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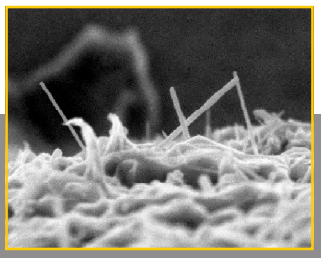

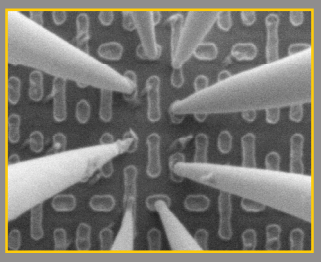

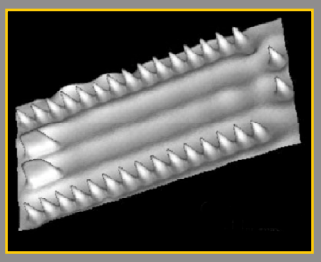

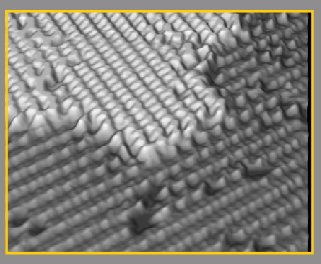

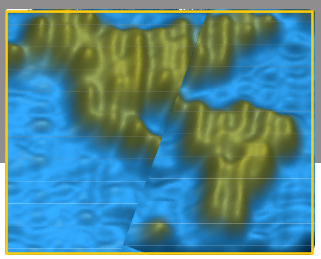

Productive Nanosystems

A Technology Roadmap

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Executive Summary

Atomically precise technologies (APT) hold the potential to meet many of the greatest global challenges, bringing revolutions in science, medicine, energy, and industry. This technology roadmap points the way for strategic research initiatives to deliver on this promise.

APT — An Essential Research Frontier

The long-term vision of all nanotechnologists has been the fabrication of a wider range of materials and products with atomic precision. However, experts in the field have had strong differences of opinion on how rapidly this will occur. It is uncontroversial that expanding the scope of atomic precision will dramatically improve high-performance technologies of all kinds, from medicine, sensors, and displays to materials and solar power. Holding to Moore's law demands it, probably in the next 15 years or less.

Atomically precise technologies are here today in diverse but restricted forms: APT structures are found throughout materials science, and APT products are common in organic synthesis, scanning probe manipulation, and biomolecular engineering. The challenge is to build on these achievements and expand them to produce a wider range of structures, providing APT systems of larger scale, greater complexity, better materials, and increasingly higher performance. Progress in this area can be used to make advances in the area of APT fabrication, which can be used to make further progress in other areas. Physics-based modeling indicates that this path will lead to the emergence of revolutionary capabilities in atomically precise manufacturing (APM).

APM Will Launch an Industrial Revolution

Atomically precise manufacturing processes use a controlled sequence of operations to build structures with atomic precision. Scanning probe devices achieve this on crystal surfaces. Biomolecular machines achieve this in living systems. In both technology and nature, the components of complex atomically precise systems are made using APM processes.

Recently identified approaches for using products of today's APM to organize and exploit other functional nanoscale components show great promise. Building on achievements in other areas of nanotechnology, they point to capabilities that could prove transformative in multiple fields, expanding the set of nanoscale building blocks and architectures for products.

Reasons why atomically precise manufacturing (APM) and atomically precise productive nanosystems (APPNs) merit high priority:

- *Atomic precision is the guiding vision for nanotechnology.*
- *Limited atomically precise fabrication capabilities exist today.*
- *Prototype scanning-probe based APM systems exist in the laboratory and demonstrate AP operations on semiconductor systems.*
- *Nanoscale APPNs exist in nature and fabricate uniquely complex AP nanostructures in enormous quantities.*
- *Improved AP technologies will enable development of next-generation APM systems.*
- *Next-generation APM systems will enable development of more advanced AP technologies.*

Atomically precise productive nanosystems (APPNs) are nanoscale APM systems that are themselves atomically precise. Biological APM systems are all APPNs. As APM technologies are drawn upon to work with a wider range of materials, APPNs will become applicable to wider and wider ranges of products. This will lead to materials and devices of unprecedented performance.

Reasons why atomically precise manufacturing (APM) and atomically precise productive nanosystems (APPNs) merit high priority (continued):

- *Nanosystems in nature demonstrate that APPNs can produce solar arrays, fuels, complex molecules, and other products on a scale of billions of tons per year, at low cost, with low environmental impact and greenhouse-gas absorption.*
- *Arrays of artificial APPN modules organized in factory-style architectures will enable fabrication of AP products on all scales and from a wide range of synthetic materials: photovoltaic cells, fuel cells, CPUs, displays, sensors, therapeutic devices, smart materials, etc.*
- *Across a wide range of devices and systems, pursuing the ultimate in high performance drives toward atomic precision, as only atomic precision can enable optimal structures.*

Robust physical scaling laws indicate that advanced systems of this type can provide high productivity per unit mass, and requirements for input materials and energy should not be exceptional. These considerations and experience with the bio-based APPNs suggest that products potentially can be made at low cost. With further development and scale-up at the systems level, arrays of APPNs will be applicable to the production of streams of components that can be assembled to form macroscale systems. These characteristics of scale, cost, and performance point to far-reaching, disruptive change that spans multiple industries.

No alternative to APPNs has been suggested that would combine atomically precise production of complex structures with the potential for cost-effective scale-up. APT development leads toward unique opportunities.

The Roadmap Workshops Opened a Unique Window on the Potential of APT

The Roadmap project provided a unique, cross-disciplinary process for exploring current capabilities and near-term opportunities in APT, and explored pathways leading toward advanced APM. Our inaugural meeting, held in San Francisco, was followed by workshops at the Oak Ridge, Brookhaven, and Pacific Northwest National Laboratories. These meetings were unusual in the breadth of disciplines and research experience brought by the participants. They were unique in their focus on integrating knowledge applicable to the development of APT and APM.

Workshop participants gained new perspectives and directions for their research. The body of this Roadmap document brings together threads from the meetings and subsequent exchanges, pointing to research directions that promise remarkable rewards.

APM Products Will Have Broad and Growing Applications

Potential products of APM are applicable to familiar nanotechnology objectives in energy production, health care, computation, materials, instrumentation, and chemical processing. These include:

- Precisely targeted agents for cancer therapy
- Efficient solar photovoltaic cells
- Efficient, high-power-density fuel cells
- Single molecule and single electron sensors
- Biomedical sensors (*in vitro* and *in vivo*)
- High-density computer memory
- Molecular-scale computer circuits
- Selectively permeable membranes
- Highly selective catalysts
- Display and lighting systems
- Responsive ("smart") materials
- Ultra-high-performance materials
- Nanosystems for APM.

The most attractive early applications of APM are those that can yield large payoffs from small quantities of relatively simple AP structures. These applications include sensors, computer devices, catalysts, and therapeutic agents. Many other applications, such as materials and energy production systems, present greater challenges of product cost or complexity. There is likewise a spectrum of challenges in required materials properties and durability in application environments. Early niche applications can provide momentum and market revenue, and we anticipate that ongoing improvements in product performance, complexity, and cost will ultimately enable the full spectrum of applications outlined in the Roadmap, as well as applications yet to be imagined.

Call to Action for APT Advancement

This Roadmap is a call to action that provides a vision for atomically precise manufacturing technologies and productive nanosystems. The United States nanotechnology advancement goal should be to lead the world towards the development of these revolutionary technologies in order to improve the human condition by addressing grand challenges in energy, health care, and other fields. The United States can accomplish this goal through accelerated global collaborations focused on two strategies that will offer ongoing and increasing benefits as the technology base advances:

1. Develop atomically precise technologies that provide clean energy supplies and a cost-effective energy infrastructure.
2. Develop atomically precise technologies that produce new nanomedicines and multifunctional *in vivo* and *in vitro* therapeutic and diagnostic devices to improve human health.

The vision expressed in this Roadmap is to use nanotechnology to improve the human condition. We believe that the most cost-effective way to do this is to develop atomically precise technologies and productive nanosystems, which enable science, engineering, and manufacturing at the nanoscale. To justify the investment, the long-term development pathway must have intermediate milestones that demonstrate real benefits.

Close cooperation between government, academia, and industry is necessary to cover the spectrum from basic to application-oriented research. To foster the necessary breakthroughs, participating universities must develop advanced study programs that address productive nanosystems. Long-term and high-risk research will require investment by government and philanthropic sources, since industry can seldom afford to invest in such research. However, an efficient approach to developing and commercializing technologies based on productive nanosystems must foster competition, since market competition has repeatedly proven to be the most efficient way to allocate the ever-scarce resources of talent, time, and money. In all areas, we must measure our success by results, not by dollars spent.

Atomically Precise Technology (APT)

- *Atomic precision is the guiding vision for nanotechnology.*
- *Required for Moore's law progress in 15 year time frame.*
- *Required for optimal materials and systems.*
- *Current forms have sharply restricted capabilities.*
- *Advances will enable expanding applications.*
- *APT development requires focused cross-disciplinary research to develop a body of engineering knowledge for systematic design and improvement of AP nanosystems.*

Close cooperation among scientific and engineering disciplines will be necessary because of the nature of the engineering problems involved. This cross-disciplinary collaboration will bring broad benefits through the cross-fertilization of ideas, instruments, and techniques that will result from developing the required technology base.

With international cooperation, the benefits of productive nanosystems will be delivered to the world faster. Coordinating a full international effort is extremely desirable in order to minimize duplication of effort in smaller national programs conducted independently.

Recommendations

As a foundation for action, establish research objectives and organizations that will be effective in developing APT systems.

- Develop a broad technology base for APT and apply this to develop improved APM, APPNs, and spinoff APT applications. Use atomic precision as a merit criterion for general research in nanofabrication. For research directed toward APM and APPNs, treat atomic precision as an essential criterion.
- Build partnerships among research institutions to coordinate the development of complex, atomically precise

nanosystems. Complement scientific exploration of novel phenomena with engineering approaches that exploit and integrate components that exhibit more predictable behavior.

- Promote collaboration aimed at satisfying the multiple requirements for building next-generation systems. The International Technology Roadmap for Semiconductors illustrates this vital role, coordinating diverse groups to develop the comprehensive sets of tools needed to fully enable next-generation technologies.

Support work on modeling and design software that facilitates AP nanosystem development.

- Prioritize modeling and design software as critical elements in the development and exploitation of APM, APPNs, and spinoff APT applications.
- Support ongoing research in multi-scale modeling to describe physical phenomena in large systems at different levels of theory and resolution. Focus this research on requirements needed to support computer-aided design software for AP nanosystems.
- Develop software that addresses domain-specific problems of modeling and design in diverse classes of AP nanosystems, including structures made by tip-directed APM and by the folding and AP self-assembly of nanoscale polymeric objects.
- Develop compilations of data organized to support design and implementation of APT systems. Classify materials, building blocks, devices, and processes, enabling search according to criteria and metrics that describe their functional characteristics. These compilations will cut across the disciplinary barriers that now impede the flow of practical knowledge.

Atomically Precise Manufacturing (APM)

- *Essential feature: programmable control of operations.*
- *Required for engineering and fabricating complex AP systems.*
- *Scanning probe devices: APM on metals, semiconductors.*
- *Biomolecular machines: APM of polymer objects.*
- *Self-assembly: large AP products from smaller ones.*
- *Near-term APM promises a growing range of applications.*
- *Advanced APM promises revolutionary applications.*

Develop tools and processes to support tip-directed APM.

- Develop stable, reproducible, atomically precise scanning tunneling microscope tips.
- Develop tool tips that capture and transfer atoms, molecules, or other building blocks in known configurations; tool tips able to sense building-block capture and release.
- Develop closed-loop nanopositioning systems with resolution < 0.1 nm and three or more degrees of freedom;

develop small-footprint systems to implement array-based parallelism

- Improve atomic layer epitaxy and atomic layer deposition.
- Seek means for highly selective depassivation and etching of surfaces and for atomically precise functionalization.
- Seek means for direct placement and bonding of atoms and molecules and for atomically precise defect inspection, repair.
- Develop robust protection layers to preserve the atomic precision of APM products.

Atomically Precise Productive Nanosystems (APPNs)

- *Essential feature: APM processes implemented by APFNs.*
- *Bio-APPNs are the central fabrication systems in living cells.*
  - *Used in biotech for bulk production: 10^{10} to >>10^{20} units.*
  - *Can now design and make 3D, 10^7-atom biopolymer objects.*
- *Advanced-generation APPNs provide a road forward.*
  - *Bootstrap the capabilities of next-gen APPNs.*
  - *Expand range of materials: ceramics, semiconductors, metals.*
  - *Increase performance of components for APFNs*
  - *Robust scaling laws predict high throughput per unit mass.*
  - *APPN arrays enable macroscale products from nano parts.*

Expand and exploit sets of building blocks for AP self- and tip-directed assembly.

- Explore and catalog diverse sources of AP components: natural and synthetic molecules, AP nanoparticles, DNA and protein objects, products of tip-directed APM.
- Expand the set of atomically precise building blocks for both AP self assembly and tip-directed methods.
- Develop monomeric building blocks for ribosome-like synthesis of AP polymer sequences with subsequent folding, binding, and cross-linking to form AP polymeric objects by self-assembly.
- Develop prototype APPNs that perform ribosome-like synthesis of AP polymer sequences.
- Make atomic precision a criterion for APT-relevant self-assembly research.
- Make systematic design methodologies a merit criterion for research in AP self-assembly.

Support the development of modular molecular composite nanosystems (MMCNs).

- Extend and exploit the recent development of configurable, 3D, million-atom-scale DNA frameworks with dense arrays of distinct, addressable, AP binding sites.
- Extend and exploit the capability of protein engineering to produce functional, relatively rigid AP polymer objects.
- Expand capabilities for engineering proteins with AP binding to DNA frameworks and functional components.

- Develop systematic methodologies for building MMCNs in which proteins bind specific functional components to specific sites on DNA structural frameworks.
- Support theoretical and experimental research to develop and exploit the ability to organize large numbers of distinct, functional nanostructures in 3D patterns on a 100 nm scale.
- Develop means to interface MMCNs with nanostructured substrates patterned by tip-directed AP fabrication and by non-AP nanolithography.
- Pursue synthetic biology approaches for bringing the cost of DNA into line with the cost of proteins and other biopolymers.

Some Enabling Technologies

- *Structural DNA nanotechnology*
- *Scanning probe manipulation*
- *Protein design*
- *Macromolecular self assembly*
- *Nanoparticle synthesis*
- *Nanolithography*
- *Organic synthesis*
- *Biotechnology and molecular biology*
- *Surface science*
- *Molecular imaging and characterization*
- *Quantum chemistry*
- *Molecular dynamics*
- *Computer-aided molecular engineering*

Explore objectives for system development.

- Extend and exploit methodologies for using modeling and design to specify APT systems well enough to indicate the requirements for their implementation.
- Use these methodologies to identify research objectives that can reasonably be anticipated to have high payoff.
- Develop objectives and requirements for implementing high-payoff APT systems, including both APT applications and next-generation APM and APPN technologies that will expand the range of APT applications.

Looking Forward

This initial roadmap explores a small part of a vast territory, yet even this limited exploration reveals rich and fertile lands. Deeper integration of knowledge already held in journals, databases, and human minds can produce a better map, and doing so should be a high priority. Some research paths lead toward ordinary applications, but other paths lead toward strategic objectives that are broadly enabling, objectives that can open many paths and create new fields. These paths are the focus of this roadmap. They demand further exploration.

Looking forward, we see both incremental payoffs and grand challenges that can be achieved through a chain of strategic objectives. Advancing from exploration, to pioneering, to full exploitation will require a great effort, but this will be a natural progression. Great rewards are already visible. They merit a commensurate investment.

Technology Development and Applications Overview

Development Area	Horizon I
Atomically Precise Fabrication and Synthesis Methods	• Bio-based productive nanosystems (ribosomes, DNA polymerases) • Atomically precise molecular self-assembly • Tip-directed (STM, AFM) surface modification • Advanced organic and inorganic synthesis
Atomically Precise Components and Subsystems	• Biomolecules (DNA- and protein-based objects) • Surface structures formed by tip-directed operations • Structural and functional nanoparticles, fibers, organic molecules, etc.
Atomically Precise Systems and Frameworks	• 3D DNA frameworks, 1000 addressable binding sites • Composite systems of the above, patterned by DNA-binding protein adapters • Systems organized by tip-built surface patterns
Applications	• Multifunctional biosensors • Anti-viral, -cancer agents • 5-nm-scale logic elements • Nano-enabled fuel cells and solar photovoltaics, • High-value nanomaterials • Artificial productive nanosystems

Horizon II	Horizon III
• Artificial productive nanosystems in solvents • Mechanically directed solution-phase synthesis • Directed and conventional self-assembly • Crystal growth on tip-built surface patterns • Coupled-catalyst systems	• Scalable productive subsystems in machine-phase environments • Machine-phase synthesis of exotic structures • Multi-scale assembly • Single-product, high-throughput molecular assembly lines
• Composite structures of ceramics, metals, and semiconductors • Tailored graphene, nanotube structures • Intricate, 10-nm scale functional devices	• Nearly reversible spintronic logic • Microscale 1 MW/cm^3 engines and motors • Complex electro-mechanical subsystems • Adaptive supermaterials
• Casings, "circuit boards" to support, link components • 100-nm scale, 1000-component systems • Molecular motors, actuators, controllers • Digital logic systems	• Complex systems of advanced components, micron to meter+ scale • 100 GHz, 1 GByte, 1 μm-scale, sub-μW processors • Ultra-light, super-strength, fracture-tough structures
• Artificial immune systems • Post-silicon extension of Moore's Law growth • Petabit RAM • Quantum-wire solar photovoltaics • Next-generation productive nanosystems	• Artificial organ systems • Exaflop laptop computers • Efficient, integrated, solar-based fuel production • Removal of greenhouse gases from atmosphere • Manufacturing based on productive nanosystems

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Acronyms and Abbreviations

3DAP	3-D Atom Probe
AES	Auger Electron Spectroscopy
AFM	Atomic Force Microscopy
ALE	Atomic Layer Epitaxy
AP	Atomically Precise
APFN	Atomically Precise Functional Nanosystem
APM	Atomically Precise Manufacturing
APPN	Atomically Precise Productive Nanosystem
APSA	Atomically Precise Self Assembly
APT	Atomically Precise Technology
CAD	Computer Aided Design
CASSCF	Complete Active Space Self-Consistent Field
CBS	Complete Basis Set
CC	Coupled Cluster
CI	Configuration Interaction
CNDO	Complete Neglect of Differential Overlap
Cryo-EM	Cryo-Electron Tomography
DCP	Disc Centrifuge Photosedimentation
DLS	Dynamic Laser Light Scattering
ESEM	Environmental Scanning Electron Microscopy
FIB	Focused Ion Beam
FRAP	Fluorescence Return After Photobleaching
FRET	Fluorescence Resonant Energy Transfer
FTIR	Fourier Transform Infrared Spectroscopy
GVB	Generalized Valence Bond
HRTEM	High Resolution Transmission Electron Microscopy
INDO	Intermediate Neglect of Differential Overlap
LED	Light Emitting Diode
MCSCF	Multi-Configuration Self-Consistent Field
MEMS	Micro Electro Mechanical System
MINDO	Modified Intermediate Neglect of Differential Overlap
MMCN	Modular Molecular Composite Nanosystem
MP	Moeller-Plesset Perturbation Theory
MRCI	Multi-Reference Configuration Interaction
MWNT	Multi-Walled Carbon Nanotube
NC-AFM	Non-Contact Atomic Force Microscopy
NMR	Nuclear Magnetic Resonance
NOPV	Nanostructured Organic Photovoltaic
OLED	Organic Light Emitting Device
PALS	Phase Analysis Light Scattering
PCS	Photon Correlation Spectroscopy
PEM	Proton Exchange Membrane; Polymer Electrolyte Membrane
PIXE	Proton Induced X-ray Emission
PN	Productive Nanosystem; Obsolete form replaced by APPN
PPP	Pariser-Parr-Pople
PV	Photovoltaic
QMC	Quantum Monte Carlo
RS	Raman Spectroscopy
SAM	Scanning Auger Microscopy
SAMMS™	Self-Assembled Monolayers on Mesoporous Supports
SANS	Small Angle Neutron Scattering
SAXS	Small Angle X-ray Scattering

SEM	Scanning Electron Microscopy
SHeM	Scanning Helium Ion Microscope
SNOM	Scanning Near-Field Optical Microscopy
SPM	Scanning Probe Microscopy
SSL	Solid-State Lighting
SSNMR	Solid State Nuclear Magnetic Resonance
STM	Scanning Tunneling Microscopy,
SWNT	Single-Walled Carbon Nanotube
TEM	Transmission Electron Microscopy
TOF-SIMS	Time of Flight Secondary Ion Mass Spectrometry
UV-vis	Ultraviolet-Visible Spectroscopy
XAFS	X-ray Absorption Fine Structure
XPS	X-ray Photoelectron Spectroscopy
XRD	X-ray Diffraction

Introduction

The two challenges Richard Feynman issued at the end of his classic lecture in 1959, "There's Plenty of Room at the Bottom," helped focus interest on the possibility of manipulating and controlling things on a very small scale. Since that time, researchers have increasingly turned their attention to achieving atomically precise manufacturing (APM). There are immense technical challenges in attaining complete control of the structure of matter, and the development path is apt to be a long one. However, even before the ultimate goal is achieved, APM is expected to provide a wide array of practical and profitable technologies and products as research and development in nanotechnology proceeds.

Leadership provided by Battelle and access to conference facilities at three U.S. National Laboratories were instrumental in enabling researchers from academia, government, and industry to map out several paths that hold promise in developing the ability to construct complex products with atomic precision. The workshop projects brought together key stakeholders who have a role in developing the next generations of nanotechnology, and gave them the opportunity to coordinate their current thinking and future APM activities. The aim of this first version of a nanotechnology roadmap is to provide a common vocabulary and framework that scientists, engineers, managers, and planners from many technical specialties can use for their own strategy, investment, research and/or development processes. This *Technology Roadmap for Productive Nanosystems* is a first attempt to map out the R&D pathways across multiple disciplines to achieve atomically precise manufacturing.

About the Roadmap Document

This Roadmap has three main parts. The first provides a broad, integrated perspective on technologies and objectives in APT and APM, together with a survey of applications and a policy-oriented call to action.

The second, *Topics in Detail,* explores contributing technologies in more depth, surveying current capabilities important to APT and APM and discussing how they might be exploited to develop next-generation capabilities and applications. It is here that we felt most acutely the limits of our time and resources relative to breadth and depth of the relevant knowledge. Important topics, major challenges and opportunities, and promising lines of development are sometimes represented as bullet points, or briefly highlighted in the discussion of a broader subject. We believe this represents an opportunity to invite

your participation in the development of a future version of this roadmap.

Finally, the *Working Group Proceedings* presents a set of papers, extended abstracts, and personal perspectives contributed by participants in the Roadmap workshops and subsequent online exchanges. These contributions are included with the Roadmap document to make available, to the extent possible, the full range of ideas and information brought to the Roadmap process by its participants.

We hope that this initial exploration of paths forward will be followed by further efforts, some more comprehensive, and others delving more deeply into topics that will, in time, become fields in themselves.

Battelle and Foresight Nanotech Institute would like to thank the Waitt Family Foundation and Sun Microsystems for financial support of the project, and the many research participants for their technical knowledge and time in producing this "first cut" at an APM roadmap.

About the Terminology in the Roadmap

The initial meeting of the Steering Committee and follow-on discussions produced the following definitions for key terms:

- **Nanosystems** are interacting nanoscale structures, components, and devices.
- **Functional nanosystems** are nanosystems that process material, energy, or information.
- **Atomically precise structures** are structures that consist of a specific arrangement of atoms.
- **Atomically precise technology** (APT) is any technology that exploits atomically precise structures of substantial complexity.
- **Atomically precise functional nanosystems** (APFNs) are functional nanosystems that incorporate one or more nanoscale components that have atomically precise structures of substantial complexity.
- **Atomically precise self-assembly** (APSA) is any process in which atomically precise structures align spontaneously and bind to form an atomically precise structure of substantial complexity.

There is no sharp and compelling line that defines the atomically precise structures within the scope of the TRPN. For example, devices made with 10,000 atoms in a specific, complex structure would be in scope, even if they have a few defects, yet a flawless water molecule would be out of scope. Somewhere between these is a gray area. Because agreement on a sharp definition would be difficult and of little use, we suggest that this question be set aside. Rather than using scale, complexity, and defect density to define threshold criteria, it will be more productive to use them as metrics for evaluating progress.

- **Atomically precise manufacturing** (APM) is any manufacturing technology that provides the capability to make atomically precise structures, components, and devices under programmable control.

- **Atomically precise productive nanosystems** (APPNs) are functional nanosystems that make atomically precise structures, components, and devices under programmable control, that is, they are advanced functional nanosystems that perform atomically precise manufacturing.

Atomic Precision: What, Why, and How?

Atomically precise structures consist of a definite arrangement of atoms. Current examples include:

- Self-assembled DNA frameworks
- Engineered proteins
- Crystal interiors and surfaces
- STM-built patterns on crystal surfaces
- Organic molecules, organometallic complexes
- Closed-shell metal clusters and quantum dots
- Nanotube segments and ends
- Biomolecular components (enzymes, photosynthetic centers, molecular motors).

This section briefly answers basic questions about atomic precision, and shows the motivation for work in the field. It also provides a framework for distinguishing near-term, mid-term, and advanced levels.

These examples illustrate some limits of fabrication capabilities today. The only large structures are simple and regular—crystals; the only complex, 3D structures are polymers—proteins and DNA. Atomically precise, STM-built patterns are at a very early stage of development. The remaining examples represent components with a broad range of functions. What is lacking is a systematic way to combine components to build complex systems.

Physical principles and examples from nature both indicate the promise of extending atomically precise fabrication to larger scales, greater complexity, and a wider range of materials. Table 1 outlines how various aspects of atomic precision (control of feature size, surface structure, etc.) enable useful properties and applications, many of which have revolutionary potential. Applications of atomically precise systems are presented in more detail later in this Nanotechnology Road Map.

The range of techniques to produce atomically precise structures is already broad, and broader applications will follow as production techniques are augmented with methods of greater power and generality. To understand the promise of atomically precise technologies, it helps to draw a clear distinction between what we can do with today's level of technology, and what we can identify as targets for longer-term research and development, requiring advances in crucial enabling technologies.

Table 1. Atomically precise structural control: kinds, results, and uses

Aspect of atomic precision:	Enabled features and applications:
Precise internal structures	Materials with novel properties (optical, piezoelectric, electronic…) with extremely broad applications
	Defect-free materials that achieve their ideal strength, conductivity, transparency…
	Absence of statistical fluctuations in dopants enabling scaling to smaller gate size
	3D bandgap engineering for systems of quantum wells, wires, and dots
	Systems of coupled spin centers for novel computer devices, quantum computing
Atomic-scale feature size	High frequency devices, new sensors, high power-density mechanisms
	High density digital circuitry, memory (up to ~10^{20} devices per cm^3)
Precise patterns of surface charge, polarity, shape, and reactivity	Unique alignment of complementary surfaces for atomically precise self-assembly of complex, many-component structures
	Precisely structured scanning-probe tips for atomically precise manufacturing, improved scanning probe microscopy
	Molecular binding, sensing of specific biomolecules
	Stereospecific and chiral catalysis
	Filtering, purification, separation
Atomically smooth, regular surfaces	Minimal scattering of electrons for low resistance nanowires, ideal electron optics
	"Epitaxial" alignment of matching surfaces for atomically precise self-alignment, high-strength interfaces
	Non-bonding, out-of-register surfaces for sliding interfaces with negligible static friction
Precisely identical structures	System designs can exploit fine-tuning of properties
	System designs can exploit symmetries among identical components
	Reproducible behavior simplifies fault identification

These apply to a range of levels of fabrication capabilities (see Table 2)

Anticipated developments may derive directly from the achievement of intermediate, enabling goals, which lends them a special strategic importance in the formulation of plans for technology development.

Techniques for implementing atomically precise systems are often based on atomically precise tools. For example, organic synthesis depends on organic reagents; atomically precise biopolymeric structures are built by molecular machine systems made of similar materials. Thus, atomically precise manipulation of surfaces could benefit from the use of atomically precise tool-tips. Some of the anticipated developments derive directly from the achievement of intermediate, enabling goals. Consequently, intermediate goals are of special strategic importance in formulating plans for technology development.

The promise of atomically precise fabrication springs from the diversity of techniques and approaches that have emerged, and from the many ways in which these might be combined to move the field forward. This diversity, however, complicates any attempt to describe pathways and levels of anticipated development. Table 2 provides a simple overview. Moving from current capabilities, two complementary lines of development emerge: one anchored in direct manipulation of atomic and molecular structures by means of scanning probe devices, the other anchored in atomically precise self-assembly of diverse components organized by folded polymers. Downstream, advances lead to atomically precise fabrication based on productive nanosystems, and a convergence of these lines of development. This schematic perspective serves to show broad directions of advance, and to distinguish near-term developments from those that can be approached only by means of intermediate stages.

Progress in this area will raise familiar constellations of challenges, such as:

- Design and modeling
- Device properties
- Spatial organization and interconnection of components
- Interfacing to macroscale systems
- Production methods, cost, and yield
- Device degradation and lifetime
- System-level defect tolerance

Later in this document we address the critical research challenges that must be met to move forward toward applications and toward enablers for a succession of next-generation technologies.

Table 2. Existing and projected capability levels in atomically precise fabrication.

Years	Fabrication methods*	Input materials	Product type	Atoms in typical product	Typical product quantity†	
					grams	units
Current Level						
2007	Tip-based APM	Small molecules	Patterned crystal surfaces	1.E+02	1.E-21	1.E+00
	Organic synthesis	Various reagents	Varied covalent structures	1.E+02	1.E+00	1.E+21
	Protein engineering, Ribosome as APPN	Biological substrates	3D folded polymers	1.E+03	1.E+00	1.E+20
	Structural DNA design, Polymer-ase as APPN	Biological substrates	3D polymer frameworks	1.E+06	1.E-06	1.E+11
	Special processes	(Diverse)	Nanocrystals, nanotubes, others (diverse)	—	—	—
Next Generation						
2 – 10	Tip-array APM	Small molecules	Layered crystalline structures, multiple materials	?	?	?
	Self-assembly of composite nanosystems	Building blocks: DNA, protein, and other	3D biopolymer frameworks, diverse components	1.E+07	1.E-03	1.E+13
Level 1						
5 – 15	Tip-array APM	Small molecules	Diverse 3D structures, diverse materials	?	?	?
	Artificial polymer-building APPNs, guided assembly	Diverse monomeric building blocks	Robust polymer-based composite nanosystems	1.E+08	1.E+00	1.E+15
Level 2						
10 – 25	Solid-building APPNs (converged technologies)	Small molecules	Robust systems built of diverse engineering materials	1.E+09	1.E+01	1.E+15
Level 3						
15 – 30	Scalable APPN-array systems, directed assembly	Small molecules	Systems at the level of complexity of 2007 macroscale products	1.E+10	1.E+02	1.E+15
Level 3+						
15 – 30+	Scaled APPN-array systems	Small molecules	Large arrays of complex systems	1.E+26	1.E+03	1.E+00

*Typically combined with other nanotechnologies: nanolithography, nanoparticles, SAMs, etc.
†Rough order of magnitude of quantity per lab-scale production run.

Atomically Precise Manufacturing

APM will play a growing role in atomically precise fabrication, expanding both the production volume and capabilities of atomically precise products. The two approaches in use today are tip-based APM, which uses STM or AFM mechanisms to pattern surfaces with atomic precision, and bio-based APM, which uses the natural, programmable molecular machinery of living cells to produce atomically precise molecular objects. These approaches are complementary because they address different problems and have potential synergies when used in combination. APM in all its forms can both exploit and extend the capabilities being developed in the broader field of nanotechnology.

Bio-based APM can be used to produce large, complex, functional nanosystems.

Potential of Bio-Based APM to Produce Large, Complex, Functional Nanosystems

The largest complex, atomically precise objects fabricated as of 2007 are made of DNA. These DNA constructions comprise helical rods linked to form combinations of sheets, tubes, and triangulated structural frameworks. For DNA constructions of established types made in well-equipped facilities, it is currently feasible to complete the design and fabrication cycle for new product in about one day, and an established type of DNA construction has been licensed for commercial use. Looking forward, DNA constructions appear able to position hundreds to thousands of distinct components to addressable locations in three-dimensional patterns.

Table 3. Functional properties and roles of DNA, protein, and specialized structures in modular molecular composite nanosystems.

	DNA	Protein	Specialized
Limitations	narrow range of functions, limited binding	small structures, difficult design, slow production	non-modular, seldom much design freedom
Strengths	large structures, easy design, fast production	broad range of functions, versatile binding	unlimited range of materials and functions
Natural roles	structural frames, large-scale pattern organization	assembly interfaces, precise alignment, diverse functions	catalytic, optical, mechanical, electronic...

Engineering protein molecules is now routine and produces complex objects built around dense polymer cores. Protein molecules can be

engineered to bind to DNA, to each other, and to a wide range of atomically precise structures. Moreover, a wide range molecules and nanostructures can be directly and covalently linked to DNA constructions. Together, these capabilities enable the development of atomically precise self-assembled modular molecular composite nanosystems.

Areas of Nanotechnology Where Bio-Based Modular Molecular Composite Nanosystems Are Applicable

In building large, self-assembled systems, these components can work together:

- DNA constructions are well suited to serve as frameworks.
- Nanometer-scale protein molecules are well-suited to serve as precision binding structures. Their mechanical properties are typically comparable to those of engineering resins such as epoxies and polycarbonates.
- A host of particles, fibers, and surfaces are well-suited to serve as high-performance structural and functional components.

Numerous fields of nanotechnology research have produced functional components. In many instances, this work may find a new level of payoff through the use of MMCNs to organize these components to form functional systems.

Main Challenges for Applications Using Self-Assembling MMCNs

The development of self-assembling MMCNs presents challenges related to the design of building blocks and of complementary interfaces between them. A major advantage of DNA is that interfaces for APSA can be provided by simply matching bases. Protein design, by contrast, requires computational search of a large combinatorial space. Special functional structures offer only highly constrained options for surface design, which must be accommodated by other system elements.

Biopolymers have a restricted range of properties and limited stability, with rigidity similar to that of engineering materials such as epoxy and polycarbonates. Although some organisms live at >100°C, the tolerance of biopolymers for high temperatures is limited. Many naturally occurring proteins, in particular, are notorious for low stability.

Increasing the stability and range of operating environments feasible for products of bio-APM is a major challenge. Progress has been made both in designing proteins for higher than natural stability and in using unnatural conditions, such as dry organic solvents, to increase their stability. In addition, designs should be sought in which biopolymers play an organizing role during fabrication, and then are no longer necessary.

For large-scale applications of MMCN, a further challenge is the cost of materials. Bulk DNA production costs are currently in the dollars per milligram range (or higher). The application of bioengineering techniques, however, promises to bring this cost down to dollars per kilogram, comparable to that of many other biopolymers.

Approaches Embraced by Tip-Based APM

The range of potential process and resulting structures associated with tip-based APM is quite broad.

Tip-based APM-style manipulation has been performed on many materials, with positioning of many kinds of atoms and molecules. The range of potential processes and resulting structures therefore may be quite broad. However, most of the work to date has involved lateral displacement of weakly bound species on surfaces. For APM to become viable, new processes must be developed that exploit the inherent resolution of scanning probe tools, but permit covalent bonding to build three-dimensional structures. Identified approaches include transfer and deposition of atoms, and removal of atoms or molecules to create reactive surfaces for precisely tailored crystal growth (patterned atomic layer epitaxy or ALE). Patterned ALE is presently a target of commercial research.

Challenges for Tip-based APM in Process Development and Scale-Up

It remains a challenge to develop a tip-APM process that operates quickly and with a low product defect rate. In terms of mass throughput, the rate of production possible by means of macroscopic tip-based APM systems is inherently low, but increases in speed expand the size and complexity of feasible products. These challenges can be addressed by a combination of advances in several areas:

- Identification of tractable combinations of surfaces and building blocks.
- Development of improved and more reproducible structures for scanning tunneling microscope tips to be used for patterned ALE.

- Development of tips that can capture and deposit atoms or molecules for mechanosynthesis.
- Improvement in the stability and control provided by tip positioning mechanisms.
- Simultaneous use of many tips to increase fabrication speeds.

One of the more promising paths for scaling up to relatively large numbers of tips is the use of micro electro mechanical systems (MEMS) –based closed loop nanopositioning systems. Recent advances in CMOS-compatible MEMS closed loop systems suggest that small-footprint intelligent scanning systems could be developed and down-scaled to produce relatively large arrays of tips that could operate at high frequencies. However, even with these advancements, macro-scale manufacturing tools that employ tip-based APM will need a throughput that will produce significant value per unit.

This suggests applications in areas such as sensors (DNA sequencing, for example), information processing (quantum encryption and computing), and the creation of atomically precise tools (such as nanoimprint templates). Perhaps the most important contribution of tip-based APM will be to make the atomically precise components required for productive nanosystems.

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Complementary Nature of Tip-Based and Bio-Based Technologies

It should be clear that tip-based and bio-based APM technologies address different problems, face different challenges, and provide different results. They are in no sense competitors, but are in fact complementary. Moreover, the MMCN vision embraces self-assembled structures that interface with the products of tip-APM systems. Each approach increases the value of the other, because both together promise to enable a broader range of products and applications.

Cascade Effect of Advances in APM and Other Technologies

Bio-APM processes in living cells build bio-APM mechanisms, and this points to the feasibility of developing biomimetic APM systems, some of which could enable the fabrication of a wider range of polymer structures than that found in biology.

Looking forward, expanding the range of feasible components will increase the performance of feasible products, including APM systems. Advances in APM can therefore be directly applicable to improving

next-generation APM. Iterating this process toward higher performance materials leads toward structures (for example, ceramics) that are denser and more stable than biopolymers. APM systems that build products of this sort are envisioned to use flexible tip-based processes, since biomimetic approaches appear to have limited value in this area.

Further development will involve broadening the range of structures that can be built, leading to nanoscale structures that by themselves provide the central components necessary for APM. As always, hybrid approaches that combine the strengths of different lines of development may prove attractive.

This anticipated convergence on tip-based inorganic systems suggests that near-term, tip-based APM methods might be more directly developed in this direction. The approaches of this kind also involve broadening the range of structures that can be built, leading to nanoscale structures that by themselves provide the central components necessary for APM. As always, hybrid approaches that combine the strengths of different lines of development may prove attractive.

It should be noted that these lines of advance remain speculative in their specifics. A case can be made that adequate tools will become available, and basic physical principles appear favorable, yet the absence of concrete designs limits conclusions that can be drawn regarding downstream objectives, development times, costs, and so forth.

Some general features are clear, however. For example, physical principles indicate the feasibility of highly productive nanosystems. Elementary mechanical scaling laws indicate that tip-based mechanisms on a 100 nm scale can be expected to operate with high motion frequencies (KHz to MHz). This rate is sufficient for an APM tip mechanism assembly to process a mass comparable to that of the mechanism itself in a practical length of time (a day or less). Taking into account requirements for power, coolant, power, control signals, and transport of feedstocks and products, one can envision planar structures that provide arrays of specialized, productive, nanoscale mechanisms, and the design and coordination of these mechanisms extrude macroscale products constructed from building blocks that are themselves sophisticated nanosystems.

As pointed out by a recent study sponsored by the US National Academies, there are uncertain constraints on the performance of APM systems. One is the error rate in the unit operations, which is related to another, which is thermodynamic efficiency. These are a function of numerous conditions, including the thermodynamic requirement that energy be dissipated to drive each step forward, and the magnitude of the energy barriers that separate paths leading to desired and undesired outcomes. To the extent that discussions in the Roadmap considers prospects for downstream products, the usual premise will be that error rates and energy costs are roughly in line with those seen in bio-based APM processes today.

Position of APM in Current Nanotechnologies

At a component level, products of bio-based APM, such as MMCNs, are naturally complementary to a host of nanotechnology products. Some provide atomically precise interfaces suitable for self-assembly, and these can in many instances join and extend the atomically precise domain of a larger system. More generally, even atomically irregular nanoparticles, fibers, and surfaces can provide functionality to be organized by an atomically precise framework. Conversely, APM products will expand the array of building blocks available for developing nanomaterials and nanosystems of all kinds. APM and other nanotechnologies lend each other greater value.

APM products will expand the array of building blocks available for developing nanomaterials and nanosystems of all kinds.

Among the most attractive prospective applications of APM, both tip-based and bio-based, are those that build on nanolithography and nanoscale electronic circuitry. There is a natural fit between these technologies in interfacing between the nano and macro worlds, enabling the flow of energy and information in one direction, and data from sensors, memories, or nanocircuitry in the other. The advances driven by APM lend further weight to the widespread view that atomically precise fabrication will become part of the ongoing revolution in microelectronics.

Atomically Precise Components and Systems

The applications of any manufacturing system depend on the structural frameworks, functional elements, and systems that can be built using it. The same holds with atomically precise manufacturing (APM). This section gives a brief overview of APM capabilities related to product structure and function. It is not intended to serve as a complete survey.

Structural Frameworks—A Limiting Factor in Applications of Nanosystems Engineering

The weakness of structural frameworks in the area of nanosystems engineering can be overcome by the development of APM-based fabrication.

The manufacture of atomically precise individual devices, such as molecular wires and switches, has been demonstrated. However, the devices have seen little use, largely because of the lag in the further development of technology to make comparably precise frameworks to hold and organize them. Transistors and conductors would have remained laboratory curiosities if the technology to organize them to form circuits would not have matured. Similarly, we know of the development of many molecular motors, bearings, and so forth, but we do not have a way to connect them to build systems.

This limiting factor is not critical in the field. Some applications of APFNs require no frameworks. For example, enzyme-like catalysts could function in solution or could be bound to conventional high-surface-area substrates, as is done with similar functional entities in current industrial practice.

Promising Results of APM-Based Fabrication

Tip-based APM exploits crystal surfaces to provide large, rigid structures. These surfaces provide a structure on which tip-based manipulation can build functional elements. One class of structures could be “sockets” that provide atomically precise interfaces able to direct the atomically precise binding (self-assembly) of diverse functional elements, exploiting components developed by other methods means of fabrication.

Self-assembly of moderately complex molecular components provides an alternative means of fabrication of atomically precise frameworks for complex nanosystems. To accomplish this, the components must be designable, in the sense that a systematic procedure enables the selection of structure from a large range of possibilities. This design freedom is required to enable the fabrication of interfaces that match other components, including the many unique, pairwise-matching interfaces required to organize the self-asssembly of information-rich,

aperiodic structures of the sort that abound in conventional engineered systems.

Ultimately, any of a range of structures built by incremental addition of different building blocks could serve this function. Today, the accessible structures of this class are restricted to polymers that are built stepwise, with a choice of monomers at each step. Wholly synthetic versions of such polymers have been experimentally realized, and these have unique properties, but the premier examples are biopolymers built by APM systems provided by nature. These are proteins and the nucleic acids, RNA and DNA. Extending this set to enable routine use of robust, non-biological polymers is an objective with potentially high payoff.

Structures that, like these polymers, are formed in a systematic way from multiple components are termed "modular." Modular molecular composite nanosystems are self-assembled systems in which several different kinds of building blocks are organized by frameworks based on self-assembling units with a modular structure. Using a combination of DNA and proteins to organize functional elements derived from other nanotechnologies appears attractive.

Advances in APM will expand the diverse set of precise, exploitable functional elements that have been developed already, providing new ways to organize and exploit them and creating nanosystems at a new scale of size, complexity, and sophistication.

Precise, Exploitable Functional Elements Now Available

In recent years, billions of dollars have been invested in exploring and developing functional elements on the nanoscale. These include:

- Organic molecules and organometallic complexes with useful optical and catalytic activities.
- Closed-shell metal clusters and quantum dots with unique electronic properties.
- Nanotubes with extraordinary strength, stiffness, and conductivity.
- Lithographically patterned electronic devices with features smaller than macromolecules.
- Biomolecular devices with the diverse photochemical, mechanical, catalytic (etc.) activities essential to photosynthesis, motion, and metabolism in living cells, including APM functionality.

APM-based fabrication will leverage past research investments by providing a new means to organize and exploit these functional elements, creating nanosystems at a new scale of size, complexity, and sophistication.

Functional Elements and Systems Enabled by APM

Advances in APM will enable a wider range of materials to be patterned with atomic precision. The resulting expansion in the range of functional devices will generically enable higher performance, greater stability, and longer functional lifetimes. A few of the devices expected to become feasible along this development path include:

- Circuitry based on integrated nanotube conductors, semiconductors, and junctions.
- Arrays of identical or smoothly graded quantum dots, promoting controlled transfer of electrons and electronic excitations.
- Digital devices based on transitions in precisely coupled spin systems.
- Nanoscale memory cells organized into 3D crystalline arrays with $\geq 10^{18}$ bits per cubic centimeter.
- Catalytic molecular machinery that couples mechanical energy to chemical transformations.

Advances in APM-enabled device fabrication will combine with other fabrication techniques to expand the technology base for development of atomically precise systems. The section on Application Highlights will explore some of the application-level capabilities that are expected to emerge.

Relevance of Physics-Based Modeling

The potential of advanced-generation nanosystems can be understood in part by physics-based modeling.

It is important to recognize that physics-based modeling can provide insights into the capabilities of physical systems whose implementation is beyond reach of current-generation fabrication technologies. Systems of this class arise naturally in considering multi-stage development of advanced fabrication systems. Physics-based modeling can provide an indication of the potential that can be unlocked by pursuing various lines of development. Placing systems of this class in the context of a multi-stage roadmap also puts them in a clarifying perspective, showing both their connection to, and their distance from, the technologies of today or the next decade.

Design, Modeling, and Characterization

Design, modeling, and characterization technologies together are intimate components of the design cycle in technology development. Design and modeling are closely intertwined, ultimately guiding fabrication. Characterization technologies—imaging and measurement—provide the data that validate or drive revision of both designs and models. Characterization technologies are crucial, but largely adequate today. Design and modeling, by contrast, will set the pace of development for many atomically precise technologies. They drive demand for more better data, models, algorithms, and computers. ("Modeling" as used here includes simulation by dynamic models.)

APT Design Requirements

By its nature, APT requires atomistic modeling. Beyond this, however, domain-specific requirements vary widely. Processes that involve bond rearrangement, unusual structures, electron transport, or electronic state transitions typically demand quantum-mechanical modeling of electron distributions and energies. Processes that involve atomic motion and molecular displacement and deformation are typically addressed by molecular mechanics and molecular dynamics methods. To reduce computational burdens, reduced models are common, treating groups of atoms as single bodies, or (in the limiting case) subsuming them into non-atomistic models of elastic or even rigid solid bodies. At this level, the techniques are those familiar in macroscale modeling and design.

Choosing a specific model always involves trade-offs of the speed of computation, the scale of the structures modeled, and the accuracy of the results. Quantum methods in particular embrace a range of models (levels of theory) that differ widely in their computational tractability: Some allow dynamical studies of thousands of atoms; others strain available computational resources in order to provide great precision in describing small molecules. Molecular mechanics and dynamics models rely on direct approximations to the forces among atoms, and currently scale to systems with up to millions of atoms. The accuracy of the latter methods (for suitably chosen classes of systems) can be judged by the fact that they are used to gain insights into the balance of weak interatomic forces responsible for the geometry and dynamics of proteins and other biomolecules.

Extending the scale, scope, and accuracy of atomistic modeling techniques is a high priority and can greatly facilitate APT design and implementation. Integrating atomistic and non-atomistic models at different levels and scales is key to enabling practical design and

Modeled Properties

Some commonly modeled properties important to AP components and systems:

- *Structural geometry, rigidity*
- *Molecular dynamics behavior*
- *Energy of reactant molecules*
- *Energy of transition state barriers*
- *Energy of protein unfolding*
- *Energy of non-covalent binding*
- *Dynamic friction, thermalization*
- *Transport of thermal energy*
- *Transport of electron, holes*
- *Electrostatic dipoles, forces*
- *Energies of electronic transitions*
- *Optical refraction, absorption*
- *Nonlinear optical coefficients*
- *Spin-spin interaction dynamics*
- *Magnetic domain dynamics*

simulation of large, complex AP nanosystems. This is an area of ongoing research activity.

Near-Term Potential for Design and Development

APT design requires multi-level, multi-scale modeling of diverse phenomena.

In assessing the near-term potential for the design and fabrication of APT systems, it is necessary to assess the adequacy of existing modeling techniques in support of the design process. This is a matter of particular concern because of the existence of many physical systems of interest for which the predictive power of existing models is very poor, often giving qualitatively incorrect results (for example, predicting stability for a system that is in reality unstable).

Design and development can succeed despite incomplete knowledge.

For design problems, the adequacy of a model cannot be assessed without considering the practical question it must answer. Design can succeed, and even be reliable, in domains where models have substantial inaccuracy and can give qualitatively incorrect results. What is required for success is not universal predictive accuracy, but instead is the ability to identify a suitable class of systems within the domain. To be suitable for the purpose of design, members of this class must be sufficiently well-behaved to be insensitive to modeling errors, and the class must include members that satisfy the relevant set of design requirements. What constitutes sufficient insensitivity, however, typically depends on whether these requirements are stringent or loose, hence the importance of knowing the practical design question before judging the adequacy of a model.

Even very incomplete knowledge can aid a technology development program. Even a weakly predictive model can speed development by directing experimental research away from likely failures and toward systems that are viable candidates for success. Experimental trial and error is often an acceptable development method, provided that success is sufficiently common, and that trials are not prohibitively slow or expensive.

Developments That Can Reducing Modeling Difficulty

Advances in AP fabrication will enable practical applications of an increasing range of structures and phenomena, increasing demands on modeling techniques by driving expansion of their scope, and increasing the demand for faster and more routine methods that are applicable in the context of system design.

However, in one important respect, advances in AP fabrication can make successful modeling less demanding. Advanced fabrication techniques can in many instances make components with improved the

stability, rigidity, and performance. These improvements tend to make the structural behavior of components less sensitive to small errors in model energies, and they can also be used to increase the margin of safety by which components satisfy design requirements. This again reduces sensitivity to errors.

Advances in AP fabrication can in some instances reduce modeling requirements.

As a consequence, currently accessible products may require more advanced modeling techniques, while analogous advanced products do not. This inverse relationship is illustrated by molecular machines, where protein-based devices remain a great challenge to modeling, but not to fabrication, while machines made of rigid AP components can be easy to model, despite being inaccessible to current and near-term fabrication techniques. This relationship facilitates, to an unexpected degree, the use of current modeling techniques to explore and evaluate the general properties of classes of systems in order to weigh their potential value as longer-term development objectives.

Innovation Needed in Computer-Aided Design

Each unique domain of atomistic modeling (see list of Modeled Properties at the beginning of this section) creates corresponding unique demands on computer aided design (CAD) tools. At all but the largest scales, conventional approaches are inapplicable because of the discrete nature of component structures: One must drop the assumption that dimensions, electrical properties, etc., can be varied in a continuous way. This is in many ways more fundamental than differences in the applicable device physics.

APT developments demand innovations in computer-aided design.

For structures to be made by means of tip-directed APM processes, product geometry results directly from a programmed sequence of motions of a tool with respect to a workpiece. This directness applies both to current and next-generation APM based on scanning-probe instruments and to envisioned advanced-generation productive nanosystems. Domain-specific CAD requirements in this area are driven chiefly by the need to model discrete structures with appropriate device and process physics.

In AP self-assembled systems, by contrast, structure and fabrication become related in a far more intimate way. At every stage of assembly, at least one component must be free to diffuse in a solvent, enabling it to explore all possible positions and orientations to find its unique, intended binding site. This process requires that the component be soluble, that it have a surface complementary to that of its intended binding site, and that all other surfaces of the workpiece and the component be sufficiently non-complementary that stable binding is

precluded. These requirements are added on top of functional requirements.

Identification of designs in which components have appropriate surfaces and matching interfaces characteristically requires an automated computation search mechanism. In many DNA structures, "sticky ends" serve as complementary interfaces, while in proteins, folding requirements can be viewed as extending self-assembly constraints to the interior of the molecule. In both instances, design tools today rely on search in the combinatorial space of alternative monomer sequences. Improving success rates and product performance will likely require improvements in this class of algorithms, chiefly in the definition of suitable objective functions.

Future-generation APSA systems, perhaps exploiting components produced by new classes of APPNs, appear likely to share this requirement for integrating search-based operations in CAD tools and design processes. A similar need for search will arise when tip-based APM systems are used to manufacture structures that satisfy surface-defined constraints by means of structures that depart greatly from crystalline order.

Multi-level modeling is motivated by the great differences in scope and computational cost associated with different modeling techniques, and this will need to be integrated into CAD tools and the design process in two distinct ways. The first is the application of different techniques to different parts of a system, for example, applying quantum methods to describe reactions, while applying molecular mechanics methods to describe the structures that support and constrain the reacting components. This has been achieved and applied, for example, in modeling enzymes. Expanding this principle to mixed models of more kinds is an important objective. The second role for multi-level modeling is design refinement. In this application, less-accurate, lower-cost techniques are used for exploratory purposed, to identify systems that are worth further investigation using more-accurate, higher-cost techniques. It will be important to provide smooth integration of this methodology into CAD tools for developing APT systems.

Characterization Methods Enable Refinement of All the Other Methods

Characterization methods enable refinement of designs, models, and fabrication methods.

The development cycle in systems engineering loops through design and modeling (for example, computational simulation) until an apparently satisfactory result is achieved. Fabrication and physical testing then provide the ultimate feedback on the success of a design.

The quality of this feedback determines its effectiveness in guiding any necessary revisions in the fabrication method, the model, or the design. It is crucial to know, for example, whether a failure results from a difference between what was designed and what was made (a fabrication problem), or from a difference between the properties predicted and the properties observed (a modeling problem). In either case, the best response may be to change the design to make it more robust, rather than to correct either the model or the fabrication process.

Improved characterization methods will aid development of AP nanosystems, but the needs and ingenuity of the scientific community have already provided remarkably capable tools. Nanoscale and atomic scale sensing, imaging, and metrology have been achieved in a plethora of ways. These methods do not solve all problems, but their capabilities are immense and growing rapidly. Improved tools for characterizing AP nanosystems will be of great value, but the present state of the art provides an adequate basis for progress.

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Applications

The scope of the Roadmap can be summarized as technologies which could either undergo major paradigm shifts with the advent of atomically precise manufacturing (APM) or themselves enable APM. Such technologies will draw on a wide range of disciplines and catalyze innovation across many markets and industries.

Technologies relevant to APM include advanced functional nanosystems, which incorporate products of APM. The application potential is significant and wide reaching.

APM includes not only advanced productive nanosystems, but also a range of nanoscale fabrication technologies that are themselves rapidly evolving:

- Atomically precise, computer-controlled deprotection of surfaces for selective growth
- Molecular manipulation using scanning probe microscopes
- Controlled self-assembly of atomically precise building blocks
- Exploitation of existing (e.g., biological) productive nanosystems
- Organic synthesis of modular, extensible nanoscale structures.

These existing APM technologies have broad utility in themselves and have been identified as enablers for productive nanosystem development. Technologies relevant to APM include advanced functional nanosystems, which incorporate products of APM. The application potential is significant and wide reaching when one considers that atomically precise functional nanosystems will impact the development and evolution of the following applications during the next 10 to 20 years:

- Energy production
- Health care
- Computation
- Smart materials
- Instrumentation
- Chemical Production (Catalysts)

These applications are the drivers for the development of APM, atomically precise functional nanosystems, and ultimately productive nanosystems. Some applications will employ hybrid systems, such as nanolithographic structures interfaced to atomically precise devices, others will leverage the hybridization of controlled self-assembly with

atomically precise targeting tools, and still others will utilize the as yet undiscovered integration of the individual pathways and technologies that are discussed in this Roadmap.

Advanced functional nanosystems—products of APM—will lead to the innovation of productive nanosystems. These, in turn, will advance APM, enabling yet more products and applications. Thus, a focus on technologies and applications relevant to APM will facilitate the emerging revolution of productive nanosystems, and hence will support the vision articulated by this Roadmap initiative. The grand challenges for clean, efficient, and cost-effective energy and long awaited breakthroughs in targeted multi-functional in-vivo and in-vitro therapeutics and diagnostic devices for cancer and other diseases are two of the most compelling drivers to advance the development of atomically precise technologies.

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From the industrial point of view, the most attractive near-term applications for Atomically Precise Technologies are those which are high-value applications that exploit the atomic precision of an APM output and are enabled with a very small volume of atomically precise matter. Good candidates for these applications are sensors, metrology standards, and quantum computing. Although an application with a very large market would be ideal, the initial applications may very well be niche applications with a modest market. This hypothetical niche market might not be worth the initial investment of developing APM, However, for a company bold enough to make that investment, once such an application demonstrated the feasibility and efficacy of APM, the investments to develop slightly more ambitious products would follow. Growing revenues from those products would start the economic drivers that would produce the manufacturing throughput and capability to capitalize on the applications listed below and many others.

Government funding to the extent that it is made available will accelerate development of APM technology, but should not be counted on to replace the market drive to more ambitious applications. Government funding is best suited to promote several to many of the more promising paths to APM, as opposed to a huge effort aimed at an outcome that will not come to fruition for many years.

The following is a brief sampling of applications that will benefit from atomically precise technologies. A more extensive overview of applications is presented in the Working Group Proceedings section.

Application Development Opportunities for Atomically Precise Technologies

Fuel Cells

PEM (proton exchange membrane) fuel cells represent a class of technology that is expected to eventually become a major source of clean energy, because of their environmentally friendly operating characteristics and uniquely high energy-conversion efficiency. Despite definitive advances in recent years, existing fuel-cell technology still has several challenges, including: (i) the lower than theoretical efficiency of energy conversion, (ii) the high platinum content of electrocatalysts, and (iii) the instability of platinum under long-term operational cycling conditions.

The solution to these three performance issues can be addressed with a combination of (i) designing catalysts using advanced theoretical methods, (ii) atomically precise manufacturing of catalysts, and (iii) further improvement of *in situ* characterization with atomic specificity and sub-angstrom resolution.

The benefits of atomically precise manufacturing may seem difficult to achieve at first given the system's complexity, however, small metal nanoparticles of 2 to 5 nm in diameter may be single crystal particles without steps and kinks. Due to a combination of quantum confinement and surface effects, such particles can have substantially different catalytic properties from bulk samples of the same material. Placing atoms of a catalyst, or catalyst modifier, on the well-ordered facets of a nanoparticle support with atomic precision can be conducive to significantly improving their properties and fuel system performance, or could mimic the catalytic properties of, for example, Pt in a material with far lower cost. Thus, we may be able to "tailor" the adlayer structure for a particular reaction to obtain the optimal "ensemble effect" for a particular reactant while optimizing the spill-over effect via the right coverage, to block the adsorption of catalytic poisons. (See Adzic, Paper 32, Working Group Proceedings.)

Energy Efficient Solid State Lighting

Artificial lighting is extremely inefficient: 22% of the nation's electricity (or 8% of the nation's total energy) was used for artificial lighting in 2001. The cost of this energy to the consumer was roughly $50 billion per year or approximately $200 per year for every person living in the U.S. The cost to the environment, furthermore, was approximately 130 million tons of carbon emissions. This inefficiency is rooted in the fact

that conventional technologies generate light as a by-product of energetic processes such as heat or a plasma.

Solid-state lighting (SSL) offers the potential to revolutionize the efficiency of artificial light. It can be defined as the *direct* conversion of electricity to light in a semiconductor. Today, SSL suitable for illumination has a power conversion efficiency significantly less than 100%, but it is steadily increasing and there is no known fundamental physical barrier to achieving high efficiencies for white light generation. SSL capabilities would be revolutionized via the controlled arrangement of the charge transporting and light emitting building blocks with atomically precise manufacturing technologies. Light emitting devices (LEDs) utilize crystalline semiconductors where the management of simgle atomic defects is important for efficient charge transport and light output. In contrast, organic light emitting devices (OLEDs) are based on largely amorphous, very thin films of molecular materials. The potential for atomic precision between the molecular building blocks of an OLED is largely unexplored territory.

For example, it is currently the relatively low efficiency of blue light emission that limits the overall efficiency and stability of white OLEDs. Using molecular engineering, however, it has recently been demonstrated that small molecular building blocks can be incorporated into larger, tractable molecules with excellent electron transport properties by using saturated linkers to extend the size of the molecule without extending its conjugation length.

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We do not currently have the synthetic techniques to combine molecular building blocks with monodisperse noble metal nanoparticles with atomic precision in an electroluminescent device. If such techniques could be developed, the efficiency of fluorescent OLEDs and conventional LEDs could likely be increased multifold via plasmonic effects, with a concomitant increase in the efficiency of solid state lighting devices.

These effects cannot currently be exploited because we lack the technology to assemble the bulk structure with molecular precision. If we could do so, the potential exists for both LEDs and OLEDs with close to 100% of the thermodynamic efficiency for conversion of electricity to light. (See Burrows, Paper 35, Working Group Proceedings.)

Solar Energy

Direct conversion of sunlight into energy using photovoltaic (PV) devices is being increasingly recognized as an important component of

future global energy production. While silicon-based PV still dominates the market, the cost on a dollar-per-watt basis remains about an order of magnitude too high to compete with power generation from fossil fuels except in certain niche applications. Thin film technologies promise low cost PV advancements. Technologies such as nano-structured organic photovoltaics (NOPV), thin film silicon, CIGS, etc. are believed to be a key to future PV systems.

Currently, the conversion efficiency of existing NOPV is close to 5% (for laboratory scale devices), which is a factor of three smaller than the best efficiency demonstrated by CdTe thin film PV systems or amorphous-silicon PV. While CdTe, Si and Grätzel cells are the most studied and widely-used PV candidates today, their processing is more technologically challenging, involving multiple steps of vacuum deposition, selenization of metal precursors, cathode sputtering or spraying, electro-deposition, and followed by the final encapsulation of PV in a polymer layer and the deposition of a protective layer of glass. The size of the PV modules made with this technology is defined by the maximum size of the vacuum chamber. The largest size of CdSe thin-layer PV demonstrated is only 30 x 30 cm^2, and operated at 12.8 % conversion efficiency. The alternative technology of thin layer PV Grätzel cells have the problem of a liquid electrolyte which lacks stability over time due to evaporation, operates in a limited range of temperatures, and has a major problems with a charge collector electrode material which degrades due to the corrosive environment of electrolyte employed. Thin film monocrystalline silicon PV cells, on the other hand, have major problems with (1) the thickness of Si, which needs to be greater than 10 μm to absorb a significant amount of light, which renders it less flexible; (2) the challenge of growth of large-area monocrystalline silicon; (3) a wire-sawing problem; and (4) a conversion efficiency degradation within the first year by 20 to 30% from the original, followed by the steady decline over next several years.

With theoretical efficiency the same as conventional semiconductor based PV and low cost structure, NOPV have a potential of achieving the goal of PV technology—economic generation of large-scale electrical power.

Low cost of NOPV, unlimited raw materials supply, low temperature processing, and possibility to make large area devices on flexible substrate cheaply make them very attractive. With theoretical efficiency the same as conventional semiconductor based PV and low cost structure, NOPV have a potential of achieving the goal of PV technology—economic generation of large-scale electrical power.

In very general terms, an optimized NOPV device requires controlling the organization of nanocomponents with the right gaps forming interfaces with the right band offsets in a structure that is thermodynamically stable. This general goal involves succeeding in several tasks, some of which are described below.

1. **Controlled synthesis of defect-free nanomaterials.** This may require development of better understanding of multivariable process of nanomaterial synthesis. The challenge calls to improve our understanding and control of defect formation and growth termination. This in turn required development and improvement of growth monitoring techniques and tools. This is a major opportunity for atomically precise technology development as conventional synthesis and directed self-assembly technologies encounter limitations.

2. **New methods for atomically precise manufacturing or controlled self-assembly of well characterized nanostructured components into meso-scale devices**. A significant advance would be to achieve synthesis nanomaterials and assembly of macroscopic structures in a single step.

3. **Macroscopic applications that require from synthesis of large amounts of materials homogeneous properties in an economical way for basic, R&D, and production efforts efforts.** New approaches for synthesis of nanomaterial at the commercial scale will have to be developed, and will require revolutionary engineering design.

4. **Quality standards ought to be developed among various research groups across the world in order to improve the quality of the starting materials and establish their precise composition.** Standardized preparation methods should be developed in order to be able to reproduce the material elsewhere.

5. **New instrumentation should be developed to characterize nanomaterials and to enable quality control.** Lack of standard quality assessment routines and the multiple instruments needed to characterize quality of a single material make these processes extremely time consuming.

6. **New methods for modeling and simulation are required across many size scales in order to understand and predict the properties of the individual components and their interactions in a working device.** Moreover, since the characterization of nonmaterial is hindered by size reduction and the convoluted structure of their interfaces theory and simulation plays a fundamental role assisting the interpretation of experimental data. (See Ivanov and Reboredo, Paper 36, Working Group Proceedings.)

Piezoelectric Energy

Piezoelectric materials can generate electrical energy from mechanical energy. This means that piezoceramics and piezopolymers can be effectively used as motion sensors, but also that they can be used to

convert otherwise unused mechanical stress or vibration into usable electrical energy. When a stress is applied to a ceramic piezoelectric element, such as a PZT (lead zirconate titanate) disc, the electrical energy created in the element is equal to the total mechanical energy applied minus the energy required to deform the element. The generated electrical energy is proportional to the elastic compliance of the piezo material (the strain produced per unit of stress applied) and to the square of the piezoelectric coupling factor of the material. This action can generate large voltages, depending on the geometry of the element, which may be reduced to lower voltages and the electrical energy stored using a parallel capacitor.

The atomically precise manufacturing of piezoelectric materials would enable unprecedented performance of and opportunities for these materials for mechanical energy harvesting. The electrical energy generated from a mechanical energy input into a piezoelectric element is proportional to the capacitance of the element. One approach that is used to increase the capacitance of a certain volume element is to employ a multiple layer stack of piezo materials alternated with electrodes rather than a single thicker element. This approach creates a larger surface to volume ratio, contributing to a higher generated charge and a comparatively lower voltage. There is difficulty in achieving ultimately thin piezoceramic layers of desired perovskite solid solutions, such as PZT, to maximize this effect using current experimental methods. With specific control over the placement of atoms in the construction of such a piezoelectric stack one could make each layer minimally thin, perhaps one unit cells, and comprised of optimal compositions of elements (Pb, Zr, Ti, O). Minimally thin electrodes between the layers could be constructed without pinhole defects. The coupling factor and elastic compliance of the assembly could be optimized. Additionally, such control in layer fabrication could conceivably enable the inclusion of piezoelectric mechanical energy harvesting thin film skins on many surfaces, such as those of automobile components, which undergo mechanical energy dissipation (vibration) that is currently untapped as an energy source. (See Fifield, Paper 31, Working Group Proceedings.)

Waveguides

Advances in waveguide technology have created the information revolution of the past 20 years. Future advances in waveguide technology due to atomically precise manufacturing (APM) could have impacts that are as large as, or larger than, what has been experienced in information technology and sensor fabrication, in addition to enabling the development of silicon photonics.

The continued expansion of the data-carrying capacity of fiber-optics networks requires the continued development of optical devices with increased functionality. Of particular interest is the development of amplifiers directly integrated into key passive components, such as star couplers and wavelength demultiplexers, and the development of components utilizing photonic band gaps or other specific arrangements of multiple materials. In the case of amplifiers, APM will allow higher dopant levels without quenching, leading to optical amplification in shorter path lengths and allowing more compact (and less expensive) device fabrication. APM will enhance the development of photonic band gap (or similar) devices by allowing more precise control of the refractive index patterns that enable the device function. Additionally, the application of APM methods to electrode fabrication may allow the realization of devices that are impossible using conventional lithographic methods.

Waveguide sensors have multiple attractive features, including compactness, robustness, resistance to electromagnetic interference, and remote connection to instrumentation using optical fibers. These sensors primarily operate using either evanescent field sensing techniques (grating couplers, waveguide interferometers, surface plasmon resonance sensors) or surface acoustic wave techniques. In both cases, the waveguide surface is treated to allow binding of the desired species, which alters the signal propagating along the waveguide. APM can enhance these sensors in multiple ways, including the fabrication of patterned surfaces on the waveguide to allow detection of multiple targets, formation of tailored binding sites to reduce the non-specific binding of other species to the surface, and the fabrication of waveguides with tailored optical or acoustical properties that would allow for improved or alternate signal transduction.

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Silicon photonics is an effort to increase the bandwidth of the connections between microprocessors by using optical transfer of data. The key is all components of the optical interconnects must be fabricated as part of the CMOS manufacturing, using standard techniques. Although silicon waveguides have been used for some time, only recently has continuous lasing been demonstrated in silicon. Because of the much smaller size of optical components in silicon as opposed to silica, APM techniques will be required to allow for the fabrication of the full range of silicon optical components (waveguides, lasers, amplifiers, filters, resonators, attenuators, modulators, etc.) needed for the complete realization of the potential of this technology. In particular, fabrication of the laser cavity, and the localized doping of the silicon to form modulators and the lasers will require the integration of APM techniques into the CMOS manufacturing process. (See Risser, Paper 39, Working Group Proceedings.)

High Q, Resonant Microcavities

Optical microcavities are resonant devices into which photons can be selectively stored or routed when certain resonant conditions are met. The microcavity Q is a benchmark parameter which is directly related to the photon storage time in the microcavity. Chip scale, microcavities are effectively closed waveguide rings, into which, when resonant conditions are met, photons can be coupled. Current chip scale, microcavities are typically on the size of tens of microns in diameter. With nominal Q values on the order of 10^{10}, photons can be stored in the microcavities for microsecond time scales and the photons will travel an effective path length on the order of kilometers. Consequently, large effective waveguide path lengths can be realized in very compact geometries through resonant recirculation of the photons within the microcavity. As cavity Q increases, the effective waveguide path length increases. The Q values of current chip scale microcavities are limited by material defects and sidewall roughness in the cavity surfaces. Atomically precise fabrication would enable ultrahigh Q values through defect free materials and atomically smooth sidewalls and enable fabrication of microcavities with small mode volumes. High Q, chip scale microcavities technology is currently being pursued to enable compact technologies in the following fields:

- **Sensors:** photons are coupled into microcavities and sense the environment through the evanescent wave. The higher the Q, the longer the photon senses the environment through the evanescent wave while circulating in the resonator ring cavity. By functionalizing the surface of the microcavity ring resonator these sensors can be configured to selectively detect target molecules such as chem/bio compounds to support defense, environmental, or medical applications. Label free, single molecule bio detection has been demonstrated using this approach by the Vahala research group at Caltech.
- **Compact, Low Threshold Lasers:** the ratio of microcavity Q to mode volume, V, is known as the Purcell factor (Q/V) and directly related to the threshold levels required for lasing. Through fabrication of ultrahigh Q cavities with small mode volumes, very low threshold laser can be fabricated on chips. The Vahala group at Caltech has demonstrated low threshold level laser on a chip with toroidal resonator microcavities. Higher Q values and smaller mode volumes achieved through atomically precise fabrication would reduce threshold lasing levels.

- **Quantum Information Sciences:** quantum networks and node configurations are currently being pursued by a wide variety of researchers which function through the strong coherent interactions of light and matter, whereby information stored in trapped atoms or quantum dots is coupled to high Q microcavities for optical information processing. Higher Q enables longer periods of strong coherent interactions with trapped atoms for accurate conversion of atomic logic to optical logic for information processing.
- **Optical Information Processing:** small mode volume, high Q microcavities reduce switching times and enhance non-linear interactions, which are required to enable high speed, all optical processing. Higher Q cavities would increase switching speeds and data process rates. (See Oesterling, Paper 38, Working Group Proceedings.)

Biological Sensors

Future sensor designs for biological monitoring and screening will need to capitalize on the enormous amounts of information resulting from genome sequencing and systems biology related efforts. Effective approaches to screening for metabolic indicators, disease associated markers, or the activity of potential pharmaceutical reagents will be enabled by biosensor technologies. Increasing the speed and accuracy of such measurements requires recognition of diverse chemical reagents. Related sensing capabilities for in situ biological monitoring will need to integrate information assessment with an appropriate compensatory response while being self-powered, self-healing and biologically compatible. Such attributes will be essential for realizing in vivo sensors aimed at ameliorating the effects of disease or for the long-term monitoring biological processes. Effective chemical sensing capabilities require controlled specificity and sensitivity to an analyte and the capability to transduce sensor information into a useful format. Atomically precise manufacturing is well positioned to meet this and other challenges posed by next generation sensing formats.

Effective chemical sensing capabilities require controlled specificity and sensitivity to an analyte and the capability to transduce sensor information into a useful format. Atomically precise manufacturing is well positioned to meet this and other challenges posed by next generation sensing formats.

Examples of atomically precise manufacturing are displayed in biological systems and serve as an inspiration for biosensor design. Biopolymers, such as proteins, nucleic acids and carbohydrates, show selective affinity to other biopolymers and small molecules through careful positioning of chemical functional groups. Potentially, new chemical recognition elements can be created by the atomically precise arrangements to form ensembles of weak interactions that can controllably recognize biomolecules. Such recognition elements are essential for chemical sensing and for the in vivo targeting of

pharmaceuticals, image contrast agents or monitoring devices. The design of molecular scale features is also critical for controlling unwanted interactions, such as those associated with false positive signals or biofouling.

Atomically precise manufacturing may allow for direct electron transfer between synthetic and natural structures, enabling new approaches for powering sensor systems or for relaying sensor information.

The molecular scale basis of biosystem function dictates that similarly sized, nanoscale materials will be effective in transducing signals between biomolecules and sensing systems. Small-scale structures will be necessary for entering cells and for interfacing to biological complexity. The atomically precise manufacturing of such nanostructures will enable controlled self-assembly of sensing system components, allowing integration of different sensing elements and diverse functions such as chemical recognition, information processing, signal transduction, and therapeutic response. Atomically precise design that bestows directed assembly would also be critical to the construction of self-healing structures and for integrating approaches to passively power sensor systems. For example, as is well recognized, the controlled synthesis of nanomaterials can be exploited for tuning the electrical or optical properties of materials. Atomically precise manufacturing may allow for direct electron transfer between synthetic and natural structures, enabling new approaches for powering sensor systems or for relaying sensor information (personal communication submitted by Mitch Doktycz, Oak Ridge National Laboratory.)

Electric Nanomotors and Nanoactuators

In 2003, the Zettl Group at Lawrence Berkeley Laboratories and UC Berkeley fabricated the smallest-known non-biological nanomotor. The device employed a multi-walled carbon nanotube (MWNT), which served as both a bearing for the rotor and as an electrical conductor, and had the following characteristics:

- Doped silicon substrate covered with 1 μm SiO2.
- Rotor, anchor pads, and electrodes—constructed lithographically; 90 nm gold layer with 10 nm Cr adhesion layer
- Rotor length 100 to 300 nm
- Bearing—MWNT, 10 to 40 nm diameter, 2 μm length between anchor pads
- Torsional spring constant of the outer nanotube, 10^{-15} to 10^{-12} N-m "as produced;" however the researchers broke the bonds with an electrical jolt (~80 V d.c.) torquing the rotor and causing the tube to rotate freely

- Speed—operated at several Hz, but potentially could run at gigahertz frequencies
- Vacuum—10^{-6} to 10^{-5} torr.

This breakthrough is highly relevant because motors based on this concept could be used to drive systems of molecular mechanical components. If the outer nanotube were fractured at the far ends rather than right next to the rotor, then this motor-driven outer shaft could be connected (e.g., by molecular gears) to other components. It's additionally significant because the operation of the motor is controlled with electrical circuitry, offering precise control from the desktop. Most importantly, the device is *individually addressable* from the desktop as opposed to broadcast architectures where light or chemical signals trigger operations on a large array of devices.

This research was additionally significant because in order to fabricate this device new technologies were developed:

- A method for peeling off successive layers of nanotubes
- Precision cutting of, and selective damage to, nanotubes
- A manipulator capable of pulling out the inner nanotube in a MWNT. This spawned a commercial product.

In 2005, the Zettl group constructed a molecular actuator able to reversibly push apart two carbon nanotubes. Mobile atoms of indium formed a nanocrystal ram between two nanotube electrodes under an applied voltage.

- Variable distance between nanotubes, 0 to 150 nm
- Cross sectional area of nanocrystal, 36 nm^2
- Force, 2.6 nN
- Extension velocity, >1900 nm/s
- Power, 5 fW
- Power density, 20 MW/m^3 to 8 GW/m^3

Mechanical devices based on levers or plates attached to the droplets or nanocrystal ram could be used to convert electricity into repetitive linear motion.

Using similar methods, the size of liquid droplets of indium on a nanotube surface could be controlled by varying the electrical current through the nanotube. These droplets are capable of exerting pressure in an oscillating manner (peak power, 20 μW, peak force 50 nN). Mechanical devices based on levers or plates attached to the droplets or nanocrystal ram could be used to convert electricity into repetitive linear motion. Again, these devices are individually addressable. (See Forrest et al., Paper 23, Working Group Proceedings.)

Photonic Nanomotors and Nanoactuators

Another class of nanomotors is that which can be controlled by photons (light and magnetic fields). There are a considerable number of examples of molecules that can be caused to rotate or change conformation with photons. In the pathway to APM, nanosystems made from these devices may be driven by arrays of motors performing operations in parallel. A broadcast of electromagnetic radiation onto the motors would provide energy for the array, which could be controlled by modulating the frequency and amplitude of the radiation.

Nanocar. One of the most prominent examples of the application of this technology is the Rice University Nanocar (and its evolving product line of wheelbarrows and trucks). What distinguishes this effort is that a Feringa motor, which powers the device, was successfully integrated with other molecular structures to create a molecular machine. The motor rotates and pushes a protruding molecular group against the substrate propelling the molecular car forward along an atomically flat surface under 365 nm wavelength light. While the utility of this particular application may or may not lead to APM, it shows that a Feringa motor (which had also been used to rotate glass rods on the surface of a liquid crystal) can be connected to a device in order to effect directed motion. One can envision alternative configurations such as Feringa motors pushing against gear teeth to rotate a shaft, or provide linear motion as in a rack and pinion.

Molecular valve. In another example, in 2005 researchers at the Biomade Technology Foundation and the University of Groningen developed a molecular valve controlled by light. To do this, they modified a protein found in *e. coli* bacteria that in nature serves as a safety valve for excessive pressure in the cell. The modifications allow it to be opened by UV light (366 nm wavelength, applied for about 2 minutes) and closed by visible light (>460 nm, for about 2 seconds) by building up and releasing localized charge. The valve operates within a lipid bilayer, is about 10 nm in external diameter, 21 nm long, and has an internal pore size of 3 nm when open. When the valve is closed it resists being forced open under pressure to nearly the breaking point of the cell wall. Although the valve has been developed and tested in an open system—embedded in the lipid bilayer of a cell wall, or more accurately, a patch clamp to measure current within this environment—one can envision fluid channels (pipes) leading to and from the valve in order to have it regulate fluid or gas transport in a closed system. (See Forrest et al., Paper 23, Working Group Proceedings.)

Carbon Nanotubes

Single-walled carbon nanotubes (SWNTs) have been at the forefront of novel nanoscale investigations due to their unique structure-dependent electronic and mechanical properties. They are thought to have a host of wide-ranging, potential applications including as catalyst supports in heterogeneous catalysis, field emitters, high strength engineering fibers, sensors, actuators, tips for scanning probe microscopy, gas storage media, and as molecular wires for the next generation of electronics devices. The combination of the helicity and diameter of SWNTs, defined by the roll-up vector, determines whether a tube is a metal or a semiconductor. Moreover, the mechanical strength of a tube is a function of its length and diameter. SWNTs have been synthesized in our lab, in gram quantities, by means of a chemical vapor deposition process although other methods including arc discharge and laser vaporization exist for generating these materials. Indeed, the advantage of SWNTs is that they are chemically, molecularly defined structures with reproducible dimensions.

The advantage of single-walled carbon nanotubes (SWNTs) is that they are chemically, molecularly defined structures with reproducible dimensions.

Many applications utilizing SWNTs require chemical modification of the carbon nanotubes to make them more amenable to rational and predictable manipulation. For example, the generation of high strength fibers is associated with the individualization of nanotubes and their subsequent dispersion into a polymer matrix. Moreover, the requirements of load-transfer efficiency demand that nanotube surfaces should be compatible with the host matrix. Secondly, sensor applications involve the tethering onto nanotube surfaces of chemical moieties with specific recognition sites for analytes with ensuing triggering of a predictable response in the nanotube's optical or transport properties. Thirdly, gas storage and lithium intercalation applications necessitate the opening of hollow cavities in nanotube sidewalls. To fulfill all of these varied stipulations at the nanoscale requires an intimate and precise understanding of the chemistry and functionality of carbon nanotubes, such as would be offered by atomically precise manufacturing.

The main problem with the majority of popular synthetic methods for growing SWNTs (i.e., laser ablation, arc-discharge, and chemical vapor deposition) is that they produce samples yielding a mixture of many different diameters and chiralities of nanotubes that are moreover contaminated with metallic and amorphous impurities. Thus, post-synthesis chemical processing protocols, that purify tubes and that can also separate individual tubes according to diameter and chirality by taking advantage of their intrinsically differential reactivity, are often the only viable routes towards rational and predictable manipulation of the favorable electronic and mechanical properties of these materials.

APM would certainly be viewed as an alternative route towards practically achieving these goals.

From a fundamental scientific perspective, chemical functionalization and APM allow for the exploration of the intrinsic molecular nature of these SWNTs and permit studies at the rich, structural interface between true molecules and bulk materials. In general, chemical modification strategies have targeted SWNT defects, end caps, sidewalls, as well as the hollow interior. APM would allow for an even more highly focused chemical targeting of nanomaterials. Representative approaches to nanotube derivatization include covalent chemistry of conjugated double bonds within the SWNT, non-covalent π-stacking, covalent interactions at dangling functionalities at nanotube ends and defects, and wrapping of macromolecules. Chemical functionalization of SWNTs attached to conventional atomic force microscopy probes has also been demonstrated as a methodology of yielding high-resolution, chemically-sensitive images on samples containing multiple chemical domains. In this last case, functionalization can be spatially localized at nanotube ends, often involving only a few molecules.

Thus, rational SWNT functionalization as well as APM provide for the possibility of the manipulation of SWNT properties in a predictive manner. The surface chemistry of SWNTs plays a vital role in enabling the dispersability, purification, solubilization, diameter and chirality-based separation, and biocompatibility of these unique nanostructures. In addition, derivatization allows for a number of site-selective nanochemistry applications such as the self-assembly of nanotubes with tailorable electronic properties, important for advances in molecular electronics. Other derivatized SWNT adducts show potential as catalytic supports and as biological transport vessels. Moreover, these systems often demonstrate novel charge transfer characteristics, the development and understanding of which have implications for photocatalysis and energy storage. Finally, rational chemical manipulation of SWNTs is critical for the hierarchical build-up of these nanomaterials into functional architectures, such as nanocomposites and nanocircuits, with unique properties.

Opportunities to research and design atomically precise catalysts and atomically precise manufacturing of carbon nanotubes will gain momentum as the demand for high quality and pure carbon nanotubes grows for energy, electronics, transportation materials, military and medical applications continues to grow. (See Wong, Paper 18; Fifield, Paper 17; and Heintz, Paper 37, Working Group Proceedings.)

Opportunities for Atomically Precise Technology Advancements in Medicine

Nano-Devices, Nano-Biosensors, NEMS, Nano-Tube, and Nano-Wire for Biological Application

Nanomaterials are exquisitely sensitive chemical and biological sensors. Nanosensors with immobilized bioreceptor probes that are selective for target analyte molecules are called nanobiosensors. They can be integrated into other technologies such as lab-on-a-chip to facilitate molecular diagnostics. Their applications include detection of microorganisms in various samples, monitoring of metabolites in body fluids and detection of tissue pathology such as cancer. The nanomaterials transduce the chemical binding event on their surface into a change in conductance of the nanowire in an extremely sensitive, real time and quantitative fashion. Boron-doped silicon nanowires (SiNWs) have been used to create highly sensitive, real-time electrically based sensors for biological and chemical species. The small size and capability of these semiconductor nanowires for sensitive, label-free, real-time detection of a wide range of chemical and biological species could be exploited in array-based screening and *in vivo* diagnostics.

Nanowires and nanotubes carry charge and excitons efficiently, and are therefore potentially ideal building blocks for nanoscale electronics and optoelectronics. Carbon nanotubes have already been exploited in devices such as field-effect and single electron transistors, but the practical utility of nanotube components for building electronic circuits is limited, as it is not yet possible to selectively grow semiconducting or metallic nanotubes. The electrical properties of the assembly of functional nanoscale devices are controlled by selective doping. (See Wei, Paper 29, Working Group Proceedings.)

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Diagnostic Nanomedicine for Cellular and Organ Imaging in Living Cells and Living Animal.

Nanomolecular diagnostics is the use of nanobiotechnology in molecular diagnostics. Nanotechnology is the creation and utilization of materials, devices, and systems through the control of matter on the nanometer (1 billionth of a meter)-length scale. Numerous nanodevices and nanosystems for sequencing single molecules of DNA are feasible. Given the inherent nanoscale of receptors, pores, and other functional components of living cells, the detailed monitoring and analysis of these components will be made possible by the development of a new class of nanoscale probes. Nanobiotechnologies are clinically relevant and have the potential to be incorporated in clinical laboratory diagnosis.

The most important current applications are foreseen in the areas of biomarker research, cancer diagnosis, and detection of infectious microorganisms.

Nanotechnologies enable the diagnosis at single cell and molecule level and some of these can be incorporated in the current molecular diagnostics such as biochips. Besides following techniques, nanoparticles, such as gold nanoparticles and quantum dots, are the most widely used. The nanotechnology-based chips on a nanoscale are related to nanomanipulation. The droplets used are 1 billion times smaller in volume than has been demonstrated by conventional methods. The levitated particles can be manipulated and positioned with accuracy within a range up to 300 nm. Use of this technology on a lab-on-a-chip would refine the examination of fluid droplets containing trace chemicals and viruses. As such, these technologies will extend the limits of current molecular diagnostics and enable point-of-care diagnosis as well as the development of personalized medicine. Although the potential diagnostic applications are unlimited, most important current applications are foreseen in the areas of biomarker research, cancer diagnosis, and detection of infectious microorganisms. (See Wei, Paper 29, Working Group Proceedings.)

Genetic Nanomedicine for Gene Detection and Gene Delivery

Gene delivery is an area of considerable current interest; genetic materials (DNA, RNA, and oligonucleotides) have been used as molecular medicine and are delivered to specific cell types to either inhibit some undesirable gene expression or express therapeutic proteins. To date, the majority of gene therapy systems are based on viral vectors delivered by injection to the sites where the therapeutic effect is desired. Viral gene-transfer techniques can deliver a specific gene to the nucleus of a cell, for expression, through integration into the geneome or as episomal vectors. Viral vectors can have potentially dangerous side effects due to unintended integration of the viral DNA into the host genome which include incorporation of the virus into the hosts immune system and hence, have been less successful than originally hoped. Liposome based gene transfer has relatively low transfection rates, are difficult to produce in a specific size range, can be unstable in the blood stream, and are difficult to target to specific tissues. Injection of naked DNA, RNA, and modified RNA directly into the blood stream leads to clearance of the injected nucleic acids with minimal beneficial outcome.

The use of non-viral vectors, because of their non-immunogenicity and easy production, represents a good alternative to viral vectors, however, most non-viral vectors have lacked the high transfection efficiency obtained with viral vectors. As such, there is currently a need for a gene delivery system that has minimal side effects but high potency and efficiency. The idea that nanosystems have unique physical and biological properties that might be used to overcome the problems of

gene and drug delivery has gained interest in recent years. Nanosystems can be designed with different compositions and biological properties. Some of these systems, such as nanoparticles, dendrimers, nanocages, micelles, molecular conjugates, liposomes and so on, have been extensively investigated for drug and gene delivery applications. One such system could be that of the self-assembled nanoparticles coated with targeting biomolecules. It uses a nanoparticle platform for diagnostic probes and effective targeted therapy. (See Wei, Paper 29, Working Group Proceedings.)

Nanotechnology-Based Regenerative Medicine: Cell Sheet Engineering

By combining preformed biodegradable polymer scaffolds and specific cell types, various tissues including cartilage, bone, and blood vessels have been reconstructed, although, so far, therapeutic use has been very limited. A method to circumvent the need for the traditional technology is "cell sheet engineering" which utilizes temperature-responsive culture surfaces. These novel surfaces are created by the covalent grafting of the temperature-responsive polymer, poly(*N*-isopropylacrylamide) by electron beam irradiation. The grafted polymer thickness and density are precisely regulated in a nanometer regime. These surfaces allow for the non-invasive harvest of cells by simple temperature reduction. Confluent cells are non-invasively harvested as single, contiguous cell sheets with intact cell-cell junctions and deposited extracellular matrix from the surfaces. These harvested cell sheets have been used for various tissue reconstructions, including ocular surfaces, periodontal ligaments, cardiac patches, esophagus, liver, and various other tissues. (See Wei, Paper 29, Working Group Proceedings.)

Oncology Nanomedicine for Early Diagnosis and Early Treatment in Cancer

Targeting and local tumor delivery is the key challenges in both diagnosis and treatment of cancer. Cancer therapies are based on a better understanding of the disease at the molecular level. Nano-biotechnology is being used to refine discovery of biomarkers, molecular diagnostics, drug discovery, and drug delivery, which are important basic components of personalized medicine and are applicable to management of cancer as well. Examples are given of the application of quantum dots, gold nanoparticles, and molecular imaging in diagnostics and combination with therapeutics—another important feature of personalized medicine. Management of cancer, facilitated by nanobiotechnology, is expected to enable early detection of cancer, and more effective and less toxic treatment, increasing the chances of cure.

Nanobiotechnology is being used to refine discovery of biomarkers, molecular diagnostics, drug discovery, and drug delivery

Nanotechnology is an emerging interdisciplinary field dedicated to the manipulations of atoms and molecules that lead to the construction of structures in the nanometer scale size range that retain unique properties. Emerging BioMicroNano-technologies have the potential to provide accurate, realtime, high-throughput screening of tumor cells without the need for time-consuming sample preparation. These rapid, nano-optical techniques may play an important role in advancing early detection, diagnosis, and treatment of disease. Recently, many nanotechnology tools have become available which can make it possible for clinicians to detect tumors at an early stage. The nanostructures can potentially enter the single tumor cell, which can help improve the current detection limit by imaging techniques. Gourley shows that laser scanning confocal microscopy can be used to identify a previously unknown property of certain cancer cells that distinguishes them, with single-cell resolution, from closely related normal cells. This property is the correlation of light scattering and the spatial organization of mitochondria. In addition, the new technology of nanolaser spectroscopy using the biocavity laser can be used to characterize the unique spectral signatures of normal and transformed cells. These optical methods represent powerful new tools that hold promise for detecting cancer at an early stage and may help to limit delays in diagnosis and treatment. Nanotechnology can help diagnose cancer using dendrimers and kill tumor cells without harming normal healthy cells by tumor selective delivery of genes using nanovectors. These and other technologies currently are in various stages of discovery and development. (See Wei, Paper 29, Working Group Proceedings.)

Pharmacological Nanomedicine for Drug Delivery and Drug Design

The application of nanotechnology in life sciences is becoming hot topic on drug design and drug delivery. The nanotechnologies, including nanoparticles and nanodevices such as nanobiosensors and nanobiochips, are used to improve drug discovery and development. Nanoscale assays can contribute significantly to cost-saving in screening campaigns. Many drugs discovered in the past could not be used in patients because a suitable method of drug delivery was lacking. Nanotechnology is also used to facilitate drug delivery. A product incorporating the NanoCrystal technology of Elan Drug Delivery (King of Prussia, PA, USA), a solid-dose formulation of the immunosuppressant sirolimus, was approved by the FDA in 2000. Abraxane™ (Abraxis™ Oncology), containing paclitaxel as albumin-bound particles in an injectable suspension, is approved for the treatment of breast cancer after the failure of combination chemotherapy for metastatic disease or after relapse within six months of adjuvant chemotherapy. It is based on nanoparticle technology,

which integrates biocompatible proteins with drugs to create the nanoparticle form of the drug (with a size ~100 to 200 nm) to overcome the insolubility problems encountered with paclitaxel. Now, the trend is to consider drug-delivery issues at the earlier stages of drug discovery and design. Potential applications of nanotechnology to facilitate drug delivery can be taken into consideration at the stage of drug design. A carrier nanoparticle can be designed simultaneously with the therapeutic molecule. Although there might be some safety concerns with respect to the *in vivo* use of nanoparticles, studies are in place to determine the nature and extent of adverse events. Future prospects for the application of nanotechnology in healthcare and for the development of personalized medicine appear to be excellent. (See Wei, Paper 29, Working Group Proceedings.)

Dendrimer-Based Nanomedicine: Its Impact on Biology, Pharma Delivery, and Polyvalent/Targeted Therapies

Dendrimers are now referred to as "artificial proteins" based on the close scaling/mimicry of their dimensions, shapes and surface chemistries to these biological nanostructures. Considering the importance of nanoscale structures, dimensions associated with proteins, DNA, antibody-antigen complexes, viral particles, to mention a few, it is safe to make the following statement: "*The positive management of human health, disease and longevity will likely be determined/controlled by a deeper understanding of critical parameters in the nano-length scale; namely: nanomedicine."* This theme will be used to present the use of precise, synthetic nanostructures (i.e., dendrimers) as critical nanoscale building blocks in a variety of nano-diagnostic, drug delivery and nano-pharma-type applications.

Dendrimers are routinely synthesized as tunable nanostructures that may be designed and regulated as a function of their size, shape, surface chemistry and interior void space. They are obtained with structural control approaching that of traditional biomacromolecules such as DNA/RNA or proteins and are distinguished by their precise nanoscale scaffolding and nanocontainer properties. These important properties are expected to play an important role in the emerging field of the nanomedicine. Recent efforts have focused on the synthesis and preclinical evaluation of multipurpose dendrimer prototype STARBURST PAMAM (polyamidoamine) that exhibits properties suitable for use as: (i) targeted, diagnostic MRI/NIR (near-IR) contrast agents, (ii) and/or for controlled delivery of cancer therapies. This dendritic nanostructure (~5.0 nm in diameter) was selected on the basis of a very favorable biocompatibility profile, the expectation that it will exhibit desirable mammalian kidney excretion properties and

Dendrimers are obtained with structural control approaching that of traditional biomacromolecules such as DNA/RNA or proteins and are distinguished by their precise nanoscale scaffolding and nanocontainer properties.

demonstrated targeting features. (See Wei, Paper 29, Working Group Proceedings.)

Cardiovascular Nanomedicine for Heart and Vascular Diseases

The future of cardiovascular diagnosis already is being impacted by nanosystems that can be both diagnose pathology and treat it with targeted delivery systems.

Cardiovascular disease remains the leading cause of death in the United States: One out of every four Americans has cardiovascular disease and every 30 seconds one person dies form heart disease. Although significant advances have been made in the management and treatment of this disease, the effectiveness of early detection and treatment in preventing heart attacks is still questionable, since few of the heart attacks could be predicted by the physicians. One of the fundamental and unresolved problems in cardiovascular biology is the in vivo detection of atherosclerotic disease and the evaluation of atherosclerotic disease activity. Current technology limits clinicians to diagnostic techniques that either image or functionally assess the significance of large obstructive vascular lesions. Techniques have been developed recently to achieve molecular and cellular imaging with most imaging modalities, including nuclear, optical, ultrasound, and magnetic resonance imaging (MRI). In addition, current imaging modalities do not allow for the possibility of imaging atherosclerotic disease at its earliest stages nor do available techniques allow routine assessment of atherosclerotic lesions susceptible to rupture and/or thrombosis. This is of particular clinical significance given that myocardial infarctions and other sequela of atherosclerotic disease are just as likely to occur from small non-obstructive coronary artery disease based on the degree of luminal obstruction is fundamentally flawed. Newer technologies must be developed that are capable of identifying earlier atherosclerotic lesions as well as atherosclerotic lesions that are active or unstable. The role of nanotechnology in cardiovascular diagnosis is expanding rapidly. It has been applied nanosystems to the area of atherosclerosis, thrombosis, and vascular biology. The technologies for producing targeted nanosystems are multifarious and reflect end uses in many cases. The results to date indicate rapid growth of interest and capability in the field. The future of cardiovascular diagnosis already is being impacted by nanosystems that can be both diagnose pathology and treat it with targeted delivery systems. To date, both advanced imaging methods and new targeted nanoparticles contrast agents for early characterization of atherosclerosis and cardiovascular pathology at the cellular and molecular levels that might represent the next frontier for combining imaging and rational drug delivery to facilitate personalized medicine. The rapid growth of nanotechnology and nanoscience could greatly expand the clinical opportunities for molecular imaging. (See Wei, Paper 29, Working Group Proceedings.)

Neurological Nanomedicine for Neuroscience Research

Applications of nanotechnology in basic neuroscience include those that investigate molecular, cellular and physiological processes including three specific areas. First, nanoengineered materials and approaches for promoting neuronal adhesion and growth to understand the underlying neurobiology of these processes or to support other technologies designed to interact with neurons in vivo (for example, coating of recording or stimulating electrodes). Second, nanoengineered materials and approaches for directly interacting, recording and/or stimulating neurons at a molecular level. Third, imaging applications using nanotechnology tools, in particular, those that focus on chemically functionalized semiconductor quantum dots. Applications of nanotechnology in clinical neuroscience include research aimed at limiting and reversing neuropathological disease states. Nanotechnology approaches are designed to support and/or promote the functional regeneration of the nervous system; neuroprotective strategies, in particular those that use fullerene derivatives; and nanotechnology approaches that facilitate the delivery of drugs and small molecules across the blood-brain barrier. Applications of nanotechnologies for neuroprotection have focused on limiting the damaging effects of free radicals generated after injury, which is a key neuropathological process that contributes to CNS ischaemia, trauma and degenerative disorders. (See Wei, Paper 29, Working Group Proceedings.)

Nanotechnology approaches are designed to support and/or promote the functional regeneration of the nervous system; neuroprotective strategies, in particular those that use fullerene derivatives; and nanotechnology approaches that facilitate the delivery of drugs and small molecules across the BBB.

Dermatological Nanomedicine for Skin Research

Several nanoparticles are used in molecular imaging: gold nanoparticles, quantum dots and magnetic nanoparticles. Gold nanoparticles are particularly good labels for sensors because a variety of analytical techniques can be used to detect them, including optical absorption, fluorescence, Raman scattering, atomic and magnetic force, and electrical conductivity. This technique can be used to detect microorganisms and could replace PCR and fluorescent tags used currently. Quantum dots (QDs) are nanoscale crystals of semiconductor material that glow, or fluoresce when excited by a light source such as a laser. QDs have fairly broad excitation spectra–from ultraviolet to red–that can be tuned depending on their size and composition. At the same time, QDs have narrow emission spectra, making it possible to resolve the emissions of different nanoparticles simultaneously and with minimal overlap. QDs are highly resistant to degradation, and their fluorescence is remarkably stable. Bound to a suitable antibody, magnetic nanoparticles are used to label specific molecules, structures, or microorganisms. Magnetic immunoassay techniques have been developed in which the magnetic field generated by the magnetically

labeled targets is detected directly with a sensitive magnetometer. (See Wei, Paper 29, Working Group Proceedings.)

Agenda for Research and Call to Action

The final report of the 2006 Congressionally-mandated review of the U.S. National Nanotechnology Initiative by the National Research Council of the National Academies and the National Materials Advisory Board includes an evaluation of prospects for molecular manufacturing based on what are here termed advanced-generation productive nanosystems. The executive summary of the review closes with a call for research in this area: Experimentation leading to demonstrations supplying ground truth for abstract models is appropriate to better characterize the potential for use of bottom-up or molecular manufacturing systems that utilize processes more complex than self-assembly. The present section includes recommendations that are responsive to this call.

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The following topics for research should be addressed in order to promote the development of atomically precise manufacturing, productive nanosystems, and their applications. This list is, of course, far from exhaustive, and reflects ideas that will evolve over time. Any agenda for research in this area must be revisited regularly.

In this section, little effort will be made to motivate our choices. The reader only has to refer to other sections of the roadmap to understand why we list these research topics. We will make an effort to suggest in broad terms what path to APM and productive nanosystems, or what enabled product or application would benefit from the research.

We recommend a useful (necessary but not sufficient) test with respect to topics that should be included or excluded from this list: If the goal of the technical challenge does not propose to lead to the fabrication of structures with atomic or molecular precision, or if it does not explore the application of atomically or molecularly precise structures then it may be worthwhile, but it should not be on the productive nanosystem roadmap. To achieve molecular or atomic precision, an approach must manipulate and exploit the quantized nature of matter.

Roadmapping and Data Integration

Knowledge, instrumentation, modeling, techniques, and components do not by themselves add up to functional engineering systems. This requires the design of system architectures, division of systems into subsystems, and the development of components that meet functional requirements determined by their context in a system as a whole. These functional requirements then set a detailed agenda for research.

The International Technology Roadmap for Semiconductors (ITRS) is a premier example of this process operating at the level of an industry as a whole. In an ongoing process, R&D leaders from across the semiconductor industry pool their knowledge to set concrete objectives for next-generation semiconductor manufacturing, to determine their requirements, and to identify and evaluate options for satisfying those requirements. This process ensures that all of the many necessary technologies will be available together. If any were missing, the rest would be of little use. Coordination gives all participants the confidence necessary to invest in equipment that must work together with equipment that does not yet exist — the light sources, etching equipment, positioning mechanisms, test equipment, design software, and so on.

The ITRS process does more than this: it looks ahead not one, but several technology generations, helping to guide the research that will create the options for developing the equipment that will implement the digital electronic systems that will revolutionize the world a decade hence. This has been an essential part of the first industry to build complex, integrated nanosystems. In this way, the ITRS process has transformed our lives.

To develop complex systems, efforts must be coordinated so as to develop all the parts they require. This entails selecting and refining objectives, determining requirements, considering options for meeting them, and thereby identifying research directions that are more likely to produce results of great value.

We cannot hope to match the ITRS achievement today, in part because of the exploratory nature of this initial roadmap, and in part because of the greater diversity and earlier stage of APT, APM, and their applications. The principle, however, is the same: To develop complex systems, efforts must be coordinated so as to develop all the parts they require. This entails selecting and refining objectives, determining requirements, considering options for meeting them, and thereby identifying research directions that are more likely to produce results of great value.

The results will always be imperfect, but it is better to try than do nothing. A vital part of the research agenda is to develop a better research agenda, and we see this as an ongoing process in which roadmapping will play a vital role.

Modeling, Design, and Data Integration

The demands of science and technology have driven vigorous development of a wide range of techniques for modeling atomically precise systems. Recognition of the promise of APT and APM adds a driver for this many aspects of this work, but it appears that this calls for little change in its overall direction.

Outside of APM and productive nanosystems there is a well documented need and ongoing effort to develop techniques that model materials and structures at the atomic and molecular level. These efforts have and will facilitate developments in AP nanotechnologies, and will play a major role in the development of APM processes and productive nanosystems. The promise of these developments calls for greater investment in applicable modeling techniques, with an increased emphasis on multilevel, multiphysics modeling that can support the design of larger and more complex systems. Present computational modeling techniques are broadly adequate for progress today, but improved techniques will be of substantial value.

Design software for APT and APM will draw on progress in the modeling community, but it presents distinct challenges that are not yet receiving sufficient attention. This is understandable because APM is in its infancy, and design software will necessarily be technology and material dependent. However, as APM techniques advance, design software will be an important and increasingly necessary enabling tool. This is an area that calls for new initiatives with the objective of developing and improving software that supports systematic design methodologies.Without sufficient investment, design software would become a bottleneck in developing AP nanosystems.

Greater investment is needed in applicable modeling techniques, with an increased emphasis on multilevel, multiphysics modeling that can support the design of larger and more complex systems.

Modeling and experimentation add to a store of knowledge regarding AP structures and processes. This knowledge, together with modeling, will inform the design process for AP nanosystems. Today, much of that knowledge is dispersed and, in effect, inaccessible to designers. It resides in a host of different journals and databases, and it is not indexed in a manner that makes it useful for design.

Designers would be greatly helped by compilations of suitably organized data relevant to nanosystems engineering. This calls for classifying and indexing data about materials, building blocks, devices, and processes according to criteria and metrics that describe their functional properties. Compilations of this kind will help designers find solutions to problems, and will help them reject unworkable options. Compilations organized around functional criteria and metrics can cut across the disciplinary barriers that now impede the flow of practical knowledge and thus can leverage the value of both past and future research. Collecting and organizing knowledge to support nanosystems engineering deserves a high priority.

Characterization

All manufacturing processes depend on inspection and metrology to control the manufacturing process. The current analytical characteriza-

tion, inspection, and metrology tools are not yet capable of sustaining scanning-probe directed APM. However, excellent progress has been made in the resolution and capabilities of these tools. While the needs of current manufacturing processes such as the semiconductor industry, and scientific research in general will continue to develop these technologies, the needs of APM would justify accelerated development of characterization, inspection, and metrology tools. The complete list of techniques and tools would be beyond the scope of this section. Some obvious candidates for consideration are listed below:

- Transmission electron microscopy
- Atom probes
- Scattering/Diffraction methods
- Scanning probes
- He beam microscopy.

Next-generation fabrication methods based on self-assembly will be outgrowths of existing methods involving biomolecules, synthetic molecules, and nanoscale particles, fibers, and so forth. These can draw on the well-established methods for macromolecular characterization that have been the basis for today's extensive knowledge of the productive nanosystems and other molecular machinery found in biology.

Early-generation APPNs are expected to roughly parallel ribosomes and DNA polymerases in scale and complexity. Current methods are now able to provide atomically precise characterization of these structures, though this remains a challenge at such a large scale (hundreds of thousands of atoms). Current million-atom class AP nanostructures are based on structural DNA technology that exploits the recent "origami" technology, and atomically detailed structural knowledge of these products derives largely from knowledge of their nanometer scale geometries combined with knowledge of smaller-scale of the same kind. Characterization of their nanometer scale geometries has proved to be the bottleneck: The premier technique today is cryoelectron tomography, but the necessary instruments are rare today and in great demand. A dedicated user facility for this purpose would speed progress, as would improvements in automation of the technique.

Overall, characterization methods in this area appear adequate to support progress and are already advancing to serve demand from other areas of molecular science and technology. However, the development of a wide range of AP can benefit greatly from faster, lower-cost methods for atomically precise characterization of macromolecular objects. The time required for this is often the rate-limiting step in the

cycle of design, fabrication, characterization, and redesign or use. The promise of AP systems and productive nanosystems therefore adds urgency to the demand for improvements.

Fabrication Methods and Enablers

AP fabrication and assembly methods are often divided into top-down (directed by scanning probe tips) and bottom-up (directed by AP self-assembly of complementary interfaces) methods, but with a gray area between. Because of the many overlaps in the technical challenges for these fabrication approaches, however, those listed below are not categorized in these terms.

Atomically Precise Tools

- Stable, reproducible, atomically precise scanning tunneling microscope tips with atomic resolution imaging capabilities.
- Atomically precise tool tips designed to capture atoms, molecules, or other building blocks in precise, reliable configurations, and to transfer them to other structures through a precise, reliable operation.
- Smart tool tips that are able to sense whether a building block has been captured by the tip and when it transfers from the tip to the desired location.
- AP stamps, molds, and nanoimprint templates that enable parallel passivation/depassivation operations.
- Closed-loop nanopositioning systems with resolution < 0.1 nm and 3 or more degrees of freedom, and small-footprint systems to implement array-based parallelism.

Atomic Resolution Processes

- Technical improvements in atomic layer epitaxy and atomic layer deposition.
- Multi-material patterned atomic layer epitaxy.
- Methods to accommodate lattice mismatch in heteroepitaxial 3D structures.
- Highly selective depassivation of surfaces (in support of multi-material ALE).
- Highly selective and layer-by-layer etches (removal of sacrificial layers deposited by multi-material ALE).
- Robust protection layers to preserve the atomic precision of the output of APM.

- Deprotection-based AP mechanosynthesis methods (for example, by tip-directed H depassivation of atomic sites on Si surfaces to direct subsequent growth steps).
- AP functionalization of surfaces.
- In situ generation and separation of radicals for atomic resolution processing.
- Atomic defect inspection.
- Atomic defect repair (adding and removing atoms).
- Atomic resolution etching.
- Additive covalent mechanosynthesis methods (direct, AP placement and bonding of reactive molecules and molecular fragments).
- Additive non-covalent mechanosynthesis methods (direct, AP placement of building blocks that self-align and bind non-covalently).
- Ribosome-like mechanosynthesis of AP polymers that subsequently fold or bind to form AP polymeric objects.
- Binding sites for collecting feedstock molecules and building blocks used in mechanosynthesis.
- All of the above in liquid phase.

Atomically Precise Components and Building Blocks

- Catalogues of atomically precise building blocks (organic or inorganic, natural or synthetic) organized by functional properties.
- Improved processes for the production and purification of these building blocks.
- Building blocks fabricated by atomically precise top down method.
- Self-aligning building blocks that enable AP results from less-than-AP positional control during assembly.
- Monomeric building blocks for ribosome-like mechanosynthesis of AP polymers (that can subsequently fold or bind to form AP polymeric objects).
- Monomeric building blocks for mechanosynthesis of highly cross-linked AP structures.
- Lower-cost production of DNA through bioengineering to exploit and improve the utility of DNA-secreting bacteria.

- Improved design software for folded protein structures, and for new classes of folding polymers based on new monomeric building blocks.

Modular Molecular Composite Nanosystems (MMCNs)

- Capabilities for engineering proteins with AP binding to DNA frameworks and functional components
- Extension to a wider range of structures of the recent "origami" technology for building configurable, 3D, million-atom-scale DNA frameworks.
- Exploiting the dense arrays of distinct, addressable, AP binding sites generated by DNA-based structures to organize 3D patterns of non-DNA components.
- Developments that exploit and extend the enormous set of DNA-like, DNA-binding polymers to expand the functional repertoire of structural DNA nanotechnologies.
- Developments in protein engineering to produce a wider range of functional, relatively rigid AP polymer objects with greater reliability.
- Systematic methodologies for building MMCNs in which proteins bind specific functional components to specific sites on DNA structural frameworks, for example, by exploiting zinc-finger based proteins with sequence-specific binding.
- Theoretical and experimental on applications that can exploit systems with large numbers of distinct, functional nanostructures organized in 3D patterns on a 100 nm scale.
- Means to interface MMCNs with nanostructured substrates patterned by tip-directed AP fabrication and by non-AP nanolithography.

Structures, Devices, and Systems

AP systems will require a range of components with functional properties as diverse as their applications, and each application area will generate its own agenda for research. These agendas will overlap in requiring a range of core capabilities, many of which are also enablers for APM systems in general, and for productive nanosystems in particular.

Because tasks and functions at the often parallel those at the macro-scale, the required components and devices likewise are often parallel. Structural frameworks require components like beams, plates, and rods,

and require means for attaching one to another. Mechanical systems require components like bearings, joints, shafts, and motors. Electrical systems will commonly use wires, insulators, capacitors, and switches. Indeed, all these are found in existing nanosystems, either in biology or in digital electronics.

Physical phenomena important at the nanoscale (tunneling, thermal fluctuations, short-range attractive forces, etc.) will often make an enormous difference in the implementation and operation of nanoscale AP systems, and will present fresh challenges and opportunities. Design, modeling, and experimentation all can contribute to expanding our understanding and capabilities in this area, and systematic exploration of nanoscale versions of familiar elements of macroscale systems will be of great value.

In this pursuit, however, it will be vital to apply engineering criteria and metrics to evaluate merit. To be a genuine motor, for example, a device must be able to deliver power to something else (a criterion), and it can be judged by metrics such as its speed, torque, and efficiency. Similarly, be a genuine logic gate, a device must be able to function as part of a network of devices that forms a digital system (a criterion), and it can be judged by metrics such as its switching speed, energy dissipation, and noise margins.

Design, modeling, and experimentation all can contribute to expanding our understanding and capabilities in this area, and systematic exploration of nanoscale versions of familiar elements of macroscale systems will be of great value.

Development of Scanning-Probe Based APM Systems

In addition to the component-level and process-level research challenges described above, the realization of scanning-probe based APM systems will require system-level development work.

The passive systems required for APM, such as mechanical framework, power distribution, information distribution, etc., must be designed, but are largely straightforward adaptations of existing technology and may be constructed with existing toolsets. We will not list passive system requirements for APM.

The active systems for APM are also within the grasp of existing technology but will be operating in regimes where production manufacturing tools have not yet tread and will require challenging system integration, especially when scaling up to higher levels of throughput through parallelism and higher-frequency operations.

While the nanopositioning system will not require atomically precise components, it will require the integration of the atomically precise tool or tools that implement the fabrication operations. Research objectives for these tools are discussed above. It should be noted, however, that developments in this area will also be applicable to advanced-generation

APPNs, which are anticipated to perform similar operations by means of nanoscale positioning mechanisms. Thus, tip-directed processes studied and developed for scanning-probe based APM systems can also be viewed as exploratory research for advanced-generation APPNs.

Designing the system architecture for a particular APM technology will set the requirements for its passive and active systems. We believe some of the nearer term areas of useful research for active systems for APM will include:

- Microscale nanopositioning systems used to carry out the spatially addressed atomically precise fabrication technique to be implemented, such as deprotection-based or additive mechanosynthesis.
- Power and information distribution systems to control arrays of microscale nanopositioning fabrication systems.
- A global alignment and nanopositioning system to control the position of an array of fabrication units relative to a workpiece.
- Inspection and metrology systems.
- Material transport systems for both feedstocks and finished products.

To extend the scope of APM based on productive nanosystems, a natural direction is to develop analogous systems that can link different kinds of monomers in order to broaden the range of materials that can be used to make AP polymer objects. This approach can enable the production of higher-performance AP products by improving the stability, predictability, rigidity, and functionality of the structures.

Development of Early-Generation Productive Nanosystems

Existing APPNs are self-assembled biopolymeric mechanisms that fabricate biopolymers (proteins and nucleic acids) under the direction of DNA. To extend the scope of APM based on productive nano-systems, a natural direction is to develop analogous systems that can link different kinds of monomers in order to broaden the range of materials that can be used to make AP polymer objects. This approach can enable the production of higher-performance AP products by improving the stability, predictability, rigidity, and functionality of the structures, accomplishing this by using (for example) novel backbone structures, denser cross-linking, and monomer side-chains with special functional properties. This approach to APM is clearly complementary to scanning-probe based methods, as each can make products that the other cannot.

An appealing approach for early-generation APPNs is to mimic biological ribosomes by using nucleic acid sequences to direct operations by binding sequences of monomeric building blocks via nucleic acid “adapters” analogous to tRNA molecules. The use of complementary sequences substantially longer than the three bases used in biology can increase reliability and obviate the need for

sophisticated kinetic proofreading like that employed by biological ribosomes. It should be noted that ribosomes are relatively simple mechanosynthetic devices: They employ no special catalysis to form bonds, relying instead simply on positional control of the reactive molecules to promote and direct bonding.

This objective suggest a range useful research challenges that are useful or necessary to meet in order to develop early-generation APPNs and products of practical utility:

- Design and evaluation of competing architectures for broadly ribosome-like APPNs, in order to prioritize options for meeting the following challenges.
- Development of competing options for backbone structures. Monomer accessibility, reactivity and cost are considerations, as well as the properties of the resulting structures.
- Development of nucleic acid (or analogous) adapters to bind sequences of monomers in accordance with base sequences in DNA strands.
- Development of mechanisms for binding and transporting sequences of monomers to a reaction site where they are linked and removed from their carrier.
- Provision of high-purity feedstocks of correctly coupled monomers and adapters (purity is a constraint on defect rates in the product structures).
- Development of monomers and linking mechanisms that enable the production of densely cross-linked AP polymeric objects of high stability, strength, rigidity, and overall robustness.
- Further development of pairs of interface structures and moities that can be covalently "locked" to give self-assembled products higher stability, strength, and overall robustness.

Pathfinding for Advanced-Generation Productive Nanosystems

Within certain limits, computational modeling can support the development and evaluation of exploratory designs for complex nanosystems. This can speed the development of advanced-generation APPNs by enabling a more efficient and coordinated application of research and development effort. Designers can explore the utility of potential developments in fabrication methods by modeling and evaluating components of the sort that those potential methods could

make. Evaluation of the projected utilities of research objectives can enable researchers to select directions that are more to produce high-value results by dovetailing with other results to enable system development.

System level design and modeling can, in turn, determine the requirements for components, enabling their evaluation. (In practice, of course, component design and system design form an iterative process in component properties also constrain system architectures.)

The challenges for modeling here differ from those in molecular biology and biochemistry. As noted in an earlier section, components that are (for example) relatively rigid, regular, and stable can be far more susceptible to atomistic modeling than are components accessible by means of current fabrication processes. Further, straw-man exploratory designs can include susceptibility to modeling as a design criterion. These considerations facilitate the design, modeling, and evaluation of important classes of potential downstream development targets, including nanomechanical systems comprising advanced-generation APPNs. The challenges are quite unlike those of modeling, for example, soft, un-designed biological systems presented by nature.

Experimentation contributes to pathfinding by testing and discovering structures, functions, and processes of kinds that will be useful later in a systems context. This motivates an enormous range of work in materials science, surface science, and chemistry. Tip-directed synthesis methods, in particular, can be seen as prototypes for operations seen as important in advanced-generation APPNs.

It is anticipated that the enabling technologies for next-generation APPNs will increasingly rely on previous generations of APPNs that, in a successful development chain, must be able to produce components and systems with expanded capabilities.

In pathfinding for advanced-generation APPNs, the overall research challenge is to identify and compare alternative chains of enabling technologies. In the earlier generations, components will be made and manipulated chiefly by techniques that are direct extensions of current laboratory practice. In the later generations, it is anticipated that the enabling technologies for next-generation APPNs will increasingly rely on previous generations of APPNs that, in a successful development chain, must be able to produce components and systems with expanded capabilities.

A modest level of effort invested in forward-looking design exercises and experimentation can leverage ongoing research by enabling it to target what are likely to be high-value objectives. It can also help identify challenges that require greater focus, missing scientific knowledge that impedes or obstructs effective modeling, and obstacles that make an otherwise attractive path very difficult or completely infeasible. Information of this kind can help define a better targeted research and development program.

A Call to Action: Policy Recommendations

The goal of this Roadmap is to accelerate the development and application of nanotechnology to improve the human condition. We believe this will require the development of Productive Nanosystems and Atomically Precise Manufacturing (APM), which enable science, engineering, and manufacturing at the nanoscale. A long-term program such as this requires strategies that deliver intermediate benefits to justify the investment. This Policy section will first sketch the opportunities, next suggest some general approaches and principles, and then present specific initiatives proposed to be undertaken by the United States:

"Strategy One" is to develop atomically precise technologies that enable clean energy supplies and a cost-effective energy infrastructure.

"Strategy Two" is to develop atomically precise technologies that result in nanostructured medicines and multifunctional therapeutic devices to improve human health.

The Opportunity

Now is the time to take the next step of accelerating the translation of our global nanoscience research into beneficial nanotechnology, by launching programs focused on the development and commercialization of APM.

This Roadmap's sketch of Atomically Precise Manufacturing offers a vision with immense leverage—and challenges—in many areas. It builds on and extends the nanoscience foundation established by the U.S. National Nanotechnology Initiative[1] and similar initiatives in other countries. While only a small subset of possible breakthroughs enabled by APM has been described in this Roadmap, success in just one of these areas would justify a major program. The economic value derived from early APM commercialization is projected to be enormous, creating huge new economic opportunities for those who succeed.

We urge involvement by responsible participants worldwide in achieving APM. Now is the time to take the next step of accelerating the translation of our global nanoscience research into beneficial nanotechnology, by launching programs focused on the development and commercialization of APM. In the U.S., the NNI has been instrumental in focusing world attention on nanoscience and has provided world leadership in establishing the necessary interdisciplinary research. A major opportunity exists to leverage the past eight years of NNI research platforms and to establish a unifying vision for the advancement of atomically precise technologies and APM. Our aim in this Roadmap is to call for the development of Atomically Precise Manufacturing Technologies that will address the grand challenges of

[1] National Nanotechnology Initiative web information at www.nano.gov

Energy, Health Care and other fields that will benefit from atomically precise technologies and Productive Nanosystems.

General Approaches and Principles

Our strategy should emphasize competition to find good ideas, and markets to reward success and to allocate scarce resources of money, time, and brainpower. Development of the Internet economy has shown the power of competition and markets to accomplish a wide range of tasks faster and cheaper than large centralized programs. Rather than creating a single, multi-billion-dollar project, we should aim for a mix of thousands of one-million-dollar efforts and hundreds of ten-million-dollar efforts, using these to lay the groundwork for tens of hundred-million-dollar efforts. Many pathways lead toward our goal, and they will inevitably lead to unexpected opportunities, difficulties, and mutual synergies. As with the commercialization of the Internet, decentralized competition and cooperation will move faster and at a lower cost than setting up and attempting to manage a single, enormous program.

Decentralized competition and cooperation will move faster and at a lower cost than setting up and attempting to manage a single, enormous program.

Cooperation between government, academia, and industry is essential. A well-designed program would fund multiple company/university groups to compete with one another in target areas, while fostering cooperation within an individual company/university cluster. Improvements in the rules and mechanisms for technology transfer between universities and companies would be highly beneficial. High speed communications will support close international collaborations that can benefit from brainpower anywhere in the world.

Industry involvement is essential for program focus and rapid deployment of the technologies developed. However, companies have a limited ability to invest in long-term research. Financial markets often punish public companies for making R&D expenditures, and small private companies lack the necessary resources. Government research funding can make a crucial difference in the scale, breadth, and time-horizon of industry-driven R&D. Tax policy could foster more R&D, but with much less focus and effectiveness than a targeted funding program.

In the U.S., new types of government funding programs are needed that support larger research budgets for longer times than programs such as Small Business Innovation Research (SBIR). The Defense Advanced Research Projects Agency (DARPA) model of R&D funding[2] works very

[2] DARPA maintains a very small staff of highly technical Program Managers who have broad discretion to propose programs, award significant contracts, and push for breakthrough results in short time horizons. Bypassing most of the bureaucracy involved in normal government R&D contracts, this model can fund risky projects that other agencies would shy away from. For two

well at funding high-impact, competitive research (such as the creation of the Internet). Creating a DARPA-like program focused on APM, fostering R&D proposals from competitive consortia of universities and companies, would create a dynamic and productive environment for rapid technology development and commercialization. Creating such an agency would be a very productive and cost-effective way for a country to launch an APM program.

Once early laboratory results have demonstrated the fundamental operations required for next-generation APM, we would expect some countries to launch a DARPA-like program to accelerate progress. The challenge will be to build programs with the right participants and incentives to take technologies from early demonstrations to scalable systems, products, and industries. A program under university control could foster research, but would not directly support system-level development. A program under government lab control could enable early system-level development, but would not bring technologies and products to market. Corporations would have incentives to bridge the final steps to market, but these same incentives would the necessary precursor stages. A well-structured consortium of these organizational forms, however, would give each participant an ability to do what it does best.

International cooperation will deliver the benefits of APM and APPNs to the world faster, and with wider applications, than a number of smaller national programs duplicating one another's work. Coordinating a full international effort is beyond the scope of this initial Roadmap, but is extremely desirable. We recommend a future international workshop on atomically precise manufacturing with representatives from countries wishing to participate in such a program.

Recommendations for the United States

The U.S. National Nanotechnology Coordinating Office[3] should coordinate both the governmental and university aspects of a national

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examples, see DARPA's "Revolutionizing Prosthetics" program to build an advanced prosthetic arm controlled by neural impulses (http://www.darpa.mil/dso/thrusts/bio/restbio_tech/revprost/index.htm) and their "Grand Challenge" program to develop self-driving vehicles (http://www.darpa.mil/grandchallenge/index.asp).

[3] The National Nanotechnology Coordinating Office (web site at www.nano.gov/html/about/nnco.html) currently assists in the preparation of multi-agency planning, budget and assessment documents. The NNCO is the point of contact on Federal nanotechnology activities for regional, state and local nanotechnology initiatives, government organizations, academia, industry, professional societies, foreign organizations, and others to exchange technical and programmatic information. In addition, the NNCO develops

program to develop APM. The NNCO should be augmented with an industry representative to coordinate this program.

The National Science Foundation should work with NNCO to structure a university program to develop APM. The NSF already manages a network of universities as part of their National Nanotechnology Infrastructure Network[4]. Created as a user facility, this network offers access to advanced tools at 13 universities around the U.S. The tools needed for APM are expected to be different from the NNIN's top-down approach to generic nanotechnology, but the collaboration model established by the NNIN would be beneficial for development of APM. Emphasis should be placed on developing effective collaborations between universities and industry.

The collaboration model established by the National Nanotechnology Infrastructure Network would be beneficial for development of APM. Emphasis should be placed on developing effective collaborations between universities and industry.

Strategy One: APM Research Targeting Clean and Low-Cost Energy Infrastructure should become a major focus of the U.S. Department of Energy. The DOE has been successful in creating five Nanoscale Science Research Centers (NSRCs) that are aligned in the support of DOE's mission by performing both basic sciences and applications research. All five centers are user facilities that provide access to industry and other research organizations:

- Center for Nanophase Materials Science at Oak Ridge National Laboratory
- Molecular Foundry at Lawrence Berkeley National Laboratory
- Center for Integrated Nanotechnologies at Los Alamos National Laboratory and Sandia National Laboratories
- Center for Nanoscale Materials at Argonne National Laboratory
- Center for Functional Nanomaterials at Brookhaven National Laboratory

These five nanotechnology centers are ideally suited to lead an "Atomically Precise Manufacturing Initiative for Energy Systems" that will also impact other industries and markets. The applications section of this Roadmap highlights a few of the huge opportunities to dramatically improve efficiency, generation, conversion, and storage of energy. Around the world, governments, universities, and industry are making growing investments in photovoltaics, fuel cells, thermoelectric and piezoelectric energy harvesting, solid state lighting, and bio-energy.

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and makes available printed and other materials as directed by the NSET Subcommittee, and maintains the NNI Web site.

[4] National Nanotechnology Infrastructure Network web information at www.nnin.org

A core program to develop Productive Nanosystems will provide enabling technology to advance all these initiatives.

A new position of "DOE Program Manager for Atomically Precise Technologies" should be created to work with the five DOE nanotechnology centers to develop a strategic plan that integrates and aligns resources in support of APM pathways discussed in this Roadmap. This program manager should also sit on the National Nanotechnology Coordinating Office board as a representative of the DOE, and would be responsible for managing a grant program to address industrial needs while also bringing in industrial cost share to accelerate the research and development of APM pathways.

The DOE has launched a program called ARPA-E to streamline its R&D. This represents an opportunity for the DOE to evaluate including APM in new ARPA-E initiatives. This would help accelerate the APM technology development for fuel cells, photovoltaics, and other renewable energy programs.

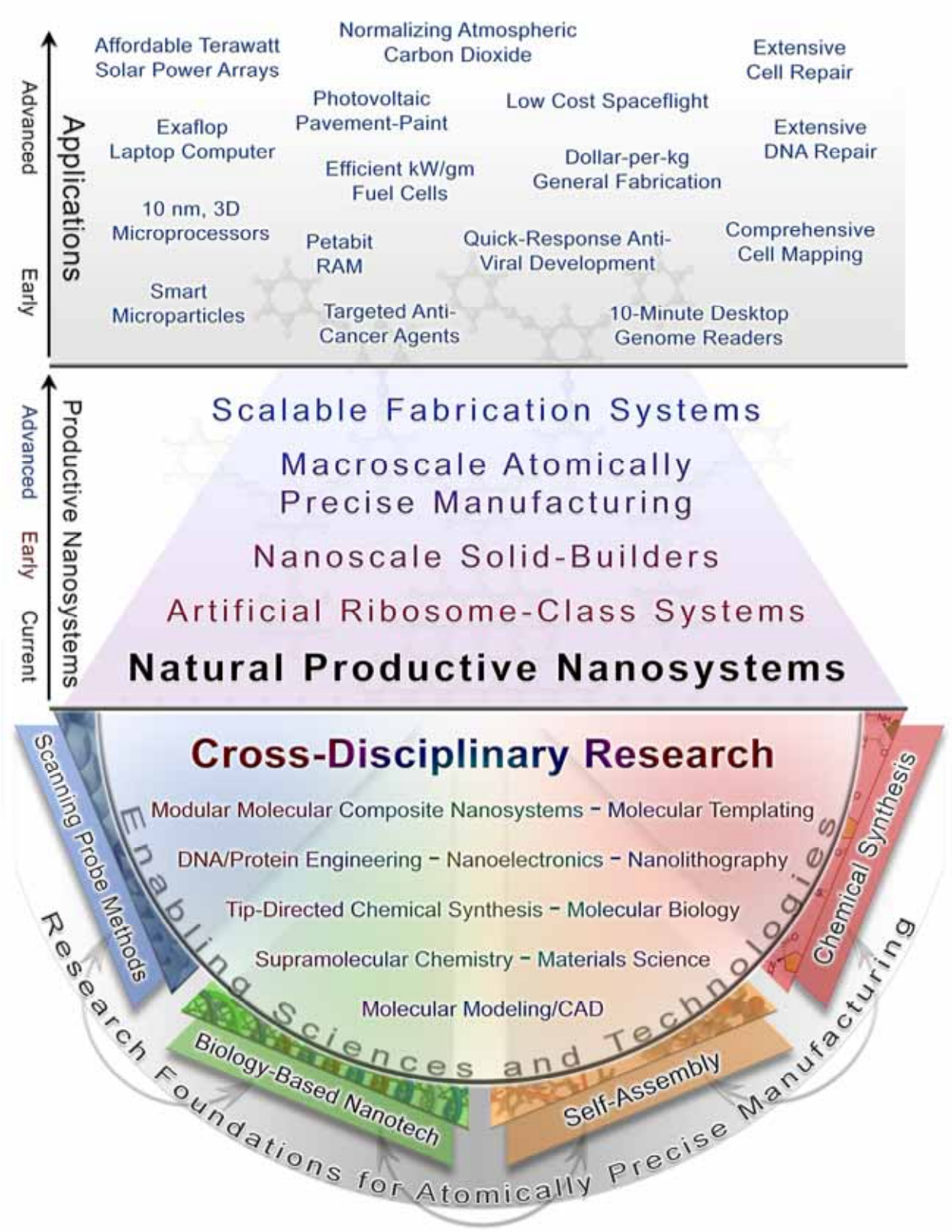
Strategy Two: Atomically Precise Nanomedicine Technologies to Improve Human Health should become a major focus of the National Institutes of Health. The NIH already has efforts in nanotechnology, but the power of APM would revolutionize our ability to analyze, synthesize, and ultimately commercialize atomically precise multifunctional *in-vivo* and *in-vitro* therapeutic and diagnostic devices. A new position of "NIH Program Manager for Atomically Precise Technologies" should be created to align NIH resources, and this person should sit on the NNCO board as a representative of the NIH.

Conclusion

The sooner we launch programs to develop APM and productive nanosystems, the sooner our vision suggests we can enjoy the benefits of cleaner energy and healthier lives. A vital next step is further development of this Roadmap by an expanded international team drawing from a wide variety of nanoscale-focused organizations.

The graphic on the following page gives an overview of the basis for collaborative research and the possible early and advanced outcomes in productive nanosystems and applications. The research areas indicated therein and the tools necessary for making progress toward developing nanotechnology applications are discussed in the next section, Topics in Detail.

Practicable Nanotechnology Research Initiatives and Outcomes



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Topic 1 Components and Devices

1.1 Introduction

This topic covers passive and active components of kinds that may prove useful in implementing atomically precise functional nanosystems. The boundary dividing "components and devices" (discussed here) from "systems" (discussed in a later section) is necessarily somewhat arbitrary. The line drawn here includes passive and active structures that have what are in some sense elementary functions. Some are structural elements that in combination could form an extended framework; others are functional elements that could (e.g., logic gates) be composed to make functional systems (e.g., computing devices).

As discussed in the Agenda for Research, it would be of great value to have an ongoing compilation of components and devices indexed by properties relevant to their fabrication and use. Classes of components can be defined by functional criteria, and within those classes, components can be characterized by both general metrics (e.g., size, mass, composition, maximum operating temperature) and class-specific metrics (e.g., motor torque, logic gate delay time). A compilation of this kind would aid designers, reveal needs, and foster cross-disciplinary communication. Today's alternative is a literature that is difficult to access and impossible to search effectively with respect to the relevant criteria and metrics: this is a major impediment to problem-solving in the development of APM and functional AP nanosytems. Better ways are needed to exploit the results of the billions of dollars of research funding that has been invested in nanotechnologies and related fields.

1.2 Structural Components

Structural components include components that are primarily used to hold parts of a system in place, to provide dimensional precision, stiffness and strength. They must resist deformation due to thermal vibration and due to the forces present during system operation. For these components, in addition to the information of interest for atomically precise components in general, parameters of interest also include:

- Stiffness
- Strength
- Granularity (the scale of the units of design: atoms, monomers…)

1.2.1 Modular Oligomers

Modular components are components that can be built of a series of independently chosen monomers, such as the nucleotides of DNA or the amino acid residues of proteins. These components are discussed at length in Topic 2 Systems and Frameworks in the context of structural systems. See Lewis, Paper 08, Working Group Proceedings; see also Mathieu et al., 1995.

1.2.2 Surfaces

Perfect surfaces of stiff crystals provide long range atomically precise positioning, effectively using the parallel chemical bonds in the bulk of the crystal to constrain the amplitude of both thermal fluctuations and the elastic deformations that may result from forces applied by a mechanical nanosystem.

Perfect surfaces of stiff crystals are attractive building platforms for atomically precise structures (see also Topic 2 Systems and Frameworks). They provide long range atomically precise positioning, effectively using the parallel chemical bonds in the bulk of the crystal to constrain the amplitude of both thermal fluctuations and the elastic deformations that may result from forces applied by a mechanical nanosystem. Today, atomically flat crystal terraces as large as 8x8 microns are available for silicon (Lee et al., 2001).

1.2.3 Sheets and Fibers

A sheet, like graphene or MoS_2 can serve as a stable substrate analogous to a crystal terrace, albeit without the mechanical reinforcement provided by the subsurface chemical bonds. In the plane of the sheet, it is still a highly fused polycyclic system.

Polymers with Covalent Backbones. This category includes DNA and proteins, which are covered in detail in Topic 2 Systems and Frameworks. More generally, any programmable 1D polymer, anything that can be built by solid phase synthesis, can be directly useful as a 3D component if it folds predictably. Even if it does not fold predictably, if it can be put under tension (e.g., by covalent bonds to DNA on both ends) it may still be useful in placing exotic functional groups in predictable 3D locations.

Fibers can include structures with a diameter of several atoms, such as carbon nanotubes (covered below in Subsection 1.2.8, Graphene Components) and a wide range of polymers. These can have high strength along the backbone, and some are available in high molecular weight. Locally, these structures are atomically precise. Some are also available as oligomers of known length. These strands are attractive tensile structural components for atomically precise nanosystems.

Non-Covalent Nanotubes. Another class of atomically precise linear structural element now available comprises a growng range of

nanotubes formed by hydrogen-bonded self-assembly. This category includes nanotubes formed from DNA. For example, studies of variations on a tube type formed by self-assembly of two types of double crossover tiles showed that diameters ranged from 7 to 20 nm. (See Lewis, Paper 08, Working Group Proceedings; see also Rothemund et al., 2004.)

Atomically precise self-assembled tubes have also been formed from peptides. For example, 8, 10, and 12 residue cyclic peptides were synthesized with alternating D and L amino acid residues, and it was demonstrated that they self-assembled into nanotubes with a beta-sheet motif (Hartgerink et al., 1996).

1.2.4 Dendrimers

Dendrimers are special polymers assembled by a branching growth process, conceptually beginning with groups A and B that will bond, e.g., after an activation step on B. Starting with a single root molecule of the form AXB_2, the two B groups are activated, then reacted with two additional molecules of the monomer to form $AX(B\text{-}AXB_2)_2$. The four B groups on this must then be activated and reacted with four molecules of the monomer to form $AX(B\text{-}AX(B\text{-}AXB_2)_2)_2$. Each of these steps is called a generation. The molecule starts from a single point, and the number of groups attached to that point grows exponentially with the generation number such that the process is eventually limited by steric congestion. If one stops short of that limit, the correctly synthesized molecules are atomically precise. A wide variety of dendrimers have been synthesized. The monomers used in each generation can differ, e.g., AXB_2 and AYB_2. This yields options somewhat like those in foldamers, but with less information per dalton because the late generation monomers are numerous and are all identical in any given generation.

Initially dendrimers were limited by the capabilities of conventional organic synthesis. Major synthetic strides have been achieved by development of self-assembly approaches that exploit hydrogen bonding, metal coordination, and pi-pi stacking interactions. Stability and utility are being enhanced via incorporation of mechanical bonds. (See Fréchet, 2002; Northrup, 2005.)

1.2.5 Biological Nanoparticles

Certain biological nanoparticles are both atomically precise and relatively large. They are therefore potential frameworks to which other atomically precise components can be attached. Examples are viral capsids, especially MS2 and TMV.

The group of Dr. Matthew Francis at the University of California, Berkeley has developed many techniques (chemical reactions) to incorporate functionalities of interest to specific, well-defined sites on the walls of the cavities inside these structures and on their external walls. These can be modified with, for example, polymers or proteins, to control solubility, antibody recognition, and other key properties. A functional example is the incorporation of MRI contrast agents within the capsids. By using specific chemistries to target specific amino acids, crystallographic knowledge of protein structure enables the functionalization of discrete sites on discrete places on these protein structures.

1.2.6 Ceramic Nanocrystals

Metal oxides. A wide variety of metal oxides have been prepared as nanoscale particles. Viewed as molecules, these particles are highly crosslinked, polycyclic structures; some have high stiffness (e.g., ~300 GPa for TiO_2). While this section concentrates on structural components, nanoparticles of metal oxides might potentially serve in

- Molecule processing (as catalysts)
- Energy conversion (as photochemical centers)
- Signal transduction (as magnetoresistive elements)
- Information storage (as magnetic dipoles)

Currently, metal oxide nanoparticles are seldom atomically precise. Over the long term, APM techniques should enable production of these components with atomically precise structures. Over a somewhat shorter term, the sol-gel oxide synthesis techniques may prove amenable to atomically precise control, for instance, via binding capping materials to crystal faces of correctly matching sizes. A modest set of large atomically precise metal oxide particles are known, notably polymolybdates (up to Mo_{368} monodisperse species) and tungstates, which have been synthesized with quite diverse structures and ligands. (See Roy, 2006; also Kong, Paper 20, Working Group Proceedings.)

II-VI semiconductors. II-VI semiconductor nanoparticles have properties somewhat similar to some of the metal oxides (and the group IIB oxides, notably ZnO, are in the intersection of the groups). They can be made in nanoscale particles with well-defined internal crystal structures, and researchers have been successful in narrowing the distribution of size, yet these are generally not available as single species of atomically precise particles. The exceptions include a modest set of "closed shell" structures.

Typically, these particles are made by precipitation from organic solvents in a reaction between an organometallic compound of the group IIB metal (e.g., dimethylcadmium) and a chalcogenide donor compound (e.g., bis-trimethylsilyl sulfide) in the presence of a capping ligand (e.g., a trialkylphosphine) (See Cao, 2004.)

While these materials are potentially useful as structural materials, they also are useful as functional components in other areas, notably in

- Photonics and signal transduction, due to their (quantum dot) fluorescence
  - Notable due to modulation of their energy levels by confinement of carriers to the dot
  - Notable due to much better resistance to photobleaching than traditional chromophores
- Logic operations, as nanoscale semiconductors suitable for transistors.

Advanced APM would enhance the usability of these components for these applications, and early AP fabrication techniques could potentially supply more sophisticated capping that would enable the synthesis of a wider range of atomically precise components made from this class of materials.

1.2.7 Metallic Nanocrystals

A number of metals are available as nanoscale crystals. On the lower end of the size spectrum, there are many known metal cluster compounds. Clusters such as Au_{55} are atomically precise and can be used as atomically precise components.

Other areas of applications for these components include

- Information processing: use as electrodes in single electron tunneling (see Chi et al., 1998).
- Signal transduction: use of plasmon resonances to greatly increase sensitivity for Raman-effect sensing of adsorbates.
- Chemical processing: use of metal nanocrystals to catalyze reactions. The trade-off between use of metal nanocrystals versus use of complexes of isolated metal atoms would need to be evaluated case by case. A very wide range of catalytic properties is available from these simpler components as well.

1.2.8 Graphene Components

There is a vast literature on graphene nanostructures. These are very stiff (with theoretical Young's modulus around 1 TPa), so they are extraordinarily attractive as rigid structural components. Roughly speaking, these components exist in the following types:

- C_{60}, C_{70}, other fullerenes, and their derivatives
- Planar, atomically precise graphene sheets, currently up to $C_{222}H_{42}$
- Larger, planar graphene flakes, atomically imprecise at their edges
- Single-walled and multi-walled carbon nanotubes (SWCNTs and MWCNTs)
- Various other structures: "nano-onions" (nested fullerenes), nanohorns, etc.

Identifying opportunities to exploit atomic-scale properties: double-walled nanotubes show physical and electrical properties, similar to single-walled tubes but possess enhanced chemical resistance owing to the additional layer of atoms.

Graphene is a two-dimensional, honeycomb structured monolayer of graphite. Defects in the regular hexagonal lattice, such as pentagons or heptagons, result in curling of the two-dimensional graphene sheet into three-dimensional structures. The most well-known is the soccer-ball shaped C_{60} fullerene, comprised of 12 pentagons and 20 hexagons.

A single-walled carbon nanotube is a seamless cylinder of graphene that possesses physical and electrical properties distinct from both graphite and multi-walled carbon nanotubes. SWCNTs possess metallic or semiconducting properties that are dependent on tube chirality and can be manipulated via doping, and that rival those of the best metals and semiconductors used in current electronics. Synthesis approaches are relatively aggressive and uncontrolled, generally involving the deposition of vaporized graphene or carbon onto a catalyst or other template, and cost of production remains a significant hurdle to more widespread utilization.

Multi-walled nanotubes are typically a set of single-walled nanotubes of progressively increasing diameter, arranged as concentric cylinders. Double-walled nanotubes show physical and electrical properties similar to single-walled tubes but possess enhanced chemical resistance owing to the additional layer of atoms. The additional layers also render multi-walled nanotubes attractive candidates for functionalization and modification, broadening further the range of potential applications.

Carbon nanotubes, particularly the single-walled variety, occupy an unusual middle ground in atomic precision. An infinitely long nanotube has its structure defined by a two-integer index called the roll-up vector,

which defines the angle and width at which one would have to (conceptually) cut a strip out of a graphene plane in order to roll it into a nanotube of this type. Amongst other properties, this roll-up vector determines if a SWCNT is metallic or semiconducting. Some progress has been made in isolating SWCNTs of desired roll-up vectors.

Preparing finite nanotube segments that are atomically precise in the same way that, e.g., anthracene, is atomically precise, will be a more challenging research goal. This will require that all of the segments be of precisely the same length, and that their terminal groups match as well.

The fullerenes and the $C_{222}H_{42}$ graphene sheets are atomically precise components today, and could be incorporated as a section of a foldamer component where a small but high stiffness part is needed.

A natural target of APM is to prepare such structures. It is possible that this may be a relatively near-term task. The conditions for producing nanotubes today are rather drastic (laser or arc vaporization, high temperature CVD), but the conditions for forming/interconnecting the aromatic rings in synthesizing $C_{222}H_{42}$ are rather mild ($FeCl_3$ oxidation) (see Kastler, 2006). A similar reaction may be feasible in early MMCNs (see Topic 2 Systems and Frameworks), potentially allowing true atomically precise SWCNT segments to be prepared.

Alternatively, SWCNTs have been grown with transition metal catalysts. MMCN techniques may potentially be used to prepare atomically precise catalyst particles that could then be used to produce tubes with a selected roll-up vector – albeit of uncontrolled length.

In addition to their use as structural components, graphene components show promise for application in multiple areas, including:

- Information processing: semiconducting SWCNTs have been used as transistors
- Power and signal transmission: metallic SWCNTs have very high current-carrying capability
- Actuators: MWCNTs have been used in a motor, with sliding rotary motion between concentric tubes
- Chemical sensors: CNTs have shown sensitivity to adsorbed molecules.

1.2.9 Inorganic Nanotubes

Spanning the periodic table in composition, inorganic nanotubes and fullerene-like particles comprise a broad range of structures and properties, sometimes analogous to their carbon counterparts. Inorganic nanotubes include boron nitride (BN), transition metal sulfides and oxides, selenides, halides, and more. WS_2 nanotubes, for example, possess lower Young's modulus but are much stronger under compression than carbon nanotubes, and undoped BN nanotubes are

uniformly insulating. Some properties, such as piezoelectric effects, are generally accessible only in non-carbon nanotubes. Similar to carbon nanotube approaches, synthesis is relatively aggressive and unspecific, particularly with respect to nanotube diameter, and there is again scope for more controlled syntheses using AP structures employing catalytic functional elements. See Pokropivnyi, 2001; Pokropivnyi, 2002; Zettl Research Group, 2007.

1.2.10 Semiconductor and Metallic Nanowires

Both semiconductors (Si, InP, etc.) and metals (Ni, Au, Pd, etc.) have been produced in the form of nanowires, structures typically a few nanometers in diameter and as much as microns long. The mechanism of formation is typically a liquid drop catalysed deposition from vapor phase material, not unlike carbon nanotube CVD growth. The semiconducting nanowires are typically crystalline and do not have an atomically precise diameter. As with other crystalline materials, the interior bonds contribute to their strength and stiffness. APM may provide mechanisms for fabricating these materials in atomically precise form. As with quantum dots, these materials are notable for carrier confinement effects on the energies of electronic states.

1.3 Motors and Actuators

For motors and actuators, there are a number of function-specific metrics of interest:

- Maximum load
  - Stall force (for a linear motor)
  - Stall torque (for a rotary motor)
- Maximum speed (unloaded linear and angular velocities, respectively)
- Energy efficiency

1.3.1 Biological

All cellular organisms contain both linear and rotary molecular motors (MM). An additional example is a bacteriophage that uses an ATP-fueled corkscrew motor to fill and pressurize a capsule with DNA. While fluorescence labeling can be used to characterize the structure and motion of MM, their localization remains a synthetic challenge. One option for a positioning template is the bacterial S-layer; another is a DNA origami based framework (see Topic 2 Systems and Frameworks), an approach that promises great control in building complex, functional structures.

Existing biological motors have diverse properties:

- Flagella
  - Contain all of the components of conventional motors (bearings, rotators, shafts, stators, fuel requirement, etc.)
  - Powered by the flow of protons across a membrane
  - Self assemble from 40 proteins
- Myosin (a muscle protein)
  - Uses ATP fuel
  - Drives linear motion of fibers, causing muscle contraction
- Kinesin
  - Uses ATP fuel, 100 steps/second, 5-7 pN force
  - Transports large cargo objects (cell organelles) along microtubules.
- ATP Synthase
  - Rotary motor, 44 pN force
  - Powered by the flow of protons across a membrane, the resulting mechanical energy is used to sythesize ATP
- DNA Translocase
  - Acts like a fishing rod reel: pulls in DNA like a line
  - Bidirectional translocation
  - When attached to a surface: directional, provides useful work-pulls DNA in
  - Motor is controllable (via methylation)

1.3.2 Synthetic

A photochemical rotary motor is an atomically precise, unidirectional motor that is steppable.

Atomically Precise. A photochemical rotary motor is an example of an atomically precise stepping motor. This motor uses a C=C double bond as an axle and operates in a four-state cycle. Upon irradiation with 280 nm UV light, state A isomerizes to state B, which then relaxes thermally into state C, characterized by the rearrangement of sterically hindered aromatic groups attached to the double bond. Upon irridation with a unique frequency of UV light, 380 nm, state C isomerizes to state D, rotating the double bond by another 180 degrees. Finally, state D thermally relaxes back to state A, completing the cycle. This atomically precise motor is unidirectional and, because of the different light frequencies used, steppable. (See Vicario et al., 2006.)

Structural DNA nanotechnology methods have been used to construct several kinds of motors and actuators that are powered and controlled by the addition of short DNA strands to the surrounding solution. Because these act on complementary sequences in the motor structure, and because different motors can have different sequences in their active sites, multiple motors in a single nanomechanical system can by this means be addressed and activated with independent control.

Atomically Imprecise. Dr. Alex Zettl and his colleagues at Lawrence Berkeley Laboratories and UC Berkeley have constructed several nanoscale devices whose motion is controlled from the desktop with changing voltage: a rotating molecular motor, a molecular actuator, and a nanoelectromechanical relaxation oscillator.

A piezoactive polymer of potential utility is poly(vinylidene difluoride), PVDF, $(CH_2CF_2)_n$. Oligomers of PVDF could serve as atomically precise actuators available in the near term. Control of strand orientation is crucial to their function, as piezoelectric activity requires asymmetry along one axis.

Piezoelectrics can be used for actuation by varying an applied field to a piezoelectric crystal, such as lead zirconate titanate. The principal near-term disadvantage for using these crystals as components is the same as for most other crystal components: they are not currently available as atomically precise components. In addition, some piezoelectrics are solid solutions, with substitutional disorder within the crystal lattice. Advanced APM is expected to benefit applications of piezoelectrics by fabricating precisely controlled phases with substituents in controlled locations, and by controlling the location and orientation of piezo-electric domains. (See Fifield, Paper 31, Working Group Proceedings.)

SWCNTs have been used as electromechanical actuators. Immersed in an electrolyte solution (to provide counterions when the tube is charged), they have exhibited strains of up to 1% (see Baughman et al., 2002).

Thermally responsive polymers provide another mechanism for using a controllable environmental property to produce motion. In small (yet far larger than nanoscale) systems, thermal time-constants can be milliseconds or less, increasing the potential utility of this approach.

1.3.3 Macroscopic

Scanning probe systems with atomically precise positioning capability typically use macroscopic positioning components (often piezoelectric ceramics). Extending the range and repeatability of these components and of systems containing them would be useful in developing atomically precise systems.

1.4 Motion Control

Motion control is fundamental to macroscale systems that move parts with respect to one another, for example, those that assemble other components to build systems. The spontaneous Brownian motion of nanoscale objects together with selective binding can be used to build systems without motion control. With motion control, however, the constraints imposed by self-assembly can be relaxed, because parts can be directed to their binding sites. Similar remarks apply to material transportation.

A motion control component controls the relative motion of parts in a system. The components considered in this section are a subset of these, distinguished from the motors in the section above in that these do not directly provide the mechanical energy for this motion. A large range of these components rely simply on rigid body kinematics and in some cases elasticity. A reasonable near-term research goal would be to construct many of them from DNA structures (albeit with modest mechanical performance).

Hinges have been fabricated from DNA. (See Lewis, Paper 08, Working Group Proceedings; see also Yurke et al., 2000.)
A near-term implementation of a clutch between a driven component and a load component may be as simple as using one single stranded DNA sequence as one component, using a second as the other component, and using the addition of a strand complementary to both sequences for the actuation of the clutch.

For these components, rigidity, energy dissipation and operating frequency are important metrics.

Examples of motion control components include:

- Bearings
  - Bonded: sigma bonds, ferrocenes
  - Non-bonded:
    - Biological examples, e.g., in flagella
    - Sliding nonbonded interfaces with systematic cancellation of lateral forces owing to rotational symmetries
- Gears: "teeth" via interlocking shapes, hydrogen bonds, dative bonds, etc. (See Lewis, Paper 08, Working Group Proceedings; see also Tian and Mao, 2004.)
- Hinges: many implementations
- Stops, detents: many implementations
- Clutches: implementations using interlocking shapes, hydrogen bonds, dative bonds, etc.

1.5 Molecule Processing

Molecule processing components transport or transform molecules. These functions are of interest in implementing APM and APPNs, and have value in a wide range of other contexts, including chemical synthesis and separations.

Metrics of interest in devices for structural transformation of molecules include:

- Reaction rates
- Error/side-reaction rates
- Required placement accuracy (where relevant)
- Selectivity of operation (determines what kinds and locations of alternative reactive sites can exist without causing substantial error rates)

1.5.1 Catalysts

A vast array of catalysts is known. In some reactions a catalyst can be as simple as a hydrogen ion. For the purpose of near-tem use in molecule-processing nanosystems, an important category of atomically precise examples is the set of metal complexes used in homogeneous catalysis.

While the homogeneous catalysts are employed in solution, for use in a nanosystem it would be advantageous to use slightly modified variations which would employ modified ligands to attach the catalytic center to a larger framework to control its location. Alternatively, noncovalent binding to a suitably designed protein would suffice.

1.5.2 Enzymes

Enzymes are a special category of atomically precise catalyst, composed of proteins, and able to catalyze a wide variety of reactions. They have been heavily studied, and many of their active sites are known in atomic detail.

Typically an enzyme surrounds part or all of the substrate(s) that participate in the reaction that it catalyses. One way of thinking about how some enzymes work is to think of them as being receptors for the transition state of a reaction. By presenting a complementary surface to the transition state of a reaction, they bind to it and lower its energy, thus lowering the barrier for the reaction and accelerating it. Some enzymes are highly specific to just one substrate.

In other instances, an enzyme is more intimately involved in a reaction, for example donating a hydrogen ion from an acidic side chain that reacts with a substrate at one step in a reaction, eventually receiving it back after several intermediate steps.

As with other catalysts, attachment of an enzyme or modified enzyme to a larger AP nanostructure or device can provide means to direct its activity to specific sites, and (in more complex systems) for it to act at specific times in a sequence of operations.

1.5.3 Atomic Ledges, Kinks, and Adatoms

Many chemical processes involve inhomogeneous catalysis, in which a reaction takes place on a solid surface. In such cases, it is often not the flat terraces of the crystal that are truly catalytically active, but instead the less coordinatively saturated surface defect sites.

In advanced APM, after atomically precise nanoscale crystals can be reliably assembled, one could expect that these functional "defect" sites can be made precisely and reproducibly, providing structures that can serve as reactive components of nanosystems. In the near term, atomically precise analogs of these sites might be accessible as potential components through metal cluster chemistry.

1.5.4 Active Tips

Many of the mechanisms discussed above are applicable to reactions directed by STM, provided that the necessary active structures are provided as tips. Further operations become possible by exploiting the high electric fields and current densities that these tips can create.

An important subset of these are tips suitable for removing passivation from surfaces for use in patterned ALE approaches (discussed in detail in Topic 3 Fabrication and Synthesis Methods). Initially, the most desirable reactions are those that remove H (and possibly Cl) passivation from Si (and possibly Ge) surfaces. An important research goal will be to atomically characterize the tip structures that participate in these reactions. Some dramatic work has recently been done in systematically fabricating and characterizing single atom Pd tips on atomically precise W{211}, three-sided pyramids on W(111) surfaces (Kuo et al., 2006). A later goal could be to align an array of such tips with atomic precision for use in Phase 3 parallel patterned ALE fabrication (see Topic 3 Fabrication and Synthesis Methods).

Other approaches employ catalysis, as shown in selective reduction of azides to amines by a Pd tip (see Blackledge et al., 2000).

1.5.6 Filtration Membrane Pores

A number of structures can serve as filtration membrane pores.

- Atomically precise examples include many ion-selective cellular channels from biology. These are typically a circular assembly of membrane-bound proteins.
- DNA meshes have been proposed as atomically precise pore structures (see Mohammadzadegan and Mohabatkar, 2007).
- Carbon nanotube segments have been found to have extraordinary transport properties of use in water purification (see Ghosh et al., 2006).

1.5.7 Soluble or Volatile Precursors

A broad range of materials that are important to the development of APM are not precisely components in that not all of their atoms will necessarily be incorporated in the final structure, but which are precursors to portions of the atomically precise structures.

The nature of these materials depends heavily on the specific fabrication chemistry in use. In the case of ALE, this could include silane and germane (GeH_4) and some of their derivatives. In the case of II-VI nanocrystals, this can include organometallic compounds and chalcogen donors.

1.6 Computation

1.6.1 Logic Operations

For logic gates, important metrics include

- Frequency
- Fanout
- Power dissipation
- Error rates.

Most amplifying elements provide a nonlinearity that can be used to perform logic. Amplifying electronic components that have been demonstrated in molecules include:

- Nanotube FETs: Semiconducting SWCNTs have been used to produce FETs of both n-type and p-type. These devices have been combined into inverters, and into other simple logic gates.

- Negative differential resistance diodes
- SETs (single electron transistors)

1.6.2 Memory

Every logic technology listed above can also be used to build cross-coupled inverters and therefore memory. Additionally:

- DNA, as well as being useful as a structural material, is also usable as an information storage medium.
- A wide range of structures with bistable energy minima are candidates for information storage:
  - Molecules exhibiting cis-trans isomerism
  - Slowly interconverting tautomeric pairs
  - Rotaxanes with two or more energy minima
  - Van der Waals bonds between elastically deformed nanotubes
  - Hydrogen bonds with double well minima
  - Electronic double minima in which an electron can be located on either of two metal ions, both of which are stable in two oxidation states

1.6.3 Mechanical Computation Components

Sliding rods with mechanical interlocks can implement systems with behavior that parallels CMOS logic circuits. With stiff components, this approach enables high frequency operation (GHz range). A larger, slower version could be made from DNA or other near-term accessible structural elements. Systems of this sort might find niche applications in contexts where the limiting factor is energy per computation rather than clock rate. Switching energies of less than 1 eV appear feasible in principle.

1.6.4 Quantum-Dot Cellular Automata

An approach to computation which uses electrostatic interactions, but which does not involve current flow over long distances is based on quantum-dot cellular automata. The components are small blocks built from a handful of quantum dots (e.g., four per block). In one scheme a pair of electrons trapped on each block selects between residence on the (four) possible dots. The blocks are placed sufficiently closely that electrostatic coupling between the blocks makes the positions of the electrons in one block set the positions of the electrons in a neighboring block. By proper arrangement of the couplings between the blocks these

interactions can be made to perform computations. Unlike the approach in the next section, this approach does not rely on phase coherence of the electrons, merely on their classical behavior, and is therefore not "quantum computing" as the term has come to be used. (See Porod et al., 1999.)

1.6.5 Coherent Quantum Computation

In this approach to computation, components of the system ("qubits") are put into a coherent superposition of states, which enables a limited but (where applicable) extraordinarily powerful form of parallel computation. The classic example is Shor's 1994 algorithm for factoring an integer N in $O(\log(N)^3)$ time, which is much faster than the comparable time on a classical computer (which is roughly $O(\exp(\log(N)^{1/3}))$. The main challenge is that quantum computation requires the maintenance of phase relationships among qubits, and these are easily destroyed by interaction with the environment. APM may be helpful in building systems where these interactions can be better controlled.

1.6.6 Signal Transmission

In a typical complex, active, integrated system, control signals must be transmitted from their point of generation to the effectors of the system; in a closed-loop system, signals from sensors need to be transmitted as well. The components mentioned in this section are examples of some of the options for implementing this function.

Metrics of interest for these components, and for the signal transduction components in the next section, include

- Data transmission rate
- Energy requirements
- Error rates.

Electrical Conductors.

- Tour wires – mixed sp^2/sp conjugated oligo(phenylene ethynylene)s. Atomically precise, including end groups. Metal junctions with these have been heavily studied (notably Au/thiol contacts). Some chemical versatility, can be built with substituents on phenylene hydrogens
- sp^2 conjugated polymers, polyacetylene, polyaniline, polythiophene. Locally, each of these is atomically precise.
- Nanotubes. There is an extensive literature on electrical conduction in carbon nanotubes. By some measures, their

conductivity exceeds that of the best room temperature metals.

Optical Waveguides. Existing optical fibers have extraordinarily low losses (0.2 dB/km). The remaining losses include contributions from Rayleigh scattering due to fluctuations inherent in the amorphous structure of their glass cores, and from absorption by residual hydroxyl groups in the glass. Replacing the glass with atomically precise structures of crystalline regularity would eliminate these causes of signal loss.

Acoustic Transmission. Many structural components can be used to transmit acoustic signals. The speed of transmission is proportional to the square root of the stiffness/density ratio, which for SWCNTs >20 km/sec.

1.7 Signal Transduction

Sensors are attractive near-term applications for AP devices and systems. Since these produce information, rather than a volume of physical product, this application is less limited by near-term restrictions on the productivity of APM. In sensing a signal, it is often important to convert it from one domain to another. The components in this section apply to that task.

Sensor applications are less limited by near-term restrictions on the productivity of APM because they produce information, rather than a volume of physical product.

- Optical to mechanical
  - Includes the cis-trans molecular motors
  - A natural example of an atomically precise optical sensor with a mechanical output is the photoreactive chromophore in rhodopsin, 11-cis retinal. On absorbing a photon it isomerizes to an all-trans state. This shape change then pushes the bound protein (opsin) into a different conformation, triggering a cascade of changes that ultimately launches a neural signal.
- Optical to electrical
  - Semiconducting quantum dots (see Hegg and Lin, 2007)
  - Atomically precise organic donor/acceptor combinations, e.g., Cu-phthalocyanine/3,4,9,10-perylenetetracar-boxylicbis-benzimidazole (see Peumans et al., 2000)
- Electrical to optical
  - Semiconducting quantum dots.
  - Organic light emitting diodes – Some examples of these contain atomically precise discrete molecules as the emitting centers, e.g., Tris(8-hydroxyquinolinato)aluminium

- Mechanical to optical [FRET]
  - An important technique for detecting changes in position in nanoscale devices is fluorescence resonant energy transfer. A photon absorbed by a donor can be transferred to an acceptor over distances of the order of 5 nm. If no transfer takes places, the donor can fluoresce in isolation. If the distance is sufficiently close, the energy is transferred to the acceptor, quenching the donor fluorescence (and replacing it with acceptor fluorescence, when present).
- Chemical to mechanical
  - Includes all the molecular motors, also includes pH sensitive polymers which will shrink or swell above or below a critical pH
- Chemical to optical
  - Trivial examples include pH indicator dyes.
  - More selective examples include, for example, a proposal to embed a binding site within a high-Q micro-scale optical resonator tuned to an optical response peak of the molecule to be detected
- Chemical to NMR
  - A wide variety are available. Basically any reaction that produces a product with a different NMR spectrum than the reactant is a candidate. Particularly large shifts come from large changes in the magnetic environment of the protons visible in NMR (changing their proximity to paramagnetic ions or to aromatic ring currents). This potentially serves as a noninvasive readout mechanism for medical applications.
- Chemical to electrical
  - Trans-pore conductivity modulation (DNA sequencing)
  - Adsorbed molecule effects on conductivity (e.g., on SWCNTs)
- Molecular sensing
  - Applies to any tight binding of a molecule to be sensed, and could result in several modes of output. In general, proteins are capable of strong selective binding. Antibodies are the classic example. The binding can result in a shape change, which can then trigger a variety of read-out mechanisms.

- Mechanical to chemical
  - Mechanochemical bond breaking (experimentally demonstrated with an AFM)
  - Modulation of steric effects, e.g., physically moving blocking groups out of the path of reactants
- Mechanical to electrical
  - The most dramatic example is the exponential sensitivity of an STM tip, with around an order of magnitude/ angstrom dependence of transmitted current on position. Within a MMCN, modulation of proximity between two atomically precise conductors could provide a detection mechanism of comparable sensitivity.

1.8 Energy Manipulation

1.8.1 Energy Storage

Important metrics for energy storage are (1) energy stored per unit mass, (2) energy stored per unit volume, (3) rate of energy storage, delivery, and (4) rate of energy loss while stored

In general, APM can be expected to weakly affect the first two parameters (a kilogram of propane continues to yield the same energy on oxidation as before, though oxidizing it in a fuel cell rather than in a heat engine is beneficial). It strongly affects the third, which blends into the subject of energy conversion. It can sometimes affect the fourth, if the storage time is limited by a defect that APM can bypass (e.g., some leakage paths in some capacitors).

1.8.2 Energy Conversion

Optoelectrical and Optochemical. Several potential components are suited for bulk conversion of optical energy to electrical or chemical energy.

- Direct bandgap nanocrystals such as II-VI compounds (typically with an absorption pathlength ~1 micron)
- Silicon nanocrystals (with an absorption pathlength ~100 microns)
- TiO_2 nanocrystals, notably for optically driven hydrogen generation
- Organic pi-systems, including analogs to natural light harvesting pigments such as chlorophyll and

bacteriorhodopsin, and donor/acceptor pairs as cited in the signal transduction subsection

Electrochemical. Electrochemical processes (e.g., in fuel cells) depend strongly on atomic and nanoscale features, which determine the rate of transport of reactants and (through catalysis) the rate of their reactions. Optimization of these structures can be expected to greatly increase the power density and efficiency of fuel cells.

1.9 Photonics

1.9.1 Ordinary (Linear) Optical Components

APM will permit forming both reflecting and transmitting optics to much finer tolerances than at present, and permit sharper bandpass and bandstop filters using dielectric stacks, particularly at short wavelengths. Performance advantages in the X-ray region of the spectrum are most promising.

1.9.2 Photonic Band Gap Materials

These are materials where a periodic pattern of refractive index changes yields ranges of wavelengths where there is no direction in which light can propagate. They require fabrication on a scale comparable to the wavelength of the light involved, so they are within reach of semiconductor lithography – but using these techniques for large or thick structures is expensive and difficult. APM might be an alternative. Advanced APM might also have an advantage in being able to interweave materials with more extreme refractive index differences than conventional fabrication can.

1.9.3 Metamaterials – Exotic Indices of Refraction

Electromagnetic responses of a dense array of conductive resonators that are substantially smaller than the wavelength of their resonance can be dramatically different from responses yielded by a uniform mix of their constituent materials. In particular, it is possible to build structures which respond as if they had a negative index of refraction. These structures are desirable because they permit, among other applications, lenses with better resolution than the normal diffraction limit. Because these structures must behave as if they had a uniform index of refraction, their components must be substantially smaller than the wavelength of the light of interest, so fabrication requirements are even more stringent than for photonic band gap materials. Consequently, these resonators are natural applications for APM.

1.9.4 Nonlinear Transmission

One application area is protective goggles which stop a high power laser pulse, but pass low power light with the same frequency. In this context, APM would be useful primarily to provide improved materials. Some of the materials are subject to damage from high intensities, and some of this results from defects that APM could avoid.

1.9.5 Nonlinear Harmonic Generation

At high intensities, some materials convert light to its second harmonic, effectively combining two photons into one. This is useful for a number of reasons, amongst others because it is easier to obtain coherent light at lower frequencies and this phenomenon provides a way to convert this laser light to double the original frequency.

A number of small organic molecules have strong second harmonic generation in isolation, notably some tetracyanoquinodimethane (TCNQ) derivatives. These molecules can serve as components for second harmonic generation. The primary difficulty in using these molecules simply as crystals is that they have strong dipole moments, and these dipole moments tend to align them into centrosymmetric crystals, which cancels out the overall nonlinear polarization required for second harmonic generation. APM could constrain the orientation of these molecules, eliminating this difficulty. (See Cole and Kreiling, 2002.)

1.9.6 Controllable Absorption, Phase Modulation

Some of the components for these functions straddle the boundary between components and systems. One of the options for a phase modulation component, for instance, would simply be two pieces of optically anisotropic material that are rotated in the path of a polarized beam.

Components for controllable absorption can be as simple as chromophores, which can be reduced or oxidized, forming or breaking a conjugated pi system. Alternatively, simply twisting one single bond in a series of conjugated double bonds can also reversibly partition the pi system.

1.10 Topic 1 References

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Topic 2 Systems and Frameworks

2.1 Introduction

This topic gives a survey of a range of atomically precise systems and subsystems that can serve roles in nanosystems engineering and its applications. It aims to give a sense of the breadth of functional system requirements and potential implementation technologies for physical systems able to satisfy those requirements.

A "system," as distinct from a "component," is taken to be a physical structure that is fabricated from multiple distinct parts to achieve a functional purpose. Discussion of systems inevitably involves their design, their components and methods for their fabrication and assembly, hence this section has a degree of overlap with the others.

Particular attention is given to atomically precise productive nanosystems (APPNs), owing to their potential role in enabling the fabrication of a wide range of advanced AP systems. Since APPNs are tools for fabrication, this discussion inevitably overlaps with, and relies on, topics explored further in the section on fabrication.

Importantly, the discussion of productive nanosystems delineates and distinguishes among distinct classes and generations of APPN development. Early generations and classes embrace systems that may be appropriate as stretch objectives for development based on current fabrication capabilities, while others would require one or more generations of intermediate APPN development for their realization. These advanced but currently inaccessible objectives are appropriate targets for exploratory design and modeling. This is of value because it can help to motivate, support, and guide ongoing research by clarifying the longer-term payoffs that can be expected from the pursuit of appropriate enabling technologies.

2.2 Structural Frameworks

2.2.1 Background

The ability to build atomically precise frameworks for organizing components is fundamental to atomically precise manufacturing (APM) of all kinds, and to the development of productive nanosystems. Also important is the ability to interface precise frameworks and components with imprecise structures, such as nanolithographically patterned substrates and circuits.

This overview describes several approaches and technologies applicable to this problem. Some technologies (e.g., large-scale patterned atomic layer epitaxy and structural DNA) have the potential to implement complex structures directly, while other technologies (for example, magic-size quantum dots and small-scale patterned atomic layer epitaxy) have the potential to play roles as components in composite nanosystems. The latter approach, in which some technologies provide a modular, extensible framework, while others provide diverse functional components, has been a useful organizing concept in envisioning directions for atomically precise functional systems.

A key distinction in what follows is between structures that are modular and those that are not. As used here "modular" refers to structures that are composed of many components that can be put together in many different ways (defining a large, combinatorial design space). Examples of modular components include monomers in polymers, and atoms or other growth species in solid structures made by tip-directed synthesis. If a set of monomers, for example, has M members, then the number of possible structures for a chain of length N is M^N. For proteins, a typical number would be 20^{300}. The size of this design space, together with the diverse properties of the 20 amino acid monomers, is what makes it possible to find protein molecules that bind selectively to any of a vast set of other structures.

2.2.2 Frameworks Made Using Tip-Directed APM

Fabrication techniques that use top down computer controlled nanopositioning devices to create atomically precise patterns on crystal surfaces, such as patterned atomic-layer epitaxy (P/ALE), are presently in an early exploratory stage, but can be expected to enable the fabrication of structures of roughly similar size and complexity, with temperature and stability metrics comparable to those of semiconductor devices and costs. For patterned ALE of Si structures, atomically precise patterns defined on a Si wafer will be the framework for fabrication. Throughput for early-generation systems will be comparable to those of other direct-write processing systems, which operate on a feature-by-feature basis, rather than performing wafer-scale patterning via mask-based processes. Use of MEMS based nanopositioning systems should allow for a significantly higher level of parallelism than is available in typical semiconductor direct write systems, but the fact that individual "pixels" are atoms will result in very limited throughput on initial APM systems of this sort. This suggests costs per device substantially above those achieved by commercial semiconductor processes, hence high-value applications that take specific advantage of atomic precision. Top down controlled scanning probe fabrication techniques (such as

patterned ALE) have the potential to create atomically precise structures that can include designed three-dimensional connectors.

Top Down Designed Modular Structures. Patterned ALE and other top down controlled APM techniques can draw on the many decades of experience in the material science and design of semiconductors, insulators, and metals used in microelectronics, MEMS, photovoltaics, and optoelectronics. These material systems provide a much wider range of material properties and operating conditions than DNA or proteins. Since these top down fabrication techniques employ directed assembly from the start, there will be a bias to continue with directed assembly to generate larger and more complex products. However, there is an opportunity to use designed modular structures produced with top down approaches in self-assembly schemes.

Currently most proposed top down controlled approaches to APM attempt to build on covalent crystalline structures. The advantages of this method include robust materials that are "simple" (compared to proteins) with well understood material properties.

A well ordered, stiff, covalent crystal structure carries with it some disadvantages. To change material properties within a given structure usually requires a change of crystal structure, lattice constant, or both. There is considerable experience in heteroepitaxy to draw on, but lattice mismatch will create strain, which can distort structures complicating their design when a specific atomically precise shape is required for inter-connectivity.

There is a possibility to use individual modular components that are each of an individual homogeneous material designed to couple with modular components of different materials. This approach would result in necessarily simpler modular structures but would avoid the lattice mismatch problem.

Perhaps the largest advantage top down designed modular structures have is that, with the freedom to design arbitrary structures that are in principle only constrained by the lattice structure and some surface atom reconstruction, combined with the well understood properties of the lattice, the design space can be very well defined and can evolve with improved technologies in the same manner that integrated circuit design rules have evolved to create ever more valuable products.

2.2.3 Frameworks Based on Atomically Precise Self-Assembled Structures

Several of the approaches below exploit biomolecular components to build APSA frameworks, and a brief overview of some properties and metrics may be in order. The state of the art in biomolecular systems provides frameworks with sizes of 100 x 100 nm or more and complexities of >10,000 bits. Their processing and operating temperatures are typically <100°C, with stability depending strongly on details of structure and environmental conditions. If they are used as scaffolds for organizing non-biomolecular components that subsequently bind or fuse to one another, the products could potentially have far wider temperature and environmental tolerances. Costs for experimental quantities of material are high (the dollars-per-milligram range), but experience with large-scale production in the biotechnology industry suggests that costs can be greatly reduced in many instances (the dollars-per-kilogram range). For 100 nm scale devices, $1000 dollars per kilogram equates to a materials cost of approximately $10^{-15} per device. This is substantially below the cost per device achieved by the commercial semiconductor industry, which are on the rough order of $10^{-9}, suggesting the potential for products that are competitive in information storage and processing.

Crystal Surfaces. As discussed above, patterned crystal surfaces provide an approach to the fabrication of large, extremely rigid framework structures. With suitable patterning, these can serve as a basis for APSA, with multiple distinct surface patterns to direct and align self-assembly of potentially complex structures.

DNA Origami

The concept of "Unique Addressing"—components in which information is encoded in structure. In the prime example of DNA frameworks, the program for assembly is encoded in the structure and thereby is the same size as the structure. The goal is a programmable system towards a generalizable self-assembly.

Unpatterned crystal surfaces have the potential to serve as supports and stiffeners for epitaxial APSA of a broad class of structures. These structures would have internal features that provide specific and potentially complex patterns of self-assembly, while the crystal surface would provide a basis for long-range alignment and precise control of distances.

DNA Frameworks. DNA, most familiar as a genetic molecule, can be used to build 3D structures. In these structures, segments of double helix are held together by strands that swap from one helix to another, forming "junctions." A striking example is Dr. Paul Rothemund's DNA origami technology, reported in *Nature* in early 2006. For this first paper, he designed and fabricated many different 100-nm scale, atomically precise structures, using design methods that consistently yielded the intended structure on the first attempt. Setting aside the time required to obtain synthetic DNA oligomers by postal order, the time required to design and make a new structure of this sort is approximately one day.

DNA engineering technologies (termed "structural DNA nanotechnology") now provide a reliable way to build large (million-atom range), complex, atomically precise frameworks. Fabrication is straightforward. DNA can be synthesized or obtained from bio-engineered organisms. In the DNA origami approach, these DNA components are dissolved and mixed in a hot buffer solution and they self assemble as the solution is slowly cooled.

DNA has only four kinds of monomers; these are bulky and similar to one another, and can form only a relatively narrow range of structural motifs. Consequently, DNA nanotechnologies enable only relatively coarse-grained control of molecular shapes and surface properties. While DNA nanotechnologies make possible large, intricate, easy-to-design, easy-to-make structures, the nature of the material limits its utility for many other applications. This limitation is addressed by the MMCN approach described below. It is further mitigated by the availability of hundreds of synthetic DNA analogs with diverse backbones: Like DNA, these polymers can bind by means Watson-Crick base pairing, yet they can display more diverse surfaces and covalently attached functional elements. Thus, synthetic DNA analogs provide another family of modular molecular materials for use in MMCN design and fabrication.

Proteins to Interface Bio-Proteins

The goal of Baker Lab work is a general protocol for design of proteins that will bind to natural proteins. An example would be an artificial antibody aimed at a pre-chosen face of an analyte protein—engineerable for increased function, stability, etc.

In terms of distinct, addressable attachment points, resolution of the structures that Rothemund has been able to construct with DNA is 3.5 nm by 6 nm, set by inter-strand spacing, and by the distance between junctions on a strand. Important to remember for interfacing of the structures is the three-dimensional nature of the helical structure of the DNA. The yield of his structures has exceeded 80 or 90% in some cases and is largely dependent on the integrity of the DNA scaffold used. Arbitrary patterns of DNA can be created and these may be marked with chemical labels.

Funding for structural DNA nanotechnology is modest, estimated to support approximately 200 researchers and students world wide. An important focus from the perspective of advanced functional nano-systems will be to extend DNA engineering to additional geometries and to use it to organize other parts in a precise way. Challenges include better characterization and control of defect rates in self-assembled DNA structures.

Protein Components. Protein engineering is an emerging design domain for a class of complex, atomically precise objects several nanometers in size. Unlike DNA, proteins can be designed to have a wide range of molecular-scale shapes and surface properties. DNA has a bulky sugar backbone with a choice of four large side-chains (the bases),

all similar to one another. Protein, by contrast, has a slim backbone with a choice of 20 side chains of many sizes, shapes, charges, and chemical properties. Proteins are polymers that typically have strengths and rigidities like those of polycarbonates, epoxies, and similar polymeric engineering materials. Silk has been used to make bullet-proof vests. In biology, proteins and self-assembled structures using proteins serve a wide range of functions, acting as structural components, catalysts, motors, and photochemical energy conversion devices.

Many natural proteins bind other molecules in precise ways. Of significance in composite systems, proteins can readily be made that bind to DNA double helices in specific locations, recognizing a sequence of base pairs from the side, without unzipping the helix.

In combination with nucleic acid polymers, protein molecules implement the naturally occurring productive nanosystems in cells. Both ribosomes and DNA polymerases use digital data to direct the assembly of small building blocks into specified sequences. The ability to engineer both proteins and nucleic acids can evidently be extended to enable the design and fabrication of productive nanosystems at this level of capability.

Protein Structures and Components

Lessons have been learned from the study of amyloid fibers—responsible for many diseases including Alzheimer's. In these fibers beta-strands from different protein monomers interact to form beta-sheets. The goal of research by Dr. Ingemar André is de novo protein architecture design: such as nanotubes, 2D hexagonal arrays, ligand-induced virus capsids, novel shapes, and moving proteins (motors).

Useful Properties. These properties enable proteins to provide mechanically stiff interfaces to DNA, providing a basis for integrating protein engineering and DNA engineering to form an expanded, more capable design domain. Further, because proteins can bind other molecules in precise ways, they can serve as a kind of atomically precise "glue" that self-assembles other structures to DNA (or other things) in a precise position and orientation. Dr. Angela Belcher has shown that peptides (the material proteins are made of) can be developed that bind specifically to different surfaces, including semiconductors.

Limitations. Protein engineering is advancing, but the technology is far from mature. Current design technology for proteins has only a moderate success rate in producing novel molecules that are stable and have an intended function. For example, the rate of success on a first try is on the order of 50% for achieving stability. The success rate for making a structure with a specific function is lower, and depends on the design objective. Successful projects have often required multiple redesigns.

Limitations Relative to DNA.

- Size: Proteins are far smaller than recent DNA structures, being only a few nanometers in size (the thousand-atom range), rather than hundreds of nanometers and millions of atoms.

- Defect rates: Protein molecules are synthesized by ribosomes with error rates of 10^{-5} to 10^{-4} per amino acid added. DNA, by contrast, can be synthesized in biological systems with error rates of 10^{-9} or less (error rates in chemical synthesis are far higher). The error rate in protein synthesis greatly limits the size and yield of perfect, atomically precise protein objects. (Purification and defect tolerance are important mitigating strategies.)
- Design: relative to DNA, it is harder to design new structures that will be stable and have the intended properties. Current design technology for proteins has only a moderate success rate in producing novel molecules that are stable and have an intended function. Successful projects have often required multiple redesigns.
- Synthesis: biological production through genetic engineering is necessary and takes many weeks. Chemical synthesis of proteins is impractical, while synthesis of DNA strands of adequate length is easy and fast (hours).
- Stability: in water, typical proteins are less stable than DNA, both physically and chemically. Artificial proteins, however, can have greater physical stability than typical natural proteins, and design for increased chemical stability shows promise. Stability can be increased by changing the chemical medium. Requirements can be relaxed by using biomolecules only as temporary scaffolding.

Much of the current work in protein engineering focuses on modifying existing functional structures, for example, to stabilize enzymes for industrial use. This circumvents the problems associated with engineering new functions directly. These and other modified biological devices could be useful in composite nanosystems, but more as functional components than as structural components or "glue".

These limitations motivate limiting the use of protein-based components to functions where their special properties are necessary, using DNA for most structural purposes. The two materials have complementary capabilities.

Some problems of stability and function may be reduced in composite nanosystems applications, however, because binding to a complementary structure tends to stabilize a protein (by stabilizing the form that does the binding), and because adhesion that is based on multiple binding interactions will be less sensitive to unexpected weakness in any single interaction. Further, the requirements for interfacing to a functional component are less stringent than those of providing a function directly.

Funding of protein engineering is primarily focused on the narrower field that modifies biological proteins to modify their functions. Challenges include refining design technologies to increase the success rate for achieving stability and specificity of binding.

To enable routine use of protein building blocks in MMCN development will require facilities organized to provide higher throughput in the design, fabrication, and test cycle for novel structures of relatively standard kinds. A focus on developing capabilities for combining specific DNA binding with specific binding of small inorganic structures will be of particular importance.

Synthetic Modular Molecular Structures. Synthetic methods can be used to make a wide variety of modular molecular systems, although these capabilities are currently less developed than those of protein and DNA engineering. Accessible structures today are polymers, typically made by means of stepwise synthesis on solid supports. Atomically precise patterning of surfaces by means of scanning probe systems also provides a way to arrange subunits in a combinatorially large set of designed patterns, and hence also fits the definition of "modular" used in this document. Looking forward, the development of productive nanosystems is expected to enable the synthesis of an increasingly broad set of modular molecular systems. The early prospects include non-biological polymers. Later prospects include structures with dense two- and three-dimensional networks of covalent bonds.

Typical polymer molecules adopt loose, fluctuating, randomly coiled conformations in solution. The molecular polymers of greatest interest in the present context are those that can be designed to fold back on themselves and collapse to form specific three-dimensional objects akin to proteins and structures engineered using DNA. Structures of this kind, sometimes termed "foldamers," are candidates for use as building blocks in self-assembling systems, provided that they can be designed to display surfaces with shapes and molecular properties complementary to those of other surfaces. A recent achievement is the engineering of a protein-like folded structure built from beta (rather than alpha) amino acids.

Some polymer molecules have substantial rigidity and maintain specific (or greatly constrained) shapes in solution. Most form straight rods or helixes, which sharply limits their utility as modular components for self-assembling structures, but polymers constructed from monomers that include a diversity of shapes have broader applicability. A polymer-building system of this kind is under development (discussed elsewhere) and has been shown to enable the design of molecules with a combinatorially large range of shapes and surface properties, and to do so without the necessity of folding first.

Synthetic monomers have relatively few constraints on their structures. They can carry diverse side-chains, some of which can be reactive groups that serve as “handles” for attaching other molecular structures

at a later time. Those with greater rigidity can contribute greater rigidity to self-assembled structures, thereby decreasing the amplitude of thermal fluctuations. Within a particular chain-building technology, the design domain can be expanded by expanding the library of available monomeric building blocks. This is a task that could easily be pursued by multiple, loosely coordinated research groups, with additive results.

A natural application of early-generation productive nanosystems will be to facilitate the design and fabrication of synthetic modular molecular systems, much as ribosomes and DNA polymerases do for the naturally occurring modular systems. Natural objectives include the synthesis of stiffer polymers, or of more advanced structures with dense two- or three-dimensional networks of covalent bonds. Productive nanosystems with these capabilities would further expand the molecular nanosystems design domain by enabling the design and use of new modular molecular structures with superior materials properties.

Schafmeister Polymeric Structures

Bis peptides are rigidified into an oligomer that has no rotatable bonds within its core structure and its shape is determined by the structure, sequence and stereochemistry of its building blocks. Bis-amino acids are coupled through pairs of bonds to create bis-peptides.

Advantages of stiff polymeric structures

- Improved thermodynamics for self assembly. Folding or binding a flexible molecule reduces its entropy by confining it to a smaller part of its configuration space. Thermodynamically, this opposes self-assembly. Stiffer polymers have lower entropy to begin with, which favors assembly.
- Stiffness may make the design process more straightforward. Because the parts have a definite shape, there is less chance that they can assume a conformation that can bind incorrectly.
- Greater stiffness in the polymer will tend to result in greater stiffness in the final structure. Because increasing stiffness reduces the amplitude of thermal fluctuations in the molecular configuration, it can help in building nanosystems with good control of component geometry.

2.2.4 Modular Molecular Composite Nanosystems (MMCNs)

To return to considerations specific to particular technologies, the emerging technology of modular molecular composite nanosystems (MMCNs) provides a way to integrate diverse nanoscale components to form complex, atomically precise systems. (DNA frameworks of the sort discussed below are revisited from a different point of view in Topic 3 Fabrication and Synthesis Methods.)

The MMCN technology discussed here aims to exploit the complementary strengths of three areas of research:

1. DNA engineering, which can rapidly design and build 3D frameworks that provide hundreds to thousands of uniquely addressable locations.

2. Protein engineering, which can make precisely tailored interfaces between DNA and a wide range of other, more specialized structures.

3. Special structures, which include components from all areas of nanotechnology that deliver high levels of functionality but resist systematic design.

To direct the atomically precise self-assembly of complex structures, building blocks must have many unique, atomically precise complementary interfaces. However, many potentially useful components (magic-size quantum dots, nanotube segments, spontaneously formed crystal-surface features...) are non-modular and have fixed surface structures that cannot be expected to fit other surfaces of interest. In MMCNs, however, modular molecular structures can compensate for this limitation by enabling designers to build an effectively infinite number of distinct, precisely tailored complementary interfaces.

Table 2-1. Characteristics of emerging MMCN technologies.

	Scale	Modularity	Surfaces	Functions
Structural DNA Framework	10^2 to 10^3 nm	Nucleotides	Semi-regular	
Proteins	2 to 10 nm	Amino Acids	Diverse	Binding, other
Synthetic chains	1 to ? nm	Diverse	Diverse	Binding, other
Patterned ALE	1 to 5 nm	Atomic	Diverse	Diverse
Special structures	1 to 10^3 nm	Little or none	Specific	Very Diverse
Nanolithography	1 to 10^7 nm	Imprecise	Imprecise	

Putting It Together: The MMCN Perspective. The range of molecular technologies outlined above includes several that meet the test for being design domains, or at least emerging design domains. All are modular molecular systems. DNA engineering is the most mature; protein engineering is established, but less mature, and the synthetic systems both through a chemical synthesis route and a top down positional fabrication approach are still emerging. Special structures, as meant here, are products of science-intensive research that involves only a very limited scope for reliable, systematic design. (Some of these functional structures result from work guided by a scientific insight, and some were found by accident.)

Each of these areas can produce structures of value by themselves, but their strengths and weaknesses indicate that they can be combined to form the basis for a broader design domain that produces composite structures.

- A natural role for DNA is as a structural framework for other components. Broad classes of DNA structures have become easy to design and make. In this role, the limited adaptability of DNA structures with respect to fine-grained shape and surface properties is unimportant. Different DNA sequences, though buried in the center of the helix, can nonetheless provide markers for distinct locations to which other structures can selectively bind. This makes locations in a framework addressable.
- A natural role for the more adaptable protein and synthetic structures is to recognize and bind to distinct locations on DNA frameworks (zinc finger proteins have already been engineered to do this). With one surface anchored to a specific location in a framework, the other surfaces can either provide functionality directly, or can serve as selective binding sites adapted to fit special structures. An important research question will be to establish how closely multiple proteins can be spaced on nearby locations before special measures are needed in their design to account for lateral interactions.
- A natural role for special structures is to provide functional properties that can be exploited in novel ways when multiple structures are held in predictable orientations and positioned with respect to one another with great accuracy. (The positioning accuracy, on a moment-by-moment basis, is limited by thermal fluctuations). A major constraint on the use of special structures is that they must be soluble (or form stable colloidal suspensions) in solvents and chemical conditions compatible with the other elements of the composite system. Solubility engineering will often be crucial.

Structures produced by top down methods have much in common with special structures in their range of functions, yet structure engineering principles can be applied to take advantage of their fine-grained modularity to create specific connectors that are designed to dock with designed sockets. A natural role for top down fabricated nanostructures is where material properties are required that are difficult or impossible to achieve with DNA or protein structures.

Notably, DNA frameworks with sizes of 100 nm or more already overlap the size range of features fabricated in commercial semiconductor manufacturing. This suggests the prospect of designing and building patterns (including 3D patterns) of nanoscale functional elements that can bind and interface to active semiconductor nanosystems.

Looking forward, the MMCN approach promises to enable the production of devices that can bind, join, and release other molecular building blocks, fabricating new components. These operations can expand the repertory of available components (both modular and special) for building next-generation MMCNs. To the extent that these devices can be seen as programmable, they satisfy the definition of productive nanosystems. Continued advances in the quality of components, the capabilities of APPNs, and the introduction of mechanically directed component assembly can provide stepping stones along a family of pathways to advanced APPNs as a basis for atomically precise manufacturing.

Global investment in special, highly functional nanoscale components now totals many billions of dollars. A premise of this investment has been the expected utility of systems built from these components. The ability to juxtapose many different kinds of highly functional nanoscale components in complex spatial patterns can be expected to leverage this investment by enabling fabrication of the kinds of systems that motivated it in the first place.

The MMCN concept includes research that is already underway, but it provides a new way to see that research in a broader strategic context. This perspective highlights ways in which diverse areas of research are complementary rather than competitive, and shows why advances in any one of them increase the value of research programs in all the rest. The MMCN concept emerged late in the roadmap development process, and will provide a useful framework for organizing future roadmapping efforts and next-generation research in self-assembling AFNs.

2.3 Machinery, Active Positioning Systems

There are many potential roles for mechanisms that drive the motion of nanoscale components and subsystems:

- To expose or protect active surfaces such as binding sites
- To position catalytic sites at specific locations where one wishes to form or break bonds

- To modulate resonant transfer of energy between chromophores in optical systems
- To use mechanical positioning to direct molecular reactivity to specific site (without resorting to protecting groups).
- To position components to construct systems that are beyond the scale and complexity possible with pure self-assembly.
- To move a nanosystem as a whole from one location to another, e.g., in medical applications

The requirements for constructing such systems may include:

- Motor components accurately bound to atomically precise structural members
- Motors that can be stopped and started on command.
- Multiple motors actuating distinct mechanisms able to start and stop their motors independently. An existing example is an actuator "fueled" by a DNA strand, specific to the particular actuator.

A significant milestone that appears feasible for the near term would be the construction of a DNA-based Stewart platform. Since DNA actuators have been demonstrated that are sequence-specific and therefore site-addressable, it appears straightforward to incorporate 6 of these actuators in a DNA octahedron and to demonstrate full control over a set of rigid body coordinates at a nanometer scale (albeit with binary control, not full analog control, of each degree of freedom).

Systems based on DNA structures have been designed that satisfy each of these requirements (albeit at low operating speeds and in a restricted environment). The mechanism used to accomplish this is selective binding and displacement of various short DNA strands, resulting in large changes in structural geometry in response to the addition or removal of strands from the solution environment.

In top-down fabricated atomically precise nanostructures, the challenge of constructing a system with multiple independently controllable actuators is in some ways simpler and in some ways more difficult. At the microscale, CMOS controlled MEMS actuators can be arrayed to create a modest amount of parallelism. However, the technology to create nanoscale actuators that would have top down control and atomic resolution has yet to be demonstrated. One path that could produce such nanoscale actuators would be to use the emerging macro/micro scaled ATM tools to create such nanoscale actuators. However, the required ability to create insulators, conductors, and sacrificial layers must first be developed. Once these material capabilities are developed, the whole spectrum of MEMS (or more appropriately NEMS) design and construction (actuators, cantilevers, etc) becomes accessible. In addition, these materials would immediately allow the independent control of multiple actuators by merely including connections to separate insulated wires, a simpler and higher bandwidth approach than using the diffusion of multiple DNA strands.

2.4 Productive Nanosystems

Atomically precise productive nanosystems are AP nanosystems that can be used to make any of a wide variety of structures under programmable control. Ribosomes and nucleic acid polymerases are examples found in nature. Metrics for productive nanosystems include:

- Block placement cycle time
- Error rate in placement
- Specific throughput (output rate per unit mass)
- Information content of products
- Metrics of the products themselves.

2.4.1 Major Subsystem Requirements

Productive nanosystems (present and projected) form a spectrum at least as broad as that of historical electronics, which has advanced from primitive crystal-diode radio receivers to teraflop computers. This spectrum can be divided roughly into early-, intermediate-, and advanced-generation systems.

Anticipated early-generation systems of one class resemble nanoscale systems found in biology today. After multiple intermediate technology generations, anticipated advanced-generation systems resemble automated factories with macroscale assembly systems fed with parts produced by macroscopic arrays of coordinated microscale productive systems that are themselves based on nanoscale components. The subsystems required for these are, of course, radically different, and their requirements must not be confused.

The paragraphs that follow consider some of the major functions that must be served in a productive nanosystem, and the kinds of subsystems required to implement them. In early-generation systems, the answer is often "nothing required."

System Architectures. The overall system architecture will depend on the technology generation of the APPN in question, and on its specific applications.

Anticipated early-generation systems are of two basic kinds, although innovative ideas may broaden this conception. One kind, associated with tip-directed fabrication pathways, relies on mechanical conveyance and positional assembly to move parts; the other, associated with self-assembly based fabrication pathways, relies on diffusion for this

purpose. In either case, early-generation APPNs are anticipated to have little parallelism and correspondingly simple architectures.

Anticipated advanced-generation systems are expected to converge on mechanical conveyance and positional assembly, which are favored by considerations of reliability, control, efficiency, product scope, and so forth. Advantages of this approach are strongly indicated by exercises in design and modeling of different kinds of components and subsystems. It must be emphasized, however, that these prospective advantages in no way force early- or intermediate-generation systems to have these features, and they are in no sense requirements or defining criteria for productive nanosystems.

Control of Operating Environments. In early-generation systems, APPN mechanisms are expected to operate exposed to an ambient environment, which has its temperature and composition controlled by external means. The APPN itself requires no subsystem that performs this task.

Paths through intermediate to advanced systems entail greater control of the environment, and at some point, transfer of more responsibility for that control to the APPN-based system. At the advanced end of the spectrum, control entails rigorous exclusion of unwanted molecules by barriers and control of transport through them. Only macroscale systems will require internal means for transport and rejection of waste heat; temperatures of nanoscale and microscale systems will characteristically be closely coupled to the surrounding medium.

Feedstock Distribution. In early-generation systems, APPN mechanisms are expected to work with feedstock molecules transported for capture (by a tool-tip or a deprotected reaction site) by diffusion from the ambient environment (a gas or liquid). The APPN itself requires no internal subsystem that performs a distribution task. Local capture mechanisms suffice.

Paths through intermediate to advanced systems entail increasing the control of feedstock distribution, as a requirement both of tighter control of operating environments and of the objectives of greater speed, reliability, and diversity of fabrication operations. This entails capture and subsequent transport. Separation of these functions can buffer internal mechanisms from statistical fluctuations in the timing of feedstock molecule capture. In macroscale APPN-based systems, as in conventional macroscale factories, the paths and control of transportation can become complex.

Power distribution. In early-generation, ribosome-class systems, "power distribution" is a consequence of the delivery of chemical free

energy together with feedstock molecules (which may be in bound forms). No internal "power distribution system" is required. Local energy coupling mechanisms suffice.

Along paths through intermediate to advanced systems (and perhaps in early-generation systems on tip-directed fabrication paths), energy sources will perform multiple functions, requiring some form of power distribution. Along the path to advanced-generation systems, these subsystems again become complex, requiring transport over macroscopic distances and distribution to a large array of productive mechanisms. Electrical power distribution has been examined and appears adequate. Energy in chemical form is a natural alternative choice.

Information distribution. In early-generation systems with a single point of activity, the problem reduces to one of external distribution of information to the devices themselves, which can be accomplished by any of several means (e.g., information molecules like nucleic acids, or modulation of light, pressure, or electric fields). No internal distribution of control information is necessary, because an external "broadcast" mechanism will suffice.

Again, advances lead to a requirement for more internal structure. At some point, multiple devices must perform different, simultaneous operations at different locations. This entails a communication network subsystem, and can benefit greatly from the use of locally stored instruction sequences, and even computation. Mechanical or electrical means appear adequate for information distribution in practical systems. There is the opportunity to use the same distribution channel for delivery of both information and power. For instance the information can be encoded as a modulation of the power delivered to the individual units.

The requirements on the information distribution subsystem will be strongly determined by the system architecture and complexity, and the system-level problems are of kinds familiar to manufacturing engineers and to programmers of parallel-processing computers.

Handling Finished Products. In solution-phase, early-generation systems, a natural approach is to simply release products that are themselves designed for self-assembly (or for "folding" of a chain of linked blocks). This avoids any requirement for a subsystem that handles products.

Along paths through intermediate to advanced systems (and perhaps in early-generation systems on tip-directed fabrication paths), product handling requires transportation, and in larger systems, the

transportation network can become complex. Anticipated macroscale APPN-based manufacturing systems employ microscale transport systems to bring small blocks together to make larger blocks, as part of a hierarchical process that results in the assembly of macroscale products from parts of substantial size. The required architectures again involve problems of kinds familiar to manufacturing engineers and to programmers of parallel-processing computers.

2.4.2 Natural Productive Nanosystems

Biological productive nanosystems include:

- Ribosomes, which convert information in RNA into proteins
- RNA polymerase, which translates DNA into RNA
- Reverse transcriptase, which translates RNA into DNA
- DNA polymerase, which copies DNA to DNA
- RNA dependent RNA polymerase, which copies RNA to RNA

Some metrics that describe the operation of ribosomes are:

- Placement frequency 20 s^{-1}
- Error rate 10^{-5} to 10^{-4}
- Specific productivity ~10^{-3} s^{-1} (this is the reciprocal of the time required for the system to produce a mass of product equal to the mass of the system itself).
- Block size 110 Daltons
- Metrics for products—maximum size ~10^5 Daltons; Young's modulus ~10^9 N/m^2; information content ~4 kbits; maximum temperature ~100°C.

2.4.3 Synthetic Productive Nanosystems

There are several different approaches to producing atomically precise 3D structures. The following paragraphs describe potential stages and system-features on pathways that lead from early- to advanced-generation APPNs and APPN-based productive systems, together with some ideas that have been considered in connection with the implementation of early-generation systems.

Ribosome-Class Artificial Systems. As with natural ribosomes, systems of this class would combine a series of selected monomers in a one dimensional chain and rely on non-covalent interactions between

the carefully selected monomers to fold them into the desired 3D geometry.

Nadrian Seeman has developed a system that is constructed of DNA, is programmed by adding strands of DNA, and builds any of several output strands according to its programming. In its current version, the device cannot select individual base pairs to be joined, but only short sequences of base pairs; however, it can build up to four different strand patterns. Seeman has expressed an interest in building similar DNA-based machines that can control the fabrication of other polymers.

2D and 3D Polymeric Component Builders. It is useful to make a distinction between productive nanosystems capable of building 1D polymers, and systems capable of building 2D or 3D polymeric components. (Strictly speaking, the components will be oligomers since an atomically precise component has a fixed number of monomers in a fixed arrangement with fixed terminations.) The latter is a desirable research goal for a number of reasons, including:

- Because the higher dimensional polymers use covalent bonds in more of their structure, the design problem is reduced in complexity. The structures have fewer thermally accessible degrees of conformational freedom. This simplifies the design space search needed to avoid misfolding.
- Also because of the additional covalent bonds in their structures, these polymers can have better mechanical properties than 1D polymers.

2D and 3D Component Construction via a Self-Assembled Productive System. Constructing 2D and 3D oligomers with atomic precision is a challenging research enterprise. Two strategies that suggest approaches towards this goal as an outgrowth of MMCN systems are:

1. For each step of the synthetic process
    - bind an MMCN DNA/protein/catalyst system to a particular location on a workpiece
    - catalyze a reaction which deposits a monomer with multiple covalent bonds on the selected location on the workpiece from a water-soluble precursor
    - unbind, apply a solution of the next MMCN system to deposit the monomer, and repeat.

    A major challenge of this approach would be to achieve sufficient productivity for practical applications

2. For each step in an alternate synthetic process
    - bind an MMCN DNA/protein/catalyst stepper system to a particular location on a workpiece
    - actuate the stepper to move the catalytic site to the next location for monomer deposition
    - catalyze a reaction which deposits a monomer with multiple covalent bonds on the selected location on the workpiece from a water-soluble precursor
    - without moving the MMCN system as a whole, use the stepper to move the catalytic site
    - repeat the last two steps until all sites accessible to the MMCN's actuators have been processed

    One challenge in this approach would be to control the molecular steppers in the MMCN to properly place each monomer in its site. One known technique of actuating multiple motors independently is to use the binding of site-specific DNA strands to drive the motors. An alternate approach to separate control is to use light, temperature, pressure, and the electric field perpendicular to a working surface to actuate distinct stepper mechanisms within the MMCN.

Finally, if the MMCN has enough independently controllable degrees of freedom, it could step over periodic features on a workpiece surface to access additional deposition sites. A crystal surface is an attractive substrate for such an operation, given its rigidity and long-range atomic precision.

2D and 3D component construction via direct manipulation technologies. A number of potential atomically precise manufacturing techniques could lead to productive nanosystems.

Patterned Atomic Layer Epitaxy (see Topic 3 Fabrication and Synthesis Methods, Subsection 3.4.3) is a mechanosynthesis technique that achieves top down control by using atomically precise depassivation to activate bonding sites on a crystalline surface. This approach avoids directly capturing and placing atoms or molecules, but instead allows reactive molecules in an ambient gas or liquid to bond to these activated sites in a direct, conventional fashion. An advantage of this technique is that it forms a densely bonded structure as a direct consequence of the epitaxial growth of a covalent crystal lattice.

Another mechanosynthesis approach discussed in this roadmap is direct manipulation of reactive molecules by capturing and placing them at specific reactive sites on a workpiece. Bonding multifunctional monomers is conceptually straightforward, and

quantum chemistry methods have been used to investigate processes that would transfer highly reactive molecular fragments (one or several atoms) to build up a densely bonded covalent structure. An attractive goal would be to extend this analysis to placement of less exotic reactive monomers to form 3D networks with mixed ionic/covalent bonding. Examples include silicic acid and other oxide-crystal growth species. Many of these reactions are compatible with aqueous conditions suitable for the use of MMCN components to provide mechanical constraints on reaction locations.

Another approach to constructing highly interconnected 2D or 3D structures would be to use larger blocks rich in potential bonding sites. For example, an MMCN framework might bind a dendrimer block in a way that imposes geometric constraints that break the symmetry of its potential bonding sites, enabling them to perform different and specific roles in a structure. This approach could enable dendrimers to be used as building blocks in highly cross-linked structures, resulting in products with more fine-grained structural control than the symmetries of the dendrimers would otherwise permit.

As the technologies develop, diverse mechanosynthesis techniques can be expected to widen the range of useful reagents on *both* ends of the scale of reactivity: precise positioning of a highly reactive reagent at a single chemical site on a workpiece should allow its use where uncontrolled solution chemistry would yield unwanted side products from reaction with other, chemically similar sites. Forceful application of a relatively unreactive reagent on a site on a workpiece can in some instances address activation energy barriers to overcome what would otherwise be unacceptably low reaction rates.

2.5 Systems for Application Areas

The following sections discuss several potential areas of application for AP nanosystems, some at the product level, some at the subsystem level, and of clear utility for products. In general, applications have the potential to expand greatly from early-generation products (sharply restricted materials, scale, and complexity; high cost) to progressively more advanced products (with materials expanding well beyond the familiar range, scale eventually growing to macroscopic, complexity limited by design capabilities, and costs potentially quite low).

2.5.1 Information Processing Systems

Add-Ons to Advanced Semiconductor Systems. Semiconductor systems are increasingly limited by the Poisson statistics of implanted impurity ions that control the electronic properties of the transistors in the system. APM would provide a number of options to solve this problem:

- Atomically precise synthesis of electrically conventional transistors, but with atomically precise positioning of impurity atoms.
- Atomically precise synthesis of exotic, but proven, active devices, such as carbon nanotube transistors. A possible alternative is the use of planar graphene as the semiconductor.
- Atomically precise synthesis of devices which have gain, but which are not directly analogous to transistors. An example is a molecular tunnel diode with negative differential resistance.

In addition to forming the active devices, integrating them into an otherwise conventional semiconductor fabrication process would require forming electrical contacts to conventional electrical conductors. Considerable work has been done on the interfaces between molecular electronics and conventional metals, as reported by Reed and associates (Reed et al., 1997).

Replacing atomically imprecise transistors with atomically precise FETS throughout a system requires moderately high productivity from APM. An earlier hybrid application area is in instrumentation, where the bulk of a system might be built by conventional techniques yet the critical sensor(s) would be built by atomically precise approaches. Patterned ALE would provide a very natural match to the substrates of modern, but atomically imprecise, electronic systems for this type of hybrid system.

Another type of hybrid of conventional microelectronics and patterned ALE might take place when the AP component of the system is capable of useful function (e.g., as STM tips) but is not yet capable of implementing logic or memory. Given some error rate in the patterning, it might be necessary to, for example, disable the nonfunctional STM tips, and the conventional FETS on the substrate might be used to do that.

Full Computational Systems. Given advanced atomically precise manufacturing, the devices described above continue to be available,

and the atomic precision can be extended to the conductors in the design and to their interfaces with the active devices. In addition, the freedom to explore configurations other than active devices on a silicon surface allows more options devices, 3D organization, integrated cooling, etc.

Information-Oriented Optical Systems. For some applications, advanced APM systems will enable construction of better devices than we currently have for electronic-to-optical, optical-to-electronic, and nonlinear optical operations.

In the specific case of nonlinear optical operations, second-harmonic crystals must have no center of symmetry, but symmetry is difficult to avoid in conventional materials fabrication. The same molecular level asymmetry that produces the nonlinear optical feature tends to force crystallization in cells which oppose molecular dipole moments, and tend to cancel nonlinear optical effects. Productive nanosystems could bypass this limitation.

For information processing, the gains likely in the optical domain are smaller than in some other domains simply because the scale of useful devices is set by the wavelength of light. The chemical flexibility of APM promises better materials, and the general manufacturing flexibility of APM promises easier integration of systems than current manufacturing allows, but this area presents fewer opportunities for strikingly new features than some of the other areas considered.

2.5.2 Medical Systems

Medical applications offer a broad scope for near-term, atomically precise systems. Several of these involve combing antibodies with labels or bioactive elements. For example, researchers have combined a magnetic moiety visible on NMR with a radioisotope and a near-IR fluorescent probe, all linked to antibodies that highlight different types of diseased tissues. (See Bumb et al., 2007.)

This is a covalently linked system with multiple functional pieces. The general availability of NMR as a position-sensitive readout mechanism (with many parallel channels at many separable chemical shifts) and the ability of in-vivo atomically precise systems to respond to many clinically interesting chemical parameters with a change in the NMR signal suggests that this is a rich area for near term applications.

The nanoscale near-term opportunities in the medical area are related to therapeutics, principally in delivery systems, as described by Dr. Chiming Wei (see Wei, Paper 29, Working Group Proceedings): “In

drug therapy, nanotechnology can dramatically improve the therapeutic potential of many water-insoluble and unstable drugs either through size reduction or encapsulation of the drug particles. In gene therapy, polymers and lipids can condense DNA into nanoparticles that can be internalized by cells, followed by delivery of the DNA into the nucleus." While these examples are not atomically precise, Dr. Wei also cites dendrimers as attractive delivery mechanisms, and these are atomically precise.

A wide variety of diagnostic applications of nanoscale technology are also cited by Dr. Wei:

- The use of semiconductor nanoparticles, quantum dots, as fluorophores which are far more resistant to photobleaching than their organic dyes predecessors. "This increased photostability is especially useful for three-dimensional (3D) optical sectioning, where a major issue is bleaching of fluorophores during acquisition of successive *z*-sections, which compromises the correct reconstruction of 3D structures."
- The use of scanning near-field optical microscopy (SNOM) to image cell ultrastructure with much less perturbation of the cell than AFM imposes.
- The integration of atomically precise binding sites for a variety of potential analate molecules with nanowires to translate the chemical binding event into a change in electrical conductivity of the nanowire.
- Targeted contrast agents—"Techniques have been developed recently to achieve molecular and cellular imaging with most imaging modalities, including nuclear, optical, ultrasound, and magnetic resonance imaging (MRI)."

Over the longer term, APM and medical applications are a natural fit. Living materials are intricately structured on the nanoscale. Many interactions between our cells involve complex nanoscale actions (e.g., the presentation of antigens in [what is the name of the cells involved?] out immune system). It seems reasonable to expect both diagnostic and therapeutic activities to involve more and more materials structured on this scale.

With very advanced APM, the potential exists to construct systems that are substantially better than the biological subsystems in healthy humans. For example, there have been theoretical studies of micron scale AP systems ("respirocytes") that would perform the same oxygen-

transport task as erythrocytes, but with an oxygen-carrying capability greater by 2 orders of magnitude.

2.5.3 Energy Conversion Systems

Opportunity to Extend the Bridge

It isn't clear what the best long term option is here. Simply using APM to manufacture conventional silicon cells, but with the system-level advantages of fabricating an array of much smaller cells connected by flexible conducting joints would preserve the high efficiency of the cells while overcoming some of their disadvantages. On the other hand, given a blank slate to choose any organic structure as the cell, one might be able to do better than silicon. Whether the degradation of the cells, of either type, can be avoided is unclear. One option that advanced APM systems might provide is to simply periodically remanufacture the cell in situ, removing any accumulated damage.

Generally speaking, APM has the largest impact on energy conversion systems where throughput is directly affected by the nanoscale or atomic scale features of energy conversion components. For example, theoretical studies of advanced-generation AP electrical motors have yielded designs with power densities $>10^{12}$ W/m^3, far above current capabilities, yet chiefly a consequence of elementary mechanical and electromagnetic scaling laws.

Bulk power conversion is not a clear near term target for APM. The *current* costs of AP fabrication from both self-assembled and scanning probe approaches are too high to be competitive in bulk energy conversion, though specialized niche applications may still find them useful. With plausible cost reductions and performance advantages, however, systems incorporating AP self-assembled structures may prove attractive in this area, and this potential is well worth exploring. Nonetheless, considerable attention has been given to solar power applications of nanoscale component technologies, both photovoltaic and photochemical.

Photovoltaic. For comparison, note that existing silicon photovoltaic cells can reach an efficiency of 24% (at 0 C) (University of Oregon,1996). The limitations on the cells include rigidity/fragility, degradation over time, and the high cost of fabrication. Near term nanoscale technology offers options such as organic photovoltaics, with lower costs, better flexibility, but with reduced efficiency (~5%).

Photochemical. Near term nanoscale approaches (albeit atomically imprecise) have yielded significant results (11% efficiency). (See Khan et al., 2002.)

Electrochemical/Fuel Cells/Batteries.

From a systems perspective, the ability to, for example, integrate transportation of solid fuels and fuel cells on a sub-millimeter scale would permit many products that would be infeasible today. For instance, it would become feasible to feed a solid graphite crystal into a fuel cell, with atomically precise coordination between the fuel feed and the electrode reactions. In the shorter term, the molecular-scale nature of the key physical processes in batteries and fuel cells has already attracted extensive research in nanostructured materials. AP nanostructures hold great promise in this area.

2.6 Topic 2 References

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Topic 3 Fabrication and Synthesis Methods

3.1 Introduction

This topic presents techniques for fabricating atomically precise components, as well as a brief survey and assessment of coarser-resolution technologies (e.g., nanolithographic methods) that can facilitate the development or application of atomically precise systems, including productive nanosystems and their products.

The products of these fabrication and synthesis methods are often tenable building blocks and components for larger-scale assemblies, aspects that are the focus of Topic 1, Components and Devices.

The process of design can be thought of as the sequence of exploring and choosing from the array of designs possible within a fabrication technique, building the target, testing it against the criteria for the application, refining the design choices, and repeating.

Ideally, an atomically precise fabrication method would provide:

- Reliable control of the 3D location of each atom in the design
- Many possible design choices
  - Many types of subunits
  - The ability to freely choose between subunits at many locations
  - The ability to build large structures, with many total design options
- Rapid turnaround times for designs
- Ability to build many instances of a design.

Table 3-1 provides a sampling of some atomically precise fabrication techniques available today.

By combining several of these methods it has proved possible to build operational molecular machines (though in some, components are not atomically precise). This approach is explored in Subsection 3.5 Hybrid Fabrication.

Table 3-1. Characteristics of Atomically Precise Fabrication Techniques Available Today.

Parameter	Self Assembly		Metal/Ligand Supramolecular	STM/Vacuum	Organic Synthesis	
	DNA	Protein			Bis-peptide oligomers	Total Synthesis
3D control	Excellent	Excellent	?	Mostly 2D	Good	Varies
Types of units	4	20	Large	Few in any single system	>14	Very large
Programmable locations, Density of choices	100% 3 bits/kD	100% 30 bits/kD	?	Some constraint, Reconstruction 20 bits/kD	100% 24 bits/kD	Constrained by side reactions 200 bits/kD
Maximum size	$3x10^6$ atoms	10^4 atoms	?	10^3 atoms	10^3 (single oligomer)	~10^2 atoms (non-polymer)
Turnaround time	Days	Months	?	Hours to Days	Days	Days to Years
Instances	10^{17}	10^{20}	10^{23}	1	10^{20}	10^{23}

3.2 Organic Synthesis

Developments in organic chemistry, which include millions of distinct synthetic structures over a period of two centuries, cannot be readily summarized in the space of a few paragraphs. Roughly speaking, if a structure of carbon, hydrogen, oxygen, nitrogen, and halogen atoms is physically stable and not too large, an organic chemist can probably synthesize it. Why then, are other, more specialized, design motifs such as DNA and proteins being considered? Because it generally takes a great deal of time and effort to synthesize an arbitrarily selected organic structure. The time needed to invent and debug a synthesis for an arbitrary (in general, polycyclic) organic structure possessing on the order of 100 atoms is on the order of months to years.

For the design of large atomically precise systems, it is best to think of classical organic chemistry as a source of a vast but finite set of functional components and building blocks on the order of 10 to 100 atoms in size. Two major exceptions to this restriction are

- The formation of chemical libraries: Some reactions (e.g., peptide bond formation, esterification) are so reliable, even in the presence of a wide variety of other chemically active groups, that given *N* starting materials with one functionality and *M* starting materials with the complementary functionality, one can be essentially assured that all *N*x*M* products of the reactions are immediately accessible.
- The formation of linear sequences of selected monomers via solid phase synthesis. This is another way of describing both

peptides and unnatural foldamers. This gives a vast range of possible products, N^M for N types of monomers and the ability to link M of them in sequence. The disadvantage is that the 1D sequence is chosen, but the 3D structure is difficult to predict and may not be a unique, stable structure at all.

3.3 Atomically Precise Self-Assembly

Although scientific studies can benefit from a focus on small, simple structures (which better reveal differences in elementary binding interactions), where atomically precise self-assembly (APSA) is concerned, design principles favor larger structures (which better conceal errors in estimating elementary binding interactions). Larger structures with larger interfaces enable a designer to control more features, offering more opportunities for strengthening or disrupting selected binding interactions. Larger interfaces also increase the tolerance for modeling errors: when adding multiple interactions, each expected to be stabilizing, cumulative errors in the total binding energy grow as the square root of area, while the expected binding energy increases linearly. This reduces sensitivity to modeling errors and enables more reliable design of strong binding.

For larger DNA strands and proteins, genetic engineering methods can be used. The problem of fabricating atomically precise 3D structures with these biopolymers largely reduces to the design problem of choosing the right monomer sequence to self-assemble into the desired 3D structure.

Constructing a system via APSA requires two steps:

1. Covalent synthesis of either components or of the primary structure of the system.

2. Assembly or folding of the system via non-covalent interactions.

For two major systems, DNA and peptides, the covalent assembly step is routine and automated. For larger DNA strands and proteins, genetic engineering methods can be used. The problem of fabricating atomically precise 3D structures with these biopolymers largely reduces to the design problem of choosing the right monomer sequence to self-assemble into the desired 3D structure.

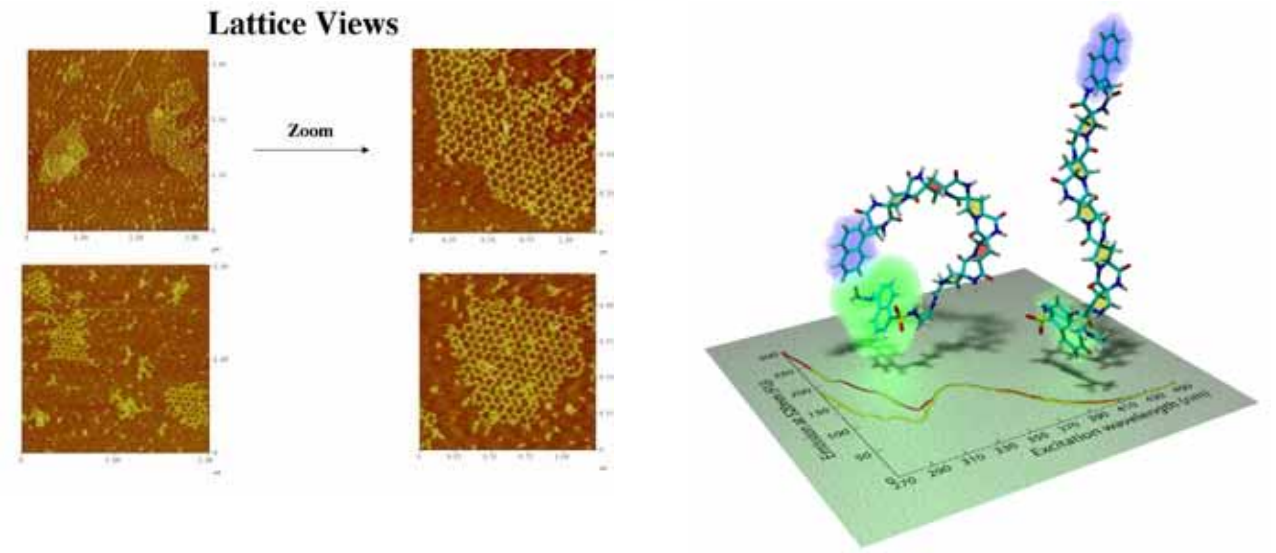

Figure 3-1. Examples of Self-Assembly. *Left*, DNA triangle motif structures self-assemble into hexagonal arrays. *Courtesy of Nadrian Seeman*. *Right*, Shape programmable bis-peptide molecules made from self-assembling subunits. *Courtesy of Christian Schafmeister.*

3.3.1 DNA Atomically Precise Self-Assembly

Self-assembly of DNA into non-linear structures (cages, decorated sheets) has enabled the design and fabrication of the most complex atomically precise structures yet made. DNA is unique in that its secondary structure is dependent on its primary structure, the order of the nucleotide bases, in a very well understood way. DNA provides precise and well-understood molecular recognition properties because the nucleotide base A specifically pairs with the base T and the nucleotide base G specifically pairs with C—termed Watson-Crick base pairing. Thus, a DNA double helix forms from the hybridization of two strands of complementary nucleotide bases. DNA base-pairing allows for a large number of specific interactions to be scripted—4^N possible sequences for a DNA strand N deoxynucleotides long. Even using short oligonucleotides a large number of specific interactions can be programmed. The simplest use of this library of precise pairings is as 'smart glue' to assemble networks of defined structure. In this way materials and devices with unique and useful properties have been created. Additional benefits of building with DNA include (i) the existence of a well-developed infrastructure of reagents and technologies provided by the biotechnology industry—especially the automated synthesis of single-strand DNA oligonucleotides of more than 100 nucleotides, (ii) the fact that the base sequence of a DNA can be read even when the double helix is intact by 'reading' the grooves along the outside of the helix, enabling in theory the determination of

absolute position along the DNA helix, and (iii) a variety of synthetic molecules are available as alternative bases and alternative backbone structures that may be chemically more useful for certain functions.

Although the base pairing between the two complementary strands of DNA can be used to assemble molecules or nanoparticles into clusters of known composition that have useful properties and functions, further modification is needed to build nanostructures with predictable geometry. The key innovation that enabled structural DNA nanotechnology was the design and implementation of stable branched structures of DNA that could be combined to form larger covalent and non-covalent structures, of diverse three dimensional geometry and with nanomechanical functionality, using base-pairing between overhanging single strand ends of DNA (or sticky ends, overhangs of several unpaired nucleotides at an end of a helix).

The key innovation that enabled structural DNA nanotechnology was the design and implementation of stable branched structures of DNA that could be combined to form larger covalent and non-covalent structures

The capacity to construct three-dimensional addressable molecular networks began with the demonstration that small DNA tiles (for example, 2 x 4 x 16 nm) can be constructed from branched DNA molecules that are rigid enough to form crystalline arrays several microns in extent (Winfree et al., 1998). These tiles were built from double-crossover (DX) molecules of DNA, in which two 4-arm branched junctions are joined at two adjacent double helical arms. The result is two side-by-side double-stranded helices linked by two crossovers. Further, sticky ends on the corners of the tiles provide intermolecular interactions that can be programmed to specify how several tiles with different structures will assemble, thus forming periodic nanometer-scale patterns in micron-scale arrays. In addition, it is possible to incorporate into a tile a third junction that forms a DNA hairpin roughly perpendicular to the plane of the other two helices. This extra structural domain provides a topographic marker that can be detected by atomic force microscopy (AFM) and so easily mark tiles in an array that have the extra domain. A useful tile can also be made from DNA triple-crossover (TX) motifs, which contain three coplanar double helices linked at each of four crossover points (that is, with each neighboring pair of helices linked by two crossovers), fitted with sticky ends at the corners to program assembly into two-dimensional arrays (LaBean et al., 2000).

In addition to the planar tiles formed from DX and TX motifs, it is possible to build DNA nanotubes from motifs designed to not be planar. By properly designing the crossovers between helical domains, a six-helix bundle can be formed from six DNA double helices that are connected to each other at two crossover sites (Mathieu et al., 2005). The six helices form a DNA nanotube with a hexagonal cross-section and a central hole about the diameter of the DNA double helix—2.0 nm.

If these motifs are designed so that overhangs on the two ends of each helix are complementary to each other, then the six-helix bundles self-assemble to form one-dimensional arrays—rather stiff wires more than 7 μm long, Such stiff nanostructures might be useful as nanomechanical struts. For productive nanosystems development, the surfaces of six-helix bundles could be used to mount other motifs and nanodevices that could be oriented in specified directions. Theoretical analysis of minimally strained nucleic acid nanotubes reveals that a wide variety of DNA-based nanotubes can serve as tubes with specific inner and outer radii and with multiple lobes (Sherman and Seeman, 2006). Such tubes could be useful as both scaffolding and custom-shaped enclosures for other nanostructures.

Two-dimensional 'nanogrids' have been shown to template the formation of periodic protein arrays (Yan et al., 2003). The large cavity size and the bulge loops, which can be chemically functionalized, at the center of each 4 x 4 tile provide each square with a potential site for conjugating a molecule so that the lattice could direct the periodic assembly of desired molecules. This capability was demonstrated by incorporating biotin to one loop on each tile and to produce a periodic array of streptavidin molecules—a protein widely used in molecular biology because of its extremely strong binding to the vitamin biotin, one of the strongest non-covalent interactions known.

Because it is possible to develop DNAzymes with diverse catalytic activities, and because it is possible to arrange DNA tiles in complex patterns, both periodic and aperiodic, it seems likely that much more complex patterns of catalytic functions can be developed.

Proteins are not the only potentially useful molecular machines that have been organized in two-dimensional arrays constructed from DNA (Garibotti et al., 2006). Through a combination of *in vitro* selection and trial and error, a DNA enzyme was developed—a bi-molecular complex in which a 29-nucleotide catalytic strand will, in the presence of Cu^{2+}, cleave a specific position in a 22-nucleotide substrate strand. This self-cleaving DNAzyme was incorporated into a two-dimensional array formed from four DX-tiles. Because it is possible to develop DNAzymes with diverse catalytic activities, and because it is possible to arrange DNA tiles in complex patterns, both periodic and aperiodic, it seems likely that much more complex patterns of catalytic functions can be developed. Two-dimensional arrays of DNA tiles can also be used to organize patterns of more than one component, including the patterning of gold nanoparticles (Pinto et al., 2005).

Rigid nanostructures make possible nanomechanical devices because a rigid object can respond to an external signal by moving in a predictable fashion, and this behavior can be observed reliably in an ensemble of molecules. Multiple crossover motifs were first used to demonstrate a DNA nanomechanical device based on the transition of the normal, right-handed B form of the DNA helix to the left-handed helix of Z-

DNA (Keren et al., 2002). Subsequent nanomechanical devices have demonstrated rotary motion and biped walking.

Structural DNA nanotechnology provides the ability to construct molecularly precise structures based upon the well-understood molecular recognition properties of DNA. Numerous molecularly precise DNA nanostructures have been demonstrated. Micron-scale and larger two-dimensional periodic arrays of DNA nanostructures have been built. At the scale of 100 to several hundred nanometers, DNA nanostructures can be arranged in an arbitrary aperiodic pattern in two dimensions, and there is reasonable optimism that this ability can soon be extended to three dimensions. Molecular biology and the biotechnology industry provide a well developed infrastructure for the technology: a wide range of DNA molecules, reagents, and methods useful for creating and characterizing DNA nanostructures. The most recently developed and perhaps the most promising approach to structural DNA nanotechnology—scaffolded DNA origami—enables quick and inexpensive implementation with ~5 nm resolution and lends itself to automated design and manufacture.

DNA Structures.

- Are now straightforward to design to a target atomically precise 3D structure
- Provide more than an order of magnitude more design choice than other available alternatives
- Produce atomically precise structures two orders of magnitude more massive than other alternatives.

DNA Limitations.

- DNA provides excellent topological control, and has substantial bending stiffness, but the flexibility of the DNA molecule is substantial and the grid size is set by base pair spacing (~0.3 nm) and the helix diameter (~2 nm), which for many applications is relatively coarse.
- DNA is not, in itself, a chemically versatile material. It is built from four nucleotides, all with similar sizes and chemical properties. In order to provide highly functional atomically precise structures, it must be linked to more highly functional components.
- Chemical synthesis is currently limited to a modest number of base pairs (<150), and biologically produced DNA strands must be used in conjunction with shorter designed strands to create larger structures. The number of base pairs that can be chemically synthesized towards a target application is

currently dependent on the project's tolerance for limited yields and for impurities, rather than only being dependent on the underlying chemistry.

- DNA is a single material with a particular set of properties. Many desirable products will require a variety of material properties that DNA does not provide and will be difficult to achieve with DNA as the primary "glue" or framework of the product.

The first and second of these items can be addressed by linking DNA to functional components.

Atomically precise self-assembly requires atomic-level complementarity between surfaces. However, many potentially useful components (magic-size quantum dots, nanotube segments, crystal-surface features...) have fixed surface structures that cannot be expected to fit other surfaces of interest. This highlights the need for linking structures of kinds that enable design of surfaces with a wide range of shapes and properties. Biopolymers, and proteins in particular, can serve this role in many instances. Many DNA binding proteins are known, and zinc fingers, in particular, can be designed to recognize and bind to specific sites without breaking the inter-base pairing.

A research target would be to build up either a library of such proteins or an efficient process for designing them – or at least for efficiently varying the relative positioning of the functional component and the DNA sequence.

In particular, the binding domains of restriction enzymes can link on the DNA side to paired DNA strands. The targets of these enzymes are DNA sequences 4 to 12 base pairs long. Examples binding to hundreds of different sequences are known.

A protein designed to bind to a DNA sequence on one side and to a functional component on the other can also be used to adjust the positioning of the functional component. Here, the higher density of design points within the protein and the greater irregularity of protein secondary structure are a help, allowing adjustment of the positioning of the functional component on a finer grid than that of DNA base pair spacing.

A research target would be to build up either a library of such proteins or an efficient process for designing them – or at least for efficiently varying the relative positioning of the functional component and the DNA sequence.

A related option, for DNA structures containing relatively short sequences from solid phase synthesis is to insert covalent bonds to at least some functional units. This technique has been routinely used to link nanoscale particles to DNA, and then to use the DNA to join particles with complementary DNA strands.

Options for increasing structural stiffness include

- Adding extra DNA strands
- Applying links to functional components to pieces which are themselves stiff, notably SWCNTs – but there are complications to avoid links to random parts of the SWCNT. For example, if one wants to use two sections of nanotube to reinforce a structure, one needs to add two linkers, then one tube, then add two linkers, then add a second nanotube. If all four linkers were active at the same time, then the identical-looking sections of the two nanotubes might get linked to the wrong places.
- Using the DNA structure as a template for stiffer materials. Metals have been deposited on DNA strands to form nanowires, e.g., DNA nanowire fabrication (Gu et al., 2006).

3.3.2 Protein Atomically Precise Self-Assembly

Proteins, like nucleic acids, have a primary structure that is built of covalent bonds that link monomer, amino acid subunits together. As with DNA, building the primary structure is routine. Proteins are comprised typically of 20 amino acids. They can have predictable, three-dimensional arrangements of atoms due to their well-defined secondary and tertiary structure, making them well-suited for atomically precise manufacturing. Proteins are also inherently highly functional due to the wide range of amino acid side chains. This combination of structural and side chain variability is responsible for the wide range of functions that proteins carry out in living organisms, ranging from catalysis, to mechanical motion, to structural components of cells and tissue. Hence, proteins are natural candidates as both building blocks and active working components of productive nanosystems.

New advances in biotechnology offer exciting prospects for custom-made proteins. Biological processes can be harnessed to construct novel structures and to tailor binding properties to other materials. For example, combinatorial libraries of short peptide sequences can be used to identify peptides with desired specificity. This is typically accomplished by manipulating an organism's DNA sequence (e.g., virus, bacteria, or yeast) to produce random peptides on the exterior of the organism. This process can be automated to create libraries containing up to a billion different peptide sequences. Through repeated exposure and selection of the biologically based library, peptides with desired affinities to chosen structures can be identified.

As researchers strive to develop new protein sequences for nanomanufacturing by employing methods such as combinatorial

selection, others are working with modified versions of existing proteins, protein fragments and *de novo* designed sequences. Computer aided, *de novo* design offers a useful approach to identifying tailored protein structures. The process of *de novo* design starts with a general structural description and then designs a sequence that will fold to produce that result. Researchers using this technique have managed to improve upon natural protein-protein interactions and to design proteins for improved biosensors.

Extending the capabilities of protein engineering is a strategic objective due to the range of functions that proteins serve, and the utility of proteins as an atomically precise "glue." The specific binding properties can be used to create self-assembled functional nanosystems that incorporate a wide range of non-protein components. These capabilities have applications to areas including (early on) catalysis for pharmaceutical production, and (with more advanced capabilities) self-assembled "circuit boards" for molecular electronics. The ability of many proteins to aggregate or self-assemble into precise, longer-range structures is extremely useful for preparing larger scale structures. Viral coat proteins and bacterial surface layer proteins are well known examples of self assembling, two-dimensional protein lattices. Genetic engineering of such proteins enables the precise placement and integration of these lattices with other structures.

The self-assembly and organizational properties of proteins stem from the specific binding properties that proteins can possess. Fusions of different peptide sequence enable multiple binding capabilities in a single polypeptide sequence. Additionally, peptide sequences can be identified that specifically bind inorganic materials, including metals, semiconductors and various nanomaterials, allowing for the directed assembly of structures other than proteins.

Proteins can have significantly different mechanical properties and can be designed for intended applications. Examples include spider silk, which can be strong and elastic, and collagen, a fibrous protein used for supporting biological structures. Further stiffness and structural support can be accomplished through mineralization of inorganic materials, as observed in marine shells, teeth, and bone. Self-assembled protein structures are observed to template and catalyze the formation of inorganic structures. Silicatein, a protein found in marine sponges, templates silica deposition and catalyzes bond formation. Silaffin peptides are thought to serve a similar function in diatoms. Synthetic peptide constructs have been shown to crystallize hydroxyapatite. In addition to control over nanometer and greater length scales, biomineralized structures can be crystalline, such as hydroxyapatite or calcium carbonate, and atomically precise. Biomineralization

approaches offer the possibility to stiffen protein subsystems by growing semiconductor lattice backbones around them, to link atomically precise protein components of nanostructures to functional semiconductor nanocrystals, or to link atomically precise protein components of nanostructures to extended (possibly lithographed) semiconductor crystal surfaces.

Protein engineering is a maturing technology for designing and fabricating complex, atomically precise objects several nanometers in size. The ability to specifically engineer proteins to bind in a defined way to other molecules, to build larger structures, and to bind biological and non-biological functional molecules presents a rich toolbox for the creation of productive nanosystems. From this perspective, an important goal of biotechnology is to develop protein engineering methods to create new proteins or modifications of existing proteins for integration into hybrid nanodevices.

An important goal of biotechnology is to develop protein engineering methods to create new proteins or modifications of existing proteins for integration into hybrid nanodevices.

3.3.3 Alternative Shape Programmable Oligomers

Protein design is advancing; nonetheless, considerable effort is still necessary to choose a sequence of amino acids which will fold into a desired 3D structure. An alternative approach to this problem is to use a less flexible polymer system which requires less work to deduce its 3D structure once the 1D sequence of monomers is chosen.

The work of Christian Schafmeister at Temple University demonstrates the use of chemical synthesis in an algorithmic fashion to produce specific structures with well controlled 3D shapes. It uses a set of modular building blocks called bis-amino acids that can be strung together in a linear chain where two covalent bonds connect each modular building block to the next. The linear chains that are formed are rigid ladder-like molecules called bis-peptides. Using building blocks of different sizes, with spatial (angular and distance) relationships between the two sets of binding sites, allows the creation of large molecules that have a rigid structure that can be predicted very rapidly. Schafmeister has developed a computer aided design tool that can select a synthesis sequence that will best fit a particular design structure. The synthesis of bis-peptides is carried out on commercially available automated peptide synthesizers. Schafmeister's group is developing building blocks that carry an additional functional group like natural amino acids do. These functionalized bis-amino acids will be incorporated into bis-peptides to create catalysts that function the way that enzymes do and to carry out complex, atomically precise self-assembly.

Bis-peptides could be used in nanotechnology in several ways. In a first generation nanotechnology they could serve many of the functions

envisioned for proteins and serve as larger building blocks and adaptors within complex nanoscale devices and machines. They could also be used to create catalysts that could assemble large, complex nano-machines from small molecules. A proposal for how bis-peptides could be used to create a second-generation nanotechnology wherein bis-peptides act as catalysts to assemble new bis-peptides under external computer control is presented in a Paper in Part 3 of the Nanotechnology Roadmap, Working Group Proceedings. The central idea is to mimic the cytoplasm of a cell using complex bis-peptide enzymes. The proposal outlines a system of bis-peptides that are controlled externally using an electronic reduction/oxidation based computer interface that would allow the rapid construction and testing of new bis-peptide based nanostructures to develop even more sophisticated nanotechnology.

More generally, a large range of foldamers systems have been examined over the years (beta-peptides, peptide nucleic acids). Roughly speaking, proteins have the advantage that

- They can be produced by genetic engineering methods
- They are more mature technologies
  - Their folding process has been intensively investigated for decades, including extensive work on modeling and design algorithms.
  - There are large databases of known tertiary structures.

Several unnatural foldamers have been developed that adopt well defined secondary structures with sequences consisting of very few monomers. The development of unnatural foldamers that can adopt well defined folded tertiary structures is yet to be developed.

Bis-peptides, by contrast, do not require folding to attain their structures and bis-peptide structures by virtue of their ladder-like covalent structure are much more robust than those of proteins.

A key requirement for stable and specific APSA using designed DNA, protein or other oligomeric molecules is that matching surfaces must be large enough to display multiple molecular features with distinct properties (of shape, charge, polarity, hydrogen bonding, etc.). These features enable the design of complementary surfaces that exhibit strong cooperative binding, while disrupting binding among other, non-complementary surfaces. This constrains the designed molecules to have a minimum size, on the order of a few nanometers along two or three of their dimensions. This means that the molecules must be at least 5 kD to 10 kD. In addition the molecules must be complex, information rich and asymmetric. Satisfying these criteria

simultaneously is difficult with organic synthesis and can only be achieved economically using solid phase oligomer synthesis or production methods that exploit the productive nanosystems found in bacteria.

The chemical variety of oligomers built with solid phase synthesis (including peptides) can exceed that achievable using only the 20 standard amino acids found in nature. An intermediate case is the addition of unnatural amino acids to the natural set, achieved by reprogramming unused codons.

3.3.4 Chemical Atomically Precise Self-Assembly

Most self-assembly processes discussed in the literature today are *not* atomically precise. The term is used to refer to the spontaneous aggregation of molecules (or particles) to form partially ordered films, fibers, and clusters. Self-assembly can be used to create sheets, ribbons, helixes and complex three-dimensional architectures, based on the nature and orientation of the contributing intermolecular forces. These structures are occasionally atomically precise, but often are not. Partially ordered systems are discussed in a later section. Examples of atomically precise self-assembly (APSA) of small chemical entities often exploit attractive intermolecular interactions like those found in self-assembled biological systems. These include van der Waals and Coulombic attraction, dipole-dipole interactions, hydrogen bonding, acid-base interactions, and binding of metal atoms. Metal-ligand self assembly, often involving non-biological motifs, has been extensively studied and sometimes used to organize structures of substantial size.

Scanning probe microscopes offer a basis for APM of several kinds, some of which are accessible to current laboratory techniques.

3.4 Scanning-Probe-Based Fabrication

Scanning probe microscopes can image individual atoms and molecules, manipulate them, and effect chemical reactions between them to form atomically precise structures. They offer a basis for APM of several kinds, some of which are accessible to current laboratory techniques.

3.4.1 Background

Starting with the Scanning Tunneling Microscope (STM) in 1982 (Binnig and Rohrer, 1982) and the Atomic Force Microscope (AFM) in 1986 (Binning et al., 1986), scanning probe microscopy has proven capable of atomically precise manipulation for approximately two decades. This generally involves direct manipulation techniques that move atoms or molecules on surfaces. These operations use mechanical positioning to direct the making and breaking of strong bonds, and thus

provide examples of mechanosynthesis (as to ribosomes in biology, but by very different means).

Direct manipulation of an atom was demonstrated in 1987 (Becker et al., 1987), using voltage pulses on an STM tip to pluck a single germanium atom from the Ge(111) surface of a sample. The first experimental demonstration that individual atoms could be manipulated into patterns was performed by IBM scientists in 1989 when they used an STM to precisely position weakly bound 35 xenon atoms on a nickel surface to spell out the corporate logo "IBM" (Eigler and Schweizer, 1990). Also using STMs, the Aono Group (working from 1989-1994) removed individual silicon atoms from a crystal surface and deposited them in different locations, and deposited hydrogen atoms. Atom removals were mediated by electric field rather than current. The group also demonstrated the ability to detect atom extraction/deposition in real time.

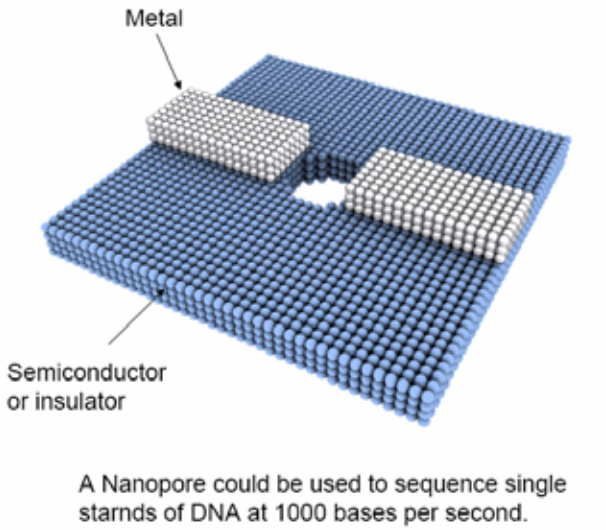

Figure 3-2. Example of Scanning Probe Fabrication. An atomically precise nanopore is one possible product made by Patterned Atomic Layer Epitaxy process. Courtesy Zyvex Corp.

In 1999, an STM was used to pick-and-place individual carbon monoxide (CO) molecules via electron tunneling (Ho and Lee, 1999). Individual iron (Fe) atoms were evaporated and coadsorbed with CO molecules on a silver (110) surface, after which a CO molecule was transferred from the surface to the STM tip and bonded with an Fe atom to form Fe(CO), then a second CO molecule was similarly transferred and bonded with Fe(CO) to form $Fe(CO)_2$ at the same surface site. In 2000, all steps of a chemical reaction induced on a copper surface via STM (Hla et al., 2000), including the separation of

iodine from iodobenzene by using tunneling electrons, bringing together two resultant phenyls mechanically by lateral manipulation and, finally, their chemical association to form a biphenyl molecule mediated by excitation with tunneling electrons. In 2003, a near-contact AFM (Oyabu et al., 2003) was used for the vertical removal of a selected silicon atom, and subsequently for depositing an Si atom into a selected Si atom vacancy on the Si(111)-7x7 surface using only mechanical forces.

3.4.2 Summary of Current Approaches

In order to construct three-dimensional atomically precise structures, a top-down nanopositioning system would have to direct bond making and bond breaking processes with atomic precision. The range of approaches that has been considered includes placement of reactive molecules of various kinds in various environments.

In solution-phase mechanosynthesis, these include placement and transfer of conventional monomers or of species involved in solution-phase crystal growth of oxides and semiconductors. Analogous mechanosynthetic placement and transfer operations taking place in inert or ultra-high vacuum environments could employ highly reactive chemical species. The latter approach would offer perhaps the widest scope, but would present the greatest difficulty, and is widely viewed as a long-term objective at best.

Alternatively, synthesis can be directed by selective deprotection, using this to create reactive sites which then react with and bind molecules (or molecular fragments) from an ambient gas or liquid. This approach to mechanosynthesis has the advantage that it avoids the need for binding and transporting reactive molecules, because the deprotection/reaction sequence requires no molecular placement and transfer operation. This deprotection-based approach is a comparatively recent innovation, and has drawn substantial commercial investment.

3.4.3 Selective Deprotection and Patterned Atomic Layer Epitaxy (PALE)

This concept employs scanning probe technology for positional control to depassivate specific atomic sites on a surface, in combination with atomic layer epitaxy (ALE) to add a single atomic layer of a second material from the vapor phase at the depassivated sites. Repeating this process can allow atomically precise three-dimensional structures to be built up one atomic layer at a time. This process is referred to as Patterned ALE or PALE.

PALE Challenges and Successes. This process has been developed by Lyding's group at the Beckman Institute. Silicon nanostructures (Lyding, 2004) and copper phthalocyanine (Cu(Pc)) and norbornadiene (Hersam et al., 1999a) were successfully grown by selectively depassivating a hydrogen-terminated silicon surface at atomically precise locations using Feedback Controlled Lithography, then depositing the atoms or molecules by adsorption onto the sites from the gas phase.

The selective deprotection processes have some significant advantages:

- The tool does not need to acquire or bind the atomic or molecular building block.
- The tool does not need to capture the atom or molecule that is the passivating species.
- The deprotection process is serial, but the delivery of building blocks either in the gas or liquid phase may proceed in parallel.
- The deprotection process, involving breaking a single chemical bond to free a passivating species, is a more general process than direct placement of building blocks and may be more easily adapted to a variety of material systems.
- Tools using deprotection by transfer of electron energy can avoid all physical contact.
- Electron tunneling and/or field emission tooltips have simple structures.

The work by Lyding and Hersam(Hersam et al., 1999b) demonstrates that atomic precision deprotection is possible with an STM tip that is not atomically precise, but is simply capable of atomic resolution imaging. However, reliable manufacturing will require a reproducible tooltip. Fortunately several technologies have emerged recently that can yield stable, reproducible atomically precise structures at the apex of a very sharp metal probe (PC-01, 2007).

PALE Objectives and Milestones.

Phase 1: Single STM Si Patterned ALE – Low Throughput

Phase 1 of Patterned ALE will be a single crystalline material process (Si is a leading candidate) that will be patterned with a single Scanning Tunneling Microscope (STM). The ALE process is likely to have a moderately long cycle time. The process will have a very low throughput but will be able to create products of value that take advantage of the atomic precision of the structures that are created.

Phase 2: Pattern Once Turn ALE crank – Dual Material ALE (Si/Ge)

Phase 2 will significantly improve the throughput of patterned ALE by removing the requirement of depassivating every bond where an atom or molecule is to be added. This can be accomplished by at least two different methods.

The first involves using two different passivating species, where one may be selectively removed without disturbing the other. For instance, both Cl and H will successfully passivate Si (100) surfaces. H will desorb from the Si surface at lower temperatures than Cl. By using the patterned Cl layer to first passivate a Si surface, ALE may be used to grow Si in that patterned area. If the ALE process is one that uses hydrogen as the passivating chemistry, then the ALE process may be continued without additional patterning by using temperature as the depassivating process for the H passivated Si. Because the Cl will remain in place, then the ALE process will only grow Si in the area that was originally patterned in the Cl passivation layer. The process may be continued for as many deposition cycles as desired for that pattern. Control of the growth on the sidewalls of the ALE grown structure may be an issue.

A Dual Material ALE process could also have a reduced patterning requirement as well as a number of other advantages. Consider an atomically flat section of Ge (100) that was passivated with some species that can be patterned. An ALE process is used to deposit a monolayer of Si in the patterned layer. (Heteroepitaxy of Si on Ge and Ge on Si has been established with ALE processes.) At this point a dual material ALE process could be used to selectively deposit Si on Si and Ge on Ge where the cyclic process would alternatively deposit a monolayer of Si and a monolayer of Ge. In this way the growth surface would stay atomically flat and there would be no sidewalls to contend with. After a designed number of deposited monolayers, the pattern could be changed and complex 3D hetero structures could be created. Since there are very selective etches to remove Ge, the Ge material could be used as a sacrificial layer, allowing for releasable structures.

Phase 3: Parallel STM (Modest Parallelization)– Si/Ge, C, Dopants, ALE (Metal, Insulator, ALD)

Phase 3 of patterned ALE would include a modest number of STM type tips operating in parallel to do the atomically precise patterning. In this context, a modest level of parallelization would be on the order of 1000 or less. A dual material ALE process such as Si/Ge would be available to create releasable complex 3D structures. Other materials such as diamond, one or more metals, and one or more dielectrics might be

available with patterned ALE or ALD if epitaxial registration could not be maintained, although there are as yet no known processes for diamond ALE. The ability to add impurity atoms (dopants) to modify the properties of the ALE deposited materials could also be exploited.

Phase 4: Moderate Parallel STM— Nanoimprint Replication

In Phase 4 of patterned ALE there would be moderate parallelism with an array of STM tips to do the atomic precision patterning. In this context moderate parallelism would mean greater than 1000 tips – up to about 1,000,000 tips. The ability to replicate atomically precise templates created by these arrays would be developed via some form of nanoimprint technology.

Phase 5: Template Based Patterning—Epitaxial Metals and Insulators

Phase 5 patterned ALE would use templates to passivate or depassivate surfaces to dramatically speed the patterning process. The atomically precise templates will be created by patterned ALE using the arrays of STM tips available in Phase 4. Phase 5 would also have developed metal and insulator deposition that was epitaxial with the other materials being deposited. Maintaining a continuous crystalline structure would have benefits for a number of applications.

Phase 6: Functional Nanosystem—Atomically Precise Nanoscale Pico Positioner Assembled from Atomically Precise Parts

Atomically precise parts made with patterned ALE can be used to assemble more complex and useful mechanisms, assuming that the atomically precise parts produced with patterned ALE will be sophisticated with respect to range of materials that can be integrated and freedom to design arbitrary 3D structures. The assembly could be handled in early stages by macroscale positioners. However, the mechanisms produced by this process could be designed to assemble these atomically precise parts into larger and more sophisticated systems.

Phase 7: Productive Nanosystems Based on Programmable Nanoscale Pico Positioner

Phase 7 is a productive nanosystem that is based on complex nanoscaled machinery built from Phase 6 capabilities. One of the most useful of these productive nanosystems is a programmable instrument that can do patterned ALE or some other form of atomically precise manufacturing. If it is programmable, it can be used to build parts for other programmable nanoscaled machines that can produce more programmable nanoscaled manufacturing machines. Through

exponential assembly, a very large number of these productive nanosystems could be produced. Once a significant quantity of these are produced, they can be programmed to produce other atomically precise articles of value.

3.4.4 Placement-Based Scanning Probe Mechanosynthesis

Mechanosynthesis by means of placement and transfer of reactive molecules or molecular fragments embraces a wide range of approaches with varying levels of capability and difficulty.

Perhaps the most accessible approaches would use binding sites at the active tip to capture reactive species from solution, eliminating the need for motions or transport systems to acquire them. This approach could be applied to a range of structures of kinds compatible with synthesis in a solution-phase environment. These include highly cross-linked polymers, oxide ceramics (ZnO, TiO_2), some semiconductors (CdSe, CdS) and metals (Cu, Ni), and, perhaps surprisingly, graphite. Many of these materials have attractive properties, such as fine-grained regularity, high rigidity, and excellent chemical and thermal stability. Many are compatible with synthesis in an aqueous environment, facilitating the exploitation of atomically precise tools derived from biopolymers.

The combination of mild conditions and processing simplicity of these approaches suggests their utility as targets for scanning-probe-based, tip-directed mechanosynthesis, as well as their suitability for early-generation implementations of productive nanosystems that employ tip-directed mechanosynthesis.

The combination of mild conditions and processing simplicity of these approaches suggests their utility as targets for scanning-probe-based, tip-directed mechanosynthesis. It likewise suggests their suitability for early-generation implementations of productive nanosystems that employ tip-directed mechanosynthesis.

This range of approaches has received too little attention relative to some of the earlier concepts for mechanosynthesis. Complexity and difficulties increase with the reactivity of the species to be positioned and with requirements for additional operations and mechanisms to effect feedstock acquisition, activation, and transport. All of these problems arise with synthetic approaches based on high-energy species, such as radicals and carbenes, of kinds ordinarily considered to be fleeting reactive intermediates. The use of these species appears to entail all of the technical difficulties of experimentation under ultra-high vacuum conditions. That initial explorations of the upper limits of what can be accomplished by mechanosynthesis have inadvertently focused attention on this class of systems to the near exclusion of others that appear more suitable for practical development may have imposed artificial bounds on progress.

Systems of this sort do have technical advantages in their control of reaction environments, and advantages in their potential capacity to synthesize strong covalent solids (structures with local bonding environments like those of silicon carbide, silicon nitride, and diamond). Further, the products of such systems lend themselves to analysis using standard tools in computational chemistry. Molecular mechanics was developed to model structures with covalent bonds among first- and second-row elements, and this circumstance has made it comparatively easy to design and characterize a wide range of components that combine high performance with synthetic inaccessibility. These properties are advantageous for exploring of the potential of advanced mechanosynthesis, but as was recognized in early work (Drexler, 1992), they are less advantageous as guides for research targeted on next-generation APM and early-generation productive nanosystems.

Atomically precise nanoparts produced with scanning probe technology could be used for more sophisticated nano-machines capable of high volume production. These productive nanosystems could then provide the massively parallel product throughput to make macroscopic objects via mechanosynthesis, selective depassivation, or some other process.

3.4.5 Scale-up of APM Production

A major limitation of scanning-probe-based APM systems will be the extremely low mass throughput that can be achieved by individual devices that perform synthetic operations in a serial manner, when productivity is measured by the metric of output per unit time per unit mass. However, initial applications that exploit the atomic precision of the fabricated structures and need only nanoscopic quantities of high value products will generate the resources to scale up manufacturing efficiencies. Such applications are discussed in more detail elsewhere, but will include metrology standards, structures designed for specific molecular interactions, quantum computing, and nanoimprint templates for producing near atomic precision structures with much greater throughput capabilities.

Current scanning probe instruments are macroscopic, but microelectromechanical systems (MEMS) could provide a path to micro scanning probes and significantly improved manufacturing throughput via parallelism. Perhaps most importantly, atomically precise nanoparts produced with scanning probe technology could be used for more sophisticated nanomachines capable of high volume production. These productive nanosystems could then provide the massively parallel product throughput to make macroscopic objects via mechano-synthesis, selective depassivation, or some other process.

3.4.6 Summary

Scanning probe fabrication is one of many viable pathways to productive nanosystems. Underscoring the promise of scanning-probe based fabrication approaches, DARPA has recently issued a Broad

Agency Announcement (BAA) soliciting proposals on Tip-Based Nanofabrication to make nanowires, nanotubes, or quantum dots using functionalized scanning probe tips (Foley et al., 1998).

For progress to be made in these approaches to APM, improvements in the automated systems that provide accuracy and stability of positioning, and improvements in atomically precise control of probe-tip structures, will be of central importance.

At this point in development, theory will be a central tool in developing the different experimental paths leading toward the realization of scanning probe based APM. For example, computational resources are now fast enough to enable the high-level study of tooltips, workspaces, and reactive intermediates in a mechanosynthetic assembly process (Sattin et al., 2004). Single atom and reactive molecule studies can be performed based on tooltip or workspace designs that are currently unachievable experimentally due to current limitations on available tooltips, workspaces, building blocks, probe stability, and other factors.

Research targets in this area include:

- Atomically precise tooltips
- Multiple degree of freedom nanopositioning
- Improved repeatability and reproducibility of positioning devices
- Increased total area over which higher precision repeatability and reproducibility limits can be met
- Manipulator tip designs for improved positioning of individual molecules and nanostructures (including gripping ability or selective stickiness, more degrees of freedom and wider ranges of motion)
- Multi-tip manipulators.

Positional assembly methods that can achieve atomic resolution such as these scanning probe fabrication pathways have the distinct advantage of being able to generate a wide variety of output structures *with the same process*, simply by changing the design of the structure and having the automated mechanisms generate that part. These methods avoid most of the limitations of self-assembly as detailed elsewhere in this roadmap. As noted by the 2006 NMAB/NRC Review Committee (NMAB, 2006): "For the manufacture of more sophisticated materials and devices, including complex objects produced in large quantities, it is unlikely that simple self-assembly processes will yield the desired results. The reason is that the probability of an error occurring at some

point in the process will increase with the complexity of the system and the number of parts that must interoperate."

Atomically precise self-assembly and protein engineering methods can and should be pursued as an early potential pathway to achieve productive nanosystems. However, scanning probe based fabrication as described above will provide APM capabilities that are unlikely to be provided with APSA techniques alone. Scanning probe fabrication provides greater flexibility for assembling small numbers of complex structures, while APSA promises the ability to produce a more limited range of atomically precise structures – but in high volume.

In their current forms, none of these scanning probe approaches has demonstrated sufficient maturity for immediate application by themselves. The set of building blocks used in any one experiment has been small and the error rates in fabrication operations have been high. The technological advances identified above will certainly improve this situation, as they emerge. In the meantime, hybrid techniques that take advantage of positional assembly, lithographic technology, self-assembly, and bulk synthesis have provided some spectacular advances. These are described in Subsection 3.5 Hybrid Fabrication.

Scanning probe fabrication provides greater flexibility for assembling small numbers of complex structures, while APSA promises the ability to produce a more limited range of atomically precise structures – but in high volume.

3.5 Hybrid Fabrication

A wide variety of atomically precise structures and reagents might usefully be incorporated as components into atomically precise structures. It is difficult to survey the possibilities without sliding into a survey of large parts of the science of chemistry, and to survey the techniques for constructing them without exploring large fractions of synthetic chemistry. Moderate sized components that have been added fairly recently to the chemical repertoire, that have useful electronic and mechanical properties, and that are reasonably stable under conditions that allow binding the DNA/protein nanostructures include:

- Graphene-based structures, C60 and CNTs
- Semiconductor nanocrystals, e.g., CdSe
- Metal clusters, e.g., Au55

These materials generally have specialized synthetic conditions which are not compatible with DNA/protein nanostructure formation (e.g., laser plama techniques for graphene nanoparticles), so near-term techniques for exploiting them would involve separate synthesis prior to incorporation into the overall system.

Hybrid fabrication takes advantage of different methods of synthesis to make atomically precise components, and then employs techniques

such as lithography, nanomanipulation, and electron microscopy to maneuver, shape, and join the components. Of particular note are the successes of the research teams of Prof. Alex Zettl and Prof. Carlo Montemagno in integrating atomically precise structures with bulk structures using lithographic and nanomanipulation techniques, highlighted below. In addition, the past efforts of researchers such as those at Zyvex and Northwestern have resulted in significant advances in the manipulation, joining, and mechanical testing of carbon nanotubes (Skidmore et al., 1999; Yu et al., 2000b).

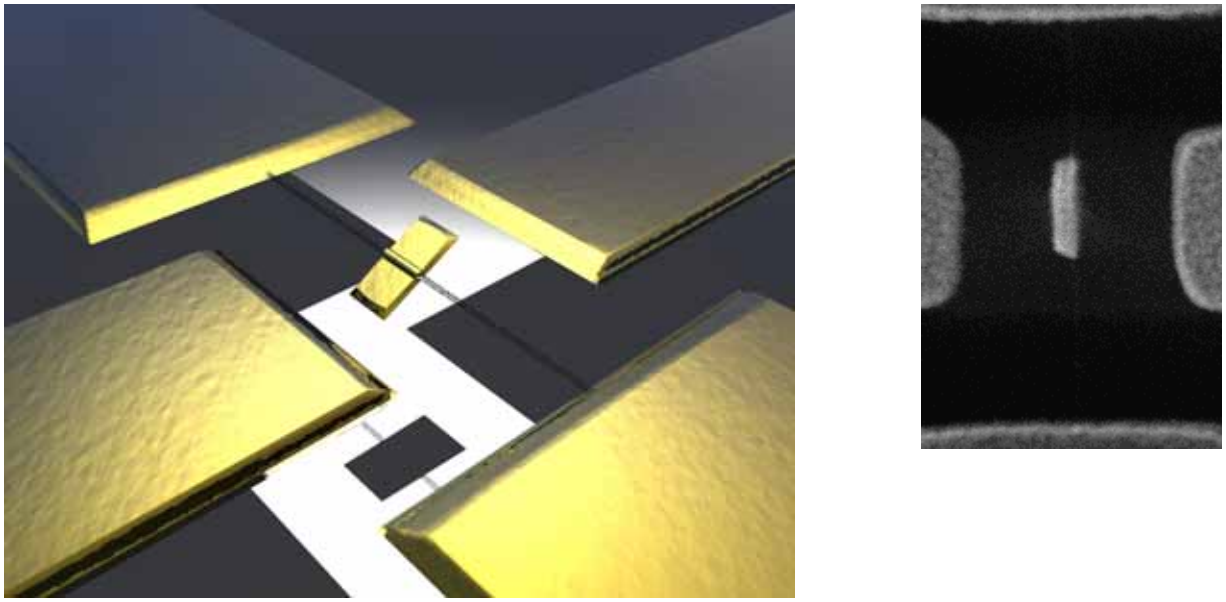

Figure3-3. Example of Hybrid Fabrication. *Left*, schematic of molecular motor. *Right*, SEM image of the working motor. A 250-500 nm rotor was suspended on a double-walled carbon nanotube (the atomically precise part in the assembly). Electrodes were lithographically fabricated on either side of the rotor, underneath the rotor (not shown), and around the ends of the nested nanotube. Varying the voltage differences between electrodes caused the rotor to spin. *Courtesy Zettl Research Group, Lawrence Berkeley National Laboratory and University of California at Berkeley.*

3.5.1 Zettl Group: Synthetic Molecular Motor

In 2003, the Zettl Group at Lawrence Berkeley Laboratories and UC Berkeley fabricated the smallest-known non-biological nanomotor (Fennimore et al., 2003). The device employed a multi-walled carbon nanotube (the atomically precise component), which served as both a bearing for the rotor and as an electrical conductor.

This breakthrough is highly relevant because motors based on this concept could be used to drive systems of molecular mechanical components. If the outer nanotube were fractured at the far ends rather than right next to the rotor (as in this experiment), then the motor-

driven outer shaft could be connected (e.g., by molecular gear teeth) to other components such as a drive belt, rack and pinion, or other rotary gears. The technology to attach gear teeth at specific positions has not yet been developed, but is one potentially important application of SPVM.

Zettl's accomplishment is additionally significant because the operation of the motor is controlled with electrical circuitry, offering precise control from the desktop. Most importantly, the device is *individually addressable* from the desktop as opposed to broadcast architectures where light or chemical signals trigger operations on a large array of devices.

In order to fabricate this device new technologies were developed:

- A method for peeling off successive layers of nanotubes (Cumings et al., 2000).
- Precision cutting of, and selective damage to, nanotubes (Yuzvinsky et al., 2005).
- A manipulator capable of pulling out the inner nanotube in a MWNT (Cumings and Zettl, 2000). This spawned a commercial product (HBS, no date).

3.5.2 Montemagno Group: Biomotor

In 2000, Soong, et al. in Montemagno's group reported the successful integration of a F_1-FTPase biomotor with a nickel substrate and a nickel propeller (Soong et al., 2000). The motor, which measured ~8 nm in diameter x 14 nm in length, was able to move the propellers (150 nm diameter x 750 to 1400 nm long) at a mean velocity of 4.8 rps. The calculated torque was about 20 pN-nm, and the energy usage was 119 to 125 pN-nm/revolution with an estimated efficiency of ~80%. In this study, the yield of working propellers was low—five out of 400 propellers in the array were able to turn when the ATP fuel was introduced into the surrounding environment.

Fabrication involved first creating Ni posts on a SiO_2 substrate using e-beam lithography. The posts measured 50 to 120 nm in diameter and 200 nm high. The F_1-ATPase biomotors (the atomically-precise components) self-attached to the nickel posts by diffusion and binding through a buffered solution. Nickel propellers measuring 150 nm in diameter and 750 to 1400 nm long were fabricated separately on silicon wafers using electron beam lithography. They were then coated with a biotinylated His-rich peptide (also atomically-precise) and then self-attached to the gamma unit of the biomotors, also by diffusion and binding through a buffered solution.

3.5.3 Hybrid Systems As a Pathway to APM

Productive nanosystems, such as those described in *Nanosystems* (Drexler, 1992), will utilize molecular motors and actuators that drive components to perform useful work. The conversion of electrical, electromagnetic, and chemical energy into mechanical motion is facilitated by the use of gears, bearings, drive shafts, springs, and other parts, to direct the motion of components and minimize energy losses. Thus, research efforts dedicated to produce and integrate these sorts of components are considered to be a direct pathway in this Roadmap.

Drexler (1981) observed that biological molecular machines and devices were functionally equivalent to macroscopic parts such as motors, bearings, pipes, drive shafts, and so forth. Table 3-2 provides a listing of existing biological nanomechanical devices. Below we highlight research on two particularly useful machine components: nanobearings and nanosprings.

Molecular bearings. Nested carbon nanotubes are a natural choice for a sleeve bearing, because they can rotate freely against each other. Measurements of the intershell friction show that the static (0.2 to 0.85 MPa) and dynamic (0.43 MPa) friction are very low (Cumings and Zettl, 2000; Yu et al., 2000a; Bourlon et al., 2004). The utility of a nested carbon nanotube bearing was proven in a working device—the molecular motor cited earlier (Fennimore et al., 2003). While there have been proposals to use nested carbon nanotubes as molecular oscillators and telescoping arms (Kang and Hwang, 2004; Kang et al., 2005; Kang et al., 2006), to date there have not been any experimental realizations of a method to drive the motion of the inner or outer tubes.

Nanosprings. As shown by Cumings and Zettl (2000), there is a restorative force between shells in carbon nanotubes due to Van der Waals forces. In the case of one nanotube on which they performed experiments, the force was calculated to be 9 nN when they used a manipulator to pull an inner nanotube out of its nested environment. Thus, a nested carbon nanotube can provide a spring-like force, but unlike a traditional Hookean spring, the nanotube force is constant (except for at the rest position) and does not increase with the length of extension.

Multi-wall carbon nanotubes can act as torsional springs, as well (Williams et al., 2003). They used lithographic methods to fabricate paddles, or torsional levers, onto nanotubes suspended at each end. From AFM measurements, for a 7.8 nm, 10 wall nanotube, they determined that the torsional spring constant was 1.5×10^{-13} N-m. The shear modulus, G, was estimated to be 600 GPa—close to the

theoretical value of 541 GPa. Subsequently, they used an applied voltage to impart an oscillating motion to ~600 x 500 nm paddles (Papadakis, 2004). The paddles were oscillated at various frequencies up to about 9 MHz. Intershell coupling varied considerably between the nanotubes, resulting in torsional spring constants ranging from 0.37×10^{-14} to 7.4×10^{-14} N-m.

We have seen from the range of examples above that some types of components that would be useful in advanced nanosystems have already been either fabricated or isolated from biological systems. This is significant with respect to the often contentious issues of both feasibility and timeline: groups are building molecular machines now.

While there has been considerable progress in the fabrication and study of individual components, significantly more progress toward the integration of various types of components into more complex systems is needed. For example, a useful advance would be the introduction of gear teeth onto carbon nanotubes to convert rotary motion into linear motion, and to transfer rotary motion from one nanotube to another.

The motors are powerful enough, and the machine components are efficient enough, to drive complex systems of molecular mechanical devices and perform useful operations at the nanoscale.[1] Carbon nanotubes have proven to be quite versatile as both structural and multi-functional materials, however, variability due to structural defects could potentially cause significant variations in the performance of nanotube devices. While there has been considerable progress in the fabrication and study of individual components, significantly more progress toward the integration of various types of components into more complex systems is needed. For example, a useful advance would be the introduction of gear teeth onto carbon nanotubes to convert rotary motion into linear motion, and to transfer rotary motion from one nanotube to another.

More advanced manipulation and construction tools are required to achieve this level of sophistication: the increased complexity means moving from a two-dimensional to a three-dimensional architecture. (For example, a simple rack and pinion operates on two separate planes.) Multiple manipulators, or some form of three-dimensional scaffolding, will likely be required to hold components in place on these multiple planes during the construction process.

[1] This includes mechanical operations of the types illustrated on the NanoRex website, http://nanoengineer-1.com/content/

Table 3-2. Representative Molecular Motors, Actuators, and Mechanical Devices.

Device	Function	Representative Reference
Nanotube Nanomotor	Motor with MWNT serving as a bearing for the rotor and as an electrical conductor	A. M. Fennimore, T. D. Yuzvinsky, Wei-Qiang Han, M. S. Fuhrer, J. Cumings, and A. Zettl, "Rotational actuators based on carbon nanotubes," Nature 424 (July 24, 2003): 408-410
Molecular Actuator	Molecular actuator able to reversibly push apart two carbon nanotubes	B.C. Regan, S. Aloni, K. Jensen, R.O. Ritchie and A. Zettl, "Nanocrystal-Powered Nanomotor," Nano Letters 5 (2005): 1730-1733.
Molecular Seal	Nanoseal that can be opened and closed at will to trap and release molecules – can be triggered and reversed by redox chemistry or changes in pH	Nguyen TD, Liu Y, Saha S, Leung KC, Stoddart JF, Zink JI., "Design and optimization of molecular nanovalves based on redox-switchable bistable rotaxanes" J Am Chem Soc. 2007 Jan 24;129(3):626-34
Molecular Bearings	Nearly frictionless bearing made from two co-rotating nested nanotubes	Cumings, J.; Zettl, A. " Low-Friction Nanoscale Linear Bearing Realized from Multiwall Carbon Nanotubes," *Science* 289 (2000): 602-604.
Nanosprings	Lithographic methods were used to fabricate paddles or levers onto multi-wall carbon nanotubes acting as torsional springs	P. A. Williams, S. J. Papadakis, A. M. Patel, M. R. Falvo, S. Washburn, and R. Superfine, "Fabrication of nanometer-scale mechanical devices incorporating individual multiwalled carbon nanotubes as torsional springs," *Applied Physics Letters*, v. 82, no. 5 (3 Feb 2003): 805-807.
Telescoping Arms	Manipulator capable of extending the inner nanotube in a MWNT	Cumings and Zettl, "Low-Friction Nanoscale Linear Bearing Realized from Multiwall Carbon Nanotubes". Science 289, 602-604 (2000)
Biomotors	Molecular motors evolved by nature that perform a variety of mechanical tasks	Montemagno, C. D., and Bachand, G. D., "Constructing nanomechanical devices powered by biomolecular motors." Nanotechnology 10 (1999): 225-331
"Nanocar"	Molecular Feringa motor rotates and pushes a protruding molecular group against a substrate, propelling a molecular chasis forward along an atomically flat surface, powered by 365 nm wavelength light	Shirai Y, Morin JF, Sasaki T, Guerrero JM, Tour JM, "Recent progress on nanovehicles". Chem Soc Rev. 2006 Nov;35(11):1043-55
DNA-based robotic arm	DNA-based robot arm inserted into a 2D array substrate and verified by atomic force microscopy to be a functional nanomechanical device with a fixed frame of reference	Ding B, Seeman NC., "Operation of a DNA robot arm inserted into a 2D DNA crystalline substrate." Science. 2006 Dec 8;314(5805):1583-5
Molecular carrier	A molecule called 9,10-dithioanthracene (DTA) with two "feet". Activated by heat or mechanical force, DTA will pull up one foot, put down the other, and walk in a line across a flat surface w/o tracks. Can carry molecular payloads of CO_2.	Wong KL, Pawin G, Kwon KY, Lin X, Jiao T, Solanki U, Fawcett RH, Bartels L, Stolbov S, Rahman TS., "A molecule carrier" *Science*. 2007 Mar 9;315(5817):1391-3.
Molecular rack and pinion	A STM tip drives a single 1.8-nm-diameter pinion molecule functioning as a six-toothed wheel interlocked at the edge of a self-assembled molecular island acting as a rack. The rotation of the pinion molecule is monitored by a chemical tag on one cog.	Franco Chiaravalloti, Leo Gross, Karl-Heinz Rieder, Sladjana M. Stojkovic, André Gourdon, Christian Joachim, Francesca Moresco, "A rack-and-pinion device at the molecular scale," *Nature Materials* 6, 30–33 (2007); http://www.nature.com/nmat/journal/v6/n1/abs/nmat1802.html

Therefore, high priority targets for new and ongoing research initiatives are:

- *Device uniformity and standardization*. Methods to reduce defects in carbon nanotubes would enable devices with more consistent performance. In addition, the development of standard devices and interfaces would enable experimentation with systems of devices.
- *Component integration*. Ongoing research to improve actuators and motors should be coupled with research to integrate these devices with other components to perform more complex nanomechanical operations.
- *Three-dimensional fabrication*. Instrumentation to manipulate and fabricate devices in three dimensions is critical to this pathway. New methods to section and join nanomaterials in 3D structures are needed, and 3D scaffolding (to support nanotubes, in particular) would be important advances.

3.6 Atomically Imprecise Techniques

The current largest atomically precise structures are roughly 500 nm in size.

This is well above the size of the finest features that can be created by top-down methods.

Some of the advantages that have been suggested for hybrid systems include:

- Bringing multiple electrical connections to atomically precise systems
- Exploiting the long-range positional control of top-down pattern generation, e.g., positioning many instances of an atomically precise system in a lattice with coherent spacing over centimeters – e.g., for X-ray diffraction studies to refine structures, or to make structures like zone plates for X-ray optics.

3.6.1 Background

Sometime before the year 2000 critical dimensions (CDs) of state-of-the-art silicon integrated circuit products crossed below 100 nm and, in doing so, entered the size realm usually associated with nanotechnology. This industry is currently at the 45 nm technology node and is encountering significant technology and cost-of-ownership

(COO) hurdles as it works towards future technology nodes at 32 nm, 22 nm, and below. The International Technology Roadmap for Semiconductors (ITRS) organization maintains and continuously updates a comprehensive roadmap for lithography for the silicon integrated circuit manufacturing community, and as a result no such roadmap will be repeated here. A summary of next-generation lithography (NGL) technologies that are addressed in that roadmap is:

- Immersion – optical lithography performed in a fluid medium that serves to reduce the effective wavelength by a factor of $1/n$, where n is the refractive index of the fluid;
- EUV – extreme ultraviolet lithography using 13.5 nm radiation, usually in conjunction with reflective optics;
- Imprint – nanoimprint lithography, in which a patterned hard mold is mechanically stamped into a resist using pressure, temperature and illumination;
- ML2 – Next-generation maskless lithography, a category that includes a number of maskless technologies such as electron beam direct patterning as well as maskless optical lithography.

A summary of possible lithography exposure tool solutions for future technology nodes is given in the 2006 ITRS update for lithography available at www.itrs.net.

3.6.2 Optical Lithography

The current limit for optical lithography stands at 30 nm (Hand, 2006). This would allow roughly 25 separate electrical contacts to a 500 nm diameter atomically precise system.

3.6.3 Electron Beam Lithography

The availability of new aberration-corrected electron optical columns for transmission electron microscopes (TEM) and scanning electron microscopes (SEM), plus the development of sample stages based on technologies developed for AFM applications, have refreshed the possibility of extremely high resolution electron beam lithography in the sub-5 nm regime. However, the lack of resist development in this area, and especially the importance of resist proximity effects in the ultimate resolution of electron beam lithography, have limited the discussion of this technology in APM. Recent activity in the local e-beam deposition of metals using carboxyl-based chemistries, and the possible hybridization of e-beam with atomic layer deposition (ALD)

technologies, may make this an interesting area of research and development for APM as well as semiconductor applications.

3.6.4 Ion Beam Lithography

Since the advent of the first practical liquid metal ion sources more than 20 years ago, the ability to form and focus beams of ions has found great utility in the semiconductor and related industries. The liquid metal ion source can produce a wide variety of ions that can be focused to fine beams, but requires a low melting point metal to form the "Taylor Cone" from which ions are emitted. There was significant work to produce ions of a wide variety by alloying them with Ga, and to use an EXB filter to mass separate the ions, but the brightness of these sources was impractically low. Most focused ion beam (FIB) microscopes use Ga as the ion of choice. The Ga ions do generate secondary electrons, and so can be used to image much like a scanning electron microscope. However, the Ga ions are heavy and have the advantage, and disadvantage, of transferring considerable energy to the sample which typically results in sputtering of the sample. This allows an FIB to ion mill samples, thereby directly patterning them. In addition the Ga beam in conjunction with gasses introduced into the FIB instrument can do both ion beam enhanced etching, and ion beam induced deposition of materials. However, the resolutions of these processes are limited to a few nms and are relatively slow processes. FIBs are extremely important for a number of relevant processes in the IC industry including photomask repair, circuit edit, and TEM and SEM sample preparation. It is unlikely that FIB tools will be able to do atomically precise fabrication because they lack the resolution to do so. In principle an FIB could be used to expose resists similar to e-beam lithography, but the heavy ions offer no significant advantages, and in fact several disadvantages compared to electron beams. They are not typically used to expose resist. However, the advent of gaseous ions sources may change this situation. See the following section for the possibilities for He ion beam lithography.

3.6.5 Helium Beam Lithography

A stable gaseous field He ion source has recently come available and has been commercialized by ALIS Corp. which was acquired by Zeiss. The import of the He beam tool is a significantly smaller spots size: ~0.25 nm for the He beam vs. 1 to 1.5 nm for electron beams. The more efficient and spatially confined manner in which light ions deposit their energy is also a significant advantage. Although no serious attempts have yet been made to produce a lithography tool with a focused He beam from this new type of source, this will surely happen and will almost surely achieve higher resolutions than possible with e-beams.

3.6.6 Nanoimprint Lithography

Nanoimprint lithography was initially developed by Chou's research group in 1996 (Chou et al., 1996a; Chou et al., 1996b) and has since evolved into several related methods with different approaches. In all cases, the fine features on a template are mechanically transferred into a resist which is then cured to retain these features. The resist pattern is then applied to metal wafers in the semiconductor manufacturing process. Nanoimprint machines with a resolution better than 50 nm (at 3-sigma) and alignment capability better than 10 nm are commercially available (Molecular Imprints, no date). Microfluidic channels measuring 100 nm wide have been fabricated for DNA stretching experiments (Tegenfeldt, 2004).

3.6.7 Dip Pen Nanolithography™

Dip-pen nanolithography, or DPN. This is a technology based on the dispense of liquid material into specialized atomic force microscope (AFM) cantilever/tip assemblies and the deposition of that material at a tip/substrate interface. The combination of the material volume dispensed, the dwell time of the tip at a location, and interactions of humidity and the material/substrate interface can result in the writing of fine lines. While the technique is quite slow and limited to specific chemistries, recent demonstration of limited parallel tip writing and plans for future large parallel tools might make this technology attractive for APM.

3.6.8 Partially Ordered Chemical Self-Assembly

When intermolecular forces combine to create a single layer of molecules on a surface or interface, the product formed is called a self-assembled monolayer (or SAM). These are among the most widely studied self-assembled system, but they characteristically lack atomic precision.

SAM formation typically involves a favorable interaction between the molecule's head group and the surface (e.g., the gold surface and a thiol). The stability of the monolayer is often dictated by the strength of this interaction – weakly held molecules produce monolayers that are easily disrupted, strongly held molecules produce monolayers that are more robust. The kinds of applications that a monolayer can be applied towards are dictated by the stability of that monolayer under those particular conditions. For example, one of the most widely studied types of self-assembled monolayers is the organothiol on gold. These monolayers are very easy to make and a wide variety have been made and characterized. They have been widely used in a variety of sensing

devices such as chemically modified electrodes, SAW devices, and QCMs. However, the thiolate head group is subject to oxidation and these monolayers are thermally labile above about 70°C, making these materials unsuitable for sensing applications that might encounter these conditions (e.g., exhaust gas monitoring). In addition, while these monolayers are locally atomically precise, even well-annealed monolayers contain grain boundaries and more complex defects. In alkylthiol layers in particular, the alkyl moiety is tilted by 30 degrees from the normal to the surface, so the SAM has a directionality, and therefore a lower symmetry than the gold (typically (111)) surface to which it is bound. This symmetry breaking allows equally stable monolayer grains to form with the alkyl groups aligned in any of several different directions, and therefore allows grain boundaries to form.

Another class of molecules that have been widely used to form self-assembled monolayers is the organosilanes. In this case, they must first be hydrolyzed to form the hydroxysilane intermediate, which is the key component that undergoes the self-assembly process. In this case, the attractive interaction between the head group and the surface is a hydrogen bond between the hydroxysilane and the oxide surface. As the hydroxysilanes aggregate, making a macromolecular aggregate, the hydroxysilanes slowly start to undergo condensation chemistry, both among themselves and with the oxide surface, ultimately resulting in a covalently anchored, and crosslinked monolayer system.

Self-assembly is not only useful in the synthesis of organized macromolecular arrays, but also in the formation of templates to make complex three-dimensional architectures. Self-assembly forces are also responsible for the formation of micelles and vesicles when surfactant molecules are dissolved in water. Micelles and vesicles can be used as templates in the synthesis of nanostructured materials (e.g., ceramic oxides, phosphates, etc.). For example, when certain types of micelles are exposed to silicate sol-gel reaction conditions, it is possible to wrap the ceramic phase around the micelle structure and make a highly porous silicate product. The pore structure of these materials is directly related to the original micelle diameter, and since these dimensions are between those commonly encountered for zeolites (15 Å or less) and macroporous materials (300 Å or more), these materials are commonly referred to as “mesoporous” materials. Polydispersity of micelle diameter is on the order of 15% (Hayter and Penfold, 1983).

The silicate coated micelle can also participate in a self-assembly process. As these macromolecular assemblies precipitate out of solution, they commonly form an ordered, organized array. Depending on reaction conditions, it is possible to make hexagonal, cubic, lamellar, or bicontinuous phase products. Thus, the first generation of self-

assembly is the orderly aggregation of the surfactant molecules to form the micelle, and the second generation of self-assembly is the aggregation of the silicate coated micelle to form the mesostructured greenbody. The surfactants are generally removed via calcination, which simultaneously serves to rigidify the ceramic backbone, exposing the latent pore structure.

This provides a very high surface area support for catalyst, sorbent and sensing/detection applications. Because these pores are generally larger than simple organosilanes, it is possible to functionalize these internal pore surfaces using a third generation of self-assembly by installing a self-assembled monolayer on this mesoporous framework. If these organosilanes are terminated with chemically specific binding sites, it is possible to create an ordered hierarchical array of binding sites that have high chemical affinity for a wide variety of target species. For example, if we line the pores with alkylthiols, we create a nanoporous sorbent that has exceptionally high affinity for "soft" heavy metals like Hg, Cd, Ag and Pb. Heavy metal sorption kinetics are quite fast (often complete in a few minutes) and selectivity in the presence of common ions (like Na, Ca, Fe, etc.) is excellent. These self-assembled monolayers on mesoporous supports (SAMMS™) are thus arrived at via three successive generations of self-assembly (surfactants to micelles, sol-gel micelles to mesostructured greenbody, and functionalization via self-assembled monolayers), and have been tailored for effective separations of a wide variety of environmentally problematic species (e.g., heavy metals, radionuclides, oxometallate anions, cesium, iodine, etc.).

Additional self-assembly motifs include electrostatic repulsion of particles dispersed in a dielectric medium. The "double-layer" repulsion thus provided allows for three-dimensional arrays of variable scale periodicity. Such is the case for simple systems where monodispersed polystyrene spheres are allowed to assemble in water or water dispersed polymer or prepolymer networks. Colloidal crystalline arrays of this kind have been known for decades, yet only recently were they exploited as effective photonic band-gap materials or photonic cystals (see Jiang et al., 2005). These photonic band-gap composites present unique polymeric materials with discrete diffraction based upon the inter-particle spacing and dielectric contrast of the two phases thereby provide sensing and optical communication platforms based on attenuation of the matrix or particle distances.

3.7 Topic 3 References

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Topic 4 Modeling, Design, and Characterization

4.1 Introduction

The processes of modeling, design, and characterization apply the discoveries of basic scientific research to support the cycles of development that drive advances in technological capabilities. These processes are interwoven and mutually supportive.

Modeling and design guide fabrication by providing a theoretical framework for generating and testing structures, devices, and entire systems by means of computational experiments. Modeling and design help choose targets for fabrication, and have proven to be valuable in areas as different as automobiles and molecules.

The characterization of raw materials and complex systems provides data with which to assess not only the utility of a design, but the accuracy of models used to derive it. The iterative comparison of theory and experiment is important because many computational models of nanoscale systems (e.g., molecular mechanics and dynamics methods) are based on adjustable parameters, and the quality of the model and its results benefit from better experimental data. Thus, the characterization process, aided by continued advancements in imaging and measurement technologies, provides the data needed to validate or drive revision of both proposed designs and the underlying physical models that describe their properties and operation.

4.2 Characterization Background

Improvements in characterization and in the computational resources vital to modeling and design have greatly advanced developments in the scientific disciplines that provide the foundations for nanoscience and nanotechnology. The available characterization methods span the range of familiar molecular study, from the investigation of bulk materials at the macroscale (refraction/reflection studies, stress and stiffness measurements, tribology), to the study of molecules in periodic systems (crystallography, electronic spectroscopy, vibrational spectroscopy), to the study of individual molecules at defined positions (atomic force microscopy, scanning tunneling microscopy). As in modeling and design, the choice of characterization method is highly dependent on the desired property to be measured, and currently available techniques can far exceed the level of detail required for the characterization and testing of materials. Currently available techniques for the characterization of nanostructures are sometimes bottlenecks in development, but are adequate to support ongoing progress in AP nanosystems and

APM: the complete characterization of atomic scale properties is not on the critical path.

In self-assembled structures, the subunits are multi-atomic and are typically independently characterized. In many instances, knowledge of their relative positions in a larger structure immediately provides atomic-scale information based on the prior characterization of the subunits themselves. With the structure and properties of individual system components defined during their initial fabrication, characterization can focus on properties at the device and component levels.

Some commonly modeled properties important to AP components and systems:

- Ground and excited state geometries
- Molecular dynamics behavior
- Energy of reactants, products
- Energy of transition state barriers
- Alternative chemical reaction products
- Protein folding and unfolding
- Electrostatic interaction energies
- Dynamic friction, thermalization
- Transport of thermal energy
- Transport of electron, holes
- Molecular transport through proteins, zeolites, and pores
- Electrostatic dipoles and higher multipoles
- Vibrational and electronic transition states and energies
- Optical refraction, absorption
- Nonlinear optical coefficients
- Spin-spin interaction dynamics

4.3 Modeling and Design Background

Nanoscience and nanotechnology are on the verge of tremendous advances in modeling and design that originate in macroscale engineering, chemistry, and computer science. The modeling and design infrastructure that has developed around macroscale engineering, including computer aided design-based mechanical and electrical engineering, provides a solid foundation of protocols and design interfaces that are now being extended to software for molecular modeling and design. The fields of quantum chemistry, molecular dynamics simulation, and molecular visualization combine to provide the modeling and design tools that enable the study of matter at the atomic scale, from molecular orbital calculations of small molecules to the study of binding interactions between biomolecules, such as DNA and proteins, that span well into the nanoscale regime.

Nanoscale modeling and design merge macroscale engineering principles with quantum mechanical and classical mechanical models of matter, all the while driving demand for more data, more accurate models, faster algorithms, and improved computational resources. Just as modeling and design will set the pace of development for many atomically precise technologies, developments in computers and algorithms are driving the extension of atomistic models, the modern basis for our understanding of matter, into the nanoscale regime.

The validity of a design and the predictive power of a theory-driven design process are heavily dependent on the accuracy of the theoretical model(s) being used. The choice of quantum mechanical, classical mechanical, or hybrid descriptions for the study of molecular and nanoscale systems is one determined by both theoretical necessity and available resources. While quantum mechanical methods exist that can approach the absolute limits of accuracy achievable by modern computational chemistry, the use of these methods is currently limited to diminutive chemical systems (< 20 atoms) because of computational cost.

The selection of a quantum mechanical or classical mechanical description of a system is one driven, within the limits of available resources, by the properties being considered, with decades of both molecular mechanics and quantum chemical developments available from which a researcher can consider a system for their properties. The difference between modeling and design for the study of both chemical and nanoscale systems is clear: while the field of molecular modeling is one that has readily accepted a formal division between quantum and classical methods for the study of materials, the field of design is not naturally subject to that constraint. While molecular modeling studies occur within the limitations of each theoretical method, the goal of nanoscale design is to produce the best structures or systems possible according to a set of value metrics, making the use of multiple modeling approaches (because of their known limitations) an integral part of the design process.

More commonly modeled properties important to AP components and systems:

- Magnetic domain dynamics
- Donor/acceptor group geometries
- Enzyme, catalysis binding modes
- Solvent-based dependences of molecular properties
- Atomic/molecular ionization energies
- Atomic/molecular electron affinities
- Molecular orbital energies, diagrams
- Chemical reaction heats of formation
- Conformational energy differences
- Molecular volumes, surface areas
- Molecular self-assembly processes
- Geometries, electrostatics at surfaces
- Crystal energies, dynamics
- Solvent-accessibility in macromolecules
- Stabilities of aggregates and ordered arrays
- Homology models, geometric relationships

4.3.1 Atomically Precise Technologies Span the Range of Available Modeling Techniques

The modeling and simulation of materials, devices, and systems within the nanoscale regime (1 to 100 nm) requires atomistic or near-atomistic ("reduced model") methods. In systems that are designed to perform chemical or mechanosynthetic operations, processes involving fundamental changes to the electronic structure of materials, the modeling and design process requires quantum chemical methods or "reactive potential" methods, empirical approaches that include as part of their parameterization process terms that account for the relative energies of chemical bonds. In systems or assemblies that do not undergo chemical reactions but instead maintain fixed atomic connectivity in the course of a series of operations, classical mechanical approaches have proven to be effective. Nowhere has this division in modeling techniques been more relevant to the study of structure and function in nanoscale systems than in the modeling of the enzymatic (quantum mechanical) and conformational (classical mechanical) properties of proteins. While the broad range of molecular modeling techniques enable the complete atomistic representation of matter across the nanoscale, the application of many techniques is limited by computational resources.

Computational chemistry must balance the advantages of accurate theoretical models to describe the properties of atoms and molecules against the limitations of available computational resources. Molecular mechanics and semi-empirical quantum chemical methods have far lower computational demands than rigorous *ab initio* methods and density functional theory. Their formulation is largely pragmatic, implemented for the interpretation, then prediction, of chemical data

during the decades when room-sized computers had a fraction of the power of the most modest personal computers today.

Improvements in resources and algorithms to reduce the computational cost of calculations have made all theoretical tools more available, yet the most exact methods are barely capable of property prediction in the nanoscale regime due to the cost of computation. Thousand-atom classical dynamics simulations and ten-atom *ab initio* calculations tested the limits of computational resources at the beginning of the personal computer revolution, yet today, entire nanoscale devices and complex biological systems (>10^6 atoms) can be simulated by classical mechanics methods, while hundred-atom systems can be readily treated by *ab initio* methods and density functional theory on computer clusters employing commodity hardware. Developments in computing power and algorithms have pushed the tools of computational chemistry into the nanoscale regime, with each new generation of processor extending the speed, scale, and accuracy of calculations.

4.3.2 Atomically Precise Technology Design Requires Multi-Level, Multi-Scale Modeling

By their nature, atomically precise technologies and their operations require atomistic models. The dependence of the properties on atomistic structure is particularly important when considering structures whose dimensions are in the nanoscale (1 to 100 nm) regime, as the atomic building blocks of these objects are within only two orders of magnitude of the size of the structures themselves. Beyond this, however, domain-specific requirements, including quantum mechanical, atomistic classical mechanical, and "reduced model" approaches, vary widely. Processes that involve bond rearrangement, unusual structures, electron transport, or electronic state transitions typically demand quantum-mechanical modeling of electron distributions and energies. Processes that involve atomic motion, molecular displacement and deformation, or any types of structural analyses that preserve the atomic connectivity of the system under investigation are typically addressed by molecular mechanics and molecular dynamics methods. To reduce computational burdens in chemically massive structures that do not require consideration of all atoms, reduced models are common, treating groups of atoms as single bodies, or (in the limiting case) subsuming them into non-atomistic models of elastic or even rigid solid bodies. At this level, the techniques are those familiar to macroscale modeling and design.

Choosing a specific model always involves trade-offs of the speed of computation, the size or amount of structures modeled, and the required accuracy of the results. Quantum methods in particular

embrace a range of models (levels of theory) that differ widely in their computational tractability: some allow dynamical studies of thousands of atoms; others strain available computational resources in order to provide great precision in describing small molecules. Molecular mechanics and dynamics models rely on direct approximations to the forces among atoms, and currently scale to systems with up to millions of atoms. The accuracy of the latter methods (for suitably chosen classes of systems) can be judged by the fact that they are used to gain insights into the balance of weak interatomic forces responsible for the geometry and dynamics of proteins and other biomolecules. The development of combined quantum mechanical and molecular mechanics methods for the study of chemical systems (QM/MM methods) is founded in the realization that the local changes to electronic structure (bond breaking, formation) in macromolecules or molecular aggregates can be dependent on the larger system. This is readily apparent in the simulation of protein function, where enzymatic activity is confined to a specific location but the geometry and dynamics of that location are a function of the protein structure as a whole. The further reduction of atomic detail, through the use of subsumed detail/rigid body models for molecules or continuum models (such as implicit solvent models and non-atomistic surface models) enable the removal of a further level of detail that would otherwise require tremendous increases in atom count and, therefore, computational cost.

Integrating atomistic and non-atomistic models at different scales is key to enabling practical design and simulation of large, complex atomically precise nanosystems.

Extending the scale, scope, and accuracy of atomistic modeling techniques is a high priority and can greatly facilitate atomically precise technology design and implementation. Integrating atomistic and non-atomistic models at different scales is key to enabling practical design and simulation of large, complex atomically precise nanosystems. This is an area of ongoing research activity, driven by areas related to, but developed in parallel with, nanotechnology, including biochemistry, supramolecular chemistry, and materials science.

4.3.3 Atomically Precise Technology Developments Demand Innovations in Computer-Aided Design

Design and molecular modeling are, at their cores, indirect tools for the prediction of chemical properties and phenomena. The process of design at the atomic level connotes the application of models, be they physical or mathematical, for the generation of new structures with desired properties. As such, design and molecular modeling are formally distinct areas within theoretical chemistry that have evolved towards tight integration, with design now commonly a process of the application of the predictive powers of the computational methods within molecular modeling for the *in silico* generation and testing of structures or whole systems. The design process for molecules and

nanosystems exploits physical descriptions based on diverse molecular modeling and continuum model techniques, with the results and interpretation of generated data subject to their approximations and computational restrictions.

The utility of design at the nanoscale depends on the adequacy of the theoretical model(s) used to describe the physical system. In many instances, potential designs can be tested and modified at timescales and expenses far below those of physical experiments. These modeling and design exercises can be of great value provided that they are accurate enough to provide guidance that yields even moderate improvements in the success rate of the more expensive physical experiments. Accordingly, even highly imperfect models can play a valuable role.

Each domain of atomistic modeling (e.g., quantum mechanical, atomistic classical mechanical, reduced model methods) creates distinct demands on computer aided design (CAD) tools. Some of these demands involve data visualization, while others involve data representation, and its integration with methods employed in subsequent analyses that may or may not be atomistic in nature. (Examples include the study of electrostatic interfaces or molecular lock-and-key binding, both of which can employ surface analyses based on previous calculations of atomic positions).

An important objective is to expand multi-level modeling and design tools, as has been achieved for enzyme systems, to mixed models of diverse kinds.

At all but the largest scales, conventional approaches to design are inapplicable because of the discrete nature of component structures: one must drop the assumption that dimensions, electrical properties, etc., can be varied in a continuous way. This is in many ways more fundamental than differences in the applicable device physics.

Multi-level modeling is motivated by the great differences in scope and computational cost associated with different modeling techniques, and this will need to be integrated into CAD tools and the design process in two distinct ways. The first is the application of different techniques to different parts of systems, for example, applying quantum methods to describe reactions, while applying molecular mechanics methods to describe the structures that support and constrain the reacting components. This has been achieved, for example, in modeling structure/property/function relationships in enzymes. Expanding this principle to mixed models of more kinds is an important objective. The second role for multi-level modeling is design refinement. In this application, less-accurate, lower-cost techniques are used for exploratory purposes to identify systems that are worth further investigation using more-accurate, higher-cost techniques, a process that maximizes throughput of designs by leveraging the speed of computation with *a priori*

knowledge of the limitations of the employed models. It will be important to provide smooth integration of this methodology into CAD tools for developing atomically precise technology systems.

4.3.4 Characterization Methods Enable Refinement of Models, Designs, and Fabrication Methods

The development cycle in systems engineering proceeds through modeling and design (for example, computational simulation) iterations until an apparently satisfactory result is achieved. Fabrication and physical testing then provide the ultimate feedback on the success of a design. The quality of this feedback determines its effectiveness in guiding any necessary revisions in the fabrication method, the model, or the design. It is crucial to know, for example, whether a failure results from a difference between what was designed and what was made (a fabrication problem), or from a difference between the properties predicted and the properties observed (a modeling problem).

In nanoscale modeling and design processes that employ the quantum and classical mechanical tools of computational chemistry, issues based on modeling accuracy are either straightforward (classical mechanics) or difficult (quantum mechanical) to overcome. As an entirely empirical class of tools, classical mechanical models of atomic motion are readily capable of being refined based on the results of experimental observation, subject to either the modification of the underlying parameters or to the increase in computational resources required to accommodate additions to the force field model used to define all atomic interactions. The same is not true of *ab initio* methods or density functional theory. In the case of *ab initio* methods, the benefits and limitations of Hartree-Fock and post-Hartree-Fock (MP*n*, CI, CC, CASSCF, etc.) methods are inherent to the mathematical approximations used to describe the quantum nature of chemical systems. For density functional theory, where the density functionals used to model the static correlation of electrons are empirically derived, the procedure of density functional optimization is far from trivial because, unlike the nearest-neighbor(s) parameter-based molecular mechanics methods, changes to density functionals are not limited to local changes in structure. Within each quantum chemical theoretical model, improvements to *ab initio* and density functional theory calculations largely come through improvements in the description of electronic wavefunctions, made possible by the selection of larger and more computationally demanding basis sets.

Improved characterization methods generally will aid in the development of atomically precise nanosystems, but the needs and ingenuity of the scientific community have already provided remarkably capable

tools that can help to refine those computational models that use experimental data in of their parameterization process. Nanoscale and atomic-scale sensing, imaging, and metrology have immense capabilities and are growing rapidly. Improved tools for characterizing atomically precise nanosystems will be of great value, but the present state of the art provides an adequate basis for progress.

4.3.5 Advances in Atomically Precise Fabrication Technologies Can Simplify Modeling Requirements

Advances in atomically precise fabrication will enable practical applications of an increasing range of structures and phenomena even beyond the nanoscale. This will, in turn, increase demands on modeling techniques by driving expansion of their scope and increasing the demand for faster and more routine methods that are applicable in the context of nanosystem design.

In one important respect, advances in atomically precise fabrication can make successful modeling less demanding by reducing the design space that must be modeled to test proposed systems. Advanced fabrication techniques can, in many instances, make components with improved stability, rigidity, and performance. These improvements tend to make the structural behavior of components less sensitive to small errors in model energies, and they can also be used to increase the margin of safety by which components satisfy design requirements. This again reduces sensitivity to errors. Constraints within the fabrication process can also be included in the modeling process and used to, for instance, remove possible degrees of freedom from a simulation. Such simplifications are difficult to incorporate into chemical simulations, where the system is inherently chaotic, but are readily included in mechanosynthetic, epitaxial, or various programmable processes at the nanoscale, where systems can be constrained to operate in a more controlled manner.

As a consequence, currently accessible products of AP fabrication may require more advanced modeling techniques, while analogous advanced products may not. This inverse relationship is illustrated by molecular machine systems, where protein-based devices remain a great challenge to modeling, but not to fabrication, while machines made of rigid atomically precise components can be easy to model despite being inaccessible to current and near-term fabrication techniques. This relationship facilitates, to an unexpected degree, the use of current modeling techniques to explore and evaluate the general properties of classes of systems in order to weigh their potential value as longer-term development objectives.

4.3.6 Atomically Precise Technology Development Can Succeed Despite Deficiencies in Modeling Techniques

In assessing the near-term potential for the design and fabrication of atomically precise systems, it is necessary to assess the adequacy of existing modeling techniques for supporting the design process. This is a matter of particular concern because there exist many physical systems of interest for which the predictive power of existing tools capable of modeling structures and properties at nanoscale dimensions is very poor, often giving qualitatively incorrect results. For instance, many quantum chemical methods are inadequate for predicting bond dissociation energies, electronic transition energies, or the association of weakly interacting molecules or structural motifs. Molecular mechanics methods are extremely susceptible to errors in atomic geometry and connectivity in the absence of algorithms to confirm the chemical accuracy of starting structures, a limitation that affects both the accuracy of calculations and the usability of such methods by untrained users across nanoscience disciplines.

For design problems, the adequacy of a model cannot be assessed without considering the practical question it must answer. Design can succeed, and even be reliable, in domains where models have substantial inaccuracy and can give qualitatively incorrect results. What is required for success is not universal predictive accuracy, but instead the ability to identify a suitable class of systems within the domain. To be suitable for the purpose of design, members of this class must be sufficiently well-behaved to be insensitive to modeling errors, and the class must include members that satisfy the relevant set of design requirements. What constitutes sufficient insensitivity, however, typically depends on whether these requirements are stringent or loose, hence the importance of knowing the practical design question before judging the adequacy of a model.

Even a very incomplete knowledge can aid a technology development program. Even a weakly predictive model can speed development by directing experimental research away from likely failures and toward systems that are viable candidates for success. While the Edisonian efforts of experimental trial and error alone can be an acceptable development method (provided that success is sufficiently common and that trials are not prohibitively slow or expensive), model-based approaches even with limited tools provide a level of rational design that can aid in the application of experimental precedent and chemical intuition.

Even a weakly predictive model can speed development by directing experimental research away from likely failures and toward systems that are viable candidates for success.

4.4 Design Considerations for Self-Assembled and Directly Assembled Nanostructures

The availability of both self-assembly and directed (mechanical, programmable) approaches at the nanoscale for the generation of new materials or complex systems provides both considerable flexibility in possible fabrication routes and considerable challenges for computational modeling and design techniques.

For structures to be made by means of tip-directed atomically precise mechanical processes, product geometry results directly from a programmed sequence of motions of a tool with respect to a workspace. This directness applies both to current and next-generation atomically precise technologies based on scanning probe instruments and to envisioned advanced-generation productive nanosystems. Domain-specific CAD requirements in this area are driven chiefly by the need to model discrete structures with appropriate device and process physics.

Design tools with improved combinatorial search algorithms can aid "supramolecular mechanosynthesis", in which blocks could be designed with complementary surfaces that strongly favor desired binding.

In atomically precise self-assembled systems, by contrast, structure and fabrication become related in a far more intimate way. At every stage of assembly, at least one component must be free to diffuse in a solvent, enabling it to explore all possible positions and orientations to find its unique, intended binding site. This process requires that the component be soluble, that it has a surface complementary to that of its intended binding site, and that all other surfaces of the workspace and the component be sufficiently non-complementary that stable binding is precluded. These requirements are added on top of functional requirements. The available materials and environmental conditions in nature favored complex structure generation by way of self-assembly methods, a general process that has been exploited with tremendous success in the field of supramolecular chemistry and, increasingly, the control of molecular crystallization.

Identification of designs in which components have appropriate surfaces and matching interfaces characteristically requires an automated computation search mechanism. In many DNA structures, "sticky ends" serve as complementary interfaces, while in proteins, folding requirements can be viewed as extending self-assembly constraints to the interior of the molecule. In both instances, design tools today rely on searches in the combinatorial space of alternative monomer sequences. Improving success rates and product performance will likely require improvements in this class of algorithms, chiefly in the definition of suitable objective functions. Such tools will also serve useful roles in the design of much larger nanoscale systems based on self-assembled components, where complementary surface interactions can be combined with control of the sequence of assembly. With

suitable nanomechanical systems, blocks with complementary surface interactions could be guided to the region where they are to bind, relying on complementarity to select a precise position and orientation within the looser, imposed constraint. By analogy with Lehn's concept of "supramolecular chemistry", in which chemists exploit non-covalent binding interactions, this might be termed "supramolecular mechanosynthesis".

Future-generation atomically precise self-assembled systems, perhaps exploiting components produced by new classes of atomically precise productive nanosystems, appear likely to share this requirement for integrating search-based operations in CAD tools and design processes. A similar need for searches will arise when tip-based atomically precise mechanical systems are used to manufacture structures that satisfy surface-defined constraints by means of structures that depart greatly from crystalline order.

4.4.1 Modeling Challenges at the Nanoscale

Modeling and design at the nanoscale is on a leading edge of developments in computational chemistry, pushing research in algorithms, visualization, and theoretical models. Nanostructures and nanoscale devices often challenge our ability to study matter by atomistic (both classical and quantum chemical) methods. Nanoscale modeling and design, like nanoscale materials and devices themselves, often straddle classical and quantum mechanical descriptions. Larger-scale models may straddle the boundary between atomistic and continuum models, where the latter are adopted because of their great computational economy.

The use of classical atomistic or even continuum approximations for modeling and design is largely pragmatic, founded in computational necessity. The cost in computational resources to handle even moderately-sized molecular systems using quantum mechanical descriptions is beyond what even the largest computational facilities can provide. The challenges of large, atomistic models can be enormous even in classical approximations, as shown by the scale of resources applied in the supercomputer and distributed computing studies of the protein fold-prediction problem.

4.4.2 Molecular Graphics Developments and the Visualization of Nanoscale Structures and Information

The visualization of chemical information is as important to the researcher as the underlying physics is to the validity of the model. Advances in molecular graphics, like advances in the scales of molecular

modeling, have a long history of expansion and improvement as a result of advances in general computational technology. While the visualization of molecules and their interactions by way of graphical molecular modeling programs have greatly aided the experimentalist in chemical research by diminishing the conceptual barriers to theoretical methods, the same graphical implementations have also aided theoreticians by providing a rapid means to identifying errors in models that can result from fundamental limitations in the theoretical methods themselves.

An important aspect of molecular graphics relevant to nanoscale design and simulation concerns the relevance of atomistic representations of chemical information. Considerable information can be obtained from non-atomistic visualizations, for example, of the DNA helix and base pairing. This reduction in model complexity extends to all areas of visualization, where the properties deemed relevant to a single calculation or simulation can be defined purely by the shape of a molecule and not its atomic constituents. Many properties important to nanoscale design, such as charge distribution, dipole moment, molecular volume, and surface geometry, need not be defined with respect to individual atoms. In the case of surface renderings for the identification of binding regions, possible interfaces for assembly, or the determination of molecular volumes, suppression of atomistic detail can provide a more useful display of the important physical properties.

Again, computational biochemistry provides excellent examples: the reduction of protein to secondary structure (ribbons and geometric objects for representing alpha helix and beta sheet motifs) or surface renderings (charge analyses, binding pocket visualization) has been vital both for understanding structure and function and for presenting this information to other researchers. Similar representational strategies will be widely applicable in the design and evaluation of AP nanosystems.

4.4.3 Smart Design Methodologies and Issues Related to Model-Based Chemical Knowledge

The visualization of molecular information has driven both open source and commercial software development that has broadly expanded the utility of molecular modeling programs to researchers that need not be familiar with the underlying theory to apply the methodologies to chemical design. The advantages and limitations of molecular modeling techniques extend into the design process, with atomistic design processes subject to both constraints imposed by the modeling limitations and an absence of “chemical knowledge” on the part of graphical programs. Simply, atom-derived properties, such as chemical reactivity and stability, are not readily accounted for within molecular

design and CAD systems, leaving proposed designs subject to critical evaluation by researchers even with exhaustive computational studies completed at high levels of theory.

A major obstacle to accurate atomistic design within the nanoscience community as a whole is also to be found in the incomplete incorporation of chemical bonding and atomic geometry information in visual molecular modeling packages. This aspect of visual molecular modeling packages has less to do with limitations of the molecular modeling methods available in the program and more to do with the chemical knowledge of the user. Any effort to greatly expand the usability of computational modeling and design systems for nanofabrication must include, as part of its functionality, the ability to identify, if not correct, flaws in atomic connectivity and geometries from "standard models," both for those users unfamiliar with the complexities of chemical bonding (a likely situation as the tools of interdisciplinary research become available in advance of knowledgeable users) and for chemists and biologists fully knowledgeable in chemical bonding but unable to readily visualize problematic locations in chemical structures due to the shear size of the structures being designed.

Efforts to expand the usability of computational modeling and design systems for nanofabrication must include the ability to identify flaws in atomic connectivity and geometries from standard models, for a diverse range of users.

In the absence of intelligent systems capable of comparing calculated geometries against databases of all known molecular motifs or theoretical models of atomic geometry and chemical bonding, the final validation of any design still lies with the researcher. The extent to which chemical knowledge can be programmed, or rules governing chemical bonding and non-covalent interactions can be developed to obviate the need for intensive pre- and post-processing by researchers, into a graphical design system to simplify nanoscale design is an important area of future study that extends from molecular modeling packages, themselves still developing such functionality.

4.5 Modeling

The predictive modeling of mechanical and electronic phenomena in the 1 to 100 nm range is being extended through improvements both in computational algorithms and computer technology. The rapid improvements in processor performance have driven theoretical work in all fields of science and are well known. However, while processor performance alone could drive the extension of theoretical studies to new size regimes, the development of efficient, scalable software has also had tremendous impact on the field of molecular modeling by enabling independent researchers to use commodity hardware in individual laboratories to approach the computational speeds of dedicated supercomputers.

Nanoscale science presents new challenges to both experimentalists and theoreticians. While experimentalists are exploring novel properties of materials at this scale, theoreticians are exploiting computational resources powerful enough to study nanoscale systems using molecular modeling tools developed for small systems in computational chemistry.

Theory and computation become useful in an area of science when their predictions become reliable enough to help improve the success rate of experiments, and they become essential to an area of technology design when their accuracy is sufficient to guide the selection of system-level implementation targets. The balance of theoretical accuracy and computational cost frequently motivates molecular researchers to perform survey-style studies of model systems using lower-quality computational methods, followed by final studies of candidate systems by high-level methods. The growth in computational resources has made this approach less important for structures of the sort to which it had been applied, but extension of molecular modeling approaches into the nanoscale reintroduces the benefits and limitations of low-accuracy models as a screening mechanism for design, and as a guide to the requirements for applying more accurate and expensive methods.

Models with substantial inaccuracies and limited applicability can nonetheless provide effective tools for system-level design in suitably selected domains. There are several reasons for this:

- System-level designs can in some instances be restricted to employ only relatively well-understood components (consider the role of DNA oligomers in structural DNA nanotechnology).
- Designs may incorporate margins of safety, making them insensitive to small errors in predicted geometry or energy.
- A system-level design may permit many alternative component-level implementation options, and modeling may strongly suggest that one or more will work, yet not specify which.

This is a particularly important realization regarding the relationship between nanoscience in general and the emerging technologies of nanosystems engineering.

4.5.1 Computational Infrastructure

Efforts in computational nanoscience span the range of resources and facilities, from individual researchers performing computational studies at academic institutions to major national laboratory investigations and method development projects using (or designing) state-of-the-art

computational resources. Further model refinements and improved computing resources will increase the reliance of researchers on theoretical methods for the design and testing of materials and complex devices.

Providing researchers with computing resources powerful enough to address their questions with the highest or most appropriate levels of theory available has been addressed at the US national level through the establishment of the National Center for Supercomputing Applications (NCSA), the support for major computational facilities at many of the national laboratories, and the provision of funding through many of the national agencies (such as NIH, NSF) for computational facilities at individual universities. A benefit of concentrating resources at national facilities is the development of communities of computational chemists familiar with the many programs available for theoretical study and the knowledge of the strengths and limitations of various theoretical methods with respect to research projects proposed by applicants.

4.5.2 Information Provided by Molecular Modeling Methods

Within the field of molecular modeling are the mathematical foundations for the property calculation of any atomic assembly, including both static properties (geometry, potential energy surfaces) and dynamic properties (excitations, transition states, electron transport). Molecular mechanics/dynamics methods, while providing the least realistic descriptions of atomistic matter by their neglect of electronic structure, have proven instrumental in computational chemistry by enabling the study of macromolecules and their interactions, the dynamics of classes of molecules in their crystal cells, and the thermal transport properties of materials, to name only a few applications.

The clearest division between the available methods in molecular modeling is between methods that provide electronic structure information and those that do not. This division separates classical and quantum mechanical descriptions of matter, a recurrent theme in much of the discussion of modeling and design. Neglecting computational demands, higher levels of theory are generally capable of calculating the properties of lower levels of theory. In the case of post-Hartree-Fock methods capable of predicting electronic transitions and excited state geometries, these same methods can also be used to calculate the ground state geometries of molecules to very high levels of accuracy. Quantum chemical methods not only can perform the same geometry and dynamics calculations as molecular mechanics methods, but provide the foundations for many molecular mechanics methods. These

derive their force field parameters from *ab initio* and density functional theory calculations.

A brief summary of some of the properties available from molecular modeling techniques are provided below. The division between classical and quantum mechanical methods, as well as quantum chemical methods suited for "static" (ground state) and "dynamic" (excited state, transition state) electronic processes, are used to divide the property prediction of the available techniques.

Non-Electronic Structure Property Prediction (Molecular Mechanics/Molecular Dynamics). Ground state geometries, dynamical behavior, conformational energies, self-assembly processes (such as protein folding and unfolding), electrostatic binding and repulsion energies, transport of thermal energy, molecular transport through materials, ligand binding geometries and positions, molecular volumes and surface areas, steric and electrostatic surface interactions, crystal dynamics and phonon energies, solvent-accessibility in macromolecules…

Static (Ground State) Electronic Structure Property Prediction (Hartree-Fock and post-HF Methods, Density Functional Theory). (Including the above non-electronic properties) energies of reactants and products in chemical reactions, energies of alternative/side products, rigorous electrostatic dipoles and multipoles, energies and intensities of vibrational transitions (IR, Raman, neutron), nonlinear optical coefficients, solvent dependences on molecular properties, ionization energies, electron affinities, occupied molecular orbital energies (and approximate unoccupied orbital energies), chemical reaction heats of formation, rigorous electron density and charge distributions (Mulliken, Löwdin, Hirshfeld, Bader, Weinhold, etc.), force constants/parameters for molecular force field calculations…

Dynamic (Excited State, Transition) Electronic Structure Property Prediction (Time-Dependent DFT, CC, CI, CASSCF, MCSCF). (Including the above properties) energies of transition state barriers, transport of electrons/holes, electronic transition energies and spectral predictions, oscillator strengths of electronic transitions, spin-spin interaction dynamics, geometries and relative energies of transition states, modeling of catalytic pathways…

4.5.3 Molecular vs. Solid-State Molecular Modeling

The defining characteristic of molecular-based modeling, as it applies to nanoscale modeling, is that the environment within which the calculation is being performed is finite. Molecular-based methods are

concerned primarily with the "system" and not the "surroundings," although some variants on molecular theory can address how a molecule/system might behave in a medium (such as through solvent modeling or the application of external electric/magnetic fields). In single molecules or discrete clusters of interacting molecules, molecular-based methods provide a wealth of information, including the relative binding energies of intermolecular interactions. When the surroundings (such as solvent) do not interact appreciably with the system, molecular-based methods can provide excellent agreement with experiment.

The isolated-molecule approximation breaks down when the system under study is bound within a periodic framework (such as a molecular crystal), as the system and surroundings are now one and the same. Solid-state theory, the application of periodic boundary conditions to include the surroundings within a calculation, is the "infinite" counterpart to molecular theory. Solid-state theory is the theory of materials, be it atomically-pure materials, mixed atomic lattices of insulating/conducting/semiconducting materials, amorphous solids, or molecular crystals. Solid-state theory provides means for studying the macroscopic properties of materials, such as those important to materials scientists and engineers.

Solid-state methods have only recently reached the level of detail and accuracy of molecular methods through the introduction of density functional theoretical implementations of solid-state code and the availability of computational resources capable of performing the calculations. Periodic boundary conditions can now be employed for the study of crystalline materials, amorphous materials modeled with periodic boundary conditions in order to artificially impose environmental constraints in a more physically realistic manner (as opposed to the solvent shell methods of molecular quantum theory), and idealized structures that exploit the spatial restrictions of the periodic boundary conditions (such as by fixing the separations of interacting structures bound along lattice planes).

4.5.4 The Multiple Levels of Modeling and Design

Theory-driven design at the nanoscale is subject to the strengths and limitations of the many methods available in computational chemistry for the study of matter. It is important to understand the limitations of each level of theory due to their approximations, as some of these limitations make the theories wholly inadequate for answering some questions. The strengths, limitations, and some of the likely future directions of many molecular modeling methods are summarized in Tables 4-1 through 4-5.

Table 4-1. Modeling, Design, and Characterization Using Empirical Methods

Capabilities	Limitations	Projected Advances	Typical Applications	Projected Applications
Subsection: Molecular Mechanics — >10^6 Atoms				
Energy minimization and optimization of ground state geometries	Most force field development and available parameters are biased to biology	The continued generalization of force fields to many types of chemical systems	Molecular structure rectification prior to quantum chemical studies	Rapid prototyping of structural motifs and mechanical processes at the nanoscale
Molecular surface generation for electrostatic maps, binding geometries	Final structures and relative energies of conformations are only as accurate as the force field being used	Computational developments, algorithm developments to push these methods into the mesoscale regime	Binding and steric interaction studies for supramolecular complexes, biological molecules	Provides the computationally feasible basis for atomistic mesoscale representations
Subsection: Molecular Dynamics — >10^6 Atoms				
Simulation of molecular motion and the sampling of conformational space	Dynamics simulations and conformational energies are only as accurate as the force field being used	Continued extension to larger and systems (beyond a complete virus)	Rapid prototyping of small molecule designs	Studies of thermal stability of non-covalent structures
Bases for explicit solvent models, periodic boundary conditions (crystals), amorphous solids, and molecular aggregates	Absence of libraries of parameters for non-biological systems means some systems cannot be studied or are treated using approximate parameters	Scaling methods and analyses to extend over various chemically relevant time scales (vibrations to protein folding); multiscale modeling integration	Thermal, vibrational, steric, and structural studies of molecules, intermolecular interactions and macromolecules	With QM/MM implementations, modeling of covalent bond assembly processes in macromolecular, nanoscale systems
Linear scaling of bonded interactions, quadratic scaling of non-bonding interactions	Inorganic clusters, solid-state species are insufficiently accounted for in most current implementations	Environmental dependence of transition state geometries with quantum mechanical integration	Simulation of molecular/ion transport mechanisms within macromolecules	Simulations of transport phenomena in nanofabrication processes
Structural accuracy achievable through parameterization of relevant terms (covalent and electrostatic)	Electronic structure properties (excited states, transition structure) cannot be accurately modeled due to lack of electron-dependent data	Enzymatic activity, bond formation/breaking, structural changes upon optical excitation with quantum mechanical integration	Ligand docking simulations, design strategies for computational drug design	Docking/interaction studies of self-assembling macromolecules, synthetic proteins
New force fields or modifications to existing force fields can be generated rapidly using experimental or theoretical methods	False minima prediction and the absence of structural/chemical knowledge bases can result in the generation of physically unrealistic minimum energy forms	The continued generalization of force fields to many types of chemical systems, periodic solids, etc.	Coarse grain, reduced model simulations that classically parameterize non-atomistic representations of atomic systems	Steric, electrostatic design basis for pseudo-real-time modeling and design of macromolecules, surfaces
Subsection: Reactive Potentials (REBO, AIREBO, BEBOP)				
Capable of modeling bond breaking, bond formation	No differentiation between spin multiplicities; no inclusion of electron-electron repulsion	Parameterization across a larger range of the Periodic Table, modes of atom binding	Surface interactions and atomic deposition, mechanosynthetic simulations	Extension to larger systems, solvent-solute or surface simulations of chemistry
Uses experimental parameters (such as ionization energies) as parameters	Extremely limited range of parameterized atoms, least element-complete MD-based method	Extension to larger unstable/metastable structures beyond quantum chemical feasibility	MD-based simulations of chemical (solution-phase) phenomena (bond breaking, formation)	Simulations of atomistic nanoscale mechanical processes, including tribological studies

Table 4-2. Modeling, Design, and Characterization Using Semi-Empirical Methods

Capabilities	Limitations	Projected Advances	Typical Applications	Projected Applications
Subsection: General Types — >1000 Atoms				
Semi-empirical methods are fast and far more computationally reasonable than ab initio calculations				
Subsection: CNDO, INDO, MNDO, MINDO/3, ZINDO, AMI, PM3, MNDO/d, OM1,OM2, PM5, RM1				
Computational cost of integral evaluation in *ab initio* methods is replaced by parameter-based evaluation, saving considerable computation time	The many limitations and known failures of semi-empirical methods are inherent to the approach. Their utility in chemical design is dependent on the properties being considered.	Application in solid-state chemistry for the property prediction of molecular and atomic solids (phonons and thermochemistry, nonlinear optical properties)	Most every commercial molecular modeling package includes semi-empirical methods because of their speed and molecular accuracy, making them broadly applied	Stepping-stone computational approaches to higher-level calculations, dry-run methodological studies in combined QM/MM studies
Non-nearest-neighbor interactions are neglected, yielding significant speed-ups in calculations of large systems (with many electrons)	As a parameterized approach based on sets of common molecules, molecules that deviate significantly from these sets (non-common organics, non-biological molecules, etc.) are subject to greater errors	Linear-scaling implementations (MOZYME) for initial quantum chemical optimizations and property prediction of macromolecules (proteins and beyond)	Rapid prototyping of molecules, transition states, excited state geometries, functional groups, and some classes of aggregate and intermolecular interactions	In the absence of MM/MD methods that have parameters for constituent atoms, semi-empirical methods become the route to energy minimization and structural studies
Lowest level of quantum chemical theory to provide chemically relevant information for molecules	Molecular properties that were not addressed in the parameterization process are not (or are poorly) accounted for (such as excited states)	Implementation of methods that consider transition metals for organometallic studies, inorganic solid studies	Prediction of electronic spectra (ZINDO), molecular vibrations, heats of formation, conformational energies	Application to quantum chemical studies of entire proteins and DNA structures (already possible)
More recent semi-empirical methods account for intermolecular interaction energies and geometries	Each semi-empirical level of theory is limited to regions of the Periodic Table (with transition metals neglected in many parameterization sets)	Implementation as the quantum mechanical component of QM/MM studies for rapid prototyping of nanoscale processes	Structure prediction and optimization (geometry beautification) prior to more computationally-demanding *ab initio* studies	Tool for solid-state crystal predictions, study of polymorphism in molecular solids, assembly processes at surfaces

Table 4-3. Modeling, Design, and Characterization Using *ab initio* (Hartree-Fock) Methods

Capabilities	Limitations	Projected Advances	Typical Applications	Projected Applications
Subsection: Hartree-Fock (RHF), Unrestricted HF (UHF), R-Open-Shell HF (ROHF), >100 Atoms				
Chemically logical interpretation of electronic structure calculations is possible via orbital-based methods	The lack of static electron correlation (beyond the Pauli exclusion principle) results in inaccurate predictions of spin states and energies	The use of HF theory as a tool for computational chemistry is dependent on algorithms and computational resources at large scales	Reasonable level of theory for survey-type computational studies of molecules and strongly interacting molecular clusters	First, most likely level of theory for first-principles quantum chemical calculations of nanoscale structures
Isodesmic energy calculations of chemical systems (direct comparisons of conformations, reactants, and products with identical basis sets)	The lack of dynamic electron correlation means dispersion energies are predicted to be too low, affecting the calculated strengths of intermolecular interactions	The key improvement to HF application in nanoscience is extension of the calculations with larger basis sets (Slater-type orbitals, all-electron sets for metals, effective core potentials for transition metals, etc.)	As no parameters are used and classes of basis sets do exist that account for most every element in the periodic table, property prediction is possible for nearly all molecules	Stepping-stone computational approaches to higher-level calculations, dry-run methodological studies in combined QM/MM studies
Reasonable scaling (N^3 possible. As implemented in many programs, N^4 scaling; N = number of basis functions) compared to post-HF methods.	When electronic states are close in energy at certain atomic geometries, the Born-Oppenheimer approximation breaks down, requiring the use of " non-adiabatic" (nuclear/electronic) wavefunctions	As the foundation for post-HF methods, any developments in non-DFT electron correlation methods will involve developments in HF (scaling of systems, parallelization of calculations)	The HF solution (wavefunction) is the formal basis for numerous electron correlation methods, variational methods	In the absence of MM/MD methods that have parameters for constituent atoms, HF methods become the route to energy minimization and structural studies
Most fundamental and theoretically sound quantum chemical treatment of molecules	Unoccupied orbital energies are not predicted well due to absence of electron correlation, making excited state and transition state calculations suspect	As the basis for hybrid HF-DFT methods ("B3LYP"), extension of these DFT approaches will follow from general improvements in HF algorithms	Rapid generation of molecular orbital descriptions for interpretive, predictive studies of chemical systems, organic chemistry reactions	In the absence of semi-empirical methods that have parameters for constituent atoms, HF methods become the fastest route to energy minimization and structural studies
The foundation for all post-HF quantum chemical methods	Chemical bond breaking and molecular dissociation are not accurately modeled	Advances in scaling and parallelization will enable HF application in macromolecule studies and, eventually, nanoscale studies	Common quantum chemical method for use in QM/MM studies of enzymatic activity, chemical assembly processes	Nanoscale simulations that do not involve changes in electron spin as part of structural changes

Table 4-4. Modeling, Design, and Characterization Using Density Functional Theory

Capabilities	Limitations	Projected Advances	Typical Applications	Projected Applications
Subsection: LAD (PWC, VWN)— >100 Atoms				
LDA - local density approximation, uses the density at points for evaluation of matrix elements				
Subsection: GGA (such as LYP, P86, B88, BP, BLYP, BOP, HCTH) — >100 Atoms				
GGA - generalized gradient approximation - uses both position and gradient of density at that position (corrects LDA over-binding)				
Subsection: Hybrid HF-DFT (such as B3LYP, B3P86) — >100 Atoms				
DFT electron correlation based on HF wavefunctions				
Static electron correlation is included in DFT calculations, recovering more of the real energy of molecules than HF methods	Static-only electron correlation means dispersion forces are not accounted for correctly, leading to the under-prediction of binding energies for weak complexes	The most important DFT limitation is the absence of dispersion forces. Numerous modeling efforts are directed at including these forces into calculations	Virtually all molecular properties are obtainable by DFT calculations, with accuracy limited by the absence of dispersion and the lack of classes of excited state density functionals	Better property prediction than HF methods for nanoscale simulations, far faster than post-HF methods for studies in the same size regime
Implementations for atom-centered (atomic basis sets) and planewave (periodic boundary condition) codes	Density functionals are derived empirically. Therefore, dozens of density functionals exist that all have strengths and weaknesses.	Dispersion force inclusion by way of the addition of empirical dispersion terms, inclusion within pseudopotentials, hybrid DFT/MPn methods	Solid-state property prediction, including geometries, phonon calculations, binding energies, general thermodynamics properties	Continued extension to the study of solid-state materials, including molecular crystals and amorphous solids
The most cost-effective (resource-based) electron correlation method available for a given level of accuracy	The molecular property in question determines the best choice of density functional at a given level of theory and choice of basis set	Linear scaling approaches to reduce the computational cost of macromolecular system and nanostructure studies	Implementations of time-dependent DFT for property prediction (electron transport through molecules, excited states, electron/molecule scattering)	Greater accuracy of deposition processes than HF methods, meaning the complete and accurate modeling of mechanosynthetic systems is possible
As commonly implemented, N^4 scaling achievable (N = number of basis functions)	Density functionals are developed for ground state systems. Excited-state DFT calculations are fundamentally suspect because of this.	Development of new density functionals for excited electronic state studies of molecules and nanostructures	Car-Parrinello molecular dynamics implmentations already allow for DFT-MD studies of solids, aggregates, conformational space sampling	With fully implemented time-dependent DFT, photophysical studies, dynamical studies, molecular electronics design and simulation becomes possible

Table 4-5. Modeling, Design, and Characterization Using Post Hartree-Fock Methods

Capabilities and Limitations, Method Summary	Scaling
Subsection: Moeller-Plesset Perturbation Theory (MP*n*)	
Inclusion of dynamic electron correlation means dispersion forces are accounted for in the optimization of weak intermolecular complexes and some intramolecular interactions	$n = 2$, M^5 $n = 3$, M^6
80% to 95% of the electron correlation of a system is recoverable depending on the order of the calculation (80% at n = 2; 95% at n = 4)	$n = 4$, M^7
Non-variational method, leading to greater basis set superposition error (BSSE) and reduced accuracy of intermolecular interaction energies, over-binding of some systems, over-stabilization of free radicals	
Subsection: Configuration Interaction (CI)	
Static and dynamic electron correlation method based on the expansion of a reference wavefunction into excited-state electronic configurations	
Complete CI calculations can achieve the exact solution to the non-relativistic Born-Oppenheimer approximation Schrodinger equation at considerable computational cost.	
Various levels of CI can be implemented in a calculation, including: CI with single electron configurations (CIS, excellent basis for electronic spectra prediction) CI with single and double electron configurations (CISD) Quadratic CI, all single and double configurations and perturbative inclusion of triple excitations (QCISD(T)) Multi-Reference CI (MRCI) CI with single, double, triplet, quartet configurations (CISDQT)	 M^5 M^6 M^7 M^8 M^{10}
Subsection: CBS/Extrapolation Methods	
Complete basis set/extrapolation methods are excellent for the accurate calculation of reaction barriers, depositions	M^7
Subsection: G2, G3	
Used to calculate thermodynamic quantities such as enthalpies of formation, atomization energies, ionization energies, and electron affinities	M^7
Subsection: Multi-Configuration Self-Consistent Field (MCSCF)	
Full CI and orbital optimizations, used for bond breaking, forming, ground-excited state calculations,	M^7
Recovers much of the static correlation energy (dynamic correlation energy obtained from CI)	
The choice of the active space to include in the calculation is not always obvious (not a black box approach, you still have to know some quantum theory)	
Subsection: Complete Active Space Self-Consistent Field (CASSCF)	
Excellent reference calculations for recovering dynamical correlation energy	M^7
The “active space” of the calculation is defined by the user, requiring testing or considerable understanding of the system and method	
Subsection: Coupled Cluster (CC)	
Possible to achieve the exact solution to the Schrodinger equation for a given basis set at high enough levels	
CC including double excitations only (CCD) CC including single and double excitations (CCSD) CC including single and double excitations with triple excitations treated approximately (CCSD(T)) CC including single, double, and triple excitations (CCSDT)	M^5 M^6 M^7 M^8
Subsection: Generalized Valence Bond (GVB)	
A limited form of MCSCF, multi-reference method	
GVB-Perfect Pairs (GVB-PP) GVB-Restricted Configuration Interaction (GVB-RCI)	
Subsection: Quantum Monte Carlo (QMC)	
Evaluation of integrals with correlated basis functions numerically using Monte Carlo methods	Indet.
Scaling values are approximate, highly method-dependent, and provided as the information is available. Provided values are only for estimation purposes; M = number of electrons	

4.6 Instrumentation and Characterization

Instrumentation and characterization techniques are being driven forward by scientific research requirements, and their applications in developing AP nanosystems chiefly add to this existing demand. This section offers a few remarks regarding the relationship between this area and the requirements for AP nanosystem development. The take-away message is that existing techniques are broadly adequate, but that improvements in some areas could be of great value.

Characterization of structure and functional properties is critical to developing components and systems on any scale, including the nanoscale. Individual high-spatial-resolution methods typically provide a subset of the total structural information desired, and artifacts and ambiguities are a pervasive vulnerability, commonly addressed by applying multiple methods to a single problem. Improvements in breadth, robustness, and precision of characterization tools are important because they can speed acquisition and improve the quality of information about products. This, in turn, can improve models and enable faster cycles of design and testing in the development process. For example, characterization is often the bottleneck in design cycles for both DNA and protein engineering. Some of these challenges could be addressed by improvements in the capabilities and the availability of cryoelectron tomography instruments.

4.6.1 Atomic-Scale Characterization

Methods that provide lower-resolution information about the nature and distribution of properties in a collection of nanoscale objects sometimes provide the necessary answers for a design process. For example, in structural DNA nanotechnology, overall geometry at or near the helix level often suffices to indicate success or failure in making a structure, and most of the atomic-scale detail is then implied by general knowledge of DNA structures.

Nontheless, atomic-scale characterization is of obvious importance to atomic-scale technologies, and a wide range of methods exist. Table 4-6 provides an overview of techniques and instruments.

Complete characterization of atomic scale properties is not on the critical path to development of, or utilization of, productive nanosystems. Rather, targeted characterization of desired aggregate properties on the device- and component-levels are needed.

Table 4-6. Characterization Methods, Sample Requirements, and Information Obtained

Method	Sample Requirements	Information Gained	Comments and Caveats
Scanning Electron Microscopy (SEM)	Placement/deposition on substrate; high vacuum compatible method	Particle size, morphology, component segregation	Must be conductive or coated (e.g., with Gold); Sample must be stable in the electron beam
Environmental SEM	Placement/deposition on substrate; high vacuum compatible method	Particle size, composition, hygroscopicity	Lower resolution in wet mode; Same general issues as SEM
Focused Ion Beam SEM	Typically up to 1" thick, up to 8" diameter	Topography, 3-D composition, crystallography	Excellent for TEM sample preparation as well
Transmission Electron Microscopy/High Resolution TEM	Placement/deposition on substrate; high vacuum compatible method < ~150 nm thick	Phase and structure, composition, chemical state in some cases	Excellent spatial resolution; Sample must be stable in the electron beam
Cryo-Electron Tomography	< ~100 nm thick	3-D structure (tomography)	Can be chemically specific (for example, a gold nanoparticle label)
X-ray Diffraction, Powder X-Ray Diffraction	On substrate (film ~20nm), as a powder (~0.1g), or as single crystals	Crystalline phase, average crystallite size, amorphous content, crystal lattice constants (space group), molecular geometry	-193 to +1000 °C temperature range; Inert atmosphere or rough vacuum sample environment
3-D Atom Probe	Conductive, needle shaped UHV compatible	3-D reconstruction of sample including minor elements to 0.1 atom %	Very high resolution; Sample preparation is often challenging
Scanning Helium Ion Microscopy	Vacuum compatible method	Topography, chemical contrast	Early stage commercialization
Secondary Ion Mass Spectrometer (NanoSIMS)	Flat, <9mm thick UHV compatible	Atomic/isotopic distribution	Usually coat sample with gold; ~50 nm resolution
Scanning Probe Microscopy[1]	Placement/deposition on substrate; Requires a fairly flat sample	Topography, nanoparticle size, shape, electrostatic, magnetic and mechanical properties	Excellent spatial resolution; low sample numbers; slow scan speeds; air, liquid or vacuum environment
Auger Electron Spectroscopy/Scanning Auger Microscopy	Placement/deposition on substrate; high vacuum compatible method	Size, shape, surface composition, 3-D composition	Conductive sample ~20 nm resolution
X-ray Photoelectron Spectroscopy	Placement/deposition on substrate; high vacuum compatible method	Average surface composition, chemical state	Modeling of complex systems improves understanding
Time of Flight Secondary Ion Mass Spectrometry	Placement/deposition on substrate; high vacuum compatible method	Average surface composition, molecular state	Molecular information; good at measuring trace contaminants ~100 nm resolution
Small Angle X-ray and Neutron Scattering	Particles in liquid	Local chemical environment, geometry and size of nanoparticles, clustering of nanoparticles	Requires synchrotron sources
X-ray Absorption Fine Structure	Particles in liquid	Oxidation state, solvation structure	Requires synchrotron sources
Proton Induced X-ray Emission	Placement/deposition on substrate; high vacuum compatible method	Elemental composition	Sample must be stable in the particle beam

Table 4-6. Characterization Methods, Sample Requirements, and Information Obtained (Continued)

Method	Sample Requirements	Information Gained	Comments and Caveats
Terahertz (THz) Spectroscopy	Solid-state, in liquid, ambient conditions	Low-frequency vibrational modes, inter- and intramolecular interactions	Many solvents are good THz absorbers (limits utility); resolution currently limits use
Raman Spectroscopy	Airborne, in solution, as solid-state samples, or deposited/mounted on substrate	Energies of vibrational modes, molecular conformation, inter- and intramolecular interactions	Low signal/noise; optical selection rules make for partial determination of molecular vibrations
Fluorescence Resonant Energy Transfer	Ambient, in liquid	Intermolecular distance	Fluorescent tag required
Fluorescence Return After Photobleaching	Ambient, in liquid	Diffusion, clustering using fluorescent probes or auto-fluorescent species	Used in biological systems
Fourier Transform Infrared Spectroscopy	Airborne, in solution, as solid-state samples, or deposited/mounted on substrate	Energies of vibrational modes, molecular conformation, inter- and intramolecular interactions	Low signal/noise; optical selection rules make for partial determination of molecular vibrations
Ultraviolet-Visible Spectroscopy	Airborne, in solution, as solid-state samples, or deposited/mounted on substrate	Electron transition states, survey of potential photochemistry, optical properties	Important characterization tool for molecular electronics applications
Coherent and incoherent inelastic neutron scattering spectroscopy (CINS, IINS)	Solid-state and powder samples	Normal modes of vibration, phonon (intermolecular) modes, molecular geometry via selective deuteration (IINS)	Absence of optical selection rules means all vibrations are observed; resolution limits at higher energies (>1000 cm^{-1})
Nuclear Magnetic Resonance (NMR)	Molecules, macromolecules in solution; selective for many isotopes (such as ^{1}H, ^{10}B, ^{11}B, ^{13}C, ^{14}N, ^{15}N, ^{17}O, ^{19}F, ^{23}Na, ^{29}Si, ^{31}P, ^{35}Cl, ^{195}Pt)	Inter- and intra-molecular structure, atomic connectivity, geometry of secondary structure, monitoring progress of chemical reactions	Experiments can take hours to days for high quality spectra; Two-dimensional methods available (COSY, EXSY, HSQC, HMQC, HMBC, NOESY, TOCSY, J-spectroscopy)
Solid State NMR	Solid-state samples; selective for many isotopes	Molecular structure, local chemical and magnetic environment	Disordered solids, interfaces can be analyzed; *operando* monitoring is a possibility
Dynamic Laser Light Scattering[2]	Particles in liquid	Size distribution down to 5 nm	Light must not be absorbed by liquid; Typically very low ionic strength liquid
Phase Analysis Light Scattering	Particles in liquid	Charge state of particle	Large ionic strength dynamic range
Disc Centrifuge Photosedimentation	Particles in liquid	Size distribution down to 3 nm	Broad range of particle size determination in complex mixtures

[1] Atomic Force Microscopy, Non-Contact AFM, Scanning Tunneling Microscopy, many derivatives.
[2] Also Photon Correlation Spectroscopy

4.6.2 Operando Characterization

Many nanoscale characterization methods cannot probe samples in native-like or desired operating-like (operando) environments. Expanding the capability to analyze nanoscale materials under such realistic conditions in real-time is a critical need. Further, many studies have demonstrated that the physical and chemical characteristics of

nanoscale materials may change over time and under varying environments. Providing the capability to image or measure these changes in real time under realistic environments would speed the rate at which new information regarding, for example, the chemical and physical structure of catalytic active sites could be determined. Observation of interactions between nanosystems and living cells presents challenge of a similar kind.

Operando nanomaterial characterization needs include monitoring the following: *in situ* particle size and shape, *in situ* composition or function (including charge; surface energy; functionalization, magnetic, electrical, or optical properties, etc.); surface chemistry at the nanoscale including fractional coverage and thickness of coatings on nanoparticles, and quality of particle dispersion in a solid phase.

4.6.3 Quality Control

Access to existing tools is on the critical path. Current characterization tools provide a broad spectrum of capabilities (ranging in resolution from the unnecessarily high to the somewhat low.

There is a need to develop deployable process-monitoring tools that can be used to ensure nanomaterials and nanoproduct consistency on a manufacturing scale. Such instruments would include real time, on-line characterization tools and rapid quality control (QC) tests for samples. Real-time, in-line measurement techniques are needed to provide reproducible control of properties such as particle size and distribution. Improved analytical tools and process control will go a long way to achieving zero defects in final materials, reducing waste, and turning nanomaterials manufacturing into a commodity.

4.6.4 Access to Tools and Multidisciplinary Effort

The need to apply multiple analysis methods stretches the ability of many researchers and students and should encourage collaboration and the use of centralized user facilities. Examples in the US include the DOE Nanotechnology User Facilities and the DOE Environmental Molecular Sciences Laboratory.

The R&D effort as a whole must closely interweave developments in fundamental understanding of nanoscale properties, new materials synthesis methodologies, new manufacturing techniques, new characterization and control techniques, and new modeling tools. Progress in nanosystems development requires iterative cycles of design, modeling, fabrication, and characterization. All these steps are necessary, and each step and field of application presents a rich and diverse set of multi-disciplinary challenges.