

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.

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.

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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.

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

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, Polymerase 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 $>100^{\circ}\text{C}$, 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

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.

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

- 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.

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.

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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-assembly of information-rich,

a-periodic 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.

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.

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.

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

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.

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

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.

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.

APT developments demand innovations in computer-aided design.

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 purposes, 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

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.

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

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.

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.

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.

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 single 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.

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

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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 cm², 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 Reboledo, 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.

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.)

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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.

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

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.

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, $>1900 \text{ nm/s}$
- 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, $20 \mu\text{W}$, 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.

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.

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

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.)

Nanowires and nanotubes carry charge and excitons efficiently, and are therefore potentially ideal building blocks for nanoscale electronics and optoelectronics.

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 genome 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. Nanobiotechnology 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 \sim 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 (\sim 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 from 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.)

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

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.

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.

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.

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 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.

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 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.

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.

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-

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.

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 nan positioning 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 nan positioning fabrication systems.
- A global alignment and nan positioning 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.

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 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, 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

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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 moieties 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.

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.

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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 Initiative¹ 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.

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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 funding² 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 be 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 Office³ should coordinate both the governmental and university aspects of a national

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/ncco.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 Network⁴. 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.

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.

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

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.

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.

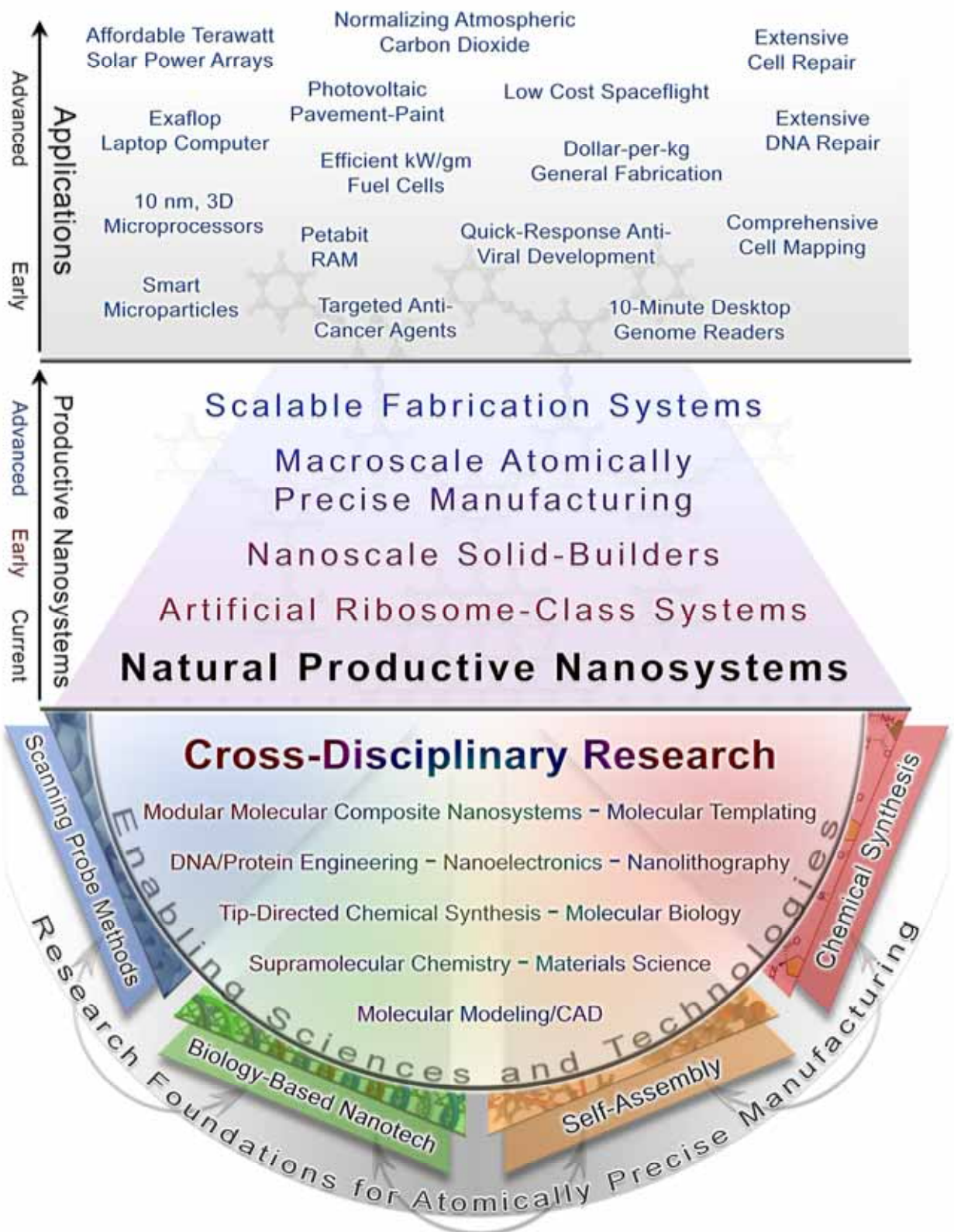
Strategy Two: Atomically Precise Nanomedicine Technologies to Improve Human Health should become a major focus of the National Institutes of Health. The NIH already has efforts in nanotechnology, but the power of APM would revolutionize our ability to analyze, synthesize, and ultimately commercialize 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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