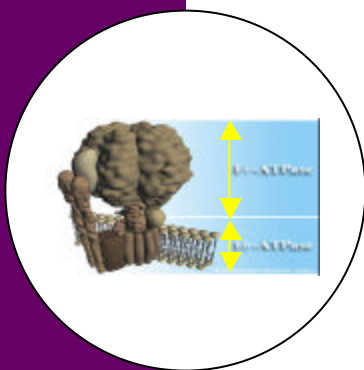


Probing Nanotechnology



A Report prepared for the Department of Natural Resources and Environment
State Government of Victoria

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This report is a review of recent work on nanotechnology reported in the publicly available scientific literature. It was prepared by staff of the Centre for Molecular Simulation (CMS), Swinburne University of Technology. The review was commissioned by the Department of Natural Resources and Environment of the State Government of Victoria.

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The picture on the cover page shows a representation of ATP-synthase which is an example of a real molecular motor capable of rotary motion.

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Executive Summary

Nanotechnology explores materials, devices and systems with feature sizes in the range of about 1 nanometer (nm) to 100 nanometers. A nanometer is one billionth of a meter (10^{-9} m) and is at the confluence of the smallest of human-made devices and the large molecules of living systems. All science, engineering and technology, focusing on nano-sized structures, components and devices and nanoscale properties, phenomena and processes etc., are in the scope of nanotechnology.

We define nanotechnology as: *The science and engineering involved directly in manipulating atoms and molecules to develop artificial molecular devices, or to harness the potential of existing biological devices with these entities, on the nanometer length scale.* This definition of nanotechnology implies a ‘bottom-up’ approach to the construction of molecular entities. ‘Bottom-up’ manufacturing, or molecular nanotechnology, applies to building organic and inorganic entities atom-by-atom and molecule-by-molecule, where the entity is held together and self-assembled controllably. Nanotechnology offers the promise of contraction from the ‘bottom-up’ by the capability of direct manipulation of atoms and molecules to create molecular machines. This strict ‘bottom-up’ definition of nanotechnology excludes some well-known ‘top-down’ approaches such as nanolithography and biosensors. We regard these as precursor technologies and they are briefly reviewed in an appendix to this report.

We have identified four core areas of nanotechnology: static, dynamic, nanoscale computing and nanobiotechnology. Most contributions to date can be considered as ‘static’ entities. Examples of static contributions are fullerenes and nanotubes, quantum dots, nanoparticles and single biomolecules that can potentially be used as the building blocks of future nanodevices and nanosystems. Such entities are static because they lack a purpose-built mechanism for motion or control. Other static contributions include the enabling nanotechnologies – the tools and methods to allow scientists to probe and manipulate individual atoms/molecules, such as scanning tunnelling microscopy, atomic force microscopy and optical tweezers. Many current advances in biotechnology, such as molecular modification and single biomolecular dynamics, can also be viewed as static contributions to nanotechnology. It is in the static area that progress has been the greatest.

In contrast, we can also identify progress in ‘dynamic’ nanotechnology. Dynamic devices are the ultimate goal of nanotechnology, namely the creation of artificial nanoscale devices capable of controlled and purposeful motion and actions. Perhaps the major examples of dynamic entities are molecular motors. Currently, work on molecular motors is focused mainly on understanding and adapting biological molecules and its assemblies.

Bridging both static and dynamic entities is work on nano-computers, which is required for the control of future nanodevices, and computational nanotechnology that is required for the design of nanosystems. Molecular computing (which uses single-molecule switches to process data) and quantum computing (which uses single electrons via quantum entanglement) are the two major forces in nano computing technology.

We regard nanotechnology and biotechnology as complimentary fields of endeavour. The distinction between the two is that nanotechnology implies the artificial manipulation of new entities whereas biotechnology involves utilizing existing biological entities. The boundary between nanotechnology and biotechnology is crossed when ‘nanobiotechnology’ involves arbitrarily changing a biological entity at the molecular level. When this occurs, say via genomic manipulation and protein engineering, or even combining biomolecular and solid state electronic components, the new science of nanobiotechnology emerges. Nanobiotechnology will enable us to recognize and control biomolecules that govern normal as well as abnormal cell activity, to implant intracellular sensing systems, to target DNA/proteins and to develop biomimic devices/systems, etc. One promising example of nanobiotechnology is the transformation of drug development into a precise molecular science capable of targeting specific genes.

It is very difficult to identify concrete examples of work on nanotechnology that is directly relevant to agriculture. Currently, the most promising molecular-based approach to improving agriculture is more appropriately classified in terms of biotechnology rather than nanotechnology per se. For example, molecular scale gene/genomics and proteomics have considerable scope in agriculture for improving control of food production and food processing. Carbon-based nanofibers offer the potential to result in lighter, stronger and longer lasting textiles. The production of agricultural chemicals is also likely to benefit from nano-aided synthesis and processing using nano-particles as a catalyst.

The main challenge in nanotechnology is to make progress in the dynamic areas (such as self-assemblers, molecular motors) and nano-computing. To meet this challenge, researchers are exploring controllable/programmable ‘self-assembly’ – molecular entities that automatically arrange themselves into the desired pattern or device. Nature provides ample examples of such dynamic entities in each living cell, e.g., DNA has been a good example of a self-assembling machine: a single molecule that, under the right conditions, creates not only replicas of itself, but remarkably complex organisms. Therefore, nanotechnology is likely to benefit greatly from the insights obtain from biotechnology. In the short term at least, progress in dynamic areas of nanotechnology is likely to come from nanobiotechnology applications. Such nanobiotechnology may include gene delivery and therapy, single biomolecular manipulation, molecular motors and quantum biology, etc.

Progress in nanotechnology is likely to result in revolutionary advances in materials, pharmaceuticals and information technology. For example, the discovery of fullerenes has led to carbon nanotubes, conducting fullerenes and assembled basic electronic components (including transistors). The discovery of the structure and behaviour of the ATP synthase molecule is leading to exceptional progress in understanding molecular motors.

Australia and Victoria in particular, has a considerable concentration of research expertise in areas such as genetics and proteomics, nanotube and nanoparticles, and molecular simulation. Possible areas for future growth and investment are:

- molecular medicine and genomics/proteomics
- nanobiotechnology – e.g., hybrid nanoparticles, smart drug delivery and molecular motors
- computational nanotechnology – e.g., molecular design, modelling and simulation.

SECTION 1 DEFINITION OF NANOTECHNOLOGY

We define nanotechnology as: *The science and engineering involved directly in manipulating atoms and molecules to develop artificial molecular devices or to harness the potential of existing biological devices with these entities on the nanometer (one-billionth of a metre) length scale.*

At the outset it should be noted that our definition of nanotechnology implies a “bottom-up” approach to the construction of molecular entities. This is in contrast to the “top-down” approach used in conventional science and engineering. The recent popularity of the term “nanotechnology” has seen it applied to conventional technologies that violate our definition. For example, work on lithography, microtechnology, advanced silicon chip production, biosensors, and surface coatings etc are increasingly being referred to as part of nanotechnology. This is misleading in two important respects. Firstly, despite the advances in miniaturization that such technologies bring they do not directly involve atomic scale manipulation. Secondly, despite their apparent sophistication, they in effect represent improvements to the conventional “top-down” engineering approach. We regard these top-down miniaturization technologies as precursor technologies. A great deal of progress has been made in precursor technologies, which may in part explain why they are often included under the label of nanotechnology. However, although the insights gained from precursor technologies may be useful, to include them in a discussion of nanotechnology would give a false measure of progress of the field. Some useful precursor technologies are described in Appendix A.

It should also be noted that nanotechnology and biotechnology are complimentary fields of endeavour. The distinction between the two is that nanotechnology implies the artificial manipulation of new entities whereas biotechnology involves utilizing existing biological entities. The boundary between nanotechnology and biotechnology is crossed when biotechnology involves arbitrarily changing a biological entity. When this occurs, say via gene manipulation, the term bionanotechnology is appropriate. Bionanotechnology satisfies our definition of nanotechnology because it involves atomic scale manipulation.

In general, we can identify two broad contributions to nanotechnology. Most contributions can be considered as “static” entities. Examples of static contributions are nanoparticles such as fullerenes and nanotubes that can potentially be used as the building blocks of future nanostructures. Such entities are static because they lack a purpose-built mechanism for motion or control. Many current advances in biotechnology can also be viewed as static contributions to nanotechnology. It is in the static area that progress has been the greatest. In contrast, we can also identify progress in “dynamic” nanotechnology. The major example of dynamic entities is the generation of molecular motors. Currently, work on molecular motors is focused mainly on understanding and adapting biological systems. Dynamic devices are the ultimate goal of nanotechnology, namely the creation of artificial nanoscale devices capable of controlled and purposeful motion and actions. Bridging the static and dynamic entities is work on quantum computing, which is required for the control of future nanodevices, and computational nanotechnology required for the design of nanosystems.

SECTION 2 PROGRESS IN STATIC NANOTECHNOLOGY

Developments in static nanotechnology include fullerenes and nanotubes, quantum dots, nanoparticles and single biomolecules, etc., that can potentially be used as the building blocks of future nanodevices and nanosystems. Such entities are 'static' because they lack a purpose-built mechanism for motion or control. Sophisticated tools such as scanning tunnelling microscopy, atomic force microscopy and optical tweezers are increasingly aiding progress in static nanotechnology, allowing researchers to probe and manipulate individual atoms and molecules.

2.1 Materials and Components

Here we discuss progress in creating molecular components that are likely to form the structural components of purpose built nano-devices. The ultimate goal of much of this work is to fabricate mechanical components such as molecular gears (Figure 1).

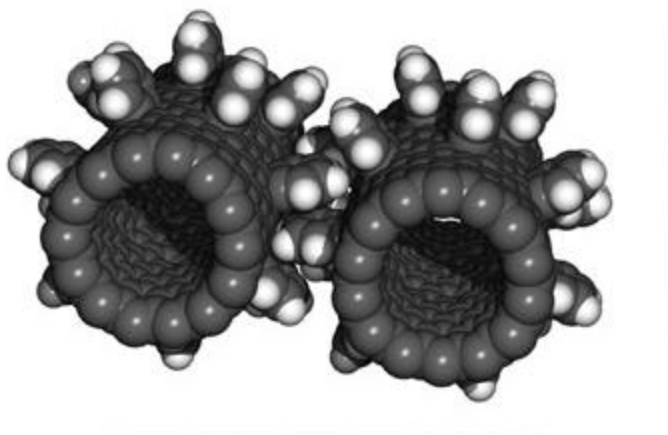


Figure 1. Carbon nanotube based molecular gears (from NASA, USA).

2.1.1 Carbon Nanotubes and Fullerenes

Fullerenes (Carbon-60) and Doped Fullerenes

Based on the knowledge that carbon has the potential to cluster in the gas phase at high temperatures, methods have been developed [Kroto et al., 1985; Smalley, 1990] to study various conformational structures of carbon by laser-vaporization of graphite. The result is that carbon atoms can be arranged to form truncated icosahedral structures, and larger geodesic cages known as fullerenes (or C_{60} , nicknamed "buckyballs"). The structure for C_{60} is an icosahedron formed by truncating each of the twelve rings of pentagons. Carbon atoms can be spontaneously bonded and assembled into fullerenes with a diameter in the range of 1 ~ 30 nm [Smalley, 1997; Dresselhaus, 1996].

The range of fullerenes has expanded considerably since this initial discovery. In addition to the icosahedron-type fullerene, many other hollow cage structures can be constructed using only pentagons and hexagons. The smallest possible fullerene would be C_{20} , containing twelve pentagons

and no hexagons, but would possess a great deal of strain, as the local structure at each carbon center would be highly non-planar. Other possible fullerenes include C_{28} , C_{32} , C_{50} , and C_{70} . Because the molecular strain tends to be concentrated in the five-member rings that are responsible for closure, structures avoiding contiguous (edge-sharing) pentagons possess greatest stability. In effect, C_{60} and C_{70} are the smallest stable carbon cages for which this can be achieved. [Curl and Smalley, 1988; Dresselhaus, 1996 and Yakobson and Smalley, 1997].

Regardless of whether fullerenes are closed or open, they can form C-O, C-N, and C-C covalent bonds that may hold and attach nearly any molecule, enzyme, membrane, or surface to the inside of the cage or the end of the tube. It is likely that in the near future a large new set of carbon or metallic fullerene-based molecules will be created in the laboratory. C_{60} and C_{70} (in toluene solution) were available commercially since early 1990.

The unique bonding ability and band structures of fullerenes make them very promising candidates for semi-conductors. Furthermore, the hollow within the cage can also encapsulate a doping atom or molecule. Therefore enormous efforts to fabricate and develop carbon fullerene-based conducting materials and inhibitor devices have been undertaken since their discovery. For example, to date, doped C_{60} superconductors have been discovered [Schon et al., 2001a; Kociak, 2001] and C_{60} inhibitors are being tested as a drug capsule.

C_{60} is widely regarded in the nanotechnology community as the first man-made nano-material or potential functioning device. It has been the catalyst for the discovery of other nano-materials and devices. The carbon nanotube is a very immediate addition, but other notable examples include nanotube single crystal growth, nanotube fibers, molecular science of nanotubes and fullerenes, advanced nanotechnology materials and applications of nanofullerenes and nanotubes in various fields [Yakobson et al., 1997].

Nanotubes and Nanotube "Ropes"

Carbon nanotubes, first discovered in 1991 [Iijima, 1991], consist of carbon-based cylinders closed at either end with caps containing pentagonal rings. During arc-evaporation synthesis of fullerenes, Iijima found that the central core of the cathodic deposit contained a variety of closed graphitic structures including nanoparticles and nanotubes. Ebbesen et al. (1992) showed how nanotubes could be produced in bulk quantities by varying the arc-evaporation conditions, which in turn led to increased research into the properties of carbon nanotubes.

A major contribution to carbon nanotube research was the synthesis of single-layer nanotubes [Iijima et al., 1993; Bethune et al., 1993]. Standard arc-evaporation methods produce only multilayered tubes [Iijima, 1991], but addition of metals such as cobalt to the graphite electrodes result in very fine tubes with single-layer walls [Iijima, 1993]. Alternatively, Thess et al. (1996) devised a method of preparing single-walled nanotubes, which, akin to the original method of preparing C_{60} , involved laser-vaporisation of graphite. Their method yielded high numbers of single-walled nanotubes with surprisingly regular diameters. These had a greater tendency to form aligned packets than those prepared using arc-evaporation, and were consequently termed nanotube "ropes" [Thess et al., 1996]. Early experiments indicated that these rope samples contained a very high proportion of nanotubes with a specific "armchair" structure. Later work [Thess et al., 1996] suggested the rope samples were less homogeneous than originally thought.

Nanotubes are so far the best block unit for nanodevices. Nanotube single crystal growth leads to nanotube fibers, and can shape the molecular science of nanotubes and fullerenes, advanced nanotechnology materials and applications of nanofullerenes and nanotubes in various fields [Harris, 1999].

Some further examples of recent work in this field include the smallest carbon nanotube [Qin et al., 2001; Wang et al., 2001], fullerene pipes [Liu et al., 1998] and hydrogen storage in single-walled carbon nanotubes [Liu et al., 1999]. By doping with metal atoms, Kociak et al. observed superconductivity in nanotube ropes [Kociak et al., 2001]. Work at IBM (see: www.almaden.ibm.com/vis/stm) used single nanotubes (with diameters of .9-2.8 nm) as extensions on the ends of atomic force microscope probes, which narrows the probe profile and produces greater spatial resolution when imaging a variety of biomolecules. When used to seek out specific molecules on a sample surface, the nanotube probe could help in studying tip-sample adhesion. Smith et al. (1998) observed enormous pressures that arise when C60 molecules are trapped inside nanotubes.

2.1.2 Nanoparticles and Dendrimers

Nanoparticles

The goal of static nanotechnology is to build tailor-made nanomaterials with a high degree of structural and compositional complexity. Colloidal nanoparticles represent potential building blocks from which to create ordered and complex nanomaterials and devices.

Much effort has been expended over the last decade to fabricate core-shell colloidal nanomaterials [Caruso, 2001]. A core-shell particle is a nano-metal particle coated with polymer shells. Core-shell particles often exhibit improved physical and chemical properties over their single-component counterparts. They are of interest in the electronics, chemical engineering, pharmaceutical and biological industries because of their unique properties. Physical and chemical functions may be readily imparted to the dispersed colloidal matter depending on the properties of the coating. Encasing colloids in a shell of different composition may also protect the core from undesirable chemical and physical changes [Boal et al., 2000].

There has been considerable progress in the synthesis of various colloidal nanoparticles, such as iron nanoparticles [Sasaki et al., 2001], platinum nanoparticles [Ahmadi et al., 1996; Joo et al., 2001], gold nanoelectrodes [Elghanian et al., 1997; Chen et al. 1998], and oxide nanoparticles [Chhowalla and Amaratunga, 2000; Poizot et al., 2000], to list a few.

A number of polymerization-based methods have been employed to produce particles that consist of solid cores within a shell of polymeric materials. These include monomer adsorption onto particles followed by subsequent polymerization [Thompson et al., 2001], heterocoagulation-polymerization and emulsion polymerization such as the nanoengineering of inorganic and hybrid hollow spheres by colloidal templating [Thompson et al., 2001; Caruso et al. 1998; and for a review, see Caruso, 2001].

Recent progress made in the engineering of nanoparticles involves assembly of nanoparticles into structured spherical and network aggregates [Boal et al., 2000; Abrahamson and Dinniss, 2000]. A DNA-based method for assembling nanoparticles into macroscopic materials has also been devised [Mirkin, 1996]. Hermanson et al. (2001) fabricated a dielectrophoretic assembly of electrically functional microwires from nanoparticle suspensions, thus demonstrating how one may engineer

nanoparticles into a functional entity.

Despite the solid work done to date, bottom-up research into the fabrication of nanoparticles and the approaches for constructing composite-colloidal entities are still in their infancy. As described above, earlier approaches focused on achieving single-component coatings on particles through surface chemical modification or conventional polymerization and precipitation reactions. More recent approaches have been based on solution self-assembly [Boal et al., 2000; Hermanson et al., 2001]. This method shows promise to be highly effective in producing multicomposite, nanostructured coatings with good control over material uniformity. This in turn ensures that the assembled components and experimental conditions can be readily reproduced and manipulated. It is likely that future research will continue to be focused on optimizing existing approaches, as well as developing new techniques to create functional, multicomposite nanoparticles and nanodevices [Caruso, 2001].

Dendrimers: Self assembly of One, Two and Three Dimensional Supramolecular Structures

Dendrimers are a new class of highly branched polymers consisting of short chain units with multifunctional groups at both ends. Starting from an initiator core, the successive reaction of the functional groups with other units generates a highly branched chain molecule, which resembles a Cayley tree. The self-assembling properties of some dendrimers also have potential implications for the fabrication of nanostructures.

Dendrimer molecules are characterised by the number of generations they contain (g), the functionality of the end groups (b), and the number of monomer segments or separator length (n) between the functional groups. Figure 2 illustrates the generational change of a dendrimer with trifunctional end groups. The number of monomers (N) in a dendrimer grows rapidly with each successive generation obeying the relationship, $N = nb[(b - 1)^{g+1} - 1]$.

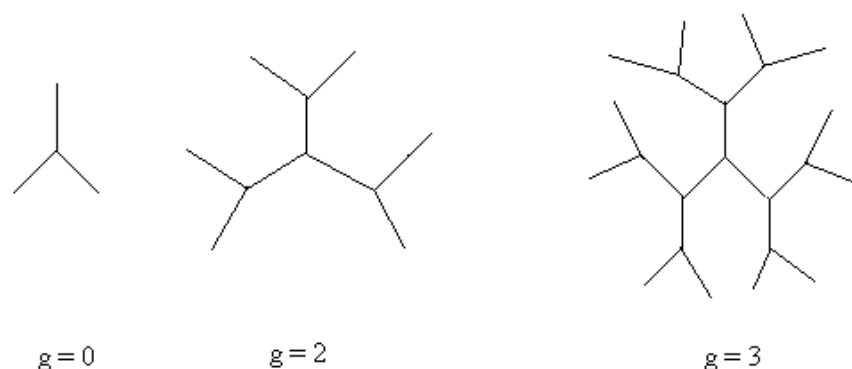


Figure 2. Schematic illustration of dendrimer connectivity with different generation number.

Dendrimers are a good example of a naturally occurring nanoparticle having a self-assembled supramolecular structure. Dendrimers represent the potential of another useful building block for nanocomponents and nanodevices. Dendrimers promise a molecular level control of size, shape, surface chemistry, topology, and flexibility of purpose-built nano-engineered materials and devices [Tomalia et al., 1990; Lang, 2001].

In general, dendrimers are monodisperse molecules (self-assembled dendrimers have typical effective diameters of 8-12 nm) that possess a regular and highly branched three-dimensional architecture. This three-dimensional fractal geometry ensures that their properties differ significantly from those of linear polymers. Apart from molecular dendrimers, other examples of dendritic structures include nerve cells, neural networks, the geometry of trees and certain grasses, and bolts of lightning. Based on these examples, dendritic macromolecules of defined size, shape, and topology can be created by classical organic and organometallic synthetic methods [Newkome et al., 1996].

Siloxane and carbosiloxane dendrimers, as well as dendrimers that contain siloxane and carbosiloxane sub-units, are the most developed synthetically generated dendrimers, since the formation of Si=O bonds can be easily generated [Lang et al., 2001]. The aim is ultimately to be able to use these systems as templates for self-assembled supramolecular structures, e.g., pseudorotaxanes and rotaxanes. They may also serve as waste stream scavengers bound to surfaces [Lang et al., 2001]. The objectives of this work are to design, synthesize and study the self-assembly of small building blocks into supramolecular pseudorotaxane complexes of controlled sizes (up to several thousand nm), shapes (linear, branched and dendritic) and functionalities, initially in solution but then in the solid state, so that these structures can be designed to meet specific requirements for nanotechnology [Tahir et al., 2000].

Dendrimers have been in the research and development stage for about a decade. Self-assembling dendritic macromolecules, either siloxane- or carbosiloxane-based, possess reactive and potentially useful organic, inorganic, or even organometallic building blocks as terminal units. They have therefore only recently attracted much more attention for promising usage in nanotechnology-based applications [Lang et al, 2001].

2.1.3 Nanofibers

A process has been recently developed [Vigolo et al., 2000] for producing macroscopic carbon nanotube fibers and strips. There are many potential applications of this technology, such as: nanotube fiber textiles, artificial muscles, supercondensators for electric vehicles, electron emitters for flat panel screens, etc.

The Argonide Nanotechnology Group [www.argonide.com] introduced the first of a new family of alumina nanofibers with a diameter of 2 nanometers and a remarkably high surface area: 500-600 m²/g. These fibers have an aspect ratio ranging from 20 to 100 (they are smaller than the size of a DNA molecule). It is generally recognized that smaller diameter fibers are more effective in strengthening metals, ceramics or plastics. It offers the potential for substantial increases in composite strength over previously available discontinuous fibers.

Lu et al. (1997) and Brinker et al. (1999) created self-assembling fibers of silica nanospheres by drying liquid droplets blowing through a furnace. This method of self-assembly improved the strength of human-created materials by sandwiching yielding layers of polymers between hard inorganic layers, increasing toughness and preventing the spreading of cracks. The durable silica spheres, which range in size from 2 to 50 nanometers and form in a few seconds, have uniform pores that could enable controlled release of drugs. The spheres can absorb organic and inorganic substances including small particles of iron, which means they can be controlled by magnets and the contents released as needed.

John et al. (2001) recently reported the first bio-based self-assembly nanofibers. Simple glycolipids derived from cardanol (obtained from *Anacardium occidentale* L, a renewable resource and a by-product of the cashew industry) were self-assembled in water initially form helical coiled nanofibers and then gradually turned into tubular structures of several tens to several hundreds of micrometers long and internal diameters of 10-15 nm. The nanofibers are found to be open ended, with uniform shape and internal diameter with a wall consisting of two to four lipid bilayers. The bio-based organic method has distinct advantages for the synthesis of new nano units, due to that they are obtainable from renewable resources and are likely to be biodegradable. This study is a good example to combine the philosophies of green chemistry and supramolecular chemistry, making use of renewable plant-derived resources for the synthesis of nanomaterials.

Huang et al. (2001) developed the use of fluidic alignment and surface patterning to arrange nanotubes and nanowires into functional structures. These techniques do not directly advance atomically precise fabrication, but they do demonstrate ordering of nanowire structure on multiple length scales - organization of nanometer diameter wires of 100-nm to micrometer-scale separations over millimeter-scale areas.

2.2 Nanoscale Electronic Devices and Computers

Nanotubes, Single-Electron Transistors, and Integrated Circuits

Carbon nanotubes have unique mechanical and electrical properties. Nanotubes have been shown theoretically to be single-electron conducting or insulating whilst having controlled structures [Mintmire et al., 1992; Hamada et al., 1992]. Besides their strong mechanical properties, nanotubes have a variety of attractive electrical properties. For example, they can sustain current densities hundreds of times greater than that of common metals, and can exist in both metallic-like and semiconducting forms. In a mixed batch of nanotubes, one can short out the metallic-like nanotubes (with a surge of voltage) while leaving the semiconducting ones unchanged for use as circuit elements. Such features make nanotubes particularly attractive for applications in nanoelectronics.

The ability of carbon nanotubes to carry electrical current can be varied by adjusting the voltage on an electrode close to the nanotube, enabling them to function as transistors in electrical circuits. A room-temperature transistor based on a single carbon nanotube has been developed [Tans et al., 1998]. Their device demonstrates very favorable electrical characteristics such as high gain (>10), a large on-off ratio ($>100,000$), and room-temperature operation. They also behave similarly to conventional silicon field-effect transistors. Single-wall carbon nanotubes serve as transistors dispersed on the wafer contact electrodes and interconnecting wires of gold on the nanotubes. The small circuits combining nanotube transistors can be used for several basic reversible logical operations used in computing electronics, including an inverter (converting a "0" into a "1," for instance), current-dependent gate operations for "AND/OR" representation, and a memory element. Very recently, logic circuits based on individual carbon nanotube molecules have been fabricated [Postma et al., 2001].

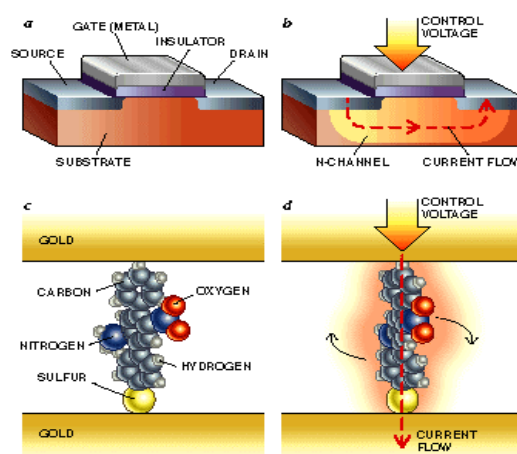
A single carbon nanotube bundle has been used to construct logic gates [Tans et al. 1988; Bachtold et al., 2001]. This work has advanced the limits of using individual molecules to build future generations of sophisticated microelectronic devices. IBM is developing integration of carbon nanotubes for logic circuits. The principal challenge is the construction of NOT gates out of nanotubes without special processing (transistors fashioned from nanotubes are normally p-type, but NOT gates require n-type transistors, the type that conducts negative charge carrier electrons). A transistor device, with a

thousand nanotubes acting like transistors, has been devised by Avouris et al. [Avouris et al., 2000; Collins et al., 2001].

The Molecular Transistor

Perhaps the most pressing challenge at this relatively early stage in nanoelectronics is the construction of a molecular device that operates analogously to a transistor. A transistor has three terminals, one of which controls the current flow between the other two. A molecular based electronic device has been devised [Reed et al., 1997; Tour, 2000] consisting of an arrangement of three benzene rings, in which the orbitals overlapped throughout. The connections between the rings are structurally weak, so that even mild twists or kinks weakened or strengthened the overlap of the orbitals. A switch to control the flow of current could thus be created if a means of controlling the twisting could be determined. This was achieved by applying an electric field to the molecule that twisted it and stemmed the current flow. Turning off the field resulted in the molecule springing back to its original shape, allowing the current to flow again. This switching from one state to the other was found to be superior to that of any comparable solid-state device.

Reed and Tour's (2000) three-terminal molecular device will make possible the chemical synthesis of tremendously efficient and complex circuits (Figure 3). Hybrids of molecular systems with conventional electronics might conceivably be used where the natural advantages of self-assembly may be harvested. But interfacing the microelectronic and the molecular will present unique challenges. Conventional computer chips have two levels of size scale. Between the macroscopic level of the chip and the intrinsic wiring, there is a factor of 1,000 in size reduction. Another 1000-fold reduction is required to get to the level of the smallest connections and components of the transistors. If molecular devices are to be added to a chip, they will represent yet another 1000-fold reduction in length scale. At this length scale thermal noise is also likely to be a significant engineering challenge. Knowing the minimum amount of heat that a single molecular device emits would place a limit on the number of devices that can be located on a chip or relevant substrate.



CONVENTIONAL MICROTRANSISTOR (a) has three terminals, known as the source, gate and drain. A positive voltage applied to the gate draws electrons to the insulator (b), enabling current to flow from the source to the drain. A molecule based on three benzene rings (c) was also used to switch an electric current. The center ring had asymmetric fragments, enabling it to be twisted by an electrical field (d). With a specific voltage applied, the electrical field twisted the molecule and permitted current to flow.

Figure 3. The molecular Transistor (Reed and Tour, 2000).

The creation of such an interconnect structure on the molecular level remains unachieved to date, but it does present the possibility of at least five orders of magnitude improvement to current silicon microtransistor chips [Reed et al., 1997; Hatzor et al., 2001]. Simple extensions of the current-day techniques used to fabricate complex microelectronics are not practical for molecular-scale electronics, because the lithography necessary for creating the interconnections to single molecules is beyond the capability of known technologies. But this represents the “top-down” approach, which, as previously discussed, is not the ideal means to manipulate devices atom-by-atom. More likely, new techniques will be invented to meet these ends, and new nanomaterials themselves used in their fabrication, such as, perhaps, nanotubes as the next generation of interconnects between molecular-scale devices [Collins et al., 2001].

Quantum Dots

Quantum Dots (QDs) are solid-state structures made of semiconductors or metals that confine a countable, small number of electrons in a 3-dimensional nanometer-sized region [Turton, 1995]. Recent progress in colloidal chemistry, epitaxial growth and lithography has made it possible to fabricate structures that are commonly defined as QDs. In QDs, the confinement of electrons is achieved by a quantum well, in which insulating material(s) is placed around a central, highly conducting region. If the insulation of the QD is good enough and if the QD is small enough quantum mechanical effects due to the discrete electron charge and/or discrete electron energies can be observed macroscopically. QDs have therefore also been called “artificial atoms”, and neighbouring weakly coupled QDs have been termed “artificial molecules” [Goldhaber et al., 1998; Turton, 1995].

Quantum dots used in electron transport experiments are typically characterized by energies needed to add a single electron. The device arrangement has to be such that the energy needed to add a single electron to the dot is large compared to the ambient thermal energy and thus represents the ultimate atomistic limit of scaled solid state devices [Bimberg et al., 1998; Petroff et al., 2001]. Nanometer-scale clusters can spontaneously form on a semiconductor substrate that has atom-like properties. They suggest novel applications in optical and optoelectronic devices, quantum computing, and information storage [Livermore et al., 1996; Bimberg et al., 1998].

Two mechanisms currently exist to grow quantum dots: self-assembled and lithographically defined quantum dots. It seems likely that self-assembled quantum dots will play the major role in the emerging fields of single-particle electronics and nano-photonics due to its “bottom-up” nature [Petroff et al., 2001].

A wide variety of quantum-dot systems have been made using epitaxial growth technologies, including group IV elemental systems (such as Si or Ge), and group III - V compound semiconductors. In practice, in-situ growth techniques such as molecular beam epitaxy or metal organic chemical-vapor deposition are used to obtain ultra clean conditions and control of deposition materials, and nanometer-sized clusters can form on the surface to minimize the total energy. For example, this technique has been used to form $\text{In}_x\text{Ga}_{1-x}\text{As}$ quantum dots [Garcia et al., 1997]. A 3D array of QDs can then be produced by repeating the deposition sequence. Furthermore, the typically randomised array of clusters can be engineered into a periodic one by controlling the quantum-dot nucleation on the surface [Lee et al., 2001; Springholz et al., 1998].

Quantum rings are a special form of quantum dots. In many respects, quantum rings are just quantum dots with a peculiar (*w*-shaped rather than parabolic) confining potential [Warburton et al., 2000]. The difference in their topology - the “hole” in their middle - becomes prominent when an external

magnetic field is applied. The magnetic flux penetrates the interior of the ring and determines the nature of the electronic states. Self-assembled InGaAs rings function in the true, scatter-free, quantum limit, and are therefore akin to ring-shaped molecular systems such as benzene. [Warburton et al., 2000; Lorke et al., 2001].

Quantum phenomena can be investigated using cavity quantum electrodynamics (cavity QED). The spontaneous emission of radiation from excited atoms can be significantly enhanced or inhibited by placing the atoms in a specially designed cavity or between mirrors. An ideal two-level system for cavity QED applications is a ground-state exciton in a self-assembled quantum dot. In contrast to the behaviour of atoms, quantum dots do not undergo random motion. Instead, they are naturally trapped in the surrounding high-bandgap-energy semiconductor. Cavity-QED techniques have a potentially important role in the area of quantum information science. A significant fraction of quantum computation and communication schemes rely on the strong-coupling regime of cavity QED [Wilczek, 2000; Gerard et al., 1998]. Experiments on quantum dots embedded in micropillar and microdisk structures have already demonstrated the enhancement of spontaneous light emission known as the ‘Purcell effect’, both for an ensemble of dots [Michler et al., 2000a] and for a single dot. This represents a major success of quantum-dot cavity QED. It indicates that self-assembled quantum dots might be used to develop a quantum-dot single-photon turnstile device [Michler et al., 2000b].

Trapping carriers in a quantum dot may be used as the basis for very-high-density memory devices where data is read and written by controlling charge storage in quantum dots [Abstreiter et al., 1999; Lundstrom et al 1999]. The idea behind this device (the dissociation of an exciton for storage in a quantum-dot pair and then reassembling it for readout) might in itself be the foundation of a viable approach for the construction of memory that is entirely optically based. With self-assembled quantum dots, quantum control of carrier injection and photon generation is now possible [Klimov et al., 2000].

It is noted that quantum dots may well play a key role in the emerging field of quantum-information science, either as building blocks where quantum information is stored in the spin degrees of freedom, or as a source of single photons for quantum communication. On the other hand, further understanding and control of physical phenomena and potentially exotic devices based on QDs are far from complete. Amongst the most significant challenges to QD technology remain reducing the QD size distribution and the observation of 3D confinement effects at room temperature [Petroff et al., 2001].

2.3 Nano Drug Delivery and Biomimetic Actuators

Conventional methods of drug delivery including injections and oral medications have limited applicability. The process of drug delivery could be greatly improved by transporting drugs through biological tissues encapsulated within a suitable nanoparticle such as a dendrimer [Kumar, 2000] (see also section 2.1.2). However, there are currently no practical applications of drug delivery by nanoparticles or dendrimers.

Another development in nano/cellular delivery is the purpose fabrication of various so-called ‘actuators’ which represent energy transfer mechanisms that can be used as a form of motive force. A DNA actuator powered by complementary pairing between DNA strands has been created recently [Yurke et al., 2000]. Such devices are approximately 7nm long and resemble motorized tweezers formed using DNA with two double- stranded arms connected by a single-stranded hinge, and two

single-stranded “handles” at the ends of the arms. These devices are widely referred to as “DNA-tweezers”.

Seeman et al. (2000) explored a systematic view of the topology of the motifs used in DNA as nanotechnology building blocks. They built up a wide variety of structures from a "reciprocal exchange" operation that joins two DNA strands by nicking them, swapping two of the free ends, and rejoining them.

Based on kinesin proteins, Hess et al., (2000) fabricated light-controlled molecular shuttles that can transport foreign molecules along microtubules. Baughman et al. (1999) also developed electromechanical actuators based on sheets of single-walled carbon nanotubes that is very capable for drug delivery and molecule transportation.

SECTION 3 PROGRESS IN DYNAMIC NANOTECHNOLOGY

Nano-materials and nano-components are examples of what we have termed “static” nanotechnology. In this section we now discuss artificial or naturally occurring nanoscale structures or molecules that have the added component of dynamical activity. Dynamic natural molecules or artificial devices are promising means of nanoscale manipulation of individual atoms and molecules. Self-assemblers and molecular motors are the most well developed areas in dynamic nanotechnology.

3.1 DNA/Nanoparticle Assembly and Diagnostics

Solution Assembly of DNA-Functionalized Nanoparticles

The unique recognition interactions of DNA have been used to direct the assembly of nanometer-sized particles [Elghanian et al., 1997; Mirkin, 1996a] enabling the production of new materials with highly tunable properties. For example, Elghanian et al. (1997) applied this strategy for the synthesis of new nanostructured materials made from metals, semiconductors (e.g., quantum dots), and inorganic and polymer insulators. Not only can the physical characteristics of these materials be designed by changing the DNA linker and the particle composition, but also the construction and deconstruction of the materials may be controlled by hybridizing and dehybridizing the linking DNA.

Nanoparticles for DNA sequence detection

A novel approach towards detecting specific DNA sequences has been developed [Taton et al., 2000]. Because nanoparticles only assemble in the presence of a complementary DNA strand, the change in material properties induced by nanoparticle assembly can be used as an indicator of whether a particular sequence is present in a sample or not. Such signatures include the changing optical, mechanical, and electrical properties of DNA-functionalized nanoparticles. For example, as illustrated in Figure 4, a DNA-mediated assembly, gold nanoparticles will change from “red” to “blue”, and this change can be correlated to the presence of a DNA target. This idea already has been applied to the detection of DNA from biological warfare agents such as anthrax, and is being extended to clinical DNA detection.

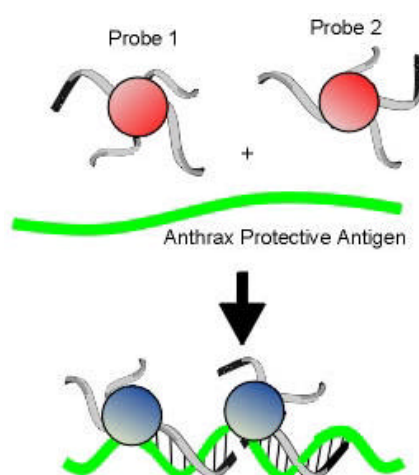


Figure 4. Detection of PCR-amplified DNA from anthrax bacteria with Au nanoparticle probes. (from Mirkin, 2000a).

Work is being undertaken [Mirkin, 2000 a & b] to extend the nanoparticle assembly strategy to analyzing combinatorial DNA arrays (or "gene chips"). It is demonstrated that DNA-functionalized gold nanoparticles will assemble onto a sensor surface only in the presence of a complementary target. If a patterned sensor surface of multiple DNA strands is used, the technique can detect millions of different DNA sequences simultaneously. Nanoparticles make 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 microscopy, and electrical conductivity.

3.2 Self-Assemblers and Synthetic Molecular Replicators

Weiss et al. [Weiss, 2001; Whitesides and Love, 2001] have created and operated the first self-assemblers and synthetic molecular motors (Figure 5). They developed a method of building less than 30 nanometer long structures in close proximity to each other. Precise spacing between the molecules was achieved using the step-by-step application of organic molecules and metal ions as size-controllers. The organic molecules serve as a ruler for scaling down a larger "parent" structure. After metal deposition and removal of the organic multilayer, an isolated smaller structure remains on the surface. This approach is used to form thin parallel wires (15 to 70 nanometers in width and 1 micrometer long) of controlled thickness and spacing. The structures obtained were imaged with field emission scanning electron microscopy. A variety of nanostructures could be scaled down, including structures with hollow patterns [Hatzor et al., 2001].

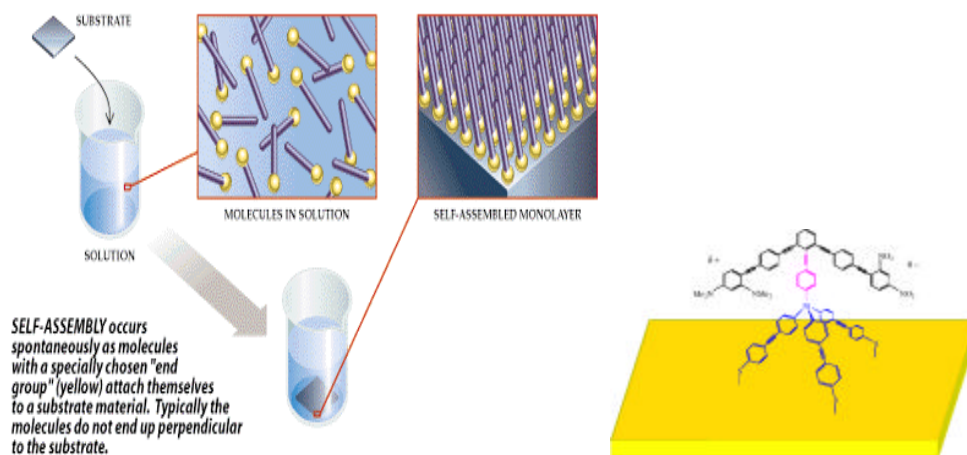


Figure 5. Self-assembler and synthetic molecular motor (from Paul Weiss, Pennsylvania State University).

Other groups have also built synthetic motors recently. A motor built by Kelly et al. (1999) consists of two major parts: three benzene ring blades and four fused benzene rings which curves back from an attachment to the axial carbon to block free rotation of the former part. Reacting the molecule with COCl_2 , the net effect of the motor is to apply the chemical energy of hydrolysis of the COCl_2 towards crossing the rotational barrier between rotamers in a predetermined direction. It currently rotates through 120 degrees.

The motor of Koumura et al. [Koumura et al., 1999] consists of two identical cyclohexane rings on both ends of the carbon-carbon double bond. These rings, in turn, have bulky groups (methyl and fused naphthalenes) pointed back towards the double bond. The steric interference between these

groups sets the direction of rotation during photoisomerization, which induces strain into the system. A full rotation of 360 degrees can be achieved by alternating photochemical and thermal steps.

Brouwer et al. (2001) recently reported the operation of a fast, photochemically powered molecular motor. The motor moves in $\sim 1\mu\text{s}$ scale (previous light-driven shuttles generally function on the time scale of minutes to hours). The motor consists of a shuttle that moves between two binding sites. The shuttle is a macrocycle, a 26-atom ring, with 4 hydrogen bond donor sites. The shuttle is threaded on to a linear molecule with two binding sites.

The significance of the above work for nanotechnology is that they provide a mechanism for controllable rotary motion machinery. Currently, the motion of these artificial dynamical devices is very limited. In contrast there are several examples of biological systems that have far more sophisticated and potentially useful dynamical properties.

3.3 Molecular Motors

Many proteins operate as either enzymes to catalyze chemical synthesis, or as ion pumps to generate electrical voltage, or as motors to generate mechanical force. Such proteins are the working machines of the cell and as such can be aptly described as 'molecular motors.' Just as mechanical motors convert chemical or electrical energy into mechanical motion, so too do naturally occurring biological molecular motors convert cellular energy into mechanical motion.

Mechanically speaking, there are two types of molecular motors: linear motors and rotary motors. Examples of linear motors include: (a) myosin (jumps along an actin filament to contract striated muscle), (b) the two-armed kinesin (walks hand-over-hand on microtubuli to pull a synaptic vesicle along the nerve axon), and (c) RNA polymerase, helicase, and ribosome (process over nucleotide strands, etc). Examples of rotary motors include: (a) ATP synthase (the enzyme that produces ATP), and (b) The flagellar drive (propels bacteria through viscous fluid). Whereas the former are powered by the hydrolysis of ATP (or other nucleotide triphosphates), the flagellar motor is powered by a cross-membrane electrochemical potential difference [Junge, 1999]. These examples of linear and rotary molecular motors are now described in detail as follows.

Myosin

Finer et al. (1994) studied myosin by suspending a single rigid actin filament held between two optical traps above a single myosin molecule. Thus they were able to measure directly the force and displacement resulting from the interaction of the molecule with the filament. When the myosin pulled on the actin fiber, the force was transmitted to microbeads anchored at the fiber's ends and held in the optical traps. The displacement of the beads from their equilibrium positions, which generated the myosin-induced movement of the fiber, was found to be discrete and load-independent. The average interaction time between myosin and actin was measured as a function of ATP concentration and found to agree with the known rates of ATP hydrolysis, and the static force developed by the myosin was also measured.

Yanagida (1998) coupled a similar system to a fluorescence microscope to observe simultaneously the displacement of the actin fiber and the hydrolysis of a fluorescently tagged ATP molecule by the myosin. The goal was to determine whether, as was generally believed, only a single ATP molecule was consumed per myosin step. Instead, they found that on average a single ATP molecule accounted

for three myosin steps. This significant experimental achievement still awaits independent confirmation.

Kinesin

In parallel to these myosin studies, Visscher et al. (1999) have been investigating the kinesin-microtubule system responsible for the movement of proteins and vesicles within cells. Here too, the central issue has been the efficiency and step-size operation of the kinesin motor. By using optical tweezers to follow the progression of a single kinesin molecule on a microtubule rail, they demonstrated that the two-headed kinesin molecule progresses in discrete steps of 8 nm for each ATP molecule consumed [Schnitzer et al., 1997; Svoboda et al., 1993]. Because kinesin can take many steps before falling off its microtubule rail, one can deduce the number of ATP molecules consumed per step from a statistical analysis of the time between steps. For kinesin, Visscher et al. (1999) found that the step-time distribution was exponential, reflecting a single rate-limiting biochemical reaction (ATP binding).

F₀F₁-ATPase

In the cells of all living organisms, a protein enzyme known as the F₀F₁-ATP synthase (ATPase) complex produces ATP at the expense of an electro-chemical potential difference across the mitochondrial membrane. It can also operate in reverse, when it generates an electrochemical difference at the expense of ATP hydrolysis [Boyer, 1997]. ATP synthase seemed to be rather well separated in the bipartite construction of the enzyme, with an ion-conducting membrane portion, F₀, and a peripheral F₁-portion that hydrolyzes ATP by itself. For some thirty odd years, it had remained a mystery how its electrochemical and chemical functions were linked to each other [Junge et al., 1997]. Boyer suggested that this machinery operated somewhat like a hydroelectric generator. The proton flow through the F₀ subunit embedded in the membrane rotates a 'shaft' in the stator like F₁ subunit to synthesize ATP. Conversely, ATP hydrolysis in F₁ causes a reverse rotation of the shaft and a reverse flow of protons [Boyer, 1981].

Now it is fully appreciated that ion transport and the synthesis of ATP by the enzyme are mechanically coupled. The enzyme is made from two rotary motors that are mounted on a central shaft and held together by an eccentric bearing. Depending on the demand for ATP or for ion-motive force, one motor operates in the forward direction and, by rotating the central shaft, drives the other motor backwards to operate as a generator. ATP synthase is of the same size as myosin but an order of magnitude smaller than the flagellar drive, and represents a natural working molecular machine enabling efficient electrical-to-mechanical-to-chemical energy conversion [Abrahams et al., 1994; Boyer, 1997; Junge et al., 1999].

The rotary mechanism has been experimentally confirmed for the isolated F₁-portion when functioning as ATPase. First evidence for a forced rotation of subunit γ relative to δ (Figure 6) was obtained by Duncan et al. (1995) and Zhou et al. (1996) who used cleavable crosslinks between subunits. Sabbert et al. (1996 & 1997) found that the rotation was compatible with enzymatic turnover.

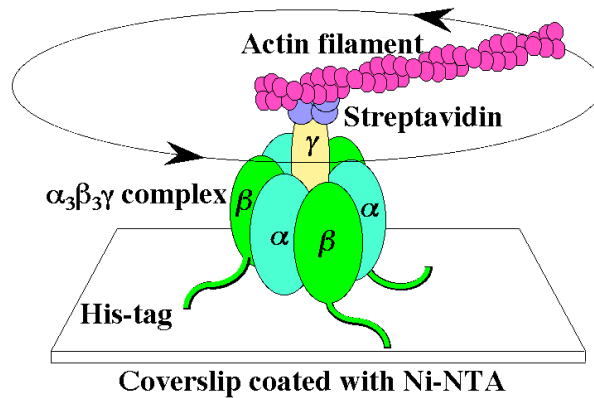


Figure 6. F₁F₀-ATPase molecular motor drives an actin filament with high efficiency (from Noji et al., 1997).

Noji et al. (1997) and Yasuda (1998) reported the first real-time study of the so-called F₁-ATPase system. They attached the protein to a cover slip and anchored a rigid, fluorescently labeled actin molecule to the enzyme rotor. When ATP was added, a 120° step-wise rotation of the actin was observed. The single exponential distribution of the dwell times between steps suggested that only a single ATP molecule was being hydrolyzed per step. In more recent experiments, they have found 90° and 30° substeps associated, respectively, with the protein binding to ATP and the release of the ATP hydrolysis products. Those results, together with an estimate of the energy dissipated by the drag on the rotated actin, imply that the efficiency of the F₁-ATPase is nearly 100% (as seen in Figure 6).

The F₀-portion of ATP synthase probably functions as a stepper motor, too, but it is twelve-stepped rather than three-stepped for the following reasons: (i) chloroplasts and cyanobacteria, the stoichiometry of translocated protons over synthesized ATP is 4:1, which amounts to 12 protons per full turn in F₁; (ii) in *E. coli*, F₀ contains 12 identical copies of the proteolipid subunit, named c [Jones et al., 1998a], arranged as a ring with a diameter of about 5 nm [Jones et al., 1998b; Singh et al., 1996].

These early experiments have demonstrated the power of single-molecule studies and generated increasing interest in the theoretical modeling of molecular motors [Ajdari et al., 1997]. Junge [Junge et al., 1997] has described how a protein domain, together with its partner, the large and transmembrane subunit c, might generate torque at the expense of proton flow. This model was quantitatively analyzed by Oster and coworkers [Dimroth et al. 1999; Elston et al., 1998; Wang, 1998], who addressed the mechanism of the electro-chemical drive in the ATP synthase of the bacterium *Propionigenium modestum*. Its F₀-portion primarily conducts Na⁺-cations, in contrast with its H⁺-translocating counterpart in photosynthetic and/or respiratory bacteria and in the chloroplasts and mitochondria of eukarya. There is no doubt, however, that the ATP synthase of *P. modestum* operates according to the same general principles as its H⁺-translocating enzymes, because of the same subunit structure and the functionality of various chimeric constructs between *P. modestum* and the F₁ of *Escherichia coli*. This has been recently corroborated for the membrane-bound H⁺-ATP synthase of *E. coli* by using engineered disulfite bridges for zero-length cross-links [Fillingame, 1998].

Berry and Berg (1999) modeled the coupling between ion flow and rotation, which has been demonstrated for the flagellar motor. In the flagellar motor, the stator is probably elastically anchored to the cell wall. In ATP synthase, there is no elastic link to the outside world; instead, the enzyme

carries out rapid and uniaxial Brownian rotation in the fluid membrane [see Sabbert et al., 1997]. Thus the stator/rotor denomination is arbitrary.

The newly emerging field of bio-nanotechnology is combining the knowledge base from conventional silicon device processing and biological life sciences, with the ultimate goal of fabricating mimic bio-nanodevices. The clear-cut assignment of any partial function of the two motors in ATP synthase to particular subunits is of great advantage for such a nanomachine. For example, Soong et al. (2000) have demonstrated that the F_1 -ATPase motion can drive a nano-propeller.

RNA and DNA polymerase

RNA polymerase was the first DNA-based molecular motor to be studied at the single-molecule level. This protein causes the transcription of DNA into messenger RNA, the template of the genetic code for protein production. The motion of RNA polymerase (RNAP) along DNA during transcription is complex and involves many phases, including initiation, elongation, pausing, backtracking, and arrest. Different studies of the molecular motor functioning of RNAP have been carried out by Block et al. (2000) who found that the dependence of the molecular motor's speed on an applied force suggested that stretching of the DNA was affecting a state that branched off the main reaction pathway, for example, by increasing the likelihood of pauses in enzyme activity [Finzi and Gelles, 1995; Yin et al., 1995; Wang et al., 1998].

Davenport et al. (2000) have used optical trap/flow-control microscopy techniques to examine the characteristics of natural single enzyme molecules, allowing them to follow the motion of the transcribing polymerase as it moves along the DNA.

DNA polymerase is a protein that synthesizes a new DNA strand on a single-strand DNA template, matching each of the four bases of the genetic code with its complement: adenine (A) with thymine (T) and guanine (G) with cytosine (C). It can also detect and correct its errors. Single-molecule studies of replication by DNAP were done independently by Bustamante, Bensimon and co-workers [Davenport et al., 2000; Wuite et al., 2000] with two proteins deficient in error-correcting activity [Allemand et al., 1998; Strick et al., 2000; Maier et al., 2000]. Essentially, the replication rate decays exponentially with increasing applied load from an initial rate of a few hundred bases per second, finally stalling at a force of about 30 pN. At forces greater than 35 pN, the error-correcting activity of the natural enzyme was enhanced, causing it to eat away at the strand it had just synthesized.

The properties of various motor proteins, linear and rotary, are summarized as follows [Junge 1999]:

- Myosin vs. kinesin. The former produces high speed at the expense of processivity, and the latter runs at high processivity at the expense of speed. The slower steps in the full reaction cycle of myosin do not limit its rate of action, because they happen while the head is detached from the actin filament.
- RNA-polymerase and flagellar motor vs. the rest. The former can operate against large loads, because they take smaller steps than the latter. In the flagellar motor, this property is even more pronounced by the joint action of eight motor elements on the wheel.
- FoF₁ vs. the rest. Although the dual motor function is normally fully sequestered in the ATP synthase, its performance matches that of the other motors. Most importantly, it rotates.

SECTION 4 NANOSCALE COMPUTATION

A dynamical nanodevice will alternatively require an instructional and control unit, along with an operational and design algorithm. This means that computers and computing methods will need to be developed on the nanoscale. Quantum computers, molecular computing and computational nanotechnology are amongst the most focused areas.

4.1 Quantum Computer

Quantum computers were first theorized about 20 years ago when Benioff (1982) considered the feasibility of creating a quantum Turing machine. The Turing machine, upon which all modern computing is based, consists of ‘tape’ of unrestricted length divided into little squares. Each square can either hold a symbol (digital ‘1’ or ‘0’) or be left blank. A read-write device gives the machine its instructions to perform a certain program. In a quantum Turing machine, the difference is that the tape exists in a quantum state, so does the read-write head. Thus the symbols on the record can be either ‘0’, ‘1’ or a superposition of ‘0’ and ‘1’. A classical Turing machine can only perform one calculation at a time, whereas a quantum Turing machine can perform many calculations simultaneously.

Quantum computers, not being limited to two states, encode information as quantum bits, or qubits. A qubit can be a ‘1’ or a ‘0’, or a superposition that is simultaneously both ‘1’ and ‘0’ or somewhere in between. Essentially, qubits represent atoms working together to act as both computer memory and a processor. Because a quantum computer can contain these multiple states simultaneously, a qubit-based processor has the potential to be millions of times more powerful than today's most powerful supercomputers.

The superposition of qubits gives quantum computers their inherent parallelism. This parallelism allows a quantum computer to work on millions of computations at the same time (a conventional classical processor can only work on one computation at a time). While parallel computation exists with classical computing, one must link an array of single processors together to achieve this. In contrast, a 30-qubit-quantum computer would equal the processing power of a conventional computer that could run at 10 teraflops, or trillions of operations per second. In contrast, the fastest civilian supercomputers now have only achieved speeds of about 6 teraflops [see <http://www.top500.org/>].

Quantum computers also utilize another aspect of quantum mechanics known as entanglement. One inherent problem with quantum computing is that if you try to measure any arbitrary property of a sub-atomic particle, you invariably disturb its state and thereby change the value of that property. However, if an external force is applied to two atoms, it can cause them to become entangled, and the second atom can take on the properties of the first atom. So if left undisturbed, an atom will ‘spin’ in all allowable directions; but as soon as it is disturbed it collapses onto one value, and at the same time, the second entangled atom will choose an opposite spin value. This gives the observer knowledge of the value of the qubits without actually looking at them [for a review see Nielsen and Chuang, 2001].

Quantum computers hold great promise to one day replace silicon chips, just like the transistor once replaced the vacuum tube. But for now, considerably more R&D needs to be invested to transform theoretical concepts into a working quantum computer. To date, the most advanced experimental quantum computers have not gone beyond manipulating more than 7 qubits [see: www.almaden.ibm.com/st/projects/quantum/intro/]. However, the potential remains that quantum

computers one day could perform, quickly and easily, calculations that are impossible for conventional computers. Furthermore, if functional quantum computers can be built, they will be valuable in factoring large numbers, and therefore extremely useful for decoding and encoding sensitive information. Quantum computers could also be used to search large databases in a fraction of the time that it would take a conventional computer.

Several key advancements have been made in quantum computing in the last four years. A few of these are summarized below:

- 1998. Groups at Los Alamos and MIT managed to spread a single qubit across three nuclear spins in each molecule of a liquid solution of alanine or trichloroethylene molecules [Lloyd, 1998; Brassard et al., 1998]. Spreading out the qubit made it harder to corrupt, allowing researchers to use entanglement to study interactions between states as an indirect method for analyzing the quantum information.
- March 2000. Scientists at Los Alamos National Laboratory announced the development of a 7-qubit-quantum computer within a single drop of liquid (see: qso.lanl.gov/qc). The quantum computer used NMR to manipulate particles in the atomic nuclei of molecules of trans-crotonic acid, a simple fluid consisting of molecules made up of six hydrogen and four carbon atoms. NMR is used to apply electromagnetic pulses, which force the particles to align themselves either in parallel or counter to the magnetic field. This allows the quantum computer to mimic the information encoding of bits in digital computers.
- August 2000. Researchers at IBM-Almaden Research Center developed what they claimed was the most advanced quantum computer developed to date [Bennett et al., 2000]. The 5-qubit-quantum computer was designed to allow the nuclei of five fluorine atoms to interact with each other as qubits, be programmed by radio frequency pulses and be detected by conventional nuclear magnetic resonance (NMR) instruments. They were able to solve in one step a mathematical problem (useful in the mathematics of cryptography) that would take conventional computers repeated cycles.
- In Australia, the Centre for Quantum Computing, founded in early 2000 with nodes at UNSW, University of Melbourne and University of Queensland, is in the process of constructing a solid-state quantum computer prototype [Kane, 1998] in collaboration with Los Alamos National Laboratory.

4.2 Towards Nanocomputers

The use of molecules for electronic devices and computing processors remained theoretical until recent advances in chemistry, physics and biology. Although significant advances towards the construction of nanoelectronic computers are foreseeable, many barriers exist and it is still too early to say it functionally works. Nevertheless, DNA computing and single molecule electronics have achieved considerable progress toward nanocomputers.

DNA-based computing may be used as a nanocomputer since DNA naturally handles genetic information in a highly parallel manner [Adleman, 1998]. More recently, an algorithm has been devised to practice DNA computing [Liu et al., 2000] in which selected DNA strands on a surface are

coupled to new DNA molecules to operate storage and switches. Molecular computation by DNA hairpin formation has also been achieved [Sakamoto et al., 2000].

Bell Laboratories developed field-effect transistors of single molecules based on two-component self-assembled monolayers of conjugated and insulating molecules. It was found that the conductance can be varied by more than three orders of magnitude by changing the applied gate bias. Using very small ratios of conjugated to insulating molecules in the two-component monolayer, devices with only a few "electrically active" molecules can be achieved. At low temperatures the peak channel-conductance is quantised, a behavior indicative of transistor action in single molecules. [Schön et al., 2001]

Huang et al. (2000) reported a "bottom-up" approach of logic gates and computation from assembled nanowire building blocks, in which functional device elements and element arrays have been assembled from solution through the use of electronically well-defined semiconductor nanowire building blocks [Huang et al., 2001]. Nanowire junction arrays were configured as key OR, AND, and NOR logic-gate structures with substantial gain and have been used to implement basic computation.

Nanotube-based molecular electronics is also a very interesting option to explore as an alternative for the common silicon computer chips, but it is too early to make a statement on whether they can surpass silicon [Tseng and Ellenbogen, 2001].

The inevitable trend towards smaller devices will probably impose a new form of electronics in which specially designed individual molecules replace conventional transistors. The minimum requirements for a workable computer are a switching device (like a transistor), memory and a means of interconnecting large numbers of the devices and memory elements. To date, only single-molecule switches and memory elements have been successfully created [Reed and Tour, 2000]. However, the switch had only two terminals, whereas complex logic circuits require a device with more than two terminals, in which, for example, current flow between two is controlled by a third, as with transistors. Another challenge that remains to be solved is how to connect large numbers of these devices.

While self-assembly (see section 3.2) represents a potential solution to the problem of connectivity [Tour, 2000; Reed et al., 1997], it is unlikely that, in the immediate future, it can alone suffice to produce useful molecular-computing systems. More likely for now, a combination of self-assembly with fabrication methods, such as photolithography will need to work in tandem.

Bumm et al. (1996) first demonstrated self-assembly in molecular electronics by mixing a small amount of a solution of molecules that were designed to have conducting properties with another containing a known inert insulating molecule. A self-assembled layer was produced in which conductive molecules were very sparsely interspersed among nonconductive ones and the electrical conductivity was greater than that of the surrounding molecules.

Reed et al. (1997) measured how much current could flow across a single molecule. Interestingly, they found that the magnitude of the current was much greater than would be expected from simple calculations of the power dissipated in a molecule, suggesting that the electrons traveled through the molecule without generating heat by interacting or colliding.

These initial demonstrations of molecular conduction were rapidly followed by construction of basic devices. The simplest electronic device is a diode, which can be thought of as a one-way valve for electrons. Metzger et al. (1999) synthesized a molecule that had an internal energetic lineup of orbitals, which varied depending on the polarity of the voltage applied to it. The lineup of orbitals was

analogous to the rungs on a ladder. If the voltage was applied in one direction, the lineup corresponded to a vertically aligned ladder, in which much effort is expended in 'climbing' it. With the opposite voltage polarity, the orbital lineup was analogous to the rungs of a horizontally aligned ladder, where it can be traversed with minimal effort.

Chen et al. (1999) adapted a nanopore structure for such a task. The structure contained a very small hole, in which an "active region" was created by self-assembling a relatively small number of molecular devices in a monolayer. In a 30-nanometer diameter hole, approximately 1,000 molecular devices were allowed to self-assemble. Evaporating a metal contact onto the top of the self-assembled monolayer completed the molecular diode device. Chen et al further moved on to more complex switching devices. A controllable switch is a minimum requirement for a functioning computer. Even more desirable is a switch that also amplifies a current. This is necessary to connect vast numbers of switches, a requirement for the construction of complex logic circuits.

The molecular equivalent of a transistor that can both switch and amplify remains undiscovered. However, molecular switches have been devised, such as the twisting switch described in section 2.2. Reed et al. (1997) observed impressive switching characteristics, such as an on/off ratio greater than 1,000, as measured by the current flow in the two different states. For comparison, the analogous device in conventional solid-state electronics has an on/off ratio of around 100. Similar behavior was observed by Collier et al. (1999), who demonstrated that the electrical conductivity of a molecular layer of rotaxanes (molecules that resemble a core with a surrounding barbell) could be predictably interrupted when a high voltage was applied to a junction containing the molecules. At this voltage, the molecules reacted and changed configuration, changing the arrangement of orbitals and interrupting the flow of current through the molecule. They built a device that performed a simple logic function by combining a series of these molecular junctions [Mahan et al., 2000].

Memory is the other indispensable component of a functioning computer. Molecular devices have already been used as effective memory elements. In Tour et al.'s twisting switch (described in section 2.2) [Tour, 2000], the internal electrically active unit (the lopsided center benzene ring with opposing NO_2 and NH_2 groups) was altered by retaining just the electrophilic nitro group, NO_2 . This made the molecular orbitals sensitive to modification, either spread out or localized depending on the charge state of the internal group. Absence or presence of charge in the internal node modified the conduction of electrons through the molecule. The molecular memory cell retained the stored bit for nearly 10 minutes, which is impressive in comparison with an ordinary silicon dynamic random-access memory element, which can retain such information for only a few milliseconds. The construction of the memory element, involving only a fairly simple modification to the twisting switch, also demonstrates the ease and flexibility in which molecular-scale devices can be redesigned [Chen et al., 1999; Donhauser et al., 2001].

4.3 Computational Nanotechnology

Fundamental understanding and accurate predictive/analytical methods are critical to the successful manipulation and manufacturing of nanomaterials and nanosystems. Currently, we have little ability to do so. Present nanomaterials and nanostructures are so small that direct measurement and controlling are still not applicable. On the other hand, they are too large to be fully described or computed by current first principle theories. Nevertheless, computational nanotechnology (theory, design, modelling and simulation) is increasingly playing key a role to advancing nanotechnology.

Computational nanotechnology may include: new theoretical understanding, innovative design, modelling and simulation, computer-aided analysis and manipulation of nanomaterials, nanostructures or nanosystems at the atomic scale. The benefits of computational nanotechnology will be realized with more powerful computers and improved algorithms for atomistic simulation. An interdisciplinary effort will be required to exploit an atomistic theoretic understanding against experimental validations, in particular on the various biomolecules and nanosystems in living cells.

Even though it is difficult today to fully simulate/model nanosystems at relatively large length and long time scales, recently there has been great progress in areas such as quantum mechanics/quantum chemistry, ‘bottom-up’ approaches to fullerenes and nanotubes, molecular dynamics and reaction molecular dynamics, structure prediction of biomolecules and ab initio dynamics of molecular motors, etc. For example, NASA has established a Division for Computational Molecular Nanotechnology [see: www.ipt.arc.nasa.gov]. Their research focuses are ‘bottom-up’ computation and simulation of various nanomaterials and nanostructures, such as carbon nanotubes (CNT), boron nitride nanotubes and protein nanotubes, CNT based electronic structures, CNT for hydrogen and fuel storage, design of CNT-based mechanical components, chemical functionalization of nanotubes, sensors, and even nanopores in gene sequencing.

The Beckman Institute at Caltech [<http://www.its.caltech.edu/~bi/>] is also a pioneer in computational nanotechnology. Their Materials Simulation Centre is leading in the design of nanoscale materials (e.g., industrial nano-catalysts) and nano-processes using a hierarchy of quantum, atomistic, mesoscale, and continuum simulations. Their other centres are conducting fundamental research in the chemical and biological sciences, such as biomolecular design and computational biology.

Progress in computational nano bio-structures is highlighted by the simulation of DNA over long times [Schlick et al., 2000], investigation of mechanical functions of proteins by steered molecular dynamics [Isralewitz et al., 2001], and the combined use of quantum mechanics and molecular mechanics techniques for calculating the hydrolysis reaction in molecular motors [Okimoto et al., 2001].

SECTION 5 NANOBIO TECHNOLOGY

We regard nanotechnology and biotechnology as complimentary fields of endeavor. The distinction between the two is that nanotechnology implies the artificial manipulation of new entities whereas biotechnology involves utilizing existing biological entities. The boundary between nanotechnology and biotechnology is crossed when ‘nanobiotechnology’ involves arbitrarily changing a biological entity at the molecular level. When this occurs, say via genomic manipulation and protein engineering or even combining biomolecular and solid electronic entities, the new science of nanobiotechnology emerges. Nanobiotechnology will enable us to recognize and control the biomolecules that govern normal as well as abnormal cell activity, to implant intracellular sensing systems, to target DNA/protein and to develop biomimic nanodevices, etc

5.1 Genetic Therapy and Molecular Medicine

The basis of genomics [Dhand, 2000] is that DNA is transcribed into RNA, which leads to the formation of proteins that provide biological function. Therefore to control the formation of proteins one needs to control the gene. Molecular biology is continuing to improve and new procedures involving molecular manipulation are being discovered. Now we can molecularly profile, copy, and manipulate the genetic basis of both plants and animal organisms. This rapidly developing field is opening wide opportunities and implications for understanding existing organisms and engineering organisms with new properties. Research is even under way to create new free-living organisms, initially microbes with a minimal genome [Cho et al.,1999].

Genomics, Genetic Profiling and Proteomics

The genomes of plants (ranging from important food crops such as rice and corn to production plants such as pulp trees) and animals (ranging from bacteria such as *E. coli*, through insects and mammals) will continue to be decoded and profiled. Over the past decade, and particularly the last three years, more than 30 organisms have had their genomes completely sequenced, and a further 100 or so are in progress [NCBI website]. The first stage of the Human Genome Project was completed in early 2001 [Dennis et al., 2001; Jasny et al., 2001; NCBI website].

DNA arrays with more than 250,000 different oligonucleotide probes or 10,000 complementary DNA (cDNA) per square centimeter are now operating [Lockhart et al., 2000]. Gene expression, or genetic profiling, is now a major determinant of cellular phenotype and function. Intense work is being undertaken to exploit genome data, develop new gene-oriented technologies, and to understand, at its molecular foundation, the complex nature of living cells. To the extent that genes dictate function and behaviour, Genomics and Proteomics are sciences that not only acquire the DNA sequencing information, but also exploit these sequences into gene expression, protein identification, translational modification, protein-protein interactions, determining protein function, and, ultimately, molecular medicine [Pandey and Mann, 2000].

The term of proteomics covers much of the functional analysis of gene products, namely ‘functional genomics’. It is complementary to genomics in that it focuses more on gene products. For this reason, proteomics directly contributes to drug development, as all drugs are targeted against specific proteins. Gene expression and its profiling into likely functions are the major themes of proteomics. More importantly, although there is a strong connection between an organism’s function and its

genotype, there are still large gaps in understanding the intermediate steps in copying, transduction, isomer modulation, activation, immediate function, and this function's effect on larger systems in the organism [Pandy and Mann, 2000]. One of the most challenging aspects for genetic profiling is whether the hypotheses and conclusions based upon the vast quantities of data generated are biologically meaningful [Martzen et al., 1999].

Cloning and Genetically Modified Organisms

Artificially producing genetically identical organisms through cloning are likely to be significant for engineered crops, livestock, and research animals. Cloning may become the dominant mechanism for rapidly bringing engineered traits to market, for continued maintenance of these traits, and for producing identical organisms for research and production [Butler et al., 1999]. Research will likely continue on human cloning in unregulated parts of the world with possible success, but ethical and health concerns will likely limit wide-scale cloning of humans in regulated parts of the world. Individuals or even some states may also engage in human or animal cloning, but it is unclear what they may gain through such efforts [RAND, 2001].

Beyond profiling genetic codes and cloning exact copies of organisms and microorganisms, biotechnologists can also manipulate the genetic code of plants and animals and will likely continue efforts to engineer certain properties into life forms, mainly for human health and food supply motivations. Traditional techniques for genetic manipulation (such as cross-pollination, selective breeding, and irradiation) will likely continue to be extended by direct insertion, deletion, and modification of genes through laboratory techniques. Targets include food crops, production plants, insects, and animals, though direct manipulation of human genes are unlikely to proceed until more profound scientific and ethical issues have been more clearly articulated, fully debated and better understood.

The engineering of genetically modified organisms (GMOs) to improve their physical robustness, extend field and shelf life, tolerate herbicides, grow faster, or grow in previously unproductive environments (e.g., in high-salinity soils, with less water, or in colder climates) is certainly of potential benefit to society [Butler et al., 1999]. Beyond systemic disease resistance, *in vivo* pesticide production has already been demonstrated (e.g., in corn) and could have a significant effect on pesticide production, application, regulation, and control with targeted release. Conceivably, organisms could be engineered to produce or deliver drugs for human disease control. For instance, bovine mammary glands could be engineered to produce pharmaceuticals and therapeutic organic compounds; other organisms might be engineered to produce or deliver therapeutics [Gurdon et al., 1999].

Experiments to clone mammals from single somatic cells are currently hampered by high frequencies of developmental abnormalities and death [Matzke and Matzke, 2000; RAND 2001]. Even cloned plant organisms display unacceptable developmental and morphological irregularities. Cloning, especially human cloning, has already generated significant ethical concerns worldwide that are likely to increase as cloning techniques become more successful. Apart from moral and ethical concerns, other valid concerns include the potential for errors and medical deficiencies of clones, questions of the ownership of good genes and genomes, and eugenics. Although some attempts at human cloning are possible, and some scientists have already signaled their willingness to participate in these trials, legal restrictions and public opinion may well limit their extent [Cho et al., 1999].

Gene therapy and molecular medicine

Proteins are the main structural elements, signaling messengers, catalysts and molecular machines of biological systems. Accordingly, manipulating specific genes for an individual protein will likely have significant structural and functional consequences for that protein and all related cellular functions. The availability of fully sequenced genomes and gene expression now opens new possibilities for molecular protein engineering [Eisenberg et al., 2000].

Gene therapy, the treatment or prevention of disease by gene control/transfer, is an immediate application of such an effort. Gene therapy will most likely revolutionize medicine by treating the cause rather than symptoms of disease. Extensive genetic profiling could significantly assist in better diagnostics for human health problems, the design of improved drugs tailored for individual treatments, more faithfully predict disease predispositions, and track disease movement and development across global populations, ethnic groups, and other genetic pools [Bock et al., 2000].

For the past decade, much progress has been made in gene therapies related to gene transfer to somatic cell *ex vivo* or *in vivo* [Mountain, 2000]. For gene transfer systems, the leading viral vectors generally give the most efficient transfection. In on-going clinical studies, approximately two-thirds of gene therapy trials are directed towards cancer treatment, and the remainder is targeted at monogenic disorders or infectious diseases (particularly HIV) [Mountain, 2000]. Currently, the most appealing features of gene therapy are [Mountain, 2000]:

- Destruction of cancerous tumor cells with genes.
- Delivery of naked DNA for preventative vaccination against infectious disease (particularly HIV).
- Naked DNA for cardiovascular disorders.
- Gene delivery for chromis disorders, such as anaemia and haemophilia.

It has been widely reported [Mountain, 2000; Roses, 2000] that the outcome of trials, in terms of gene therapy and biological consequence, is currently disappointing and considerable effort will be required to develop effective gene therapies.

Developments in genomics and proteomics have been the impetus behind the growing field of Pharmacogenetics, which explores how genetic differences influence the variability in patients' responses to medicines. Through the use of pharmacogenetics, it is likely that profiling variations between individuals' DNA will become the basis for a particular medicine for a particular individual. Molecular medicine is indeed founded on such an individualized genetically oriented medicine [Roses, 2000; Reiss, 2001]. Molecular medicine, in its true sense, no longer targets the symptoms of disease like conventional drugs do today. Rather it will target the specific functional proteins of diseased cells via genomic and genetic approaches.

A major challenge is just how to find the particular target for a particular drug. Roughly half of the genes that have been sequenced are completely unknown genes that appear to be species specific. Another issue is the accepted principle that one gene leads to a transcript RNA which in turn leads to one protein with a single function. Current evidence suggests this functionality is much more complicated – one gene may have a variety of outcome functions [Bock et al., 2000]. The total number of protein-encoding genes is estimated at ~ 30,000 for human being [Dennis et al., 2001; Jasny et al., 2001], and the total number of known diseases is estimated at ~1500 [Peltonen and McKusick, 2001; NCBI website]. While impressive progress has been made in this field, it is clear

that target validation and its applications in molecular medicine still have many years of work ahead of it [Reiss, 2001].

5.2 Single Biomolecule Dynamics and Manipulation

Recent advances in the detection and manipulation of single molecules, such as SPM, laser tweezers, and high-resolution laser fluorescence microscopy, offer great promise for an increased understanding of the behavior of individual biological molecules in cells and allow real-time observations of molecular interactions and movement within living conditions [NIGMS, 2000]. Single molecule biomechanical studies have been used to manipulate individual molecules and to measure the force generated by molecular motors or covalent bonds [Strick et al., 2001].

Probing and Visualization of Single Molecules in Cells

Scanning probe techniques allow imaging of single molecules on surfaces, and specialized optical tweezer techniques enable their characterization and manipulation in complex environments. These tools enable individual members of a population to be examined, identified, and quantitatively compared within cellular sub-populations and substructures. Single molecule studies have the potential to provide spatio-temporal information that is impossible to obtain using conventional static techniques. [Mehta et al., 1999]. For example, X-ray crystallography, NMR, and electron microscopy provide enormous amounts of information on molecular structure, yet none of these methods can be used to make measurements on the *in vivo* dynamics of single molecules in intracellular conditions or to observe the behavior of single molecules over extended periods of time.

Single molecule methods should make it possible to study time trajectories and reaction pathways of individual molecules in a cellular assembly without averaging across populations. Cellular processes, such as exocytosis, flux through channels, or the assembly of transcription complexes, could be visualized. Individual differences in structure or function generated by allelic polymorphisms should be detectable at the level of the single molecule [Song et al., 1996]. Monitoring the coordinated expression of a gene or group of genes in specific tissues, or at certain developmental stages, is within reach using these technologies [Simmons et al., 1996].

Potentially any biological molecule is a candidate for study. Typical molecules chosen for study are members of multicomponent systems that change in response to environmental conditions or specific cellular signals. Current examples of experimental systems include: Single-molecule study of protein catalysis and folding [Zhuang et al., 2000; Liphardt et al., 2001]; conformational changes [Fisher et al., 2000]; pathways, existence of intermediates [Davenport et al., 2000]; single molecule study of transcription of RNA polymerase [Yin et al., 1999]; kinetics, heterogeneity and mechanism of enzyme catalysis [Lu and Xie, 1998]; Ion channels, kinetics, phosphorylation dynamics; DNA mechanics [Bustamante et al., 2000; Baumann et al., 2000], protein-protein interactions in real time [Viani et al., 2000]; and binding constants, and regulation of gene expression [Meller et al., 2001].

Meller et al. (2000 & 2001) devised a technique for probing, and eventually sequencing and manipulating individual DNA molecules using single-channel recording. This technology is based on a very high-speed method that first translates the characteristics of a polynucleotide into electronic signals. This then has the potential to sequence DNA at very high frequencies and can probe very long stretches of DNA or RNA. It is a high throughput, single molecule technique compatible with high levels of nanofabrication, and has particular promise applied to bio-nanotechnology.

Performing 3-D visualizations of single biomolecules in real time at high resolution is not an end in itself. More importantly, one wishes to use that information to analyze complex cellular processes, such as signaling, transcription, or translation, etc. A better understanding of the spatio-temporal regulation of individual cellular events, movements and trafficking within the cell, can be achieved through single molecule studies. Specialized instrumentation and methodologies are required to meet the challenges of detecting single molecules in complex 3-D environments, such as whole cells, tissues and blood. Probing and visualization of single biomolecules is also leading to the understanding of complex cellular structures (e.g., transcription complexes) and functions (e.g., enzymatic catalysis) [Strick et al., 2000 & 2001].

Dynamics and Manipulation of Biomolecules

Based on the progress in probing and visualization of single biomolecular properties, the study of molecular interactions and dynamics on large ensembles of molecules is being actively pursued. This is being driven by developments in understanding complex cellular structures and their functions, and the sciences of genomics and proteomics. Dynamical studies on biomolecules may assist in uncovering the mechanisms of protein folding, RNA/DNA folding, single molecule enzymology, and molecular motor proteins.

Protein folding is one of the most fundamental and complex problems in modern biology. Understanding and controlling protein folding/unfolding are essentially the basis for future genomics, proteomics and bio-nanotechnology. Protein folding is a particularly good target for the application of single-molecule methods. Different folding pathways and transition states for the folding reaction cannot be singled out in a heterogeneous ensemble of molecules. Fluorescence resonance energy transfer (FRET) has been used for years to make spectroscopic distance measurements on protein folding [Weiss, 1999]. Recent advances in new fluorescent dyes and optical methods have increased the spatial resolution, distance range, and sensitivity of this method so that it continues to be one of the few tools available for measuring nanometer-scale distances in biological molecules. In FRET, energy is transferred from a donor to an acceptor fluorophore over a range of 2-10 nm. An excellent model system for FRET studies is the single-molecule folding of chymotrypsin 2 inhibitor (C12), which has been analyzed by Weiss and colleagues [Bruchez et al., 1998; Weiss, 1999].

Enzymatic dynamics is also a key subject of biomolecular dynamics. Xie and co-workers have probed single molecule enzymatic dynamics [Xie et al., 1996; Lu et al., 1998]. They observed enzymatic turnovers of single cholesterol oxidase molecules in real time by monitoring the emission from the enzyme's fluorescent active site, and analyzed the single-molecule trajectories, revealing a significant and slow fluctuation oxidation. Static disorder and dynamic disorder, which are indistinguishable in ensemble-averaged experiments, were determined separately by the real-time single-molecule approach. A molecular memory phenomenon, in which an enzymatic turnover was not independent of its previous turnovers because of a slow fluctuation in protein conformation, was also observed. Their work of single-molecule experiments under natural biological conditions also revealed that the active site of the enzyme involves a flavin adenine dinucleotide (FAD). The FAD emission turned on and off, each on-off cycle corresponding to an enzymatic turnover. The conformational changes caused the rate fluctuation. The rate fluctuation is not described by the macroscopic Michaelis-Menten mechanism of enzymology, but rather by single molecular dynamics [Xie and Lu, 1999].

Another key dynamical and functional biomolecule is the molecular motor [see section 3.3 Molecular Motors]. A complete understanding of how molecular machinery works requires characterization of the individual activities, when and why they occur, what structural components are required in each

case, and what the biochemical parameters are. Since ensemble measurements will give only averages across a mixture of molecules engaged in a variety of these different behaviors, single molecule measurements may be the only way to examine the characteristics of each type of behavior independently.

The ability to control and manipulate individual biomolecules can have very profound effects in nanobiotechnology. The general objectives in this newly emerging science of nanobiotechnology are combining the knowledge base from silicon-based electronic devices and biological life sciences, and developing systems which can be used for the characterization and manipulation of individual polynucleotide molecules, such as of DNA and mRNA. For example, the use of DNA as molecular wires in a complex bio-electronic system, measurements of important properties of DNA, and realization of DNA/electronic interface devices [Borath et al., 2000; Drekker, 2001] are important long-term goals in molecular medicine, functional proteomics and bio-nanotechnology.

The goals of single biomolecule research are to observe the dynamic behavior of individual molecules, to explore heterogeneity between molecules, and to determine mechanisms of molecular/cellular action. Single molecule studies are uniquely designed to yield information about molecular motion, behavior, and fluctuations over time and space. An important aspect of research in this field will be to measure features of individual molecules otherwise shrouded in ensemble measurements. Real-time dynamics of single molecules in live cells, relative to *in vitro* studies, will be particularly useful [NIGMS, 2000].

5.3 Quantum Biology

Quantum physics and molecular biology are two disciplines that have evolved relatively independently. Recent evidence [Ritz et al., 2002; Seife, 2000] has demonstrated the importance of quantum mechanics for biological systems and thus a new field of quantum biology is emerging. Living systems routinely make and break chemical bonds, a unique quantum mechanical phenomena. Absorbance of frequency specific radiation (e.g., photosynthesis and vision), conversion of chemical energy into mechanical motion (e.g., ATP dynamics) and single electron transfers through biological polymers (e.g., DNA or proteins) all involve quantum mechanical effects. It is likely that the merging of disciplines known collectively as nanotechnology will remove the traditional interface between quantum physics and biology.

Tegmark (2000 a & b) sought to prove that the brain is too warm to maintain the coherence required for quantum computation, and thus concluded that classical approaches to neural network simulations are valid. This statement contradicts the hypothesis that the brain functions as a quantum computer, originally proposed by Penrose (1998). However, the computations carried out by Tegmark relied on a value of 310K for the temperature in his model of the neuron. While the temperature of an entire brain cell may be 310K, life does *not* exist under conditions of thermal equilibrium and thus, our statistical method for measuring temperature breaks down at small sizes, particularly at the nanoscale.

Biological systems are known to have ways of manipulating local temperatures. For instance, it has been calculated that actomyosin complexes (existing in the axons of nerve cells) can reach local temperatures as low as 0.0016 K [Matsuno, 1999]. It is claimed they function as a heat engine (a device that converts heat energy into mechanical energy) that is able to maintain a constant velocity due to quantum mechanical coherence and entanglement.

While most biochemical studies of actomyosin and other proteins ignore subtle quantum mechanical effects such as superposition, coherence and entanglement, there may be much to be gained from such models. For example, regulatory molecules and pharmaceuticals may interact with the protein not only as a lock and key, but also as several locks and several keys. However, the exact geometry upon which coherence and entanglement would depend (if indeed significant) is not yet known.

5.4 Nanotechnology in Agriculture

It is easy to speculate on potential applications of nanotechnology to agriculture but concrete examples of research currently in progress are difficult to identify. Applications to agriculture are centred on biotechnology or gene technologies rather than nanotechnology per se. For example, molecular scale gene/genomics and proteomics is being applied to agriculture for the purpose of improving control of food growing and food processing. Carbon-based nanofibers could result in lighter, stronger and longer lasting textiles. Agriculture could also benefit from the nano-aided synthesis and processing of agricultural chemicals such as chemicals using nano-particles as catalysts.

Due to the scarcity of concrete scientific achievements in applying nanotechnology to specific agricultural goals (apart from genomics/proteomics and genetically modified organisms already described) we are reluctant to comment on the more speculative and unsubstantiated claims being raised in the literature. Suffice it to say that this application of nanotechnology is still in an embryonic stage.

SECTION 6 CONCLUSIONS AND RECOMMENDATIONS

Considerable progress has been made in the static aspects of nanotechnology such as nano-materials and precursor technologies (detailed in Appendix A). The main challenge is to make substantial progress in the ‘dynamic’ areas, such as self-assemblers, molecular motors, and in nano-computing. Researchers are exploring self-assembly – molecular designs that automatically arrange themselves into desired patterns or devices. Nature provides ample examples of such dynamic entities in each living cell. For example, DNA is a remarkable self-assembling machine: a nano system that, under the right conditions, creates not only replicas of itself, but incredibly complex organisms. Therefore, nanotechnology is likely to benefit greatly from the insights obtain from biotechnology. In the short term at least, progress in dynamic areas of nanotechnology is likely to come from nanobiotechnology applications, such as gene delivery and therapy, single biomolecular manipulation, molecular motors and structural and quantum biology, etc. Ultimately, the usefulness of molecular devices will depend on progress in developing suitable control and instruction mechanisms such as nanoscale computers. It is apparent that nanotechnology will benefit greatly from insights gained from molecular computation, quantum computing and nanobiotechnology.

Australia, in particular Victoria, has considerable expertise in some nanotechnology-related areas such as genomics and proteomics, nanotubes and nanoparticles, and molecular simulation. However, we do need both national and state strategies to embrace and fully participate in the emerging science.

Given our strength and national interest in nanotechnology, we would recommend investing resources into the following areas:

- molecular medicine, genomics and proteomics;
- nanobiotechnology – e.g., hybrid nanoparticles, smart drug delivery and molecular motors; and
- computational nanotechnology – e.g., molecular design, modelling and simulation.

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APPENDIX A. PRECURSOR TECHNOLOGIES

A.1 Nanolithography and NEMS

Lithography and NEMS involve techniques designed to carve and fabricate smaller and thinner devices. Sub-micro (or Nanoscale) lithography has been specifically required by the immediate needs for the manufacture and constant minituarisation of computer chips.

IBM, as part of its "Sub-100nm Interferometer Lithography Project" [IBM, 2001] is enabling fabrication, stability and determination of physical properties of small structures down to below 100nm. Despite reaching into the nanometer length scales and being termed 'nanolithography', this technology is a natural extension of mature microelectronics and computer technologies.

Progress in 'nanolithography' has also been made across the computer industry for optical or electron beam lithography. Similarly, advances in this field are still along the traditional track of 'cut and carve' and not with the serious manipulation of individual atoms and molecules.

NEMS

NEMS stands for 'Nano Electromechanical Systems'. It has been shown that manipulating carbon nanotubes changes their electrical properties. This might be exploited to build nanometer scale strain devices, and may be achievable within 3-5 years. Computer simulations along these lines are in progress and show promise. Similar results have been achieved experimentally with C₆₀ [Joachim 97], i.e. the electrical properties of a C₆₀ molecule were changed by applying pressure to the molecule with an SPM.

A.2 Biosensors

The earliest biosensors were catalytic systems integrating enzymes, cellular organelles, tissues or whole microorganisms with transducers that converted a biological response into a digital electronic signal. The principal transducers used were electrochemical, optical, or thermometric. Affinity biosensors were the successors of catalytic systems, and used piezoelectric transducers (that interconvert mechanical deformation and voltage to measure mass or viscoelastic effects) and magnetic transducers. Affinity biosensors deliver real-time information about the binding of antibodies to antigens, cell receptors to their ligands, and DNA and RNA to nucleic acid with a complementary sequence. Both types of sensors may be used to measure blood glucose levels, detect pollutants and pesticides in the environment, monitor food-borne pathogens in the food supply, or to detect biological warfare agents. The design of semi-synthetic receptors in biosensors may in the near future be superseded by synthetic ligands produced with the aid of computational and combinatorial chemistry, molecular imprinting, self-assembly, rational design, or combinations thereof.

A.3 Genechip and Lab-on-a-chip

'Lab-on-a-chip' devices are based on silicon chip technology, with some already in commercial production, dramatically shortening the timescales for all kinds of analysis. On a silicon chip, micro-scale channels direct picolitres of sample fluid into active sensing sites that can be from 10-200

micrometres in diameter. These channel widths are already shrinking as the technology improves. The miniaturisation of all components has the immediate effect of speeding up the whole analytical process, giving results in minutes rather than hours.

Lab-on-a-chip technology has a variety of applications, from fast throughput DNA analysis and cell separation to new drug discovery based on measuring the reaction of single cells to various therapeutic compounds. Hand-held devices are heralding the way to the creation of miniature diagnostic laboratories. Preventive medicine could be made cheaper by widespread application of this technology, whilst applications in defence are being pursued, for example, as advance warning systems for chemical or biological weapons.

The advent of biochips means that in less than a decade a device may well become available enabling, almost instantaneously, an individual's entire genetic code to be mapped from a single drop of blood – in this case, it is called the 'Gene-chip' or 'DNA-chip'. These chips also have applications in agriculture, enabling scientists to understand why some strains of plants are hardier and more disease resistant than others.

A future development in chip technology may well be in the timed release of measured doses of drugs from inside a microchip, triggered by a microprocessor, remote control, or inbuilt sensor. This so-called 'pharmacy-on-a-chip' idea has the potential to monitor conditions such as diabetes, causing an automatic dose of insulin to be administered. This technique might similarly act as an artificial means of regulating and maintaining the body's own hormonal balance. We point out here that, while desirable, these ideas are just that: ideas. They are yet to be realized, and there are significant technical hurdles to be overcome .

A.4 Fabrication, manipulation and manufacturing

Varied approaches to fabricating nanostructures have emerged in recent years. Like so-called 'nanolithography', top-down practitioners chisel out or add bulk material to a surface. In contrast, bottom-up manufacturers, to manipulate atoms or molecules one by one, or use self-assembly processes to put together larger structures of atoms or molecules that spontaneously make ordered arrangements, require revolutionary tools and methods. Examples of such tools are scanning probe microscopes (SPM), the scanning tunneling microscope (STM) and the atomic force microscope (AFM). These instruments are capable of creating pictures of individual atoms or moving them from place to place. Besides SPM, other ways to manipulate single molecules are also highly sought, such as optical or magnetic tweezers, or glass microfibers [Whitesides and Love, 2001].

A.4.1 SPM, STM and AFM

The SPM Technique

It is well known that the properties of the surface of a solid differ dramatically from those of the bulk, due to the difference in nearest neighbour numbers, types, and hence, interactions. As an example, surface atoms often arrange themselves differently from the other atoms in a solid to ensure that their energy is minimised.

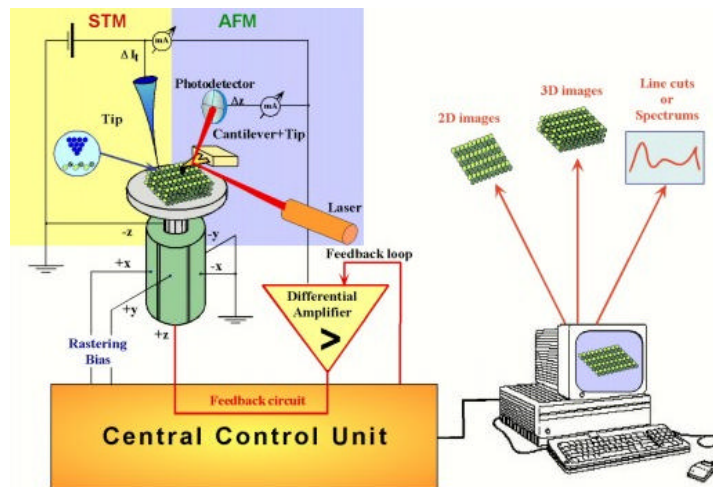


Figure A.1 Illustration of the integration of key components of STM/AFM.

Scanning Probe Microscopy (SPM) evolved from the Scanning Tunneling Microscope (STM) [Binnig et al., 1982a,b,c,d; 1984] (Figure A.1). The STM genuinely revolutionized the study of solid surfaces, and enabled for the first time tracking images and performing spectroscopy of surfaces with atomic resolution. As the STM is limited in its operation to conducting surfaces, an entire family of imaging technologies based on various physical interactions appeared. Such technologies include the Atomic Force Microscope (AFM) [Binnig et al., 1986], which can image insulating surfaces with near-atomic resolution, the Lateral Force Microscope (LFM) [Mate et al., 1987], the Magnetic Force Microscope (MFM) [Martin et al., 1987], the Force Modulation Microscope (FMM) [Albrecht et al., 1992], the Phase Detection Microscope (PDM) [Albrecht et al., 1992], the Electrostatic Force Microscope (EFM) [Stern et al., 1988], the Scanning Capacitance Microscope (SCM) [Matey et al., 1985], the Thermal Scanning Microscope (TSM) [William et al., 1986], the Scanning Electrochemical Microscope (SECM) and the Scanning Near-Field Optical Microscope (SNOM) [Pohl et al., 1984; Durig et al., 1986].

The SPM gives scientists a closer than ever before view of the atomic world, allowing visualization and manipulation of single atoms or molecules. The two most widely used of the three dimensional atomic resolution SPMs are the STM and the AFM, which generates images by measuring the atomic forces of interaction between its scanning tip and the sample's surface atoms. However, only STM allows the study of both topographical and electrical properties of materials, important for understanding the behaviour of microelectronic devices. The STM is also the only instrument with the ability to remove single atoms from the sample surface and relocate or otherwise manipulate them.

Current resolution with optical nanolithographic techniques is of the order of about 250 nm. These methods are expected to reach their limit at around 100 nm in the next few years. This is due to the wavelength restriction of the ultraviolet light used to project the circuit image onto a chip. In contrast, the STM can easily make devices in the sub-100nm resolution range. Recently it has been used to produce chemically modified silicon surfaces with 2 nm resolution. In these experiments, electrons from the STM tip were used to trigger local chemical reactions between the surface and adsorbed gas molecules.

A.4.2 ‘Dip-Pen’ Nanolithography (DPN)

Dip-Pen Nanolithography (DPN) [Piner et al., 1999] is a new AFM-based, direct-write soft lithography technique. It is used to create nanostructures on a substrate by delivering collections of molecules by capillary transport from an AFM tip to a surface.

Creating nanostructures using DPN is a single step process not requiring the use of resists. Using a conventional AFM it is possible to achieve ultra-high resolution features as small as 15 nm linewidths and ~ 5 nm spatial resolution [Hong et al., 2000]. For nanotechnology applications, it is not only important to pattern molecules with high resolution, but also to functionalize surfaces with patterns of two or more components. In a DPN the same device is used to image and write a pattern. Hence, patterns of multiple molecular ‘inks’ can be formed on the same substrate with very high alignment. Such a feature was recently used to create a DPN nanoplotter capable of writing any type of complicated pattern [Ivanisevic et al., 2001].

Other applications of DPN include:

- ?? Using DPN to probe fundamental surface science questions as well as to create technologically relevant nanostructures.
- ?? To form solid, three-dimensional nanostructures, even with different adsorbate-substrate combinations, in particular for systems important to nanofabrication, molecular electronics, optoelectronics, and bio-related materials.
- ?? To build customized structures in arrays consisting of several to thousands of components that can be combinatorially screened for certain processes, for instance catalysis.

A.4.3 Optical Manipulation of Molecules and Nanoparticles

Besides AFM cantilevers, optical or magnetic tweezers are the most successful techniques to manipulate single atoms or molecules. In particular, laser tweezers are very powerful for nanoparticles [Chu, 1991] or DNA, proteins, or other biopolymers that have one end bound to a surface and the other to a force sensor [Kuo et al. 1993; Mehta et al., 1999].

Laser tweezers were first used in manipulating single cells [Ashkin et al., 1987a&b]. The force sensor is usually a micron-sized bead or a cantilever. The sensor’s displacement allows one to determine the magnitude of the force. The sensor behaves like a noisy damped oscillator. For any given temporal resolution, the force measurement depends solely on the dissipation due to viscous drag. To reduce noise in the measurement of force, smaller sensors are better. To reduce noise in measurements of displacement, one wants to use shorter, more rigid molecules. Different optical operation addresses different scales of displacement, time, and force on single nanoparticles or biomolecules [Simmons et al., 1996].

Compared with AFM cantilevers, that can measure angstrom length-scales, millisecond events and forces larger than 10 pN, optical tweezers allow the measurement of piconewton forces and nanometer displacements. Magnetic tweezers can measure femtonewton forces. They can also twist a molecule by rotating the attached magnetic bead or an attached microfiber.

In the tweezing and pulling of DNA molecules and their associated proteins and enzymes, it has been demonstrated that the tweezers technique is both simple and powerful [e.g., Finer et al., 1994]. Briefly, it consists of stretching a single molecule while it is anchored at one end to a surface and, at the other end, to a magnetic bead whose diameter is on the order of a micron. Small magnets whose position and rotation can be controlled are used to pull and rotate the microbead, thus stretching and twisting the molecule [Strick et al., 2001].

A.5 From Lithography to Molecular Electronics

Solid-state and silicon-based electronics follow one of the most famous axioms in technology: Moore's Law. It states that the number of transistors that can be fabricated on a silicon integrated circuit (and hence the computing speed of such a circuit) is doubling every 18 to 24 months. After being faithful to this law for four decades, solid-state microelectronics has evolved to the point at which now a thin slice of silicon of just a few square centimeters contains some million transistors, with key features measuring 0.18 micron. In a dozen years silicon transistors are likely to shrink to about 150 nanometers in length. Thus traditional microelectronics is approaching the technology limit for a 'top-down' lithography-based fabrication process. 'Bottom-up' molecular electronics, or nanoelectronics, emerges at the end of limit of Moore's Law.

Nanoelectronics is based on electronically functional structures that are fabricated on an atomic and molecular length scale, to perform functions identical or analogous to transistors, diodes, conductors and other key components of existing microcircuits. Such structures can be created with a variety of methods (most promisingly, self-assembled) in a variety of different material systems. The interfaces between different materials at such a nano scale enable device designers to confine single electrons, and control quantum mechanical interactions/transitions between different electronic quantum mechanical states. The emergence of nanoelectronics is highlighted by the latest progress in nanotube-based transistors, quantum computers, molecular computing, and ultrahigh density data storage and display, etc.

Appendix B: Glossary of Terms

Assembler: a general-purpose device for molecular manufacturing capable of guiding chemical reactions or biological processes by positioning molecules.

Atom: the smallest unit of a chemical element, about a third of a nanometer in diameter. Atoms make up molecules and larger objects.

Atomic Force Microscope (AFM): an instrument able to image surfaces to molecular accuracy by mechanically probing their surface contours. A kind of proximal probe.

Automated Engineering: Engineering design done by a computer system, generating detailed designs from broad specifications with little or no human help.

Automated Manufacturing: as used here, nanotechnology-based manufacturing requiring little human labor.

Bacteria: single-celled microorganisms, about one micrometer (one thousand nanometers) across.

Biomolecular Nanotechnology (nanobiotechnology): nanotechnology existing in living systems and resulting from our ability to use biomolecules as components for molecular nanotechnology.

Bottom-Up: building larger objects from smaller building blocks. ‘Bottom-up’ nanotechnology seeks to use atoms and molecules as blocks to build up nanodevices or systems via self-assembling or direct manipulation of molecules. The advantage of bottom-up design is that the covalent bonds holding together a single molecule are far stronger than the weak interactions that hold many molecules together.

Bulk Technology: technology in which atoms and molecular are manipulated in bulk, rather than individually.

Cell Pharmacology: delivery of drugs by medical nanomachines to exact locations in the body.

Cell Surgery : modifying cellular structures using medical nanomachines.

Conformation: the shape of a molecule. Since the covalent bonds connecting each atom within a molecule can rotate and bend, a single molecule can take on numerous conformations. Due to entropy, the lowest energy conformation is the most likely.

Disassembler: an instrument able to take apart structures a few atoms at a time, recording structural information at each step.

DNA: deoxyribonucleic acid. DNA consists of two associated polynucleotide strands that wind together in a helical fashion, thus often called the double helix. DNA chains consist of deoxyribose, phosphoric acid and organic (nitrogenous) bases. The sequence of bases normally is referred as the genomic information. In addition to functioning as building blocks of nucleic acids, nucleotides are important because they are used to store and transfer chemical energy.

Electron Beam Lithography (EBL): a method of fabricating sub-micron and nanoscale features by exposing electrically sensitive surfaces to an electron beam. The method is similar to photolithography, but uses electrons rather than photons. Since the wavelength of an electron is far smaller than that of a photon, diffraction is not a limit to the resolution. While EBL is more expensive and less parallel than photolithography, its resolution is higher and it is frequently used to create photolithographic masks.

Enzymes: molecular machines found in nature, made of proteins, which can catalyze (speed up) chemical reactions.

GM: genetically modified.

GMO: gene modified organism.

Immune Machines: medical nanomachines designed for internal use, especially in the bloodstream and digestive tract, able to identify and disable intruders such as bacteria and viruses.

Limited Assembler: assembler capable of making only certain products faster, more efficient, and less liable to abuse than a general-purpose assembler.

Molecular Electronics: any system with atomically precise electronic devices of nanometer dimensions, especially if made of discrete molecular parts rather than the continuous materials found in today's semiconductor devices.

Molecular Machine: any machine with atomically precise parts of nanometer dimensions. Can be used to describe molecular devices found in nature.

Molecular Manipulator: a device combining a proximal probe mechanism for atomically precise positioning with a molecule binding site on the tip; can serve as the basis for building complex structures by positional synthesis.

Molecular Manufacturing: manufacturing using molecular machinery, giving molecule-by-molecule control of products and by-products via positional chemical synthesis or other means.

Molecular Medicine: a variety of pharmaceutical techniques and therapies to target diseases with a molecular understanding of drug functions.

Molecular Motor: generically a single or an assembly of natural or synthetic molecules operating as enzymes to catalyze chemical synthesis, as ion pumps to generate electrical potential, as shuttles to transport molecules, and as motors to generate mechanical force. They are the working machines of cells. Just as mechanical motors convert chemical or electrical energy into mechanical motion (or vice versa), so too do biological molecular motors convert cellular energy into mechanical motion and fulfill cell functions.

Molecular Nanotechnology: thorough, inexpensive control of the structure of matter based on molecule-by-molecule control of products and byproducts; the products and processes of molecular manufacturing, including molecular machinery.

Molecular Recognition: a chemical term referring to processes in which molecules adhere in a highly specific way, forming a larger structure; an enabling technology for nanotechnology.

Molecular Surgery or Repair: analysis and physical correction of molecular structures in the body using medical nanomachines.

Molecular Systems Engineering: design, analysis, and construction of systems of molecular parts working together to carry out a useful purpose.

mRNA: messenger RNA. mRNA carries the genetic information out of the nucleus for protein synthesis. (RNA: ribonucleic acid. RNA is a linear chain in which the monomers (nucleotides) are linked together by means of phosphodiester bonds. It consists of ribose, phosphoric acid and organic (nitrogenous) bases).

Nano-: a prefix meaning one billionth (1/1,000,000,000).

Nanocomputer: a computer with parts built on a molecular scale.

Nanoelectronics: electronics on a nanometer scale, whether made by current techniques or nanotechnology; includes both molecular electronics and nanoscale devices resembling today's semiconductor devices.

Nanomachine : an artificial molecular machine of the sort made by molecular manufacturing.

Nanomanufacturing: see Molecular Manufacturing.

Nanosurgery: a generic term including molecular repair and cell surgery.

Nanotechnology: see Molecular Nanotechnology.

NEMS: Nano-electromechanical systems.

Positional Synthesis: control of chemical reactions by precisely positioning the reactive molecules; the basic principle of assemblers.

Protein Design/Protein Engineering: the design and construction of new proteins; an enabling technology for bio-nanotechnology.

Proximal Probes: a family of devices capable of fine positional control and sensing, including scanning tunneling and atomic force microscopes; an enabling technology for nanotechnology.

Quantum Computer: a computer based on quantum mechanical materials and operations, such as superposition and entanglement resulting from nanoscale, molecular, atomic and subatomic components.

Qubit: in quantum computers, the logical states are not limited to two states; they encode information as quantum bits, or qubits. A qubit can be a '1', a '0', or it can exist in a superposition that is simultaneously both '1' and '0' or somewhere in between.

Replicator: a system able to build copies of itself when provided with raw materials and energy.

Scanning Tunneling Microscope (STM): An instrument able to image conducting surfaces to atomic accuracy; has been used to pin molecules to a surface.

Self-Assembly: a method of integration in which the components spontaneously assemble, typically by moving in a solution, gas phase or interface until a stable structure of minimum energy is reached. Components in self-assembled structures find their appropriate location based on their structural properties (or chemical properties in the case of atomic or molecular self-assembly), with an energy difference between the starting and finished state being the driving force. Self-assembly is by no means limited to molecules or the nanoscale and can be carried out on just about any scale, making it a powerful bottom-up method for nanotechnology.

Self-organisation: the spontaneous order arising in a system when certain parameters of the system reach critical values. Self-organisation occurs in many systems in physics, chemistry and biology. Self-organisation can occur when a system is driven far from thermal equilibrium. Since a self-organising system is open to its environment, the second law of thermodynamics is not violated by the formation of an ordered phase, as entropy can be transferred to the environment. Self-organisation is related to the concepts of broken symmetry, complexity, nonlinearity and nonequilibrium statistical mechanics. Many systems that undergo transitions to self-organisation can also undergo transitions to chaos.

Sealed Assembler Lab: a general-purpose assembler system in a container permitting only energy and information to be exchanged with the environment.

Smart nano-Materials and Products: materials and products capable of relatively complex behavior due to the incorporation of nanocomputers and nanomachines. Also used for products having some ability to respond to the environment.

Top-down: building smaller objects from larger building blocks. ‘Top-down’ nanotechnology refers to making nano-scale structures by machining and etching techniques, similar to traditional manufacturing and fabrication processes that apply machinery forces to cut, bend, mould, glue, bolt or otherwise connect materials together.

Appendix C: Major Web Resources

Major nanotechnology-related web sites are listed below.

- Foresight Institute, <http://www.foresight.org/>
- Institute of Nanotechnology, UK, <http://www.nano.org.uk/>
- Nanoscale Science and Engineering Program, The National Science Foundation, USA, (<http://www.nsf.gov/nano/>)
- Nanotechnology at www.about.com, <http://nanotech.about.com/library/>
- Nanotechnology Magazine
- Nanotechnology: Science of Small Things (www.futurist.com).
- NASA: nanotechnology <http://www.nas.nasa.gov/Groups/SciTech/nano/index.html>
- National Nanotechnology Initiative, 2000, USA, <http://www.nano.gov/>
- Nanotechnology in Australia, <http://www.nanotechnology.gov.au/>