Chapter 4

SYNTHESIS, ASSEMBLY, AND PROCESSING OF NANOSTRUCTURES

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4.1 VISION

Synthesis and processing of nanostructures will employ a diverse array of material types—organic, inorganic, and biological—well beyond examples already realized. The driving forces will be creativity, applications, opportunities, and economics in broad areas of science, medicine, and technology. Increasing emphasis will be placed on synthesis and assembly at a very high degree of precision, achieved through innovative processing. The result will be control of the size, shape, structure, morphology, and connectivity of molecules, supermolecules, nano-objects and nanostructured materials and devices. Integration of top-down physical assembly concepts with bottom-up chemical and biological assembly concepts may be required to create fully functional nanostructures that are operational at mesoscopic scales. The combination of new nanoscale building blocks and new paradigms in assembly strategies will provide nanostructured materials and devices with new, unprecedented capabilities limited only by our imagination.

4.2 CURRENT SCIENTIFIC AND TECHNOLOGICAL ADVANCEMENTS

Recent Scientific Advances

Synthesis of Individual Building Blocks

Polymeric materials, dendrimers, and block copolymers. The last decade has seen tremendous advances in the preparation of organic building blocks of considerable complexity (Matthews et al. 1998; Stupp et al. 1997; Tomalia 1994). The discovery of a new topology for polymers, dendrimers, has led to an exciting new class of nanoscale component, with interesting optical and mechanical properties. Precise nanoscale architectures ranging between 10 and 100 nm have been successfully synthesized. These constructions involve the reaction of an excess of dendrimer shell reagent with a reactive dendrimer core reagent. The new compositions are referred to as tecto (dendrimer) core-shell molecules. These molecules have demonstrated potential as unique nanoscale reactors, intermediates for new coatings/controlled delivery, compatibilizers, and building blocks for higher order nanoscale constructions. There have also been steady advances in engineering new phases using block copolymers; the recent development of tri-component block copolymer is noteworthy in this regard.

Nanocrystals. There has been significant progress made in the preparation of nanocrystals in recent years (Brus 1996; Martin 1996). Many common materials, such as metals, semiconductors, and magnets, can be prepared as nanocrystals, using colloidal chemistry techniques. The concepts of ligand exchange and surface derivatization have been well developed, and these methods permit nanocrystals with narrow size distribution (typically 5-15% variation in diameter) to be isolated and then used further as chemical reagents. This field has been aided greatly by improved understanding of size-dependent scaling laws, which have emerged from fundamental studies in chemical physics and condensed matter physics. The fact that a simple property like light emission depends so strongly upon size in semiconductors has greatly facilitated the development of reliable preparations. The same size dependence has also led to a wide range of applications in unexpected areas, such as in biological tagging (Chan and Nie 1998; Bruchez et al. 1998).

Nanotubes and rods. The exciting discovery of the fullerenes was followed closely by the discovery of nanotubes of carbon (Terrones et al. 1999). Nanotubes show tremendous promise as building blocks for new materials. Because of their topology, nanotubes have no dangling bonds, and so despite being very small, they do not exhibit "surface effects." As a consequence, individual nanotubes exhibit nearly ideal electrical, optical, and mechanical properties. Nanorods are also under extensive development and investigation.

Nanoparticle structures. Controlled particle formation is an important synthetic route to nanoscale building blocks relevant to many technologies from ceramics to pharmaceuticals. Some interesting new nanoparticle structures are composed of chain-like arrays of nanoparticles of relatively low coordination number. There are two main types: agglomerates (or aggregates) and aerogels. In particular, these structures can be characterized by their morphology (for example, fractal dimension and coordination number) and the energies of the bonds that hold the primary (individual) particles together.

Processing of Nanostructures

Assembly. The development of self-assembly methodology, which is the archetypal bio-inspired synthesis route, has greatly expanded the methods of construction of nanostructures. In the design of complex materials such as electrical devices, we currently rely on our ability to create designed patterns lithographically. New ways of bonding, assembly, and linking macromolecules and nano-objects have been developed that are based on interactions that are both more complex and individually weaker (e.g., steric, electrostatic, hydrophobic, and hydrogen bonding) than the classical electronic bond. Multiple bonding interactions are often needed to stabilize complex nanostructures. These interactions are the basis for coding information into nanostructures. In the last decade, nanoscale objects such as nanoparticles or nanocrystals have been assembled into periodic arrays, or supercrystals. Such arrays exhibit novel optical and electrical characteristics. Several proposals have been put forward for how to pattern nanocrystals and nanotubes using biological molecules (Mucic et al. 1998; Alivisatos et al. 1996; Braun et al. 1998).

Templated growth of mesoporous materials. In the last decade, tremendous advances have occurred in the preparation of mesoporous inorganic solids (Antonelli and Ying 1996). The initial work showed that it is possible to use organic surfactant molecules to prepare a complex pattern. That pattern can serve as the template for the formation of an inorganic phase. This has led to many exciting discoveries in chemical synthesis and to immediate practical advances in catalysis. Nanoporous media science (the control of void space) has advanced in some very important ways. For example, new scaffolds and matrices for tissue repair and engineering have been realized, and a large range of tailored porous catalysts and membranes, such as Mobil's MCM-41, have achieved commercial success. In another example, Nylon-6 nanocomposite with only two volume percent clay nanoparticles has a heat deformation temperature of 150°C, as opposed to 60°C for traditional Nylon-6.

Direct structuring. The ability to direct the assembly and organization of materials with nanomanipulation and nanolithography, based, for example, on scanning microprobe techniques, has achieved directed assembly and structuring of materials at the molecular level. New methodologies in this area include 3-D printing and various forms of soft lithography.

Nanoimprint lithography. Nanoimprinting will allow for patterning at scales up to 10 nm on large surfaces and with a relatively low cost (see section 4.7.2).

Recent Technological Advances

One key to advanced technology emerging over the past decade has been nanomaterials. The aggressive advance of smart materials, solid state devices, and biomimetic technologies and the concurrent push towards miniaturization are making the understanding and development of materials on the nanometer level critical and are encouraging the design of nanoscale structure and functionality into materials systems. The focus on nanostructuring of materials systems has been further sharpened by the need to develop materials having novel and/or enhanced properties without resorting to new synthetic chemistries with the associated environmental and cost issues. Enhancements in mechanical performance, wear resistance, integrity under thermal stress, flammability, and transport properties have *all* been linked to nanostructure in materials systems within the past five years, demonstrating that the technology has reached a level of maturity where it is ripe for exploitation in systems demanding both high performance and reliability.

A very important technological advance in recent years has been in the area of large-scale, reliable production of uniform, nano-sized particles. This has been particularly important in the high-performance ceramic materials and the pharmaceutical areas, where materials properties, through defect control, drug delivery, and control of uptake, have been favorably influenced by nanoparticle production. Aerogels are normally fabricated by condensed phase (sol-gel) methods, even though the final product is a gas/solid system. Recently, aerogel-like structures have been fabricated directly by gas-phase processes without passing through the sol-gel state. This could lead to less expensive fabrication processes, use of a wider range of materials in aerogel fabrication, and excellent control of multilayer deposition processes, with applications in magnetic (giant magnetoresistance, GMR) and optical devices. Soft lithography and nanoimprinting have been developed and identified as low-cost patterning approaches, with several new applications on the horizon. Nanostructured zeolite catalysts can be tailored to perform oxidation reactions more efficiently than enzymes. While not strictly speaking a nanotechnology, the tremendous advances in organic electronics, such as organic light-emitting diodes, must be noted, since that field is highly likely to benefit from advances in organic nanoscale synthesis in the future.

Potential Impact

New nanostructured materials have the potential to significantly reduce production costs and the time of parts assembly, for example, in the automotive, consumer appliance, tooling, and container industries. The potential of significant reductions in weight due to these new materials as they are applied in the transportation industries will have great impact on energy consumption and the environment. Understanding nanoparticle formation is paying dividends in dealing with environmental issues such as atmospheric particulate formation as well.

Many fundamental phenomena in energy science, such as electron transfer and exciton diffusion, occur on the nanometer length scale. Thus, the ability to arrange matter, i.e., to inexpensively pattern and to develop effective nanostructuring processes, will be a vital asset in designing next-generation electronic devices, photovoltaics, and batteries.

Size and cost reduction due to advances in the design and manufacture of healthcare-related diagnostic systems has the potential to empower individuals to diagnose and treat diseases in their own homes, decentralizing the healthcare system.

Sensors based on nanotechnology will revolutionize healthcare (e.g., via remote patient monitoring), climate control, detection of toxic substances (for environment, defense, and healthcare applications), and energy consumption in homes, consumer appliances, and power tools.

The ability to assemble and interconnect nanoparticles and molecules at nanometer dimensions will enable the development of new types of nanoelectronic circuitry and nanomechanical machinery.

4.3 GOALS FOR THE NEXT 5-10 YEARS: BARRIERS AND SOLUTIONS

New Discoveries and Applications Anticipated in the Next Decade

There is broad opportunity in the next decade for synthesis and processing in applications at the interface with biology. Specific areas include biological synthesis using coded self-assembly and guided assembly using biorecognition capabilities of DNA and proteins; nanoparticles for drug delivery, gene therapy, and immunotherapy; and a wide range of biological probes and sensors. Increasing success is anticipated with bio-inspired processes that interface assembled nanostructures with biological systems.

High-throughput screening methods, that is, methods that measure properties or activities rapidly in spatially addressable ways, will be necessary in order for combinatorial chemistry methods to realize their full potential in new drug and materials development.

New nanotechnology is both an enabler and a result of the development of new high-throughput screening. For example, robotics is expected to be very important in achieving these goals.

Nanotechnology and synthesis will open new frontiers in the design of catalysts and catalyst technology for the petroleum, chemical, automotive, pharmaceutical, and food industries. The design of catalyst supports commensurate with biological structures will be an important bridge between conventional and enzymatic catalysis. In fact, oxidation catalysis can be performed today more efficiently in a zeolite, "ship-in-a-bottle" catalytic complex than with natural enzymes. This is but one example of an entire array of anticipated future developments.

New discoveries are expected and needed in studies of single objects with nanoscale dimensions ranging in size from single molecules, clusters, and particles to organelles and cells. Researchers will learn more about the opportunities for and limits on the synthesis of large, precisely structured objects and clusters. Controlling purity and scale-up of products emanating from such precision syntheses is a major barrier that must and will be tackled in the near future. Many of the important properties of nanostructures depend on obtaining precise building blocks; means of creating and analyzing purity and homogeneity in such products are vitally needed. Furthermore, if production of these materials cannot be done at a sufficiently large scale, this will eventually limit utility in some applications.

While current microfluidics approaches will be effective for manipulating single objects on the scale of one micron or more, new techniques must be developed for single-object manipulation at smaller scales. The ability must be developed to do nanomanipulation in three dimensions to guide nanoassembly in bulk as well as on surfaces. There will be increasing interactions between nanoscale scientists and system designers. An important element of this interaction will be prototyping methods, an intermediate level of implementation between lab-scale demonstration and mass production.

The new nanomaterials will impact not only the performance of the most advanced computational and electronic devices, but also objects of daily use familiar to every consumer, such as cars, appliances, films, containers, and cosmetics.

Paradigm Changes

A significant paradigm shift is expected, owing to our improved ability to address, manipulate, and activate individual molecules and objects. Increasingly, important developments will be made with hybrid or nanocomposite materials, that is, combining very different materials systems (organic, inorganic, and biological) in one integrated structure.

The integration of nanotechnology in medicine, supported by fundamental science bridging the gap between nanotechnology and biology, will be critical in bringing the impact of nanotechnology to the attention of the public. This integration can be expected to bring about revolutionary changes in healthcare as well as advances in biology itself. Further detailed ideas on this are given in Section 4.7.6.

New computer architectures will require new approaches to synthesis and assembly, reflecting the idea (expressed at the IWGN workshop by Horst Stormer) that “wiring” may be more important than “wires” or “switches” in assembling functional nanostructures for computing. New methods for connecting elements of nanostructures will be required. The strain-directed assembly of nanoparticle arrays in a solid (Figure 4.7, after Kiehl et al. 1996), where a top-down physical process (lithographically defined surface structure) is integrated with a bottom-up chemical assembly process (strain and compositionally controlled precipitation), represents an example of a significant trend of integrating fabrication techniques that will be crucial for the fabrication and interconnection of wires and switches. Such integration techniques will provide the means for introducing functionality in the substrate that is coupled to functionality on the surface. A new form of information technology is emerging characterized by ubiquitous interaction with information and the physical world. Full implementation of this will require enormous numbers of sensors and actuators in addition to very small computers.

The education and training of young scientists and engineers in environments conducive to exploring these new paradigms will be essential. This will require some creative approaches to interdisciplinary education.

4.4 SCIENTIFIC AND TECHNOLOGICAL INFRASTRUCTURE

In the area of synthesis, assembly, and processing of nanostructures, several kinds of infrastructure are very important. State-of-the-art characterization tools underpin all efforts to synthesize and manufacture high-precision, high-purity substances; advanced characterization methods must be accessible to those doing this type of work. These include, but are not limited to, neutron, X-ray, and light-scattering tools (some of which require advanced sources such as reactors, spallation sources, and synchrotrons); surface and interface analytical tools; particle characterization; microscopy of all types; and rheological methods. Equally important are synthesis tools themselves, such as nanofabrication facilities. New synthesis facilities, particularly those that might make new materials widely available to a broader range of investigators, could advance the field significantly. Large-scale scientific computation facilities are very important in the design and characterization of nanostructures.

4.5 R&D INVESTMENT AND IMPLEMENTATION STRATEGIES

The guiding principles of R&D investment should be (1) support work that crosses all traditional boundaries, and (2) maintain appropriate balance between centers, teams, and single-investigator grants, and between basic science work and device/applications work. Boundaries to be crossed include those between traditional academic disciplines, between universities and industry, and between countries. Nanoscience and technology requires a spectrum of diversity of talent and approaches that cannot be achieved without crossing boundaries.

4.6 PRIORITIES AND CONCLUSIONS

The large variety of avenues in this broad area of research makes it a richly diversified area for investment objectives. Synthetic chemistry now has the most diverse set of research targets. Priority in future research should be given to projects with clearly articulated interdisciplinary tools. Research on synthesis should endeavor to link itself with research on scale-up or on advanced processing, or with research in fundamental biology. No one field has a monopoly on the tools that will be created to solve these problems: the more interdisciplinarity that can be brought to bear the better. Nanotechnology is perhaps the one field with the most to exploit from bringing all disciplines closer together. Scaleup of processes, and related chemical engineering research, are particularly neglected areas that are necessary to realize the full potential for effective synthesis, assembly, and processing of nanostructures.

4.7 EXAMPLES OF CURRENT ACHIEVEMENTS AND PARADIGM SHIFTS

4.7.1 Fullerenes and Nanotubes

Contact person: D.T. Colbert, Rice University

Fullerene nanotubes hold tremendous promise for numerous applications, owing to their remarkable materials properties, including strength, stiffness, toughness, chemical robustness, thermal conductivity, and perhaps most interestingly, electrical conductivity. Depending on their precise molecular symmetry, some nanotubes are semiconducting, while others exhibit truly metallic conductivity. This behavior, coupled with their nanoscale geometry, makes them ideal—perhaps unique—candidates for wires, interconnects, and even devices for true molecular electronics.

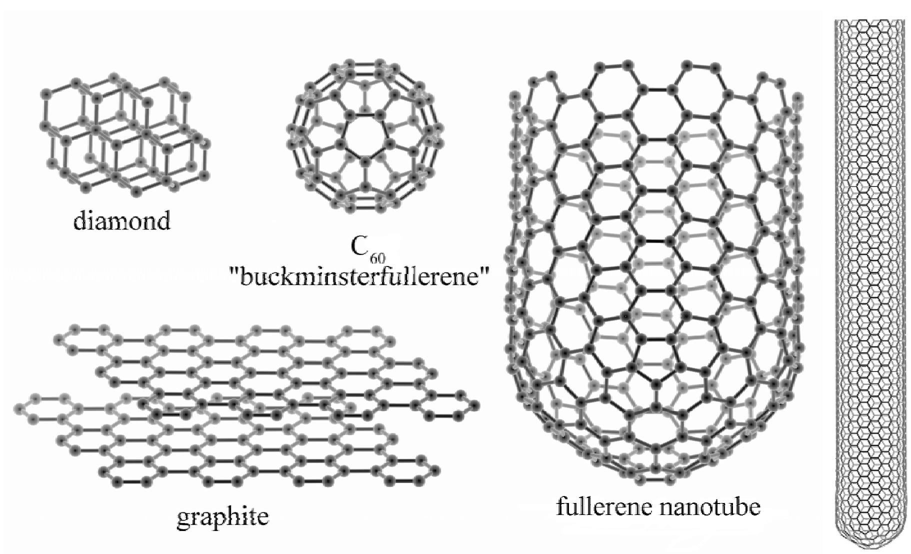

Figure 4.1. Fullerene nanotubes.

One application of nanotubes—as probe tips in scanning probe microscopy (Dai et al. 1996; Wong et al. 1998)—has already been developed. Many others, such as field-emission displays (Rinzler et al. 1995; de Heer et al. 1995); high-strength composites, and various electronic applications, are being pursued vigorously now, largely enabled by the discovery in 1995 (Guo et al. 1995; Thess et al. 1996) of the laser-vaporization process for producing single-wall nanotubes in high yield. In the three years since this breakthrough, a tremendous amount has been learned about the fundamental physical characteristics of fullerene nanotubes, mostly consistent with early expectations of extraordinary material properties. The gram quantities of nanotubes provided by the laser process, and now by the arc process as well, are enabling a period of research on chemical methods for manipulating and assembling short lengths of nanotubes (Liu et al. 1998; Chen et al. 1998). These are expected, in turn, to provide the enabling technologies for the applications exploiting the material properties discussed above. It must be stressed that the full realization of most applications exploiting these properties will be made possible by the very high degree of structural perfection exhibited by nanotubes. This *molecular* aspect of fullerene nanotubes permits us to develop chemical strategies for assembling them into useful structures, materials, and perhaps molecular electronic devices.

4.7.2 Nanoimprint Lithography

Contact person: S. Chou, Princeton University

Nanoimprint lithography (NIL) is a revolutionary approach to low-cost and high-throughput nanolithography (Chou 1998; Chou et al. 1996). NIL patterns a resist by physically deforming the resist shape with a mold (i.e., embossing), rather than by modifying the resist chemical structures with radiation as in a conventional lithography (Figure 4.2). This fundamental difference in principles frees NIL from many problems suffered in conventional lithography, such as diffraction limit, scattering, and chemistry. As a result (see also Figure 4.3), NIL can achieve sub-10 nm structures over large areas with low cost and high throughput—a feat currently unachievable using existing lithographies.

Successful development of NIL will bring a revolution to nanostructure research, because NIL will remove the key obstacle—cost—to nanostructure commercialization and will make nanostructures easily accessible to everyone. To a great extent, one can compare the impact of NIL with that of personal computers, which have made computation so widely accessible. Therefore, NIL will not only impact future integrated circuit development, but will also impact many other disciplines, such as biology, chemistry, medicine, and materials, to name a few.

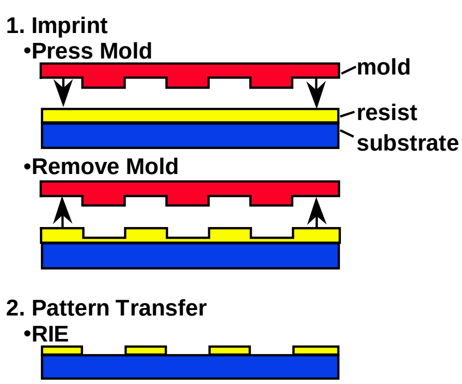

Figure 4.2. Schematic of nanoimprint lithography process: (1) imprinting using a mold to create a thickness contrast in a resist, and (2) pattern transfer using anisotropic etching to remove residue resist in the compressed areas (reprinted with permission from Chou et al. 1996, ©1996 American Association for the Advancement of Science).

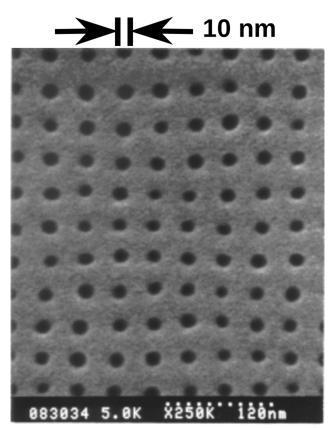

Figure 4.3. SEM micrograph of a top view of 10 nm minimum diameter and 40 nm period holes imprinted into PMMA (60 nm deep) (reprinted with permission from Chou et al. 1997, ©1997 American Vacuum Society).

4.7.3 Lithographically Induced Self-Assembly

Contact person: S. Chou, Princeton University

Lithographically-induced self-assembly (LISA) is a recent discovery that will have a great impact on science and technology (Chou and Zhuang 1997, 1999). In LISA, a mask is used to induce and control the self-formation of periodic supramolecular pillar arrays in a thin polymer melt that was initially flat on a substrate. The mask was initially placed above the polymer film with a gap. The pillars, formed by rising against the gravitational force and surface tension, bridge the two plates. The boundary of the pillar array is precisely aligned to the bounding contour of the patterns on the mask (Figure 4.4). The principle for LISA is, although still unclear, fundamentally different from self-assembly by phase-separation and surface chemistry modification. It is believed that LISA is related to electrostatic forces and electrohydrodynamic instabilities (Chou and Zhuang 1999).

LISA opens up exciting new areas for fundamental scientific study and practical applications. Scientifically, understanding of the LISA principle requires combining several disciplines. Technologically, LISA offers a solution to the two long-sought goals: (a) precise control of the orientation and location of a self-assembled polymer structure, and (b) making the self-assembled features smaller than those of mask patterns (Figure 4.5). Furthermore, the LISA process should, in principle, be applicable to other polymers and perhaps even other single-phase materials, such as semiconductors, metals, and biological materials. The periodic arrays formed by LISA have many applications, such as memory devices, photonic materials, and new biological materials, to name a few. Finally, LISA offers a unique way to pattern polymer electronic and optoelectronic devices directly without using the detrimental photolithography process.

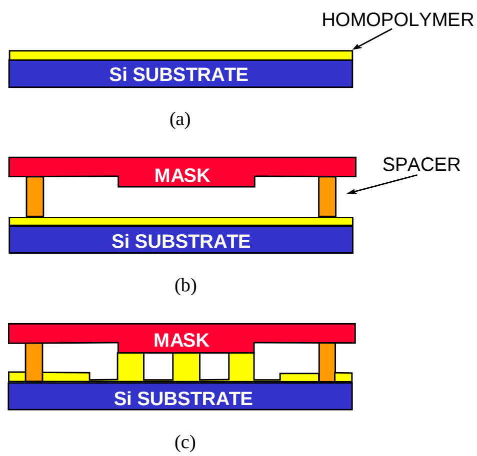

Figure 4.4. Schematic of lithographically-induced self-assembly (LISA). A mask is used to induce and control the self-formation of supramolecular pillar array in a thin polymer melt (reprinted with permission from Chou and Zuang 1999, ©1999 American Vacuum Society).

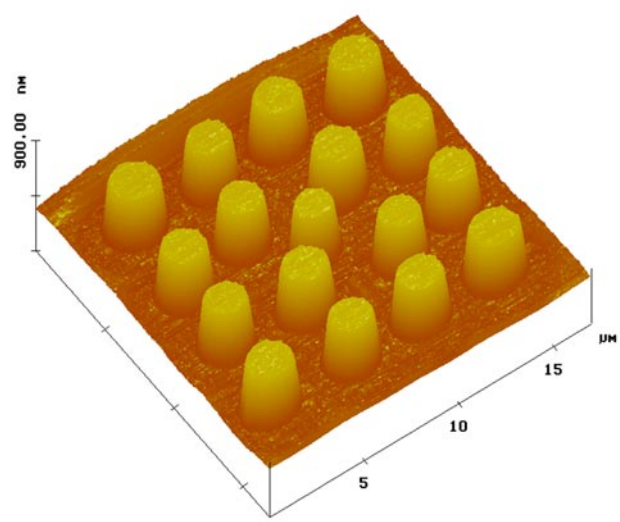

Figure 4.5. AFM image of PMMA LISA pillar array formed under a square pattern (reprinted with permission from Chou and Zuang 1999, ©1999 American Vacuum Society).

4.7.4 DNA-Directed Assembling: Potential for Nanofabrication

Contact Person: M.J. Heller, Nanogen

DNA chips and microarrays represent a technology which has immediate applications in genetic research and diagnostics. DNA array technology may also play a future role in enabling nanofabrication. DNA chips or arrays are devices in which different DNA sequences are arrayed in a microscopic format on a solid support (glass, silicon, plastic, etc.). DNA arrays can have anywhere from 100 to 100,000 different DNA sites (pixels) on the chip surface. Depending on the chip, the sites can range in size from 10 microns to over 100 microns (smaller sites are possible). Each DNA site can contain from 10^6 to 10^9 DNA sequences. In a DNA hybridization assay, the DNA array is contacted with a sample solution that contains the unknown target DNA sequences. If any of the sequences are complementary to those on the array, hybridization occurs and the unknown sequence is identified by its position on the array. A number of companies are now involved in the development of DNA chips and arrays, including Affymetrix, PE Applied Biosystems, HySeq, Nanogen, Incyte, Molecular Dynamics, and Genometrix. Present DNA chip devices will have applications in genomic research, pharmacogenetics, drug discovery, gene expression analysis, forensics, cancer detection, and infectious and genetic disease diagnostics.

Newer generations of electronically active DNA microarrays (under development by Nanogen) that produce controlled electric fields at each site may have potential applications for nanofabrication. These active microelectronic devices are able to transport charged molecules (DNA, RNA, proteins, enzymes), nanostructures, cells and micron-scale structures to and from any test site on the device surface. When DNA hybridization reactions are carried out, these devices are actually using electric fields to direct the self-assembly of DNA molecules at specified sites on the chip surface. These active devices are serving as semiconductor hosts or motherboards for the assembly of DNA molecules into more complex three-dimensional structures. The DNA molecules themselves have programmable and self-assembly properties and can be derivatized with a variety of molecular electronic or photonic moieties. DNA molecules can also be attached to larger nanostructures, including metallic and organic particles, nanotubes, microstructures, and silicon surfaces. In principle, active microelectronic arrays and DNA-modified components may allow scientists and engineers to direct self-assembly of two- and three- dimensional molecular electronic circuits and devices within the defined perimeters of larger silicon or semiconductor structures (Figure 4.6). Thus, electronically directed DNA self-assembly technology could encompass a broad area of potential applications from nearer term heterogeneous integration processes for photonic and microelectronic device fabrication to the longer term nanofabrication of true molecular electronic circuits and devices.

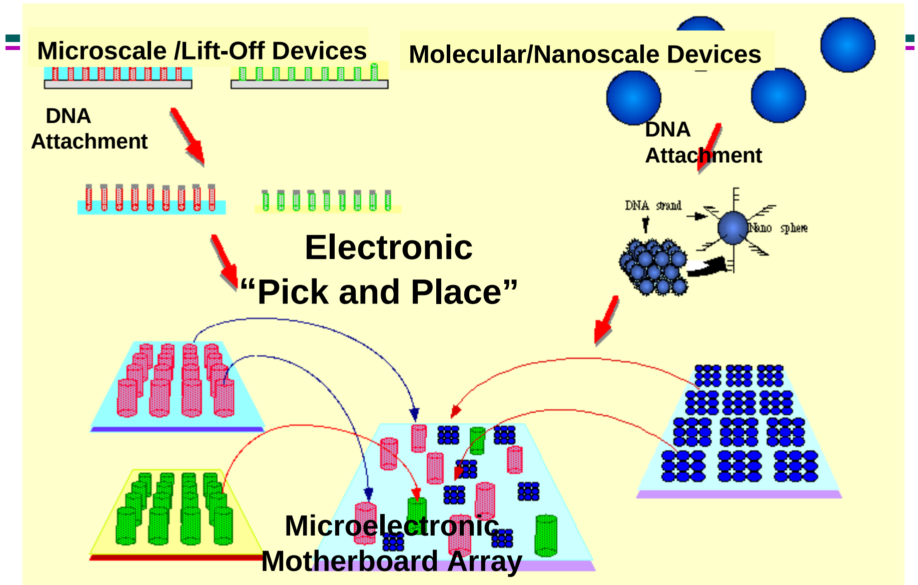

Figure 4.6. Directed nanofabrication on a chip (Nanogen, Inc.).

4.7.5 Strain-Directed Assembly

Contact person: R. Kiehl, University of Minnesota

The integration of top-down physical and bottom-up chemical or biological assembly methods will be crucial for the fabrication and interconnection of wires and switches. The strain-directed assembly of nanoparticle arrays in a solid (Figure 4.7), where a top-down physical process (lithographically defined surface structure) is integrated with a bottom-up chemical assembly process (strain and compositionally controlled precipitation), represents a step in this direction. More generally, the development of such techniques will provide the means for introducing functionality in the substrate that is coupled to functionality on the surface. Strain-directed assembly of arsenic precipitates in an AlGaAs/GaAs heterostructure is sketched in Figure 4.7. The horizontal positions of the 20 nm particles are controlled by the 200 nm surface stressors, while the vertical positions are confined to a 10 nm GaAs layer. One-dimensional arrays of closely spaced particles are formed along lines running into the plane (Kiehl et al. 1996).

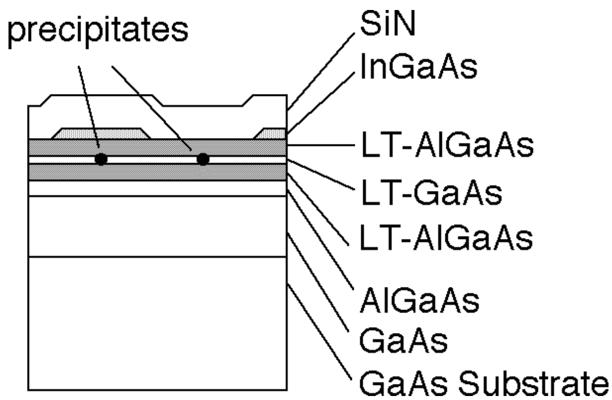

Figure 4.7. Strain-directed assembly.

4.7.6 Nanotechnology Synthesis and Processing in Drug and Gene Delivery

Contact person: K. Leong, Johns Hopkins University

Almost half of therapeutically useful drugs are hydrophobic. Administration of these water-insoluble drugs is problematic. The bioavailability of these drugs can be significantly enhanced by reducing the size of the drug particles to the nanoscale. Thus small enough to pass through the capillaries, the drug may even be administered via intravenous injection. The benefit to the pharmaceutical industry of this nanotechnology processing has been enormous.

Genetic medicine continues to hold exciting promise in the future of healthcare. A major challenge for successful gene therapy has been the development of safe and efficient gene vectors. While viruses in some cases can efficiently deliver exogenous genes to cells in vivo, the long-term safety of this approach remains a major concern. Non-viral vectors have been increasingly proposed as alternatives. Nanoparticles composed of complexes between polycationic lipids or polycationic polymers with DNA have shown efficacy in many animal models. The lipid-DNA complexes are being tested in several clinical trials, notably the delivery of the CFTR gene to the lung airways for correcting the chloride transport defect that leads to cystic fibrosis. These DNA nanoparticles may potentially be the most practical vehicles for fulfilling the promise of genetic medicine.

Nanotechnology Synthesis and Processing in Drug/Gene Delivery

Producing drug particles down to the nanometer scale, uniform in size and distribution, non-aggregated in solution, and manufacturable in industrial scale remains a significant challenge. Continuing advances in nanotechnology, particularly the fundamental aspects, will be needed to meet this challenge. New nanosynthetic approaches may be needed to improve current techniques such as controlled crystallization, and improvements over the milling and scale-up processes will be important.

Nanotechnology may also help reach the hitherto elusive goal of active drug targeting. The “magic bullet” concept has mostly been tested on soluble complexes or targeting ligands conjugated to ill-defined particles. Limited success has been documented in the literature on delivering polymer-coated nanoparticles across the blood-brain barrier or increasing the lymphatic drainage of nanoparticles to target the lymph node. Advances in nanotechnology that can further reduce the size and reproducibly attach targeting ligands to the drug-loaded nanoparticles may improve the targeting efficiency. These nanoparticles may also be valuable tools for molecular biologists to study the cellular processes of receptor-mediated endocytosis and intracellular trafficking. A potentially important application of these nanoparticles may be altering the way an immunogen can be presented to the immune system of the host. An antigen adsorbed to or encapsulated in nanoparticles may be used to optimize the immune response in vaccine applications.

Current non-viral gene vectors are far from perfect. Ideally, DNA nanoparticles with controlled composition, size, polydispersity, shape, morphology, stability, encapsulation capability, and targetability would be needed to optimize the transfection efficiency in vivo. Scaling up of the DNA particle synthesis is also a serious challenge. Only with significant advances in nanotechnology will the potential of these DNA nanoparticles be realized.

There is a strong need to expand the effort to investigate the fundamental aspects of nanosynthesis and processing related to drug and gene delivery. Nanosynthesis by complex coacervation remains an inexact science. A theoretical framework that can describe and predict the phase separation behavior of such polyelectrolytes will greatly aid the choice of polycationic carriers and the synthesis. A clear picture of the self-assembly of the DNA-polycation complex, such as the studies conducted on lipid-DNA complex, will help correlate the physico-chemical properties with the transfection efficiency. A detailed biological transport analysis of these nanoparticles will help define the mechanism and identify the rate-limiting steps of the transfection process. A better understanding of colloidal behavior in biological fluids will also facilitate the rational design of these nanoparticular drug and gene delivery systems.

4.7.7 Nanostructured Polymers

Contact person: S.I. Stupp, Northwestern University

Nano-sized polymers shaped as rounded bricks, cones, mushrooms, and plates have been prepared in laboratories and found to self-assemble into tubular, spherical, layered, and lamellar constructs, respectively. These new types of polymers may eventually be useful in applications ranging from sophisticated sensors to de-icing agents (Stupp 1998).

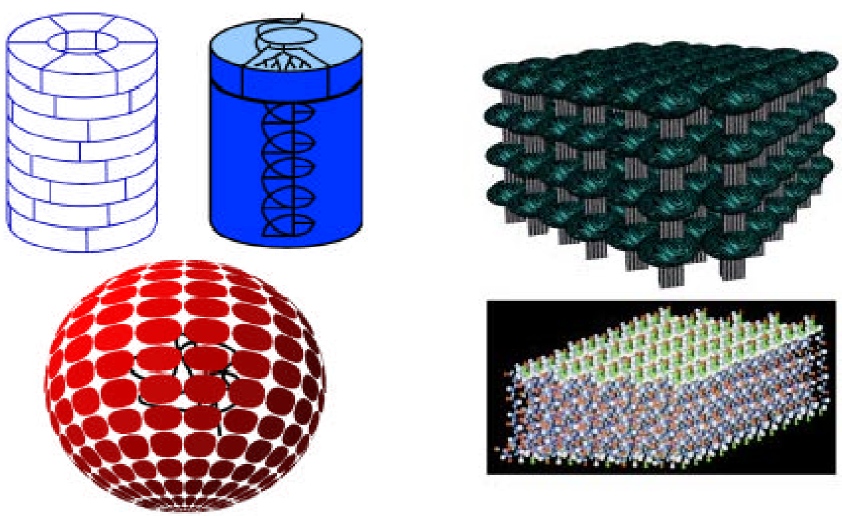

Figure 4.8. Nano-sized polymers self-assembling into functional structures.

4.7.8 Replication of Nanostructures by Polymer Molding

Contact persons: R.J. Celotta and G. Whitesides

A key element in the utilization of nanostructures for as many applications as possible is the ability to inexpensively mass-produce them. The technique of polymer molding, long used for replication of micron-sized structures in such devices as diffraction gratings, compact disks, and microtools, has now been shown to work on the nanoscale as well (Xia et al. 1997). Beginning with a master nanostructure, a mold is made using an elastomer such as polydimethylsiloxane (PDMS). The mold is then used to produce replicas in a UV-curable polymer such as polyurethane. As seen in Figure 4.9, which shows atomic force microscope images of the original master and a replica, high-quality reproduction is possible on a scale of tens of nanometers.

The demonstration that this replication process works on the nanoscale was carried out using a master pattern fabricated via a unique new process known as laser-focused atomic deposition (McClelland et al. 1993). In this process, a laser standing wave forms an array of atomic "microlenses." These concentrate chromium atoms as they deposit onto a surface, building nanoscale objects "from the bottom up" in a single step without the use of any resist.

Replication of the laser-focused chromium structure is only one example of the use of polymer molding on the nanoscale. For example, nanostructures with ~30 nm lateral dimensions have been produced based on gold patterns made using conventional lithography.

Given these demonstrations, it is now clear that a new tool is available for nanoscale fabrication, with a direct avenue to mass production. As applications for nanostructured materials continue to expand, this technology stands ready for implementation in a manufacturing setting, enabling the type of inexpensive production techniques that new technologies critically depend on.

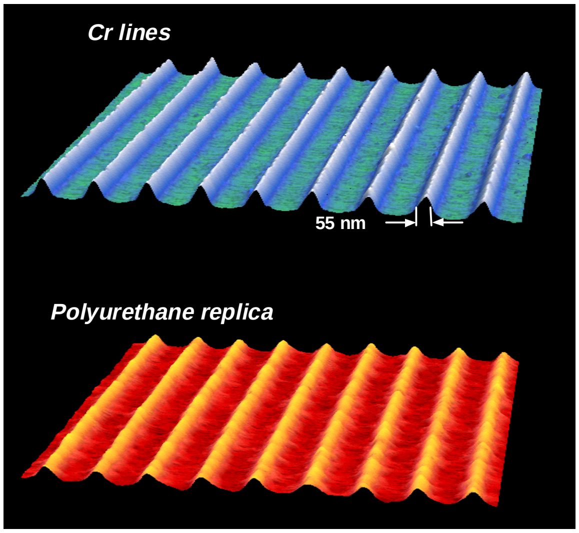

Figure 4.9. Soft lithographic nanostructure (courtesy J.J. McClelland, NIST).

4.7.9 Molecular Self-assembly

Contact person: M. Reed, Yale University

Figure 4.10 depicts a single molecule bridging the gap between two metallic contacts, forming the smallest and ultimate limit of an electronic device. The illustration points to a potentially powerful new fabrication strategy for self-assembly. The molecule is designed with end groups (dull gold spheres) of sulfur atoms, which automatically assembly onto the gold wire contacts. The blue fuzz above and below the atoms represents the electron clouds, through which the current actually flows. Figure 4.10 is a representation of the experiments that demonstrated the first electrical measurement of a single atom (Reed et al. 1997).

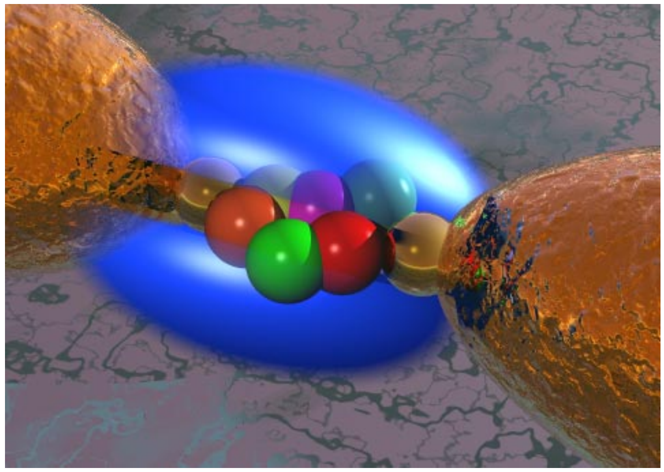

Figure 4.10. A single molecule bridging the gap between two metallic contacts, forming the smallest and ultimate limit of an electronic device (©1999 Mark Reed; all rights reserved).

4.7.10 Robotic Assembly of Nanostructures

Contact person: Ari Requicha, University of Southern California

Nanoparticles may be positioned accurately and reliably on a surface by using the tip of an atomic force microscope (AFM) as a robot. The AFM images the original, random distribution of particles in dynamic (non-contact) mode, and then pushes each particle along a desired trajectory by moving against the particle with the feedback turned off. Potential application of nanomanipulation to NanoCDs by using ASCII language has been illustrated. The new type of digital storage could have with densities several orders of magnitude larger than those of current compact disks. Nanomanipulation of nanoparticles with AFMs has been demonstrated at room temperature, in ambient air and in liquids. The resulting structures can be linked chemically, e.g., by using di-thiols or DNA as glue, to produce nano-components that can themselves be manipulated as sub-assemblies (Resch et al. 1998, Requicha, 1999). Robotic operations with standard, single-tip AFMs have low throughput, and are useful primarily for prototyping. Large-scale production requires massively parallel tip arrays, which are under development at several laboratories (see Section 3.2).

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