

INTRODUCTION

A system is a composite of different elements that when brought together yield results that are not obtainable from the elements alone. The function of systems engineering is to guide the development of individual components into robust and efficient systems capable of autonomous operation as complex systems, where complex systems are defined as systems in which elements are diverse and have intricate relationships with each another. Nanotechnology refers to the creation of functional materials, devices, and systems via control of matter on the nanometer-length scale (nominally 1–100 nm) and exploitation of novel phenomena and properties (physical, chemical, biological) at that length scale. In general, nanotechnology begins with nanoscience: the study of material properties and their interactions at the nanoscale and how they can be exploited. Once the properties of nanostructures are well characterized and can be reproducibly fabricated, those properties can be exploited as a technology.

Two important concepts define a system:

1. The system has properties or attributes that cannot be associated with any of its components.
2. The description of the system function is less complex than the functional descriptions of the system components. These concepts or properties are called emergent properties of the system.

Emergence in the engineering disciplines is an expected outcome. Emergence can also occur in nano-material systems.

For example, a microprocessor chip system can perform millions of arithmetical functions per second.
under precise control of a software program. These mathematical functions are a straightforward manifestation of the input and output behavior of the software code. This description is much simpler than a description of the microprocessor chip states through which the chip would pass as the function is computed under the direction of the software code. Such component descriptions—regardless of the level considered, from individual quantum levels to gate or machine language functions—are much more complex than the description of the mathematical function itself. Microprocessors, however, are typically part of multiscale systems such as cellular phones and automotive sensors and similarly could be part of systems linking nanotechnology to society.

This article will describe the development of nanotechnology for small systems or components at APL. Examples include physiologically responsive polymers, which release drugs only in response to a need-based physiological stimulus;\(^4\) nanoporous DNA sensors, which electrically detect DNA segments binding to a known segment;\(^5\) and biologically generated nanoscale cellulose composites, which provide strong transparent materials for structural or biomedical applications.\(^6\) All of these technologies are currently under development at APL.

**COMPLEX SYSTEMS**

Complex systems or complex adaptive systems have been studied extensively for almost 40 years.\(^7\) They trace their origins to the beginnings of chaos theory in 1890 by Jules Henri Poincaré\(^8\) (1854–1912), a professor of mathematics at the University of Paris from 1881 to 1912, and to the work in the 1960s of Edward Norton Lorenz\(^9\) (1917–2008), mathematician, meteorologist, and professor at Massachusetts Institute of Technology. To define a complex system we must consider the concept of upward predictability. Upward predictability implies that an analysis of interactions at the component level will yield a simple explanation of the phenomena observed at the system level. Systems that can be analyzed in this manner are upwardly predictable. Complex systems often are not upwardly predictable. The effects of interactions at the component level are correlated in complex ways to the phenomena occurring at the system level. This lack of upward predictability, coupled with emergence concepts, is the hallmark of a complex system.

Complex systems can be engineered by humans or they can occur naturally. Representative human-engineered systems include many APL systems, including missile defense and spacecraft systems such as the Standard and Tomahawk missiles, the Midcourse Space Experiment (MSX, a DoD satellite), and the MESSENGER Surface, Space ENvironment, GEOchemistry and Rang-
exploit the self-assembling material properties of DNA to enable a small “robot” to perform functions such as walking down a track.16

APL researchers have developed functional nanomaterials and devices to address critical challenges in homeland protection. For example, one project, the Nanoporous DNA Sensor, uses nanotechnology to achieve rapid, straightforward DNA matching. Nanoscale pores are functionalized with complementary DNA, and the size of the pores is small enough that DNA binding inside the pore will change impedance through the porous membrane in a detectable way. This technology is envisioned as an alternative to DNA microarray technology, providing the advantage of reduced sample preparation requirements, which will be useful in rapid screening scenarios. Another APL project uses electro-deposited bismuth nanowires to detect radiation. Incident gamma rays generate detectable electrical current in these materials. These bismuth nanowire arrays have the significant advantage of being less expensive to produce than the current technology, which involves large single-crystal semiconductor detectors. In addition to these sensor nanowire applications, metal nanotubes are being investigated at APL for high-energy-density thin-film battery applications. These thin-film battery nanotubes are filled with battery chemicals, and they can be geometrically engineered to minimize battery inefficiencies such as diffusion-limited transport between anode and cathode.17

Researchers hoping to mimic the desirable functionalities of naturally occurring biological systems have created various nanomaterial systems. For example, the gecko lizard demonstrates the remarkable ability to defy gravity by scaling walls and walking on ceilings despite its relatively high mass (especially when compared with insects). Furthermore, this organism can scale surfaces of varying roughness in varying ambient environments such as low or high humidity. Research into the biological gecko foot and the structures of insects’ feet has revealed the presence of small hair-like structures whose sizes scale inversely with the creatures’ mass-to-pad area ratio, with the gecko’s foot hair structures consisting of flexible nanofiber-shaped hairs. Attempts to replicate these naturally occurring structures have integrated many types of lithography and materials, from microelectromechanical system (MEMS) foot hairs to high-aspect-ratio polymer nanofiber structures created from a self-assembling polymer microsphere templated lithographic technique.18 At APL, researchers are mimicking nature to produce an “eye patch” for battlefield eye injuries. Biologically generated nanoscale cellulose fiber composites are being used to mimic the strong mechanical properties and simultaneously transparent optical properties of the natural cornea.19

The types of materials described above can be considered individual components of larger systems, rather

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**Figure 1.** Nanoscale particles have a much larger percentage of atoms at the surface (76%) than macroscopic (millimeter-sized) particles, which have approximately 0% of atoms at the surface.11

Quantum confinement, or confinement of electrons in a material as a result of finite size (rather than bulk “infinite” size), leads to many interesting nanoscale effects. Semiconductors exhibit size-dependent optical properties as a result of quantum confinement. The term “quantum dot” is used in the context of referring to these materials, as they fluoresce at size-dependent wavelengths. These materials have been applied commercially as fluorescent biomarkers used for biomedical imaging, and they have been used at APL for sensing and tagging applications.

There are many nanoscale devices that perform functions in response to stimuli or integrate the functionality of multiple counterparts to perform a function or make a measurement. These are small, complex nanosystems. Three primary examples are nanowire sensors, biomimetic nanomaterial systems, and DNA “walkers” that
than nanosystems themselves. Roco\textsuperscript{20} has classified nanotechnology into four generations: (i) nanomaterials fabrication, (ii) nanoscale phenomena exploitation, (iii) nanotechnology-based devices, and (iv) complex nanosystems. As a field, nanotechnology to date has certainly reached the third generation. The achievement of the fourth generation will likely challenge the field of systems engineering to accommodate these dynamic, reconfigurable nanosystems with properties that do not necessarily scale with size.

**INTERFACING NANOTECHNOLOGY WITH THE MACROSCOPIC WORLD**

At the time of this writing, several systems involving nanotechnology are under development for commercial use, including lab-on-a-chip (LOC) technology and hybrid nanoelectronics.

LOC technology has received considerable attention in the last two decades\textsuperscript{21} as a promising, highly functioning diagnostic tool capable of providing fast diagnostic information to medical professionals and requiring minimally invasive sample collection. LOCs incorporate many types of technology at many scales, from sample collection (e.g., blood draw) to microfluidic chip-level sample processing (e.g., separation of cellular blood components from serum), to sensors for detecting biomarkers in the samples, to user interfaces. Thus LOCs incorporating nanosensors or other nanotechnology are an example of nanotechnology interfacing with the micro- and macroscales at the systems level.

Much has been reported about the potential of nanostructure-based electronics, including devices consisting of supramolecular chemistry-based molecules connected to nanostructures as a new molecular electronics-based computing paradigm\textsuperscript{22} and devices that exploit the semiconductor properties combined with the small diameter and high aspect ratios of nanostructures such as carbon nanotubes (CNTs).\textsuperscript{23} Commercial nanoelectronic devices are available (e.g., Nantero, Inc., http://www.nantero.com/). However, manufacturability issues remain a challenge for integrating some nanoelectronic materials with current CMOS technology. Specifically, it remains challenging to control the electronic structure of CNTs during the growth process, often requiring the separation of semiconducting tubes from metallic tubes or the time-intensive wiring of only the semiconducting tubes (after identification) in place. In addition, many nanostructure growth procedures require high temperatures (600–1000°C) or gases not typically compatible with conventional CMOS technology. Because the CMOS device infrastructure is enormous, these nanodevices have not made it into the mainstream and thus are an example of a nanotechnology challenge with respect to integration into a larger system.

To incorporate nanoelectronic materials into mainstream device technology, the nanoelectronic materials must be integrated into hybrid devices by using conventional integrated circuit processes. This process is very challenging with CNTs, as a result of their varied electronic properties, but may not be as prohibitive with graphene. Graphene consists of a single sheet of graphite, and it can be deposited at lower temperatures onto silicon or transferred mechanically.\textsuperscript{24} APL researchers are working with graphene for several projects.

In addition to manufacturing challenges associated with nanotechnology, the nanotechnology itself may require additional considerations in the systems engineering process. Nanomaterials, because of their very small size, are much more susceptible to thermal fluctuations and to weak, reversible forces than are their macroscopic counterparts.

These susceptibilities can be exploited to create materials and devices by using self-assembly. Self-assembly is a process that nanomaterials undergo through which weak, reversible forces such as van der Waals attractions, capillary forces, electrostatic interactions, and hydrophobic/hydrophilic interactions are exploited to assemble larger structures from nanoscale counterparts. Self-assembled monolayers (SAMs) are an example of an early studied self-assembling system in which molecules spontaneously form monolayers onto substrates for which they have an affinity, e.g., sulfur-containing thiol molecules onto gold. With the invention and maturity of atomic imaging techniques such as scanning tunneling microscopy, these self-assembled monolayers were used initially to study the positional bonding and thermal migration of molecules on surfaces. Soon thereafter, however, it was discovered that these films could also be used to passivate nanoparticles, thus preventing their aggregation, or could be exploited to introduce new functionalities to material surfaces.\textsuperscript{25}

Beyond SAMs, self-assembly has been exploited to create nanoparticle-based colorimetric DNA sensors, precisely shaped microstructures from the folding of components engineered to self-assemble,\textsuperscript{26} complex structures made out of DNA (which readily self-assembles to strands with corresponding base pairs), and metalized DNA grids with nanoscale dimensions.\textsuperscript{27} Because a strand of DNA will automatically form a helical structure with its corresponding base pair-matched counterpart, computer scientists and materials scientists have been able to exploit this material for its innate self-assembling properties rather than for its biological function. In fact, it is possible to simply order the desired strands so that one must only design the proper sequence to create imaginable structures. DNA “smiley-face” structures have been formed in this way, by engineering small crossing strands to force a long strand to fold in programmed ways into the desired structure.
When the DNA structure also performs a complex function, this structure becomes a system.

Self-assembly has also been exploited on a wide variety of APL projects, most recently for self-healing paint applications and drug delivery. The self-healing paint has been created by APL researchers for naval applications. The paint contains essentially miniature metal “paint” cans, which actually contain uncured polymer that cures upon contact with air. The process of scratching the paint breaks open these “cans” and releases the polymer, and the polymer flows to fill up the scratch and then cures. The emulsification of the paint into (nearly) identical microscopic droplets is a wet chemical self-assembly process. Self-assembly is being exploited to create physiologically responsive polymers, which release a drug only in response to a physiological stimulus. Binding of the allergen or antibody of interest causes a conformational change in the polymer, which releases the drug. Also at APL, chemiluminescent solid lipid nanoparticles have been created by using self-assembly, and these are being explored as a fluorescent or colorimetric assay for inflammatory markers in the skin that may be indicative of disease, such as peroxides in skin cancer.\(^{28}\)

Self-assembly is of interest when nanotechnology is being considered for use as a component of a greater system. Because self-assembly is a naturally dynamic process that exploits forces that in many cases are of a magnitude similar to the thermal energy of the system, care must be taken to understand and account for the dynamic nature of the nanotechnology being used when engineering the system. Nanomaterials and related devices may be more dynamic than micro- or macro-devices with similar functions. For this reason, strategies such as redundancy or capability-based design (rather than requirements-based design) might be necessary in the systems engineering process.

**SYSTEMS ENGINEERING APPLICATION TO SMALL, COMPLEX SYSTEMS**

Successfully managing the issues surrounding emergence, system complexity, and the top-down vs. bottom-up design philosophy is a key factor in determining the viability of microelectronic- and nanotechnology-based products. Systems engineering principles provide the framework for the implementation of working complex systems at micro- and nanoscales. These same principles also help the integration of micro- and nanosystems into the building blocks of larger-scale engineered systems. Figure 2 illustrates the emergence and the evolution of the complexity of systems as the size of the system’s compositional entities increases and the entities’ environments change. Timescales of development also increase with increasing system complexity and the expected emergence behavior.

Scale (or size) is a key element in all microelectronic- and nanotechnology-based systems. Not only has shrinking size improved the performance of electronic devices (integrated circuits), but it has also reduced particle size (diameter, surface area-to-volume ratio) in all material systems and has allowed significant breakthroughs in many fields. Today these breakthroughs range from materials and medical breakthroughs to devices that emulate nature.\(^{28}\)

Just as the invention of the planar process and the integrated circuit attributed to Kilby\(^{29,30}\) and Noyce\(^{31,32}\) more than 50 years ago were seminal moments in the microelectronic industry, the discovery of the CNT by Iijima\(^{33,34}\) in 1991 and the preceding development of the atomic force microscope by Binnig, Quate, and Gerber\(^{35}\) in 1986 were defining moments in nanotechnology. The atomic force microscope has allowed engineers and scientists to view atoms. This ability to “see” has led to various investigations and the ability to manipulate individual atoms.

The issue of scale and the possibility of manipulating the structure of materials on an atomic basis
While nanotechnology applications and funding are increasing, there is growing concern about the health risks associated with nanoparticles and nanomaterials. These concerns spring from lack of knowledge about certain factors that are necessary for predicting human health risks. Such factors include the types of exposure and particle entrance into the body, movement of particles from the entry site (translocation), and interaction of the material with the body’s biological systems. Once exposed, the health risks are related to the level and time of exposure, the material’s toxicity, persistence of the material in the body, and the body’s susceptibility to the biological effects. Experimental studies in animals and with cell cultures have shown that the toxicity of ultrafine or nanoparticles is greater than the toxicity of the same amount (mass) of larger particles of the same chemical composition.

Inhalation is the most common route for exposing the body to airborne particles. The deposition of nanoparticles in the respiratory tract is determined primarily by the particles' size and shape (aerodynamics) rather than by their composition. Nanoparticles, being so small, are not readily exhaled like their larger counterparts; thus they can build up at faster rates in the respiratory tract and lungs. More research is needed on the effects of nanoparticle inhalation on health.

Ingestion is another way nanoparticles can enter the body. Unless special precautions are taken, the accidental transfer of materials from hand to mouth is common in handling of most substances. Similarly, ingestion could occur by swallowing mucous that contains particles inhaled through the respiratory tract. The effects of ingestion of nanoparticles are unknown.

Recent reports indicate that nanoparticles can penetrate the skin. They penetrate by a standard diffusion process and tend to collect in the epidermal and dermal layers. Potential harmful effects of these nanoparticle accumulations in the body’s outer covering are again unknown. However, studies of cells have shown that CNTs can enter cells and cause release of cytokines, which cause inflammation, produce oxidative stress, and decrease culture viability—thus indicating potential occupational hazards. One study (based on animal models) estimated that a 20-day exposure to single-wall CNTs at the Occupational Safety and Health Administration (OSHA) permissible exposure limit posed a high...
risk of development of lung lesions. Given the potential risks, workers should take every precaution to avoid inhalation, ingestion, and contact of skin with nanotubes and particles.

**FUTURE**

Many issues must be explored before nanosystems can be realized and integrated into society. As the potential for large-scale integration is considered, for example, the following issues will be relevant:

- System design tools: new tools may be required
- Material suppliers and their consistency: standardization of nanomaterials may be needed
- Reliability: smaller scaling may lead to higher failure rates
- Architecture: redundancy may counter effects of smaller scaling
- Circuit manufacturing technology
- Circuit architectures
- Toxicity
- Public fear/marketing
- Cost
- Profit margin
- Unforeseen risks

Organizations exist to address most of these issues, from organizations devoted to raising awareness of the benefits, dangers, and possibilities for responsible use of advanced nanotechnology to organizations tracking nanotechnology-based consumer products, their toxicity, and their geographical manufacture. Nanoarchitectures have prompted extensive research, as self-assembling components may lead to cheaper manufacture but higher defect densities. Such self-assembling components could be incorporated into the designs by using architectural redundancy or software algorithms (as discussed in the conference proceedings at http://www.nanochip.org). All these factors may enable or inhibit the integration of nanosystems into mainstream application, regardless of their inherent promise.

**REFERENCES AND NOTES**


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