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The BRIDGE

LINKING ENGINEERING AND SOCIETY

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The BRIDGE
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LINKING ENGINEERING AND SOCIETY

Editor's Note

Features

NAE News and Notes

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Editor's Note

George Bugliarello is President Emeritus and University Professor at Polytechnic University in Brooklyn, New York, and foreign secretary of NAE.

The Biotechnology Revolution

The rapid growth of bioengineering since the first academic programs were initiated in the early 1960s is a measure of its importance both to the life sciences and medicine and to engineering. The achievements of bioengineering have been dramatic, not only new instrumentation, diagnostic and therapeutic devices, medical imaging, biotechnology, and increasingly sophisticated prostheses, but also a deeper understanding of living systems, from physiology to genetics. Studies of the highly complex and efficient processes developed by biological organisms over four billion years are also leading to opportunities for new engineering designs.

At the NAE National Meeting at the Beckman Center last February, NAE held a symposium on biotechnology organized by NAE member **Satya Atluri**, Samueli/Von Karman Chair in Aerospace Engineering and director of the Center for Aerospace Research and Education at the University of California, Irvine.

In the words of Dr. Atluri in his opening remarks, "Mechanics and chemistry are fundamentally linked together in the science and engineering of biological systems. The aims of this symposium were to help establish a better understanding of mechanochemical coupling in living cells, to facilitate studies of the mechanics of biomolecules, including proteins and nucleic acids, and to provide a knowledge base for the engineering of biosystems, such as hybrid bio/abio nano- and micro-mechanical systems." Dr. Atluri stressed the engineering challenges in addressing the multi-time, multi-length scales of phenomena in biological systems. Biomechanics pioneer **Yuan-Cheng Fung** (NAE) described the vistas opened by advanced concepts in the engineering discipline of continuum mechanics, which can lead to a better understanding of biosystems from the molecular to the macroscopic scale.

Three of the papers presented in this issue are based on presentations given at the symposium. Donald Ingber addresses the mechanochemical basis of cell and tissue generation. He explains how the integration of the physical structure of a cell—its hardware—and the cellular information-processing network—its software—enables the cell to respond to its environment. Lester Martinez-Lopez discusses biotechnology as an enabler for the Soldier System of Systems, integrated technologies that can protect soldiers through improved vaccine design and construction, drugs to protect against malaria, biosensors that can identify impending degradation in physical and cognitive performance, sensors to detect and diagnose exposure to biological hazards, and inoculations against toxic agents. John Parmentola explains how paradigms based on biotechnology contribute to the Army's process of transformation by making possible, for example, dramatic reductions in the size and weight of equipment while increasing the lethality of weapons and improving soldiers' survivability.

To broaden the picture of the role of bioengineering, we have included two papers that were not presented at the symposium: one on impact biomechanics, that is, the science of preventing and controlling injuries from impacts (**Albert I. King**, NAE) and the other on how bioprocess engineering translates molecular-scale bioprocesses into production-scale quantities of bioproducts and bioenergy (**Michael Ladish**, NAE).

As engineering becomes more intimately involved with living systems, the combinations of machines and biological organisms will offer an alternative to a purely robotics-influenced future. Biotechnology and bioengineering are ushering in a technological revolution, opening a myriad of possibilities in areas such as manufacturing, computating, sensing, tissue engineering, and motion control, just to mention a few.

George Bugliarello

The hierarchical molecular structures that comprise living cells, tissues, and organs are based on tensegrity principles.

Mechanochemical Basis of Cell and Tissue Regulation

Donald E. Ingber is Judah Folkman Professor of Vascular Biology, Departments of Surgery and Pathology, Harvard Medical School and Children's Hospital Boston.

Donald E. Ingber

The burgeoning fields of tissue engineering and nanotechnology offer exciting new approaches to address fundamental questions in biology and improve human health. But these fields are limited because we do not understand how living cells and tissues are constructed so that they exhibit their incredible organic properties, including their ability to change shape, move, grow, and self-heal. So far, we have not been able to construct man-made materials that mimic these features or to design drugs or devices to control these behaviors selectively. To accomplish this, we must first uncover the underlying design principles that govern how cells and tissues form and function as hierarchical assemblies of nanometer-scale components.

One aspect of this challenge is to understand the "hardware"—the physical structure of the whole cell. The second is to comprehend how the "software" (cellular information-processing network) functions so cells can make discrete cell-fate decisions, such as whether to grow, differentiate, or die, even when confronted by conflicting signals. The ultimate goal of this research is to explain how structural and information networks are integrated so that cells can sense their physical and chemical environments and respond appropriately.

Cellular Hardware

Because a mammalian cell has a flexible membrane surrounding its cytoplasm and nucleus, people have tended to think of cells as squishy blobs, like balloons filled with molasses. However, the sculpting of tissues and organs that occurs in the embryo is an extremely physical process. Various regions of the growing cellular aggregate independently move, stretch, and pull against one another through the action of cell-generated forces. Mechanical distortion does more than change the shape of cells; it also influences cellular biochemistry and gene expression, and thereby actively controls tissue development. Adult tissues exhibit a similar sensitivity to physical forces. Compressive forces due to gravity shape bones; tension molds muscle; and hemodynamic forces govern the form and function of the cardiovascular system.

Cells could not exhibit these behaviors if they were structured like balloons. In reality, the cell has a molecular framework or "cytoskeleton" hidden within its surface membrane that mechanically stabilizes the cell and actively generates contractile forces through an actomyosin filament-shortening mechanism similar to that of muscle. Cells apply these forces to their adhesions to other cells, as well as to extracellular matrix (ECM) scaffolds that hold cells together within living tissues. These tensional forces also promote structural rearrangements within the cytoskeleton that govern multiple cellular activities (e.g., movement, contraction, intracellular transport, mitosis) at the molecular level.

The cytoskeletal network is composed of three classes of biopolymers: microfilaments, intermediate filaments, and microtubules. The challenge is to understand how the mechanical properties of a cell emerge through collective interactions among these molecular filaments. Most work on cell mechanics focuses on the gel properties of the cytoskeletal lattice, but gels made from isolated cytoskeletal filaments do not mimic complex cell behaviors. In contrast, we have explored the possibility that cells structure their cytoskeletons using "tensegrity"—the architectural principle used in Buckminster Fuller's geodesic domes. This idea may seem strange, but molecular geodesic domes have been observed in the microfilament cytoskeletons of living cells (Figure 1).

The stable shape of tensegrity structures is attributable to continuous tension, rather than continuous compression. For example, a simple tensegrity structure may be constructed from a continuous series of strings

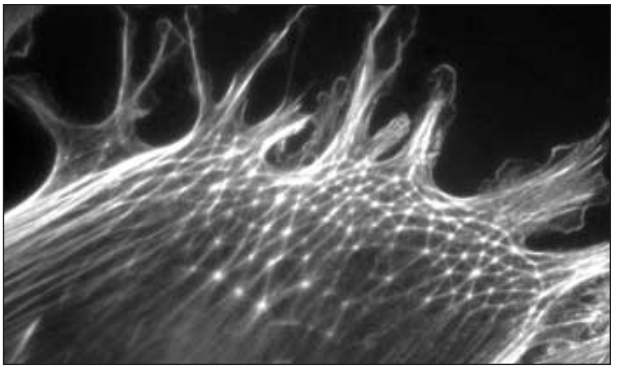

FIGURE 1 Molecular geodesic dome in the cytoskeleton of a human cell.

under tension pulling toward the center of the object, but balanced by other filaments or struts that resist being compressed. Thus, the stable shape of the entire structure depends on the presence of isometric tension or a tensile "prestress," just like the stability of my arm depends on my muscle tone. The key role of prestress for shape stability is the most fundamental feature of tensegrity structures. Prestress is essentially ignored in models of the cytoskeleton that focus on gel properties.

Another fundamental property of living materials, as opposed to man-made materials, is that their structures are hierarchical. For instance, when an intact nucleus is removed from one living cell and placed in another enucleated cell (e.g., to clone an embryo), both the nucleus and cytoplasm maintain their structural integrity in isolation. Once a nucleus is in the recipient cell, however, it reconnects with the surrounding cytoskeleton and regenerates a new structurally and functionally integrated cell. Moreover, smaller structures in the cells, such as organelles, transport vesicles, and enzyme complexes, exhibit similar autonomy, even though physical coupling to surrounding structures also affects their function. Whole cells are similarly integrated within tissues, tissues within organs, and organs within a whole organism. Moreover, when stress is applied at the whole organism level (e.g., gravity), there are coordinated structural and functional changes on many other levels.

Many of the properties of living systems are mimicked by simple tensegrity structures. For example, hierarchical tensegrity models of a cell containing a nucleus can be constructed by linking larger and smaller tensegrity structures composed of elastic sticks and strings, with additional tensile connections (Figure 2). Because they are prestressed, when these tensegrity models are not anchored, they take on a round shape. However, both the cell and nucleus spontaneously flatten out and spread

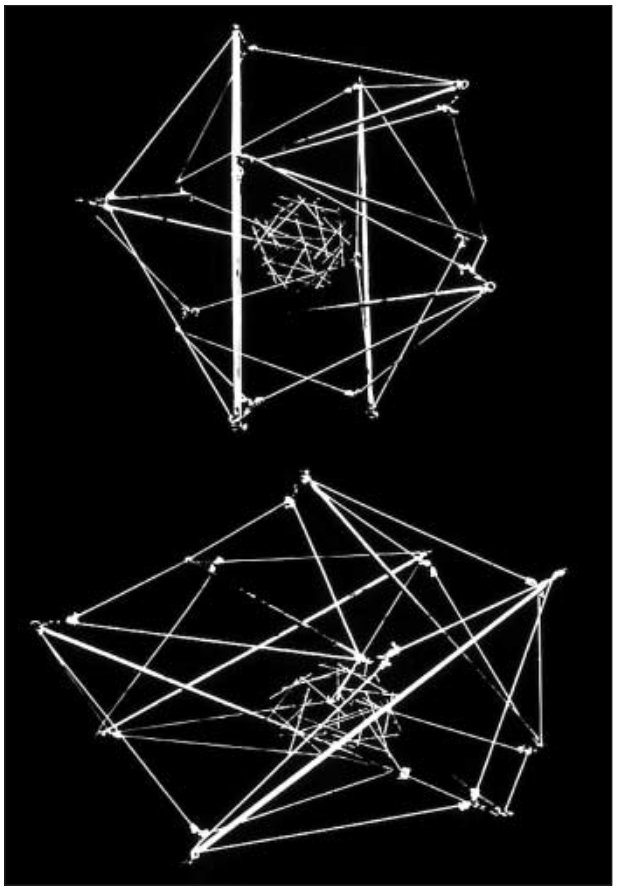

FIGURE 2 Like a living cell, a hierarchical tensegrity cell model with a nucleus fabricated from sticks and strings takes on a round shape when unanchored (top) but spreads when attached to a substrate (bottom).

in a coordinated way when they are attached to a rigid substrate. Furthermore, when their anchors are clipped, both the cell and the nucleus spontaneously retract into a round shape. This is exactly what is observed when cells adhere to and detach from a culture substrate. Analysis of these structural models also reveals that applying stress locally on the surface of a hierarchical tensegrity results in global structural rearrangements in various locations and on several levels.

Experimental studies from various laboratories support the possibility that cells use tensegrity to structure themselves. These experiments confirm that cell shape is stabilized through a balance of mechanical forces. Cytoskeletal contractile forces are resisted and balanced by internal cytoskeletal struts and by external adhesions to ECM and to other cells, thereby generating prestress that stabilizes the cell. The cytoskeletal lattice connects to the ECM and neighboring cells via transmembrane adhesion receptors, known as "cadherins" and "integrins," that form spot weld-like adhesion sites on the cell surface. The tensed strings of the tensegrity model mimic the contractile microfilaments of the cytoskeleton; the struts represent other cytoskeletal elements that resist compression, such as microtubules and stiffened (e.g., cross-linked) bundles of actin microfilaments. Intermediate filaments act like molecular guy wires to help individual microtubules resist buckling under compression and link the nucleus to the surface membrane, thereby ensuring hierarchical coordination. Finally, the surface membrane and underlying cortical cytoskeleton (a thin shell composed of actin, ankryin, and spectrin molecules) form a third level in the structural hierarchy of the cell. This submembranous cytoskeleton is also a prestressed molecular lattice that is highly flexible, except where the membrane connects with the microfilament-microtubule-intermediate filament lattice at sites of cell-cell and cell-ECM adhesion.

Tensegrity also appears on both smaller and larger scales in the hierarchy of life. Viruses, enzyme complexes, transport vesicles, actin geodomes (Figure 1), the submembranous cytoskeleton, transport vesicles, enzyme complexes, and viruses all exhibit geodesic forms. On a larger scale, specialized ECM components, including elastic (elastin) fibers, stiffened (cross-linked) collagen bundles, and compression-resistant (hydroscopically swollen) polysaccharide gels, interplay with contractile cells to maintain a stabilizing tensile prestress at the tissue and organ levels. Bones, muscles, tendons, and ligaments organized in a similar way stabilize the shapes of our bodies; tensegrity even has been invoked to explain structural stability in insects and plants.

Cellular Mechanotransduction and Tissue Morphogenesis

One prediction based on the cellular tensegrity model is that adhesion receptors linked to the deep cytoskeleton, such as integrins and cadherins, provide preferred paths for mechanical signals to enter the cell. For instance, if one were to pull on a transmembrane protein that only connects to the flexible submembranous cytoskeleton, stress would dissipate locally. In contrast, if one were to tweak a receptor linked to the internal microfilament-intermediate filament-microtubule lattice, the entire cytoskeletal network would bear the load and become stronger as a result of structural rearrangements at multiple levels.

To test this prediction, we developed microengineering approaches to apply mechanical stresses to specific receptors on the surface of living cells. Magnetic fields were applied to cells bound to micrometer-sized magnetic beads precoated with receptor ligands, and bead displacements were measured simultaneously. With Ning Wang (Harvard School of Public Health) and Dimitrije Stamenovic (Boston University), we have used this approach to demonstrate that the mechanical behavior of mammalian cells is like the behavior of tensegrity structures. A theoretical formulation of the tensegrity model starting from first mechanical principles also yields accurate qualitative and quantitative predictions of many static and dynamic mechanical behaviors.

But the cytoskeleton is more than a structural scaffold; it also orients much of the biochemical machinery of the cell, including many of the enzymes and substrates that mediate signal transduction. This type of "solid-state" biochemistry has important implications for the way cells sense mechanical signals and transduce them into a biochemical response, a process known as mechanotransduction. For example, when molecular (e.g., enzymatic) components of cytoskeletal filaments that bear mechanical loads are deformed, their thermodynamic and kinetic properties change. In this way, tensegrity provides a way for cells to channel mechanical forces in distinct patterns and focus them on specific sites where mechanochemical conversion may take place.

Some of the major cellular sites for solid-state signaling are "focal adhesions" where integrin receptors mediate the transfer of mechanical force between the cytoskeleton and the ECM. When mechanical forces are applied directly to integrin receptors (e.g., using magnetic forces), cellular biochemistry and gene expression are altered in a stress-dependent way. Forces applied to integrins activate many signaling pathways in these sites, including protein tyrosine phosphorylation, ion fluxes, cAMP production, and G protein signaling. In contrast, if the same stress is applied to a peripheral membrane receptor, there is no effect. Thus, cells use specific transmembrane receptors that link to the deep cytoskeleton—in this case, integrins—to mediate mechanochemical transduction.

However, the tensegrity model suggests that a local stress may also produce global structural responses. In fact, when tension is applied to surface integrins (e.g., with a micropipette), this results in stress-dependent displacements of mitochondria, focal adhesions, and even molecular realignment of nucleoli inside the nucleus. Moreover, as predicted by tensegrity, this type of force transduction is mediated by cytoskeletal filaments and modulated by the level of cytoskeletal prestress. Thus, a mechanical force applied on one point at the surface may alter cell behavior by influencing biochemical activities at multiple sites.

These actions at a distance are important physiologically. For example, although cells may sense mechanical forces locally within focal adhesions, the whole cell must process this information before orchestrating a concerted functional response. This was demonstrated by controlling cell distortion independently of other factors (e.g., soluble hormones), by plating cells on different sized adhesive islands created with a microcontact printing technique originally developed by George Whitesides' laboratory (Harvard University) as an inexpensive way to fabricate microchips for the computer industry. The islands, made adhesive for cells by coating them with ECM molecules, were surrounded by nonadhesive regions covered with polyethylene glycol. The cells spread to take the shape of the island to which they adhered as a result of pulling themselves flat against the ECM substrate. Cells appeared round on circular islands and literally displayed 90-degree corners when cultured on square islands (Figure 3). Thus, if we hold the shape of the island constant and vary its size, we can control the degree of cell distortion.

The cytoskeleton orients much of the biomechnical machinery of the cell.

Spread and round cells cultured on different sized islands produce similar intracellular signals (e.g., cAMP production) when their integrin receptors are magnetically stressed. A flattened cell takes in this signal, integrates it with other cues conveyed by its overall structural state, and switches on a growth (proliferation) program, whereas a round cell shuts off growth and activates a suicide program, known as "apoptosis." Furthermore, when spreading is only partially restricted on an intermediate-sized island, the cell neither grows

nor dies; instead, the cell differentiates and expresses tissue-specific features (e.g., capillary endothelial cells form hollow capillary tubes, liver cells increase production of specialized blood proteins).

Cell distortion also impacts cell movement. When cells on square islands are stimulated with motility factors, the cells preferentially extend new motile processes from their corners, whereas they extend from all points along the edge of round cells (Figure 3). These methods have led to new approaches to tissue engineering using microfabricated substrates, in which it is possible to direct cell migration, growth, and differentiation in specific locations by modifying the surface chemistry and topography of artificial materials, instead of adding soluble stimulants.

Regional variations in cell distortion may similarly drive tissue patterning in the embryo. For a capillary network to form, for example, only a subset of cells must respond to soluble growth factors by proliferating locally and sprouting outward relative to neighboring non-growing cells. This process is repeated along the sides of the newly formed sprouts, and then is repeated over time; this is how the fractal-like patterns of all tissues develop. This process is mediated by regional changes in ECM structure; the ECM thins in regions where new sprouts will form due to local enzymatic degradation. Because tissues are prestressed, a local region of the tensed ECM may thin out more than the rest, like a "run" in a nylon stocking. Cells anchored to this region will also stretch, whereas neighboring cells on intact ECM remain unchanged. If cell stretching promotes growth, then this would generate local cell growth differentials. In short, these studies suggest that tissue morphogenesis may be controlled *mechanically*, and recent experimental studies in embryonic systems support this possibility.

Cellular Software

Biologists commonly speak of a "growth pathway" versus "differentiation pathway" and assume that cell-fate switching is controlled through activation of a specific series of regulatory events that "instruct" the cell to express one distinct phenotype or another. Work on controlling cell shape suggests that this model does not take into account the larger frame of reference that is critical for understanding cell structure and function—the framework of the *whole cell*. Sui Huang in my group has noted that when a single control parameter—cell shape—is varied continuously, abrupt all-or-none changes in cell fate are produced reminiscent of a "phase transition" in physical systems (e.g., water going from solid to liquid to gas when temperature is varied). Macroscopic (system-level) features of simple inorganic materials are *emergent* properties of the network of interactions among multiple components (e.g., a single water molecule has no boiling point). Given that different stable cell fates similarly emerge out of a network of gene and protein regulatory interactions, we began to ask if this could work in a similar manner.

Systems biologists interested in nonlinear dynamics have begun to address the question of stable cell states by modeling isolated regulatory circuits consisting of a

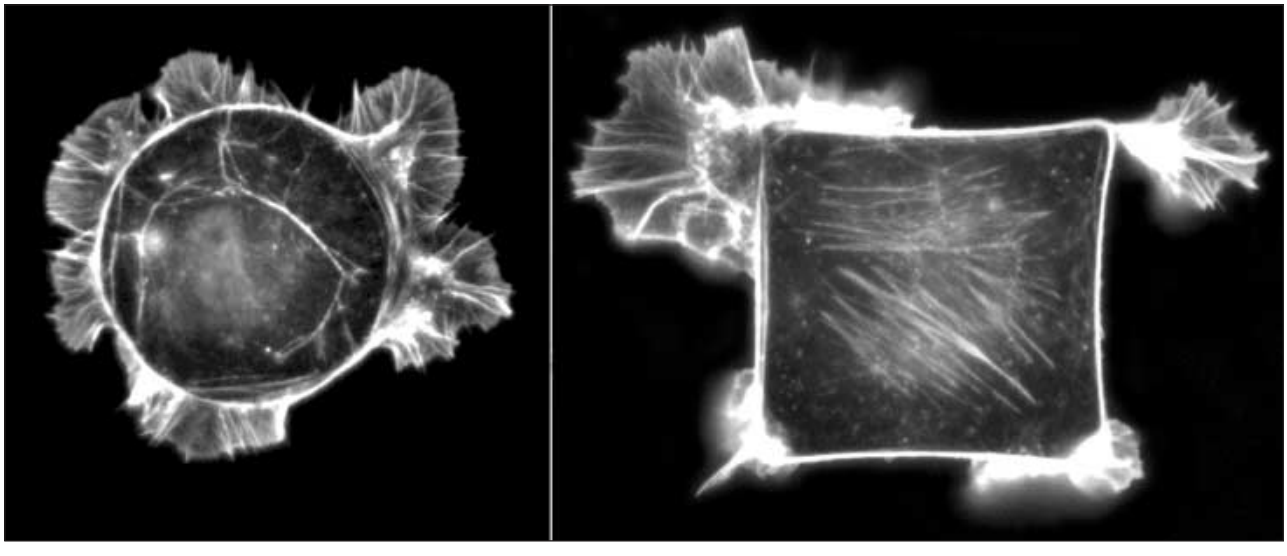

FIGURE 3 The photos show cells cultured on round and square micrometer-sized adhesive islands and stimulated with motility factors.

few mutually regulating genes. These low-dimensional models explain bistable, switch-like decisions (bifurcations) between stable network states that arise because of nonlinear relationships between the circuit components. However, they do not explain the coordinated changes of thousands of genes across the entire genome, which occur during a phenotypic switch in mammalian cells.

Genomic and proteomic studies also suggest that molecular pathways in the cell form a single large connected network ("giant component") that spans almost the entire genome. Yet, cells are able to reliably integrate multiple, simultaneous, often conflicting signals that perturb genes across the entire genome and respond by selecting one of just a few possible stable cell fates. Moreover, the very same cell-fate transition can be triggered by a broad variety of unrelated signals (e.g., different hormones and adhesive molecules), including those that apparently lack molecular specificity, such as distortion of cell shape.

Theoretical models of generic networks have revealed that stable states known as high dimensional "attractors" self-organize in large interconnected networks containing thousands of elements, if they exhibit a particular class of network architecture. Virtually all biomolecular networks analyzed to date have this architecture. Stable, high-dimensional attractor states arise at the *whole system level* as a consequence of the particular regulatory interactions between the network components (e.g., genes) that impose constraints on the global dynamics of the network; thus, the cell cannot occupy any arbitrary network state. Stuart Kauffman (Sante Fe Institute) has proposed on these theoretical grounds that different cell types (e.g., lung vs. liver) represent different attractor states in the gene regulatory network.

Based on these observations, we proposed that the different stable cell phenotypes (e.g., growth, differentiation, motility, apoptosis, etc.) similarly represent high-dimensional attractor states, or "default" states, in the regulatory network of mammalian cells. To pursue this idea, we developed new bioinformatics software that could simultaneously visualize and compare multiple time series composed of high-dimensional, genome-wide gene profiles. Using this tool and novel nonlinear dynamics approaches to analyze the process of cell-fate switching in human blood cell precursor cells induced to differentiate into neutrophils by two different stimuli (all trans-retinoic acid and DMSO), we have obtained experimental evidence that directly supports the attractor hypothesis.

The existence of attractors in the genome-wide regulatory network that confer stability with respect to thousands of dimensions (e.g., gene expression levels) is important because it explains how cells can simultaneously sense multiple chemical, adhesive, and mechanical inputs and yet only switch on one of a limited number of specific, reproducible behavioral responses. A key feature of the attractor model is that multiple regulatory elements (e.g., ensembles of genes and signaling proteins) must change at the same time to produce an attractor switch. Given that mechanical forces and cell shape distortion probably impact many cytoskeletal-associated signaling molecules simultaneously, this may explain how global changes in shape are able to control cell-fate switching.

The cytoskeleton is a mechanochemical scaffold that is both structure and catalyst.

Conclusion

The riddle of how cells form specialized tissues and organs is more a problem in structural design, systems engineering, and architecture, than a question of chemistry. Because the hierarchical molecular structures that comprise living cells, tissues, and organs are stabilized based on tensegrity principles, cells are perfectly poised to sense physical signals, to respond mechanically, and to orchestrate a spatially coordinated biochemical response at the molecular level. For this reason, structure dictates function in living cells—cells can be switched between growth, differentiation, and death solely by varying the degree to which the cell physically distorts its shape. Thus, although a cell may be able to sense mechanical signals locally through adhesion receptors, such as integrins, the overall response of the cell is governed at the whole cell level where the mechanical status of the entire cytoskeleton is also taken into account.

The cytoskeleton can integrate these diverse signals because it is a mechanochemical scaffold that is both structure and catalyst. This structural design principle conveys mechanosensitivity to the cell because stress-dependent changes in the shape of molecules and

enzymes that bear loads in these cytoskeletal structures alter their thermodynamic and kinetic parameters, thereby converting mechanical signals into a biochemical response. Cells also change their shape and move by changing their level of internal prestress, shifting forces back and forth between internal struts and external tethers, and by using these localized forces to drive biochemical remodeling events. By integrating structural networks with biochemical assemblies and information processing networks, the cell can function simultaneously as sensor, processor, and actuator, while at the same time moving, growing, and producing the energy required for these processes. The future challenge in "living materials science" is, therefore, to define the principles that govern how molecules self-assemble to form the multifunctional structural hierarchies we call living cells and tissues. If we could incorporate these principles into artificial nanomaterials, biomedical devices, and engineered tissues, we could revolutionize the way medicine is practiced in the future.

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The goal of impact biomechanics is to protect vehicle occupants from serious injury.

Impact Biomechanics

Albert I. King is Distinguished Professor and Chair of the Department of Biomedical Engineering at Wayne State University.

Albert I. King

Vehicle safety is on the minds of many would-be car buyers these days, and most of us have either been injured in a crash or know someone who has been injured or even killed in a collision. Impact biomechanics, the science of injury control, is research dedicated to injury prevention through environmental control. The goal of impact biomechanics is to protect vehicle occupants from serious injury at a price the general population can afford. The research is based on the principles of mechanics and an understanding of the physiology and pathophysiology of the human system. Research ranging from the testing of whole-body cadavers to the study of flux of ions across a cell membrane has been going on for at least 65 years.

History

The study of accidents began in the 1920s when Hugh DeHaven of Cornell set out to understand how people survive falls from great heights. De Haven, a combat pilot in World War I, had survived a free fall from a great height (Andreasson and Backstrom, 2000). Laboratory research began in 1939 at Wayne State University when Steve Gurdjian, a neurosurgeon, and Herbert Lissner, a professor of engineering mechanics, initiated a study on head injuries and skull fractures using anesthetized dogs and cadaveric skulls (Gurdjian and Lissner, 1944). Research on impact biomechanics is now being done in many countries around the world. Centers of biomechanics research include the

Bioengineering Center at Wayne State, one of the most versatile research centers in the world, and research laboratories at the University of Michigan, the University of Virginia, the Medical College of Wisconsin, Duke University, and the University of Pennsylvania; new laboratories are being established at the University of California San Francisco, Virginia Polytechnic Institute and State University, and Kettering University.

Because research is still mostly on the macroscopic scale, impact equipment must be able to generate sufficient force or acceleration to cause injury. Wayne State has two pneumatically driven, full-scale impact sleds. The HYGE sled (Figure 1a) is accelerated from a standstill, and the impact occurs as soon as the sled starts to move. To simulate a frontal impact, the subject faces rearward. The second sled (Figure 1b) is a deceleration sled that is accelerated up to speed and stopped by a hydraulic snubber to produce the impact. With either sled, the impact pulse can be designed to simulate a certain vehicle or type of crash. Other impact equipment can include linear impactors, which accelerate a moving mass into a body region, or minisleds, which can be transported to a remote facility where a high-speed x-ray unit can be used to measure the motion of internal organs during impact.

The most common parameter measured is body-fixed acceleration of the regions of interest. Other parameters include the force of impact, pressure, strain, displacement, and stretch. In addition, angular acceleration, a parameter thought to be a major cause of brain injury, can now be accurately measured. Before the days of 3-D angular accelerometers, angular acceleration was measured using uniaxial linear accelerometers. For a rigid body, a minimum of six accelerometers are necessary to measure the three linear and three angular components of accelerations. However, the equations used to calculate angular acceleration were in the form of nonlinear differential equations that require a numerical solution. In theory, this method worked fine with six accelerometers, but errors in the measured accelerations tended to magnify errors in the computed acceleration. Thus, if the integration process went on for any period of time, the solution could be far off the mark, especially if low-sensitivity accelerometers were used to measure small accelerations.

In 1975, Padgaonkar et al. developed a new method using nine accelerometers placed on a mount, which has the form of a rectangular Cartesian coordinate system. There were two accelerometers at the end of each axis, normal to that axis, and three at the origin. With this 3-2-2-2 arrangement, the equations become algebraic, thus eliminating the need for integration. Even with the advent of the angular accelerometer, the 3-2-2-2 method is still considered the gold standard against which transducers are compared. This method is just one contribution of biomechanics to applied mechanics. Perhaps in the future, we will find an elegant method of using six accelerometers to measure angular acceleration accurately.

Basic Principles

There are four basic areas of research in impact biomechanics: injury mechanisms; mechanical response; injury tolerance; and simulation of human impact. Cadavers and animals are used to obtain data in the

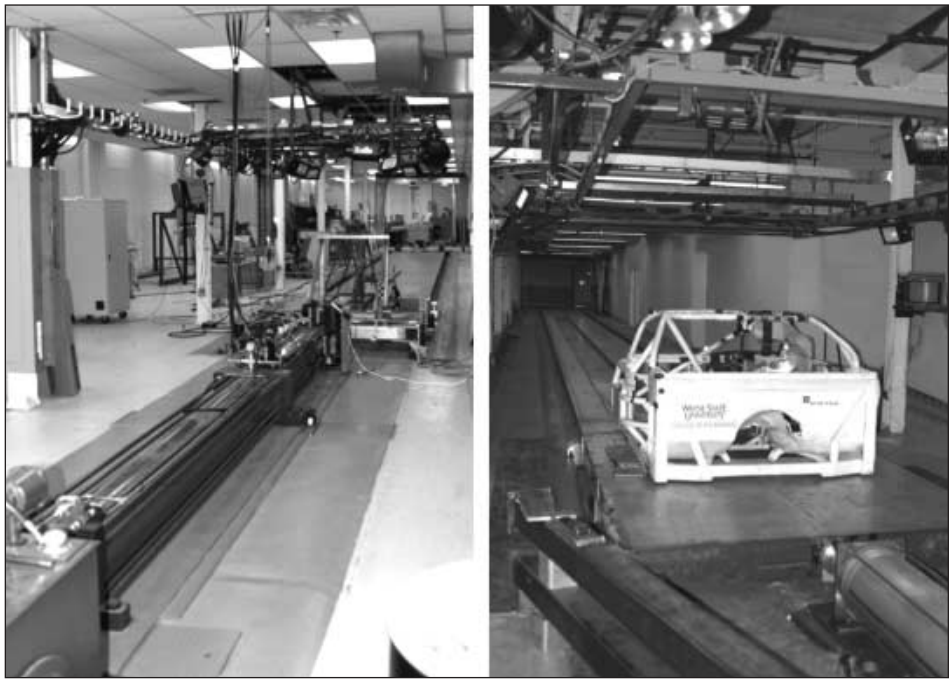

FIGURE 1 1a. HYGE acceleration sled. 1b. Deceleration sled with snubber (bottom right corner).

first three areas, but these surrogates are not perfect. For one thing, cadavers lack muscular response, although this does not usually cause serious problems. However, scaling data from animals to humans is prone to error. Tests with volunteers are generally not severe enough to study injury.

Injury Mechanisms

We must understand how an injury occurs before we can find a way to prevent it. A case in point is the so-called whiplash injury, which can cause intractable neck pain in some people, even after a very minor impact. (Whiplash is discussed in more detail below.)

Mechanical Response

To design and build realistic surrogates, we must first quantify the mechanical responses of various body regions. The crash dummies seen on TV are finely tuned measuring instruments that can indicate to a safety engineer if a body region is likely to be injured in a crash. The response data are also used in the development of computer models that simulate an occupant involved in a crash.

Human Tolerance

Understanding the tolerance level of every body region is crucial for the design engineer. However, human tolerance varies greatly with age and gender. To narrow the range, the tolerance is usually defined for a 50th-percentile, middle-aged male. This means that elderly people, women, and children may be less well protected, and efforts are under way to change government standards to consider tolerance levels of women and children. Information on the responses and tolerances of children is sparse because child cadavers are not readily available.

Simulation of Human Impact

Automobile manufacturers use crash dummies as human surrogates for evaluating safety systems in their vehicles. The Hybrid III family of dummies is shown in Figure 2. The 50th-percentile male dummy, which was designed using frontal impact cadaveric data, has relatively good human-like responses for frontal impact simulations. For side impact simulations, we use side impact dummies, but none of them is really biofidelic at present.

Auto manufacturers do not use cadavers for two reasons. First, there are obvious ethical problems and availability problems associated with their use by a commercial enterprise. Second, cadaveric responses and tolerances are too variable for an efficient evaluation of vehicle safety systems. Thus, human models that simulate human occupants are becoming more popular. The current slogan is "Make the car safe for people, not for dummies." Rapid increases in computing power and advances in finite element analysis have made it possible to simulate the entire human occupant. The whole body THUMS model developed by Toyota a few years ago is being evaluated by safety professionals around the world (Iwamoto, et al, 2002). Yang (2001) has reviewed all finite element models of the human in the literature.

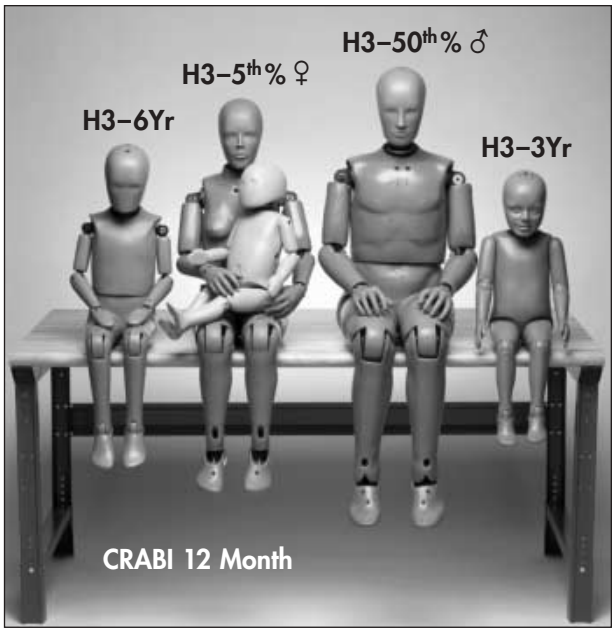

FIGURE 2 The Hybrid III (H3) frontal-impact family. Courtesy of First Technology Safety Systems.

Examples

Before the advent of air bags, 50 percent of automotive fatalities resulted from head injuries. Since then, the fatality rate has declined, but minor and moderate head injuries continue to be a problem. Even mild head injuries can have devastating consequences, such as memory loss, inability to concentrate and process information, increased irritability, and clinical depression. The current Federal Motor Vehicle Safety Standards use a head injury criterion (HIC) limit of 1,000. According to best estimates, the probability of sustaining a life-threatening injury at a HIC of 1,000 is 15 percent (Prasad and Mertz, 1985). We do not have a widely accepted tolerance for a mild traumatic brain

injury (MTBI). The HIC has been controversial ever since it was introduced in the early 1970s, because it does not account for the effects of angular acceleration, which is believed by many to be the principal cause of brain injury (Gennarelli et al., 1972; Ommaya and Hirsch, 1971). In fact, Ommaya used animal data to deduce the level of human tolerance for severe brain injury at 1,800 rad/s^2.

Recently, researchers at Wayne State University put together the results of several studies and came up with predictors of brain injury (King et al., 2003). First, with the help of a high-speed biplanar x-ray device, the motion of the brain was quantified for mild to moderate impacts, involving a peak linear acceleration of 100 g and a peak angular acceleration of several thousand rad/s^2 (Hardy et al., 2001). Figure 3 shows

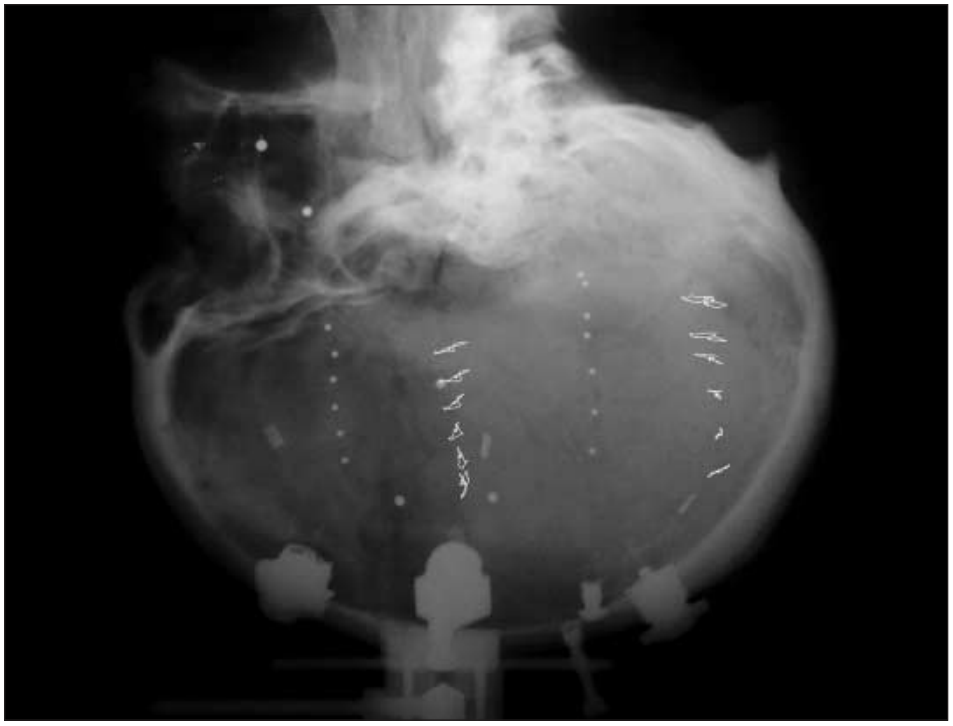

FIGURE 3 Brain motion shown by biplanar high-speed x-ray.

figure-eight motion patterns of several radio-opaque targets implanted in a cadaveric brain. Brain displacement was ±1 mm due to linear acceleration and as much as ±5 mm due to angular acceleration. However, regardless of the magnitude of the angular acceleration (in excess of 10,000 rad/s^2), the displacement did not exceed ±5 mm. Also, the motion was larger near the center of the brain than near the periphery. Another experiment showed that wearing a helmet decreases linear acceleration by more than 20 percent but does not appreciably decrease angular acceleration. Thus, if angular acceleration is the cause of brain injury, how does the helmet protect the brain? We still do not have a satisfactory answer to this question.

A third experiment by Biokinetics, Inc. of Ottawa, Canada, involves the re-creation of head impacts sustained by NFL players as recorded on video game films. Stereophotogrammetric techniques were used to estimate the velocity impact between helmeted heads and between the helmeted head and the ground. Newman et al. (1999) duplicated the impacts using crash dummies in the laboratory to measure the linear and angular accelerations of both players (one of whom usually suffered a concussion) or of a single player for ground impact. The acceleration data were then fed into a finite element model of the brain to compute brain response, including strain (ϵ), strain rate ($d\epsilon/dt$) and the product of strain rate ($\epsilon \cdot d\epsilon/dt$) (Zhang et al., 2001). These and other response variables, as well as input variables, were subjected to a Logist analysis to determine the strongest predictor of concussion (MTBI), which was found to be $\epsilon \cdot d\epsilon/dt$, followed by $d\epsilon/dt$. Surprisingly, HIC was third, and in the most recent analysis of all available cases, angular acceleration was ninth. These studies show that brain response is a better predictor of injury than input and that a computer model of the brain is essential for understanding brain injury. We also found that the value of HIC to produce a 50-percent probability of an MTBI was 235 and that the average value for angular acceleration to cause an MTBI was 6,400 rad/s^2. Thus, the dangers of scaling animal data are obvious.

Another unsolved problem in impact biomechanics is whiplash. Many hypotheses have been proposed to explain neck pain following an accident, the most logical of which appears to be shear in a rear-end

impact. The seat back pushes the torso forward leaving the head behind unless a shear force is generated at every level of the cervical spine to bring it along. Experiments carried out by Deng et al. (2000) using the same high-speed x-ray system showed that there is substantial relative motion between the adjacent cervical vertebra, both in translation and rotation, and that the estimated stretch in the facet capsules, particularly in the lower cervical spine, were extremely high, reaching a peak of almost 100 percent. Although it has long been established clinically that facet capsules are a source of neck pain (Wallis et al., 1997), the majority of physicians do not believe in facet pain. Therefore, the controversy continues.

Despite the uncertainty about the cause of whiplash injuries, several attempts have been and are being made to redesign car seats and head rests to prevent or minimize whiplash injuries. Trying to prevent an injury without knowing its cause could potentially put the user at risk. Although engineers do not take the Hippocratic oath, they should obey the maxim—above all else, do no harm.

Importance of Biomechanics

Knowing that the results of my research may save lives and reduce injury is very rewarding. An estimated 12 lives have already been saved as a result of one cadaver test, and the results of that research will continue to save lives (King et al., 1995). Of course, cadaver testing is not the most glamorous job in the world, but young engineers can now use computer models of human responses to study impact. The spine model by Prasad and King (1974) predicted large compressive loads in the thoracolumbar spine when a belted individual was subjected to a frontal impact. At first, this was thought to be an anomaly of the model, but Begeman et al. (1973) showed that the model was correct when they fractured the spine of shoulder-belted cadavers in a series of horizontal sled tests. The explanation after the fact was simple. The thoracic spine is convex rearward, and when the restrained torso is loaded inertially in a frontal impact, it tends to straighten out the curved thoracic spine, causing it to push down on the lumbar spine.

Experimental attempts by several laboratories to cause aortic ruptures in cadavers have been unsuccessful, so Shah et al. 2001 developed a computer model to find the most likely scenario. It is hoped that an improved version of the model can be used as a guide to create this injury and determine the mechanism of injury.

Conclusions

The most obvious thing one can do to protect oneself against injury is to wear a seat belt. If the driver has to sit close to the steering wheel to reach the pedals, the seat should be leaned back as far as is comfortable so the driver is not too close to the air bag. All children should be in the back seat and should use child seats appropriate for their age and weight.

In addition, a word to a senator or congressman can sometimes do wonders to support research. Despite the common occurrence of automotive injuries, no large constituency is clamoring for support on Capitol Hill, and funding for injury research is a miniscule fraction of the federal research budget—one reason improvements in automotive safety have been slow and irregular. Even with air bags, more than 40,000 people are killed every year, and injury is the leading cause of loss of productive years of life, exceeding cancer and heart disease combined. Finally, the cost to society from injury is extremely high, not only in pain and suffering, but also in high taxes and insurance premiums.

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Biotechnology-based strategies are key to transforming a soldier into a Soldier System of Systems.

Biotechnology Enablers for the *Soldier System of Systems*

Major General Lester Martinez-Lopez, M.D., M.P.H., is the Commanding General of the U.S. Army Medical Research and Materiel Command.

Lester Martinez-Lopez

The Army has historically recognized that the individual soldier, the critical element of operational success, is an integral component of weapons, transportation, and other hardware systems and that military hardware (and software) must be designed with human factors in mind. Today, we think of the soldier as a system; taken together with his or her equipment, the soldier is a *system of systems*. This more holistic approach encompasses not only the human-system interface, but also the full range of biological, environmental, and occupational factors that can affect a soldier's health and performance. Soldiers today face more environments and threats than the soldiers of yesteryear, and we anticipate that the challenges will continue to increase. To maximize a soldier's performance and prevent disease and injury in this changing operational setting, the U.S. Army is pursuing research, development, and engineering to transform the individual soldier into a fully protected and integrated *Soldier System of Systems*. Biotechnology-based strategies are key to achieving this goal.

Challenges

Soldiering remains a dangerous business, involving a wide variety of threats to health and performance (Figure 1). To protect the soldier, we must counter traditional threats from ballistics weapons, as well as from chemical and biological weapons. However, we often overlook the fact

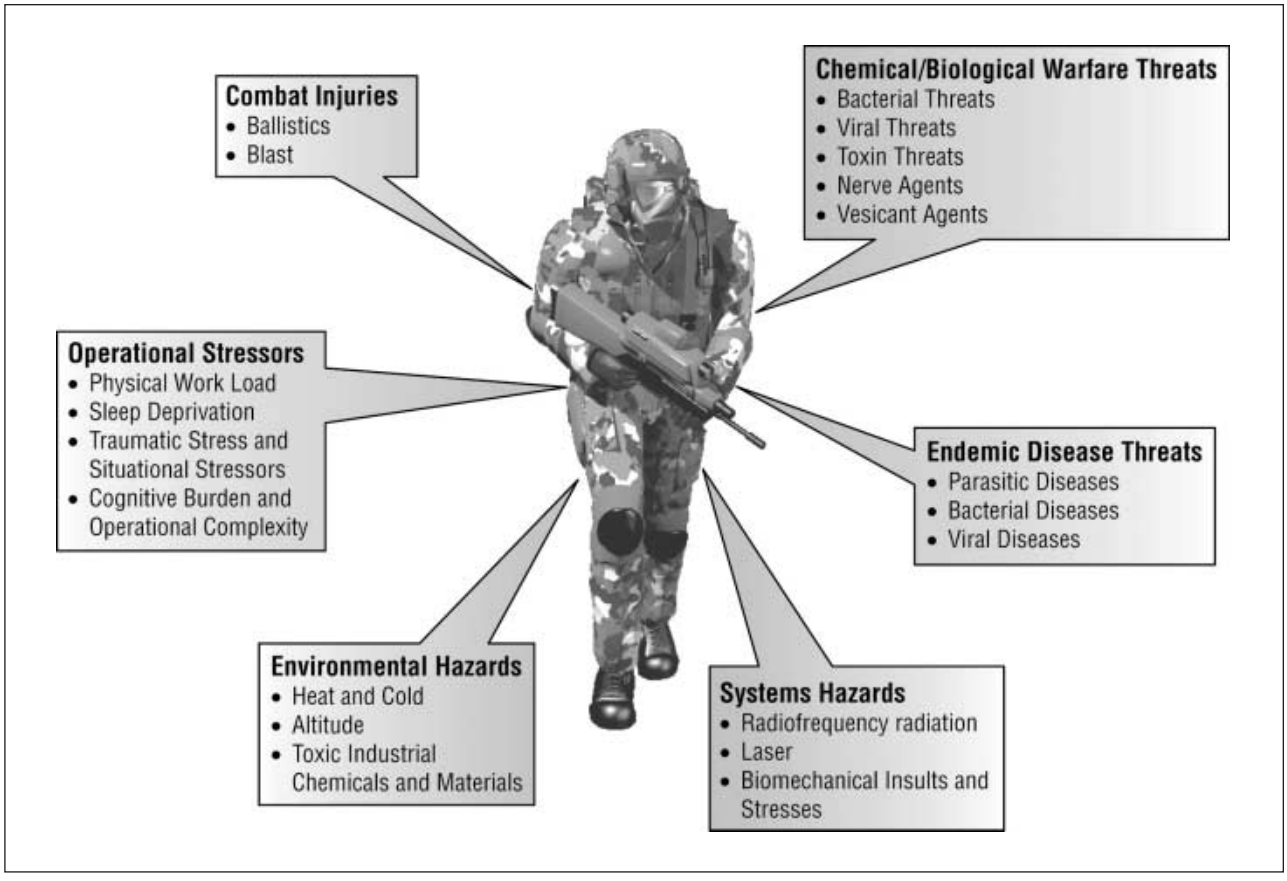


FIGURE 1 Threats faced by the soldier of today and the future.

that the majority of casualties have historically resulted not from enemy weapons, but from diseases (especially infectious diseases), non-battle-related injuries, and stress. For example, in the Vietnam War, 83 percent of all hospital admissions were for disease and non-battle injuries. A traditional rule of thumb is that there is one combat-stress casualty for every three physical casualties.

It is also important to recognize the unique features of the military environment that adversely affect human performance without directly causing casualties. If performance degradation is severe enough, however, missions can be compromised, which can lead to serious consequences, including casualties. The soldier's occupational environment is extremely stressful, both physically and mentally. Work is conducted outdoors in all types of weather and at all altitudes. The workload continues around the clock and is subject to sudden, rapid changes in intensity. Soldiers are required to remain attentive and vigilant and process increasing amounts of information very quickly.

In the future, even greater demands will be made upon soldiers. Future operational concepts call for highly mobile forces enabled by increasingly sophisticated weapon and information systems. Currently, the military must be able to deploy one division (10,000 to 18,000 troops) into an operational theater on 120 hours notice and five divisions within 30 days. The soldier of the future must be physically ready to deploy on a moment's notice; upon arrival, he or she must be ready to fight, anywhere in the world. Soldiers may also be required to change rapidly from humanitarian to peacekeeping to warfighting roles (as in Iraq). These requirements will make substantial cognitive, perceptual, and emotional demands on soldiers. Highly mobile operations will also increase the dispersion and isolation of small units and individual soldiers, changing the way support services, such as medical support, are delivered and making it imperative that soldiers remain fit and healthy. Future soldiers will have to be capable of going without sleep or resupply for extended periods of time and more reliant on self- or buddy-aid in the event of illness or injury.

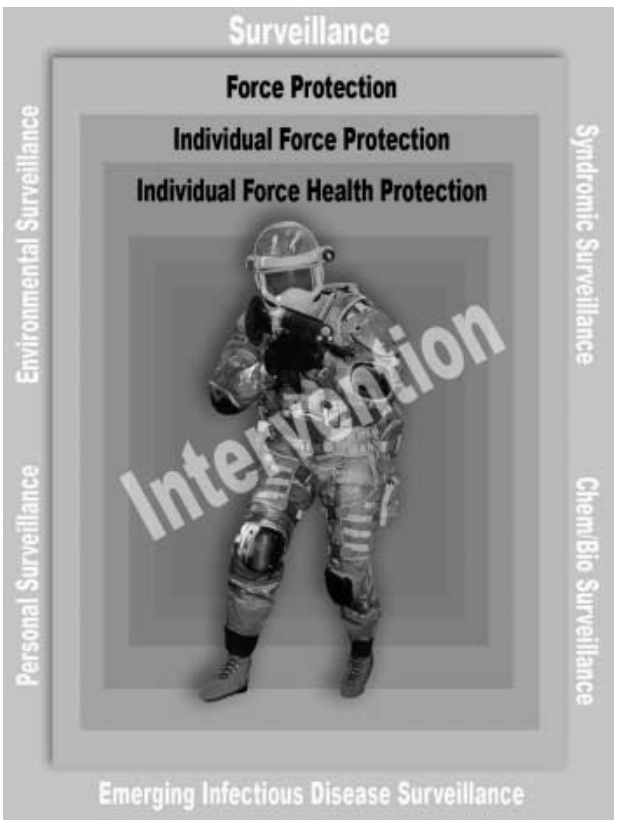
The *Soldier System of Systems*

The *Soldier System of Systems* is a multi-tiered strategy in which the soldier and his or her weapon and support systems are considered as a unified system that encompasses the full range of medical and nonmedical systems for protecting and enhancing the soldier's health and performance. This strategy consists of three levels of defense: *Protection*; *Surveillance*; and *Intervention*. *Protection* is subdivided into the three categories: *Individual Force Health Protection*; *Individual Force Protection*; and *Force Protection* (Figure 2).

Role of Biotechnology

The key to realizing the *Soldier System of Systems* is biotechnology. In 2001, the U.S. Army commissioned a National Research Council (NRC) committee, the Committee on Opportunities in Biotechnology for Future Army Applications, chaired by NAE member Michael R. Ladisch of Purdue University, to accomplish the following goals:

- Examine trends in the bioscience and engineering industries, including small business involvement and university and other institutional research activities in biology, biomimetics, and related areas.
- Determine whether trends in research, technology transfer, and commercialization could be used to predict advances likely to be useful for the Army through 2025.
- Identify the bioscience and engineering technologies with the most potential for Army applications, based on affordability and the likelihood of leveraging commercial research and development.
- Identify critical barriers to the development of biotechnologies with strong potential for Army applications, especially barriers that could be surmounted by appropriate investments in science and technology.
- Recommend research initiatives that could help the Army exploit promising developments in biotechnologies and engineering.



Level of Defense

Protection

Individual Force Health Protection

Physiologically based systems and practices to make the soldier more intrinsically resilient. Examples include medical technologies that improve the fitness and stress resistance of the individual soldier in the face of occupational and operational stresses and environmental hazards, as well as medical technologies, such as vaccines, drugs, and early diagnostics, that can protect against biological and chemical warfare agents and endemic infectious diseases.

Individual Force Protection

Individual systems worn by the soldier, including armor systems to protect against ballistic and blast injuries, physical protection against chemical and biological weapons, and integrated thermal-control systems, and biological and physiological sensors to monitor individual health and performance capability.

Force Protection

Larger scale protective systems, including early-warning systems, vehicle armor, active protection, and signature reduction and evasion technologies to protect against large-scale munitions; and collective (group-level) protection against chemical and biological warfare agents.

Surveillance

Unit- and theater-level systems that provide early warning to avoid injury and/or limit the spread of disease.

Intervention

Casualty-care systems to improve survival in the event of injury and reduce levels of short- and long-term disability.

FIGURE 2 The multi-tiered *Soldier System of Systems* for protection and enhancement of soldiers.

TABLE 1 Biotechnology Applications for Investment by the Army

Camouflage and concealment using biomaterials with stealth characteristics and nonilluminating paints and coatings

Combat identification via biological markers that can distinguish friendly soldiers

Computing with DNA computers that can solve special problems and biological models that lead to new algorithms

Data fusion using protein-based devices and artificial intelligence technologies

Functional foods, such as edible vaccines and food additives, that can lead to improved nutrition and digestion or aid in battlefield identification

Health monitoring via devices that provide feedback on soldier status, enable remote triage, and provide intelligence on chemical and biological warfare agents

High-capacity data storage using individual soldier-based computers with rugged memories

High-resolution imaging to replace semiconductor-based imagers

Lightweight armor for ballistics protection constructed from biopolymers and bioceramics

Novel materials inspired by natural products and modified by genetic engineering, including biodegradable consumables and renewable resources

Performance enhancement through drugs, cortical implants, and sensory enhancement

Radiation-resistant electronics including protein-based components and biomolecular hybrid devices

Reductions in size and weight brought about by cell-based processes, molecular electronics, biochips, and nanotechnology

Sensing of battlefield environments by laboratories-on-a-chip that can detect and identify chemical and biological threats

Sensor networks that include remote sensors mounted on vehicles and carried by soldiers to augment threat intelligence

Soldier therapeutics that are targeted and genomics-based, including therapeutics that can counteract shock and optimize responsiveness to vaccines

Soldier-portable power generated by cell-based energy systems

Target recognition using protein-based devices for pattern recognition and artificial intelligence

Vaccine development that is more rapid and can meet small-scale requirements for diseases encountered in exotic locales

Wound healing aided by engineered skin, tissue, and organs along with dressings and treatments that curtail bleeding and accelerate healing

Source: NRC, 2003.

The results of the NRC study published in 2003 identified 20 prospective applications for Army investment over the short term, midterm, and long term (Table 1).

Biotechnology in the Army

Based on the recommendations of the NRC Committee and internal assessments of technology readiness and soldiers' needs, the Army is currently investing in several broad areas that cut across multiple technology applications (Table 2). The Army's intramural biotechnology effort is being conducted at facilities that fall under the U.S. Army Medical Research and Materiel Command (USAMRMC) and the U.S. Army Research, Development and Engineering Command (RDECOM). USAMRMC focuses on medical and human performance applications; RDECOM focuses on nonmedical systems applications. Extramural basic research is being coordinated by the Army Research Office (ARO), based in Research Triangle Park, North Carolina. ARO oversees two major collaborative ventures with academia that are focused on biotechnology enablers: the Institute of Collaborative Biotechnologies, which includes the University of California at Santa Barbara, California Institute of Technology, and Massachusetts Institute of Technology (MIT), to provide the Army with core competencies and expertise; and the Institute of Nanotechnologies, a $50-million research collaboration between the Army and MIT. The remainder of this article highlights examples of biotechnology-based systems being developed for the *Soldier System of Systems*.

Vaccine-Based Protection against Endemic Diseases and Biological Agents

Current efforts to develop improved vaccines for *Individual Force Health Protection* are focused on molecular recognition and vaccine design and construction. In addition to potentially protecting against diseases for which little or no protection is currently available, molecular biology-based vaccines are expected to avoid

causing some of the side effects commonly associated with traditional vaccines, which are based on whole killed or attenuated live organisms. DNA-based vaccines are being developed by the U.S. Army for several diseases, including dengue fever, malaria, and *Hantaan* virus, and for biowarfare agents, including anthrax, botulinum neurotoxins C through G, and staphylococcal enterotoxins A and B. Genetic and genomic technologies have shifted research and development efforts away from whole pathogens to specific viral or bacterial components that confer long-term immunity in those who survive infection. Army-sponsored vaccine research is currently being conducted at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the Walter Reed Army Institute of Research (WRAIR), and the U.S. Naval Medical Research Center (USNMRC).

As an example of the current state of the art, DNA vaccines are being developed at USAMRIID to protect against hantaviruses, which cause hemorrhagic fever with renal syndrome (HFRS) or hantavirus pulmonary syndrome (HPS). Both HFRS and HPS are acute febrile illnesses that are lethal in 5 to 15 percent and 40 to 50 percent of victims, respectively. DNA sequences that code for specific hantavirus genes have been inserted into nonpathogenic viral vectors, precipitated onto gold microbeads, and injected into the skin of test animals with a needleless gene gun (Hooper et al., 2001). Hamsters injected with the vaccine were protected against challenge infection, and rhesus monkeys produced antibodies that neutralized virus particles. Hamsters injected with monkey serum as much as five days after viral challenge were protected from developing HPS (Custer et al., 2003).

Existing methodologies are continually being refined for more rapid identification of the immune-response-producing components of pathogens, the isolation of genes that code for these components, and large-quantity production of component-coding genes. Rapidly formulated DNA vaccines that are effective against multiple strains of the same organism or combinations of multiple organisms can render the soldier of the future resilient against threats posed by emerging diseases and genetically engineered biowarfare agents.

TABLE 2 Current Biotechnology Focus Areas

Genomic detection, patterns of gene expression that can be used as diagnostics and prognostics, as well as guides to improving preventive medicine and enhancing performance
Molecular recognition, generation of oligonucleotide probes, peptide libraries, and monoclonal antibodies as potential recognition elements for sensor systems
Vaccine design and construction, DNA-based approaches to vaccine design and needleless delivery systems
Drug design and testing, functional studies and genomic and proteomic approaches to identifying novel targets
Catalytic enzymes, recombinant and engineered enzymes for medical prophylaxis, physical protection, and small- and large-scale decontamination
Molecular toxicology, mechanisms of toxicity at the cellular, proteomic, and genetic levels—cytosensor microphysiometer studies for determining effects of nerve agents on human cells; fingerprints of toxic exposures
Bioderived electronic and photonic materials, soluble, conducting, and optically active polymers for biosensors, lightweight power sources, electromagnetic interference shielding, stealthy fabrics, and coatings that protect against corrosion
Bioderived nanoceramics, replications and modifications of the mechanisms for synthesizing ceramic materials in nature

Source: NRC, 2003.

Drug-Based Protection against Endemic Diseases and Biological Threat Agents

Non-vaccine-based efforts in *Individual Force Health Protection* are based on molecular recognition and drug design and testing. The Army is currently focusing on preventive and therapeutic drugs for malaria, a disease for which vaccine-based approaches have not been effective. To ensure that the *Soldier System of Systems* includes protection against this common tropical disease, the Army is pursuing both vaccine-based and non-vaccine-based strategies. The recent completion of the malaria parasite genome sequence (Gardner et al., 2002) has opened the search to the full spectrum of gene-based drug discovery, coupled with more conventional biotechnological, pharmacological, and medicinal methods of drug optimization.

Drugs could also be potentially tailored to specific subpopulations to improve safety and increase effectiveness. When a large number of individuals receive identical doses of the same drug, their responses and side effects vary greatly. These differences are attributed to presumed variabilities in drug-metabolizing enzymes, receptor subtypes, and other genetic factors. Pharmacogenomic and toxicogenomic profiling can

facilitate the identification of subpopulations of individuals for whom a given drug is less effective or more toxic. In some cases, differences may be correctable by introducing minor changes into the chemical structure of the drug.

Monitoring of Physiological Status

To further *Surveillance and Intervention* through the identification of impending degradations in physical or cognitive performance and improved casualty assessment, the Army is investing in molecular recognition technologies. Current prototypes of monitoring systems of physiological status are based on electrical or mechanical sensing of measures of physical activity, heart rate, temperature, and other parameters. A goal for the future is the detection of biomolecules in perspiration or other accessible body fluids that correlate with a soldier's potential to execute a mission. This could be accomplished through biosensors for physiological surveillance or casualty diagnosis integrated into soldier ensembles.

At present, little is known about which, if any, secreted biomolecules are appropriate for sensing. The molecules being investigated include proteins, such as growth factors, metabolites, such as glucose or lactate, and stress hormones, such as cortisol. With proteomics, researchers can profile the expression of all proteins in a tissue and identify patterns and relationships among them under specific performance environments.

Novel approaches are being considered for preventing environmental injuries.

Investigators at the Natick Soldier Center are attempting to identify performance-relevant markers and develop additional types of biosensors. An example of the latter is a project at Georgetown University, cosponsored by the Army and the Defense Advanced Research Projects Agency, that has resulted in the development of a biofluidic chip that extracts molecules, such as glucose, that do not usually diffuse across skin, from subepidermal interstitial fluid.

Protection against Environmental Injury

As part of *Individual Force Health Protection* and *Intervention*, genomic detection and drug design and testing technologies are being pursued for protection against environmental injuries. Genomic methodologies are being used to identify molecular regulators that enhance a soldier's adaptation to environmental stressors, such as extreme heat, cold, and altitude, and biomarkers that predict increased or decreased susceptibility to environmental injuries. Investigators at the U.S. Army Research Institute of Environmental Medicine have characterized gene-expression patterns in peripheral blood mononuclear cells (PBMCs) isolated from soldiers who exhibit signs and symptoms of exertional heat injury (Sonna et al., 2004), as well as PBMCs isolated from health volunteers and then exposed to heat or cold under controlled conditions in the laboratory (Sonna et al., 2002a,b). They have also characterized changes in cultured human liver cells exposed to low oxygen tensions to mimick high altitude (Sonna et al., 2003). More than 50 proteins are affected by heat stress; fewer than 20 are affected by cold; and more than 380 are affected by hypoxia. Novel approaches being considered for preventing environmental injuries include nutritional supplements and smart suits with sensing capabilities.

Host-Based Detection and Diagnosis of Exposure to Chemical and Biological Hazards

Army investment in genomic detection, molecular recognition, and molecular toxicology is funding the development of host-based detection systems in support of *Individual Force Health Protection* and *Surveillance*. A fundamental concept in toxicology is the dose-toxicity relationship, in which the adverse effects elicited by a toxic substance are dependent on the level of exposure to the toxic substance. Exposure levels too low to cause outwardly observable changes in health often cause changes at the molecular level. By detecting molecular changes in the soldier before observable signs and symptoms of toxicity appear, it becomes possible to prevent further exposure and initiate a protective or intervention-based strategy to avert or ameliorate adverse events.

DNA microarray technology is being used at the U.S. Army Center for Environmental Health Research, the Edgewood Chemical and Biological Center (ECBC), and WRAIR to identify genetic markers of response to different classes of toxic hazards and long-term changes in gene expression following asymptomatic, low-level exposures

to chemical warfare agents. An interesting finding is that male and female rats show different alterations in gene expression following whole-body inhalational exposures to low doses of sarin vapor (Sekowski et al., 2002).

DNA microarray technology is also being used at USAMRIID and WRAIR to assess immune system responses to a variety of biological agents. The expression patterns of isolated PBMCs exposed to biological agents in the laboratory setting support discrimination of agents that include bacteria (e.g., anthrax, plague, and brucella), toxins (e.g., staphylococcal enterotoxin B, cholera toxin, and botulinum neurotoxin A), and viruses (e.g., Venezuelan equine encephalitis and dengue fever) (Das et al., 2002). Furthermore, PBMCs isolated from nonhuman primates exposed to anthrax in vivo reveal patterns of gene expression that correlate with the impending onset of symptoms. The latter approach could be beneficial for detecting exposures to genetically modified organisms that cannot be detected by pathogen-based methods.

Hazard-Based Detection and Diagnosis of Exposure to Biological Hazards

Another element of *Individual Force Health Protection* and *Surveillance* is the combination of molecular recognition and bioderived electronic and photonic materials to detect pathogenic organisms in the environment. Investigators at the Natick Soldier Center are leveraging the electrical conduction and optical properties of polymers that have been complexed with single-stranded DNA or RNA to form sensitive gene chip biosensors. When the nucleic acid of a pathogenic organism hybridizes to a complexed nucleic acid probe, the properties of the polymers change. Investigators are also developing peptide-based receptors that bind selectively to pathogenic bacteria. Investigators at ECBC are working on peptide-based receptors that bind toxins, such as ricin and staphylococcal enterotoxin B, and on designing and fabricating a DNA/RNA microarray capable of detecting and identifying pathogens down to the level of different strains. These technologies can also be used for monitoring food and water for contamination.

Catalytic Inactivation of Toxic Agents

Individual Force Health Protection, Individual Force Protection, and *Force Protection* are being addressed through investment in catalytic enzymes and drug design and testing to protect against toxic chemical and biological agents. At the U.S. Army Medical Research Institute of Chemical Defense, bioengineered recombinant butyrylcholinesterase is being investigated for use as prophylaxis against the adverse effects of exposure to nerve agents, such as sarin, soman, tabun, and VX. This enzyme mimics acetylcholinesterase and competes with it for binding nerve agents, thus reducing the level of acetylcholinesterase inactivation. It is anticipated that a single dose of this enzyme will be capable of scavenging nerve agent through stoichiometric binding for up to eight hours. Current efforts are directed at engineering the enzyme so that it has catalytic activity in vivo and exploring the use of a transgenic goat model for generating sufficient quantities of engineered enzyme to conduct clinical trials.

Enzymes for hydrolyzing G-type and V-type nerve agents have been identified, cloned, and optimized.

At ECBC, recombinant enzymes are being incorporated into fabrics and polyurethane foams for nonmedical protection and into sprays, detergents, degreasers, and other matrices for decontamination following exposure. Enzymes for hydrolyzing G-type and V-type nerve agents have been identified, cloned, and optimized. Organophosphorus acid anhydrolase, which works against the G agents sarin, soman, and tabun, is in large-scale process development. Random and site-directed mutagenesis has resulted in variants of organophosphorus hydrolase enzyme with increased activity against the V-type agent VX. Organophosphorus hydrolase is also currently in process development. In addition, a bacterial enzyme has been identified that hydrolyzes sulfur mustard, and a collaborative project is under way with Rockefeller University to assess the effectiveness of using bacteriophage lysins to destroy anthrax spores (Schuch et al., 2002).

Biomembrane and Fiber Generation

The Army is investing in bioderived materials and molecular recognition as part of *Individual Force Protection, Force Protection,* and *Intervention.* A process called

electrospinning is being used at the Natick Soldier Center to produce high-surface-area nanofiber membranes with unique reactive sites for selective immobilization of biological recognition elements. The current focus is on including immobilized antibodies and antimicrobial peptides on electrospun nanofibrous poly(epsilon-caprolactone) (PCL) for selective binding to pathogens. These materials can be used in the development of clothing-based biosensors and in filtration of pathogens from food, water, and clothing. Other electrospun polymeric materials include polyurethanes and polyvinyl chloride.

Biomembranes and fibers are also being investigated at the Institute for Soldier Nanotechnologies. There, electrospun polymers are being used as extracellular matrix-mimicking scaffolds to support tissue regeneration and as vehicles for delivering drugs and biologics that promote tissue healing after injury.

Protection against Ballistics

Hard and lightweight ceramic materials, such as boron carbide, are incorporated into body armor and other forms of protective shielding. Research is now focusing on bioderived nanoceramics in support of *Individual Force Protection* and *Force Protection*.

In nature, organisms can form ceramics under mild conditions using protein-directed templated crystallization mechanisms. Identifying novel peptides that control inorganic ceramic architecture is a technical challenge being addressed at the Natick Soldier Center. Based on our current understanding of how nature nucleates inorganic nanocrystallization, researchers are attempting to use biomimetic approaches to create novel materials not found in nature. For example, the proteins that direct crystallization for generation of sea urchin spicules are being genetically modified to favor ions, such as boron and aluminum, rather than the naturally incorporated ions of calcium and silica.

Systems Engineering Issues

A key challenge to realizing the *Soldier System of Systems* is to provide a comprehensive range of capabilities while simultaneously meeting stringent military requirements to minimize weight and power consumption. Today's soldiers may carry as much as 100 pounds of equipment. In keeping with requirements for increased mobility, the objective is to reduce the effective load to less than 40 pounds by developing efficient multifunctional systems for the *Soldier System of Systems*. Examples include a single system for detecting exposures to chemical warfare agents, toxic environmental chemicals, biowarfare agents, and/or infectious pathogens and a single vaccine system for protecting against multiple pathogenic organisms.

The problem is complicated because of potential interactions among drugs and vaccines that can decrease their effectiveness or increase their toxicity. Another concern about biologically based systems is their stability and durability. Many biological molecules are susceptible to degradation, and it remains to be seen whether bio-based materials and sensors will be able to perform well under rugged field conditions in which they are exposed to extremes of temperature and humidity, the possibility of oxidation, and other stresses. Biomaterials must also have a reasonably long shelf-life, because perishable materials could be logistically insupportable or unaffordable if stockpiles must be frequently refreshed.

Other major challenges to realizing the *Soldier System of Systems* are gaps in our knowledge. Despite substantial progress in the enabling technologies for engineering sensors and DNA vaccines, questions remain about which biomolecules are appropriate for sensing and why some vaccines fail to elicit a protective response. We will certainly need more basic research on enabling technologies and their applications. By continually monitoring progress in basic and applied research in the academic, governmental, and industrial communities, the Army can hope to fill these knowledge gaps, identify the most promising enabling technologies, and promote their development by carefully directing its investments.

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Bioprocess engineering is the discipline that puts biotechnology to work.

The Role of Bioprocess Engineering in Biotechnology

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Biotechnology involves using organisms, tissues, cells, or their molecular components (1) to act on living things and (2) to intervene in the workings of cells or the molecular components of cells, including their genetic material (NRC, 2001). Biotechnology evolved as a means of producing food, beverages, and medicines. More than 8,000 years ago, it was used to make leavened bread. Some 5,000 years ago, moldy soybean curd was used to treat skin infections in China. The malting of barley and fermentation of beer was used in Egypt in 2500 BC (Ladisch, 2002).

Biology is central to biotechnology. Louis Pasteur proved in 1857 that yeast is a living cell that ferments sugar to alcohol; in 1877, he showed that some bacteria kill anthrax bacilli. In 1923, Banting and Best showed that insulin from animals could be used to treat people suffering from diabetes. In 1928, Alexander Fleming showed that growing colonies of *Penicillium notatum* inhibit *Staphylococcus* cultures. Beginning in 1939, Florey and Chain rediscovered that Fleming's *Penicillium* could lyse bacteria, but the yield of penicillin was small; in addition, the penicillin it did produce was unstable (Matales, 1998). They realized that producing *Penicillium* on a large scale would require isolation and purification procedures that minimized product loss. Early bioprocess engineers found solutions to this problem (Aiba et al., 1973) when researchers in the U.S. Department of Agriculture (USDA) laboratory in Peoria, Illinois, discovered that mold on

a cantaloupe (*P. chrysogenum*) could be grown in large tanks in submerged cultures (Shuler and Kargi, 1991).

During World War II, government incentives encouraged several pharmaceutical companies to develop cost-effective manufacturing processes for penicillin (Hacking, 1986). Chemical engineers, industrial chemists, and microbiologists quickly devised methods of countercurrent extraction, crystallization, and lyophilization to recover penicillin in an active, stable form and established the viability of submerged fermentations (Matales, 1998).

The benefits of biotechnology might be an anomaly if it were not for engineering, specifically bioprocess engineering, the discipline that puts biotechnology to work (NRC, 1992). To quote Louis Pasteur, bioprocess engineering is to biotechnology "as the fruit is to the tree." Neither can exist without the other. The realization of the benefits of penicillin required the development of methods of transforming microbial growth on the surface of a moldy cantaloupe to cultures grown in large stirred tanks fed by sterile air (Aiba et al., 1973).

It took engineers to design the tanks, impellers, pumps, compressors, columns, pipes, and valves that have made biotechnology products available to large numbers of people. The lifesaving benefits of insulin required engineering for the extraction and purification of insulin from cow and pig pancreas, and later, the large-scale propagation of bacteria engineered to make human insulin, as well as methods of recovery, refolding, and purification to obtain an active molecule (Ladisch, 2001). Biochemical manufacturing and bioseparations have made it possible to purify products derived from biotechnology on a large scale.

High-Fructose Corn Syrup and Bioethanol

In 1957, scientists at USDA reported the discovery of an enzyme with the amazing ability to transform glucose to fructose (although it required arsenic as a cofactor). In 1965, a version of this glucose isomerase enzyme that did not require arsenate was discovered in a species of *Streptomyces*. Once it was possible to grow this organism using corn-steep liquor to produce a thermally stable enzyme in a cost-effective way, sugars from corn with sweetness similar to sugar from sugar cane became feasible.

Glucose isomerase (which also transformed xylose to xylulose) was used to generate the first commercial shipment of corn syrup containing 42 percent fructose in 1967. Bioprocess engineers invented systems of fixed beds of the glucose isomerase enzyme and demonstrated the utility of biocatalysts for the large-scale industrial production of biochemicals. They also adapted industrial-scale liquid-chromatography separations used in the petrochemical industry to enrich the fructose content in corn syrup from 42 percent to 55 percent (UOP Sarex process), creating 55-percent high fructose corn syrup (HFCS). When a "taste challenge" sponsored by a soft-drink company showed that consumers preferred soft drinks made with 55-percent HFCS, HFCS became a major sweetener in many popular soft drinks. The HFCS industry grew quickly, particularly after 1975, when patent coverage for using xylose (glucose) isomerase to convert glucose to fructose was lost due to a civil action suit (described in Ladisch, 2002).

The benefits of biotechnology could not be realized without bioprocess engineering.

The biotechnology developed for HCFS production intersected with increases in U.S. agricultural productivity to set the stage for the large-scale production of bioethanol as a liquid transportation fuel. In 1988, yields of corn were 85 bushels per acre; by 1990, they had jumped to 119 bushels per acre. Today, yields range from about 130 to 138 bushels per acre. The wet mills that produced HFCS had the infrastructure, integrated processing, biotechnology, and bioprocess engineering expertise to make million-gallon fermenters conceivable. They also had access to glucose from corn to fill these tanks with substrates for the production of fuel ethanol, which was introduced in the 1980s (NRC, 1998). The 81 million acres of corn planted in 2004 will provide renewable raw materials, not only to make sugar, but also to make fuel ethanol and other bioproducts, such as monomers and biodegradable plastics.

DNA, Genetic Engineering, and the Biotechnology Industry

In 1953, Watson and Crick showed that DNA consists of a double helix with a code of triplets of nucleotides that correspond to specific amino acids and

the sequence in which they were assembled.[1] Spectacular developments followed. Genes in chromosomes were mapped to the genetic bases of diseases. Cellular processing of DNA and other nucleotides derived from it were beginning to be understood. A breakthrough came in 1970 when Smith et al. showed that a restriction endonuclease (i.e., an enzyme that hydrolyzes DNA) from *Haemophilis influenzae* could recognize specific DNA sequences. Restriction enzymes were then used to cut plasmids (circular DNA found in bacteria) in a way that allowed scientists to insert new genes. By 1973, Cohen et al. had put a plasmid with an inserted gene back into a cell, making it possible to produce a wide range of new products.

Bioprocess and bioseparation engineering were critical in bringing human insulin to market.

One widely used plasmid is PBR 322. Its 4,362 nucleotides were completely sequenced in 1979. PBR 322 contains unique restriction sites and has genes for antibiotic resistance that allows for the selection of transformed bacteria. Thus, specific regions (restriction sites) cleaved by specific restriction enzymes could be identified and foreign genes inserted. In other words, the engineering of genes, or genetic engineering, became possible. When the reconstructed plasmid was reintroduced into a microorganism, *E. coli*, the molecular machinery in the cell transcribed and translated the instructions to make a human protein in a bacterial cell. Here's how it worked.

PBR 322 carried instructions (genes) for making enzymes that rendered the antibiotics ampicillin and tetracycline harmless (Old and Primrose, 1994). Only about 1 percent of *E. coli* cells, however, retain the engineered plasmids inserted into them. Thus, cells that were successfully transformed by inserting the plasmids could be identified by their ability to grow in media containing ampicillin and/or tetracycline. Cells that contained the plasmid had built-in resistance to the antibiotic; cells that did not contain the plasmid were killed. Thus, biologists had found a way to select for transformed cells. Because the plasmid could be "constructed" in a test tube, and because the construction involved genes, the term genetic engineering was used to describe the process.

The stage was now set for the first human protein, human insulin, to be produced in *E. coli* in a sequence identical to the human pancreatic peptide. In 1978, separate insulin A and B chains were achieved in *E. coli K-12*, using genes synthesized for the insulin A and B chains and cloned in plasmid PBR 322. Later, human insulin was produced as a preprohormone, using one fermentation instead of two (Chance et al., 1981). Eli Lilly licensed the technology and quickly developed the process, and the first recombinant product, human insulin, was marketed in 1982. By 1991, human insulin provided an estimated 70 percent of the demand for insulin in the United States.

The production of human insulin required 31 major processing steps, 27 of which are associated with product recovery and purification (Prouty, 1991). Bioprocess and bioseparation engineering, which provided technology for carrying out complex, biological processes on a large scale, were critical in bringing human insulin to market.

Monoclonal Antibodies

In 1975, Kohler and Milstein reported that hybrid cells derived from mouse B lymphocytes (which secrete antibodies) fused to mouse myeloma malignant cells will grow in submerged cultures. The fused cells, called hybrid myelomas, or hybridomas (NRC, 2001), had the capability of growing and dividing, and hence producing, monoclonal antibodies in cell culture. The cells derived from the founder cell are identical to it and produce the same antibodies, which are referred to as monoclonals. Here was an example of living things acting on livings things (and with each other) to make a part of a living thing (an antibody) that had therapeutic uses.

Initially, monoclonal antibodies were considered tools for detecting or diagnosing pathogenic microorganisms or cancer cells because of their ability to bind specifically to protein biomarkers that label these cells. When monoclonal antibodies were linked to toxins to deliver them specifically to cancer cells and other

[1] The polymers of amino acids are self-assembling, and their sequences determine their three-dimensional conformations. These macromolecules are endowed with catalytic capabilities under atmospheric conditions and temperatures between 10°C and 50°C.

therapeutic uses were discovered, demand for their manufacture increased dramatically. Bioprocess engineers are working to scale up processes of cell culture to enable manufacturing facilities to meet that demand.

Biopharmaceuticals and Bioproducts

Biopharmaceuticals (biological molecules with medicinal value) include treatments for cancer, heart disease, and autoimmune diseases. Bioproducts are commodity-scale products that often have a lower molecular weight (e.g., fuel ethanol, monomers for manufacturing biodegradable plastics and carpet fibers, and biocatalysts used in food processing and laundry detergents). Other types of future bioproducts might include functional foods that improve nutrition or contain edible vaccines, biomaterials for paints and coatings, and optical-holographic high-density memories (NRC, 2001). Bioprocess engineering puts biotechnology to work by providing manufacturing systems to generate bioproducts in large volume, at low cost, and with acceptable purity.

Mapping the Human Genome: Genomics

Genomics "provides a means of identifying, in any cell, tissue, or organism, all of the important genes and regulatory regions in the DNA, all of the mRNAs, and all of the proteins in different states of cell and organ function. Genomics has transformed the science of biology by enabling the discovery of new links between protein structure and function" (NRC, 2001). Proteomics addresses "information about RNA and protein products of genes" (NRC, 2001).

The grand challenge of sequencing the human genome required that many existing bioprocessing tools—fermentation, enzymology, and bioseparations—be mapped onto new biotechnologies—cloning, polymerase chain reaction (PCR), and automation of DNA sequence analysis—and used with information-age tools that connected computers through the Internet. The goal was to generate sequences (the order of nucleic acids in DNA) and piece them together to discover genes and the nature of information stored in DNA. To produce enough genetic material, DNA was propagated in microbial cells using bacterial artificial chromosomes.

The human genome consists of chromosomes made of DNA associated with a protein that wraps around it to protect it from the effects of mechanical forces. First, the DNA had to be separated from this protein so that it could be disassembled one nucleic acid at a time. The process was accelerated by a so-called "shotgun" technique. Restriction enzymes were used to break up DNA into small fragments of 300 to 500 base pairs. The fragments were then sequenced and the sequences compared to find overlapping fragments. Computers were used to reassemble the sequences of these overlapping fragments into the original DNA code.

By replicating the procedure in different laboratories, comparing the results against existing databases, and using the Internet and computers to make comparisons, the sequencing task was completed by 2000, several years ahead of schedule. It took another year to determine the number of genes in the human genome (now believed to be about 30,000 but once thought to be 100,000). The engineering of automated instruments and software for analyzing nucleic acid sequencing played a major role in achieving this milestone.

Future bioproducts might be foods that contain edible vaccines and optical-holographic high-density memories.

The cost of sequencing has decreased from $2 per base pair to 20¢ per base pair. By 2025, perhaps sooner, it may be possible to sequence the entire human genome for $6,000, making it practical to compare a person's complete DNA sequences with a reference DNA sequence to identify a biological "dog tag" unique to each person. Not only would this preserve the identity of the individual, but it could also lead to the identification of genetic risk factors and an individual's tolerance to environmental conditions (e.g., heat, cold, high altitude, radiation) or chemotherapy (NRC, 2001).

Identification of differences in DNA is in part made possible by PCR (see Box 1). PCR requires a thermally stable enzyme that catalyzes DNA formation. The enzyme (first isolated from microbes growing in hot springs) enables researchers to make millions of copies of a DNA fragment in as little as an hour, enough to sequence or identify the DNA sequence.

BOX 1 The Polymerase Chain Reaction

The polymerase chain reaction (PCR) is an enzyme-mediated, *in vitro* amplification of DNA for purposes of analysis. Since about 1985, this method has significantly increased the ease and speed of isolating DNA sequences *in vitro*. Developed by scientists of Cetus Corporation in 1984 and 1985, PCR is an enzyme-catalyzed reaction that facilitates gene isolation and eliminates the need for the complex process of cloning, which requires the *in vivo* replication of a target DNA sequence integrated into a cloning vector in a host organism. PCR is initiated by DNA denaturation, followed by primer annealing; a DNA polymerase and deoxynucleoside triphosphates are then added to form a new DNA strand across the target sequence. When this cycle is repeated *n* times, it produces 2^n times as much target sequence as was initially present. Thus 20 cycles of the PCR yields a one million-fold increase or amplification of the DNA. Applications of PCR include comparisons of altered, uncloned genes to cloned genes, diagnoses of genetic diseases, and retrospective analyses of human tissue.

Source: Arnheim and Levenson, 1990.

Biotechnology and Agriculture

In the past, plant and animal breeding were used to enhance agriculture by taking advantage of the natural variability of characteristics or inducing mutations (or using natural mutations) in genes. Today, genes from other species can be engineered into plants or animals. For example, antiworm protein from the bacterium *Bacillus thuringiensis* can be engineered into corn or cotton, thus reducing the need for pesticides. Biotechnology has provided the tools for engineering crops resistant to pests or herbicides and animals capable of producing therapeutic proteins. Another example is sheep that produce human antibodies that can boost the immune system. Organisms with genes transferred from one species to another are called transgenic.

The tools of molecular biology, described in this paper, which were developed largely for medical applications, are being used for cloning genes into microorganisms to produce bioenergy and bioproducts, as well as for the study and modification of metabolic pathways in microorganisms. These studies require gene sequencing and relating protein function to its structure, much as pharmaceutical properties are related to protein structure in the development of new pharmaceuticals. There is a major difference, however. Outputs of bioenergy (such as ethanol) will be measured in tons per day, whereas outputs of biopharmaceuticals may be measured in kilograms per year.

A yeast has been engineered to produce ethanol from xylose, including the formation of xylulose by xylose isomerase (an enzyme that also isomerizes glucose to fructose). The xylulose then enters an ethanol-producing pathway. Glucose has been fermented to ethanol for millions of years, but when xylose isomerase and other enzymes are cloned into yeast, both glucose and xylose can be fermented. Similarly, a genetically engineered *E. coli* is also capable of fermenting xylose to ethanol. When combined with a suite of other bioprocessing technologies, pentose fermentation increases the yield of ethanol from plant materials by 50 percent, moving us a step closer to the transformation of renewable, agricultural residues into fuel-grade ethanol. Imagine the potential in the United States alone, where an estimated 20 million tons of residues could produce 1.6 billion gallons of ethanol.

The goal of metabolic-pathway engineering is to understand, and ultimately direct, metabolic pathways in microbial cells to make value-added bioproducts. Some transgenic animals and plants have been engineered to produce therapeutically important proteins (although these are not yet commercial). Agriculture could become a producer of large volumes of therapeutic compounds using small amounts of land. Engineering will play an important role in the extraction, recovery, and purification of these products.

Eighty-one percent of U.S. soybean acreage and 15 percent of corn acreage is already planted with genetically engineered, herbicide-tolerant crops. These crops can survive the application of specific herbicides that would otherwise destroy them, as well as targeted weeds. Insect-resistant cotton and corn contain a gene from the soil bacterium, *Bacillus thuringiensis*, that produces a protein toxic to certain lepidopteran insects (insects that go through a caterpillar stage) and protects the plant over its entire lifetime. Some plants have "stacked" traits (i.e., both insect and herbicide resistance). In 2003, 27 percent of the cotton planted was insect and herbicide resistant. Corn with stacked traits made up only 4 percent of the corn planted in 2003. Corn with the *Bacillus thuringiensis* trait made up 41 percent in 2003 and appears to be leveling off. Considering that these crops only became available in 1996, their impact has been remarkable. One of the challenges for engineers will be keeping genetically engineered crops separate from other crops, because

commercial developers must address consumer resistance to some engineered bioproducts, particularly some types of foods.

On the Horizon

The newest frontiers for bioprocess engineers are biotechnology on the nanoscale. Bionanotechnology involves defining fundamental phenomena for investigating the macroscopic world on a submicroscopic scale. Stem cells, gene therapy, functional foods, edible vaccines, pharmacogenomics, and biosensors are on the horizon for biotechnology. Designing robust manufacturing processes to produce large quantities of these bioproducts will require bioprocess engineering. The absolute scales of these processes will be measured in volumes ranging from nanoliters to cubic meters.

For example, sensors with micron-scale features and nanoliter-sized volumes must be able to sample colloidal fluids with submicron-scale virus particles or microbes and process fluid without becoming plugged up or otherwise inactivated. Sensors used for pathogen detection must be integrated into a system that concentrates a large-volume sample (100 to 200 milliliters) into a small-volume sample (10/μL), perhaps in less than an hour. This will require amplification of the target species by culture or by concentration (filtration) and recovery of the sample. The integrated system will have to be able to concentrate a sample as much as 10,000 fold prior to its being introduced or interrogated by a miniature analytical device. Bioprocess engineering will be required to develop a knowledge base of fluidics at a microscale, self-assembly processes of biological molecules, and microscale bioseparations. The challenge to engineers will be relating properties of the macroscopic world to microscale devices built from submicron, nanoscale components.

Other bioproducts will involve biotechnology (i.e., parts of living things acting on living things) to enhance human performance in emergency situations, to generate electricity from biological molecules or living cells, to use proteins to store holographs of maps, to develop strong, lightweight materials from nanostructured components, to embed physiological monitors, and to stop bleeding. A recent study identified 45 areas of biotechnology that could be useful to the U.S. Army (NRC, 2001).

Summary

Biotechnology is defined by the tools used to practice it. By programming DNA and directing cellular machinery, we can obtain products that were unimaginable even 10 years ago. With biotechnology, we can direct the nanoscale machinery of living cells to produce self-contained factories that perform on a characteristic scale of one micron. To be useful to people, however, bioproducts and bioenergy must be produced in immense quantities. Genetic engineering, for example, is carried out at a molecular scale but is amplified through bioprocess engineering to transfer the technology from the test tube to the bottle through a sequence of integrated steps that generate, recover, purify and package the product (NRC, 1992). The challenge facing bioengineers is to redirect genetic and cellular machinery to make economically important molecules when the cells are placed in controlled environments. Engineers must design, build, and operate hardware and integrated systems that can multiply a cell's output by a factor of one trillion, as well as recover and purify the products in a cost-effective manner. Bioprocess engineering is the next frontier.

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The Army is investing in biotechnology to realize the goals of Transformation.

Army Transformation: Paradigm-Shifting Capabilities through Biotechnology

John A. Parmentola is Director for Research and Laboratory Management, U.S. Army.

John A. Parmentola

The U.S. Department of Defense (DOD) has embarked on an extraordinary process of change called Transformation, that is, the creation of a highly responsive, networked, joint force capable of making swift decisions at all levels and maintaining overwhelming superiority in any battle space. In support of this process, the Army is developing the Future Combat System (FCS), a major element of its Future Force, which will be smaller, lighter, faster, more lethal, and smarter than its predecessor. Transformation will require that the Army make significant reductions in the size and weight of major warfighting systems, at the same time ensuring that U.S. troops have unmatched lethal force and survivability. It also means that the Army and other military services (as well as coalition forces) will be interdependent.

Challenges

To meet the Army's goals for "strategic responsiveness," that is, the ability to deploy a brigade combat team in 96 hours, a division in 120 hours, five divisions in 30 days, and to fight immediately upon arrival, the Army must overcome a number of technical challenges. These include: reducing the weight of soldier equipment while improving soldier protection; making lightweight combat systems survivable; and ensuring that command-and-control centers are mobile and much more capable.

The Weight of Equipment

Today, soldiers must carry as much as 100 pounds of equipment, which has a dramatic effect on their agility and endurance. The Army's goal is to reduce the effective fighting load to 40 pounds, while improving protection against threats from the enemy and the environment. As a first step, the Army is developing robotic "mules" that can follow soldiers into battle and carry a good part of the load.

Robotic "mules" will carry some of the soldier's load into battle.

Improved Soldier Protection

The Army is also pursuing novel ways to use nanomaterials to protect against ballistic projectiles and chemical and biological attacks and to enable a soldier's ensemble to perform triage through active-control materials and diagnostic sensors. An immediate challenge is to protect against injuries to the extremities, the most prevalent injuries on the battlefield.

The Army Research Laboratory, in collaboration with the Army Center of Excellence in Materials at the University of Delaware, has developed a new Kevlar-based garment by applying shear thickening liquids to the material. These substances are composed of nanoparticles of silica suspended in a liquid, such as polyethylene glycol. When a high-speed projectile is injected into these liquids, the nanoparticles are compressed into a rigid mass that resists penetration. At slow speeds, the nanoparticles are able to move around the projectile, offering little or no resistance to a slow-moving projectile. The result is a garment with normal flexibility that is completely stab resistant. The garment is currently being assessed to determine its effectiveness with respect to other types of injuries to the extremities.

Recently, the Army's Institute for Soldier Nanotechnology at the Massachusetts Institute of Technology (MIT) discovered a novel, active-control material, dubbed "exomuscle," that might be used as a prosthesis to help soldiers handle and lift heavy objects. Exomuscle might also be embedded in the soldier ensemble, along with physiological monitoring and diagnostic sensors. The soldier's uniform could then act as a tourniquet to limit blood loss or perform CPR, as needed on the battlefield.

Stronger, Lighter Weight Armor

Currently, the most advanced combat system is the Abrams tank, which weighs more than 70 tons and can only be deployed either by C-5 aircraft (two per aircraft) using special runways, C-17 aircraft (one per aircraft), or ship and rail. The Abrams tank has a remarkable record of limiting casualties (only three in combat since its deployment nearly 20 years ago). To meet the new deployment goals, however, the Army must use C-130-like intratheater cargo aircraft to transport troops and equipment.

Traditional approaches to survivability have relied heavily on armor, which has driven up the weight of ground combat systems. Because of the weight limits of FCS, the Army must develop a new survivability paradigm that relies on speed, agility, situational understanding, active protection systems, lighter weight armor, signature management, robotic systems, indirect precision fire, terrain masking, and various forms of deception rather than heavy armor.

Realizing this new paradigm will require sophisticated research tools. For example, suppose for each of the 10 parameters listed above there are 10 points to explore. This means there are 10 billion points representing varying degrees of survivability. So where in this 10-dimensional volume are the acceptable levels of survivability for light combat systems in desert terrain, rugged terrain, urban terrain, and jungle terrain, taking into account the environmental conditions associated with them? Analyzing this complex 10-dimensional volume experimentally is both unaffordable and impractical. Therefore, we must rely on modeling and simulation. Fortunately, with focused research, emerging technological developments, and advances in high-performance computing (HPC), the Army will be able to conduct trade-off analyses to help resolve this critical issue.

Armor will undoubtedly remain an important aspect of survivability, and many innovative approaches are under development, including advanced lighter weight composite armors and ceramic armor that can sustain greater loading for longer periods of time, thus increasing its ability to dissipate energy. These novel materials have enabled engineers to trade levels of protection for reductions in armor weight.

Mobile, More Capable Command-and-Control Centers

Another challenge is making command-and-control centers mobile and capable of maintaining the momentum of the fighting force. Currently, these centers are massive and relatively immobile—they move at less than 10 miles per hour—not quite as slow as the air traffic control center at a major airport. One of DOD's top five goals is network-centric warfare, the central element in fully realizing Transformation in this century. The network must include individual soldiers on point, operations centers in the theater of operation, and the home station, which can be anywhere in the world. Communications and the network are the key foundational elements of FCS and the Future Force.

Trends in Science and Technology

Because the Army's strategy for transformation is strongly dependent on the continuous infusion of new technologies, trends in technology are continually monitored and assessed to determine their applicability to meeting the Army's needs. Certain trends are expected to persist well into this century. These trends include: time compression; miniaturization; and the understanding and control of increasingly complex systems.

Time Compression

Time compression involves the conveyance of information at the speed of light, and, more importantly, the ubiquitous availability of HPC that can process information very rapidly. Knowledge management, data processing, data interpretation, information routing, and link restoration for assured communications will be essential to situational awareness. Real-time, multisensor, data-fusion processing will be possible with embedded HPC capabilities. This technology will also be important for autonomous unmanned systems and reliable autonomous seekers for smart munitions.

Advances in silicon-based HPC are likely to be overtaken by rapid developments in molecular electronics, and possibly DNA and quantum computing, with speeds that will make current supercomputers seem like ordinary pocket calculators. According to futurist and inventor Dr. Ray Kurzweil, we can expect a steady, exponential progress in computing power. At that rate of advance, we could have embedded HPC with remarkable speeds within the next decade. If Dr. Kurzweil is correct, computing ability will exceed the ability of all human brains on the planet by 2050.

Miniaturization

Space continues to be "compactified," as more and more functions are performed by devices that take up smaller and smaller spaces. Golf-ball-size systems on the horizon include advances in microelectromechanical systems (MEMS). These systems will improve sensor systems and lead to low-cost inertial-navigation systems, diagnostics, prognostics, microcontrol systems, and so forth.

Miniaturization will also improve logistics. Maintenance of warfighting systems on the battlefield will be managed in real time through predictive capabilities involving sophisticated prognostic and diagnostic systems, all connected and communicating on the FCS mobile wireless ad hoc network. Further advances in miniaturization will result in inexpensive, self-contained, disposable sensors, such as smart dust (Figure 1). These small, inexpensive sensors will be dispersed by soldiers on the battlefield in handfuls over an area where they will self-organize and self-configure to suit the particular situation.

Miniaturization will also have a major impact on flexible display technology, conformal displays that can be placed on a soldier's face plate or wrapped around a soldier's arm. The Army's Flexible Display Center at Arizona State University leads the field in research in this area. Within this decade, we expect to realize a wireless device contained in a six-inch long, one-inch diameter tube (Figure 2). Anticipated advances in

FIGURE 1 Smart dust, a miniaturized, inexpensive, self-contained disposable sensor. Source: Dr. Kenneth Pister, University of California at Berkeley.

miniaturization, computer memory, computational speed, and speech recognition should lead to a compact device capable of video recording, speech recognition, embedded mission-rehearsal exercises, stored illustrative manuals, wireless communications, and real-time situational awareness through a flexible display, all in a compact form that will easily fit into a soldier's pocket.

We will also be working on the development of very small complex machines, such as nanobots that can perform microsurgery, prostheses that can enhance soldier capabilities, and machines that can go into places that are dangerous to humans. The development of micro unmanned aerial vehicles (UAVs) the size of a human hand, or even smaller, is within our grasp (Figure 3). Micro UAVs will enable soldiers to gather information about threats and provide both lethal and nonlethal capabilities, while keeping soldiers out of harm's way.

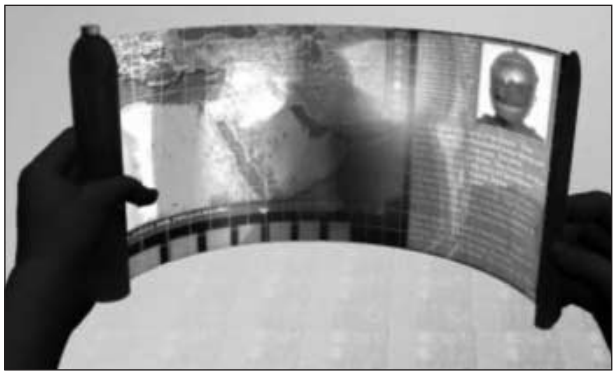

FIGURE 2 Wireless flexible display for use by the soldier on the battlefield. Source: Eric Forsythe and David Morton, Army Research Laboratory.

Our inspiration for this system is the common bumblebee (Figure 4). This small creature, with a body weight that is essentially all nectar, has a horizontal thrust of five times its weight and is capable of flying at a speed of 50 km per hour with a range of 16 km. Recently, researchers have discovered that the bumblebee navigates by balancing information flow from its left and right optical systems. Our current challenge is to understand the control system that enables this small creature to land precisely and exquisitely with zero velocity under turbulent conditions. Achieving this capability in a micro UAV will require extensive research on small-scale instabilities at low Reynolds numbers, the development of lightweight, durable materials, and sophisticated control systems that can work in turbulent environments. We will also have to develop highly efficient active-control materials and low-noise propulsion systems with compact power and energy sources that can operate reliably and for extended periods of time.

Through biotechnology, we have a real opportunity to take advantage of four billion years of evolution. Biotechnology could lead to the engineering and manufacturing of new materials for sensors and other electronic devices for ultra-rapid, ultra-smart information processing for targeting and threat avoidance.

Dr. Angela Belcher of MIT has tapped into the biological self-assembly capabilities of phages (viruses that infect bacteria) that could potentially enable precise, functioning electrical circuits with nanometer-scale dimensions. By allowing genetically engineered phages to self-replicate in bacteria cultures over several generations (Figure 5), Dr. Belcher has identified and isolated the phages that can bind with particular semiconductor crystals with high affinity and high specificity. These phages can then self-assemble on a substrate into a network forming exquisitely precise arrays. The ultimate

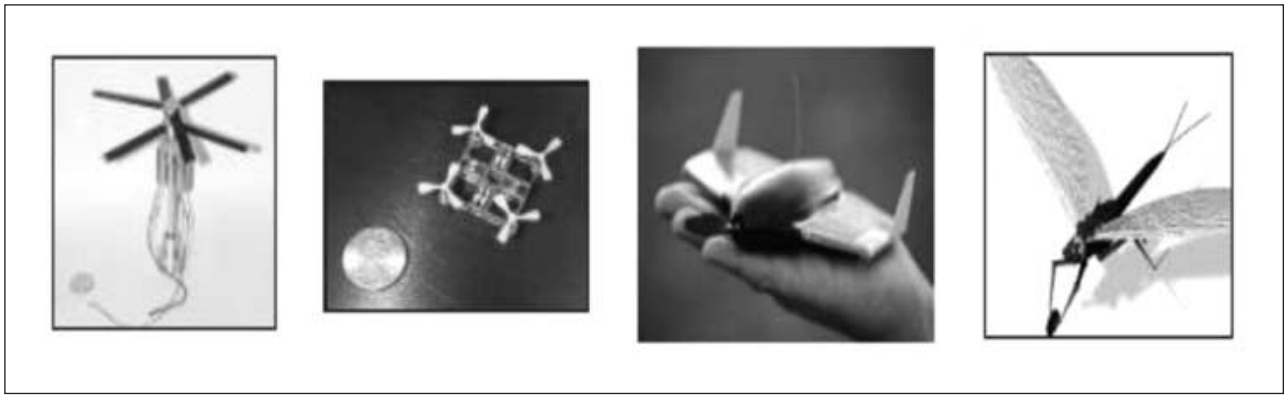

FIGURE 3 Micro unmanned aerial vehicles (UAVs). Source: M.J. Tarascio and I. Chopra, University of Maryland.

FIGURE 4 The bumblebee—a highly agile and efficient navigator. Source: M.V. Srinivansan, M. Poteser, and K. Kral, Australian National University.

goal of this research is to replace the arduous fabrication of electronic, magnetic, and optical materials with genetically engineered microbes that can self-assemble exquisitely precise nanoscale materials based on codes implanted in their DNA.

By exploiting living organisms as sensors, we are making advances in detection and identification. After all, why invent a sensor when evolution has already done it for you? The U.S. Army Medical Research and Materiel Command has developed a technique for using common freshwater blue gills to monitor water quality in several towns around the country. The system successfully detected in real-time a diesel fuel spill from a leaking fuel line at a New York City reservoir. Fortunately, the reservoir intake was off line at the time of the incident, and no contaminated water reached consumers. A Belgian research organization, APOPO, has developed a way to detect land mines using giant African pouched rats. In Tanzania, these rats have been trained to detect land mines with extraordinarily high detection rates. Research is ongoing on the detection of explosives by parasitic wasps, the early diagnosis of pulmonary tuberculosis by rats, and the detection of certain types of cancers in humans by dogs.

Control of Increasingly Complex Systems

Our understanding and control of increasingly complex human-engineered and biologically evolved systems continues to improve. Besides creating new materials from the atom up and managing these new configurations through breakthroughs in nanotechnology and biotechnology as described above, we are improving our control of the communications network to support the Future Force. The FCS network will be a network of humans collaborating through a system of C4ISR (command, control, communications, computers, intelligence, surveillance, and reconnaissance) technologies.

Humans process sensory information and respond through an ad hoc communication network, which affects network performance and, in turn, feeds back into human behavior. For the network to meet the Army's goals, we need a better understanding of the best

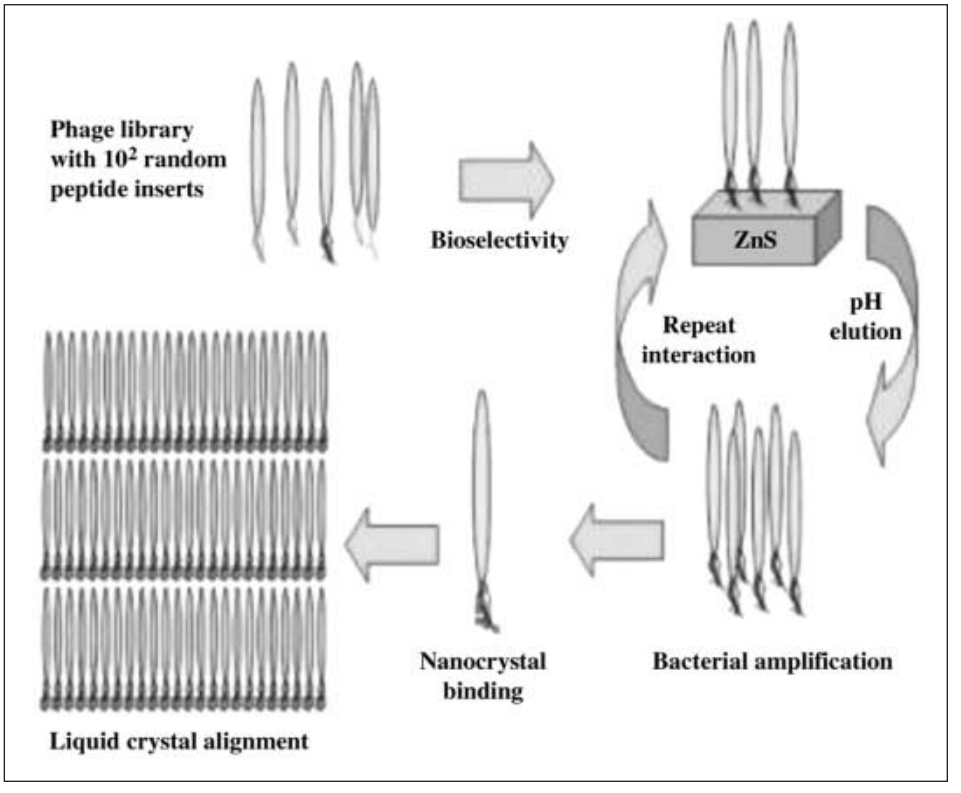

FIGURE 5 Self-assembly characteristics of genetically modified phages. Source: Dr. Angela M. Belcher, MIT.

way for humans to behave and collaborate on such a network. Although multi-hop mesh networks hold out the promise of self-organizing, self-configuring, self-healing, and higher bandwidth performance, we still need considerable research to understand network performance in a wide range of conditions to optimize protocols for military operations. We especially need to identify network instabilities to ensure that the network remains invulnerable to attack.

Network Science

The network is the centerpiece of network-centric warfare and the Army's transformation to the Future Force. There are networks in all aspects of our daily lives and throughout the environment, such as the Internet (we are still trying to understand how it works), power grids (we could have used a common operating picture in the Northeast last year to avoid a blackout); and transportation (cars, trains, and airplanes). There are also social networks composed of people and organizations. Studies of social networks focus on understanding how interactions among individuals give rise to organizational behaviors. Social insects, such as bees, ants, wasps, and other swarming insects, also operate as networks.

There are networks in ecosystems as well as in cellular (the human brain) and molecular (e.g., metabolic) systems. We are learning how information is processed throughout the prefrontal cortex of the brain and where various types of events occur in this region of the brain (Figure 6). There are about 100 billion neurons in the brain, approximately half of them in the cerebellum. Modeling and simulation at the University of Pennsylvania has resulted in a depiction of the dynamic activity of approximately 10,000 neurons in the cerebellum (Finkel, 2004). Although this is only a small fraction of the total, we continue to advance our understanding of how neuronal networks function and affect human behavior. One goal is to understand how the brain and cognition work to learn about the software of the brain and its application to artificial intelligence. This knowledge will significantly affect virtual reality, robotics, human-factors behavioral science, and smart munitions, all of which are likely to be important to the Army's transformation to the Future Force. However, we currently lack a fundamental understanding of how networks operate in general.

The network of network-centric warfare will be a system of connections between humans organized and

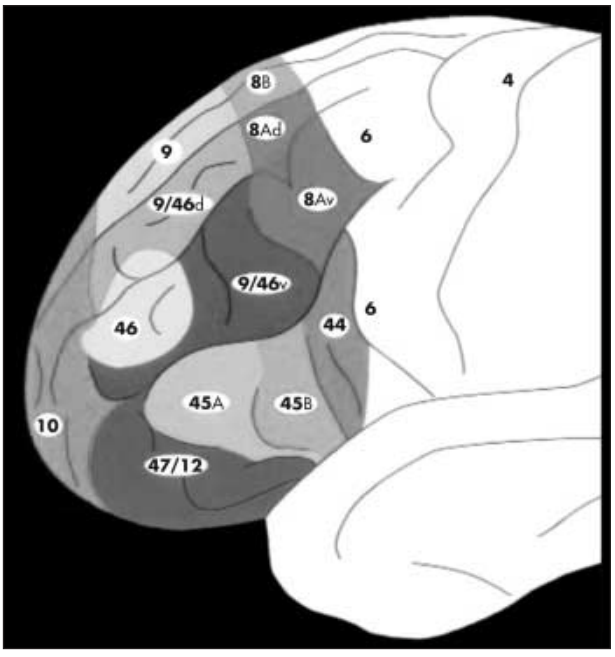

FIGURE 6 Information flow between regions of the prefrontal cortex.
Source: Adapted from Helmuth, 2003.

interacting through a system of technologies. This network will be a highly nonlinear sense-and-response system about which little is known and for which there are few research tools to enable us to predict performance. Although the main focus is on C4ISR technologies and associated concepts, they are only part of the picture. At a very basic level, the rules or principles governing the behavior of this complex system are not well understood. Consequently, we do not have a language appropriate for describing the dynamics or a systematic mathematical formalism to make predictions of network performance for comparison with experimental data. We will need a multidisciplinary approach to advance our knowledge.

This network is an example of an entire class of complex systems that exhibit network behavior. Therefore, rather than focusing research on the network of network-centric warfare, there may be an opportunity to advance knowledge and develop synergies along a broader front that will improve many complex systems and processes that exhibit network behavior. This new front could be called "network science," and progress in network science could have significant impacts on many fields, including economics and sociology.

Research in network science could address a number of intriguing and important questions. Do seemingly diverse systems that exhibit network behavior have the same or similar underlying rules and principles? Is there

a common language that can give us insight into the behaviors of these systems? Is there a general mathematical formalism for a systematic study of these systems? What should the Army focus on in the near term (0–10 years), midterm (10–20 years), and long term (beyond 20 years) to advance Future Force capabilities?

Conclusions

The Army faces formidable technical challenges on its path to Transformation. We are already seeing the emergence of a paradigm-shift in capabilities that will save soldiers' lives and lead to a smaller, lighter, faster, and smarter force. The Army's partnerships with academia, industry, and U.S. allies are essential to advancing science and engineering to realize the vision of the Future Force. Our investments in science and technology will enable us to overcome the many technical challenges associated with Transformation, but more importantly, to ensure that when our soldiers are called upon to defend freedom and liberty anywhere in the world, they come home safe and victorious.

Acknowledgement

The author is deeply indebted to Irena D. Szkrybalo for her creative comments and careful editing of the original transcript associated with my NAE Symposium briefing. She also made several important suggestions, which significantly improved this paper.

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NAE News and Notes

NAE Newsmakers

Alice M. Agogino, professor of mechanical engineering at the University of California, Berkeley, was recognized by the National Science Foundation with the **Director's Award for Distinguished Teaching Scholars**, the foundation's highest honor for excellence in teaching and research. The award, worth about $300,000 over the next four years, can be used to support new projects or to continue current projects in ways that will benefit students in the field.

In November 2003, **Norman R. Augustine**, retired chairman and CEO, Lockheed Martin Corporation, received the **ASME Medal** for outstanding leadership in engineering, particularly for his teaching and mentoring the next generation of leaders. **Karl J. Springer**, retired vice president, Automotive Products and Emissions Research, Southwest Research Institute, was also honored on that occasion. Dr. Springer was named an **Honorary Member** of ASME for the development of test methodologies for measuring emissions of smoke, odors, and particulate matter from internal combustion engines and for extensive publishing in the field.

Albert L. Babb, Professor Emeritus of Nuclear Engineering and Chemical Engineering, University of Washington, was the recipient of the 2003 **Special Award for Lifetime Achievement in Hemodialysis Engineering** presented during the 23rd Annual Dialysis Conference in Seattle, Washington, on March 2, 2003.

John J. Cassidy, consultant in hydraulic and hydrologic engineering, Walnut Creek, California, was presented with a **Lifetime Achievement Award** by the American Society of Civil Engineers (ASCE). The presentation was made at the ASCE Congress of Environmental Water Resources Institute held in Salt Lake City, Utah, on June 29, 2004. The award was presented to Dr. Cassidy in recognition of his lifelong contributions to the disciplines of environmental engineering and water resources engineering through practice, research, and public service.

William Cavanaugh III, chairman, World Association of Nuclear Operations, received the **William S. Lee Award for Industry Leadership**, the nuclear energy industry's most prestigious individual award. The award was presented May 13, 2004, at the Nuclear Energy Institute annual conference in Washington, D.C.

Richard A. Conway, retired senior corporate fellow, Union Carbide Corporation, received the **Gordon Maskew Fair Award** from the American Academy of Environmental Engineers for his contributions to environmental engineering through exemplary professional conduct, achievements in the profession, and contributions to the quality control of the global environment.

Nick Holonyak Jr., John Bardeen Chair Professor of Electrical and Computer Engineering and Physics, University of Illinois, received the **2004 Washington Award** from the Western Society of Engineers. The award was presented to Dr. Holonyak "for his pioneering contributions to the development of power silicon electronics and invention of the first semi-conducting light-emitting diodes in a visible part of the spectrum."

Mary Jane Irwin, A. Robert Noll Chair in Engineering, Pennsylvania State University, will be honored as this year's winner of the **Marie R. Pistilli Women in EDA Achievement Award**. Named for the former organizer of the Design Automation Conference, the award is presented annually to an individual who has advanced women in the electronic design automation (EDA) industry.

John L. Junkins, George J. Eppright Distinguished Professor of Aerospace Engineering, Texas A&M University, was awarded the 2004 **Tycho Brahe** Award from the Institute of Navigation (ION). ION gives the award annually in recognition of outstanding contributions to the science of space navigation, guidance, and control. The award cites Dr. Junkins' fundamental advances, which have supported more than a dozen spaceflight missions.

Alan C. Kay, senior fellow, HP Labs, Hewlett-Packard Company, won this year's **Kyoto Prize** for paving the way for the development of personal computing technology. The award, bestowed by Japan's Inamori Foundation, cites Dr. Kay's "creation of the concept of personal computing and contribution to its realization." The prize includes $450,000 in cash, a gold medal, and a diploma.

Leslie B. Lamport, senior researcher, Microsoft Research, received the **IEEE Emanuel R. Piore Award** for seminal contributions to the theory and practice of concurrent programming and fault-tolerant computing.

Robert C. Lanphier III, president and CEO, AGMED Inc., was inducted as a **fellow** of the American Society of Agricultural Engineers at its Annual International Meeting on August 3, 2004. Dr. Lanphier was honored for his contributions to applications of electronic technologies to agriculture and his visionary leadership in the establishment of the "precision agriculture" industry.

James K. Mitchell, University Distinguished Professor Emeritus, Virginia Polytechnic Institute and State University, and independent geotechnical consultant, has been selected by the American Society of Civil Engineers (ASCE) Geo-Institute to receive the 2004 **H. Bolton Seed Medal**. The medal recognizes an individual for outstanding contributions to teaching, research, and/or practice in geotechnical engineering. Dr. Mitchell was cited for contributions to the fundamental understanding and professional practice of geotechnical and geoenvironmental engineering.

Van C. Mow, Stanley Dicker Professor and chair, Department of Biomedical Engineering, Columbia University, was elected to the **Academia Sinica of Taiwan** on July 8, 2004. On the same day, the American Society of Mechanical Engineers (ASME) established a named medal in his honor, the **ASME Van C. Mow Medal for Bioengineering**. The medal will be awarded annually to an outstanding bioengineer at mid-career (10 to 20 years after earning a Ph.D. or equivalent).

Robert M. Nerem, Parker H. Petit Professor and director, Institute for Bioengineering and Bioscience, Georgia Institute of Technology, received the 2004 **Benjamin G. Lamme Medal** on September 3. The medal is awarded annually to a graduate of the Ohio State University College of Engineering for "meritorious achievement in engineering."

E. Gail de Planque, president, Strategy Matters Inc., and **Patricia G. Selinger**, vice president, Data Management Architecture and Technology, IBM Silicon Valley Laboratory, were inducted into the **Hall of Fame** of Women in Technology International (WITI). The WITI Foundation Hall of Fame honors and promotes contributions by women that have a positive impact on society. Dr. de Planque was honored for her role in promoting diversity in engineering, which led to the formation of the National Academy of Engineering Diversity Forum. Dr. Selinger was honored for advances in relational database management and the invention of cost-based query optimization.

John M. Prausnitz, professor of chemical engineering, University of California, Berkeley, received an **honorary Doctor of Engineering degree** from the University of Padua on April 16, 2004. The colorful ceremony was held in the Palazzo Bo where Galileo lectured nearly 400 years ago.

Joseph A. Yura, Cockrell Family Regents Chair in Engineering, University of Texas at Austin, received a **Lifetime Achievement Award** from the American Institute of Steel Construction at the North American Steel Construction Conference in March.

Awards were presented to several NAE members on June 19 at the annual Honors Ceremony of the Institute of Electrical and Electronics Engineers (IEEE). **David Atlas**, Distinguished Visiting Scientist, NASA Goddard Space Flight Center, received the **Dennis J. Picard Medal for Radar Technologies and Applications** "for exceptionally outstanding leadership and significant individual technical contributions to the application of radar for the observation of weather and other atmospheric phenomena." **Craig R. Barrett**, president and CEO of Intel Corporation and NAE chair, received the **Robert N. Noyce Medal** for his "contributions to semiconductor manufacturing technology and leadership in business and in industry initiatives." **Federico Capasso**, Gordon MacKay Professor of Applied Physics and Vinton Hayes Sr. Research Fellow in Electrical Engineering, Harvard University, received the **Edison Medal** for "a career of highly creative and influential contributions to heterostructure devices and materials." **Frederick H. Dill**, Distinguished Engineer, Hitachi Global Storage Technologies, received the **Jun-ichi Nishizawa Medal** "for lifetime contributions to microelectronics processing, including lithographic simulation, semiconductor lasers and magnetic recording." **Mildred S. Dresselhaus**, Institute Professor of Electrical Engineering and Physics, Massachusetts Institute of Technology, received the IEEE **Founders Medal** for "leadership across many fields of science and engineering through research and education, and for exceptional and unique contributions to the profession." **Paul R. Gray**, executive vice chancellor and provost, University of California,

Berkeley, received the **James H. Mulligan Jr. Education Medal** "for exemplary contributions to electrical engineering education through mentoring of students, an influential textbook, and university-wide academic leadership." **Barbara H. Liskov**, Ford Professor of Engineering, Massachusetts Institute of Technology, received the **John von Neumann Medal** "for fundamental contributions to programming languages, programming methodology, and distributed systems." **Tadahiro Sekimoto**, chairman of the Institute for International Socio-Economic Studies and former chairman of the NEC Corporation, received the IEEE **Medal of Honor** for his "contributions to digital satellite communications, promotion of information technology R&D, and technical and corporate leadership in computers and communications." **Jack Keil Wolf**, Stephen O. Rice Professor, University of California, San Diego, received the **Richard W. Hamming Medal** "for fundamental contributions to the theory and practice of information transmission and storage."

The following NAE members have been elected **Fellows** of the American Academy of Arts and Sciences: **Arden L. Bement Jr.**, director, National Institute of Standards and Technology; **Mark E. Dean**, vice president, Storage Technology, and IBM Fellow, IBM Corporation; **Paul A. Fleury**, dean, faculty of engineering, Yale University; **James L. Massey**, adjunct professor of information technology, University of Lund, Sweden; **C. Dan Mote Jr.**, president and Glenn Martin Institute Professor of Engineering, University of Maryland; and **Henry Samueli**, chairman and chief technical officer, Broadcom Corporation.

Report of the Foreign Secretary

George Bugliarello

The past six months have been a time of intense activity in my area of responsibility.

- In April, I attended the German-American Frontiers of Engineering Symposium in Washington, D.C. The topics this year were engineering and art; the Internet; quality management in product design, innovation, and logistics; and bioengineering and the food industry.
- In April, I attended meetings with the Mexican-American Foundation for Science. The discussions focused on collaborative projects with the National Academies.
- In May, I attended a meeting in London with European NAE foreign associates. President **Wm. A. Wulf** presided over the meeting; NAE Executive Officer **Lance Davis** and NAE Home Secretary **Dale Compton** also attended. The NAE group later visited the Royal Academy of Engineering (RAE) and exchanged views with RAE members at a meeting chaired by NAE President Wulf and RAE President **Lord Broers**. The group also visited Imperial College.
- In May, there was a meeting in Dublin, Ireland, of the National Academies Presidents' Circle, a group of distinguished leaders in industry and business. Dale Compton, Lance Davis, and I were also present. The purpose of the meeting was to familiarize the group with the goals of the National Academies (NAS, NAE, IOM, and NRC) and to enlist their support.
- In May, I participated (with Wm. A. Wulf and Lance Davis) in a meeting in Stavanger, Norway, of the Council of Academies of Engineering and Technological Sciences (CAETS). (President Wulf is CAETS' immediate past president—a position that rotates every year.) The meeting in Stavanger was followed by an international symposium on energy organized by the Norwegian Academy of Engineering; the U.S. presentation was made by NAE member **John Ahearne**. The consensus of the meeting was that (1) coal will remain an irreplaceable resource for the foreseeable future; (2) meeting the mushrooming energy demand, particularly from developing countries, will require safe nuclear energy; and (3) that the use of alternative energy sources will increase substantially, but

concentration levels of CO_2 and other atmospheric pollutants will continue to rise.

- At the beginning of June, I represented President Wulf and NAE at a celebration in Beijing of the 10th anniversary of the Chinese Academy of Engineering (CAE). The President of China, Hu Jintao, met with the Chinese members of CAE, and Prime Minister Wen Jiabao met with delegates from other countries. At CAE, I participated in a discussion on behalf of the National Academies on collaborative projects on air pollution and sustainable cities.
- The foreign secretaries of NAS and IOM and I participated in the initial meeting of the Board on Science for Africa to frame a project to increase health care capacity in Africa. The project is supported by a $20 million grant from the Bill and Melinda Gates Foundation.
- In April, I delivered the opening remarks at a meeting hosted by NAE on the Iraqi marshlands. Preserving what is left of this unique ecological area, which was largely destroyed between the two Iraqi wars, will be a major social-engineering challenge. I also participated in a meeting with the minister of technology in the Iraqi provisional government to identify areas in which U.S. engineers could be of assistance.
- In the last six months, I participated in meetings with leaders of the French Academy of Science (hosted by NAS President Bruce Alberts), members of the Australian Academy of Engineering, and the president of the Korean Academy of Science and Technology (both hosted by NAE President Wm. A. Wulf).
- I made several presentations in the last six months at meetings sponsored by the World Federation of Engineering Organizations, UNESCO, the American Association for the Advancement of Science, the American Association of Engineering Societies, the American Society of Civil Engineers, and the American Society of Engineering Education. My talks focused on engineering and sustainability, the role of engineering in economic development for developing countries, and engineering to fight poverty. NAE member **Henry J. Hatch** is actively involved in the leadership of these organizations.
- On behalf of the NAE Council, I participated in meetings of the NRC Division on Engineering and Physical Sciences and the Executive Committee of the Transportation Research Board.

As you know, the election of distinguished foreign associates is an important aspect of NAE international activities. I am happy to report that in the current cycle, we have received 56 nominations for screening by the peer committees. Nominees include several from countries either not represented at all or not well represented in NAE. In October at our next annual meeting, 11 new foreign associates will be inducted.

In closing this brief report, I would like to emphasize the importance of NAE's international relations at this moment of heightened national concern. Our country faces major challenges in the international arena that involve technology, such as the shift in international economic and technological power with the emergence of China and India and an expanding European Union, the weakening of the U.S. manufacturing base, our troubling relations with North Korea and the Islamic world, the enduring global gap between affluence and abject poverty, the growing global demand for energy, and our dependence on energy from abroad. History cannot preordain the future, but we must heed the lessons of great empires that fell under the double onslaught of internal hubris and external challenges. The strength of our nation rests on two pillars—our form of government and our science and technology. If either pillar is weakened, both could collapse. The challenge to U.S. engineers, and especially to NAE, is to help our nation hold the high moral ground through participation in the global community to make the world more sustainable and more prosperous, while preserving and enhancing our technological strength.

Donna Dean Honored by Washington Academy of Sciences

Donna J. Dean

Dr. Donna J. Dean recently received the Award for Scientific Achievement in Health Sciences from the Washington Academy of Sciences "in recognition of visionary leadership and pivotal roles in fostering new arenas of research endeavor at the National Institutes of Health." Dr. Dean was cited for her professional contributions as researcher, regulatory scientist, administrator, and manager of NIH's peer review process and founding/acting director of the National Institute of Biomedical Imaging and Bioengineering. Her activities related to workforce issues, research on women's health, and professional societies were also highlighted. A chemist/biochemist by training, Dr. Dean is currently senior advisor for engineering in the NIH Office of the Director and senior scholar in residence at NAE.

NAE Calendar of Meetings and Events

August 11	News and Terrorism: Communicating in a Crisis Workshop Chicago, Illinois
August 17	Committee to Assess the Capacity of the U.S. Engineering Research Enterprise Meeting
August 24	NAE Nominating Committee Meeting
September 9–11	10th U.S. Frontiers of Engineering Symposium Irvine, California
September 13–14	User Authorized Handgun Technology Committee Meeting
September 15	NRC Governing Board Meeting/Executive Committee Meeting
September 21	News and Terrorism: Communicating in a Crisis Workshop Kansas City, Missouri
September 24	NAE Congressional Luncheon
September 29	Technological Literacy Workshop
September 30	Assessing Technological Literacy Committee Meeting
October 1	NAE Finance and Budget Committee Meeting
October 1–2	NAE Council Meeting
October 2	NAE Peer Committee Meetings
October 3–4	NAE Annual Meeting
October 6	NRC Governing Board Meeting/ Executive Committee Meeting
October 12	Russ Prize Committee Meeting
October 14	News and Terrorism: Communicating in a Crisis Workshop Portland, Oregon
October 19	Draper Prize Committee Meeting
	CASEE Advisory Committee Meeting Savannah, Georgia
October 20	CASEE Dane & Louise Miller Symposium Savannah, Georgia
October 26	News and Terrorism: Communicating in a Crisis Workshop Philadelphia, Pennsylvania
November 4–6	Japan-America Frontiers of Engineering Keihanna, Japan
November 9–10	NRC Governing Board Meeting/Executive Committee Meeting
December 1–2	Committee on Diversity in the Engineering Workforce Meeting
December 4	NAE Committee on Membership Meeting
December 9	News and Terrorism: Communicating in a Crisis Workshop Miami, Florida

All meetings are held in the Academies buildings in Washington, D.C., unless otherwise noted.

Council and Staff Awards Luncheon

NAE recently held its annual Staff Awards Luncheon at the National Academy of Sciences Building. President **Wm. A. Wulf** hosted the ceremony. Copies of the Council Resolution and gifts were presented by Dr. Wulf to retiring members **George M.C. Fisher** (chair, four years of service) and **Robert Nerem** (six years of service) for their dedication to the organization. Three NAE Service Awards were presented to NAE staff members **Lance Davis**, executive officer (five years of service); Mary Kutruff, assistant awards administrator (10 years of service); and Maribeth Keitz, senior associate working on public understanding of engineering (15 years of service).

Staff Achievement Awards were also presented to Mary Resch, senior financial officer; Dennis Thorp, membership staff officer; and Doug Denning, contract manager for the Office of Contracts and Grants. All three received certificates of appreciation and cash awards.

In Memoriam

RICHARD H. BOLT, 90, retired professor of acoustics, Massachusetts Institute of Technology, and retired Chairman, Emeritus, Bolt Berenek and Newman, Inc., died on January 13, 2002. Dr. Bolt was elected to NAE in 1978 for contributions to acoustics and leadership in engineering enterprises and public service.

HARVEY BROOKS, 88, Professor of Technology and Public Policy, Emeritus, Harvard University, died on May 28, 2004. Dr. Brooks was elected to NAE in 1968 for contributions to solid-state engineering and nuclear reactors and leadership in national technological decisions.

BURTON P. BROWN, 86, retired systems consultant, General Electric Company, died on May 24, 2004. Mr. Brown was elected to NAE in 1973 for original contributions to the advancement of the art and science of radar systems.

ERNST R. ECKERT, 99, Regents' Professor, Emeritus, University of Minnesota, died on July 15, 2004. Dr. Eckert was elected to NAE in 1970 for contributions to the solution of basic problems in heat and mass transfer.

NICHOLAS J. GRANT, 88, Professor Emeritus and senior lecturer, Massachusetts Institute of Technology, died on May 1, 2004. Dr. Grant was elected to NAE in 1980 for contributions to the science and technology of high-temperature alloys.

WILMOT N. HESS, 77, retired associate director, high energy and nuclear research, U.S. Department of Energy, died on April 16, 2004. Dr. Hess was elected to NAE in 1976 for applications of nuclear, space, and geophysical sciences in support of engineering, industrial, and public needs.

CSABA HORVÁTH, 74, Roberto F. Goizueta Professor of Chemical Engineering, Department of Chemical Engineering, Mason Laboratory, Yale University, died on April 13, 2004. Dr. Horváth was elected to NAE in 2004 for pioneering the concept and the reduction to practice of high-pressure liquid chromatography (HPLC) and for leadership in the development of bioanalytical techniques.

JOHN D. KRAUS, 94, Taine G. McDougal Professor Emeritus of Electrical Engineering and director, Radio Observatory, Ohio State University, died on July 18, 2004. Dr. Kraus was elected to NAE in 1972 for advancements in engineering applications of antennas and electromagnetic theory in space communications and exploration.

WALTER B. LABERGE, 80, chief scientist, Institute for Advanced Technology, died on July 16, 2004. Dr. LaBerge was elected to NAE in 1987 for outstanding contributions to national security through technical leadership in industry and public service.

The National Academies Update

Presidents' Comment on U.S. Visa Policies

On May 13, 2004, Wm. A. Wulf, President, National Academy of Engineering; Bruce Alberts, President, National Academy of Sciences; and Harvey Fineberg, President, Institute of Medicine, issued the following statement expanding on the "Statement and Recommendations on Visa Problems Harming America's Scientific, Economic, and Security Interests" document issued on May 12 (available online at: http://www.aau.edu/resources/JointVisaStatement.pdf).

We believe that implementation of the proposals made in the May 12 statement about U.S. visa policies—issued jointly by 25 national education, science, and engineering organizations—would resolve many of the urgent problems posed by the nation's current policies. We are pleased to be among the signers of this important document.

Several points of special interest to our research communities, however, are not addressed explicitly in this document. We list them here for consideration by the government agencies that are concerned with these issues.

We believe there is a compelling need for a special visa—most likely an expansion of the O visa—for foreign scientists and engineers who are well-known to the research community, who have proven track records as participants in international research activities, and who need to make multiple visits to the United States. Such scientists and engineers should be eligible for long-term, multiple-entry visas; and they should be able to revalidate those visas from within the United States. Requiring such scientists to submit repeated visa applications has added substantially to the costly delays in the system without improving national security.

The screening tools that are used to identify visa applicants who might pose threats to the United States must be specific to those threats, and must be used by consular officials who understand the relevant technical considerations. Specifically, the Technology Alert List, which identifies sensitive fields of research and is used by consular officials to determine the need for "Visas Mantis" security checks, is too broad in its definitions and is of questionable benefit.

Our visa processing system should be informed by scientific and technical experts who are able to evaluate the potential threats and the technical merits of individual cases. We offer the assistance of the National Academies in providing documentation for foreign citizens who are working with our scientists and engineers, in providing advice on which technical specialties might actually be sensitive and therefore require careful monitoring, and in providing information about scientific meetings and educational events.

In order to stay secure and prosperous, our nation must remain open to the best scientists and engineers from around the world. Our visa processing system not only must provide genuine security against those who might do us harm, but also keep our borders open to the stream of scientific and technical talent that fuels our progress. While no visa system can completely eliminate all risk, we believe an enhanced visa process can provide many benefits to our nation and to our security without materially affecting the risks we face. Because of the urgency of the present problems, we intend to give highest priority to working with federal agencies to achieve these goals.

Managing the Los Alamos and Lawrence Livermore National Laboratories

In recent years, concerns have been raised about security and operations management at Los Alamos and Lawrence Livermore national laboratories (LANL and LLNL). To address these concerns, Congress directed the U.S. Department of Energy (DOE) to accept competitive bids for the management and operations contracts for both LANL and LLNL. To ensure that a change would not adversely affect the quality of science and engineering, the DOE National Nuclear Security Administration (NNSA) asked the NRC to recommend qualification and selection discriminators. The report fulfilling that request, *Maintaining High Scientific Quality at Los Alamos and Lawrence Livermore National Laboratories*, was recently published.

A single contractor currently manages both laboratories, and the consensus among scientists and engineers is that this has facilitated coordination and cooperation and advanced the work of both laboratories. The committee did not conclude that a single contractor should necessarily manage both organizations but recommended that NNSA select contractor(s) with experience running a large science and technology organization; that can plan, construct, and operate major facilities; and whose management team members have credentials comparable to those of people in similar positions at other national laboratories. In addition, the contractor(s) should ensure that the laboratories continue to attract, retain, and nurture world-class science and technology staffs. This will require that interactions between the laboratories and the outside technical community be encouraged and that innovations by the laboratory staff be rewarded.

NAE member **Paul C. Jennings**, California Institute of Technology, chaired the study committee. Other NAE members on the committee were **Lloyd A. Duscha**, U.S. Army Corps of Engineers (retired); **Paul A. Fleury**, Yale University; **Cherry A. Murray**, Lucent Technologies; and **Harvey W. Schadler**, GE Corporate Research and Development Center (retired).

Assessment of the National Aerospace Initiative

The National Aerospace Initiative (NAI) was conceived as a joint effort between the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) to ensure that the United States retains its leadership position in aerospace research and development. NAI funds and otherwise supports the accelerated development of selected aerospace technologies, such as hypersonic flight, technologies that will increase access to space, and other technologies. However, the U.S. Air Force is concerned that if NAI priorities differ from Air Force priorities, Air Force programs and budgets could be adversely affected. Therefore, the Air Force asked the NRC to conduct an independent review of NAI to examine the issue. This report focuses on three questions asked by the Air Force: is NAI technically feasible in the scheduled time frame; is NAI financially feasible over that period; and is NAI operationally relevant. The study committee concluded that NAI is keeping the United States in the forefront of research but that the program faces many technical and financial hurdles.

Research on high-speed hypersonic flight is focused on the development of jet-like vehicles that can fly at Mach 12 by around 2014. The study committee concluded that the development of high-speed vehicles may be technically feasible in that time frame but that NAI needs a more comprehensive plan that includes a range of activities, from fundamental research to critical technology development to flight demonstration.

The committee believes that NAI's efforts to develop new rocket propulsion systems could dramatically increase access to space and decrease costs. In addition, NAI's phased-funding approach to this research is likely to result in significant payoffs, such as more frequent flights, high numbers of test flights, and low marginal costs per flight, but not by NAI's target goal of 2008.

To ensure that an adequate workforce is available, the committee recommends that NAI establish a stable, predictable source of funding to help the program weather cyclic hirings and layoffs in the aerospace industry and to encourage the creation of stable, career-oriented jobs. DOD and NASA should strive to stabilize the amount of funding available and increase it, if possible, to support long-term research on reusable launch vehicles and aerospace propulsion and power.

The study committee also recommends that DOD and NASA develop a top-down, comprehensive road map that defines the objectives, challenges, technologies, research, and funding required to implement these recommendations and achieve NAI goals. The road map should then be distributed to decision makers and stakeholders, including the public. Independent experts should review the plan on a regular basis.

NAE member **Edsel D. Dunford**, TRW Inc. (retired), chaired the committee that wrote the report. Other NAE members on the committee were **Wesley L. Harris**, Massachusetts Institute of Technology; **Hans G. Hornung**, California Institute of Technology; **Neil E. Paton**, Liquidmetal Technologies, and **Peter Staudhammer**, TRW Inc. (retired).

Publications of Interest

The following reports have been published recently by the National Academy of Engineering or the National Research Council. Unless otherwise noted, all publications are for sale (prepaid) from the National Academies Press (NAP), 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055. For more information or to place an order, contact NAP online at <*http://www.nap.edu*> or by phone at (800) 624-6242. (*Note: Prices quoted by NAP are subject to change without notice. Online orders receive a 20 percent discount. Please add $4.50 for shipping and handling for the first book and $0.95 for each additional book. Add applicable sales tax or GST if you live in CA, DC, FL, MD, MO, TX, or Canada.*)

Investments in Federal Facilities: Asset Management Strategies for the 21st Century. Facilities owned by the federal government are valued at more than $300 billion, and the federal government spends more than $25 billion per year for the acquisition, renovation, and upkeep of facilities. Despite these huge expenditures, a growing number of problems with federal facilities is putting a drain on the federal budget and compromising federal services. The Federal Facilities Council (FFC) asked the National Research Council (NRC) to develop guidelines for making decisions about investments in new federal facilities and in the renewal, maintenance, and replacement of existing facilities. This report includes a review of public and private practices to support decision making and identifies appropriate objectives, practices, and performance measures. The study committee's recommendations are intended to improve management and investment decision making by federal agencies and departments. Paper, $34.75.

The Marine Transportation System and the Federal Role: Measuring Performance, Targeting Improvement. Special Report 279. This report calls upon the U.S. Department of Transportation (DOT) to take the lead in assessing the performance of the marine transportation system and in improving it. The report recommends that DOT immediately begin to conduct assessments of the condition, performance, and uses of the marine transportation system and seek a mandate from Congress to produce these reports on a regular basis (as is already done for the nation's highway and transit systems). Paper, $24.00.

New Directions in Manufacturing: Report of a Workshop. Manufacturing processes and techniques continue to evolve. To examine the potential impact of recent changes, the U.S. Department of Commerce asked the NRC to design a workshop to focus on the changing nature of manufacturing. The workshop brought together a number of experts to present papers and discuss the current status of manufacturing in the United States and to identify the challenges facing manufacturing enterprises. The key challenges that emerged from the workshop discussed in this report include: understanding trends in manufacturing; problems arising from the globalization of manufacturing; taking advantage of opportunities in information technology; developing strategies for maintaining innovation; strengthening small and medium-sized enterprises; improving workforce education; and meeting rising infrastructure costs. Print-on-demand, $34.00.

Review of the Desalination and Water Purification Technology Roadmap. The Bureau of Reclamation and Sandia National Laboratories jointly developed this road map to provide a strategic research pathway for desalination and water purification technologies. The report recommends that the road map be more sharply focused on the research and technological advancements necessary to reach the long-term objectives. The report also suggests that the environmental, economic, and social costs of energy associated with increased dependence on desalination be examined. Strategies for implementing the road map are also provided. Print-on-demand, $23.00.

A Review of the FBI's Trilogy Information Technology Modernization Program. The Federal Bureau of Investigation (FBI) is in the process of developing a modern information technology (IT) system—the Trilogy Program—that includes a high-speed network, modern workstations and software, and an application—the Virtual Case File (VCF)—that will make it easier for agents to organize, access, and analyze information.

The implementation of this system has been plagued by substantial difficulties, however, and has been the subject of many investigations. To help the FBI address these problems, the National Research Council (NRC) was asked to undertake a quick review and assessment of the program. The current status of four major aspects of the program—the enterprise architecture, system design, program management, and human resources—are discussed in this report, and recommendations are provided to address the problems. Paper, $18.00.

Setting Priorities for Large Research Facility Projects Supported by the National Science Foundation. In 1995, the National Science Foundation (NSF) created a special account to fund large (several tens of millions of dollars) research facilities, which now represent a substantial portion of the nation's R&D portfolio. Recently, concerns about the way NSF selects projects for this account have intensified. In 2003, six U.S. Senators, including the chair and ranking member of the Senate Subcommittee on VA, HUD, and Independent Agencies Appropriations, expressed these concerns in a letter asking the NRC to "review the current prioritization process and report to us on how it can be improved." The study notes that NSF has improved its processes for setting priorities but that further improvements are necessary. Detailed recommendations are provided to help NSF achieve that goal. Paper, $41.50.

The Workforce Challenge: Recruiting, Training, and Retaining Qualified Workers for Transportation and Transit Agencies. Special Report 275. This report calls upon surface transportation agencies, the private sector, educational institutions, unions, and employees to make training a key priority. The report recommends that a broad coalition of these organizations work toward expanding existing federal and academic resources, establishing an institutional focus on training, and making human-resources management a strategic function in the transportation community. Paper, $23.00.

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