Future Directions in Chemical Engineering and Bioengineering

January 16-18, 2013
Austin, Texas
Chair: John G. Ekerdt, The University of Texas at Austin
Sponsored by Department of Defense,
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Executive Summary

Chemical and biological engineers use math, physics, chemistry, and biology to develop chemical transformations and processes, creating useful products and materials that improve society. In recent years, the boundaries between chemical engineering and bioengineering have blurred as biology has become molecular science, more seamlessly connecting with the historic focus of chemical engineering on molecular interactions and transformations.

This disappearing boundary creates new opportunities for the next generation of engineered systems – hybrid systems that integrate the specificity of biology with chemical and material systems to enable novel applications in catalysis, biomaterials, electronic materials, and energy conversion materials.

Basic research for the U.S. Department of Defense covers a wide range of topics such as metamaterials and plasmonics, quantum information science, cognitive neuroscience, understanding human behavior, synthetic biology, and nanoscience and nanotechnology. Future Directions workshops such as this one identify opportunities for continuing and future DOD investment. The intent is to create conditions for discovery and transformation, maximize the discovery potential, bring balance and coherence, and foster connections. Basic research stretches the limits of today's technologies and discovers new phenomena and know-how that ultimately lead to future technologies and enable military and societal progress.

This workshop sought, within the disciplines of chemical engineering and bioengineering, to identify current knowledge gaps and critical pathways, determine where and how creative intellectual and funding leadership could enable transformative progress in the next 10 to 20 years, and anticipate what is required to make that progress a reality.

Attendees began by discussing major breakthroughs in the past 10 years or so, as well as emerging developments and breakthroughs likely in the next 10 or so. We began by focusing on four themes that define current and emerging foci of chemical engineering and bioengineering research:

- Materials
- Molecules
- Modeling
- Systems

In subsequent breakout sessions, these groups evolved into four key emerging areas:

- Sensors
- Molecules and materials designed from building blocks
- Emergent systems
- Energy

These four concepts led us to three key themes:

- Bottom-up chemical and materials synthesis
- Better optimization methods for large-scale problems
- *In silico* discovery of materials properties and processing routes

The group consensus is that research in these areas will lead to tactical, strategic, and economic advancement and security; improved intelligence; and improved monitoring of human health, all of which will provide the modern warfighter with more autonomy and self-sufficiency.

Finally, the group identified new advances requiring focused investment now:

- Bottom-up synthesis
- Systemic integration and scalable manufacturing
- Cell-free synthesis

Conference Report

The conference opened with a summary from each attendee of our areas of expertise and current research. Each attendee also outlined significant recent and emerging breakthroughs and research needs.

Recent major breakthroughs (See complete list in the Appendix)

Significant research and application breakthroughs in the past few decades in both chemical engineering and bioengineering have had significant impact on the military and society at large. Chemical engineering and bioengineering are naturally interdisciplinary and many of these breakthroughs have occurred because of that convergence. Key advancements include development of high-performance algorithms for continuous and discrete optimization; synthesis and characterization of new molecules designed from quantum mechanics and molecular simulations; the ability to sequence, synthesize, read and write DNA; synthesis of artificial proteins and viruses; the development of new, cell-free biomanufacturing approaches that separate catalyst synthesis from catalyst utilization; development of adaptive and self-learning systems; continued progress in using nanomaterials as building blocks with controlled size, shape, composition and function; the capacity to describe rare events; real-time optimization of industrial processes; and increasingly specific sensors.

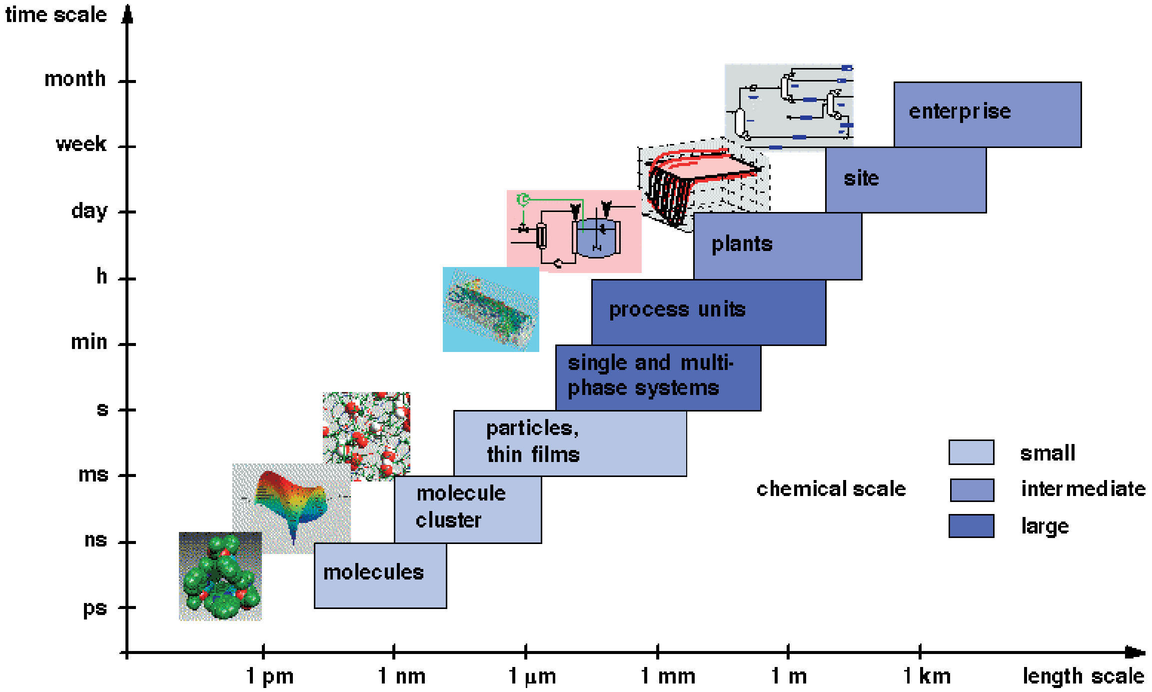
Today, we have the ability to make nearly any shape on any scale out of virtually any kind of material, and the ability to decorate or functionalize these shapes with an assortment of materials, including biomolecules. The palette of “patchy particles” available today is limited solely by our imaginations.

“If we can build anything, what should we build?”

Emerging breakthroughs and needs (See complete list in the Appendix)

Continued advances in basic research will be informed and amplified by breakthroughs just on or over the horizon. Key among these:

- Integrated multiscale optimization, to integrate time and length scales, permit fast fullspace optimization, and support high-potential integrated decision-making
- Creation of new molecules and functional materials: for example, as catalysts for water splitting and reduction of CO_2
- Formation of nominally thermodynamically unstable yet kinetically stabilized phases over wide composition ranges, which would open a broad array of new materials
- Compatible and manufacturable fabrication of organics and inorganics, including 3D printing
- Greater understanding and predictive ability for zoonoses and the immune response
- Transformation of food, energy, chemicals, materials, and medicine through the ability to biomanufacture them
- Full realization of synthetic molecular recognition
- Multi-scale, rare-event simulations
- Application of real-time informatics to industrial processes

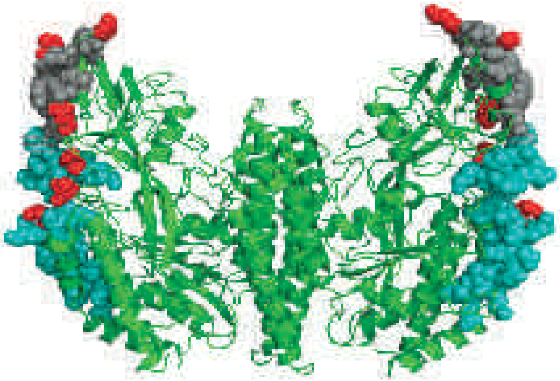


Long-term goal: decision-making for multi-scale problems integrated from molecule to enterprise. Copyright © 2000 American Institute of Chemical Engineers (AIChE). Used with permission.

The breakthroughs and future advances will require:

- Novel strategies that accelerate the engineering design cycle and make biological systems easier to engineer
- A cell classifier circuit that triggers a response only in a predetermined cell type profile
- A synthetic detection, signaling, and read-out system to detect a human-made chemical in plants
- A new science of catalysis of solid-state transformations
- Predictive models of assembly, structure, and activity
- Increased throughput and quality of experimental validation
- Computational tools, force fields for chemical systems, and a focus on complex multi-step processes
- Better understanding of the mechanisms and dynamics of catalyzed transformations
- A new science for cell-free biomanufacturing without intact cells
- Evolution study for phylogenetic structure-based prediction of host-pathogen interactions, and the ability to predict what five amino acids are most likely to interact with a receptor

"We're only marginally good at engineering simple systems in single-celled organisms because cells evolved to evolve."



Host-pathogen interaction. Image Copyright: © 2013 A. Demogines et al. Dual Host-Virus Arms Races Shape an Essential Housekeeping Protein. PLoS Biol 11(5): e1001571. Used with permission.

Four breakout groups discussed emerging technologies that could cause major shifts in how things are done. The groups then considered what emerging technologies and methodologies will be needed to make these shifts possible. The groups formed around the four themes: materials, modeling, molecules, and process/systems. Summaries of those discussions are in the Appendix, and highlights follow.

Emerging Technologies and Methodologies Needed for Materials

-In the energy realm, research is needed for carbon-free hydrogen at all scales, high density storage, distributed diverse feedstocks, and improved CO_2 absorption and release. New computing technologies will enable CO_2 capture, hydrogen generation, improved heat transfer for power generation, and lightweight materials for increasingly connected and autonomous vehicles.

-For sensors, research is needed to develop platforms for single molecule detection, robust transduction of information from sensing to use of the data, and seamless transmission and analysis of the data. Possible applications include massive, cheap, pre-symptom screening for disease markers in individuals from certain populations and platforms that allow rapid assay of large numbers of single cells. New materials will be developed based on how scalp electrodes work.

-We increasingly need to interpret massive numbers of stochastic signals. Quantum computing materials and multi-state devices are needed to make this a reality. We need breakthroughs including self-assembly of materials (rather than starting with large, perfect crystals), materials breakthroughs and manufacturing (for example, quantum computing photonic circuits), integration of dissimilar materials to enable devices and computers of the future, reproducibility of devices, information flow from ubiquitous connected devices, and manufacturing-reproducible nanodevices. We need new computing technologies in quantum computing and multi-state devices.

Emerging Technologies and Methodologies Needed for Modeling

This breakout group and many workshop participants have been influenced by the *Materials Genome Initiative for Global Competitiveness*, a white paper from the Office of Science and Technology Policy in 2011. Ideas represented throughout this report contain elements of the Initiative because of their synergy with chemical engineering and bioengineering.

-We will be moving from a computer-driven to data-driven design era, with community metadata standards needed for open-access data banks. We will use data to inform and set parameters for predictive theoretical and empirical models to guide experiments. A major need is the creation of tools to get the data, mine the data, and find patterns.

-Liquid-solid interfaces will be modeled from first-principles. There will be improvements in exchange-correlation in first-principles density functional theory (DFT); reliable and reactive force fields; nonequilibrium multiscale methods (coarse-graining, rare events); theories of dissipative systems; directing evolution *in silico* and *in vivo;* and models to control self-assembly at nano-, micro-, and meso-scales and emergent structure, function, and rate of formation (kinetics).

-Methodology is needed for discovery and design of materials in real-time, developing reliable physics-based models and simulations for different properties, fast computability of properties, fast data I/O, inter-operability with cloud data and mining tools and techniques, and fast interactive visualization and manipulation.

A common theme: data, data, data.

Emerging Technologies and Methodologies Needed for Molecules

-The discussion led to proposing a “chemical Legos”™ approach to the design of new molecules from standard building blocks that would feature high-efficiency coupling and seek biomolecular processing routes done without water. The Legos™ approach should offer a rich molecular architecture versus the more linear biological polymers, great stereoselectivity, and the ability for self-replication (i.e., non-biological evolution).

-Because water is problematic as a solvent, synthetic routes are needed that involve tunable non-aqueous media, no solvents, organic solvents, ionic liquids, surfaces, or solids.

-This new approach to molecule design and synthesis will be enabled by:

- modeling to design the molecule and synthesis route;
- modeling to design molecule synthesis through the development of a new chemistry toolbox that uses a building block approach;
- modeling to design molecule characterization that encompasses electronic visualization of a single molecule such as NMR-like fingerprints; and
- development of theory to integrate biological and organic molecules with inorganic molecules and circuits through modeling of surfaces and interfaces.

"To do things to more complex organisms, we need to get better at the simple things. Advances will come in the simple things, then move to the more complex, robust systems that can translate from the lab to the real world."

Emerging Technologies and Methodologies Needed for Systems

-Biological systems lack reliable behavior models, which is a fundamental modeling problem, not a problem with molecules and materials. We don't have enough understanding for models of open systems such as wastewater treatment and agricultural systems.

-Adaptive control is taking a model and using data to turn the model around to control something. This is currently a popular paradigm, but if we over-train the model, we will get unique solutions. To some extent the answer is to draw a box around what we look at. Population biologists and ecologists might be helpful in this area, because they are experienced in open systems in evolution. Perhaps engineers could talk to population biologists.

-We need a broader view of what we are trying to achieve and how to get there. We need to change how we think about modeling and systems. A simple example: the best model for an individual's risk of getting the flu this season isn't high-level epidemiology, it is a Google search of "flu" that reveals the location of outbreaks in real time.

-There are so many problems and classes of problems, where are the big breakthroughs coming? It is actually possible now to imagine that we could get all the data we wanted on something, to measure everything about a particular system. Then what? How would that change what we do? Would it mean we could better understand things? What is the use of predicting things if we have no idea why? Are there areas where we could understand something if we had all the data?

-Defining "everything" is a challenge in and of itself. We have to ask: what data do we need in order to understand something so we can re-engineer it?

Looking forward, the groups envisioned:

- Adapting models from emerging data sets for non-living and living systems
- Designing non-living systems that go the way of chemicals and fuels, leverage and extend advanced systems technology, develop related enablers, and use big data
- Living systems that use big data, improve measurement technology, accelerate the design-build-test cycle, and decouple evolutionary aspects from engineering objectives

"What can we get out of the science of decision-making that we don't have today?"

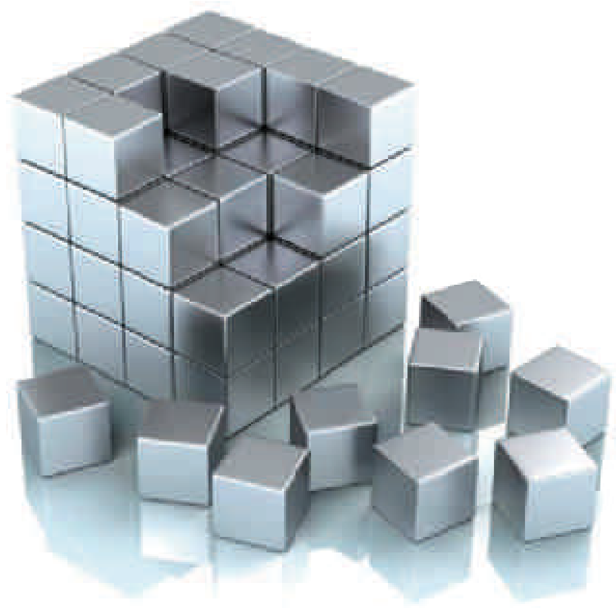
A full group discussion of the breakout group reports led to creation of new working group themes: Materials, Sensors, Emergent behavior, and Building blocks. Building blocks are the smallest constituents that are necessary for a function, such as the four nucleotides – A, C, G, and T – that comprise DNA to define the functioning of genes.

Attendees then broke into the new working groups for discussions, summarized here.

Materials Group Discussion

Modern materials research focuses largely on understanding how the properties and function of a given material arise from constituent atoms and molecules. New trends are shifting research to bottom-up design, where one identifies elementary building blocks (e.g., atoms, molecules, clusters, and nanoparticles) for a target structure with a particular desired property. A more comprehensive approach would take a well-defined set of buildings blocks, or so-called primitives – the smallest constituent necessary to resolve the problem at hand – and create a knowledge space of all possible architectures, properties, and functions that could be created from the finite set of primitives. The set could expand over time.

This approach would have the benefit of focusing communities around such factors as models, force fields or interaction rules, and measurement and characterization techniques needed for that particular set of primitives.



What are the optimal sets of primitives for a given community or application and how can they be determined? As an example, the 20 amino acids from which all biological proteins are built are apparently sufficient to achieve all protein functions necessary for life. Likewise, the four nucleotides that comprise DNA – A, C, G, and T – form a sufficient set for the functioning of genes. For other, engineered applications, is it possible to identify all desired properties or functions and from that, the complete set of primitives required? Moving beyond that, can we then predict the new space of outcomes from the addition or substitution of a primitive?

Of course, the proposed approach of prescribing*, a priori*, a given set of primitives for investigation limits the possibilities to those outcomes (structures, properties, and functions) that can emerge from various combinations of primitives within the set. However, the approach also offers a well-defined, finite space to help focus the work.

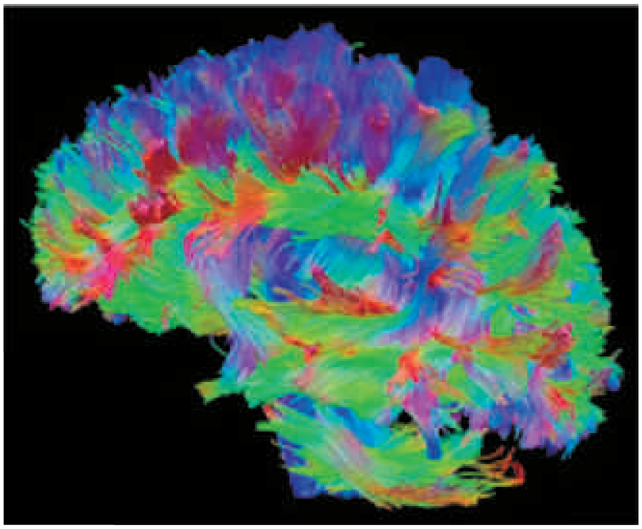
"What do I need, and what materials breakthroughs get me there?"

Sensors Group Discussion

The panel addressed a number of issues that were revisited in the final working group on sensors. There was a sense that properly posed problems can be solved and what the sensor community needs is to understand the challenges that are more relevant for defense. Examples suggested for development and implementation included new materials and ways to integrate them (e.g., for infrared imaging and radiation detection and dosage; molecular sensors that can detect volatile compounds, trace molecules in water, and biomolecules in blood; sensing arrays monitoring the physiological condition; glycol-profiling sensors that would allow one to recognize protein, bacteria, and viruses; and, deployable nanoparticles for physiological sensing).

The design and deployment of robust, specific integrated sensors and sensor systems that are producible, manufacturable, portable, and compact will require development of materials to enable stand-off detection of molecules or pathogens at a distance, and adaptation of proteins for recognition in extreme environments. Essentially that means taking proteins that work in the ideal environment and adapting them to work in harsh environments. A novel sensor system was suggested that monitored brain activity to amplify the performance of an individual by reacting to electrical signals in the brain.

This sensor system would require understanding how nervous system electrical signals are collected with remote (e.g., scalp) electrodes.

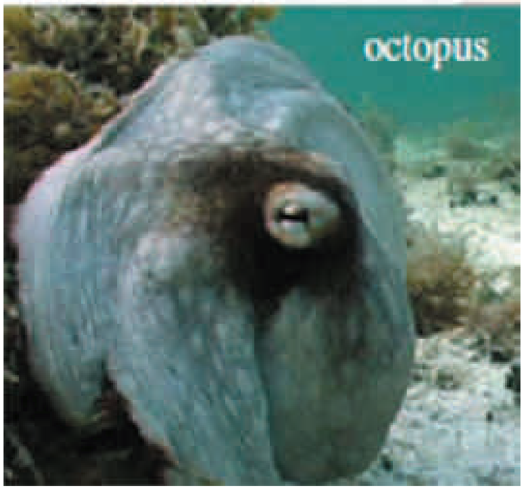


High-definition fiber-tracking map showing a million brain fibers in an uninjured brain. Credit: University of Pittsburgh Medical Center. Used with permission.

Emergent Behavior Group discussion

Complex systems and patterns arise out of a multiplicity of relatively simple interactions among primitives that in this context are called agents. Examples of such systems include crystals of atoms, molecules or nanoparticles; flocks of birds; schools of fish; and swarms of ants. The behavior exhibited by one of these systems is emergent because it cannot be intuited in a trivial way from knowledge of the agents alone. If we understand and can predict how behavior emerges from interactions among agents comprising the system, we can then start with target functions and use inverse design to discover the agents and interactions needed to achieve the targets.

Important DOD-specific challenges that might benefit from such an approach include the design of clothing that changes its mechanical and optical properties in response to electrical current or voltage, adaptive sensors, active wound healing, and adaptive "real-time" camouflage.



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One approach to discovering materials with target emergent properties would be *in silico,* directed evolution using genetic algorithms, in which reproduction, mutation, and selection pressure in building-block populations are used to screen for compositions that result in the target emergent properties. This approach leverages computational power and uses principles of natural selection to discover emergent and unexpected function at large scales from primitives and interaction rules, while at the same time leveraging the inverse materials design paradigm.

Challenges here include evolving *in silico* building blocks that are optimized with respect to shape, symmetry, and interactions, and that are also achievable in the lab, as well as minimizing the set of primitives and rules needed to achieve novel properties and functions, in the same way that nature has evolved a compact alphabet of 20 amino acids with which to work. Another challenge is developing the algorithms to perform efficient, unstructured searches with convergence, ergodicity, and optimality.

Building Block Group Discussion

The group discussed a radical new approach to design and synthesis based upon defining minimal sets of primitives or building blocks highly optimized for building a target system with desired properties and behavior. A common syntax for molecular transformation – micro to macro – is primitives (building blocks) to modules (larger units comprised of building blocks) to motifs (emergent patterns) to systems (where the properties or functions are expressed). A new molecular transformation-type approach based on building blocks involves developing a toolkit of the appropriate primitives optimized for the targeted system. Such a toolkit would need to provide:

- assurance of the propensity for molecular transformation or assembly,
- commercially available primitives at reasonable cost and high purity,
- well-characterized properties of the primitives, and
- fast, specific coupling kinetics with no need for separation of an impure product.

New opportunities based on this toolkit approach include small molecules in solvents other than water, nonlinear structures and long-range sequence specificity of chains, and primitives at multiple length scales and combinations. The idea is to build defined architectures with sequence specificity by selecting the primitives *a priori*. This approach represents a disruption to traditional chemical synthesis and could be used to design, for example, molecular recognition sites, molecular actuation, membranes, gas adsorption, antifouling, surfactants, lubricants, organic transistors, and hybrids of synthetic chemistry/biology.

The group recommended investing in bottom-up materials synthesis, moving from primitives to stable hierarchical structures to libraries, with large databases for design of materials and primitives. Challenges to designing a set of primitives include modeling with experimental verification, characterizing single molecules, modular chemistry for structure and function, and a culture of standardized synthesis. It's a design-ahead strategy rather than a reactive one.

The time is ripe for such an approach for several reasons. Many of the technologies that will help us choose desirable primitives are on the cusp, and posing this challenge could drive that capability to completion. Through the toolkit, it would be possible to achieve vertical integration of parties: vendor/theory/synthesis/characterization/end users/regulators.

Other groups also discussed the concept of building blocks or "primitives." Key concepts from those discussions include:

- Choose a set of primitives and identify all architectures that could be built with those principles. In the context of sensors, what sensors could be created? The set of primitives could increase over time as people developed the ability to use them.
- What are the optimal building block sets? What are the optimal models for predicting in advance what they will do? How do we define the building blocks for the target, geometry and symmetry, and interactions? How do we perform efficient, unstructured searches with convergence, ergodicity, and optimality? How do we formulate a structured set of alternatives for searching from the unstructured problem?
- What features are gained by expanding the set of primitives, and what is the path to identifying the primitives we need? The sets of primitives required by different communities will be dictated by the target system. One suggestion was to focus the problem on a societal problem such as rapid screening, sensing, or predicting and controlling emergent behavior.
- Emergent properties of large collections of building blocks cannot be intuited in a trivial way, making it challenging to know, *a priori*, what properties will be achieved by making changes to the set of primitives.
- *In silico*, directed evolution might be a powerful approach to optimizing sets of primitives. There, reproduction, mutation, and selection pressure in building

block populations are used to screen for compositions that result in the target emergent properties. This leverages computational power and uses principles of natural selection to discover emergent and unexpected function at large scales from simple subcomponents and interaction rules. It leverages the inverse materials design paradigm.
- Challenges include translation of knowledge gained *in silico* to the lab setting; in other words, replication, mutation, and selection pressure.

Final Working Groups

By consensus, three final working groups were formed: Sensors, Building Blocks, and Emergent Issues. Each considered the emerging challenges and directions.

1. Sensors. Develop the concept for the threat/target, which will define the approach to develop the solution and a path to put it into action. Smart, creative people can answer well-posed questions, so we need to define and pose the questions.

What are we measuring and why? What is a representative sample – a single molecule, or many? And if many, how many?

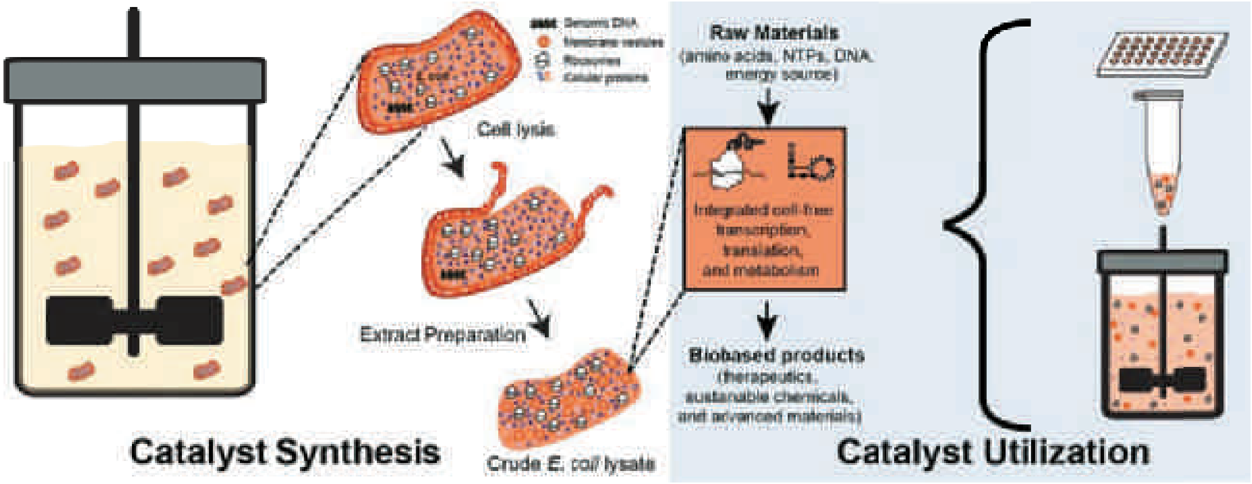
We need new concepts for weapons detection. If we know what concentration or signature is needed, and what gives a positive response, then we can make the detector. What are the targets, the right concentration?

We need centers of excellence or centers for new concepts, combinations of expertise across geographic and discipline borders, collaborations that take different forms from those currently in existence (i.e., multidisciplinary teams). There are clusters of bright people at major universities, but they are not organized or managed for this activity. Within a center the fundamental issues must be addressed first. Then add experts as needed, such as tissue specialists for electrodes attached to the skin, or computer scientists to address speed of response with the computer.

2. Building Blocks. Develop the concept/procedure through Multi-disciplinary University Research Initiatives. Teams would define their application or system and develop primitives relevant for achieving the modules, motifs, and, ultimately, the target system through simulation-based design. Important tasks include understanding the robustness of primitive-to-system pathways and stability to variations; synthesis; and testing of the primitives and iteration/optimization among theory, simulation, and experiment.

Fund teams that have the ability to characterize primitives in real time, *in situ*, and develop and apply modeling methods for the assembly of primitives into systems through multiple scales.

Questions that cannot be asked yet: What is the theory describing inorganic/organic surfaces and interfaces? How will elegantly designed and built materials adapt, function, and change in working environments? What's happening on the surface of the primitives that can affect their arrangement into modules and motifs, or for systems to adapt? How do we make molecules for molecular recognition, sensing, or actuation economically and in a short time? How can we make replicating materials that can evolve? Accomplishments needed in the next ten years include automated synthesis of optimized primitives and their combination into functioning systems.



A cell-free vision. Image courtesy of Michael C. Jewett, Northwestern University.

3. Emergent issues. Define the building blocks for the target emergent properties and behavior. Systems engineering is needed to determine how to formulate a structured set of alternatives for searching from an unstructured problem; how to perform efficient searches with convergence, ergodicity, optimality guarantees; how to determine whether our current library or set of primitives is too small, meaning we need new primitives. How do we expand the alphabet of primitives? Start with the function, use evolutionary search, and modify the parts to figure out what they should look like. Define new alphabets of primitives, such as biology's amino acid alphabet. Explore all of what nature has as its primitives, and actually control and design.

To fully understand – and eventually predict – emergent phenomena we must be able to see the emergence as it is happening, to visualize assembly pathways. Identify a set of problems and issue a call for proof-of-concept of *in situ* monitoring, such as high-throughput, *in situ,* online or web-based transition electron microscopy (TEM). Test evolutionary algorithms of simple targets. All of this requires infrastructure investment for dynamic, *in situ* TEM, highly parallelized code optimized on graphics processors, data mining/correlation tools, and real-time characterization of self-assembly and kinetics of materials formation.

Final Group Discussion
Our consensus as a discipline of where to focus our resources in the next 10 to 15 years

-For energy innovation, accelerate commercialization of new technologies, such as occurred with integrated circuits. Develop the omnivorous mini-refinery on a scale applicable to fixed and forward bases, using biomass, waste, and stranded gas. We need reaction kinetics, separation science, and engineering to handle diverse feedstocks at the local base scale. Modularize components that are the size of a shipping container to create units that are moveable on those scales. Conventional industry will not do it because it is hard to make an economic case for it.

-Bottom-up chemical and materials synthesis. Current chemical synthesis takes too long and no one is happy with it. Have an infrastructure investment in modeling and databases and a group of people working on a finite number of chemicals. Control flow in and out of the process; do not just make the building blocks. Life cycle control and supply chain management. With a finite number of chemicals we will know a lot more about this.

-Earth-abundant, unconventional resources, non-toxic feedstocks for chemicals and materials. Move away from petroleum-based and rare feedstocks. Design processes and products that are mindful of carbon flow and choose the appropriate process for the feedstock – carbon-negative processes and products where possible.

-Because systems are embedded in everything, we need better optimization methods for large-scale problems. In systems theory, what tools and methods are needed to solve a problem? The best way to answer that is to solve a problem then go back and see what tools it required. Anticipate the need for advances in systems engineering, which will be informed by the applications. We do not know what we need until we start working on it. Addressing a larger problem with greater complexity than what we are doing now. Our need to handle large amounts of data continues to grow.

-In silico materials properties and processing routes from familiar classes of materials but away from equilibrium, creating different yet kinetically stable structures

-Tremendous impact will result from unknown materials and their properties – what are the unknown materials properties for *x*? We need centralized databases and a way of understanding the data generated in order to know where to look. Make unknown materials from the classes of familiar materials, the ones we are used to using.

Emerging areas:

Sensors

Molecules and materials, including organic ones, by design from building blocks

Emergent systems

Energy

New advancements in 10-20 years that require focused investment now:

Bottom-up synthesis. This includes analytical techniques for *in situ* monitoring of single molecules and nanoparticles and rapid models for predicting properties and robust synthetic routes. Invest in bottom-up materials design and synthesis to disrupt traditional chemical synthesis and do things ten times faster.

Systemic integration and scalable manufacturing to meet product specifications and handle variability. Take these materials and fabricate them in a commercially viable way, with reproducibility and precision. Integrate new materials into established platforms. Invest in process platforms that are capable of insertion into existing manufacturing platforms. There is a major opportunity here where bottom-up synthesis meets additive manufacturing (3D printing). Design appropriate user-fabrication facilities.

Cell free synthesis. For primitives or systems-based engineering. Primitives could include biological pieces, such as amino acids, and could even be organisms, perhaps viruses. Nothing says the building blocks tool kit could not work in a cell-free setting. In fact, cell-free environments open the aperture to game-changing, disruptive capabilities by offering unprecedented freedom of design to control and modify biosynthesis.

The overall idea is to speed up design and concept, to move from a device with the property and performance we want, to a product. Not just to make it faster, but to make it possible.


FUTURE DIRECTIONS IN
CHEMICAL AND
BIOENGINEERING

Appendix

Attendees and areas of expertise

Mark A. Barteau, University of Michigan. Catalysis and energy, focusing on rationally designed catalysts for high selectivity.

Mark Bathe, Massachusetts Institute of Technology. Synthetic structural biology and Materials Genome Initiative for functional DNA-based materials.

Lorenz T. Biegler, Carnegie Mellon University. Optimization strategies in process engineering systems, interfacing biology, chemistry, physics, dealing with two issues: developing fast algorithms and applications to enable decision-making for integrated multi-scale problems.

Joan F. Brennecke, University of Notre Dame. Ionic liquids for energy applications such as CO_2 separation from flue gas, other gas separations, refrigeration applications, absorption refrigeration, electrochemical applications, and liquid-liquid separations.

John G. Ekerdt, University of Texas at Austin. Kinetics and reaction engineering applied to growth of electronic materials surface and materials chemistry.

Andrew D. Ellington, University of Texas at Austin. Synthetic biology for high-throughput gene and operon synthesis, protein design, and electronic input/output and genome engineering for site-specific, high efficiency insertion of recombination sites and reorganization of genomes.

Kristen A. Fichthorn, Pennsylvania State University. Multi-scale theory and simulation of the growth and assembly of nanoscale materials, at surfaces and in colloidal nanoparticles, focused on oriented attachment, or the specific ways single atoms aggregate and add, or particles aggregate with one another, and ways we can organize and control that growth.

Justin P. Gallivan, Emory University. Working toward the ability to use any molecule to control the expression of any gene in order to reprogram how an organism behaves, to affect fundamental biology, metabolic engineering, and synthetic biology problems.

Venkat Ganesan, University of Texas at Austin. Studying structure of multicomponent polymers, properties of nanocomposite membranes, and polymers in energy applications.

Karen K. Gleason, Massachusetts Institute of Technology. Chemical vapor deposition of insoluble, grafted, conformal, and substrate-independent polymers to produce, for example, vapor printed devices and coatings for anti-biofouling.

Sharon C. Glotzer, University of Michigan. Simulation–enabled assembly science and engineering, studying self-assembly of shapes to work toward predictive colloidal crystal assembly.

Tobias Hanrath, Cornell University. Fundamental conceptual framework for nanocrystal quantum dot solids with properties by design, and emerging energy nanotechnologies such as quantum dot-based photovoltaics and light emitting diodes.

Adam Heller, University of Texas at Austin. Developing biosensors to interface computers with the brain.

Michael C. Jewett, Northwestern University. Cell-free biological systems as a platform for advanced manufacturing, researching ribosome construction and evolution, translation system engineering/evolution, cell-free protein synthesis, and cell-free metabolic engineering to develop therapeutics, advanced materials, and sustainable chemicals.

Thomas F. Kuech, University of Wisconsin-Madison. Synthesis of new optical and electronic materials and structures via chemical methods, including semiconductor surface chemistry and biomedical applications of semiconductor structures.

Kevin Morey, Colorado State University. Biosensor and synthetic signaling system in plant synthetic biology, working toward biofuels, metabolic engineering for improved nutrition, pathogen and pest resistance, crops better able to withstand environmental stresses, and biopharmaceuticals.

James B. Rawlings, University of Wisconsin-Madison. Systems engineering, especially process control theory, model predictive control, and state estimation, developing algorithms for implementation in real time, with uncertainty.

Stuart E. Strand, University of Washington. Engineering transgenic grasses for *in situ* treatment of RDX and TNT on live fire training ranges, and phytoremediation of atmospheric methane using transgenic plants.

Michael S. Strano, Massachusetts Institute of Technology. Chemical engineering of low dimensional materials, molecular recognition using the nanoparticle corona as a basis for medicine and human health, catalysis and biocatalysis, and directed assembly of materials.

Navin Varadarajan, University of Houston. Single-cell, high-throughput assays, including adoptive cell-based immunotherapy, molecular engineering of biocatalysts, and isolation of fully human antibodies. Proteomics, detection of post-translational modifications at low cell numbers.

U.S. Department of Defense representative: J. Aura Gimm, AAAS Diplomacy, Security, and Development Policy Fellow, Office of the Secretary of Defense for Research & Engineering.

Recent major breakthroughs:

Development of high performance algorithms, continuous optimization, discrete optimization.

Synthesis and characterization of new molecules designed from quantum mechanics and molecular simulations, which enabled doubled capacity (1 mole CO_2 per mole IL versus 1 mole/2 moles amine) and eliminated viscosity increase upon reaction with CO_2.

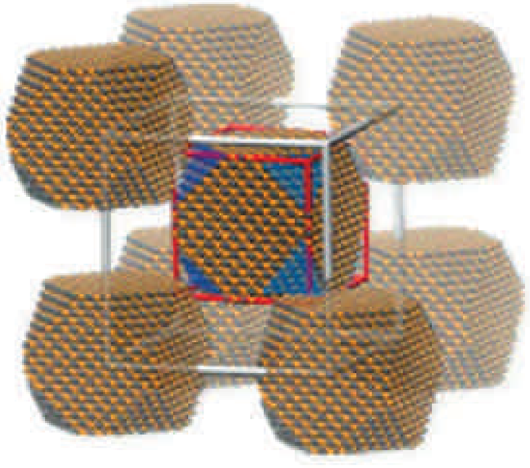
The ability to read and write DNA is transforming the way we engineer biological systems now.

Adaptive and self-learning systems.

High performance algorithms, both continuous and discrete.

Development of nitride semiconductors, revolutionizing solid state lighting and power transmission.

Access to nanomaterial building blocks with controlled size, shape, composition, aka a nanoparticle vending machine. We moved from ordinary atoms and crystals to designer atoms and crystals.



Designer Crystal. Reprinted with permission from T. Hanrath, Colloidal nanocrystal quantum dot assemblies as artificial solids, J. Vac. Sci. Technol. A 30, Article 030802 (2012). Copyright 2012, American Vacuum Society.

Artificial viruses. The ability to make a lot of DNA. Synthesizing variants of extant viruses, which will equal better understanding of infectivity and pathogenesis, viral evolution, and adaptation.

Revolution in capacity to describe rare events. Nudged elastic band and transition path methods. Revolution in capacity to describe van der Waals interactions in first-principle density-functional theory.

Extensively used length and time scales, providing methodologies to link different scales and understanding of the scale needed to describe problems, which isn't always the nanoscale.

Real-time optimization of industrial processes.

A light-controlled synthetic gene circuit that increased insulin in diabetic mice.

A cell classifier circuit that triggers a response only in a predetermined cell type profile. Allows detection of a human-made chemical *in planta* using synthetic detection, signaling, and read out system.

We shifted from making one kind of particle in one kind of shape to being able to make any shape on any scale out of virtually any kind of material, with the capability of coating it and attaching other materials to it. We are able to be predictive and have moved from assembly science to assembly engineering.

Speed of a graphics processor has increased much more than CPU speed, changing fundamentally what we can do with simulations, turning computer-limited problems into data-limited problems.

Epitaxial growth of $SrTiO_3$ on Si.

Atomic layer deposition moved from a research tool to a production tool, and enabling precursor molecules are now broadly available (they can be purchased rather than made).

Artificial viruses.

We've become skilled at DNA sequencing, genetic tools, DNA synthesis, all enabling technologies that will get better, faster, and cheaper. However, we're only marginally good at engineering simple systems in single-celled organisms because cells evolved to evolve.

"Anything found to be true of E. coli must also be true of elephants." Jacques Monod.

Emerging breakthroughs and needs:

In the next ten-plus years, food, energy, chemicals, materials, and medicine will be transformed by the ability to biomanufacture them.

Integrated, multiscale optimization. To integrate time and length scales, permit fast fullspace optimization, and lead to high potential, integrated decision-making.

Formation of nominally thermodynamically unstable yet kinetically stabilized phases over wide compositional ranges, which would open a wide array of new materials. There is a tremendous amount of potential in looking at these materials that are nominally unstable.

Moving from a fossil-fuel powered economy with separate energy systems for transportation and electric power to an energy resource base that may still be majority fossil fuel, but is used in less GHG intensive ways. This may be driven by CAFE standards and the dramatic increase in domestic gas and wet gas supplies.

Multiplexing, single-cell resolution, kinetics.

Multi-scale, rare-event simulations. Accelerated molecular dynamics “superbasin” kinetic Monte Carlo.

Crystallize developments in growth and assembly of nanoscale materials and proceed to practical applications – catalysis, organic thin films, colloidal systems, and soft condensed matter.

Full realization of synthetic molecular recognition. Synthetic nanomaterials as substrates for biomolecules. Functional DNA origami devices. Real-time informatics applied to industrial processes.

Data-drive correlation and prediction, with relevant, information-rich simulations in minutes creating huge amounts of data.

Create new molecules from quantum mechanics and multiscale for technologically relevant systems. Catalysts for water splitting and reduction of CO_2, for which we need computational tools, force fields, a focus on complex multi-step processes, and skilled molecule and materials synthesis. Chemical engineers have transformed the petroleum world, now need to tackle the non-petroleum world.

We need improved batteries to electrify our vehicle fleets and direct solar hydrogen to produce carbon-free hydrogen as a fuel and as a feedstock for upgrading other energy resources. A “transportation internet” to enable autonomous and grid-connected vehicles and transportation systems. An “omnivorous” refinery to integrate renewables and alternative resources into a base for liquid fuels.

Design and controlled synthesis of catalytic structures. Understanding the mechanisms and dynamics of catalyzed transformations.

Compatible and manufacturable fabrication of organics and inorganics; meld education perspective between organic and materials chemistry; characterization of interfaces, as opposed to surfaces, and directional, interfacial properties; theory and modeling appropriate to both material types and their interfaces.

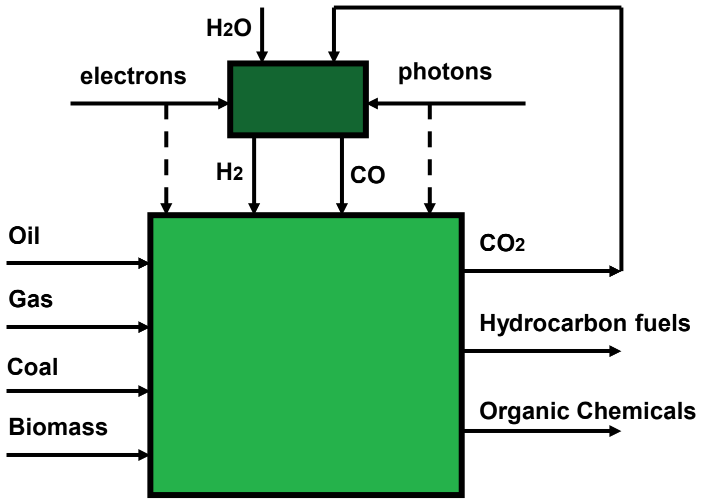
Scalability of process is important moving forward. Concept of programmable/designer solids. Understanding surfaces is critical, so we need to determine what is really going on at a surface. Coupling between quantum dots and properties of the entire assembly.

Prediction of zoonoses. Phylogenetic and structure-based prediction of host-pathogen interactions. Deep analysis of immune responsivity to develop countermeasures in advance of disease emergence and to predict the immune response to that disease. Design for medical preparedness. One thing needed is evolution study. What five amino acids are most likely to interact with a receptor?

The challenge is that engineering biology is costly, risky, and slow, and there is a need to expand the chemistry of life. To have an appreciable impact on modern life and DOD capabilities, we need novel strategies that accelerate the engineering design cycle and make biological systems easier to engineer.

We need new catalytic upgrading processes, co-processing of carbon-based resources, integration of carbon-free resources. Pay more attention to making fuels converge upfront – oil, gas, coal, biomass. Logistical fuels we can count on. Look at how to get renewables in ways besides in the obvious ones.

A new science – catalysis of solid-state transformations – is needed.



- New catalytic upgrading processes
- Co-processing of carbon-based resources
- Integration of carbon-free resources

Image courtesy of Mark A. Barteau, University of Michigan

We need novel programmable materials, and predictive models of assembly, structure, and activity; predictive functional models; increased throughput of computational materials screening and quality of feedback to design; and increased throughput and quality of experimental validation.

Increased shale gas production in North America has led to increased production of natural-gas products and decreased supply of co-products from naptha cracking. We are extracting gas from extremely impermeable shale, creating new needs for water treatment and purification and leading to a de-emphasis on cleaner energies.

Modeling challenges include new, “designed” catalysts for making the reduced supply of chemicals, macroscopic modeling of fluid flow in highly fractured media, and connections between chemical structure and macroscopic transport properties of polymer membranes used for water purification.

Desalination of water to overcome impending worldwide shortages of water. Purification of fracking water is likely to become an important issue. Nonfouling polymer membranes may be a solution. Design of water purification membranes will take quantum mechanics, molecular dynamics, mesoscale models, continuum models, and process models, including multiscale modeling of multiphase (gas, liquid) flow modeling, translating from nanosized pore scales to rock scales.

Significant investment in research into plant molecular biology and application of enzyme modeling and molecular engineering to genetically modify plants.

Ramped-up basic research into symbiosis. Funding for microbial catalysis of rare pollutants for wastewater treatment and water recycling. Increased focus on mechanisms of phage infection and resistance and horizontal gene transfer.

The need to develop and grow a new modulated work-function device. Devices get smaller and smaller, but not faster, creating intrinsic limits on switching speed of individual devices. Changing the physics of underlying devices to reduce power dissipation by operating FETs at lower voltages.

To do things to more complex organisms, we need to get better at the simple things. Engineer complex, robust systems that can translate from the lab to real world. Advances will come in the simple things, then move to the more complex.

Study of atmospheric carbon removal technologies.

Initial Breakout Group Discussions

Materials. This group discussed biological and self-assembled materials, sensing, and information needs.

Research is headed toward engineering for self-assembly. While materials make a huge difference in all areas, we still seem limited by the things that we can build. Many of the materials we make today are still petroleum-based. Biology has unique features, such as the capability to make sequence polymers, which offer, for example, unique architectures for self-healing. We should investigate the chemical palette in biology. We're just now reaching the capability to read and write DNA, harnessing greater chemical diversity to get to different materials.

Can we engineer a new immune system, or create new prophylactic antibodies? How do we engineer recognition in space, because that's how the immune system works? Advanced armor and perfect information are no match for a biological created in the lab.

In many living systems, when we know what to measure and have a sensor to measure it, the problem is solved. Use-inspired research is about solving a problem. What are the problems that need to be solved?

One application area is sensing or screening molecules, such as sensing a type of bacteria to determine who is exposed. If we had these sensors, what would we measure, and what advances are needed?

Technology challenges include mapping the distance-dependence of electrical signals from a nerve; achieving signal magnitude, fidelity, and noise; and tools for arrays and spatial and temporal resolution.

Sensing research needs to develop nanotech platforms for single molecule detection, robust transduction of information from sensing to use of the data, and seamless transmitting and analyzing. Possibilities include massive, cheap pre-symptom screening for markers of disease in individuals in certain populations and platforms that allow rapid assay of large numbers of single cells. We are beginning to understand how scalp electrodes work and will likely see new materials based on that understanding.

Different force fields work in different ways and that is a problem. We need to understand where the control knobs are, wand hat spaces we will never get a handle on. Some things we will never predict.

We need to embrace fudge factors as we move toward more complex systems. Models that are quasi-predictive in certain schemes can be miserable failures in others. We want models that are reliable predictors in the right areas.

In the energy realm, research needs to seek carbon-free hydrogen at all scales, high-density storage, distributed diverse feedstocks, and improved CO_2 absorption and release. New computing technologies will enable CO_2 capture, hydrogen generation, improved heat transfer for power generation, and lightweight materials for autonomous vehicles.

In the information realm, we increasingly need to interpret massive numbers of stochastic signals. Quantum computing materials and multi-state devices are needed to make this a reality. We need breakthroughs that include self-assembly of materials (rather than starting with large, perfect crystals), materials breakthroughs and manufacturing (for example quantum computing photonic circuits), integration of dissimilar materials to enable devices and computers of the future, reproducibility of devices, information flow from ubiquitous connected devices, and manufacturing-reproducible nanodevices. We need new computing technologies in quantum computing and multi-state devices.

Modeling. This group discussed moving from a computer-driven to data-driven design era.

A key premise: saving data is cheap; experimentally generating or computing new data is expensive. We need community metadata standards for deposition in data banks. Use data to inform and guide experimental design, to test and classify predictive theoretical versus necessary empirical models. Machine learning data classification, feature identification/extraction, genetic algorithms. Having the data isn't enough, we need tools to get the data, mine the data, and find patterns.

Crowd-sourcing *de novo* materials design and innovation. The goal – games, social media, challenges, prizes. The tool – black-box design tools to commoditize design (iPad apps). The language – community accepted metadata standards for input and outputs. Performance metrics – how well does it work, how useful is it. We can have different standards for different databases as long as we have a standard-to-standard translator. This would be done through consensus.

Discipline-based needs: improved exchange-correlation in first-principles density functional theory (DFT); liquid-solid interfaces from first-principles; reliable and reactive force fields; nonequilibrium multiscale methods (coarse-graining, rare events); theories of dissipative systems, directing evolution *in silico* and *in vivo*; and models to control self-assembly at nano-, micro-, and meso-scales, emergent structure, function, and rate of formation (kinetics).

Real-time materials discovery and design: reliable physics-based models and simulations for different properties, fast computability of properties, fast data I/O, inter-operability with cloud data and mining tools and techniques, and fast, interactive visualization and manipulation.

Molecules. This group discussed design versus evolution.

Chemical engineers have transformed the petroleum world; now we need to apply quantum mechanics and multiscale modeling to the design of molecules for the non-petroleum world. In doing so, it will be important to use theory as a predictive design tool, to develop systematic approaches to construct and characterize the designed molecules at the atomic level, and to develop the necessary understanding to control or direct the chemical reactions in complex media.

Still mimicking nature, but not IN nature. Making nature better. Differences between living and non-living (synthetic) systems. Because living cells are living, they are different.

Integrating and recycling complicated the process greatly. We went from one loop at a time to many integrated loops. We routinely collect huge amounts of data and use it in real-time, but then pretty much ignore it. We could use data better.

Systems. This group discussed adapting models from emerging data sets for non-living and living systems.

We have very powerful capabilities for trying different things, with software and hardware contributing in major ways to our ability to look at thousands of variables. We can continue improving along that route, but we should become better at optimizing high-level things. For example, rather than optimizing the temperature in this room, we should optimize the energy use in this building.

Non-living systems: go the way of chemicals and fuels, leverage and extend advanced systems technology, develop related enablers, use big data.

Biological systems involve so much adaptation that we can't get our hands around. With adaptive materials, we need to determine a feasible level of adaptation to work up toward on the materials side and down to on the biological side. Limited, achievable adaptation requires not only chemistry and physics, but modeling and control. We may be tempted to say something is impossible, but many of today's technologies would have looked impossible ten years ago.

Is bioengineering the best tool for the progress that we want to make? Modeling had very little impact on the vast progress made in managing diabetes, for example. We can talk about large, global concepts, but need to be specific about exactly what we want to do.

Living systems: use big data, improve measurement technology, accelerate the design-build-test cycle, decouple evolutionary aspects from engineering objectives, develop on-site distribution in the field. Model development is the major challenge. We need to be able to program in a meaningful way beyond the tinkering level.

Initial Questions for Attendees

OBJECTIVE: Where and how could creative intellectual and funding leadership enable transformative progress in 10 to 20 years?

- What research is moving the fastest?
- Where is there room to grow?
- What new areas do you see emerging in the next 10 to 20 years?
- What are the particular challenges to success?
- Are there particular infrastructure needs that the U.S. Department of Defense should be investing in? Why?
- If you were the DOD and an incremental 5% increase in funds was made available for bleeding-edge, but potentially high payoff research areas, where would you place the mad money?
- What questions do you want to ask today, but cannot?
- What have been the major breakthroughs in chemical and bioengineering over the last decade?
- What accomplishments or capabilities will be attainable in 5 to 10 years?
- Where are existing and emerging global centers of excellence in chemical and bioengineering?
- Chemical engineering and bioengineering are naturally interdisciplinary and many of the past and future breakthroughs this workshop will explore come from the concept being promoted – convergence, which is "the merging of distinct technologies, processing disciplines, or devices into a unified whole that creates a host of new pathways and opportunities." Which convergences will create the greatest impact?