Unsolved Problems in Biomolecular Engineering

Biographical sketch of Michael L. Shuler

Michael L. Shuler is the Samuel B. Eckert Professor of Chemical Engineering, Director of the School of Chemical Engineering, and Director, Bioengineering Program at Cornell University He joined the faculty at Cornell in 1974 after receiving his doctorate in Chemical Engineering from the University of Minnesota. He holds a B.S. in Chemical Engineering from the University of Notre Dame. Shuler has held visiting appointments at ETH (Zurich, Switzerland, 1995), Boyce Thompson Institute (1995/96), University of Wisconsin (1988/89), and the University of Washington (1980/81). He has held short-term distinguished visiting professorships at the University of Florida, Osaka University, and the University of Newcastle upon Tyne. Shuler was the Director of the School of Chemical and Biomolecular Engineering from 1998 to 2002.

Shuler has current research interests in several aspects of bioengineering, particularly bioreactors. These interests include production of secondary metabolites from plant cell cultures (e.g. Taxol), structured mathematical models of cells (e.g. a "minimal" cell model to relate genomic structure to cell function), microfabricated, heterologous protein expression systems, and *in vitro* toxicology using cell culture analogs and physiologically-based pharmacokinetic models. He authored or co-authored over 200 refereed papers, and 7 books, including a textbook, "Bioprocess Engineering: Basic Concepts", now in its second edition

He was elected to the National Academy of Engineering in 1989, an Inaugural Fellow for the American Institute of Medical & Biological Engineers in 1992, and American Academy of Arts and Sciences (1996). He has served on numerous taskforces and committees for the National Research Council, including the committee responsible for "Beyond the Molecular Frontier, Challenges for Chemistry, and Chemical Engineering". He also has been an active member of the ACS, American Society for Microbiology, American Society of Pharmacognosy, and AICHE (Fellow, 1997). He is currently a member of AIChE's board of directors and headed a recent taskforce on how to better integrate bioengineering into AIChE.

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Abstract:

The growing interface of biology with that of chemical engineering principles is a major challenge in chemical engineering education (esp. curriculum) and research. The "problem" for the chemical engineering profession is how do we best exploit these emerging opportunities. The most critical driver of change is the advent of molecular biology, genomics, and related technology. Biology is evolving from a data poor to a data rich science where the underlying molecular mechanisms of life are becoming clearer. Traditional strengths of chemical engineers are their ability to think across length and time scales and integrate descriptions of molecular level phenomena into an understanding of macroscopic systems. Chemical engineers are well positioned to contribute to biological discovery because of their skills in systems integration across length scales. Chemical engineers will be major players in the emerging field of systems biology. Further, chemical engineers are key contributors to the tools necessary for rapid, accurate and cost effective analysis of biomolecules. Finally, chemical engineers will increasingly convert the basic insights from the emerging understanding of biology into useful processes, diagnostics, therapies, and devices that will be of broad benefit to human kind. Some key examples are improved, lower cost cell culture processes to make therapeutic proteins that are more authentic, devices that allow rapid and more accurate assessment of disease, methods to evaluate pharmaceuticals for toxicity to reduce the cost of drug approvals, and more accurate ways to deliver drugs and genes to specific target tissues.

These intellectual drivers are also changing the nature of chemical engineering education. While the core chemical engineering principles will remain intact, biology (esp. biochemistry) will become a foundational science for all chemical engineers. Examples from biomolecular engineering as well as other emerging areas such as electronics and materials need to permeate the core courses supplementing examples from petrochemicals. Ultimately, I predict that within chemical engineering departments there will emerge an identifiable track for those students who wish to focus on biomolecular engineering.

Introduction

The grand challenge for the chemical engineering community is how to best exploit the emerging opportunities at the interface of biology and chemical engineering principles.

The "Problem" or "Challenge"

Biology is undergoing a revolution. The emergence of molecular biology followed by high throughput analytical techniques is generating data at rates that were inconceivable 15 years ago. Biology is evolving from data poor to a data rich science. This abundance of data will drive biology towards formulation of theoretical constructs to summarize these data efficiently and to form general principles and models. Biology is moving from an observational, descriptive science towards a mechanistic and quantitative science. As it does so, the opportunities for chemical engineering science to be relevant to biology and biology to chemical engineering increase significantly. Biomolecular engineering emerges from this interface. Biomolecular engineering was defined by National Institute's of Health for a December 1992 meeting as "…research at the interface of chemical engineering and biology with an emphasis at the molecular level."

Why Are Chemical Engineering Principles Key to Biology?

Life obeys all the rules of chemistry and physics. Living cells are complex chemical plants. While mechanical and electrical forces (and their transformation into chemical signals) are important, the dominant science in cells is chemistry. Biology, especially at the molecular and cellular level, is primarily the study of chemical systems. Cellular regulation – information sensing and control of the corresponding chemical reactions – is typically done

using chemical signals and signal transduction pathways.

Analysis of cell function calls upon all of the principle components in a chemical engineering education: mass and energy balances, thermodynamics, reaction kinetics, transport processes (esp. mass transfer), separations (esp. natural membranes), and process control. The chemical engineering education is also unique in its emphasis on integrating from molecular to the macro scale as in the design of a chemical plant. These principles and the ability to work quantitatively across both length and time scales places chemical engineers in an unique situation to contribute to both using biology to create devices or developing useful therapeutic strategies and to discover more clearly how living organisms function.

Basic Biological Concepts

While some readers will have an in depth knowledge of biology, others may not. Consequently I cover some elementary concepts and vocabulary to insure that the remainder of the discussion is readily accessible. (Greater detail is available in Shuler & Kargi, 2002)

Molecular biology is principally concerned with the storage, replication, and use of information. A living cell must process information from the external world and act upon it to ensure survival and replication of the organism. The primary challenge to an intact cell is the flow and control of information. The primary tenant of molecular biology is known as the Central Dogma. The information necessary for a cell is encoded in the double helix of DNA (deoxyribonucleic acid). DNA acts as template for its own *replication*. Segments of DNA that encode information for the primary structure (i.e., sequence of amino acids) in a protein are called genes. The information for production of the protein is first transcribed from DNA through synthesis of a messenger RNA (ribonucleic acid) molecule by the process of *transcription*. Regulatory elements on the DNA determine when and how often a particular gene is transcribed. The information on the messenger RNA is converted to a protein through a process known as *translation*. If the physiological conditions in the cell are correct, the nascent protein folds into its proper 3-dimensional shape. Proteins act as catalysts, transporters, receptors of information, regulators, and structural elements in the cell.

The language of biology consists of four letters (A, T, C, and G corresponding to four different nucleotides) in DNA and three letter words. Each three letter word specifies a particular amino acid (or start or stop translation). Other combinations of DNA letters (of various lengths) combine with proteins in the cell to block or encourage transcription of genes; these combinations of letters constitute regulatory elements. The language of the processes in the Central Dogma is universal; the same language applies to humans, plants, and microbes. The universality of this language is essential to modern biotechnology.

Simple bacterial cells (or procaryotes) are small (ca. 1μm) and have no internal organelles. A single, double stranded DNA (or chromosome) encodes the organism's genetic blueprint. In higher organisms (e.g. humans, plants, insects, even yeast) cells are larger (ca. 10 μm) and have distinct organelles. The nucleus is one such organelle. Multiple double-stranded DNA molecules, or chromosomes, are present and maintained within a nuclear membrane. The minimal cell to be discussed later is a simple bacterial cell while eucaryotic cells are used in the "animal-on-a-chip" described at the end of this article.

Genomics and Systems Biology

The major advances in biology have led first to understanding the molecular basis of life, then to molecular techniques to manipulate cells (e.g. recombinant DNA technology) in a predictable manner and now to genomics. "Genomics" is the set of experimental and computational tools which allow the genetic blueprints of life to be read. By this statement we mean that we know the sequence of all the letters in genome or the total inheritable DNA in an organism. We have full genomic sequences for over 100 organisms. While most of these are for bacteria with only a single chromosome, full genomic sequences are available for representations of higher and more complex organisms (e.g. insects, plants, mammals and humans). As the technology for sequencing DNA improves, many additional species will be sequenced.

The emerging challenge is to understand this sequence data in terms of how an organism works. The term "functional genomics" is often used to suggest the range of activities necessary to relate genetic blueprints (genomic sequence) to the structure and behavior of organisms.

To fully understand regulation and physiology, DNA information is insufficient. Interactions among the expression of different genes requires complete knowledge of DNA sequence, mRNA expression, and protein content. Microarrays for determining time and situation dependent expression of mRNAs have been developed. A microarray is a high-density oligonucleotide array. Each oligonucleotide hybridizes with a corresponding m-RNA. For each known gene (eg

from sequence analysis) an oligonucleotide (eg 40 bases in length) can be synthesized that binds uniquely the m-RNA from that gene. Using the techniques of photolithography, arrays for about 10,000 genes can be made that are less than 2 cm^2 in area. Binding with a m-RNA can alter a fluroscent signal allowing the array to be read optically.

A study of the total protein content (proteome) of biological systems provides a unique protein fingerprint for a system and permits an elucidation of the key genes involved in a phenotype (eg functional features displayed by a cell). Hatzimanikatis et al. (1999) have shown that an understanding of the regulatory structure/response requires simultaneous data on DNA, RNA, and protein. Proteome analysis is slow, difficult, and expensive. Consequently, DNA and RNA are often obtained in the absence of protein information resulting in an incomplete understanding of the relation of genes and cellular regulation.

Even with complete knowledge of DNA, RNA, and protein, the full analysis of cellular function requires a knowledge of the small molecules in a cell or tissue, the physical structure of the cell, and the structure of metabolic pathways. The nature of a living cell is also dynamic (time-dependent) and requires a knowledge of current environmental state and past history to fully describe.

It is also critical to understand how these components work together. As an example, Bhalla and Iyengar (1999) have shown that when individual well-defined biochemical signaling pathways share common elements to form a network, new properties emerge when the network is analyzed. As this example illustrates the full properties of a cell or organism are more than a sum of identifiable components, but result from the complex non-linear interactions of the components. Understanding biology will mean understanding both which components are involved and the non-linear dynamics of how they interact. It is with respect to systems integration and analysis that engineering approaches may prove critical to biological discovery.

These considerations lead to the concept of "systems biology." A goal of systems biology is the integration of genomics, high throughput, organism-wide data on cell composition and observations of physiology/function into a comprehensive mathematical model. Such a model of a living organism can predict the behavior of the organism in response to internal and external perturbations.

Why Is This Important?

The interface of chemical engineering with biology provides the best basis to develop "systems biology." One of the most fundamental questions asked by humans is: "What is life?" What is the essence of being alive? Systems biology cannot ignore this question; a natural consequence of building a systems model is to ask what are the essential functions for life. Those biomolecular engineers engaged in developing systems biology will be leaders in this aspect of scientific discovery.

Biomolecular engineers will also create the devices and therapeutic strategies that arise from the "new" biology. One aspect of creation will simply be the tools necessary to more efficiently sequence DNA, to build microfabricated array systems to more effectively determine mRNA expression, or to better separate, purify and analyze all the proteins in a tissue or cell. The more critical aspect will be to couple engineering analysis and systems biology to create for example: cells that more effectively produce therapeutic proteins in large scales; to devise not only new vectors for gene delivery, but the overall predictive analysis to make gene therapy an useful clinical tool; to build new methods to separate different cells on a large scale to diagnosis and treat cancer; to grow artificial organs that can replace living tissues; and so forth.

Perhaps this point is a good place to ask what separates biomolecular engineering from biology. A key feature of biomolecular engineering is the emphasis on design: the ability to predict the output from controllable inputs. Another is to do the design in a macroscopic system using explicit links of the molecular scale to the macroscopic system. While engineering design, especially in the area of systems biology, may be lead to biological discovery, the essential role of the biomolecular engineer is to create what has never been (e.g. a device, a computer model, or a therapeutic procedure). Scientists are primarily interesting in discovering what exists (e.g. a new organism or novel protein).

What Is Known?

The origins of biomolecular engineering arise from the development of large-scale processes to produce antibiotics during World War II. Companies began to pair chemical engineers and microbiologists to gain the integrated knowledge of process engineering and microbiology necessary to produce these new compounds. The rise of processes to produce antibiotics induced students to seek combined training

in chemical engineering and microbiology. These students became the parents of biochemical engineering.

Somewhat in parallel, chemical engineers sought to apply the basic principles of chemical engineering to human health (e.g. development of the artificial kidney). This second group worked as biomedical engineers. From the 1950s to the 1980s these activities were thought to be rather separate. In the 1980s and beyond it became increasingly apparent that common principles from molecular and cellular bioengineering were foundational to both activities. For example, in both medical and non-medical applications it became important to understand how cells responded to different surface chemistries, or how they would respond to alterations in gene number of deletion, or how fluid shear would alter cell physiology, etc. By 1990 biochemical engineering had come to mean bioprocess engineering and seemed to exclude biomedical engineering. There was a need for a new word that would recognize that common principles supporting both medical and non-medical applications at the chemical engineering and biology interface. In 1992 (as described earlier) the term biomolecular engineering was coined to include all activities at the chemical engineering and biological interface with special emphasis on the emergence of molecular and cellular biology as the common linkage independent of area of application.

Biomolecular engineering is perhaps best defined by what biomolecular engineers do. There are four activities in which those with a chemical engineering background dominate:

- Bioprocesses (biochemical reaction engineering; bioreactors with associated bioseparations). Bioprocesses produce pharmaceuticals, chemical commodies and energy products and are an integral part of waste treatment.

- Bioseparations support bioprocesses and have important medical applications such as cell separations (e.g., stem cell recovery) and proteomics (e.g., total analysis of protein content in a cell).

- Metabolic engineering is the analysis and redirection or enhancement of the metabolic activities of a cell. Chemical engineers are currently playing a leading role in this area, often for the purposes of supporting bioprocess development for more efficient production of pharmaceuticals or chemicals.

- Biocatalysis concerns the generation of protein catalysts (enzymes) with novel or enhanced activities often in unusual environments, such as at high temperature or in organic solvents. These enzymes can be used to synthesize novel chemicals.

In addition biomolecular engineers are key contributors to research activities such as:

- Drug delivery is an area in which chemical engineers have had a major impact, particularly for controlled delivery of pharmaceuticals to specific target sites (e.g., a tumor).

- Gene therapy is really metabolic engineering combined with drug delivery. The right genes need to be delivered to the desired tissues, and proteins from that gene need to be made at the right time in the right amount. The lack of success with gene therapy is, at least in part, due to the inability of medical scientists to deal with these issues of well-controlled gene delivery and gene expression. The solution lies in a quantitative analysis of the entire system.

- Biomaterials (particularly for controlled release of bioactive compounds or surface modifications to become biologically compatible or to actively direct biological activities).

- Cell and tissue engineering combines biomaterials and broad concepts from metabolic engineering and analysis of chemical signaling. The issues for manufacturing (e.g., artificial skin) are very similar to those for bioprocesses.

- Systems biology, especially to computer models of cells and to rapid separation, purification and measurement of cell components such as proteins.

- Nanobiotechnology (e.g., “lab-on-a-chip” type devices; chemical engineers have played key roles in development of these devices which are basically small-scale chemical plants).

If the reader is interested in another listing of challenges to be solved by biomolecular engineers, they are referred to the new book just released by the National

Research Council (2003) on “Beyond the Molecular Frontier: Challenges for Chemistry and Chemical Engineering”

The next section details two programs our research group has undertaken that illustrate our response to the challenges arising from the new biology-chemical engineering interface.

Examples of Biomolecular Engineering

The Minimal Cell Model

We are constructing a mathematical model of a "minimal cell" to provide a platform to better understand the "design logic" of cellular regulation. The model, which contains kinetic and thermodynamic constraints as well as stoichiometric constraints, will be used as a tool to identify the organizing principles which relate the static linear sequence information of the genome to the dynamic non-linear functioning of the cell. A minimal cell will be a prokaryote with the minimum number of genes necessary for growth and replication in an "ideal" environment (i.e. a rich medium with preformed precursors, constant temperature and pH, and at a sufficiently low cell concentration that no metabolic by-product becomes inhibitory). Kooin (2000) provides a review of the minimal cell concept.

The success of whole organism genome sequencing and high-throughput measurements provides an opportunity for system-level analysis of whole organisms or what has been termed "systems biology" e.g. (Ideker, T., et al 2001). The emphasis in our project is on modeling the complete functionality of a cell and its explicit response to perturbations in its environment (Browning & Shuler, 2001). Our attempt to generate a "complete" model that predicts time-dependent responses in a cell differentiates this project from others.

The model we are developing focuses on essential functions while finding examples of gene products that can perform those functions. While the set of minimal genes we postulate may change (for example if a new multifunctional protein is found), we believe we can find a set of truly essential functions. Further, the technical difficulties associated with generating an experimental minimal cell and the ambiguities in interpretation of comparative genomic data argue for the establishment of a theoretical computer model of a minimal cell that is explicit in regard to minimal function and includes a realistic set of gene products to accomplish these functions. This is, in essence, the primary objective of the project.

We have previously developed a “complete” cell model of *E. coli* that contains all of the functional elements for the cell to grow, divide, and respond to a wide variety of environmental perturbations. This model serves as the basis for a minimal cell model, but does not qualify as a minimal cell model for two reasons. First, it is specific to a particular species (*E. coli*). Second, chemical species are lumped into a single model component so that the dynamic function of the cell cannot be mapped directly back to the genome. Basically, the model is a good summary of the functionality required for a minimal cell, but it does not capture explicitly the physical chemistry that supports those functions. We described our first mathematical model of a single *E. coli* cell in 1979 (Shuler, et al, 1979); at the time of its publication, it was the only model of an individual cell which did not include artificially-imposed constraints on aspects such as mode of growth, timing of cell division (e.g. growth rate), and cell size. Also, it was unique in its ability to respond explicitly to concentrations of nutrients in the environment (Bailey, 1998). This base model (Domach, et al 1984) has been embellished with additional biological details to allow prediction of a wide-range of microbial responses to environmental and genetic manipulations (Shuler, 1999). The initial model included only 18 components, and most components represented large groups of related chemical species; the mathematical description of cellular function, which is the core of the model, is based on time-variant mass balances for each component. Each mass balance takes into account the component's synthesis (as a function of availability of precursors and energy, and in some cases, relevant enzymes), utilization, and degradation. Stoichiometric coefficients for relating components through mass balances were derived primarily from published research, and in some cases, from our own experiments. It is important to note that the model was not developed by using adjustable parameters to fit model predictions to experimental results, nor did the stoichiometric mass balances assume a steady state (i.e., the amount of each component was allowed to vary with time). Despite the simplifications that were made in describing cell composition and relationships, the model can accurately predict changes in cell composition, cell size, cell shape, and the timing of chromosome synthesis as a function of changes in external glucose and ammonium concentration.

While the minimal cell model differs from the *E. coli* model (primarily in that each component in the minimal cell model will be directly related to an actual component in a living cell), the *E. coli* model has been an excellent starting point from which to construct a minimal cell model. The *E. coli* model is “complete” in terms of function and is “modular”. By modular we mean that we can “delump” a pseudochemical species

into individual components while still maintaining the essential connectivity to other functions in the cell. This allows us to add detail in parallel efforts on different "modules" and then have confidence that they can be recombined into a functional and functioning whole.

We have tested the hypothesis that it is not the exact values of parameters in the model that determine function, but that the relative values to one and another is critical. We tested this hypothesis by varying all kinetic rates by a scaling factor (or kinetic ratio). The growth rate scales directly with the kinetic ratio over about two orders of magnitude. At low values of growth rate the terms for maintenance due to membrane energization become important, and these factors are not directly influenced by the kinetic ratio and the linearity is lost. Cell composition (e.g. protein/cell, RNA/cell, etc.) remains constant for a wide range of kinetic ratios. Further, relative growth rate changes for models with different kinetic ratios are essentially the same for a wide variety of perturbations to cell function. All together these findings suggest that "…a minimal cell based on a hypothetical set of properties using dimensionless parameters should provide realistic insight into cellular regulation" (Browning & Shuler, 2001).

A particularly important aspect of the original Cornell *E. coli* model was a model that mechanistically coupled cell growth, chromosome replication, and cell division. We have updated the model for control of chromosome replication based on new experimental evidence over the last 25 years. While the revised model is significantly different in terms of biological mechanism (positive vs. negative control), the mathematical characteristics are quite similar. Indeed it may be that any functional mechanism for control of replication must satisfy similar mathematical characteristics.

We have nearly completed our model for nucleotide metabolism and have demonstrated that a functional system can be achieved with significantly fewer gene-encoded functions (13) than estimated previously. This "module" has been integrated into the whole cell minimal model and the resulting cell functions in a biologically realistic manner confirming the modularity of the model. We are currently extending the model to describe other "modules" with genetic level detail.

While this project focuses on the cellular level, it is possible to build useful models of complex, multicellular organisms, including humans.

An "Animal-on-a-chip"

Our ultimate goal is construction and validation of an *in vitro* device (cell culture analog or CCA) that realistically and inexpensively mimics uptake, distribution, metabolism, and biological response of humans to exposure to various chemicals and drugs (Ghanem & Shuler, 2000). A cell culture analog (CCA) is a device that is a direct physical replica of a physiologically based pharmacokinetic (PBPK) model. A PBPK model is a mathematical model that represents the body as interconnected compartments representing the functions of selected organs or tissues. The CCA uses living cells in "organ/tissue" compartments to represent some aspects of metabolism in that organ. Coupling of a CCA and corresponding PBPK can provide insight into molecular mechanisms of toxicity. This device will impact biomedical research by providing a cost-effective, pre-clinical system to estimate human response to a wide range of drug leads and assist in risk assessment for environmental exposure to chemicals while reducing dependence on animal studies.

While our initial experiments were on macroscale systems, there are a number of advantages to greatly reducing the size of the CCA device to microscale. Our design calculations for a prototype chip system have shown that we can achieve physiologically realistic organ residence times and ratio of fluid to tissue in an "organ" compartment, and maintain fluid flow rates at values that create only physiologic values of shear stress on cells. Only by going to the dimensions of a microsystem can we attain a physiologic design. Further, the microscale reduces the cost of the device and makes effective use of expensive reagents or difficult cell cultures.

We have constructed prototype microCCAs in silicon with 3 (liver-lung-other tissue) compartments. The constraints placed on the design were: (1) it should fit on a 2cm X 2cm silicon chip; (2) the ratio of the organ compartment sizes and the liquid residence times in each compartment should be physiologically realistic; (3) each compartment should have a minimum of 10,000 cells to facilitate analysis of chemicals and enzyme activity; and (4) the hydrodynamic shear stress on the cells must be within physiologic values (2dynes/cm^2 for body cells and 6-14 dyne/cm^2 for endothelial cells). We have also extended this technology to a 4-compartment system (liver-lung-fat-other tissues). Initial studies have been done with naphthalene as the model toxicant. These studies have used two-dimensional cell cultures (i.e., monolayers) of established cell lines. The models demonstrate the production of reactive, relatively stable metabolites in the liver compartment that circulate to the lung compartment and cause preferential cell death in the

lung compartment. When a fat compartment is present the level of toxicity is reduced due to adsorption of hydrophobic compounds into the fat compartment. Further we have identified napthaquione as the toxic metabolite.

We are currently adapting this approach to evaluate chemicals for the potential usefulness as compounds to suppress multidrug resistance in cancer cells. If successful we may find chemical mixtures, including chemotherapeutic agents, that will allow treatment of cancers that currently do not respond to chemotherapy.

These two examples of work at the chemical engineering biology interface demonstrate the need for biomolecular engineers to be expert in chemical engineering with significant biological knowledge. In the next section we discuss some implications for chemical engineering education.

Implications for Chemical Engineering Education

I believe that all chemical engineers (indeed all educated citizens) should have a basic college level understanding of biology and biochemistry. Without a basic understanding of biology, chemical engineers will be excluded from certain types of jobs, particularly in the pharmaceutical and biotechnology sectors. More importantly they will be unable to understand the basis for environmental and health regulations while they are responsible to meet those standards in the operation or design of any chemical facility, whether it is biologically based or not. Further, many of the great debates in our society will arise from advances in biology (e.g. stem cell therapies). It is also important for the unity of the discipline that all chemical engineers have biology as one of the supporting sciences.

It must be recognized that learning biology is not simply a matter of new vocabulary, but also understanding a different culture. What constitutes "proof" of a concept in biology is different than the typical approach in engineering. In particular, biologists have had to make progress in the absence of a quantative theoretical framework. Thus biologists are particularly sensitive to the use of appropriate experimental controls; a concept not stressed in traditional engineering education where experiments are usually evaluated by comparison to theoretical expectations. I believe chemical engineers will become better chemical engineers as they broaden their perspective to incorporate both approaches to testing hypotheses.

As biomolecular engineering emerges all chemical engineering departments are faced with two problems: how to offer specialized education in biomolecular engineering and how to integrate biomolecular engineering into traditional courses that teach the basic principles of chemical engineering.

For those students who wish to focus on biomolecular engineering, they need not only basic biology courses, but also courses in molecular and cellular principles of biomolecular engineering, quantative analysis of physiological systems and bioprocess engineering (metabolic engineering, bioreactors, bioseparations). I believe the biggest unmet need is course material for molecular and cellular bioengineering. No textbooks are yet available to support such courses. It is material at this level that will define the intellectual foundations for biomolecular engineering.

Even students who do not intend to work in biotechnology or health are looking for inclusion of biomolecular engineering into the curriculum. The absence of biological based examples and context in textbooks is a barrier to the true integration of biology into chemical engineering. All of the chemical engineering principles can be developed in the context of biological systems. In addition to the need for modified textbooks, many chemical engineering faculty are uncomfortable with the intersection of chemical engineering and biology. While good textbooks would relieve some of the faculty anxiety, short courses specifically targeted to this issue would be helpful. Chemical Engineering as a sustainable unified discipline will require a professorate that are comfortable with biology as a core science of chemical engineering.

Chemical engineering education has undergone many changes over the last fifty years. Evolution to incorporate biology and biomolecular engineering into chemical engineering education should be a natural process. I believe that this evolution will be accomplished within less than a decade.

Concluding Thoughts

I believe that it is important to recognize that the intellectual revolution in biology provides a basis for fostering biomolecular engineering. Chemical engineers who embrace the basic concepts in biomolecular engineering are well prepared to become leaders in the field of systems biology.

In addition biomolecular engineers will continue to be leaders in bioprocess and bioreactor engineering, bioseparations, and metabolic engineering. Further biomolecular engineers will be critical in the development of the molecular and cellular aspects of

biomedical engineering. Particularly important will be opportunities in controlled drug delivery, gene therapy, tissue engineering, diagnostics (based on separations technology), and nanobiotechnology.

For the health of the chemical engineering profession, biology must be integrated into the curriculum. Chemical engineering principles should be developed throughout the curriculum in the context of biology as well as in the context of more traditional areas. Finally the academic enterprise should provide opportunities for specialization in biomolecular engineering which will require development of new courses which integrate biology and engineering in the same way chemistry and engineering were integrated at the beginning of the profession.

The opportunities and challenges to chemical engineering that arise from the biological revolution will invigorate the profession and attract students who otherwise might not select chemical engineering. Many of humankind's oldest problems may be solved by combining chemical engineering principles with opportunities emerging from the new biology.

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