The Institute of Biological Engineering

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Inside

Spring 2007 Volume 11.1

Mark Your Calendar Now
IBE 2007 Annual Meeting
March 30-April 1, 2007, St. Louis, MO

The President's Message

Dear IBE Members:

I hope that your year is going well. The IBE Council met in St. Louis Missouri on August 31st to review IBE progress and to prepare for the 2007 meeting. We had an opportunity to review the hotel and surrounding communities and we believe that you will find hotel and the St. Louis location an excellent place to network and meet with your colleagues during the 2007 Annual meeting. The meeting will be hosted in St. Louis by the University of Missouri-Columbia and local arrangements are being Shelia Grant and Mark Haidekker. The meeting dates are March 30th and April 1st, 2007. Last count we had over 80 papers and 50 poster presentations. Areas such as biology-Inspired Sensors and Biofuels and Biproducts and Biological Engineering will each have strong sessions.

The deadline for abstract submission is December 1, 2006 however this has been extended until mid-December. Please check the website or with the session chairs as to the availability of specific sessions. We hope you plan to attend and present at this meeting.

Another area where we have made progress is in the development of a Journal of Biological Engineering (JBE). Mark Riley has stepped up to the plate and indicated that he would be willing to lead the effort for the first couple of years. The journal is proposed to be an open source journal. We hope to see a number of your papers from the 2007 meeting in the Journal in the coming year, so please stay tuned.

IBE has recently negotiated for and is in the process of purchasing the url domain name "ibe.org" which will be our official and exclusive web site. Please stay tuned for more information as we increase our presence on the web and in the electronic media.

I wish to thank Art Johnson and all of the IBE members who contributed to this excellent Newsletter.

It is an honor to be a part of the leadership team of IBE, and I look forward to many great things this year as we move ahead.

Hope to see you in St. Louis !!

Vince Bralts
2006 President

Editor, Art Johnson

Professional Registration for Bio-based Engineers

The hottest item of discussion at the BMES meeting this fall was the proposal to compose a professional registration exam for Biomedical, Biological, Bio-, Biochemical, Bioprocessing, and other similar engineers. This is an issue that should be of extreme interest to IBE members. As with many other people I have talked to, I have an opinion on the matter. Accordingly, I have included two editorials that were previously published, the first from the AIMBE Newsletter (Can the Chasms Be Bridged?) and the second from the BMES Bulletin (Our Fundamental Commonality). These two put forth my position on the matter. Any written comments from the IBE membership are welcome.

Reprinted from the AIMBE News

Can the Chasms Be Bridged?

Arthur T. Johnson

Earlier this summer the Biomedical Engineering Society (BMES--an AIMBE member) received a letter from the National Council of Examiners for Engineering and Surveying (NCEES) about interest in a meeting to discuss beginning a Professional Engineers examination common to all bio-based engineers. The American Society of Agricultural and Biological Engineers (ASABE--an AIMBE member) had initiated this inquiry. Also involved was the Society for Biological Engineering (AIChE-SBE--an AIMBE member). Invited to the meeting, in addition, were the American Society of Mechanical Engineers (ASME--an AIMBE member), the Engineering in Medicine and Biology Society (IEEE-EMBS--an AIMBE member), National Institute of Ceramic Engineers, and the American Academy of Environmental Engineers. Not invited was the Institute for Biological Engineers (IBE--an AIMBE member), and other AIMBE member societies that may or may not be interested in a licensure exam).

The responses to the invitation that I have heard go something like this: it is probably a good idea to have professional registration for biological and biomedical engineers whose work relates to public health and safety, but. . .

BUT, how can we expect biomedical engineers to know about ventilation requirements of stored fruits and vegetables, how to operate a compost pile, or how to optimize a bioreactor? How can we possibly expect biomedical engineers to know about environmental toxins, biochemical extractions and enzyme kinetics?

But, how can we expect biological engineers to know about medical practice? about imaging? about bioinformatics? How can we possibly expect biological engineers to know about Markov chains, surgical techniques, and automatic cardiac defibrillators?

Well, excuse me, but aren't these the wrong questions to ask? Isn't this like asking how mechanical engineers can know all about engine design, refrigeration, and electronic controls? Isn't it true that electrical engineers can deal with energy grids, electrical motors, nanofabrication of computer chips, and communications systems? Isn't there just one PE exam for all mechanical engineers and another for all electrical engineers? Why is there no one from each of these groups questioning how everyone from their respective field could possibly take the same PE exam?

The answer, of course, is that mechanical engineers, electrical engineers, and all of the others, focus on common knowledge: that which all members are expected to know. There may be some applications-specific questions that make their way on the PE exam, but the exam is structured in such a way that anyone in that field should be able to pass as long as they have had the expected common education.

One thing is clear from sessions at the American Society for Engineering Education, from Rob Linsenmaier's Delphi studies of required BME courses, from the Whitaker Foundation educational summits, and from intersociety discussions related to biological engineering and biomedical engineering. That is that there is no fundamental agreement about core knowledge for bio-based engineering fields. Each academic program approaches education of its students in a different way. Some, especially those located close to associated medical schools with teaching hospitals, mandate that their students should spend a lot of time learning medical technology. Others require several laboratories on bioreactors and bioseparations. It occurs to me that both of these are preparing their students for particular types of careers, and only for those careers.

Perhaps the problem is that faculty members who designed and administer these programs were themselves not educated as bio-based engineers. The great advances in biology over the last few decades came during a time when their formal educations had ended. They had only enough time to learn the one small portion of biology relevant to their research area, and that constituted their view of what a bio-based engineer should know. And, then again, perhaps the problem is this and a host of other factors.

I believe that any bio-based engineer who doesn't appreciate how any living being (or system) interacts with, reacts to, and is affected by its total chemical, physical, and biological environment is not well prepared. I believe that almost any engineer can work with living things, and, most likely, produce credible products and processes involving those living things. Perhaps right away, or perhaps eventually. That doesn't make that engineer a biomedical engineer or biological engineer, or whatever.

What distinguishes a true bio-based engineer from the others, I believe, is the essential study of biology forming an intrinsic part of the foundational knowledge base of that engineer. This bio-based engineer has a biological-science based understanding at least equal to the understanding of engineering sciences.

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Biological Engineering Achieves ABET Recognition

James H. Dooley

The biological engineering profession achieved a major milestone in late October when the ABET Board of Directors, representing 28 engineering and technical societies, approved the creation of a stand-alone program criteria for the discipline of Biological Engineering. Formal recognition of biological engineering as one of the foundational engineering disciplines is the culmination of more than ten years of effort by IBE members and their peers from numerous related technical organizations.

Beginning in January 2007, undergraduate academic programs in the United States may seek ABET accreditation under the new criteria. Concurrently with the approval of the new biological engineering criteria, the ABET Board made changes to several other bio-related program criteria.

The new Biological Engineering program criteria apply to undergraduate academic programs with the name "biological," "biological systems," and similar modifiers such as "biosystems." Curricula for biological engineering programs "*must demonstrate that graduates have proficiency in mathematics through differential equations, a thorough grounding in chemistry and biology and a working knowledge of advanced biological sciences consistent with the program educational objectives. Competency must be demonstrated in the application of engineering to biological systems.*"

Central to the application of the biological engineering criteria is an understanding that the discipline is engineering applied in the context of biology as the foundational science. This interpretation parallels those of the other pure engineering disciplines of mechanical and chemical. While graduates of a biological engineering program may complete an emphasis in one of many applications, there is an expectation that students will be able to broadly apply their accumulated knowledge and design skills.

ABET broadened the scope of the Chemical Engineering criteria to include "biochemical" and "biomolecular" emphasis areas. The revised chemical engineering program criteria specifically discuss preparation of graduates to "… *design, analyze, and control physical, chemical, and biological processes…*" Chemical engineers have long been involved in the biomaterials and bioprocess industries. The ABET approved change provides increased recognition of the evolution of chemical industries to organic feedstocks and bio-based processes.

ABET narrowed the scope of Agricultural Engineering program criteria to the discipline's historic strengths in agriculture, aquaculture, forestry, and human / natural resources. Graduates of agricultural engineering programs are recognized for their ability to utilize engineering science, analysis, and design skills to protect and improve the human condition while preserving or enhancing our natural resources. The separation of Agricultural and Biological engineering program criteria may stimulate a renewed excitement about the agricultural engineering profession.

Previously approved program criteria for bioengineering and biomedical engineering were unchanged in this latest ABET Board action.

How will this affect the Institute of Biological Engineering and its members?

Over the longer term, additional engineering educational programs are likely to form under the biological engineering name, both in the United States and around the world. ABET's worldwide leadership of quality assurance and curricula development provides a level of legitimacy for the discipline that cannot be obtained otherwise. The burgeoning cadre of graduates from biological engineering programs, and others who have developed biological engineering competency later through lifelong learning, will be increasingly recognized by the public, agencies, and regulatory bodies as having a unique skill set. In time, the membership of IBE may grow, and its stature as the representative of those in the profession may justify the Institute seeking a seat on the ABET Board and leadership of the Biological Engineering program criteria.

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This bio-based engineer is equipped to deal with the vagaries of living things. This bio-based engineer is versatile and valuable and able to look ahead to a long career filled with adjustments of technology and capability. But, maybe that's just my expectations.

Apparently, the people considering the common PE exam didn't see it that way. They were apparently looking at the application more importantly than the science. They saw the divisions, but didn't see the commonality.

As long as those perceptions pervade, there will be a divide that cannot be bridged. There will be at least one group on one side of the crevass and at least one group on the other. Each group will, in turn, believe it is superior, and that the other group has no validity. The chasm will prevent common communication, and misunderstanding will prevail. It will not be apparent to either group why they want exchange with the other.

That is, until we have a bridge. We need to build a bridge.

Reprinted from the BMES Bulletin

Our Fundamental Commonality

Arthur T. Johnson

I last wrote about disunity for expectations of bio-based engineers, and decried the fact that many of us seem to assess expectations of these engineers based upon the application areas with which we are familiar. However, application areas can only define applications based engineering disciplines, not science-based engineering disciplines. If we are an engineering discipline based upon the science of biology, and I think most of us would prefer to think of ourselves that way, then we must stop thinking primarily of applications when we describe who we are.

That is not easy to do. Bio-based engineers work on problems confined to some small locus within the biological realm. They are thus experts in some particular applications areas. They think first and foremost about their areas of specialization and are not always comfortable thinking outside the confines of these little boxes. So, sticking with the familiar, they have little to say about what they may share in common with those inhabiting other little boxes.

Duane Bruley used to talk of the four basic pillars of bioengineering: physics, chemistry, mathematics, and biology. We can start there when listing those features that define bioengineering or biological engineering. Biomedical engineering tends to be focused primarily on applications in medicine and may or may not fit the construct we are about to offer.

Physics was the first pillar on the list, and we have all studied physics. Bioengineers need to know a lot about physics. They need to know about optics, mechanics, fluids, electricity, and thermodynamics. They need to know about the difference between potentials and things that flow in response to a potential. They need to know about forces, velocities, and accelerations. They need to know about mechanical strengths of different materials, stresses created in these materials, and deformations that result. They need to know about fluid pressures exerted equally in all directions, about vessel resistances, and about input/output relationships. They need to know about material diffusion, convection (advection), and osmosis. They need to know about interactions among like and unlike charges, ionic currents, and electrical hazards. They need to know about the equivalence between work and energy, the second law of thermodynamics, and energy conversions. They should know about the states of matter and how each serves a different purpose in living things. They should appreciate that the order inherent in living things requires energy to maintain that order. Further, bioengineers should know about the methods physicists used to arrive at scientific truths, their quantitative methods, and their ingenious experimentation.

Bioengineers need to know about chemistry, how chemical compounds are formed, and energy transfer among different chemicals. They should know something about chemical equilibrium and disequilibrium, and how chemicals can be used as energy-storage repositories. They should know about normal metabolic pathways and metabolic and chemical efficiencies. They should know about classes of biochemicals, general characteristics of each, and where they are normally found in living things. They should know about physical chemistry, the differences in physical attributes that accompany different chemical compositions. They should know about surface energies and bioactivity. They need to know about molecular shape effects, geometrical conformation, and the physical basis for enzyme reactions and complementary DNA formation. They should know about pH effects, and appreciate the uniqueness of carbon chemistry and water as a solvent. They should also appreciate the meaning of free energy and what it means for living things. In addition, some appreciation of the methods of chemical detection and quantification should be retained.

Bioengineers should know mathematical concepts. They should know about the basis for differential and integral calculus, and when to switch from continuum to discreteness. They should be familiar with first-and second-order responses. They should know about randomness, probability, and statistics. They should be familiar with the concept of chaos, and path-based outcomes. And, certainly, they should be aware of the differences between different modeling approaches, especially between theoretical and empirical models, and the limitations of each. Methods of mathematical manipulation should also be committed to memory.

Bioengineers should also draw knowledge from the engineering sciences. Many of these are based on physics, and won't be repeated. Others are more mathematical in nature. Information theory is one of those, and the equality between information and biological order should be appreciated. Control systems are extremely important for living things, and bioengineers should have a thorough understanding of the elements of a control system (including means of communication among elements). They should also know about redundancy, optimization, amplification techniques, sensory discrimination, and reliability. Pattern recognition is important, as is just noticeable difference.

From the science of biology come important concepts for bioengineers to know. First and foremost is the first law of biology: survival and reproduction. What should bio-based engineers know about biology? They should certainly know that form and function are related. They should be familiar with genes as information storage units, but also aware of intergenerational information transfer by cultural means (learning). They need to know about competition and selection pressures, and about necessary conditions

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High Throughput Cell Culture Process Development

by Brigitte A. Van der Haegen, M.D., Ph.D.

The development, scale up and optimization of a manufacturing process that relies on cell culture for the production of therapeutic biologicals is referred to as cell culture process development. Cells can be engineered to produce antibodies or recombinant proteins, and infected to produce viruses and vaccines. Alternatively, the final biological product might be the cultured cells per se, as during the in vitro expansion of stem and progenitor cells. Process development comprises an upstream and a downstream phase. Upstream refers to the production phase in cell culture, while downstream refers to the processing phase, i.e. the isolation and purification of the final product.

Process development associated with the production of biologicals is a low throughput operation, i.e. lengthy, labor intensive and costly. In the U.S., the market for therapeutic biologicals is estimated at $56 billion and is expected to grow at an annual rate of 12%. As a response to the increasing demand for biologicals, cell culture has undergone major improvements in process development aiming at more efficient production output. This article discusses the application of statistical design of experiment and automated microbioreactors for improved process development.

The process starts with the generation of cell clones, which are then selected for high specific productivity levels. In general, these clones are derived from established cell lines easily adaptable to culture conditions such as Chinese Hamster Ovary (CHO) and hybridoma cell lines. The selection of properly engineered cell lines for high producer clones with efficient screening techniques cannot be over emphasized. While factors such as formulation composition, feed rates and process control will affect final product yield at a later stage, these factors will not "redeem" a low producer cell line. The next stage is the development of a system for optimum growth and productivity of cells in culture. This stage includes formulation design, scale up and process control, and seeks to achieve at least one of the following purposes: High cell densities ($\geq 1 \times 10^7$ cells/ml), extended culture span ($\geq$10 days), and high production yields ($\geq$1g/L). Traditionally, cell line generation and cell culture development have been accomplished independently of each other. Molecular biologists have been mostly responsible for the former while cell culturists and process engineers have dealt with the latter. Current trends however point to the benefit of integrating these stages early during process development.

To design a formulation capable of sustaining accelerated cell growth, high cell densities and high product titers is one of the major challenges of cell culture. Often, formulations optimized for growth are not suitable for production and vice versa, leading to the use of "feeds" of different compositions throughout the process to account for the changing metabolic states. The growing trend (and challenge) to develop formulations devoid of animal-derived products, such as bovine serum, has been one of the catalysts for the introduction of statistical tools that minimize the guesswork involved in defining the nutrient requirements of cells whose metabolic needs are close to unknown.

The development of a manufacturing process involving live cells is complex. Little is known about the physiology of cells in culture and their specific interaction with the environment. The process under study can be equated to a black box providing no information of the events happening inside. Rather than trying to understand the mechanisms inside the box, focus should be on determining which factors affect the process.

As illustrated in Figure 1, the input of factors into the black box affects the response (output) at the other end. Determining which factor(s) affect specific target(s) is the essence of process development and control. Traditionally, characterization of factors and their response has been carried out with a combination of trial and error with the OFAT ("one factor at a time") approach. Trial and error is obviously time-consuming guesswork but still used by many in the field. OFAT, which is widely accepted by scientists and engineers as a valid scientific approach to experimentation, requires

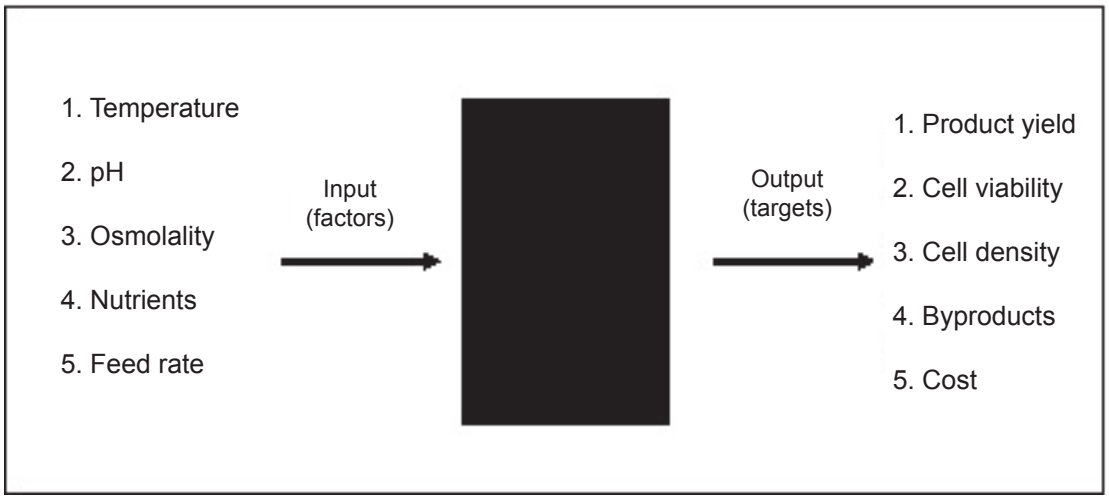

Figure 1. The Process Development Black Box.

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CELL CULTURE *continued from pg. 5*

that all factors be kept constant except for that under study. In Figure 1 for example while temperature is varied, all other factors (pH, osmolality, nutrients, and feed rate) are kept constant. OFAT also assumes that all factors have the same relevance to the process, i.e. temperature is as important as pH, which is as important as osmolality, etc. A factor that is completely irrelevant to a particular process may become critical when interacting with another factor. OFAT is bound to fail when data is subject to experimental error and factors are likely to interact. To sort through this complex maze of probabilities requires the use of statistical tools of design of experiment (DOE).

DOE can be defined as a statistical method to plan and analyze data so that the maximum amount of information is obtained with the fewest number of runs. The best way to define DOE however is to list what it does, namely (a) It screens unknown factors and select the critical ones, (b) It determines how critical factors interact and affect the process, and (c) It defines the factor settings for optimal performance. DOE is a powerful statistical tool whether used alone or in combination with automation. In fact, most automation devices such as those used in drug screening utilize some form of DOE software. Statistical methods however are only tools, not replacement for experienced professionals.

High throughput automated devices have been used in drug discovery for quite some time, allowing for drug screening at a very fast pace. Automation has recently reached the field of cell culture, in particular process development. Most cell culture high throughput devices have been used for clone and formulation screening, and are adaptations of their drug screening counterparts. Screening tests use multi-well plates containing a few milliliter of culture medium and do not reliably reproduce the environment of bioreactors. Therefore, scalability issues arise when moving to larger vessels. To minimize these issues, cell culture developmental work is carried out in culture flasks and bench top bioreactors before further scale up. This is a labor intensive, lengthy and costly operation limited by equipment availability. Thus, the advantages provided by high throughput automation are curtailed by scalability issues, while attempts to improve scalability lead to increased developmental time. To solve this predicament requires a robust scale-down model that operates with very small volumes of culture medium in an environment comparable to production bioreactors.

The SimCell™ Robotic Workstation from BioProcessors Corporation (www.bioprocessors.com) is a cell culture platform for high throughput process development. It consists of small microfluidics-based operational units called SimCell™ MicroBioreactor Arrays or MBA's (Figure 2).

Each unit harbors 6 microbioreactors with a working volume capacity of 30-500 microliters. Microbioreactors are connected to ports for sampling and feeding. Gas exchange is performed through a semi-permeable membrane, and optics system measurement for gas, pH and cell density takes place directly in the MBA's.

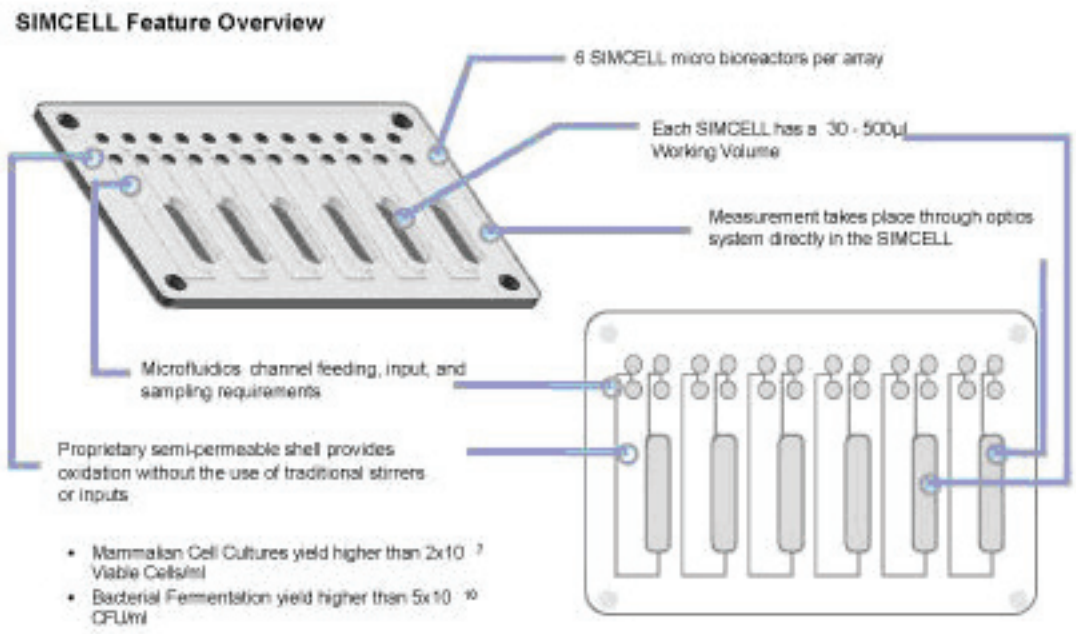

Figure 2. A SimCell™ MicroBioreactor Array (Courtesy of BioProcessors, Co).

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CELL CULTURE *continued from pg. 6*

These miniaturized bioreactors can operate in the same batch, fed batch and perfusion modes as their larger counterparts. The robotic workstation handles automatic feeding, sampling, process control, and data management. It interfaces with DOE software and can operate hundreds of microbioreactors in parallel. Validation data has consistently demonstrated high reproducibility between replicates and excellent comparability with production bioreactors. The advantages of integrating DOE with high throughput microbioreactors are obvious. Hundreds of microbioreactors can be run in parallel allowing the use of full factorial designs in replicates, eliminating the issue of equipment limitation. All phases of process development (screening, optimization and validation) can be carried out in SimCell™ microbioreactors using all modes, to determine optimal performance at the lowest possible cost. Excellent data comparability allows for trouble-free scale up resulting in reduced developmental time and cost.

In summary, the application of innovative tools such as DOE and microbioreactors results in superior handling and control over the development of cell-based production processes, transforming a laborious tasks into an efficient and automated operation.

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COMMONALITY *continued from pg. 4*

for evolution. They should appreciate the different contributions of information legacies and environmental effects on biological outcomes, including genetic expression. Lastly, biological engineers or bioengineers should be aware of the difficulty defining what life is or isn't.

I know that this list is a long one. There are many facts and concepts that I have enumerated that many would consider unnecessary. Likewise, there are others that might be added to the list. In particular, I can imagine some readers who would add a number of physiological facts to this list. But, remember, I am writing here of foundational knowledge for a science-based discipline instead of information necessary for particular applications. There are additional facts and concepts necessary for specific sub-fields, and these must be learned later, in addition to foundational knowledge.

ABET RECOGNITION *continued from pg. 3*

In the short term, IBE can continue to participate in forums, continuously improve the educational offerings and experiences of our undergraduate programs, and join with our peer technical societies to support the new ABET Biological Engineering program criteria. Our peer society, the American Society of Agricultural and Biological Engineers (ASABE), is an ABET member society and is the ABET designated lead and steward for the biological engineering program criteria. ASABE is in the process of forming a stakeholder council to include representatives from all bio-related engineering societies to cooperatively explore, discuss, and develop criteria improvements. IBE should seek a seat at the biological engineering criteria council, and actively contribute on behalf of our members.

Final Thoughts

The discipline of biological engineering probably can be traced through the millennia to the brewers and enologists who understood biology and process design to provide abundant high quality beverages. Electrobiology brought us the electrocardiograph, cauterization and other useful medical devices a century ago. Within the past five decades, advances in biological sciences, modeling and computing enabled the creation of an engineering discipline wholly based on the science of biology. Today, nearly a thousand students graduate with degrees in biological engineering in the United States each year. With their action this fall, the ABET Board of Directors, and their Engineering Accreditation Commission, launched the first stand-alone program criteria for the discipline. Program criteria are living documents, subject to continuous improvement and adaptation to contemporary contexts. IBE should be proud of the role its members played in the creation of ABET-worthy curricula and educational programs. We should look forward to an ongoing role to ensure the quality and continuous of programs around the world.

Biological Engineer at Work

by Eve Rubenstein

Jewel Davis, graduated from the Biological Resources Engineering program at the University of Maryland in 1998.

Have you always known what you wanted to do? Why did you choose Biological Engineering?

I have always known I wanted a medically related career. I knew right away that I wanted to do the biomedical track of Biological Resources Engineering. Now looking back it was not as big of a field then as it is now. Many more people I graduated were interested in the water resources and environmental side of the Biological Resources degree.

How did you go about the job searching process?
I used the many of the University of Maryland resources and kept in contact with many people I had met throughout college. I used job-searching sites, such as Monster, and found my first job with a consulting company. A short time later, I changed paths and accepted a job as an IT engineer at Air Products & Chemicals, Inc, a medical and health care manufacturing company.

Do you use what you learned in your Biological Engineering education?
I had a good background in engineering; however, the major is very broad. Not many courses offered were focused in the biomedical area. However, once I accepted my most recent job, I was trained on everything I needed to know. I did not have an in depth computer or technology background, but I was able to learn quickly since I have

What was the most beneficial part of your undergraduate studies?
The junior year curriculum, when you start focusing on more biologically related parts of engineering was probably the most beneficial part to undergraduate studies. It was near this time when most of my classmates actually decided what aspects of engineering interested them most. The senior design project was very helpful in finally putting to use everything we had learned the past four years. We spent countless hours studying the biology and calculating the physics necessary to make our project work. Getting to build the actual product was one of the best experiences as an undergrad because you could actually see a product of your work. The full exposure to the engineering design process was a very significant part to my undergraduate education.

Does it limit your career to have a B.S. degree? Do you have or want to get an advanced degree?
Yes, it is very, very limiting to have only a B.S. degree. In this upcoming field, I find it especially hard to move up in your career or obtain certain biomedical or pharmaceutical degrees without a Masters or Ph.D. I do not have an advanced degree. I am currently taking classes, but am not enrolled in a graduate program. One day I hope to go back to school and continue my education. It will be much easier to get the job you want with more education.

Did you take the fundamentals exam your last semester? Did you or are you pursing a PE certification?
I did not take the fundamentals exam. I do wish I had because it is a great attribute to have on a resume. It will really help you get a job and stay in the engineering field. You should definitely take the test during school or as soon as you can after graduations while the information is still fresh in your head. I am not pursing a PE.

Do you feel the Biological Engineering field is up to date with society, now with bioengineering being an up and coming area?
There is so much to bioengineering now. Biological Resources Engineering gives a great background and the students will be well prepared to go into work, but on-the job training in every job is where you will learn the specifics you will need to be successful.

What do you see as the most prominent up coming fields in bioengineering?
Bioinformatics and nano-technology are very prominent fields. New lab-chips and biochips are very modern technologies that are becoming of more interest to many companies. Biotechnology does not seem to be as big as it used to be, as it is breaking down into individual, more specific fields. The bio-pharmaceutical is also a continuously growing field.

Do you have any advice for up coming Biological Engineering graduates?
Stay in school. The more education you have, the more you can do with your career. Stay in the biomedical field or whichever field you want to pursue. Once you get into another area, it is very hard to come back to technical work because you have not had any relevant experience. Most biotechnology and pharmaceutical companies require an advance degree or at least 2-3 years of experience in the fields. If you are pursing a career after graduation, just continue to update your education and become familiar with new technologies. It can only help you as you continue your career.

Visualization of Genetic Circuits

Stephen Davies

An effective graphical means of depicting genetic circuits offers many advantages. Standardization facilitates efficient communication between designers and among the synthetic biology community. Abstraction permits assessment of the circuit at different levels of detail. Inclusion implies the capture of relevant effects not on the path of the main information flow of the circuit.

One may argue that useful means of describing genetic circuits already exist. There is the cartoon depiction of promoter and gene on a line with floating protein balls, arrows and deadheads indicating interactions. There's little standardization in these depictions. They quickly become unmanageable as circuit size increases. And parameter values are rarely included in these depictions.

Figure 1 is just such a depiction for one of the first engineered genetic circuits, the toggle switch [1] or more formally, Set Reset (SR) latch. This circuit maintains one of two states as when one promoter is on gene transcription leads to a protein that turns the other promoter off. Applying the corresponding inducer permits the state to change. Note that this depiction neither indicates how these products are removed nor allows one to deduce the transition dynamics.

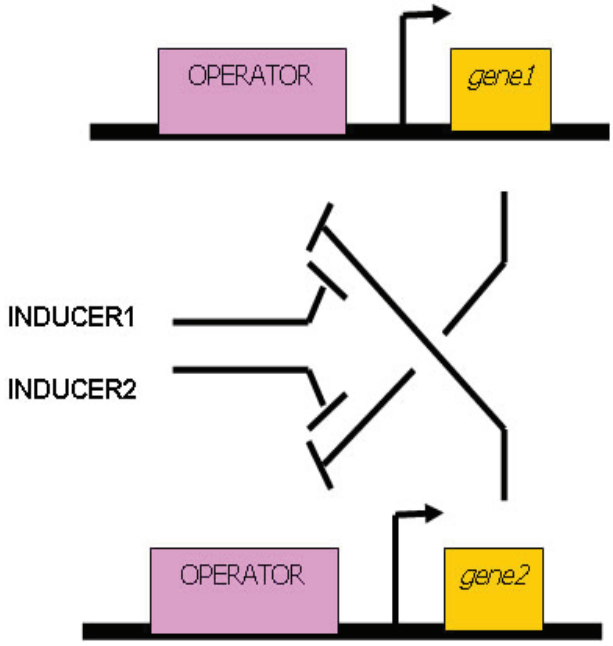

Figure 1. "Cartoon" depiction of a genetic circuit Set Rest (SR) latch.

At another level, there is the block diagram. Figure 2 shows the block diagram depiction of the SR latch of Figure 1. Here, each block provides the logic NOR function; its output may be high only when both inputs are low. When one NOR block's output is high, the feedback ensures that the other NOR block's output will be low.

This format is useful for very high-level design of mostly digital complex functions. It is virtually a direct mapping of the depictions used in digital electronics. Indeed, the lower level implementations are hidden from the designer such that the ultimate implementation could be genetic or electronic. Implicit in design at this level is that: the signals are standardized; the circuit does not load down its "power supply"; the "power" is appropriate and constant; and that there is no interference between circuit components. In the case of genetic circuits, the "power" corresponds to the supply of RNA polymerase, nucleotides, ribosomes, etc.

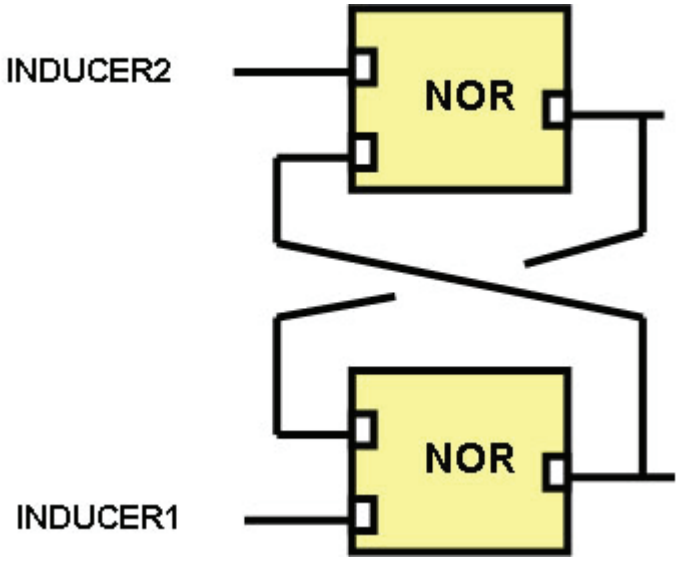

Figure 2. Block diagram for SR latch of Figure 1.

At the other extreme is the description of the genetic circuit as a complete set of chemical reactions, perhaps going so far as to form a model of the complete cell. Assuming the required parameter values are available, this yields a high fidelity model. Here the level of detail is overwhelming to the casual viewer. The big picture is hidden in the detail. In our lab, circuits with only slightly greater complexity than that of Figure 1 have required some 40 equations for their model.

In the more mature field of electronics, designers have developed a range of depictions to match the task at hand. Figure 3 illustrates three such depictions. On the left is a composite of the lithographic masks that determine the electronic components and their interconnection. This is analogous to the sequence of DNA in a genetic circuit. On the right is a high-level depiction with the blocks replaced by standardized logic symbols. In the middle is the schematic diagram. It supplies the level of detail necessary to determine dynamics and loading. Typically, component

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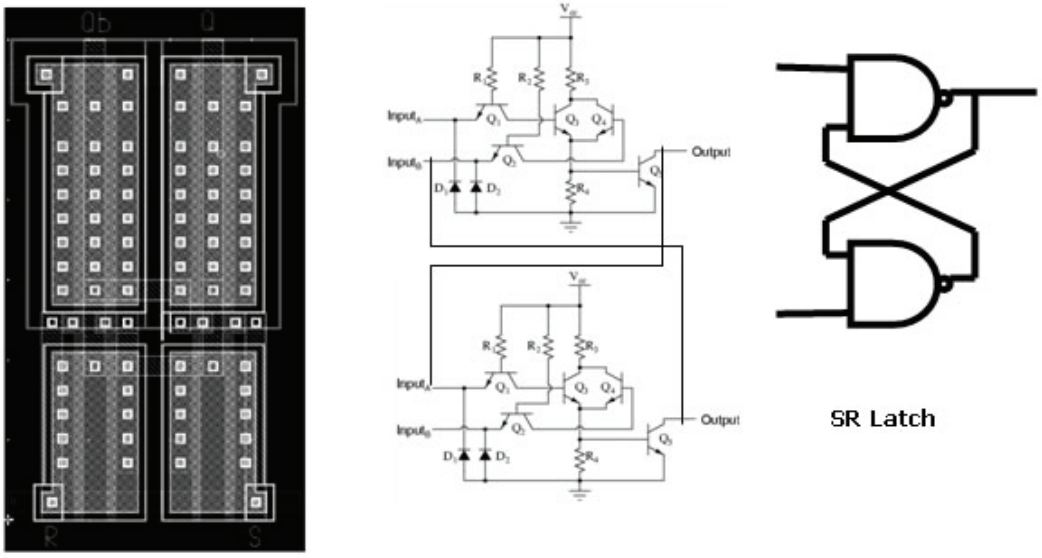

Figure 3. Three different depictions of an electronic SR latch:composite layout (left), schematic diagram (center), and, high level digital depiction.

parameter values are written beside them so that all the necessary information is available at a glance.

There is a role for a genetic circuit depiction at a level in between the block diagram and the complete chemical reaction model. At this level, signal and "power supply" effects would be considered. The depiction would allow easy extraction of dynamic parameters such as signal rise times. A scheme based on the schematic diagram of electrical circuits is proposed. It builds on our earlier work [2]. It is distinct from work that has used electrical engineering circuit simulators to efficiently model large cell networks [3]. The focus is on an effective means for the designer to organize, conceptualize and intuitively analyze his/her developing design, and to further communicate that design to the synthetic biology community.

To illustrate the idea, let us consider a simple sub-circuit where the output of one stage (promoter) controls the output of the next. At the left of Figure 4, the arrow in a circle represents a source producing protein at rate Is1. In this diagram, the analog of electrical current is rate of change in number of protein molecules.

These protein molecules accumulate in the cellular compartment. This is the same as the way charge accumulates on an electrical capacitor. The number of molecules divided by the volume (and Avogadro's number) yields protein concentration. Charge divided by capacitance is the voltage across the capacitor. Let us use protein concentration as the analog of voltage. So the compartment volume may then be represented by capacitor Cs.

Protein molecules are degraded, typically at a rate proportional to the protein concentration. This degradation is modeled by a flow of current through the resistor, Rd. Note that the value of this resistance is simply one over the degradation reaction rate constant.

With resistance and capacitance so defined in our genetic circuit, we can reap one of the benefits of this depiction. The product RC is the time constant in electric circuits and it is the same in genetic circuits. Thus knowing RC, we can say to first order how fast things change in this circuit. We gain insight into the dynamics of the system simply through seeing R, C and their values on the diagram.

Finally, we introduce the input to the second stage. Protein molecules can bind to the operator(s) of the second promoter. The bound proteins exist in equilibrium with the free proteins and in a sense they are stored at the operator sites as if there was an additional compartment. So the operators are modeled as an additional capacitance, Cop, in parallel with Cs. The net effect is to slow the dynamics of the system and the new time constant is Rd(Cs+Cop). The rate of production for this second stage, Is2, is simply a function of protein concentration, f([protein]).

One thought that occurs with respect to the difference between electric and genetic circuits is that electric current is totally generic whereas in genetic circuits we have different flows (and concentrations) for each protein. However, the first step in electric circuit analysis is to label the

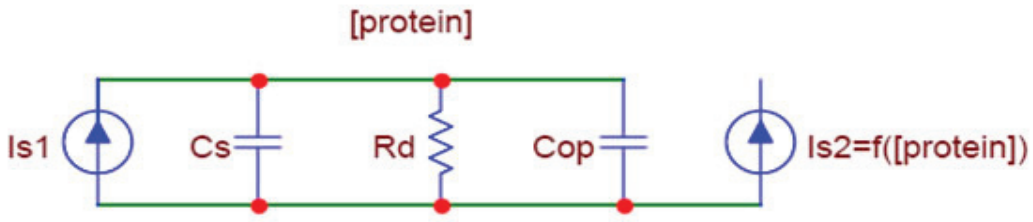

Figure 4. Genetic circuit schematic diagram.

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currents and voltages. In genetic circuits, this is automatically done by the species involved. In larger circuits, the circuit diagram will have a different node for each protein involved.

Also the depiction here is what is known as the small signal model in electronics. It can be extended to a full model by replacing the controlled sources by transistors that modulate the flow of current from a power source. This is how demand for key reagents such as NTP's, amino acids and RNA polymerases would be captured in the schematic. While its discussion is beyond the level of detail possible in this short note, we have found that such an encompassing depiction is indeed possible, effective and useful.

1) Gardiner, T.S., Cantor, C.R., Collins, J.J., "Construction of a genetic toggle switch in Escherichia coli", Nature, Vol. 403, pp. 339-342, 2000.
2) S.W. Davies, "The genetic transistor", ASM Conf. Bio-,Micro-, and Nanosystems, New York, USA, July 7-10, 2003.
3) R. Schiek E. E. May, "Examining tissue differentiation stability through large scale, multi-cellular pathway modeling", 2005 Nano Science and Technology Institute Nanotechnology Conference, Anaheim, California, USA May 2005.

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