THE FUTURE OF CHEMICAL ENGINEERING RESEARCH: BIOLOGICAL ENGINEERING

Directed Evolution in Chemical Engineering

K. Dane Wittrup
Dept. of Chemical Engineering and Division of Biological Engineering, Massachusetts Institute of Technology, MIT 66-552, Cambridge, MA 02139

Entropy, Disease, and New Opportunities for Chemical Engineering Research

Michael W. Deem
Rice University, 6100 Main Street-MS 142, Houston, TX 77005

Metabolic Engineering: Developing New Products and Processes by Constructing Functioning Biosynthetic Pathways *in vivo*

Gregory Stephanopoulos and Kyle L. Jensen
Massachusetts Institute of Technology, Dept. of Chemical Engineering 77 Massachusetts Avenue, Cambridge, MA 02137

Perspective

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K. Dane Wittrup
Dept. of Chemical Engineering and Division of Biological Engineering, Massachusetts Institute of Technology, MIT 66-552, Cambridge, MA 02139

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"*Predictions are hard to make, especially about the future.*" Niels Bohr, and Yogi Berra

A role for prediction?

Top-down exercises in research area prognostication often miss the mark. The most general predictions can be platitudinously unfalsifiable; the most specific are often amusingly wrong in retrospect. Given the primacy of investigator-initiated efforts in the successful definition and exploitation of new research areas, it is fair to question the utility of "the future of. . ." pieces, such as this one.

I well recall sitting through keynote presentations by eminent senior colleagues in the biochemical engineering field at national meetings in the late 1980s and early 1990s, the tenor of which was that the essential premise of my research program was an enormous mistake, straying too far from the hard ChE core. A particularly memorable assertion was that "It is better to be a first-rate chemical engineer than a second-rate biologist." (Fortunately these do not appear to be the only two available options.) Editorializing is an ineffective means of squelching initiative, by comparison to the ruthless efficiency of the existing marketplace of ideas. Successful research directions are determined, over a sufficient time span, by peer-reviewed funding and publication, the interest of new students, and the willingness of academia and industry to hire students trained to perform such research. If exercises such as this one are capable of serving a useful purpose, perhaps it is to constructively recognize incipient grass-roots movements and highlight exciting challenges.

Synthesis in Chemical Engineering

A shift from process to product engineering within ChE has been noted previously, and has been embraced systemically in U.S. academic departments. Synthetic capabilities are an essential tool for invention, as evidenced by numerous accomplishments of ChE researchers applying and developing synthetic tools in the fields of electronic materials, polymers, MEMS devices, and drug delivery. A new opportunity for ChE contributions beckons with the explosive growth in the development of protein biopharmaceuticals. Proteins play a central role in biological function and many pathologies. The therapeutic efficacy of a protein drug is inextricably linked to its binding properties, and consequently tools for engineering protein binding are indispensable, as well as analytical tools to properly determine biophysical design criteria.[1]

At present the most powerful and robust approach to engineering protein properties is Directed Evolution, and the field of chemical engineering has quietly gone about becoming the predominant academic home for Directed Evolution research. A cursory examination of departmental web sites reveals over 20 ChE faculty in the U.S. (most of whom began their careers in the past 15 years) whose research programs are extensively dedicated to developing or using Directed Evolution. Combinatorial polypeptide library screening consists of a series of equilibrium and/or transient biochemical transformations that are well suited to analysis with classical chemical reaction engineering tools.[2-5] Widely-practiced innovations in protein screening methodology have originated from ChE research groups.[6-8] The fundamental structure of the fitness landscape, and improved search methods for it, has been a fruitful source for interesting research problems.[9-14] A growing direction is the use of chemical engineering analyses to guide the development of optimized protein biopharmaceuticals.[1, 15-19] In terms of analytical contributions, cellular signaling pathways,[20, 21] metabolism,[22, 23] and immunology[24, 25] hold tremendous promise for chemical engineers, and these approaches are likely to contribute to rationalization of protein drug pharmacology.

Curricular development in chemical and biological engineering

There has been a significant level of angst in the ChE community with respect to the Whitaker-driven expansion of academic biomedical engineering programs, with concomitant reductions in ChE undergraduate enrollments. However, allowing the ChE curriculum to be driven by the actions of external communities is existentially unsatisfying and unlikely to be a recipe for innovation.

At the risk of Pollyanna optimism, the ChE discipline is in a very strong position on the ground with respect to biomolecular engineering. If the ChE analytical toolkit did not exist, it would be necessary to invent it in order to solve many of the problems in modern bioengineering. Critical foundations of biomolecular processes are the rates of biochemical conversions and their

K. D. Wittrup's e-mail address is wittrup@mit.edu.

equilibria, and the rates of biomolecular movement by diffusion and convection. The ChE triumvirate core of kinetics, thermo, and transport are the required tools for such analyses. Although BME curricula generally include transport coursework, BME training programs in general do not incorporate kinetics and chemistry to the extent necessary for modern biomolecular engineering.

ChE should not rest on its laurels, however; incorporating biology into the ChE curriculum is not so simple as adding a few new examples or homework problems, because there are new intellectual principles from biochemistry, biophysics, and cell biology that must be integrated throughout the toolkit. The most effective means for syllabus evolution will be to staff courses with champions dedicated to change; given the large numbers of young ChE faculty with biological interests now disseminated throughout the U.S., this is already occurring. These efforts will be amplified by the emergence of new textbooks incorporating biological principles in an integrated fashion rather than grafted onto existing outlines.

Précis and outlook

There are an extraordinary number of significant opportunities in biomedicine to engineer proteins by directed evolution.[1, 26-28] Many chemical engineers have recognized this opportunity and are exploiting it with vigor, making chemical engineering the academic center of mass for the burgeoning field of Directed Evolution.

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