Editor's Choice: Introductory Retrospective

A Tribute to Professor Jay Bailey: A Pioneer in Biochemical Engineering

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This article, and this issue of the AIChE Journal, is a tribute to Professor James (Jay) E. Bailey who, as an intellectual leader of biochemical engineering, has had a profound impact on chemical engineering. Over his 30-year career, Bailey pioneered many new approaches that have become cornerstones of modern metabolic engineering, enzyme engineering, and cell culture engineering. We highlight some of these seminal contributions as well as his legacy as a research mentor.
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Introduction

Professor James (Jay) E. Bailey was a thought leader in biochemical engineering and pioneered the development of metabolic engineering. His many contributions focused on the application of engineering principles to biological systems. One of his most long-lasting contributions is the textbook, Biochemical Engineering Fundamentals, which Jay coauthored with David Ollis. This landmark text is widely credited to have brought engineering rigor to a new field that had undergone transformational changes with the advent of recombinant DNA technology, and had a huge impact on biochemical engineering education as well as industrial biotechnology. Over his 30-year career at the University of Houston (1971–1980), the California Institute of Technology (1981–1992), and the Swiss Federal Institute of Technology (1992–2001), Jay made groundbreaking contributions in many key areas of biochemical engineering. His original ideas and approaches laid the foundations in the field of metabolic engineering, enzyme engineering, and cell culture engineering.

Metabolic Engineering

In a farsighted article written in 1991,[1] Jay Bailey defined metabolic engineering as "the improvement of cellular activities by manipulation of enzymatic, transport, and regulatory functions of the cell with the use of recombinant DNA technology." He then went on to articulate the relevance of this activity to biotechnology by emphasizing that "this capability enables construction of metabolic configurations with novel and often beneficial characteristics" in any cell that catalyzes chemical transformations of value to society.

Over the past three decades, both the toolbox and the list of success stories associated with metabolic engineering have grown beyond imagination. Virtually every chemical engineering department in the country has one or more faculty members who pursue research in this field, while training young scholars who in turn aspire to push its frontiers to new heights. Although even Jay Bailey may not have anticipated such dramatic growth from the seeds he planted, there is no question that the core value proposition of metabolic engineering to the practice of biotechnology has remained well aligned with Jay's original vision. More than anything else, this is a hallmark of a true visionary.

As we look to the future of metabolic engineering, its frontiers will likely gravitate toward more complex systems. With gene editing in humans around the corner,[2] one can anticipate that deadly metabolic diseases like Tay Sachs disease or even liver cirrhosis could be transformed into manageable conditions. At the same time, the metabolic engineer's mastery of simpler living systems could result in equally profound societal impacts. For example, engineering bacteria to convert municipal waste into biodegradable plastics via processes that can be cost-effectively operated at multiple scales could have the impact of breaking our dependence on fossil fuel-derived polyolefins.[3] And of course, to a chemical engineer what can be more appealing than harnessing metabolic engineering to transform row crops into factories capable of producing all kinds of value-added chemicals? Regardless of where the science of metabolic engineering takes us over the next decades,

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Figure 1. Four different generations of the Bailey academic family at the 2017 AIChE meeting.
[Color figure can be viewed at wileyonlinelibrary.com]

future students will be well-advised to launch their journey into this field by reading some of Jay Bailey's classic papers.

Enzyme Engineering

Jay transitioned into the field of biochemical engineering during the late 1970s and early 1980s, during which a significant part of his research focused on enzyme engineering. At that time, enzyme engineering was a different field than it has evolved into today, with its major topics including enzyme and cell immobilization, along with industrial, biomedical, and analytical applications of enzymes. It has of course since expanded to encompass the field of protein engineering, which centers on the modification of protein structure and function stemming from random or systematic changes at the genetic level and/or the *de novo* design of new enzyme active sites. It was a time of great excitement and promise for the incorporation of immobilized enzymes and cells as catalysts into industrial chemical processing, and Jay arrived on the scene with new ideas and a sophisticated outlook that remain fresh and relevant even against the modern backdrop of the field in its present, more advanced stage of development.

Jay immediately recognized important opportunities to advance the field to a higher level of scientific relevance and practical potential. Drawing from his own background and academic training in classical reaction engineering, he and his group applied rigorous mathematical analysis and modeling to account for and remove transport effects in examining the impact of immobilization on enzyme kinetics and cellular metabolism.[4,5] Determination of intrinsic enzyme activity and cell productivity was combined with advanced physicochemical methods, and analyses of system heterogeneity, to elucidate immobilized enzyme structure-function relationships and immobilized cell behavior with a level of accuracy and molecular detail that stands out even today.

As Jay's research expanded to encompass many other aspects of biochemical engineering, including the new frontier of metabolic engineering, there was a marked shift in his program away from heterogeneous biocatalysis. However, his work in this area remains timely, and foreshadowed his approach to the study and development of metabolically engineered cells, as well as other complex systems that fell within Jay's expanding repertoire. Thus, not only did enzyme engineering provide a logical and opportune entry for Jay into a field he would change forever, it also benefited from the same striking creativity, scientific rigor, exacting standards, and infectious enthusiasm that Jay brought to everything he did throughout his career.

Cell Culture Engineering and Advance Analytical Techniques

The use of CHO cell technology for biopharmaceutical production was first demonstrated by the approval of human tissue plasminogen activator in 1986. This excitement generated significant interest within the biochemical engineering community to further a fundamental understanding of CHO cell biology and biotechnology. Unlike most initial efforts, Jay was one of the first biochemical engineers to embrace the power of molecular biology for investigating the cellular impact of recombinant protein production on CHO cell cultures. Those early insights into how gene dosage affected cell productivity have led to genetic strategies for enhancing the overall product yield.[6] For example, the use of cyclins to prolong cell proliferation and cell productivity is an idea that remains highly relevant even today.[7]

Jay and his students also pioneered the engineering of CHO glycosylation via the coordinated up- and down-regulation of glycosyltransferases. Drawing from his expertise in metabolic engineering, Jay quickly recognized the importance of recruiting foreign transferases into CHO cells to create new and more desirable glycoforms. Using this new framework, his group

generated a chimeric IgG1 with substantial antibody-dependent cellular cytotoxicity suitable for neuroblastoma treatment.[8] This initial breakthrough created the foundation for the formation of a new company, Roche Glycart AG, one of the world's leading glycoengineeirng companies, focusing on engineering new antibodies with the desirable glycoforms. Jay's far-reaching impact in this area is another example of his creativity and ability to inspire students during his career.

In addition to cellular engineering, Jay made significant contributions to developing new methods for probing cell function. For example, he adapted emerging capabilities of high-field nuclear magnetic resonance to probe metabolism *in situ.*[9] His research group went on to further improve the scope of this method for metabolic analysis by implementing ^{13}C tracer labeling techniques.[10] This approach remains one of the most widely used methods for estimating metabolic fluxes noninvasively, and parallels Jay's many other insightful contributions in metabolic engineering and enzyme engineering.

Long-Lasting Legacy as a Mentor

Perhaps the greatest aspect of Jay's legacy is represented by the 100+ doctoral and postdoctoral trainees he mentored over his 30-year career. His passion in fostering their independence, creativity, and research ambition continues to influence biochemical engineering, as many of them have had successful careers in industry and academia, thus extending Jay's heritage to a new generation (Figure 1).

Literature Cited

1. Bailey J. Toward a science of metabolic engineering. *Science*. 1991; 252:1668-1675.
2. Ma H, Marti-Gutierrez N, Park SW, et al. Correction of a pathogenic gene mutation in human embryos. *Nature*. 2017;548:413.
3. Anderson LA, Islam MA, Prather KLJ. Synthetic biology strategies for improving microbial synthesis of "green" biopolymers. *J Biol Chem*. 2018;293:5053-5061.
4. Clark DS, Bailey JE. Structure-function relationships in immobilized chymotrypsin catalysis. *Biotechnol Bioeng*. 1983;25:1027-1047.
5. Doran PM, Bailey JE. Effects of immobilization on growth, fermentation properties, and macromolecular composition of *Saccharomyces cerevisiae* attached to gelatin. *Biotechnol Bioeng*. 1986;28:73-87.
6. Pendse GJ, Karkare S, Bailey JE. Effect of cloned gene dosage on cell-growth and hepatitis-B surface-antigen synthesis and secretion in recombinant CHO cells. *Biotechnol Bioeng*. 1992;40:119-129.
7. Renner WA, Lee KH, Hatzimanikatis V, Bailey JE, Eppenberger HM. Recombinant cyclin E expression activates proliferation and obviates surface attachment of Chinese hamster ovary (CHO) cells in protein-free medium. *Biotechnol Bioeng*. 1995;47:476-482.
8. Umaña P, Jean–Mairet J, Moudry R, Amstutz H, Bailey JE. Engineered glycoforms of an antineuroblastoma IgG1 with optimized antibody-dependent cellular cytotoxic activity. *Nat Biotechnol*. 1999; 17:176.
9. Pendse GJ, Riedy G, Bailey JE. NMR spectroscopy of recombinant Chinese hamster ovary (CHO) cells in a packed bed reactor. *Biotechnol Tech*. 1991;5:193-198.
10. Fiaux J, Andersson CIJ, Holmberg N, et al. ^{13}C NMR flux ratio analysis of *Escherichia coli* central carbon metabolism in microaerobic bioprocesses. *J Am Chem Soc*. 1999;121:1407-1408.

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