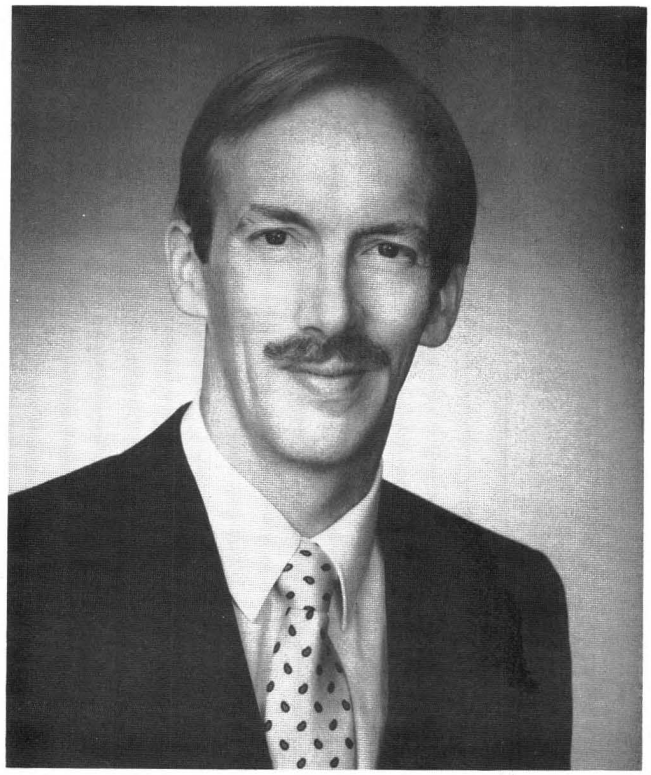
ChE educator

JAMES E. BAILEY

of Caltech

ROBERT FINN
California Institute of Technology
Pasadena, CA 91125



HIS COLLEAGUES describe James E. (Jay) Bailey as a man open to new ideas. Trained as a classical chemical engineer (Bailey did his doctoral work on chemical reactor theory, optimization theory, and nonlinear mathematics) he soon developed an interest in the relatively young field of biochemical engineering. Lately, Jay has turned even more biological in his approach, pioneering a brand new field he calls metabolic engineering. His graduate students, who have joined in this odyssey, are well prepared to combine the techniques of molecular biology with more traditional engineering methods in the chemical engineering problem-solving armamentarium.

Jay ascribes many of the twists and turns of this intellectual odyssey to fortunate encounters with bright students and interesting colleagues. One of these chance encounters took place at the University of Houston in 1972 when Jay, then on the UH faculty, happened to meet biochemical engineer David Ollis. (Ollis was at Princeton University at that time; he is now Distinguished Professor of Chemical Engineering at North Carolina State University.) As Jay recalls it, "I was really impressed by the breadth of Dave's knowledge in biochemical engineering. I didn't know what a protein was in those days, but after a 30-minute conversation and a couple of phone calls, we decided to write a textbook."

The result was *Biochemical Engineering Fundamentals*, which has by now become the required text in almost every biochemical engineering course in the United States and in much of the rest of the world. It is now in its second edition. "Writing the first edition of this text was a tremendous learning experience," Jay recalls. "I didn't know much biochemistry, microbiology, or biochemical engineering at that time. I read texts and review articles, and I went to Elmer Gaden's short course. All this convinced me that we had to emphasize the background material in biochemistry, physiology, and genetics that differentiates biochemical engineering from chemical engineering. A lot of other texts assume that you know what a protein is, what a bacterium is, what a gene is. We decided to define those terms, and others, very explicitly. I think that my entry into the field as a beginner made the text suitable for other beginners. The second edition, prepared after I had been heavily involved in biochemical engineering research for more than a decade, provided an opportunity to inject some personal perspectives into the text, in addition to improving its organization and updating its content."

Jay's own education as a chemical engineer was typical enough. He did both his undergraduate and graduate work at Rice University, earning his doctorate working on reactor theory and optimization with Fritz Horn. After a two-year stint with Shell Development in Emeryville, California, Jay established his own laboratory in the Department of Chemical Engineering at the University of Houston. It was there that he first let himself be nudged in the direction of biochemical engineering.

"In the late 1960s and the early 1970s, the National Science Foundation sponsored a major effort in en-

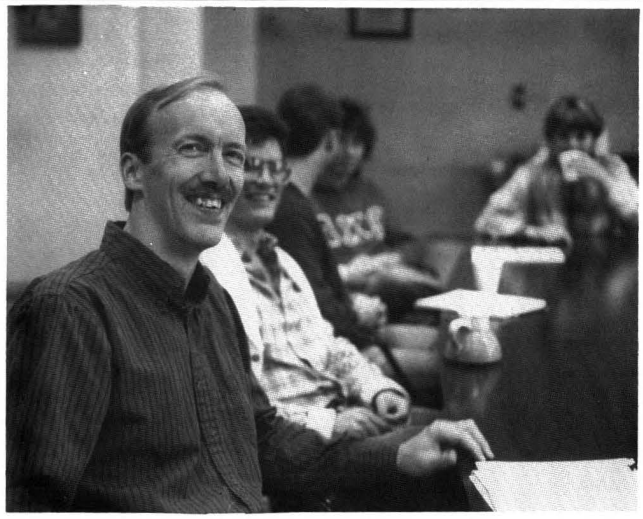
Trained as a classical chemical engineer, [Jay] soon developed an interest in the relatively young field of biochemical engineering. Lately, he has turned even more biological in his approach, pioneering a brand new field he calls metabolic engineering. His graduate students, who have joined in this odyssey . . . combine the techniques of molecular biology with more traditional engineering methods . . .

zyme engineering," Jay notes. "I was doing computational and theoretical work on immobilized enzyme catalysis and on some diffusion-reaction problems with unusual properties. Two of my graduate students at UH had interesting backgrounds—Mike Cho had a background in biochemistry, and Jila Fazel-Madjlessi had a background in microbial fermentation. They helped me start experimental programs in those areas."

With Cho, for example, Bailey made major theoretical and practical advances in the area of immobilized enzymes. Their work involved the first application of the carbodiimide-mediated covalent attachment of enzymes to activated carbon. Using this approach they constructed hybrid catalysts that combined an enzyme's activity with the catalytic action of the support surface. Specifically, they looked at the oxidation of glucose by the enzyme glucose oxidase. A byproduct of this reaction is hydrogen peroxide, which tends to deactivate the enzyme. Bailey and Cho discovered that activated carbon decomposes the peroxide and also assists in the supply of oxygen to the enzyme sites within the porous catalyst. They also discovered, however, that loading too much enzyme onto the support compromises its efficiency in deactivating peroxide, and they were able to characterize the tradeoff between higher enzyme loading and peroxide decomposition in some detail.

Jay's experimental work on immobilized enzymes continues to this day. One of his most significant discoveries was accomplished in collaboration with Ph.D. student Doug Clark (now an assistant professor and NSF Presidential Young Investigator at the University of California, Berkeley). Clark and Bailey combined classical activity studies with electron paramagnetic spin resonance measurements of spin-labeled immobilized enzymes. Using this technique, they were able to establish direct evidence of active site modification caused by immobilization and to show the relationship between the degree of modification and the activity of the enzyme.

Bailey's collaboration with Clark characterizes Jay's philosophy of graduate education. He firmly believes that graduate students should participate heavily in their research projects and in formulating strategies for solving their problems. He observes, "Graduate students are here to learn how to do research—not just how to do experiments or calculations, but how to identify a particular problem within an important general area. I encourage them to consider the method of accomplishing a solution and its feasibility as well as the ultimate impact that the solution will have. Besides, since I've been fortunate to work with many excellent students, it would be foolish of me to presume that I have all the necessary ideas and knowledge. I depend on my students to contribute substantially to all aspects of their projects. On many occasions, including Doug Clark's work, my students have transformed my vague suggestions into highly original and productive research."



Jay enjoys weekly group seminars to discuss progress and problems in the lab.

Jay's work on periodic processes and biochemical engineering during nine years on the faculty of the University of Houston was recognized in 1979 by the Allan P. Colburn Award of the American Institute of Chemical Engineers. He came to Caltech in 1980. According to John Seinfeld, a close friend of Bailey's and Caltech's Louis E. Nohl Professor and Professor of Chemical Engineering, "I first met Jay about twelve years ago at an AIChE meeting and we became friends. Around 1979 I realized that Jay might consider moving. He was quickly establishing himself as one of the leading people in biochemical engineering in the United States."

Jay has been good for Caltech, and the intimacy and informality of the Caltech environment have apparently been very good for him as well. "The biggest qualitative change in my work came after I arrived at Caltech. Here my students and I can learn from and

interact with some of the top people in biochemistry, molecular biology, and cell biology, not to mention chemical engineering. Cross-disciplinary collaboration happens almost automatically at Caltech."

It was at Caltech that the techniques of genetic engineering began influencing Jay's work. The revolution in recombinant DNA technology that began in the late 1970s has been widely seen as the biologist's show. But Bailey realized that if these techniques were to realize their commercial potential, chemical engineers would have to get intimately involved.

He also realized that modeling concepts from traditional chemical reaction engineering could be effectively applied in a new context—viewing a single cell

A sophisticated flow cytometer-cell sorter, here operated by Dane Wittrup and Elaine Meilhoc, has supported many PhD projects in Bailey's laboratory.

as a complex chemical reactor and transport apparatus. Working in Jay's group, Sun Bok Lee (now at the Korea Advanced Institute for Science and Technology) and Steve Peretti (currently an assistant professor at North Carolina State University) formulated powerful new mathematical models that included genetic level regulation.

Another consequence of Jay's interest in genetic engineering was his collaboration with Caltech's Judith Campbell, associate professor of chemistry and biology, who studies basic mechanisms of DNA replication in yeast. Genetic engineers often use the technique of inserting recombinant "plasmids" into yeast cells to get them to produce desired proteins in quantity. Plasmids are relatively small, circular segments of DNA that contain regulatory genes and genes that code for proteins. There is one important problem with foreign plasmids, however: As the recombinant yeast cells divide, they tend to lose their plasmids generation by generation, gradually becoming less and less productive.

Bailey and Campbell have made a concerted effort to understand this process using flow cytometry measurements to provide unprecedented detail on single-cell plasmid content in recombinant populations. In flow cytometry individual cells are sent past a laser beam, one by one, but very rapidly. In a process that takes about one millisecond per cell, flow cytometry permits determinations of cell size, shape, internal structure, and the concentration of specific compounds in individual cells. Many graduate students and postdoctoral fellows have contributed to a growing body of flow cytometry research in Jay's lab, and several of these collaborators, including Friedrich Srienc at Minnesota and Jin-Ho Seo at Purdue, are now extending these methods in their research labs.

Some of Jay's work in progress involves sharpening the focus of the genetic engineering studies to more subtle and interesting problems. For example, he's gotten interested in the details of what exactly happens to a protein after synthesis. There are essentially three possibilities: The protein can be degraded, it can be exported from the cell, or it can remain in the cell in solution or in an aggregate. If genetic engineering is to fulfil its economic promise, these alternatives must be understood and the factors that control protein targeting must be better characterized in quantitative terms.

Typically, genetic engineers concern themselves with attempts to make cells produce certain proteins in quantity. But chemical engineers are well aware of the fact that proteins are not the only compounds of economic importance made by cells. Realizing this, Jay's group is concentrating on a brand new field that Jay calls metabolic engineering. "Metabolic engineering involves the application of genetic engineering techniques to alter or enhance the metabolism of cells," Jay explains. "The goal is to overproduce specific amino acids, acetone, vitamins, certain biopolymers, or other important chemicals made in cells. Metabolic engineering requires a lot better understanding of what a cell is doing.

"First, we must understand all the pathways available to an organism for producing the target compound and determine what additional pathways we could make possible by introducing new enzyme activities into that organism. Then, it's important to judge which regulatory points along the pathway are most important, since these determine the rate and the selectivity for the target compound. After determining the most promising target enzymes, we must clone the gene for that enzyme, attach the gene to a suitable vector, and insert it into the organism. Then, of course, we must investigate the effects of our genetic manipulations on the production of the target compound and its intermediates."

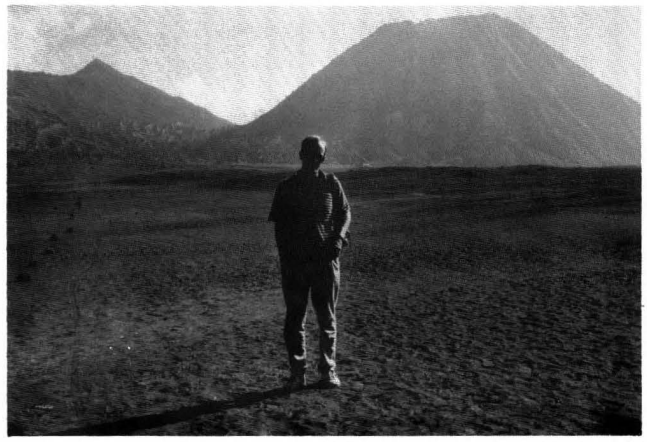
Jay's group has made significant advances in all

steps of this process. In terms of understanding metabolic pathways in detail, Alex Seressiotis, a former student of his who's now at Columbia University, developed a computer program called MPS (Metabolic Pathway Synthesis). The program contains a database system that stores enzyme and substance descriptions. "MPS can be used on a qualitative basis to examine the effects of adding or deleting enzyme activities to or from the cellular environment, to classify pathways with respect to cellular objectives, and to extract information about metabolic regulation," Jay says. In an illustration of the power of MPS, Seressiotis and Bailey had it consider the conversion of pyruvate to the amino acid L-alanine. MPS came up with a route to L-alanine that does not incorporate the enzyme alanine aminotransferase, which is commonly assumed to be a required step for alanine biosynthesis.

Jay's lab has the distinction of being one of the first chemical engineering labs in the world with full cloning facilities. "The traditional way of producing strains of an organism with desired properties was to use a mutagenesis program," notes Bailey. This involves exposing the cells to radiation or other mutagens and assaying the resulting organisms for the property in question. "But this is a very random, time consuming, and sloppy technique. By using recombinant DNA technology we can make the whole process far more rational. Furthermore, students with cloning experience are more equipped to consider genetic as well as process solutions to engineering problems. And they'll be far better prepared to interact productively with molecular biologists in the future."

To investigate the effects of genetic manipulations made in his lab, Jay's group has recently developed novel data analysis methods for use with his new, 300 megahertz, wide-bore NMR. These methods allow important measurements to be accomplished simultaneously from a group of living cells. In a single experiment, Jay's students can estimate intracellular *p*H, the concentration of several key sugar phosphate metabolic intermediates, and the concentrations of adenosine di- and triphosphate (ADP and ATP).

At present, Bailey's lab is working on three projects in metabolic engineering. In the first of these projects, the lab is attempting to enhance the uptake of the sugar hexose in the yeast *Saccharomyces cerevisiae*. Hexose uptake is the rate-limiting step for growth in this economically important organism, which is used for ethanol production and in the genetically engineered production of other compounds. The second project involves engineering the bacterium *Escherichia coli* to produce ethanol by inserting genes



Jay explored the crater of Mt. Bromo in Java, Indonesia, in April 1987.

for pyruvate decarboxylase and alcohol dehydrogenase. In a third project, the group is trying to improve production of ATP (the cell's energy currency) in *E. coli*.

Not all chemical engineers agree with the direction Bailey's research has taken. According to John Seinfeld, there are still a few diehards out there who express skepticism about chemical engineers who get involved with essentially biological techniques. But, Seinfeld says, there are fewer and fewer naysayers. "I think biochemical engineering is going to mature. People are recognizing that it will take its place as a firm field in chemical engineering and, in a sense, settle down. It is difficult for biochemical engineering to be as rigorous as some other fields of chemical engineering that are closer to physics. That level of rigor is being supplied by people like Jay Bailey. There will be more biology in the education of future chemical engineers as a result of his work."

The education of chemical engineers is a subject that's important to Bailey. He's particularly proud of the fact that many of his former graduate students have become faculty members at important universities around the world. Frances Arnold, assistant professor of chemical engineering at Caltech and Bailey's wife says, "Jay takes a personal interest in each of his students. He's always willing to sit down with them and tell them the 'facts of life' of the chemical engineering profession. His students show a lot of loyalty as a result of his interest in them."

Important institutions to Jay's group of students and postdocs are Friday afternoon group seminars and, following that, the traditional "Ho-Ho" in the Rathskeller of the Athenaeum, Caltech's faculty club. "Gathering outside the lab for conversation and a few

Continued on page 102.

Simulation—An Introduction, 2nd Ed., Ulrich's Bookstore, Ann Arbor, MI, 1977.
3. Clark, J. P., and J. T. Sommerfeld, "Use of FLOWTRAN Simulation in Education," *Chem. Eng. Ed.*, **10**, No. 2, 90 (1976).
4. Schriber, T. J., *Simulation Using GPSS*, Wiley, New York, 1974.
5. Franta, W. R., *The Process View of Simulation*, Elsevier North-Holland, New York, 1977.
6. Wyman, F. P., *Simulation Modeling: A Guide to Using SIMSCRIPT*, Wiley, New York, 1970.
7. Morris, R. C., "Simulating Batch Processes," *Chem. Eng.*, **90**, No. 10, 77 (1983).
8. Blaylock, C. R., C. O. Morgan, and J. T. Sommerfeld, "GPSS Simulation of DDT Manufacture," *Proc. 14th IASTED Intl. Conf. on Appl. Sim. and Mod.*, Vancouver, June, 1986, p. 314.
9. Passariello, I., and J. T. Sommerfeld, "GPSS Simulation of Chocolate Manufacturing" in *Tools for the Simulation Profession*, Soc. for Computer Simulation, San Diego, 1987, p. 1.
10. Barnette, D. T., and J. T. Sommerfeld, "Discrete-Event Simulation of a Sequence of Multi-Component Batch Distillation Columns," *Comp. & Chem. Eng.*, **11**, 395 (1987).
11. Kenvin, J. C., and J. T. Sommerfeld, "Discrete-Event Simulation of Large-Scale Poliomyelitis Vaccine Production," *Process Biochem.*, **22**, 74 (1987).
12. Bales, W. J., J. R. Johnson, and J. T. Sommerfeld, "Use of a Queuing Simulator in Design of a Batch Chemical Production System," *Prodn. and Inventory Mgmt.*, accepted for publication (1987).
13. Adebekun, A. K., Z. Q. Song, and J. T. Sommerfeld, "GPSS Simulation of PVC Manufacture," *Polymer Process Eng.*, **5**, 145 (1987).
14. Glenn, S. L., R. T. Norris, Jr., and J. T. Sommerfeld, "Discrete-Event Simulation of Sequencing Batch Reactors (SBR) for Wastewater Treatment," *J. Water Poll. Cont. Fedn.*, submitted for publication (1987). □

ENTROPY

Continued from page 97.

Zenzen, *The Nature of Irreversibility*, D. Reidel Pub. Co., Dordrecht, Holland, 1985.
9. Teilhard de Chardin, P., *The Phenomenon of Man*, Harper and Row, New York, 1975. A good summary of Teilhard's arguments is presented in Barrow, J. D. and F. J. Tipler, *The Anthropic Cosmological Principle*, Ch. 3, Clarendon Press, Oxford, 1986.
10. Adams, Henry, *The Degradation of Democratic Dogma*, Reprint of the 1919 ed., Harper Torchbooks, New York, 1969.
11. Levi-Strauss, C., *Tristes Tropiques*, translated by J. and D. Weightman, Jonathan Cape, London, 1973.
12. Georgescu-Roegen, N., *The Entropy Law and the Economic Process*, Harvard University Press, Cambridge, 1971.
13. Daly, Herman E., *Steady-State Economics*, W. H. Freeman & Co., San Francisco, 1977.
14. Rifkin, J., *Entropy: A New World View*, Bantam Books, New York, 1980.
15. Tanner, Tony, *City of Words*, Chap. 6, Harper and Row, New York, 1971, and Lewicki, Zbigniew, *The Bang and the Whimper*, Greenwood Press, Westport, CT., 1984.
16. Greenland, Colin, *The Entropy Exhibition*, Routledge and Kegan Paul, London, 1983.
17. Wiener, Norbert, *Human Use of Human Beings*, Houghton-Mifflin, Boston, 1950.
18. Whether entropy can be linked to the information in a message is still an undecided question. The views of Brillouin and the Denbighs typify the pro and con, respectively. Brillouin, L., *Scientific Uncertainty and Information*, Academic Press, New York, 1964. Denbigh, K. G. and J. S. Denbigh, *Entropy in Relation to Incomplete Knowledge*, Cambridge University Press, Cambridge, 1985.
19. Arnheim, Rudolf, *Entropy and Art*, University of California Press, Berkeley, 1971.
20. de Santillana, G., and H. von Dechend, *Hamlet's Mill*, Gambit Inc., Boston, 1969.
21. Romans 8:21.
22. For lucid and concise discussion of the philosophical problem of time, see Denbigh, K. G., *Three Concepts of Time*, Springer-Verlag, Berlin, 1981.
23. Whorf, B. L., *Language, Thought and Reality*, M.I.T. Press, Cambridge, 1956.
24. See, for example, Capra, F., *The Tao of Physics*, Bantam Books, New York, 1975.
25. Both the external and internal views are discussed by Morris Kline in *Mathematics and the Search for Knowledge*, Oxford University Press, Oxford, 1985. The internal view is examined by Roger S. Jones in *Physics as Metaphor*, New American Library, New York, 1982. □

EDUCATOR: Bailey

Continued from page 61.

pitchers helps my students know each other better," Jay notes. "It also helps me maintain a friendly and open relationship with my group that's important in our work together."

Research by Bailey and his students was recognized by the Curtis W. McGraw Research Award of the American Society of Engineering Education in 1983, by Jay's election to the National Academy of Engineering in 1986, and by the AIChE Professional Progress Award in 1987.

Bailey does have interests outside of the lab. Everyone who knows him remarks on his devotion to Sean, his 18-year-old son, who's now a freshman at the University of Colorado, Boulder. Jay's an avid amateur musician—the guitar is his instrument—and he loves active sports such as tennis, racquetball, and bicycling. He and Arnold also love to travel. Says Bailey, "We went to Malaysia and Indonesia last summer and just wandered around for four weeks for absolutely no professional reason whatsoever. It was wonderful."

Frances Arnold sums up Jay Bailey's influence on his profession in the following way, "Jay stands out in the field as a pioneer in new techniques in the 8,000-year-old discipline of biochemical engineering. You won't find many new products coming out of his lab, but you will find many new ideas." □