flux analysis. General principles applied for particular bioreactors models are included in the second part. The book concludes with examples of modeling selected processes of industrial importance. The general models are applied to describe the kinetics and control strategies in the production of baker's yeast, beer, lactic acid, recombinant proteins and β-lactam antibiotics. The last section includes some applications for metabolic flux analysis and metabolic design for yeast, bacterial and mammalian cells.

The book introduces the methods used in the various stages of designing industrial processes. It offers an overview of the different types of biological models at various levels of complexity, beginning with simple formal-kinetic models over structured models, and moving on to segregated population models. Improvements in understanding cellular metabolism are well illustrated using current methods for flux quantification, and the book introduces several existing techniques, such as metabolic balancing and isotopic labeling combined with NMR spectroscopy methods. The importance of the accuracy and reliability of measured data for process modeling and control is carefully discussed in the text. Also, an introduction to automatic control for optimizing production efficiency and the design of adaptive linearizing control of bioprocesses are adequately outlined.

The physiological state of microorganisms and their behavior is intimately bound to the mixing effects and the transport effects in bioreactors. The application of various approaches to bioreactor modeling is outlined, covering the computational fluid-dynamic technique, stirred tank and bubble column bioreactor with results good enough to serve as basic reactor models.

The book is well written, well structured and easy to read and contains relevant references. This is a useful book that gives a good global view of the modeling and control of bioprocesses. It is highly recommended for anyone who wants to know the most important current and future perspectives in bioreaction engineering.

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Profile

Profile – Richard A. Mathies

Richard A. Mathies (Fig. 1) is a professor of chemistry at the University of California (UC) at Berkeley. His early work at UC was on the use of resonance Raman and time-resolved optical spectroscopy to elucidate the structure and reaction dynamics of energy and information-transducing photoactive proteins called rhodopsins. His work on the Human Genome Project led to the development of high-throughput platform technologies including capillary array electrophoresis and energy transfer fluorescent dye labels for DNA sequencing and analysis. He has also pioneered the development of microfabricated capillary electrophoresis devices, capillary array electrophoresis microplates and microfabriated integrated sample preparation and detection methods. He is the co-founder of the Center for Analytical Biotechnology at UC Berkeley. Mathies was interviewed at the BIOMEMS and Biomedical Nanotechnology conference in Columbus, Ohio, 21–25 September 2001, where he gave a talk about capillary array electrophoresis-based microprocessors. Such devices could be used as point-of-care clinical and genetic analyzers, in integrated microfluidic sequencing chips and in DNA-based computing.

Who awarded your first grant and what was it for?
My first award was an NIH grant to examine the molecular basis of visual excitation in rhodopsin using resonance Raman spectroscopy. This basic science project led to our development of high-sensitivity confocal detection systems as well as a better understanding of the fundamental detection limits imposed by photodestruction. These new understandings provided the underpinning for our work applying high sensitivity confocal fluorescence scanning to DNA sequencing and diagnostics.

Fig. 1. Prof. Richard A. Mathies. (Photograph courtesy of The Mathies Lab.)

What is the biggest obstacle or challenge in the field?
There are social as well as technical issues to be overcome. On the technical side, the big challenge is the integration of the plethora of microfluidic technologies that have been developed into robust analysis systems. Although this challenge is significant, I think that great progress will be made on the integration issue in the next five years. On the more challenging social side we must address the ethical, legal and social issues that will arise from the wide application of microfluidic technologies. Microtechnologies such as point-of-care genetic analysis and portable forensic analyzers raise issues about privacy, insurance discrimination and so on. Also, the Human Genome Project is often erroneously associated in the press with human cloning technology thereby raising concerns among the public. The difficult legal and legislative issues need to be resolved and the public needs to be educated about what these new measurements and technologies mean and what they don't mean. Education will also be important in the medical community; doctors need to understand and trust the new technology before they can advise and inform their

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patients about it. Educational issues could take up to 10 years or more to resolve so this is a big obstacle in getting our microfluidic analysis devices into everyday use.

Is bioinformatics a bottleneck for this research community?

To a certain extent, informatics is always an issue but much of the necessary groundwork has been driven by the genome project so this is not rate determining for the development of current micro- and nanofluidic technologies. The big issue will occur at a later date when vast databases of genetic and medical information must be interrogated in the context of personalized molecular medicine enabled by microfluidic technologies.

Do you intend to patent your findings or keep them in the public domain?

The recent explosion of work on the development of micro- and nanofluidics technologies has been driven in part by the ability of companies to obtain or license patents, secure funding and develop products. However, as this field develops I think that the approach to intellectual property will have to change from the current climate where the focus is on blocking patents and litigation. Like the microelectronics industry, micro- and nanofluidics will advance more rapidly if the intellectual property paradigm is altered to emphasize nonexclusive or cross licensing. In this alternative model, success is driven by the development of better products and time to market. This is better for the field and for the consumer.

Who has most inspired your work?

Star Trek! This show emphasizes the idea that 'anything can be done'. Microfluidics technologies are so new that many clever things have not yet been done and rapid exponential advancement of the field continues. Do it!

What are your scientific plans over the next five years?

One of the critical goals will be to capitalise on the technology we have developed thus far – to develop prototypes of fully integrated analysis devices. There are two or three different areas of application. My approach is to pick a provocative target and pursue that as a way of driving technological innovation. One of our foci is what we call the GATTACA machine. This is a microdevice that performs real-time forensic identification. We're getting very close to the development of a working device – it remains provocative but is a really nice vision for a technical goal. Another point-of-care technology we're working on is in cancer diagnosis. The idea is to genotype tumour cells (a tumour mass is a clonal poplulation of cells). Once we've genotyped that tumour we have a very efficient way of generating markers and diagnostic measurements to tell us where that tumour is invading. If we could couple this analysis with one of these point-of-care devices it would enable simple genotyping of tissue samples in 5 or 10 mins and provide the opportunity to do molecular pathology and tell the surgeon exactly where the tumour has invaded.

A third area that we're working on is extraterrestrial exploration for chemical signs of life. We have joint projects with Scripps and JPL to build prototype chemical analysis devices that can test for the presence of amino acids. This molecular test is based on the hypothesis that life is built up of homochiral amino acids (which is not dependent on the specific sidechains but is dependent on essentially amide linkages that have chiral alpha carbons). The idea that if the polymer makes a viable structure it must be homochiral, whether its D or L doesn't matter. We have built a microfluidic electrophoretic system that can perform amino acid analysis as well as chiral discrimination.

What is the most exciting aspect of all those?

Unquestionably the space exploration project. The big challenge here is to get the microanalysis system working well enough so that it is selected as a payload on a flight mission. If we could drop one of these analysis devices on Mars, and detect homochiral amino acids, that would provide the chemical proof for extraterrestrial life. The importance of such a result is on the scale of the human genome project, and in the big scheme of 'science' would be the most spectacular of all. There are not many people working on these directions but they are dedicated to this important goal. My entry is sort of by the back door, because of the technology we developed for the human genome project. It may sound a little crazy but it's very real and exciting new project.

Which aspects of this conference most interest you?

I get interesting vibes from all of the talks that bring new technologies into the field. Probably the most valuable interaction is when you can pick up something from a talk that fundamentally changes the way you think and helps you to solve a problem. In that respect, the topic that I found particularly fascinating was the idea of coupling microfluidic systems with cell culture – the engineering of the surfaces so that you can really control where the cells go down and what their shape are, and make them viable. If such technologies could be coupled with, for example, nanopores, it presents the possibility of establishing electrical contact with cells and working with them to fashion a bionic interface.

What is the time-scale of the point-of-care analysis devices?

From a technical point of view you have to first wait until a device has been shown to work practically in an academic lab as a breadboard. From that point it typically takes five years to move the devices from working on a bench to something you can sell. For clinical analysers you have to add some time for such issues as regulatory approval and market acceptance. In part, the time-scale can be driven by attention the user community. We've seen this with the AIDS community and certain constituency groups. If one focussed on a device in an area where early detection is critical, such as in cancer diagnosis, and where consumers are active and really pushing the regulatory community for access to the technology, then I think it could be done faster. From a technical point of view, in five years time such devices will be available.

Richard Mathies was interviewed by Suzanne Berry (suzanne.berry@eslo.co.uk).

Erratum

In the recent article by U. Kragl and T. Dwars (*TIBTECH* 19, 442–449) there was a mistake with the reference citation numbering. In the legends of Figs 2, 3 and 4 Ref. 61 should be Ref. 63, 62 should be 64, 64 should be 66, 65 should be 67 and 66 should be 68. We apologise to the authors and the readers for this error.

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