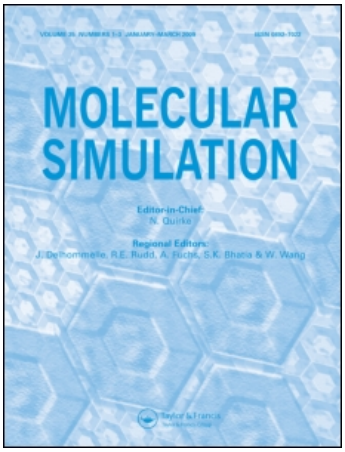

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Chemical engineers at the frontiers of computational biology

M. R. King[a]
[a] University of Rochester, Rochester, NY, USA

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Chemical engineers at the frontiers of computational biology

M. R. KING

University of Rochester, 601 Elmwood Avenue, Box 639, Rochester, NY 14642, USA

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At the 2005 Annual Meeting of the American Institute of Chemical Engineers (AIChE), held in Cincinnati, Ohio from October 31 to November 4, 2005, three platform sessions on Computational Biology were organized as part of the Computational Molecular Science and Engineering Forum. We heard from over 20 speakers on theoretical and computational studies of biological systems such as protein/DNA and protein/protein interactions, genetic networks, metabolic pathways, and signal transduction pathways. Emerging behavior of these systems in response to changes in their kinetic and thermodynamic properties was discussed. Chemical engineering laboratories from the US and Europe are making important contributions to several different areas of computational biology.

The simulation and prediction of gene networks is a particularly active area of research currently. Ian Laurenzi of Lehigh University has developed a new approach to identifying networks called "Transcriptional Dynamics", based on relating genes via the local clustering of time fluctuations of their Pol II transcription rates. These transcription rates are calculated from RNA expression timeseries and mRNA degradation information. Joao Natali and Jose Pinto from Polytechnic University presented a reconstruction of transcriptional regulatory networks via integer linear programming. Their framework, based on optimization methods and logical relationships modeling, represents the system as a bipartite network and is designed to interpret experimental evidence on genome wide regulatory networks. Kelvin Lee and coworkers at Cornell University have developed a deterministic model of circadian gene network oscillations in *Drosophila*. They use the "SloppyCell" package to deal with the challenge of fitting experimental data sets from the literature with 16 coupled differential equations containing 76 adjustable parameters. David Schaffer's group at the University of California, Berkeley has investigated stochastic gene expression in a lentiviral positive feedback loop [1]. Through combined experimental and theoretical work, they have obtained evidence that stochastic delays in HIV gene expression enable the virus to convert to a latent state. Yiannis Kaznessis and coworkers at the University of Minnesota have developed a multiscale stochastic-discrete and stochastic-continuous algorithm, that enables simulations of thousands of species involved in thousands of reactions with disparate kinetic constants. They have made their hybrid "Hy3S" algorithm available over the internet at hysss.sourceforge.net

There were several talks on molecular dynamics simulations in the AIChE computational biology sessions, ranging from course-grained simulations, to full atomistic simulations, to hybrid approaches. Simulations of lipid membranes and membrane/protein interactions were of particular interest. While researchers are making great strides in developing full atomistic simulations of macromolecule interactions in realistic situations [2], there will remain a regime of molecular interactions most efficiently handled by coarse-grained, bead-and-spring simulations. An example of this is the flow of extremely long ($L > 100$ nm) DNA chains in water, as considered by Juan de Pablo's group at the University of Wisconsin.

As explained in Michael Shuler's acceptance lecture for the inaugural James E. Bailey Award from the Society of Biological Engineering, for decades chemical engineers have been innovators in the field that has come to be known as "systems biology". Unfortunately, this important role that pioneering chemical engineers have played in systems biology is often overlooked by systems

Corresponding author. Tel: + 1-585-275-3285. Fax: + 1-585-273-4746. Email: mike_king@urmc.rochester.edu

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biologists composing more recent reviews on the subject. The Cornell *E. coli* model was one of the first predictive models of a real bacterium that directly linked genomic structure to cell physiology [3]. The systems biology approach to simulating the whole cell is now being extended to complex "animal-on-a-chip" assays that can rapidly screen drug candidates and potentially accelerate the drug approval process.

My own laboratory's research focuses on multiscale simulations of receptor-mediated blood cell adhesion under flow [4,5]. In this area of computational biology, some of the critical issues being addressed today involve incorporating the proper catch-slip bond kinetic models for receptor-ligand dissociation, and the nanoscale rheology of cell membrane attachments. To enable scale-up to physiologically realistic conditions, efficient computational algorithms must be used that enable multicellular simulations to be carried out on inexpensive computing clusters, rather than some currently used approaches that require the use of less accessible supercomputing resources even for single cell calculations.

To summarize, the 2005 AIChE Annual Meeting featured many excellent studies involving molecular simulation applied to biological systems. However, most talks in the AIChE computational biology sessions focused on the development of new methodologies rather than on results obtained from these methods. The next "frontier" of computational biology must be aimed at applying the newly developed methods towards the solution of biomedical problems of real clinical relevance. This will require chemical engineers and others, many of whom have received their own training in non-biological fields, to commit to earnestly learning the biological complexities of the systems that funding agencies pay us to study. I believe that we as a professional community are up to this challenge.

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