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Instrumentation Challenges for Systems Biology

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Summary

Burgeoning genomic and proteomic data are motivating the development of numerical models for systems biology. However, specification of the almost innumerable **dynamic** model parameters will require new measurement techniques. The problem is that cellular metabolic reactions and the early steps of intracellular signaling can occur in ms to s, but the 100 to 100k s temporal resolution of measurements on milliliter culture dishes and well plates is often limited by diffusion times set by the experimental chamber volume. Hence the instruments themselves must be of cellular dimension to achieve response times commensurate with key intracellular biochemical events, as is done with microelectrode recording of ion-channel conductance fluctuations and fluorescence detection of protein binding. The engineering challenge is to develop BioMEMS and molecular-scale sensors and actuators to study the breadth of mechanisms involved in intracellular signaling, metabolism, and cell-cell communication.

Motivation

Much of the effort in systems biology is focusing on development of numerical models for biological systems[1-6] – a logical response to the burgeoning wealth of genetic and proteomic data. However, this approach will falter unless new techniques are developed to acquire the dynamic information necessary to specify the extraordinary large number of model parameters which accompany these complex models: the complete modeling of a single mammalian cell may require 10^5 variables and equations, cell-cell interactions are critical to system function, and some organs have 10^9 interacting cells. Models could easily require a mole of PDEs (a leibnitz), requiring an exaFLOPS-year of computation. The most pressing modeling limitation will be the absence of adequate data on the 10^{-3}-10^{-6} s dynamics of cellular processes, as required by the Shannon theorem.

What is not yet widely recognized is that existing techniques used in the biology and biochemistry laboratory are ill-suited to obtain the dynamic data that are required to drive these new, highly interconnected models. The fundamental problem is that the temporal resolution possible for measurements made on milliliter-volume culture dishes and well plates is limited by diffusion times, and hence the volume of the experimental chamber. In order to obtain instrument response times that are commensurate with key intracellular biochemical events, the instruments themselves have to be of cellular dimensions. A few techniques can accomplish this – microelectrode recording of the conductance fluctuations of a single ligand-gated ion channel, or the fluorescence detection of a protein binding event. However, the vast majority of biological measurements are made with time constants of minutes, hours, or days, rather than the milliseconds to seconds typical of cellular metabolism and the early steps of intracellular signaling.

Although the national emphasis in systems biology is primarily based on effective integration of the biological and computational sciences, there is a clear need to add a

third dimension, one which focuses on sound dynamic measurement principles and on the design of sensors and instruments used to capture and control the dynamics of intracellular events. Just as the closed-loop study of single ion channels revolutionized electrophysiology and allowed separation of the stochastic behavior of single channels from the ensemble average of an entire nerve or cardiac cell, and the study of receptor binding revolutionized pharmacology, the study of the rapid dynamics of the physiology of single cells will allow identification of specific physiological events lost in slow biochemical measurements averaged over a population of cells. We recognize that we must measure single cells not only in isolation, but in highly instrumented microenvironments that allow interactions between cells and their neighbors and invaders. More importantly, we have come to appreciate that great advances in physiology, for example the explanation of the nerve impulse, the discovery of the role of insulin in glucose regulation, and the elucidation of the mechanisms of cardiac hemodynamic control, often involved the interruption of normal, biological feedback mechanisms, and the insertion of artificial, external controls that could be monitored and adjusted.

In the rapidly evolving world of systems biology, we need to develop devices that will allow us to not only measure dynamical physiological quantities at the cellular level, but also seize control of them. This in turn will require advances in microfluidics, nanoscience, microscopy, optics, electronics, and electrochemistry. Therein lies the challenge to the engineering community: apply Biological MicroElectromechanical Systems (BioMEMS) and molecular-scale sensors and actuators to address problems in intracellular signaling, metabolism, and cell-cell communication that are difficult to study with more conventional biological laboratory techniques. This in turn will require a interdisciplinary team that includes biologists, bioengineers, chemists, chemical, mechanical, and electrical engineers, mathematicians, pharmacologists, physicists, physiologists, and physicians. However, the key driver to this entire endeavor will undoubtedly be sensors that are small, robust, inexpensive, and capable of operating in a harsh biological environment. Most importantly, sensor arrays must allow the high-bandwidth measurement of a very large number of tissue and intracellular variables, either *in vitro* and, eventually, *in vivo*.

Literature Cited

1. Ideker,T, Galitski,T, Hood,L. A New Approach to Decoding Life: Systems Biology, Ann.Rev.Genom.Hum.Genet., 2, 343-372, 2001
2. Ideker,T. Systems Biology 101 - What You Need to Know, Nat.Biotechnol., 22, 473-475, 2004
3. Arkin,AP. Synthetic Cell Biology, Curr.Opin.Biotechnol., 12, 638-644, 2001
4. Endy,D and Brent,R. Modelling Cellular Behaviour, Nature, 409, 391-395, 2001
5. Tyson,JJ, Chen,K, Novak,B. Network Dynamics and Cell Physiology, Nature Reviews Molecular Cell Biology, 2, 908-916, 2001
6. Schilling,CH, Covert,MW, Famili,I, Church,GM, Edwards,JS, Palsson,BO. Genome-Scale Metabolic Model of Helicobacter Pylori 26695, The Journal of Bacteriology, 184, 4582-4593, 2002