FOCUS ISSUE: Molecular, Metabolic, and Genetic Control

Molecular, metabolic, and genetic control: An introduction

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(Received 19 December 2000; accepted for publication 19 December 2000)

The living cell is a miniature, self-reproducing, biochemical machine. Like all machines, it has a power supply, a set of working components that carry out its necessary tasks, and control systems that ensure the proper coordination of these tasks. In this Special Issue, we focus on the molecular regulatory systems that control cell metabolism, gene expression, environmental responses, development, and reproduction. As for the control systems in human-engineered machines, these regulatory networks can be described by nonlinear dynamical equations, for example, ordinary differential equations, reaction-diffusion equations, stochastic differential equations, or cellular automata. The articles collected here illustrate (i) a range of theoretical problems presented by modern concepts of cellular regulation, (ii) some strategies for converting molecular mechanisms into dynamical systems, (iii) some useful mathematical tools for analyzing and simulating these systems, and (iv) the sort of results that derive from serious interplay between theory and experiment. [DOI: 10.1063/1.1350441]

Exploiting the power of modern genetics and biochemistry, molecular biologists have been wildly successful in identifying the molecular components of the regulatory systems that control many crucial processes within the living cell. These components have been painstakingly pieced together into schematic ''wiring'' diagrams of great complexity. To derive the physiological properties of a cell from these wiring diagrams is beyond the power of casual biochemical intuition, so a call has gone out for theoretical methods to describe these control systems in precise mathematical terms. The theory of nonlinear dynamical systems, familiar to readers of *Chaos*, provides a set of tools that seem custom made for this challenge. If you would like to know how to apply your expertise in dynamical systems and control theory to modern problems in molecular cell biology, this Special Issue is for you.

The living cell is a marvelous chemical machine. Within the confines of a few microliters of densely packed cytoplasm, bounded by a semipermeable membrane, the cell carries out thousands of chemical and physical transformations that permit its own survival and reproduction. The cell must respond to its environment and to its own internal state, searching out raw materials and energy, avoiding toxins and predators, repairing damaged parts, and producing exact replicas of itself. Every chemical and physical process within the cell must be exquisitely regulated to meet the demands of life. Genes must be copied and read out, proteins must be assembled and their activities controlled, metabolites must be broken down and recombined, food must be imported and waste products excreted, signals must be generated, relayed and interpreted. All of these regulatory processes are carried out by the same sort of molecular machinery that is being regulated: the genes, proteins and metabolites within the cell. A fundamental goal of molecular cell biology is to uncover these molecular control circuits and to understand how they orchestrate the observed physiological properties of the living cell.[1]

For example, consider the ability of bacterial cells to swim toward food sources and away from toxins. This behavior is controlled by an enzymatic ''information processing'' unit (see Fig. 1) that transduces a chemical signal (attractants or repellants in the environment) into a cellular response (straight-line swimming, or a tumbling motion that reorients the direction of motion of the bacterium). The response is determined by the direction of rotation of the motor that turns the bacterium's flagellum: when the motor turns counterclockwise, the bacterium swims in a straight line; when clockwise, the bacterium tumbles. The default state of the motor, straight swimming with occasional tumbles, can be modified by the presence of small molecules or ions (e.g., amino acids or toxic metals) in the external medium. When a signal molecule binds to a protein receptor (Tar) that spans the cell membrane, it changes the catalytic activity of Tar inside the cell. When bound to a repellant (such as Ni^{2+}), Tar stimulates the autophosphorylation of CheA, which transfers its phosphate group to CheY, which then interacts with the

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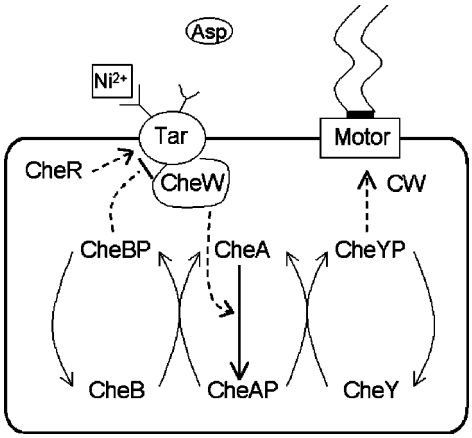

FIG. 1. The information processing system that controls bacterial motion in response to small molecules in the environment. Adapted from Bray *et al.*[2] Phosphoproteins (CheA and CheY) transduce a chemical signal (binding of chemoattractants or repellants to a membrane receptor, Tar) into either counterclockwise (CCW) or clockwise (CW) rotation of the flagellar motor. CCW rotation produces straight-line swimming, whereas CW rotation induces a tumbling motion that allows the bacterium to choose a new direction of motion. Proteins CheB and CheR control the methylation of Tar, which is involved in adaptation of the response to constant high levels of signal molecules.

flagellar motor to increase the probability of clockwise rotation (i.e., tumble and pick a new direction). Hence, the bacterium tends to swim away from repellants. Chemoattractant binding, on the other hand, favors the unphosphorylated form of CheY, counterclockwise rotation, and straight swimming.

If we are content with such a hand-waving explanation of bacterial chemotaxis, then intuitive notions of protein interactions are sufficient. But the chemotactic response is much more subtle than we have described. For instance, cells respond not to absolute concentration of a chemoattractant or repellant but to temporal changes in its external concentration. If the concentration is maintained at a constant high level, the cell will adapt to the signal and return to default swimming. Furthermore, if mutations are introduced into the genes coding for proteins Tar, CheA, CheY, etc., then the mutant cells display characteristic behavioral defects, for example, abnormally frequent tumbles or inability to adapt. To account for these quantitative properties of bacterial chemotaxis in detail requires a comprehensive, mathematical model of the signal transduction pathway. In a trend-setting paper in 1993, Bray, Bourret and Simon[2] presented the first thorough computer simulation of this control system. Since then, others have contributed significantly to our understanding of this paradigmatic case of molecular regulation.[3–5]

Other problems are crying out for similar mathematical analysis and simulation. For excellent examples, we suggest perusal of the ''Millenium Reviews'' issue of *Cell* (January 7, 2000).

Fraser and Harland[6] describe the molecular basis of pattern formation in worms, frogs, fruit flies, and chick wings. They conclude, ''Results to date show a dizzying array of signaling systems acting within and between cells... . In such settings, intuition can be inadequate, often giving incomplete or incorrect predictions... . In the face of such complexity, computational tools must be employed as a tool for understanding.''

Hanahan and Weinberg[7] describe the molecular pathways underlying the seven pathological characteristics acquired during tumor development. In their opinion, ''For decades now we have been able to predict with precision the behavior of an electronic integrated circuit in terms of its constituent parts... . Two decades from now, having fully charted the wiring diagram of every cellular signaling pathway, it will be possible to lay out the complete 'integrated circuit of the cell'... . We will then be able to apply the tools of mathematical modeling to explain how specific genetic lesions serve to reprogram this integrated circuit... so as to manifest cancer.''

Nurse,[8] after describing the complex network of protein kinases that regulate DNA synthesis and cell division, concludes, ''Perhaps a proper understanding of the complex regulatory networks making up cellular systems like the cell cycle will require a... shift from common sense thinking. We might need to move into a strange more abstract world, more readily analyzable in terms of mathematics.''

Brent,[9] after reviewing modern developments in genomics and proteomics, points out that ''For a few prokaryotes and subsystems within eukaryotic cells, we are at or near a level of description where we can enumerate key players... . Better predictive ability may depend on representations [of the key players] that incorporate kinetic information. The classical frameworks for this are, of course, systems of differential equations that describe the rates at which enumerated species change.''

Clearly, the world's foremost molecular biologists now recognize that their spectacular success in tracing out molecular pathways has created a pressing demand for theoretical and computational tools to make sense of the dynamical interactions among proteins in these fundamental regulatory networks. Of course, there is no need to wait twenty years, as Hanahan and Weinberg suggest, before beginning this program. Indeed, the program is already off to a good start, as illustrated by this collection of articles.

To show how theoretical biologists currently make connections between molecular interactions and cell physiology, we have assembled a group of papers that describe both useful methods and successful applications. The papers that are primarily methods-oriented are the following.

(1) Kohn, on molecular interaction maps as tools for organizing experimental information and templates for constructing mathematical models.
(2) Schaff *et al.*, on a computational tool (the Virtual Cell) for simulating spatial as well as temporal interactions within a cell.
(3) Herzel *et al.*, on extracting information about coregulated gene expression from cDNA microarrays.
(4) Edwards *et al.*, on using piecewise-linear differential equations to model genetic switching networks.
(5) Savageau, on using S systems (a special class of nonlinear ODEs) to model elementary genetic circuits.

(6) Thomas and Kaufman, on the analysis of molecular feedback circuits by differential equations and discrete dynamical systems.
(7) Goldbeter *et al.*, on ODE models of simple and complex oscillations in metabolic and genetic control systems.
(8) Samoilov, Arkin and Ross, on deducing chemical reaction pathways from time-series measurements.
(9) Roussel and Fraser, on automated methods for reducing the dimensionality of complex metabolic models.

The application-oriented papers cover the following topics: calcium oscillators (Bindschadler and Sneyd); cell cycle (Aguda; Novak *et al.*); signal transduction pathways (Ferrell and Xiong; Bhalla and Iyengar); bacterial operons (Hasty *et al.*; Santillan and Mackey); development (Gursky *et al.*); and neural networks (Mihaliuk *et al.*).

We hope that, for a host of dynamical systems theorists, these papers will provide an entry into the fascinating field of molecular regulatory systems within living cells. Your services are sorely needed! But one word of warning: this field is not for the faint-hearted or the dilettante. To make a significant contribution, you must roll up your sleeves and plunge into the arcane world of genes, proteins, and metabolites. There is no point in applying sophisticated dynamical reasoning to a poorly designed mathematical model. First, you must get the science straight and develop a model that can give useful insights into a problem of current biological interest. Then your analytical and computational efforts will be a guaranteed success. The field is wide open to anyone who is willing to learn the language of molecular cell biology and collaborate effectively with experimentalists.

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