COMPUTATIONAL PROBLEMS IN CELL BIOLOGY

Obtaining a predictive understanding of cell behavior will require new computational methods, as well as adaptations of traditional techniques of optimization and system analysis. The authors discuss the challenges cell biologists face in their effort to control information transfer in cells.

The biological sciences have crossed a cultural watershed, driven in large part by the Human Genome Project and its associated high-throughput technologies for identifying and sequencing genes and their products.[1] Currently, 17 complete prokaryotic and two complete eurcaryotic genomes have been sequenced (visit *www.tigr.com*), and genomes of autonomous organisms are appearing at a rate of nearly one per month.

With the emergence of microarray technologies, it's likely that entire genomes will soon be available on a single chip, allowing dose-response studies of entire sets of expressed genes as a function of time. This opens many possibilities for understanding disease states, discovering drug targets, and unraveling genetic circuitry (see *www.smi.stanford.edu/projects/helix/psb99/* and *http://library.genetics.nature.com/server-java/Propub/genetics/ng0199supp.contents*).

Even as researchers continue to identify genes and their products, other experimental advances have made it possible to amplify trace quantities of proteins and rapidly determine their structure,[2] function,[3] and interactions.[4] During the next decade, the combined effect of these and other remarkable technological advances will dramatically increase the identification, quantitative characterization, and structural elucidation of proteins and their complexes. This information will not only provide an atomic-level understanding of the fundamental units (proteins) of information transfer in and between cells, but it will also let us develop deep insight into the topology (connectivity) of the various pathways by which cells process information, and the circuitry that regulates their behavior.

This article outlines some major problem areas related to controlling and transmitting information in active cells. The problems fall into two broad categories: proteins and their immediate interactions, and the control circuits and pathways those interactions define.

Proteins: molecular machines

Just as nucleic acids encode and transmit information between generations, proteins transmit, regulate, and store information in active cells and provide the fundamental units for memory and control circuits in cells.[5] They are, in effect, molecular machines—the hardware encoded by DNA software.

A predictive understanding of the way a cell transmits and controls information requires sufficient knowledge of molecular recognition to recognize desired targets. The molecules of interest include proteins, nucleic acids, and polysaccharides. While much progress has been made in understanding proteins in atomic de-

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tail,[6] less is known about a structure's dependence on sequence in nucleic acids, and a predictive understanding—even in its most circumscribed sense—of polysaccharide structure is essentially nonexistent.[7] We limit our discussion to proteins.

The ability to identify gene products and their expression levels in a specified cell provides an immediate impetus to identify reactive protein partners. A given protein can interact with several other proteins, but at any moment it is most likely to be associated with only one or two other large molecules. The cataloguing of all possible partners is being approached experimentally using new high-throughput techniques, notably yeast two-protein hybridization,[4] and through advances in docking algorithms.[8] Computational methods require a good first approximation of the putative reactants' structure. This leads to the first major computational challenge.

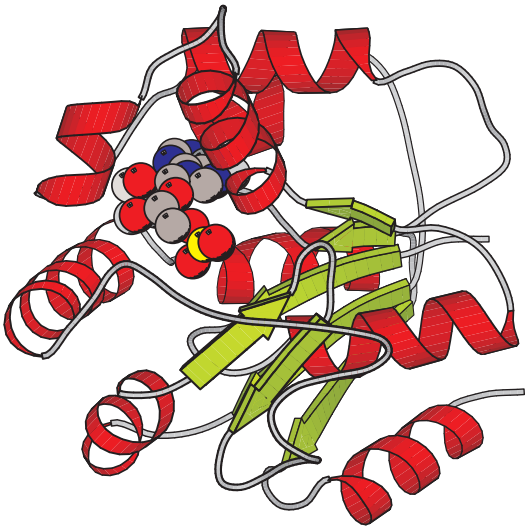


Figure 1. The structure of an adenylate kinase, an enzyme that catalyzes the reaction AMP (adenosine monophosphate) + ATP (adenosine triphosphate) = 2 ADP (adenosine diphosphate). The alpha helixes are red, and the beta strands are light green. All atoms are shown for a bound AMP molecule in which the atoms are colored by the following scheme: carbon, gray; oxygen, red; nitrogen, blue; and phosphorus, yellow.

Determining protein-domain structures

Proteins often consist of congeries of compact domains, which pack upon one another but fold independently.[6] The folded domains contain partially ordered secondary structural regions—alpha helixes and beta strands—interspersed with one another and with partially ordered regions at which they turn in space (see Figure 1). Domains are said to have the same fold if they have the same secondary structural elements in the same order, arranged in the same topology.[9] Recent estimates indicate that the protein domains whose folds are known have been sampled more or less randomly from a universe with fewer than a thousand folds.[10] The next 15 years will see the elucidation of several examples of each fold in that universe.

Although protein domains with the same fold have the same general architecture, they can differ substantially in geometric detail. The importance of having at least one structure for every fold is that we should be able to obtain, through computation, the geometry of other proteins with the same fold. Obtaining a generally reliable *homologous extension* methodology[11] is one of the next decade's great computational challenges. Solving this problem requires progress on two subproblems, one chemical and the other algorithmic. The first requires rapidly and accurately calculating the free energy of any conformation of the protein;[12] the second requires an algorithm to effectively search a rugged free-energy landscape for its global minimum.[13]

Another problem involves determining a protein-complex structure from its monomeric units—that is, the noncovalent association of two single domain proteins whose structures are known. In this problem's simplest version, the proteins are known to associate and their binding sites are approximately known.[14] The solution again requires chemical and algorithmic progress.

Progress is also being made on the more difficult problem of identifying the binding sites at which the putative pair will associate. One promising method for rapid exploration uses the fast Fourier transform.[15] However, the method does not allow for conformational change, which occurs frequently with macromolecular association.[16] Conformational change also occurs when small hormones and signaling molecules that are flexible in solution acquire a well-defined conformation when bound to their protein receptor.[17] Obtaining a widely applicable, reliable method for the more general problem of identifying binding sites will require at least another decade; when it is obtained, we will have control over a fundamental unit of information transfer in and between cells.

Control circuits and pathways

Structural biology is now a well-developed field, and during the past 15 years, computation has assumed a well-established place. By comparison, relatively few descriptions of complete molecular circuits are available, and fewer still are the number of detailed analyses.[18]

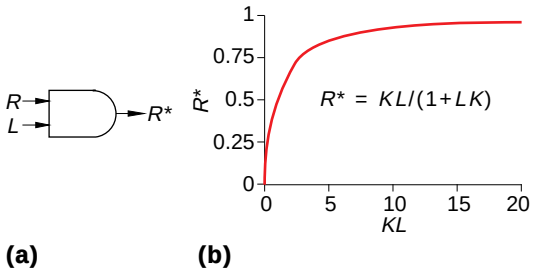


Figure 2. Binding of the monovalent ligand *L* to a monovalent receptor *R*; (a) a gating scheme representation; (b) the input-output response.

The state of knowledge in cell-systems analysis corresponds roughly to where structural biology was 30 years ago. Then, only a handful of researchers were ready to start developing a theoretical understanding of protein structure and the associated computational methods. Structural biology, however, was not about to undergo the explosion that cell-systems analysis will in the coming decade, nor was today's computing power imaginable.

In what follows, we attempt to convey no more than a gestalt of signaling within cells, and even that is confined to some special examples, arbitrarily chosen. We hope, however, that it provides sufficient background to motivate and direct future research.

Cell circuits

A cell's control and information-processing circuits are analogous to conventional electrical circuits. In a conventional circuit, the *current* (particles per second crossing a surface) comprises electrons or photons, and the flow is transport driven. In a cell, ions or molecules mediate the current, and the flow is driven by coupled diffusion-reaction-transport processes, constrained by the cell's complex interior.

In a conventional circuit, transistors switch states in response to an applied voltage. In a cell, molecules switch states in response to association with other molecules, pH changes, or an energy flux, such as light. The hardwired circuitry and the voltage applied at some subset of inputs determines an electrical device's outputs. A cell's state of differentiation and the states of its receptors determine its outputs. The state of differentiation can be considered the expressible subset of its genes, and once it is achieved, it is generally irreversible and, therefore, essentially hardwired.

Gating elements and representations

Gating elements in a cell are protein complexes. For information processing and control, logic gates (for example, AND or OR) can be represented in a number of ways; we use the standard notation of digital electronics. With this notation, we do not imply that the cell should be thought of as a central processing unit (nor do we imply the opposite). We use it to maintain the logic of connectivity (as opposed to the details of gating) and because we find it convenient.

Noncooperative receptor-ligand interactions. We use the word receptor with no particular reference to function: it's a molecule that, when it binds some other molecule (ligand), changes in conformation, thereby signaling the presence of a new spatial pattern of atoms not present prior to binding.[19] An enzymatic reaction understood in atomic detail is the structural modification in hexokinase when it binds glucose. Other examples include the conformational change in the cytosolic domain of the *epidermal growth factor* receptor, induced by binding the EGF to its extracellular domain.

We represent these reactions as an AND gate with two inputs (R and L), and a single output, R^*, dimensionless and normalized to unity (see Figure 2). For a simple unimolecular reaction, $R^* = \beta/(1+\beta)$, where $\beta = KL$, K is the receptor-ligand equilibrium constant, and L the free ligand concentration. Response functions have the same form for the rate of product produced by the simplest enzyme-substrate reactions.[20]

Cooperative interactions. There are two types of cooperative interactions: positive and negative. Both require that the receptor be multivalent for the ligand, so that the presence of a bound ligand at one site influences the thermodynamics and kinetics of binding at another site. It is easy to show that unless the receptor has three or more sites, the input-response function cannot have an inflection point. In general, as the number of sites becomes very large, the slope of the curve increases and the response function approaches that of an on-off switch. Calmodulin is an example of a molecular switch.[21] It is has four calcium binding sites and changes conformation and affinity for Ca^{++} as a function of the extent of chelation.

The molecule's degree of occupancy influences the binding affinities in these examples. The output rises nonlinearly with input, providing one of the simplest forms of biological *amplification*. Feedback loops also provide sharp nonlinearities, but they are fundamentally different. Figure 3 shows a simple negative-feedback loop.

The response function is relatively compli-

cated and in the discrete case it cannot be represented by equilibrium equations. With continuous variables, the feedback loop can be stable. However, the response will oscillate if feedback is delayed and inhibition is strongly cooperative yielding high amplification.

An additional element in the loop would provide the basis for building long-term memory.[22] For example, R^* could activate a kinase that phosphorylates the enzyme, rendering it inactive unless a specific phosphatase rescues it. More generally, R^* will not feed back directly as shown but will be the initiating event in a complex network, one or more of whose products will inhibit the enzyme.

The nature of biological signals

As the previous discussion indicates, molecules are by definition activated or deactivated as the result of local and global structural modifications, such as:

- conformational changes in receptors when they bind hormones and other ligands;
- the addition of recognition sites or changes in local charge density when small chemical groups are covalently attached to side chains;
- protonation or deprotonation when molecules move between cellular compartments having different pH; or
- enzymatic cleavage.

Each of these changes constitutes a signal, which is the input for a subsequent signal. Thus, relatively few input/output mechanisms can be selected combinatorially to form information-processing pathways and control loops. The many different kinds of expressed proteins (several thousand including signaling molecules and their targets in a committed cell), and the combinatorial selection of signaling molecules, allow the possibility of extremely complex networks.[23]

Among the signaling mechanisms that are of particular importance is the addition or removal of phosphate groups on serine, threonine, and tyrosine sidechains. This directly changes local structure by adding new atoms and, perhaps more importantly, by adding two negative charges per phosphate, which can shift the conformation of spatially proximate acidic and basic sidechains. Phosphorylation is enzyme catalyzed; for example, kinase transfers a phosphate group from adenosine triphosphate (ATP) to an unphosphorylated sidechain. Similarly phosphatase catalyzes *dephosphorylation*—the removal of phosphates. Molecular modification by adding phosphates can also occur nonenzymatically, such as when guanosine triphosphate (GTP) displaces guanosine diphosphate (GDP) in trimeric G proteins. We now briefly discuss paths involving these processes.

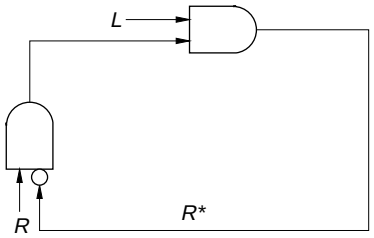


Figure 3. Gating representation of a simple feedback scheme. The small circle represents the NOT operation—that is, the maximum input signal present when *R is absent (both inputs to the lower gate are then 1). Here, *R* is an enzyme, *L* a substrate, and *R** the product, which is also a regulator of the enzyme.**

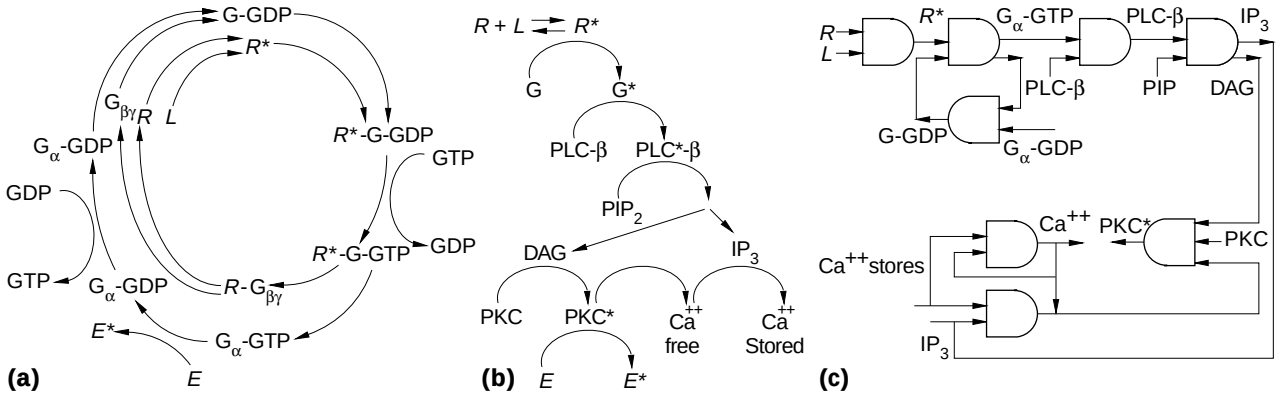
A widely used signaling pathway. Ligation of plasma membrane receptors often induces a conformational change in the receptor, which trimeric G proteins can detect. In its off state, the trimeric G protein consists of α, β, and γ subunits, with GDP noncovalently bound by the alpha subunit. In the presence of an activated receptor and GTP (inputs), a lower free-energy state has α-GTP bound to the receptor, with the β and γ subunits and GDP released (outputs). The relevant output signal is α-GTP as a function of the activated receptor concentration, with GTP and total-G-protein subunits held fixed.

α-GTP can initiate, nonexclusively, at least two major paths—one mediated by adenylyl cyclase and the subsequent production of cAMP (*a*denosine *m*ono*p*hosphate), the other by phospholipase C-β. We describe only the latter—the so-called inositol phospholipid pathway (see Figure 4b).

Activated phospholipase C-β hydrolyzes phosphatidylinositol biphosphate to produce diacylglycerol (DAG) and inositol triphosphate (IP_3). DAG activates protein kinase C (PKC), but that activation is modulated by Ca^{++}, which IP_3 regulates. The particular PKC that is activated depends on cell type, and perhaps also external conditions and the cell's health. The molecules it phosphorylates and the pathways it activates are also cell-type dependent. Pathways typically lead through a series of phosphorylations or regulatory binding events, to the activation or deactivation of gene regulatory proteins. Figure 4c shows the gating mechanism that includes the important steps shown in Figures 4a and 4b.

Challenges

There are, of course, many types of cells—and many kinds of activity, even for a well-characterized cell. A predictive understanding of initial events in cell activation must be developed, as well as methods to analyze diverse biological cir-



GDP: Guanosine diphosphate
GTP: Guanosine triphosphate
PLC-β: Phosholipase-β
E*: Activated enzyme (PLC* in this case)

PIP: Phosphatidylinositol
DAG: Diacylglycerol
IP: Inositol triphosphate
PKC: Protein kinase C

Ca^{++}: Calcium
R: Receptor
R*: Activated receptor
G: Trimeric G-protein

Figure 4. Activating G-protein coupled receptors and the phospholipase pathway; (a) activating G-proteins by bound receptors; (b) summarizing the phospholipase pathway; (c) a gating scheme representing the main interactions in G-protein activation of the phospholipase pathway. Notations: G_α, G_β, and $G_{\beta\gamma}$ are alph, beta, and beta and gamma subunits of the Trimeric G-protien, respectively. (Notice that the two AND gates on the lower left side of Figure 4c represent the release of calcium from cellular stores, induced by calcium itself and by IP_3, respectively.)

cuits that store information (memory) and modulate signals (amplification and damping). We limit discussion to T lymphocytes, in particular cytotoxic T cells, and consider early events.

Initial events in cell activation

T lymphocytes utilize the inositol phospholipid pathway, except that phospholipase C-γ hydrolyzes phosphatidylinositol biphosphate, and the events leading to phospholipase C-γ activation are different from those leading to activated phospholipase C-β. The events are fairly complex, even at this early stage, but essentially involve receptor dimerization, which allows autophosphorylation of T-cell-receptor (TcR) associated kinases. They, in turn, activate phospholipase C-γ. Whatever the cell's activity at a given time, it is determined by conditions on the surface at a previous time. Do we know enough to explain the range of responses in terms of the range in the set of *initial* conditions on the surface?

The complexes of interest are TCRs interacting with so-called peptide MHC complexes on an infected cell surface.[24] Among the variables of interest are the number of peptide MHC targets on a cell; the TcR dissociation rate; the TcR dimer lifetimes; the possibility that trimers and dimers transduce different signals; variations in the kinds of molecules that can be recruited as the result of variations in the lifetimes of complexes; and modulation of lifetimes of complexes by downstream events that modulate membrane fluidity and the number and nature of surface proteins—just to name a few.

What is equally interesting is how even an abstracted and highly oversimplified model of surface events can lead to a relatively rich range of behavior. For example, Bray and Lay[25] show that even with only two types of signaling molecules—a receptor and an intracellular target protein—we can generate a wide range of dose-response patterns, depending on the dissociation rates of ligand and target from the receptor.

More specifically, it would not be difficult to trace biphasic response curves (where activity rises and falls as a function of antigenic dose) widely observed in immune cells,[26] to a balance between pathways, one leading to apoptosis and the other to secretion. Activating the tyrosine kinases ZAP-70 and fyn is known to depend on the degree of phosphorylation of proteins in the CD3 complex, which is associated with TcRs. Hypothetically, the extent of phosphorylation could depend, in different ways, on the ternary complex's stability or its degree of aggregation. Models of this sort would have to quantitatively explain the observed data, and they could therefore suggest possible candidates for signaling molecules (in this case, two particular kinases),

which could be tested experimentally. Related models would seek to explain, in conjunction with the experiment, the response's simultaneously near-perfect antigenic specificity and sensitivity and the circuitry that encodes adaptation (for example, receptor down regulation[19]), tolerance, and other kinds of memory.[22]

Diverse biological circuits

Memory occurs at several levels and is of several types. It can be stored in networks formed of systems of neurons; that is, between cells. It can also be embedded in cell circuits. Here, we briefly describe adaptation and transduction in the chemotactic response of bacteria, for which the circuitry is well-understood.

Bacteria respond to temporal rather than spatial concentration gradients,[27] and do so with an efficiency that is fairly constant over a seven order-of-magnitude variation in absolute concentration. In fact, bacteria will adapt within minutes to a change from one uniform concentration to another by methylating receptors. This desensitization mechanism is distinct from—and several orders-of-magnitude faster than—desensitization by receptor-down regulation, which is common in eucaryotic cells.

A motor arm that comprises a bundle of a single type of protein—flagellin—propels bacteria. The relation between the motor's supramolecular structure and the way it propels is relatively well-understood. When the bundle rotates counterclockwise, the flagella work cooperatively, resulting in more or less unidirectional movement. When it rotates clockwise, the packing loosens, the proteins move more or less independently, and the bacterium tumbles randomly. A concentration gradient produces a bias in favor of counterclockwise rotation, and this drives the bacterium up or down stream, depending on whether the gradient is an attractant or repellant. When several gradients are present simultaneously, the responses are integrated.

The circuitry is relatively simple. Besides the motor, which consists of some 40 proteins but can be thought of as a single unit, there are four proteins of interest. Briefly, a receptor bound by a ligand activates a protein kinase, CheA, which self phosphorylates in the presence of another molecule CheW. CheA transfers the phosphate to CheY, which binds the motor and biases the direction in which the flagellar motor arm rotates. A phosphatase, CheZ, also controls the build-up of CheA. Another phosphorylase cycle, coupled to the CheA cycle, methylates receptors, and thereby mediates adaptation. Bray and his colleagues[28] have modeled the nonadaptive response in *E coli* to aspartate (attractant) and Ni^{++} (repellant), and they were able to produce, among other things, the observed patterns of runs, tumbles, and pauses.

During the coming decade, new high-throughput technologies will dramatically increase our knowledge of control loops and the structure of their elements. We will begin to have in hand the information needed to develop a predictive understanding of macromolecular recognition, and to simulate the behavior of cellular control circuitry. The complexity of cell dynamics poses, however, daunting computational challenges.

Traditionally, signaling mechanisms have been modeled and simulated in isolation restricting consideration to a few interacting variables with a limited number of connections to the environment. However, it has become increasingly clear that interactions between pathways might significantly affect signaling pathways interacting with one another and the observable biological responses.[18] It's likely that obtaining a predictive understanding of cell behavior will require new computational methods, as well as adaptations of traditional techniques of optimization and systems analysis. CiSE

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