Theory in Biology

Computational biology: A propagating wave of interest

Albert Goldbeter

Systems biology, computational biology, integrative biology... many names are being used to describe an emerging field that is characterized by the application of quantitative theoretical methods and tendency to take a global view of problems in biology. This field is not entirely novel, but what is clear and significant is that the life sciences community recognizes its increasing importance. This is the really new aspect: many experimentalists are beginning to accept the view that theoretical models and computer simulations can be useful to address the dynamic behavior of complex regulatory networks in biological systems.

Theoretical or mathematical biology has existed for many decades, as attested by the journals that carry these terms as part of their names. Until recently, however, these journals were outside of the mainstream and largely ignored by the majority of molecular and cell biologists. As the attitude to theoretical approaches in biology is shifting, it is not surprising to see their revival under new names, if only because a change in name is often needed to focus attention. After all, even at the cellular level, many sensory systems are built to respond to changes in stimulus intensity and adapt to constant signals.

The hype that currently surrounds computational and systems biology has the beneficial consequences of triggering further interest and creating a momentum for new opportunities, but it also carries some dangers (see [1]), in particular that of making the field appear merely a fashion. The French stylist Coco Chanel once said “la mode, c’est ce qui se démode” — “fashion is what comes out of fashion”. In my view, this does not apply to computational approaches to biological dynamics, which are here to stay. I would like to address the need for computational models in molecular and cell biology, building on my own experience in theoretical studies of rhythmic behavior and other dynamic phenomena at the biochemical and cellular levels.

Regarding the surge of interest in theoretical approaches to biology it is natural to ask: why now? One triggering factor is undoubtedly the completion of genome projects for a number of species and realisation that the sequences alone cannot tell us how cells and organisms function. Understanding dynamic cellular behavior and making sense of the data that are accumulating at an ever increasing pace requires the study of protein and gene regulatory networks. This network approach naturally encourages one to take a more integrative view of the cell and, at an even higher level, of the whole organism.

Quantitative models show that certain types of biological behavior occur only in precise conditions, within a domain bounded by critical parameter values. This can contrast with the intuitive expectations from simple verbal descriptions. This is well illustrated by cellular rhythms [2,3]. Thus, cytosolic Ca^{2+} oscillations are triggered in various types of cell by treatment with a hormone or neurotransmitter. But repetitive Ca^{2+} spiking only occurs in a range of stimulation bounded by two critical values: below and above this range, the intracellular Ca^{2+} concentration reaches a low or a high steady-state level, respectively. Another example is the well-known generation of oscillations in models based on negative feedback. It is straightforward to explain in words why oscillations can readily be generated by negative feedback; but this verbal explanation largely misses the point, as it fails to explain why oscillations only occur in precise conditions, which critically affect both the degree of cooperativity of repression and the delay in the negative feedback loop.

Moreover, models can show how — and explain why — different types of dynamic behavior can occur in closely related conditions. A good example of this is the wave-like aggregation of amoebae of the cellular slime mold *Dictyostelium discoideum* after starvation, in response to chemotactic signals of cyclic AMP (cAMP). These signals are emitted in a pulsatile manner by cells that behave as aggregation centers, while other cells relay the signals to the periphery of the aggregating field. There is no need to invoke different molecular mechanisms to explain the relay *versus* oscillations of cAMP. Models show that — much as with the excitability and pacemaker behavior of nerve cells — relay and oscillations can be explained by the same regulatory mechanism operating with slightly different values of the control parameters.

The different outcomes could result, for example, from small modifications in the activities of adenylate cyclase or phosphodiesterase, enzymes involved in cAMP synthesis and degradation, respectively. Theoretical approaches further show how the progressive increase in these enzyme activities during the hours that follow starvation causes a switch in dynamic properties of the cAMP signaling system in the course of development, from no relay to relay (excitability), and then to autonomous oscillations. Waves of cAMP develop as soon as a critical density of relay cells is reached. The change in slime mold dynamics provides us with a metaphor for the change in responsiveness to computational and systems biology: here, as well, the new

conditions may correspond to the onset of wave propagation.

Modeling becomes necessary when sheer intuition reaches its limits. We have seen that this can be true of relatively simple situations, where one is trying to understand why certain types of dynamic behavior occur in very precise conditions. It applies even more forcefully to more complex situations, common in biological systems, where there are a large number of variables coupled through multiple regulatory loops.

Another case in which models are clearly needed is where a dynamical system (and biological systems are dynamical systems) has multiple 'attractors' — points or trajectories within 'phase space' to which the state of the system is gradually attracted when it starts from some point (the 'initial condition') within a particular subset of that space. To put it in somewhat less mathematical language: a theoretical approach is required to understand why a system can evolve towards one of several possible steady states, depending on the system's history (which define its initial conditions). Examples of such multistability have long been discussed in the context of theoretical models, in fields ranging from cell differentiation [4] to the control of Cdc2 kinase in the embryonic cell cycle [5,6].

As with experiments, computational modeling can sometimes provide serendipitous insights. I will give two examples drawn from personal experience. The first relates to the occurrence of threshold phenomena in phosphorylation-dephosphorylation cascades. Before it was analyzed theoretically or experimentally, this phenomenon — referred to as 'zero-order ultrasensitivity' [7] — was observed by chance in the course of numerical simulations in a model which was formulated to explain the role of reversible receptor methylation in bacterial chemotaxis.

A second example comes from work on a computational model of the mammalian circadian clock [8]. Initially, this model failed to yield entrainment by light–dark cycles — one of the most important properties of circadian oscillations. It turns out this failure points to a possible molecular basis for the non-24 hour sleep–wake cycle syndrome, a clinical disorder associated with abnormalities of circadian rhythms in humans.

One of the most powerful aspects of theoretical models is that, by virtue of their common mathematical structure, they allow one to make connections between phenomena that occur in widely different contexts but that are nevertheless fundamentally similar. This is well illustrated by the case of bistability arising from mutual inhibition. This situation was first studied in population dynamics by Volterra, and has become a classic in ecology textbooks: when two animal populations exert an inhibitory effect on each other, depending on the strength of mutual inhibition they can either coexist in a unique stable steady state corresponding to suboptimal levels of the two populations, or one population can eliminate the other. The latter situation is an example of bistability: depending on the initial conditions, one or the other population eventually evolves to its maximum level, while the other is driven toward extinction. In a markedly different context, bistability was demonstrated theoretically and experimentally in the formally related situation of a synthetic gene network involving two repressors coupled through mutual inhibition [9].

When three, instead of two, inhibitory interactions are coupled in a cyclical manner, oscillations, rather than bistability, may occur. This phenomenon, first studied theoretically and referred to as 'recurrent cyclic inhibition', underlies the rhythmic operation of some neural networks [10]. A similar regulatory arrangement is at the core of oscillations in the 'repressilator', a synthetic gene regulatory network containing three repressors acting on each other in a cyclical manner [11].

Making such connections provides additional insights into dynamic phenomena of similar nature that occur in widely different biological settings, from genetic to metabolic and neural networks, and from cell to animal populations. This global perspective represents one of the strengths of the theoretical approach in biology.

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Faculté des Sciences, Université Libre de Bruxelles, Campus Plaine, C.P. 231, B-1050 Brussels, Belgium.
E-mail: agoldbet@ulb.ac.be