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End of the interlude?

“In one way, you could say all the genetic and molecular biological work of the last 60 years could be considered a long interlude... We have come full circle—back to the problems left behind unsolved. How does a wounded organism regenerate exactly the same structure it had before? How does the egg form the organism? In the next 25 years, we are going to have to teach biologists another language... I don’t know what it’s called yet; nobody knows...”

Sydney Brenner

Delivered over 30 years ago, Brenner’s cautionary words resound even more forcefully today. Although we may now have a term, ‘systems biology,’ for his ‘language’ (the focus of this issue), the central problem remains: how to transform molecular knowledge into an understanding of complex phenomena in cells, tissues, organs and organisms? In the intervening decades, we have become spectacularly successful at creating inventories of genes, proteins and metabolites, but remained spectacularly average at pinpointing key points for medical intervention in disease pathways or determining which recombinant gene(s) to add to generate a complex trait. There is no clear connection between molecular description and such ‘systems’ phenomena.

The need to tackle system complexity has become even more apparent since completion of the various genome projects. These reveal that we have only around 5,000–15,000 more genes than less urbane and sophisticated relations in the worm or weed worlds. Although some of this complexity deficit may be restored by the subtleties of alternative splicing, gene duplication, domain splicing and more multidomain proteins, this does not easily translate into how different mammals with similar proteomes and similar embryologies produce the morphological and behavioral variation that is seen, for example, in whale sonar, bat echolocation or human speech. It is the interactions and relationships among the parts—whether protein-protein, protein-gene/metabolite/lipid, protein-cell, cell-cell, or brain subsystems—that produce the ‘emergent’ properties of a living system. These are not evident from an inspection of the parts list.

Thus, complexity appears to arise partly as a result of emergent properties of the ‘system.’ The problem, as this issue makes clear, is that a mammal or even a single eukaryotic cell is a rather complicated ‘system,’ too complicated certainly to build up from components of molecular knowledge; we need to first learn how to understand and construct smaller modules. Eukaryotic cells represent a particular challenge because they live in tissues. Modeling embryology or the nervous system is daunting. In practical terms, integrating from the genome to cognition, or understanding perceptual categorization or consciousness, involves a combination of nervous system development and emergent neuropsychiatric phenomena that are currently in the ‘too hard’ basket.

Just how hard is illustrated by perhaps the best studied of the human subsystems, the red blood cell. Simplified by the absence of genetic

regulation and the need to generate biomass, models of red blood cells need only include a limited number of metabolites and metabolic reactions. Nevertheless, despite 30 years of research, current erythrocyte models still lack validation; many of the predictions the models make are inaccurate. Clearly, models of whole eukaryotic cells, where transcriptional control and growth (let alone other cells) are also part of the system, remain some way off.

Current systems models are often gross simplifications that ignore huge amounts of knowledge. Most metabolic models, for instance, regard the cell pretty much as a bag of enzymes and neglect spatial heterogeneity and compartmentalization. Furthermore, most integrative models struggle to resolve the 10–12 order-of-magnitude span of timescales for events in the system, whether molecular (ion channel gating; 10^{-6} s), cellular (mitosis; 10^3 s) or physiological (cancer progression, aging; 10^5 s).

If one accepts that most physiological systems of interest are just too complicated to model at the moment, then the way forward for systems biology will continue to be to develop methods for studying subsystem networks, over subsystem timescales, the complexity of which might be addressable. The task of systems biology then would not be to build the system from its molecular components, but to build subsystems from molecules and then the system from the subsystems.

This is not a straightforward proposition. There will be no standardized ‘cookie cutter’ modeling methods that can be automatically applied, even to the simplest problems. The good news is that Occam’s razor often applies: adding more equations to include more details of interactions does not usually help. The bad news is that identifying the few relevant variables is still often a matter of intuition on the part of the modeler. Systems biology needs a more stringent way of identifying the most relevant elements of a model.

Then it needs to be able to define a hierarchy of subsystems and the way they interact. What do solutions at one level (e.g., metabolic pathways) mean to solutions at another (e.g., cells, tissues, organisms, populations)? In order to start to understand a problem that involves many interacting systems within the same organism, we will need to determine the type of data at each level of organization that needs to be collected, the boundary conditions to use when describing a disease (*i.e.*, a perturbed system), and the technologies and approaches best suited to uncover the disease etiology.

It will not be straightforward for mainstream biology and biomedicine to integrate computer modeling. Although the magnitude of the experiments required to validate models will require enormous investment, the frequent failure of clinical decision-making, the dismal success rates of drug discovery programs, and poor returns for investors should provide strong incentive. And for those who do make the leap, the chance to glimpse what lies beyond biology’s interlude will be its own reward.