Next-Gen Biophysics: Look to the Forest, Beyond the Trees

A modest proposal for cell biophysics going forward. In terms of the classic *forest-and-the-trees* metaphor, we humbly encourage more big-picture, top-down modeling (i.e., the "forest"), in contrast to details-first, bottom-up modeling (i.e., the "trees"). The difference is expressed (tongue-in-cheek) in Yuri Lazebnik's classic piece "Can a Biologist Fix a Radio?" (15). In the bottom-up approach, you snip out individual resistors, capacitors, or other individual components to see which ones cause the radio to stop working. But living systems are complex, and engineers of complex systems—like TVs, computers, smartphones, and modern airplanes—don't learn that way. Engineers reason from the top down, understanding first the large functional pieces—amplifiers, oscillators, tuners, and processors—followed by the details. This approach reveals what the device *is trying to do* at each scale. Cell biophysics needs more of this kind of reasoning too.

We've become pretty good at seeing the trees. Today's structural biology, of inferring function from structure, is a juggernaut of bottom-up knowledge generation. We know the detailed sequences of biomolecules; we know protein native structures angstrom by angstrom; we have molecule-by-molecule maps of biochemical pathways; we design pharmaceuticals atom by atom; and we have single-nucleotide polymorphism (SNP)-by-SNP comparisons of sequence–disease relationships in genome-wide association studies. This approach is powerful because discovering drugs and mechanisms requires atomistic granularity, because our underpinnings in molecular physics and chemistry are so solid, and because it harnesses the efficiency of the pharmaceutical industry. Bottom-up approaches are growing ever more powerful: Cryo-electron microscopy, deep learning, and molecular dynamics (MD) continue reaching to bigger and more complex molecules, assemblies, and systems.

But seeing the forests should be a major goal too. Biology has plenty of big-picture questions. What drives cellular aging and death? What determines a cell's fitness for its environment? What advantage does a cell gain by being cancerous? How do we understand those adaptations—like in aging and cancer—where hundreds of a cell's genes change expression levels loosely together? How can one cell be so combinatorially different from another cell in its mutations and still be the same cancer? Like engineers with radios, reasoning down from the top is crucial for fixing what's broken. But it's also more than that. It allows us to ask not just "*What Is*?", but also "*What If*?" Imagine a

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future biology industry where—like in today's semiconductor industry—it is possible to design cellular life at will, to your specification.

Bottom up, *even in principle*, might never give the view from the mountaintop. Science is filled with examples of emergent properties, like phase transitions, where properties at one scale cannot be inferred from properties at the next-smaller scale. Philip Anderson, in a famous paper, "More Is Different" (1), argued that the behavior at each scale requires new concepts. Valence electrons, Cooper pairs, the Debye screening length, reptation in polymers, supply and demand curves in economics, and the R_0 infectivity in epidemiology are examples of theoretical concepts that convert incomprehensible complexity at the small scale to workable understanding at the larger scale. Living systems are the epitome of more-is-different complexity, with pathways of bucket-brigade-like linked functionalities, with global balances of expression levels across whole proteomes, and with the temporal sequences of events that assemble them.

The paradigm for top-down modeling is theoretical physics. We need theory, as distinct from—and complementary to—either experiments or computations. Theory is often hypothesis driven; i.e., the modeling comes before experiments, resting on assumptions not yet proven, and validation comes from testing the implications and not the premises. Consider the metaphor of scientific understanding as if it were a broad multicolored fabric (principles) of single-colored patches (particular results). While experiments, database methods, and MD simulations can illuminate one patch or another, theoretical modeling is the broader multicolored fabric. Theoretical modeling seeks the connections, principles, forces, causalities, and emergent behaviors through the exploration of variables. What is the essence? What matters most? Which "knobs" turn big dials, and which knobs turn small dials? Sometimes, details matter, and sometimes they don't. Theoretical models can help sort these situations out.

Theoretical modeling has a venerable history in physics. Top-down modeling can glean principles of matter that bottom-up simulations cannot show. Consider phase transitions and critical phenomena. You could compute the gas-to-liquid transitions of particular molecules, say, nitrogen or argon. But from the critical-phenomena revolution precipitated by the Ising model (12; see also 3) and Renormalization Group theory (21), we learned the universal principle—now applicable across physics, chemistry, biology, and social phenomena—that details often don't matter and macroscale order–disorder transitions emerge from nearest-neighbor interactions. From theories of Einstein (8), von Smoluchowski (20), and Fokker-Planck related to Brownian motion, we learned how to treat diffusion, fluctuations, and distributions in small things from single molecules to cells. From polymer theories and lattice models (6, 9, 11), we learned how the folding of proteins, RNA, and chromatin, as well as the assembling of membraneless organelles, is less about the atom-by-atom details and more about the general nature of flexible, bead-like chains (2, 18, 19). From Debye-Huckel and Poisson-Boltzmann theories (5, 7, 10), we learned how to separate generic electrostatic screening effects from molecule-specific solvation forces.

Cell biology, too, has benefitted from theory. Theories have shown that biology, too, is not always about details, particulars, and evolutionary frozen accidents. Peter Mitchell's (17) chemiosmotic hypothesis, awarded the 1978 Nobel Prize in Chemistry, proposed that the energy source for ATP production was stored in concentration

gradients across membranes, not in chemical bond energies. Frank Macfarlane Burnet (4) and Niels Jerne (13, 14) predicted, in Nobel Prize–winning research, how the immune system could produce antibodies specific to a foreign antigen without targeting host proteins and give a broad immune response. Biologist Salvador Luria and physicist Max Delbrück (16) developed the Luria-Delbrück probability distribution, recognized by the 1969 Nobel Prize in Physiology or Medicine (shared with Alfred Hershey), asking whether mutations in bacteria are truly random or are pre-biased for fitness. It arguably initiated today's field of quantitative bacteriology. More such insights would be quite welcome.

For best results, trust the practitioners. Every field has its own culture and standards of acceptance. Theory has its culture too. But outsiders can't always tell the features from the bugs. (*a*) Assumptions and approximations are assertions of what's important. Good models should boldly probe the unknown. Assumptions, approximations, and parameters are ways of "putting knobs" on our ignorance. Of course, these should be as controlled and sensible as possible. But models serve us best when they make significant, falsifiable, and unexpected predictions. (*b*) It can be an advantage when predictions precede and drive experiments. The best theories can guide further thinking, suggest new experiments, and make unexpected predictions in advance of experiments. The Higgs boson was predicted in 1964 but not observed until 2012. Einstein's general relativity prediction of the perihelion of Mercury was predicted in 1915 and confirmed by Eddington in 1919. This theory led to today's understanding of curved space-time, LIGO's detection of gravity waves in 2016, and GPS positioning that can tell us precisely where we are. (*c*) Simplification is a source of power. Theories often strip out details deliberately, as a way of learning about what does and doesn't matter, not just because it's too hard to include them. Simplified theories include the hydrogen atom, Einstein's clocks on a train, modeling polymers as beads and rods, and approximating motions with harmonic oscillators. Good theories can reduce complexities to understandable simplicities.

Summary. We urge tomorrow's cell biophysicists to look beyond the trees to the forests, to top-down conceptual frameworks. Theoretical modeling will be key. And assumptions, approximations, and simplifications are often features, not bugs.

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