development of the single molecule technology and science in general.

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Putting the Cell Biology Establishment on the Stand

Cells, Gels and the Engines of Life
By G.H. Pollack
Seattle, WA: Ebner & Sons (2001).
305 pp. $27.95

When I was a graduate student, I set out to get a handle on cell biology by carrying out an extensive review of the literature, beginning with the earliest citations I could find. By observing how the field progressed over time, I hoped to get a better sense for where the field would move in the future. I read the preface of the first edition of a biochemistry textbook from the early 1900s which explained that, for simplicity, it was assumed that all reactions took place in a well-stirred solution in a test tube in the section on thermodynamics and kinetics. The authors clearly recognized that life was not a structureless chemistry and thus, they explicitly warned the reader that this limitation must be addressed in the future. However, when I read the preface of the second and third editions of the same textbook, this warning was nowhere to be found. I realized that generations of scientists were being trained without any awareness of this fundamental flaw in their understanding of what governed chemical reactions within a living cell. For this reason, I was not shocked when the cell biology "establishment" was taken aback by the suggestion that structural (cytoskeletal) scaffolds and mechanical forces play critical roles in virtually all aspects of cell regulation; they just never read the preface. In *Cells, Gels and the Engines of Life*, Gerald Pollack has done us all a service: he has provided us with a 305 page preface to the future of cell biology which warns us all—students and establishment alike—that there will always be a fine line between understanding and assumption.

While our knowledge of the molecular widgets that comprise living cells has exploded beyond our wildest dream, our understanding of cell architecture and the relation between structure and function still remain rudimentary. For example, one mainstream cell biology textbook defines the cell as "a small membrane-bounded compartment filled with a concentrated aqueous solution of chemicals," like a balloon filled with molasses. In fact, many biologists who work with molecules in isolation still share this view, as do virtually all lay people, including the congressmen and women who decide which science projects the government will invest in. Pollack views this image as a dragon that must be slain and I cannot agree more.

The living cell is a chemo-mechanical machine and it uses all forces and devices at its disposal—physical as well as chemical and electrical—to carry out its miraculous tasks. The reality is that the cytoplasm is a molecular lattice, known as the cytoskeleton, that is permeated and insufflated by an aqueous solution. The different molecular filaments that comprise the cytoskeleton—microfilaments, microtubules, and intermediate filaments—position the cytoplasmic organelles. But this is not a passive support system. The same scaffolds orient many of the enzymes and substrates that mediate critical cell functions, including signal transduction, glycolysis, protein synthesis, transport, and secretion; analogous insoluble scaffolds mediate RNA processing and DNA replication within the nucleus. This use of "solid-state" biochemistry greatly increases the efficiency of chemical reactions because they are no longer diffusion limited, and it provides a means to compartmentalize different cellular activities. The cytoskeletal system also can dynamically grow and shrink within different microcompartments as a result of the action of specific molecular regulators. Finally, the entire cytoskeleton is always mechanically tensed as a result of the action of contractile forces that are generated within cytoskeletal microfilaments. Because thermodynamic and kinetic parameters are sensitive to changes in molecular mechanics, physical distortion of load-bearing molecules can directly alter biochemical activities. Thus, both changing the level of the tension in the cytoskeleton and chemically modifying cytoskeletal architecture can significantly impact cell form and function. Indeed, it is through these varied functions of the cytoskeleton that living cells can exhibit behaviors that are far beyond anything observed in man-made materials. The abilities of a cell to move its entire mass upstream against the flow of blood or contract against hundred pound weights are two simple examples.

Given these novel features of the cytoskeleton and the global orchestrating role that it plays in cell regulation, it is surprising that none of these features are ever mentioned by Pollack. In fact, he rarely uses the term cytoskeleton when discussing the cytoplasm. Instead, the revolutionary concept he presents is that the cytoplasm is a gel. At first glance, it would seem that we have merely changed the model of the cell from a balloon filled with molasses to one filled with jello. However, there is something deeper and much more important in his message. While cell biology focuses on the molecular components that comprise living cells, Pollack centers his attention on the water molecules that swell the cytoskeletal gel and which, up to now, have been virtually absent from the cell biology radar screen.

In the beginning of the book, we are introduced to new and important findings from fields as wide as engineering, drug delivery, and nanoscale chemistry that demonstrate previously unexpected properties of water when it is in a bound state. Pollack explains that much, if not most, of cellular water exists in a highly structured state in tight association with the hydrophilic surfaces of cytoskeletal proteins. This state lies somewhere between ordinary liquid water and ice. In fact, water molecules assemble into higher order geodesic structures

because their dipole charge distribution exhibits a tetrahedral form much like the electron clouds of carbon.

The remainder of the story flows from this simple observation that cellular water exhibits structural richness and biophysical information content. For example, we learn that the difference between the solvency of structured water and that of bulk water is sufficient to provide a basis for the partitioning of solutes and a means to sustain ion gradients across the cell surface in the absence of membrane integrity. Herein lies one of the most provocative arguments of the book: perhaps it is because the cytoplasm is a hydrogel that cells maintain high internal K^+ and exclude Na^+, rather than through the use of specific transmembrane ion channels and pumps. This insight could explain our inability to unequivocally demonstrate tight ion selectivity of these molecules as well as the observation that many cells remain functional and sustain ion gradients after membrane integrity is lost. In Pollack's view, the ion channels and pumps exist; they just take on a more passive role with the gel properties of the cell providing the driving force. He also extends this argument to describe how phase transitions within the water phase drive electromechanical changes in the cytoskeletal gel that result in the generation and propagation of the action potential. The story is exciting and thought provoking; however, we never hear about the conventional side of the story, which has demonstrated that specific ion channels exhibit both functional specificity and clinical relevance. Yet, in a way, this is understandable because without laying out the story in these black and white terms—good guys versus bad guys—Pollack's message may never be heard above the din of convention.

Armed with this unifying concept, Pollack takes on the remaining dragons of cell biology and slays them one by one. Secretion becomes an explosive phase transition resulting from entrance of ions and water into a polyanionic gel; the cross-bridge model of muscle contraction is thrown out the window and replaced by a phase-transition-driven reptation model of acto-myosin filament sliding (undulation); and so on. The story always begins with a historical perspective, highlighting how multiple alternative hypotheses emerged at the beginning of each field, but most died away once the dominant model took hold. He reminds us how we tend to grasp tightly to conventional models, even when confronted by examples of conflicting results. It is hard not to appreciate his point. Many of our current beliefs in cell biology are ephemeral and will undoubtedly be replaced, whether we like it or not, by new and improved views, just like the epicycles which explained the planets' movements around the earth was replaced by Galileo's heliocentric model of the universe.

Given all my enthusiasm, I must say that, in the end, the unifying theme of phase transitions and water structuring may not be relevant for many biologists who only seek to focus on molecular binding interactions, chromosome mapping, or clustering genes. It may, however, be extremely valuable for cell biologists who are interested in more complex behaviors, for those who study cell and tissue physiology, and for bioengineers who seek to mimic the properties of living cells and tissues. A simple example is the important role that cytoplasmic pH plays in cell growth control. The conventional experimental approach has been to search for key molecules that exhibit a pH sensitivity that is similar to that of cell cycle progression. Pollack's insight provides an alternative path: perhaps the abrupt change in growth associated with a tiny increase in pH (0.2–0.4 units) that we observe in living cells is indicative of a phase transition within the entire cytoskeletal lattice or within a particular microdomain. This is a testable hypothesis; the same can be said for his elegant alternative models for secretion and actomyosin-based contractility. However, phase transitions and water structuring cannot explain all cell behavior. In the end, there is no real physiological relevance without molecular specificity. Thus, while the themes Pollack has uncovered and now champions are an important part of the equation, they are only one part of the solution. The challenge for the future is to follow this preface with a more detailed and thorough story that takes the good from both sides of the aisle and combines them to paint a more detailed and richer portrait of how cells work.

In the end, I would say that *Cells, Gels and the Engines of Life* takes the reader on a voyage through cell biology that is not unlike listening to the team of prosecuting attorneys play out their hand in the O.J. Simpson trial. The evidence laid out before you is shocking, unnerving, even titillating, to the point where it is hard to pull yourself away; at the end, you are so convinced of the defendant's guilt that you question whether you ever again can accept what you see in the world at face value. The difference in this case, is that we never get to hear the defense's side of the argument (whether worthy or not). Herein lies both the strength and weakness of this nicely sculpted and wonderfully illustrated polemic against complacency in the cell biology establishment.

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