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COMMENTARY (AND BOOK REVIEW)

POLLACK'S GEL PHASE-TRANSITION PARADIGM OF CELL FUNCTION

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The premise on which Pollack (2001) bases his exposition may be relatively unfamiliar to many and the question arises as to whether such ideas as gel-phase transitions are tenable. In this regard, we ought to consider these matters more closely because they are of such fundamental importance to our concept of the physico-chemical basis of the cell (and life).

Pollack's new book is divided into five sections, each of which is briefly reviewed. In the first section the author reviews and challenges the generally accepted textbook presentation that the relatively impermeable cell membrane with its ion selective channels and pump proteins explain the well accepted ion concentration differences between the intracellular and the extracellular environment (Alberts *et al.*, 1994). Much of his argument is based on the fact that cells with disrupted plasma membranes do not quickly equilibrate their ion concentration differences with the extracellular environment as might be expected by simple diffusion. The experimental evidence supporting his arguments are convincing. This leads to his conclusion that an impermeable membrane with its pumps and channels may not play the role envisioned by most cell biologists.

But if ions and proteins don't quickly leak from a cell with major holes in the plasma membrane, what is keeping them from diffusing out of the cell? This question is addressed in the second section of the book. Here the author emphasis the interactions of water and protein surfaces. In this section Pollack freely acknowledges the influence of Gilbert Ling (1984) and participants at a symposium he attended in 1986 (Tigyi *et al.*, 1991 and Edelmann, 2001). The physical properties of much of the water in cytoplasm are reported to differ from that of bulk water. Here I caution the reader that cited evidence for structuring of multilayers of water on inanimate surfaces of mica, quartz plates or on polymers with charged surfaces of linearized proteins and synthetic polymers may not fully equate with phenomena that take place on protein surfaces within the cell. However the author does present enough data on cell-water properties to support the conclusion that a large fraction of cell water has properties that differ from bulk water. As the distances between protein surfaces in most cells is small, there is only room for about 8–15 water molecule diameters between protein surfaces, thus only 4 to 8 layers of perturbed water on the protein surface would be enough to account for all of the water in most cells. Clearly a relatively fixed linear polymer or protein can perturb or polarize water for several molecular layers but most of the proteins in cells are globular and are not in an extended filament state. Here one must ask how much water can globular proteins motionally perturb. The answer may be more than the author envisions (Cameron *et al.*, 1997). The reason the author devotes so much attention to a perturbed 'structured' state of water in cells concerns its selective solvency for solutes of different size and charge. At the same time he reminds us that intracellular proteins have a net negative charge. Thus a case is made that Na^+ with a hydration diameter of 5 Å is excluded from the large fraction of structured water on protein surfaces in the cell but that K^+ with a hydration diameter of 3.8 Å is not excluded from this structured water and K^+ is therefore better able to approach and be adsorbed to the negative charge sites on the protein surface. *Viola!* We have an explanation for low intracellular Na^+ and high K^+ concentration without

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employment of membrane pumps or ion selective channels and no energy is required to run a pump to maintain ion content gradients. Even cell potentials can be accounted for by this model. Have we been run down the garden path with this cytoplasmic model? Certainly Pollack has placed a greater role on protein surfaces in the cytoplasm than on the membrane. Let me caution the reader that expression of ion concentration gradients based on a wet weight, as is most commonly reported to represent an ionic gradient, is not necessarily a measure of an ionic chemical activity gradient (Cameron *et al.*, 1990). If the activity gradient is less than thought, then membrane pumps, like the energy-requiring sodium pump, may not have so much work to do given that most of the job of Na^+ exclusion from the cell is done by solute exclusion from structured water.

Why not a hybrid model of the cytoplasmic and of the membrane models? An argument can be made that a cytoplasmic model is more parsimonious in explaining the existing data than is the membrane model. Indeed, key information on chemical activity of ions in cellular compartments is limited and controversial. However, to ignore membranes, pumps and channels is to make quite unhappy those that have devoted much of their life work and teachings to this popular paradigm. This seems especially so now that pumps and channels are being studied at the Å level of structure and function by crystallographic enzymology and genetic manipulations (Miller, 2001). The answer to which paradigm is the right one is that both are right because cells need multiple backup support systems just as do astronauts in space ships. As for me, as a living organism, parsimony be damned, give me multiple life support backup systems.

The third and fourth sections of the book build on section two and is a valiant attempt by the author to explain cell functions: secretion, action potentials, transport, cell division, and muscle contraction on the basis of commonality of properties of polymer gels and cytoplasm. Here Pollack selects gels and their ability to undergo phase-transitions under the influence of stimuli, i.e. pH, temperature, chemical agents, electromagnetic fields, pressure and mechanical force to explain the functional dynamics of cells. Clearly polymer gels can be used to mimic many functions performed by cells, but is this analogy more apparent than real? Throughout chapters 9 and 10 emphasis is placed on linear negatively charged polymeric matrices and their phase-transitions to explain secretion and action potentials. One can again question the evidence for linear proteins in living cells as the vast majority of cellular proteins are in a folded globular form. Does ATP and/or other solutes bind to globular protein and thereby cause extension of tight helix to a more extended confirmation, and if so is this conformational change adequate to perform a phase-transition in the cell? The polymerization of globular actin molecules into a string of globules (an actin filament) is not to be confused with the linearization of a single protein molecule. Or is filamentous actin just super good at structuring multilayers of water? Some evidence for the latter is offered in the book. What may be important about filamentous actin is its relative lack of mobility thus providing a stable enough platform to allow the time needed to build up multiple layers of structured water. It is a fact that actin selectively binds more than 60 proteins over many other proteins. Certainly the binding of specific proteins to actin can cause filaments of globular actin to break and to undergo bending. The author makes the case that actin gel contraction and solvation is an established feature of cell migration and filamentous actins ability to facilitate vectorial transport.

Chapters 12 and 13 deal with transport microtubules and cell division. The processes of transport on microtubule and their assembly and disassembly are described much as in most textbooks except that phase-transition is proposed as the mechanism for kinesins movement along microtubules while polymerization and depolymerization of tubulin is looked at as a phase-transition process to account for mitosis.

Chapter 14 on muscle contraction is the most authoritative in the book. The popular sliding filament concept of muscle contraction, where myosin heads attach or cross bridge to actin, swing and then detaches in the presence of ATP, is challenged and replaced by a model where all three of the filaments (i.e. thick, thin, and connecting) shorten. Thus muscle contraction is explained as a phase-transition involving monomeric condensation, helix-coil transition, or fold-unfold transition. All three filament types are demonstrated to shorten in discrete increments or steps. This chapter presents an alternative to the all familiar sliding filament model and deserves careful scrutiny and serious consideration as its replacement.

The fifth and last section of the book deals with energy that powers the phase-transition and a brief review of the preceding chapters leading to the pervasiveness of phase-transition as a mechanism of cell functions. ATP is discussed in terms of its ability to first tightly bind to proteins then to split

into ADP and Pi which drives contiguous proteins into their extended state causing surface change that induces bulk water into a multilayered structure, not in terms of ATP being a source of high energy upon hydrolysis into ADP and Pi. For example the binding of ATP to hemoglobin is known to reduce hemoglobins affinity for oxygen without hydrolysis of ATP. It is well known that the human erythrocytes change shape (crenate) when depleted of ATP (see Ling, 1984) and it is also reported that water and hemoglobin are both relatively immobile within the erythrocyte for many minutes following disruption of the plasma membrane (Cameron *et al*., 1991). These authors attributed their finding to associations between hemoglobin molecules resulting in reduced mobility of hemoglobin and in the reduced mobility of water in the membrane permeabilized erythrocyte. The conclusion being that retention of hemoglobin and associated water within the erythrocyte is not due to an intact plasma membrane. Are specific binding sites present to link hemoglobin molecules together or does binding with ATP cause a conformational change in hemoglobin to increase its structured water sphere perhaps leading to frictional resistance to motion? Pollack posits that the highly charged ATP molecule binds to protein and is then split into ADP and Pi which transduces metabolic energy into the structuring of multilayers of water. The entropy of the structured water is thus primed to do work.

The last chapter is a review of the main themes of the book: cytoplasm is gel-like and gels structure multilayers of water. Structured water excludes larger solutes while the gel matrix polymer with its change groups selectively adsorbs small solutes like potassium. Membrane pumps and channels may be present but are relegated to lesser functional roles than current dogma purports. Phase-transition is offered as a new paradigm to account for many cell functions normally attributed to membrane pumps and channels. Phase-transition may take the form of sol-gel or between condensation-expansion states with or without cross-linking. The role of the divalent cation in cross-linking gel filaments and in phase-transition is emphasized. In this regard Heilbrunn (1952) made clear the importance of calcium in studies of the colloidal chemistry of cytoplasm and one would do well to revisit his publications on viscosity, sol-gel transformation and the surface precipitation reactions.

The gel phase-transition model of the cell's cytoplasm has been questioned based on results obtained by attaching ferromagnetic beads to the cell's surface where they are held in place with optical tweezers then subjected to oscillating electromagnetic fields. The properties of cytoplasm were determined not to respond like a gel but rather to respond like a class of non-crystalline materials referred to as 'soft glass' which includes slurries, foams and toothpaste. The implication being that cytoskeletal proteins regulate cell mechanical properties mainly via modulating the effective noise temperature of the matrix. More information is needed to distinguish the true physical and molecular nature of cytoplasm (Fabry *et al*., 2001).

Ultimately the goal of cell biologists is to understand living cell dynamics in terms of information encoded in the cell's genome. Complex sets of interacting proteins are already being studied based on genome sequences. The types of protein interactions are being correlated to gene sequences leading to completely predictable functional proteosomes (Walhout and Vidal, 2001). It seems likely that molecular genetic approaches and computer modeling will become a key tool to understanding the complex dance of life.

I do recommend that cell biologists and cell physiologists read Gerald Pollack's new book because it presents important experimental findings that have either escaped the attention of most modern biologists or have often been ignored. The book presents much of this body of missing information in one place in a pleasant readable style with many insightful and colorful illustrations. My search of web-sites gave list prices for soft cover ranging from 35$ down to 18.50$ U.S. and hard cover from 74$ down to 45$ U.S.

Is the book a balanced presentation of facts? No, because the author's aims are to bring forth underrecognized experimental facts and to offer new ideas on how cells function. In this attempt he has been successful. Realize that the book is not a comprehensive textbook of molecular cell biology. To be fair, current cell biology textbooks sometimes mention that the state of water and ions in cells may be different than under dilute aqueous conditions but that is as far as the subject goes. I hope many of my cell physiology colleagues will read, think, discuss, challenge and teach the facts and ideas presented in Pollack's book. It seems apparent that anyone attempting to explain a phenomenon like cell volume regulation based solely on the modern membrane paradigm or solely on the cytoplasmic gel phase-transition paradigm is doing so based on unfounded assumptions. Will the thesis put forth in this book lead to a revolution in our understanding of cell function? As Pollack puts it 'stay tuned'.

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