Book Review

Cells, Gels, and the Engines of Life

A Oberst

Cell Death and Differentiation Rome Editorial Office: Correspondence to: drew_oberst@hotmail.com

Cell Death and Differentiation (2003) 10, 266–268. doi:10.1038/sj.cdd.4401201

Cells, Gels, and the Engines of Life. By Gerald H Pollack. Ebner and Sons Publishing, Seattle, Washington, USA: 2001. pp 305. ISBN: 0-9626895-2-1. US\$27.95

My introduction to cellular biology was accompanied by a schematic drawing of a generic mammalian cell, a diagram that has been reproduced thousands of times in textbooks and journals. The colors vary, but the idea remains the same: The cell appears like a tiny balloon, with a pink nucleus, red mitochondria, blue Golgi, and so on, all surrounded by a thin line labeled 'cellular membrane'. The cell's key players float in a pale yellow sea called the 'cytoplasm', and beyond filing this word away for possible exam-day use, I had never really paid much attention to the seemingly innocuous solution in which the cellular drama unfolds. Of course, I later learned about cellular signaling, ion partitioning and pumping, and intracellular trafficking, but in each case, the cytoplasm itself stayed in the background. This was a naive oversight, and one that has been resoundingly remedied by a recent publication by Dr. Gerald H Pollack, grandly entitled 'Cells, Gels, and the Engines of Life'. In this book, Dr. Pollack argues that the structured state of cytoplasmic water is of central importance to a huge array of cellular processes, from ion pumping (a term whose intrinsic meaning Pollack challenges) to essential cellular structure and motility.

As this introduction should make clear, I'm not sufficiently expert on this topic to offer an informed critique of Pollack's hypothesis. However, I also have no prejudice, and I belong to the book's apparent target audience: generally well-informed biologists schooled in the traditional dogma of cell function. The book itself, comprising five major sections subdivided into 16 chapters, does an excellent job of walking the fine line between 'boring' hardcore scientific tome and 'insubstantial' pop-science rag. It is a beautifully produced volume full of color pictures, whimsical, cartoonish illustrations, and fanciful pictures (a car shaped like a stiletto high-heeled shoe opens a chapter called 'transportation with flare'), and Pollack keeps the tone light and readable throughout. Casual readers thus placated, Pollack also gives a nod to his more critical readership with a 14-page reference section and plentiful allusions to 'further readings' on all major topics addressed.

The first section, headed 'Toward Ground Truth', is an eye opener indeed. In the initial pages, the author compares the current state of cell biology with that of pre-Galilean astronomy, in which increasingly complex models of planetary motion were required to explain the mistaken hypothesis of an earth-centered solar system. This leads briskly into a

challenge of the function of membrane-based ion pumps and channels; while the author concedes that proteins with pump- and channel-like properties do exist, he argues that the evidence that these proteins are actually responsible for observed cellular ion partitioning is sketchy at best. Pollack complains that the current models are based on a series of unfounded assumptions made to explain the phenomenon of ion partitioning. For example, intracellular sodium concentration is low, despite the fact that sodium can pass through the cell membrane; a pump was hypothesized to rid the cell of sodium, and the hypothesis stuck. The well-known patch-clamp technique, a long-held gold standard for the pumps-and-channels model, is also criticized, in that silicon rubber, a polyethylene terephthalate filter, and a pure lipid bilayer all yield the distinctive current pattern thought to indicate the presence of an ion channel. The existence of 'proteins exhibiting pump-like or channel-like behavior' is justified by possible signaling roles.

Storming ahead, Pollack next challenges the current thinking that the cell membrane is a continuous barrier that keeps small molecules in or out of the cell. This challenge is buttressed by the observation that ripping substantial holes in the cell membrane, and even cutting cells in half, does not cause the contents of the cell to gush out, deflating the victim like a ruptured beach ball; instead, cells can survive such assaults with little consequence. Finally, the nature of the cytoplasm itself is considered: cytoplasmic water freezes at lower temperatures than pure water, and ions do not diffuse as readily in the cytoplasm as in a beaker, leading to the enigmatic and ominous conclusion that 'the cytoplasm is not the aqueous solution it is cracked up to be'. The first section ends leaving a significant gap in current theories of cell function: the idea of the cell as a membrane-bounded entity with pumps and channels that regulate the chemical makeup of its aqueous cytoplasm is called into question. To Dr. Pollack's credit, he ends the chapter with a 'perspective', which urges the reader to reflect on the obviously unconventional message presented thus far, and refers to standard texts on conventional cell function to help skeptics make an informed decision regarding the central message of his hypothesis.

The second section of the book, entitled 'Building from Basics', begins filling the holes in current cellular theory

created by the first section. First, water is considered, with special attention given to the ability of water to form several structured layers along charged surfaces. Indeed, the argument goes, it seems possible that the majority of cytoplasmic water is structured in most cells, given current calculations of charges and proximities of protein and DNA in the cellular environment. This structuring is cited as the reason for the nonliquid nature of the cytoplasm, which allows it to remain both largely intact in the event of membrane trauma, and largely unfrozen even significantly below zero. The riddles of the first section thereby partially solved, the discourse shifts to the implications of a structured-water cytoplasm for cytoplasmic solutes. It is postulated that solutes should be excluded from structured water based on their solvated size, that is, the size of the solute plus that of the shell of structured water that it carries. This idea is confirmed in experiments using gels, which are suggested to approximate the cytoplasm, and physiological potassium and sodium concentrations bear out this hypothesis: sodium exclusion is more pronounced than that of potassium, because sodium's hydration shell is larger. Finally, the cell potential is considered in the context of the structured-water hypothesis: Cytoplasmic proteins bear a net negative charge that is partially, but not totally, balanced by positive sodium and potassium ions, and the total cell potential therefore rests on the electronic makeup of the cell's proteins. This model thereby hypothesizes a cell whose ion exclusion and cell potential are intrinsic properties of the gel-like cytoplasm; the cell is in equilibrium, and no barriers or 'special widgets', as the author says, are required to keep ions in or out.

The brief third section of the book examines gels, with attention to gel phase-transitions and the possibility that similar mechanisms govern cell function. Several reasons for the gel phase-transition's attractiveness in this context are cited. First, gel phase-transitions have been shown to produce a variety of distinct, widespread changes in properties including permeability, solute composition, and shape, in response to subtle environmental shifts relatively in pH or temperature. Second, if cellular processes are based on the phase transition, the cell would be governed by the same well-known laws that apply to nonbiological systems, rather than, as Pollack puts it, 'special inventions of the celestial committee', leading to a sort of biological-chemical grand unification theory. Third, in Pollack's vision the phase transition would be the key mechanism in a wide variety of cellular processes, thereby uniting and simplifying our understanding of apparently diverse cellular processes such as motility, transport, division, and secretion.

In the book's sprawling fourth section lies the real meat of Pollack's argument, in which the carefully constructed hypothesis of a gel-like cytoplasm, in which the phase transition plays a central role, is applied to several cellular processes: secretion, the action potential, transport, division, and muscle contraction.

First off secretion, for which Pollack proposes an elegant mechanism. The author observes that all secretory vesicles studied to date export cations (Ca^{2+} , histamine, adrenaline, etc.); furthermore, significant vesicular volume expansions have been observed upon secretion. Pollack therefore proposes a 'jack in the box' mechanism, by which the negatively charged

protein polymer matrix within the vesicle is crosslinked by the very multivalent cations being released, leading to condensation of the matrix. This condensed-matrix export packet is encased in a lipid bilayer and shipped to the cell surface; once it is outside the cell and free from the bilayer, the high extracellular concentration of monovalent sodium ions displaces the divalent crosslinkers by virtue of sodium's higher affinity for negative surface charges. The monovalent sodium ions are incapable of effectively crosslinking the polymer matrix, leading to its rapid expansion; the lipid shell encasing the vesicle, while it is inside the cell, serves to protect the vesicle from monovalent potassium, which could cause premature expansion. A similar model is proposed to explain the action potential: The peripheral cytoskeleton, which lies just below the cell membrane, is condensed by divalent calcium ion crosslinkers, forming an impenetrable barrier. Upon the receptor-mediated local influx of monovalent sodium ions, the crosslinkers are displaced and the peripheral cytoskeleton expands, leading to increased permeability and more sodium influx; unlike the matrix found in secretory vesicles, the peripheral cytoskeleton is covalently crosslinked independent of calcium, and the expansion is therefore controlled. Eventually, the influx of sodium destabilizes the structured water bound to the expanded matrix, and the matrix recollapses, expelling the matrix-bound sodium and re-establishing the resting state of the cell.

A phase-transition explanation is also put forth for 'streaming', the primitive form of transport that carries substances through the cell in a flowing stream along actin filaments. The streaming organelle comprises crosslinked strands of actin, with associated myosin proteins. Pollack proposes a 'propagative melting' mechanism to explain the flow of substances along these filaments: It has been observed that the binding of certain substances (such as the protein gelsolin) to the end of actin filaments leads to a structural change in the filament, which propagates along its entire length. Actin filaments have a high propensity to induce order in surrounding water, and this local organization would presumably be disturbed as the structural change propagated along the filament's length. As this 'window' of melted water sweeps along the length of the filament, nearby solutes would be swept along as well because of their increased solubility in unstructured water relative to structured water. A conceptually similar model is proposed for microtubule-mediated transport. In the classical model, microtubules are able to transport cargo molecules specifically thanks to the action of kinesin and dynein proteins, which 'step' along the microtubule. Dr. Pollack proposes a counter model, in which binding of these proteins to the microtubule induces a local, asymmetrical 'melting' of the tubule's associated structured water, briefly freeing the cargo molecule to move in the direction determined by the melt's asymmetry. The water then restructures, 'freezing' the cargo into its new position. A subsequent chapter applies these concepts to the cytoskeletal dance required for successful cell division and chromosome partitioning.

Finally, Dr. Pollack dedicates a chapter to his own field of muscle contraction, a topic which he has already addressed in a book and several reviews. Not surprisingly, he attacks the established view that thin filaments are driven past thick by a

series of ATP-dependent protein steps, in which the filaments themselves do not change length. Instead, Dr. Pollack tackles the question of contraction with the hypothesis of a series of phase transitions in the thick, thin, and connecting filaments, all of which entail length-changes in the filaments themselves. Thin filaments are hypothesized to behave in a manner similar to the 'streaming' actin microfilaments already mentioned, while thick and connecting filaments are hypothesized to function via a protein folding mechanism involving helix-coil and fold-unfold transitions, respectively, both associated with disordering of vicinal water. In effect, the proteins are held in their extended state by vicinal water, and are subsequently induced to 'melt' into shorter coiled states by, you guessed it, a phase transition.

Finally, the book ends with a section entitled 'Tying Up Loose Ends', the highlight of which is the energetic hypothesis upon which the above-mentioned ideas are based. All the hypotheses for cell function put forth by Dr. Pollack, from the expansion of the condensed matrix in the secretory vesicle to the contraction-inducing collapse of muscle proteins, involve the cashing in of potential energy in the form of order in exchange for action resulting in loss of order. Dr. Pollack likens the cell to an entropic battery, in which ATP generates energy by inducing order in cellular water, which in turn extends proteins into higher-energy states, preparing the cell for action. When action is needed, this order can be broken down, using up the potential energy of the ordered state in a 'domino effect' of action. ATP from the mitochondria can then go forth and bind to the relaxed proteins, re-extend them by reinducing order in vicinal water, and thereby recharge the cell for a new cycle of action. While Dr. Pollack's theory maintains that ATP is the energetic currency of the cell, he hypothesizes that it exerts its action not by liberating chemical energy, but rather by inducing order in the cell's water molecules, which can later be broken down to do work.

This book is, without doubt, an impressive example of informed scientific dissent. Dr. Pollack has obviously thought long and hard about all these questions; his obvious enthusiasm for his hypothesis is matched by an impressive depth of research, and he is obviously intimately familiar with the seminal works from the last 100 years on both sides of the

debate. While my brief summaries of the mechanisms proposed by Dr. Pollack may make them seem outlandishly unconventional, the text itself contains extensive explanations of why current theories have been called into doubt, and why the author's hypothesis deserves consideration. Throughout, the author avoids the embittered tone often adopted by those whose cherished theories run against accepted dogma, adopting instead an admirably patient explanatory tone and urging readers to decide for themselves which fundamental hypothesis deserves acceptance. The mechanisms proposed by Dr. Pollack are extremely elegant and well-conceived, and if the abbreviated explanations presented in this review pique your curiosity, be it in the form of inspiration or incredulity, I strongly recommend that you take a closer look at the text itself.

That said, Dr. Pollack's work is far from complete. His book tends to shy away from the details of certain mechanisms; while this is perfectly understandable given its hypothetical nature, the blanks must be filled in if the theories are to be accepted. While the models presented are functional and at times beautiful, they are too often preceded by disclaimers (this *could* be a *possible* mechanism), and too rarely followed by references to studies where the mechanisms are explored at the bench. While Dr. Pollack often presents studies demonstrating that the physical and chemical principles underlying his models are sound, direct tests of the models themselves are often lacking. While the very breadth of the author's vision makes its proof a daunting undertaking, the fact that his hypothesis calls for a re-evaluation of fundamental aspects of biology ranging from membranes to energetics means that ironclad proof is absolutely necessary for its acceptance. The simplicity and unity of Dr. Pollack's hypothesis is beguiling, but biological systems are the result of billions of years of herky-jerky evolution, not rational design, and the prettiest explanation is not always the correct one (just look at the shamefully cluttered state of any mammalian genome). Ultimately, modern science involves forming a plausible, informed hypothesis and then experimentally verifying it; Dr. Pollack has done an admirable job at the former, but only time will tell if he and others succeed at the latter.