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BOOK REVIEW

Mathias Grote, *Membranes to Molecular Machines: Active Matter and the Remaking of Life*. Chicago: The University of Chicago Press, 2019

Grote opens *Membranes to Molecular Machines* (Figure 1) by challenging us to think of ourselves not as flesh and blood, but rather as an assemblage of diverse molecular machines which can be manipulated to slow, accelerate, or refine specific functions and, thereby, improve the human condition. The book suggests that our thinking has evolved to view biology and medicine in molecular-mechanical terms rather than in holistic or Linnaeus-Darwin-Mendelian ones. The author argues (page 20) we should "forget about founding fathers altogether" and "confront the diversity and heterogeneity of recent science, asking new questions pertinent to our day."

To make his case, Grote outlines the evolution of our understanding of molecular machines by exploring those found in biological membranes. His focus on membrane molecular machines is useful for several reasons. Although he could have chosen to explore the history of our understanding of the ribosome, DNA polymerases, or any other molecular machine, the study of membrane molecular machines (carriers, pumps, hormone and light receptors and the photosynthetic reaction centers) became "molecularized" only after 1970. Their study not only illuminates a much broader field but also permits an analysis of the rise of the molecular life sciences as we know them today, with its orientation to molecular machinery.

The book is divided into two parts. In the first, Grote describes how our understanding of membranes and the methods we use to study membranes evolved as biologists dismantled them to isolate and analyze their constituents. In part two, the author describes how we learned to remake membranes and the broader impact that these emerging skills and understandings have had on society.

Part one begins with an historical perspective on biological membranes. Grote quotes (page 29) E. Newton Harvey's forward to Hugh Davson and James Danielli's 1952 article on "The permeability or natural membranes": *Just as chemistry could not have developed without test tubes to hold reacting substances, so organisms could not have evolved without relatively impermeable membranes to surround the cell constituents*.

It was clear to all that without membranes, cells would not be discernible, leaving us with some ill-defined protoplasm or surface within or upon which metabolism and heredity take place. One obvious consequence of enveloping a cell within a membrane (ie, living in a container) is that this boundary or membrane must be traversed for metabolism to occur. Thus, membranes contain transport systems (carriers, pumps, and channels) to deliver and export metabolites and receptors for communication between the outside world and the cell's interior and, thereby, stabilize the "milieu intérieur."[1]

Grote takes a dim view of the state of knowledge of membrane molecular mechanisms in the 1960s. At that time, scientists were trying to synthesize "order" out of the disorder embodied in an imperfect understanding of membranes, surfaces, and ionic gradients. Delbrück and others sought to uncover a general mechanism for how membranes mediate signals between organisms and their environments or how they transport substances. The futility of this goal at the time was illuminated when Efraim Racker humorously opined (page 35) that "Anyone who is not thoroughly confused just does not understand the situation." The search for a unifying hypothesis would later evaporate in light of the diversity of membrane molecules and mechanisms discovered.

The author points to Arthur Pardee, who suggested (page 34) that the details of membrane activities such as the transport of substances into cells were "completely mysterious" and that the existing "black box approach" of physiology did not allow one to decide the central issue of mechanisms.[2] However, molecular mechanisms cannot be established without overarching data describing the functional behavior of an enzyme. Molecular models, no matter how detailed today, remain sophisticated attempts to explain black box data or biological behavior and by the 1960s a growing number of transport systems had been described in exquisite mathematical detail.

Grote suggests that by the mid 60s, membrane pumps were no longer metaphors without a material substrate; however, what mechanism(s) accomplished the pumping of substrates remained elusive. Pumps and membranes were still far from being recognized as discrete molecular objects. Nonetheless, it is worth emphasizing the challenges that biochemists and physiologists at that time faced in studying membrane activities. Their attempts to explain membrane transport systems drew heavily from their understanding of molecular systems known to function in the aqueous environment. They surmised that membrane transporters and receptors were enzymes and, understanding that enzymes are

proteins, concluded that membrane proteins did this work. They lacked the necessary tools to isolate and visualize their protein[s] of interest.

The author proceeds to discuss his concept of active matter in an engaging Chapter 2 that narrates of the discovery of bacteriorhodopsin (BR) and the studies giving rise to our understanding of BR function and structure. As such it reveals the personalities and motivations of the major figures in the field. These include but are by no means limited to George Palade, Walther Stoeckenius, Dieter Oesterhelt, Allen Blaurock, Maurice Wilkins, Richard Henderson, and Nigel Unwin. It also illuminates the development of new technologies that allowed the field to advance as it did. In many ways, BR is an unusual choice through which to explain the development of our understanding of pumps. Proton transfer via a light-activated proton relay may not be representative of most channels or carriers whose substrates are often significantly larger than protons and thus necessitate much greater conformational changes in either the translocation pathway, the gating mechanisms or both to effect transport. Multi-drug resistance (MDR) proteins (notable given how they limit the effectiveness of many cancer drugs and antibiotics), the major facilitator super-family, the e_1e_2ATPases, or the voltage-gated cation channels might have been better choices. However, the choice of BR is justified not only by the first-hand insights the author provides, but also by his recounting of the use of X-ray diffraction and crystallographic electron microscopy of purple membranes (2-dimensional arrays of BR-rich membranes) to analyze BR structure. Grote recounts Henderson and Unwin's pioneering treatment of electron micrographs not as images for inspection by eye but rather as data sets for mathematical analysis to aid in the reconstruction of protein structure. These approaches would give rise to cryo-electron microscopy techniques to expose BR structure—the latter method currently, radically, and altogether transforming the field of structural biology.

Part 2 turns to how we learned to remake membranes and molecular machines. In Chapter 3 Grote recalls the transition from chemical and biophysical to molecular biological approaches to analyze the membrane machines and how we, thereby, became masters of the molecules we study.

Today one approach to studying membrane proteins is to chemically tag a genetically modified protein then add substrate to observe how the protein responds (eg, through a change in shape). This requires that we can isolate and reassemble all the parts of a membrane as individual molecules—lipids and proteins. The author suggests that the availability of such molecules and thus the "materiality" of life's molecules have changed. An alternative view is that their materiality has not changed—just our perception of their "molecularity." Grote goes on to suggest that life has become mechanical because it can be taken apart and put back together at the level of molecules and cells. Can the essence of living things be explained by their materiality? Millennia of natural selection have shaped the adaptability of cells and organisms which often react to stress in unexpected ways. Reductionism may explain cellular responses but does not always predict them.

Grote places great emphasis on our ability to make any protein we want and that these molecules are self-organizing. Khorana's cloning of BR allowed us to map primary and secondary structure onto Henderson's BR tertiary structure—a truly remarkable advance. While lipid bilayers are self-assembling, macromolecular structures whose formation is entropically driven by the hydrophobic effect, protein insertion is more complex, may be enthalpically or entropically driven depending on the composition of the lipid bilayer and, in nature, occurs co-translationally.[3] The author neither discusses how the thermodynamics of membrane molecular machinery assembly and insertion permit self-organization nor the involvement of the co- and post-translational molecular machinery required for protein maturation. Grote argues that because we can reconstitute wild-type and mutant membrane proteins into synthetic lipid bilayers, we now have a plug and play approach to life. But do we? Just as we domesticated cattle, crops, and fungi to provide for our nutritional needs, we have now domesticated cells to further our study and production of molecular machines. We still need biologically vital cells or their organelles to transcribe the redesigned gene, translate its RNA into protein, then fold and secrete the protein. Grote calls protein engineering a man-made process. But is it? While we can now create self-assembling artificial lipid bilayers from synthetic lipids and use the resulting "liposomes" for membrane protein reconstitution or for targeted drug and nucleic acid delivery to cells and organs, is not the design and production of novel proteins still a human-designed but cell-executed process? Nevertheless, Grote's view that molecular cloning, sequencing, and expression techniques transformed modern biology is fundamentally correct. Life's materiality has changed before our eyes during recent decades.

Chapter 4 is titled "Biochip fever: Life and technology in the 1980s." The first part of this chapter follows the visionary idea that biochips (eg, a light sensitive BR array) could replace computer chips not only in material form but also in their ability to undertake parallel computing. This has not been realized for several reasons. First the idea was impractical. To be useful, it would be necessary to manufacture robust, light sensitive BR films coupled to computer circuitry. This was not achieved on a commercial scale. Second, silicon-based computer CPUs have continued to follow Moore's law, can be assembled as multicore structures and their miniaturization now exceeds what may be possible with proteins. Molybdenum disulfide and carbon nanotubes, for example, promise the construction of transistor gates smaller than 1 nm. Parallel computing is now served by super-fast, multicore, silicon-based CPUs, but the slower, most powerful biological, parallel computers (humans), unlike their

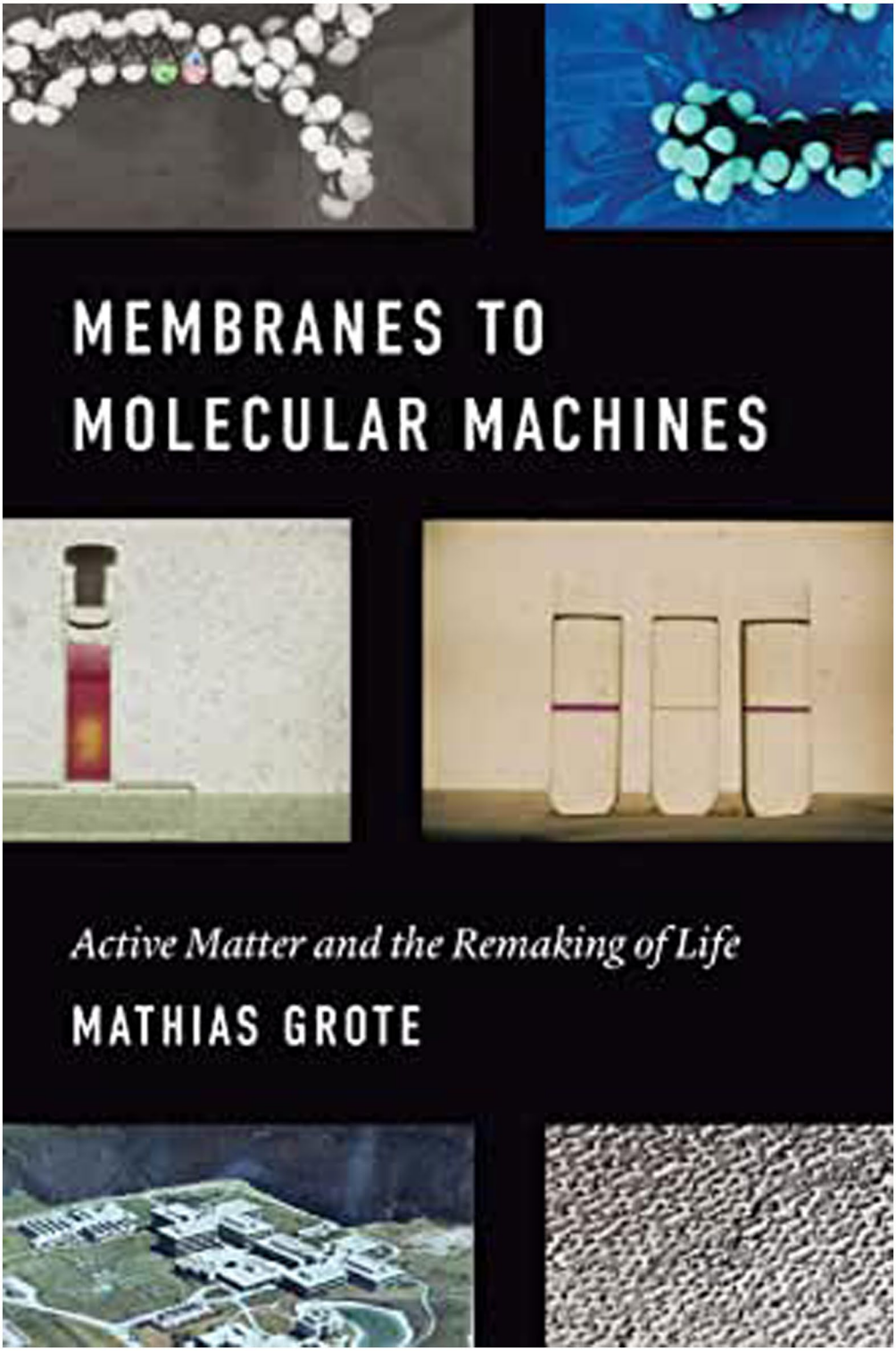

FIGURE 1 Cover to "Membranes to Molecular Machines" by Mathias Grote.

silicon counterparts, are also capable of self-replication and self-improvement.

Grote tells the story of the leaders in the biochip field and describes how little of their work was peer-reviewed. Indeed, for many life sciences practitioners, large parts of this chapter will feel like reading science fiction. There is also an interesting discussion of how governments responded to fears of falling behind in the international biocomputing race with increased research funding. All was not lost, however. Grote points out that the financial promise of biotech was eventually realized through its application in the life sciences and medicine if not in biocomputing.

The author concludes with several provocative theses.

1. *The life sciences have revealed that the intrinsic property of matter leads to the formation of self-organizing complex structures*. This thesis omits any discussion of the thermodynamics of the process and how materiality can give rise to self-repairing, self-replicating biological systems.
2. *Life is now unmade and remade by the human hand and mind*. This reviewer would prefer *Some building blocks of life can now be unmade and remade by the human hand and mind*.
3. *Molecular life sciences are not just an "engine of discovery" but rather are equal to human activities that dismantle and rebuild organisms and their components and, thereby, alter the makeup of both the living and chemical realms*.

Grote boldly considers that his discussion of molecular machines has not yet revealed how they were designed or reproduced. Currently, their refinement is via evolution through natural selection. This, echoing Virchow, implies that the cell is both prior and primary for the design and production of molecular machines.[4] The author suggests that scenarios for the molecular origin of life (eg, the RNA world) may provide alternative explanations and solutions to this contradiction. This is, of course, a central question that, in different ways, challenges the thinking of scientists, the lay public, philosophers, and theologians alike.

Grote offers a path forward by pointing out that although the quest for general principles or laws for how organisms work on the molecular level might have been abandoned by many of the contributors to the advances described in his book (with the exception perhaps of contemporary systems biologists), the underlying assumption that life processes can be explained by molecular-mechanical interactions and reactions remains widely endorsed. Rather than call this assumption "reductionism" Grote (page 199) prefers "materialism" or "chemicalism."

This is a very readable book which explores how our understanding of the composition, structure, and function of membranes has evolved during the last century. The author successfully draws on his proximity to the field and his professional relationships with several of its key scientists to provide a rich history of the how the field advanced and to offer insights into the personalities and motivations of the major figures in the field.

In describing the molecules and detailed structures emerging from membrane studies, Grote argues that that life has *become* mechanical in a new sense because it can be taken apart and put back together at the level of molecules and cells. Grote attributes this to a new, or at least revised, understanding of life's materiality. What remains unanswered is whether the essence of living things can be explained by their so-called "materiality" or how we might interrogate the meaningfulness of this materiality. While the rationale for exploring the evolution of our understanding of membrane molecular machines as a means of illustrating the materiality of life is sound, the selection of BR as the central focus of exploration is somewhat arbitrary although entirely forgivable given the author's professional history. Other membrane molecular machines such as the voltage-gated channels,[5] the aquaporins[6] or the channel rhodopsins[7] (the latter being especially resonant given their experimental and potential medical applications in opto-genetic control of CNS function) may have proven equally fertile material for discussion.

These quibbles aside, this is a well-written book that will find a wide readership among students and practitioners of cell biology, biochemistry, molecular biophysics, structural biology, and the history of science.

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