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Biological Membrane Ion Channels: Dynamics, Structure and Applications

Springer

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Preface

Ion channels are water-filled, biological "sub-nanotubes" formed by large protein molecules. They constitute a class of membrane proteins that serve as conduits for rapid, regulated ion movement across cellular membranes. Ion channels thereby provide the molecular substrate for rapid, electrical signaling in excitable tissues. In addition to playing this important role, ion channels regulate the release of hormones and neurotransmitters and control cell and body electrolytes and volume homeostasis. They are also involved in the transduction of external stimuli to sensory signals. Proper ion channel function is a prerequisite for normal cell, organ and body function—and disorders in ion channel function, channelopathies, underlie many human diseases, such as, cardiac arrythmias, cystic fibrosis, some cases of diabetes mellitus and epilepsy, myotonias and myasthenias. The list is growing. Not surprisingly, ion channels, which long were considered to be rather specialized entities studied by electrophysiologists, are attracting increasing interest.

In most, maybe all, ion channels, ion movement occurs as an electrodiffusive barrier crossing by which selected ions move through a water-filled pore. As the free energy profile the permeating ions have to traverse is relative flat, the throughput is high, of the order of 10^7 ions per second. It thus becomes possible to observe the function of single ion channels in real time using electrophysiological recording methods. Indeed, the first single-molecule measurements were single-channel measurements made almost 40 years ago on ion channels incorporated into planar lipid bilayers (Bean, R.C., W.C. Shepherd, M. Chan, and J. Eichner. Discrete conductance fluctuations in lipid bilayer protein membranes. *J. Gen. Physiol.* 53:741–757, 1969)—and the first single-channel recordings in biological membranes were made 30 years ago (Neher, E. and B. Sakmann. Single-channel currents recorded from membrane of denervated frog muscle fibers. *Nature* 260:779–802, 1976).

Electrophysiological methods improved, the power of molecular and structural biology was unleashed, and ion channels are no longer "black boxes" but molecular entities. Mutations in the DNA sequences encoding channel subunits cause well-defined changes in channel function, which range from mutations that compromise the delivery of the channels to their proper destination, over mutations that cause dysregulation of channel function, to mutations that alter the rate of ion movement. The mechanistic interpretation of these studies is guided by the availability of atomic-resolution structures of a growing number of channels, as well as by increasingly sophisticated computational studies ranging from *ab initio* calculations, over molecular and Brownian dynamics simulations, to continuum descriptions. Taken together these different approaches provide for unprecedented insights into molecular function.

Preface

The current interest in ion channels, however, arises not only from their biological importance; their high turnover numbers make ion channels well suited to serve as switches in sensors. Ion channels also are targets for a growing number of drugs. In many cases ion channels are the desired target(s), but serious side effects may arise from unintended (and unexpected) drug-induced changes in channel function. It is important to develop methods that allow for efficient screening for unintended side effects.

Though the basic functions ion channels are well understood, at least in comparison with other classes of membrane proteins, ion channels continue to pose a wide range of problems for which the principles and practices of biophysics, nanotechnology design, statistical signal processing ~~and~~ can provide elegant and efficient solutions. Indeed, the cross fertilization of ideas in these disparate disciplines will eventually enable us to relate the atomic structure of an ion channel to its experimentally measurable properties through the fundamental processes operating in electrolyte solutions or the basic laws of physics.

The aim of the present book is to provide an introduction to ion channels as molecular entities. It is aimed at researchers and graduate students in the life sciences, biophysics, engineering and computational physics who are interested in acquiring an understanding of the key research results in ion channels. Given the breadth of the field, we do not aim for a comprehensive coverage but focus on the physical description of channel function, the power of computational approaches toward obtaining mechanistic insight into this important class of molecules, and the possibility of the future developments in ion channel research. Thus, this volume is intended extract from the vast literature in ion channels~~,~~ the central ideas and essential methods regarding the dynamics, structure and application of ion channels.

The chapters in this book are organized as follows. P. Jordan in the first chapter gives a lucid account of the major advances made in the ion channel research over the past 50 years. In the following 11 chapters, some of the current issues in the main classes of ion channels are reviewed. These are: the gramicidin channel (O. Andersen, R. Koeppe II, and B. Roux), voltage-gated ion channels (F. Bezanilla), voltage-gated potassium channel (S. Korn and J. Trapani), BK~~Ca~~ channels (D. Cox), voltage-gated sodium channels (D. Hanck and H. Fozzard), calcium channels (B. Corry and L. Hool), ClC channels (M. Pusch), ligand-gated channels (J. Lynch and P. Barry), mechanosensitive channels (B. Martinac), TRP channels (T. Voets, Owsianik, and Nilius) and ion channels in epithelian cells (L. Palmer). These are followed by four chapters dealing with theoretical and computational approaches to studying the permeation of ions across biological ion channels. These chapters highlight the strengths and weaknesses of the main tools of physics that are employed in this endeavor, together with examples of how they are applied. The theoretical approaches that are covered here are the Poisson-Nernst-Planck theory (R. Coalson and M. Kurnikova), semi-microscopic Monte Carlo method (P. Jordan), stochastic dynamics (S. Chung and V. Krishnamurthy) and molecular dynamics (A. Grottesi, S. Haider, and M. Sansom). The final three chapters deal with new emerging technology in microfabricated patch-clamp electrodes (F. Sigworth and K. Klemics), an ion channel based biosensor device (F. Separovic and B. Cornell) and hidden Markov model signal processing techniques for extracting small signals from channel currents (V. Krishnamurthy and S. Chung).

The chapters appearing in this book thus comprehensively summarize our current understanding of biological ion channels and the state-of-the-art experimental and computational methodologies used in this field. We hope that the chapters contained in this volume will assist in advancing the boundaries of our understanding of the workings of ion channels and enhance multi-disciplinary research in ion channels.

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