Generally Physiological

A new standard: A review of *Handbook of Ion Channels*

Handbook of Ion Channels (2015)
Jie Zheng and Matthew Trudeau, editors
CRC Press, 691 pp.

The publication in 1984 of Bertil Hille's *Ionic Channels in Excitable Membranes* (Hille, 1984) marked a milestone and turning point in the field of ion channel biophysics and physiology. Not only did it provide a scholarly, comprehensive, and clearly written summary of the historical and conceptual framework of the field, it provided an essential introduction for beginners, including, importantly, scientists from other areas of biochemistry and biophysics who were not used to thinking about molecules in terms picoamps and millivolts. I wrote at that time, in a review of the book (Aldrich, 1985):

"Channels have traditionally been the territory of membrane biophysicists, who have used electrical measurements of membrane currents to make inferences about the functional and structural properties of the underlying channel molecules. Recently, however, biochemical techniques have been brought to bear on these channels and the most well-studied of them have been cloned and sequenced. The future will bring a valuable confluence of these molecular techniques with the biophysical study of engineered structural mutants of ion channels."

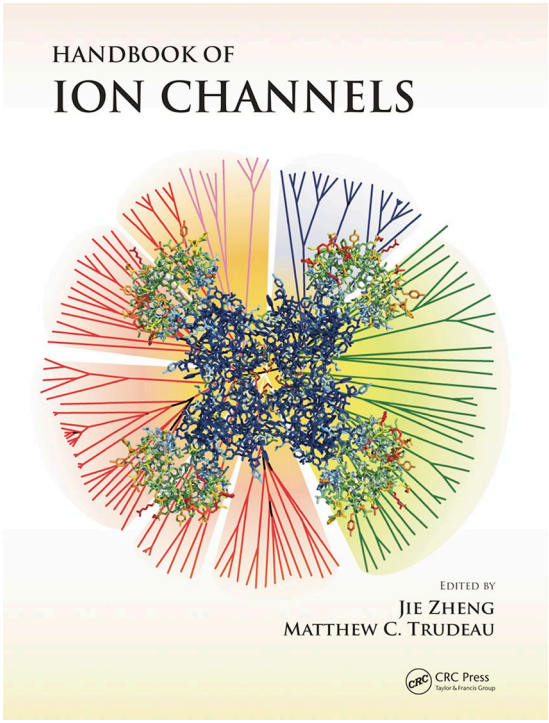
Although it did not take exceptional foresight to make this prediction in 1985, the last 30 years in ion channel research have been truly astounding, as these essential and fascinating molecules have been subjected to all available methods of visualizing, probing, illuminating, altering, mutating, calculating, radiating, activating, inhibiting, hybridizing, resonating, modeling, and evolving.

Hille's book, in no small part because of his exceptional scholarship and exposition, has been the standard work on the subject. However, the last edition was published in 2001, about halfway between the original volume and the present. Other books that stand out as tremendous resources and landmarks in the field are also rather old: Sakmann and Neher's *Single Channel Recording* (second edition; Sackmann and Neher, 1995) and Ashcroft's *Ion Channels and Disease* (Ashcroft, 1999), for example.

Thus, for several years now, researchers have discussed the need for a new updated and modern standard work for the field, particularly given the explosion of new approaches to channel research, some of which barely existed in 2001.

And now we have it. Jie Zheng and Matthew Trudeau have organized an authoritative multi-author "*Handbook*" covering much of the ion channel field, encompassing the conceptual, technical, organizational, and pathophysiological aspects of ion channel function, essentially expanding and updating the bulk of the material covered by Hille, Sakmann and Neher, and Ashcroft.

Zheng and Trudeau (2015) aimed for a comprehensive treatment of modern ion channel research, written by leaders in the field. They and their 71 expert authors, from 10 countries, have delivered a substantial treatment of contemporary ion channel research at 660 pages, consisting of 43 chapters divided into five parts: Basic Concepts (5 chapters), Ion Channel Methods (10 chapters), Ion Channel Families (18 chapters), Ion Channel Regulation (5 Chapters), and Ion Channel Physiology and Disease (5 chapters). Given the difficulties in organizing and author wrangling, Zheng and Trudeau, and their authors, have done an outstanding job, producing a volume that will become the essential ion channel reference for years, until the rapid advances of the field render parts of it out of date. May we hope for further editions.



Brief historical perspectives are provided by Bertil Hille, in a foreword about the Early Days of Ion Channels, and by Clay Armstrong in a chapter

that traces animal electricity from the 18th century work of Galvani to present-day structural biology. These two perspectives nicely trace the field from its beginnings, when ion channel research relied almost exclusively on electrophysiological methods by experimenters who built their own amplifiers and voltage clamps, to its current state where voltage-clamp recording is but one of a wide range of techniques that essentially encompass all appropriate methods of molecular biology, biochemistry, biophysics, and computational biology. It would not be inaccurate to describe contemporary channel research as a subfield of molecular biophysics that uses voltage-clamp electrophysiology, the best available method to measure and analyze the dynamic conformational changes essential for protein's biological functions. This exceptional ability to study biophysical function by the means of electrical signals exemplifies the value of ion channel research to the general understanding of protein biophysics.

The growth and progression of the ion channel field is nicely illustrated by tracing the treatment of molecular approaches as depicted by Hille's editions up to the current *Handbook*.

The first edition of Hille's book in 1984 contained a brief chapter on "Molecular Properties of Ionic Channels" that discussed the (then) recent progress on the purification and (very) low resolution structure of the nicotinic acetylcholine receptor along with the recently reported amino acid sequences of its subunits. Further inklings of the future consisted of mentions of purification of the sodium channel and characterization of *Drosophila* Shaker alleles that eliminated a particular component of potassium current from muscle, suggesting that it might be an ion channel gene.

By the time of the third edition 17 years later (Hille, 2001), biochemical and molecular approaches had become near equals with electrophysiology. Channel crystal structures were depicted, along with treatments of gating and permeation mechanisms derived from site-directed mutagenesis, and entire chapters are devoted to relations among channel families, protein structures, and cell biology of channels. The tables of important quantities and equations (physical constants, ionic radii, Ohm's law, and the Nernst and Goldman–Hodgkin–Katz equations) on the inside covers were joined, with equal prominence, by properties of the amino acids and dendrograms and gene names of sodium, potassium, and calcium channel families.

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After another 14 years, the current *Handbook* has fully integrated molecular measurements and thinking. Most of the chapters, except for some of those devoted exclusively to methods, freely incorporate multidisciplinary approaches to understanding function, as is the case in most laboratories studying channel function, represented appropriately and nicely by the authors.

These authors represent a selection of forefront researchers and leaders in the field, writing on areas of their expertise. The material is, with a few exceptions here and there, contemporary and authoritative. As is unavoidable in large multi-author texts, the level of exposition varies. I would classify most of the text to be at the advanced beginner or intermediate level. I find that the chapters on basic concepts would likely require elementary familiarity with mechanisms of gating and selectivity, as well as a bit of the underlying physical and chemical concepts to be the most effective. That said, I find these chapters to be first-rate, including some advanced concepts explained in a clear and valuable manner. It is curious, however, that inactivation gating is not discussed.

The 10 chapters on methods cover a wider range than most treatments of channels, aptly dealing with the state of the field, including electrophysiological methods, structural biology, kinetic and molecular modeling, spectroscopy, pharmacology, genetics, and high-throughput screening. I see most of these chapters as particularly appropriate for workers familiar with one area, say patch clamp, to understand what is involved with another, say cryo-electron microscopy.

The chapters on Ion Channel Families provide excellent summaries of the structure, function, and physiological role of the myriad families. This section will be exceptionally useful. However, it suffers from perhaps the biggest flaw in the book. In such a comprehensive handbook, it is distressing that some prominent classes of channels are not included among the 18 chapters, which includes 4 (!) on the subfamilies of TRP channels. There is NO chapter on three of the most important and best studied channel types/families: acetylcholine receptor channels, voltage-gated calcium channels, or voltage-gated K_v channels, by far the most well-studied and well-understood class. A few other classes are also missing, including one of my favorites, the small-conductance (SK) calcium-activated potassium channels. This deficit is somewhat alleviated by the prominence of K_v channels in the chapters on basic concepts, and of calcium channels as a regulatory target of calmodulin in the channel regulation section, but it is a substantial problem with what aspires to be such a comprehensive handbook.

An authoritative book such as this should include an accurate depiction of the development of the field in terms of citations to the important contributions. I find, as I am sure as

others would, a few annoying missing citations and unusual attributions, but overall the *Handbook* provides an outstanding source for the important primary literature. Most chapters contain extensive bibliographies. I do feel compelled, however, to point out two repeated (in several chapters) missing attributions. Olaf Pong's laboratory made substantial contributions to the original cloning of the Shaker potassium channel, and Richard Keynes and colleagues did important work in the early days of gating currents. Surprisingly, their work on these topics is rarely acknowledged or cited.

There are a few problems with production that are worth pointing out. The figures are black and white, although colors are often mentioned in the text. The online edition has color figures. There are a few text references to nonexistent figures or figure panels, and references to nonexistent chapters. The bibliographic style is not uniform (some chapters are alphabetical, others are numbered). These are small problems that undoubtedly reflect the chaos of getting all of the chapters in and edited toward the publication deadline, but they should be corrected if possible.

So will the *Handbook of Ion Channels* become the much needed new and modern authoritative reference in the field? I am confident that it will. I enjoyed reading it and learned a lot, particularly in areas that I haven't kept up with. It will be a great reference. It will not fare quite as well as an introductory text, because much of the material requires substantial previous knowledge and more appropriate introductory texts are available. I do expect it will be a valuable supplemental text for introductory courses on ion channels. It has much to offer to readers at all levels, and I expect that most workers in the field will find it useful and will want to have it readily available in their offices and laboratories. The quality of the individual chapters is particularly high given the wide variety of authors, and the breadth of coverage is unprecedented. Despite the rather serious, and inexplicably mysterious, flaw of leaving out three of the most important families of ion channels, what is here is outstanding. Zheng, Trudeau, and the authors should be commended for contributing a first-rate and highly important volume to the ion channel field. Given the continuing rapid pace of research, perhaps they should start planning the second edition.

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