Contemporary Physics
Vol. 00, No. 00, , 1–5

ESSAY REVIEW

Handbook of Ion Channels

Peter V. E. McClintock and Igor Kh. Kaufman

Department of Physics, Lancaster University, Lancaster LA1 4YB, UK

(*v7.0 released 9 April 2018*)

A review of **Handbook of Ion Channels**, CRC Press Taylor & Francis Group, 2015, pp. xx + 671. Scope: reference, £124.00, ISBN 978 1-4665-5140-4 (Hardback; eBook also available). Level: professional researchers, postgraduate students.

Just lifting a finger involves the coordinated opening and closing of billions of ion channels. These natural nanotubes play an essential role in the physiology of all living creatures, from bacteria to humans [1, 2]. By providing for the exchange of ions across cellular membranes, they control a vast range of biological processes, and their dysfunction leads to numerous diseases. Permeation of a channel by a positive ion is affected by the ion's radius, hydration properties, and valence. The permeating ion interacts with a thermal bath, with fixed and induced charges on the channel walls, and with other permeating ions [3]. Furthermore, the channel wall is flexible and continuously fluctuating in random thermal motion. So the analysis of channel dynamics is far from simple.

One of the most striking functional features exhibited by many ion channels is the ability to select between different species of ion [4–8]. The underlying selectivity mechanism is extraordinarily efficient. Specialized ion channels allow their favoured species to permeate freely, with little discernible delay in their passage, i.e. almost as though the channel were an open hole. Yet they largely prohibit permeation by other ions. For example a calcium channel favours Ca^{2+} over Na^{+} ions by a factor of up to 1000× even though the ions are almost the same size, and a potassium channel favours K^{+} over Na^{+} ions by a similar factor despite the K^{+} ion being significantly larger than Na^{+}. This selectivity is associated with a narrow negatively-charged region, called the selectivity filter. Altering the magnitude of the charge by mutating the channel may destroy the functionality of the channel by stopping it from conducting altogether, or it can alter its selectivity by e.g. changing a sodium channel into a calcium channel, or *vice versa*.

The understanding of puzzling phenomena of this kind, and of the conduction processes that operate in channels, has evolved slowly. In the classic work on the propagation of action potentials (nerve impulses) by Hodgkin and Huxley in the 1950s [9] it was unclear whether ion channels *per se* existed, or whether the ions passed through the cell membrane directly in some way. Later, even when the existence and general nature of ion channels as transmembrane proteins had become well-established, the mechanisms of conduction and selectivity remained mysterious. It was generally assumed that they would become obvious as soon as the ion channel's structure had been discovered.

It is now understood that the structure consists of "a protein with a hole down the middle" [3], with the protein molecule embedded in the plasma membrane surrounding the cell such that the hole accesses the intracellular domain at one end, and the extracellular domain at the other. It is also appreciated that there are several hundred different kinds of ion channel. Some of the channel proteins have been crystallised and their detailed structures determined by X-ray crystallography or, more recently, by cryo-electron microscopy [10]. The first one was the KcsA

ISSN: 0010-7514 print/ISSN 1366-5812 online

DOI: 10.1080/0010751YYxxxxxxxx
http://www.informaworld.com

potassium channel [11], but several others followed and new channel structures now seem to be reported every few months. However, knowledge of the structure did not immediately bring the anticipated understanding of either the conduction process or the mechanism underlying the selectivity. Thus, although ion channels have been the subject of intensive research for over half a century, and more than 300,000 scientific papers have been published, many aspects of their functional mechanisms have remained mysterious, with several still unresolved puzzles and paradoxes.

The seemingly paradoxical preference of potassium channels for the larger K^+ ion can, however, readily be accounted for in terms of hydration energy. In aqueous solution, water is bound electrostatically to ions in a hierarchy of hydration shells [12]. The narrowness of the potassium channel requires permeating ions to shed their hydration shells in order to be able to pass through. Being smaller, the Na^+ ion's first hydration shell is more tightly bound, so significantly more energy is needed to remove it than in the case of K^+, and thus the permeation event is correspondingly much less probable.

In the early days of research on cellular electricity and ion-permeable pores, it was mostly researchers with a physical science orientation who made the running but, as Hille points out in his Foreword to the *Handbook* [1], a much broader range of scientists has become involved in the last three decades, including "...in addition to biophysicists... physiologists, biologists, biochemists, anatomists, molecular biologists, structural biologists, and physicians". This is excellent, and wholly appropriate, given the wide interdisciplinary importance of channels, but the physical scientists are still needed because it is physical mechanisms that give rise to the selective conduction.

Perhaps unsurprisingly, there is some difference in underlying attitude and motivation between the two main groups of channel researchers. The physical scientists are primarily looking for fundamental principles, generally applicable to a variety of different channels, whereas those on the biomedical side tend to focus more on the details of particular channels that interest them and they may spend a significant proportion of their whole research lifetime working on a single channel or a small sub-family of channels. Yet despite their differing philosophies and outlooks, it is essential for the two groups to continue working together, as their contributions are wholly complementary. In this context, we comment that the present *Handbook* [1] is in large part edited and written by physiologists and biomedical researchers for physiologists and biomedical researchers.

How does one produce a volume encompassing the significant results of more than 300,000 research papers? It is an almost insuperable challenge. What Zheng and Trudeau have actually done is to pull together a collection of 43 separately authored or co-authored chapters on particular topics, grouped into 5 parts, involving some 71 contributors in total. It is a huge enterprise, and the resultant *Handbook* [1] is correspondingly a substantial tome. It is constructed as follows:

- The 5 chapters of Part I "Basic Concepts" are intended to be a preparation for what follows, and they include some interesting history together with fundamental ideas and mechanisms underpinning selectivity and gating. From our own (physics-based) point of view, the most interesting chapter would be expected to be "2. Ion selectivity and conductance". In fact, this chapter is mostly devoted to the selectivity of K^+ channels, with a short addition about Na^+ channels. To our way of thinking, the presentation could usefully have been fuller and more detailed and would have benefitted from a more extensive bibliography. Part I also (perhaps a little surprisingly) includes a chapter "6. Mechanosensitive channels...".
- The 10 chapters of Part II "Ion Channel Methods" are also in a sense preparatory, as they describe the diversity of tools and models that have been applied to bring us to where we now are in the understanding of ion channels, their structures, and how they function. Importantly, Part II includes chapters describing modern physical methods like fluorescence spectroscopy and cryo-electron microscopy. It also covers computational/simulation methods for studying ion channels.
- With all that under his/her belt, the reader is then ready to grapple with the 28 chapters

that form the rest of the book, which are focused on what has been discovered and how this knowledge is being used. Part III discusses "Ion Channel Families", and describes the properties of several particular ion channels, including TPRV/TPRM/TPRC and some exotic channels. Surprisingly, calcium channels are not included in the list (though they are partially described in later sections).

- Part IV deals with "Ion Channel Regulation", and Part V describes "Ion Channel Physiology and Diseases". These sections relate to special ion channel problems and, in particular, to their physiological features in health, disease, and drug targeting. Some of the chapter titles (especially in Part V) appear extremely interesting though they are far from our own areas of expertise.

Does the scheme work? To a large extent we think it does. There is a staggering amount of information here, and it is quite well organised and classified. Most of the authors try to present the current state-of-the-art in their own laboratories, without deep historical background or wide comparison with alternative approaches and models. The reader is thus introduced to front-line research in the areas in question – front-line at the time of writing, of course. However, it can be argued that the rapid advances currently being made will soon render obsolete this snapshot of the subject area it was in 2013–2014, that the era of "handbooks" is now over, and that it is better for researchers to access readily-available and frequently-updated on-line resources. Nonetheless, it seems to us that there is great value in bringing together a collection of this kind in hard copy. It provides a baseline for future developments, and the existence of the editors provides for subject coverage as well as a measure of quality control (in comparison, on-line resources can in practice be more uneven in availability and quality). Perhaps inevitably, there is a significant degree of inconsistency of convention and format between the different groups of authors, and not very much cross-referencing between chapters which tend to be relatively self-contained; some authors italicise variables in what (for physical scientists) is the conventional way, whereas others do not, giving rise to occasional ambiguities. But these are minor niggles. The most important aspects are the coverage and content.

One example of new research that mostly appeared and developed while the *Handbook* [1] was in preparation was the use of results from semiconductor physics and, in particular, incorporation of the effects of ion charge/entity discreteness into the electro-diffusion model of selectivity. Allowing for the fact that ion channels are in many respects closely analogous to transistors [13], and also taking account of charge discreteness, leads one logically to the phenomena of ionic Coulomb blockade (ICB) [14, 15], which is closely analogous to the electronic Coulomb blockade that occurs in quantum dots or single-electron transistors [16, 17]. Based on first-principles electrostatics, the ICB model of permeation takes explicit account of the discreteness of the ionic charge and the existence of a dielectric self-energy barrier that arises on account of the huge mismatch in dielectric constant ε between the water ($\varepsilon \sim 80$) and the protein walls of the channel ($\varepsilon \sim 2$) [18, 19]. This self-energy barrier is in itself enough to prevent ions from entering an uncharged channel. With an appropriate value of fixed negative charge in the channel, however, the self-energy barrier is cancelled and the ion can then permeate in a barrier-less fashion [4, 6, 19, 20]. In valence selectivity, e.g. the L-type calcium channel's preference for Ca^{2+} over Na^{+}, electrostatic energy dominates and the roles of the fixed charge and its precise value are paramount. If the effective fixed charge is $-2e$ so that it exactly neutralises an incoming Ca^{2+} ion, the latter will get trapped in a deep potential well from which it cannot escape and the channel is effectively blocked. For a fixed charge of e.g. $-3e$, however, the dielectric self-energy barrier can be almost exactly balanced: if one Ca^{2+} ion is trapped in the channel, a second Ca^{2+} can enter, knocking the first one forwards. The result is resonant barrier-less conduction for the favoured ionic species, very much in accord with what is seen experimentally. Generally, the ICB model predicts/explains well the phenomena of valence selectivity, including the famous divalent blockade of monovalent currents [15, 21] in Ca^{2+} channels, which has also been observed and investigated in the NaChBac channel and its mutants [22, 23]. The ICB model was recently extended on the firm basis of very general statistical principles [24].

For many ion channel researchers, the conventional reference to use in the introductions of their papers has for many years been the book by Bertil Hille [2], which was first published in 1984 and which went through three editions. So a natural question to ponder is whether the present compilation by Zheng and Trudeau [1] will take Hille's place as the standard general reference for ion channels? They are very different kinds of work. Hille's book, being extremely well-written by a single individual, is readable, coherent, and internally self-consistent. But it is ageing. In comparison, the *Handbook* by Zheng and Trudeau [1] has the enormous advantage of being 14 years (and a few hundred thousand papers) more up-to-date, and it also carries an *imprimatur* from Hille in the shape of his Foreword. On the other hand, as Hille points out, there is "some bias towards the biomedical side" and, by implication, not enough about the physical science (physics and physical chemistry) of channels.

It is practically impossible to read through such an extensive and heterogeneous book in full detail, partly because of its sheer volume, but more particularly because almost any given reader will lack the expertise needed to comprehend certain parts of the exposition. Nevertheless, what we were able read and understand provides a timely, useful and very interesting snapshot of the current state of the art in channel science as viewed from a biomedical perspective. Most of the *Handbook* [1], and especially Parts III "Ion Channels families" and V "Ion Channels in physiology and decease", is likely to age relatively slowly and thus have continuing usefulness in a conventional handbook sense over the next several years.

The work was supported by the Engineering and Physical Sciences Research Council UK [grant No. EP/M015831/1] and by a Leverhulme Trust Research Project Grant RPG-2017-134.

Peter V. E. McClintock
Igor Kh. Kaufman
Lancaster University
p.v.e.mcclintock@lancaster.ac.uk

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