



Article

Introduction to the Physics of Ionic Conduction in Narrow Biological and Artificial Channels

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Abstract: The permeation of ions through narrow water-filled channels is essential to life and of rapidly-growing importance in technology. Reaching an understanding of the mechanisms underlying the permeation process requires an interdisciplinary approach, where ideas drawn from physics are of particular importance and have brought encouraging progress in recent years. This Introduction sets into context the several ground-breaking papers presented in the *Entropy* Special Issue on “The Physics of Ionic Conduction in Narrow Biological and Artificial Channels”.

Keywords: ion channel; nanopore; ionic selectivity; Coulomb blockade; hydration energy; molecular dynamics; Brownian dynamics; nonlinear dynamics; stochastic process.

“There is plenty of room at the bottom”

Richard Feynman

Understanding, predicting and optimising the ionic selective transport properties of nanopores remains a critical challenge, both to nanotechnology and to biophysics. The last few decades have witnessed substantial progress in the analysis of such transport based on the use of a variety of experimental, numerical, and theoretical methods. Indeed, it would require several books to do full justice to the current state of the art in the field.

In some cases, the crystal structures, e.g. those of potassium, sodium, and calcium voltage-gated channels, have been discovered. This has provided invaluable insight but has also thrown into sharp relief the structure-function problem: how to predict the conduction/selectivity properties of a known structure; or conversely how to design a structure with required properties. A reliable solution to the problem offers to open new horizons in terms of pharmaceutical applications and in improved fabrication of solid-state nanopores for the sensing of molecules, desalination, DNA sequencing and the other developments that together are marking a new era in nanotechnology.

Novel numerical methods and computer hardware nowadays enable microsecond-long simulations of systems with hundreds thousands of atoms and the exploration of polarizable and quantum mechanical force fields. They provide unprecedented capabilities for reaching an understanding of experimental data and for the development of novel devices and techniques. Theoretical advances not only underlie many developments in molecular dynamics, including enhanced sampling and advanced force fields, but are also opening up new research frontiers and shedding fresh light on a number of longstanding problems such as binding probabilities, knock-on mechanisms of conduction, gating, electric double-layers, and local dielectric permittivity, just to mention a few.

32 It is now appreciated that selective conduction in biological ion channels has a great deal in
33 common with that in artificial nanopores. In each case, there are intriguing analogies with the physics
34 of quantum dots leading to the development of the theory of ionic Coulomb blockade. We dedicate
35 this issue to the memory of our late colleague, Dr Igor Kh. Kaufman, who developed an elegant
36 theory of ionic Coulomb blockade in biological ion channels and suggested a simple classification of
37 voltage-gated channels based on the charge of the selectivity filter.

38 At the same time it is known that specific features of ionic conduction – such as dehydration,
39 ion-specific binding affinities, protonation, the multicomponent and competitive nature of ion
40 dynamics, the complex and adaptive structure of the ionic pathway, long range interaction, local
41 variation of the effective dielectric constant, highly correlated motion of more than one ion within a
42 narrow channel, electric double layers, and water layering at the channel entrances – add many layers
43 of complexity to the fundamental physics analogies.

44 This Special Issue brings together original high-quality papers on ionic permeation through
45 narrow water-filled channels, both biological and artificial, from some of the best researchers in the
46 field. It includes papers on the statistical physics of the process, on molecular dynamics and Brownian
47 dynamics simulations, and on relevant experiments. Although any selection of papers can only be
48 a narrow slice of the field, our aim is to emphasize the complexity and mutual interdependence of
49 recent multifaceted progress in understanding the physics of ion channels and nanopores. The time is
50 ripe for bringing together these complementary approaches, and we anticipate that they will facilitate
51 major breakthroughs, enabling the design of nanopores to meet particular technological requirements
52 as well as improvements in drug design and perhaps in personalised medicine.

53 Importantly, the Poisson-Nernst-Planck (PNP) and kinetic models remain among the principal
54 tools for predicting current through nanopores both in biology and nanotechnology. An example of
55 the classical application of the PNP model to the analysis of reversal potentials and zero-current fluxes,
56 in a system with a fixed profile of permanent charges and two mobile ion species, is provided by the
57 paper by Mofidi et al [1]. Rigorous analytic and numerical results establish the dependence of the
58 electric and chemical potential profiles on voltage and permanent charge.

59 At the same time it is well known that classical Poisson-Boltzmann (PB) and PNP theories do
60 not take account of short-range ion-ion, ion-wall, or ion-water interactions in ion channels. Efforts to
61 eliminate, or ameliorate the effects of, this deficiency of the continuum models have a long history. This
62 stream of research is represented by the interesting paper of J.-L. Liu and R.S. Eisenberg [2] featuring
63 the development of a molecular mean-field theory – a fourth-order Poisson–Nernst–Planck–Bikerman
64 theory for modeling ionic and water flows in biological ion channels. The theory treats ions and
65 water molecules, in channels of any volume or shape, with interstitial voids, polarization of water,
66 and ion-ion and ion-water correlations. It can be applied to electrolyte solutions in the nanopores of
67 batteries and fuel cells.

68 Modelling ionic currents with reduced models is extensively analysed by Boda et al [3]. They
69 show that channels are especially amenable to reduced modelling because their functions and
70 the relationships between input parameters (e.g. applied voltage, bath concentrations) and output
71 parameters (e.g. current, rectification, selectivity) are well-defined, allowing one to focus on the physics
72 of input-output relationships rather than on the atomic-scale physics inside the pore. Based on decades
73 of research, the authors propose four rules of thumb for constructing good reduced models of ion
74 channels and nanopores, focusing on the physics of input-output relationships rather than on atomic
75 structure. The proposed rules relate to the importance (1) of the axial concentration profiles, (2) of
76 the pore charges, (3) of choosing the right explicit degrees of freedom, and (4) of creating the proper
77 response functions. Examples demonstrating the application of these rules are provided. Further
78 improvements in predicting the capabilities of reduced models can be achieved by incorporating
79 into the solution of the one-dimensional electro-diffusion model the potential of the mean force
80 obtained from MD simulations. The performance of two such methods is examined by A. Pohorille
81 and M. A. Wilson1 [4] using stochastic simulations. These methods require neither knowledge of

82 the diffusivity nor simulations at multiple voltages, which greatly reduces the computational effort
83 needed to probe the electrophysiology of ion channels. They can be used to determine the free energy
84 profiles from either forward or backward one-sided properties of ions in the channel, such as ion fluxes,
85 density profiles, committor probabilities, or from their two-sided combination. In this work large
86 sets of stochastic trajectories were generated individually designed to mimic the molecular dynamics
87 crossing statistics of models for channels of trichotoxin, p7 from hepatitis C and a bacterial homolog of
88 pentameric ligand-gated ion channel, GLIC. The authors found that the free energy profiles and the
89 current–voltage curves obtained from the generated trajectories reproduce with good accuracy results
90 obtained in molecular dynamics simulations.

91 The charged particles of which matter is composed move when an external electric field is
92 applied, and their changed distribution is traditionally described in terms of a polarisation field. For
93 insulators, it is usually possible to define a relative permittivity (dielectric constant) to quantify the
94 material’s responsiveness to the electric field. In ion channels, for example, the protein walls and
95 the water are usually treated as dielectric continua with relative permittivities of around 2 and 80
96 respectively. This approach can be very helpful and revealing, but it involves greater approximation
97 than just that of spatial averaging because, as R.S. Eisenberg points out [5], the material’s response
98 to the electric field may be both nonlinear and time-dependent. In order to accommodate such
99 phenomena – simultaneously challenging physicists to review their knowledge of electromagnetism
100 in biological dielectrics – he proposes and discusses an apparently minor change in Maxwell’s first
101 equation. It produces a major consequence when joined with Maxwell’s second equation in that
102 conservation of total current (including the displacement current) then emerges as a general principle.
103 In one dimensional systems, like ion channels or electronic circuit components, the consequences are
104 profound: there, total currents are equal at all locations at any given time, so the space variable does
105 not appear in the description of total current.

106 There follow two papers reporting MD simulations of ion currents in biological and artificial
107 channels. First, S.M. Cosseddu et al [6] present an extended MD-based analysis of ion motion within
108 the KcsA channel. They reveal complicated patterns of potassium currents that are governed by
109 the structural variability of the selectivity filter. They show that ion motion involves the complex
110 dynamics of a strongly-correlated network of residues and water molecules. Intriguing features of
111 self-organisation and readjustment of the network are analysed statistically and discussed in detail.

112 Secondly, we note that ionic transport in nano- to subnano-scale pores is highly dependent on
113 translocation barriers and potential wells. These features in the free-energy landscape are primarily
114 the result of ion dehydration and electrostatic interactions. For pores in atomically thin membranes,
115 the ionic dynamics both inside and outside the geometrical volume of the pore can be critical in
116 determining its transport properties. S. Sahu and M. Zwolak [7] examine regimes of transport that are
117 highly sensitive to pore size due to the interplay of dehydration and interaction with pore charge, where
118 picometer changes in the size, e.g. due to a minute strain, can lead to a large change in conductance.

119 We have already remarked upon the crucial importance of water, the electric double-layer,
120 water-layering, polarisation, and the resultant changes of local dielectric permittivity at the entrances
121 of nanopores. Another approach to this problem is illustrated in the paper by T.-L. Horng [8]. Starting
122 from the classical Helmholtz free energy functional for an electrolyte, including the solvation energies
123 for anions and cations, the author follows the Bikerman modification by adding an entropy term to the
124 functional, and he then extends the Bikerman approach by introducing ion-size-specific corrections to
125 the theory.

126 The approach based on density functional theory (DFT), which works well near charged walls
127 and in bulk electrolytes, can be extended to the analysis of the orientational ordering of water dipoles
128 in membrane nanotubes. M. Drab et al [9] analyse water ordering in nanotubes by minimizing the
129 corresponding Helmholtz free energy functional, also including the orientational entropy contribution
130 of water dipoles, and deriving the modified Langevin Poisson-Boltzmann (MLPB) model of the
131 electric double-layer. The MLPB equation is solved in cylindrical coordinates to determine the spatial

132 dependences of the electric potential, relative permittivity and average orientations of water dipoles
133 within charged tubes of different radii. Results show that, for tubes of a large radii, the macroscopic
134 (net) volume charge density of cations and counterions is zero on the geometrical axis. This is attributed
135 to effective electrolyte charge screening in the vicinity of the charged inner surface of the tube. For
136 tubes of small radii, the screening region extends into the whole inner space of the tube, leading to
137 non-zero net volume charge density and non-zero orientational ordering of water dipoles near the axis.

138 The DFT results mentioned above are examples of statistical physics yielding insight into the
139 function of ion channels and nanopores. This theme is continued and extended, first by Gibby et
140 al [10] who apply their recent derivation of an effective grand canonical ensemble and linear response
141 theory of ion channels to analyse the conduction of the bacterial NaChBac selectivity filter. The authors
142 compare their theory to experimental current-voltage and current-concentration dependences for
143 a single channel and for a whole cell. They find that the statistical theory in the linear response
144 regime predicts correctly many important properties of the NaChBac filter including the concentration
145 dependence of the reversal potential and the current-voltage relations. They also show that the
146 theoretical results are consistent with MD simulations of the filter population at each binding site.

147 Secondly, analysis of quantum mechanical effects in ion channels is another important direction,
148 supported by the extended capabilities of modern quantum mechanics/molecular mechanics
149 simulations. In this respect, interesting perspectives are opened by mapping the statistical mechanics
150 of ion channels onto an effective quantum mechanics. Such investigations are reviewed by T. Gulden
151 and A. Kamenev [11], who study the dynamics and thermodynamics of ion channels, considered as
152 effective 1D Coulomb systems whose statistical mechanics is dominated by entropic effects that may
153 be taken accurately into account by mapping onto an effective quantum mechanics. The corresponding
154 semiclassical calculations for non-Hermitian Hamiltonians are conducted by applying tools from
155 algebraic topology. The relationship of the solutions to the thermodynamics and correlation functions
156 of multivalent solutions within long water-filled channels is discussed.

157 The actual properties of real nanopores are, of course, discovered by experiment, which has been
158 leading the research in this area especially since the discovery of the structure of the KcsA channel. In
159 our Special Issue, experimental insight is provided by two of the leading research groups in the field.

160 O. Fedorenko et al [12] discuss the properties of voltage-gated sodium channels (Navs).
161 These channels play fundamental roles in eukaryotes but lack structural resolution, which renders
162 understanding their structure-function relationships a challenging problem. Bacterial Navs,
163 representing simplified homologues of their eukaryotic counterparts, have enabled both structural
164 resolution and electrophysiological characterization. However, their homotetrameric structure leads to
165 an EEEE locus in the SF that is at odds with the DEKA locus of eukaryotic Navs. Indeed, prokaryotic
166 Navs have long been considered more similar to eukaryotic calcium channels (Cavs) than to Navs,
167 leading to the formulation of the "EEEE paradox". This was arguably solved by Kaufman et al by the
168 realisation that there is a critical D residue close to the EEEE ring of eukaryotic Cavs generating an
169 effective EEEED locus of charge $-5e$. Fedorenko et al. present a follow-up of a previous study, aimed
170 at mimicking the SF of eukaryotic Navs by engineering radial asymmetry into the SFs of bacterial
171 channels. This goal was pursued with two approaches: co-expression of different monomers of the
172 NaChBac bacterial channel in mammalian cells, to induce the random assembly of heterotetramers;
173 and the concatenation of four bacterial monomers to form a concatemer that can be targeted by
174 mutagenesis on specific strands of the SF, thereby introducing asymmetry. Patch-clamp measurements
175 and MD simulations showed that an additional gating charge in the SF leads to a significant increase
176 of Na^+ and a modest increase in Ca^{2+} conductance in the NavMs concatemer in agreement with
177 the behaviour of the population of random heterotetramers with the highest proportion of channels
178 with charge $-5e$. This study confirms that, although the charge at the SF is important, it is not the
179 only factor affecting conduction and selectivity. It also offers new tools extending the use of bacterial
180 channels as models of eukaryotic ones.

181 The work by A. Chernev et al [13] reviews the most promising approaches to the fabrication of
182 artificial nanofluidic devices capable of reproducing properties of single ion channels. It is shown that
183 modern technologies have great potential in allowing one to test various theoretical models of ion
184 channels. The review aims to highlight ionic Coulomb blockade — the phenomenon which (see above)
185 can often be key player in ion channel selectivity. The authors discuss the most critical obstacles
186 associated with these studies and suggest possible solutions to further advance the field.

187 The rapid interdisciplinary advances in nanotechnology can be characterised as the beginning of
188 a new industrial revolution, where novel devices and materials are fabricated and controlled on the
189 atomic level. Ion- and water-selective nanopores represent an important frontier in these advances.

190 The selected papers in this Special Issue provide both a snapshot of the present and strong
191 indications of how the subject is likely to evolve over the coming years. We may, for example, anticipate:
192 major developments in the theory at a fundamental level, based on statistical mechanics and quantum
193 mechanics; substantial improvements in “intermediate level” theories like PNP, modified CKE and
194 DFT which promise quantitative predictions of the properties of real channels; together with much
195 faster and more capacious MD modelling of larger ensembles of atoms on longer timescales, more
196 accurate due to use of polarizable force field and QM/MM, encompassing gating and permeation
197 events at a statistically useful level. This progress is expected to lead to the first-principles design
198 and fabrication of structures optimised for many important applications including ion pumps, energy
199 harvesting, and field effect ionic transistors as well as those mentioned above at the beginning. Many
200 of these will require theory and experiment on small scales where disciplinary distinctions have mostly
201 faded away, but where physics predominates.

202 An additional impulse propelling these developments forwards is expected due to the fusion of
203 physics-based approaches with artificial intelligence. The latter has already been proven to be a very
204 useful for accelerated learning of the force fields in MD, as well as for reconstruction of the potentials
205 of the mean force and neural-network-based discovery of partial differential equations. Remarkably, it
206 also underlies a recent breakthrough in the solution of the protein-folding problem.

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