Predicting complex multi-species phase structure for ionic conduction in nanopores

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***Abstract*—Using a statistical linear response theory, we present a complex phase structure describing ionic conduction through a nanopore as a function of pore structure. This picture sheds light on the permeation mechanism, and selectivity between ions of alike and differing charge; and is calculated explicitly from first principles via the statistical properties including particle number fluctuations. We therefore expect the theory to be applicable to the functionalisation and design of highly selective nanopores.**

***Index Terms*—selective conduction, ionic Coulomb blockade, resonant conduction**

I. INTRODUCTION

Understanding, predicting, and controlling how ions permeate nanoscale pores is increasingly important in the fields of nano- and biophysics with applications such as water treatment [1], biological ion channels [2], and health and medicine [3]. In general, pores need to fulfil the following criteria: (i) to discriminate effectively between ionic species, including ions that share valence; and (ii) the ability to conduct the selected ions at a high rate.

In [4, 5], we introduced an equilibrium statistical theory, relating both the kinetic and thermodynamic properties of permeation directly to pore structure. It differs from earlier insightful theories [6, 7, 8, 9] to name a few, which are often focused on either conductivity or selectivity, and have neglected the multi-component nature of transport. Briefly, our theory accounts for the multi-ion and multi-species (including different valences) nature of conduction, calculating it directly from the fluctuations in particle number. We have applied this theory to the selectivity filters of K^+ and Na^+ biological pores. By careful comparison with experimental data, we show that it can model the effect of point mutation on conduction rates, demonstrating highly selective and efficient conduction, and thereby resolving the long-standing selectivity-conductivity paradox, and the complex anomalous mole fraction effect in Na^+ channels. Furthermore, it describes the conduction mechanism and relates it to ionic Coulomb blockade, an emergent phenomena observed experimentally [10] and via simulations [11] in artificial nanopores and biological pores respectively. Finally, the theoretical framework provides a basis for the development of non-equilibrium kinetic models and the calculation of self-consistent transition rates [12].

In this report, we consider a system of 0-1 ions in the pore; but we allow for the presence of three possible conducting ions K^+, Na^+, and Cl^-. We show that a complex phase structure exists and that it describes the nature of the permeation mechanism, and selectivity between ions of alike and differing charge. This structure is shown as a function of pore capacitance and charge, strength of chemical interactions, and bulk concentrations. As such, it allows users to identify crucial parameters required for a desired pore function.

II. THEORETICAL APPROACH AND RESULTS

We consider two bulk reservoirs with aqueous solutions containing ionic species s, in this instance K^+, Na^+, and Cl^-. The reservoirs are diffusively and thermally coupled via a narrow pore of volume V_c, where due to the narrowness of the pore, ionic motion is confined to one dimensional conduction. The pore houses n_s ions, although total occupancy is at most 1 ion. As a result there are four discrete energy states, $\{n_j\}$, corresponding to the pore being empty or being occupied by one of the ions.

The electrochemical potential in the bulk takes the standard form [13] i.e. the sum of ideal, excess, and electrostatic parts. It is a similar picture inside the pore where it is defined from the discrete difference in the energy to add an ion. As in [4, 5], we can write an effective grand canonical ensemble by separating the degrees of freedom from the bulk and pore phases. If we consider identical concentrations of ionic species in either bulk, then the total Gibbs free energy reads as,

$$G(\{n_j\};n_f) = \mathcal{E}(\{n_j\};n_f) - \sum_s n_s \Delta\tilde{\mu}_s + \sum_s kT \ln{(n_s)!}. \tag{1}$$

where: k and T are the Boltzmann constant and system temperature respectively and $\mathcal{E}$ provides the electrostatic interaction between ions and wall charges. We shall consider $\mathcal{E}$ in the form $\mathcal{E} = U_c(n_f + \sum_s z_s n_s)^2$, originally taken from [14]. In this expression, the prefactor U_c is inversely dependent on pore capacitance and thus geometry, and n_f is the total wall charge in the pore. In low capacitance systems the level of quantisation is high because the Coulomb gap i.e. $U_c \gg 1kT$, in this type of system we would expect to observe *strong Coulomb Blockade* [11]. It is of interest to note that this interaction is identical to that used in electron transport through quantum dots [15]. In the supplementary material of [4] we considered an alternative interaction (from that in [8]) and show comparable results. In the future, we plan to further validate the theory through comparison to Brownian dynamics models. The term $\Delta\tilde{\mu}_s$ is the summation of the difference in excess chemical potential between bulk and pore $\Delta\bar{\mu}_s = \bar{\mu}_s^b - \bar{\mu}_s^c$ plus the natural logarithm of the mole fraction of the ionic species. The final term represents the entropy of mixing. Here, $\bar{\mu}_s^b$ provides the non-polar (surface tension and excluded volume) and electrostatic (Born and Debye-Hückel) contributions to the solvation free energy [13].

The energy barrier ΔG impeding addition an ion to the pore is

$$\Delta G = \Delta\mathcal{E} - \Delta\tilde{\mu}_s + kT\log(n_s + 1). \tag{2}$$

The final term is relatively small, and so clearly the energy barrier to add an ion is a balance between the 'electrostatic' cost $\mathcal{E}$, and the 'chemical' $\Delta\tilde{\mu}$ cost. We have also shown a method for connecting $\Delta\tilde{\mu}_s$, to the potential of mean force (PMF), $\mathcal{W}$. The PMF represents the reversible thermodynamic work needed to move the ion adiabatically through the pore [6]. It is measurable in simulations, and we plan to perform such studies in future work. Given that, at most, only one ion can occupy the pore at any time, then we have the following relation,

$$\bar{\mu}_s^c = -\left(kT\log\left(\int_c dr_1 e^{-\mathcal{W}(r_1)/kT}\right) + \Delta\mathcal{E}\right). \tag{3}$$

Note, here that we have reduced $\Delta\tilde{\mu}_s$ down to its value in the pore, by cancelling the bulk electrochemical potential contribution.

Conductivity at linear response is derived rigorously through comparison to Kubo and Zwanzig [16, 17]. It is calculated directly from the fluctuations in particle number, and is directly proportional to the susceptibility χ_s which we plot below in our main results,

$$\chi_s \propto \left(\frac{\partial\langle z_s n_s\rangle}{\partial\Delta\bar{\mu}_s} + \sum_{j\neq s}\frac{\partial\langle z_j n_j\rangle}{\partial\Delta\bar{\mu}_s}\right). \tag{4}$$

As can be seen, the susceptibility and thus conductivity, for a given species depend on the cross correlations between ions of different species (the second term), note that z is ionic valence. Now, these cross-terms become small in the highly selective limits, but they can be important if the pore is minimally or non-selective. In the full relation there are ionic diffusivities in the pore, but the overall difference in value between our three conducting ions is fairly small and so it is ignored here and a constant value will be assumed; but it will be included when we do full comparisons with experiment. Finally, it is worth noting that if the pore is expanded to include several binding sites then it is also expanded to include cross correlations between ions at these sites as well.

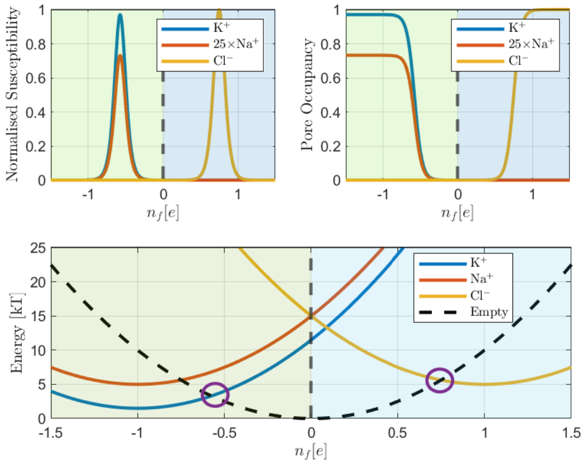

Fig. 1. Top, normalised susceptibility (left), and pore occupancy (right). Bottom, energy spectra of the empty and three possible excited states. In this figure, blue, red, and yellow curves denote K^+, Na^+ and Cl^- respectively, and in the energy spectra graph the dashed black line denotes the zeroth ion i.e. empty state. These plots are made with the following parameters: $\Delta\tilde{\mu}_{K,Na,Cl} = -1.5, -5, -5[kT]$ and $U_c = 10kT$, and plotted $vs.\ n_f$.

III. RESULTS

In Fig. 1 we show the results, in the top left and right figures we show the normalised susceptibilities (proportional to conductivity) and the pore occupancies respectively, and below we show the energy spectra in this system, all as functions of n_f. We consider the following parameters $\Delta\tilde{\mu}_{K,Na,Cl} = -1.5, -5, -5[kT]$ and $U_c = 10kT$, thus both Cl^- and Na^+ face a small chemical barrier relative to K^+ of 3.5kT. Susceptibility peaks, and occupancy steps form as functions of n_f. Peaks maximise when the energy barrier between neighbouring states is minimal corresponding to the midpoint of the occupancy step and the purple circles in the energy spectra figure. This is an example of *ionic Coulomb Blockade*, because n_f plays the role of the gate voltage in electronic systems and when it reaches the critical value we see resonant $n \leftrightarrow n+1$ transitions, and when n_f is far from his critical value we see significantly reduced conduction and even blockade. The critical value of n_f is around half-integer and equal and opposite in sign to the conducting ion, as it electrostatically attracts the ion.

To discuss these results further, we first need to understand the role of selectivity in the system. Broadly speaking, the properties of the pore can be split into two selective regimes: cation selectivity for $n_f < 0$ and anion selectivity for $n_f > 0$, although there are exceptions to this which will be considered below. As discussed above, there is a chemical barrier impeding entry of both Cl^- and Na^+. Thus, when $n_f < 0$, Cl^- ions are completely blocked from entering the pore because the combined chemical and much larger electrostatic barrier is $>$ 25kT. Similarly, cations face a large electrostatic barrier when $n_f > 0$, thus prohibiting entry. When $n_f < 0$, Na^+ ions can and do enter the pore, albeit at a reduced rate compared

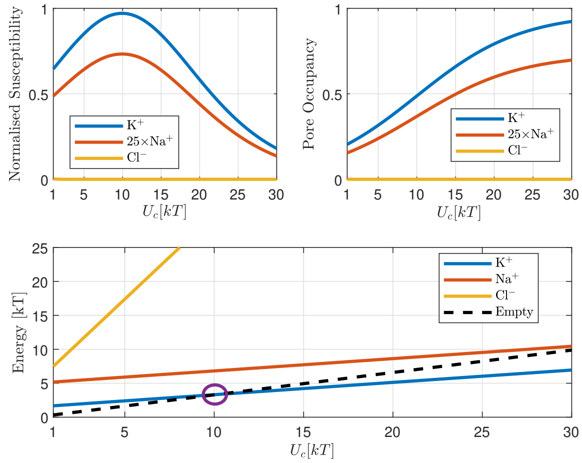

Fig. 2. Top, normalised susceptibility (left), and pore occupancy (right). Bottom, energy spectra of the empty and three possible excited states. Colour conventions are the same as in Fig. 1. These plots are made with the following parameters: $\Delta\tilde{\mu}_{K,Na,Cl} = -1.5, -5, -5[kT]$ and $n_f = -0.57$, and plotted $vs.$ U_c starting at $U_c = 1kT$.

to that for positive n_f. The Na$^+$ peak is centred at the same location as K$^+$ because this value of n_f still corresponds to the location with the smallest barrier, however, because this barrier is $3.5kT$ Na$^+$ conductivity is exponentially suppressed by this amount resulting in a selectivity ratio of ≈33:1. An interesting case occurs when this barrier is smaller but still non-zero e.g. $\sim 1kT$. The location of the peak is not then at the location of the midpoint of the favoured ion's step or barrier-less condition but, rather, at the midpoint of the total occupancy step.

To see how finely tuned these parameters are, let us consider the original conditions, except that we fix n_f at $n_f^* \sim -0.6$ i.e. the resonant conduction point for K$^+$, and we allow U_c to vary equally amongst all species. We remind readers that this term is inversely proportional to the pore capacitance, so that its increase amounts to a decrease in the pore radius or to an increase in its length. It also governs the level of quantisation in the pore, and thus the overall importance of the electrostatics in the pore. In Fig. 2 we again plot normalised susceptibility and occupancy top left and right respectively and energy spectra (below). We observe susceptibility peaks and occupancy steps $vs.$ U_c, again resonating when $U_c = 10kT$ as we expect, and linear energy spectra. As a result of this linearity in the energy spectra, the susceptibility peak is broader and the occupancy step smoother than in Fig. 1. In the low U_c limit the electrostatic effects become less important compared to the differences in $\Delta\tilde{\mu}$; however, the energy barrier to add Cl$^-$ is still above $5kT$, and so the ion cannot enter the pore.

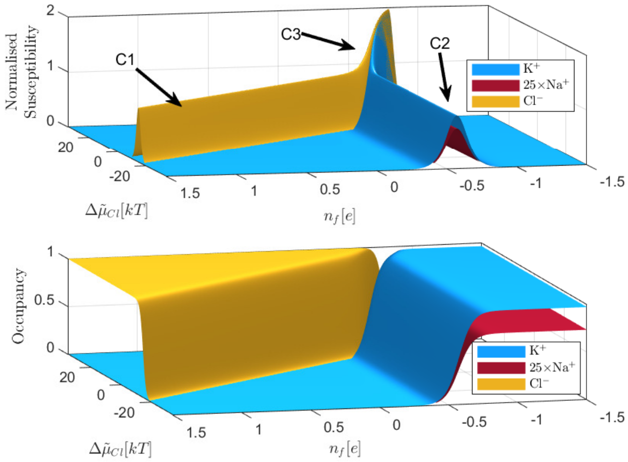

Fig. 3. Complex phase structure of Na$^+$, K$^+$ and Cl$^-$ permeation in a given nanopore. Top, we show the normalised susceptibility (with respect to maximal Cl$^-$ susceptibility in the anion selective limit such that only it is entering the pore), and (bottom) we show the respective occupancies. All plots are made with the following parameters: $\Delta\tilde{\mu}_{K,Na} = -1.5, -5, [kT]$ and $U_c = 10kT$, and $\Delta\tilde{\mu}_{Cl}$ and n_f are allowed to vary. In this figure, blue, red, and yellow faces denote K$^+$, Na$^+$ and Cl$^-$ respectively, and three conductivity regimes are identify C1-3. C1 and C2 correspond to anion and cation selectivity respectively, and C3 corresponds to non-selectivity whereby K$^+$ and Cl$^-$ ions are involved in the conduction process.

If we now extend this picture, allowing $\Delta\tilde{\mu}_{Cl}$ as well as n_f to vary, then we start to see an interesting and complex phase structure (see Fig. 3). The fixed parameters here are: $\Delta\tilde{\mu}_{K,Na} = -1.5, -5[kT]$ and $U_c = 10kT$. Species-specific susceptibilities (top) and occupancies (bottom) are shown. The normalisation used is the same as in the earlier figures, i.e. with respect to maximal Cl$^-$ susceptibility in the anion-selective limit such that only it is entering the pore. As a result one can immediately identify a region (labelled C3) where the susceptibility exceeds unity, which will be discussed below. The colour convention is maintained with blue, red, and yellow faces denoting K$^+$, Na$^+$ and Cl$^-$ respectively. Three conductivity regimes C1-3 are highlighted, C1 and C2 correspond to anion and cation selectivity respectively with the properties as described above. An additional point of interest here is that the Cl$^-$ maximal conductivity location shifts in n_f because the value of $\Delta\tilde{\mu}_{Cl}$ is varying.

The final condition, C3, corresponds to an interesting new phenomena. It occurs for very large positive values of $\Delta\tilde{\mu}_{Cl}$, and negative values of n_f. The electrostatic penalty to add Cl$^-$ to the negatively charged pore, is then being compensated by $\Delta\tilde{\mu}_{Cl}$, and as result the pore is non-selective between K$^+$ and Cl$^-$. However, because of the conditions in the pore, the pore is always occupied with 1 ion, unlike previously where we had 0-1 ion conduction and so we predict direct K$^+$ $\leftrightarrow$ Cl$^-$ transitions: the increased susceptibility arises because the cross-correlation terms are no longer small.

IV. CONCLUSION

We have used a statistical theory, to model selective ionic conduction through a nanopore. Even in the simple case of 0-1 ions present, complex phenomena and phase structure exists for varying parameter choices. We consider monovalent ions

Na$^+$, K$^+$ and Cl$^-$, and show regions of resonant conductivity, blockade (and ionic Coulomb blockade), and variable selectivity. Each phase, can be described through comparison of the energy spectra and occupancies within the pore, and its location can be calculated and predicted from within the theory. We plan to test this further in future research including relationship between the only undetermined parameter $\bar{\mu}_s^c$ and the measurable PMF, but we expect the theory to be insightful in the successful design and functionalisation of nano-pores.

To further develop this work, we want to: compare function to simulations and experiments with known structure, and this will allow us to test the predictive capability of the theory. We also want to allow multiple ions into the pore, to investigate the role that mixed states can play in the conduction mechanism, and we want to consider divalent selectivity i.e. Ca^{++}/Na$^+$ to ultimately predict the full range of selectivity sequences. Finally, we would like to explore the relationship of our cross correlation terms to the cross diffusion coefficient.

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