

Selective resonant diffusion of ions in an artificial analogue of a biological filter

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Abstract—We study selective ionic diffusion in a single-walled carbon nanotube (CNT). The wall is charged so as to mimic the structure of the selectivity filters in biological ion channels. We use all-atom molecular dynamics simulations to demonstrate that a charged CNT can closely reproduce many of the selectivity and conductivity properties of the KcsA biological channel. A K^+/Na^+ selectivity ratio $\gtrsim 150$ and a conduction current $I_{\text{table}} \gtrsim 50$ pA are demonstrated. It is shown that ionic Coulomb blockade is the key phenomenon underlying the CNT conduction properties. Coulomb blockade theory is used to estimate the excess chemical potential of the ions in the channel and the channel capacitance.

Index Terms—ionic Coulomb blockade, carbon nanotube, resonant diffusion

I. INTRODUCTION

Single-wall carbon nanotubes (CNT) have strong potential for future nanofluidics applications including sequencing single-stranded DNA [1], ion pumps [2], and integration with biological nanopores [3]. CNTs bear structural and functional similarity to biological KcsA [4] channels and can thus serve as biomimetic devices for reproducing KcsA functionality in nanotechnology systems [1, 5, 6]. For example, a short CNT functionalized with carbonyl oxygen atoms [7] shows strong K^+/Na^+ or opposite selectivity, depending on the arrangement of the carbonyl atoms. Current blocking of a CNT by surface charge was recently reported [8]. However, the function of biological channels still outstrips by far that of artificial channels, because understanding and controlling diffusion through these nano-pores present significant challenges, both theoretical and experimental [9].

Here we use all-atom molecular dynamics (MD) simulations and statistical theory to investigate Na^+/K^+ permeation in a short CNT, designed to mimic the selectivity-filter of the highly K^+ -selective KcsA channel. The simulations yield selectivity and conduction properties approaching those observed in biological channels [10]. We compare the results with our statistical theory, and demonstrate good agreement for the primary conducting ion.

II. METHODS AND MODEL

The system, shown in Fig.1, is comprised of a short CNT (length $L_c = 1.13$ nm, radius $R_c = 0.39$ nm), limited at either entrance by graphene layers with pores. The carbon atoms

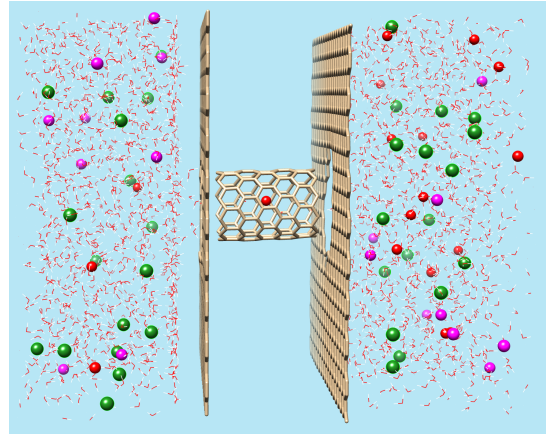


Fig. 1. All-atom model view generated by ChimeraX [11]. Potassium ions are shaded red, chloride ions are shaded green, and magenta balls represent sodium ions. Carbon atoms and connecting bonds are shaded light brown. Water bonds are shown by red (oxygen) and white (hydrogen) sticks.

are fixed in place. The dimensions of the simulation box are $4.43 \times 4.26 \times 5.44$ nm, and the system is hydrated by a mixture of 0.46M KCl and NaCl solutions equally on both sides. These are slightly stronger than physiological concentrations, but are representative of the values commonly used in experiments [10]. An electric field 0.2 V/nm was applied in the z -direction, resulting in diffusion and drift of ions through the CNT.

As already stated, we designed the system to mimic the highly-conserved selectivity filter of common biological K^+ channels e.g. KcsA. It is a narrow pore with 4/5 binding sites, each formed by 8 charged carbonyl and hydroxyl oxygen groups [4, 12], and it selects between K^+ and Na^+ by a factor of order 1000:1 [10]. Thus, in our CNT we introduce four charged planes each with 5 equally-charged carbon atoms. Hence, the total wall charge, Q_{ex} , varies from $-0.8e$ to $-2.5e$ in our pore. The length of our CNT is comparable with a KcsA-like channel. The graphene sheets at the entrances serve to prevent particle leakage, possibly causing interaction with the outside walls of the CNT. Their pores are of radius $R_p = 0.45$ nm and rim charge $-1.52e$, where e is the elementary charge. This rim charge encourages ions to approach the entrance of the channel and it mimics the vestibules of a

biological channel. In this work the geometry and charge of the graphene pores is fixed and in themselves they are non-selective.

The model was built using J-OCTA software [13] with the Amber20 [14] force field for water, ions, and graphene sheets, and the Dreiding force field [15] for the CNT. The simulations were performed using GROMACS software [16] on in the NPT ensemble with a 2 fs time step and run for 320 to 620 ns.

III. RESULTS

Fig. 2 plots the K^+ (red) and Na^+ (blue) currents (top) and occupancies (bottom) of the CNT as functions of wall charge. The ionic currents were calculated directly from the trajectories: see inset of Fig. 2 (top).

There is clear selectivity in favour of K^+ -ions. The K^+ current has a broad peak maximising at ≈ 80 pA when the wall charge $Q_{ex} \approx -2e$, and its occupancy forms a discrete step between the channel being empty and being fully occupied. This represents the first observation of the resonant barrierless ion diffusion peak through the CNT predicted earlier in the theory of *ionic Coulomb blockade* (ICB) [17].

Na^+ ions also show this behaviour with a current peak which, however, is much smaller than that for K^+ due to the selectivity in the system. It maximises at $Q_{ex} \approx -2.2e$ at ≈ 5.6 pA. In fact, the Na^+ current still remains under-resolved even after 620 ns of simulation time.

Our estimates of the CNT currents and selectivity are summarised in Table I. The Na^+ current remains zero (up to 620 ns) for wall charge $Q_{ex} \geq -1.6e$, and it only forms a small conduction peak of ≈ 5 pA. The simulations reveal selectivity of more than 100:1 and K^+ currents exceed 50 pA at the three values of Q_{ex} highlighted by red circles in the inset of the Fig. 2 (bottom). In particular, the selectivity was estimated to exceed 200:1 with the K^+ current of 54 pA at $Q_{ex} = -1.6e$. More accurate estimation requires simulation times far beyond 1 μs , and are currently being planned. However, the results already obtained demonstrate clearly that the system closely mimics the well-known selectivity/conductivity behaviour of the biological KcsA filter [10].

TABLE I
SUMMARY OF K^+ -CURRENT AND K^+/Na^+ SELECTIVITY OF THE CNT

Q_{ex}	-2.5	-2.4	-2.2	-2.0	-1.8	-1.6
Simulation time, ns	320	520	460	460	420	620
# K trans	135	175	177	220	181	211
# Na trans	1	1	8	9	5	0
Selectivity	135	175	22	24	36	$\gtrsim 211$
K current, pA	≈ 68	54	64	77	69	54

System behaviour of this type can also be estimated analytically using the statistical ICB theory introduced in our earlier work [18, 19]. The key quantity of this theory is an effective

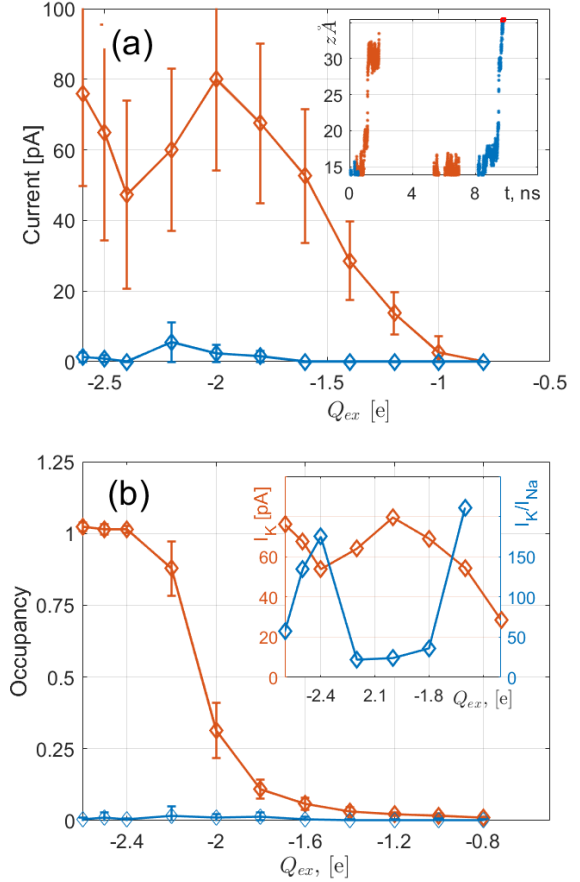


Fig. 2. (a) Current through the CNT as a function of the surface charge Q_{ex} for potassium (red diamonds) and sodium (blue diamonds) in mixed 0.46M KCl and NaCl bulk solutions. The inset shows examples of potassium (brown lines) and sodium (blue lines) trajectories crossing the CNT at $Q_{ex} = -2.2e$. (b) Occupancies of the CNT for potassium (red diamonds) and sodium (blue diamonds) ions. The inset shows selectivity (blue diamonds) and potassium current (brown diamonds, the same as in the top figure) as a function of Q_{ex} .

grand canonical ensemble with Gibbs free energy, $G(\{n_j\})$ calculated for each configuration of ions $\{n_j\}$ as

$$G(\{n_j\}) = \mathcal{E}(\{n_j\}) + kT \left(\ln(n_0)! + \sum_{s=1}^S \ln n_s! \right) + \sum_{s=1}^S \sum_{m=1}^M n_{sm} (\Delta \bar{\mu}_{sm}^b + e\phi_m + kT \log(x_s^b)), \quad (1)$$

where n_{sm} is the number of s -type ions at the m -th site and n_s is the total number of s -ions in the channel, while n_0 is the number of empty sites. This energy contains two major contributions: (1) the electrostatic interaction energy between the ions and the fixed charge \mathcal{E} , and (2) the chemical interactions of the ions and the pore via the excess chemical potential (the difference between bulk and site m in the channel is denoted by $\Delta \bar{\mu}_{sm}^b$). Other important contributions are the ionic concentration or mole fraction x_s^b , and the applied potential at each site ϕ_m .

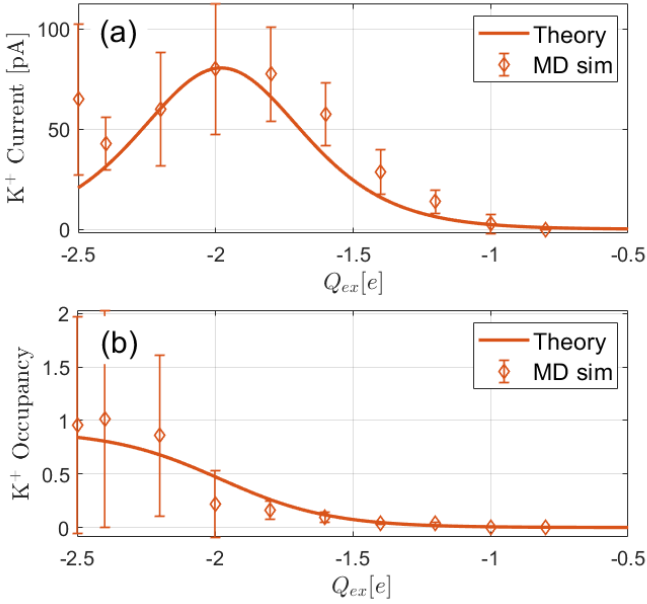


Fig. 3. Comparison of simulation (diamond), to theory (coloured solid line). Theory, agrees well with the main conduction ion K^+ and shows a current peak (a) and occupancy step (b) *vs.* pore charge.

Within this theory, the current through the CNT is given by the particle number fluctuations, calculated directly from the grand potential $\Omega = -kT \ln G$, and these take into account the cross correlations between all particles. Because we only observe one ion to be in the channel, which has a singular binding site, the expression for current reduces to

$$I_s = -\frac{e^2 D_s}{2L_c^2 kT} \left(\frac{\partial^2 \Omega}{\partial \Delta \bar{\mu}_s \partial \Delta \bar{\mu}_s} + \sum_{j \neq s} \frac{\partial^2 \Omega}{\partial \Delta \bar{\mu}_j \partial \Delta \bar{\mu}_s} \right) \mathcal{V}. \quad (2)$$

Here, D_s is the species specific diffusivity, and $\mathcal{V} = \sum_m \phi_m$ is the total applied voltage across the pore. Using ICB theory, the electrostatic interaction energy can be approximated as

$$\mathcal{E} = U_c \left(z_{ex} n_{ex} + \sum n_s \right)^2$$

where U_c is the charging energy parameter dependent on the CNT capacitance and $Q_{ex} = e z_{ex} n_{ex}$ is the total charge with $z_{ex} = 1$ in our case.

We showed earlier that these nano-channel systems exhibit ICB behaviour analogous to that of single-electron transistors, with the total wall charge playing the role of the gate voltage in electronic systems. The set of states of such systems is quantised. The strength of the quantisation is dependent on U_c and inversely dependent on the capacitance, so that higher-capacitance systems display weaker Coulomb blockade effects [18]. As a result, when plotted *vs.* channel charge, we observe a set of current peaks and occupancy steps, with the current maximising when the wall charge is such that the total energy barrier to enter or leave the channel is zero.

We compare the MD results to the theory in Fig. 3. In doing so, we consider the channel diffusivity of potassium

ions $D_K = 6.5 \times 10^{-10} \text{m}^2 \text{s}^{-2}$, $U_c = 2.5kT$ and, using $\Delta \bar{\mu}_K$ as a fitting parameter we find its best fit value $-2.7kT$. The K^+ curves fit the MD data well, for both occupancy and current. We successfully recover the current peak (including its location), and find the occupancy step.

Proper comparison of the Na^+ peak with theoretical predictions will become possible after accurate resolution of the Na^+ -current in simulations, which will require extension of the simulation time beyond $1 \mu\text{s}$. However, the proposed theory allows direct estimation of all the key parameters of the system, including the diffusivities $D_{K,Na}$, differences in chemical potentials $\Delta \bar{\mu}_{K,Na}$, and charging energy U_c or channel capacitance C since $U_c = e^2/2C$.

Indeed, our theory gives the selectivity ratio $S = I_K/I_{Na}$ in the form

$$S = (D_K/D_{Na}) e^{(\Delta \bar{\mu}_K - \Delta \bar{\mu}_{Na} + kT \ln(x_K/x_{Na}))/kT}. \quad (3)$$

Therefore, measuring S for two different ratios x_K/x_{Na} allows for estimation of $\ln(D_K/D_{Na})$ and $\Delta \bar{\mu}_K - \Delta \bar{\mu}_{Na}$.

In turn, values of $\Delta \bar{\mu}_K$ and $\Delta \bar{\mu}_{Na}$ can be estimated by measuring the ICB bias voltage ϕ_{ICB} . The latter is given by the condition $G(0) = G(1)$ meaning that there is no energy cost in adding an ion to the empty channel [20]

$$e\phi_{ICB} = U_c(1 + 2n_{ex}) - [\Delta \bar{\mu}_K^b + kT \ln(x_K^b)]. \quad (4)$$

This includes an electrostatic component, alongside chemical terms related to the bulk mole fraction and the $\Delta \bar{\mu}_K^b$ of ions entering the pore. For a given applied field the condition (4) corresponds to a wall charge $Q_{ex}^{ICB} = e n_{ex}^{ICB}$ at the location of the resonant conduction peak (see top of Fig. 2 and Fig. 3). Values of U_c and $\Delta \bar{\mu}_K^b$ can thus be determined by measuring the location of the peak for two different values of the mole fraction x_K^b .

Finally, using the above estimates and measuring the current I_s for each type of ion, one can determine values of the diffusivities D_K and D_{Na} . Comparison of the results obtained with the theory demonstrates the strong potential of this approach for analysis of the key physical parameters of ionic conduction in narrow artificial and biological channels.

In practice, however, care must of course be exercised, and it must be borne in mind that the approach is based on linear response theory. The theory will be extended to encompass finite field effects, dehydration barriers at the channel entrances, and the role of the charge distribution.

IV. CONCLUSION

In summary, our all-atom MD model of an artificial ion channel exhibits selectivity/conductivity properties closely resembling those of the biological KcsA selectivity filter. The artificial system exhibits resonant diffusion of K^+ exceeding that of Na^+ at the ratio $K^+/Na^+ \geq 100$ at a rate $\sim 5 \times 10^8$ ions per second. The ionic conduction occurs through a mechanism analogous to electronic Coulomb blockade in solid state devices. It is broadly explainable within our statistical theory and ICB model, introduced in [19]. The close similarity to electronic Coulomb blockade, and the results obtained,

confirm our conjecture [18, 19] that ICB is one of the key phenomena controlling ionic diffusion in artificial as well as in biological ion channels. It also confirms that CNTs are very promising nanodevices for mimicking the functions of biological selectivity filters.

Future work will include extension of the charge range beyond $-2.5e$. We would expect, and preliminary results confirm this, that additional current peaks and blockade regions will be present with a corresponding occupancy staircase. We also plan to further investigate the PMF and the differences between ions by doing a decomposition of terms, and we plan to incorporate it into a Brownian dynamics model that will further illuminate the permeation process.

We will also extend the theory to incorporate fully the shape and properties of the energy profile, which affect the transport mechanism. We will continue developing the self-consistent kinetic theory (initiated in [21]), whereby the results will be extended far beyond equilibrium. The proposed approach is suitable for the analysis of ionic conduction through CNTs in experimental systems of the type [2, 22] and can be further extended to the investigation of biological KcsA like channels.

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