Fast-ion transport in peptide nanochannels

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Abstract
This review summarizes recent results of the ion transport in narrow peptide nanochannels (PNCs) conducting ions and water molecules at various densities. The molecular structure of the nanochannel is a periodic continuation of the short selectivity pore of a biological potassium channel. The ion conductivity of a PNC can reach ion velocities up to 50 m/s. This phenomena is based on a fine tuned interplay between the three constituents of the PNC: the ions, the water molecules, and the flexible carbonyl groups of the channel’s backbone, which represents a one-dimensional fluctuating lattice potential for ions and water. The unidirectional transport is based on hopping processes of bound ion–water pairs (‘permons’) mediated by the lattice potential.

1. Introduction
The transport of microscopic particles, including atoms, ions, molecules, and colloids, through nanotubes and nanochannels, is significant for fundamental biological processes and industrial applications. Examples include molecular or ionic permeation in zeolites [1,2], in carbon nanotubes [3–5], in cyclic peptide nanotubes [6,7], in superionic conductors [8–11], in biological ion channels [12–15], and in others [16,17]. Recently, carbon nanotubes, stabilized as arrays in solid membranes [18–21], have been demonstrated experimentally and by simulations as ultra-efficient gas and liquid transporters [21–23]. Similarly for cyclic peptide nanotubes [24]. The main theoretical challenge is to predict possible molecular realizations of nanotubes or nanochannels where the highly correlated motions of ions or molecules lead to very selective and fast transport.

Recently, a model of a peptide nanochannel (PNC) [25,26] has been proposed which is predicted to provide ion conduction based on highly correlated motions with ion velocities up to 50 m/s. This nanochannel shares essential molecular details and the molecular ion conduction mechanism with a biological potassium ion channel [12,27,28]. It is known that many biomolecular nanoscale devices, so-called ‘bionanomachines’ [29,30], have extraordinary properties which are superior to many man-made devices. Such an example is the ion conduction in biological ion channels. Potassium ion channels reside in cell membranes and they work by selecting specific ions and by catalyzing the passive diffusion through the selectivity filter. The selectivity filter facilitates the diffusion of ions at rates approaching $10^8$ ions/s, which corresponds to ion velocities of the order of 0.1 m/s, under physiological electrochemical gradients [31]. This high throughput rate was suggested to be achieved by some collective motion of all ions in the filter (‘multi-ion permeation process’) [32]. Recent theoretical studies on a PNC [25,26,33] have shown that the high ion conductivity is based on concerted movements of the three constituents of the PNC: the ions, the water molecules, and the flexible carbonyl groups of the channel’s backbone. The unidirectional transport is based on correlated hopping processes of bound ion–water pairs (‘permons’) mediated by the ion-correlated dynamics of the lattice potential of the PNC.

2. Model
The PNC is based on the atomic coordinates of the selectivity filter of the potassium channel KcsA taken from X-ray diffraction at high resolutions [27,28]. The channel protein is a tetramer composed of four identical monomers each containing 160 amino residues. The selectivity filter is the central structural element of the KcsA channel and consists of four strands of peptides with the amino acid sequence Thr, Val, Gly, Tyr, and Gly. They are arranged with their oxygen atoms of the carbonyls, CO$^-$, pointing inward towards the ion conduction pathway. The PNC (Fig. 1) is constructed by a finite continuation of the original KcsA selectivity filter [25,26]. At each binding site an ion or a water molecules is stably coordinated by eight carbonyl oxygens, four on each side. The width of such a binding site along the channel axis is about 3 Å. The periodicity of the binding sites represents a one-
dimensional ‘lattice potential’ provided by the carbonyl groups of the backbone. According to experimental findings [27,28,34] it can be assumed that the PNC contains potassium ions and water molecules in an alternating sequence (Fig. 1). The model and charges of the peptide unit of the channel’s backbone is shown in Fig. 2.

The backbone atoms are restrained at their positions by harmonic forces in order to provide a certain rigidity of the one-dimensional structure. Under experimental conditions this could be thought to be provided by an external embedding matrix of dimensional structure. Under experimental conditions this could be thought to be provided by an external embedding matrix of dimensional structure.

2.1. Potentials and driving force inside the channel

The potential energy of a single ion along the channel axis $z$ has a gradient towards the N-terminus which is a result of the electric field between C- and N-termini. This is a slight, but not the dominant driving force for the ion. The lattice potentials, $U_{K}(z)$ and $U_{W}(z)$ for one ion and one water molecule, respectively, are periodic with potential wells of about 2–8 $k_{B}T$. The detailed forms of the potentials differ in both cases. The potential $U_{W}(z)$ for a water molecule depends significantly on its orientation $\Omega$. The ion conduction is strongly influenced by the quasi-one-dimensional Coulomb repulsion among the ions along the channel’s axis. By introducing a certain numbers of unoccupied binding sites (‘vacancies’) in the channel, the symmetry (‘incommensurability’) between the periodicity of the PNC’s lattice potential and the inter-ionic Coulomb repulsion is broken. This causes a driving force for ion displacements, similarly as discussed for superionic conductors [8–10] in the context of the Frenkel–Kontorova model [8,9,35–38]. The term ‘commensurable’ is used for ion configurations in which the equilibrium distance of the potassium ions coincides with the periodicity of the lattice potential. In this case, without any other influences, the ions would rest exactly in the energetic minima (binding sites) of the lattice potential. Fig. 3(a) illustrates a commensurable occupation where the commensurability can be characterized by the ‘ion occupation number’, $\nu = \frac{\text{number of binding sites}}{\text{number of ions}}$. For commensurable ion distributions the number is an integer. Incommensurable conditions (Fig. 3(b)), however, induce a driving force due to the competition between the periodicity of the lattice potential and the aperiodic distribution of ions. This causes random jumps of ions among the binding sites.

3. Simulations

3.1. Water-filled channel

In order to understand the correlated movements of ions and water in the channel, it is of interest to distinguish correlated movements from the intrinsic movements of water alone. It was observed [26] that the water molecules move rather freely inside the channel and sometimes even occupy the same binding site. Obviously, the influence of the channel potential on the water molecules is rather weak. This is a consequence of the overall neutral charge of each water molecule. The interaction between the dipoles and the carbonyl groups, separating the binding sites, are not sufficient to induce significant correlated movements. The orientations of the water dipoles are essentially parallel, all dipoles point approximately towards the N-terminus. A significant influence of the periodic potential on the dipoles is not apparent. It is interesting to note that there is a correlation between orientational and positional changes. Most of the time a positive orientation, is preferred, but at the moment the molecule moves, its orientation changes transiently to the opposite direction. This seems to be a general feature of water translocation in this type of narrow protein channel and has been observed also for the KcsA potassium channel [33].
3.2. Ion-filled channel

In the case when the nanochannel contains only potassium ions at various densities, the simulations show that the Coulomb repulsion among the commensurably distributed ions keeps the ions at rest at their binding sites. The thermal fluctuations are too small to move the ions along the potential gradient towards the C-terminus. Even a single ion does not perform long-range diffusion, which indicates that the potential barriers imposed by the carbonyls are larger than the driving force exerted by the potential gradient originating from the electric field between the N- and C-termini. In the case of an incommensurable situation, there is no long-ranged unidirectional motion of the vacancy, but rather an equilibration. If some vacancies are located near one side of the channel, then the hopping of the ions leads to a rearrangement such that the vacancies become located near the middle of the channel where they perform random hoppings about their equilibrium positions.

3.3. Permons at low densities

Consider the situations where the initial configurations consist of ion–water pairs separated by one or more vacancies. A typical case of trajectories is shown in Fig. 4. In the dilute incommensurable case with occupation number $v = 5.75$ the ion–water pairs remain in their bound state and move together with no preferred direction. In fact, the hopping of the ion–water pairs do not destroy the integrity of the bound state of the ion–water pairs. The appearance of a stable bound state of ion–water pairs is an important feature of this peptide nanochannel. One reason for the stability of the ion–water pair is their Coulomb attraction. The potential energy $U_{KW}(z)$, consisting of Coulomb and van der Waals interactions, between an ion and a water molecule as function of their distance $z = |z_{\text{water}} - z_{\text{ion}}|$ (in Å), is given approximately by [39]

$$U_{KW}(z) = -114\mu\Omega/\varepsilon z^2 + \varepsilon(z/\varepsilon)^{12}$$

in units of $k_B T$, where $\mu = 1.84$ is the dipole moment in Debye, $\varepsilon$ is the dielectric constant, and $\Omega$ is the water orientation with respect to the $z$ axis, and $\varepsilon$ and $\sigma$ are the van der Waals parameters. The potential exhibits energy minima at a characteristic distance of $\approx 3$ Å, which is smaller than the periodicity of the lattice potential formed by the carbonyl groups of the nanochannel (Fig. 1). Therefore, at equilibrium the potassium ions and the water molecules are located at the minima of the lattice potential (“binding sites”) where they are stably coordinated by eight carbonyl oxygens, four on each side.

3.4. Permons at high densities

In situations where the nanochannel is almost fully occupied with potassium ions and water in an alternating sequence, a typical ensemble of trajectories of potassium ions and water molecules is shown in Fig. 5. The ions and water molecules exhibit a long-range unidirectional motion from the N-terminus towards the C-terminus (from top to bottom) of the nanochannel. A closer inspection of the trajectories indicates that the movements of ions and water molecules take place as hopping events of permons. This is more easily observed by analyzing the corresponding trajectory of the single vacancy in the system (Fig. 6), which shows the long-range drift of the vacancy and hence of the permons.

4. Theory

4.1. Role of water molecules

The role of water during the hopping processes is very important. Without the support of water molecules the ions do not perform a long-range drift along the nanochannel [26]. The reasons...
for that are not well understood. One possibility is that the long-range polarized state of the water molecules plays a role. Another possibility is the hypothesis that a water molecule may act as ‘pawl’ in a ratchet mechanism [40]. Let us consider this mechanism in a simple pair approximation picture where we assume that the ion–water pair hops as a stable entity by one binding site. The initial configuration is depicted in Fig. 1 and we denote the sequence from bottom to top by: \( W_1, K_2, W_3, \) vacancy, \( K_4, W_5, K_5. \) In this situation the water \( W_3 \) can be assumed to have the tendency to be polarized by \( K_2 \) with \( \Omega = -1 \) due to the lack of a neighboring ion at site 4, and forms a stable polarized bound state with \( K_2 \) (‘permon’). The interaction of the pair \( K_2–W_3 \) with the ion \( K_3 \) is repulsive. If solely \( W_3 \) would hop to the vacant site 4, it would have to change its orientation to \( \Omega = +1, \) which corresponds to an energy barrier of \( \approx 30 \text{ kT} \). Eq. (1) for breaking the \( K_2–W_3 \) permon binding. Therefore the hopping of this pair or \( W_3 \) towards the vacancy is less probable. Since \( W_3 \) is essentially responsible for this prohibition, it may be considered as a ‘pawl’ in this ratchet model. The situation for the opposing pair \( K_3–W_6, \) however, is different. Due to the influence of \( K_3 \) and \( K_7 \) on \( W_6, \) this water molecule has orientations fluctuating around \( \Omega = 0 \) forming transiently bound pairs of \( K_5–W_6 \) and \( W_6–K_7. \) Influenced by the gradient of the channel potential, the movements of the ion \( K_5 \) are biased towards the vacancy. Therefore, if the transiently formed permon \( K_5–W_6 \) with \( \Omega = -1 \) moves towards the vacancy, then its state becomes stabilized in the same way as the preceding pair \( K_2–W_3. \) From this new situation the whole process as described above will take place again for \( K_7–W_8, \) and so on. This leads to the unidirectional movements of ions and water in the nanochannel. It should be noted that the described hypothetical ratchet model for the correlated movements of ions and water is different from the variety of ratchet models discussed in the literature (see, e.g., [41–45]). Almost all ratchet models rely on the principle that the directed motion of particles in spatially periodic structures under the influence of a weak external (constant or periodic) force can be induced if the periodic potential or the fluctuations are asymmetric. A typical example of such a ratchet model is the over damped Angevin equation of a single particle at coordinate \( x(t) \)

\[
\frac{dx}{dt} = -\frac{dU}{dx} + F + \xi(t),
\]

where \( \xi(t) \) is a Gaussian white noise of zero mean, \( F \) is a constant homogeneous force, and \( U(x) \) a periodic asymptotic potential (e.g., an asymmetric saw-tooth potential). This is different from the present model where the asymmetry is related to the ‘particle’ itself (ion–water pair with water acting as a pawl), rather than to the fluctuating channel potential \( U(x) \), which is on the average spatially symmetric. The formulation of this model corresponding to Eq. (2) is a formidable task.

4.2. Role of carbonyls

The flexibility of the carbonyl groups, which represent a periodic one-dimensional fluctuating lattice potential for ions and water molecules, has a significant influence on the movements of the occupants in the channel. If the thermal fluctuations of the peptide nanochannel are frozen in, then movements of the occupants are suppressed [26], which means that the potential barriers imposed by the carbonyl atoms are higher than the inter-ionic Coulomb repulsion. The effects of the dynamics of the carbonyls on the movements of ions and water have been addressed recently in more details [33,25]. Consider again the situation as depicted in Fig. 1 and the sequence \( W_1, K_2, W_3, \) vacancy, \( K_4, W_5, K_5, \ldots \), from bottom to top. The moving ion \( K_5 \) induces a tilt of its neighboring carbonyl groups due to the Coulomb interaction between \( K^+ \) and \( CO^- \). The corresponding lattice potential \( U_k(z) \) changes and facilitates the movement of the ion. Of course, the ion-induced tilt of the carbonyls is not restricted to the nearest neighbors, but the general scenario of one moving ion along the one-dimensional lattice of the nanochannel resembles a polaron, known from solid state physics, where a traveling electron induces accompanying local deformations of the crystal lattice. One important consequence of the ion-induced local deformation of the carbonyls is that the local lattice potential \( U_W(z) \) of the neighboring water molecule \( W_6 \) is changed as well. This is illustrated in Fig. 7 for \( \Omega = 1 \). Due to the ion-induced tilt of the carbonyls, the potential for the water molecule becomes bistable and the energy barrier is reduced from \( \Delta U_W \approx 40 \text{ kT} \) to \( 10 \text{ kT} \) at \( \theta = 30^\circ. \) Since the ion–water attraction is about \( 30 \text{ kT} \) (for \( \Omega = 1 \)), the water molecule \( W_6 \) prefers to maintain its bound state and follows its preceding ion towards the vacancy site. A backflow of the permon \( K_5–W_6 \) is prevented by the high energy barrier for the water molecule, \( \approx 40 \text{ kT}. \) The presented theoretical considerations are thought to provide a molecular basis for a mathematical theory of ion conduction in PNCs, eventually following a quasi-particle concept as is common in solid state physics [13].

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References