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SIMPLIFIED STRUCTURE-BASED MODEL
OF THE POTASSIUM CHANNEL SELECTIVITY FILTER

Recent x-ray structures of bacterial Kcsa K+ channel revolutionized the ion channel science. A widely used theoretical model, based on the conception of discrete binding sites in the channel, appears to be inconsistent with the structural data. We developed a model of multiply occupied Kcsa-like selectivity filter based on the best available data. The model explicitly considers ion-ion interactions. Parameters of the ion-ion interactions, such as shielding constant, are determined. The model correctly describes barrierless knock-on conduction in the filter and allows to study the influence of the large-scale filter motions on its properties. It is shown that the concerted motion of multiple ions in the filter may be described as a motion of single "quasi-ion" in the effective energy profile which is easily calculated numerically.

Introduction

Ion channels are classical objects of biophysics [20, 21, 22]. Their exceptional biological significance for cell functionality, complex behavior and intriguing physical properties makes them very interesting for both experimental and theoretical studies. However, theoretical investigation of ion channels was long hampered by the lack of the detailed three-dimensional structure of the channel forming proteins. High-resolution crystal structures of bacterial Kcsa K^+ channel, first published in 1998, brought new insights into the ion channels science [6]. It was established that the most important feature in the Kcsa structure is a narrow (~3 Å) selective filter. It is responsible for selectivity [1–4], conduction [1–4] and possibly for fast flickerry gating of the channels [10, 11] and their C-type inactivation [13, 14, 16–18].

The filter has 5 more or less distinct binding sites occupied by K^+ ions or water molecules, however only $3K^+$ ions may be accommodated in the filter due to ion-ion repulsion [1–4, 6, 12, 15]. Numerous molecular dynamics (MD) and Brownian dynamics (BD) studies revealed barrierless «knock-on» conduction mechanism in the filter and exceptional role of ion-ion forces in energy balance of different ion configurations on the conduction pathway [1–4].

MD data suggest some degree of local flexibility in the filter. Recent x-ray structures of Kcsa-Fab complex revealed dramatically different filter conformations in the open and closed states of the channel [1]. Finally, experiments on the defunct *Shaker* channels and C-type inactivation studies of related K^+ channels suggest an existence of large-scale concerted radial motions of the filter walls which may have gating effect on ion conduction [12, 13, 19]. Although, the question of the filter mobility and it's influence on conduction is of great importance now, direct all-atom description of large scale slow filter dynamics is unavailable, so the simplified models of the process may be especially useful.

Although selective filter of K^+ channels is a multi-ion pore, existing theoretical models fail to describe it. Conventional models of multiply occupied channels treat them as a system of binding sites which may contain only one ion each. Ion-ion interactions are treated implicitly as kinetical interactions, or restrictions which allow one ion in each binding site [5, 23–26]. This model is absolutely inconsistent with the real energy profile in the filter, which is rather extended and deep energy well containing several strongly interacting ions [1–4, 6]. However existing models allow to consider flexible structure of the channel protein resulting in self-organization phenomena leading to gating behavior [5, 23–26]. So, it seems to be promising to combine the vital ideas of previously developed models with the modern structural data. This approach require the consistent model of conduction in the selectivity filter able to operate with different energy profiles and conformational states of this structure.

In the present study we proposed a simplified model of the Kcsa-like selective filter based on realistic filter design, energetics and explicit ion-ion interactions. It gives a correct description of the conduction in the filter and allows to study the states with different filter radius which is vital for understanding the role of the radial filter motions.

Although we try to make the model as close to the structure as possible, it is not limited to Kcsa channel. The model is formulated in terms of approximated energy profiles rather than explicit atomic-resolution potentials which makes it general enough to describe the whole class of channels with the homologous structure of selective filter.

The model of Kcsa selective filter

Selective filter of the Kcsa may contain up to 3 ions [1–4, 6–9]. The size of the extended energy well along the pore axis is approximately $L = 30$ Å [4]. Energy profile for the ion in the channel consist of the interaction with the pore walls and interaction with the other ions.

Interaction of the single ion with the pore walls were calculated in MD simulations more or less

accurately. We used the data of the latest MD studies of J. Mashl et al [4]. It is necessary to say, that depth of energy profiles obtained in brawnian dynamics simulations (see for example [7]) may be quite different from the used here due to large uncertainty in the values of macroscopic constants used for simulations. However, the shape of potential remains the same. Our model may be made consistent with any energy estimate by corresponding change of parameters. Energy profile for single permeating potassium ion may be quite accurately approximated by the inverted Gaussian-like curve:

$$E(x) = -a \exp\left(-\frac{x^2}{s^2}\right),$$

where a is the lowest energy in the center of the well, s is the characteristic well width. Comparison with the MD data of [3–4] gives $s \approx 7$ Å.

Since we are interested in the radial filter motions («breathing» of the filter) we should deduce the changes in energy profile associated with the change of the pore radius. MD simulations performed for various pH values [4], which influence side-chain effective charges, show, that the *shape* of energy well in the filter is preserved but the maximal well depth is changed. Motion of the filter walls may also be interpreted as the change of effective charges of the walls, so the Gaussian shape of the well should be preserved, but parameter a becomes radius-dependent. We approximate this dependence as,

$$a(r) = \frac{q \cdot Q}{4\pi\varepsilon_0 \cdot r},$$ (1)

where r is a filter radius, Q is some effective charge of the filter wall, q is an electron charge, ε_0 is vacuum dielectric constant. Although, filter wall have distributed charge rather than local one, our approximation is accurate enough, because the amplitude of the filter wall motions should be quite small (~1 Å) and the effective value of Q can not change significantly on this scale. The value of effective charge Q is calculated for the average distance $r \approx 3$ Å and $a \approx 15kT$ observed in short-run MD studies [4].

The influence of the membrane potential should also be included into the single-ion part of the energy. We separate the total electric flied in the pore into two parts: the field caused by the membrane potential and the filed of the other ions in the filter. It was shown [1–4] that the membrane potential drops linearly mainly in the region of the selective filter, so the Goldman assumption of the linear voltage drop is valid for the part of the filed caused by the membrane potential. Ion-ion interactions are accounted explicitly below. The energy profile felt by the ion in the presence of membrane potential is

$$E(x,r,\phi) = -\frac{qQ}{4\pi\varepsilon_0 \cdot r} \exp\left(-\frac{x^2}{s^2}\right) + \frac{q\phi(L-x)}{2L} \cdot \Theta(L-|x|) +$$
$$+ \Theta(-L-x),$$ (2)

where ϕ is membrane potential, q is an electron charge. $\Theta(x)$ is a Heaviside step function: $\Theta(x) = 0$ for $x < 0$, $\Theta(x) = 1$ otherwise. Membrane potential is negative constant equal to $q\phi$ inside the cell, linearly change to zero in the filter region and is zero in the external solution as it is adopted in electrophysiology.

Ion-ion interactions may be approximated as shielded Coulomb repulsion of two equal charges

$$E_{int}(x_i, x_j) = \frac{q^2}{4\pi\varepsilon_0} \frac{\exp\left(\frac{|x_i - x_j|}{d}\right)}{|x_i - x_j|},$$ (3)

where q is an electron charge, ε_0 is vacuum dielectric constant, d is effective shielding constant which describe shielding by the pore wall and water molecules situated between potassium ions. The value of d is evaluated from the assumption of the barrierless conduction (see below). We used the value $d = 2$ Å.

Occupancy states and equilibrium ion positions

Let us first calculate an equilibrium ion positions x_1 and x_2 and the energy E_2 of the state with two ions inside the filter.

It is clear that in the equilibrium when membrane potential is zero the ions are situated symmetrically around the energy minimum, so $x_1 = -x_2$ and the energy of the system may be written as

$$E_2(x,r,0) = 2E(x,r,0) + E_{int}(2x),$$

where x – is the distance from the center of the well to each of the ions (fig. 2). This equilibrium state is referred as $2I$ state below. Equilibrium ion positions x_2 in the state $2I$ are given by

$$\frac{\partial E_2(x,r,0)}{\partial x} = 0.$$

The same considerations for the state with three ions in the filter lead to expressions

$$E_3(x,r,0) = 2E(x,r,0) + E(0,r,0) + E_{int}(2x) + 2E_{int}(x),$$

$$\frac{\partial E_3(x,r,0)}{\partial x} = 0,$$

where $\pm x_3$ are the equilibrium positions of two ions, while the third ion is situated in the center of the well (fig. 1). This state is referred as $3I$ state below.
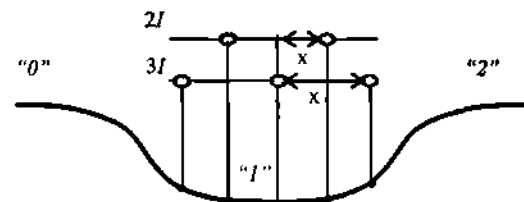

Fig. 1. Equilibrium positions of the ions in $2I$ (double occupancy) and $3I$ (triple occupancy) states. Solid lines correspond to zero membrane potential, dashed lines to some small positive potential
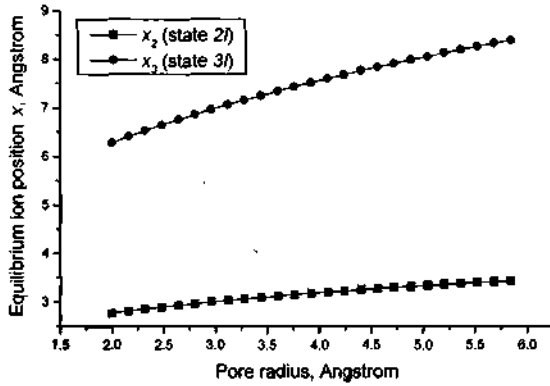
Fig. 2. Equilibrium positions of the ions in the filter for zero membrane potential as a function of the pore radius. In the case of double occupancy (state 2*I*) the ions are placed symmetrically on the distance x from zero. In the state 3*I* one ion is located at $x = 0$, and two other are placed symmetrically at the distance x

Fig. 3. Escape energies in different occupancy states for zero membrane potential as a function of the pore radius

Equilibrium positions x_2 and x_3 and their dependencies on the pore radius can be easily calculated numerically and are presented in the fig. 2.

With the increase of the pore radius the depth of the energy well decreases and the ion-ion repulsion become more and more important, so the equilibrium distances between the ions increase. In the case of double occupancy these changes are very small, however for triple occupancy they reach more than 1 Å. It means that the state with triple occupancy is much more sensitive for the changes of the energy profile.

Let us consider the ion which is escaping the pore. In this case escaping ion have to surmount an energy barrier which is a difference between its energy in solution and energy in equilibrium position inside the filter. Escape energies may be evaluated under assumptions that the escape process is much faster than relaxations inside the pore, so the positions of the remaining ions are approximately fixed:

$$U^{(1)}(r) = E(0,r,0)$$

$$U^{(2)}(r) = E(x_2,r,0) + E_{int}(2x_2) \qquad (4)$$

$$U^{(3)}(r) = E(x_3,r,0) + E_{int}(2x_3) + E_{int}(x_3),$$

where $U^{(n)}$ is a height of the escape energy for the occupancy state with n ions in the channel. The values of escape barriers are easily calculated numerically. The dependence of the escape energies on the pore radius is presented in the fig. 3.

Escape energy for the single ion is simply a dependence of the well depth on the pore radius given formula (3). With the increase of the pore radius the depth of the well decreases which lead to decrease of the escape energies. In the native conditions, corresponding to $r = 3$ Å, the depth of the energy well is 15 k_BT. The ion-ion repulsion reduces the escape
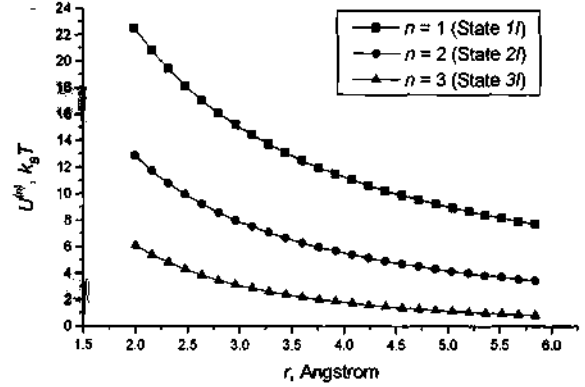
energies significantly to 9 k_BT in the state 2*I* and to 3 k_BT in the state 3*I*.

Barrierless conduction

It was shown in recent MD studies of Kcsa channel [1-4] that conductance trough the selective filter is essentially barrierless. The incoming ions are pushing the ions and water molecules, residing in the filter, along rather than waiting for the vacancy in the adjacent filter site. This «knock-on» collective motion provide simultaneous substitution of the outgoing ion by the incoming one which eliminates large free energy changes associated with the single-ion transitions. Estimated barriers on this conduction pathway are less than 2–3 kT [3–4], so the process has diffusion-limited rather than activational kinetics. To investigate the possibility of knock-on conduction in our model we have constructed total energy function in the following form:

$$E_t(x,y,z) = E(x) + E(y) + E(z) + E_{int}(|x - y|) +$$
$$+ E_{int}(|y - z|) + E_{int}(|x - z|), \qquad (5)$$

where x, y, z are positions of three ions, $x < y < z$. In the absence of membrane potential, if $x = -\infty$, $y = 0$, $z = +\infty$ we have an equilibrium state with the single occupancy; $x = -x_2$, $y = +x_2$, $z = +\infty$ corresponds to equilibrium double occupancy, and finally $x = -x_3$, $y = 0$, $z = +x_3$ to equilibrium triple occupancy. Membrane potential breaks the symmetry of the energy profile given by eq. (4), thus equilibrium positions of the ions become asymmetric.

Let us consider the state with double occupancy when the third ion is approaching from $+\infty$. For each given position of the third ion we equilibrate two ions in the filter. If total energy E_t will not change significantly during this process up to the equilibrium state with triple occupancy, than knock-on barrierless conduction is possible.
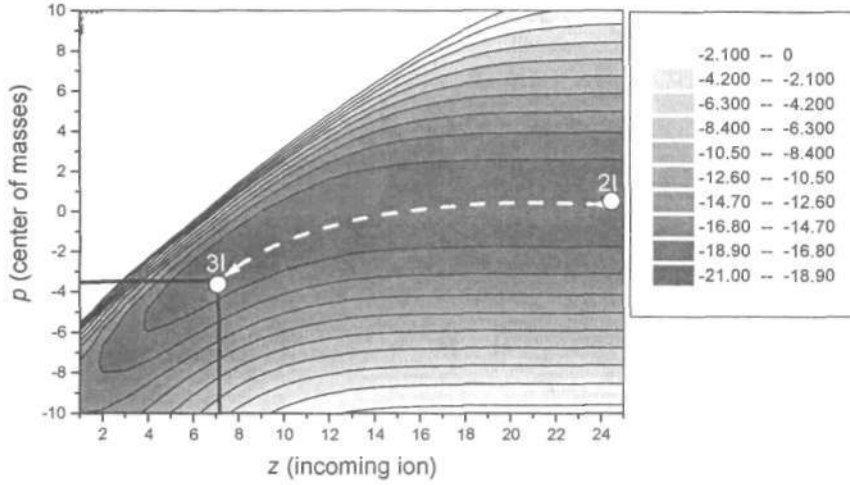
Fig. 4. Total energy as a function of the incoming ion position (z) and the center of masses of two ions in the pore (p). Distances in Å, energies in $k_B T$. No membrane potential is applied. Dashed line shows the barrierless isoenergetic pathway connecting the occupancy states $2I$ and $3I$. Regions with the positive energies, which correspond to strong repulsive forces, are not shown for clarity

The existence of barrierless conduction in real channel was used in the present study to estimate the value of the shielding constant d for ion-ion interactions. We constructed a series of energy profiles adjusting this parameter to obtain approximately the same energy values for the states $2I$ and $3I$, which is necessary for barrierless conduction. The value $d = 2$ Å used in all calculations gives the energies $E_2(x_2) \approx E_3(x_3) \approx 21\ k_B T$.

We will consider the case with no membrane potential applied and with the pore radius $r = 3$ Å first. In this case, as it is seen from fig. 2, the distances between ions in the states $2I$ and $3I$ are almost the same (~3 Å). Let us introduce new coordinates p and q such as

$$p = \frac{x+y}{2}$$

$$q = \frac{|x-y|}{2},$$

then $2 \cdot q \approx 3$ Å = const, and p is a center of masses of the ions in the filter. Total energy is rewritten as

$$E_t(p,\ z) = E(p+q) + E(p-q) + E(z) + E_{\text{int}}(2q) +$$

$$+ E_{\text{int}}(|p-q-z|) + E_{\text{int}}(|p+q-z|). \qquad (6)$$

A contour plot of the function (8) is presented in fig. 4.

Broad energy minimum connecting the states $2I$ and $3I$ is observed. The motion of the incoming ion does not change the total energy of the system due to the rearrangement of the ions in the pore. When the system enters the area around $3I$ state, the first ion may move out. If we will change x and z in (8) the graph above will show the outward motion of the first ion as well. So, our model really allows knock-on mechanism of conduction.

Conduction as a motion of quasi-ion

Used parameterization is not valid in the case of membrane potential applied because the equilibrium placement of the ions become asymmetric and the distances between them become variable. In addition, occupancy state $3I$ may become unstable for large voltages as it is shown below.

We performed numerical simulations of the quasistatical ion conduction through the channel to investigate the conduction in general case. We considered the case when the third ion is approaching the doubly occupied channel from right and push the first ion out to the left. On each step of this process the i-th ion is chosen as a *leading ion*, $i = 1, 2, 3$. Leading ion is assumed to move from the right to the left in small discrete steps Δx separated by equal time intervals Δt. On each step leading ion is fixed while two remaining ions are set *free*. They relax to the equilibrium positions $x_{j(i)}$ and $x_{k(i)}$ which correspond to minimal possible energy of the system with the fixed leading ion. Second index in parenthesis shows the number of the leading ion used for equilibration. The time step of the leading ion motion is assumed to be much larger than the relaxation time of the free ions: $\Delta t \gg t_{free}$, so free ions are fully equilibrated at the end of each step. The whole process may be treated as a slow quasistatical motion of the leading ion accompanied by the fast relaxation of the free ions. The leading ion is chosen on each step according to the following rule:

1. Current positions of the ions, achieved on the iteration n, are $x_1^{(n)}$, $x_2^{(n)}$, $x_3^{(n)}$, which correspond to the energy $E^{(n)} = E(x_1^{(n)}, x_2^{(n)}, x_3^{(n)})$.

2. The first ion is moved one step to the left and then fixed in a new position $x_1^{(n)} - \Delta x$. Two other ions are equilibrated and the energy cost of transition $x_1^{(n)} \to x_1^{(n)} - \Delta x$ is calculated as $\Delta E_1 = E(x_1^{(n)} - \Delta x, x_{2(1)}, x_{3(1)}) - E^{(n)}$.

3. The procedure is repeated with the fixation of the second and third ions and the energy costs $E_2 = E(x_{1(2)}, x_2^{(n)} - \Delta x, x_{3(2)}) - E^{(n)}$ and $E_3 = E(x_{1(3)}, x_{2(3)}, x_3^{(n)} - \Delta x) - E^{(n)}$ are calculated.

4. The ion i, which provide the minimal energy cost is chosen as a leading ion and the ion positions on the next iteration are calculated as $x_i^{(n+1)} = x_i^{(n)} - \Delta x$, $x_j^{(n+1)} = x_{j(i)}$, $x_k^{(n+1)} = x_{k(i)}$.

Free ions are allowed move according to the forces acting on them as described by the Langevien equations in the overdamped case:

$$\begin{cases} \dfrac{\dot{x}_j}{\lambda} = -\dfrac{\partial E(x,r,\phi)}{\partial x}\bigg|_{x=x_j} - \dfrac{\partial E_{int}(x)}{\partial x}\bigg|_{x=x_i-x_j} - \dfrac{\partial E_{int}(x)}{\partial x}\bigg|_{x=x_k-x_j} \\[2ex] \dfrac{\dot{x}_k}{\lambda} = -\dfrac{\partial E(x,r,\phi)}{\partial x}\bigg|_{x=x_k} - \dfrac{\partial E_{int}(x)}{\partial x}\bigg|_{x=x_i-x_k} - \dfrac{\partial E_{int}(x)}{\partial x}\bigg|_{x=x_j-x_k} \end{cases}, \quad (7)$$

where λ is a friction coefficient. We are interested only in the equilibrium positions of the free ions, so the value of λ may be adjusted to achieve the fastest convergence toward the equilibrium state.

The system (9) is solved numerically by the standard finite-difference Euler method. Simulation continue until the energy minimum is reached with the given accuracy or one of the ions cross the boundary $|x| = 30$ Å. Simulation was performed for the position of the leading ion from $X = 15$ Å to $X = -15$ Å with the step 0.2 Å.

Results obtained for the case $r = 3$ Å, $\phi = 0$ are shown on the fig. 5.

It is clearly seen that one ion is entering the channel pushing the other one out in a «knock-on» manner. The process is almost isoenergetic – the energy changes are much less than $k_B T$.

The conduction through the channel can not be presented as a motion of the single ion, since the incoming and outcoming ion are different. The process can be described as a motion of the center of
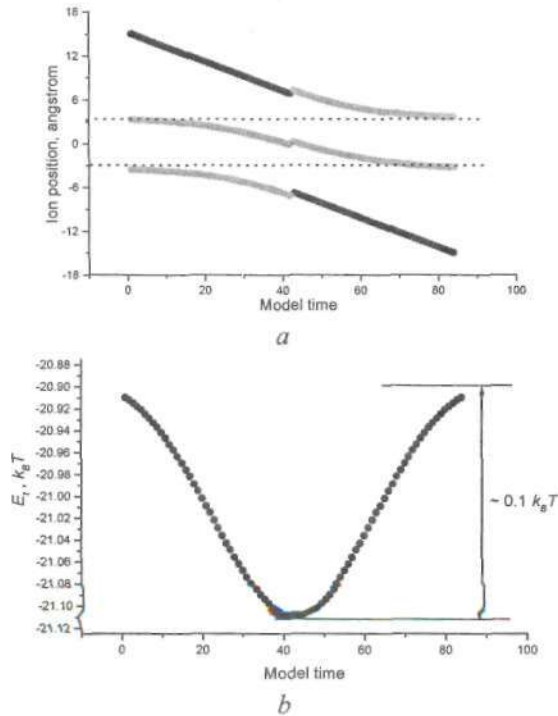
masses of all three ions instead. If we introduce the coordinate of the center of masses as

$$x = \frac{1}{3}(x_1 + x_2 + x_3)$$

the conduction may be described as the motion of some *quasiparticle* with the mass of three ion masses along the coordinate x. Each position of this «quasi-ion» correspond to unique arrangement of three real ions in the channel.

Energy profiles obtained in numerical simulations may be easily presented as a functions of x. Profiles for different values of membrane potential are shown in the fig. 6.
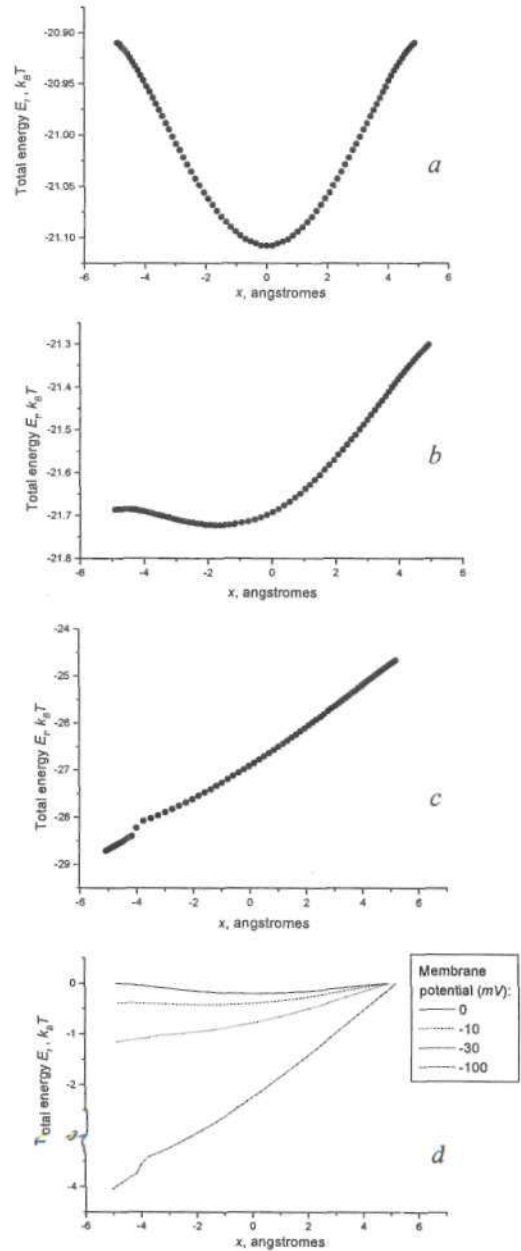

Fig. 5. Equilibrium ion positions (*a*) and total energy (*b*) as a function of the model time. Black parts of the curves in (*a*) correspond to the motion of the leading ion. Small displacements are consequences of the numerical errors. Dashed lines show the equilibrium positions of 2 ions in the filter in the occupancy state 2*I*

Fig. 6. Effective energy profiles seen by the quasi-ion when it moves through the channel for the membrane potentials (*a*) 0 mV, (*b*) –10 mV, (*c*) –100 mV. The same curves are aligned by the ion energy in the external solution in (*d*) for comparison

For zero membrane potential the energy profile is symmetrical. The depth of the energy well, which corresponds to the equilibrium occupancy state *2I* is only 0.1 *kT* in comparison with the energy in the state "2*I*plus the ion in solution", so the conduction is essentially barrierless. With the decrease of the membrane potential the energy of the ions in internal and external solutions become different and the shape of the energy profile become asymmetric. If the membrane potential is smaller than -20-25 mV the minimum on the potential profile disappears, so the state 3 I *u n s t a b l e* .

The formalism of quaiparticles allow to solve the problem of multi-ion conduction through the channel easily. It is not necessary to consider the motion of all the ions in the pore explicitly. The motion of the single «quasi-ion» in the effective potential may be considered instead.

Conclusion

We develop a simplified model of the multiply-occupied selective filter of potassium Kcsa channel based on the latest structural data. Ion-ion interactions are treated explicitly, which allows to estimate the shielding of ionic electrostatic fields in the pore. Our model allows to investigate the conduction in various conditions, particularly it **is** possible to investigate its dependencies on the pore radius. This data can not be extracted from x-ray structures and MD simulations so far. Our data confirmed that the multi-ion conduction in the selectivity filter is essentially barrierless and performed by the "knock-on" mechanism. Stability of the occupancy states for various membrane potentials is investigated. It is shown that the state of triple occupancy become unstable for large membrane potentials, which is consistent with the available data. Our data suggest that the concerted motion of multiple ions in the filter may described as a motion of the single "quasi-ion" in the effective energy profile which allow to reduce the multi-ion problem to the diffusion of single quasi-particle.

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СПРОЩЕНА МОДЕЛЬ СЕЛЕКТИВНОГО ФІЛЬТРУ КАЛІЄВОГО ІОННОГО КАНАЛУ, ЩО БАЗУЄТЬСЯ НА СТРУКТУРНИХ ДАНИХ

Визначення кристалографічної структури бактеріального калієвого каналу Kcsa стало революційним етапом у вивченні іонних каналів. Усталені теоретичні моделі іонних каналів, що базуються на концепції дискретних місць зв'язування іонів, виявилися несумісними із структурними даними. У даній праці розроблено нову модель Kcsa-подібного селективного фільтра з множинною заселеністю, що базується на найновіших експериментальних даних. У моделі явно розглянуто міжіонні взаємодії та визначено константу екранування поля іонів. Модель правильно описує безбар'єрний виштовхувальний механізм провідності у фільтрі й дає змогу вивчати вплив великомасштабних рухів селективного фільтра на його властивості. Було показано, що провідність здійснюється за рахунок колективних рухів іонів, які можна представити як рух «квазііона» в ефективному потенціалі, який легко піддається моделюванню.