# Semi-quantitative model of the gating of KcsA ion channel. 2. Dynamic self-organization model of the gating

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***The aim*** *of this series of papers is to develop the semi-quantitative theory of the gating of KcsA channel.* ***Methods****. For this purpose available structural and electrophysiological data and the results of molecular dynamics simulations were used in the context of the concept of dynamical self-organization. In the second paper we describe the principles of dynamic self-organization and develop the theory of KcsA channel gating based on this concept.* ***Conclusions****. Present work is the first successful attempt of combining the structure and dynamics of real protein and the general concept of dynamic self-organization.*

*Keywords: on channel, KcsA channel, dynamic self-organization, channel gating.*

**Introduction**. The theoretical framework of the Dynamic Self Organization (DSO) was developed for the flux of any moieties, which interact with the protein structure strong enough to cause considerable conformational changes. This can include ions, electrons, charged or neutral ligands, etc. [1–3]. The DSO was applied with great success to the bacterial photosynthetic reaction centers, where the photo-excited electrons interact with the flexible protein structure and causes various non-trivial dynamic effects [4, 5].

The DSO was formulated initially as purely phenomenological theory, with no direct relation to the real structure of particular proteins. In this work we make the first attempt to apply the concept of the DSO to real molecule of the KcsA ion channel.

The permeating ions create very strong local electrostatic field, which polarizes the surrounding protein and changes its structure. The changes in the protein structure influence the energy profile «seen» by each permeating ion. As a result the ionic occupancy becomes dependent on the current conformation of the protein, which in turn depends on the occupancy. This scenario can lead to the DSO phenomena. According to this DSO-based theory, the open state of the channel appears dynamically in the course of self-organizing interaction between the permeating ions and the channel structure [3, 6, 7]. As a result the open state of the channel exists in strongly non-equilibrium environment only and can vanish completely in certain conditions.

It is shown that the KcsA channel may not exhibit gating behavior for small ion fluxes, which is in perfect agreement with the DSO concept [8].

The appearance of the crystal structures of the closed state of KcsA channel [9, 10] and a large approaches to determining the structure of its open form [11] allows one to search for the possible sites responsible for DSO effects in the real channel. In this work we propose possible molecular mechanism, which can lead to the DSO in the KcsA channel: The ions push the M2 transmembrane helices of KcsA channel by means of their local electrostatic field. The motion of the M2 helices changes the effective energy profile for permeation of ions and influences the ionic flux, creating the dynamic feedback. Resulting self-organization leads to the appearance of the steady, but non-equilibrium, dynamic open state of the channel.

The theory is based on the results of the first paper [12] of this series, where the geometry and the energetic of the gating motions were analyzed.

**Theory**. *Conformational potential*. It is possible to rewrite the equation for structural potential (eq. (9) in the first paper [12]) as following:

$$\dot{\varphi} = -\frac{D}{k_B T} \frac{\partial V_{\text{conf}}(\varphi, z_q, z_w, r, U)}{\partial \varphi} + \sqrt{2D}\,\xi(t), \quad (1)$$

where

$$V_{\text{conf}}(\varphi, z, z_q, z_w, r, U) = V_{\text{str}}(\varphi) +$$

$$+ \int_{\varphi'=0}^{\varphi} \int_{z_{\min}}^{z_{\max}} m(\varphi', z, z_q, z_w) \times$$

$$\times c(\varphi', z, r, U)\,dz\,d\varphi'. \quad (2)$$

The last expression defines the *conformational potential* for the M2 helix. The conformational potential is a free energy of the self-consistent system, which consists of two parts. The first part is structural potential, which is intrinsic to the channel protein itself and does not depend on the occupancy of the channel pore. The second part is the energy of interaction between the ions in the pore and the M2 helix. This interaction energy is responsible for non-trivial behavior of the system and for appearance of DSO phenomena.

*Probabilities of the closed and open states*. The main quantities computed in our model, which can be compared with experimental results, are the probabilities of the closed and open states. Let us assume that

the conformational potential possesses two distinct energy wells. The channel is assumed to be closed if it resides in the left well and to be open otherwise. Let us first compute the probability of the channel to reside in a small interval of opening angles from $\varphi$ to $\varphi + \Delta\varphi$ as $P(\varphi)\Delta\varphi$, where:

$$P(\varphi) = \frac{\exp(-V_{\text{conf}}(\varphi, z, z_q, z_w, r, U)/k_B T)}{\int_{\varphi=\varphi_{\min}}^{\varphi_{\max}} \exp(-V_{\text{conf}}(\varphi, z, z_q, z_w, r, U)/k_B T)\,d\varphi}, \quad (3)$$

and $\varphi_{\min}$ and $\varphi_{\max}$ are minimal and maximal possible values of the opening angle respectively.

Using the equation one can compute the probability of the channel to reside in one of the potential well of conformational potential as follows:

$$P_{\text{closed}} = \int_{\varphi=\varphi_{\min}}^{\varphi_{\text{barrier}}} P(\varphi)\,d\varphi;$$

$$P_{\text{open}} = \int_{\varphi=\varphi_{\text{barrier}}}^{\varphi_{\max}} P(\varphi)\,d\varphi, \quad (4)$$

where $\varphi_{\text{barrier}}$ is the position of the energy barrier on the conformational potential.

*Current through the channel*. The current through the channel can be expressed as the first integral of the Focker-Plank equation (1) from the first paper under stationary conditions $\partial c(\varphi, z, C_{in}, C_{ex}, U)/\partial t = 0$. Accounting for the boundary conditions leads to the following final expression for the current

$$J(\varphi, C_{in}, C_{ex}, U) =$$

$$= D \frac{C_{in}\, e^{\frac{V_{ion}(-z_{\min})}{k_B T}} - C_{ex}\, e^{\frac{V_{ion}(z_{\max})}{k_B T}}}{\Xi(\varphi, z_{\max}, U)}, \quad (5)$$

where $\Xi$ is given by equation (3) from the first paper.

**Results and Discussion**. We have analyzed large number of possible combinations of parameters and found that three major scenarios of the channel functioning can be obtained in our model. In all scenarios the shielding constant of electrostatic interactions is $d = 5$ Å, the membrane potential is $U = 2\,k_B T$ (equivalent of ~ 50 mV), $C_{in} = 0.02$ Å$^{-1}$ (real concentration $C_{in}^0 =$
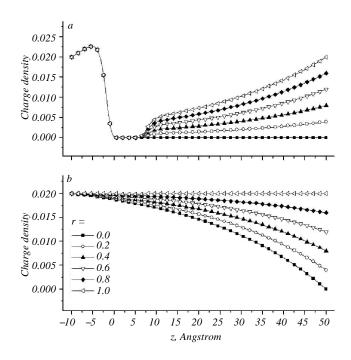
Fig. 1. Distributions of the ionic charge density along the channels in scenario 1 for various values of concentrations ratio: *a* – closed state; *b* – open state

= 200 mM). The values of other parameters are indicated below.

S c e n a r i o 1. *Permanent open state*. In this scenario the open state of the channel is present permanently regardless of the ionic concentrations and the value of ionic flux, however, the probability of the open state depends strongly on these factors. If the ionic flux is small, the probability of the open state becomes negligible, but the open steady state itself does not disappear. However, if there are no ions in the channel, the open state disappears in agreement with the general ideology of DSO. This can not happen under physiological conditions, thus the open state can be considered permanently present.

We present the most prominent case observed for $_q = 0.49$; $l_w = 1.0$; $_w = 0.1$; $w_0 = 1 \cdot 10^{10}$.

*Charge distributions.* Quasi-equilibrium charge distributions along the channel in the closed and open states are shown in Fig. 1 for various values of $r$ ranging from equal ionic concentrations $r = C_{ex}/C_{in} = 1$ to zero external concentration $r = C_{ex}/C_{in} = 0$. If the concentrations are equal the ionic charge distribution inside the channel is determined solely by the effective energy profile $V_{ion}$. The energy barriers on $V_{ion}$

correspond to the decreases of the charge density. The dramatic depletion of the charge density near $z = 5$ Å in the closed state corresponds to the VDW particle, which blocks the pore sterically. The ions can not surmount the barrier created by the VDW particle, thus the charge density at the left of the barrier is determined solely by $C_{in}$ and thus does not change with $r$. Once the blocking VDW group moves away in the course of opening, the ions redistribute along the whole channel. In the open state the charge density drops smoothly and monotonously from the larger value of $C_{in}$ to $C_{out}$. The charge density is sensitive to $r$ along the whole channel in the open state.

*Necessary condition of DSO – the regulatory region*. The first prerequisite for the appearance of non-trivial DSO effects is the direction of the angular momentum, which act on the M2 helix and moves it along structural coordinate     (see first paper of the series). This momentum should change its sign depending on the value of the structural coordinate. If the structure is close to the closed state, the momentum caused by the ions should stabilize this state by closing the channel. If the structure is nearly open, the momentum should act at the opposite direction to drive the channel toward the open state.

Thus, the first test, which shows the possibility of DSO effects, is the analysis of the momentum, which acts in the opening plane. If this momentum changes its sign in the interval of opening angles, which correspond to the gating transition, then the DSO effects are possible in the system. Since the force, which act between the ions and the charged or VDW group of the helix is always repulsive, it is enough to consider the projection of the distance between the ion and the charged group on the moving ort $j(\;)$.

Fig. 2, *a*, shows the dependence of $R(z, \;)$ on the position of the ion (as it was mentioned above this projection is independent on the position of the charged group   ). The ions located in the intracellular part of the pore ($z < 11$ Å) are opening the channel regardless of its current state. Similarly, the ions, which are located in the extracellular part of the pore ($z > 17$ Å) are always closing the channel. It is clearly seen that there is a range of $z$ values (approximately from $z = 11$ Å to $z = 17$ Å) where $R$ changes its sign upon opening. The ions, which are located in this region (which coincide
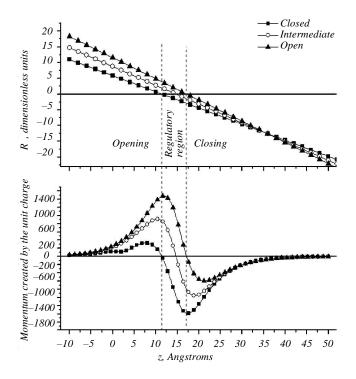
Fig. 2. Analysis of the angular momentum, acting from the ion located in the point $z$ of the channel axis on the M2 helix: $a$ – projection of the distance between the group and the ion on the moving ort $j(\ )$; $b$ – projection of the angular momentum created by the VDW and charged groups on the moving ort $j(\ )$. Opening, closing and regulatory regions are indicated. See text for details

with the vicinity of the channel central cavity), will close the channel if it is nearly closed and open the channel if it is nearly open. The saddle point is located approximately halfway of the opening. The ionic charge density in this region is thus critical for possible DSO effects. We will call this region «regulatory region» hereafter.

Fig. 2, $b$, shows the angular momentum acting on both VDW and charged groups from the ion located at the point $z$ on the channel axis. The sign of the momentum is in agreement with the analysis given above, however, the magnitude shows several important features. In the closed state the VDW closes the pore sterically. The $K^+$ ions do not fit into the narrow gating region, which causes very strong repulsive force, which «tries» to widen the pore. However, the population of the gating region is extremely small, which means that it does not contribute into the net momentum weighted over ionic distribution along the channel. However, this high energy barrier affects the

distribution of the ions along the pore as it is shown below. The momentum, caused by the charged group, falls into the vicinity of the regulatory region and thus changes significantly upon opening.

Our analysis shows that the necessary condition for the DSO effects is fulfilled in our model – the regulatory region exists and is located *inside* the channel. This fact can not be considered as a coincidence. This allows us to speculate that the geometry of the channel opening is tuned by the evolution to allow the DSO effects (see discussion for details).

*Conformational potential and the probability of residence.* The conformational potential of the system with the parameters specified above appears to be bistable with two well-defined energy wells (Fig. 3, $a$). The shape of the conformational potential depends on the concentration ratio $r$. The increase of $r$ leads to the deepening of the left energy well, which corresponds to the closed state of the channel. The open state energy well becomes shallower with the increase of $r$, but this dependence is very weak in comparison to the well of the closed state. The changes of the shape of the conformational potential leads to dramatic redistribution of the probability of residence if the channel stays in particular range of opening angles (Fig. 2, $b$). In the case of equal concentrations ($r = 1$) the channel is mostly closed. With the decrease of $r$ the probability density of the open state increases until the closed state becomes barely detectable for $r = 0$. This dependence is summarized in Fig. 6, $c$, which shows the probabilities of the open and closed state computed using eq. as a function of $r$.

It is interesting to compare our dependencies with the experimentally determined ones (Fig. 5 of the work [8]). Although there is no quantitative correspondence, the qualitative similarity is remarkable.

*The current.* For the given set of parameters the dependence of the current on the opening angle (given by equation (14)) is shown in Fig 4. It is clearly seen that the current is essentially zero for small opening angles and reaches the maximum for nearly open angles. This confirms that two steady states in our model can be interpreted as real closed and open states.

S c e n a r i o 2. *Emerging open state.* In this scenario the open state of the channel disappears if the ionic flux becomes smaller then certain critical value.
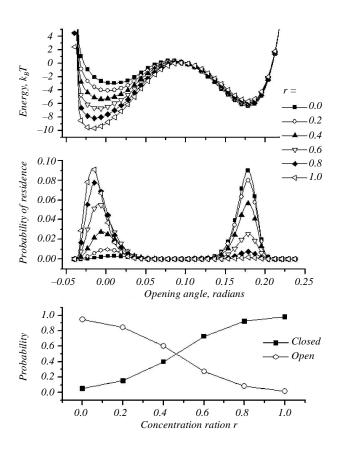
Fig. 3. Conformational potential (*a*), probabilities of residence (*b*) and probabilities of the open and closed states (*c*) for scenario 1. Conformational potentials are aligned by the positions of the energy barrier to aid the comparison

In this case the interaction between the permeating ions and the channel structure is rather weak. As a result small changes in the ionic charge density, caused by the changes of ionic concentrations in solutions, can lead to the disappearing of the open state.

The results observed for $\varepsilon_q = 0.43$; $l_w = 0.7$; $\varepsilon_w = 0.1$; $w_0 = 1 \cdot 10^{11}$ are presented. We postulate that there is a potential well in the effective energy profile for permeating ions, which is located in the vicinity of the central cavity ($z = 32$ Å). The depth of the well is assumed to be $A = 3 \, k_B T$, the half-width $\sigma = 5$ Å. The plots of angular momentum and the current are not shown for this scenario because they are very similar to the corresponding plots for scenario 1. Particularly the regulatory region is also present and has the same characteristics as in the scenario 1.

*Conformational potential and the probability of residence.* In this scenario the conformational potential

shows the «classical» transition from the monostability to bistability with the appearance of the open state. If the parameter *r* is large there is only single energy well in the conformational potential, which corresponds to the closed state of the channel. The right hand part of the potential possesses a pronounced shoulder, which is the precursor of the second energy well (Fig. 5, *a*). With the decrease of *r* this shoulder become more and more pronounced and, finally, the derivative at this point reaches zero for $r = 0.6$. The value $r = 0.6$ corresponds to the bifurcation point in the system. Further decrease of *r* leads to the formation of the second energy well, which corresponds to the open state of the channel. Finally, for small values of *r*, the well of open state become deeper then the well of the closed state. The same sequence of events can be observed in the plot of probability of residence (Fig. 5, *b*). The probability of the open and closed states in this scenario behaves very much like in experiment (Fig. 5, *c*), however the correspondence is still only semi-quantitative.

It is clearly seen that there is no stable open state of the channel if *r* is larger then 0.6. This means that the open state emerges from the non-linear interaction between the ionic charge density and the channel structure in the physiological range of concentration ratios. In the previous scenario the transition from the mono- to bistability occurs outside the physiological region (negative values of *r*).

S c e n a r i o 3. *Subconductance state*. In this scenario the system becomes not bistable but tristable. There are three steady states, which correspond to the closed, the subconductnace and the open states of the channel. The subconductunce state appears between the closed and open states and can only be observed for large ionic fluxes.

The results obtained for $\varepsilon_q = 0.46$; $l_w = 1.0$; $\varepsilon_w = 0.25$; $w_0 = 1 \cdot 10^9$ are shown. The energy well on the effective energy profile for the permeating ions is located at point z = 20, has the depth of $A = 1 \, k_B T$ and the half-width of $\sigma = 5$ Å. The plots of the charge distributions, momenta and the current in this case are very similar to the corresponding plots for scenario 1 and thus not shown.

In this case the shape of the conformational potential (Fig. 6) become more complex than in the previous cases. Particularly, there are three steady
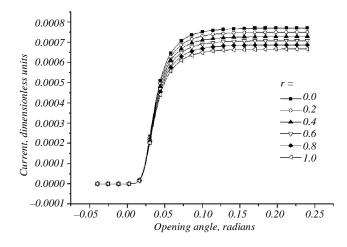
Fig. 4. Current through the channel as the function of the opening angle for various values of the concentration ratio $r$

states instead of two. The third steady state is located between the closed and open states and can be classified as a subconductance state.

It is clearly seen that the subconductance state is present for small values of $r$ and disappears starting from $r = 0.3$. There are experimental data, which show the existence of the subconductance states in KcsA channel [8], thus our model can be considered as a possible explanation of the appearance of these states.

The DSO was developed as a general physical theory, which explains complex dynamical properties of the biological macromolecules in a simple and physically consistent way. It allows deriving the kinetic constants of the channel gating from the simple physical principles and the atomistic channel structure in a bottom-up manner.

Experimental data obtained on various channels (including KcsA), show that the probabilities of the open and closed states depend strongly on the ionic flux through the channel [6, 8, 13, 14]. Furthermore, it is possible that the open state of KcsA disappears completely if the ionic flux is smaller than certain critical value [8]. It is hard to explain such behavior from the traditional point of view, when the existence of open and closed states is considered to be intrinsic to the pore-forming protein. The DSO provides very elegant and general framework for describing the systems with emerging steady states. However, this picture is inevitably somewhat simplified and describes the functioning of the single channel only. It
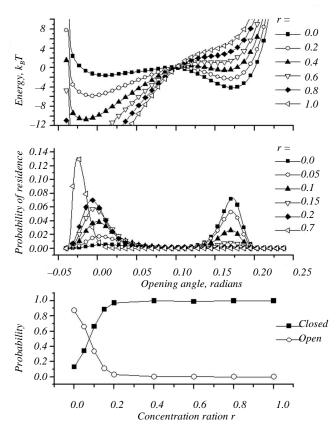


Fig. 5. Conformational potential (*a*), probabilities of residence (*b*) and probabilities of the open and closed states (*c*) for scenario 2. Conformational potentials are aligned by the positions of the energy barrier (or position of the former barrier) to aid the comparison

is now widely recognized that voltage-gated $K^+$ channels exist not as independent units merely responding to changes in transmembrane potential but as macromolecular complexes able to integrate a plethora of cellular signals that fine tune channel activities. Proteins that associate with $K^+$ channels may do so dynamically with regulated on- and off-rates, or they may be constitutively complexed for the lifetime of the channel protein. The functional result of interactions with these accessory proteins includes altered channel assembly, trafficking, protein stability, gating kinetics, conduction properties, and responses to signal transduction evens [16]. These aspects of the channel functioning are not addressed in our approach, which is focused on the physical mechanisms of functioning of the single channel proteins.

Although the theoretical basis of DSO is well established and tested [1–3, 7, 15], its implementation
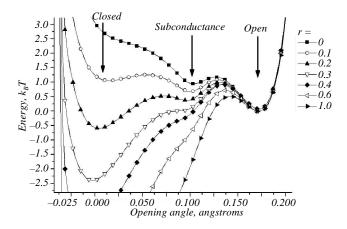
Fig. 6. Conformational potential in scenario 2 for various values of concentration ratio $r$. Conformational potentials are aligned by the positions of right energy well to aid the comparison

for particular molecular system is still challenging. To our knowledge the current work is the first attempt to use the ideas of DSO in conjunction with the high-resolution structural data and the results of all-atom MD simulations.

We demonstrate that our model produces various scenarios of dynamical self-organization in the channel. The interaction between the ionic flux and the channel structure can lead to the emergence of the open state or the open and the subconducting states. These emergent states are not intrinsic to the protein itself. They appear due to the self-consistent interaction with the permeating ions and cannot exist without this interaction. The open state of the channel is sensitive to the ratio of ionic concentrations. The sensitivity can vary from the subtle change of the open state probability to complete disappearance of the open state if the concentration ratio exceeds certain threshold. The latter case is in complete agreement with experimental data [8].

The appearance of the subconductance state in our model is very intriguing. It is well known that the subconductance states are generally hard to study and to explain. We can speculate that the DSO can be responsible for the appearance of at least some of the observed subconductance states in the ion channels.

There is a region in the middle of the channel where the direction of momentum created by the ions can change its sign (regulatory region). Such region is present in the wide range of channel geometries, which

allows us to conclude that it is likely to be the general feature of all tetrameric channels. The regulatory region makes the channel sensitive to the ratio of ionic concentrations and is vital for DSO phenomena. The existence of this region is determined by the geometry of opening only and serves as a necessary condition for DSO. This allows us to conclude that DSO phenomena *in principle* can exist in the wide range of the ion channels. We can also speculate that the channels were evolutionary designed to have the regulatory region and thus to allow the DSO processes.

Finally, the DSO can clarify one of the most intriguing features of the ion channels – the existence of at least two distinct functional states (closed and open). The majority of selective ion channels function by switching between conducting and not conducting states even in the cases when such behavior can hardly be subjected to evolutionary pressure. This allows speculating that there is some very general physical mechanism, which causes the existence of two distinct functional states of the channel. The DSO is a good candidate for such mechanism.
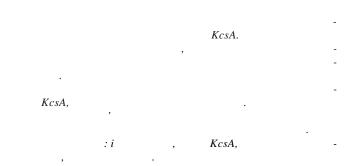
**Conclusions**. We developed the first semi-quantitative theoretical model of the gating of KcsA channel based on the concept of dynamical self-organization. In our model the channel forming protein and the ionic flux through the pore are considered as a self-consistent system, which exhibit complex dynamic behavior. The model is built using the latest experimental data on the channel gating and the results of all-atom MD simulations. The DSO leads to the appearance of the open state of the channel, which is not intrinsic to the channel forming protein itself and can only exist due to the ion-conformational interaction in non-equilibrium conditions. Our model provides an elegant explanation of the experimentally observed disappearance of the open state of KcsA channel in the conditions with small ionic fluxes. The model can describe a series of different self-organization scenarios, including formation of the subconductance states. The results of the present work allow us to speculate that the DSO can be a general physical principle, which guides the functioning and the evolution of the ion channels.

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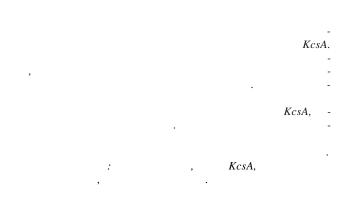
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