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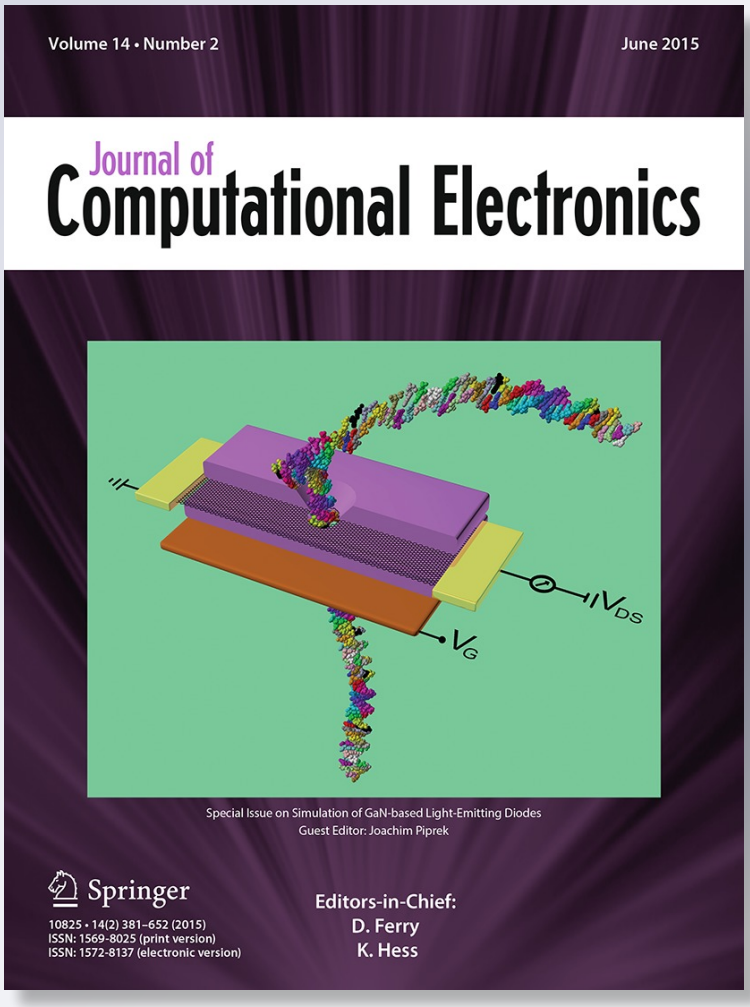

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A transport equation for confined structures applied to the OprP, Gramicidin A, and KcsA channels

Amirreza Khodadadian · Clemens Heitzinger

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Abstract A transport equation for confined structures is used to calculate the ionic currents through various transmembrane proteins. The transport equation is a diffusion-type equation where the concentration of the particles depends on the one-dimensional position in the confined structure and on the local energy. The computational significance of this continuum model is that the $(6+1)$-dimensional Boltzmann equation is reduced to a $(2+1)$-dimensional diffusion-type equation that can be solved with small computational effort so that ionic currents through confined structures can be calculated quickly. The applications here are three channels, namely OprP, Gramicidin A, and KcsA. In each case, the confinement potential is estimated from the known molecular structure of the channel. Then the confinement potentials are used to calculate ionic currents and to study the effect of parameters such as the potential of mean force, the ionic bath concentration, and the applied voltage. The simulated currents are compared with measurements, and very good agreement is found in each case. Finally, virtual potassium channels with selectivity filters of varying length are simulated in order to discuss the optimality of the filter.

Keywords Boltzmann equation · Confined structures · Ionic transport

A. Khodadadian · C. Heitzinger
Institute for Analysis and Scientific Computing, Vienna University of Technology (TU Vienna), Vienna, Austria
e-mail: Amirreza.Khodadadian@TUWien.ac.at

C. Heitzinger (✉)
School of Mathematical and Statistical Sciences, Arizona State University (ASU), Tempe, AZ, USA
e-mail: Clemens.Heitzinger@ASU.edu;
Clemens.Heitzinger@TUWien.ac.at

1 Introduction

The fundamental transport equation for large-scale systems is the Boltzmann transport equation [6,16]. Its independent variables are time, three space, and three momentum dimensions; therefore, calculating numerical approximations to its solutions is very computationally expensive. Popular approaches to the calculation of currents through ion channels such as molecular dynamics and Brownian dynamics are valuable to elucidate various aspects, but also require a huge computational effort when currents are calculated. However, only currents are measured in experiments. In order to overcome this problem, we have derived a $(2+1)$-dimensional transport equation from the $(6+1)$-dimensional Boltzmann transport equation to simulate geometrically complicated structures and to decrease the computational cost of current calculations [11].

Here confined structures are understood as long, narrow 3D geometries where the transport of the particles occurs in one space dimension, namely the longitudinal direction, due to the presence of a potential wells in the two transverse dimensions. The potential wells responsible for the confinement can vary along the transport direction and are given as functions of position. The independent variables in the $(2+1)$-dimensional transport equation are position along the longitudinal direction, local particle energy, and time. In the case of harmonic confinement potentials, i.e., when they are quadratic functions of position, it was even possible to find explicit expressions for the transport coefficients.

This is an essential feature of the present model: the confinement potentials determine the local fluxes and hence the transport coefficients. This is an important improvement compared to using bulk transport coefficients for the simulation of extremely small structures and it means that the physical properties of the channels and especially their selectivity

filters are captured. Since the transport coefficients are given by explicit expressions, the numerical solution of the transport equation is as computationally expensive as the solution of a diffusion equation with constant transport coefficients so that currents are obtained with relatively small computational effort. Therefore this transport equation for confined structures is ideally suited for the simulation of ion channels.

Due to the physiological importance of ion channels [15], this transport model is applied to three transmembrane proteins here, namely the phosphate specific channel OprP (an antibiotic), the Gramicidin A channel (another antibiotic), and the well-known KcsA ionic channel. In each case, the model is validated by comparison with current measurements of various ions. Then we elucidate physiological properties of the channels. For example, the selectivity of potassium channels between sodium and potassium is its primary physiological function and therefore it is investigated in the simulations. The model reproduces selectivity. We also constructed virtual ion channels by changing the length of the selectivity filter in order to answer the question if and in which respect the natural KcsA channel is optimal.

The rest of the paper is organized as follows. In Sect. 2, the transport equation is presented. In Sect. 3, the three transmembrane proteins are simulated. Finally, in Sect. 4, conclusions are drawn.

2 The transport equation

We recapitulate the transport equation and its relation to the given confinement potential in this section. Throughout [11], the calculations were performed using dimensionless variables and the theoretical feasibility of this approach was demonstrated. In [12], the derivation of the transport equation was extended so that all variables have physical units and a complete discussion of all the units can be found there as well.

The starting point is the Boltzmann transport equation in the form

$$\partial_t f + \{E,\ f\}_{XP} + \mathcal{Q}[f] = 0, \tag{1}$$

where the Poisson bracket is defined as

$$\{g,\ f\}_{XP} := \nabla_P g \cdot \nabla_X f - \nabla_X g \cdot \nabla_P f. \tag{2}$$

Here $f(X,\ P,\ t)$ is the kinetic particle density, $X \in \mathbb{R}^3$ is position, $P \in \mathbb{R}^3$ is momentum, t is time, $E(X,\ P)$ is the energy, and $\mathcal{Q}$ is the scattering operator. The energy is defined as

$$E(X,\ P) := V(X) + \frac{|P|^2}{2m},$$

being the sum of the potential energy V of the confinement and the kinetic energy. m denotes the mass of a particle.

The spatial multiscale problem arises, since the structures are much narrower than long. We write the confinement potential as

$$V(x,\ y) = V_0(x) + V_1(x,\ y), \tag{3}$$

where V_0 is the applied potential, and we will rescale in (4a) below.

Here we consider 3D structures that are confined in two dimensions such that transport occurs in one dimension. Therefore we split position X and momentum P into

$$X = (x,\ y) = (x,\ y_1,\ y_2),$$
$$P = (p,\ q) = (p,\ q_1,\ q_2),$$

where x is the longitudinal direction of charge transport and y_1 and y_2 are the two transverse directions of confinement. Accordingly, p is the momentum in the longitudinal direction and q_1 and q_2 are the momenta in the transverse directions. We also split the energy E into two contributions E_x and E_y from the longitudinal and transverse directions, respectively, i.e.,

$$E(X,\ P) = E_x(x,\ p) + E_y(x,\ y,\ q),$$
$$E_x(x,\ p) := V_0(x) + \frac{|p|^2}{2m},$$
$$E_y(x,\ y,\ q) := V_1(x,\ y) + \frac{|q|^2}{2m}.$$

The scattering operator $\mathcal{Q}$ is defined such that it describes the physical system correctly. In the transport (longitudinal) x-direction, it relaxes the density towards a Maxwellian distribution, whereas in the confinement (transverse) y-direction it conserves the local energy so that the particles do not lose or gain energy on average by colliding with the sidewalls of the structure, i.e., there is no net energy transfer between the particles and the sidewalls. The scattering operator is a relaxation operator and it has the form

$$\mathcal{Q}[f](x,\ y,\ p,\ q,\ t) := \frac{1}{\tau}\left(f - M(p)\frac{u_f(x,\ E_y(x,\ y,\ q),\ t)}{N(x,\ E_y(x,\ y,\ q))}\right).$$

The details of the operator can be found in [11, Sect. 2.1]. Relaxation towards a Maxwellian distribution in the transport direction leads to the final diffusion-type behavior in this direction similar to the derivation of the drift-diffusion equations from the Boltzmann transport equation.

Then, in [11, Sect. 2.2], all variables were scaled and transformed into a dimensionless formulation. Here, however, we only scale the confinement direction y and time t by setting

$$y_s := \frac{y}{\epsilon}, \tag{4a}$$

$$t_s := \epsilon t. \tag{4b}$$

We consider the limit $\epsilon \to 0$. Regarding the spatial multiscale problem, this means that the width $\epsilon \ll 1$ of the structure is very small corresponding to pores that are much longer than wide. Regarding the temporal multiscale problems, this scaling in conjunction with the scattering operators means that we are interested in time scales where diffusion is the dominant mechanism. We now simplify notation by using the same variable names as before the scaling; additionally, in order to be consistent with the notation in [11], we set $v := p$ and $w := q$, but note that v and w denote momenta.

Dramatic simplifications are possible when assumptions on the form of the confinement potential, and especially on the form of $V_1(x,\ y)$, are made. We assume that $V_1(x,\ y)$ has the quadratic form

$$V_1(x,\ y) = \frac{1}{2}(y - b(x))^\top B(x)(y - b(x)), \tag{5}$$

where $y,\ b \in \mathbb{R}^2$ and the diagonal matrix $B(x)$ is given by

$$B(x) = \begin{pmatrix} B_1(x) & 0 \\ 0 & B_2(x) \end{pmatrix}.$$

In this case, the confinement potential is called harmonic. Of course it is required that $B_1(x) > 0$ and $B_2(x) > 0$ for all x so that the particles are indeed confined.

Finally, a diffusion-type equation for transport through a confined structure can be found. Its coefficients are given by the coefficients of the confinement potential. The equation is the conservation law

$$\partial_t \rho(x,\ \eta,\ t) + \partial_x F^x(x,\ \eta,\ t) + \partial_\eta F^\eta(x,\ \eta,\ t) = 0, \tag{6}$$

where the three independent variables are x, the longitudinal position, η, the local energy in the transverse direction, and time t. The two fluxes F^x and F^η are

$$\begin{aligned} F^x(x,\ \eta,\ t) = &-\frac{4\pi^2 kT\tau\eta}{\sqrt{B_1 B_2}} T_1 \\ &- \frac{\pi^2 kT\tau\eta^2}{\sqrt{B_1 B_2}} \left(\partial_x (\ln B_1) + \partial_x (\ln B_2)\right) T_2, \end{aligned} \tag{7}$$

and

$$\begin{aligned} F^\eta(x,\ \eta,\ t) = &-\frac{\pi^2 kT\tau\eta^2}{\sqrt{B_1 B_2}} \left(\partial_x (\ln B_1) + \partial_x (\ln B_2)\right) T_1 \\ &- \frac{\pi^2 kT\tau\eta^2}{6\sqrt{B_1 B_2}} \left(\frac{12 m B_1 (\partial_x b_1)^2}{m + \tau^2 B_1} \right. \\ &+ \frac{12 m B_2 (\partial_x b_2)^2}{m + \tau^2 B_2} + 2\eta \partial_x (\ln B_1)\, \partial_x (\ln B_2) \\ &+ \frac{\eta(3m + 8\tau^2 B_1)(\partial_x (\ln B_1))^2}{m + 4\tau^2 B_1} \\ &\left. + \frac{\eta(3m + 8\tau^2 B_2)(\partial_x (\ln B_2))^2}{m + 4\tau^2 B_2} \right) T_2, \end{aligned} \tag{8}$$

where

$$T_1 := \mathrm{e}^{-V_0/kT} \nabla_x \left(\mathrm{e}^{V_0/kT} \frac{\rho}{N} \right),$$

$$T_2 := \mathrm{e}^{-\eta/kT} \partial_\eta \left(\mathrm{e}^{\eta/kT} \frac{\rho}{N} \right).$$

The computational significance is that this $(2+1)$-dimensional equation can be solved fast numerically in contrast to the original $(6+1)$-dimensional problem. Then the total current is immediately found by integrating the flux F^x in the longitudinal direction over all local energies η, i.e., the total current I is

$$I = \int_{\eta=0}^{\infty} F^x\ (x_0,\ \eta)\, \mathrm{d}\eta,$$

which does not depend on the particular cross section given by x_0.

3 Simulation of transmembrane proteins

Ion channels are of essential physiological importance. They are located in cells membranes and manage the concentration gradients of ions across the membranes. Hence they are the fundamental regulators, amplifiers, and transducers of the nervous system. Ion channels are small enough that interactions between the ions and the channel protein are important for their operation, while they are large enough that it is impossible to calculate all such interactions at the atomistic level on realistic time scales where ionic conductance occurs.

All organisms have ion channels for Na^+, K^+ and Cl^-. These are significant in osmoregulation and the transmission of signals via the transmembrane potential between the inside (potassium) and the outside (sodium and chlorine) of the cell. Because of their important role in physiology, we simulate currents through three different ion channels. The channels considered are the phosphate selective OprP channel, the Gramicidin A channel, and the *Streptomyces lividans* KcsA channel. In each case, the calculated currents are compared with measurements. We also discuss virtual KcsA channels in order to elucidate if and how the structure of the natural channels is optimal with respect to its selectivity.

3.1 Determination of the confinement potential

The confinement potential enters the transport model via Eqs. (3) and (5). For each channel type and each ionic species, the potential of mean force (PMF) and the channel width

completely determine the confinement potential, i.e., the PMF and the channel width determine the functions V_0, b and B in the confinement potential V in (3). In other words, the microscopic structure of the channel as it is experienced by each ionic species is fully described by the PMF and the channel width.

Harmonic confinement potentials can always be constructed by calculating the best approximation from given forces according to [11, Sect. 5.1]. Here the channels are considered to be straight for simplicity so that $b_1(x) = b_2(x) = 0$ holds for all x. The minimum energy, i.e., the minimum of each parabola, at each x along the channel is then given by $V(x,\ (0,\ 0)^\top) = V_0(x)$. These energies are taken from the literature for each structure considered here, e.g., they are PMFs [8]. Applied potentials can be added to V_0.

Finally, the coefficient function B is determined from the known width of the structure. For simplicity, we assume that the channels have a rotational symmetry so that $B := B_1 = B_2$. The width r of the structure at x for the present purposes is the distance $r(x)$ in y-direction from the center of the cross section where the confinement force reaches a constant value F that may depend on channel type. In order to determine the coefficient B from the known width $r(x)$, we first calculate the gradient as

$$\nabla_y V(x,\ y) = \nabla_y \left(V_0(x) + \frac{1}{2} B(x) \left(y_1^2 + y_2^2 \right) \right) = \begin{pmatrix} B(x) y_1 \\ B(x) y_2 \end{pmatrix}.$$

Therefore, the confinement force F at x is

$$|F| = \left| \nabla_y V(x,\ y) \right| = |B(x)| \sqrt{y_1^2 + y_2^2} = B(x) r(x),$$

so that the sought coefficient is

$$B(x) = \frac{|F|}{r(x)}.$$

This procedure is used to determine the functions V_0, b, and B in (3) and (5) from the given structure in all of the following simulations. The channel width is known from structures in the Protein Data Bank (PDB) and the energy landscape along the channel from data in the literature for the PMF, where is has been calculated, e.g., from molecular-dynamics simulations.

3.2 Simulation of phosphate specific OprP channels

Pseudomonas aeruginosa is a versatile gram-negative outer membrane bacterium, which can live in various environments and leads to diseases in humans and animals such as pneumonia, osteomyelitis, and meningitis. OprP is a transmembrane beta-barrel protein of this bacterium and forms a highly selective phosphate channel. The selectivity of the pore for molecular interactions and the permeability of OprP for small anions or antibiotics in the absence of phosphate were studied in [18,19].

We simulate the passage of potassium and chlorine ions through the OprP channel. The PMFs as well as the width of the channel were determined in [17]. The PMFs are shown in Fig. 1. The figure illustrates that the potential barriers have their extrema in the middle of the pore, between R226 and K121 for chlorine and R59 and D94 for potassium, whereas the barriers are smaller and the pore is wider near R220, K30, and K322. These areas are entrance funnels to OprP allowing chlorine and potassium ions to move easily [17].

In Fig. 2, the measured and simulated K^+ and Cl^- conductivities are shown as functions of the applied voltage for an ionic bath concentration of 0.1 M. The simulations indicate that the conductivities increase mostly linear between 50 and 100 mV; however, the increases show exponential behavior for larger applied voltages meaning that the currents become voltage driven in this regime. Furthermore, the considerable difference between the conductivities shows that the current in OprP is mostly chlorine. The simulations show good agreement with the experimental data points in Fig. 2, although the potassium current is overestimated.

3.3 Simulation of Gramicidin A channels

More measurements are available for Gramicidin A channels. Gramicidin channels are polypeptide antibiotics active against gram-positive bacteria such as, e.g., *Escherichia coli*, *Shigella*, and *Stenotrophomonas*. They are selective for monovalent cations [3]. Their effect is to increase the cation flow through the target bacterial membrane due to the formation of bilayer spanning channels. Figure 3 shows the Gramicidin A channel from the side with its alternating L–D amino-acid sequence. The structure of the bilayer spanning channel is well known and the ion permeability can be modulated by defined chemical modifications whose influence on the structure can be specified experimentally.

In order to validate the simulation approach, we compare the simulated sodium current as a function of applied voltage and bath concentration with measurements [2,14]. Figure 4 shows the results for various ionic concentrations from 10 to 1000 mM, and Fig. 5 shows the results for positive and negative applied voltages. In both figures, very good agreement between the simulated and measured Na^+ currents is observed.

The selectivity of Gramicidin channels with respect to different ion species is also an important property. In order to investigate this effect, we calculated the potassium current and compared the results with experimental data [2]. Very good agreement was found and is shown in Fig. 6. The potential barrier inside the channel leads

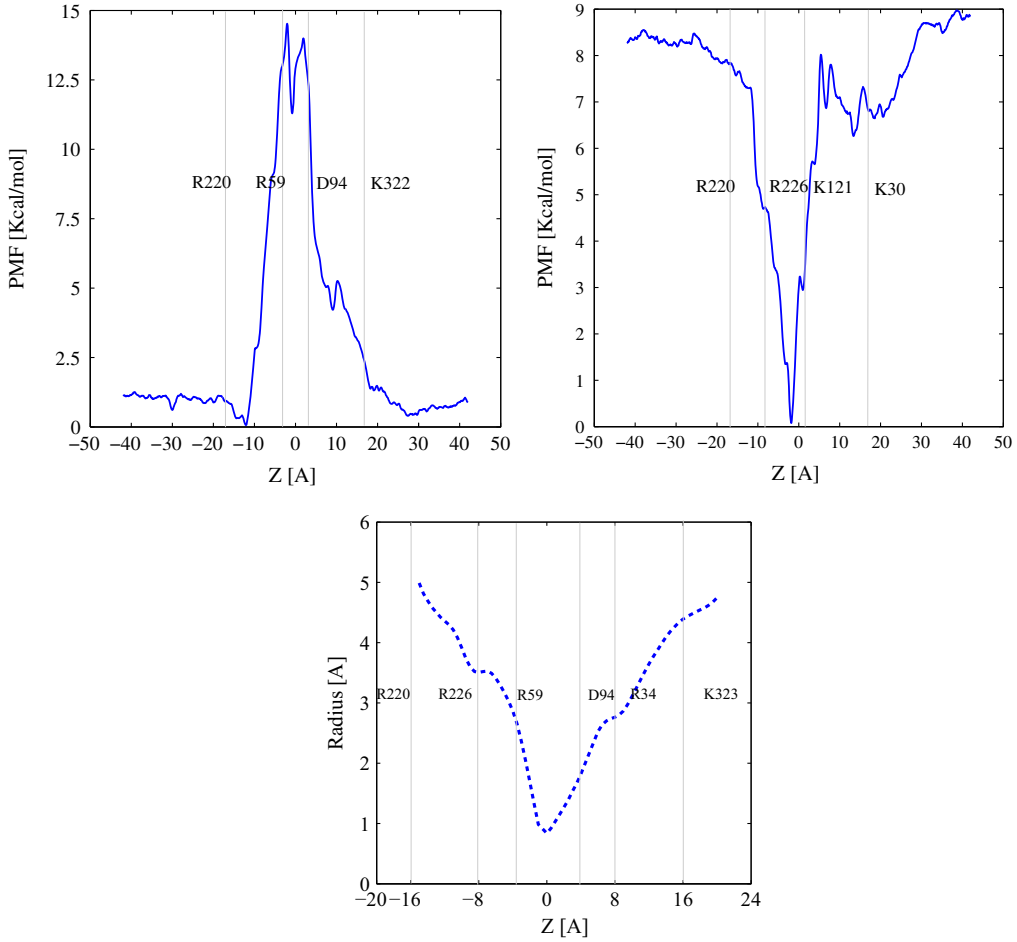

Fig. 1 Potentials of mean force (*top*) of potassium (*left*) and chlorine (*right*) in the OprP phosphate channel, and the corresponding channel radius (*bottom*). Arginine *ladders* are additionally shown

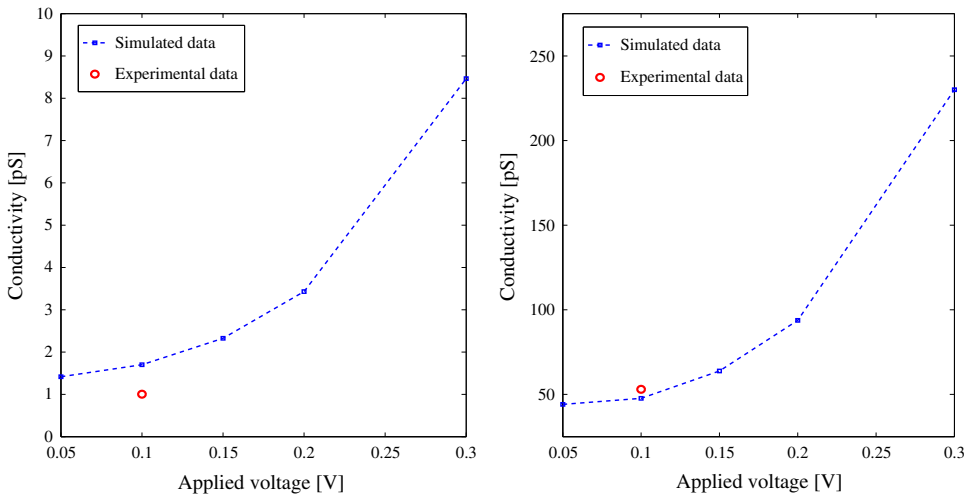

Fig. 2 The simulated potassium (*left*) and chlorine (*right*) conductivities versus experimental data as functions of applied voltage for one of the monomers of the porin

to higher selectivity for K^+ ions compared to Na^+ ions, and the current ratio varies between 2.5 and 3 depending on applied potential. The PMFs are from [1,13], respectively.

In order to model the transport of anions, we used the PMF of Cl^- in Gramicidin A from [9, Fig. 3]. The PMF in the channel is approximately two times larger than the PMF of potassium, which greatly reduces the Cl^- current. Using

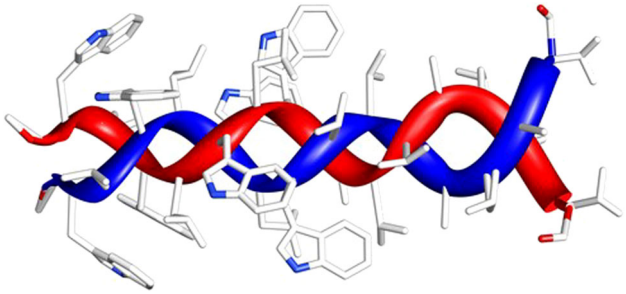

Fig. 3 Structure of the Gramicidin A channel (PDB code 1MIC)

an ionic concentration of 0.1 mM and an applied voltage of 0.1 mV yields a negligible Cl^- current of 1.5577×10^{-7} pA, which agrees well with experimental data [9].

3.4 Simulation of KcsA channels

The transduction of potassium ions through transmembrane channels plays an important role in cell metabolism. In contrast to sodium, potassium is intracellular. Potassium channels enable and control the flux of potassium ions across cell membranes and are found in most cell types. They regulate a wide variety of cell functions; for example, the high selectivity of the KcsA channel with respect to potassium is fundamental for signal conduction in nerve cells.

The potassium channel of *S. lividans*, KcsA (PDB id 1K4C), is a membrane protein with sequence similarity to all known potassium channels, implying that the selectivity filter is highly conserved. The KcsA channel consists of four identical subunits that form an inverted pyramid surrounding a large central cavity and leading to a narrow pore at the extracellular end. The pore region consists of an inner pore, a large cavity near the middle of the pore, and the selectivity filter that separates the cavity from the extracellular liquid (see Fig. 7) [5,10]. The inner pore and the internal cavity are hydrophobic, while the selectivity filter is lined exclusively by chain atoms belonging to the conserved sequence. Mutation experiments demonstrated that this signature sequence is responsible for potassium selectivity. The selectivity filter

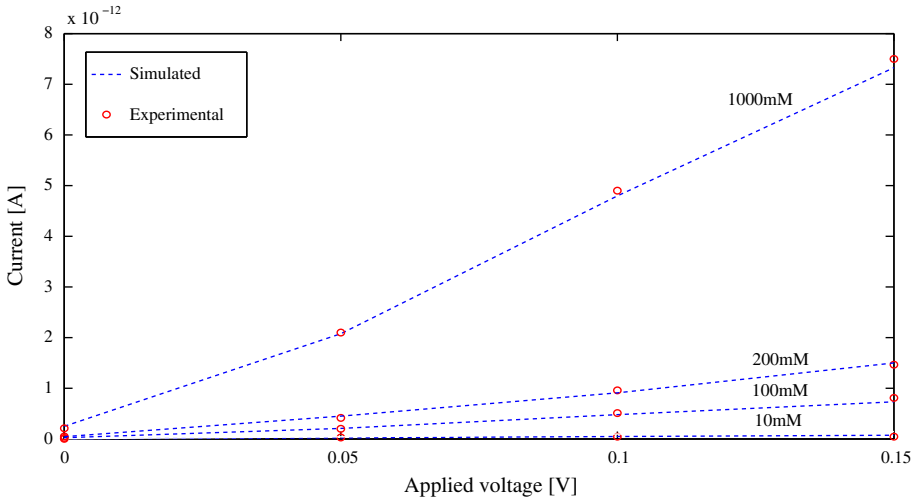

Fig. 4 Comparison of experimental [14] and simulated Na^+ currents through the Gramicidin A channel as functions of applied potential for different bath concentrations

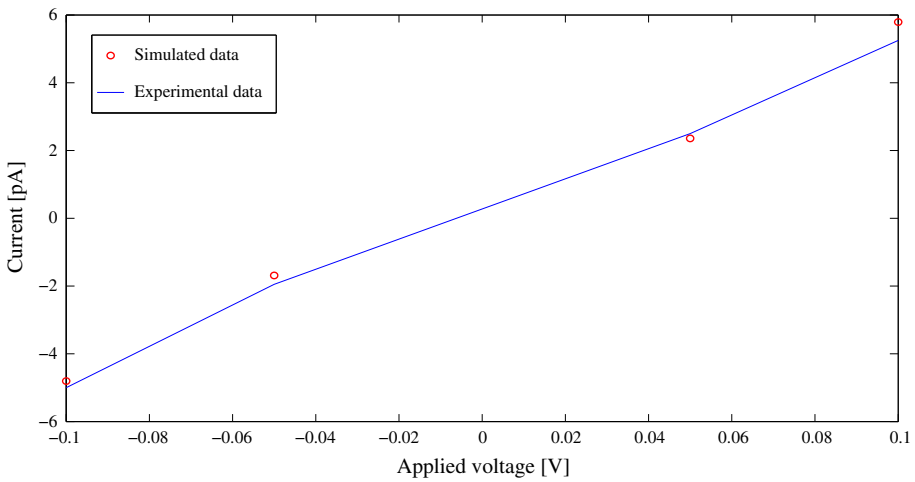

Fig. 5 The measured [14] and simulated Na^+ currents through the Gramicidin A channel for positive and negative applied voltages

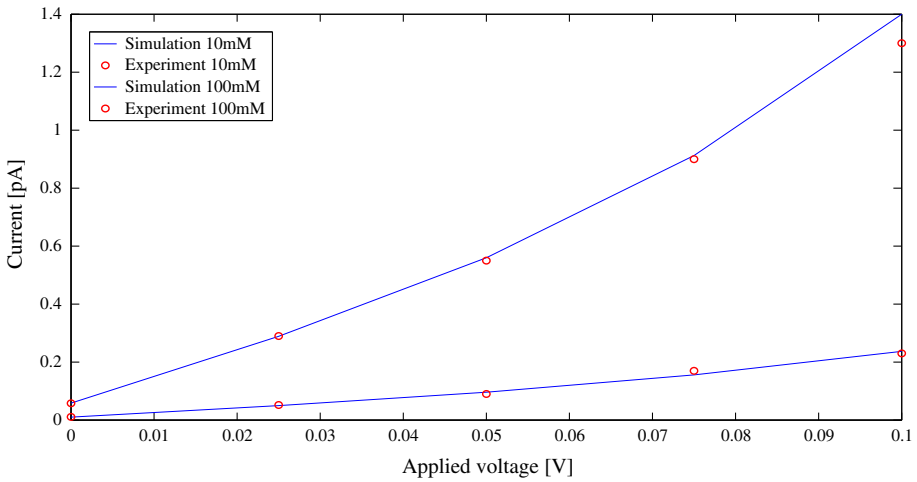

Fig. 6 The simulated versus the experimental [2] K^+ current for different applied voltages

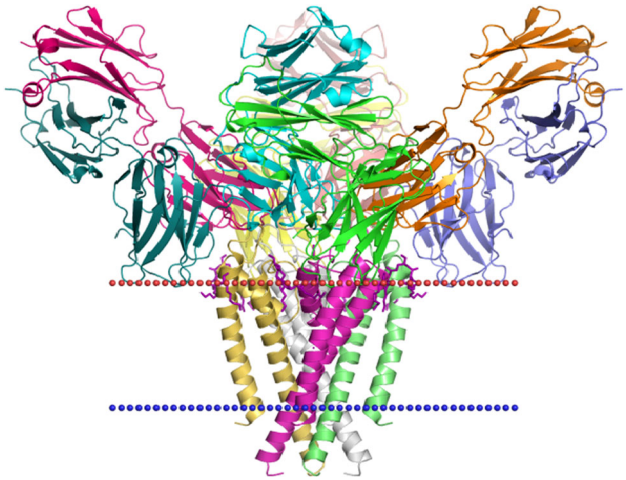

Fig. 7 The 1K4C potassium channel KcsA with a radius of 0.28 nm and a length of 12.4 nm. The extracellular space and the cytoplasm are illustrated with *red* and *blue dotted lines*, respectively (Color figure online)

has four binding sites which can be occupied by monovalent cations or water molecules. The geometry of the KcsA channel is much more complicated than other transmembrane pores. The coefficient functions were again determined as described in Sect. 3.1 according to the geometry of the protein.

Numerical investigations show that the current as a function of applied voltage is larger compared to the other pores underlining the selectivity of the channel for potassium (see Fig. 8). In the next step, we simulate the transduction of sodium ions through the channel. As is well-known, their conductivity is much smaller and the sodium current is much lower even at high sodium concentrations. This is also seen in the simulations in Fig. 9 using the correct potential barrier for sodium ions [20]. Moreover, in order to simulate the transport of the ions, we used the experimental data in [4] and the PMF in [20].

Having validated the simulations in this manner, we can now discuss the selectivity of the KcsA channel. We pose the question why the rings of oxygen atoms in the selectivity filter are repeated four times. The oxygen atoms in the selectivity filter provide binding sites for the cations and they imitate the hydration shells of cations in bulk water. In the natural protein, the oxygen atoms are arranged in four rings with the coordination distance varying from 0.27 to 0.308 nm [21]. The length of the selectivity filter in the continuum model corresponds, of course, to the number of binding sites in the filter.

The natural selectivity filter is approximately 1.2 nm long [5]. Since the length of the natural selectivity filter cannot be changed in experiments (huge modifications of the protein would be necessary) but can be changed quite easily in simulations, we have investigated the effect of filter length here. In other words, we have simulated virtual channels that have shorter and longer selectivity filters. An applied voltage of 100 mV is applied across the channel for bath concentration of 100 and 200 mM. The numerical results for the ratio of potassium–sodium current, used here as a measure of selectivity, are shown in Fig. 10.

If there is only a selectivity filter shorter than the natural one, the selectivity decreases. On the other hand, for filters longer than four oxygen rings, the selectivity remains essentially constant. This behavior is observed independent of bath concentration. Because of the selectivity for potassium, the Na^+ current is more than 20 times smaller than the K^+ current.

These results mean that a filter length of four oxygen rings is the optimal filter length: longer filters would not be advantageous compared to the natural selectivity filter, but they would be harder to assemble and stabilize in a lipid bilayer and would be generally wasteful, while shorter filters would have the disadvantage of allowing larger sodium currents and reducing selectivity, diminishing the physiological purpose of the KcsA channel.

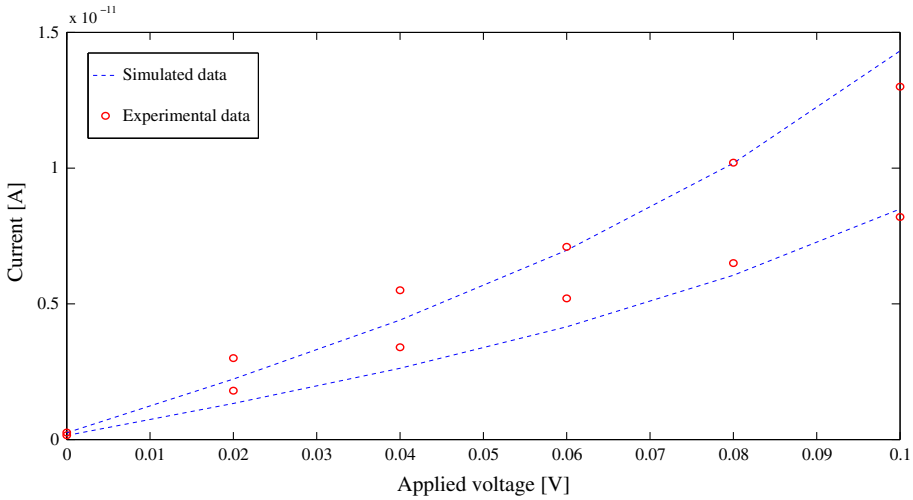

Fig. 8 Comparison of simulated and measured [4] K^+ current through a KcsA channel for bath concentrations of 100 and 200 mM

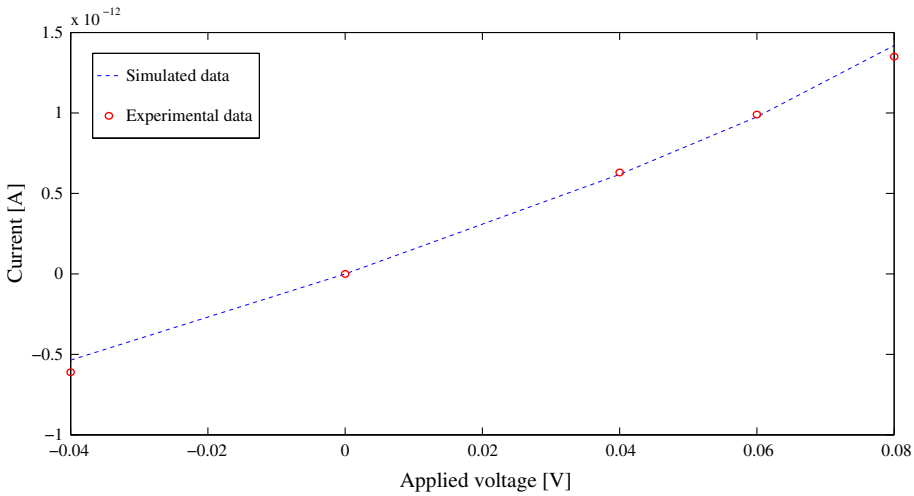

Fig. 9 Comparison of simulated and measured [7] Na^+ current through a KcsA channel for a 500 mM bath concentration

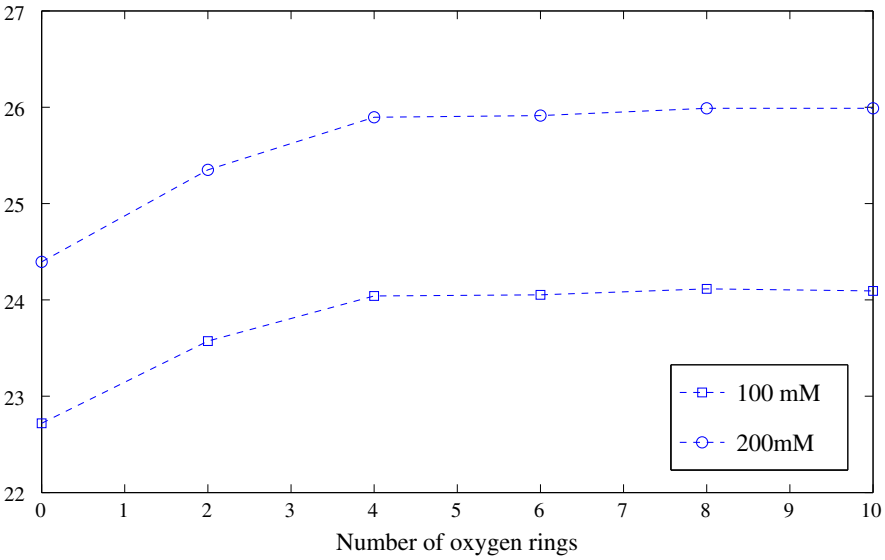

Fig. 10 The ratio of potassium–sodium currents as a function of the length of the selectivity filter. For filters longer than four oxygen rings, the ratio is constant, while it decreases as the filter length decreases below this length

4 Conclusions

We have used a continuum transport model for confined structures to investigate three kinds of transmembrane channels. The main feature of this diffusion-type transport equation is that the geometry of the confining protein directly determines the transport coefficients in the equation. Its great advantage as a continuum model is the fact that the currents are obtained immediately from the 2D numerical solution by integration over local energy; the numerical solutions of this 2D equation can be calculated quickly.

The model was validated by the application to three kinds of channels. In all cases, very good agreement between simulation and experiments was found, implying that the potential barriers (PMFs) inside the channel and the widths of the channels already capture the essential features of their functioning.

In the case of the OprP porin and Gramicidin A, this simulation capability can be used to further our quantitative understanding of antibiotics. For example, mutations can be investigated by first calculating the potential barrier that ions experience and then calculating ionic currents through the proteins.

The KcsA channel was considered as the third example. The main physiological function of the KcsA potassium channel is its selectivity between sodium and potassium ions. Here the geometry of the protein is much more complicated than the geometry of other pores. Nevertheless, the simulated sodium and potassium currents match the measured data very well. The optimal selectivity filter length was determined by simulating virtual channels and agrees well with the natural filter length. Hence it is possible to explain why the KcsA channel has this particular geometry.

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