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Mathematical models of ion transport through cell membrane channels

Abstract We discuss various models of ion transport through cell membrane channels. Recent experimental data shows that sizes of some ion channels are compared to those of ions and that only few ions may be simultaneously in any single channel. Theoretical description of ion transport in such channels should therefore take into account stochastic fluctuations and interactions between ions and between ions and channel proteins. This is not satisfied by macroscopic continuum models based on the Poisson-Nernst-Planck equations. More realistic descriptions of ion transport are offered by microscopic molecular and Brownian dynamics. We present a derivation of the Poisson-Nernst-Planck equations. We also review some recent models such as single-file diffusion and Markov chains of interacting ions (boundary driven lattice gases). Such models take into account discrete and stochastic nature of ion transport and specifically interactions between ions in ion channels.

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1. Introduction Every living cell is an open system. Continuous transfer of energy and mass between cells and their surroundings constitutes a necessary condition for a sustained life. Cell membranes, which ensure the autonomy of separated compartments, should be endowed by mechanisms of a selective transport of substances indispensable for the life of cells. In particular, a fundamental phenomenon is a transport of ions through cell membranes which ensures that the ion content of a cell is different from the one outside the cell.

In evolutionary processes, structures, and mechanisms have been formed in membranes, which lower locally an energy barrier for penetrating ions.

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Such structures consist of molecules of integral proteins whose hydrophobic parts interact with two-lipid layers and polar hydrophilic parts form:
a) relatively wide non-selective hydrated pores which penetrate membranes, b) specific ion channels, often endowed with special structural elements which form gates sensitive to an electric field, chemical ligands, or to the mechanical stress, c) ion-binding centers (on one or both sides of a membrane) called carriers or transporters which interact with ions and transport them to the other side of the membrane where ion-carrier complexes dissociate. Such transport can use the energy obtained by metabolic reactions (mainly ATP hydrolysis), then it is called the active transport, or an interior energy in this case it is called the facilitated diffusion.

All above mentioned transport mechanisms are essential for cell homeostasis, that is for securing the content of the interior of a cell, its volume, and an electric potential of the membrane. In the stationary state, the membrane potential is the result of a constant number (on average) of open channels. In the excitable state, the number of open channels change in time [49]. Conductivity of the membrane is the product of the number of channels, probability of opening a channel and conductivity of a single channel [25]. The channel gate is charged and its position in a channel is crucial for channel opening [6].

In this paper we review three basic models of ion transport in ion channels: molecular dynamics, Brownian dynamics, and continual electro-diffusion theory based on Poisson–Nernst–Planck equations and discuss problems of these approaches. We also describe the Kawasaki dynamics — a simple model of a one-dimensional boundary driven lattice gas.

2. Ion channels In the late forties and early fifties of the last century, Hodgkin and Huxley in the collaboration with Katz [54–57, 85] worked out their phenomenological theory of nerve impulses and put up a hypothesis that transport of potassium and sodium ions in excitable biological membranes takes places in selective ionic paths, different for different ions. These paths, besides a high selectivity, displayed the dependence of the conductivity on the membrane voltage. Although, such paths have not been called ion channels in these papers, yet a widely accepted hypothesis was formulated that ions penetrate membranes through specific ion channels made of proteins. Channel properties as well as transport mechanisms were deducted from macroscopic measurements. Particularly useful was the voltage-clamp method which consists of registering electric currents through a certain macroscopic surface of a membrane for fixed values of the membrane potential. There are many channels on a given surface and therefore their individual properties can be only deducted from current-voltage characteristics obtained in concrete experimental conditions. One can read about the voltage-clamp method for example in [115].

The patch-clamp worked out by [90] make possible measuring currents through individual channels. In this method, the ending of a glass pipette

(of the diameter of 1 μm and the resistance of the contact of 109 ohms) is attached to the membrane. One can register electric currents through the surface adhered to the pipette for fixed voltage between measuring electrodes. There should be only one ion channel located on such a small surface and therefore one can obtain transport characteristics of individual channels. Details of this method can be found in the very good monograph of [103].

Investigations using the patch-clamp method confirmed a high selectivity of ion channels. Transport velocity of ions, obtained from these measurements, equals to about 10^7 ions per second (a number of ions crossing a channel during one second) appeared to be close to values observed in the diffusion in water solutions of electrolytes with the thickness compared to that of cell membranes. Such high velocity of ions in membranes indicates that the transport mechanism cannot be of a carrier type which is the case in the active transport realized by ion pumps or in the passive exchange transport (for example realized in the case of anions by band 3 protein in the erythrocyte membrane). Channels in excitable membranes are highly selective for univalent cations (Na^+ and K^+). Such selectivity cannot be therefore the effect of electrostatic interactions between ions and charges of the inner surface of the channel. It results from interactions with chemical residues of channel proteins directed towards the interior of the channel [8, 51, 77, 82, 97, 98, 120]. Biochemical studies tell us which proteins form particular channels. We know their aminoacid sequences and ternary and quaternary structures. It is known which parts of channel proteins are responsible for hydrated pores, which parts form a filter responsible for the channel selectivity and which ones play the role of a voltage sensor which can change the state of a voltage-dependent channel from the conductive to the non-conductive one (and vice versa). Bibliography discussing these issues is immense and we will not cite it here but rather refer readers to the new edition of an excellent monograph [53] and review papers [105, 113, 119] new idea on this matter is presented in MacKinnon's papers [70, 106].

Scientists who worked out theoretical description of ion transport in open channels had to base their models on biochemical data and experimentally obtained channel transport characteristics. Until recently we had lacked directly obtained channel images. First reports of such images appeared in the end of nineties of the last century. There have been obtained X-rays images of potassium and chlorine channels, an acetylocholin receptor, and water channels (aquaporins). Particularly important is a paper [33] whose authors were able to crystallize the protein of a potassium channel, KcsA, from the membrane of the bacteria Streptomyces lividans, and obtained its three-dimensional X-ray image with 0.32 nm resolution. Results obtained in this paper were confirmed in [84, 121] with images with 0.2 nm resolution. Despite the fact that the KcsA channel is not voltage-dependent and its image corresponds to the non-conductive state, it has become the base for con-

structing realistic models of ion channels (mainly potassium ones) [105, 111] and the literature cited therein).

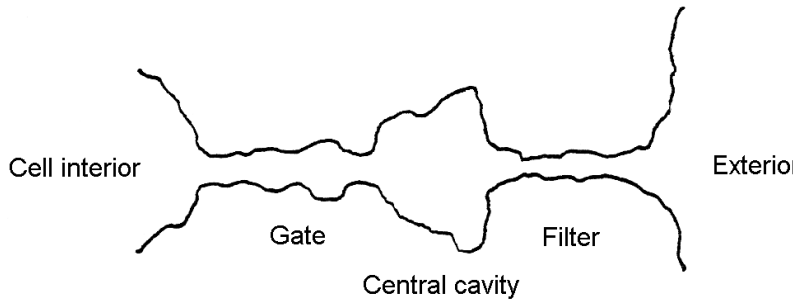

Figure 1: Schematic cross-section of a ion channel

The general scheme of the potassium channel following from the above papers is presented in Fig. 1. One can see that the channel cross-section changes along its axis. In the channel part directed toward the outside of the cell there is located a filter responsible for channel selectivity (of the length of 1.2 nm length and the diameter of 0.3 nm). In the middle part there is a relatively wide cavity of the length of about 1 nm which is capable of containing tens of water molecules. In the part of the channel directed toward the interior of the cell (of the length of about 2 nm) there are subunits of the protein channels responsible for the opening and closing the channel (a channel gate). In the closed channel, the smallest diameter of this part of the channel is 0.24 nm, whereas the diameter of K^+ ion is equal to 0.26 nm. The surface of this part of the channel is hydrophobic. The above data come from [19]. It is seen from the X-ray image of the channel that there can be at most two potassium ions in the filter (separated by a water molecule). In the middle cavity of the channel there can be a third potassium ion. Such distribution of ions in a channel is confirmed by Brownian dynamics [20], and molecular dynamics [2, 12, 105] and the literature cited therein).

Detail studies of channel proteins indicate that a filter part is the same in all potassium channels [53, 75, 84]. It is formed from segments of polypeptide chains (two or four subunits of a channel protein) with the amino acid sequence TVGYG. One can distinguish four centers (S1, S2, S3, and S4) in which oxygen atoms of the carbonyl residues exactly correspond to the coordination bond of potassium ions and can substitute oxygen atoms of water molecules around the hydrated K^+ ion [83]. X-ray studies [121] and molecular dynamics [9] indicate that there exists another center (S0) in the exterior of the channel entrance domain. his is schematically illustrated in Fig. 2. The presence of such a filter in all potassium channels allows the construction of a uniform theoretical description of the ion transport in all open potas-

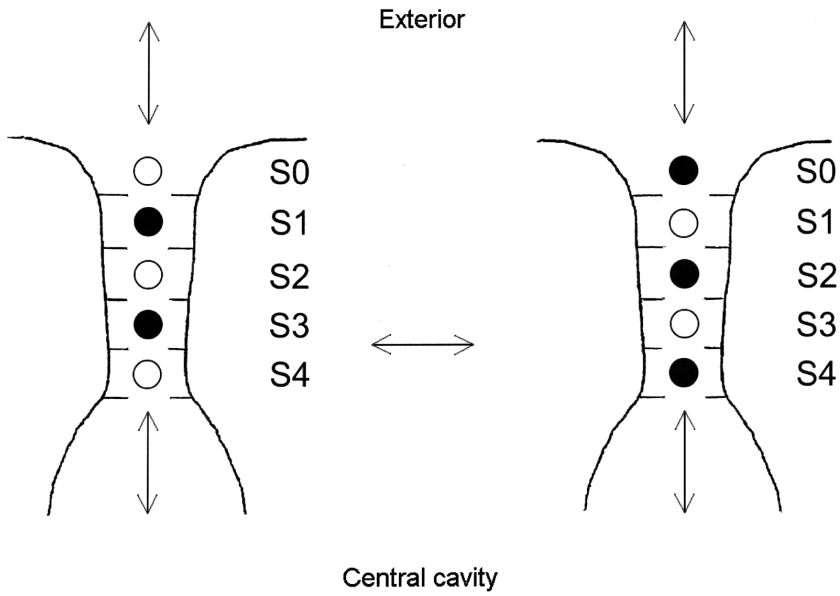

Figure 2: Schematic distribution of K^+ ions (•) and water molecules (◦) in the channel filter

sium channels. It was shown in [22] that such description can also be used in calcium channels.

3. Ion transport in channels

A fundamental model aspiring to provide a realistic description of ion transport in channels of excitable membranes is the molecular dynamics [2,3,9,18,19,73,88,101,102]. Ions and molecules of water and of channel proteins are treated as individual objects. Newton equations of motion of ions interacting with other ions, water molecules, and the surface of a channel, are solved. Unfortunately, the computer time needed to solve these equations and to calculate properties of channels (like their conductivity) is so far prohibitively large (years for the fastest computers). In such a situation, even if one could have a realistic model of channels and a proper physical theory describing interactions between molecules in a channel, then limitations of computer power prevent us from using the molecular dynamics to describe ion transport.

3.1. Brownian dynamics

A model which is less fundamental but still describing motion of individual ions is the Brownian dynamics. In order to reduce the number of equations, the force acting on a given ion (originated from water molecules) is decomposed into the sum of a deterministic friction force and a random force (a white noise) with the zero average. Now in a standard Newton equa-

tion, a random force appears, such an equation is called a Langevin equation [15, 62], see discussion and (21) in Appendix A,

$$m\frac{dv}{dt} = -m\gamma v + L(t) + qE + F_s, \tag{1}$$

where m, q, v are respectively a mass, a charge, and a velocity of a given ion, E is the electric field. The friction, $m\gamma v$, (where γ is the friction coefficient per unit mass) and a stochastic force, L, are results of random collisions of ions with water molecules and the channel surface, F_s is the force of a short-range non-electrostatic interaction between the ion and the channel. The electric field responsible for the force exerted on ions, is computed numerically from the Poisson equation in the form

$$\nabla[\epsilon(r)\nabla\phi(r)] = -\rho(r), \tag{2}$$

where $r = (x, y, z)$ is a position vector, ρ is the total charge of ions and channel proteins, ϕ is the potential of the electric field, ϵ — the electric permittivity and $\nabla = (\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z})$ — the gradient operator. One adds to the obtained electric field, an exterior field connected with the membrane potential.

In a very narrow selective channel, in an axon of a nerve cell for example, there can be only few ions of the same type. In such membranes, ions of different types are separated and their transport takes place in different channels. The electric field inside such channels is a sum of fields coming from surface charges and individual ions. The first field is an exterior field, the second one is a result of interactions between ions. The Langevin equations (1) were derived under **the assumption that Brownian motion of ions is independent of the presence of other ions**. The problem of interaction between ions in very narrow channels requires a separate discussion.

In the first paper [21], where Brownian dynamics was used to describe ion transport, one assumed that ions movement is one-dimensional. Such assumption is far from realistic models of ion channels. Papers published since 1998, mainly by a group of physicists from the Australian National University in Canberra, contain numerical simulations in a three-dimensional space. A detailed list of references devoted to this issue can be found in extensive reviews [18, 19, 66–68, 102].

Parameters required in equations (such as an electric permittivity or a diffusion coefficient) are taken from molecular dynamics. One very often uses parameter fitting based on an optimization principle [22, 34, 80, 81]. Geometrical dimensions of channels are often taken from experimentally obtained images or from molecular dynamics. In a recent paper [63], a stochastic optimization algorithms were constructed to estimate certain structural parameters of ion channels.

In Brownian dynamics, Langevin equations are solved to describe trajectories of all ions. In order to do so in very short time intervals (steps) of few

femtoseconds (10^{-15} s), Langevin equations are integrated to find velocities and locations of all ions before the next step. This procedure is repeated for a sufficiently long time, usually few microseconds (10^{-6} s), to find the number of ions (Δn) passing through the channel in time (Δt) (naturally, Δn includes ions with velocity v which are not further than $v\Delta t$ from a given channel cross-section). This gives us the flux of ions,

$$J = \frac{\Delta n}{\Delta t}. \tag{3}$$

Details of this method can be found in a review paper [67], see also a mathematical monograph on computational methods for micro and nano-flows [60] and recent mathematical papers on Langevin dynamics [71, 72]. Fluxes obtained for different values of a membrane potential for a fixed ion concentration or for different concentrations but a fixed membrane potential, allow us to describe current-voltage and current-concentration characteristics. Such characteristics can be confronted with an experimental data.

In the introduction to [22], the authors declare that in their model, based on Brownian dynamics, ion chemical potentials and other channel parameters were neither assumed ad hoc or fitted to experimental data. It seems that they cannot really justify it. An optimization of channel parameters and their calculations based on molecular dynamics are not free from necessary approximations (for example treating water in a channel as a continuum, putting the relative electric permittivity of a channel protein to 2 or treating channel proteins as static structures).

Despite many simplifications, the description of ion transport in ion channels based on Brownian dynamics explains many experimentally observed channel characteristics [34]. In particular, it predicts, in the agreement with experiments, current-voltage and current-concentration characteristics (including the observed flux saturation with respect to the ion concentration in a solution near the membrane [75, 82], caused by the independence of the time of the ion passage through a selective filter of the concentration [10, 19, 66–68, 101].

When we realize that proteins form dynamical structures whose pores, allowing ion transport, have cross-sections of atomic sizes, then we understand that using statistical macroscopic parameters (like an electric permittivity ϵ and a diffusion coefficient D inside the channel) to describe their functions is not justified. This may constitute a fundamental limit of usability of Brownian dynamics to describe the ion transport in channels. Moreover, it is argued in [12, 108] that one cannot define an electric permittivity of protein molecules and a solution near their surface of contact. In particular, one cannot characterize a protein molecule by an average permittivity (an estimated permittivity varies in space and it depends on the method of calculation). Protein channels are commonly treated as equilibrium structures with a time-independent permittivity. In reality, ion channels are non-equilibrium struc-

tures in which moving ions induce a time-dependent electric permittivity of channel proteins [12]. The above described problem of the electric permittivity of ion channels concerns in the same degree models of Brownian dynamics and molecular dynamics [87].

We would like to pinpoint still another problem. Brownian dynamics describes movements of individual ions. Results of experimental papers [84] and of molecular dynamics [9,10,101,109] suggest that potassium ions are moving collectively together with a water molecule between them — they pass from S1 and S2 centers to S2 and S4. Such collective transport cannot be described in a simple way within models based on molecular dynamics. A kinetic theory of collective transport was presented in by Nelson in [92–94]. He assumed that transport barriers exist at the channel entrance and exit and there no barriers inside the channel (which is consistent with molecular dynamics). Results of the above papers display a saturation in current-concentration characteristics. We would also like to point out that ion sizes are compared to those of water molecules, therefore treating ions in channels as Brownian particles is not justified [50].

3.2. Poisson-Nernst-Planck equations

Here we present continual electro-diffusion theory, proposed by [48] and then developed in many papers, a comprehensive bibliography can be found in monographs [53,110]. It is a mean-field theory. It can only be used to describe ion transport in channels of sufficiently large diameters and for solutions of dilution ensuring that ions do not interact with themselves.

We assume that ions passing through a channel are subject to a severe dumping which justifies neglecting the inertial term ($\frac{dv}{dt} = 0$) in (1). One obtains a reduced Langevin equation for a given ion:

$$m\gamma v = L(t) + qE + F_s, \tag{4}$$

where q is a charge of the ion, $E = -\frac{\partial \phi}{\partial x}$ is the electric field and $F_s = -\frac{\partial V}{\partial x}$ is the force of a short-range non-electrostatic interaction between the ion and the channel [65, 74, 99, 102]. For wide multi-ion channels, of diameters exceeding several times the Debye radius, one can neglect F_s.

Of course, one also has to assume, for (4) to have a sense, that exterior forces do not vary substantially during dumping. This assumption is dubious in narrow channels — a cross section of such channels is not a constant and therefore ion-channel interactions vary on short distances.

In the dumping case, the probability density of finding a ion at a certain location x at the time t, $p_i(x,t)$, is a solution of the Smoluchowski equation [15] (which is a particular case of the Fokker–Planck equation [100], see (30) in Appendix A, where the Fokker–Planck equation for the probability density

of finding ions with certain velocities is given),

$$\frac{\partial p(x,t)}{\partial t} = \frac{\partial}{\partial x}\left[\frac{kT}{m\gamma}\frac{\partial p}{\partial x} - \frac{qp}{m\gamma}\frac{dU}{dx}\right], \tag{5}$$

where $U = q\phi + V$.

Continuity equation for the probability $p(x,t)$ reads

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial}{\partial x}J, \tag{6}$$

where J is the ion flux. From (5) and (6) we get the following formulae for probability flux:

$$J = -\frac{kT}{m\gamma}\frac{\partial p}{\partial x} + \frac{qp}{m\gamma}\frac{dU}{dx}. \tag{7}$$

For wide multi-ion channels, their interior can be treated as a continuous media and therefore the probability $p(x,t)$ can be then replaced by ion concentrations $c(x,t)$ and we get:

$$J = -\frac{kT}{m\gamma}\frac{dc}{dx} - \frac{qc}{m\gamma}\frac{dU}{dx}. \tag{8}$$

From the fluctuation-dissipation theorem we get the relation between γ and the diffusion coefficient D,

$$D = \frac{kT}{m\gamma}, \tag{9}$$

hence

$$J = -D\left[\frac{dc}{dx} + \frac{qc}{kT}\frac{dU}{dx}\right]. \tag{10}$$

This is the one-dimensional Nernst-Planck (NP) electro-diffusion equation for the ion flux [48].

We supplement it with the Poisson equation for the electric potential ϕ,

$$\epsilon\frac{d^2\phi}{d^2x} = -c(x)q - N(x), \tag{11}$$

where ϵ is the electric permittivity and N — a fixed charge of the membrane.

The above two equations form the Poisson–Nernst–Planck (PNP) theory.

If we assume that the electric field is constant in the channel, then the right-hand side of (11) is zero (electro-neutrality). In the stationary state, (10) can be integrated. One then obtains the following expression for the flux J:

$$J = \frac{\frac{Dq}{kT}\frac{V_m}{d}\left[c_i - c_o e^{-\frac{qV_m}{kT}}\right]}{e^{-\frac{qV_m}{kT}} - 1}, \tag{12}$$

where d is the thickness of the layer, V_m — a membrane potential, c_i ion concentration on the boundary inside the membrane and c_o — ion concentration on the boundary outside the membrane.

Eisenberg and his coworkers [16,17,35–38,44,95,108] and Kurnikova with her coworkers [14, 50, 65, 80] developed a three-dimensional electro-diffusion theory based on the Nernst-Planck equation and the Poisson equation for the potential of electrostatic interactions. This theory, called PNP (Poisson–Nernst–Planck) theory, is still a mean-field theory and as it was shown in [23,86], it cannot be used in channels of dimensions described above. It can be applied to channels of dimensions exceeding twice the value of the Debye radius. The PNP theory cannot be used to describe the transport in channels discussed here because the average number of ions observed in such channels is compared to the size of fluctuations and therefore the concept of concentration ceases to have a sense. This problem was pointed out in [83, 108]. However, this was not taken into account in proposed theories and in the case of the second paper, this problem was bypassed by averaging over a long time. In [45,46], the PNP equations were generalized by adding to the chemical potential of ions, an "excess" responsible for interactions between ions and non-electrostatic interactions between ions and the surface of a channel.

The PNP theory fails to explain an experimentally observed saturation of the ion flux as a function of the concentration of ions in the solution adjacent to the membrane for the fixed membrane potential. According to the PNP theory, this dependence should be linear. It is worth to point out once again that using the continuous description of the ion transport in channels with atomic dimensions is inherently inappropriate. Macroscopic parameters of channels such as the diffusion coefficient (equivalently ions motility), concentration and electric permeability, taken from continual theories cannot be rationally justified. This is confirmed by Monte-Carlo simulations of a double electric layer in 2 nm nano-pores [116,117]. The above remarks about continual description of ion transport in open channels, based on the PNP theory suggest that it should not be used for channels with dimensions observed experimentally. Accidental agreement of this theory with an experimental data can follow from cancellation effects of assuming wrong channel parameters and wrong assumptions about the physics of channels [23]. The importance of ions interactions in modeling ion channels was discussed recently in [39–41].

Finally, we would like to emphasize once again the fundamental problem present both in continuum models of the PNP type as well as in the Brownian dynamics. In channels containing several ions simultaneously, it seems to be essential to take into account interactions between them. In Langevin equations, random collisions between ions and water molecules and the surface of the channel are represented by a sum of a deterministic friction force and a purely random force. Relations between friction and fluctuations of random interactions are described by a dissipation-fluctuation theory. Such theory requires the system to be in a thermodynamic equilibrium and particles not to interact. Then the diffusion coefficient (which measures the size of fluctuations) is given by the Einstein relation, $D_i = kT/m_i\gamma_i$, where T is the

temperature of the system. However, if we take into account ion interactions, then random forces acting on ions are no longer independent. Also the division of a force into a deterministic and a random part becomes problematic.

In [107], authors claim channel solutions are very diluted and therefore one can neglect correlations between random forces exerted on particular ions (however, they explicitly consider interactions between ions). Then they introduce appropriate electro-diffusion equations with a self-consistent electric field a solution of Poisson equations. Let us observe, however, that solutions in channels, in comparison to diluted surrounding solutions where ions are far apart, are not diluted. Despite that fact that there are only few ions in the channel, due to atomic sizes of channels, ions are close to each other and therefore their interactions cannot be neglected. Moreover, the concept of a self-consistent field treats concentration as a statistical quantity. In the case of a low number of ions, concentration fluctuations are of the order of the concentration itself.

Different approach is contained in [13]. The authors analyze there a motion of interacting ions in electrolyte solutions. In the appropriate Langevin equation, a friction force has the form of an integral dependent upon a history. Friction with a memory is also used if sizes of Brownian particles are compared to sizes of solution particles [64] which takes place in ion channels.

Taking into consideration interactions between ions in the description of ion transport in channels requires further studies. Ion interactions cause dependence between fluxes of different ion types. However, interactions between ions of the same type within one channel does not lead to interactions between channels. This was used in [12] where an additivity principle was invoked.

In conclusion, one can say that only a truly microscopic description of ion channels (based for example on molecular dynamics) can fully explain mechanisms of their functioning [19]. Further development of computational techniques, better computational methods for stochastic ordinary differential equations in particular, more detailed knowledge of a molecular structure of ion channels, and also advances of physics of nano-systems are needed to achieve this goal.

4. Ions as interacting random walkers in ion channels

Some ion channels are very narrow hence ions move in a one-dimensional array and they cannot pass each other. Such a situation is modeled by the so-called single-file diffusion and it is discussed in [24, 26–29, 42, 61, 91]. Authors of these papers solve either numerically or analytically Langevin equations which include interactions between ions. They showed that the mean square displacement of a particle grows at long times with the square root of time, rather than linearly as in the standard diffusion. The coefficient in front of the square root, the so-called single-file mobility, can be derived from the

fluctuation-dissipation theory based on the generalized Smoluchowski equation.

To simplify things even further, we discretize the space to model narrow ion channels by continuous-time Markov chains (Markov jump processes) with finite number of states. Namely, consider a one dimensional array of lattice sites. Every lattice site can be either empty or occupied by one particle. Particles may hop with certain rates (depending on their interaction energy) to neighboring empty sites. If hoping rates to the left and to the right are different, then such a process is called an asymmetric simple exclusion process (ASEP) [30, 31]. In addition, particles from outside of the system may appear at the empty array endpoints, particles which occupy endpoints may disappear from the system. Physically speaking, array endpoints are coupled to particle reservoirs. Such models are called boundary driven lattice gases. They may serve as models of narrow ion channels, where hoping asymmetry is due to the external electric field (we assume that particles are charged). Calculating mean current and its fluctuations in such systems is a challenging problem. Mathematically speaking, we have an ergodic continuous-time Markov chain with a finite number of states. It has a unique stationary probability distribution (a stationary state). Such a stationary state cannot be called an equilibrium, there is an average current (flux of particles) in the system. It is one of the simplest examples of a non-equilibrium system of interacting particles with a non-equilibrium stationary state (NESS).

Below we describe in more detail a particular version of a driven lattice gas — the so-called Kawasaki dynamics, we follow closely the description in [79].

Let $\Lambda_N = \{1, \dots, N\}$. Every site of Λ_N can be either occupied by one particle or be empty. $\Omega_N = \{0,1\}^{\Lambda_N}$ is the configuration space, if $x \in \Omega_N$, then $x(i) \in \{0,1\}$, $i \in \Lambda_N$. The energy of interaction between particles is given by the Hamiltonian, $H\colon \Omega_N \to R$,

$$H(x) = -\kappa \sum_{i=1}^{N-1} x(i)x(i+1), \tag{13}$$

$\kappa > 0$ implies attraction between particles (two neighboring particles have a negative energy) and $\kappa < 0$ means repulsion between particles (two neighboring particles have a positive energy).

We allow particles to hop to neighboring empty sites. The easiest way to implement such a dynamics is to consider interchanging of occupation of two neighboring lattice sites. Namely, let

$$x^{i,i+1}(k) = \begin{cases} x(k) & \text{if } k \neq i,\, i+1, \\ x(i) & \text{if } k = i+1, \\ x(i+1) & \text{if } k = i. \end{cases} \tag{14}$$

We define $k(x \to x^{i,i+1})$ to be the probability of transition per unit time. More precisely, $k(x \to x^{i,i+1}) = \lim_{h\to 0} \frac{\text{probability}(x(t+h)=x^{i,i+1}|x(t)=x)}{h}$. We set

$$k(x \to x^{i,i+1}) = e^{-\frac{\beta}{2}[H(x^{i,i+1})-H(x)]}, \tag{15}$$

where β is the inverse of the temperature of the system.

We constructed a continuous-time Markov chain. One can easily show that the following Gibbs state (the canonical ensemble of equilibrium statistical mechanics),

$$\rho(x) = \frac{e^{-\beta H(x)}}{\sum\limits_{y\in\Omega_N} e^{-\beta H(y)}} \tag{16}$$

is its stationary state. It is enough to demonstrate that the chain satisfies the so-called detailed balance condition (see Appendix B),

$$e^{-\beta H(x)} k(x \to x^{i,i+1}) = e^{-\beta H(x^{i,i+1})} k(x^{i,i+1} \to x). \tag{17}$$

Now we allow the system to absorb a particle from a reservoir at sites $i = 1, N$ or expel it to a reservoir from sites $i = 1, N$. Such a flipping of occupation we denote by $x \to x^i$, where

$$x^i(k) = \begin{cases} 1 - x(i) & \text{if } k = i, \\ x(k) & \text{if } k \neq i \end{cases} \tag{18}$$

and the rates are given by

$$k(x \to x^i) = e^{-\frac{\beta}{2}[H(x^i)-H(x)-\mu_i(1-2x(i)]}, \quad i = 0,\ N. \tag{19}$$

It is an easy exercise to show that the Markov chain of the above boundary-driven dynamics satisfies the detailed balance condition if and only if $\mu_1 = \mu_N = \mu$. If this is the case, then the stationary state is given by

$$\rho(x) = \frac{e^{-\beta[H(x)-\mu N(x)]}}{\sum\limits_{y\in\Omega_N} e^{-\beta[H(y)-\mu N(y)])}}, \tag{20}$$

where $N(x) = \sum_{i=1}^{N} x(i)$ is the number of particles in the configuration x.

Assume that $\mu_1 > 0$ and $\mu_2 < 0$. Then we expect a current of particles from the left to the right even in the stationary state of the Markov chain with the rates (15) and (19), the steady state of the open system coupled to two reservoirs. The mathematical analysis of the above steady state in the limit of low temperatures (large β) can be found in [79]. The Kawasaki dynamics was analyzed recently in [32], where an exact current — particle density relation was derived. For the general treatment of the detailed balance

condition in non-equilibrium statistical mechanics we refer readers to [59] (see also Appendix B), see [5,89] for a discussion of the detailed balance condition in the transport of ions in ion channels.

The more realistic model of ion channels should include interactions between neighboring ions but not necessarily at the distance 1. The work is in progress.

5. Discussion In our paper we reviewed various models of ion channels. We emphasized the need of construction of new models which would take into account interactions between ions. This is especially important in narrow channels where the number of ions is very small and standard continuous Poisson-Nernst-Planck theory cannot be applied. We also discussed simple discrete one-dimensional models of non-equilibrium statistical mechanics, the so-called boundary driven lattice gases. They may serve as toy models of narrow ion channels.

A. Langevin, Ito, and Fokker–Planck equations We consider a particle (a macromolecule) immersed in a liquid and therefore subject to forces exerted by surrounding liquid molecules (micromolecules). For simplicity we will discuss one-dimensional model. Our particle is described by its position x and velocity v and it moves according to the Newton dynamics, $a = dv/dt = F/m$, where m is the mass of the particle and F is the sum of all forces exerted on it. Instead of solving such an equation together with analogous equations for liquid molecules (Molecular Dynamics approach), we decompose the force acting on our particle into the sum of a deterministic friction force proportional to the velocity of the particle and a random force (a white noise) with the zero expected value. In this way we pass from the deterministic Newton equation to the stochastic Langevin equation [114]:

$$\frac{dv}{dt} = -\gamma v + \frac{L(t)}{m}, \tag{21}$$

where γ is the friction coefficient per unit mass and $L(t)$ is a stochastic force for which we assume that the expected value and the correlation function are given respectively by $\langle L(t)\rangle = 0$ and $\langle L(t)L(t')\rangle = \Gamma\delta(t-t')$. The Langevin equation is simply the Newton equation plus a random force. It can be written in the precise mathematical way as the Ito equation:

$$dv = -\gamma v dt + \frac{dW}{m}, \tag{22}$$

where W is the Wiener process.

We will continue the informal (physical) discussion of the Langevin equation. For a given realization $L(t)$ of the Wiener process we may simply solve the linear equation (21) with the initial condition $v(0) = v_o$,

$$v(t) = v_o e^{-\gamma t} + e^{-\gamma t}\int_0^t e^{\gamma t'} L(t')\, dt'. \tag{23}$$

We use the properties of L and get the expected values of the velocity,

$$\langle v(t)\rangle = v_o e^{-\gamma t} \tag{24}$$

and the expected value of the square of the velocity,

$$\langle v^2(t)\rangle = v_o^2 e^{-2\gamma t} + \frac{\Gamma}{2\gamma}(1 - e^{-2\gamma t}). \tag{25}$$

For the infinite time t at the equilibrium we get

$$\lim_{t\to\infty} \frac{m\langle v^2(t)\rangle}{2} = \frac{m\Gamma}{4\gamma} \tag{26}$$

and from the equipartition principle it should be equal to $kT/2$, where k is the Boltzmann constant and T the temperature of the system.

Finally we get he following relation in the equilibrium:

$$\frac{\Gamma}{2\gamma} = \frac{kT}{m}. \tag{27}$$

This is an example of the fluctuation-dissipation theorem which relates friction to thermal motion.

On the other hand, for a small time t we have:

$$\langle v(t) - v_o\rangle \sim -\gamma v_o t \tag{28}$$

$$\langle (v(t) - v_o)^2\rangle \sim \Gamma t. \tag{29}$$

This enables us to write a Fokker-Planck equation, a partial differential equation for the probability density $P(v,t)$ that the particle will have a velocity v at time t [100, 114],

$$\frac{\partial P(v,t)}{\partial t} = \gamma \frac{\partial v P(v,t)}{\partial v} + \frac{\Gamma}{2}\frac{\partial^2 P(v,t)}{\partial v^2}. \tag{30}$$

B. Time-irreversibility and the detailed balance It is well-known that Newtonian dynamics of interacting particles is time-reversible. If we reverse the momenta of all particles, then the system will travel back to its past along the trajectory by which it arrived at a given point. Here we will discuss what we mean by time-reversible Markov chains (we follow [52]). Let $\{X_n, -\infty < n < \infty\}$ be an ergodic discrete-time Markov chain with a transition matrix P and a unique stationary probability distribution μ. Assume now that X_n has distribution μ for every n.

Definition B.1 Let $Y_n = X_{-n}$, then Y is the time-reversed chain of X.

DEFINITION B.2 Markov chain X is time-reversible if X and Y have the same transition matrix.

DEFINITION B.3 Markov chain X satisfies the detailed balance condition if there exists a function f on its states such that

$$f(i)p_{ij} = f(j)p_{ji}$$

for all states i, j of the chain.

We encourage readers to prove the following theorems (proofs are elementary).

THEOREM B.4 *Markov chain X is time-reversible if and only if its stationary distribution satisfies the detailed balance condition.*

THEOREM B.5 *If a positive and normalized to one function f satisfies the detailed balance condition, then it is a stationary distribution of a given Markov chain.*

THEOREM B.6 *Markov chain X is time-reversible if and only if for every three states i, j, k we have that*

$$p_{ij}p_{jk}p_{ki} = p_{ik}p_{kj}p_{ji}.$$

Definition B.3 and Theorem B.5 hold also for continuous-time Markov chains (Markov jump processes) if by p_{ij} we mean not probabilities but transition rates. We leave as an exercise for readers to define time reversibility of continuous-time Markov chains.

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Matematyczne modele transportu jonów w kanałach komórkowych

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Streszczenie

W naszej pracy przeglądowej przedstawiamy różne modele transportu jonów w kanałach komórkowych. Rozmiary niektórych kanałów jonowych są rzędu średnicy jonów, a więc tylko kilka jonów może jednocześnie znajdować się w danym kanale. Opis transporu w tak wąskich kanałach powinien brać pod uwagę stochastyczne fluktuacje liczby jonów oraz oddziaływania między nimi. Ciagłe modele makroskopowe oparte na równaniach Poissona–Nernsta–Plancka nie spełniają tych warunków. Bardziej realistyczne modele, takie jak dynamika molekularna i dynamika brownowska, uwzględniają mikroskopową dyskretną strukturę kanałów jonowych. Przedstawiamy wyprowadzenie równań Poissona–Nernsta–Plancka. Przedyskutowujemy również modele łańcuchów Markowa oddziałujących jonów. Modele takie biorą pod uwagę dyskretny charakter transportu jonów i oddziaływania między nimi.

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Jacek Miękisz was hiking Tatra Mountains at the age of minus 6 months and then he was born in Wrocław in 1956. He investigated interacting suspensions in ferrofluids and received Master degree in physics from Wrocław Technical University in 1979. Then he moved to Blacksburg, Virginia Tech, studied interacting spins in Ising models of ferromagnetism and got PhD in mathematics in 1984. He spent postdoctoral years at the University of Texas at Austin, in Louvain-la-Neuve and Leuven, studying interacting particles in lattice-gas models of quasicrystals. Now he works at the Institute of Applied Mathematics and Mechanics of the University of Warsaw and deals with interacting agents in evolutionary games and interacting proteins in genetic regulatory networks, sometimes with time delays.

Jan Gomułkiewicz is a professor emeritus at the Institute of Physics of Wrocław University of Technology. He received PhD in physics at University of Wrocław in 1966. He specialized in physics of dielectrics, in electret effect in particular. Then he became interested in biophysics of ion transport through cell membrane channels. He obtained habilitation in this area in the Experimental Biology Institute of Agricultural Academy (now Wrocław University of Environmental and Life Sciences) in 1972. He worked in the Institute of Physics of Wrocław University of Technology from 1978 to 2005.

Stanisław Miękisz is a full professor emeritus at the Department of Biophysics of Wrocław Medical University. He received PhD at the Faculty of Mathematics, Physics and Chemistry of University of Wrocław under the supervision of Roman S. Ingarden in 1960. The PhD thesis was entitled "Nonlinear problems of viscous fluid flow through vessels with elastic walls". He worked for some time on applications of the fluid theory to hemodynamics and received habilitation in this area in 1966. Then he became interested in biophysics of ion transport in the framework of thermodynamics of irreversible processes. He was the main organizer of the first school on Biophysics of Membrane Transport. He collaborated with I. W. Richardson (then in the Dalhousie University — Halifax, Canada), they have written together papers on thermodynamics of irreversible processes.

Stanisław Miękisz worked in the Agricultural Academy (now Wrocław University of Environmental and Life Sciences) and in the Academy of Medicine (now Wrocław Medical University) where he was a head of the Department of Biophysics from 1975 untill 1997.

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