# BROWNIAN DYNAMICS SIMULATIONS OF SINGLE-FILE MOTION THROUGH NANOCHANNELS

# I.D. Kosińska, A. Fuliński

## M. Smoluchowski Institute of Physics, Jagellonian University Reymonta 4, 30-059 Kraków, Poland

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Algorithm is constructed which models single-file motion of particles interacting with each other and with the surroundings. As an example, we present the results of Brownian Dynamics simulations of the motion of cations moving through a short very narrow channel containing a device called "gate", which may open and close the channel.

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### 1. Introduction

Nanochannel transport and physical mechanisms of its regulation are among leading open problems in nanoscience. Its importance results from the fact that controlled and selective flow of matter through proteins in the cell membrane — achieved by active and passive channels [1] — is one of the most important biophysical processes in living cells. On the other hand, similar functions may be performed by synthetic nanopores which also can rectify the ionic currents [2–4] and pump the ions against their concentration gradients [5] and, therefore, may be used as simple models of biological (protein) channels, and, on the other hand, may serve as devices for manipulating the transport in the nanoscale. Therefore, it is important to understand the conditions and properties of material transport inside the nanopore.

The well-known and rather obvious property of the transport of material through very narrow pores is that the particles (ions, molecules  $\dots$ ) can pass through such channels in the form of single file only [6].

In the absence of noise (*i.e.*, in standard Molecular Dynamics simulations) time increments  $\delta t$  can be made arbitrarily small. This feature makes easy (in principle, at least) to keep all particles in prescribed unchanged order. In the Brownian Dynamics (BD) the action of random forces may result in arbitrarily high velocities and arbitrarily long jumps, time increment

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being irrelevant in this respect. Therefore, it is impossible to keep particles in still the same ordering by reducing time increments, the more that in the presence of noise the time increments cannot be arbitrary [7,8]. Some additional procedures are needed.

We present here the developed by us algorithm which models single-file motion of particles interacting with each other and with the surroundings, moving in a short very narrow channel containing a device called "gate", which may open and close the channel. To be specific, we shall discuss in this paper the electrostatic and soft-sphere interactions, though the formulas and the algorithms themselves can be easily adapted to any (sensible) form of interactions.

## 2. The model

We use the simplified model which does not take into account the details of the channel's structure. Full MD simulations of a K<sup>+</sup>-channel, including its molecular structure, water inside, all ions in the immediate vicinity, *etc.*, requires use of total number of atoms in the simulation system above  $4 \times 10^4$ , and time-steps 0.2 fs [9,10]. Such simulations have also some other drawbacks [11].

Little is known about the details of the gating mechanism, the more that the motions of dangling ends [12] in synthetic pores are probably quite different from the motions of the subunits of proteins constituting the biological channels. Therefore, without entering into details of equations of motion for the channel's walls, we model the gating process by introducing inside the channel the artificial device called "gate" which can either allow or prevent the flow of particles through the channel.

The main assumptions are:

- (i) We simulate the motions of the particles inside the Simulation Zone (SZ) of the length L, narrow enough to force the particles inside SZ to move in the single-file order. Knowledge of the detailed shape (e.g. cylinder, cone, hour-glass) is not necessary from this point of view. Regions outside are treated as reservoirs for particles both outcoming from and ingoing into SZ.
- (ii) We neglect the motions in radial directions, and describe the particles as moving along the z-axis of the SZ only (quasi-one-dimensional motion). However, the physical system (electrostatic interactions, etc.) remains three-dimensional.
- (*iii*) The opening and closing of the channel (so-called gating process) is modeled by the presence of the charged "gate" located inside SZ. The state of the gate is determined by its Brownian motion (Wiener process

of intensity  $Q_b$ ), and by electrostatic interactions with the ions inside SZ and with external electric field. The gate opens when the net force exceeds some threshold value, and closes otherwise. Minimal approach distance between particle and gate is  $d_{cg}$ .

- (*iv*) The real channels exhibiting the flicker noise are asymmetric and charged. We model these properties by the mentioned above gate, and by additional charges located outside SZ.
- (v) Water molecules are not modeled explicitly but are described electrostatically by an effective dielectric constant and as the source of friction and noise — as is frequently done [13].

No periodic boundary conditions are imposed. Instead, in our simulations we assumed (when other rules are satisfied) that:

- (i) Particles can leave and enter the simulation zone through both apertures.
- (ii) Particle leaves the simulation zone (and can be counted to the current balance at the given aperture) when its center-of-mass position is smaller than the lower threshold, or greater then the higher threshold. In our case we accepted as thresholds the particle diameter  $d_c$  and simulation zone length L minus  $d_c$ .
- (*iii*) Single-file assumption implies that when one particle leaves the simulation zone, another cannot enter through the same aperture in the same time (*i.e.*, during the same time-step).
- (*iv*) When rule (*iii*) allows, particle may enter SZ when nearest particle is farther that the prescribed smallest distance. In our case the smallest distance is  $d_{\rm c} + \varepsilon$  ( $\varepsilon = 0.00001$  nm).
- (v) Particles enter SZ with prescribed finite probabilities P(0) and P(L), which may be different for different apertures (*i.e.* at x = 0 and x = L). The probabilities of entrance simulate concentrations outside SZ, the lower concentration, the lower probability.

In our simulations we assumed that (when other rules are satisfied) during one time-step only one particle may enter the SZ through a given entrance, and, when entering, that it is located at the distance  $d_c$  from the aperture. This rule can be changed.

The Langevin-type equations of motion for the particles (cations) moving along the channel reads:

$$m_{i}\dot{v}_{i} = -\gamma_{i}v_{i} + R_{i}(z_{i}) + F_{i}(z_{i}), \dot{z}_{i} = v_{i},$$
(1)

where  $v_i$  is the velocity of *i*-th ion,  $z_i$  the position,  $m_i$  the mass,  $\gamma_i$  the friction coefficient,  $F_i(z_i)$  sum of deterministic forces, and  $R_i(z_i)$  the random force.

The gate is charged to prescribed value  $q_g = Z_g e$ , where  $Z_g$  is the valence and can be in two states: open and closed, respectively. In our simulation important is the absolute value of the force  $F_g$  acting on the gate. We assume  $F_g$  to be sum of deterministic and random forces described below.

The deterministic force  $F_i(z_i)$  experienced by the cations and the gate consist of the applied external force (voltage), and the internal Coulomb force from other charges. The Coulomb interaction between two ions is modified by the addition of a short-range repulsive  $1/r^{10}$  force, where r is the ion-ion distance [8].

The random force  $R_i$  acting on ions is assumed to be the thermal noise represented by the Gaussian white noise. On the other hand the random force experienced by the gate  $R_g$  is given by the Wiener process (gate's Brownian motion)  $R_g = \sum_n R_{i,n}$  where *n* denotes the *n*-th step of iteration.

In the Brownian Dynamics calculations,  $\delta t$  should be of the order of  $m_i/\gamma_i$  [7,14,15]. Using the Euler scheme for the Eq. (1)

$$m_i \frac{v_i(t+\delta t) - v_i(t)}{\delta t} + \gamma_i v_i(t) = F_i(t) + R_i(t), \qquad (2)$$

would lead to obviously wrong result:  $v_i(t + \delta t) = F_i(t) + R_i(t)$ . Therefore, we use the following scheme of discretization:

$$m_{i} \frac{v_{i}(t+\delta t) - v_{i}(t)}{\delta t} + \frac{\gamma_{i}}{2} [v_{i}(t+\delta t) + v_{i}(t)] = F_{i}(t) + R_{i}(t),$$
$$\frac{z_{i}(t+\delta t) - z_{i}(t))}{\delta t} = v_{i}(t+\delta t).$$
(3)

This computational scheme is similar, though not identical, with that described recently in Ref. [7, 14]. The "forward evaluation" (Eq. (3)) has stability and accuracy implications, and [14] suggest using it for each extrapolative force calculations.

#### 3. Numerical results

The length of the simulation zone is L = 10 nm. This corresponds to the real length of biological channels and, roughly, to the length of the narrow part of the synthetic channel reported in [12]

The net flow of particles, the particles are the potassium cations, through the channel (simulation zone) was calculated either by keeping the balance of particles entering and leaving both apertures, or by counting the particles passing the gate in both directions. Both procedures lead to the same results.

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Initial values of velocities of cations were drawn from the Maxwell distribution with the variance  $k_{\rm B}T/m_{\rm c}$ . The results are insensitive on the exact values of temperature and mass within rather wide range of temperatures and masses.

A list of the parameters used in the BD simulations is given below:

 $\begin{array}{l} \mbox{Temperature: } T = 298 \mbox{ K and } k_{\rm B}T = 4,12 \times 10^{-21} \mbox{ J}, \\ \mbox{Mass of cation: } m_{\rm c} = 6.5 \times 10^{-26} \mbox{ kg}, \\ \mbox{Friction constant: } \gamma_{\rm c} = 2.08 \times 10^{-12} \mbox{ kg/s}, \\ \mbox{Dielectric constant: } \varepsilon_w = 81, \\ \mbox{Voltage: } U = 1.77 \times 10^{-2} \mbox{ V} \\ \mbox{Ion diameter: } d_{\rm c} = 0.266 \times 10^{-9} \mbox{ m}, \\ \mbox{Ion-gate min. distance: } d_{\rm cg} = 2.5 d_{\rm c}, \\ \mbox{Valences: } Z_{\rm c} = +1, \quad Z_{\rm g} = -50, \\ \mbox{Intensity of short-range force: } F_{\rm SR}^0 = 18 \times 10^{-9} \mbox{ N}, \\ \mbox{Intensity of noise: } Q_{\rm c} = 0.47 \times 10^{-9} \mbox{ N}, \quad Q_{\rm g} = 0.01 Q_{i}. \end{array}$ 

Intensity of the gate's noise  $Q_{\rm g}$  is different from cations' one  $Q_{\rm c}$  (and is taken as a free parameter) due to the difference of masses, and also due to a kind of "stiffness" of (or hindrances in) the motions of channel's walls constituents.

In all simulations first  $10^6$  steps were rejected. The power spectrum was calculated from runs of length  $10^7 \delta t$ . The power spectrum of the series  $\{m_1, \ldots, m_N\}$  is

$$S(f) = \frac{1}{N} \left| \sum_{n=1}^{N} m_n e^{-2\pi i f n} \right|^2,$$
(4)

where  $m_n$  denotes either the net number of particles leaving SZ during the *n*-th step (then  $m_n$  can be either positive, zero, or negative), the number of particles inside SZ at the end of the *n*-th step ( $m_n = N_p \ge 0$ ), or the state of the gate during the *n*-th step (then  $m_n = \{0, 1\}$ ). All these power spectra are dimensionless.

There are data that suggest that inside very narrow pores the physical properties of aqueous solutions, such as dielectric constant, density, diffusion coefficient, viscosity, solvatation of ions (*i.e.*, their effective diameters), *etc.* may differ from their bulk values [17]. Therefore, we checked how the changes of such parameters influence our model. We found that the quantitative changes of calculated values of net currents and of frequency spectra resulting from reasonable variations of these parameters are within the limits of quantitative differences resulting from different realizations of the noise. The results are shown in Figs. 1–3. These observations suggest robustness of the model.



Fig. 1. Power spectra S(f) of the stochastic series of subsequent values of the net number of cations  $m_n$  leaving the simulation zone. Panel A: S(f) for 7 different realizations of the intrinsic noises, the same values of all parameters in every series:  $\varepsilon = 81$ ,  $m_c = 6.5 \times 10^{-26}$  kg,  $U = 17.7 \times 10^{-3}$  V,  $\delta t = 31 \times 10^{-15}$  s,  $Q_g = 0.01 Q_c$ ,  $F_{\rm SR}^0 = 18 \times 10^{-9}$  N, gate thresholds  $= \pm 1.1 \times 10^{-9}$  N. Panel B: S(f) with the same realizations of the intrinsic noises, for 7 different values of all parameters in every series. In every series only one parameter is changed:  $\varepsilon = 0.93 \varepsilon^0$ ,  $m = 0.77 m^0$ ,  $U = 1.33 U^0$ ,  $\delta t = 0.8 \delta t^0$ ,  $Q_g = 0.75 Q_g^0$ ,  $F_{\rm SR} = 0.6 F_{\rm SR}^0$ , where  $p^0$  denotes the value of the given parameter from the panel A.



Fig. 2. Power spectra S(f) of the stochastic series of subsequent values of the number of cations  $N_p$  inside the simulation zone. Notation and values of parameters the same as in Fig. 1.

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Fig. 3. Power spectra S(f) of the stochastic series of subsequent values of the state of the gate. Notation and values of parameters the same as in Fig. 1.

On the other hand, the model is sensitive with respect to the changes of relative strength of random and deterministic forces — decrease of the dielectric constant with noise unchanged, or increase of noise with electrostatic forces unchanged changed significantly the results. *E.g.*, either too strong gate noise or too strong electrostatic force (*i.e.*, low dielectric constant) dampen the flicker noise.

When the single-file limitations are removed, all the power spectra shown in Figs. 1–3 become  $S(f) \sim f^{-1.5}$ , *i.e.*, the corresponding processes behave like the Wiener process.

The code for the single-file motion is presented at the WWW site http://arxiv.org/abs/physics/0603238.

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