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Biological Transport: Membrane Channels, a white noise flashing ratchet model

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Abstract

We explore biological transport across membrane channels from a physical point of view. The main objective is to use the tools available to a physicist from non-equilibrium thermodynamics and apply them to a concrete biological problem. In this case, we focus our attention in trying to build simple physical models, yet not trivial, that match the behavior of real channels, or ones that can be synthetically accomplished.

The model of a channel studied in here consists on a symmetric sawtooth potential with multiplicative noise. The introduction of multiplicative noise into the system makes it dramatically change its behavior, yet it remains analytically solvable. We also present a simulation framework applicable to more complex and realistic models for channels that can be easily mapped to real experiments and does not require cumbersome theoretical developments.

1 Introduction

1.1 Transport across biological membranes

Any living organism divides the world into two regions: itself and the rest of the universe, and it does so through a well defined boundary. This boundary allows the organism to differentiate itself and have its own identity. On the other hand, a living organism is also an open system, constantly exchanging three magnitudes with its environment: matter, energy and information [1]. From these exchanges, clearly the most important one is matter, since it can also act as a source of energy and information.

The most fundamental boundary found in living organisms is the cell membrane. It could be said that *the first cell came into being when a membrane formed, enclosing a small volume of aqueous solution and separating it from the rest of the universe* [2]. The cell membrane consists mainly of amiphatic lipid molecules arranged in a bilayer structure, with the polar heads of the lipids in the exterior of both layers. The cell membrane is a flexible structure, self-sealing and highly impermeable to ions, polar molecules and large compounds. But the cell is an open system, and it needs to exchange matter with its surroundings through the membrane, mostly ions, but also proteins and other substances. Since the membrane is highly impermeable to them, it needs of other structures to allow transport.

Transport across the membrane is done through transmembrane proteins. These proteins attach to the lipid bilayer and are in contact with both the exterior and the interior of the cell. There are mainly two classes of proteins involved in transport: pumps and channels. Pumps involve active transport, using an energy source to transport ions or molecules against a free energy barrier, usually against a concentration gradient. On the other hand, channels involve passive transport, allowing transport in the same direction as the concentration gradients, in the same way free diffusion does,

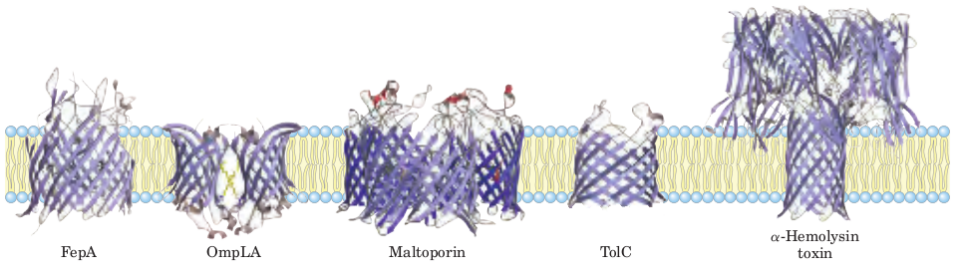

Figure 1: Different examples of membrane proteins. All of these include a β-barrel structure forming a pathway between both sides of the membrane (Ref. [2]).

also they do not require an energy source to facilitate transport, although energy is needed for opening and/or closing (gating) the channel.

Channels, being passive transporters, have some key features that make them special. While pumps can transport ions and molecules at rates approaching several thousand ions per second, channels are capable of reaching speeds up to a thousand times higher, being very close to the speed of free diffusion [3]. Yet, they are not just tubes that allow diffusion across the membrane, they are sophisticated molecular machines that respond to changes in their environment and undergo precisely timed conformational changes.

Channels are also highly selective. For example, some channels allow very effectively the flow of K^+ but do not allow the flow of Na^+, there are specific channels for each susbstance that needs to cross the membrane. Another key feature of channels is that they exist in two states, open and closed. In the closed state, channels do not allow any substantial flow. The transitions between the two states is regulated by external factors, in some channels it is done by ligand-binding (ligand-gated channels) or directly by ATP hydrolysis, while on others, this regulation is done by response to an electric potential (voltage-gated channels).

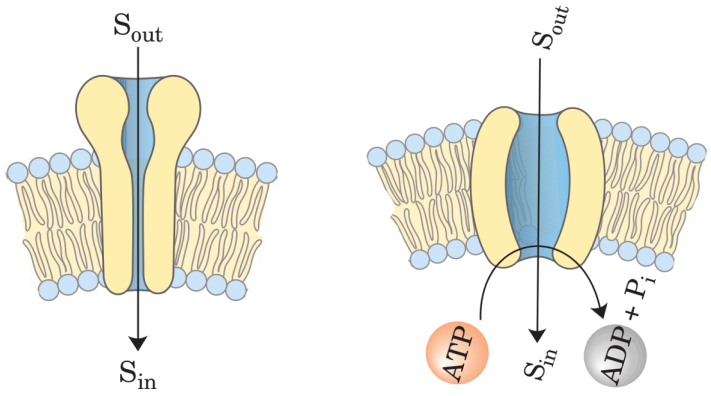

Figure 2: Cartoon representation of a membrane channel and a pump. On the left we can see the channel, which facilitates diffusion down the concentration gradient. On the right we have the pump, working against the gradient and consuming energy in the process (Adapted from Ref. [2]).

1.2 The Biophysical approach to membrane channels

The introduction of the patch-clamp technique by Erwin Neher and Bert Sakmann [4] in 1976 made possible the study of single channels. With this technique one can measure the activity of a single channel. The flow of

ions through a single channel and transitions between the open and closed states of a channel can be monitored with a time resolution of microseconds. Also, the channel can be studied in its native environment, even in an intact cell. This technique, and newer ones, makes possible a quantitative analysis of channels. From this point of view, it is also important to theoretically describe the processes involved in the transport through channels, using models more accurate than simple diffusion or chemical kinetics, but still far from molecular dynamics simulations.

A good understanding of channel transport is needed from a medical point of view. One clear example is the CFTR (Cystic fibrosis transmembrane conductance regulator) chloride channel, whose failure causes cystic fibrosis [5]. Channels, which play an essential role in the nervous system, are the main target of many toxins attacking the organism, such as poisons and venoms, that block the channels. Also, since channels govern the fastest processes in cellular transport, they are the favorite target in the drug research industry. Creating drugs and compounds that have a high affinity with channels can improve and speed up the process of drug delivery.

Theoretical models also play an important role on recent advances in the design and construction of synthetic channels and nanopores [6, 7]. Identifying and isolating the key components involved in channel transport we can, later on, produce synthetic compounds that mimic the effects of biological channels, and also change them and make them more suitable for other tasks. Applications in this field range from the biological level, for example, to replace faulty channels, to the industrial level, allowing for example, to separate substances in a solution. Properties like the high selectivity, speed, and the fact that they can be easily controlled at will, makes them specially interesting for the industry.

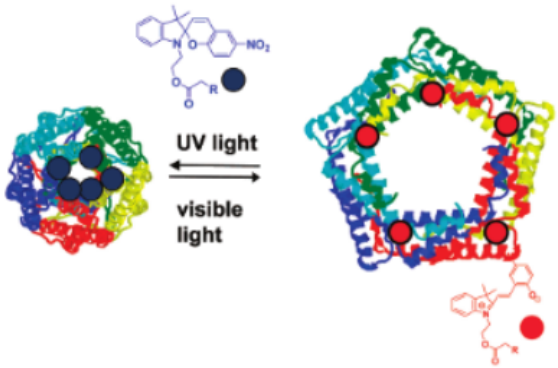

Figure 3: Example of a light-actuated synthetic channel. Exciting the channel with different wavelengths opens and closes the channel (Ref. [6]).

Physicists have been studying the process of transport for centuries, but molecular transport in biological systems makes it substantially different from the rest. From a physical point of view, living organisms are systems very far from equilibrium, continuously exchanging matter, energy and information with its surroundings. This is already a challenge from a physical point of view, since one is used to study systems in equilibrium, or close to it, where linear relations hold; in the biological world, as we will see in later chapters, linear relations do not hold anymore. Also, at the molecular level, biological systems are found in the low Reynolds regime [8]; in this regime, friction dominates inertia, the systems are highly dissipative and noisy, and the laws governing movement are slightly different from the macroscopic ones.

2 Membrane channel as a symmetric pump

2.1 Introduction

In this section we introduce our first approach to studying biological channels from a physical point of view. From a coarse-grained perspective, the main difference between channels and pumps is the breaking of spatial symmetry in their effective potential. At the same time, most models of active transport in biophysics are based on Feynman's ratchet mechanism [9], and we will make use of these premises to model our channel. We will apply the framework introduced by A. Gomez-Marin and J. M. Sancho [10] for Brownian pumps and apply it to channels.

The basis of this model is a white-noise flashing potential (symmetric in our case). The flashing potential is modeled as a normal potential $V(x)$, modulated by a time dependent stochastic process (see Figure 4). Even if this modulation is small, it introduces new features to the model that make it behave quite different as it would do without it. Although a white-noise stochastic modulation cannot take into account channel gating, it can be considered as the effect of an external fluctuation (i.e. an oscillating electric field in voltage-gated channels), as the limit of a dichotomic noise, or just as the inherent fluctuations in the conformational structure of the channel [11]. On the other hand, the symmetry makes it behave as a passive transport mechanism, the flux always goes against the concentration gradient, from higher to lower, being the equilibrium state the one in which the concentrations at both sides of the potential are the same.

To study this model we start by considering a simple potential, a symmetric sawtooth, for which we can find an analytic solution by means of Langevin dynamics. After a theoretical analysis, both in and out of equilibrium, we introduce a simulation scheme based on the introduction of reservoirs and "natural" boundary conditions, which we can apply to more complex potentials. Then we find the complete analytical solution for the symmetric sawtooth plus reservoirs, and compare it with the results of the simulation.

2.2 Theoretical analysis for a symmetric sawtooth

As stated in the introduction, biological systems (at the molecular level), belong to the low Reynolds number regime, in which friction dominates inertia. Given that, our starting point for the theoretical analysis will be a general Langevin equation in the over-damped limit

$$\gamma \dot{x} = -V'(x,t) + \eta(t), \tag{1}$$

which describes a single particle moving through the channel, where γ is the friction, $\dot{x}$ the velocity, $V(x,t)$ is the complete potential, and $\eta(t)$ is a

Gaussian white noise with autocorrelation $<\eta(t)\eta(t')>= 2\gamma k_B T\delta(t-t')$. To introduce the flashing ratchet we take a potential of the form

$$V(x,t) = V(x)\left(1+\chi(t)\right), \tag{2}$$

where $V(x)$ is a symmetric sawtooth potential, and $\chi(t)$ is the flashing part, also a Gaussian white noise with autocorrelation $<\chi(t)\chi(t')>= 2Q\delta(t-t')$. A scheme of the potential can be seen in Fig. 4.

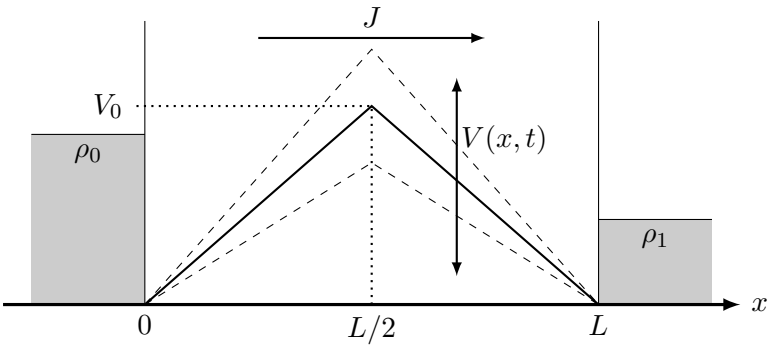

Figure 4: Structure of the channel. The channel is modeled as a symmetric flashing potential $V(x,t)$, being ρ_0 and ρ_1 the particle concentrations at each side of the channel. When the concentrations are different, there is a net flux.

The exact form of our sawtooth potential is

$$V_L(x) = \frac{2V_0}{L}x, \quad x\in\left(0,\frac{L}{2}\right), \tag{3}$$

$$V_R(x) = \frac{2V_0}{L}(L-x), \quad x\in\left(\frac{L}{2},L\right). \tag{4}$$

Using the potential from (2) the Langevin equation (1) can be expressed as

$$\dot{x} = -V'(x) - V'(x)\chi(t) + \eta(t), \tag{5}$$

where we have taken $\gamma = 1$ for convenience, since its only effect is a change in the time scale[1]. Being $\chi(t)$ and $\eta(t)$ stochastic processes, and both Gaussian white noise, we can easily combine them, since the convolution of the two PDF[2] is still Gaussian. Taking this into account, we can further simplify the previous expression

$$\dot{x} = -V'(x) + g(x)\xi(t), \tag{6}$$

$$g(x) \equiv \sqrt{k_B T + QV'(x)^2}, \tag{7}$$

[1]It can be easily seen by making the substitution $t' = \gamma^{-1}t$ in the Langevin equation
[2]Probability Density Function

where $\xi(t)$ is also a Gaussian white noise with zero mean and unit autocorrelation strength, but now it is a multiplicative noise.

Due to the multiplicative noise $\chi(t)$ previously introduced, it is worth saying that we are going to analyze our stochastic processes following Itô rules. Since we have not fully explained the origin of the multiplicative noise[3], the choice might seem arbitrary, but it is more natural to work under Itô interpretation, both from the analytical point of view, and from the simulation, since it does not require any additional terms, like drifts. Under Itô interpretation, the Fokker-Planck equation for the process $x(t)$ defined by the previous Langevin equation becomes [13]

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}\left[P(x,t)V'(x)\right] + \frac{\partial^2}{\partial x^2}\left[g^2(x)P(x,t)\right], \tag{8}$$

and from the conservation of probability we also have $\partial_t P(x,t) = -\partial_x J(x,t)$, where $J(x,t)$ is the particle flux. Forgetting about the normalization of probability and considering the global behavior of the channel as the sum of N independent single-particle processes we can safely move from probabilities to particle concentrations $\rho(x,t)$,

$$J(x,t) = -V'(x)\rho(x,t) - \frac{\partial}{\partial x}\left[g^2(x)\rho(x,t)\right]. \tag{9}$$

We now proceed to find solutions in the steady-state, where J becomes position independent. In this case, the last equation becomes a first order differential equation, which has for solution,

$$\rho(x) = Z(x,c_0,J)\exp\left[-\int_0^x dz\left(\frac{V'(z)}{g^2(z)} + 2\frac{g'(z)}{g(z)}\right)\right], \tag{10}$$

$$Z(x,c_0,J) = c_0 - J\int_0^x \frac{dz}{g^2(z)}\exp\left[\int_0^z dy\left(\frac{V'(y)}{g^2(y)} + 2\frac{g'(y)}{g(y)}\right)\right] \tag{11}$$

where c_0 and J are constants yet to be determined. c_0 being the concentration at $x = 0$ and J the particle's flux. This solution is quite general as long as the function $g(x)$ remains continuous and differentiable, when moving through different domains special care is needed to handle the discontinuities. For our symmetric sawtooth discontinuities will appear between the channel and the reservoirs, but not inside the channel, since $g(x)$ is continuous inside the whole channel, and the concentration jumps only occur when there's a discontinuity in $g(x)$.

[3] See for example [12] for a full discussion

2.3 Simulation framework

Although we have been able to find a steady-state solution for the Fokker-Planck equation, working with it, is often cumbersome, since one has to take extra care of discontinuities and the integrals inside (10) cannot always be solved. Based on the last Langevin equation (7) we implement a simulation framework that makes finding solutions, for any system and potential, much easier than using analytical expressions or solving equations (10) and (11) numerically.

2.3.1 Algorithm

Many algorithms exist for Brownian dynamics simulations [14], but since we are dealing with non standard equations with multiplicative noise we will go back to the core [15] and stick with Euler's first order. Integrating (7) between t and $t + dt$ we obtain,

$$x_i(t + dt) = x_i(t) - V'[x_i(t)]dt + g[x_i(t)]X_i(t) \tag{12}$$

where $X_i(t)$ is the numerical representation of the stochastic integral

$$X_i(t) = \int_t^{(t+dt)} \xi(t')dt' = \sqrt{2dt}\alpha_i, \tag{13}$$

namely a random number with zero mean and variance $2dt$, which we can write as a function of α_i, being α_i random numbers from the standard normal distribution, due to the properties of the normal distribution.

We have the algorithm ready to simulate the movement of a particle in our system, but we still need a way to deal with the boundaries.

2.3.2 Reservoirs model

In our model for the channel we have three parameters to work with, the concentrations at both sides of the channel and the flux (only two of them being independent), and we need a method to introduce them in the simulation. The most common method of generating Langevin trajectories between fixed concentrations is called particle injection [16], but the method is unpractical, since it requires the knowledge of the temporal dependence on the particle probability distribution to avoid the generation of spurious boundaries, and we are interested in doing a general simulation, one that matches possible physical experiments, not a simulation that depends on the specific form of the distribution. Our approach to the boundary conditions is the introduction of reservoirs (zones around the channel where particles can diffuse freely), and the insertion of reflective or periodic boundaries at the end of the reservoirs, depending the case. This method increases the simulation time, but is applicable to more situations and is easily understood.

In the original work of A. Gomez-Marin and J.M. Sancho [10] the introduction of the reservoirs was enough to simulate all the possible cases, equilibrium and out of equilibrium (steady) states since their potential was asymmetric, but in our case this is only half the story. We are working with a symmetric potential, and no matter how the reservoirs and the boundaries are, the system will always reach the equilibrium state with zero flux. To be able to study situations with $J \neq 0$ we also introduce a pumping device to our system. In the most simple case, this is just a new zone where a constant force is applied to the particles. Now our complete system is as follows: from left to right, diffusive zone (left reservoir), pumping device, diffusive zone, channel, diffusive zone (right reservoir), see also Fig. 5. But if the system is closed with reflective walls, we will still be in equilibrium, detailed balance will be satisfied. To be able to study the system in steady-states we connect both ends of the system, as if we had periodic boundary conditions, so particles that exit from the right enter again by the left and vice versa, this way, due to the general asymmetry of the complete potential, a net flux will appear in the direction of the pumping force.

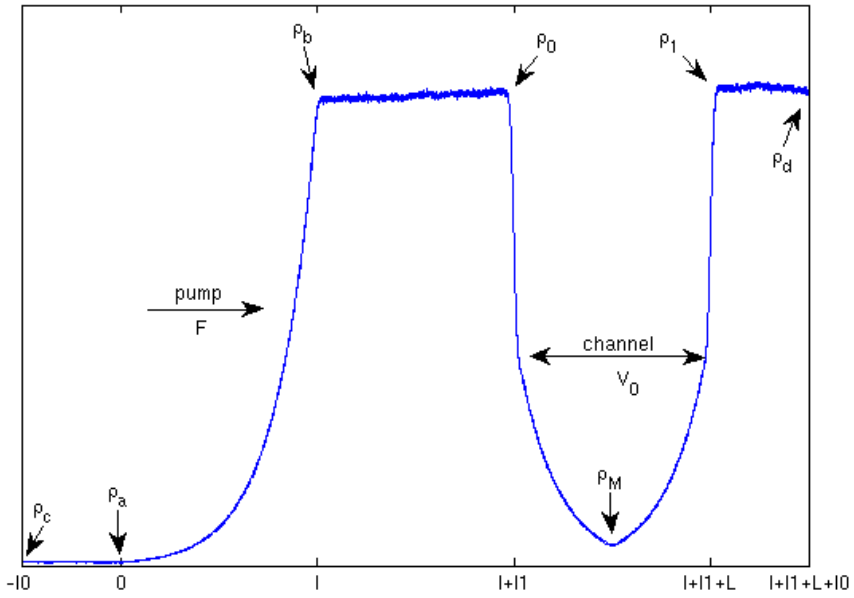

Figure 5: Scheme of the whole system. A constant force is acting as a pump in the region $(0, l)$ and the channel of length L is found on the right. This corresponds to the concentration profile for the system in equilibrium, $J = 0$ (reflective walls).

The only problem with this simulation scheme is that there is no easy way to control the concentrations at the sides of the channel and the global flux beforehand (the system is not linear), and to do a full comparison between

theory and simulation the complete analytical solution is required.

2.4 Complete analytical solution

Given the piecewise linear form of our potential for the channel, the Fokker-Planck equation of the whole system (channel, pump and reservoirs) is solvable analytically . The solution is found by solving eq. (10) for each part of the system and applying continuity to join the parts together when possible[4]. Following the notation introduced if Fig. 5 we present the final expressions of the analytical solution,

$$\frac{\rho_1}{\rho_0} = \frac{J}{\rho_0}\left[\frac{1}{F}\left(1-e^{-f}\right)+\frac{l_1 e^{-f}+2l_0}{k_BT}\right]+e^{-f} \tag{14}$$

$$\frac{J}{\rho_0} = \left(1-\frac{\rho_1}{\rho_0}\right)\frac{v}{e^v-1}\frac{k_BT}{L}, \tag{15}$$

where we have used

$$f \equiv \frac{Fl}{k_BT} \tag{16}$$

$$v \equiv \frac{V_0}{g_1^2} \tag{17}$$

$$g_1^2 \equiv k_BT + 4Q\frac{V_0^2}{L^2}. \tag{18}$$

Although the last two expressions of the analytical solution[5] can be combined, the expression becomes quite cumbersome and hard to read. Also, we have chosen these expressions so the first one only involves parameters of the simulation helper (pump + reservoirs) and the second one only involves parameters of the channel. As we can see from the two expressions, the dependence between the concentrations is not linear, but it is linear between the ratio of concentrations ρ_1/ρ_0 and the "normalized' flux J/ρ_0. A single expression for the ratio of concentrations can be obtained by redefining some parameters

$$\alpha \equiv \frac{1}{F}\left(1-e^{f}\right)-\frac{l_1+2l_0e^{f}}{k_BT} \tag{19}$$

$$\beta \equiv \frac{v}{1-v}\frac{k_BT}{L}, \tag{20}$$

such that the final expression now becomes

$$\frac{\rho_1}{\rho_0} = \frac{1+\alpha\beta}{e^f+\alpha\beta}, \tag{21}$$

[4]Due to the form of the function $g(x)$ special care is needed when joining the reservoirs with the channel, discontinuities in the concentrations will appear

[5]It is worth saying that these expressions are only valid in the case $J \neq 0$ (although the second one is always valid). This arises from the fact that you cannot both satisfy periodic boundary conditions and $J = 0$ (unless there is no pumping, $F = 0$).

which is useful for studying limiting cases. For example, it is easily seen that in the limit $f \to 0$ (no pumping) the system reaches equilibrium, $\rho_1 = \rho_0$.

2.5 Results

Next we show the most noteworthy results available for our model, namely the particle density function for steady states and an exploration on the channel's behavior based on the different parameters.

2.5.1 Equilibrium, $J = 0$

We start with the most simple case, the system is at equilibrium, there is no net particle's flux. We accomplish this by setting reflective walls at the boundaries of the system. The results for the particle density function along the system for a simulation can be seen in Fig. 6, both in normal and logarithmic scales. As it is clear from the logarithmic one, the concentration is either constant or shows an exponential behavior, and it is the same in both sides of the channel, clearly satisfying detailed balance. The ripples on the left reservoir are due to the simulation time being small, and that the reservoir has almost no particles in it. It can also be seen from the zones of free diffusion that there is no flux; which is consistent with the common knowledge obtained from Fick's law: a net flux in a free diffusion zone requires a concentration gradient to exist.

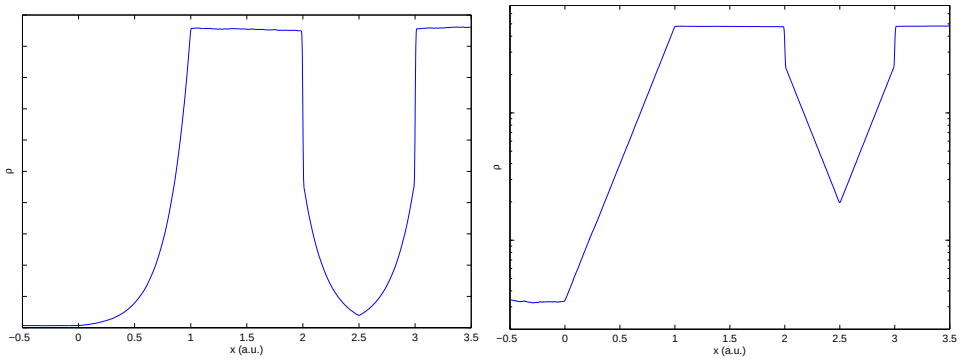

Figure 6: Particle density distribution for equilibrium. Image on the right is on logarithmic scale. See text for further explanation.

2.5.2 Non-Equilibrium Steady-State, $J \neq 0$

Now we move to solutions involving $J \neq 0$ that have relaxed until they show no time dependence. To accomplish this, we connect both ends of the system as explained previously to introduce a net flux in the system. Now we can

also compare the simulation results with those obtained in the theoretical section. The histogram for the particle density of one simulation run can be seen in Fig. 7. together with the theoretical predictions. As it can be seen in the figure, both results match perfectly, including the discontinuity found between the channel and the system. Also, since now there is a net flux in the system, the zones of free diffusion show the expected linear behavior of Fick's law, and a careful examination shows the continuity between the two ends of the system.

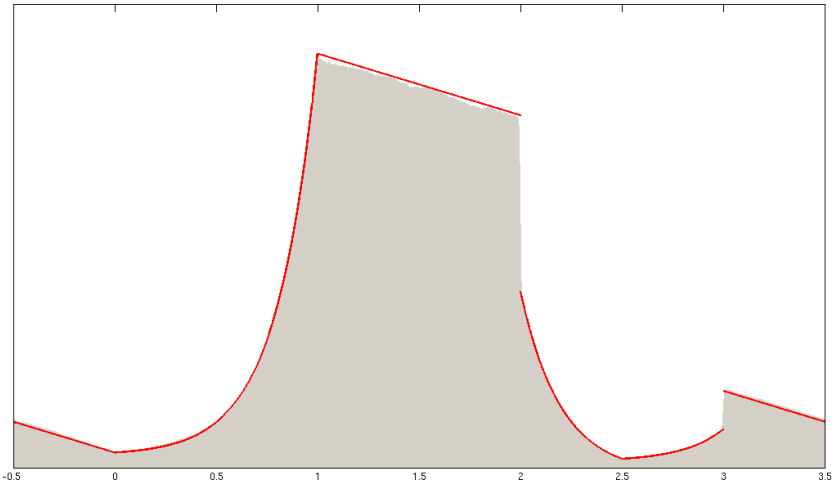

Figure 7: Particle density distribution for a steady state, $J \neq 0$. The thick contour line belongs to the analytical results and the grey shade to the histogram of one simulation run.

2.5.3 The effect of multiplicative noise

The main difference of this model with previous ones based on free diffusion is the presence of multiplicative noise in the system. Even if the strength of this multiplicative noise is small it has a big impact on the system's behavior, as can be seen in Fig. 8.

Using the analytical results, we have explored the flux dependence with the channel's barrier height V_0 for different values of the multiplicative noise strength Q, while keeping it small. When there is no multiplicative noise, the flux falls exponentially to zero as V_0 increases, since particles have a small probability of crossing through the channel's barrier with only Brownian motion (V_0 is in units of k_BT). In fact, this situation corresponds to a typical problem of barrier crossing. On the other hand, the presence of multiplicative noise allows particles to always be able to cross the barrier. Also, for very high barriers, the flux becomes independent of the barrier

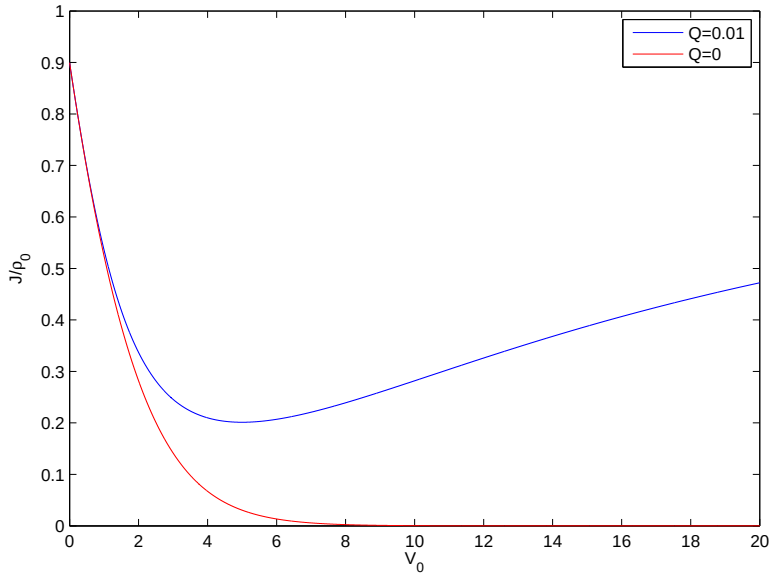

Figure 8: Flux as a function of the channel's barrier height for different values of the multiplicative noise strength.

height, which can be easily understood with the following argument: when the barrier is high, the only chance a particle has to cross the barrier, is to wait until the barrier disappears (due to fluctuations of the multiplicative noise), and the frequency of this fluctuations is independent of the barrier height, only depends on the strength of the multiplicative noise.

Another interesting effect of the multiplicative noise is the presence of a minimum in the normalized flux. The position of this minimum actually belongs to the regime in which the contribution to the effective diffusion coefficient of the thermal fluctuations and the multiplicative noise is the same, $QV'^2(x) = k_B T$.

2.5.4 Parameter exploration

Since we are interested in the non-equilibrium behavior of the system we proceed to study the flux dependence as a function of the different 'tunable' parameters of the system. To try to mimic real channels, we have to consider that parameters like the channel's length, and the temperature will be fixed. Our tunable parameters will be mainly the barrier's height and the multiplicative noise strength. Also, to establish a direct correspondence between theory and simulation we will perform all our calculations using the analytical expressions previously found for the periodic system, eq. (15). Although on a real situation we would work at fixed concentration ratio between both ends of the channel, since the relationship between the concentration's ratio

and the normalized flux is linear, the behavior of the system will remain the same.

We start by studying the normalized flux as a function of the barrier height. This is the same plot we already showed on the study of the effect of the multiplicative noise, but now we fix all the system parameters, including Q. The comparison between simulation and analytical results can be seen in Fig. 9. As we can see, the results obtained from the simulation match

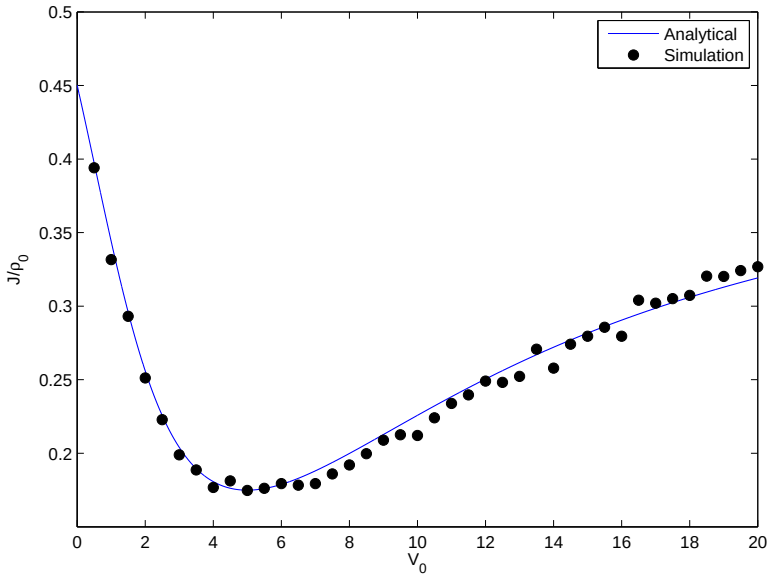

Figure 9: Flux as a function of the channel's barrier height. Comparison between simulation and analytical results ($Q = 0.01$).

perfectly the analytical predictions. Needless to say, for the simulation the flux has been calculated as one would do in a real experiment, measuring the number of particles crossing a given surface perpendicular to the channel per unit time. We also tried calculating the flux by adjusting a linear fit to the zones of free diffusion, but this result was surprisingly less accurate.

Next we proceed to study the flux as a function of the multiplicative noise strength Q. We use the same procedure as before, but now we fix all the parameters but Q. The results can be seen in Fig. 10.

Again, both predictions match. We can see on Fig. 10 how for $Q = 0$ the flux is very small (we are working with a barrier of height $V_0 = 5k_BT$), and for $Q \neq 0$ the flux quickly grows with Q until it saturates. The saturation can be easily explained, since for high values of the multiplicative noise the particles can always cross the barrier, and the system mostly behaves as

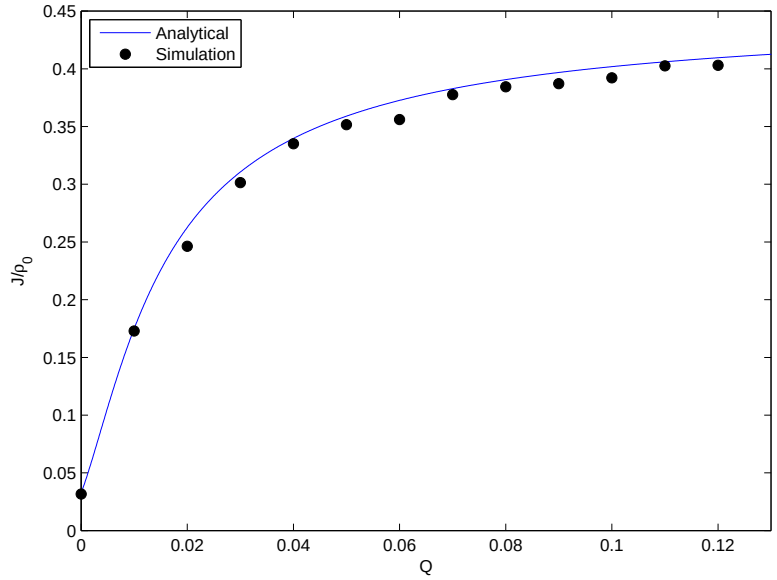

Figure 10: Flux as a function of the multiplicative noise strength. Comparison between simulation and analytical results ($V_0 = 5k_BT$).

with free diffusion, but with a different effective diffusion coefficient.

3 Conclusions

From the brief study done on this model we can already see some interesting results. The most important one being the effect of multiplicative noise in our system, how such a small noise can have a very strong effect in the behavior of the channel. Even if this model does not take into account important aspects in passive transport like gating and selectiveness, it captures its essence, it maintains fluxes of the same order of magnitude as free diffusion while showing a completely different behaviour. The presence of a minimum in the normalized flux for a given barrier height is also interesting, this minimum also corresponds to a maximum in the difference of ratio concentrations. In fact, this is the most interesting regime, in which the system deviates the most from pure passive transport due to diffusion.

Also important is the introduction of the simulation framework, which allows us to explore a wide range of potentials and systems for which analytical solutions are not possible, and this framework will also be employed in future projects.

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