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Two-state flashing molecular pump

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Abstract – Here we study a pumping device capable of maintaining a density gradient and a flux of particles across a membrane. Its driving mechanism is based on the flashing ratchet effect powered by the random telegraph process in the presence of thermal fluctuations. Unlike Brownian motors, the concentrations at both reservoir boundaries need to be implemented as boundary conditions. The residence transition rates of the dichotomic flashing are related to the binding and hydrolysis of ATP molecules. The model is exactly solved and explored. The pump energetics is discussed and the relevant parameter values are tuned within a biological scale.

Introduction. – Active-transport processes are ubiquitous in living matter. In fact, the cell cannot survive when specific out-of-equilibrium tasks inside cease, mainly carried out by proteins such as kinesin, RNA-isomerase, dynein or rotatory ATP-ase. For instance, in order to maintain a suitable osmotically regulated state, the pumping of ions across the cell membrane is a crucial job that is performed by molecular pumps, which are, in turn, powered by the hydrolysis of ATP molecules. Stemming from the studies on active transport in noisy environments [1], the stochastic features of pumps were originally addressed in [2,3] and applied to chemically driven electron pumping [4]. An experiment on artificial ion pores showing rectification was presented in [5], where the observations were interpreted by a model containing flashing ratchets. Also in [6], experimental realizations of synthetic nanoscopic devices transporting potassium ions against their concentration gradient when stimulated with external field fluctuations were built. Recently it has been directly demonstrated that the ratchet mechanism is indeed of use in a biological system where molecular transport driven by fluctuations occurs in a membrane channel [7]. Other theoretical works have studied the gating kinetics of ionic channels, based on the effect of non-equilibrium fluctuations combined with the ratchet effect [8]. A Brownian device with cyclic steps accounting for its configurational changes has been shown to reproduce the main features of experiments on the Na,K-ATP-ase ion pump [9]. Moving to more simplistic descriptions, the study of active transport in an idealized Brownian pump focusing on the concentration gradient created and maintained at both sides of a membrane has been analytically and numerically discussed in [10].

Despite its relevance for modeling molecular pumps, the ratchet effect and its transport features against a concentration gradient have drawn very little attention. In this letter we introduce a simple, yet revealing, two-state theoretical model for a machine which pumps particles against a concentration gradient. The model is inspired by recent experimental works where the operating cycle of a channel has been shown to involve two steps (opening and closing) related to the ATP binding and hydrolysis, respectively [11,12]. The pumping device we present consists of a ratchet potential, embedded in a membrane and bounded by particle reservoirs, which exhibits dichotomic fluctuations controlled by the ATP concentration. We do not focus on the precise structural details of the pump, but do it at the level of energetics. We consider the asymmetric ratchet profile as an energy barrier. Alternatively, one could also think of modeling the particle binding site as an energy well. In the steady state, we exactly calculate the concentration ratio between both reservoirs and the particle flux. We relate the performance of the device with ATP concentration, study its energetics and finally place it in a biological context.

The model. – Let us consider a pumping mechanism based on a flashing potential embedded in a membrane of length $L$, whose boundaries are infinite reservoirs

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of particles with fixed mean densities $\rho_0$ and $\rho_1$. The dynamics of a particle in the membrane is determined by the following Langevin equation in the over-damped regime:

$$\dot{x} = -U'(x, t) + \xi(t),$$

where $U(x, t)$ is a time-dependent potential (the prime denotes the position derivative) and $\xi(t)$ the random force arising from the thermal fluctuations. It has zero mean and its autocorrelation is given by the fluctuation-dissipation theorem,

$$\langle \xi(t)\xi(t') \rangle = 2\gamma k_B T \delta(t - t'),$$

where $\gamma$ is the friction coefficient and $T$ the temperature of the environment. Whereas in the reservoirs the particles can diffuse freely, in the membrane they experience the potential

$$U(x, t) = V(x)\zeta(t),$$

where $V(x)$, as depicted in fig. 1, is a piecewise linear asymmetric ratchet potential:

$$V_1(x) = V_0 \frac{x}{\delta L}, \quad x \in [0, \delta L],$$

$$V_2(x) = V_0 \frac{L - x}{(1 - \delta)L}, \quad x \in [\delta L, L].$$

$V_0$ is the energy barrier height and $\delta$ controls the spatial asymmetry by taking values between zero and unity.

The flashing modulation $\zeta(t)$ is a stochastic forcing in time which randomly switches the ratchet potential between two states [1,2]. It is distributed according to a random telegraph (dichotomous Markov) process, flipping between values $\zeta_a = 1$ (closed state) and $\zeta_b = 0$ (open state), with residence probability transitions $w_a$ and $w_b$ respectively [13,14]. Its mean value and correlation are

$$\langle \zeta(t) \rangle = \frac{w_a}{w_a + w_b},$$

$$\langle \Delta\zeta(t)\Delta\zeta(t') \rangle = \frac{w_a w_b}{(w_a + w_b)^2} e^{-\{w_a + w_b\}|t-t'|},$$

where $\Delta\zeta(t) \equiv \zeta(t) - \langle \zeta(t) \rangle$. While the asymmetric potential breaks the spatial symmetry, the flashing transitions between states are responsible for the breaking of detailed balance in the system.

**Transition rates and ATP concentration.** – The hydrolysis of ATP molecules provides the energy input. It creates the necessary out-of-equilibrium conditions to drive molecular pumps. As a first level of approximation to include the effect of ATP consumption into the model, we relate the ATP concentration, its binding and its hydrolysis processes to both residence transition rates. This two-state picture has been described in experiments in channels [11,12] and it is a valid paradigm for the mathematical characterization of mechano-chemical energy transduction. We consider that, when the pump is in the closed state ($\zeta_a = 1$), it is the binding of an ATP molecule to a certain pocket center of the pump which induces conformational change to the open state ($\zeta_b = 0$). The transition rate $w_a$ is thus dependent on the ATP concentration available in the surroundings, which can be modeled as a Michaelis-Menten kinetics law:

$$w_a = w_0 \frac{[\text{ATP}]}{k_M + [\text{ATP}]} = \frac{w_0}{1 + 1/\sigma},$$

where $k_M$ is the so-called affinity constant and $[\text{ATP}]$ is the concentration of ATP molecules. Only their ratio is relevant: $\sigma = [\text{ATP}]/k_M$. The rate $w_b$ is given by the inverse of the machine’s intrinsic time, which we consider constant:

$$w_b = w_0.$$

In the limit of a saturating $[\text{ATP}]$, both transition probabilities are equal ($w_a = w_b = w_0$) indicating that the pump cannot operate faster. Medium $[\text{ATP}]$ values imply a longer average time in the closed state. At low concentrations, $w_a$ is small and the pump seldom starts the cycle. Diffusive leak losses dominate and its pumping capacity is then very low. See scheme in fig. 2.

**Numerical simulations.** – As a first test to show that the model just introduced can indeed create and maintain a concentration gradient, we use the simulation framework discussed in [10]. This method allows for the numerical implementation of the reservoir boundary conditions, which is not trivial. We then simulate non-interacting particles following the Langevin equation (1),

Fig. 1: Pump model: an asymmetric potential $V(x)$ flashes its shape at random between a blocking (closed) and a flat (open) configuration with transitions rates $w_a$ and $w_b$.

Fig. 2: Illustrative representation of the effect of ATP concentration in the switching rates of the dichotomic flashing ratchet mechanism.
under thermal white noise and the random telegraph process. In fig. 3, we plot the histogram of the position of the particles, being illustrative of the density profiles typically obtained in the steady state at zero net flux. It is clear that the pump is able to generate and maintain a concentration ratio \( \rho_1 \neq \rho_0 \), while the edges emulate particle reservoirs with uniform concentrations.

**Theoretical analysis.** – Consistent with the Langevin equation (1), the corresponding partial differential equations for the time evolution of the concentration of particles in each flashing state, \( P_{i \lambda} \equiv P_{i \lambda}(x,t) \) and \( P_\lambda \equiv P_\lambda(x,t) \), originate from a combination of the Fokker-Planck description for the continuous variable \( x \) and the Master equation for the discrete states \( a \) and \( b \). They read [2,3,13,14]

\[
\begin{align*}
\partial_t P_a &= \gamma^{-1} \partial_x [V'(x) + k_B T \partial_x] P_a - w_a P_a + w_b P_b, \\
\partial_t P_b &= \gamma^{-1} \partial_x [k_B T \partial_x] P_b - w_b P_b + w_a P_a.
\end{align*}
\]

\( \text{(10)} \)

It is convenient to work with dimensionless quantities. We first re-scale space and time: \( z \equiv x/L \) and \( s \equiv (k_B T)/(\gamma L^2) \). Consequently, the new transition rates are \( f \equiv w_0(\gamma L^2)/(k_B T) \) (for \( w_a, w_b \) and \( w_0 \)) and \( L \) is absorbed in the concentration distributions. We introduce the following densities: the total density of particles \( \rho \equiv P_a + P_b \) and the auxiliary function \( \pi \equiv P_a - P_b \). In the steady state, eqs. (10) are governed by a new set of equations for each region (indicated by the subindex \( i = 1, 2 \)):

\[
\begin{align*}
\rho_i' &- F_i [\rho_i + \pi_i] = -J, \\
\pi_i'' &- F_i (\rho_i' + \pi_i') = \pi(f_b - f_a),
\end{align*}
\]

\( \text{(11)} \)

where \( F_1 = -v_0/2\delta \) and \( F_2 = v_0/2(1-\delta) \). \( v_0 \equiv V_0/k_B T \) measures the relative strength of the potential with respect to the thermal energy. \( J \) is the physical total flux of particles across the membrane.

Substituting (11) in (12) one gets a linear ODE for \( \rho_i(z) \):

\[
\rho_i''(z) - 2F_i \rho_i'(z) - (f_a + f_b) \rho_i(z) + 2f_b F_i \rho_i(z) = J(f_a + f_b),
\]

\( \text{(13)} \)

whose solution has the standard form

\[
\rho_i(z) = C_{i1}e^{\lambda_{1i}z} + C_{i2}e^{\lambda_{2i}z} + C_{i3}e^{\lambda_{3i}z} + (J/F_i)\alpha,
\]

\( \text{(14)} \)

where \( \alpha \equiv (f_a + f_b)/2f_b \). The constants \( C_{ij} \) are, so far, unknown parameters. Instead, the constant coefficients \( \lambda_{ij} \) are found by inserting \( \rho_i(z) \) back in (13) and solving the algebraic equation

\[
\lambda_{ij}^2 - 2F_i \lambda_{ij}^2 - (f_a + f_b) \lambda_{ij} + 2f_b F_i = 0.
\]

\( \text{(15)} \)

Plugging (14) in eq. (11) and defining \( s_{ij} \equiv (\lambda_{ij}/F_i - 1) \) and \( \beta \equiv (f_b - f_a)/2f_b \), one finds

\[
\pi_i(z) = s_{11} C_{i1} e^{\lambda_{11}z} + s_{12} C_{i2} e^{\lambda_{12}z} + s_{13} C_{i3} e^{\lambda_{13}z} + (J/F_i)\beta.
\]

\( \text{(16)} \)

**Boundary conditions.** – The relevance of the boundary conditions in this problem was emphasized in [2]. The formal solution of the concentration of particles in the steady state depends on seven unknown constants (the coefficients \( C_{ij} \) and the flux \( J \)), whose value is determined by boundary conditions. In contrast with models for Brownian motors, in the present Brownian pump one should not impose normalization nor the periodicity condition for the probability. Instead, the total concentrations at left and right boundaries, \( \rho_0 \) and \( \rho_1 \) respectively, are externally fixed: \( \rho_1(0) \equiv \rho_0 \) and \( \rho_2(1) \equiv \rho_1 \). At the boundaries (in contact with the particle reservoirs) the state probabilities can be factorized as the total concentration times the stationary weight the state, complying with \( P_{a}(0) = \rho_0 f_b/(f_b + f_a) \) and \( P_{b}(0) = \rho_0 f_a/(f_b + f_a) \) (and analogously at \( z = 1 \)). Rewritten in terms of \( \pi(z) \), this supplies two new conditions: \( \pi_1(0) = r \rho_0 \) and \( \pi_2(1) = r \rho_1 \), where \( r \equiv (f_b - f_a)/(f_b + f_a) \). Third, \( \rho(z) \) and \( \pi(z) \) must be continuous functions connecting both regions: \( \rho_1(\delta) = \rho_2(\delta) \) and \( \pi_1(\delta) = \pi_2(\delta) \). The last, the total flux \( J \) associated to \( \rho(z) \) has implicitly been assumed continuous across both zones. The same holds for the one associated to \( \pi(z) \) in (12), which in practice yields to impose continuity on \( \pi_1'(z) - F_i[\rho_1(z) + \pi_1(z)] \). This last boundary condition can be recast as a property of the \( \pi(z) \) derivatives: \( (F_2 - F_1)[\rho_1(\delta) + \pi_1(\delta)] = \pi_2'(\delta) - \pi_1'(\delta) \).

**Solution.** – Following the technical procedures in [3], the solution to the problem is feasible. The above cumbersome boundary conditions can be compactly written as a system of linear equations:

\[
\text{see eq. (17) on the next page}
\]

from which the flux \( J \) (and also the density profile \( \rho(z) \) by means of \( C_{ij} \)) can be obtained as a function of the system parameters. New constants are defined for compact notation: \( \Delta F \equiv (1/F_1 - 1/F_2) \) and \( h_{ij} \equiv \lambda_{ij}(s_{ij} + F_2/F_1 - 1) \). In the zero-flux case (\( J = 0 \)) such linear system has to be rearranged. The ratio of concentrations \( \rho_1/\rho_0 \), which is then the relevant observable, is easily found by imposing a minor of the coefficient matrix equal to zero (ensuring that the solution of the problem exists):
Pumping is possible, thus leading to a non-zero net flux of particles against the concentration gradient, if the flashing time is higher, the decay is softer due to a more powerful functioning of the pump (at the expense of more energy). Even if the pump is able to carry a non-zero net flux of particles against the concentration gradient, if $ρ_1$ is sufficiently increased, the particle flux can be reversed.

The analytical prediction of the flux $J$ as a function of the rate $f_0$ for several values of $ρ_1$ (where $ρ_0 = 1$) is shown in fig. 5 (bottom). When $ρ_1 = ρ_0$ and $f_0 = 0$, the device is stopped and the net flux vanishes. As the pumping rate is increased, transport starts. The higher $ρ_1$, the lower the parameter exploration: Non-zero–flux case. — In fig. 5 (top) we plot the flux $J$ as the concentration $ρ_1$ is increased (given a fixed $ρ_0 = 1$) for several values of $ρ_0$. A restoring entropic force appears opposing the pumping and leading to a decrease of the total flux. The decrease of the flux is linear. When the barrier $ρ_0$ is higher, the decay is softer due to a more powerful functioning of the pump (at the expense of more energy). Even if the pump is able to carry a non-zero net flux of particles against the concentration gradient, if $ρ_1$ is sufficiently increased, the particle flux can be reversed.

The analytical prediction of the flux $J$ as a function of the rate $f_0$ for several values of $ρ_1$ (where $ρ_0 = 1$) is shown in fig. 5 (bottom). When $ρ_1 = ρ_0$ and $f_0 = 0$, the device is stopped and the net flux vanishes. As the pumping rate is increased, transport starts. The higher $ρ_1$, the lower the flux $J$, even becoming negative for great concentration values. In that case, if the flashing rate is increased, the machine can reverse the sign of the flux back to $J > 0$ so that particles are then pumped against the concentrations imposed by the reservoirs. Finally, for very high rates the flux steadily tends to zero because, when the flashing is almost instantaneous, there is no effective pumping.

![Graph showing concentration ratio $ρ_1/ρ_0$ vs. characteristic frequency $f_0$ for different $σ$ values ($δ = 0.33$ and $v_0 = 10$).](image-url)
Energetic characterization. – The energetic aspects are relevant and abundant in the literature of motor modeling [15–17] and should definitely be addressed in their pump counterparts. A suitable definition of efficiency for pumps is not obvious. It is unclear how to interpret and quantify the payoff achieved from the pumping process as a whole. However, from a purely energetic point of view, meaningful quantities can still be defined consistently.

First, the input source of energy can be conveniently studied as follows. Working in the overdamped approximation, every time the potential is lifted (due to the ζ(t) modulation) energy is injected into the system. This energy is used to actively create the concentration profile and maintain it. When the pump flashes down to the open configuration, no energy is injected nor recovered. In such situation, the pumping energy input per unit of time is mathematically quantified as

$$\dot{E}_{\text{in}} = \int_0^L dxV(x)w_bP_b(x).$$

(19)

The mean power input that the dichotomic flashing inserts into the system is a controllable feature of the model by a judicious choice of its pameter values. An explicit expression for the above quantity (in dimensionless variables) can be obtained by splitting it into two parts, each corresponding to the piecewise linear potential:

$$\frac{\dot{E}_{\text{in}}}{v_0f_0} = \int_0^\delta dz \frac{[\rho_1(z) - \pi_1(z)]}{\delta/z} + \int_\delta^1 dz \frac{[\rho_2(z) - \pi_2(z)]}{(1-\delta)(1-z)}.$$  

(20)

By using the state probabilities (14) and (16) we are left with sums of exponentials, whose integrals are trivial. In fig. 6 we show the behavior of $\dot{E}_{\text{in}}$ at zero flux as the typical frequency $f_0$ is varied (solid line) for several values of $v_0$. The faster the flashing, the more energy per unit of time is inserted in the system. Similarly, when the barrier $v_0$ is increased, the power input rises very quickly.

Secondly, the power output produced by the machine can be quantified as the product $\dot{E}_{\text{chem}} = J\Delta \phi$, where $J$ is the particle current and $\Delta \phi = k_BT \text{ln}(\rho_1/\rho_0)$ is the chemical potential difference between both reservoirs. Note that at zero flux, the power output vanishes, namely, the pump is using energy but it is not performing work. This is equivalent to the stalling regime in motors, where the energetic efficiency is zero since there is consumption but no work performance.

On the whole, the benefit pursued by a pump is often not an energetic one. For instance, maintaining a concentration gradient at zero flux can indeed be very important for biological functions. The energetic input can still be used to constrain the biophysical tuning of the model, which we address as follows. In connection to real biomachines, one ought to require the input energy per cycle not to be greater than the energy released from the hydrolysis of one ATP molecule, which is approximately $20k_BT$. Given that the typical period of the pump cycle is $\tau_{\text{cycle}} = w_a^{-1} + w_b^{-1}$, the power released by the ATP is $\dot{E}_{\text{ATP}} = E_{\text{ATP}}/\tau_{\text{cycle}}$ which, in dimensionless units, yields

$$\dot{E}_{\text{ATP}} = f_0 \frac{20}{2+1/\sigma} \geq \dot{E}_{\text{in}}.$$  

(21)

In fig. 6 we plot the above expression (dashed line) as a function of the frequency $f_0$.

Biophysical scale. – So far we have solved the equations of the model and examined the behavior of the pump as a function of dimensionless parameters. Can all that be placed in a biophysical scale [18–21]? We use a tuning approach that combines constraints and
optimization criteria. Let us consider the length of the molecular pump of the order of $L \approx 5$ nm and an effective opening section of $S \approx 1$ nm$^2$. At biological conditions ($T = 310$ K) the thermal energy is $k_B T \approx 4.28 \times 10^{-21}$ J. Given an effective viscosity inside the membrane two orders of magnitude bigger than that of the water, the resulting diffusion constant of the medium yields $D = k_BT/\gamma \approx 10^{-12}$ m$^2$/s. This leads to a typical time scale associated with diffusion of the order $\tau = L^2/D \approx 10^{-5}$ s.

Then, when the optimal fluctuating rate $f_0$ found in our explorations is mapped to dimensional units, we find $v_0 \approx 10^6 \sim 10^7$ Hz, which is compatible with typical reported rates of functioning of the Na,K-ATP-ase pump under the effect of an oscillating electric field [22]. Guided by the energetic calculations developed previously, we impose that the energy spent per cycle is close but not higher than the one obtained from the ATP hydrolysis. See the black dot in fig. 6. This sets the possible space of parameters. For instance, a plausible potential barrier $V_0$ is expected to be of the order of a few tens of $k_BT$. Higher values can lead to greater concentration ratios but their energetics is not biologically meaningful. In this way, by recursively adjusting the parameter space where the pump functions optimally, bearing in mind biological constrains, the model is shown to be consistently translated into dimensional units of the order of those of a real molecular pumps.

**Final remarks and conclusions.** – The interplay between experimental observations and theoretical models substantially helped to understand the basic features of molecular motors. We believe that applying now the basic mechanisms of the ratchet effect to molecular pumps will contribute to understand the fundamental working principles of protein machines embedded in cell membranes.

Although the model presented here is a dramatic simplification of the great complexity and richness of a biological pump, it contains many interesting and new elements that capture its basic biophysical aspects. First, the explicit implementation of concentrations as boundary conditions at both ends of the membrane, leading to the characteristic quantity $\rho_1/\rho_0$. Second, the use of the simulation framework developed in [10], which is prone to be applied in models whose an analytical solution is not possible. Third, a simple coarse-grained connection between transition rates and ATP binding and hydrolysis processes. Fourth, the energetic characterization of the model and its connection to biophysical values. Finally, it is worth commenting on the straightforward extension of this approach for particles of charge $q$ in a membrane potential $\Phi$ by including an electrostatic force $F_q = q\Phi/L$ in the equations of motion. The pump then needs to supply extra energy, reducing the flux and the concentration ratio accordingly.

On the whole, we expect that the present work will be of use as a starting point to make progress, from a physical point of view, towards future investigations of active processes in membranes.

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