Focusing in Multiwell Potentials: Applications to Ion Channels

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We investigate out of equilibrium stationary distributions induced by a stochastic dichotomous noise on double and multi-well models for ion channels. Ion-channel dynamics is analyzed both through over-damped Langevin equations and master equations. As a consequence of the external stochastic noise, we prove a non trivial focusing effect, namely the probability distribution is concentrated only on one state of the multi-well model. We also show that this focusing effect , which occurs at physiological conditions, cannot be predicted by a simple master equation approach.

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I. INTRODUCTION

Interaction of physical, chemical or biological systems with fluctuating stimuli, both random and/or periodic, has in recent years received a lot of attention in a variety of contexts. It gives rise to new effects in nonlinear systems that cannot be observed under stationary perturbation. One of the most studied examples of such phenomena is the stochastic resonance [1–8]. It is an effect when a noise with suitable properties, either intrinsic or added to the system, improves the system response to weak time-dependent signals. The signal-to-noise ratio can paradoxically be boosted by increasing the level of noise present in the system. The SR was first suggested as an explanation for the cyclic ice ages observed in the earths climate [1] but has been since expanded as a plausible explanation of various effects in other areas. Of particular interest seems to be the application to explain the detection of very weak signals in noisy environments observed in biological systems, e.g. ion channels [3, 5, 6].

Another example is the dynamics of ratchets. The term refers to spatially asymmetric potentials which, interacting with Brownian fluctuations generate a directed drift in the system. The scale of the effect can be controlled by adjusting the properties of the noise. A similar ratchet-like effect has been observed in spatially symmetric potentials subject to temporally asymmetric noise (so-called correlation ratchets) [9].

An interesting example of such fluctuation-induced phenomena is called the resonant activation [10, 11]. It is an effect where the diffusion over a fluctuating potential barrier is correlated with the fluctuation rate and a resonant effect is observed. As noted in [10] if the barrier fluctuations are slow compared to the natural time scale of barrier crossing then the effect can be described using an adiabatic approximation. For very fast oscillations the barrier crossing rate would be that for the average barrier height. For intermediate barrier fluctuation rates a resonance-like enhancement of barrier crossing rate is observed. This has been applied e.g. to chemical reaction rates [12] and ion transport through channels [13].

A related effect, and the one we investigate in this paper is the nonequilibrium kinetic focusing first proposed in [14]. It is an effect where a particle moving in a ratchet-like potential subject to external dichotomous noise fluctuations gets trapped in one of the energy wells. This mechanism was applied to gating kinetics of voltage-gated ion channels, achieving a focusing of the channels into a particular conformational state corresponding to this energy well. First experimental study of this effect in Shaker K+ channels was reported in [15]. The phenomenon of particle trapping in correlation ratchet was also investigated in [9].

Ion channels are membrane proteins in biological cells that form gated channels for a controlled exchange of physiologically important ions, such as sodium or potassium, between the cytosol and the extracellular medium [16]. They play a very important role in various physiological processes (nerve impulses, muscle contraction etc.), and several human and animal disorders have been linked to malfunctioning ion channels. Therefore there have been numerous studies aimed at better understanding of channel gating kinetics and ultimately controlling it. Kinetic focusing of ion channels seems to be very promising for both of these goals.

Gating kinetics of voltage-gated ion channels is a reflection of conformational changes of the channel molecule. From a physico-chemical standpoint the gating process has been modeled as a particle (so-called gating particle) moving in a certain multi-well energy landscape (the energy of molecular conformational states). Mathematically, the most commonly used description is a discrete Markov chain, where different Markov states correspond to minima in the energy profile and the transition rates between the states reflect the height and width of the energy barrier. The time evolution of the system is described by the master equation. These types of models dominate the literature about ion channels and have been reasonably successful in explaining physiologically relevant channel effects (see e.g. [17]). However, they are

coarse approximations only, completely disregard intra-well motions of the gating particle, and work only if the energy barriers separating the wells are sufficiently high. More accurately the process can be described by the over-damped Langevin equation [1].

In this paper we study both approaches to simple models of ion channel gating. In Section II we introduce the model, in Section III we consider a two-state (two-well) model which may represent an ion channel with two stable conformational states only: one open (where the ions can go through the cell membrane) and one closed. In Section IV we analyze a more realistic model of gating kinetics for a *Shaker* potassium channel developed by Bezanilla et al. [17] based on patch-clamping experiments with ionic and gating currents. This model was also used in [14] to show the existence of the focusing effect.

II. THE MODEL

In the model we use, the potential minima are the possible states of the ion channel, while the barriers heights between two neighboring states are chosen so to reproduce the correct transition rates. It is is described by the overdamped Langevin equation

$$\gamma\dot{x}(t) = -u'(x) + \sqrt{2\gamma k_B T}\xi(t) \tag{1}$$

where $\xi(t)$ is a white noise with $\langle\xi(t)\rangle = 0$ and $\langle\xi(t)\xi(0)\rangle = \delta(t)$, $u(x)$ is the potential landscape, γ is the friction coefficient and T is the temperature of the bath.

We will consider the effect of a time dependent stochastic external potential on the out of equilibrium stationary distributions of our model. When an external voltage, $v_{ext}(t)$, is applied across the cell membrane, the particle behaves as if it had a charge valence, z, and the Langevin equation becomes (see [14]),

$$\gamma\dot{x}(t) = -u'(x) + zv_{ext}(t)/\lambda + \sqrt{2\gamma k_B T}\xi(t), \tag{2}$$

where the length scale, λ, is the cell membrane thickness. Using the rescaled variables

$$\begin{aligned} X &= \frac{zx}{\lambda}, \quad \tau = \frac{z^2 k_B T}{\gamma\lambda^2}t, \\ V_{ext}(t) &= \frac{v_{ext}(t)}{k_B T}, \quad U(x) = \frac{u(x)}{k_B T}, \end{aligned} \tag{3}$$

we finally get the Langevin equation in the dimensionless form

$$\dot{X}(\tau) = -U'(X) + V_{ext}(\tau) + \sqrt{2}\,\xi(\tau). \tag{4}$$

In this equation we see that the membrane potential, V_{ext}, changes the potential shape in a linear way:

$$U(X) \to U(X) - V_{ext}\,X. \tag{5}$$

The specific choice of the external stochastic potential is a a dichotomous noise :

$$V_{ext}(\tau) = V_0 + V_{DN}(\tau), \tag{6}$$

where V_0 is a constant term and $V_{DN}(\tau)$ represents a is time-dependent random and asymmetric switching between to fixed values of the potential, $V_{\pm}$,:

$$V_+ = \sqrt{\frac{D}{\tau_v}\left(\frac{1+\epsilon}{1-\epsilon}\right)}, \qquad V_- = -\sqrt{\frac{D}{\tau_v}\left(\frac{1-\epsilon}{1+\epsilon}\right)} \tag{7}$$

with transition probabilities, w_+ (from plus to minus state), and w_- (from minus to plus state),

$$w_+ = (1+\epsilon)/2\tau_v, \qquad w_- = (1-\epsilon)/2\tau_v. \tag{8}$$

It is easy to show that such DN has a null time average

$$\langle V_{DN}(\tau)\rangle = 0, \tag{9}$$

and correlation function

$$\langle V_{DN}(\tau)\,V_{DN}(0)\rangle = (D/\tau_v)\exp(-\tau/\tau_v),$$

so that it can be fully characterized by three dimensionless parameters: *correlation time* τ_v, *intensity* or *amplitude* D/τ_v and *asymmetry* ϵ (with $-1 < \epsilon < 1$).

III. FOCUSING IN A DOUBLE-WELL POTENTIAL

In this Section we consider a two state model for an ion channel, represeting open/close configurations. Even if it is too simple to adequately represent the function of real channels, It is commonly used as toy models, to demonstrate various phenomena [12, 18–21]. A two-state model can also be understood as a sub-model of a larger system, see Section IV.

The double well potential landscape here considered is:

$$u(x) = -\frac{1}{2}ax^2 + \frac{1}{4}bx^4, \tag{10}$$

which has two minima in $\pm x_m = \pm\sqrt{a/b}$, and a central barrier with height $\Delta u = a^2/(4b)$; see Fig. 1.

Due to thermal fluctuations, the particle is forced to jump between the two wells with a rate that for $\Delta u/k_B T \gg 1$, is given by the *Kramers formula* [1]:

$$w_K = \frac{\omega_0\omega_b}{2\pi\gamma}\exp\left(-\frac{\Delta u}{k_B T}\right), \tag{11}$$

where $\omega_0^2 = |u''(x_m)|$, $\omega_b^2 = |u''(x_b)|$ (evaluated at the top x_b of the central barrier).

In this Section we consider the effect of a DN perturbation with $V_0 = 0$, see Eq.(6). Depending on the state of the DN, there are two possible configurations for the

potential: a (−) configuration and a (+) configuration, as depicted in Fig. 1. For each configuration there are two different thermal transition rates: for example, in the (−) configuration $w^L(-)$ stands for the transitions from the left to the right well and $w^R(-)$ for the transitions from the right to the left well; and similarly in the (+) configuration.

In order to study the stationary probability distribution one has to solve the stochastic equation, Eq.(4). In our case the Langevin equation (4) has been solved numerically with an *order 1.5 strong Ito-Taylor scheme* (in explicit form), described by Platen and Wagner in [22]. Starting with different initial conditions (random distribution of initial position) and integrating in time the Langevin equation, it is possible to compute the probability $P_{L/R}(\tau)$ to be found at the time τ in each potential well. After a transient time, we verified that this probability reaches a stationary value, P_L^{eq}, dependent on the DN parameters.

Because of the DN, the potential switches between two configurations, so it is possible to define four thermal transition times in the system: $\tau^{L/R}(+/-)$, where, for example, $\tau^L(+)$ is the mean time after which a particle jumps from the left to the right well when the potential is in the (+) configuration (that is when $V_{DN} = V_+$). Note that in this Section we consider a regime in which both the DN amplitude and the thermal fluctuations are not too large, compared to the height of the potential barrier. Small thermal fluctuations w.r.t. the potential barrier correspond to physiological conditions at room temperature for ion channels, [14]. Moreover also moderate DN amplitude is a realistic regime since a large amplitude would destroy the ion-channels. Under these assumptions, the thermal transition times can be computed through the Kramers rates, $w^{R/L}(\pm)$ see Eq.(11), for the perturbed potential, so that we have:

$$\tau^{L/R}(\pm) = 1/w^{L/R}(\pm). \tag{12}$$

We should also take into account that there are two more characteristic times, given by the DN, namely,

$$\tau_v^{\pm} = \frac{1}{w_{\pm}} = \frac{2}{(1\pm\epsilon)}\tau_v, \tag{13}$$

where $w_\pm$ are given by Eq.(8). Note that $\tau_v^{\pm}$ are an estimate of the times spent in each configuration between two DN switchings.

The results of Langevin equation are shown in Fig. 2 at fixed DN intensity, D/τ_v, asymmetry, ϵ, and varying the DN correlation time, τ_v. Each data in the graph represents the left well equilibrium probability, P_L^{eq}. As one can see there is a minimum of P_L^{eq}, which means that the 90% of probability is concentrate in the right well, at some peculiar value of τ_v. This is the *nonequilibrium kinetic focusing*, which should not be confused with the trivial focusing which occurs at large τ_v, where $P_L^{eq} \sim 0.8$. Indeed this focusing for large τ_v can be understood based on equilibrium consideration. Indeed, when the DN transition times, $\tau_v^{\pm}$, are much larger than the thermal transition times, $\tau^{L,R}$, we can assume that the system reaches

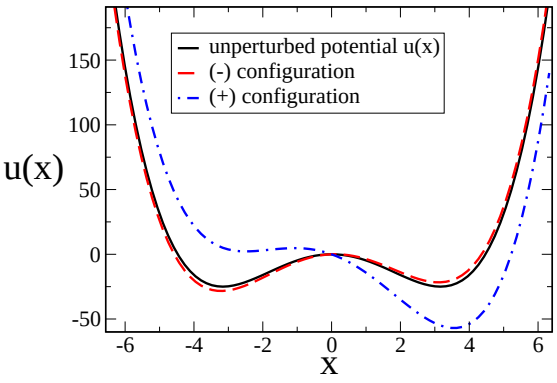

FIG. 1. (Color online) The unperturbed double-well potential $u(x)$ of Eq. (10) and the two configurations of the potential when it is modified by the dichotomous noise, as indicated in the legend. Potential parameters are $a = 10$ and $b = 1$, while the DN shown refers to: $D/\tau_v = 0.71$, $k_BT = 0.15\Delta u$, $\epsilon = 0.8$.

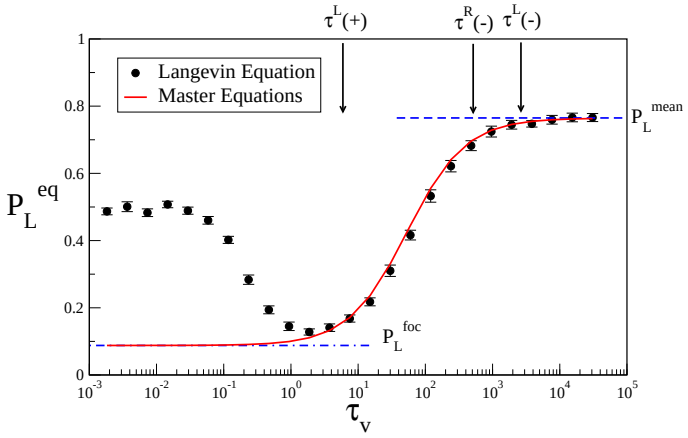

FIG. 2. (Color online) Equilibrium probability in the left well versus the DN correlation time τ_v. Full (black) circles have been obtained from the Langevin equation, while full (red) line has been obtained from a master equation approach. Thermal transition times $\tau^{L,R}(\pm)$ are shown as arrows (except from $\tau^R(+)$, which is found to be of order 10^6 and is out of scale). The horizontal upper dashed line represents the limit P_L^{mean}, computed with Eq. (14), while the dot-dashed horizontal lower line isP_L^{foc}, see Eq.(27). Here we have $\epsilon = 0.8$, $k_BT = 0.15\Delta u$, $D/\tau_v = 0.71$, as in Fig. 1.

separately the thermal equilibrium in each potential configuration.

Therefore if $P_{L/R}(\pm)$ are the thermal Gibbs probabilities for each well in the $(+)$ and $(-)$ configuration, then it is reasonable to assume that, for $\tau_v^{\pm} \to \infty$, the probability P_L^{eq} approaches the mean value

$$P_L^{eq} \to \frac{\tau_v^+}{(\tau_v^+ + \tau_v^-)} P_L(+) + \frac{\tau_v^-}{(\tau_v^+ + \tau_v^-)} P_L(-) \equiv P_L^{mean}. \tag{14}$$

P_L^{mean} is shown as the dashed horizontal line in Fig. 2 and agrees very well with numerical data.

On the other side, in the limit of fast switching of the DN ($\tau_v \to 0$), the probability distribution becomes symmetric:

$$P_L^{eq}, P_R^{eq} \to 1/2, \tag{15}$$

which is the value obtained with our numerical simulations of the Langevin equation, see Fig. 2. The limit $\tau_v \to 0$ can be understood using the Langevin equation, by assuming, for simplicity, a periodic, rather than a stochastic switching, between the two potential configurations. Indeed, after the first step, assuming we are in the $(+)$ configuration, we can write, see Eq.(4):

$$(\Delta X)^+ = [-U'(X) + V_+ + \sqrt{2}\,\xi]\tau_v^+, \tag{16}$$

and after the second step

$$(\Delta X)^- = [-U'(X) + V_- + \sqrt{2}\,\xi]\tau_v^-, \tag{17}$$

neglecting the terms proportional to $\tau_v^+\tau_v^-$. The total variation after a time $\tau_v^+ + \tau_v^-$ is then:

$$\begin{aligned} \Delta X &= (\Delta X)^+ + (\Delta X)^- \\ &= [-U'(x) + \sqrt{2}\,\xi](\tau_v^+ + \tau_v^-) + (v_+\tau_v^+ + v_-\tau_v^-). \end{aligned} \tag{18}$$

and, dividing by $\tau_v^+ + \tau_v^-$, we get the Langevin equation for a fast oscillating potential:

$$\dot{X} = -U'(X) + \sqrt{2}\,\xi + \frac{V^+\tau_v^+ + V^-\tau_v^-}{\tau_v^+ + \tau_v^-}. \tag{19}$$

The last term corresponds to the time average of the DN, which is zero (see Eq. (9)): this proves that for fast oscillations of the perturbing potential the Langevin equation does not feel the perturbation, namely it behaves symmetrically, as anticipated.

In the intermediate regime we have a non trivial result: from Fig. 2, it is clear that the left well probability P_L^{eq} has a minimum (i.e. there is a "focusing" in the right well) for a particular choice of the DN correlation time τ_v. The focusing effect is an interesting result, since the applied DN has zero mean (Eq.(9), and nevertheless it can induce stationary distributions which focus the system in one well.

In order to understand what are the conditions for the focusing, we can attempt a simple explanation through a master equation approach:

$$\dot{\mathbf{P}} = W(\tau)\,\mathbf{P}, \tag{20}$$

where $\mathbf{P}(\tau) = (P_L(\tau), P_R(\tau))$ and the time dependent transition matrix $W(\tau)$, which switches between the two configurations :

$$W(\pm) = \begin{pmatrix} -w^L(\pm) & w^R(\pm) \\ w^L(\pm) & -w^R(\pm) \end{pmatrix} \tag{21}$$

with the same rates as in Eq. (8). In Fig. 2 we compare the results obtained through the Langevin equation with those obtained via the master equation, Eq.(20). As one can see, there is a good agreement between the two approaches when the DN correlation time τ_v is larger than the value at which the best focusing occurs, while, when $\tau_v \to 0$ the master equation gives a complete different result.

This is a limitation of the master equation formalism, for which we can give an explanation by assuming, as was done above for the Langevin equation, a periodic switching. At the initial time the matrix is in the $W(+)$ configuration, and after a time τ_v^+ it changes into the $W(-)$ configuration, where it stays for a time τ_v^-; and so on. Thus assuming that τ_v^+ and τ_v^- are both infinitesimal, after the first step we can write:

$$(\Delta\mathbf{P})^+ = W(+)\,\tau_v^+\,\mathbf{P}(0), \tag{22}$$

where $(\Delta\mathbf{P})^+ = \mathbf{P}(\tau_v^+) - \mathbf{P}(0)$. Similarly, after the second step we have:

$$(\Delta\mathbf{P})^- = W(-)\,\tau_v^-\,\mathbf{P}(\tau_v^+) = W(-)\,\tau_v^-\,\mathbf{P}(0), \tag{23}$$

where the last term holds neglecting the terms proportional to $\tau_v^+\tau_v^-$. The total variation after a time $\tau_v^+ + \tau_v^-$ is:

$$\begin{aligned} \Delta\mathbf{P} &= (\Delta\mathbf{P})^+ + (\Delta\mathbf{P})^- \\ &= [W(+)\tau_v^+ + W(-)\tau_v^-]\,\mathbf{P}(0), \end{aligned} \tag{24}$$

and, dividing both sides by $\tau_v^+ + \tau_v^-$, we get a system of differential equations with an *averaged* transition matrix:

$$\langle W\rangle = \frac{W(+)\tau_v^+ + W(-)\tau_v^-}{\tau_v^+ + \tau_v^-}. \tag{25}$$

This averaged matrix is different from the unperturbed transition matrix, that we would expect for $\tau_v \to 0$, and determines the following equation for the probabilities:

$$\begin{aligned} \dot{P}_L &= \langle W\rangle_{11}\,P_L + \langle W\rangle_{12}\,P_R \\ &= (\langle W\rangle_{11} - \langle W\rangle_{12})P_L + \langle W\rangle_{12}. \end{aligned} \tag{26}$$

and the stationary solutions $\dot{P}_L^{eq} = 0$, is given by:

$$P_L^{eq} = \frac{\langle W\rangle_{12}}{\langle W\rangle_{12} - \langle W\rangle_{11}} \equiv P_L^{foc}. \tag{27}$$

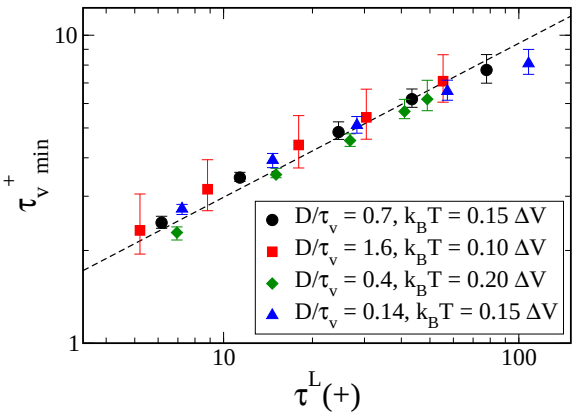

FIG. 3. (Color online) Correlation time $\tau^+_{v\ min}$, for which we observe focusing, *vs* the transition time $\tau^L(+)$. Each data set refers to simulations with different ϵ but same intensity D/τ_v and temperature T as indicated in the legend. The dashed line indicates a square root dependence. Error bars describe the variation of $\tau^+_{v\ min}$ for which P_L^{eq} changes by 0.1% from its minimum value.

Therefore this average transition matrix in general does not have a symmetric solution. In Fig. 2 the value of P_L^{foc} is shown to agree with the master equation solution in the limit $\tau_v \to 0$, and, interestingly, it is close to the focusing value of P_L^{eq} at the minimum. This coincidence will be used below to determine the dependence of the focusing intensity on the parameters of the model.

An intuitive explanation of the failure of the master equation approach for $\tau_v \to 0$, is that the system does not have time to equilibrate in each well before the switching and thus the two-state model becomes inappropriate.

The fact that a master equation approach cannot explain the focusing effect which occurs for fast switching of the DN, shows that the focusing is highly non trivial, being a truly non-equilibrium effect. For a better understand this focusing we need to consider the interplay of several time scales. Physically, we can expect focusing when τ_v^+ (mean time for which the potential is in (+) configuration) is of the same order than $\tau^L(+)$ (i.e. the time the particles need to jump towards the right well in the (+) configuration) and, at the same time, τ_v^- should be much smaller than the time $\tau^R(-)$ the particles need to jump towards the left well. Roughly speaking we can thus write the *focusing conditions* at the right well as,

$$\begin{cases} \tau_v^+ \approx \tau^L(+) \ll \tau^R(+) \\ \tau_v^- \ll \tau^R(-) \ll \tau^L(-). \end{cases} \tag{28}$$

We now study how the switching time, $\tau^+_{v\ min}$, at which a minimum of P_L^{eq} is found, depends on the thermal transition time, $\tau^L(+)$ for different asymmetry ϵ, the intensity D/τ_v and the temperature T. Data are shown in Fig. 3. Each value of $\tau^+_{v\ min}$ has been computed from a graph like Fig. 2, by making a quadratic fit of the function $P_L^{eq}(\log(\tau_v))$ around its minimum. In the same figure each curve at fixed D/τ_v and k_BT, has been obtained varying the asymmetry parameter ϵ. We have the remarkable result that $\tau^+_{v\ min}$ depends on the amplitude of noise and temperature only through $\tau^L(+)$. Interestingly, the relationship between $\tau^+_{v\ min}$ and $\tau^L(+)$ is more complicated than what is suggested in Eq.(28). Indeed in Fig. 3 the dashed line indicates a square root dependence, so that we have:

$$\tau^+_{v\ min} \propto \sqrt{\tau^L(+)} \tag{29}$$

We have no theoretical arguments suggesting the scaling law above, and more investigation is required.

Up to now, we have only studied the probability distribution induced by the DN as a function of τ_v. Now we intend to analyze the dependence of the focusing on the other parameters, such as ϵ and k_BT. In Fig. 4 (upper panel) we show the left well probability at the focusing, P_L^{eq} *vs* the DN asymmetry parameter, ϵ. We observed that the focusing decreases as the asymmetry decreases ($\epsilon \to 0$). This can be explained by notecing that the distance between the two thermal transition times $\tau^L(+)$ and $\tau^R(-)$ decreases as the asymmetry decreases, therefore the second focusing condition in Eq.(28) is not met. In Fig. 4 (lower panel) we show the left well probability at the focusing, P_L^{eq} *vs* the temperature. Obviously the temperature destroys the focusing effect.

From Fig. 2 we noticed that the master equations fail to fit the data when τ_v is smaller than the value at which a minimum is found. After that point, the equilibrium probability computed with the master equations reaches the limiting value, P_L^{for}, given in Eq.(27), which is close to P_L^{eq}, evaluated at the focusing. Thus we can use Eq.(27) to analytically estimate the value of the focusing as a function of the parameters. The result is shown in both panels of Fig. 4 as dashed curves, which are in good agreement with our numerical results, as long as the asymmetry, ϵ, and the temperature, k_BT, are not too large. Indeed in these cases the Kramers formula (11) is no longer applicable since the energy barriers are not well defined.

The results of our investigations on a double well potential can be summarized as follows:

- a stochastic perturbing potential with zero time average can induce an unbalanced stationary probability distribution between the two wells.
- conditions for the right-well focusing are: $\tau_v^+ \simeq \tau^L(+)$ and $\tau_v^- \ll \tau^R(-)$, see Eq.(28). Similarly for the left-well focusing.
- At fixed DN intensity the focusing can be improved by increasing the asymmetry ϵ or decreasing the

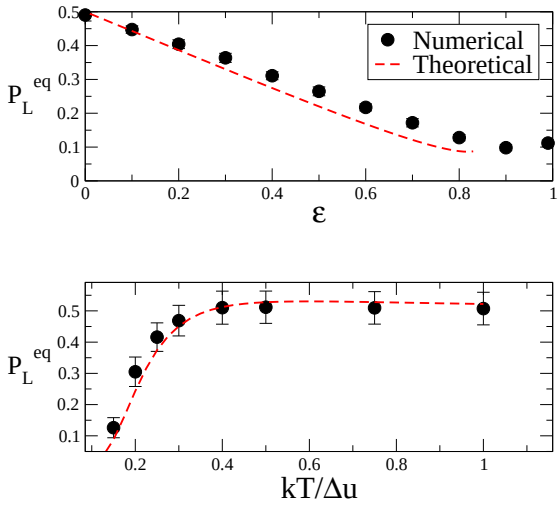

FIG. 4. (Color online) Upper panel: P_L^{eq} at focusing (black dots) is plotted *vs* ϵ for $D/\tau_v = 0.71$, $k_BT = 0.15\Delta u$. Lower panel: P_L^{eq} at focusing (black dots) is plotted *vs* $k_BT/\Delta u$ for $D/\tau_v = 10(k_BT)^2$, $\epsilon = 0.8$. In both panels the dashed lines represent the theoretical predictions obtained from the master equation, see text.

temperature. Analytical estimation of the focusing intensity is given in Eq.(27).

- The master equation approach completely fails for fast DN perturbations (small τ_v) and is unable to describe the *nonequilibrium kinetic focusing*.

IV. EIGHT-WELL POTENTIAL: A MORE REALISTIC MODEL FOR ION CHANNEL GATING

In the previous Section we showed that it is possible to modify the *stationary* probability distribution in a double-well potential, and particularly to increase the probability to find the system in one well, by introducing a stochastic perturbation. Although a potential with only two states can be a useful starting point, a multiwell potential is a more realistic model for ion channels. As an example, we consider, as in [14], the Shaker K^+ channel, for which there exists a simple kinetic model, proposed by Bezanilla, Perozo and Stefani (BPS) [17]: in this model, there are eight states, or conformations, and the system can jump between them. All the states from 1 to 7 correspond to closed conformations, and the state 8 is the only one for which the ion channel is open (which means that the ions can go through the channel). The allowed transition rates for the Shaker K^+ ion channel are known from experimental measurements. Since transitions occur only between nearest neighboring states, this can be represented by an eight-well potential landscape $u(x)$, as depicted in Fig. 5. The eight potential minima are the possible states of the channel, and the barriers heights are chosen so to reproduce the correct exponential transition rates.

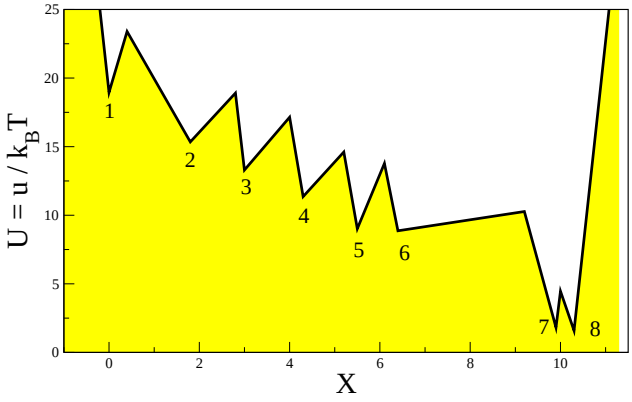

FIG. 5. The potential u used by Millonas and Chialvo in [14] as a model of the Shaker K^+ channel. For the definition of the rescaled potential $U(X)$, see Eq. (3). In this Figure we assumed $T = 300K$.

In the following we present some preliminary discussion on the effect of stochastic noise on a multiwell potential landscape, leaving a deeper analysis for future work.

The problem of focusing in this eight-well model has been already considered by Millonas and Chialvo [14]. Based on a probabilistic treatment of the Langevin equation (4), Millonas and Chialvo claimed that, for very low temperature and large amplitude of the DN, it is possible to induce *stationary* probability distributions located in a chosen potential well: they called this effect *nonequilibrium kinetic focusing*. These two conditions (low temperature and large DN) are not physiological, since the ion channel would be destroyed under these conditions. For this reason, we will first investigate whether a *nonequilibrium kinetic focusing* can occur in an eight-well potential in physiological conditions (room temperature and moderate DN amplitude) as it was considered in the double well case in the previous Section. We will also compare the analytical predictions of Ref. [14] for low temperature and large DN intensity with our numerical simulations.

A. Room temperature and low DN intensity

Our starting point is the Langevin equation (4), and the analysis of the results will concern the equilibrium probabilities P_i^{eq} in each well, defined as in the previous Sections.

In Fig. 6 we report our simulations concerning the equilibrium probability distribution P_i^{eq} as a function of τ_v for each well, at fixed asymmetry ϵ, intensity D/τ_v and mean external potential V_0. Here we can see that some kind of focusing occurs only close to the potential edges (states $1, 2$ or $7, 8$), while the equilibrium probabilities of the central wells are almost independent of τ_v.

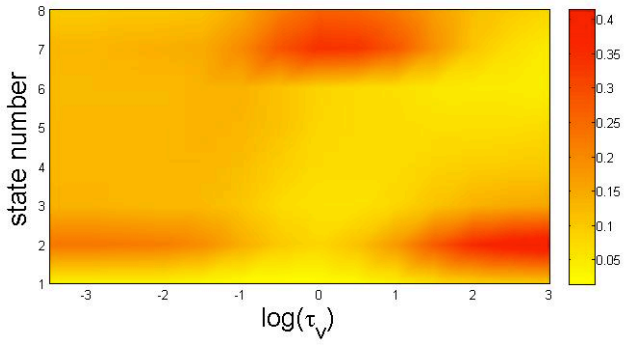

FIG. 6. (Color online) Density plot of the equilibrium probabilities P_i^{eq} in the i-th well versus the DN correlation time τ_v. Darker color intensities stand for higher probabilities. Data are: $D/\tau_v = 1$, $\epsilon = 0.8$, $V_0 = \langle V_{ext} \rangle = (-45 \text{ mV})/k_B T$, and $T = 300$ K.

From the same figure it is also possible to recover the usual observations made in the double-well case about the limits of very small and very large τ_v. We checked that when $\tau_v \to 0$, the DN averages to zero, so that the probability distribution the thermal Gibbs distribution for $V_{ext} = V_0$. On the other hand, for $\tau_v \gg 1$ the probabilities can be evaluated, as in Eq.(14), by

$$P_i^{mean} = \frac{\tau_v^+}{(\tau_v^+ + \tau_v^-)} P_i(+) + \frac{\tau_v^-}{(\tau_v^+ + \tau_v^-)} P_i(-), \qquad (30)$$

where the probabilities $P_i(\pm)$ are the thermal Gibbs probabilities for each well in the $(+)$ and $(-)$ configuration.

The non trivial focusing in the intermediate τ_v regime, resembles the one found in the double well case. Indeed the conditions given in Eq.(28) seem to work also in the multi-well case if we consider the edge wells $1, 2$ as a left well; the edge wells $7, 8$ as the right well and the central wells as an effective barrier between them. Nevertheless a more detailed analysis is necessary to understand how to relate the focusing in the double well with that in the multi-well case.

We also considered many other situations, with different values of the DN asymmetry parameter ϵ and of the DN intensity D/τ_v: in all cases, we could only observe some probability increase in the wells on the edges, while, to the best of our effort, we were not able to obtain focusing in the central wells. Such a result would be desirable since it would allow a complete control of the ion channel dynamics under a stochastic perturbations.

B. Low temperature and large DN intensity

An analytical solution (Eq.(7) in Ref. [14]) for the stationary probability distribution induced by a DN, were derived under the following assumptions:

- the amplitude of the driving, must be larger than the thermal fluctuations,
- and larger than the maximal potential jump, $\sqrt{D/\tau_v} > \sup |U'|$;
- the temperature should be very small (that is $T \to 0$).

In the above Section, we did not take these conditions into account, because we considered them not physiologically feasible, nevertheless in this Section we take this regime into consideration in order to understand the range of validity of the analytical prediction given in Ref. [14]).

In Fig. 7 we compare our numerical results (hystogram) with the theoretical results (dots) given in Ref. [14] for different temperatures while fixing all the other parameters. As we can see, while at low temperature (panel a) and b)) there is a good agreement, on increasing the temperature (panel c) and d)) the theoretical distribution starts to fail even for temperature well below room temperature ($T = 40$ K). Interestingly we notice a good focusing in the central wells: in panel (c) Langevin equation gives approximately 90 % of probability in the wells 5 and 6), even when the theoretical equation of Ref. [14] does not work. The presence of some focusing in this case seems to indicate that the conditions given in Ref. [14], could be too restrictive in order to have focusing.

V. CONCLUSIONS

In this work we considered two different kinetic models of ion channels subjected to dichotomous noise perturbation, with zero time average. The first is a simple model consisting of two wells separated by an energy barrier, while the second is the physiologically relevant eight-well model proposed by Bezanilla et al. [17]. In both cases an highly non trivial non equilibrium focusing has been found under physiological conditions (room temperature and moderate external perturbation intensity), which cannot be described by a master equation approach, but the analysis of the full Langevin equation turns out to be necessary. Conditions for the focusing and dependence on the external perturbation parameters have been given for the double well case. In the eight-well case more analysis is needed in order to address this question.

We also analyzed the results of Millonas and Chialvo in [14], showing that the *nonequilibrium kinetic focusing* does not survive in physiological conditions.

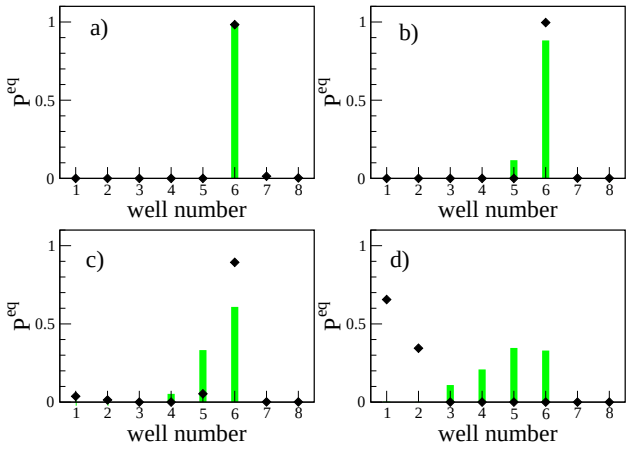

FIG. 7. (Color online) Probability distributions at different temperature computed with the Langevin equation (green bars) and theoretically (black diamonds) with Eq.(7) in Ref. [14]. The parameters are: $D/\tau_v = 10^5$, $\epsilon = 0.6$, $\tau_v = 10^{-4}$, $v_0 = -142$ mV$/k_BT$. Temperature is : $T = 20K$ (a), $T = 25K$ (b), $T = 30K$ (c), $T = 40K$ (d).

In perspective our analysis leaves still open the question of whether it is possible to focus an ion channel in any well, thus completely controlling its dynamics, under physiological conditions. Nevertheless we have shown both that focusing is possible in physiological conditions and also we gave a preliminar evidence that focusing in the central wells of a multi-well potential is also possible.

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