# Motion Reversal of Molecular Motor Assemblies due to Weak Noise

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Bidirectional motion is an example of collective behavior of molecular motors. It occurs at finite noise level in a nonequilibrium system. We consider this problem as a first exit problem. We identify the noise strength by doing an expansion of a master equation and apply the Wentzell-Freidlin theory to define an effective nonequilibrium potential and provide analytical estimates of the reversal time. Our results match very well with the results of stochastic simulations.

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Molecular motors are proteins that convert chemical energy into mechanical work [1]. In many biological situations, molecular motors acting on cytoskeletal filaments are connected together by rigid elements, and the state of one motor depends on the state of all the others. Motor assemblies display complex collective dynamical properties which are not observed at the single motor level such as hysteresis [2,3] and spontaneous oscillations [4–6].

In an assembly with a finite number of motors, noise leads to a collective effect called bidirectional motion [7] when the assembly shows successive phases of motion in opposite directions. This typically occurs in nonpolar systems with a spatial ‘‘left-right’’ symmetry, for example, when an external force opposes the motion of the motors, or when two groups of motors with opposite polarities act on the same filament in a ‘‘tug-of-war’’ geometry. In this last case, the state of vanishing velocity is a steady state, which is not necessarily stable: a spontaneous symmetry breaking can lead to two possible stable velocities with opposite signs and the finite noise induces transitions between the two states, leading to bidirectional motion. In some circumstances, bidirectional motion requires the presence of proteins playing the role of a coordination complex [8], possibly inactivating one group of motors while the other one is active [9]. However, it is also observed in minimal *in vitro* experiments [3,10], where it can only result from the collective behavior of the motors.

Bidirectional motion gives an example of the importance of noise in nonequilibrium systems. It has been studied numerically by solving a master equation [11] or by using stochastic simulations [7,12]. In the limit of a large number $N$ of motors, the mean reversal time increases as $t_{\mathrm{rev}} \sim e^N$. This Arrhenius-like behavior can be understood by comparing the motor assembly to a particle diffusing in a bistable potential. The particle escapes a metastable state within a time proportional to a Boltzmann factor, the noise intensity being proportional to temperature. For the motor assembly, the noise intensity is inversely proportional to the number of motors, leading to an exponential variation in $N$ of the reversal time.

In this Letter, we study bidirectional motion analytically. We identify the noise strength and define an effective potential to calculate the reversal time. As a first step, we describe the motor assembly by the rigid two-state model of Ref. [2]. Other theories of molecular motor assemblies such as the cross-bridge model [5] or our soft motor model [13] also show dynamic instabilities and could possibly be studied by the same approach. In this Letter, we give only the main steps of the calculations and refer to Ref. [14] for details.

In the rigid two-state model, the motors are represented as particles rigidly attached to a common rigid backbone. Each particle can be in two states, in which it interacts with the filament. We consider here that one of the states is a ‘‘weakly bound’’ state, where there is no interaction with the filament. In the other state, the interaction potential $W(x)$ is a periodic function of the coordinate $x$ along the filament with a period $\ell$ of the order of a monomer size, reflecting the filament periodicity. A motor switches between the two states with transition rates $\omega_{\mathrm{on}}(x)$ and $\omega_{\mathrm{off}}(x)$, which are also periodic in $x$. A key hypothesis is that the motor assembly is a nonequilibrium system: detailed balance is not satisfied ($\omega_{\mathrm{off}}/\omega_{\mathrm{on}} \neq e^{W/k_BT}$).

In an experiment, the motors are either regularly spaced with a period incommensurate to the filament period (as in muscles) or uniformly distributed (as in a motility assay). The random position of the motors introduces then a quenched disorder. We simplify this situation by assuming that the motors are positioned on $m$ sites $i = 1, \ldots, m$ whose coordinates along the backbone are $z_i = i\Delta$, where $\Delta = \ell/m$ is the distance between two sites. All the motors at a given site are not physically at the same place, since all positions on the filament separated by an integer number of periods are equivalent.

Earlier studies show that thermal noise has little influence on the reversal time [7]. Here, we neglect thermal

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noise and focus on the stochasticity associated with binding and unbinding events. Under this assumption the filament position $X$ evolves in a deterministic way between two transition events. Let us assume that, at each site $i$, there are $n_i$ attached motors, whose positions in the reference frame of the filament are $z_i - X$. Then, in the absence of any external force, the force balance equation reads $N\lambda v = \sum_{i=1}^{m} W'(z_i - X)n_i$, where $\lambda$ represents the friction per motor and $v = \dot{X}$ is the velocity of the filament. We introduce the joined probability $P(\{n_i\}, X, t)$ to find the filament at position $X$ with $n_i$ attached motors at site $i$ at time $t$. By using an expansion method exposed by Van Kampen [15], the master equation that describes the evolution of $P$ can be simplified and transformed into a Fokker-Planck equation in the limit where the number of motors at each site $N/m$ is large. We take the continuum limit $\Delta \rightarrow 0$, and define the motor density in the reference frame of the filament $\rho(x) = n_i/(N\Delta)$, with $n_i$ the number of motors at the site located at $z_i = x + X$. The filament velocity is then $v[\rho] = \int_0^\ell dx W'(x)\rho(x)/\lambda$, it is a functional of $\rho$ but it does not depend on $X$; this allows us to integrate over $X$ and to obtain a Fokker-Planck equation for the probability $P([\rho(x)], t)$ to find the motor assembly with a density $\rho(x)$ at time $t$:

$$\frac{\partial P}{\partial t} = \int dx \frac{\delta}{\delta\rho(x)} AP + \int dx \int dy \frac{\delta^2}{\delta\rho(x)\delta\rho(y)} \frac{BP}{2N}, \tag{1}$$

where the functions $A$ and $B$ are defined by

$$A = \omega_{\mathrm{off}}(x)\rho(x) - \omega_{\mathrm{on}}(x)\left(\frac{1}{\ell} - \rho(x)\right) + v[\rho]\frac{d\rho}{dx}, \tag{2}$$

$$B = \delta(x-y)\{\omega_{\mathrm{off}}(x)\rho(x) + \omega_{\mathrm{on}}(x)[1/\ell - \rho(x)]\}. \tag{3}$$

In the limit of large $N$, the noise is weak and the deterministic evolution of the average density is given by $\dot{\rho} = -A$.

The functional Fokker-Planck equation (1) is difficult to study in the general case. We choose to investigate the model for a particular choice of parameters, where the potential is sinusoidal: $W(x) = U[1 - \cos(2\pi x/\ell)]$ and the transition rates are $\omega_{\mathrm{on}}(x) = \omega[\eta - \alpha\cos(2\pi x/\ell)]$ and $\omega_{\mathrm{off}}(x) = \omega[1 - \eta + \alpha\cos(2\pi x/\ell)]$. With this choice, the sum of the two rates does not depend on $x$. The variable $\eta$ is the mean fraction of bound motors, sometimes called the duty ratio, whereas $\alpha$ represents the amplitude of variation of the transition rates. These hypotheses can be seen as an approximation of $\omega_{\mathrm{on}}$ and $\omega_{\mathrm{off}}$ by their first Fourier mode, which is valid only if they are weakly varying in space. For this reason, we assume in the following that $\alpha \ll 1$. Our choice of transition rates respects the left-right symmetry and is therefore suitable to describe a tug-of-war situation or "symmetric motors." We choose $\alpha > 0$: the motors detach more at the bottom of the potential than at the top, thus breaking detailed balance. At constant small filament velocity, the mean motor force amounts to a negative friction $N\xi_a v$ [2]. We introduce the dimensionless activity parameter $\gamma = \xi_a/\lambda = 2\pi^2 U\alpha/(\ell^2\omega\lambda)$. The force-velocity relation is nonmonotonic only above the critical value $\gamma = 1$, at which there is a dynamical phase transition. Bidirectional motion can therefore occur only if $\gamma > 1$. Finally, we use dimensionless variables by setting $\ell = \omega = \lambda = 1$.

We now describe the state of the motor assembly by the Fourier coefficients of the density defined by $\rho(x)/\alpha = \sum_n a_n \cos(2\pi nx) + b_n \sin(2\pi nx)$. In the absence of noise, the evolution of the coefficients $a_n, b_n$ is found from the equation $\dot{\rho} = -A$ [Eq. (2)]. We find that $a_0 \rightarrow \eta/\alpha$ and that, for $n \geq 2$, $a_n$ and $b_n$ relax to 0 at least as fast as $\omega^{-1}$. These modes fluctuate around their equilibrium position by a distance $N^{-1/2}$. After integration over the modes $n = 0$ and $n \geq 2$, we find a Fokker-Planck equation, which describes the evolution of the quantities $a_1 = a$ and $b_1 = b$ that we consider as the components of a vector $\vec{y}$:

$$\partial_t P = -\vec{\nabla} \cdot (\vec{u}P) + [D/(2N)]\nabla^2 P, \tag{4}$$

where the velocity field $\vec{u}$ has components $u_a = -(a + 1 - \gamma b^2)$ and $u_b = -(b + \gamma ab)$. At lowest order in $\alpha \rightarrow 0$, the diffusion constant is $D = 4\eta(1-\eta)/\alpha^2$. This clearly shows that the noise is proportional to the variance of a two-state variable $\eta(1-\eta)$ and that it is reduced when the amplitude of variation of the transition rates $\alpha$ is increased. The filament velocity is proportional to $b$, $v = \gamma b/(2\pi)$, whereas $a$ characterizes the internal state of the motor assembly. The trajectories in the absence of noise are given by the solutions of the dynamical system $\dot{\vec{y}} = \vec{u}$, and are displayed in Fig. 1 for $\gamma = 2.3$. There are two stable fixed points $F_+$ and $F_-$, with attraction basins separated by the separatrix $b = 0$. The separatrix contains a hyperbolic unstable point $H$. The two stable fixed points correspond to the states of positive and negative velocities of the filament. At weak but finite noise level, the system does not remain indefinitely close to one of the stable fixed points: large excursions due to fluctuations eventually bring it close to the separatrix. Once the separatrix is crossed, it falls to the other stable point,

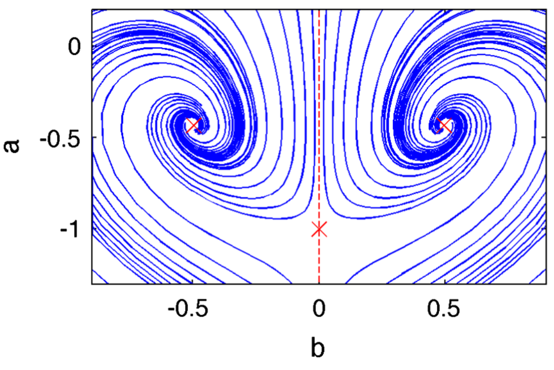

FIG. 1 (color online). Blue continuous lines: Trajectories in the absence of noise (solutions of the dynamical system $\dot{a} = u_a$, $\dot{b} = u_b$) for $\gamma = 2.3$. The red crosses indicate the position of the fixed points. The red dotted line represents the separatrix.

corresponding to a reversal event of the filament velocity. The mean reversal time is therefore the mean first passage time from one stable point to the separatrix.

An important remark is that the vorticity of the velocity field $\vec{u}$ does not vanish ($\vec{\nabla}\times\vec{u}\neq\vec{0}$), so that there is no potential $V$ such that $\vec{u}=-\vec{\nabla}V$. This is expected since molecular motor assemblies are far from equilibrium systems. It is therefore not possible to estimate the reversal time from Kramer's rate theory. However, an effective nonequilibrium potential can be defined from the Wentzell-Freidlin theory [16], which can be used to estimate the reversal time [17]. We now briefly present this method.

In order to define a quasipotential, we assume that the stationary probability distribution $P_S$ of the Fokker-Planck equation (4) can be approximated by $P_S = K\exp(-NS/D)$. Inserting this WKB ansatz into Eq. (4) and expanding at lowest order in $1/N$ gives an equation of the form $\mathcal{H}(\vec{y},\vec{\nabla}S)=0$, which can be interpreted as a Hamilton-Jacobi equation, with $S$ the classical action and $\mathcal{H}$ the "Wentzell-Freidlin" Hamiltonian $\mathcal{H}(\vec{y},\vec{p})=\vec{u}\cdot\vec{p}+\vec{p}^2/2$ [16]. The momentum $\vec{p}$ is related to the action by $\vec{p}=\vec{\nabla}S$. The dynamical system formed by Hamilton's equations ($\dot{\vec{y}}=\vec{\nabla}_{\vec{p}}\mathcal{H}$, $\dot{\vec{p}}=-\vec{\nabla}_{\vec{y}}\mathcal{H}$) defines trajectories that minimize the action and therefore maximize the probability $P_S$: these trajectories are the *most likely paths*. Among them, one finds the flow lines or anti-instantons, that follow the flow, and the instantons which are the most likely escape trajectories and go against the flow. A particle observed at a point $M$ far from the stable state is highly likely to have come from the stable point by following the most likely trajectory that reaches $M$ [18]. The action $S$ can be calculated along each instanton and is a measure of the difficulty to reach a point by using fluctuations. The most likely paths emanating from the fixed point $F_+$ are shown in Fig. 2. The action is minimal on the separatrix at the hyperbolic point $H$: the most likely escape path is therefore the instanton joining the fixed point $F_+$ and the hyperbolic point $H$. These trajectories are analogous to the classical trajectories obtained from the WKB approximation of the Schrödinger equation in quantum mechanics.

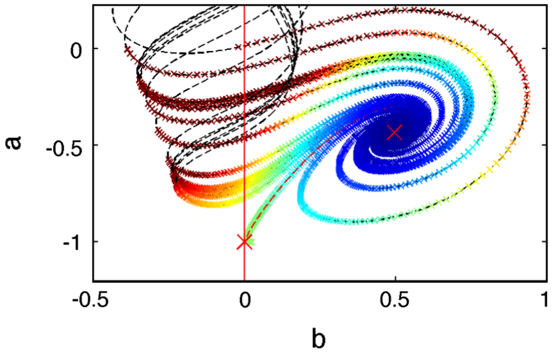

FIG. 2 (color online). Most likely paths emanating from the stable fixed point $F_+$ for $\gamma = 2.3$. The effective potential $S$ is represented by a color code.

The definition of the effective potential $S$ can be used to calculate the mean escape time in the weak noise limit. The mean first escape time is evaluated as twice the inverse of the smallest eigenvalue $\lambda_1$ of the Fokker-Planck equation (4) with an absorbing boundary condition at the separatrix $[P(a, b=0, t)=0]$ [17]. The eigenfunction associated with $\lambda_1$ is evaluated by using the WKB approximation, except near the separatrix where one has to do asymptotic expansions to take into account the absorbing boundary condition. A key parameter is the ratio $\mu = |\partial_a u_a/\partial_b u_b|_H = (\gamma-1)^{-1}$ of the stable and unstable eigenvalues of the velocity field at the hyperbolic point $H$. If $\mu > 1$, the escape path is perpendicular to the separatrix, the effective potential $S$ is quadratic in the vicinity of $H$, and the reversal time follows an Eyring formula [17]:

$$2t_{\rm rev}^{-1}=\lambda_1=\frac{K(H)}{2\pi}\sqrt{\mu^{-1}\det[S_{,ij}(F_+)]}e^{-S_H N/D}. \qquad (5)$$

In this equation, $S_H$ is the value of the action at $H$. The reversal time therefore follows an Arrhenius law with a preexeponential factor depending on the curvatures of the potential $S$ at the hyperbolic and stable points. The prefactor $K(H)$ is calculated by integration along the most likely escape path of the transport equation: $\dot{K}=-(\partial_i u_i + S_{,ii}/2)K$ with the initial condition $K(F_+)=1$. Here, the coefficients $S_{,ij}$ are the components of the Hessian matrix $S_{,ij}=\partial_{y_i}\partial_{y_j}S$ and can be numerically integrated along the most likely escape path [17]. The opposite case ($\mu < 1$ or $\gamma > 2$) is less similar to an equilibrium problem: the most likely escape path is tangent to the separatrix (see Fig. 2) and the effective potential is singular at $H$. The prefactor $K$ tends to 0 when approaching the hyperbolic point and the Eyring formula (5) is incorrect. The mean escape time still follows an Arrhenius law:

$$2t_{\rm rev}^{-1}=\lim_{a,b\to a_H,b_H}\frac{\mu K(a-a_H)}{2\pi(b-b_H)}\sqrt{\det[S_{,ij}(F_+)]}e^{-S_H N/D}. \qquad (6)$$

Equations (5) and (6) are derived in Ref. [17], but we have corrected factors of 2. The reversal time of a motor assembly can then be written as

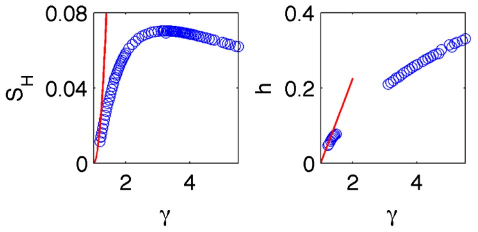

FIG. 3 (color online). Circles: Functions $S_H(\gamma)$ and $h(\gamma)$ defined in the text in Eq. (7). Red lines: Analytic estimations of $h$ and $S_H$ close to the dynamic phase transition threshold $\gamma\to 1$ $[S_H(\gamma)\simeq(\gamma-1)^2/2$ and $h(\gamma)\simeq(\gamma-1)/(\pi\sqrt{2})]$.

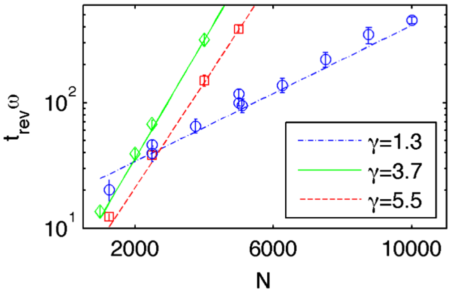

FIG. 4 (color online). Lines: Analytic estimation of the mean reversal time [using Eq. (7)]. Markers: Results of simulations (circles, $\gamma = 1.3$; diamonds, $\gamma = 3.7$; squares, $\gamma = 5.5$). The error bars indicate the 95% confidence intervals. Parameter values: $\eta = 0.5$, $\alpha = 1/8$.

$$t_{\rm rev} = \omega^{-1}h^{-1}(\gamma)e^{NS_H(\gamma)/D}. \tag{7}$$

The dimensionless functions $S_H$ and $h$ can be computed by numerically evaluating all quantities appearing in Eqs. (5) and (6). They are shown in Fig. 3. An interesting result is that the effective potential barrier, $S_H$, reaches a maximum value at $\gamma \simeq 3$. Noting that one must have $\alpha^2 < \eta(1-\eta)$ so that the transition rates remain positive, the characteristic number of motors $N_0$ required to observe bidirectional motion (defined by $t_{\rm rev} \sim e^{N/N_0}$) is always larger than $N_0 > 4/[\max S_H] \simeq 60$. One of our results is therefore that bidirectional motion cannot be observed for a small number of motors within our hypotheses. This prediction is to be compared to the small number of motors required for bidirectional motion in other models [11].

We also obtained asymptotic expressions for $S_H$ and $h$ when $\gamma$ is close to its critical value 1. In this limit, the problem can be reduced to a one-dimensional problem and the first escape time can be calculated using the equilibrium Kramer's rate theory. We find $S_H(\gamma) \simeq (\gamma-1)^2/2$ and $h(\gamma) \simeq (\gamma-1)/(\pi\sqrt{2})$. These asymptotics are plotted in Fig. 3. In this limit, the effective potential barrier vanishes at the dynamic transition threshold, $S_H \rightarrow 0$, whereas the characteristic time scale near the transition diverges, as expected for a second order phase transition. At fixed value of $N$, however, the small noise approximation does not hold infinitely close to the threshold, and a detailed study of the joined limits $N \rightarrow \infty$ and $\gamma \rightarrow 1$ would require a more accurate expansion method of the master equation [19].

In Fig. 3 we do not give values of the prefactor $h$ for $\gamma \in [3/2; 3]$ (or $\mu \in [1/2; 2]$). In this range of parameters, we did not observe the behavior of the prefactor $K$ predicted in Ref. [17]. This might be due to numerical uncertainties, although we used a symplectic numerical integration scheme that efficiently conserves the energy [20]. The function $h(\gamma)$ seems, however, to be continuous and smooth in this range.

We have also performed stochastic simulations of the model using the Gillespie algorithm [21], with the same choice of parameters. The results are shown in Fig. 4. The analytical estimates match very well with the results of the simulations, with no adjustable parameters.

In conclusion, we have shown in this Letter that the reversal events of a molecular motor assembly can be considered as a first exit problem from the attraction basin of a stable fixed point. In the WKB approximation, most reversal events take place on an optimal trajectory, which brings the system in the vicinity of a hyperbolic fixed point. This trajectory is a classical path of a Hamiltonian system and can be numerically estimated to calculate an effective nonequilibrium potential and provide estimates of the reversal time, which correspond very well to the result of stochastic simulations. For motor assemblies, we find no deviation from an Arrhenius law for the reversal time, although the system is out of equilibrium. We do not know whether deviations from an Arrhenius law could be observed with other sets of hypotheses. The methods that we have presented here could be applied to more realistic models of molecular motors in order to provide a better understanding of fluctuations in molecular motor assemblies.

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