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Analytic descriptions of stochastic bistable systems under force ramp

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Solving the two-state master equation with time-dependent rates, the ubiquitous driven bistable system, is a long-standing problem that does not permit a complete solution for all driving rates. Here we show an accurate approximation to this problem by considering the system in the control parameter regime. The results are immediately applicable to a diverse range of bistable systems including single-molecule mechanics.

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I. INTRODUCTION

There are plenty of examples of physical systems which appear to switch between two stable states when subject to environmental or experimental forcing. These include both macroscale systems, such as ocean circulation [1] and social behavior [2], and several microscale systems, such as neuron firing [3], bond dissociation [4], and biopolymer unfolding [5]. In reality, few precious examples exist which truly possess only two states. But when a system's phase space can be reduced to two discrete states and transitions from one state to another are memoryless, the process can be described by the master equation with instantaneous transition rates. It should then be possible to predict the collective behavior of normally complex systems from well-defined transition rates. However, the master equation with time-dependent rates, which is required for dynamic forces, cannot be solved for most relevant statistical quantities. Since the solution contains the important link between equilibrium and nonequilibrium behavior, approximations within those limits have been carried out [4,6–9]. Here we derive a complete analytic approximation which emerges only by considering the system within the control-parameter domain.

We consider a bistable system which is embodied by the two-state master equation,

$$\frac{dp_1(t)}{dt} = -k_1(t)p_1(t) + k_2(t)p_2(t), \tag{1}$$

where $k_i(t)$ is the instantaneous transition rate out of state i and $p_i(t)$ represents the probability of finding the system in state i at time t. The transition rates are assumed to follow an Arrhenius rate of escape,

$$k_i(t) = k_i^0 \exp\{-\beta[V(x_t,t) - V(x_i,t)]\}, \tag{2}$$

where $V(x,t)$ is an external biasing potential and $\beta^{-1} = k_B T$ is the inverse thermal energy. The positions x_i and x_t represent the ith state minimum and transition state, respectively, and k_i^0 is the rate of escape from state i in the absence of an external potential. For the derivation that follows we consider the process as a function of the control parameter, here force, $f = -\partial V(x,t)/\partial x$, where the rate of changing force $\dot{f}(t) = df/dt$ is not necessarily constant in time. When the force is held fixed for long times, the left side of Eq. (1) vanishes, and we have the steady-state equilibrium probability,

$$p_1^{eq}(f) = \frac{k_2(f)}{k_1(f) + k_2(f)} = \frac{1}{1 + \exp\{\beta[\Delta V(f) - \Delta\mu]\}}, \tag{3}$$

where $\Delta\mu = \beta^{-1}\ln\frac{k_2^0}{k_1^0}$ is the unperturbed free energy difference and $\Delta V(f) = V(x_1,f) - V(x_2,f)$ is the applied bias between the two state minima. When the external bias increases, the function $p_1^{eq}(f)$ decreases from 1 to 0, passing through $p_1^{eq}(f_{1/2}) = 1/2$, where $f_{1/2}$ marks the coexistence force at which the two rates are equal,

$$k_1(f_{1/2}) = k_2(f_{1/2}). \tag{4}$$

It will prove useful to rewrite the master equation [Eq. (1)] such that $p_1^{eq}(f)$ is explicit. Using $p_1 + p_2 = 1$ and Eq. (3), we express the differential system as the excess probability $\Pi(f) = p_1(f) - p_1^{eq}(f)$ driven by the derivative of the equilibrium probability,

$$\frac{d\Pi(f)}{df} + \frac{k_T(f)}{\dot{f}}\Pi(f) = -\frac{dp_1^{eq}(f)}{df}, \tag{5}$$

where

$$k_T(f) = k_1(f) + k_2(f) \tag{6}$$

is the total relaxation rate of the system. To remove the effects of particular initial conditions we start the process at infinite negative force, $f_0 \to -\infty$, and with $p_1(-\infty) = p_1^{eq}(-\infty) = 1$ we have the probability of finding the system in state 1 at force f,

$$p_1(f) = p_1^{eq}(f) - \int_{-\infty}^{f} \frac{dp_1^{eq}(f'')}{df''} \times \exp\left[-\int_{f''}^{f} \frac{k_T(f')}{\dot{f}} df'\right] df''. \tag{7}$$

Equation (7) is convenient in that it decomposes the distribution into a sum of two essential terms: the quasistatic, adiabatic (equilibrium) limit of the process $p_1^{eq}(f)$ and the nonequilibrium contribution. For finite loading rates ($\dot{f} > 0$) the second, nonequilibrium term in Eq. (7) enables state 1 to persist to higher forces; how high depends on the ratio $k_T(\delta f)\delta f/\dot{f}$, where δf is a characteristic force scale for the transition. When the loading rate is significantly slower than the relaxation rate [$\dot{f} \ll k_T(\delta f)\delta f$], the exponent forces the second term to zero, which physically means the system is able to adapt to the relatively slowly changing force. At faster loading rates the potential changes before the system can relax, and thus the second term describes the lag of the system's relaxation behind the changing potential landscape [10].

As graphically illustrated in Fig. 1, the equilibrated distribution $p_1^{eq}(f)$ is a sigmoid which transitions from 1 to 0 over

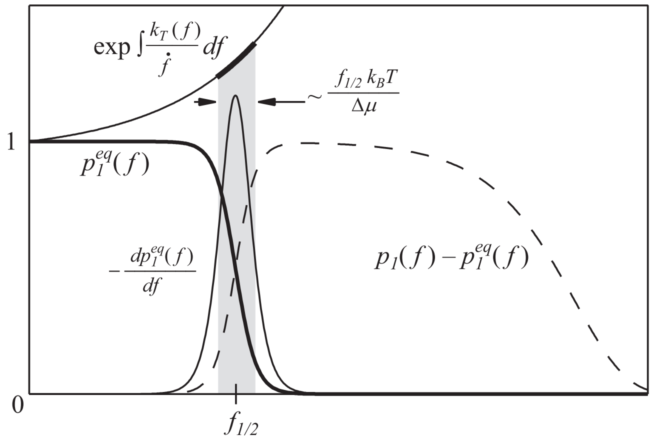

FIG. 1. The total distribution $p_1(f)$ as expressed in Eq. (7) is a sum of the equilibrium distribution $p_1^{eq}(f)$ and a nonequilibrium process which lags behind the changing force in proportion to the loading rate (dashed line). The derivative of the equilibrium distribution appearing in Eq. (7) acts as an aperture, allowing a narrow band of forces around $f_{1/2}$ to initialize the nonequilibrium term of the process (upper curve). In the limit of very small width (FWHM $\sim f_{1/2}k_BT/\Delta\mu$) a single force is sifted out, effectively initializing the nonequilibrium term at $f_{1/2}$.

a relatively narrow band of the control parameter, centered at $f_{1/2}$. Assuming a sufficiently large barrier ($\beta\Delta\mu \gg 1$), we can approximate the equilibrium distribution as a step function at the expense of a coarser resolution of $p_1(f)$ around $f_{1/2}$,

$$p_1^{eq}(f) \approx \theta(f_{1/2} - f), \qquad \theta(x) = \begin{cases} 1, & x > 0, \\ 0, & x \leqslant 0, \end{cases} \tag{8}$$

where $\theta(x)$ is the Heaviside step function. Inserting Eq. (8) in (7), we see that the derivative $dp_1^{eq}(f)/df \to d\theta(f_{1/2} - f)/df$ functions to sift out the lower integration limit within the exponent at $f_{1/2}$ (see Fig. 1),

$$p_1(f) \approx \theta(f_{1/2} - f) + \int_{-\infty}^{f} \frac{d\theta(f'' - f_{1/2})}{df''} df'' \times \exp\left[-\int_{f_{1/2}}^{f} \frac{k_T(f')}{\dot f} df' \right]. \tag{9}$$

Completing the integration, we have

$$p_1(f) \approx \theta(f_{1/2} - f) + \theta(f - f_{1/2}) \exp\left[-\int_{f_{1/2}}^{f} \frac{k_T(f')}{\dot f} df' \right]. \tag{10}$$

Equation (10) is a key result of this article. It shows that the two-state master equation [Eq. (1)] can be approximated as a *delayed* first-order rate process, with rate $k_T(f) = k_1(f) + k_2(f)$ provided that the derivative of the equilibrium distribution is sharply peaked relative to the forces explored in the system (and, more practically, narrow relative to the experimental force resolution). The delay is not in time, but force, and is approximately equal to the coexistence force $f_{1/2}$. Thus the effect of both forward and reverse transitions is to maintain the population of state 1 until $f_{1/2}$ is overcome. The opposite step functions ensure this by imposing $p_1(f < f_{1/2}) = 1$. In cases where $k_2(f)$ decreases rapidly beyond $f_{1/2}$, its contribution can be regarded as negligible. This leads to a simpler expression with $k_T(f) \approx k_1(f)$, and thus the effects of $k_2(f)$ are entirely contained in $f_{1/2}$. As an example, we show in Fig. 2 a plot of Eq. (10) using the rates defined in Eqs. (11) below for a range of loading rates extending from equilibrium to far from equilibrium.

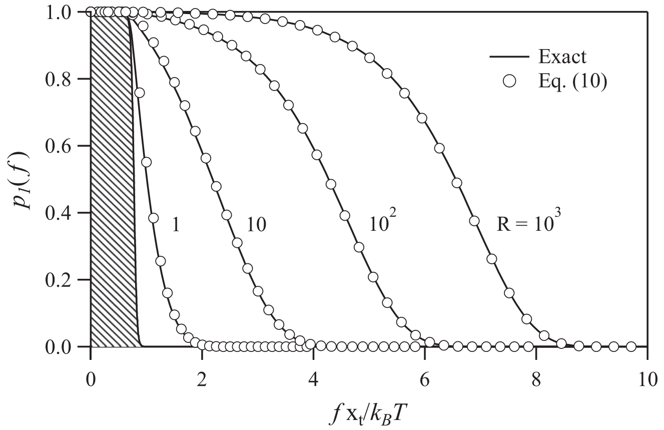

FIG. 2. Exact and approximate solutions to the master equation using the transition rates in Eqs. (11). Solid curves are numeric solutions to the differential equation (1). Circles show Eq. (10). The hatched region denotes the area under the quasistatic distribution, $p_1^{eq}(f)$. Parameters used are $k_1^0 = 1$, $\beta\Delta\mu = 15$, $\beta k x_t^2/2 = 0.01$. The coexistence force is thus $f_{1/2} \approx 0.775 k_BT/x_t$. The noted loading rates are normalized according to $R = \dot f x_t/k_BTk_1^0$.

II. FORCE RAMP INTERMOLECULAR BOND RUPTURE

Here we will treat the case of intermolecular bonding under force, where two interacting species are pulled apart by a spring-like potential: the archetype of single-molecule dynamic force spectroscopy (DFS). In this scenario, state 1 designates the formed intermolecular bond, while state 2 designates the unbonded case which is energetically defined by the external pulling potential. Therefore $k_1(t)$ represents the rate of a particle escaping a potential well under force, while $k_2(t)$ represents the rate of the particle escaping the potential defined by the pulling spring.

In a previous publication [11] we used heuristic arguments to find an interpolation to the mean rupture force of this two-state process. Here we will show that the solution found in [11] is directly obtained from Eq. (10).

We apply an external potential given by $V(x_i, f) = \frac{1}{2}k(x_i - f/k)$, with transition state x_t, state 1 placed at the origin $x_1 = 0$, and $x_2 = f/k$ moving with the applied potential minimum. Hence f is defined as the force on state 1. The loading rate $\dot f$ is constant. Using the prescription from the previous section, we have the quantities

$$\begin{aligned} k_1(f) &= k_1^0 e^{\beta(f x_t - \frac{1}{2}k x_t^2)}, \\ k_2(f) &= k_2^0 e^{-\beta \frac{k}{2}(f/k - x_t)^2}, \\ f_{1/2} &= \sqrt{2k\Delta\mu}, \end{aligned} \tag{11}$$

and the equilibrium distribution follows as

$$p_1^{eq}(f) = \frac{1}{1+\exp\left[\beta\left(\frac{f^2}{2k} - \Delta\mu\right)\right]}. \tag{12}$$

Figure 2 shows Eqs. (12) and (10) plotted using Eqs. (11). The derivative of this distribution, $dp_1^{eq}(f)/df$, has a FWHM of approximately $0.88 f_{1/2} k_B T/\Delta\mu$. Therefore from the definition of $f_{1/2}$ in this scenario, the requirement of Eq. (10) for a narrow FWHM is satisfied with decreasing transducer stiffness k and increasing $\Delta\mu/k_B T$.

In the quasistatic limit the mean force, $\langle f\rangle_{eq} = \int_0^\infty p_1^{eq}(f)df$, is not analytic. We can approximate the integral by recognizing that the term $f^2/2k$ is the energy that the bound state is raised with force. Changing the variable of integration to dimensionless energy, $\epsilon = \beta f^2/2k$,

$$\langle f\rangle_{eq} = \sqrt{\frac{k}{2\beta}}\int_0^\infty \frac{\epsilon^{-1/2}d\epsilon}{1+\exp[(\epsilon-\beta\Delta\mu)]} \tag{13}$$

$$= \sqrt{\frac{k}{2\beta}} F_{-1/2}(\beta\Delta\mu), \tag{14}$$

where $F_j(x)$ is the Fermi-Dirac integral of order j. Assuming strong bonds ($\Delta\mu \gg k_B T$), we use the asymptotic series expansion for the integral $\lim_{x\to\infty} F_{-1/2}(x) \to 2\sqrt{x}$ [12],

$$\langle f\rangle_{eq} \cong \sqrt{2k\Delta\mu} = f_{1/2}. \tag{15}$$

We see that for $\beta\Delta\mu$ significantly larger than unity, the mean force recovered under quasistatic pulling coincides with the coexistence force which balances the populations of the bound and unbound states. To evaluate the nonequilibrium component to the mean we take $k_2(f) \approx 0$ for $f > f_{1/2}$. Therefore, using $k_T(f) \approx k_1(f)$ in Eq. (10), the mean rupture force $\int_0^\infty p_1(f)df$ evaluates to our previous result [11],

$$\langle f\rangle = \sqrt{2k\Delta\mu} + \frac{k_B T}{x_t}\exp\left[\frac{k_1(f_{1/2})k_B T}{\dot f x_t}\right]E_1\left[\frac{k_1(f_{1/2})k_B T}{\dot f x_t}\right], \tag{16}$$

where $E_1(z) = \int_z^\infty \frac{e^{-s}}{s}ds$ is the first-order exponential integral [$E_1(z) \approx e^{-z}\ln(1+e^{-\gamma}/z)$, where $\gamma = 0.577\ldots$ is Euler's constant].

III. FORCE RAMP INTRAMOLECULAR TRANSITIONS

Transitions *within* the molecule under study, such as configurational switching in protein folding and RNA/DNA hairpins, have been extensively studied thermodynamically and kinetically and very often are reducible to a two-state system [13].

In this case we again set $x_1 = 0$; however, unlike intermolecular bond rupture, the second state is a fixed distance away from the first, $x_2 = \Delta x$. As before, the external potential is parabolic $V(x_i,t) = \frac{1}{2}k(x_i - vt)^2$, and from Eqs. (2)–(4) we have

$$\begin{aligned} k_1(f) &= k_1^0 e^{\beta(f x_t - \frac{1}{2}k x_t^2)}, \\ k_2(f) &= k_2^0 e^{-\beta[f(\Delta x - x_t) - \frac{1}{2}k(\Delta x^2 - x_t^2)]}, \\ f_{1/2} &= \frac{\Delta\mu}{\Delta x} + \frac{1}{2}k\Delta x. \end{aligned} \tag{17}$$

The equilibrium distribution follows as

$$p_1^{eq}(f) = \frac{1}{1+\exp\left[\beta\left(f\Delta x - \frac{1}{2}k\Delta x^2 - \Delta\mu\right)\right]}. \tag{18}$$

The FWHM of the derivative, $dp_1^{eq}(f)/df$, is approximately $1.76 f_{1/2} k_B T/\Delta\mu$. Note $f_{1/2}$ is defined immediately above and differs from that of the intermolecular bond rupture case discussed in the previous section. Here again the derivative of p_1^{eq} becomes narrower with decreasing transducer stiffness k and increasing energy, $\Delta\mu/k_B T$. The FWHM is not monotonic in Δx. It decreases with increasing Δx until a minimum is reached at $\Delta x^* = \sqrt{2\Delta\mu/k}$, then gradually increases.

Owing to the same form of $k_1(f)$ for both the intramolecular and intermolecular cases, under the approximation $k_T(f) \approx k_1(f)$ the mean rupture force for this intramolecular switching example is identical to that found in Eq. (16), with the exception of the definition of the coexistence force,

$$\langle f\rangle = \frac{\Delta\mu}{\Delta x} + \frac{1}{2}k\Delta x + \frac{k_B T}{x_t}\exp\left[\frac{k_1(f_{1/2})k_B T}{\dot f x_t}\right]E_1\left[\frac{k_1(f_{1/2})k_B T}{\dot f x_t}\right]. \tag{19}$$

IV. DISCUSSION

Realizing an approximation such as that of Eq. (10) would not be possible in the time domain. This is due to problems which arise near equilibrium, where a quasistatically driven process requires infinite time to complete, and hence critical parameters like coexistence, $t_{1/2} = f_{1/2}/\dot f$, are undefined when $\dot f \to 0$. The same quasistatic process in the control parameter domain is well defined at every relevant parameter value, regardless of rate.

How reasonable are these assumptions for the single-molecule examples treated here? Approximating $p_1^{eq}(f)$ as a step function and its derivative as a δ function brings negligible error if the experimental force resolution is much greater than the spread around the transition, typically defined as the FWHM of the derivative (see Fig. 1). The error is manifested as a small overestimate of $p_1(f)$ around $f_{1/2}$ due to a sharp, instead of gradual, transition near $f_{1/2}$. Figure 3 illustrates this error at the most problematic loading rate, the loading rate $\dot f_\times$ which marks the crossover from near-equilibrium to kinetic regimes. In the approximations of Eqs. (16) and (19) this rate is essentially where the external energy exerted on the system $\dot f x_t$ matches the energy exchanged between the system and the thermal bath, $k_1(f_{1/2})k_B T$ [14],

$$\dot f_\times x_t = k_1(f_{1/2})k_B T. \tag{20}$$

Figure 4 shows the error with loading rate for large and small values of the free energy. For loading rates less than $\dot f_\times$ the error is less than 4% even for the nonideal case of low free energy ($\beta\Delta\mu = 5$).

Using typical laboratory parameters for the intermolecular adhesion case of atomic force microscope (AFM) cantilever stiffness $k = 0.1$ N/m and $\Delta\mu = 10\, k_B T$, the FWHM equals 8 pN. For the intramolecular switching case, we consider the unfolding of RNA [5] as an example; with optical trap stiffness

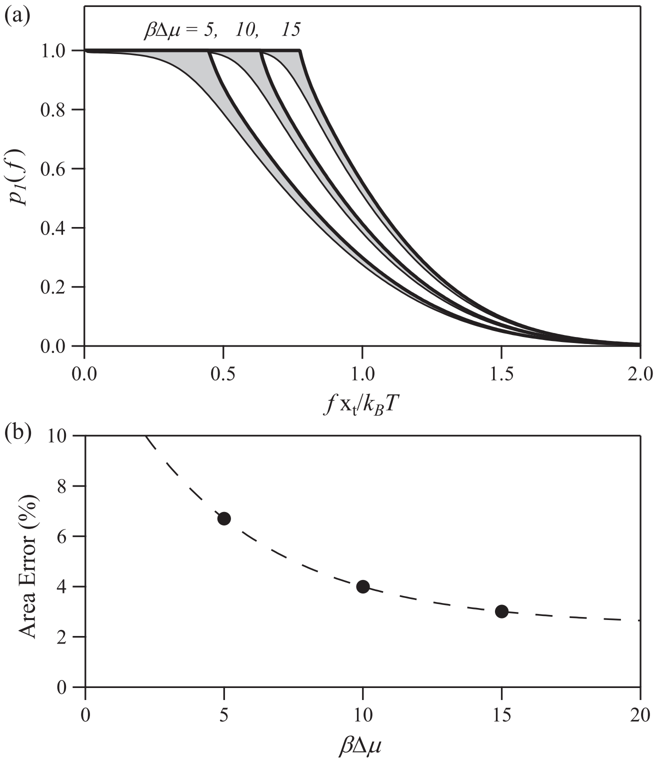

FIG. 3. (a) The probability of state 1 vs normalized force, evaluated at the crossover loading rate, $\dot{f}_\times x_t/k_BTk_1(f_{1/2}) = 1$, for three values of the energy barrier $\Delta\mu$. Exact solutions (thin lines) and approximations (thick lines) are shown using Eq. (10) with the rates defined in Eqs. (11). The area between the curves equals the difference in mean force for that loading rate. (b) The error as a percent of the exact solution is shown for three different free energy values. An exponential fit (dashed line) is shown as a guide. Parameters used are $k_1^0 = 1$ and $\beta k x_t^2/2 = 0.01$.

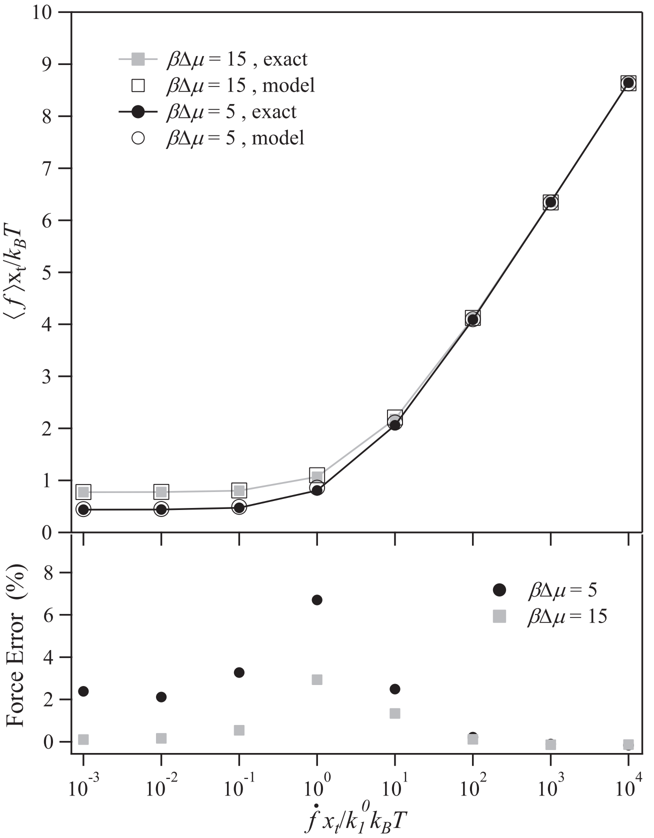

FIG. 4. Normalized mean force vs loading rate evaluated by Eq. (10) compared against the exact numerical solution for large and small free energy values. The error, $(\langle f\rangle_{\rm model} - \langle f\rangle_{\rm exact})/\langle f\rangle_{\rm exact}$, is greatest at a normalized loading rate of unity, $\dot{f}x_t/k_1^0k_BT \approx 1$, and diminishes with higher free energy values. Parameters are the same as in Fig. 3.

$k = 0.01$ pN/nm, $\Delta\mu = 10k_BT$, and $\Delta x = 20$ nm we find a FWHM of 0.5 pN. Both of these widths are below the typical noise floor of their respective experimental techniques.

It is also important to recognize that one cannot derive a probability density function (PDF) for the above processes from the approximation in Eq. (10). Away from equilibrium the PDF is trivial since the probability becomes a first-escape time distribution. In general, however, the PDF of the total force expended to drive a transition is not simply the negative derivative of $p_1(f)$ as it is defined in the master equation (1). Such a relationship would require that $p_1(f)$ is a cumulative distribution function (CDF) of the total exerted force, which it is not. Instead, $p_1(f)$ is only the probability of finding the system in state 1 at force f. As a result, the mean force $\langle f\rangle$ found in (16) from integrating over $p_1(f)$ has an important distinction. Since, in principle, the system may transition any number of times between the two states before finally resting in state 2, the transition force for any individual realization of the process should be defined as the sum of increasing force increments while in state 1. This is the force analog to the total sojourn time of a two-state process. Therefore the mean transition force is the ensemble average of the sum of force increments exerted on state 1 while the system resides in state 1.

In summary, the two-state master equation with time-dependent rates, the stochastic model often used in describing driven bistable processes, has a simple approximation when considering the process in terms of the control parameter. The process can be reduced to a first-order rate process with a delay set by the coexistence force. While the applied examples here deal with single-molecule transitions (DFS), the approach can be extended to other driven systems whose phase space can be reduced to a two-state Markov process.

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