The viscosity dependence of passage through a fluctuating bottleneck

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We generalize the model of a rate process involving the passage of an object through a fluctuating bottleneck. The rate of passage is considered to be proportional to a power function of the radius of the bottleneck with exponent $\alpha > 0$. The fluctuations of the bottleneck are coupled to the motion of the surrounding medium and governed by Langevin dynamics. We show numerically and also explain analytically that for slow bottleneck fluctuations the long time decay rate of the process has a fractional power law dependence on the solvent viscosity with exponent $\alpha/(\alpha+2)$. The results are consistent with the experimental data on ligand binding to myoglobin, and might also be relevant to other reactions for which exponents between 0 and 1 were reported.

I. INTRODUCTION

The rates of reactions in overdamped environments can often be understood in terms of Kramers' theory of diffusion over a potential barrier[1,2]. Kramers' theory predicts that the rate constants are inversely proportional to the friction coefficient characterizing the reaction coordinate along the reaction pathway. When the main source of friction is the solvent, then the friction coefficient is expected to be proportional to the solvent viscosity. It is, however, not obvious how the viscosity of the solvent affects the rate constant if the reaction is accompanied by the internal reorganization of the molecules involved (e.g., during protein conformational changes, or ligand motion in enzymes).

For many enzymatic reactions[3,4], first observed in case of ligand binding to myoglobin[5], the rate constant μ appears to be inversely proportional to a fractional power function of the solvent viscosity η with exponent p (where $0 < p < 1$):

$$\mu \propto \frac{1}{\eta^p} \ . \tag{1}$$

The exponent is difficult to interpret, and several alternative concepts were proposed to explain the observations. One such possibility is that because the solvent viscosity is usually controlled by the addition of viscogenic cosolvents, the microviscosity in the vicinity of the molecule can be different from the measured macroviscosity of the solvent[6–8]. Another possible explanation concerns the frequency-dependence of the friction[9].

Inspired by the ligand binding experiments of Beece et al.[5], a third possibility was introduced by Zwanzig[10], who assumed the primary process to be passage through a fluctuating bottleneck. This model considers two perpendicular reaction coordinates[11]. One of them is the position of the ligand inside the protein, and the other one is the radius of the bottleneck which the ligand has to get through. The ligand's motion inside the protein is supposed to be independent of the solvent, whereas the bottleneck is assumed to follow the proteins' conformational fluctuations, which are coupled to solvent motion.

Under specific conditions (quadratic potential for the radius of the bottleneck, and quadratic dependence of the escape rate on the radius) Zwanzig could show analytically that (1) the decay curves are not exponential at short times, but change to exponential at long times; and (2) the long time decay rate is inversely proportional to the square root of the solvent viscosity, i.e., $p = 1/2$. Here we generalize this model (allowing a more general potential for the bottleneck, and a more general dependence of the escape rate on the radius), then show numerically how the exponent p depends on the system parameters, and finally, we justify our numerical results by analytical arguments.

II. THE MODEL

In Zwanzig's model[10] the ligand concentration C decays according to a simple rate equation

$$\frac{dC}{dt} = -K(r)C \ , \tag{2}$$

where the decay rate $K(r)$ is proportional to a power function of the radius r of the bottleneck:

$$K(r) = kr^\alpha \tag{3}$$

with prefactor k and exponent $\alpha > 0$.

The radius fluctuates, and its time evolution is given by the Langevin equation

$$\frac{dr}{dt} = -\frac{1}{\gamma}\frac{dU(r)}{dr} + F(t) \ , \tag{4}$$

where the friction coefficient γ is proportional to the solvent viscosity η, and the potential $U(r)$ experienced by the radius has the form

$$U(r) = \frac{1}{\beta}\kappa r^\beta \tag{5}$$

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with strength κ and exponent $\beta > 0$. A hard reflecting barrier is imposed at $r = 0$ so that only positive radii are involved. The thermal (Gaussian white) noise $F(t)$ has the usual autocorrelation function

$$\langle F(t)F(t')\rangle = 2\frac{k_{\mathrm{B}}T}{\gamma}\delta(t-t') \ , \tag{6}$$

where k_{B} is the Boltzmann constant and T is the absolute temperature.

To be able to solve the model analytically, Zwanzig chose the specific values $\alpha = \beta = 2$. For generality, here we keep both of these exponents as free parameters, and investigate their effects on the rate process.

The goal is to find the noise-averaged concentration $\langle C(t)\rangle$. First we have to define a noise-averaged concentration $\overline{C}(r,t)$ for a given bottleneck radius r, so that

$$\langle C(t)\rangle = \int_0^\infty \overline{C}(r,t)\ dr \ . \tag{7}$$

$\overline{C}(r,t)$ satisfies the Smoluchowski equation with a sink[12]:

$$\frac{\partial\overline{C}}{\partial t} = -K(r)\overline{C} + \frac{\partial}{\partial r}\left(\frac{k_{\mathrm{B}}T}{\gamma}\frac{\partial\overline{C}}{\partial r} + \frac{1}{\gamma}\frac{dU(r)}{dr}\overline{C}\right) . \tag{8}$$

A reflecting boundary condition is imposed at $r = 0$. The initial condition is that $\overline{C}$ has its equilibrium distribution in the absence of the reaction sink. After plugging Eqs. (3) and (5) into the Smoluchowski equation and introducing the notations $\lambda = \kappa/\gamma$ and $\theta = k_{\mathrm{B}}T/\kappa$ we arrive at

$$\frac{\partial\overline{C}}{\partial t} = -kr^\alpha\overline{C} + \lambda\theta\frac{\partial}{\partial r}\left(\frac{\partial\overline{C}}{\partial r} + \frac{r^\beta}{\theta}\overline{C}\right) , \tag{9}$$

which is the generalized form of Eq. (7) of Zwanzig's original article[10]. This equation has three dimensional parameters (k, λ, and θ), out of which two can be scaled out (e.g., setting $k = \theta = 1$) by rescaling time and space accordingly. In other words, only their dimensionless combination

$$\widetilde{\lambda} = \frac{\lambda}{k\theta^{(\alpha-\beta+2)/\beta}} \tag{10}$$

is relevant to the model.

For $\widetilde{\lambda} \gg 1$, i.e., when the bottleneck equilibrates much faster than the ligand escapes, then r remains close to its equilibrium distribution at all times, and C decays exponentially with a viscosity independent rate constant $\langle kr^\alpha\rangle$. On the other hand, for $\widetilde{\lambda} \ll 1$, i.e., when the dynamics of the bottleneck is slow, the behavior of the model is more interesting. As Zwanzig pointed out, the decay of C is not exponential at short times, but changes to exponential at long times. In fact, it is the exponential decay of the slowest eigenmode that is observed in the long run. Zwanzig determined that the long time exponential decay rate for $\alpha = \beta = 2$ is $(k\theta\lambda)^{1/2}$, i.e., it is inversely proportional to a fractional power function of the solvent viscosity η with exponent $p = 1/2$.

III. RESULTS AND DISCUSSION

For general values of α and β the Smoluchowski equation cannot be solved analytically. Therefore, we spatially discretized the equation (up to a sufficiently large value of r) to obtain a set of stationary (Markovian) master equations, and determined its dominant eigenvalue (i.e., the one closest to unity, corresponding to the slowest eigenmode) by applying either the scaled power method or a root finding technique. The continuum limit was extrapolated through successive refinement of the discretization. For $\widetilde{\lambda} \ll 1$ we found that the decay rate of the slowest egienmode is proportional to $\widetilde{\lambda}^p$ or, equivalently, inversely proportional to η^p. Surprisingly, the exponent p appears to be independent of β, and follows the relationship

$$p = \frac{\alpha}{\alpha+2} \ . \tag{11}$$

remarkably well (Fig. 1).

This simple formula can be understood by realizing that for slow bottleneck dynamics (which is the case for $\widetilde{\lambda} \ll 1$) those are the small bottlenecks that retain the ligand for the longest times (due to $K(0) = 0$). So systems starting near $r = 0$ will decay only after r fluctuates to larger values. The diffusive motion of r is practically independent of the potential $U(r)$ as long as $U(r) - U(0) \ll k_{\mathrm{B}}T$, thus, for short diffusion the potential can be ignored. Escape will occur near position r^*, where the escape time $1/K(r^*) = 1/(kr^{*\alpha})$ becomes comparable to the characteristic diffusion time $r^{*2}\gamma/(k_{\mathrm{B}}T) = r^{*2}/(\lambda\theta)$ from position 0 to r^* along a flat potential. Equating these two times results in

$$r^* = \left(\frac{\lambda\theta}{k}\right)^{1/(\alpha+2)} , \tag{12}$$

from which the decay rate is

$$\mu \approx K(r^*) = k\left(\frac{\lambda\theta}{k}\right)^{\alpha/(\alpha+2)} , \tag{13}$$

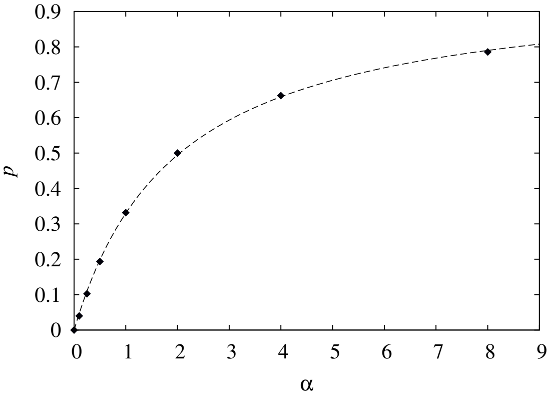

FIG. 1. The numerically obtained values of the exponent p as a function of α (symbols). The values are independent of β. The data points follow the curve $p = \alpha/(\alpha+2)$ (dashed line).

providing the anticipated $p = \alpha/(\alpha + 2)$ value for the exponent.

IV. CONCLUSION

We have shown that for passage through a fluctuating bottleneck the long time decay rate is inversely proportional to the power function of the solvent viscosity with exponent $0 < p < 1$, and the exponent is sensitive to the dependence of the escape rate on the size of the bottleneck for narrow bottlenecks. This generalized version of Zwanzig's original model[10] can be applicable to systems with two coupled perpendicular reaction coordinates, where only one of the reaction coordinates is directly affected by solvent motion. Examples include not only ligand motion inside an enzyme, but also protein conformational changes where an internal part of the protein slides with respect to the rest of the molecule or, more generally, a considerable internal reorganization of the protein occurs.

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