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The dynamics of single enzyme reactions: A reconsideration of Kramers' model for colored noise processes

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The utility of an approximate heuristic version of Kramers' theory of reaction rates that was earlier used [Chaudhury and Cherayil, J. Chem. Phys. **125**, 024904 (2006)] to successfully describe the nonexponential waiting time distributions of the enzyme β-galactosidase is reassessed. The original model, based on the Smoluchowski equation, is reformulated in terms of the phase space variables of the reaction coordinate, without neglecting inertial contributions. A new derivation of the Fokker–Planck equation (FPE) that describes the dynamics of this coordinate is presented. This derivation, based on functional methods, provides a more direct alternative to the existing distribution function approach used by Hanggi and Mojtabai [Phys. Rev. A **26**, 1168 (1982)]. The time-dependent coefficients in the FPE, when incorporated into the exact expression for the transmission coefficient obtained from a reactive-flux formalism [Kohen and Tannor, J. Chem. Phys. **103**, 6013 (1995)], are found to yield virtually the same results as the earlier heuristic model. © *2008 American Institute of Physics*. [DOI: 10.1063/1.2969767]

I. INTRODUCTION

In an early and incomplete effort at understanding observations of stochasticity in the reactions of single enzymes,[1] we had proposed a simple model of catalytic activity based on the generalized Langevin equation (GLE) and Kramers' theory of thermally activated barrier crossing.[2] The model proved to be surprisingly successful in reproducing nonexponentiality in the measured waiting time distributions of the enzyme β-galactosidase.[3] Unlike Kramers' approach, which was formulated in terms of the phase space dynamics of a reaction coordinate evolving under white noise near a harmonic barrier, our own approach employed a reduced description, in which the reaction coordinate evolved in position space alone (under overdamped conditions), its motion governed by power-law correlated random forces that were intended to reflect the multiple time scale dynamics of the surrounding protein.[4] In this approach, the calculation of the waiting time distribution was reduced to the calculation of a time-dependent barrier crossing rate from the generalized diffusion equation to which the GLE could be exactly transformed. The rate was calculated as the ratio of the flux of particles over the barrier to the population of particles in the metastable well, exactly as in Kramers' method, except that these quantities were no longer evaluated in the stationary limit. This meant that the flux and population in our method were time dependent, and their ratio—the barrier crossing rate—was time dependent as well (and hence not strictly a rate at all.) However the use of this rate in the calculation of waiting time distributions led to a good agreement with data from the experiments on β-galactosidase by English *et al.*[3]

The various approximations in this approach were largely *ad hoc*, but we did show that in the long-time limit its results agreed qualitatively with the corresponding results of two *exact* formulations of a non-Markovian generalization of Kramers' barrier crossing model: one by Hanggi and Mojtabai[5] and the other by Kohen and Tannor.[6] We also showed,[7] in an extension of our approach, that a model based on the subdiffusive dynamics of a particle in a double well potential led to an expression for the waiting time distribution that reproduced its earlier scaling structure, but this second calculation also used approximations (including a short-time limit) whose validity was not entirely clear.

The aim of the present note is to show, first of all, how the functional methods of our earlier calculations can be used to exactly re-express the GLE model as an equivalent phase space Fokker–Planck equation (FPE) without neglecting inertial contributions. Such methods are amongst the most direct and economical routes to the derivation of diffusion equations from Langevin equations, and their importance as a calculational tool can be gauged by the number of reviews that have been written about them.[8] Their application to the GLE model leads to a FPE that is identical (as it should be) to the equation obtained by Hanggi and Mojtabai[5] using a different approach based on the distribution function of the phase space variables.[9] Our derivation of the FPE is new and sets down what we believe are important guidelines for the proper conversion of the coupled equations for positions and momenta to the equivalent equation for their joint probability density when these variables are governed by Gaussian colored noise. A second aim is to reconcile the results of our earlier approximate calculations with the results of Hanggi and Mojtabai[5] and Kohen and Tannor.[6] In particular it is to show that when the results of the FPE are combined with the exact results of Kohen and Tannor[6] to calculate the transmission coefficient, the expression that is then obtained is virtually identical to the expression obtained from the original flux-overpopulation method, suggesting that the approxima-

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tions used in its derivation were not necessarily as severe as previously believed. Waiting time distributions determined from the approximate transmission coefficient compare as favorably with data from Ref. 3 as those determined from the present expression.

There are three sections in this paper: Section II A below briefly recapitulates the main results of Ref. 1, Sec. II B describes the results of the present calculations, and Sec. III discusses their implications. The Appendix provides details of the derivation of the phase space FPE using functional methods. The Appendix may be omitted by readers not interested in the technical minutiae of the calculations.

II. DYNAMICS OF THE ENZYMATIC REACTION COORDINATE

A. Recapitulation of some results from Reference 1

Assuming that the fluctuations of a single stochastic distance variable $x(t)$ are the underlying cause of the fluctuations in the rate at which single enzymes convert substrates to products during one catalytic turnover cycle, the time evolution of enzyme activity can be described by the time evolution of $x(t)$, which we assume is governed by the following GLE[10] for a particle of mass m moving in a potential $U(x)$:

$$m\dot{v}(t) = -U'(x) - \zeta \int_0^t dt' K(t-t')v(t') + \theta(t). \tag{1}$$

Here $v(t) = \dot{x}(t)$ is the velocity of the particle, ζ is its friction coefficient, and $\theta(t)$ is a Gaussian colored noise with the moments $\langle\theta(t)\rangle = 0$ and $\langle\theta(t)\theta(t')\rangle = \zeta k_B T K(|t-t'|)$, where $K(t)$ is a memory function, k_B is Boltzmann's constant, and T is the temperature.

In Ref. 1, the potential was chosen to correspond to the inverted parabola $U(x) = U(x_b) - m\omega_b^2(x-x_b)^2/2$, where x_b is the location of the barrier top, ω_b is a frequency, and $\theta(t)$ was chosen to correspond to fractional Gaussian noise[11] (to model the effects of protein conformational fluctuations), so the memory function was given by[12] $K(|t-t'|) = 2H(2H-1)|t-t'|^{2H-2}$ (for $t \neq t'$), with H a phenomenological parameter lying between $1/2$ and 1 that is a measure of the extent of temporal correlations in the noise. Furthermore, it was assumed that the friction was sufficiently large that the inertial term in Eq. (1), $m\ddot{x}(t)$, could be neglected. The resulting equation could then be exactly transformed to the following Smoluchowski equation for the probability density $P(x,t)$ that the particle is at x at time t,

$$\frac{\partial P(x,t)}{\partial t} = \eta(t)\left[\frac{\partial}{\partial x}(x-x_b) - \frac{k_B T}{m\omega_b^2}\frac{\partial^2}{\partial x^2}\right]P(x,t), \tag{2a}$$

where $\eta(t) \equiv -\dot{\chi}(t)/\chi(t)$, with $\chi(t)$ the inverse Laplace transform of the function

$$\hat{\chi}(s) = \frac{\zeta\hat{K}(s)}{s\zeta\hat{K}(s) - m\omega_b^2}. \tag{2b}$$

Here the Laplace transform $\hat{g}(s)$ of a function $g(t)$ is defined by the relation $\hat{g}(s) = \int_0^\infty dt e^{-st}g(t)$. It was found that to fit the results of this model to the dynamic distance data of the protein complex fluorescein-antifluorescein,[13] the parameter

H had to be assigned the value of $3/4$. For this special value of H, the function $\chi(t)$ was found [from Eq. (2b)] to equal[14] $E_{1/2}(\sqrt{t/\tau})$, where $E_\alpha(z)$ is the Mittag–Leffler function and $\tau \equiv (3\zeta\sqrt{\pi}/4m\omega_b^2)^2$ is some relaxation time.

From the solution of Eq. (2a), under the initial condition $P(x,0) = \delta(x-x_0)$, a time-dependent flux and a time-dependent population were determined, from which, using Kramers' method, the transmission coefficient $\kappa(t)$ was found to be

$$\kappa(t) = -\frac{\eta(t)}{\omega_b}. \tag{3}$$

The distribution of waiting times, $f(t)$, between barrier crossing events was then calculated from

$$f(t) = -\frac{d}{dt}\exp\left[-k_{TST}\int_0^t dt'\,\kappa(t')\right], \tag{4}$$

where k_{TST} is the barrier crossing rate calculated from transition state theory. The above distribution, after setting H to $3/4$ and adjusting the other phenomenological parameters in k_{TST} and $\kappa(t)$ for best fit, was found to agree very well with the waiting time distribution determined from the single-molecule experiments on β-galactosidase.[3]

B. Exact treatment of Equation (1)

Without neglecting the inertial term in Eq. (1), and assuming only that $\theta(t)$ is Gaussian, with the same moments as defined above, the phase space FPE analogous to Eq. (2a) (after setting x_b to 0 for convenience, but without loss of generality), is shown in the Appendix (and by Hanggi and Mojtabai in Ref. 5) to be given by

$$\frac{\partial P}{\partial t} = -v\frac{\partial P}{\partial x} + \Xi\frac{\partial}{\partial v}vP - \Omega^2 x\frac{\partial P}{\partial v} + (\Omega^2 - \omega_b^2)\frac{k_B T}{m\omega_b^2}\frac{\partial^2 P}{\partial v\,\partial x}$$
$$+ \Xi\frac{k_B T}{m}\frac{\partial^2 P}{\partial v^2}, \tag{5}$$

where $P \equiv P(x,v,t)$, and Ξ and Ω^2 are time-dependent coefficients, which, from the definitions given in the Appendix, can be shown to be

$$\Xi(t) = \frac{\chi(t)\dddot{\chi}(t) - \dot{\chi}(t)\ddot{\chi}(t)}{\dot{\chi}(t)^2 - \chi(t)\ddot{\chi}(t)} \tag{6a}$$

and

$$\Omega^2(t) = \frac{\dot{\chi}(t)\dddot{\chi}(t) - \ddot{\chi}(t)^2}{\dot{\chi}(t)^2 - \chi(t)\ddot{\chi}(t)}, \tag{6b}$$

where $\chi(t)$ is the inverse Laplace transform of the function

$$\hat{\chi}(s) = \frac{s + \zeta\hat{K}(s)/m}{s^2 + s\zeta\hat{K}(s)/m - \omega_b^2}, \tag{7a}$$

and the dots on $\chi(t)$ denote derivatives with respect to time. Equation (7a) is the generalization to the inertial regime of the function $\hat{\chi}(s)$ introduced in the preceding section [see Eq. (2b)] and reduces to it in the overdamped limit.

As shown by Hanggi and Mojtabai,[5] Kramers' flux-overpopulation method can be applied directly to Eq. (5) to determine the barrier crossing rate k in the stationary limit. From their analysis, it immediately follows that

$$k = \frac{\omega_0}{2\pi\omega_b}\left[\sqrt{\frac{\Xi_\infty^2}{4} + \Omega_\infty^2} - \frac{\Xi_\infty}{2}\right]\exp(-\Delta E/k_B T), \qquad (7b)$$

where ω_0 is the oscillator frequency at the bottom of the well, ΔE is the barrier height, and Ξ_∞ and Ω_∞^2 are the $t \to \infty$ limits of $\Xi(t)$ and $\Omega^2(t)$, respectively.

Furthermore, since $x(t)$ and $v(t)$ are Gaussian random variables, the solution of Eq. (5) is given by

$$P(x,v,t) = \frac{\sqrt{C}}{2\pi}\exp\left\{-\frac{1}{2}[D_{11}(x-\bar{x}(t))^2 + 2D_{12}(x-\bar{x}(t))\right.$$
$$\left. \times (v-\bar{v}(t)) + D_{22}(v-\bar{v}(t))^2]\right\}, \qquad (8a)$$

where the constants D_{ij} are the elements of the matrix

$$\mathbf{D} = \begin{pmatrix} C\sigma_v^2(t) & -C\sigma_{xv}(t) \\ -C\sigma_{xv}(t) & C\sigma_x^2(t) \end{pmatrix}, \qquad (8b)$$

with $C = \det \mathbf{D} = [\sigma_x^2(t)\sigma_v^2(t) - \sigma_{xv}^2(t)]^{-1}$. The time-dependent coefficients in Eqs. (8a) and (8b) are the moments of P; i.e., $\bar{x}(t) = \int dx \int dv\, x P(x,v,t)$ and $\bar{v}(t) = \int dx \int dv\, v P(x,v,t)$, while $\sigma_x^2(t) = \int dx \int dv\, x^2 P(x,v,t) - \bar{x}(t)^2$, $\sigma_v^2(t) = \int dx \int dv\, v^2 P(x,v,t) - \bar{v}(t)^2$, and $\sigma_{xv}(t) = \int dx \int dv\, xv P(x,v,t) - \bar{x}(t)\bar{v}(t)$. From Eq. (5), these moments are seen to satisfy the following equations:

$$\frac{\partial \bar{x}(t)}{\partial t} = \bar{v}(t), \qquad (9a)$$

$$\frac{\partial \bar{v}(t)}{\partial t} = -\bar{v}(t)\Xi(t) + \Omega^2(t)\bar{x}(t), \qquad (9b)$$

$$\frac{\partial \sigma_x^2(t)}{\partial t} = 2\sigma_{xv}(t), \qquad (9c)$$

$$\frac{\partial \sigma_v^2(t)}{\partial t} = -2\Xi(t)\sigma_v^2(t) + 2\Omega^2(t)\sigma_{xv}(t) + \frac{2k_B T}{m}\Xi(t), \qquad (9d)$$

and

$$\frac{\partial \sigma_{xv}(t)}{\partial t} = \sigma_v^2(t) + \Omega^2(t)\sigma_x^2(t) - \Xi(t)\sigma_{xv}(t) + \frac{k_B T}{m\omega_b^2}(\Omega^2(t)$$
$$- \omega_b^2). \qquad (9e)$$

By directly solving Eq. (1) for $x(t)$ and $v(t)$, as done, for example, in recent papers by Viñales and Despósito,[15] these equations can be shown to be satisfied by

$$\bar{x}(t) = x_0\chi(t) + \frac{v_0}{\omega_b^2}\dot{\chi}(t), \qquad (10a)$$

$$\bar{v}(t) = x_0\dot{\chi}(t) + \frac{v_0}{\omega_b^2}\ddot{\chi}(t), \qquad (10b)$$

$$\sigma_x^2(t) = -\frac{k_B T}{m}\left[\frac{1}{\omega_b^4}\dot{\chi}(t)^2 - \frac{1}{\omega_b^2}(\chi^2(t)-1)\right], \qquad (10c)$$

$$\sigma_v^2(t) = \frac{k_B T}{m}\left[1 + \frac{1}{\omega_b^2}\dot{\chi}(t)^2 - \frac{1}{\omega_b^4}\ddot{\chi}(t)^2\right], \qquad (10d)$$

and

$$\sigma_{xv}(t) = \frac{k_B T}{m}\left[\frac{1}{\omega_b^2}\chi(t)\dot{\chi}(t) - \frac{1}{\omega_b^4}\dot{\chi}(t)\ddot{\chi}(t)\right], \qquad (10e)$$

where x_0 and v_0 are, respectively, the initial position and velocity of the particle. Kohen and Tannor[6] showed how an exact expression for the transmission coefficient $\kappa(t)$ can be derived from a bivariate Gaussian distribution function having the structure of Eq. (8a) using the reactive flux formalism;[16] their results immediately establish that

$$\kappa(t) = \frac{\dot{\chi}(t)}{\omega_b^2\sqrt{\dfrac{\dot{\chi}(t)^2}{\omega_b^4} + \dfrac{m}{k_B T}\sigma_x^2(t)}}, \qquad (11)$$

which from Eq. (10c) simplifies to

$$\kappa(t) = \frac{\dot{\chi}(t)}{\omega_b\chi(t)\sqrt{1-\chi(t)^{-2}}}. \qquad (12)$$

Equations (7b) and (12) are among the main results of the paper.

III. DISCUSSION

From the expressions for $\Xi(t)$ and $\Omega^2(t)$ given in Eqs. (6a) and (6b), it can be shown that in the overdamped limit—for the special case of fractional Gaussian noise—with $H = 3/4$ [and $\chi(t)$ therefore given by $E_{1/2}(\sqrt{t/\tau})$], Eq. (7b) reduces to

$$k = \frac{\omega_0}{2\pi\omega_b\tau}\exp(-\Delta E/k_B T), \qquad (13)$$

where τ is defined after Eq. (2b). This is *exactly* the expression that the barrier crossing rate in Ref. 1 also reduces to, but in that reference it had not been possible to show that the limit was identical to the result obtained from the Hangi–Mojtabai rate expression.

Further, comparing Eqs. (12) and (3) [and recalling that $\eta(t) \equiv -\dot{\chi}(t)/\chi(t)$], one sees that apart from the factor of $\sqrt{1-\chi(t)^{-2}}$, the two expressions for the transmission coefficient are also of the same form [the $\chi(t)$'s in these expressions are, of course, different], and they become exactly the same when the overdamped limit is taken in Eq. (7a) and t is made large. In this limit, then, both the flux overpopulation method and the reactive flux formalism yield a $\kappa(t)$ that scales as $\dot{\chi}(t)/\chi(t)$. If the distribution of barrier crossing times, $f(t)$, is now determined from Eq. (4) (which is a consequence of defining the rate as a flux over a population[1]), with $\kappa(t)$ having the form above, one sees that $f(t) \sim \dot{\chi}(t)/\chi(t)^\mu$, where μ is some nonuniversal constant that contains details of the potential, the temperature, etc. This is also exactly the scaling structure of $f(t)$ that we had obtained from another model of barrier crossing;[7] that model used an

approximate Smoluchowski equation to determine $f(t)$ as the solution to a first passage time problem for the dynamics of an overdamped particle evolving under fGn in a *continuous* symmetric double well potential in which the barrier height was fixed by a single real number A (where $-1/2 < A < 0$).

The present calculations therefore establish *quantitatively* what it had earlier only been possible to suggest qualitatively, that Eq. (3) is entirely consistent with the results of the Hanggi–Mojtabai barrier crossing rate,[5] the Kohen–Tannor transmission coefficient,[6] and the first passage time distribution for the double well potential.[7] They also confirm, therefore, that the approximations used earlier to simplify Kramers' treatment of barrier crossing were reasonable and well motivated. Furthermore, by showing that the methods of functional calculus can be extended without approximation to phase space variables in the inertial regime, the calculations also complete and unify the program begun in Refs. 1 and 7 to describe single enzyme dynamics in the framework of Kramers' theory of chemical reaction rates.

However, these remarks must be qualified by an important caveat. With $f(t)$ in our calculations given by $N\dot\chi(t)/\chi(t)^\mu$, N being a time-independent prefactor, the mean barrier crossing time $\langle t \rangle = \int_0^\infty dt\, t f(t)$ is

$$\langle t \rangle = \frac{N}{1-\mu} \lim_{t\to\infty} t\chi(t)^{1-\mu} - \frac{N}{1-\mu} \int_0^\infty dt\, \chi(t)^{1-\mu}. \quad (14)$$

Now for both the inverted parabolic potential of Ref. 1 (which is also the potential used in the present calculations) and the symmetric double well potential of Ref. 7, the factor $1-\mu$ is negative and the function $\chi(t)$, given by $E_{2-2H}((t/\tau)^{2-2H})$, *grows* as an exponential at long times; so $\langle t \rangle$ in Eq. (14) is finite. This means that, asymptotically, a well-defined barrier crossing rate exists. However in a recent exact calculation,[17] Goychuk and Hanggi showed that in overdamped conditions the survival probability of a particle driven by $1/f$ noise in a cusp-shaped parabolic potential is asymptotically a power law in the time and that the escape time out of the potential, $\langle t \rangle_{GH}$, is therefore infinite, implying the *absence* of a well-defined barrier crossing rate.

The divergence of $\langle t \rangle_{GH}$ in these calculations has an interesting source: it comes from the integral shown below,

$$\langle t \rangle_{GH} \sim \int_0^\infty dt\, \chi_{GH}(t)^\nu, \quad (15)$$

where $\chi_{GH}(t) = E_\alpha(-(t/\tau_D)^\alpha)$, and α, ν, and τ_D are constants. The parallels between Eqs. (14) and (15) are obvious, but the difference in the sign of the arguments of the two Mittag–Leffler functions (which reflects the differences in the shapes of the respective potentials) leads to drastically different predictions because, on the one hand, $E_\alpha(-z) \overset{z\gg1}{\to} z^{-1}$, whereas on the other, $E_\alpha(z) \overset{z\gg1}{\to} \exp(z^{1/\alpha})$.

A meaningful rate description is recovered from the Goychuk–Hanggi model if an exponential cutoff at low frequencies is incorporated into the expression for the memory kernel, in which case the survival probability decays exponentially at long times [as in Eq. (14)] and the integral in
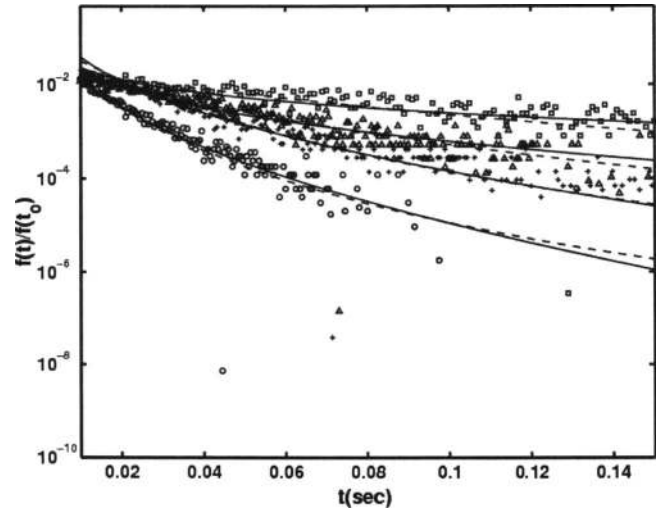

FIG. 1. Comparison of the theoretical waiting time distribution $f(t)$, normalized to a time t_0, calculated from Eq. (12) (full lines) with the corresponding experimental data of English *et al.* (Ref. 3) on the enzyme β-galactosidase (symbols) at four different substrate concentrations (10 μM, open squares; 20 μM, open triangles; 50 μM, plus signs; and 100 μM, open circles). The theoretical curves were constructed by adjusting the well frequency ω_0 and the barrier height $\Delta E/k_B T$ for best fit to these data after fixing $m\omega_b^2$ to 1 (in appropriate units) and $\zeta/m\omega_b^2$ to 0.714 s$^{1/2}$. The best fit values of ω_0 and $\Delta E/k_B T$ at the four substrate concentrations are given in the text. Also shown are normalized curves (dashed lines) derived from a fitting function discussed in Ref. 3.

Eq. (15) no longer diverges. One way of ensuring finiteness of the barrier crossing rate is to increase the height of the barrier, which would entail a clear separation of time scales between barrier crossing and equilibration within the metastable well. It is presumably exactly this condition that is implicit in the equation [Eq. (4)] that we have used to determine $f(t)$. These facts must be borne in mind whenever one considers escape processes governed by subdiffusive dynamics.

Other theoretical developments in the field of single-molecule enzyme dynamics have occurred over the past few years, including extensions of our model[1] that consider reaction and diffusion within the Michaelis–Menten mechanism[18] and that consider particle dynamics on free energy surfaces of two dimensions,[19] to cite two recent examples.

By way of conclusion, and for the sake of completeness, we now use Eq. (12) in the overdamped limit to recompute $f(t)$ from Eq. (4) for the case of fractional Gaussian noise, with H chosen to be 3/4 as before and $\chi(t) = E_{1/2}(\sqrt{t/\tau})$. The calculated curves of the distribution are shown as full lines in Fig. 1, where they are compared with data on β-galactosidase from Ref. 3 at four different concentrations of added substrate: 10 μM, open squares; 20 μM, open triangles; 50 μM, plus signs; and 100 μM, open circles. In constructing these curves [which have been normalized by the value of $f(t)$ at some t_0 chosen to ensure that they coincide with the experimental data at the same initial time], the well frequency ω_0 and the barrier height ΔE were adjusted for a best fit to the data, keeping $m\omega_B^2$ and $\zeta/m\omega_B^2$ fixed, respectively at 1 (in suitable units) and 0.714 s$^{1/2}$. (The decay constant τ thus assumes the fixed value of 0.9 s.) The

best fit values of ω_0 and $\Delta E/k_B T$ were found to be, respectively, $3.8\pi \times 10^{11}$ s^{-1} and 25.0 (for the 10 μM data), $8\pi \times 10^{11}$ s^{-1} and 24.8 (for the 20 μM data), $1.45\pi \times 10^{12}$ s^{-1} and 24.67 (for the 50 μM data), and $2\pi \times 10^{12}$ s^{-1} and 24.67 (for the 100 μM data). These values are physically reasonable and very close to the corresponding values determined earlier.[1] Also shown in the figure are curves obtained from the fitting function discussed in Ref. [3] (dashed lines). The theoretical curves obtained from Eq. (12) are seen to be in very good agreement with the experimental data at all concentrations, and their fits are indistinguishable, for all practical purposes, from the fits found in the corresponding calculations of Ref. [1].

Owing to the limited time span over which the data on β-galactosidase have been collected, the agreement between experiment and theory in Fig. 1 is not necessarily a validation of our model, and other simpler models might do equally well in fitting the data. However, the present results should be seen in the context of the success that the model (or its variants) has had in characterizing the dynamics of other complex soft matter system.[20]

ACKNOWLEDGMENTS

APPENDIX: THE PHASE SPACE FOKKER–PLANCK EQUATION

To derive the phase space FPE shown in Eq. (5) using functional methods,[8] the definition $v(t) = \dot{x}(t)$ is first substituted into Eq. (1), and the equation then solved for $x(t)$, using Laplace transforms. With $U(x)$ an inverted parabola, the result is

$$x(t) = x_0\chi(t) + v_0\int_0^t dt'\chi(t-t')\bar{\xi}(t') - x_b\omega_b^2\int_0^t dt'\chi(t-t')$$
$$\times\bar{\beta}(t') + \frac{1}{m}\int_0^t dt'\chi(t-t')\bar{\gamma}(t'), \qquad (A1)$$

where $\hat{\bar{\xi}}(s) = 1/[s + \zeta\hat{K}(s)/m]$, $\hat{\bar{\beta}}(s) = \hat{\bar{\xi}}(s)/s$, $\hat{\bar{\gamma}}(s) = \hat{\bar{\xi}}(s)\hat{\theta}(s)$, and $\hat{\chi}(s) = 1/[s - \omega_b^2\hat{\bar{\xi}}(s)]$. An equation for $\dot{x}(t)$ in which x_0 has been eliminated is now derived by multiplying all but the first term on the right hand side of Eq. (A1) by $\chi(t)/\chi(t)$ and then differentiating the equation with respect to t. This yields

$$\dot{x}(t) = -\eta(t)x(t) + v_0\bar{\xi}(t) - x_b\omega_b^2\bar{\beta}(t) + \bar{\gamma}(t). \qquad (A2)$$

Here $\eta(t) = -\dot{\chi}(t)/\chi(t)$, $\bar{\xi}(t)/\chi(t) = (d/dt)\Delta_\xi(t,t')$, $\bar{\beta}(t)/\chi(t) = (d/dt)\Delta_\beta(t,t')$, and $\bar{\gamma}(t)/\chi(t) = (1/m)(d/dt)\Delta_\gamma(t,t')$, with $\Delta_z(t,t') \equiv 1/\chi(t)\int_0^t dt'\chi(t-t')Z(t')$ and $Z(t)$ standing for $\xi(t)$, $\beta(t)$, or $\gamma(t)$.

The function $\bar{\xi}(t)$ can be simplified to $\bar{\xi}(t) = -\chi(t)\dot{\eta}(t)/\omega_b^2$ by evaluating $\int_0^t dt'\chi(t-t')\xi(t')$ from

$\mathcal{L}^{-1}\hat{\chi}(s)\hat{\xi}(s)$ ($\mathcal{L}^{-1}$ being the inverse Laplace operator) after replacing $\hat{\xi}(s)$ by its expression in terms of $\hat{\chi}(s)$. In the same way, $\bar{\beta}(t)$ can be reduced to $\bar{\beta}(t) = -\eta(t)/\omega_b^2$. Equation (A2) is the defining equation for the evolution of $x(t)$.

A related equation for the evolution of $v(t)$ in which v_0 has been eliminated is obtained by multiplying all but the second term on the right hand side of Eq. (A2) by $\bar{\xi}(t)/\bar{\xi}(t)$ and then differentiating the equation with respect to t; after substituting $\bar{\beta}(t) = -\eta(t)/\omega_b^2$ into the equation and collecting terms, it is found that

$$\dot{v}(t) = -\Xi(t)v(t) + \Omega^2(t)(x(t) - x_b) + \lambda(t), \qquad (A3)$$

where $\Xi(t) = \eta(t) - \dot{\bar{\xi}}(t)/\bar{\xi}(t)$, $\Omega^2(t) = -\bar{\xi}(t)(d/dt)[\eta(t)/\bar{\xi}(t)]$, and $\lambda(t)$ is a new random variable: $\lambda(t) \equiv \bar{\xi}(t)(d/dt)[\bar{\gamma}(t)/\bar{\xi}(t)]$. Equation (A3) is the defining equation for $v(t)$.

The equations for $\dot{x}(t)$ and $\dot{v}(t)$ are substituted into the expression obtained after differentiating (with respect to t) the definition of the phase space probability density, $P(x,v,t) \equiv \langle\delta(x-x(t)\,\delta(v-v(t)\,\rangle$; the use of Novikov's theorem[21] in the result yields

$$\frac{\partial P}{\partial t} = -v\frac{\partial P}{\partial x} + \Xi(t)\frac{\partial}{\partial v}vP - \Omega^2(t)(x-x_b)\frac{\partial P}{\partial v} + \frac{\partial^2 P}{\partial v\partial x}Y_1$$
$$+ \frac{\partial^2 P}{\partial v^2}Y_2, \qquad (A4)$$

where $Y_1 \equiv \int_0^t dt'\langle\lambda(t)\lambda(t')\rangle[\delta x(t)/\delta\lambda(t')]$ and $Y_2 \equiv \int_0^t dt'\langle\lambda(t)\lambda(t')\rangle[\delta v(t)/\delta\lambda(t')]$. The functional derivatives in Y_1 and Y_2 are obtained as follows. First, Eq. (A2) is functionally differentiated with respect to $\lambda(t')$, producing $(d/dt)[\delta x(t)/\delta\lambda(t')] = -\eta(t)[\delta x(t)/\delta\lambda(t')] + \delta\bar{\gamma}(t)/\delta\lambda(t')$. The equation for $\lambda(t)$ is next rewritten as $d\bar{\gamma}(t)/dt = [\dot{\bar{\xi}}(t)/\bar{\xi}(t)]\bar{\gamma}(t) + \lambda(t)$ and similarly differentiated with respect to $\lambda(t')$ to give $(d/dt)[\delta\bar{\gamma}(t)/\delta\lambda(t')] = (\dot{\bar{\xi}}(t)/\bar{\xi}(t))\times[\delta\bar{\gamma}(t)/\delta\lambda(t')] + \delta(t-t')$. The solution of this equation is $\delta\bar{\gamma}(t)/\delta\lambda(t') = H(t-t')\exp[\int_{t'}^t ds[\dot{\bar{\xi}}(s)/\bar{\xi}(s)]]$, where $H(x)$ is the step function. From these equations, it is easily shown that

$$\frac{\delta x(t)}{\delta\lambda(t')} = \frac{1}{\bar{\xi}(t')}\int_{t'}^t ds\bar{\xi}(s)\exp\left[-\int_s^t ds'\,\eta(s')\right]. \qquad (A5)$$

The relation $\bar{\xi}(s) = -\chi(s)\dot{\eta}(s)/\omega_b^2$ is now substituted into the term $I_1 \equiv \int_{t'}^t ds\bar{\xi}(s)\exp[-\int_s^t ds'\,\eta(s')]$, and the result is integrated by parts to produce $I_1 = (1/\omega_b^2)(\dot{\chi}(t) - \chi(t)\times[\dot{\chi}(t')/\chi(t')])$, which is then substituted into the integral Y_1, along with Eq. (A5) and the definition of the random variable $\lambda(t)$ [defined after Eq. (A3)]. This leads to

$$Y_1 = \frac{1}{\omega_b^2}\left\langle \lambda(t)\int_0^t dt'\bar{\xi}(t')\left(\frac{d}{dt'}\frac{\bar{\gamma}(t')}{\bar{\xi}(t')}\right)\right.$$
$$\left.\times\frac{1}{\bar{\xi}(t')}\left(\dot{\chi}(t) - \chi(t)\frac{\dot{\chi}(t')}{\chi(t')}\right)\right\rangle. \qquad (A6)$$

After the integration of Eq. (A6) by parts, substitution of

$\bar{\gamma}(0)=0$ (as indicated later, $\bar{\xi}(0)=1$), and use of the relation $d\eta(t)/dt=-\omega_b^2[\bar{\xi}(t)/\chi(t)]$, it is found, after some algebra, that

$$Y_1 = \left\langle \bar{\xi}(t)\chi(t)\frac{d}{dt}\left(\frac{1}{\bar{\xi}(t)}\int_0^t dt'\frac{\bar{\gamma}(t)\bar{\gamma}(t')}{\chi(t')}\right)\right\rangle - \langle\bar{\gamma}(t)^2\rangle. \tag{A7}$$

Double Laplace transforms are introduced into the definition of $\bar{\gamma}(t)$ [defined after Eq. (A2)] to evaluate the correlation function $\langle\bar{\gamma}(t)\bar{\gamma}(t')\rangle$. In this way it can be shown that

$$\langle\bar{\gamma}(t)\bar{\gamma}(t')\rangle = \frac{1}{m^2}\chi(t)\chi(t')\left[\frac{mk_BT}{\omega_b^2}\frac{\dot{\chi}(t')}{\chi(t')^2}\right.$$
$$\times\left\{-\frac{\dot{\chi}(t)}{\chi(t)^2}\chi(|t-t'|)+\frac{1}{\chi(t)}\frac{d}{dt}\chi(|t-t'|)\right\}$$
$$-\frac{mk_BT}{\omega_b^2}\frac{1}{\chi(t')}\left\{-\frac{\dot{\chi}(t)}{\chi(t)^2}\frac{d}{dt'}\chi(|t-t'|)\right.$$
$$\left.+\frac{1}{\chi(t)}\frac{d}{dt}\frac{d}{dt'}\chi(|t-t'|)\right\}-\frac{mk_BT}{\omega_b^4}\dot{\eta}(t)\dot{\eta}(t')\left.\right]. \tag{A8}$$

From the definition of $\bar{\xi}(t)$, it can also be shown that $\bar{\xi}(0)=\xi(0)=1$ and that $\ddot{\chi}(0)=\omega_b^2$. So, from Eq. (A8), we eventually find

$$\langle\bar{\gamma}(t)^2\rangle = -\frac{k_BT}{m\omega_b^2}[\eta(t)^2-\omega_b^2]-\frac{k_BT}{m\omega_b^4}\chi(t)^2\dot{\eta}(t)^2. \tag{A9}$$

The integral $I_2 \equiv \int_0^t dt'[1/\chi(t')]\langle\bar{\gamma}(t)\bar{\gamma}(t')\rangle$ in Eq. (A7) is now written as $I_2=(1/2m^2)\langle\chi(t)(d/dt)[1/\chi(t)^2]\int_0^t dt_1\int_0^t dt_2\chi(t-t_1)\chi(t-t_2)\gamma(t_1)\gamma(t_2)\rangle$ by substituting the definitions of $\bar{\gamma}(t)$ and $\bar{\gamma}(t')$ and rearranging. The application of double Laplace transforms to the result yields $I_2=(k_BT/m\omega_b^2)[\dot{\chi}(t)/\chi(t)^2]-(k_BT/m\omega_b^4)\chi(t)\eta(t)\dot{\eta}(t)$. Substituting I_2 into Eq. (A7), using $\bar{\xi}(t)=-\chi(t)\dot{\eta}(t)/\omega_b^2$, and simplifying further, we have

$$Y_1 = \int_0^t dt'\langle\lambda(t)\lambda(t')\rangle\frac{\delta x(t)}{\delta\lambda(t')}$$
$$= \frac{k_BT}{m\omega_b^2}\left[\frac{\dot{\chi}(t)\dddot{\chi}(t)-\ddot{\chi}(t)^2}{\dot{\chi}(t)^2-\chi(t)\ddot{\chi}(t)}-\omega_b^2\right]. \tag{A10}$$

The above relation leads to the identification, $\Omega^2(t)=[\dot{\chi}(t)\dddot{\chi}(t)-\ddot{\chi}(t)^2]/[\dot{\chi}(t)^2-\chi(t)\ddot{\chi}(t)]$. For the purely Markovian case, the memory function in Eq. (1) is delta correlated, and $\chi(t)$ is the sum of two exponentials; in this case, $\Omega^2(t)$ reduces to ω_b^2, so the mixed derivative contribution to the phase space FPE vanishes, as it should.

The evaluation of Y_2 [see Eq. (A4)] is carried out along much the same lines. Since $\dot{x}(t)=v(t)$, the expressions for $d\bar{\gamma}(t)/dt$, $\delta x(t)/\delta\lambda(t')$, and I_1 together yield

$$\frac{\delta v(t)}{\delta\lambda(t')} = -\frac{1}{\omega_b^2}\frac{\eta(t)}{\bar{\xi}(t')}\chi(t)[-\eta(t)+\eta(t')]+\theta(t-t')\frac{\bar{\xi}(t)}{\bar{\xi}(t')}. \tag{A11}$$

Therefore,

$$Y_2 = \frac{1}{\omega_b^2}\left\langle\lambda(t)\int_0^t dt'\left(\frac{d}{dt'}\frac{\bar{\gamma}(t')}{\bar{\xi}(t')}\right)[\eta(t)^2\chi(t)\right.$$
$$\left.-\eta(t)\chi(t)\eta(t')+\omega_b^2\bar{\xi}(t)]\right\rangle \equiv I_A - I_B + I_C, \tag{A12}$$

where I_A can be found at once, $I_A=(1/\omega_b^2)\langle\lambda(t)\eta(t)^2\chi(t)\times[\bar{\gamma}(t)/\bar{\xi}(t)]\rangle$. I_B is evaluated by first substituting $\bar{\xi}(t)=-\chi(t)\dot{\eta}(t)/\omega_b^2$ into the expression, after which it is written as $I_B=I_A+I_B^{(1)}$, where $I_B^{(1)}=\langle\lambda(t)\eta(t)\chi(t)\int_0^t dt'[\bar{\gamma}(t')/\chi(t')]\rangle$. This integral, after introducing $\lambda(t)$ and simplifying, produces $I_B^{(1)}=\bar{\xi}(t)\eta(t)\chi(t)(d/dt)[1/\xi(t)]I_2-\eta(t)\langle\bar{\gamma}(t)^2\rangle$. Here, I_2 is the same integral defined after Eq. (A9). Finally, I_C can be immediately reduced to $I_C=-[\dot{\bar{\xi}}(t)/\bar{\xi}(t)]\langle\bar{\gamma}(t)^2\rangle+(1/2)(d/dt)\langle\bar{\gamma}(t)^2\rangle$. After putting these results for I_A, I_B, and I_C back into the expression for Y_2, substituting for $\langle\bar{\gamma}(t)^2\rangle$, and simplifying, the result is

$$Y_2 = \int_0^t dt'\langle\lambda(t)\lambda(t)'\rangle\frac{\delta v(t)}{\delta\lambda(t')} = -\left(\frac{\dot{\bar{\xi}}(t)}{\bar{\xi}(t)}-\eta(t)\right)\frac{k_BT}{m\omega_b^2}\omega_b^2, \tag{A13}$$

which leads, finally, to the identification $\Xi(t)=\eta(t)-\dot{\bar{\xi}}(t)/\bar{\xi}(t)=[\chi(t)\dddot{\chi}(t)-\dot{\chi}(t)\ddot{\chi}(t)]/[\dot{\chi}(t)^2-\chi(t)\ddot{\chi}(t)]$. For the purely Markovian case, $\Xi(t)$ reduces to the constant ζ/m, as it should.

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