

# A minimal model of the internal friction of proteins based on two elastically coupled reaction coordinates

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Based on two elastically coupled reaction coordinates, representing the surface motion and the internal rearrangement of a protein, we introduce and analyze a simple model for the interpretation of the viscosity dependence of the rate constant of a broad range of conformational transitions. We show how the short-wavelength components of the roughness of the protein’s energy landscape can combine together to provide an internal friction. Our model reproduces and explains a variety of experimental observations, including the Arrhenius-like temperature dependence of the apparent internal friction coefficient. A consequence of the model is that the activation energy of the transition is reduced by that of the internal friction.

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The temperature dependence of reaction rates usually follows the Arrhenius equation remarkably well. Furthermore, in case of strong friction (i.e., in the over-damped regime), valid for most enzymatic reactions and protein conformational changes, Kramers showed that the rate constant ( $k$ ) of a reaction is inversely proportional to the friction coefficient ( $\gamma$ ) characterizing the reaction coordinate [1, 2]:

$$k = \frac{1}{\gamma} A_0 \exp\left(-\frac{\Delta E_a}{k_B T}\right), \quad (1)$$

where  $\Delta E_a$  is the activation energy of the reaction,  $k_B$  is the Boltzmann constant,  $T \approx 300$  K is the absolute temperature, and  $A_0$  is a temperature- and friction-independent prefactor.

The origin of friction is poorly understood. For protein conformational changes it has two main ingredients. One is the external friction caused by the displacement of the molecules of the surrounding medium (mostly water), and a concomitant reorganization of a large number of non-linear intermolecular interactions, through which mechanical energy is dissipated into heat. The other one is the *internal friction*, resulting from a similar reorganization of non-linear intramolecular interactions (bonding and non-bonding alike) inside the protein. How these two friction sources couple to each other to produce a single friction coefficient ( $\gamma$ ) is not obvious. Several experiments have been performed to separate the effects of the external friction by varying the viscosity ( $\eta$ ) of the external medium through the addition of viscogenic cosolvents (for a comprehensive review see Ref. [3]). In many cases [4–7] a simple linear contribution of the viscosity to the friction coefficient was observed:

$$\gamma \propto \eta + \sigma, \quad (2)$$

where the parameter  $\sigma$ , which characterizes the relative contribution of the internal friction, can be referred to as the “apparent internal viscosity.” Note that the authors of Refs. [5, 6] attributed the viscosity dependent and independent terms of the

reciprocal rate constant to “solvent friction-controlled” and “internal friction-controlled” time scales, respectively, and thus considered the transitions to be composed of two sequential, rather than parallel processes. Their clearly mono-exponential relaxation data, however, contradicts to this picture, and better support a single process that is affected by both external and internal friction in parallel.

Some of the experiments performed at different temperatures [5–7] indicated that this internal viscosity parameter (similarly to the viscosity of liquids) also follows an Arrhenius-like temperature dependence:

$$\sigma = \sigma_0 \exp\left(\frac{\Delta E_\sigma}{k_B T}\right) \quad (3)$$

with an apparent activation energy  $\Delta E_\sigma$  and prefactor  $\sigma_0$ . Recent experimental evidences on the activation of trypsin [7] indicated that single point mutations in the hinge region of the protein can alter the apparent activation energies of both the conformational change ( $\Delta E_a$ ) and the internal friction ( $\Delta E_\sigma$ ), but in such a way that their sum remains essentially unaltered.

In other cases [8, 9] the friction coefficient exhibited a decreasing slope as the viscosity was increased, and could be better fitted by a power function  $\gamma \propto \eta^p$  with exponent  $p$  (where  $0 < p < 1$ ). This exponent, however, is difficult to interpret. Several concepts were proposed to explain the power-law dependence, including the difference between macroviscosity and microviscosity [9–11]; or the possibility of frequency-dependent friction [12]; or the presence of a second, slowly fluctuating, *perpendicular* reaction coordinate [13]. For a specific model Zwanzig showed [14] that if it is only this second reaction coordinate that is influenced by the viscosity of the external medium, then the viscosity dependence of the reaction rate can indeed follow a power-law. Note also, that in a narrow viscosity range near the viscosity of water the two (linear and power-law) formulae fit the experimental data equally well, and for large viscosities the

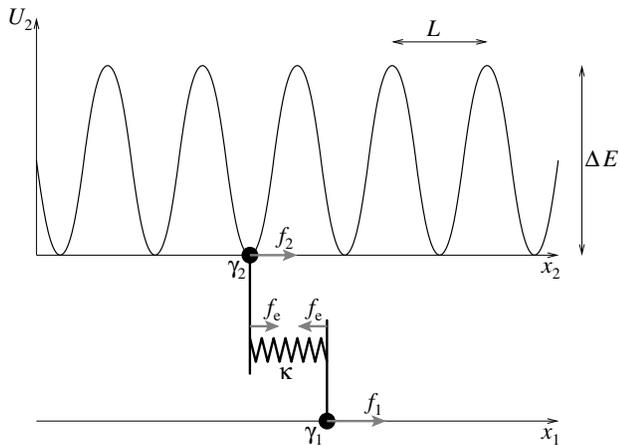


FIG. 1. Schematic representation of the model of two reaction coordinates coupled by a harmonic potential with spring constant  $\kappa$ . The external reaction coordinate ( $x_1$ ) characterized by friction coefficient ( $\gamma_1$ ) experiences a flat potential, whereas the internal one ( $x_2$ ) characterized by friction coefficient ( $\gamma_2$ ) moves in a sinusoidal potential, representing one of the short wavelength components of the rough energy landscape of the protein. The pulling forces ( $f_1$  and  $f_2$ ) and elastic forces ( $-f_e$  and  $f_e$ ) are denoted by gray arrows.

observed deviation from linearity might be attributed to the adverse effects of the high concentrations of the cosolvent. It is well possible that no unified theory exists for the description of the viscosity dependence of reaction rates, but rather, different enzymatic reactions and conformational changes can be grouped into several different classes.

Based on two elastically coupled *parallel* reaction coordinates (corresponding to the surface motion and the internal rearrangement of the molecule, respectively), here we introduce and analyze a new concept for the interpretation of the viscosity dependence of the rate constant of a broad range of reactions. This concept explains the Arrhenius-like temperature dependence of the apparent internal friction, as well as the invariability of the sum of the apparent activation energies of the reaction ( $\Delta E_a$ ) and the internal friction ( $\Delta E_\sigma$ ). Under certain conditions it also provides a decreasing slope to the friction coefficient ( $\gamma$ ) as a function of the external viscosity. Our analytical calculations supplemented with numerical simulations demonstrate that depending on the coupling strength between the two reaction coordinates (which is related to the flexibility of the molecule) there exists a cross-over length scale, below which all the short-wavelength components of the roughness of the energy landscape blend into the apparent internal friction.

During a conformational change not only the surface of the protein moves with respect to the external aqueous environment, but its interior also rearranges. It is thus natural to distinguish two reaction coordinates: an external one ( $x_1$ ) characterizing the motion of the surface, and an internal one ( $x_2$ ) corresponding to the internal rearrangement. The two reaction coordinates are not independent of each other, as the elastic body of the protein couples them together. Their coupling is

characterized by a harmonic potential

$$U_{12}(x_1, x_2) = \frac{\kappa}{2}(x_1 - x_2)^2, \quad (4)$$

with coupling strength  $\kappa$  (Fig. 1). The external reaction coordinate represents the interaction of the surface of the protein with the solvent, so it experiences a flat potential and its friction coefficient  $\gamma_1$  is considered proportional to the viscosity ( $\eta$ ) of the external medium. The internal reaction coordinate, on the other hand, is hidden from the solvent, and it experiences the hierarchically organized, rough energy landscape of the protein [15, 16]. Our aim is to show that the short wavelength components of the roughness constitute a viscosity independent friction coefficient of this reaction coordinate. To this end we assume that all components below wavelength  $L$  are already incorporated into the internal friction coefficient  $\gamma_2$ , and we take the component with wavelength  $L$  into consideration explicitly:

$$U_2(x_2) = \Delta E \frac{1 - \cos(2\pi x_2/L)}{2}, \quad (5)$$

where  $\Delta E$  is the height (i.e., twice the amplitude) of this component. All longer wavelength components (including the transition barrier of the conformational change) are omitted from now on, because we are only interested in the contribution of this selected component of the landscape roughness to the internal friction coefficient.

Let us recall [17, 18] that if  $x_2$  were decoupled from  $x_1$  (which is equivalent to setting  $\gamma_1 = 0$ ) and, thus, moved in a one-dimensional sinusoidal potential, then on the long scale it would exhibit a diffusive motion with effective friction coefficient

$$\gamma_2 I_0^2\left(\frac{\Delta E}{2k_B T}\right) \approx \gamma_2 \frac{k_B T}{\pi \Delta E} \exp\left(\frac{\Delta E}{k_B T}\right), \quad (6)$$

where  $I_0$  is the modified Bessel function of the first kind, and the approximation holds for  $\Delta E > k_B T$ .

Now we can turn to the questions of how the long-scale diffusion of the coupled system – which governs the time scale of any long-scale processes, including the crossing of the transition barrier of the conformational change – depends on the external friction coefficient ( $\gamma_1$ ); and under what conditions the periodic potential of the internal reaction coordinate merges into the internal friction coefficient. Based on the fluctuation-dissipation theorem, instead of determining the diffusion coefficient of the unperturbed system directly, we apply small forces  $f_1$  and  $f_2$  on the two reaction coordinates, respectively, and determine their average drift velocity, which is also proportional to the diffusion coefficient. This latter method is numerically more efficient and accurate. The drift velocity, due to the coupling, must be the same for both reaction coordinates, and it is expected to be proportional to the sum of the two forces,  $f = f_1 + f_2$ , as long as their energetic perturbation per period is much smaller than  $k_B T$ , i.e.,  $f_1, f_2 \ll k_B T/L$ .

In two limiting cases the drift velocity can be calculated analytically [7]. For strong coupling ( $\kappa L^2 \gg \Delta E$ ), i.e., when

the separation of the two reaction coordinates over the period-length requires much larger energy than the height of the periodic potential, the two reaction coordinates behave as a single one and, thus, their average speed is:

$$v_{\kappa \rightarrow \infty} = \frac{f}{(\gamma_1 + \gamma_2) I_0^2 \left( \frac{\Delta E}{2k_B T} \right)} \approx \frac{f}{(\gamma_1 + \gamma_2) \frac{k_B T}{\pi \Delta E} \exp \left( \frac{\Delta E}{k_B T} \right)}. \quad (7)$$

For weak coupling ( $\kappa L^2 \ll \Delta E$ ) the change of the elastic energy is negligible (relative to the barrier heights) when the separation of the two reaction coordinates changes by an amount comparable to the period-length, thus, an essentially position independent elastic force ( $-f_e$  and  $f_e$ , respectively) can be assumed between them. The drift velocity for

$$v_{\kappa \rightarrow 0} = \frac{f_1 - f_e}{\gamma_1}, \quad (8)$$

$$v_{\kappa \rightarrow 0} = \frac{f_2 + f_e}{\gamma_2 I_0^2 \left( \frac{\Delta E}{2k_B T} \right)}, \quad (9)$$

from which, after eliminating  $f_e$ , we arrive at

$$v_{\kappa \rightarrow 0} = \frac{f}{\gamma_1 + \gamma_2 I_0^2 \left( \frac{\Delta E}{2k_B T} \right)} \approx \frac{f}{\gamma_1 + \gamma_2 \frac{k_B T}{\pi \Delta E} \exp \left( \frac{\Delta E}{k_B T} \right)}. \quad (10)$$

In both limits the drift velocity takes the form

$$v = \frac{f}{\gamma_1 + \gamma_2^{\text{eff}}(T)} A(T), \quad (11)$$

where  $\gamma_2^{\text{eff}}(T)$  is the apparent internal friction of the system, and  $A(T)$  is the apparent activation function of the diffusion process. For strong coupling the periodic potential leaves the internal friction unaffected, and the potential height contributes to the activation energy of the process. For weak coupling the exact opposite occurs, as the potential affects only the apparent internal friction, and the potential height contributes to the activation energy of the internal friction.

To determine the cross-over between the two limits, we numerically determined the steady-state probability distribution and current density of the discretized version of the corresponding Fokker-Planck equation (using lattice constant  $\Delta x$ ) for  $f_1 = f_2 = 0.01 k_B T / L$ . For symmetry reasons (i.e., to satisfy that the velocity is an odd function of the force) the leading term of the discretization error of the drift velocity has to scale as  $(f \Delta x)^2 / (k_B T)^2$ . We used this scaling property to extrapolate to the continuum limit. We verified that for small forces ( $f_1, f_2 \ll k_B T / L$ ) the resulting drift velocity was indeed proportional to  $f = f_1 + f_2$ , and it was independent of how  $f$  was distributed among  $f_1$  and  $f_2$ .

Our model has three independent parameters, which, in dimensionless form, are  $\gamma_1 / \gamma_2$ ,  $\kappa L^2 / \Delta E$ , and  $\Delta E / k_B T$ . We explored a wide range of  $\gamma_1 / \gamma_2$  and  $\kappa L^2 / \Delta E$  values, and to determine the temperature dependence of the measured quantities, we applied three different temperatures (or potential heights):  $\Delta E / k_B T = 10, 11$ , and 12. This temperature range

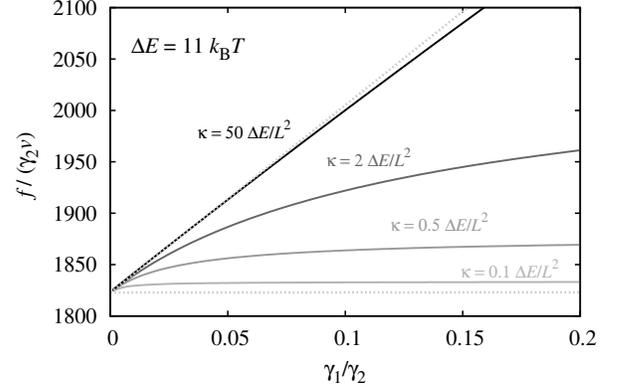


FIG. 2. The reciprocal of the drift velocity ( $1/v$ , in units of  $\gamma_2/f$ ), which is proportional to the total friction coefficient ( $\gamma$ ), as a function of the external friction coefficient ( $\gamma_1$ , in units of  $\gamma_2$ ) for  $\Delta E = 11 k_B T$  and four different values of  $\kappa$ . The lower dotted line represents the  $\kappa = 0$  limit, whereas the upper one shows the  $\kappa \rightarrow \infty$  limit. The curves start from the common value of  $I_0^2[\Delta E / (2k_B T)]$  at  $\gamma_1 = 0$ , and converge to straight lines of different slopes for  $\gamma_1 \rightarrow \infty$ .

allowed the potential height to exceed the thermal energy scale considerably, yet it ensured high numerical accuracy.

We found that the reciprocal of the drift velocity ( $1/v$ ), which is proportional to the total friction coefficient ( $\gamma$ ), as a function of the external friction coefficient ( $\gamma_1$ ) has dual characteristics (Fig. 2). For large values of the external friction coefficient ( $\gamma_1 \gtrsim \gamma_2$ ) it converges to a straight line (with a slope depending on  $\kappa$ ) and recovers Eq. 2, which is consistent with the existence of an apparent internal viscosity [4–7]. For smaller values ( $\gamma_1 \lesssim \gamma_2$ ) it exhibits an unexpected, non-linear behavior, with a decreasing slope, resembling to some of the experimental observations [8, 9]. It is uncertain, however, if it is this non-linearity that is manifested in the observed power-law dependence of these experiments. The reason of the deviation from linearity is that for  $\gamma_1 \ll \gamma_2$  the fast external reaction coordinate is slaved by the slow internal one and, thus, the system behaves as if the external reaction coordinate was rigidly coupled to the internal one (i.e.,  $\kappa L^2 / \Delta E \gg 1$ ). This is why each curve converges to the  $\kappa \rightarrow \infty$  line for small  $\gamma_1 / \gamma_2$ , and then takes the value of  $I_0^2[\Delta E / (2k_B T)]$  at  $\gamma_1 / \gamma_2 = 0$ .

Since  $1/v$  is an almost linear function of  $\gamma_1$  for  $\gamma_1 \gtrsim \gamma_2$ , it can be well fitted by Eq. 11. The resulting values of  $\gamma_2^{\text{eff}}(T)$  and  $A(T)$  as functions of the coupling strength ( $\kappa$ ) are plotted in Fig. 3 at three different temperatures and four selected values of  $\gamma_1 / \gamma_2$ . Both  $\gamma_2^{\text{eff}}(T)$  and  $A(T)$  have Arrhenius-like temperature dependence:

$$\frac{\gamma_2^{\text{eff}}(T)}{\gamma_2} = c_\sigma I_0^2 \left( \frac{\Delta E_\sigma}{2k_B T} \right) \approx c_\sigma \frac{k_B T}{\pi \Delta E_\sigma} \exp \left( \frac{\Delta E_\sigma}{k_B T} \right), \quad (12)$$

$$A(T) = c_a I_0^{-2} \left( \frac{\Delta E_a}{2k_B T} \right) \approx c_a \frac{\pi \Delta E_a}{k_B T} \exp \left( -\frac{\Delta E_a}{k_B T} \right), \quad (13)$$

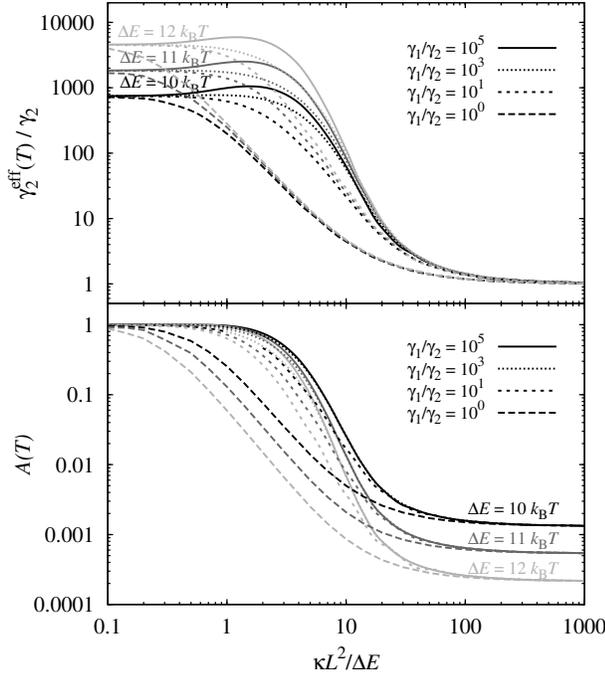


FIG. 3. The apparent internal friction coefficient ( $\gamma_2^{\text{eff}}(T)$ , in units of  $\gamma_2$ , top panel) and apparent activation function ( $A(T)$ , bottom panel) as functions of the coupling strength ( $\kappa$ , in units of  $\Delta E/L^2$ ) at three different temperatures (distinguished by gray-scale) and four selected values of  $\gamma_1/\gamma_2$  (distinguished by line-type).

where  $c_\sigma$  and  $c_a$  are two fitting coefficients (of the order of unity). The apparent activation energies of the internal friction ( $\Delta E_\sigma$ ) and the diffusion process ( $\Delta E_a$ ) are plotted in Fig. 4 as functions of the coupling strength ( $\kappa$ ). They converge to the analytically predicted values (see Eqs. 7 and 10) in the limits of weak and strong coupling. One can also notice that these apparent activation energies cross over from one of the limiting values to the other one in a narrow range of  $\kappa$ , and that  $\Delta E_\sigma + \Delta E_a \approx \Delta E$  throughout the entire parameter range.

For  $\gamma_1 \gg \gamma_2$  the value of  $\Delta E_a$  can also be estimated, as under this condition it is the fast internal reaction coordinate that is slaved by the slow external one, so at any position  $x_1$  of the external reaction coordinate the position  $x_2$  of the internal one can be integrated out, providing the restricted free energy

$$F_1(x_1) = -k_B T \ln \int_{-\infty}^{\infty} \exp \left[ -\frac{U_2(x_2) + U_{12}(x_1, x_2)}{k_B T} \right] dx_2 \quad (14)$$

to the external reaction coordinate. The height of this free energy ( $F_1(L/2) - F_1(0)$ ) is plotted as circles in Fig. 4, and indeed it approximates  $\Delta E_a$  remarkably well for  $\gamma_1 \gg \gamma_2$ .

In conclusion, our simple model of elastically coupled internal and external reaction coordinates can reproduce a variety of experimental observations and, thus, sheds light on the physical origin of the viscosity and temperature dependence of the rate constant of a broad range of enzymatic reactions and protein conformational changes. When the inter-

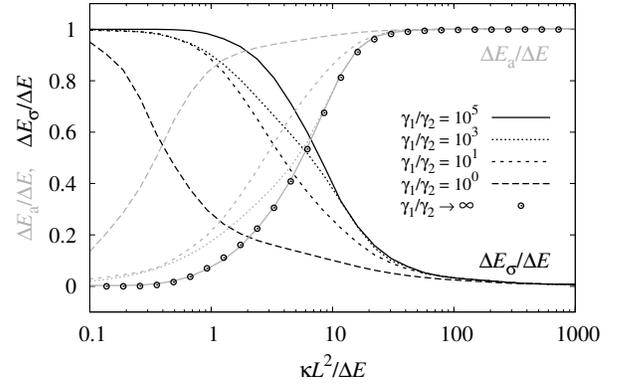


FIG. 4. The apparent activation energies (in units of  $\Delta E$ ) of the internal friction ( $\Delta E_\sigma$ , black lines) and the diffusion process ( $\Delta E_a$ , gray lines) as functions of the coupling strength ( $\kappa$ , in units of  $\Delta E/L^2$ ) at four values of  $\gamma_1/\gamma_2$  (distinguished by line-type). The approximation in the  $\gamma_1/\gamma_2 \rightarrow \infty$  limit is plotted as circles.

nal friction dominates (e.g., the reaction involves mostly the rearrangement of the interior of the protein), the total friction coefficient ( $\gamma \propto 1/v$ ) can exhibit a decreasing slope as the external friction is increased. On the other hand, when the external friction is more relevant, then up to a wavelength  $L \approx \sqrt{\Delta E/\kappa}$ , the roughness of the internal potential merges into a well defined apparent internal friction coefficient, and provides an additive contribution to the external friction coefficient. Intuitively, the flexibility of the protein smears out and seemingly eliminates the short-scale roughness of the internal potential (leaving all the long-scale components intact) and, at the same time, blends it into an apparent internal friction. The most important consequences of this phenomenon are that the internal friction follows an Arrhenius-like temperature dependence, and that its apparent activation energy reduces the apparent activation energy of the conformational transition by about the same amount. This latter effect is consistent with one of the most recent experiments [7], in which changing the flexibility of the protein (by introducing a point mutation) the apparent internal friction coefficient changed in such a manner that the sum of the apparent activation energies of the internal friction and of the reaction remained largely intact. For nanometer-sized protein domains with Young moduli of a few gigapascals, and for landscape roughness of the order of 10 kJ/mol, the cross-over wavelength falls into the physically reasonable angstrom range, justifying the relevance of our concept and its predictions.

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