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VISCOSITY SCALING AND PROTEIN DYNAMICS

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The rates of molecular motions in the interior of some proteins were found to scale with an inverse power of the external solvent viscosity. The data were explained by a flexible protein structure whose dynamics is partially controlled by the solvent. Reaction dynamics in the presence of structural fluctuations with finite lifetimes lead to a dynamic friction coefficient defined by a generalized Langevin equation and a fluctuation-dissipation theorem. A model for the dynamic friction is derived assuming that the fluctuation spectrum at the reaction site involves two components: solvent-independent diffusion of local structural defects in the protein matrix and global fluctuations coupled to the solvent. The theory is applied to the viscosity dependence of molecular oxygen-binding rates in sperm whale myoglobin.

1. Introduction

The conformation and stability of proteins depend critically on the equilibrium properties of the solvent like chemical composition, pH, ionic strength, etc. However, proteins are dynamic systems with molecular motions extending over a time scale between 10^{-13} and 1 s. The dynamic aspect of protein solvent interactions, the influence of Brownian motion of solvent molecules on mobility and reaction rates in proteins, is of considerable interest. It has been suggested that solvent-induced structural fluctuations trigger catalysis in enzymes [1]. The situation is rather special, since the active site of most proteins is well shielded from the solvent and the effect of solvent fluctuations has to be transmitted to the reaction site through protein structure. Thus, in addition to the kinetics of the ligand or substrate, structural dynamics, solvent dynamics and their interaction have to be considered. The simplest approach theoretically and experimentally is to study the effect of the solvent viscosity η on reactions and diffusion in proteins. Experimental data are available for a number of systems and over a broad viscosity range ($1-10^5$ cP). Catalysis of carboxypeptidase [2], binding of molecular oxygen and carbon monoxide to myoglobin and protoheme [3] and some steps in the photocycle of bacteriorhodopsin [4] have rates that vary with the solvent viscosity. The reaction rates listed in refs. 3 and 4 were obtained from isoviscosity plots in different solvents. Possible effects of solvent composition could be minimized. The results were represented by a Kramers equation in the high-damping limit [5]:

$$k = \frac{\omega_1 \omega_2}{2\pi f/m} \exp(-H/RT) \qquad (1)$$

where m is the mass of the ligand, f the local friction coefficient of the reaction, ω_1 and ω_2 the frequencies of the parabolic wells at the top and bottom of the barrier, respectively, H the barrier height, R the gas constant and T the temperature. The friction coefficient f scales (for all systems

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studied) with the solvent viscosity η in the following way:

$$f \propto \begin{cases} \eta^{\kappa} & \eta < \eta_t \\ \text{constant} & \eta > \eta_t \end{cases} \quad (2)$$

with the constant κ, $0 \leqq \kappa \leqq 1$, and η_t a transition viscosity depending on the specific reaction. Only the recombination rate of carbon monoxide with protoheme has a friction coefficient in agreement with Stokes' law: $\kappa = 1$, $f \propto \eta$ [3]. This fact together with the observation that κ is independent of the solvent imply that the scaling law (eq. 2) is a property of the protein structure. It appears that the protein transmits or shields the external viscosity to an extent characterized by the exponent κ. Reactions with κ close to 1 are tightly coupled to surface motions while reactions with κ close to zero are well shielded by rigid protein structure. In this view eq. 2 is a consequence of protein dynamics [3,6]. The plateau at high viscosities, $\eta > \eta_t$, suggests that not all protein modes are controlled by the solvent viscosity. Gavish [6] proposed that the power law in the low-viscosity regime, $\eta < \eta_t$, is the result of a position-dependent friction coefficient across the barrier. This approach, however, does not provide a molecular explanation for eq. 2. In the present paper it is proposed that the friction coefficient of the ligand is nonlocal in time as a consequence of protein fluctuations with a finite lifetime.

2. Solvent-coupled fluctuations

Protein motions that are most likely coupled to the solvent are large-scale fluctuations like hinge-bending motions of two domains, volume fluctuations of large cavities and motions on the surface. McCammon and Wolynes [7] specifically modeled the hinge-bending mode of lysozyme by a Langevin equation of damped harmonic oscillator:

$$\dot{x}_s = u_s$$
$$m_s \dot{u}_s = -f_s u_s - m_s \omega_0^2 x_s + R_s(t), \quad (3)$$

where x_s is the displacement of the protein coordinate from equilibrium. The reduced mass m_s and the restoring force constant ω_0^2 are determined by the static structure of the protein. The friction coefficient f_s is proportional to the solvent viscosity η and is assumed to be frequency independent in this section. $R_s(t)$ is the random force generated by the impacts of solvent molecules. Eq. 3 is valid only if a clearcut separation of time scales between solvent and surface dynamics exists. The friction coefficient f_s and the correlation function of the random force, $\langle R_s(0)\ R_s(t)\rangle$, are related by a fluctuation-dissipation theorem [8]:

$$\langle R_s(0) R_s(t)\rangle = 2k_B T f_s \delta(t) \quad (4)$$

k_B is Boltzmann's constant. The random forces have to be δ-correlated and Gaussian. The dynamic properties of the solvent are thus given by a single parameter: $f_s \propto \eta$.

As a second class of solvent-coupled processes we consider fluctuations which are governed by a harmonic barrier. The relaxation rate k_s then follows a Kramers equation [5]. At high damping one obtains in both cases relaxation rates k_s proportional to f_s^{-1} [9]:

$$k_s = A/f_s \quad (5)$$

with

$$A = \begin{cases} m_s \omega_0^2 \text{ (damped harmonic oscillator)} \\ \omega_1 \omega_2 m_s \exp(-H_s/RT)/2\pi \text{ (Kramers equation)} \end{cases} \quad (6)$$

3. Internal mobility and ligand motion

Consider the migration of a small ligand molecule like molecular oxygen through a protein matrix. The migration can be modeled by continuous diffusion or jumps of a particle across successive barriers. As mentioned in section 2, the Langevin description breaks down for very rapid motions. The local motion of a small ligand can be as fast or even faster than conformational fluctuations of its protein environment. If position and velocity (x,u) of the ligand do not form a complete set of slow dynamic variables one has to account for memory effects. The ligand motion can be treated by a generalized Langevin equation [8]. The random forces $R(t)$ are not necessarily δ-correlated which leads to a time-dependent friction coeffi-

cient [10]:

$$\dot{x} = u$$

$$m\dot{u} = -\int_0^t \tilde{f}(x(t-t');u(t-t');t';\Gamma)u(t-t')\mathrm{d}t' - \frac{\partial V}{\partial x} + R(t) \tag{7}$$

where $V(x)$ and m are potential and mass of the ligand, respectively. The complexity of the dynamic problem is contained in the dynamic friction coefficient $\tilde{f}$ which can depend in particular on the dynamic variables of the protein Γ. In the following we consider two simple cases where $\tilde{f}$ is only a function of time: Homogeneous diffusion ($V(x) = 0$) and the escape over a harmonic barrier in the presence of a memory with a finite lifetime. With this restriction one finds that the random force correlation function, $\langle R(0)R(t)\rangle$, and the dynamic friction are related by a fluctuation-dissipation theorem [8]:

$$f(z) = \frac{1}{k_B T}\int_0^\infty e^{-zt}\langle R(0)R(t)\rangle \mathrm{d}t, \tag{8}$$

with z being the frequency. The frequency-dependent diffusion coefficient $D(z)$ is given by:

$$D(z) = \int_0^\infty e^{-zt}\langle u(0)u(t)\rangle \mathrm{d}t = \frac{k_B T/m}{z + f(z)/m} \tag{9}$$

with $m\langle u^2\rangle = k_B T$ and $D(0) = k_B T/\mathrm{f}(0)$. $\langle u(0)u(t)\rangle$ is the velocity autocorrelation function. Starting with a linear generalized Langevin equation, with Gaussian noise $R(t)$, Grothe and Hynes [11] derived a modified Kramers law for the escape rate, k, of a particle in a potential well:

$$k = \frac{\omega_1\omega_2}{2\pi(\lambda + f(\lambda)/m)}\exp(-H/RT) \tag{10}$$

λ is the frequency of the unstable reactive ligand motion in the barrier region. $f(z = \lambda)$ is given by eq. 8. Eq. 10 yields Kramers equation in the limit $\lambda \to z = 0$ (high damping) and turns into the transition-state approximation for $f(\lambda)/m \ll \lambda$. λ defines the time scale of the ligand motion and is at high damping simply the relaxation rate in the barrier region:

$$\lambda = m\omega_2^2/f(\lambda). \tag{11}$$

The underdamped regime is excluded. The formula of activated escape rate in the presence of long-time memory has also been investigated in ref. 12 using a generalization of Kramers method. In particular eq. 10 has been recovered for exponential memory-type kernels. In section 4 a relationship is established between the empirical scaling law of the friction coefficients, eq. 2, and the behavior of $\langle R(0)R(t)\rangle$ at long times. The time dependence of $\langle R(0)R(t)\rangle$ is then explained by a dynamic friction resulting from two types of protein motions: Solvent-independent diffusion of local structural defects and global solvent-coupled fluctuations. Throughout the treatment the high-damping limit is assumed: $\lambda \ll f(\lambda)/m$.

4. The long-time behavior of $\langle R(0)R(t)\rangle$

For a stationary random force one can write:

$$\langle R(0)R(t)\rangle = \langle R^2\rangle g(t) \tag{12}$$

where $g(t)$ is the normalized time-dependent part of the force autocorrelation function. $\langle R^2\rangle$ is an equilibrium property and should not depend on transport coefficients. From eqs. 2 and 5, one obtains: $f \propto \eta^\kappa \propto k_s^{-\kappa}$, $\eta < \eta_t$. The dynamic friction is introduced by defining f as the low-frequency limit of $f(z)$:

$$f = \lim_{z\to 0} f(z) = C\frac{\langle R^2\rangle}{k_B T}\alpha^{\kappa-1}k_s^{-\kappa} \tag{13}$$

where C is a numerical constant and α a rate coefficient introduced for reasons of dimensionality. The second equality comes from the fluctuation dissipation theorem, eqs. 8 and 12. $f(z)$ and $g(t)$ are (apart from a constant, $\langle R^2\rangle/k_B T$) a Laplace transform pair. α and k_s are thus rate coefficients associated with the time dependence of $g(t)$. At sufficiently high solvent viscosities one has $\alpha \gg k_s$, since $k_s \propto f_s^{-1}$ and α is independent of f_s. $f(z)$ at low frequencies is then approximately given by:

$$f(z) = C\frac{\langle R^2\rangle}{k_B T}\cdot\frac{\alpha^{\kappa-1}}{(z + k_s)^\kappa} \qquad z \to 0 \tag{14}$$

which has the correct limit (eq. 13) and involves a minimum number of parameters. The long-time behavior of $g(t)$ then follows from $f(z)$ at low

frequencies [13]:

$$g(t) \propto (\alpha t)^{\kappa-1} \exp(-k_s t) \quad t \to \infty \tag{15}$$

$g(t)$ has a long-time tail multiplied by a cutoff function. Eq. 15 allows a simple interpretation: The rate coefficient α which had to be introduced to match dimensions in eq. 2 is not a function of the solvent viscosity and indicates the existence of solvent-decoupled protein modes. $g(t)$ can be separated into statistically independent parts: $\exp(-k_s t)$ represents the relaxation of solvent-dependent global fluctuations discussed in section 2. The power law in time $(\alpha t)^{\kappa-1}$ is then the result of local internal modes. This concept is discussed in the following sections.

5. A dynamic friction model

Assume that the exchange of thermal energy between internal degrees of freedom in a protein involves diffusion of local structural defects (LD) with a diffusion coefficient, D, independent of the solvent viscosity. Examples could be correlated fluctuations along the main chain as detected by molecular dynamic simulations on a picosecond time scale [14] or diffusion of small cavities introduced by Lumry [15,16] to explain hydrogen exchange and fluorescence quenching in proteins. LDs could explain why reaction rates are finite at 'infinite' external viscosity when the protein is suspended in a solid environment like PVA *, frozen solvents or dry films [3,19]. Global fluctuations (GF), by contrast, involve larger parts of the protein, and are thus necessarily coupled to the solvent. Examples could be relative motions of two domains or volume fluctuations of large cavities. We characterize the dynamics of GF by an exponential relaxation with a single rate coefficient k_s. Fig. 1 shows a scheme of the model. It is assumed that LD and GF are the main components of the fluctuation spectrum at the reaction site and are responsible for the decay of the random force autocorrelation function $\langle R(0)R(t)\rangle$. The processes LD and GF are assumed to be statistically independent. Their combined autocorrelation function $g(D,k_s,t)$ then factorizes:

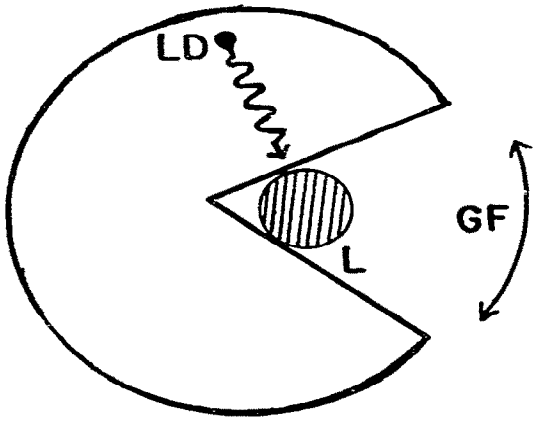

Fig. 1. Schematic 'Pac Man' model of a protein and its dynamics. The ligand (L) experiences solvent-dependent global fluctuations (GF) and solvent-independent internal modes (LD).

$$g(D,k_s,t) = g_{LD}(D,t)\, g_{GF}(k_s,t) \tag{16}$$

For process LD we take into account only the first passage of the defect nearest to the reaction site. The correlation function then has the form:

$$g(D,k_s,t) = \int_0^\infty \mathrm{d}x\, p(x) F(x,t) e^{-k_s t} \tag{17}$$

where $F(x,t) = \mathrm{erf}(x/\sqrt{4Dt})$, $(F(x,t=0)=1)$ is the probability that a defect initially at x has not been absorbed at the reaction site $(x=0)$ at time t [20], and $\mathrm{erf}(y)$ the error function. $p(x)$ is the one-dimensional distribution of defect distances at $t=0$ and D the one-dimensional defect diffusion coefficient. $F(x,t)$ is proportional to $t^{-0.5}$ at long times. The model is similar to that proposed by Glarum [21], Hunt and Powles [22] and Doster and Kimmich [23] to explain dielectric and nuclear magnetic relaxation in polymers and supercooled liquids. Hunt and Powles also discuss the three-dimensional case and conclude that extremely accurate data are required to distinguish between one-dimensional and three-dimensional defect diffusion. The form of $p(x)$ has no significant influence on the results. Consider first $p(x) = \delta(x - x_0)$. $2x_0$ is the average distance between two defects. Eqs. 8 and 17 yield the following dynamic friction at $z = \lambda$:

* PVA, poly(vinyl alcohol).

$$f(\lambda) = \frac{\langle R^2 \rangle}{k_B T(\lambda + k_s)}\left(1 - \exp\left(-((\lambda + k_s)/\gamma)^{0.5}\right)\right)$$

$$\gamma = D/x_0^2 \qquad (18)$$

λ is determined by eq. 11. $1/\gamma$ is a measure of the time for a defect to travel a distance $2x_0$. The result for an exponential defect distribution $p(x) = \exp(-x/x_0)/x_0$ is easily obtained:

$$f(\lambda) = \frac{\langle R^2 \rangle}{k_B T \gamma \beta (1 + \beta)}$$

$$\beta = ((\lambda + k_s)/\gamma)^{0.5} \qquad (19)$$

The ligand diffusion coefficient, $D(z)$, can be calculated from eq. 9. Instead of considering only the internal defect (LD) nearest to the reaction site at $t = 0$, one can take into account all defects if they diffuse independently of each other. It has been shown that the corresponding correlation function $g_{LD}(t)$ has the form (assuming a uniform defect distribution) [24]:

$$g_{LD}(t) = e^{-(4\gamma t/\pi)^{1/2}} \qquad (20)$$

which decays faster at long times than does $F(x,t)$. Eq. 20 is the empirical William Watts relaxation function ($\kappa = 0.5$) and describes structural relaxation in glasses [25]. The resulting low-frequency friction coefficient is given by (eqs. 8 and 20):

$$f(0) = \frac{\langle R^2 \rangle}{k_B T} \cdot \frac{w}{\gamma}\left(1 - (\pi w)^{1/2} e^{w} \operatorname{erfc}(w^{1/2})\right)$$

$$w = \gamma/4 \cdot k_s \qquad (21)$$

where $\operatorname{erfc}(y)$ is the complementary error function.

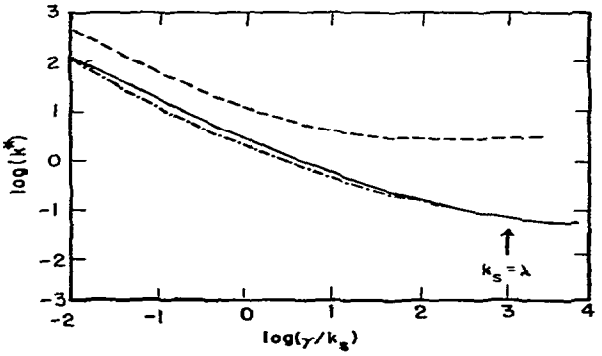

Fig. 2. The reduced rate coefficient, $k^* = f(\lambda)^{-1}\langle R^2 \rangle/(\gamma k_B T)$ is plotted vs. a reduced solvent viscosity, $\gamma/k_s \propto f_s$, for the three models: (·–·–·) eq. 18, (———) eq. 19, (- - - - -) eq. 21. $\lambda/\gamma = 10^{-3}$ was kept constant.

Fig. 2 shows the resulting theoretical curves for the three cases: Eqs. 18, 19 and 21. The reduced reaction rate $k^* \propto f(k_s,\gamma)^{-1}$ is plotted vs. a normalized external friction, $\gamma/k_s \propto f_s$. λ/γ was kept constant. λ could be determined numerically in a self-consistent way by inserting eq. 11 into eqs. 18 and 19. However, $f(\lambda)$ is independent of λ for $k_s \ll \lambda$ and $k_s \gg \lambda$. In the transition region $k_s \equiv \lambda$, the variation of λ with viscosity is small and can be neglected. The viscosity dependence of λ is discussed in section 6). The two distributions $p(x)$ of the nearest-defect model lead to almost identical results. The transition at $\gamma = k_s$ is smoother for the exponential-defect distribution. In the low-viscosity regime ($\gamma \ll k_s$), one finds for all three models that $k^* \propto f_s^{-1}$, because in this case the thermal-exchange rate with the solvent (GF) dominates over the internal exchange (LD). For the nearest-defect model one obtains an extended intermediate-viscosity regime: $\gamma \gg k_s \gg \lambda$, which is dominated by defect diffusion (LD). In this region k^* is proportional to $f_s^{-0.5}$. At high external friction ($\lambda \gg k_s$), k^* levels off because the intrinsic relaxation rate of the ligand λ is faster than GF. If all defects are taken into account (eq. 21), the intermediate viscosity region is narrow and k^* becomes independent of f_s for $\gamma \gg k_s$. The model is attractive because it does not involve the frequence dependence of $f(\lambda)$. It fails, however, to explain an extended intermediate viscosity regime which is observed experimentally (eq. 2).

6. Comparison with experiments

Theory and experiment are compared in Fig. 3. The data were taken from ref. 3 and show recombination rates of molecular oxygen, k_{ij}, with sperm whale myoglobin as a function of the solvent viscosity η. The binding kinetics were analysed by a four-state model:

$$A \overset{k_{BA}}{\leftarrow} B \underset{k_{BC}}{\overset{k_{CB}}{\leftrightarrow}} C \underset{k_{CS}}{\overset{k_{SC}}{\leftrightarrow}} S + O_2$$

A, B and C are protein states with the ligand at specific sites in the matrix, and S is the ligand free state. The rates k_{BC}, k_{CB}, k_{CS} and k_{SC} depend on η as shown in fig. 3. k_{BA} is taken to be indepen-

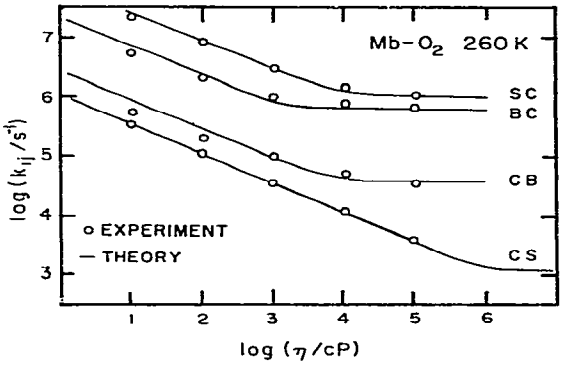

Fig. 3. Rate coefficients k_{ij} for recombination of molecular oxygen with myoglobin after flash photolysis as a function of the solvent viscosity and theoretical curves. The data were taken from ref. 3 and fitted with eqs. 10 and 18.

dent of η. The theoretical curve was obtained from eqs. 10 and 18. The intersection with the ordinate is determined by the parameters of the barrier: ω_1, ω_2, H and T. The theory reproduces the experimental results reasonably well. The exponent κ in the power law region ($\eta < \eta_t$) is close to 0.5 in agreement with the defect-diffusion model. A more detailed analysis requires the knowledge of one of the three parameters λ, γ and k_s from other experiments. The rest then follows from $\lambda = k_s$ at $\eta = \eta_t$ and $k_s = \gamma$ at $\eta = \eta_t'$. The data, however, do not extent to sufficiently low viscosities to determine η_t'. η_t for k_{SC}, k_{BC} and k_{CB} is between 10^3 and 10^4 cP. The theory predicts: $\lambda \propto f_s^{-0.5}$ and $k_s \propto f_s^{-1}$. Taken together it follows that λ at 1 cP (viscosity of water) is 1.5–2 orders of magnitude smaller than k_s. The activation enthalpy H obtained from the temperature dependence of k_{ij} is about 35 kJ/mol [3]. Assume that a large contribution to H comes from the protein motions LD and GF through $f(\lambda)$. In the limit of a small ligand barrier (however, $H_L \gg RT$), one has at $\eta = \eta_t$: $k_{ij} \lesssim \lambda = k_s$. Substituting the plateau rate for k_{ij}, one finds by extrapolation to 1 cP: $k_s = 10^9$ s^{-1} for B → C and C → B and 10^{10} s^{-1} for C → S as lower limits. The assumption made above is supported by the observation that the transition viscosity η_t for a given barrier increases with decreasing ligand rate. η_t for k_{CS} should be 10^6 cP (fig. 3). From eq. 18 or 19 one can obtain an estimate of the internal viscosity if Stokes' law is assumed:

$$f(0) = \frac{\langle R^2 \rangle}{k_B T} (k_s \gamma)^{-0.5} = 4\pi\eta_i r \qquad (22)$$

A typical value of $\langle R^2 \rangle / k_B T = 10^4$ erg/cm^2 is taken from simulations of molecular dynamics [26]. $\gamma = 10^{12}$ s^{-1}, $k_s = 10^{10}$ s^{-1} and $r = 2$ Å, the size of molecular oxygen, yield an internal viscosity $\eta_i =$ 40 cP which is consistent with the assumption of an overdamped regime.

7. Conclusion

The solvent viscosity dependence of reaction rates in proteins can be understood as a consequence of the fluctuation-dissipation theorem. The friction coefficient of the ligand is essentially given by the power spectrum of the noise generated by structural fluctuations. The friction is dynamic or frequency dependent if the noise is not 'white'. Chemical reactions and diffusion driven by 'coloured noise' have been studied by a number of authors [11,12,27]. The generalized Langevin equation proved to be useful to explain molecular dynamics of fluids [28]. A memory kernel analysis of molecular dynamics in proteins was suggested recently [29]. The present treatment is oversimplified. The two-parameter description (α,k_s) of high-frequency fluctuations in proteins is obviously not realistic. A possible frequency dependence of f_s has been neglected [7]. Inclusion of this effect would lead to a continued fraction expansion [8]. Only small high-frequency fluctuations were considered. Large fluctuations can govern the motion of the ligand completely, for instance, by opening or closing a gate [3,30]. The theory then applies to the dynamics of the gate rather than to the ligand. Nevertheless, the phenomenological scaling law of the friction coefficients (eq. 2) can be understood if the power spectrum of structural fluctuations has two main components: Solvent-coupled modes with rates $k_s \propto f_s^{-1} \propto \eta^{-1}$ and solvent-independent internal fluctuations. Diffusion of structural defects can account for the power law relationship with $\kappa = 0.5$. A distribution of internal modes would be a more general explana-

tion. More experimental data especially in the low-viscosity regime are required before more specific models can be designed. The low solvent viscosity regime deserves a special comment: If γ is the fastest rate in the protein, all defects are limited in rate by defect diffusion and, consequently, $f(\lambda)$ is independent of f_s at low viscosity. On the other hand, if the surface process is not overdamped, k_s is proportional to f_s [9]. If the ligand still is in the overdamped regime one obtains from eq. 8 a ligand rate increasing with f_s because the damping impact on the ligand lasts a shorter time with increasing solvent viscosity. Eq. 10 has to be used and λ has to be calculated explicitly if the ligand is not overdamped [11]. Thus, the model fails to give a unique prediction for the low-viscosity regime. At first sight, the power law of eq. 2 suggests that the ligand is somewhere in between the transition state regime, $\kappa = 0$, and the high damping limit with $\kappa = 1$. This model predicts that κ increases with increasing solvent viscosity to its limit $\kappa = 1$ while actually the opposite is observed. It is interesting in this context that the velocity correlation function and the memory function associated with the bulk viscosity in one-dimensional harmonic liquids decay with $t^{-0.5}$ at long times. The dissipative effect is associated to structural fluctuation which leads to the lack of crystalline long-range order [31]. In conclusion, our analysis suggests that proteins, in addition to providing static environments quite different from the solvent, can have autonomous internal dynamics.

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