A Fractional Calculus Approach to Self-Similar Protein Dynamics

Walter G. Glöckle and Theo F. Nonnenmacher

Department of Mathematical Physics, University of Ulm, D-89069 Ulm, Germany

ABSTRACT   Relaxation processes and reaction kinetics of proteins deviate from exponential behavior because of their large amount of conformational substates. The dynamics are governed by many time scales and, therefore, the decay of the relaxation function or reactant concentration is slower than exponential. Applying the idea of self-similar dynamics, we derive a fractal scaling model that results in an equation in which the time derivative is replaced by a differentiation $(d/dt)^\beta$ of non-integer order β. The fractional order differential equation is solved by a Mittag-Leffler function. It depends on two parameters, a fundamental time scale τ_0 and a fractional order β that can be interpreted as a self-similarity dimension of the dynamics. Application of the fractal model to ligand rebinding and pressure release measurements of myoglobin is demonstrated, and the connection of the model to considerations of energy barrier height distributions is shown.

INTRODUCTION

Apart from the prominent importance for biological functions, proteins provide qualified objects to study the dynamics of complex systems. Because of the aperiodic arrangement of the amino acids, their conformational states consist of many substates with nearly the same energy (Frauenfelder et al., 1988). Thus their energy surface is a rough hypersurface in a high dimensional configuration space with an immense number of local minima. Proteins share this feature with other complex systems like spin glasses, glass-forming liquids, macromolecular melts, etc. However, compared with these examples, a protein is a relatively small system that is identically reproduced by nature. Therefore in recent years, proteins, especially myoglobin, have become model systems to study dynamics of complex systems. Several physical concepts known from those systems are applied to proteins. Millhauser (1990), for example, estimates time constants of the dynamics of ion channels by applying the reptation model for polymer melts, and Doster et al. (1991) used the mode coupling theory of the glass transition to interpret inelastic neutron scattering data of proteins.

In this paper we will consider reaction kinetics and relaxation dynamics of proteins. This type of protein dynamics deviates from the exponential behavior of simple systems. Experimentally one finds a slower decay that may be represented by a stretched exponential or by a power law. Therefore reaction kinetics and relaxation of proteins are not described by a first order differential equation (kinetic equation of a first order process and standard relaxation equation, respectively). Our purpose is to derive a fractional order relaxation equation for protein dynamics based on self-similar processes. Up to now, equations containing non-integer orders of differentiation or integration have been successfully applied to relaxation in the area of linear viscoelasticity (Glöckle and Nonnenmacher, 1991) and to diffusion in disordered materials (Giona and Roman, 1992; Metzler et al., 1994).

Scaling laws and self-similar behavior are supposed to be fundamental features of complex systems. Recently it was shown by Shlesinger et al. (1993) that anomalous transport and slow relaxation occur in chaotic dynamical systems on a kinetic level. It was demonstrated how Lévy statistics, scaling laws, and multifractal properties emerge as a consequence of kinetic averaging. Scaling behavior was also derived by Agmon and Rabinovich (1991, 1992; Rabinovich and Agmon, 1993) via a theoretical analysis of two-dimensional diffusive dynamics. In particular, they investigated the myoglobin CO binding on a model potential energy surface and found scaling in an intermediate time region. In the model of Wang and Wolynes (1994), the slowing down of the exponential reactant decay is produced by fluctuating environments with non-Markovian statistics. For Gaussian fluctuating environments they obtained stretched exponential behavior if the rate coefficients vary slowly with the environmental variables. In the case of rapidly varying coefficients a more complex behavior was found.

In proteins, according to their biological function, two states can be distinguished; e.g., an ion channel can be open or closed, a hemoglobin or myoglobin protein can have bound oxygen or not. The transition between the two states may either be regarded as a reaction kinetic process or a relaxation process. The reactant population or the relaxation function is the probability of a protein to be in the excited state. The nonstandard behavior that is observed is often modeled by functions containing a few parameters like

$$\phi(t) = (1 + t/\tau)^{-n} \tag{1}$$

where n and τ are fit parameters depending on temperature, pressure, pH value etc. (Austin et al., 1975). It differs from the reaction kinetics of a first order process or from the standard relaxation. On a more microscopic level, the deviation from the exponential law is regarded to be a consequence of the large number of conformational substates (Frauenfelder et al., 1988; Frauenfelder, 1987). Each of the two experimentally

distinguishable states is realized by many substates separated by energy barriers. Therefore, the reaction kinetics and relaxation may be described by using a distribution $g(E)$ of energy barrier heights. The relaxation function $\phi(t)$ is then given by

$$\phi(t) = \int_0^\infty g(E)\exp(-k(E)t)\,dE \qquad (2)$$

where for $k(E)$ an Arrhenius activation law

$$k(E) = A\exp(-E/RT) \qquad (3)$$

is assumed. Whereas Eq. 1 provides a description of the process with few easily manageable empirical parameters, Eq. 2 gives a more molecular picture in terms of an energy barrier height distribution $g(E)$. In this case a continuous function is used for the description.

The fractional calculus approach is based on the idea of self-similar dynamics. Besides structures with fractal geometry, processes with self-similar behavior on many different time scales are widespread in nature (Goldberger et al., 1985; Goldberger and Bhargava, 1991; Nonnenmacher and Nonnenmacher, 1989). Starting from a model with self-similar dynamics, we will derive a fractional order equation. In particular, a well posed fractional initial value problem is derived. In comparison with modeling processes by using an energy barrier distribution function, the fractional model depends on a few parameters only. The influence of physical properties, like temperature, on the protein dynamics can easily be studied by considering those parameters. Like the empirical function Eq. 1, the fractional approach works on a global level but, in contrast to the power law fitting curves, its parameters possess a foundation in the context of self-similar dynamics. Thus, our description works on a middle position between the detailed energy barrier height consideration and the purely empirical power laws. As the standard equations for relaxation and first order reaction kinetics are equivalent, their fractional generalization models both nonstandard relaxation and nonstandard reaction processes. For the sake of simplicity, the resulting fractional order equation will be denoted by a fractional relaxation equation.

The paper is organized as follows. First, a self-similar dynamical model is presented. Next, it is shown that this fractal model corresponds to a fractional order relaxation equation that is solved by a Mittag-Leffler function. In addition, the general fractional equations for the linear response behavior are derived. Then, the fractional relaxation is applied to the dynamics and reaction kinetics of myoglobin. The temperature dependence of the model parameters are discussed for temperatures in the vicinity of the glass transition temperature T_g of the solution as well as far below T_g. In the final section, some conclusions are presented.

RESULTS

Self-Similar dynamics

The absence of an internal scale is one of the main features of fractals. One can also say that in fractals a great number

of scales coexist in a self-similar manner. A comparable situation is known from thermodynamic systems at the critical point. The divergence of the correlation length at the critical point, e.g., can be mathematically treated by assuming a composition of subsystems with a special coupling constant (Wilson, 1979). Each of the subsystems is, again, built up by sub-subsystems with another coupling constant and so on. The central idea of the renormalization group theory is that a change of the scale should lead to the same behavior apart from a renormalization of the coupling constant.

The coexistence of many scales is not only found in geometrical objects but also in the time course of processes. For the latter case the term fractal time process was coined (Shlesinger, 1988). Fractal time effects are observed, e.g., in the anomalous electron transport in amorphous materials (Scher and Montroll, 1975) and in the dielectrical and mechanical relaxation of polymers and glass-forming liquids (Shlesinger, 1988; Glöckle and Nonnenmacher, 1993). Our goal here is not to study conditions for the occurrence of fractal time in proteins. In the examples mentioned, the fractal time, i.e., the self-similar dynamics, is explicable by an underlying triggering process with Lévy statistics. Common features of the materials are, among others, disorder, rough energy surface, glass transition, and frustration. On the one hand a protein is a small system consisting of only one macromolecule. On the other hand, however, the configurational space of a protein is high dimensional and its energy surface is a rough landscape in this space that is additionally modified by the surrounding solvent molecules. Therefore, as far as a protein shares features of glasses, the concept of self-similar dynamics may be suitable to its reaction and relaxation processes.

The renormalization idea will now be applied to processes in proteins. For a single exponential relaxation $\phi(t) = \phi_0\exp(-t/\tau)$ a time scale τ is given. Because many conformational substates are accessible to a protein, it is not relaxing with a single time constant τ but with many time constants τ_n leading to

$$\phi(t) = \sum_n w_n\exp\left(-\frac{t}{\tau_n}\right). \qquad (4)$$

Self-similar dynamics means that the weights w_n and the time constants τ_n are not independent, but correlated. If the time scale is changed by $t \to \lambda t$ ($\lambda > 1$), the behavior of the system should be the same, apart from a renormalization of the statistical weight ($w \to \tilde{w}$). Depending on the choice of $\tilde{w}$, different models can be discussed:

(i) The case of $w \to \tilde{w} = \lambda^{-\beta}w$ leads to the geometric progression

$$\tau_n = \lambda^n\tau_0 \qquad (5)$$

$$w_n = p^np_0 = (\lambda^{-\beta})^np_0 \qquad (6)$$

($\lambda > 1$, $\beta > 0$, $p < 1$), which has been previously discussed by Montroll and Shlesinger (1982) in an economical context. If there are infinitely many processes, the sum in

Eq. 4 represents a modified version of a Weierstrass series. In the continuum limit one obtains the relaxation function

$$\phi(t) = \int_0^\infty p_0 \lambda^{-\beta x} \exp\left(-\frac{t}{\lambda^x \tau_0}\right) dx$$

$$= \frac{p_0}{\ln \lambda}\left(\frac{t}{\tau_0}\right)^{-\beta} \gamma\left(\beta, \frac{t}{\tau_0}\right) \tag{7}$$

expressible by the incomplete γ-function (Nonnenmacher and Nonnenmacher, 1988, 1989). For large t, an algebraic decay

$$\phi(t) \sim \frac{p_0 \Gamma(\beta)}{\ln \lambda}\left(\frac{t}{\tau_0}\right)^{-\beta} \tag{8}$$

is found. This continuous scaling with geometric progression can be related to the description by energy barrier heights leading to the distribution

$$g(E) = p_0 \exp\left(-\frac{\beta E}{RT}\right) \tag{9}$$

with $\tau_0 = 1/A$ and $\ln \lambda = 1/RT$. One recognizes that Eq. 9 is independent of the temperature T if the parameter β is proportional to T. The model with geometric progression (Eqs. 5 and 6) has been applied to ion channel gating processes. Results going beyond the continuum limit are given with the help of the Poisson summation formula (Nonnenmacher and Nonnenmacher, 1988). Especially, oscillations winding around the power law trend are obtained.

(ii) Our purpose is to point out a connection between self-similar processes and fractional order relaxation equations. Therefore we start from a slightly different self-similar process, here called fractal scaling. According to the renormalization group idea, in addition to the standard relaxation $p_0 \exp(-t/\tau_0)$, processes with time scales

$$\tau_n = \lambda^n \tau_0 \tag{10}$$

stretched by a factor λ ($\lambda > 1$) are taken into consideration. Instead of Eq. 6, the weights are now modified in the form

$$w_n = p_0 \frac{p^n \sin(\pi\beta)}{p^{2n} + 2p^n \cos(\pi\beta) + 1} \tag{11}$$

with $p = \lambda^{-\beta} < 1$ ($\beta > 0$). The difference between the scaling model with geometric progression and the fractal scaling model are shown in Fig. 1. Here, $p_0, p_1, \cdots$ are the weights of the former model whereas the weights $w_0, w_1, \cdots$ of the fractal model are given by $w_n = a_n/b_n^2$. As b_n tends toward 1 for large n, both models are asymptotically equivalent: $w_n \sim p_n \sin(\pi\beta)$ for large n. In terms of the renormalization group theory, the two models belong to the same class of universality where the universality in connection to these time processes is the asymptotic power law decay with the power $-\beta$.

There is no a priori reason to prefer fractal scaling. The choice of fractal scaling (Eqs. 10 and 11) instead of geo-
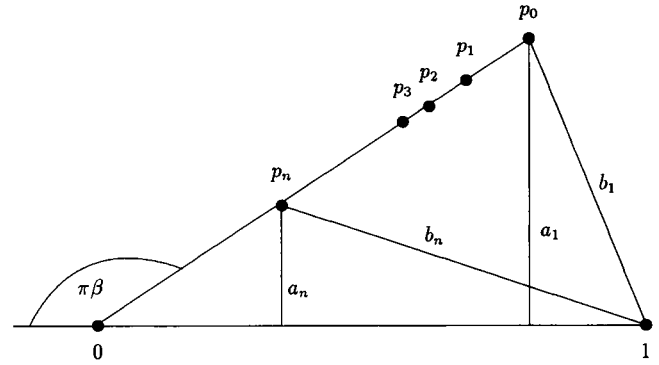

FIGURE 1   Statistical weights $w_n = a_n/b_n^2$ of the fractal model in comparison with the weights p_n of the model with geometric progression.

metrical scaling (Eqs. 5 and 6) is motivated by the intention to derive a consistent mathematical formulation of the process in form of a fractional order differential equation. This will be done in the following section. From experiments apart from the asymptotic power law that is reflected by the scaling $w_n \sim \lambda^{-\beta n}$, a limitation τ_0 of the scaling behavior towards small times is indicated. For times $t < \tau_0$ the relaxation process is dominated by the initial value whereas for $t > \tau_0$ the scale-invariant power law behavior is found. But up to now it is impossible to prefer on grounds of experimental evidence one of the two scaling models. Of course both types are ideal models of a real process. Furthermore, besides the limitation τ_0, the self-similar process is limited at large times as well. Like geometrical fractals in nature the time fractals are "fractal between limits" (Nonnenmacher, 1994). In the models presented here, however, an upper limitation is not provided.

Again we are restricting ourselves to infinitely many processes in the continuum limit. In this case, the total process of fractal scaling type takes the form of Eq. 2 by identifying $\lambda = \exp(1/(RT))$ and $A = 1/\tau_0$ where $g(E)$ is given by

$$g(E) = p_0 \frac{e^{-\beta E/RT}\sin(\pi\beta)}{e^{-2\beta E/RT} + 2e^{-\beta E/RT}\cos(\pi\beta) + 1}. \tag{12}$$

Thus Eq. 12 can be interpreted as an energy barrier distribution of the fractal scaling model in the continuum limit. As a consequence of the asymptotic power law decay $\phi(t) \sim t^{-\beta}$, the distribution function $g(E)$ shows a decay $\sim \exp(-\beta E/RT)$ for large values of E. Asymptotically $g(E)$ agrees with the Poisson type of distribution

$$g(E) = C\left(\exp(\alpha(E_{peak} - E)) - \frac{\alpha}{\beta}\exp(\beta(E_{peak} - E))\right) \tag{13}$$

used by Frauenfelder and co-workers (Alberding et al., 1976) to parametrize the energy barrier distribution. On the other hand a motivation for the γ-distribution

$$g(E) = c(E - E_{min})^{3\nu-1}\exp(-\alpha(E - E_{min})) \tag{14}$$

($E > E_{min}$) was given by Young and Bowne (1984). They assumed conformational substates with potential bottoms following the anharmonic potential $V_\nu(x) \propto x^{1/\nu}$. Recently

Straub et al. (1994) presented a method for deriving the energy barrier distribution in systems with complex energy landscapes consisting in solving a homogeneous Fredholm integral equation. For proteins they utilized the ansatz

$$g(E) = a\Theta(E_{\text{low}} - E) + bE \exp(-E/E_0) \qquad (15)$$

and determined the parameters by solving the corresponding integral equation. Because of the Heaviside Θ-function, the distribution Eq. 15 shows a constant value a for small barrier heights E and a Poisson-type decay for large E. Whereas in the asymptotic (large E) region the distributions (Eqs. 12, 13, 14, and 15) are equivalent, they differ in the small E region. In the cases of Eqs. 13 and 14 the number of small barrier heights is small. On the contrary, in Eqs. 12 and 15 (for typical values of a) a large number of small barrier heights occur that, however, do not influence the long time kinetics. Although up to now the experiments are not good enough to decide between the two possibilities, in the picture of the energy surface it is plausible that apart from high barriers an immense number of small barriers are present.

Derivation of a fractional equation

The idea of generalizing the differential calculus to non-integer orders of derivation is going back to Leibniz (see Oldham and Spanier, 1974). Since then, various types of fractional derivatives and integrals have been proposed. The most famous one is the Riemann-Liouville calculus based on the fractional integral (Oldham and Spanier, 1974)

$$_aD_t^{-\beta}f(t) = \int_a^t \frac{(t - t')^{\beta-1}}{\Gamma(\beta)} f(t') \, dt' \qquad (16)$$

which is defined for $\mathfrak{R}(\beta) > 0$ where $\mathfrak{R}$ denotes the real part. The fractional differentiation is reduced via

$$_aD_t^q f(t) = \frac{d^n}{dt^n} {}_aD_t^{q-n} f(t) \qquad (17)$$

$(n > \mathfrak{R}(q))$ to a fractional integration followed by an ordinary differentiation of the integer order n. As, for the lower limit $a = 0$, the integral in Eq. 16 is a Laplace convolution, the Laplace transform of the fractional integral is given by

$$\mathcal{L}(_0D_t^{-\beta}f(t), p) = p^{-\beta}\mathcal{L}(f(t), p) \qquad (18)$$

indicating a relation between non-integer powers of the Laplace variable p and fractional order differentiation or integration. In several works of recent years (Schneider and Wyss, 1989; Glöckle and Nonnenmacher 1991), attention has been paid to the formulation of well posed fractional initial value problems. This is achieved by formulating differential or integral equations with incorporated initial values.

To come up with a differential equation reflecting the self-similar behavior of the fractal model, we calculate the

Laplace transform of $\phi(t)$

$$\frac{Q(p)}{p} = \mathcal{L}(\phi(t), p) \qquad (19)$$

which results in

$$Q(p) = \frac{\phi_0}{(\tau_0 p)^{-\beta} + 1} \qquad (20)$$

with $\phi_0 = \pi p_0 RT$ (Appendix). The non-integer exponent $-\beta$ refers to a fractional integration. It is easily verified that the fractional integral equation

$$\tau_0^{-\beta} {}_0D_t^{-\beta}\phi(t) + \phi(t) - \phi_0 = 0 \qquad (21)$$

leads to Eq. 20. Applying the fractional differential operator $_0D_t^\beta$ on Eq. 21, the equivalent fractional differential equation

$$\tau_0^{-\beta}\phi(t) + {}_0D_t^\beta\phi(t) - \frac{\phi_0 t^{-\beta}}{\Gamma(1 - \beta)} = 0 \qquad (22)$$

is obtained. In Eqs. 21 and 22 the initial value $\phi_0 = \phi(t = 0)$ is incorporated. For $\beta \to 1$, both equations lead to the standard relaxation. The inhomogeneity in Eq. 22 then produces a singular term $-\phi_0\delta(t)$.

The solution $\phi(t)$ of the fractional equations (Eqs. 21 and 22, respectively), can be calculated from Eq. 20 via inverse Laplace transformation which results in (Glöckle and Nonnenmacher, 1993)

$$\phi(t) = \phi_0 E_\beta(-(t/\tau_0)^\beta) \qquad (23)$$

in terms of a Mittag-Leffler function E_β. From series and asymptotic expansions of E_β (Erdélyi et al., 1955), the representations

$$\phi(t) = \phi_0 \sum_{k=0}^{\infty} \frac{(-1)^k}{\Gamma(1 + \beta k)} \left(\frac{t}{\tau_0}\right)^{\beta k} \qquad (24)$$

and

$$\phi(t) \sim \phi_0 \sum_{k=0}^{\infty} \frac{(-1)^k}{\Gamma(1 - \beta - \beta k)} \left(\frac{t}{\tau_0}\right)^{-\beta-\beta k} \qquad (25)$$

$(0 < \beta < 1)$ are found. One recognizes that the algebraic decay $\phi(t) \sim t^{-\beta}$ is governed by the same parameter β that occurs as an order of the fractional operators. For $\beta \to 1$, again, the solution reduces to the exponential function.

Up to now we have considered a freely decaying process starting at time $t = 0$ from a prepared initial value. Usually, relaxation processes are discussed in the framework of linear response theory (Dattagupta, 1987) in which the dynamics of a variable $x(t)$ is regarded on which an external force $E(t)$ is acting. Then, the relaxation function is defined by $\phi(t) = x(t)/E_0$ where E_0 is the strength of a constant force that is switched off at $t = 0$. In the range of the validity of the linear response theory, i.e., for small values of $E(t)$, the Fourier components $\hat{x}(\omega)$ and $\hat{E}(\omega)$ are connected by

$$\hat{x}(\omega) = \chi(\omega)\hat{E}(\omega) \qquad (26)$$

with a frequency dependent susceptibility $\chi(\omega)$. A difficulty that arises in deriving a fractional equation consists in the difference between the relaxation function and functions that are handled by Laplace transforms. The relaxation process we would like to describe is a switching off process. A typical example is dielectric relaxation for which the relaxation of the polarization of a material is measured after switching off a constant electric field E_0 at $t = 0$. The function $\phi(t)$ is then given by $\phi(t) = P(t)/E_0$. Thus, it is a constant nonvanishing function for $t < 0$ and a decaying function for $t > 0$. On the contrary, the Laplace transform deals with functions vanishing for $t < 0$. Mechanical stress relaxation of a viscoelastic material after imposing a constant strain is an example proper to the Laplace transform. Here, both the stress function $\sigma(t)$ and the strain function $\epsilon(t)$ are equal to zero for $t < 0$. To overcome this difficulty we define new variables $\bar{x}(t) = x(t) - x_0$ and $\bar{E}(t) = E(t) - E_0$ measuring the deviation of x and E from the equilibrium state $x_0 = \chi_0 E_0$ for $t < 0$.

For the fractional relaxation the Laplace transform $x(p)$ of $x(t)$ is given by (cf. Eq. 19 and Eq. 20)

$$x(p) = \frac{1}{(\tau_0 p)^{-\beta} + 1} \frac{x_0}{p}. \tag{27}$$

Inserting $x(p) = \bar{x}(p) + x_0/p$ in Eq. 27 and inverting the Laplace transform leads to

$$\tau_0^{-\beta}{}_0 D_t^{-\beta} \bar{x}(t) + \bar{x}(t) = \tau_0^{-\beta}{}_0 D_t^{-\beta}(-x_0) \tag{28}$$

which corresponds to Eq. 21. But now the initial value x_0 will be regarded to be a consequence of the force $E(t)$. This is achieved by

$$\tau_0^{-\beta}{}_0 D_t^{-\beta} \bar{x}(t) + \bar{x}(t) = \chi_0 \tau_0^{-\beta}{}_0 D_t^{-\beta} \bar{E}(t) \tag{29}$$

Because in the case of relaxation, $E(t)$ jumps from E_0 to 0 at $t = 0$. Eq. 29 reduces to Eq. 28. However, it is not necessary to interpret Eq. 29 to be a relaxation equation. It is a linear, fractional order integral equation that connects the two conjugate variables $\bar{x}$ and $\bar{E}$. In the original variables x and E the general equation reads as

$$\tau_0^{-\beta}{}_0 D_t^{-\beta} x(t) + x(t) - x_0 = \chi_0 \tau_0^{-\beta}{}_0 D_t^{-\beta} E(t) \tag{30}$$

which contains an inhomogeneity x_0. Applying the differential operator $_0 D_t^\beta$ on this equation, the fractional differential equation

$$_0 D_t^\beta x(t) + \tau_0^{-\beta} x(t) - x_0 \frac{t^{-\beta}}{\Gamma(1 - \beta)} = \chi_0 \tau_0^{-\beta} E(t) \tag{31}$$

results. For $\beta \to 1$, Eq. 31 is the standard equation known from magnetic or dielectric relaxations. In the special case of switching off a constant E_0 field, the general equations (Eqs. 30 and 31) reduce to the fractional relaxation equation.

Apart from relaxation, harmonic oscillation experiments and other experimental realizations can be studied as well. The central property for such experiments is the dynamic susceptibility. Fourier transforming the fractional equation,

the susceptibility

$$\chi(\omega) = \frac{\chi_0}{(i\tau_0 \omega)^\beta + 1} \tag{32}$$

is obtained which was first used in a phenomenological model by Cole and Cole (1941) in the context of dielectric experiments. As the inhomogeneous term proportional to x_0 falls off $\sim t^{-\beta}$, this transient part does not contribute to the steady-state oscillation.

The approach via the variables $\bar{x}$ and $\bar{E}$ is used here to get a description suitable for the Laplace transform with well posed initial conditions. In the ordinary differential calculus such indirect procedures are in general not necessary because derivatives of constants vanish. However, fractional derivatives of constants cannot be neglected.

Dynamics of myoglobin

As a typical process, we consider the ligand rebinding to the heme iron of myoglobin (Mb) after flash dissociation. In the experiment (Austin et al., 1975) the ligand-iron bond is broken by a laser pulse and the rebinding is measured afterwards optically in the Soret band. According to our point of view two states are distinguished, the protein having the ligand bound or not. Both states are built up by a hierarchy of substates that contribute to the transition kinetics by different rate constants or relaxation times. If the substates occur in a self-similar manner as proposed above, the amount of Mb that has not bound in a ligand follows Eq. 21. The solution is given by Eq. 23 with $\phi/\phi_0 = N$. In Fig. 2 experimental data from CO rebinding to Mb are shown for different temperatures. The solid lines correspond to the fractal model in which the temperature dependence of β is taken proportional to T

$$\beta(T) = \frac{0.41}{120\text{K}} T. \tag{33}$$

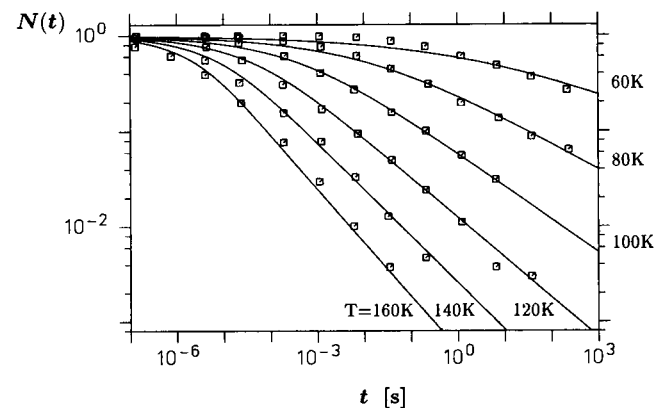The time constants $\tau_0(T)$ determined by a least-squares fit

FIGURE 2 Three-parameter model Eq. 32 for rebinding of CO to Mb after photo dissociation. The parameters are $\tau_m = 8.4 \times 10^{-10}$s, $\alpha = 3.5 \times 10^{-3}$ K^{-1} and $k = 130$, the data points are from Austin et al. (1975).

agree well with an Arrhenius law

$$\tau_0(T) = \tau_m \exp\left(\frac{E^*}{T}\right) \tag{34}$$

where the activation energy $E^* = 1470K \hat{=} 12.3$ kJ/mol is of the order of a characteristic energy barrier height $E_{peak} \approx 10 \cdots 11$ kJ/mol (Young and Bowne, 1984) and $\tau_m = 3.4 \times 10^{-10}$ s is a time constant of molecular motion.

Because of this temperature dependence, the fractional equation Eq. 21 can be transformed to the three-parameter model

$$k_0 D_z^{-\beta} \phi(z) + \phi(z) - \phi_0 = 0 \tag{35}$$

with the dimensionless time $z = t/\tau_m$, the fractional order $\beta = \alpha T$, and a constant k that is independent of the temperature. Thus, the whole temperature dependence is expressed by the fractal parameter β that increases proportional to T. In Fig. 2 this three-parameter model is applied to the Mb-CO rebinding. A least-squares fit leads to $\tau_m = 8.4 \times 10^{-10}$s, $\alpha = 3.5 \times 10^{-3}$ K^{-1}, and $k = 130$ ($\hat{=} E^* = 11.5$ kJ/mol). For temperatures T far below the glass transition temperature $T_g \approx 178$ K (Iben et al., 1989) of the Mb solution, the reaction kinetics and the temperature dependence are well described by the three-parameter model.

Whereas the photo dissociation experiment was performed on temperatures below the glass temperature, Iben et al. (1989) measured relaxation of Mb in the vicinity of T_g. They studied the relaxation of the protein after pressure release in the infrared stretch bands. The data for the relaxation function $\phi_1(t)$ determined from the center frequency of the A_0 band are given in Fig. 3. The solid lines correspond to the fractional model with $\beta = 0.4$. The temperature dependence is incorporated by $\tau_0 = \tau_0(T)$. The fit of the three-parameter model (Eq. 35) to the data provides agreement, but the parameters $\tau_0 \approx 10^{-42}$s and $E^* \approx 150$ kJ/mol obtain unrealistic values. The reason for this deviation is the dependence of $\tau_0(T)$. Instead of the Arrhenius form of Eq. 34, the activation in the neighborhood of the glass temperature follows a Vogel-Fulcher law

$$\tau_0(T) = C \exp\left(\frac{E}{T - T_0}\right) \tag{36}$$

(Fig. 4). The Vogel temperature $T_0 = 129$ K is in good agreement with the empirical rule $T_0 = T_g - 50$ K (Adam and Gibbs, 1965). We remark that instead of Eq. 36 the relation

$$\tau_0(T) = \tau^* \exp\left(\left(\frac{T^*}{T}\right)^2\right) \tag{37}$$

fits the data as well. Although Eq. 37 involves only two parameters $\tau^* \approx 6 \times 10^{-20}$s and $T^* \approx 1237$ K, we prefer the Vogel-Fulcher form (Eq. 36). In comparison with Eq. 37 the Vogel-Fulcher law (Eq. 36) is motivated by a molecular kinetic theory based on the configurational entropy of glass-forming liquids (Adam and Gibbs, 1965).

Because the glass temperature of the protein depends strongly on the glass transition of the solvent, it is called slaved glass transition. For a solution of Mb in a 75% glycerol and water mixture, which was used for the measurement in Fig. 3, the slaved glass transition is approximately $T_g \approx 178$ K (Iben et al., 1989). In the pressure release experiment the change of the molecule conformation is detected. Due to the glass transition of the solvent, the motion of the protein is slowed down. Each molecule shows slow relaxation dynamics according to the Vogel-Fulcher law Eq. 36 for $T > T_0$. The slow decay is a feature of each molecule and the fractional equation describes the relaxation dynamics of a more or less homogeneous ensemble (sequential process).

In the rebinding experiment, however, the temperature was far below T_g. Thus each protein is frozen in one of the many substates of the conformation. The conformational change connected with rebinding is a Debye process controlled by the Arrhenius law. In this case the slow reaction dynamics is a consequence of a heterogeneous ensemble (different parallel processes). As the only presumption for the fractional relaxation is the rough energy surface, the model works for both sequential and parallel processes. Hence the
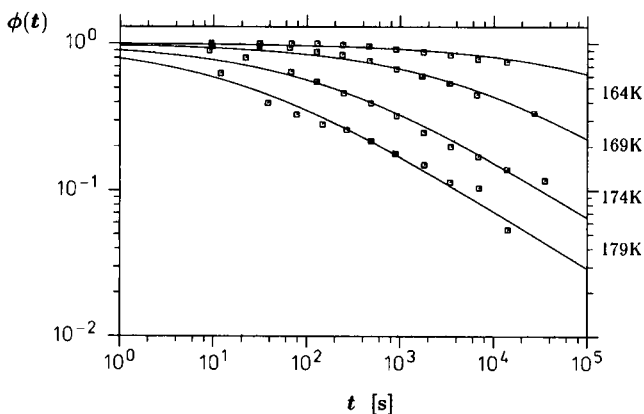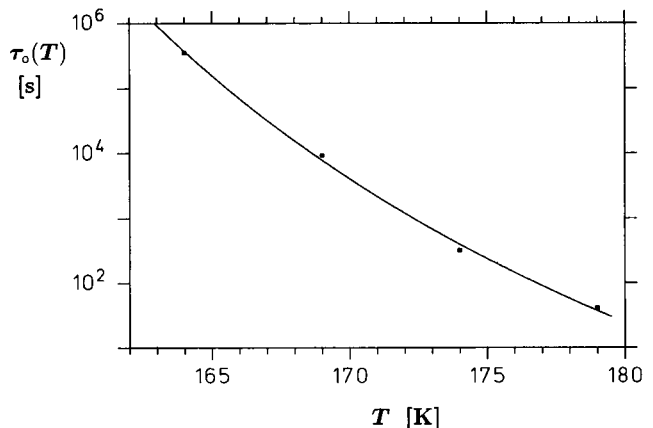

FIGURE 3 Relaxation of Mb after pressure release with data points from Iben et al. (1989). The solid lines are according to Eq. 20 with $\beta = 0.4$ and τ_0 given in Fig. 4.

FIGURE 4 Parameters $\tau_0(T)$ used in Fig. 3. The solid line shows the Vogel-Fulcher law Eq. 36 with $T_0 = 129.5$ K, $E = 1040$ K, and $C = 2.5 \times 10^{-8}$s.

model cannot be used to distinguish between the two limiting cases of processes. Furthermore, the model covers pure relaxation and pure reaction kinetics as well as mixed forms that are considered in the model of Agmon and Rabinovich (1992) in detail.

DISCUSSION

A characteristic feature of slow relaxation processes is the algebraic decay $\sim t^{-\beta}$ for large t whereby the parameter β plays the role of a fractal dimension in the time domain. There are several processes imaginable leading to the same long-time asymptotic that are, however, different at short times. Accordingly, different models of self-similar processes can be proposed obeying a close relationship due to the $t^{-\beta}$ law. In terms of the renormalization group theory we can say that they belong to the same class of universality. In this paper, apart from the model with geometric progression, the fractal scaling model was proposed as one representative of the universality class. The main advantage of the fractal scaling model is its close connection to a fractional order differential or integral equation. We showed that the model can be derived from an equation leading to a well posed initial value problem.

The fractal model shows good agreement with experimental results on conformational relaxation of Mb caused by ligand rebinding as well as by pressure release. It provides a description on a phenomenological level with two parameters, the characteristic time scale τ_0, and the fractional order β. Thus it can be used to analyze the parameter dependence on the temperature or other properties. In particular, for Mb the dynamical process shows an Arrhenius activation for temperatures far below the glass transition temperature and a Vogel-Fulcher activation in the vicinity of T_g. The fractal model applies to both sequential and parallel processes.

The parameter β that characterizes the universality class and describes the statistical weights of the model turns out to be the order of the fractional Riemann-Liouville operator. Hence, in time fractals the non-integer order in the equation takes the function of a fractal dimension that determines the scaling behavior. Another interpretation of β can be given in the picture of energy barriers. For large energies E the barrier height distribution $g(E)$ given by Eq. 12 decays like exp-$(-E/RT^*)$ with $T^* = T/\beta$. The property T^* is a measure of the roughness of the energy surface. Thus the parameter β describes the ratio of the temperature T to the roughness T^*. Such a Poisson-like decay was previously asserted as the characteristic of complex energy surfaces and as a universal aspect of all proteins (Straub and Thirumalai, 1993). Hence, this property also confirms the applicability of the fractal model to proteins.

Of course, the fractal language is a rough description and more details can be found in analyzing experimental data like those in Fig. 2. The fractional equation is an ideal construction that occurs in nature just as seldom as Sierpinsky gaskets, Koch curves, or Cantor sets. However, the shapes of

objects in nature are in general better described in the language of fractal geometry than by Euclidian geometry. The fractional relaxation equation should therefore be assumed as a mathematical construct that reflects the main features of processes in complex systems like proteins.

APPENDIX

For estimating the Laplace transform $Q(p)$ of the relaxation function $\phi(t)$, we start out with Eq. 2. Instead of $g(E)$ the distribution $b(k)$ of reaction rates k can be used as well, leading to

$$\phi(t) = \int_0^A b(k) \frac{RT}{k} \exp(-kt) \, dk. \tag{38}$$

Both distributions are related by $g(E) = b(A \exp(-E/RT))$, i.e.,

$$b(k) = p_0 \frac{(k\tau_0)^\beta \sin(\pi\beta)}{(k\tau_0)^{2\beta} + 2(k\tau_0)^\beta \cos(\pi\beta) + 1} \tag{39}$$

for the fractal model. In what follows, we consider observation times t much greater than the time scale of molecular motions $1/A$. Thus A can be substituted by ∞ in Eq. 38 and $\phi(t)$ is the Laplace transform

$$\phi(t) = \mathcal{L}\left(\frac{RTb(k)}{k}, t\right) \tag{40}$$

of $b(k)/k$.

The calculation of $Q(p)$ from $b(k)$ just consists in performing twice a Laplace transform

$$RT \frac{b(k)}{k} \xrightarrow{\mathcal{L}} \phi(t) \xrightarrow{\mathcal{L}} \frac{Q(p)}{p}.$$

However, because of the non-integer exponent β in Eq. 39, the necessary expressions are not listed in standard handbooks. Instead of the iteration of two Laplace transforms, one can use the Stieltjes transform given by

$$S(f(k), p) = \int_0^\infty \frac{f(k)}{p + k} \, dk \tag{41}$$

to calculate $Q(p)$ by

$$\frac{Q(p)}{p} = S\left(\frac{RTb(k)}{k}, p\right). \tag{42}$$

Further we use the relation (Oberhettinger, 1974)

$$\mathcal{M}(S(f(k), x), z) = \frac{\pi}{\sin(\pi z)} \mathcal{M}(f(x), z) \tag{43}$$

connecting an arbitrary function and its Stieltjes transform by their Mellin transforms which are defined by

$$\mathcal{M}(f(x), z) = \int_0^\infty f(x) x^{z-1} \, dx. \tag{44}$$

From

$$Q(p) = p\mathcal{M}^{-1}\left(\frac{\pi}{\sin(\pi z)} \mathcal{M}\left(\frac{RTb(k)}{k}, z\right), p\right) \tag{45}$$

the result

$$Q(p) = RT\pi p_0 \frac{1}{(\tau_0 p)^{-\beta} + 1} \tag{46}$$

is found from tables of Mellin transforms and inverse Mellin transforms (Oberhettinger, 1974).

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