Short communication

Stochastic Description of Protein Conformational Motion

P. BABINEC and M. BABINCOVÁ

Department of Biophysics and Chemical Physics,
Faculty of Mathematics and Physics, Comenius University,
Mlynská dolina F1, 842 15 Bratislava, Slovakia

Abstract. Green function analysis of the Fokker-Planck equation was used to describe protein conformational motion for approximate variational derivation of typical rate constant of protein relaxation from excited nonequilibrium state to the equilibrium. This approach was illustrated on a simple one-dimensional conformational potential.

Key words: Protein — Conformational motion — Fokker-Planck equation — Green function

Proteins are extremely complex systems with large numbers of energy valleys (substates) separated by energy barriers (Frauenfelder et al. 1991; Frauenfelder and Wolynes 1994). Despite the great success in the determination of protein structure at the atomic level of resolution, it is still impossible to use these data for quantitative prediction of e.g. reaction rates of enzyme catalysis (Demchenko 1992). The relaxation of a protein from an excited nonequlibrium state toward equilibrium exhibits characteristics that distinguish complex systems from simple ones which allowed to used analogies between proteins and glasses (Iben et al. 1989) or spin glasses (Binder and Young 1986) and also analogies from the disordered systems in condensed matter physics (Iori et al. 1991). This conformational relaxation is essentially an elementary act of such processes as enzymatic catalysis and the energy coupling of intracellular chemical reactions.

In this paper we have used statistical description for the motion of proteins considered as transitions between conformational substates which may be described by the Fokker-Planck diffusion equation (Bryngelson and Wolynes 1989).

$$\frac{\partial P(x,t)}{\partial t} = D\left(\frac{\partial^2 P(x,t)}{\partial x^2} + \beta \frac{\partial U(x)}{\partial x}\,\frac{\partial P(x,t)}{\partial x} + \beta\, P(x,t)\,\frac{\partial^2 U(x)}{\partial x^2}\right) \qquad (1)$$

where $P(x,t)$ is probability density to find the protein in conformation with coordinate x, $U(x)$ is conformational potential (for simplicity we have restricted to

the one-dimensional case, and $U(x)$ represents now a cut through the conformational hypersurface), D is the conformational diffusion constant, and $\mathcal{J}$ is absolute temperature.

Equation (1) may be rewritten in the form

$$\frac{\partial P(x,t)}{\partial t} = -D\,F(x)\;P(x,t) \tag{2}$$

where diffusion operator F is defined as

$$F(x) = -\frac{\partial^2}{\partial x^2} - \beta\left(\frac{\partial U}{\partial x}\,\frac{\partial}{\partial x} + \frac{\partial^2 U}{\partial x^2}\right) \tag{3}$$

Diffusion operator is non-Hermitian, and its Hermitian conjugate is

$$F^{+}(x) = -\frac{\partial^2}{\partial x^2} + \beta\left(\frac{\partial U}{\partial x}\,\frac{\partial}{\partial x} - \frac{\partial^2 U}{\partial x^2}\right) \tag{4}$$

Equation (2) may be resolved using the Green function $G(x,x';\;t,t')$ which obey the equation (Risken 1984)

$$\left(\frac{\partial}{\partial t} + D\;F(x)\right) G = \delta\,(x - x')\,\delta\,(t - t') \tag{5}$$

Explicit form of the Green function is

$$G = \sum_n \theta(t - t')\,\mathrm{e}^{-D\lambda_n (t-t')}\,\phi_n^*(x')\,\phi_n(x) \tag{6}$$

where θ is the Heaviside function ($\theta(t) = 0$ if $t < 0$ and $\theta(t) = 1$ if $t \geq 0$).

Let us consider that initially ($t' = 0$) was a protein in conformation with coordinate x_o, then we have

$$P(x,t) = \sum_n \theta(t)\;\mathrm{e}^{-D\lambda_n t}\,\phi_n^*(x_o)\;\phi_n(x) \tag{7}$$

Where the set $\{\lambda_n;\; n = 1,2\ldots\}$ are eigenvalues of $F^{+}(x)$ corresponding to eigenfunctions $\phi_n(x)$

$$F^{+}\;\phi_n\,(x) = \lambda_n\,\phi_n\,(x) \tag{8}$$

$\phi_0\,(x) = 1$ and $\lambda_o = 0$ for all $U(x)$.

If the next eigenvalues are positive, then next terms in the sum (7) decay exponentially with time.

The typical relaxation rate constant K_r is intimately connected with the first subdominant eigenvalue λ_1 (Hänggi et al. 1990)

$$K_r \sim \lambda_1 \tag{9}$$

Calculations of the set $\{\lambda_n\}$ for a given conformational potential is important for the understanding of the dynamical behaviour of the proteins.

Simplest conformational potential $U(x)$ is

$$U(x) = x^2 \tag{10}$$

with corresponding eigenvalue equation

$$\phi''(x) - 2x\,\phi_n'(x) + \lambda_n\ \phi_n(x) = 0 \tag{11}$$

This equation has solutions

$$\lambda_n = 2\beta n \quad \text{and} \quad \phi_n(x) = H_n\,[(\beta)^{1/2}x] \tag{12}$$

where H_n are Hermite polynomials defined recurrently as $H_0(x) = 1$, $H_1(x) = 2x$, $H_{n+1}(x) = 2xH_n(x) - 2nH_{n-1}(x)$.

To determine $\{\lambda_n\}$ for a more realistic potential, we must resort to approximate methods. We employed variational method with the basis given by the set of functions (12). Variational ansatz may be written in the form

$$\phi_n(x) = \sum_{l=0}^{m} c_{n\,l}\ H_l\,[(\beta)^{1/2}x] \tag{13}$$

According to the Ritz principle, the optimal solution is obtained from equation

$$\sum_l (f_{jl} - \lambda_k\ s_{jl})\,c_{k,l} = 0 \qquad j = 0, 1, \ldots, m \tag{14}$$

where $f_{jl} = \int H_j\,[(\beta)^{1/2}x]\ \ F^+\ H_l[(\beta)^{1/2}x]\,\mathrm{d}x$
and $s_{jl} = \int H_j\,[(\beta)^{1/2}x]\ H_l\,[(\beta)^{1/2}x]\,\mathrm{d}x$

For a given potential these integrals may be solved numerically.

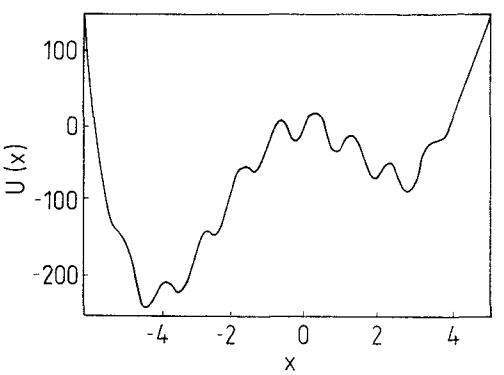

Figure 1. One-dimensional model conformational potential.

Let us consider conformational potential $U(x)$ (Fig. 1.) which is similar to the one-dimensional cross section of protein energy landscape

$$U(x) = x^4 + 2x^3 - 22x^2 + 20 \sin 6x \tag{15}$$

The calculated ($m = 12$) temperature dependence of the first subdominant value λ_1 is shown in the Fig. 2. Even for this simple system this dependence has a strongly non-Arrhenius character, which is similar to that obtained experimentally e.g. in the study of CO and O_2 rebinding kinetics in myoglobin, where the relaxation pathway is essentially one-dimensional (Iben et al. 1989). This theory may be directly applied only to such problems which may be of importance especially in the site specific excitation of protein conformational motion, similar like in small molecules (Zewail 1993).

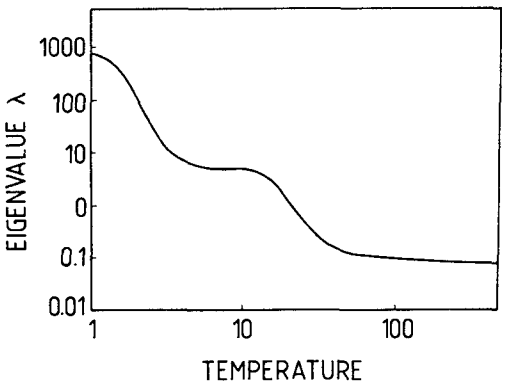

Figure 2. Dependence of the first subdominant eigenvalue λ on absolute temperature.

In the presence of several relaxation pathways the Fokker-Planck equation (1) may be generalized to multi-dimensional cases and solved approximately using the generalization of the proposed variational ansatz (13). If there are for example two relevant conformational coordinates, with substantially different relaxation rate constants, further approximation previously used in the study of electron transfer in proteins (Onuchic 1987) may be employed to reduce the problem to one renormalized conformational coordinate.

The proposed method has similar features like the Wilson FG-analysis of molecular vibrations (Wilson et al. 1955), where each vibration is given as a sum of normal vibrational modes. In our case probability density $P(x,t)$ is given as an infinite sum of the "normal conformational modes".

Applications of this approach to simple proteins are in progress. This may be useful in the interpretation of e.g. temperature-derivation spectroscopy, flash photolysis or pressure jump experiments (Young et al. 1991; Blumenfeld 1983)

where the conformational relaxation of proteins after local chemical changes may be regarded as a motion along specific mechanical degree of freedom Another possible application is the calculation of typical time scales of protein folding from the first principles (Honeycutt and Thirulamai 1992) and the study of the influence of protein conformational motion on the electron transfer (Babincova and Babinec 1993)

References

Babincova M Babinec P (1993) Influence of protein vibrations on electron transfer Acta Phys Polon A **84,** 365 367

Binder K Young A P (1986) Spin glasses Rev Mod Phys **58,** 801—976

Blumenfeld L A (1983) Physics of Bioenergetic Processes Springer Verlag New York

Bryngelson J D Wolynes P G (1989) Intermediates and barrier crossing in a random energy model J Phys Chem **93,** 6902—6915

Demchenko A P (1992) Does biocatalysis involve inhomogeneous kinetics? FEBS Lett **310,** 211—215

Frauenfelder H Sligar S Wolynes P G (1991) The energy landscapes and motion of proteins Science **254,** 1598—1603

Frauenfelder H Wolynes P G (1994) Biomolecules Where the physics of complexity and simplicity meet Phys Today **47,** 58—64

Hanggi P Talkner P , Borkovec M (1990) Reaction rate theory Rev Mod Phys **62,** 251—340

Honeycutt J D Thirulamai D (1992) The nature of folded states of globular proteins Biopolymers **32,** 695—709

Iben I E T Braunstein D , Doster W Frauenfelder H , Hong M K Johnson J B Luck S , Ormos P Schulte A , Steinbach P J Xie A H Young R D (1989) Glassy behavior of a protein Phys Rev Lett **62,** 1916—1919

Iori G Marinari E Parisi G (1991) Random self-interacting chains a mechanism for protein folding J Phys A **24,** 5349 –5362

Onuchic J N (1987) Effect of friction on electron transfer The two reaction coordinate case J Chem Phys **86,** 3925 –3943

Risken H (1984) The Fokker-Planck Equation Springer Verlag, New York

Wilson E B , Decius J B , Cross P C (1955) Molecular Vibrations McGraw-Hill, New York

Young R D , Frauenfelder H , Johnson J B , Lamb D C , Nienhaus G U , Philipp R Scholl R (1991) Time- and temperature dependence of large-scale conformational transitions in myoglobin Chem Phys **158,** 315—327

Zewail A (1993) Femtochemistry J Phys Chem **97,** 12427—12446

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