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Fluctuation relations, effective temperature, and ageing of enzymes: The case of protein electron transfer

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ABSTRACT

Proteins catalyzing chemical reactions are glassy systems in which the reaction time is often below the time of conformational relaxation. The protein is not able to sample its configuration space on the reaction time, leading to nonergodic ensemble averages. This phenomenology makes the effective configurational temperature of the protein significantly higher than the kinetic temperature of the bath. The effective temperature is expressed in terms of the fluctuation-dissipation ratio quantifying the violation of the fluctuation dissipation theorem (FDT). For reactions of protein electron transfer, the ratio of configurational and kinetic temperatures is given by the ratio of two reorganization energies related to, correspondingly, thermal fluctuations of the thermal bath and linear response of the bath to electron arriving to the active site. The violation of the FDT leads to a significant depression of the activation barrier achieved trough nonergodic exploration of the protein configuration space. The time of conformational dynamics, leading to equilibration, establishes the ageing time during which the enzyme has to be reset to its original configuration. Experimental evidence and numerical simulations indicate a factor of 2–3 violation of the FDT for protein electron transfer at physiological temperatures. Lowering temperature freezes the protein into a state consistent with the FDT through a glass transition. Design principles of physiological energy chains are discussed by postulating the need to maintain FDT violated to support catalytic function.

1. Introduction

We discuss here some general principles of how the statistics and dynamics of individual proteins contribute to the overall efficiency of energy production in biology. The problem of physiological energy flow embraces many scales, but it starts at the level of individual molecules converting the energy of light (photosynthesis) or chemical redox potential (mitochondria) into the movement of even smaller subatomic particles, electrons and protons, across the cellular membrane [1].

Our main hypothesis is that proteins, being a specific form of a folded linear-chain polymer, possess properties distinguishing them from simple organic molecules used for redox chemistry in man-made devices. Specifically, we entertain the notion, advocated in the past [2,3], that proteins are fundamentally glassy materials. This means that their relaxation times, related to conformational transitions, are significantly longer than the time-scale required to perform a specific function, a protein-catalyzed chemical reaction in this case.

The glassy state of a protein, or of any other material, implies that some parts of its phase space cannot be visited on the observation time-scale. Constraints imposed on the phase space available to a given observable property are often described as ergodicity breaking [4]. A convenient cartoon visualizing the issues involved is in terms of the configuration landscape of the system [5]. The complete energy landscape is the potential energy of the system $U(\mathbf{q})$ as a function of its all degrees of freedom $\mathbf{q}$ [6]. Since the complete landscape is hard to imagine or even compute, a one-dimensional cartoon is often used for illustration and is shown in Fig. 1. The main feature of this picture is that, in contrast to ergodicity implicit to the Gibbs distribution, the system can explore only a small portion of its phase space known as a component [4]. As a result, the statistical averages performed to calculate the observables should be restricted to the phase space of a given component, or a cluster of them visited on the observation time.

The transition from the ergodic Gibbs statistics to the nonergodic statistics of glassy systems brings in a number of observable consequences. The most important in the present context is the violation of the fluctuation-dissipation theorem (FDT) [7] connecting the response of a material to a small perturbation with the breadth of spontaneous fluctuations caused by thermal agitation [8].

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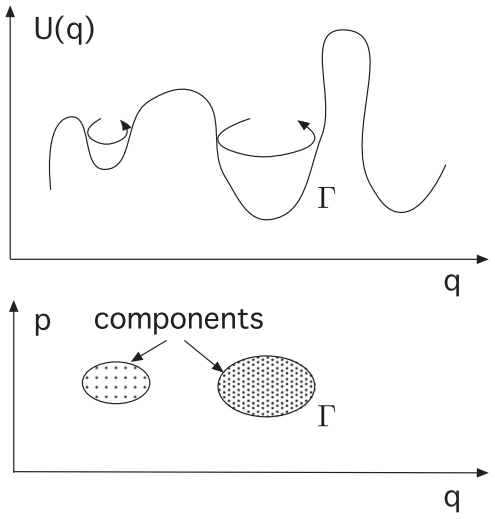

Fig. 1. Cartoon of the energy landscape of a glassy system, which is locked in a local minimum on the observation time-scale. The phase space available to the system is limited to a single component Γ within a constrained part of the available phase space (q, p). As the system ages on the time-scale of its α-relaxation, it visits an increasing number of components, thus asymptotically approaching the Gibbs statistics in configuration space.

The essence of the linear response theory and the FDT is illustrated in Fig. 2. It shows a step perturbation by an external force and the time response of the dynamic variable A, with its average value equal to zero before the perturbation has been applied. The ratio of the time-dependent response $\langle A\rangle_t$ (the average is taken with the time-dependent distribution function [7] $f(\Gamma, t)$ evolving on the phase space Γ) to the external force step $\Delta f_{\rm ext}$ provides the time-dependent susceptibility $\chi(t) = \langle A\rangle_t/\Delta f_{\rm ext}$. It can be found from the FDT according to the relation [7,9]

$$\chi(t) = \beta[C(0) - C(t)]\,. \tag{1}$$

Here, $\beta = (k_{\rm B}T)^{-1}$ is the inverse temperature and $C(t) = \langle A(0)A(t)\rangle_{\rm eq}$ is the time autocorrelation function of the variable $A(t)$, $\langle A\rangle_{\rm eq} = 0$. Here and below, the angular brackets denote an ensemble average, which can be either the equilibrium Gibbs ensemble or an ageing nonequilibrium ensemble specific to averages performed over the states of a protein or of a quenched glass former. The former is specified with the subscript "eq" and no subscript is given for the latter.

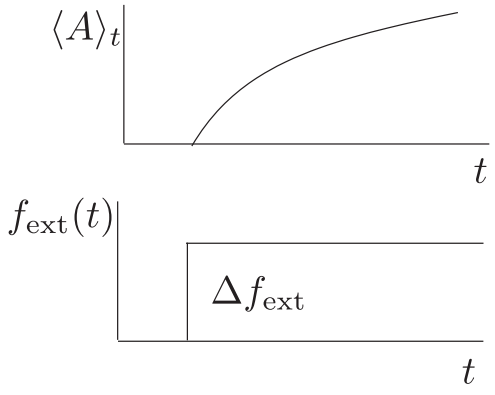

Fig. 2. Step perturbation of the external force $f_{\rm ext}(t)$ and the linear response of the dynamic variable $\langle A\rangle_t$. The response function $\chi(t)$ is the ratio of $\langle A\rangle_t$ and the force step $\Delta f_{\rm ext}$.

Two predictions come from Eq. (1). First, one expects a linear relation between $\chi(t)$ and $C(t)$ with the slope equal to $-\beta$ (Fig. 3a). This is the FDT relation between the dynamic variables. Second, the correlation function $C(t)$ vanishes when $t \to \infty$ and one arrives at the relation between the static response and the static variance of A

$$\chi = \chi(\infty) = \beta\langle A^2\rangle_{\rm eq}. \tag{2}$$

This relation is of main interest in application to protein's function discussed below. Before we turn to those issues, it is useful to outline a general phenomenology of glassy materials and related signatures of the FDT violation. We turn to the problem of structural recovery of glasses exposed to ageing [10-13]. The main phenomenological issues are summarized in Fig. 3.

The linear relation between the susceptibility $\chi(t)$ and the correlation function $C(t)$, with the slope of $-\beta$ [Eq. (1)], is shown in Fig. 3a. In a nonequilibrium system ageing through the waiting time t_w, the time translational invariance of the dynamic correlation functions is lost [9] and the correlation function $C(t, t_w)$ depends on two times, t and t_w, instead of their difference $t - t_w$. The second, ageing time refers to the system's evolution from an originally created (quenched) nonequilibrium state toward equilibrium. The FDT is violated during the ageing process [14-16]. This violation is reflected by the slope $-\beta_{\rm eff}$ between $\chi(t)$ and $C(t)$ distinct from $-\beta$ predicted by Eq. (1) (Fig. 3b) [17]. As t_w becomes longer, the portion of the plot with the slope $-\beta_{\rm eff}$ shrinks, eventually leading to the standard equilibrium expectations.

The nonequilibrium quenched state of a glass former is created by experimental preparation placing the system in a local minimum higher in energy than the global minimum of the equilibrium state. The ageing process then corresponds to the evolution of the energy or the enthalpy of the system from the high value of the trapped glassy state H_0 to the equilibrium value H_∞ consistent with the bath temperature T (Fig. 3c) [10]. Quenching of glass formers is typically achieved by rapid cooling, but any nonequilibrium preparation of the system will create a quenched state. For instance, for physiological energy flow considered here, the instantaneous, on the time-scale of nuclear motions, tunneling of the electron to an active site of a protein creates an initial nonequilibrium quenched state.

The temperature at which the system was quenched can be specified as an effective, or fictive [10], temperature. Alternatively, one can use the fluctuation-dissipation ratio, i.e., the slope $\beta_{\rm eff} = 1/(k_{\rm B}T_{\rm eff})$ between $\chi(t)$ and $C(t, t_w)$ to define $T_{\rm eff}$ [12,14,17]. In this paper, we will use a somewhat different definition, also based on Eq. (1), but referring to the static limit of the FDT [19]

$$\frac{T_{\rm eff}}{T} = \frac{\beta\langle A^2\rangle}{\chi}. \tag{3}$$

Such defined fluctuation-dissipation ratio involves the effective temperature $T_{\rm eff}$, which can be associated with the "configurational temperature" since it, like the fictive temperature of glass science [10,20,21], characterizes the position of the system in the configuration landscape. This effective temperature does not carry a universal character, in contrast to the kinetic temperature at equilibrium, and instead depends on the variable A used to establish it [22,23]. This difficulty is also shared by the phenomenological fictive temperature [21]. This problem does not complicate our formulation since we use the effective temperature in a very specific context of an activated chemical reaction catalyzed by the protein. The dynamic variable A becomes the reaction coordinate monitoring the transition over the activation barrier. As we show below, such defined effective temperature quantifies the depression of the activation barrier