Mechanism of Solvent Control of Protein Dynamics

Saumyak Mukherjee, Sayantan Mondal, and Biman Bagchi*
Solid State and Structural Chemistry Unit, Indian Institute of Science, Bengaluru 560012, India

(Received 23 May 2018; published 7 February 2019)

We find that the coupled interactions between protein and water polarization fluctuations play a dominant role in driving the configuration space random walk of solvated proteins. We perform atomistic molecular dynamics simulations on five proteins. Owing to a very low dielectric constant of protein, its dipolar groups experience forces from water along with local forces due to protein atoms. Energy fluctuations reveal a pronounced anticorrelation between protein and water contributions. The protein energy spectrum shows bimodal $1/f$ noise, which can be attributed to the influence of water on the dynamics of protein.

DOI: 10.1103/PhysRevLett.122.058101

In their seminal work on the nature of protein secondary structures, Pauling and Corey mentioned that β sheets are long-lived structures that display the characteristics of a crystal, whereas α helices are mobile and exhibit liquidlike properties [1,2]. This suggests that internal protein motions are partly determined by its architecture. Conformational fluctuations of proteins are manifested in their biological functions [3]. Hence, the following question arises: What forces are responsible for these ceaseless motions? Along with the structural fluctuations, surrounding water molecules play a pivotal role. Protein-water interactions and diffusion of water on a protein surface are known to control the conformational fluctuations in protein [4,5]. But, how far is the reach of water? Earlier computational (molecular dynamics simulation) and experimental (terahertz spectroscopy) studies showed that the static properties of the hydration layer are perturbed by protein only up to a distance of 3 Å. But, its influence in the dynamics is long ranged and can be observed up to 10 Å or more [6–8].

Frauenfelder and coworkers proposed that conformational fluctuations in proteins are *slaved* to the dynamics of solvent (primarily water) molecules [9–12]. According to their proposition, large-scale protein motions are slaved to fluctuations of bulk water, whereas small-scale motions are controlled by fluctuations of the hydration layer. These resemble the α and β fluctuations observed in glassy dynamics [13,14]. The similarities between the energy landscapes of proteins and glasses have stimulated several theoretical studies [15–18]. Water itself is a liquid with a rich energy landscape. It exhibits correlated large-scale fluctuations [19–22]. Thus, the interactions between water and protein allow enormous kinetic and thermodynamic possibilities that become useful in the protein's functions [8,23–27].

The protein backbone and side-chain atoms contain partial charges [28]. However, the static dielectric constant of the protein core is small [29], due partly to the lack of orientational degrees of freedom of the peptide bonds that are held relatively fixed in their native positions, albeit with small conformational motions. These dipole moments and partial charges of the protein interact with the surrounding water molecules. Because of the long-range nature of polar interactions, even relatively distant molecules interact with the protein core, aided by its low static dielectric constant. The strong interaction of charged groups with surrounding water molecules is also manifested in the Stokes shift studies of natural probes like tryptophan [30,31]. This is interesting because water may exert local forces inside the protein core that might lead to conformational transitions. However, the total force, because of cancellations, might still be small.

The dynamics of this coupled complex system can be understood by using a generalized Langevin approach [Eq. (1)] for order parameter vector $\mathbf{A}$:

$$\frac{d\mathbf{A}(t)}{dt} = i\mathbf{\Omega}\cdot\mathbf{A}(t) - \int_0^t d\tau \mathbf{K}(\tau)\cdot\mathbf{A}(t-\tau) + \delta\mathbf{F}(t). \quad (1)$$

Here, $\mathbf{\Omega}$ is the frequency matrix, $\mathbf{K}(t)$ is the memory kernel, and $\delta\mathbf{F}(t)$ is random force. $\mathbf{K}(t)$ is related to the stochastic force $\delta\mathbf{F}(t)$ by the fluctuation-dissipation theorem [32]. $\mathbf{K}(t)$ is a tensor because $\delta\mathbf{F}(t)$ comprises two distinct components: one from self-energy of the protein, and another from interactions with water molecules. These give rise to what are often referred to as internal and external frictions, respectively [33–36]. The cross-correlation between the two different sources is of interest. Forces exerted by solvent partly guide the configuration space diffusion of proteins and the flow of energy between the two [15,37–40].

A holistic study of this coupled dynamics is difficult to perform with forces acting on individual particles. Not only is this approach too detailed, but the inherent stochasticity also increases the complexity of the problem. Hence, we

choose energy fluctuations as the convenient order parameter. Although several studies have probed the vibrational energy flow within proteins [41–45], the energy flow between a protein and its surrounding solvent remains relatively unexplored. Here, we address this complex coupling by performing atomistic molecular dynamics simulations on five protein-water systems, namely, myoglobin (Mg), lysozyme (Lz), plastocyanin (Pc), insulin (In), and HP36 (Hp). This choice of proteins covers a wide range of functionalities, sizes, shapes, and internal structures (Supplemental Material [46]).

We divide the whole system into two subensembles, i.e., protein (P) and water (W). Water is farther classified into two subdomains, viz., the hydration layer (HL) and bulk water (BW). This classification allows us to decompose the total energy of the system into separate contributions [Eqs. (2) and (3)].

$$E_T = E_P + E_W, \tag{2}$$

$$E_W = E_{\mathrm{HL}} + E_{\mathrm{BW}}. \tag{3}$$

The total contribution from any of part of the system (α) is calculated by adding the self-energy of that domain ($E_{\alpha\text{-}\alpha}$) to half of the cross-interaction energies of that domain with the rest of the system ($E_{\alpha\text{-}\beta}$) [Eq. (4)].

$$E_\alpha = E_{\alpha\text{-}\alpha} + \frac{1}{2}\sum_\beta E_{\alpha\text{-}\beta}. \tag{4}$$

Here we compute the Coulomb interactions. We find that, in all five protein-water systems, the energy of water fluctuates to a greater extent than that of proteins (Fig. 1). This observation is a manifestation of the huge number of water molecules in the systems (~25 000). The extended hydrogen-bond network in water results in large-scale collective oscillations that give rise to large-scale fluctuations [20].

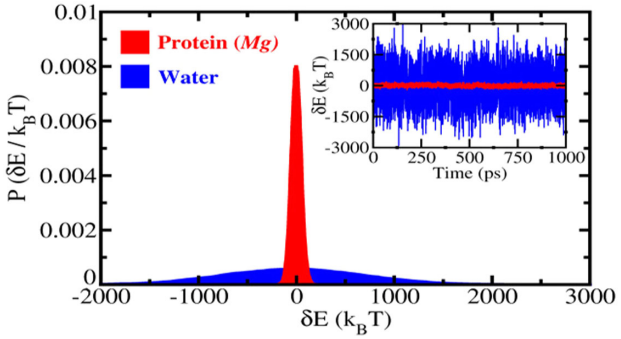

FIG. 1. Distributions of energy fluctuations in protein (Mg) and water that show the following form: $P(\delta E) = e^{-[(\delta E)^2/(2k_BT^2C_V)]}/\sqrt{2\pi k_B T^2 C_V}$. Corresponding energy fluctuation trajectories are shown in the inset. Fluctuation is greater in water (standard deviation = 701.91 k_BT) than in protein (standard deviation = 49.58 k_BT). Results for other proteins are provided in the Supplemental Material [46].

δE denotes the fluctuation in energy. $C_V = \langle \delta E^2 \rangle / (k_B T^2)$ is the specific heat that is related to the width of the distribution. Consequently, the specific heat of protein is substantially lower than that of water [27,56–59]. Hence, water is less sensitive to sudden temperature fluctuations as compared to proteins. As a result, the hydration layer acts a protective shield that maintains the structural integrity and, consequently, the dynamics of a protein. This leads to the following question: How are energy contributions from protein and water correlated?

We quantify the correlation between E_α and E_β by the Pearson correlation coefficient [Eq. (5)].

$$\rho_{\alpha\beta} = \frac{\langle \delta E_\alpha \delta E_\beta \rangle}{\sqrt{\langle (\delta E_\alpha)^2 \rangle \langle (\delta E_\beta)^2 \rangle}}. \tag{5}$$

A positive $\rho_{\alpha\beta}$ signifies correlated contributions, whereas a negative value indicates anticorrelation. The two quantities are uncorrelated if $\rho_{\alpha\beta}$ is "zero." The values of $\rho_{\alpha\beta}$ between protein self-energy ($E_{P\text{-}P}$) and protein-water interaction energy ($E_{P\text{-}W}$) for the five protein-water systems are found to be ~ -0.9. Hence, the two energy contributions exhibit strong anticorrelation. The exact values are provided in the Supplemental Material [46].

In Fig. 2(a), we present the trajectories of $\delta E_{P\text{-}P}$ and $\delta E_{P\text{-}W}$ for aqueous myoglobin. This clearly shows anticorrelated fluctuations. These energy fluctuation trajectories resemble spectral diffusion in energy space, as has been shown by earlier spectroscopic studies [60–62]. Furthermore, the slope of the major axis of the elliptical contour of the bivariate distribution is negative [Fig. 2(b)] (other systems are shown in the Supplemental Material [46]), which indicates anticorrelation.

We rationalize the observed anticorrelations in terms of a coupled anharmonic oscillator model. Here, protein and water are connected by springs that allow transfer of energy between them. As a consequence of the law of energy conservation, the increase in protein's energy causes a

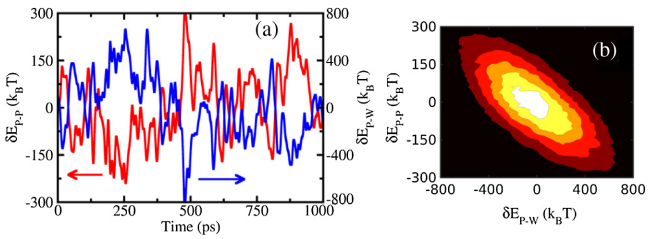

FIG. 2. (a) Protein (Mg) self-energy fluctuations ($\delta E_{P\text{-}P}$) and protein-water interaction energy fluctuations ($\delta E_{P\text{-}W}$); (b) contour representation of bivariate distribution of these two energy contributions. Energy trajectories and contour diagram denote strong anticorrelation. Similar results are obtained for other proteins (Supplemental Material [46]).

decrease in that of water. Because the protein experiences higher energy barriers in traversing its configuration space, a single transition in the protein landscape results in multiple transitions in the water configurational space (Supplemental Material [46]).

A significant anticorrelation is particularly observed between the self-energy of protein ($E_{P\text{-}P}$) and the cross-interaction energy of protein and a hydration layer ($E_{P\text{-HL}}$) in every system studied ($\rho_{P\text{-}P,P\text{-HL}} = -0.41$, Mg). On the other hand, the correlation of the former is weak with that of the protein-bulk interaction energy ($E_{P\text{-BW}}$; $\rho_{P\text{-}P,P\text{-BW}} = -0.41$, Mg).

Although significant anticorrelation is observed between the $E_{P\text{-}P}$ and $E_{P\text{-}W}$ contributions, $E_{P\text{-}P}$ and $E_{W\text{-}W}$ are weakly correlated. We rationalize this apparently conflicting observation in terms of the energy autocorrelation function to be described later. Structural rearrangements in proteins and water often lead to extensive cancellations of interaction energies [63]. Besides, with the overall polarization of bulk water being close to zero, the effects on protein as a whole are decreased to a great extent. Also, polarization of the hydration layer water molecules, especially around charged or polar side chains on the protein surface, screens the effects of bulk water on protein.

However, if we focus on a local probe for a microscopic picture, the effect of such cancellations is minimized to some extent and the scenario becomes clearer. Myoglobin and plastocyanin possess metal ions (iron at the heme center in myoglobin and copper in plastocyanin) that can be used as local probes. Because of the low dielectric constant of protein, especially the core [29], these charged metal ions are poorly screened. This allows the ions to interact with water molecules, both in the hydration layer and bulk.

We calculate the electrostatic interaction energies of these metal ions (M) with different subsystems and compute the correlation coefficients between them. This provides a rational insight into the nature of coupling between the different contributions. We find that M-P and M-W interactions are strongly anticorrelated, with $\rho = -0.71$ for iron in Mg and -0.91 for copper in Pc. Protein atoms reside in closer vicinity to copper in Pc than that of Fe in Mg, which is caged inside a porphyrin ring. Hence, a variation in ρ arises because of the different neighborhoods. We show the energy fluctuations in Fig. 3, which demonstrate the observed anticorrelation.

Because we consider a probe inside the protein to study energy coupling at a microscopic level, we classify the protein into two further subdomains, namely, side chain (SC) and backbone (BB). The values of the correlation coefficients for M-SC vs M-W and M-BB vs M-W interactions are provided in Table I.

This shows that the principal sources of negative coupling between protein and water are the amino acid side chains. Higher anticorrelation for side chains is a consequence of greater solvent exposure as compared to the backbone. Water molecules in the immediate vicinity of side chains are often found to execute coupled motions with side-chain fluctuations (Supplemental Material [46]). Therefore, energy flows from protein to water (and *vice versa*) aided by the side-chain conformational fluctuations. We observe similar anticorrelations for several other local sites as well.

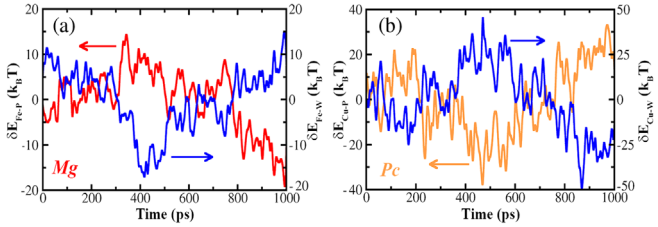

FIG. 3. Anticorrelated energy fluctuations of (a) Fe-myoglobin and (b) Cu-plastocyanin interactions along with interactions with water.

The structural fluctuations of protein in its native state are consequences of these multiple interactions. The forces acting on the protein backbone from water impart flexibility to the system. With the average total polarization of bulk water being small, the total force experienced by the protein because of interactions with water might be small. However, we find that forces experienced by individual dipolar groups in the backbone (such as peptide C = O and N-H) from interaction with water molecules are comparable in magnitude to that from the other protein atoms. For instance, although the mean square force experienced by a peptide C = O group in myoglobin due to interaction with water is 2.24×10^{-24} dyn^2, that due to protein atoms is 1.87×10^{-24} dyn^2. Moreover, the average relaxation time of the force autocorrelation function (related to time-dependent friction) from the water contribution (22.7 ps) is also of the same order as that from protein atoms (60.2 ps).

Several water molecules that reside inside the hydration layer show correlated displacement (d_w) along with energy fluctuations in protein. Such a correlation is shown in Fig. 4. This shows that energy fluctuations in proteins are coupled to positional fluctuations of hydration layer water molecules. The vibrational correlation between protein and water has been reported earlier [6].

Although the correlation coefficient gives the measure of static correlation, a dynamic correlation is quantified by time correlation function (TCF) [Eq. (6)].

TABLE I. Correlation coefficients for interactions between metal and water with metal-SC and metal-BB contributions separately.

Interactions	ρ
Fe-SC and Fe-W; Fe-BB and Fe-W (Mg)	−0.71; −0.31
Cu-SC and Cu-W; Cu-BB and Cu-W (Pc)	−0.91; −0.09

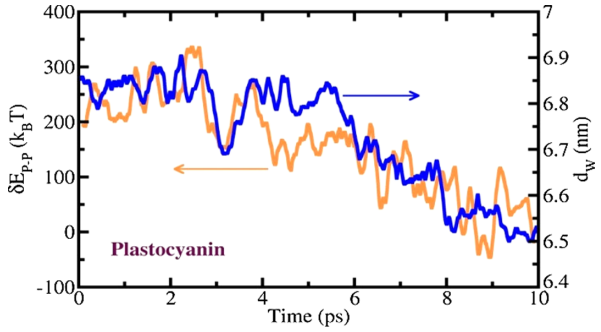

FIG. 4. Protein self-energy fluctuation of Pc along with displacement of a selected water molecule in HL. The two trajectories are strongly correlated ($\rho = 0.75$). Several other water molecules in HL show similar behavior.

$$C^{\text{cross}}(t) = \langle \delta E_\alpha(0) \delta E_\beta(t) \rangle. \tag{6}$$

Figure 5(a) shows the cross-TCF of protein self-energies and protein-water interaction energies for five protein-water systems. The amplitudes ($t = 0$) of the TCF are mentioned in the figure. Negative values of these amplitudes in all the systems represent strong anticorrelation.

The scenario is similar for interactions with local probes, as presented in Figs. 5(b) and 5(c) for Fe in Mg and Cu in Pc, respectively. We note that the local dynamics is slower than the global picture.

We quantify the nature of these dynamics by calculating the relaxation timescales of the energy fluctuations. We compute the autocorrelation functions defined in Eq. (7):

$$C(t) = \frac{\langle \delta E_\alpha(0) \delta E_\alpha(t) \rangle}{\langle \delta E_\alpha(0) \delta E_\alpha(0) \rangle}. \tag{7}$$

We plot $C(t)$ for protein (P) and water (W) in the five protein-water systems in Fig. 6(a). Although relaxations of proteins differ from system to system, that of water remains almost unchanged. Hence, we show $C(t)$ of water for only the Mg-water system. The inset shows average relaxation times (τ) of the protein autocorrelation function (ACF) as a function of protein size. The decay of energy autocorrelation is slower in larger proteins. The long-time decay of energy autocorrelation is slower for proteins than for water. The decay timescales are given in the Supplemental Material [46].

In Fig. 6(b), we show the ACFs of protein-water cross ($E_{P\text{-}W}$), protein-self- ($E_{P\text{-}P}$), and water-self- ($E_{W\text{-}W}$) energies. The average relaxation times of these are 29.53, 22.32, and 0.43 ps, respectively. We note that the relaxations of $E_{P\text{-}P}$ and $E_{P\text{-}W}$ are comparable. However, $E_{W\text{-}W}$ relaxes ~50 times faster than $E_{P\text{-}P}$. As a result, the two energy fluctuations cannot be compared in the same temporal frame. The transferred energy to the water dissipates immediately. Hence, we cannot capture the signature of anticorrelation between these two subensembles.

The power spectra of energy fluctuations provide a valuable window into the correlations present in the system. The energy spectral densities of both protein and water are found to be proportional to $1/f^\alpha$, where f is the frequency and α is a constant between 0.5 and 1.5 [19,20,22,64–66]. Such behavior, known as $1/f$ noise, signifies multiple relaxation processes [65]. It also indicates the possible intermittent transitions among multiple energy states of the system [20]. Bizzarri and Cannistraro observed $1/f$ noise in the energy spectrum of plastocyanin with $\alpha = 0.94$ [65]. Ohmine *et al.* reported similar behavior in the energy spectrum of water with $\alpha = 0.75$ [20,22]. We plot such spectrum in Fig. 7 for the total energy of Pc in water. It shows a bimodal character with two slopes having values 0.97 and 0.68. The former is the inherent property of the protein [Fig. 7(b)]. However, the latter arises because of the influence of water [Fig. 7(a)]. Clearly, water wields considerable influence on the energy spectrum, and consequently the dynamics of protein. Although the presence of $1/f$ noise has been noted before, the correlation between protein and water is presented here for the first time. Such behavior is also observed for the other proteins (Supplemental Material [46]). We note that the influence of water is observed at a lower frequency. This accounts for the collective structural rearrangements in water [67].

It is well known that interaction energetics and dynamics have a cause-effect relationship [63]. In processes like electron/proton transfer, solvent reorientation and consequent changes in donor-acceptor interaction energy plays a

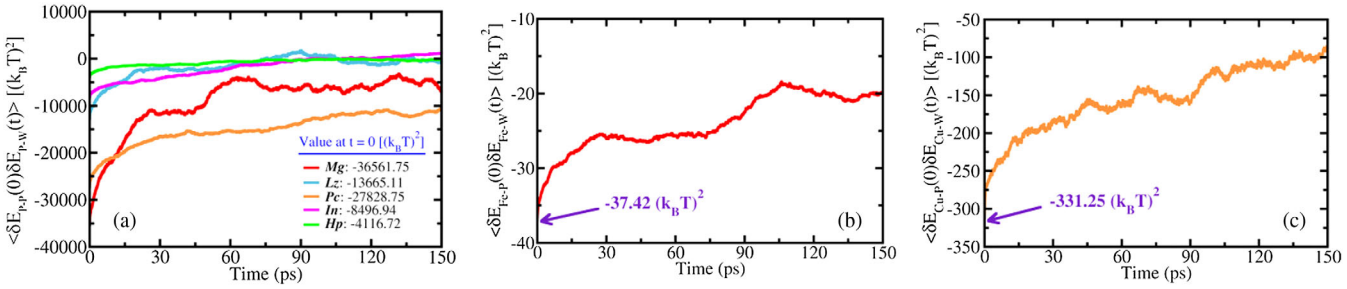

FIG. 5. (a) Cross-TCF of protein self-energy and protein-water interaction energy fluctuations in five protein-water systems. Cross-TCF of (b) Fe-protein interaction in Mg and (c) Cu-protein interaction in Pc. Figure reveals strong anticorrelation between corresponding energy terms with high negative amplitudes.

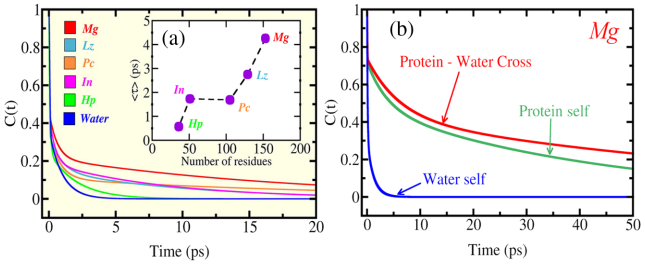

FIG. 6. (a) Energy ACF of five proteins and water. Inset shows average relaxation times of protein ACF as a function of protein size. Relaxation is slower for protein energy and is system dependent. Water energy relaxation is invariant of the different systems. Decay timescales are given in the Supplemental Material [46]. (b) Autocorrelation function of protein-water cross ($E_{P\text{-}W}$), protein self- ($E_{P\text{-}P}$), and water self- ($E_{W\text{-}W}$) energies. The relaxation of $E_{W\text{-}W}$ is faster than those of $E_{P\text{-}W}$ and $E_{P\text{-}P}$, with the latter two being comparable. Consequently, $\delta E_{P\text{-}P}$ is apparently uncorrelated with $\delta E_{W\text{-}W}$, whereas a strong anticorrelation is observed between $\delta E_{P\text{-}P}$ and $\delta E_{P\text{-}W}$. The results in this figure are shown for the *Mg*-water system. Other systems also show similar behaviors.

vital role [68,69]. Hence, the coupled interaction between protein and water must have significant effects on the dynamics of these two domains. We find that, instead of a particle-level microscopic approach, energy as a collective variable imparts better clarity to the protein-water dynamical coupling. Furthermore, water exerts substantial force on the local sites of the protein backbone that imparts flexibility to the biomolecule. We observe that fluctuations of the energy contribution from water are higher than those from protein. Moreover, the energy autocorrelation relaxation of water is faster than that of protein. Protein's energy spectrum reveals bimodal $1/f$ noise that displays characteristics of both protein and water. The coupling between

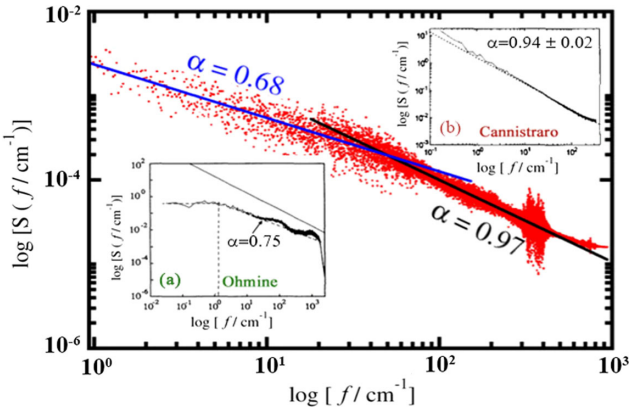

FIG. 7. $1/f$ noise behavior of spectral density of total energy fluctuations in plastocyanin. In the presence of interaction with water, the power spectrum shows two slopes: one corresponding to protein, and the other due to water. Spectra for water [19] and plastocyanin [64] are shown in insets (a) and (b), respectively.

protein and water has been investigated earlier by terahertz spectroscopy [7,8]. Our study provides new insights to the reported coupling and long-range interactions between protein and water. Here, we show that fluctuations in water drive the configuration space random walk of proteins. This naturally gives rise to a friction that is dependent, partly, on the dynamics of water. This work, to the best of our knowledge, is the first theoretical investigation that addresses these issues of protein-water coupling.

This work was partly supported by grants from DST, India. B. B. is thankful for financial support from the Sir J. C. Bose Fellowship, DST, India. S. Mu. is thankful for support from a research fellowship from INSPIRE, DST, India. S. Mo. is thankful for support from a research fellowship from UGC, India.

*bbagchi@iisc.ac.in

[1] L. Pauling and R. B. Corey, Proc. Natl. Acad. Sci. U.S.A. **37**, 729 (1951).
[2] L. Pauling and R. B. Corey, Proc. Natl. Acad. Sci. U.S.A. **37**, 235 (1951).
[3] G. R. Welch, *The Fluctuating Enzyme* (John Wiley & Sons, New York, 1986), Vol. 5.
[4] M. Tarek and D. J. Tobias, Phys. Rev. Lett. **88**, 138101 (2002).
[5] G. Schirò *et al.*, Nat. Commun. **6**, 6490 (2015).
[6] M. Heyden and D. J. Tobias, Phys. Rev. Lett. **111**, 218101 (2013).
[7] S. Ebbinghaus, S. J. Kim, M. Heyden, X. Yu, U. Heugen, M. Gruebele, D. M. Leitner, and M. Havenith, Proc. Natl. Acad. Sci. U.S.A. **104**, 20749 (2007).
[8] K. Meister, S. Ebbinghaus, Y. Xu, J. G. Duman, A. DeVries, M. Gruebele, D. M. Leitner, and M. Havenith, Proc. Natl. Acad. Sci. U.S.A. **110**, 1617 (2013).
[9] P. W. Fenimore, H. Frauenfelder, B. H. McMahon, and F. G. Parak, Proc. Natl. Acad. Sci. U.S.A. **99**, 16047 (2002).
[10] H. Frauenfelder, G. Chen, J. Berendzen, P. W. Fenimore, H. Jansson, B. H. McMahon, I. R. Stroe, J. Swenson, and R. D. Young, Proc. Natl. Acad. Sci. U.S.A. **106**, 5129 (2009).
[11] H. Frauenfelder, P. Fenimore, G. Chen, and B. McMahon, Proc. Natl. Acad. Sci. U.S.A. **103**, 15469 (2006).
[12] H. Frauenfelder, P. W. Fenimore, and R. D. Young, IUBMB Life **59**, 506 (2007).
[13] P. G. Debenedetti and F. H. Stillinger, Nature (London) **410**, 259 (2001).
[14] V. Lubchenko, P. G. Wolynes, and H. Frauenfelder, J. Phys. Chem. B **109**, 7488 (2005).
[15] J. D. Bryngelson and P. G. Wolynes, J. Phys. Chem. **93**, 6902 (1989).
[16] H. Frauenfelder, S. G. Sligar, and P. G. Wolynes, Science **254**, 1598 (1991).
[17] D. Vitkup, D. Ringe, G. A. Petsko, and M. Karplus, Nat. Struct. Mol. Biol. **7**, 34 (2000).
[18] J. Chahine, H. Nymeyer, V. B. P. Leite, N. D. Socci, and J. N. Onuchic, Phys. Rev. Lett. **88**, 168101 (2002).
[19] I. Ohmine and S. Saito, Acc. Chem. Res. **32**, 741 (1999).
[20] I. Ohmine and H. Tanaka, Chem. Rev. **93**, 2545 (1993).
[21] I. Ohmine, J. Phys. Chem. **99**, 6767 (1995).

[22] M. Sasai, I. Ohmine, and R. Ramaswamy, J. Chem. Phys. **96**, 3045 (1992).

[23] B. Bagchi, *Water in Biological and Chemical Processes: From Structure and Dynamics to Function* (Cambridge University Press, New York, 2013).

[24] P. Ball, Proc. Natl. Acad. Sci. U.S.A. **114**, 13327 (2017).

[25] P. Ball, Chem. Rev. **108**, 74 (2008).

[26] K. Bhattacharyya, Chem. Commun. **2018**, 2848 (2008).

[27] S. Mondal, S. Mukherjee, and B. Bagchi, J. Phys. Chem. Lett. **8**, 4878 (2017).

[28] C. Oostenbrink, A. Villa, A. E. Mark, and W. F. van Gunsteren, J. Comput. Chem. **25**, 1656 (2004).

[29] T. Simonson and C. L. Brooks, J. Am. Chem. Soc. **118**, 8452 (1996).

[30] S. Mondal, S. Mukherjee, and B. Bagchi, Chem. Phys. Lett. **683**, 29 (2017).

[31] S. Mondal, S. Mukherjee, and B. Bagchi, J. Chem. Phys. **147**, 154901 (2017).

[32] R. Zwanzig, *Nonequilibrium Statistical Mechanics* (Oxford University Press, New York, 2001).

[33] J. O. Daldrop, J. Kappler, F. N. Brünig, and R. R. Netz, Proc. Natl. Acad. Sci. U.S.A. **115**, 5169 (2018).

[34] D. De Sancho, A. Sirur, and R. B. Best, Nat. Commun. **5**, 4307 (2014).

[35] W. Zheng, D. De Sancho, T. Hoppe, and R. B. Best, J. Am. Chem. Soc. **137**, 3283 (2015).

[36] I. Derenyi, A. Rauscher, G. J. Szollosi, Z. Simon, L. Graf, and A. Malnasi-Csizmadia, Biophys. J. **98**, 237a (2010).

[37] K. A. Dill and H. S. Chan, Nat. Struct. Mol. Biol. **4**, 10 (1997).

[38] J. D. Bryngelson, J. N. Onuchic, N. D. Socci, and P. G. Wolynes, Proteins **21**, 167 (1995).

[39] S. S. Plotkin and P. G. Wolynes, Phys. Rev. Lett. **80**, 5015 (1998).

[40] A. Garcia, R. Blumenfeld, G. Hummer, and J. Sobehart, *Proceeding of the 9th Conversation in Biomolecular Stereodynamics* (Albany, New York, 1995).

[41] D. M. Leitner, Annu. Rev. Phys. Chem. **59**, 233 (2008).

[42] M. Kondoh, M. Mizuno, and Y. Mizutani, J. Phys. Chem. Lett. **7**, 1950 (2016).

[43] K. Moritsugu, O. Miyashita, and A. Kidera, Phys. Rev. Lett. **85**, 3970 (2000).

[44] L. Bu and J. E. Straub, J. Phys. Chem. B **107**, 12339 (2003).

[45] T. Lian, B. Locke, Y. Kholodenko, and R. M. Hochstrasser, J. Phys. Chem. **98**, 11648 (1994).

[46] See Supplemental Material at http://link.aps.org/supplemental/10.1103/PhysRevLett.122.058101 for simulation details, energy distributions and fluctuations, coupled oscillator model, energy ACF timescales, SC-W coupled dynamics, bimodal 1/f noise of proteins and an explanation of high anti-correlation in metalloproteins, which includes Refs. [28,47–55].

[47] B. Hess, C. Kutzner, D. Van Der Spoel, and E. Lindahl, J. Chem. Theory Comput. **4**, 435 (2008).

[48] F. C. Bernstein, T. F. Koetzle, G. J. Williams, E. F. Meyer, M. D. Brice, J. R. Rodgers, O. Kennard, T. Shimanouchi, and M. Tasumi, J. Mol. Biol. **112**, 535 (1977).

[49] H. Berendsen, J. Grigera, and T. Straatsma, J. Phys. Chem. **91**, 6269 (1987).

[50] W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery, *Numerical Recipes: The Art of Scientific Computing*, 3rd ed. (Cambridge University Press, Cambridge, England, 2007).

[51] S. Kirkpatrick, C. D. Gelatt, and M. P. Vecchi, Science **220**, 671 (1983).

[52] W. G. Hoover, Phys. Rev. A **31**, 1695 (1985).

[53] M. Parrinello and A. Rahman, Phys. Rev. Lett. **45**, 1196 (1980).

[54] B. Hess, H. Bekker, H. J. Berendsen, and J. G. Fraaije, J. Comput. Chem. **18**, 1463 (1997).

[55] T. Darden, D. York, and L. Pedersen, J. Chem. Phys. **98**, 10089 (1993).

[56] S. Mukherjee, S. Mondal, and B. Bagchi, J. Chem. Phys. **147**, 024901 (2017).

[57] J. Gomez, V. J. Hilser, D. Xie, and E. Freire, Proteins **22**, 404 (1995).

[58] G. Makhatadze and P. Privalov, J. Mol. Biol. **213**, 375 (1990).

[59] N. V. Prabhu and K. A. Sharp, Annu. Rev. Phys. Chem. **56**, 521 (2005).

[60] K. Fritsch, J. Friedrich, F. Parak, and J. L. Skinner, Proc. Natl. Acad. Sci. U.S.A. **93**, 15141 (1996).

[61] P. D. Reilly and J. L. Skinner, Phys. Rev. Lett. **71**, 4257 (1993).

[62] J. L. Skinner, B. M. Auer, and Y.-S. Lin, Adv. Chem. Phys. **142**, 59 (2009).

[63] A. Kumawat and S. Chakrabarty, Proc. Natl. Acad. Sci. U.S.A. **114**, E5825 (2017).

[64] A. R. Bizzarri and S. Cannistraro, Physica (Amsterdam) **267A**, 257 (1999).

[65] A. R. Bizzarri and S. Cannistraro, Phys. Lett. A **236**, 596 (1997).

[66] P. Carlini, A. Bizzarri, and S. Cannistraro, Physica (Amsterdam) **165D**, 242 (2002).

[67] M. Cho, G. R. Fleming, S. Saito, I. Ohmine, and R. M. Stratt, J. Chem. Phys. **100**, 6672 (1994).

[68] B. Bagchi, *Molecular Relaxation in Liquids* (Oxford University Press, New York, 2012).

[69] R. A. Marcus and N. Sutin, Biochim. Biophys. Acta **811**, 265 (1985).