

A unified model of protein dynamics

Hans Frauenfelder^{a,1}, Guo Chen^a, Joel Berendzen^a, Paul W. Fenimore^{a,1}, Helén Jansson^b, Benjamin H. McMahon^a, Izabela R. Stroe^c, Jan Swenson^d, and Robert D. Young^e

^aLos Alamos National Laboratory, Los Alamos, NM 87545; ^bThe Swedish NMR Center, Göteborg University, SE 405 30 Göteborg, Sweden; ^cDepartment of Physics, Worcester Polytechnic Institute, Worcester, MA 01609; ^dDepartment of Applied Physics, Chalmers University of Technology, SE 412 96 Göteborg, Sweden; and ^eDepartment of Physics and Astronomy, Northern Arizona University, Flagstaff, AZ 86011

Contributed by Hans Frauenfelder, January 15, 2009 (sent for review December 5, 2008)

Protein functions require conformational motions. We show here that the dominant conformational motions are slaved by the hydration shell and the bulk solvent. The protein contributes the structure necessary for function. We formulate a model that is based on experiments, insights from the physics of glass-forming liquids, and the concepts of a hierarchically organized energy landscape. To explore the effect of external fluctuations on protein dynamics, we measure the fluctuations in the bulk solvent and the hydration shell with broadband dielectric spectroscopy and compare them with internal fluctuations measured with the Mössbauer effect and neutron scattering. The result is clear. Large-scale protein motions are slaved to the fluctuations in the bulk solvent. They are controlled by the solvent viscosity, and are absent in a solid environment. Internal protein motions are slaved to the beta fluctuations of the hydration shell, are controlled by hydration, and are absent in a dehydrated protein. The model quantitatively predicts the rapid increase of the mean-square displacement above ≈ 200 K, shows that the external beta fluctuations determine the temperature- and time-dependence of the passage of carbon monoxide through myoglobin, and explains the nonexponential time dependence of the protein relaxation after photodissociation.

beta process | dielectric | hydration | solvent

Proteins are dynamic systems that interact strongly with their environment (1). Most texts and publications show proteins in unique conformations and naked, without hydration shell and bulk solvent, while fluctuations are rarely mentioned. The unified model of protein dynamics presented here is a radical departure from this picture. In this model, the protein provides the structure for the biological function, but it is dynamically passive. The fluctuations in the bulk solvent power and control the large-scale motions and shape changes of the protein in a diffusive manner (2–4), whereas the fluctuations in the hydration shell power and control the internal protein motions such as ligand migration (5, 6). The hydration shell consists of ≈ 2 layers of water that surround proteins as shown in Fig. 1 (7–12). Protein functions depend on the degree of hydration, h , defined as the weight ratio of water to protein. Dehydrated proteins do not function. Some proteins begin to work at $h \approx 0.2$ (11) but full function may require $h > 1$. The controls exerted by the bulk solvent and the hydration shell are possible because the protein interior is fluid-like (13); the intrinsic viscosity of a protein is small, about like water (14–16). The image of the protein being essentially passive and being slaved to the environment is not an idle speculation. It is based on experiments using myoglobin (Mb) that led to the seminal concepts that underlie the present work: (i) Proteins do not exist in a unique conformation; they can assume a very large number of conformational substates (CS) (17, 18). (ii) The CS can be described by an energy landscape (17). (iii) The landscape is organized in a hierarchy; there are energy valleys within energy valleys within energy valleys (19). The description of the effects of the bulk solvent and the hydration shell is based on these concepts. Because knowledge of the fluctuations in glass-forming liquids and of the energy landscape of proteins is essential for understanding these results, we discuss these topics first.

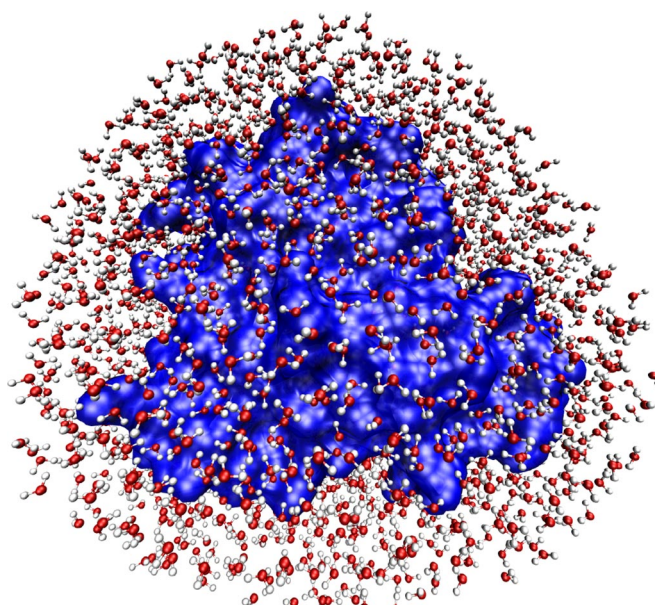


Fig. 1. The hydration shell of myoglobin (Mb). Diagram of myoglobin (blue surface) with 1,911 water molecules (CPK model), the approximate number needed for optimal function ($h = 2$). The waters form a shell ≈ 5 Å thick around the protein. Approximately 200 water molecules are distinguishable from background with high-resolution X-ray crystallography.

The α and β Processes (20, 21)

Glass-forming liquids have two types of equilibrium fluctuations, α and β .^{*} One tool to study these fluctuations is dielectric relaxation spectroscopy (21). The sample is placed in a capacitor, a sine-wave voltage $U_1(\nu)$ of frequency ν is applied, and the resulting current is converted into a voltage $U_2(\nu)$ that characterizes the dielectric spectrum. Our spectra exhibit two prominent peaks that characterize α , or primary, and β , or secondary, relaxations. The α process describes structural fluctuations. The mechanical Maxwell relation,

$$k_\alpha(T) = G_0/\eta(T), \quad [1]$$

connects the rate coefficient $k_\alpha(T)$ for the α fluctuations to the viscosity $\eta(T)$. Here, G_0 is the infinite-frequency shear modulus that depends only weakly on temperature and on the material.

Author contributions: H.F., G.C., J.B., P.W.F., H.J., B.H.M., I.R.S., J.S., and R.D.Y. designed research, performed research, contributed new reagents/analytic tools, analyzed data, and wrote the paper.

The authors declare no conflict of interest.

Freely available online through the PNAS open access option.

¹To whom correspondence may be addressed. E-mail: frauenfelder@lanl.gov or paulf@lanl.gov.

^{*}Systems undergo thermal fluctuations even in equilibrium. When moved out of equilibrium, the system relaxes toward equilibrium. So long as detailed balance is obeyed, relaxations and fluctuations are related by the fluctuation–dissipation theorem.

In a solid, where the viscosity is extremely large, Eq. 1 implies that the α fluctuations are essentially absent. The rate coefficient $k_\alpha(T)$ can usually be approximated by the Vogel–Tammann–Fulcher (VTF) relation,

$$k_\alpha(T) = A_\alpha \exp[-DT_0/(T - T_0)]. \quad [2]$$

D , A_α , and T_0 are experimentally determined coefficients. Theoretical models for the effect of the α process on protein dynamics exist (4, 22). In contrast, the β processes in supercooled liquids and glasses are essentially independent of the solvent viscosity and exist even in the glassy state (23, 24). Two classes of β fluctuations occur in molecular liquids (25–27). The Johari–Goldstein (J-G) fluctuations are related to the α fluctuations; at some temperature, the two merge. In contrast, the “statistically independent” β fluctuations do not merge; they are faster than α at temperatures below a crossing temperature T_{cr} , cross at T_{cr} , and are slower above T_{cr} . Their rate coefficient $k_\beta(T)$ can be approximated by a standard Arrhenius relation, $k_\beta(T) = A_\beta \exp[-H_\beta/(k_B T)]$.

Proteins are subject to α and β processes (5, 28–30). These do not originate in the protein, but in the bulk solvent and the hydration shell. We have measured dielectric spectra of Mb from <140 to >300 K in different solvents. Fig. 2A displays the peak rate coefficients ($k = 2\pi\nu$) of α and β in a 50/50 (wt/wt) glycerol/water solvent as a function of $1,000 \text{ K}/T$. The two processes cross at $T_{cr} \approx 210 \text{ K}$. The α process behaves like a typical α relaxation in supercooled liquids. The β process behaves like the “statistically independent” process in molecular glass formers. β is easy to observe well below T_{cr} where α is extremely slow. In the crossing region, α and β are difficult to separate and we only show the continuation well above T_{cr} . We retain the name “ β relaxation,” but label it with a subscript h . Fig. 2C shows β_h relaxation spectra at 160 K in 50/50 (wt/wt) glycerol/water samples without and with Mb at different hydration levels. Already the sample without Mb is inhomogeneously broadened. Adding Mb broadens the spectrum, shifts the peak to lower frequencies, and adds substates at both the low and high part of the spectrum. We assign the additional substates and β_h to the hydration shell of the protein. The fact that β_h can be observed well below 200 K where the solvent becomes solid means that it does not depend on viscosity. Thus, α is eliminated if Mb is embedded in a solid. We therefore measured the dielectric relaxation of Mb embedded in solid poly(vinyl alcohol) (PVA) at different levels of hydration (Fig. 2B). The parameters for the β_h relaxation depend on hydration, as shown in Table 1. At small values of hydration, the activation enthalpy is very large. With increasing hydration, the activation enthalpy moves toward typical values of β relaxations. For hydration levels above $h = 0.5$ a transition occurs at $\approx 270 \text{ K}$ (not shown in Fig. 2B). It is likely due to the melting of small ice crystals. Ice crystals cannot form if water is closely confined. For $h < 0.5$, the water molecules are indeed closely confined to the hydration shell. At $h > 0.5$, there is enough water to permit the formation of small ice crystals.

The Energy Landscape

Proteins can assume a very large number of conformational substates that are organized in the energy landscape (17, 18, 31). At any instant of time, the structure of a protein, including its hydration shell, is given by the set of coordinates of its N atoms, where N is of the order of 10^3 . The set of coordinates is a point in a $3N$ -3-dimensional conformation space. The number of CS in a protein and its hydration shell is extremely large. Assume that each of 100 side chains and each of 200 water molecules in the hydration shell can assume two positions. The number of CS, or points in the conformation space, then is $2^{100}2^{200}$ or $\approx 10^{100}$. These points, together with the barriers between them, form the

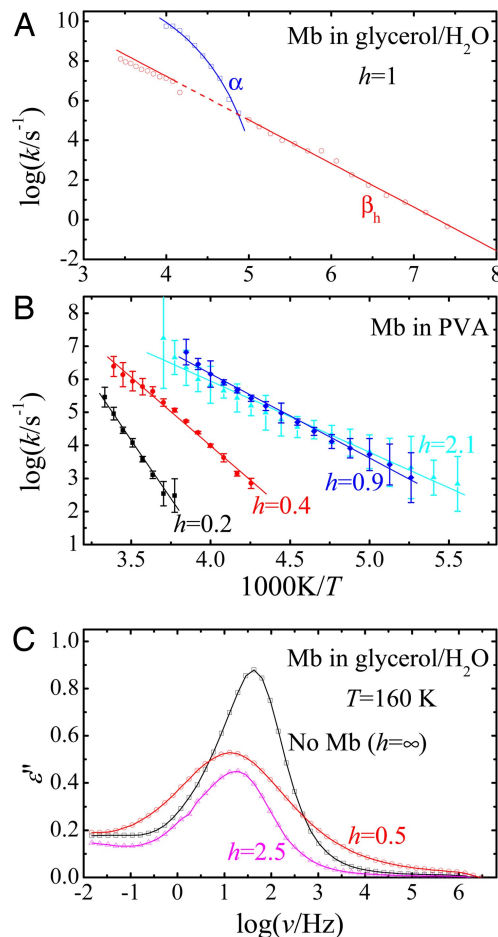


Fig. 2. Relaxation processes in Mb. (A) Arrhenius plot of the α and the β_h processes of Mb embedded in a 50:50 (wt/wt) glycerol/water solvent with a water–protein weight ratio $h = 1$, measured with dielectric relaxation spectroscopy. The α process (blue) follows a VTF relation (Eq. 2). The β_h process (red) approximately follows an Arrhenius law. (B) Arrhenius plot of the β_h processes for Mb embedded in PVA for various values of the hydration h . (C) Dielectric spectra of 50:50 (wt/wt) glycerol/water samples at 160 K for $h = 0.5$, 2.5, and ∞ (no Mb).

EL. A change of the protein structure in real space appears as the motion from one point to another in the conformation space. What has been gained by the introduction of the EL? If the EL were featureless, not much, apart from expressing the fact that proteins exist in a large number of conformations. However, the EL is structured into a number of tiers (19). The top three tiers are relevant for function. Lower tiers have been discovered in cryogenic experiments (32), but we do not consider them. Fig. 3A gives a 1-dimensional cross-section through the Mb energy landscape, drawn ≈ 20 years ago (33). The top tier, CS0, contains three taxonomic substates, so called because they can be fully

Table 1. H_β , A_β , and $\Delta\varepsilon$ of the β relaxations for Mb embedded in PVA at various h

h	H_β , kJ/mol	$\log(A_\beta/s^{-1})$	$\Delta\varepsilon^*$
0.2	135.5 ± 7.0	28.9 ± 1.3	14.1 ± 2.5
0.4	79.2 ± 2.2	20.5 ± 0.4	15.0 ± 0.5
0.9	48.7 ± 1.3	16.3 ± 0.3	24.4 ± 17.8
2.1	41.2 ± 1.7	14.6 ± 0.4	31.0 ± 15.5

* $\Delta\varepsilon$ (Eq. 5) varies with T . The values given are at $T = 265 \text{ K}$ for $h = 0.2, 0.4$, and 2.1 and $T = 260 \text{ K}$ for $h = 0.9$.

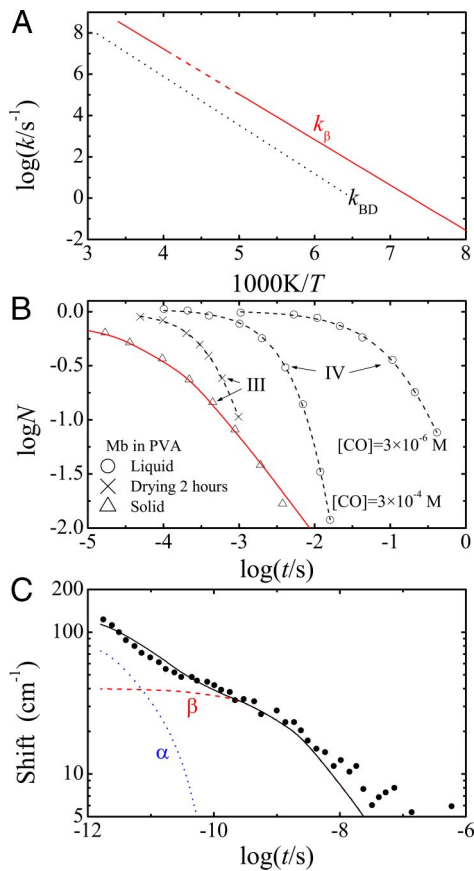


Fig. 6. The β_h relaxation predicts internal motions. (A) The rate coefficient $k_{BD}(T)$ for the passage of CO from the heme pocket to the Xe-1 cavity follows $k_\beta(T)$ over nearly 8 orders of magnitude. (B) Rebinding of CO to Mb in PVA. The data are from figure 6 of ref. 17. The curves denoted by IV are obtained in a freshly prepared sample of Mb in PVA while the sample is still liquid. After drying for ≈ 2 h, process IV disappears and the exponential but [CO]-independent and faster process III appears. On complete drying, when PVA is solid, the nonexponential curve III is obtained. The red solid line is the time dependence as predicted by the β_h fluctuation data. (C) The relaxation of the charge-transfer band III in Mb after photodissociation at room temperature (48). The shift of band III after photodissociation is plotted versus time. The highly nonexponential time dependence of the band position shift can be reproduced with the sum of an α process predicted by Eq. 8 and a β_h process predicted by Eq. 9.

with the β_h fluctuations in the hydration shell, we note that $N(t)$ gives the fraction of CO molecules that have not rebound at time t . $N(t)$ should be proportional to the area $a_\beta(t)$, like that plotted in Fig. 4, but now calculated at a fixed temperature as a function of time. We further expect $N(t)$ to be slower than $a_\beta(t)$ because the CO visits the internal cavities many times before binding (17, 44). We therefore set

$$N_{III}(t) = a_\beta(ct). \quad [7]$$

On the log-log scale in Fig. 6B the slowing corresponds to a shift of $\log(N_{III}(t))$ by $\log(c)$. The result, shown as a red curve in Fig. 6B, gives $\log(c) = -4$. The fact that Eq. 7 holds proves that the transit of CO through the protein is indeed controlled by the hydration shell fluctuations.

The relaxation of Mb after photodissociation is a third example of the role of α and β_h . The structures of deoxyMb and MbCO differ. After a laser flash dissociates the CO from the heme iron, Mb is still in the MbCO structure, but it relaxes to the deoxyMb structure. The relaxation can be followed by monitoring the wavenumber of the heme-charge transfer band III (47). Anfinrud and collaborators have measured the shift of the peak wavenumber as a function of time after photodissociation (48). A close look at their data in Fig. 6C suggests that two distinct processes are involved. We postulate that the fast process is α , which changes the protein shape to the deoxyMb form, and that the slow process is β_h , which relaxes the internal structure. These two processes can be measured separately. Consider α first. Its time dependence is usually described by a stretched exponential (49),

$$N_\alpha(t) = N_\alpha(0) \exp[-(k_\alpha t)^p]. \quad [8]$$

For the glycerol-water solvent used by Anfinrud et al. the parameters are approximately $k_\alpha = 10^{11} \text{ s}^{-1}$ (25) and $p = 0.65$ (49). For β_h we set

$$N_\beta(t) = N_\beta(0) a_\beta(t). \quad [9]$$

To calculate $a_\beta(T)$ we use the spectrum for $h = 2.5$ in Fig. 2C and $k_\beta \approx 10^{8.7} \text{ s}^{-1}$ as estimated from Fig. 2A for the peak at $T \approx 300$ K. The spectrum shifted to this peak value then permits the calculation of $a_\beta(t)$. Eqs. 8 and 9 predict the time dependence of the fast and the slow component in Fig. 6C and only $N_\alpha(0)$ and $N_\beta(0)$ must be taken from the data. A crude evaluation gives $N_\alpha(0) \approx 100 \text{ cm}^{-1}$ and $N_\beta(0) \approx 40 \text{ cm}^{-1}$. With these values and Eqs. 8 and 9 the predicted relaxation functions and their sum can be calculated and plotted in Fig. 6C. The sum agrees remarkably well with the experimentally determined relaxation function. We repeat that the solid curve in Fig. 6C is a prediction, and not a fit.

The unified model justifies the picture of proteins as picomachines (50). The protein provides the exquisite structural machinery that moves nearly without friction. The α fluctuations in the bulk power and control the shape of the protein. The β_h fluctuations in the hydration shell power and control protein internal motions. This model implies that β_h permits a broader range of control of protein function than α . The latter is essentially determined by the viscosity of the bulk solvent, which in cells probably does not vary much. The former, however, can be changed in many ways because the hydration shell is not uniform; it is highly structured. Protein surfaces have been designed by evolution and are craggy, contain outcrops and pockets, and have both charged and neutral residues (51, 52). Pockets and channels open and close (53). Addition of salts, sugars, or nucleic acids may change β_h . Many molecules attach covalently to protein surfaces. Allostery, phosphorylation, and palmitoylation (54) are examples of candidates for the study of the effect of external factors on β_h . The possibilities are endless.

Finally a caveat. Although the data used here can be explained with the α and the β_h fluctuations, other motions exist and are important for protein function (51). The famous boson peak fluctuations may also play a role (55).

ACKNOWLEDGMENTS. We thank Albert Migliori and Jon Betts for experimental assistance and discussions, and Angel Garcia, S. Gnanakaran, Vas Lubchenko, Feri Mezei, Stephen Sligar, and Ranko Richert for discussions and comments on the manuscript. This work was supported by Department of Energy Contract DE-AC5206NA25396. J.S. and H.J. were supported by the Swedish Foundation for Strategic Research.

- Henzler-Wildman K, Kern D (2007) Dynamic personalities of proteins. *Nature* 450:964–972.
- Fenimore PW, Frauenfelder H, McMahon BH, Parak FG (2002) Slaving: Solvent fluctuations dominate protein dynamics and functions. *Proc Natl Acad Sci USA* 99:16047–16051.

- Frauenfelder H, Fenimore PW, Chen G, McMahon BH (2006) Protein folding is slaved to solvent motions. *Proc Natl Acad Sci USA* 103:15469–15472.
- Lubchenko V, Wolynes PG, Frauenfelder H (2005) Mosaic energy landscapes of liquids and the control of protein conformational dynamics by glass-forming solvents. *J Phys Chem B* 109:7488–7499.

5. Fenimore PW, Frauenfelder H, McMahon BH, Young RD (2004) Bulk-solvent and hydration-shell fluctuations, similar to α - and β -fluctuations in glasses, control protein motions and functions. *Proc Natl Acad Sci USA* 101:14408–14413.
6. Chen G, et al. (2008) Protein fluctuations explored by inelastic neutron scattering and dielectric relaxation spectroscopy. *Phil Mag* 88:3877–3883.
7. Rupley JA, Careri G (1991) Protein hydration and function. *Adv Protein Chem* 41:37–172.
8. Halle B (2004) Protein hydration dynamics in solution: A critical survey. *Philos Trans R Soc Lond B* 359:1207–1224.
9. Levy Y, Onuchic JN (2006) Water mediation in protein folding and molecular recognition. *Annu Rev Biophys Biomol Struct* 35:389–415.
10. Helms V (2007) Protein dynamics tightly connected to the dynamics of surrounding and internal water molecules. *Chem Phys Chem* 8:23–33.
11. Careri G, Gratton E, Yang PH, Rupley JA (1980) Correlation of IR spectroscopic, heat capacity, diamagnetic susceptibility and enzymatic measurements on lysozyme powder. *Nature* 284:572–573.
12. Brovchenko I, Oleinikova A (2008) Which properties of a spanning network of hydration water enable biological functions? *Chem Phys Chem* 9:2695–2702.
13. McCammon JA, Gelin BR, Karplus M (1977) Dynamics of folded proteins. *Nature* 267:585–590.
14. Ansari A, Jones CM, Henry ER, Hofrichter J, Eaton WA (1992) The role of solvent viscosity in the dynamics of protein conformational changes. *Science* 256:1796–1798.
15. Shibata Y, Kurita A, Kushida T (1998) Real-time observation of conformational fluctuations in Zn-substituted myoglobin by time-resolved transient hole-burning spectroscopy. *Biophys J* 75:521–527.
16. Ansari A (1999) Langevin modes analysis of myoglobin. *J Chem Phys* 110:1774–1780.
17. Austin RH, et al. (1975) Dynamics of ligand binding to myoglobin. *Biochemistry* 14:5355–5373.
18. Frauenfelder H, Petsko GA, Tsernoglou D (1979) Temperature-dependent X-ray diffraction as a probe of protein structural dynamics. *Nature* 280:558–563.
19. Ansari A, et al. (1985) Protein states and protein quakes. *Proc Natl Acad Sci USA* 82:5000–5004.
20. Donth E (2001) *The Glass Transition* (Springer, Heidelberg).
21. Kremer F, Schönhals A (2002) *Broadband Dielectric Spectroscopy* (Springer, Heidelberg).
22. Lubchenko V (2006) Quantitative theory of structural relaxation in supercooled liquids and folded proteins. *J Non-Cryst Solids* 352:4400–4409.
23. Richert R (2002) Heterogeneous dynamics in liquids: Fluctuations in space and time. *J Phys Condens Matter* 14:R703–R738.
24. Ngai KL, Paluch M (2004) Classification of secondary relaxation in glass-formers based on dynamic properties. *J Chem Phys* 120:857–873.
25. Hayashi Y, Puzenko A, Feldman Y (2006) Slow and fast dynamics in glycerol-water mixtures. *J Non-Cryst Solids* 352:4696–4703.
26. Capaccioli S, Ngai KL, Shinyashiki N (2007) The Johari-Goldstein beta relaxation of water. *J Phys Chem B* 111:8197–8209.
27. Mandanici A, Huang W, Cutroni M, Richert R (2008) Dynamics of glass forming liquids. XII. Dielectric study of primary and secondary relaxations in ethylcyclohexane. *J Chem Phys* 128:124505.
28. Swenson J, Jansson H, Hedström J, Bergman R (2007) Properties of hydration water and its role in protein dynamics. *J Phys Condens Matter* 19:205109.
29. Cervený S, Schwartz GA, Bergman R, Swenson J (2004) Glass transition and relaxation processes in supercooled water. *Phys Rev Lett* 93:245702–245705.
30. Swenson J, Jansson H, Bergman R (2006) Relaxation processes in supercooled confined water and implications for protein dynamics. *Phys Rev Lett* 96:247802.
31. Frauenfelder H, Sligar SG, Wolynes PG (1991) The energy landscape and motions of proteins. *Science* 254:1598–1603.
32. Leeson DT, Wiersma DA, Fritsch K, Friedrich J (1997) Energy landscape of myoglobin: An optical study. *J Phys Chem B* 101:6331–6340.
33. Frauenfelder H, Steinbach PJ, Young RD (1989) Conformational relaxation in proteins. *Chem Scripta* 29A:145–150.
34. Alben JO, et al. (1982) Infrared spectroscopy of photodissociated carboxymyoglobin at low temperatures. *Proc Natl Acad Sci USA* 79:3744–3748.
35. Ansari A, et al. (1987) Rebinding and relaxation in the myoglobin pocket. *Biophys Chem* 26:337–355.
36. Yang F, Phillips GN Jr (1996) Crystal structures of CO-, deoxy- and met-myoglobins at various pH values. *J Mol Biol* 256:762–774.
37. Frauenfelder H, McMahon BH, Austin RH, Chu K, Groves JT (2001) The role of structure, energy landscape, dynamics, and allostery in the enzymatic function of myoglobin. *Proc Natl Acad Sci USA* 98:2370–2374.
38. Parak FG, Achterhold K (2005) Protein dynamics on different timescales. *J Phys Chem Solids* 66:2257–2262.
39. Parak FG, Achterhold K, Croci S, Schmidt M (2007) A physical picture of protein dynamics and conformational changes. *J Biol Phys* 33:371–387.
40. Chong S-H, et al. (2001) Dynamical transition of myoglobin in a crystal: Comparative studies of X-ray crystallography and Mössbauer spectroscopy. *Eur Biophys J* 30:319–329.
41. Parak F, Hartmann H, Schmidt M, Corongiu G, Clementi E (1992) The hydration shell of myoglobin. *Eur Biophys J* 21:313–320.
42. Doster W, Cusack S, Petry W (1989) Dynamical transition of myoglobin revealed by inelastic neutron scattering. *Nature* 337:754–756.
43. Engler N, Ostermann A, Niimura N, Parak FG (2003) Hydrogen atoms in proteins: Positions and dynamics. *Proc Natl Acad Sci USA* 100:10243–10248.
44. Kleinert T, et al. (1998) Solvent composition and viscosity effects on the kinetics of CO binding to horse myoglobin. *Biochemistry* 37:717–733.
45. Tetreau C, Lavalette D (2005) Dominant features of protein reaction dynamics: Conformational relaxation and ligand migration. *Biochim Biophys Acta* 1724:411–424.
46. Schotte F, et al. (2003) Watching a protein as it functions with 150-ps time-resolved x-ray crystallography. *Science* 300:1944–1947.
47. Stavrov SS (2001) Optical absorption band III of deoxyheme proteins as a probe of their structure and dynamics. *Chem Phys* 271:145–154.
48. Jackson TA, Lim M, Anfinrud PA (1994) Complex nonexponential relaxation in myoglobin after photodissociation of MbCO: Measurement and analysis from 2ps to 56 μ s. *Chem Phys* 180:131–140.
49. Böhmer R, Ngai KL, Angell CA, Plazek DJ (1993) Nonexponential relaxations in strong and fragile glass formers. *J Chem Phys* 99:4201–4209.
50. Astumian RD (1997) Thermodynamics and kinetics of a Brownian motor. *Science* 276:917–922.
51. Pal SK, Zewail AH (2004) Dynamics of water in biological recognition. *Chem Rev* 104:2099–2123.
52. Zhang L, et al. (2007) Mapping hydration dynamics around a protein surface. *Proc Natl Acad Sci USA* 104:18461–18466.
53. Eyrich S, Helms V (2007) Transient pockets on protein surfaces involved in protein-protein interaction. *J Med Chem* 50:3457–3464.
54. Kang R (2008) Neural palmitoyl-proteomics reveals dynamic synaptic palmitoylation. *Nature* 456:904–909.
55. Lubchenko V, Wolynes PG (2003) The origin of the boson peak and thermal conductivity plateau in low-temperature glasses. *Proc Natl Acad Sci USA* 100:1515–1518.