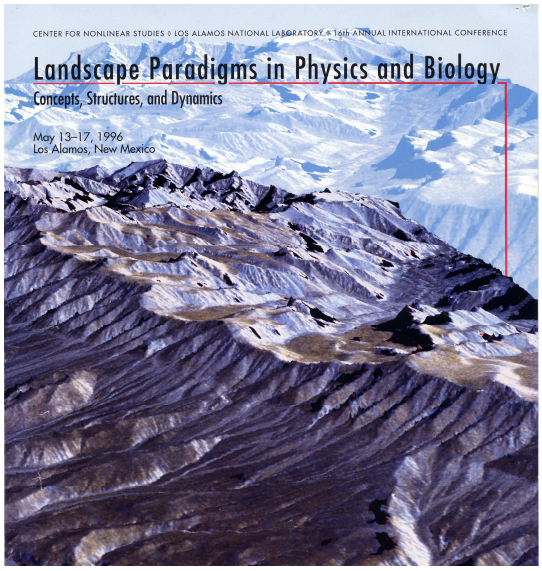
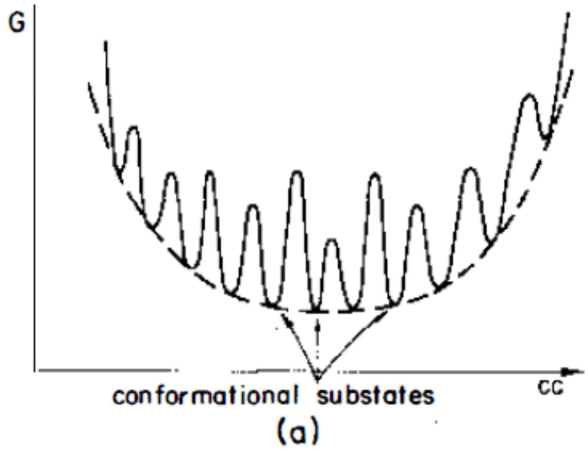
The energy landscapes and motions in proteins

Hans Frauenfelder, S. Sligar and P. Wolynes, Science 254 (1991) 1598



Here the protein substate model is introduced as a paradigm of protein dynamics, completely determined by the energy landscape. The solvent does not play a significant role, it is not even mentioned. All anomalous dynamic properties are associated with the landscape: non-exponential relaxation, non-Arrhenius temperature dependence of relaxation rates, structural distributions. The glass transition is visualized by a particle which is trapped in a local well of a complex landscape. The onset of anharmonic displacements by Mössbauer spectroscopy



was thus interpreted as an amplitude controlled enhancement of molecular motions by detrapping from local wells. Already in 1986 (Doster et al. Bioph. J) we had proposed a different model of dynamic cross-over analogous to a protein-water glass transition.

. In 2002 (PNAS) Frauenfelder completely changed his mind, now the protein is “slaved” by the solvent. The solvent starts to dominate over the landscape.

This paper does not discuss neutron scattering experiments. But the multiple substate model is still heavily cited as background of bio-molecular neutron scattering for instance by Zaccai in

the book “Biophysical Methods” of Zaccai and Zaccai. The SM is so deceptively simple. Anybody can understand the issue without much work. It says, protein dynamics is simple and can be understood easily, if you use my notation.

The landscape model reduces the many dimensional conformational space to a 2-D surface with multiple minima. Protein dynamics is described by a single particle, migrating across a rigid free energy surface. This is a drastic simplification of collective many particle effects, which could lead to artefacts. Sometimes it is assumed that the surface fluctuates, but then it loses its relevance to dynamics, since the transition will occur, when the local barrier is transiently low. Besides being visually attractive, what does it predict? Nothing specific, thus it is hard to prove it wrong! My counter-argument was that the solvent does not fit in, it is a liquid, which cannot be characterized by a fixed landscape.

It is thus not really puzzling that the solvent in this paper plays a minor role. All anomalous dynamic properties of the protein, non-exponential kinetics and non-Arrhenius temperature dependence are explained as the result of multiple substates and migration within a complex landscape. There are other deficiencies: Glasses are non-equilibrium structures, proteins are equilibrium structures. Even equilibrium structures can display a large number of conformational states, for instance real gases. Non-exponential kinetics reflects mainly multiple ligand positions and do not provide much insight into structural disorder. The heme interacts directly with the solvent and is thus a poor monitor of protein motions (Lichtenegger, BJ 1999).

This paper is in between ideology (paradigm) and science. The existence of multiple conformational states does not help very much. Specially neutron scattering has the power to determine the exact nature of molecular motions. In 1989 we identified two types of motions, rotational transitions of side chains and small scale water-coupled librational displacements of residues. In 2005, we proposed a model with three components (1) rotational transition of side chains mostly methyl groups, (2) fast local H-bond fluctuations and (3) water-assisted librational relaxation of protein residues. The substates model is just too general to be useful. It cannot be wrong.

For the first time Frauenfelder mentions α and β-relaxation of glasses, without reference to our work, (Doster et al. Nature 1989*): “In glasses different probes reveal two types of motions, denoted by α and β-relaxation: The α-relaxation is usually characterized by…., involves large scale motions..”* This is not correct, it is the elementary step of translational diffusion, the disintegration of the cage of nearest neighbors on a microscopic scale. “*The β-relaxation is typically closer to an Arrhenius temperature dependence and is attributed to motions of local region. In protein, the motions operating in tiers 0 and 1 to involve large segments of the protein structure and are similar to the α-relaxation in glasses. Motions in lower tiers may involve only local regions..”*

The α and β-relaxation are attributed by Frauenfelder to internal protein processes, small scale and large scale, detached from the solvent. Proteins are interpreted in analogy to glasses. By contrast the α-relaxation of Doster et al. Nature 1989, was assigned to structural relaxation of liquid hydration water coupled by hydrogen bonds to protein residues. Not the protein is a

glass. The glass property of hydration water was introduced in 1986 based on specific heat experiments and infrared data.

In 2004 Frauenfelder changed his notation again with “Bulk solvent and hydration shell fluctuations..” (PNAS). α and β relaxation within the protein are discarded. Now α-relaxation is assigned to the bulk solvent only, while β-relaxation refers to the hydration shell (see Comment). The Frauenfelder model of protein dynamics of 2004: