Solvent fluctuations dominate protein dynamics and function (Fenimore PNAS 2002)

The secret behind the slaving model:

Kleinert et al. 1998

“Solvent fluctuations dominate...” “Proteins are slaved to solvent”

This solvent dominated model represents a complete revision of the original “Energy Landscapes and Motions in Proteins” model published by Frauenfelder in Science 1991. Here the solvent does not play a major role, the glassy features, nonexponential kinetics and the Ferry law are all attributed to multiple substates of the protein landscape. Glassy means: multiple states. In the new model, the landscape is replaced by the solvent, the solvent not the landscape dominates the dynamics.

Is it true? Of course not, in fact, the opposite is true: the active site of proteins is well shielded from the solvent by rigid protein structure. The essential internal kinetic steps at the active site are usually independent of the solvent, which is the biological function of the protein structure. This was demonstrated in the particular case of myoglobin by Kleinert et al. (Biochem. 1998) in “Solvent composition and viscosity effects on the kinetics of CO-binding to myoglobin”, which is the substance behind the slaving paper. The trick is to republish the main ideas and data of a competitor under a different name. “Slaving” is a catch word without a special physical meaning according to the comment of a PRL referee of the first “slaving paper” in 1989. Frauenfelder published a series of non-peer reviewed paper in PNAS, which have captured the field.

Kleinert et al demonstrated that ligand exchange rates of myoglobin with the solvent depend on the solvent viscosity according to Kramers law of activated escape. There was still a barrier involved. By contrast the internal transfer rates were independent of the solvent. In Frauenfelder’s previous work (solvent viscosity and protein dynamics, Beece et al. Biochem. 1980) also Kramers law and the solvent viscosity were celebrated, but also internal rates would depend on the solvent viscosity but as fractional power laws. In the PNAS 2002 paper, the viscosity and Kramers law are not even mentioned. Instead different quantities are introduced to hide the origin of the material:

a) Instead of the solvent relaxation rate $k_s(T)$, determined in our experiments, Frauenfelder uses the dielectric relaxation rate $k_{\text{diel}}$, which is identical to our experimental $k_s$. Of course we are cited, but only some buried data and not for our interpretation.

b) The viscosity dependence is replaced by the term slaving, which has no precise physical meaning.
c) The Kramer’s law of activated escape:
\[ K_{CS} = \frac{A}{\eta} \exp \left( -\frac{H_{CS}}{RT} \right) \] (Kleinert et al.)
is replaced by the new “Frauenfelder law”
\[ K_{DS}(T) = \frac{k_{\text{diele}}(T)}{n(T)} \] which does not refer to the viscosity.
d) Only Arrhenius plots of certain rate coefficients of a single solvent are shown. By contrast the viscosity dependence of rates in five solvents is discussed by Kleinert et al. 1998 (Biochem), which is much more involved. The escape rate shows a stronger temperature dependence than \( k_s \), which can be corrected with the activation energy of Kramer’s law.

\[ T / K \quad 80\% \text{ sucrose/water} \]

\[ 426 \quad 321 \quad 282 \quad 261 \quad 248 \quad 239 \quad 232 \quad 227 \]

\[ T / K \quad 90\% \text{ glycerol/water} \]

\[ 367 \quad 285 \quad 245 \quad 221 \quad 206 \quad 194 \quad 186 \quad 179 \]

\[ T / K \quad 75\% \text{ glycerol/water} \]

\[ 321 \quad 255 \quad 222 \quad 203 \quad 190 \quad 181 \quad 174 \quad 169 \]

\[ T / K \quad 60\% \text{ ethylene glycol/water} \]

\[ 275 \quad 209 \quad 181 \quad 165 \quad 156 \quad 149 \quad 144 \quad 140 \]

The relevant parameter for protein processes at the surface is the surface viscosity $\eta_s$, which can be very different from the bulk $\eta_b$ due to partial demixing of cosolvent and water (preferential hydration, Timasheff). This is particularly relevant in sucrose water which is strongly excluded from the protein domain. The escaper rate of CO in 80 % S/W (sucrose-water) is much weaker depending on the solvent viscosity as in glycerol.

CO escape rates from myoglobin in different solvents versus viscosity and ligand binding kinetics at 240 K with the internal state B and C and the solvent dependent step involving the ligand in the solvent S (adapted from Kleinert et al. 1998, in Doster, Longeville, Dynamics of Soft Matter ch. 8, Springer 2012).