"Lights, Computer, Action"
Probing Protein Dynamics with QM/MM Techniques and Femtosecond Laser Spectroscopy

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Abstract
The dynamics of a protein are of fundamental importance in understanding the relationship between its function and structure. We have used electronic structure calculations of excited states coupled to molecular dynamics simulations to track the fluctuations in the ground to excited state energy of a system as a function of time and so study time dependent properties of the system. Through the use of our QM/MM framework for predicting optical spectra based on linear response theory[1] it is possible to make direct comparisons between theory and experiment and ultimately provide a method for calculating free energies of reactions for protein based systems without the need for a detailed knowledge of the transition states.

CIS electronic structure calculations have been employed to derive the fluctuations in the ground to excited state energy gaps for dihydro−Nicotinamide Adenine Dinucleotide (NADH) embedded within the Horse Liver Alcohol Dehydrogenase (LADH) protein matrix and Zinc substituted horse heart Myoglobin. Classical molecular dynamics trajectories for the LADH+NADH dimer and Zinc Myoglobin, both in water, have been used to obtain the steady−state absorption and emission spectra, as well as 3 pulse echo peak shifts, to an accuracy within 10 % of experiment by utilising CIS QM/MM calculations coupled to our framework for predicting optical spectra based on linear response theory[1]. The magnitude of the Stoke's shift between absorption and emission is significant as it is a direct measurement of the reorganisation energy. It has been found that the accuracy of the results obtained is very dependent on the quality of the molecular dynamics trajectory, especially in the parameterisation of the nicotinamide moiety for the LADH+NADH dimer. The results are the first example involving a protein based system to show that linear response theory can work for proteins, such as LADH, which have very large reorganisation energies (Stoke's shift ~ 1 eV) . The method is also sensitive enough to provide a way of validating molecular dynamics force fields for chromophores.

[1] Walker, R.C., Melanie M. de Souza, Ian P. Mercer, Ian R. Gould, David R. Klug, J. Phys. Chem. B., *106*, 11658−11665, 2002.