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Conferencia: Ockham's razor and multi-conformer models of enzyme dynamics and catalysis

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Ockham's razor and multi-conformer models of enzyme dynamics and catalysis

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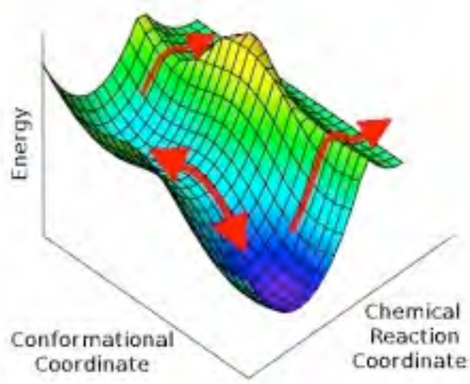

Along with protein folding, understanding enzyme catalysis continues to be one of the driving 'grand challenges' of chemical biology. Evolution has made enzymes superb catalysts, but the underlying physical principles remain hotly debated. In particular, the extent to which protein dynamics couple to enzyme catalysis is a matter of intense current debate. Enzyme-catalysed reactions that involve significant quantum tunnelling can give rise to experimental kinetic isotope effects with complex temperature dependences. In some well-studied enzymes including soybean lipoxygenase (SLO), dihydrofolate reductase (DHFR), aromatic amine dehydrogenase (AADH), and methylamine dehydrogenase (MADH), it is certainly the case that simple canonical transition state theory (TST) is unable to describe the experimental observations. This has raised questions as to the adequacy of standard statistical rate theories like TST for explaining these enzymatic systems. In this talk, I will introduce aspects of TST relevant to the study of enzyme reactivity, taking cues from chemical kinetics and dynamics studies of small molecules in the gas phase and in solution – where breakdowns of canonical TST have received significant attention and their origins are relatively better understood.[1,2] I will discuss recent theoretical approaches to understanding enzyme activity and show how experimental observations for a number of enzymes may be reproduced using a simple course-grained kinetic model built from thermal TST using physically reasonable parameters. A key ingredient of this simple model is the inclusion of: (1) appropriate temperature dependences in the tunnelling transmission coefficients, and (2) multiple enzyme-substrate conformations with different reactivity and fast interconversion kinetics.

(1) Greaves, S. J.; Rose, R. A.; Oliver, T. A. A.; Glowacki, D. R.; Ashfold, M. N. R.; Harvey, J. N.; Clark, I. P.; Greetham, G. M.; Parker, A. W.; Towrie, M.; Orr-Ewing, A. J. *Science* **2011**, *331*, 1423.
(2) Glowacki, D. R.; Lockhart, J.; Blitz, M. A.; Klippenstein, S. J.; Pilling, M. J.; Robertson, S. H.; Seakins, P. W. *Science* **2012**, *337*, 1066.