Aromatic aminoacids and Substrates as Probes of Local Environment and Dynamics in Proteins

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The lock-and-key model of enzyme function proposes that an enzyme catalyses reaction by preferentially binding and stabilizing the transition states of the reactants (substrates). We then expect that the structure of the enzyme should be rigid and highly complementary to a particular reactant. However, there are many enzymes than can bind to several different substrates (one at a time) and catalyze them. This conundrum is resolved by acknowledging the fact that enzymes are not rigid structures but dynamic and flexible ones. Our research is aimed at understanding the mechanism through which enzymes can accomplish multiple substrate specificity and still retain catalytic efficiency. Some of the questions we are currently addressing are: What is the nature and strength of the interactions between the substrate and enzyme? How are these interactions modulated for different substrates of the same enzyme? How do enzyme-substrate contacts compare in structurally homologous enzymes with differing substrate specificities? We have addressed these questions through high-resolution measurements of vibrational spectra and quantum chemical modeling of enzyme-substrate complexes. I will present a couple of examples where we have been able to observe distortions of substrate structures that are too subtle to be seen by more popular methods. Our results allow us to connect the flexibility of structurally analogous enzymes to their differing substrate specificities.

In experiments and computational studies outlined above, we analyze the enzyme-substrate complexes in steady state. However, it has long been suspected that the dynamics of enzymes is also relevant to function. I will outline a novel approach, through which we extract ultrafast dynamical responses of proteins by simulating Raman Intensities.