Calculated Free Energy Differences for Protein Loop Conformational Changes

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Formyl-CoA;oxalate CoA transferase (FRC) is a bacterial enzyme that catalyses the formation of oxalyl-CoA and formate from formyl-CoA and oxalate. FRC is active as a homodimer in which the two FRC monomers adopt an unusual, "interlocked" fold, and a series of X-ray crystal structures have been reported that correspond to "snapshots" of the enzyme as it undergoes its catalytic cycle. Computational methods offer an approach to determining the thermodynamics and free energy barriers to motions of active site loops but enhanced sampling is required in order to overcome the "lagging" Hamiltonian problem. In this lecture I will present the results of Orthogonal Space Random Walk (OSRW) calculations on the energetics of an active site tetraglycine loop in FRC and a series of site-specific FRC mutants that have been kinetically characterized. Not only do the calculated free energy profiles correlate well with with steady-state kinetic observations but the calculations also predicted the observed active site loop conformation in the G260A FRC mutant. The implications of these calculations for understanding the role of active site loop conformations in catalysis will also be discussed.

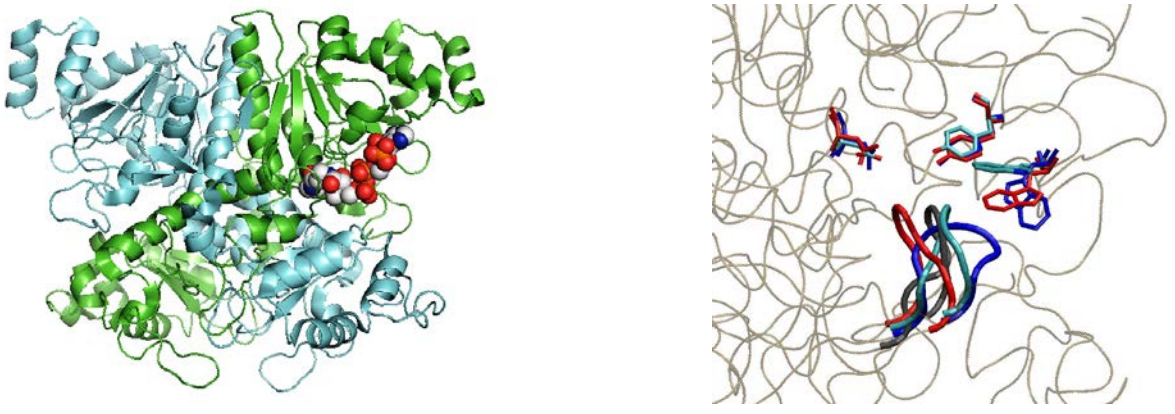

Figure: **(Left)** Cartoon representation of the formyl-CoA transferase/CoA complex, showing the location of the active site. Protein monomers are shown in green or blue ribbon representations. Bound coenzyme A is rendered in a space-filling representation. **(Right)** Cartoon showing superimposed active site loops for observed (2VJN) (cyan) and calculated "open" (blue), "intermediate" (black) and "closed" (red) loop conformations in the G260A FRC mutant.

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