

Novel Mathematical Approach to Calculating Acetylcholinesterase Reaction Rates

Yuhui Cheng & J. Andrew McCammon

Center for Theoretical Biological Physics, University of California, San Diego

Acetylcholinesterase is a type of enzyme. An enzyme is a protein macromolecule which modifies, synthesizes and/or degrades other molecules, e.g. synthesizing large molecules from many smaller molecules (“substrate”), etc., and are involved in practically all aspects of life. Understanding the mechanism(s) of enzyme reactions (“catalysis”) and how fast these reactions occur (“reaction rates”) is important in developing a higher understanding of biological function. Enzyme reaction rates are largely governed by diffusion (the movement of the enzyme and its substrates in an aqueous environment) and the subsequent binding of enzyme and substrate (also called a ligand). Computational models of diffusion have been widely studied using both discrete and continuum methods. Discrete methods concentrate on stochastic processes (those based on analyzing the movements of individual molecules), e.g., Monte Carlo, Brownian dynamics and Langevin dynamics. Whereas, continuum modeling describes diffusion processes via a concentration distribution probability (an “averaging” of the movements of many thousands to millions of molecules).

Our research has focused developing a numerical solution to the time-dependent Smoluchowski equation to study diffusion in biomolecular systems. Specifically, we have used finite element mathematical methods to calculate substrate binding rate constants for large biomolecules. We have applied these new methods towards understanding monomeric (single protein) and tetrameric (many proteins) mouse acetylcholinesterase (mAChE) activity. Reaction rates for mAChE were calculated at various aqueous environment ionic strengths with several different time steps. Our calculated rates show very good agreement with experimental and theoretical steady-state studies. And these methods are much less computationally challenging (require less computer time and resources to calculate), yet robust for complicated geometries (broad array of different shape and size enzymes and substrates).

The key finding of biological importance in this work is that the rate accelerations of the monomeric and tetrameric mAChE that result from electrostatic steering are preserved under non-steady state conditions that are expected to occur in physiological circumstances.

See also:

- Cheng et al., 2006, 2007, Biophysical Journal (*In Press*)
- Demo movie showing how the +1e charged ligand diffuses to mAChE, the red represents high concentration and blue represents the low concentration:
http://mccammon.ucsd.edu/smol/doc/demo/mache_conc.mpg
- Demo movie showing how the [-log(concentration)] depends on the time in the diffusion
http://mccammon.ucsd.edu/smol/doc/demo/log_conc.mpg