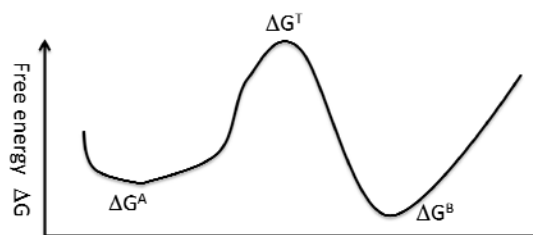


Free Energy & Kinetics from Molecular Dynamics

14.6.10

Objective: To give a presentation of about 60 minutes at the end of the week covering the key aspects of how to get kinetic parameters from molecular dynamics experiments.



Simulating biological systems is a field on the rise and driven by two major factors: the increased ability to simulate biological systems and availability of highthroughput OMICS-data. In simulating biological systems it is important to make reductions data groups a large assembly of things into an entity with its own dynamics as this can give rise to huge savings in computational needs. An example is to represent a large number of molecules by their concentrations instead of tracing their individual actions.

Molecular Dynamics (MD) has recently allowed the description of the behaviour of individual macromolecules in great detail. One interesting application of is the possibility of determining macroscopic parameters by simulations. One of the most important examples would be free energy and rate constants. The above illustration is the standard description of free energy and rates of going between two states *A* and *B*, but is also treacherous in being in 1 dimension, while the real molecules might need in excess of 10^4 dimension to be described. The free energy will related to how much time is spent in a state, while rates can be evaluated by considering all paths from a state to another. Both computationally very hard questions. This would allow simulations of individual molecules to be translated into whole cell simulations. What needs to be simulated would be the full atomic trajectory of for instance $A + B \rightarrow C$, sufficiently many times and under conditions enabling the evaluation of the rate of this reaction. $A + B \rightarrow C$ will often involve bond breaking, which needs a quantum mechanical description in contrast to motion of the molecules which can be deon by classssical descriptions. A serious problem here is that $A + B \rightarrow C$ can occur on time scales (milliseconds) that are 6 orders of magnitude larger than fine grained MD typically deals with (nanoseconds and less). Ie accelerations that bridges this gap are key to the success in this endeavour. There are many approaches to this, but clearly a combined description, where motions are described by classical potentials, while bond breaking by QM. Coarse grained descriptions are approximations to full atomic descriptions that all further necessary accelerations.

The Big Questions Are

- How big an acceleration is this?
- What is lost in a major reduction like this?
- What are the main problems in application of this simple idea?

Possible Contents of Presentation

1. History of MD and its applications
2. History of Enzyme Kinetics and its application
3. Key principles of MD
4. How is MD used to determine kinetic parameters?
5. Key examples of applications of this
6. The Possibility of large scale applications of this

Recommended literature

Benkovic et al. (2003) Perspective on Enzyme Catalysis Science 301, 1196 (2003);
Benkovic et al (2008) Free-Energy Landscape of Enzyme Catalysis Biochemistry 2008, 47, 3317–3321
Deng and Roux (2009) Computations of standard binding free energies with molecular dynamics simulations. J Phys Chem B.113(8):2234–46.
Gao and Truhlar QUANTUMMECHANICALMETHODS FOR ENZYME KINETICS Annu.Rev.PhysChem. 2002. 53:467–505
Hamelberg et al. (2005) Relating kinetic rates and local energetic roughness by accelerated molecular-dynamics simulations J. J Chem Phys. 122(24):241103.
Hammes-Schiffer and Benkovic (2006) Relating Protein Motion to Catalysis Annu. Rev. Biochem. 75:519–41
Hu et al. (2008) Free Energies of Chemical Reactions in Solution and in Enzymes with Ab Initio Quantum Mechanics/Molecular Mechanics Methods AnnuRev of Phys Chem. 59, 573-601
karplus et al. (1965) Exchange Reactions with Activation Energy. I. Simple Barrier Potential for (H, H2) t jchemphys 43 3259 1965
Nagel & Klinman (2009) A 21st century revisionist's view at a turning point in Enzymology Nat Chem Biol 5 8. 543-
Oliveira et al. (2007) Estimating kinetic rates from accelerated molecular dynamics simulations: Alanine dipeptide in explicit solvent as a case study J CHEM PHYS 127, 175105
Psachoulia et al. (2009) Molecular Dynamics Simulations of the Dimerization of Transmembrane alpha-Helices. Acc Chem Res 43.3388-396
Warshel COMPUTER SIMULATIONS OF ENZYME CATALYSIS Annu. Rev. Biophys. Biomol. Struct. 2003. 32:425–43

“Big Questions”, “Contents” and “Recommended Literature” are only suggestions from which the student is welcome to depart from or completely ignore.