Molecular Dynamics (and Thermodynamics) of Biomolecules

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A **single** protein structure is not the whole story

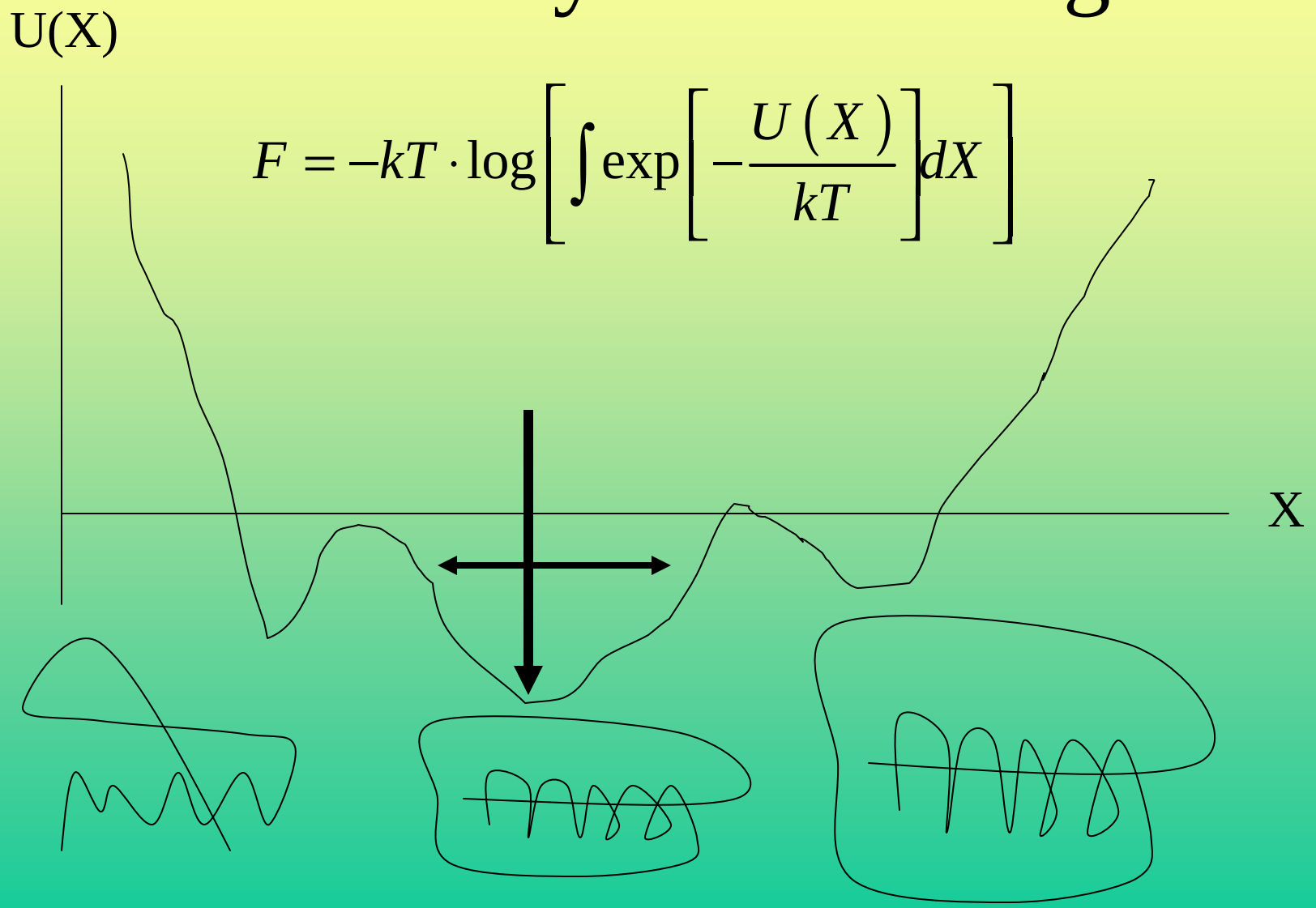
- A transient protein conformation may be responsible for activity.
- Some biomolecules do not have “structure” (lipids)
- Induced fit upon ligand binding.
- Computing kinetic properties: Reaction path, rate constants
- Computing thermodynamic properties
  - Protein stability and mutation
  - Strength of protein-protein interactions, protein-ligand interactions
  - Free energy profile during enzymatic reaction

To compute thermodynamics and kinetic properties, we need

- An energy, U(X), that describes the microscopic state of the protein chain
- A way to sample important conformations of the protein chain (that are sampled in the life time of the protein)

Thermodynamic averages

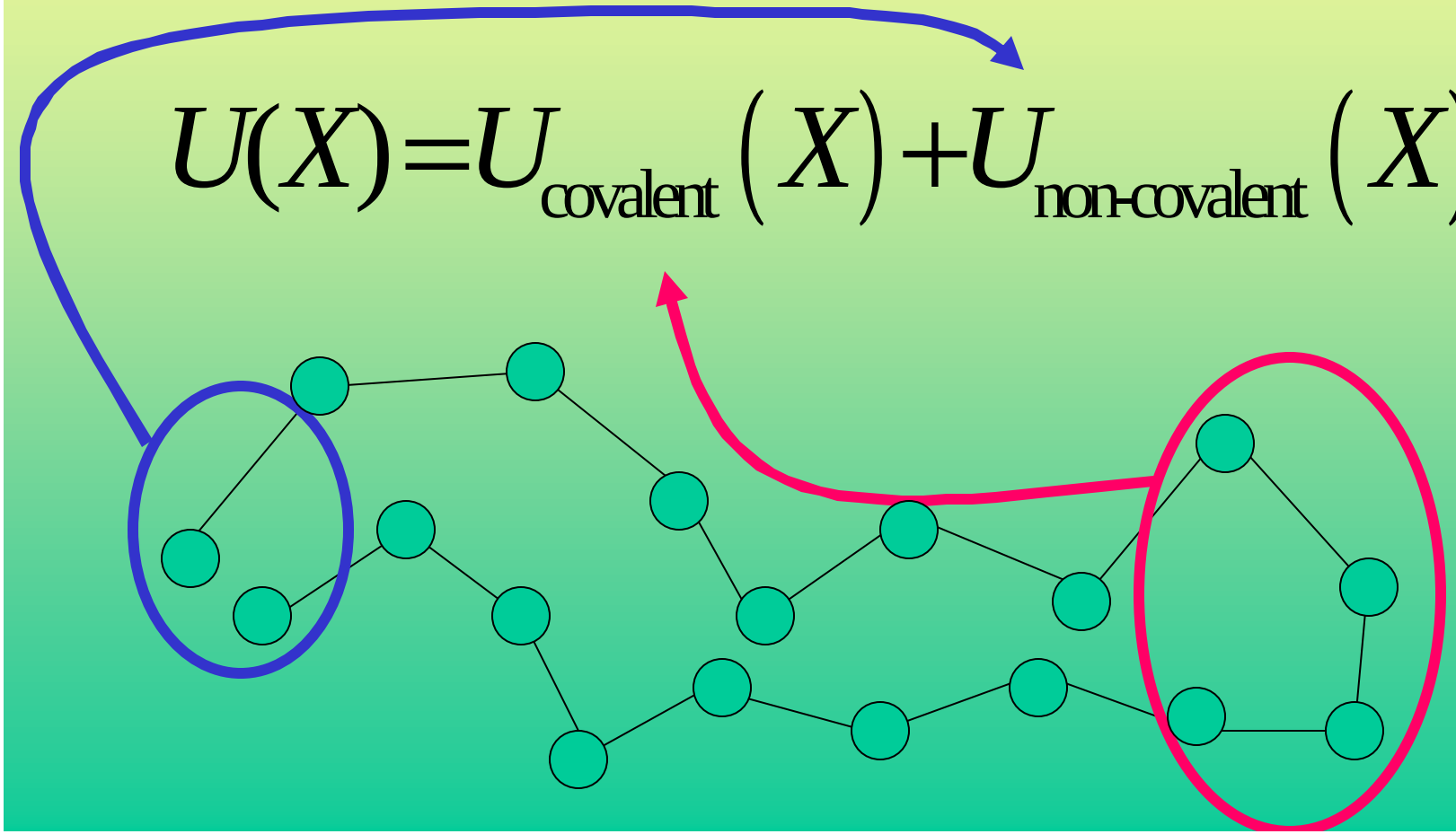
$$F = -kT \cdot \log\left[\int \exp\left[-\frac{U(X)}{kT}\right] dX\right]$$



The potential U(X)

A sum of two terms: Covalent and non-covalent

$$U(X) = U_{\text{covalent}}(X) + U_{\text{non-covalent}}(X)$$



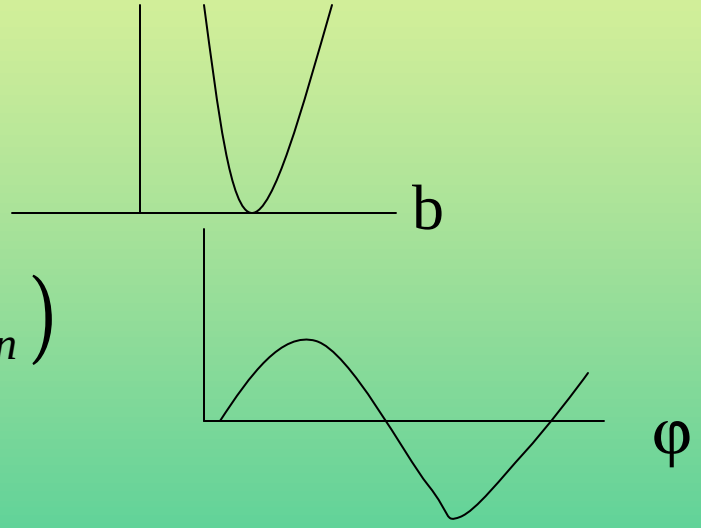
Interaction potential: More details (I)

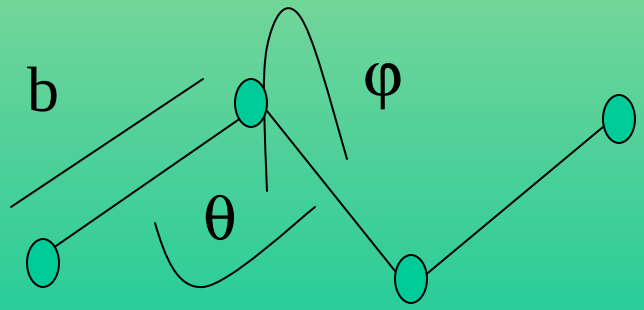
$$U_{\text{covalent}} = \sum U_{bond} + \sum U_{angle} + \sum U_{torsions}$$

$$U_{bond} = k_b (b - b_0)^2$$

$$U_{angle} = k_q (q - q_0)^2$$

$$U_{torsion} = \sum a_n \cos(nj + d_n)$$

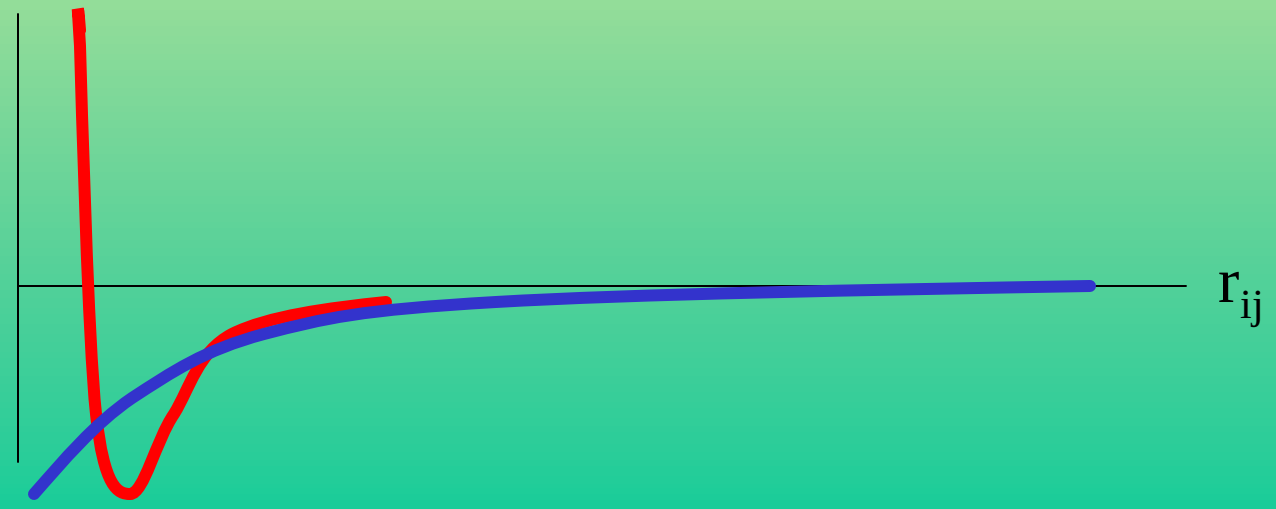




Interaction potential: More details (II)

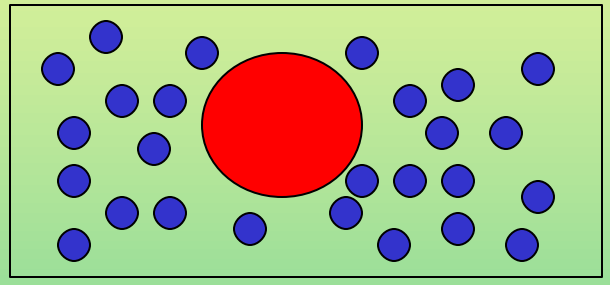
$$U_{non-bonded} = \sum U_{LJ} + \sum U_{elec}$$

$$U_{LJ} = \frac{A}{r_{ij}^{12}} - \frac{B}{r_{ij}^{6}} \qquad U_{elec} = \frac{q_i q_j}{r_{ij}}$$

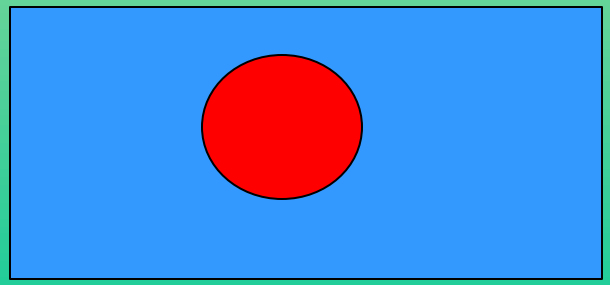


Approximate calculation of solvation

- Computing non-bonded interactions for water molecules (periodic boundary conditions is expensive



- Using continuum model instead (Poisson Boltzmann, Generalized Born model)



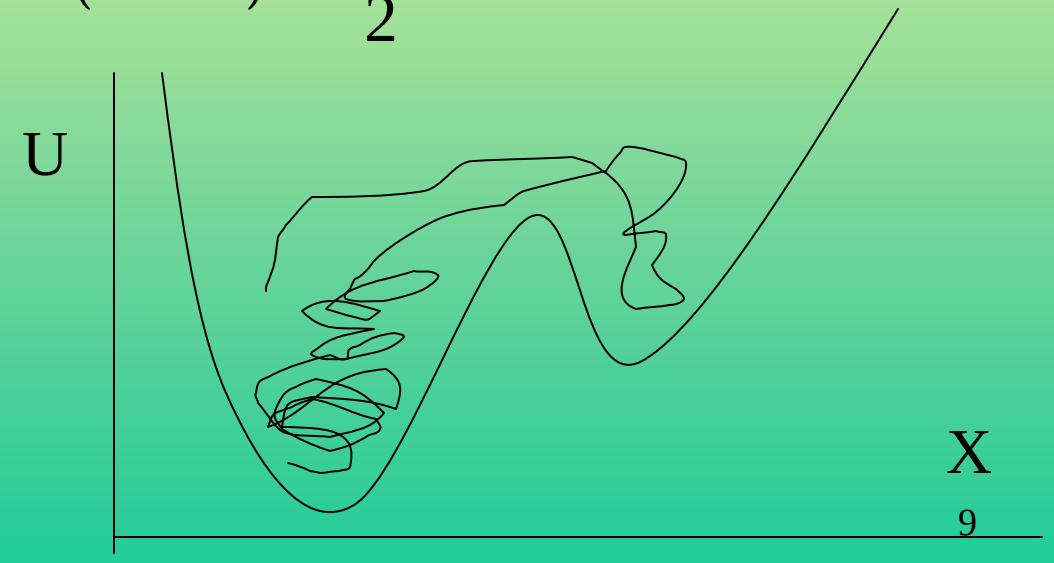
Classical mechanics is assumed

$$M\frac{d^2X}{dt^2} = -\nabla U(X)$$

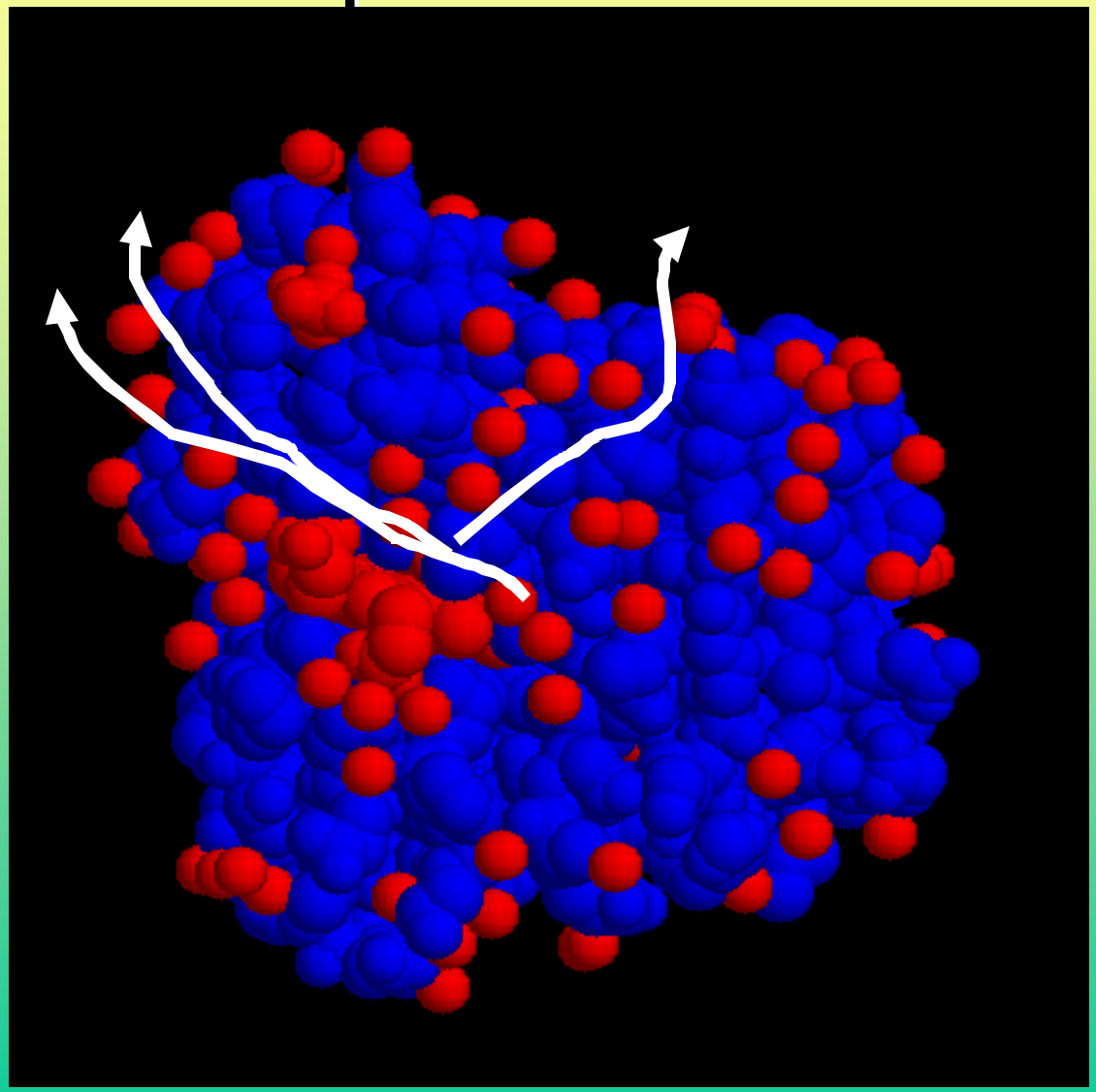
$$X(t+\Delta t) = 2X(t) - X(t-\Delta t) - \frac{\Delta t^2}{2} M^{-1}\cdot\nabla U$$

Sampling is over time

$$\int ...dX \rightarrow \int ...dt$$



Searching for transient ligand exits in protein structures

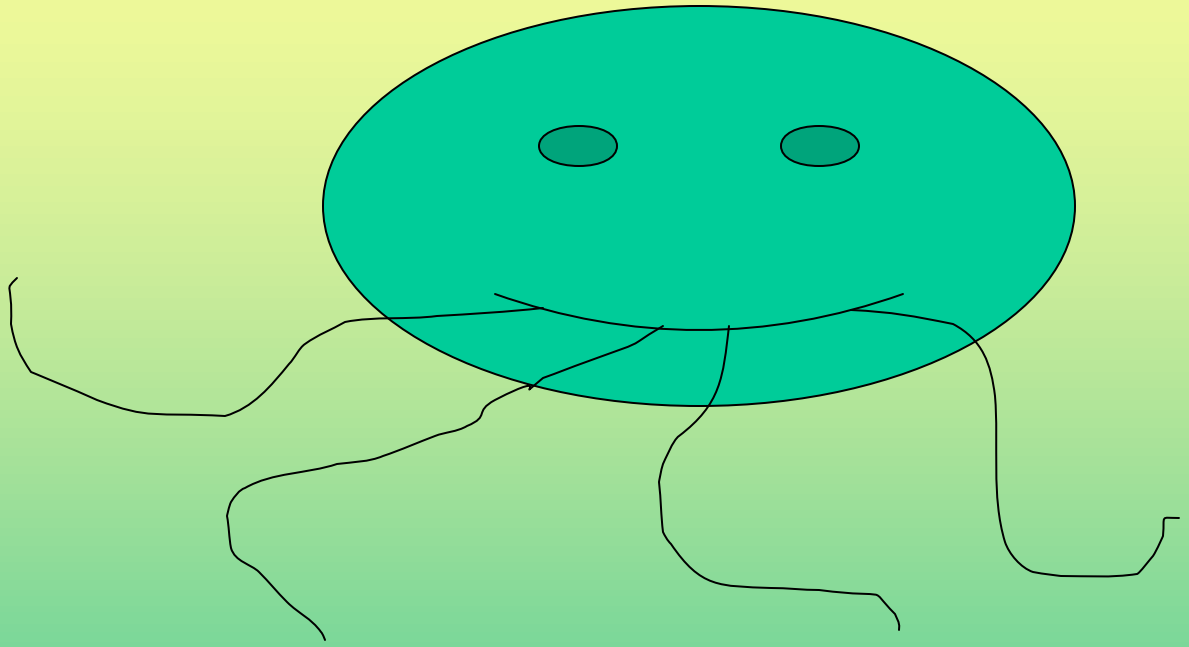


Sampling problems

Carbon monoxide diffusion in globins

- Ligand dissociation and recombination: Gibson, Eaton, Hochstrasser, Frauenfelder
- Time resolved X-ray crystallography: Moffat, Phillips
- Experiments on mutants: Sligar, Olson, Boxer

Locally Enhanced Sampling: A Mean Field Approach



Computational effort is dominated by protein atoms. Run a single trajectory for the protein, many trajectories for the small ligand

Ligand diffusion in a globin

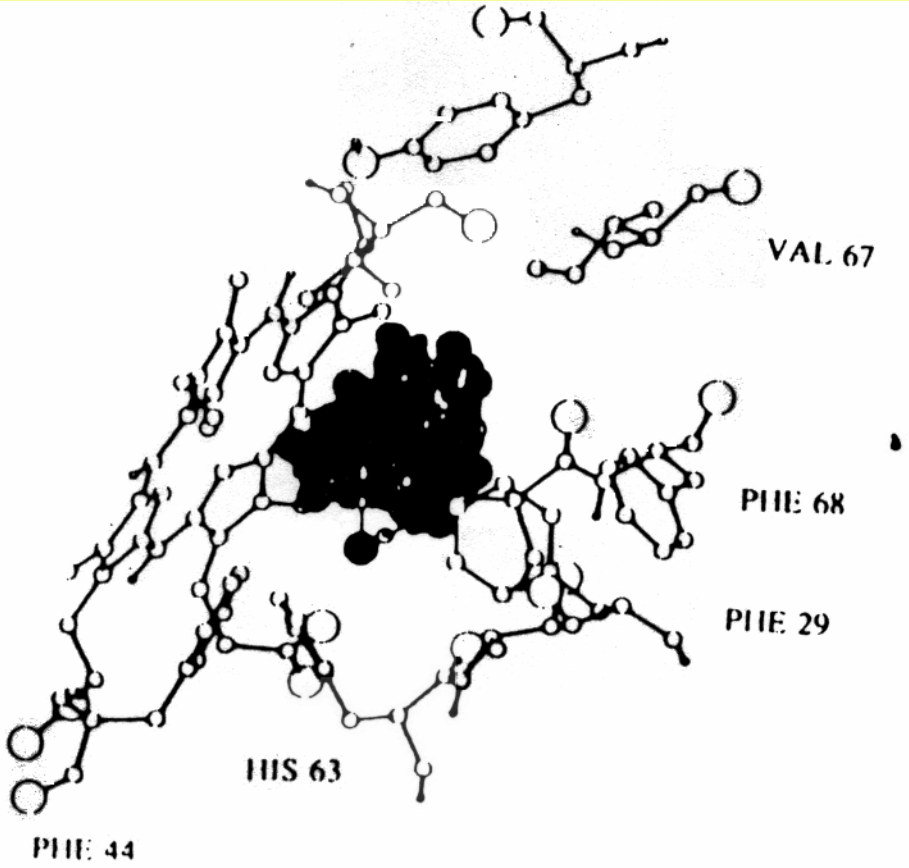
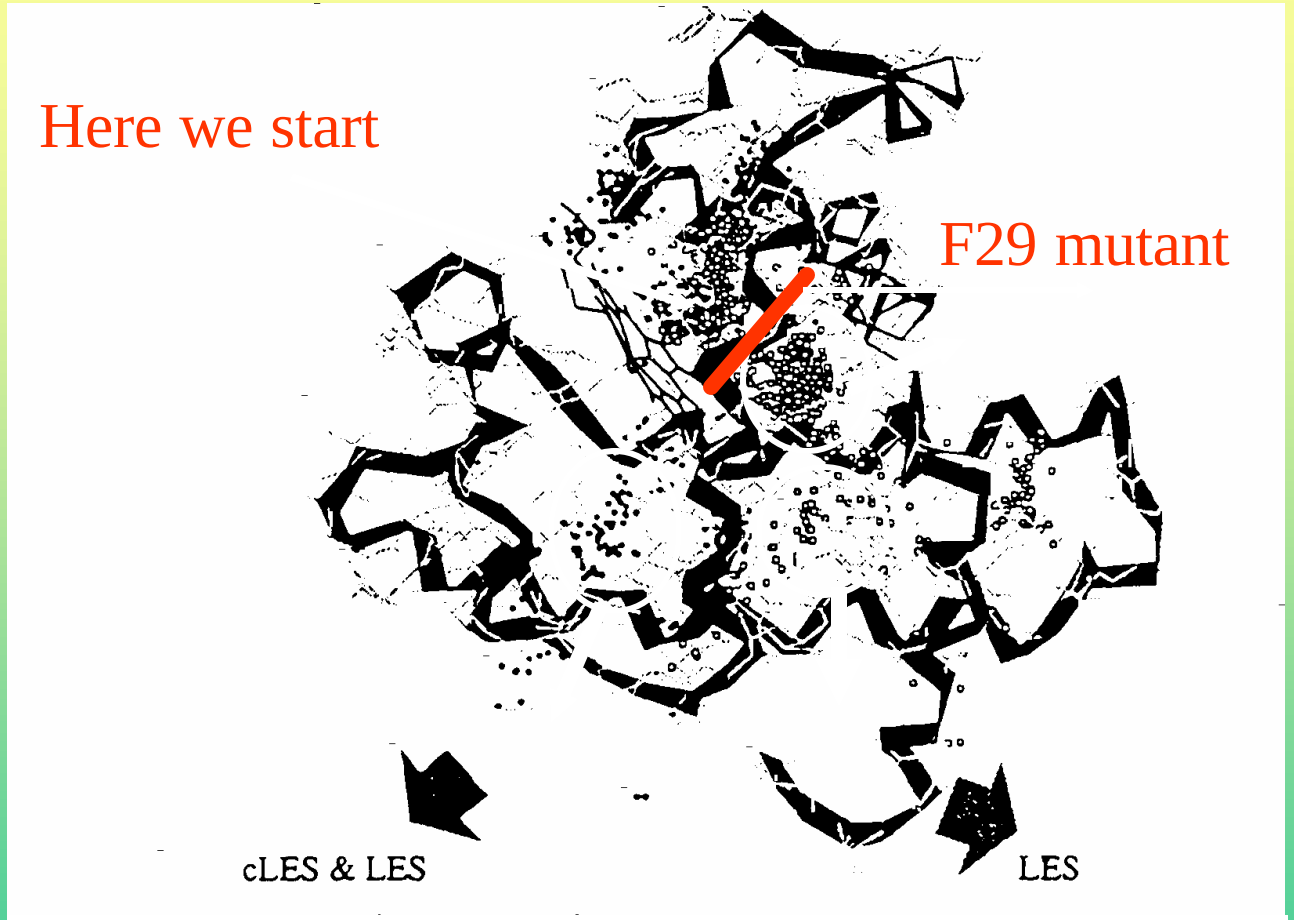


Fig. 4. A model of sticks and balls for the heme environment in leghemoglobin. The structure is after 20 psec simulation (trajectory A). The black circles are the ligand copies which are still in the pocket at this time (105 replica).

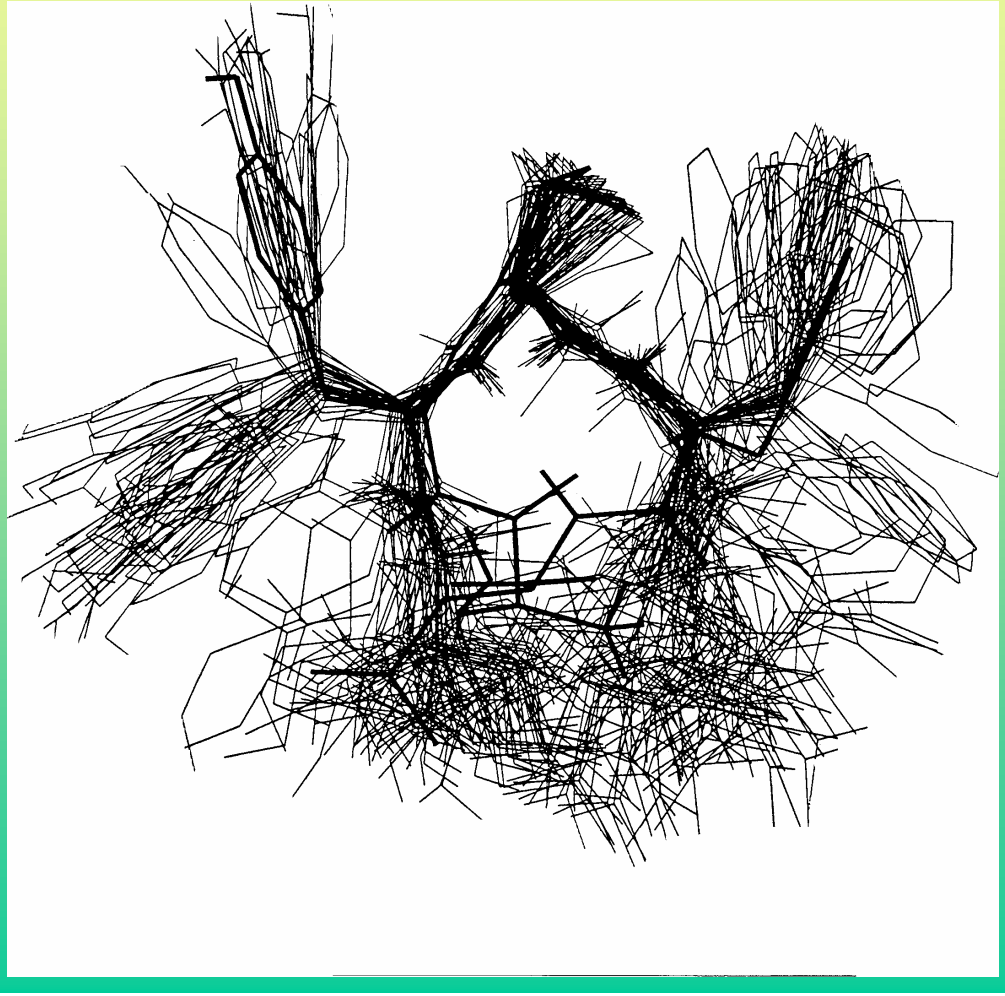
Ligand diffusion in myoglobin



Quick summary of ligand diffusion in globins

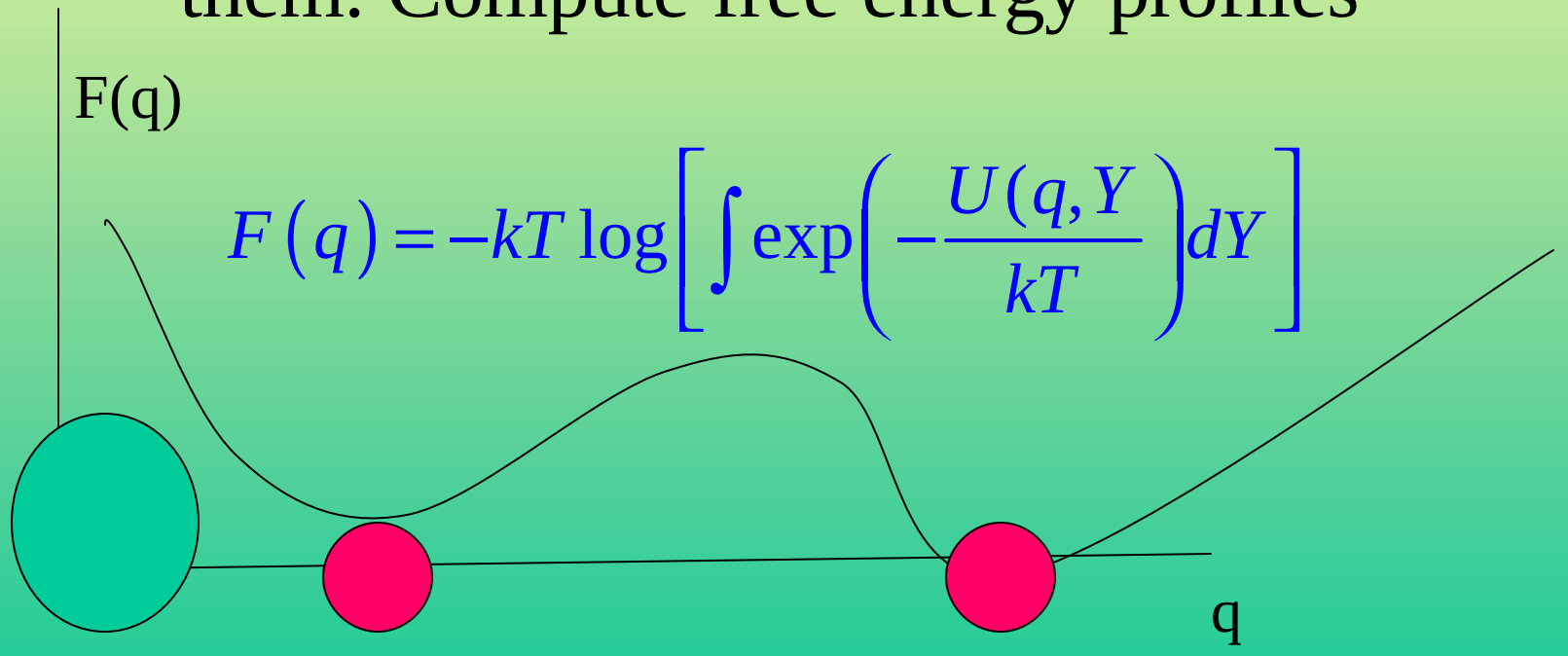
- Extensive network of cavities and pathways for a ligand demonstrated for myoglobin
- Early view of ligand in a single pocket and short exit pathway, incorrect.
- Numerous cavities that are occupied by the ligand confirmed by X-ray crystallography
- Alternative diffusion pathways demonstrated by protein mutations

Determine peptide conformation in solution: Folding nucleation sites?!



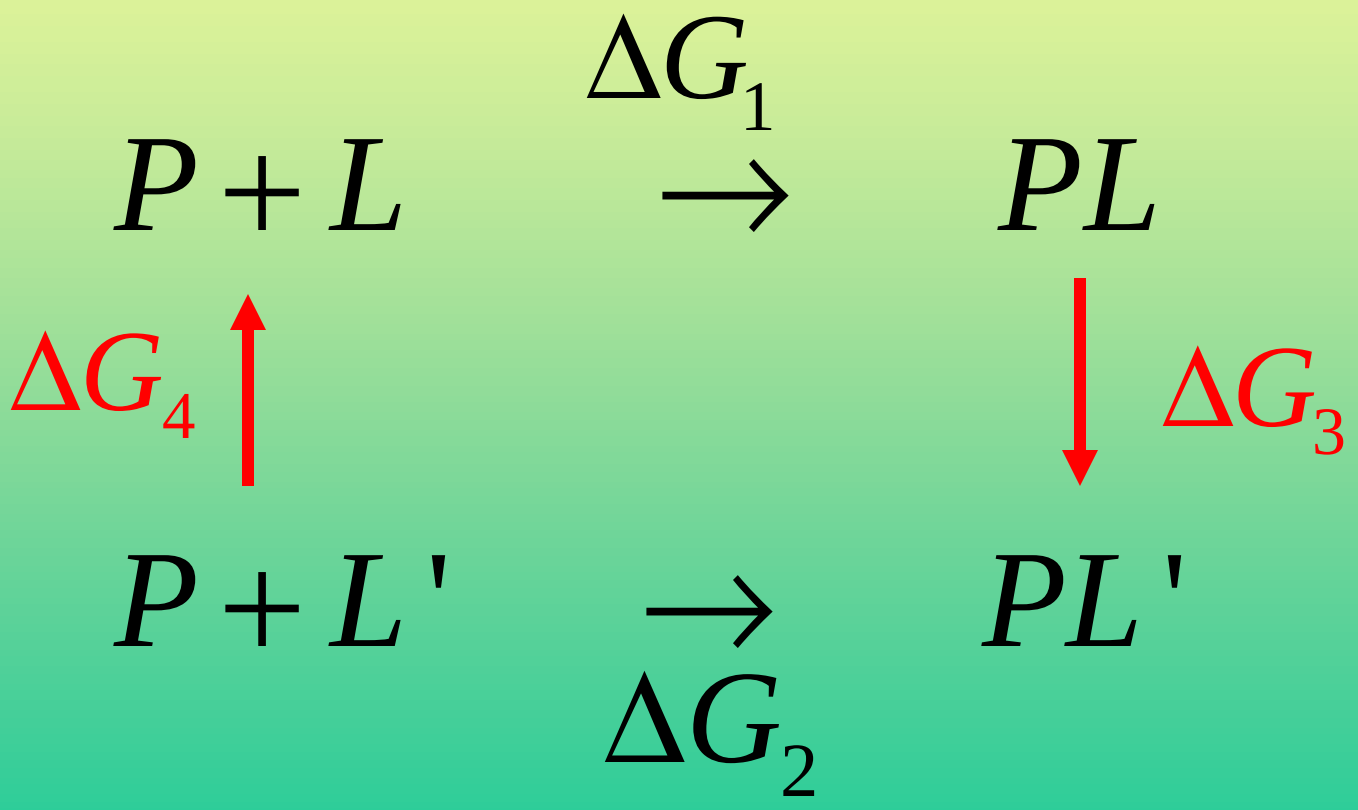
Free energy profiles along reaction coordinates

- To understand relative stability of reactant and products and the barrier separating them. Compute free energy profiles



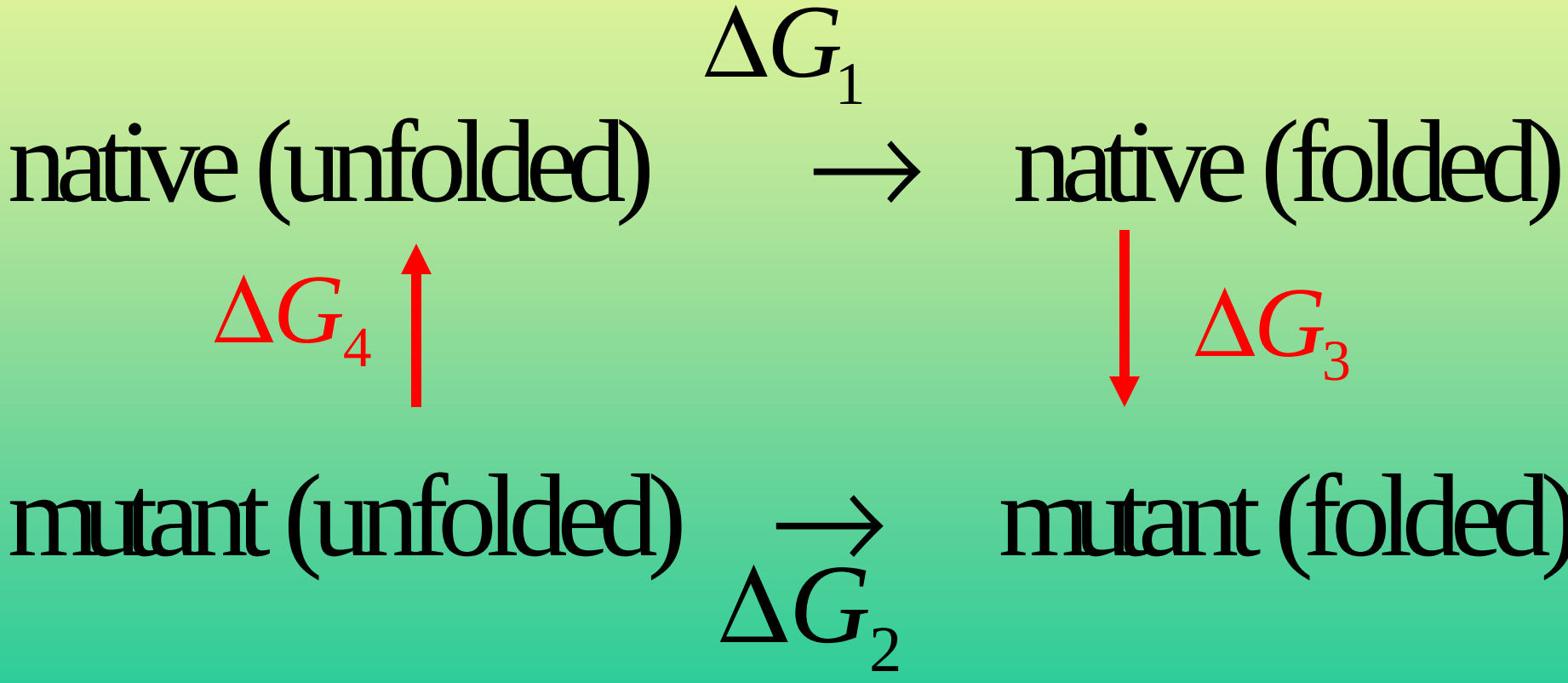
The thermodynamic cycle: Protein mutants or ligand variations

$$\Delta G_1 - \Delta G_2 + \Delta G_3 + \Delta G_4 = 0$$



Structure stability of mutants

$$\Delta G_1 - \Delta G_2 + \Delta G_3 + \Delta G_4 = 0$$

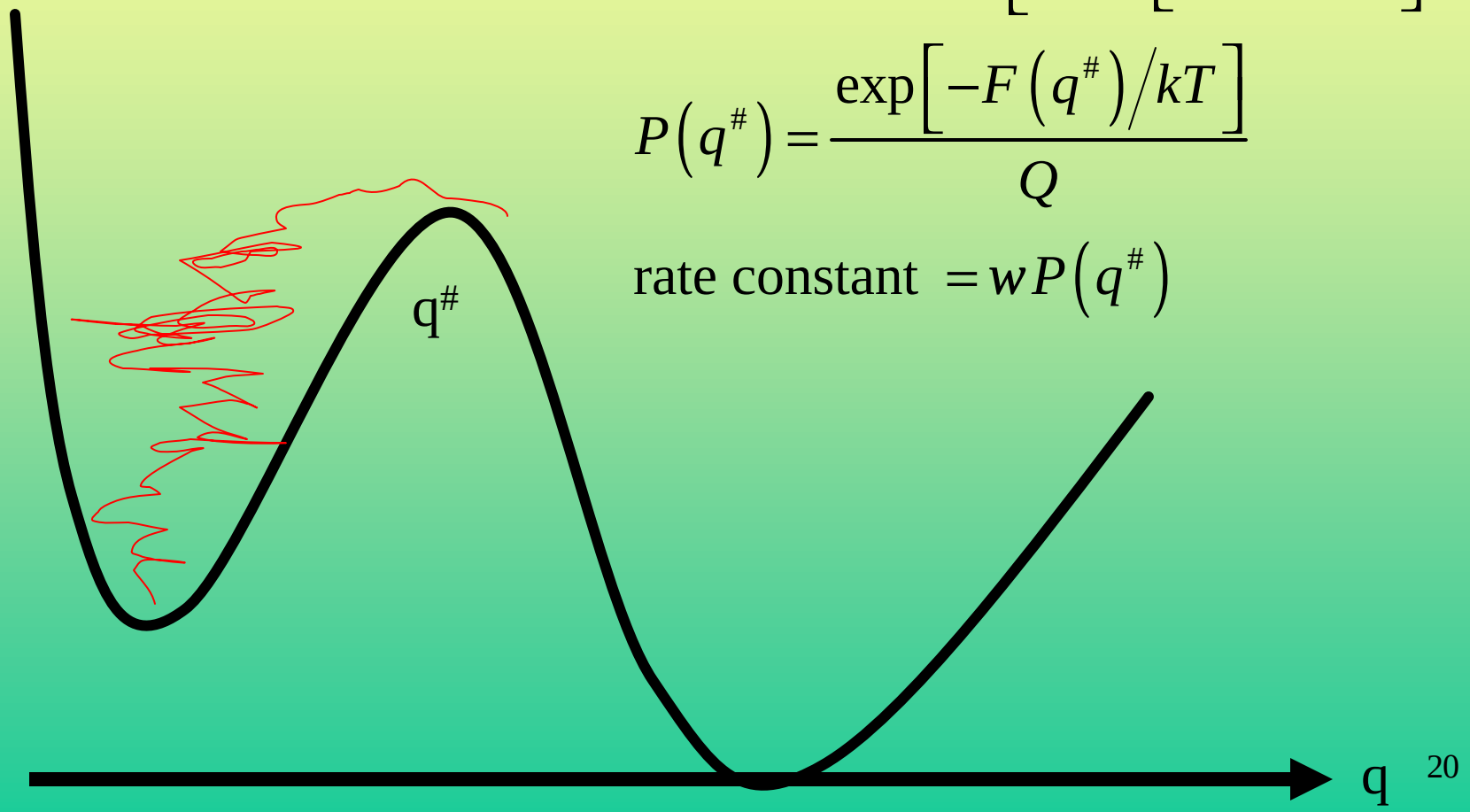


Rate theory

$$F(q^{\#}) = -kT \log\left[\int \exp\left[-\frac{U(q^{\#},Y}{kT}\right] dY\right]$$

$$P\left(q^{\#}\right) = \frac{\exp\left[-F\left(q^{\#}\right)/kT\right]}{Q}$$

$$\text{rate constant} = wP\left(q^{\#}\right)$$



Summary

A pictorial view of protein flexibility and reaction mechanisms

Molecular dynamic simulations provide the statistics for thermodynamics calculations and kinetic studies. Computations of

– Binding constants and free energies

– Rate constants

– Relative stability of mutants