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LEADERS IN IDEAS AND SOLUTIONS

Modelling Polyphenol-Protein Interactions

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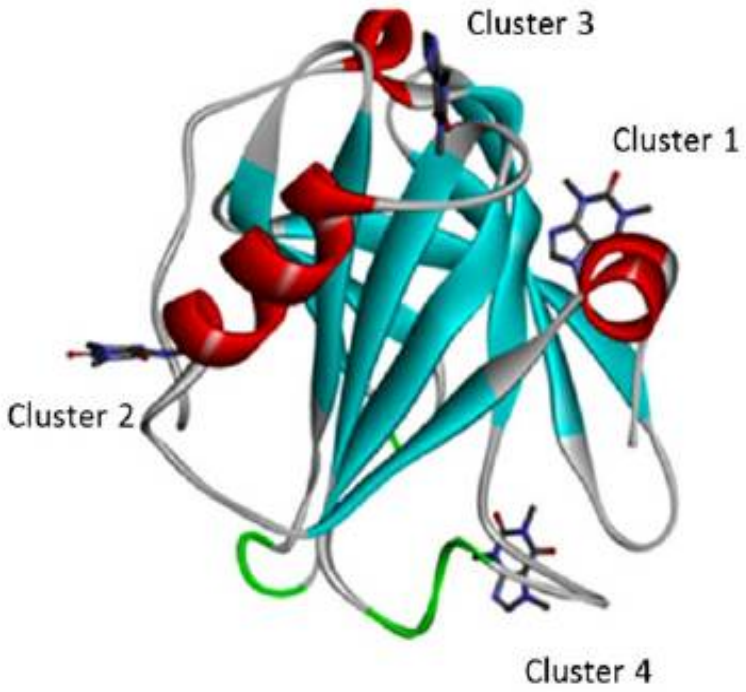
Protein-Polyphenol Interactions

- Evidence that protein-polyphenol interactions/complexes improve stability/bioavailability
- theoretical methods for determining binding site and binding free energy
  - Molecular simulation
  - Molecular docking



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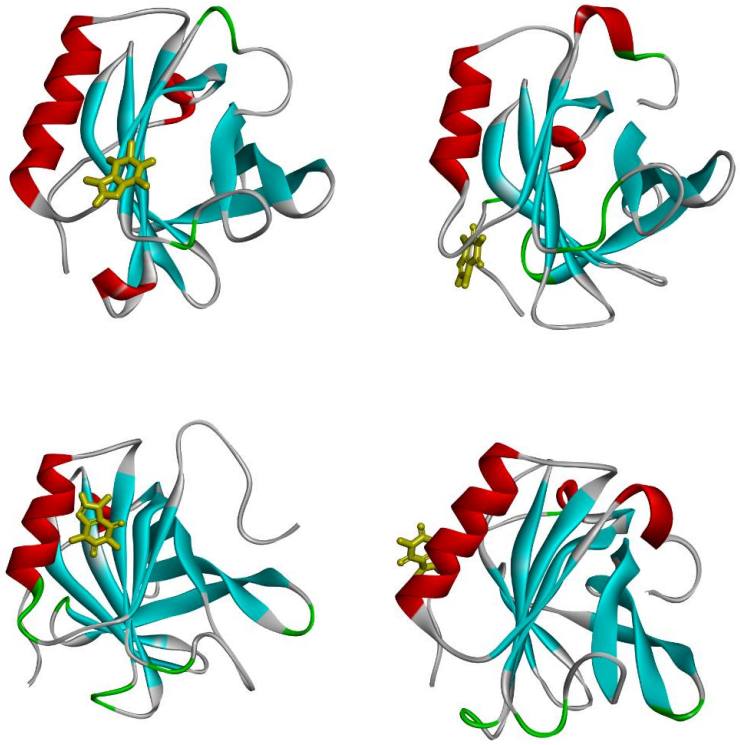
Molecular Dynamics Simulation

- Identifies binding site
  - Uses explicit solvent (water)
  - Explicit flexibility of protein and ligand
  - Can enter metastable binding states
  - Time consuming (long simulations)
    - Use accelerated MD to improve sampling
      - Meta-dynamics
      - Replica-exchange MD



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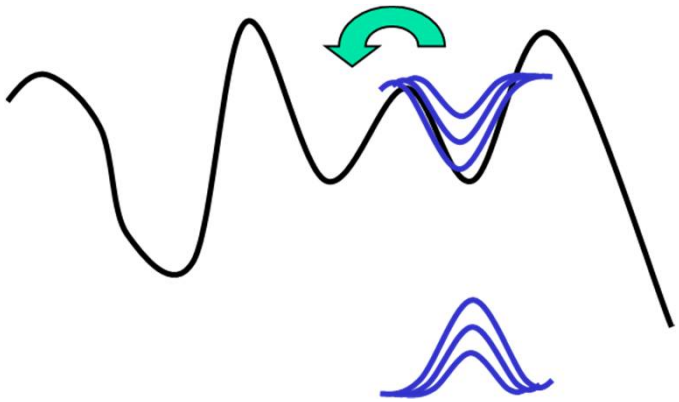
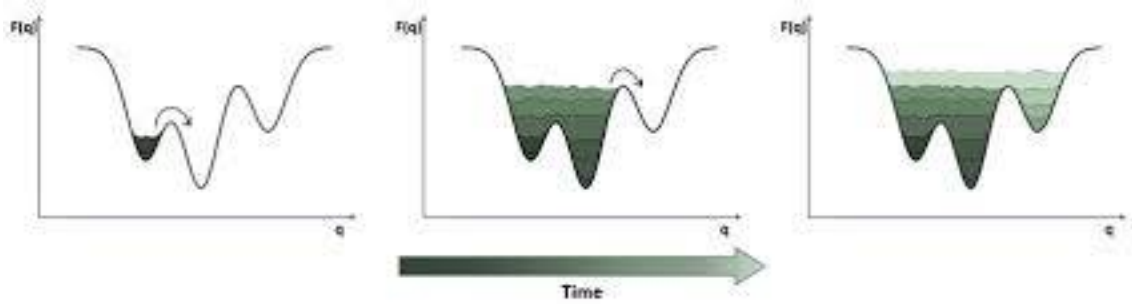
Metadynamics

- atoms in the system are exposed to a bias force in the form of Gaussian potentials designed to drive the system away from its current configuration to a new one
- Over the simulation, the Gaussians build up and exclude an increasing number of conformations





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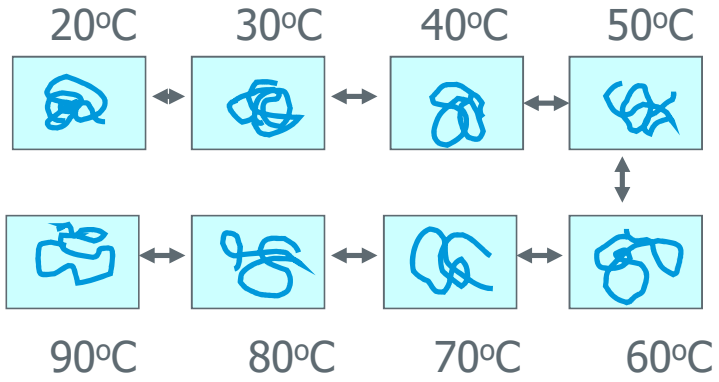
Replica Exchange MD

- Have a system where high T simulations overcome barriers to conformational change, coupled to low T exploration of minimum energy states of those conformations



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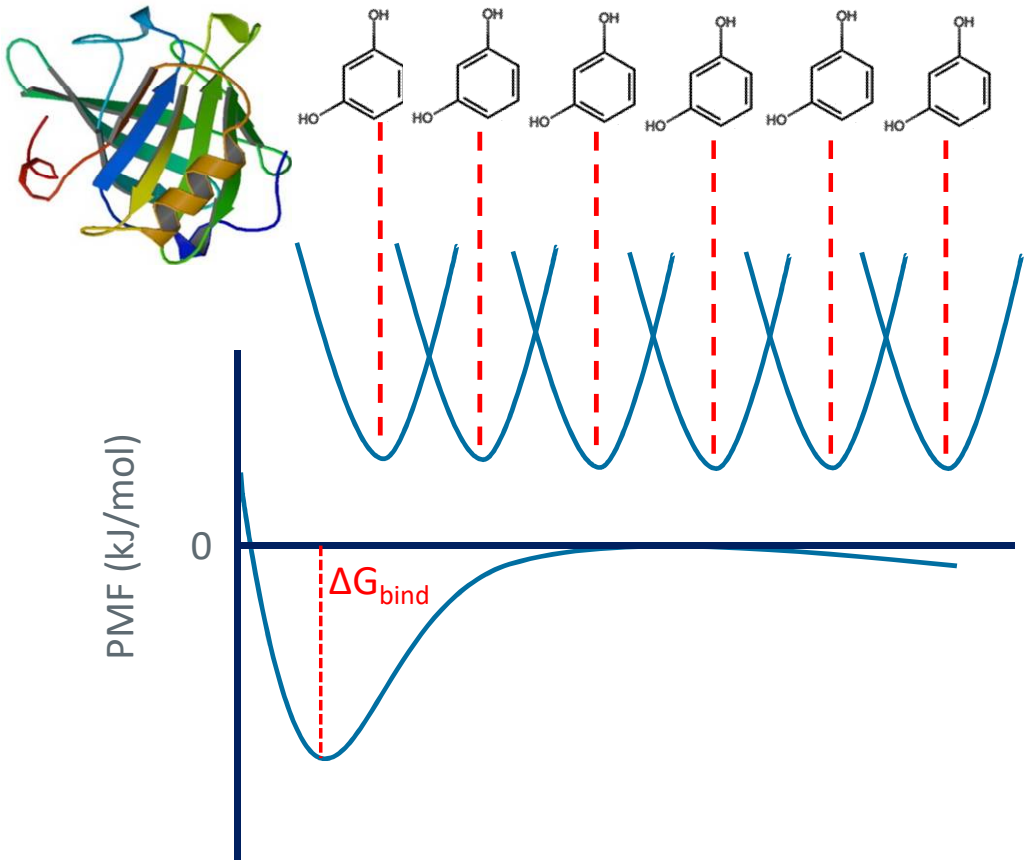
Binding Free Energy from MD

- Can determine binding free energy using various methods
  - umbrella sampling is popular
    - Potential of mean force (PMF) along a reaction coordinate
  - Analysed using weighted histograms method (WHAM)



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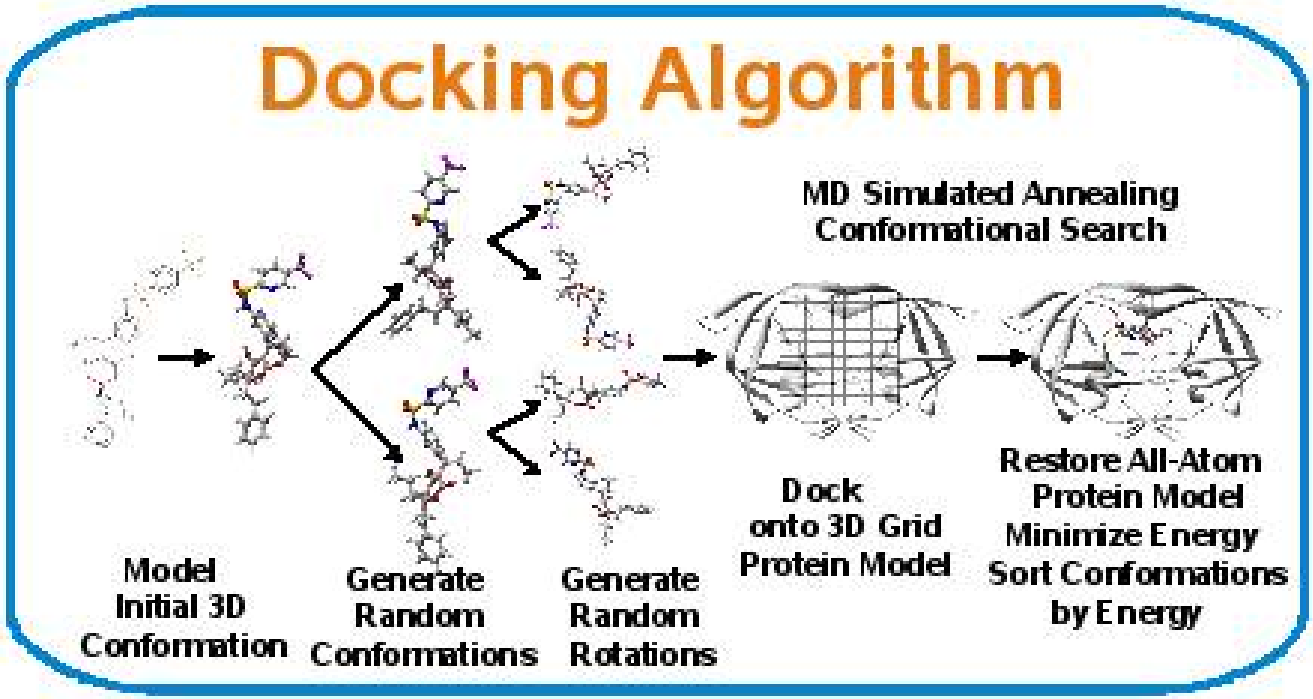
Molecular docking

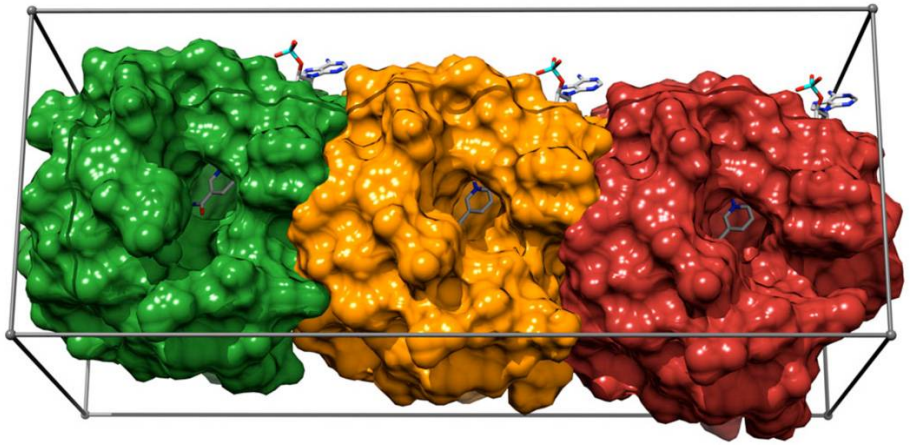
- Number of freeware programs
  - Autodock/Autodock Vina
  - FlexX
  - Ligandfit etc
- Rigid-body or flexible docking



Docking @ home
http://docking.cis.udel.edu/about/science/index.html

Molecular docking

- Three parts to docking
  - defining the surface of the protein
  - Search algorithm (protein surface searching)
  - Scoring function (ranking of the different docked poses)



Cosconati, S., Forli, S., Perryman, A.L., Harris, R., Goodsell, D.S. and Olson, A.J., 2010. Virtual screening with AutoDock: theory and practice. Expert opinion on drug discovery, 5(6), pp.597-607.

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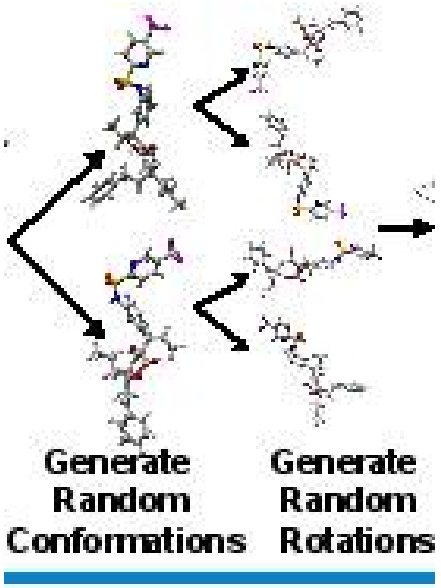

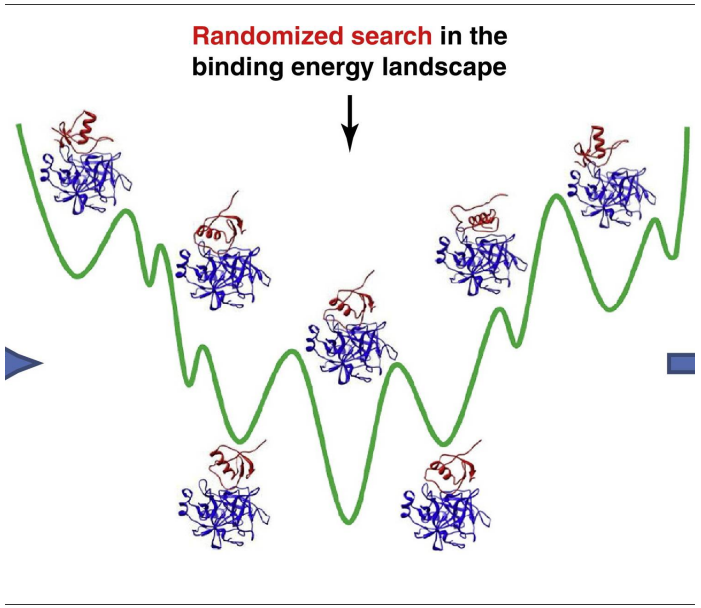

Huang, S.Y., 2014. Search strategies and evaluation in protein–protein docking: principles, advances and challenges. Drug discovery today, 19(8), pp.1081-1096.

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Molecular docking

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- Scoring = assigning binding energy
  - Forcefield based
    - Similar to MD
  - Empirical
    - Sum of energy terms (H-Bond, electrostatic, hydrophobic)
    - fast
  - Knowledge based
    - Database of potential based on pair interaction of atoms

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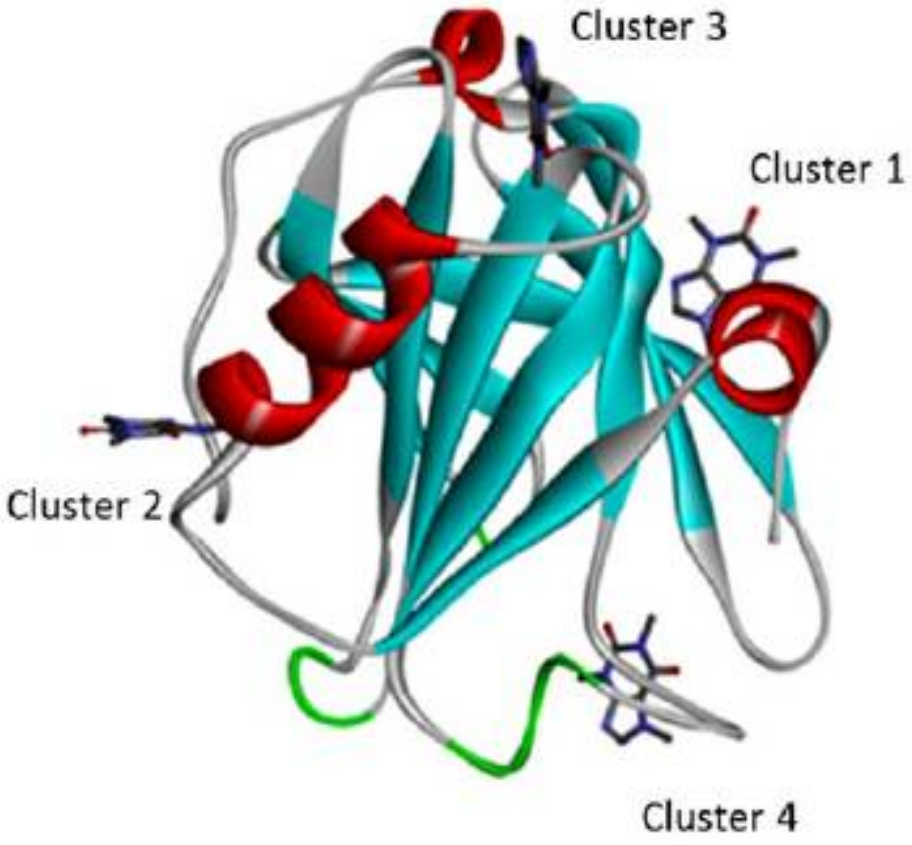
Molecular docking

- Net result of docking
  - Clusters of docking poses ranked on binding energy
  - Cluster on RMSD tolerance



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Conclusions

- Theoretical methods are useful in estimating binding site location and free energy of binding
  - Can be used for automated screening

- Methods are approximate
  - Accuracy of force-fields
  - Limitations of rigid body approximation