

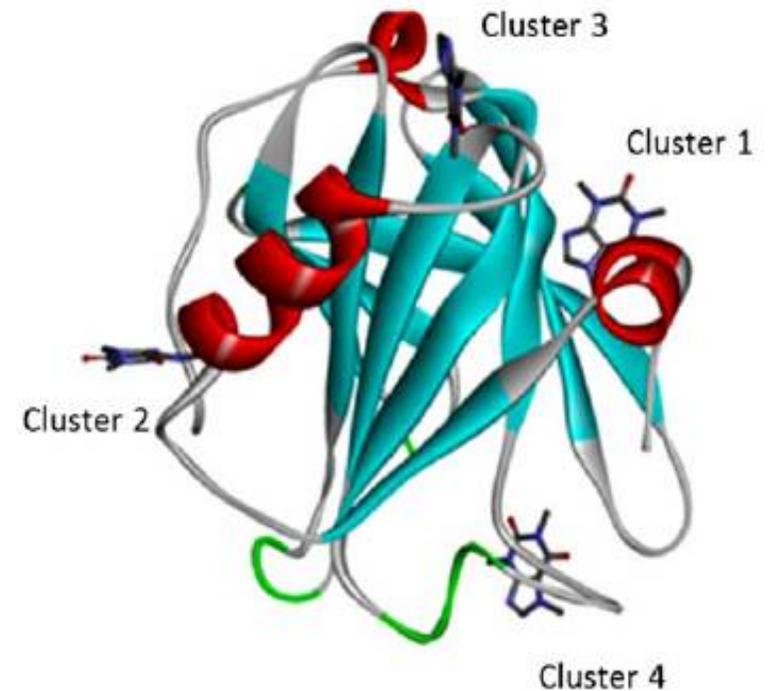
Modelling Polyphenol-Protein Interactions

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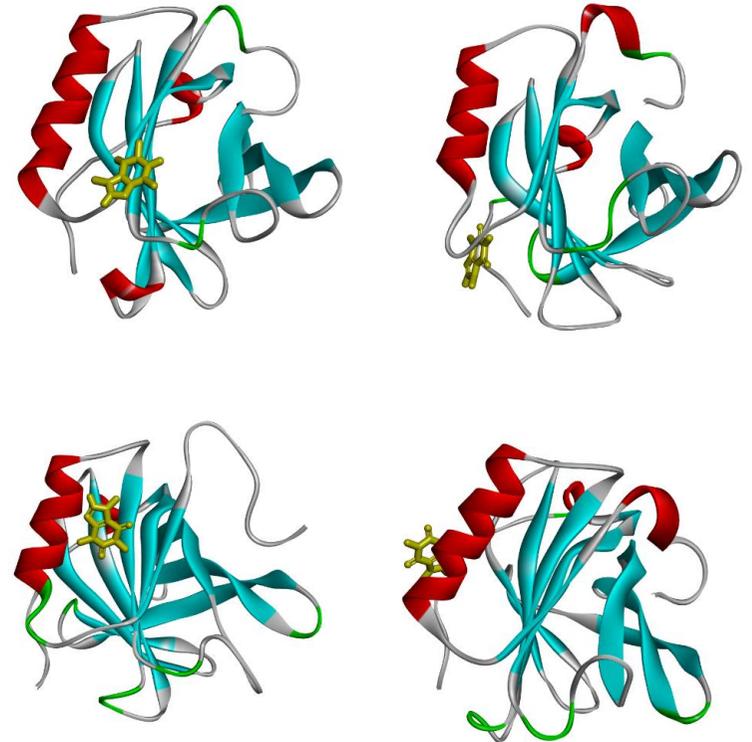
Protein-Polyphenol Interactions

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



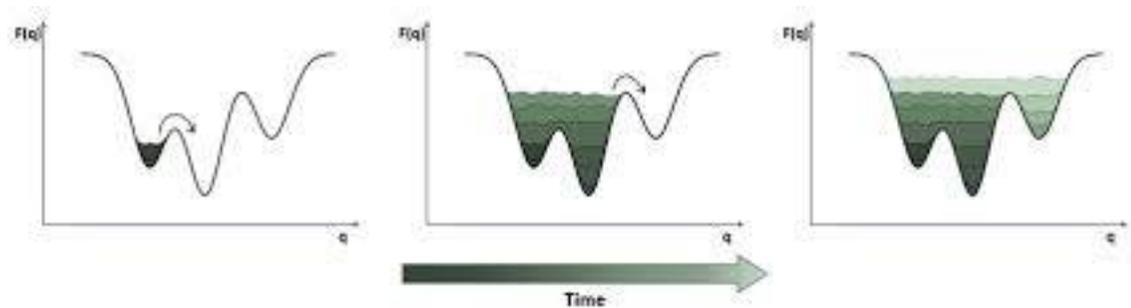
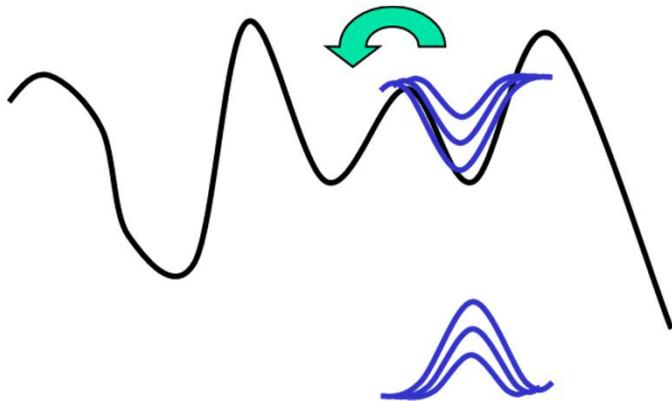
Molecular Dynamics Simulation

- 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



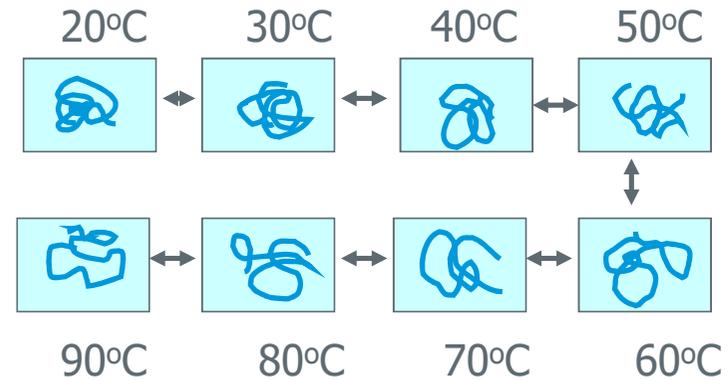
Metadynamics

- 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



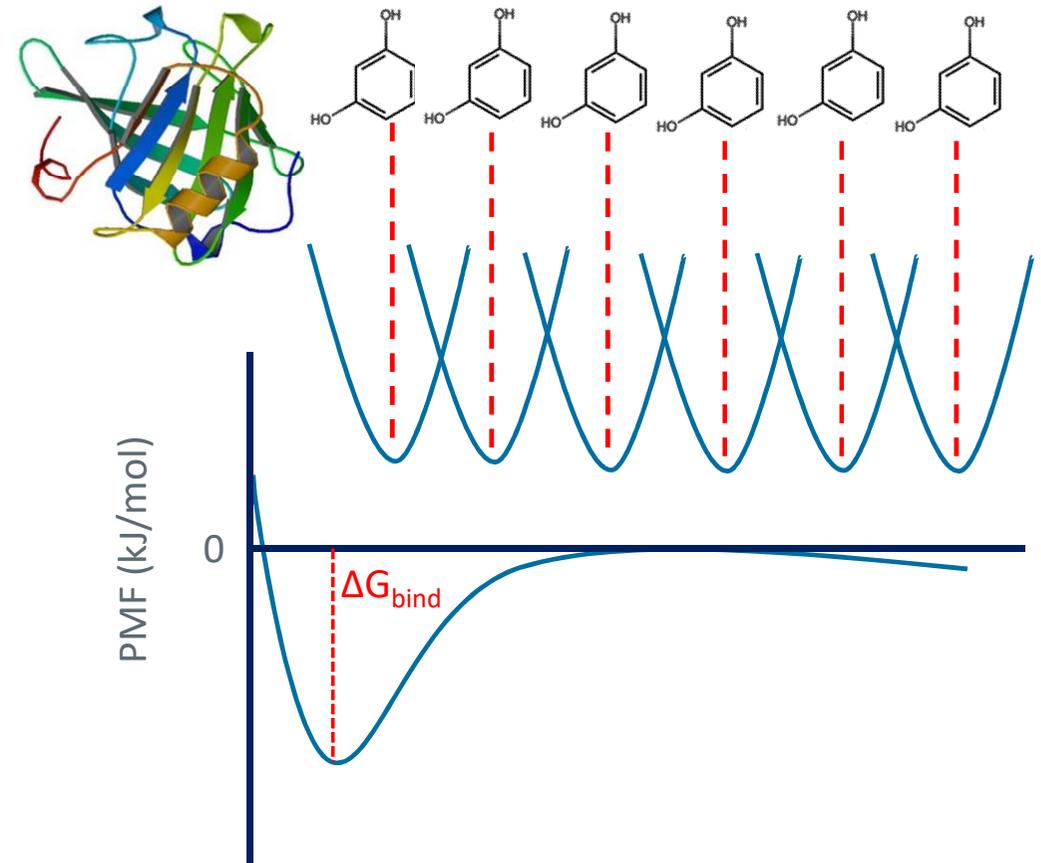
Replica Exchange MD

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



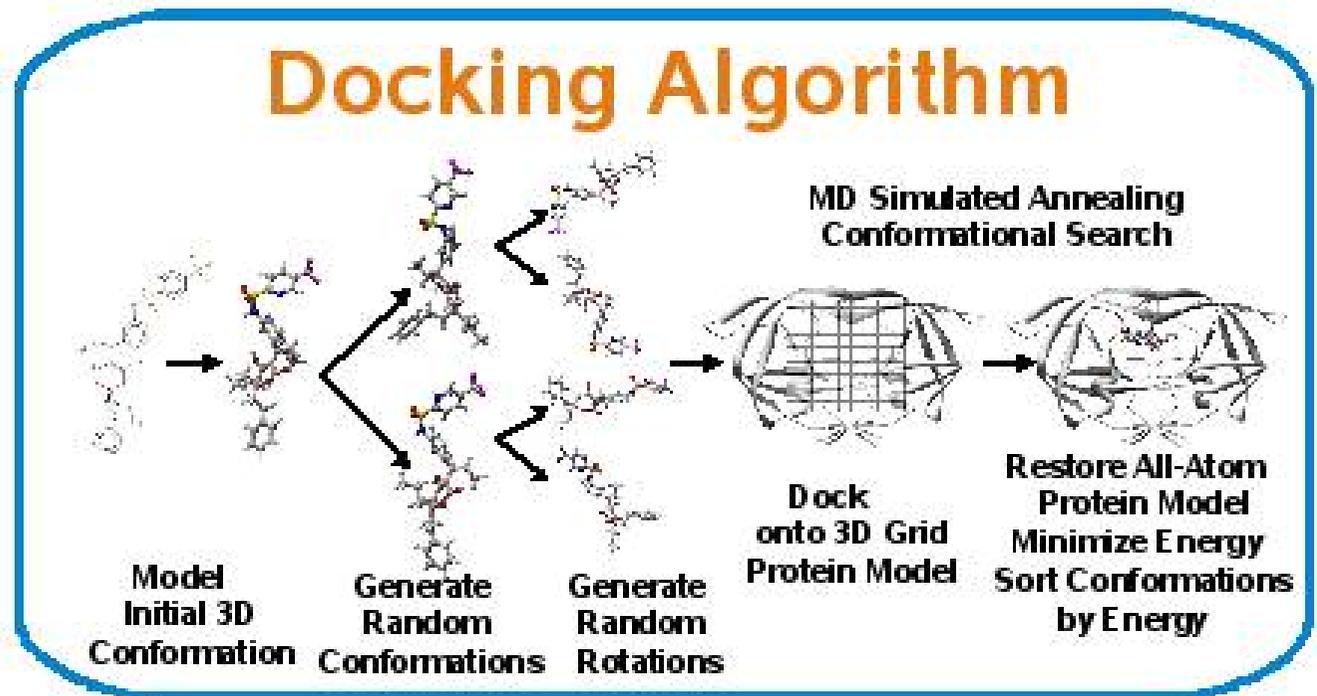
Binding Free Energy from MD

- 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)



Molecular docking

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

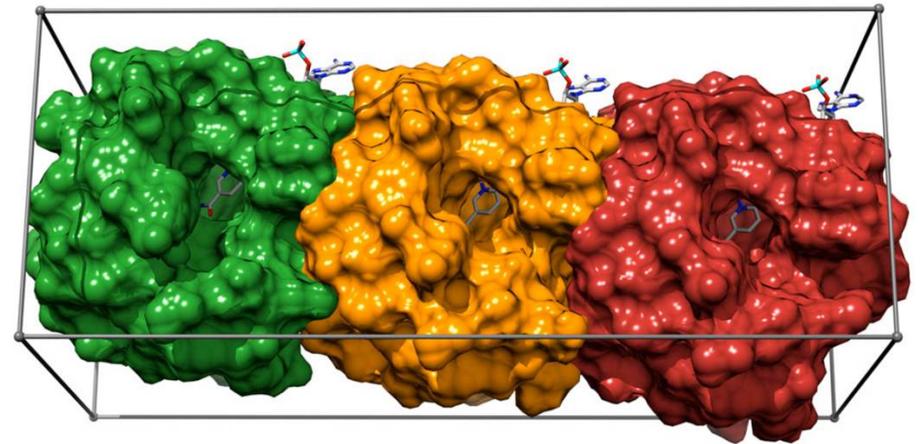


Docking @ home

<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)

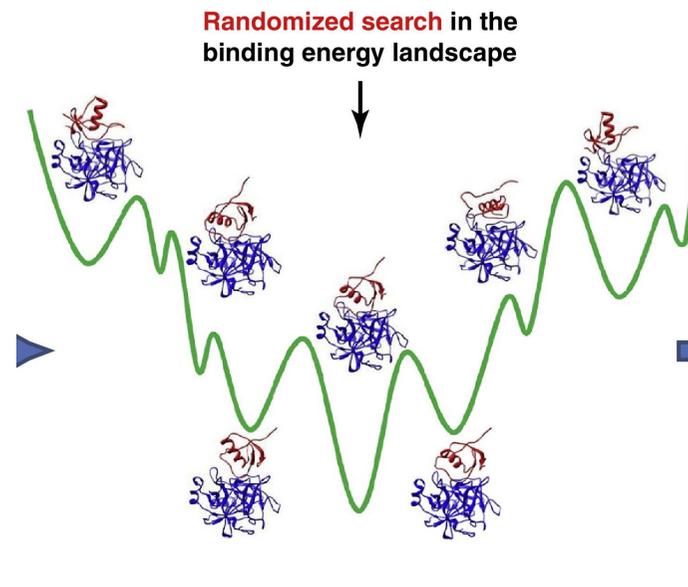
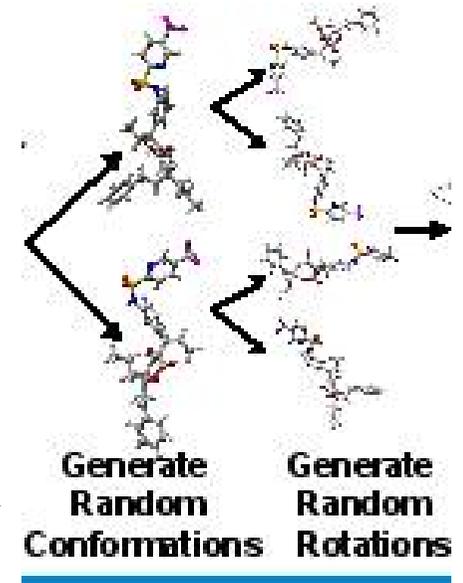


Cosconati, S., Forli, S., Perryman, A.L., Harris, R., Goodsell, D.S. and Olson, A.J., 2010. Virtual screening with AutoDock: theory and practice. *Expert opinion on drug discovery*, 5(6), pp.597-607.

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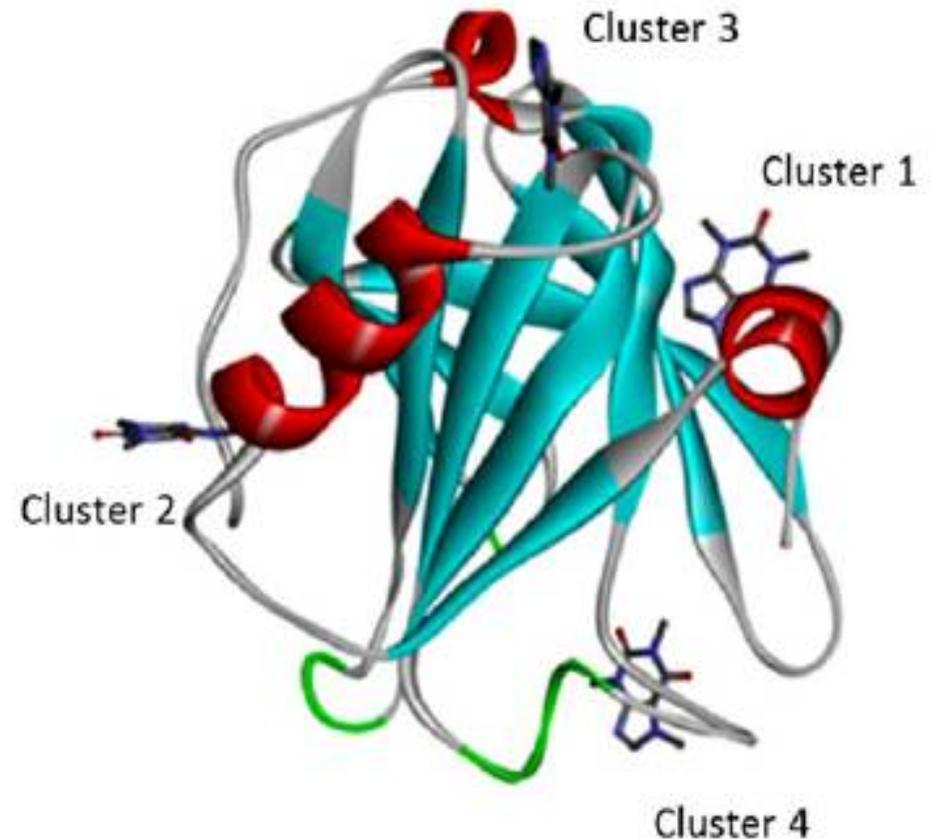
Huang, S.Y., 2014. Search strategies and evaluation in protein-protein docking: principles, advances and challenges. *Drug discovery today*, 19(8), pp.1081-1096.

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)
- 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

Molecular docking

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



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