Binding Free Energy Calculations

- This module will introduce you to:
  - What binding free energy is, and why it is useful to predict.
  - Different types of free energy calculations, and their relative accuracy.

- At the conclusion of this module, you will:
  - Understand the application of binding free energy calculations in research.
  - Review a binding free energy calculation by the replica exchange software, YANK.

This Presentation

What is **binding free energy**?

Free energy of a reaction, and of a binding reaction.
Selectivity and **Affinity**.

Why is it useful to predict **binding free energy**?

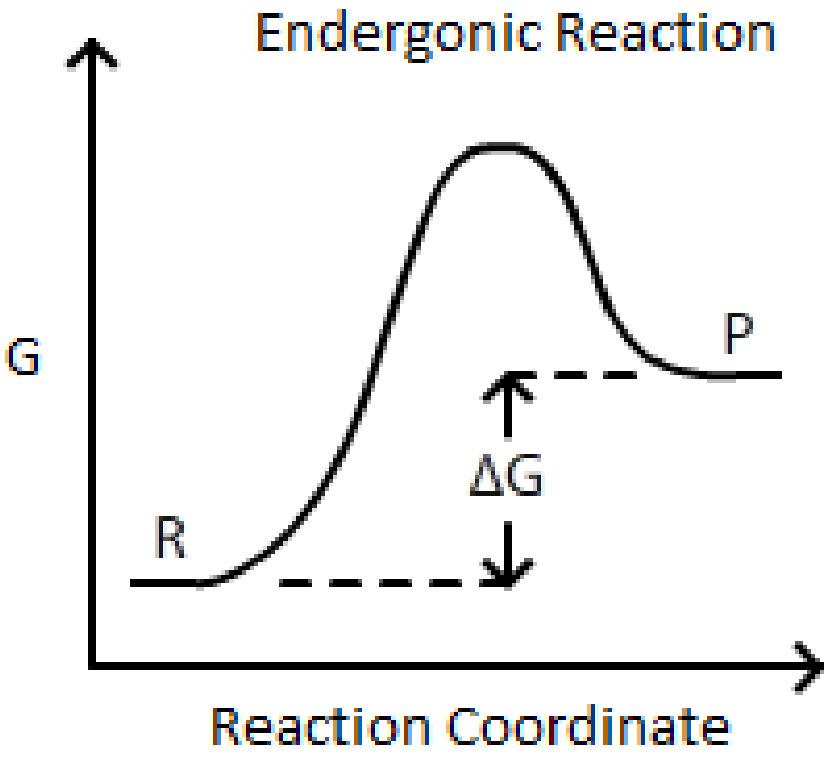
Methods of **predicting binding free energy**.

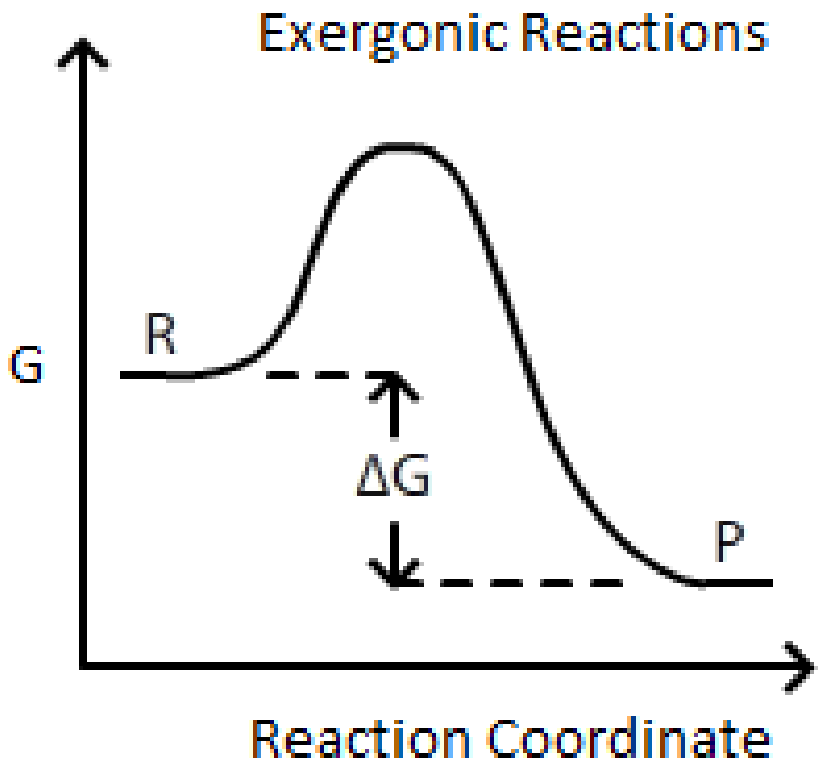
End-Point methods

Alchemical ("Phase space overlap") methods

What is the free energy of a reaction?

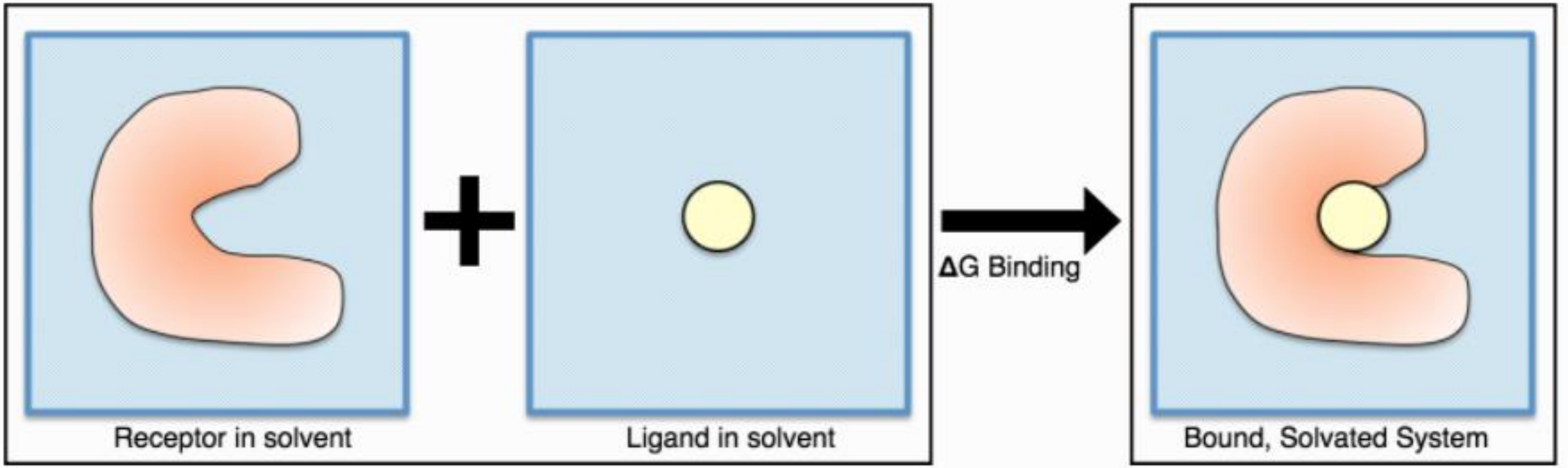
$$\Delta G = \Delta H - T\Delta S = RTln(K_d)$$





https://www.google.com/url?sa=i&url=https%3A%2F%2Fchem.libretexts.org%2FBookshelves%2FAnalytical_Chemistry%2FSupplemental_Modules_(Analytical_Chemistry)%2FElectrochemistry%2FElectrochemistry_and_Thermodynamics&psig=AOvVaw19TUHfYXk_UXc63ZrRB9GY&ust=1647023570005000&source=images&cd=vfe&ved=0CAsQjRxqFwoTCJCPia-XvPYCFQAAAAAdAAAAABAD

What is binding free energy?



Binding free energy is the free energy of a binding reaction.

http://getyank.org/0.22.2/theory.html

Selectivity and Affinity

An effective drug should:

Bind highly selectively, and with high affinity

Selectivity – The ability of the drug to bind to it's target, but not other targets.

Affinity – The ability of the drug to remain bound to the target.

In terms of a stoichiometric reaction:

$$Drug + Protein_{Target} \overset{Kda}{\longleftrightarrow} Complex; \quad Drug + Protein_{NonTarget} \overset{Kdb}{\longleftrightarrow} Complex$$

Affinty – Minimize Kda

Selectivity – Maximize Kdb

$$K_d = \frac{[Drug][Protein]}{[Complex]}$$

Enthalpy and Entropy of Binding

What do you think that the signs of $\Delta G, \Delta H, \Delta S$ are for the following rxn?

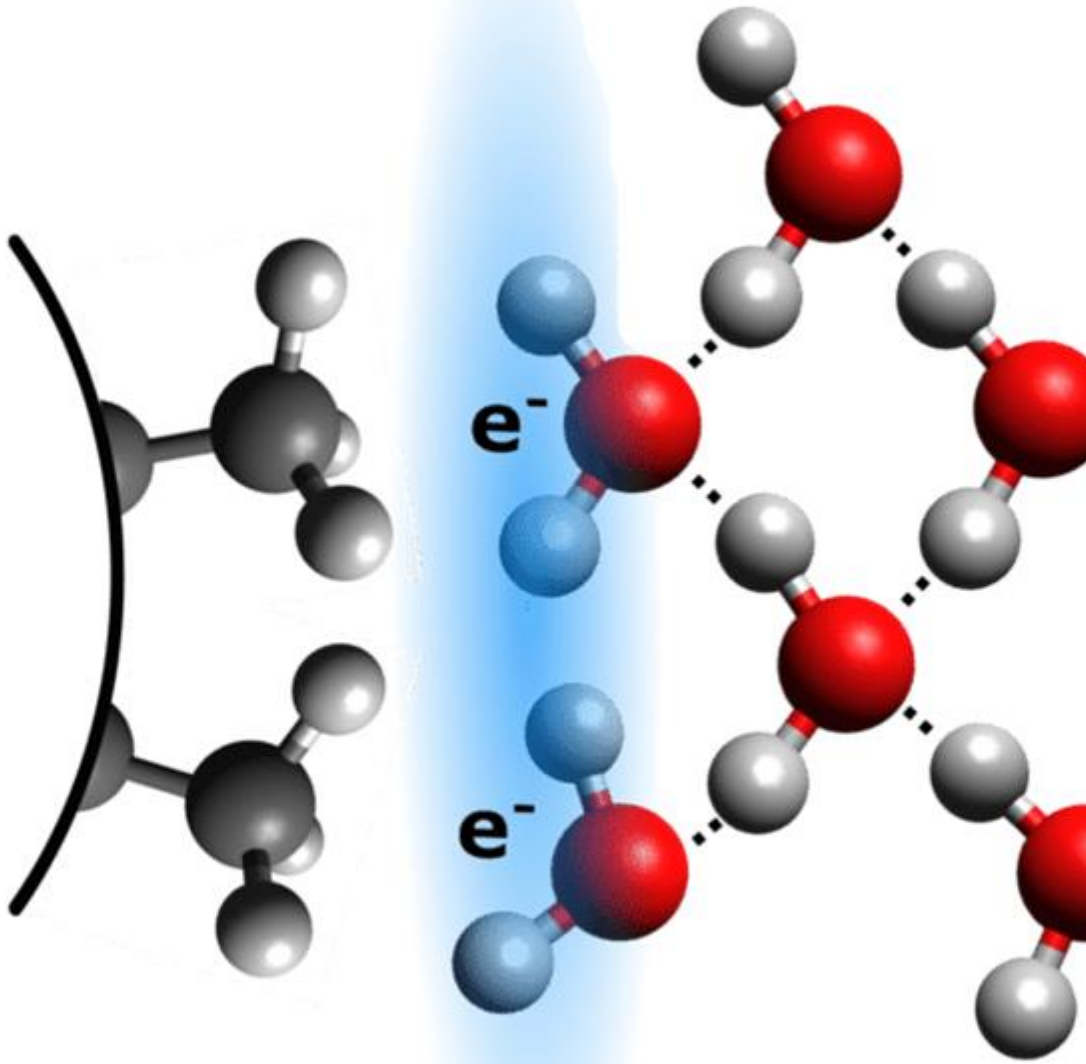
$$\boldsymbol{Drug_{aq} + Protein_{aq} \leftrightarrow Complex_{aq}}$$

The Hydrophobic Effect – An entropically driven process

Fats do not engage in hydrogen bonds with water.

The surface area of the "vacant" space left by the lack of interaction between water and hydrophobic is the basis of Hydrophobic Surface Area

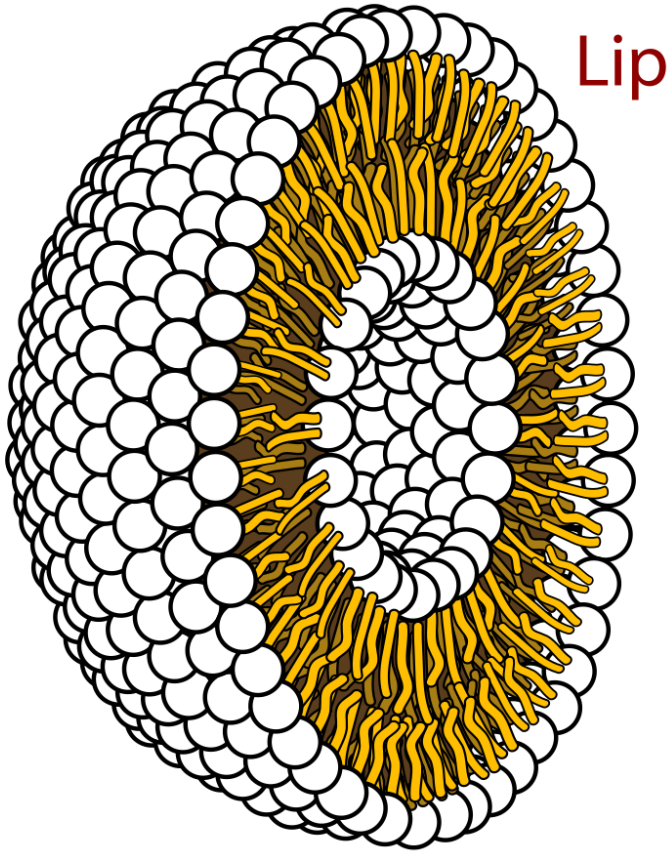
Hydrophobic Surface Area in contact with water is entropically unfavorable and is therefore "buried" whenever possible. This is the basis of the Hydrophobic Effect.

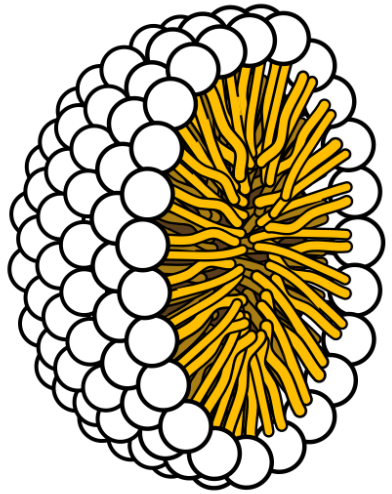


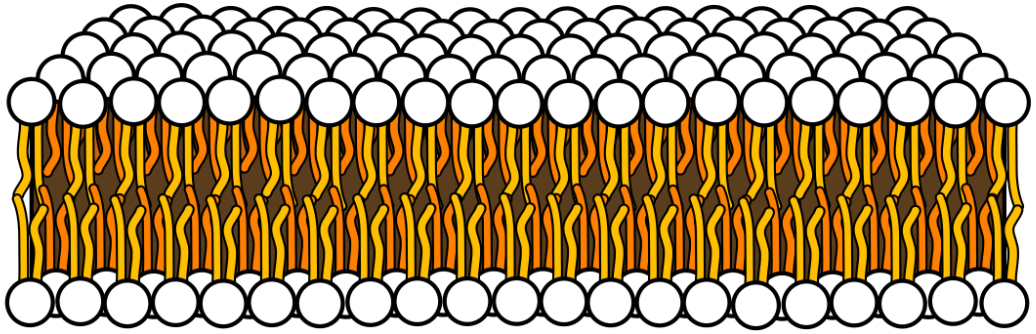
Burial of Hydrophobic Surface Area by Aggregation

The Hydrophobic effect is responsible for the aggregation of fats (lipids) in water.

The structures presented at right all derive stability from the hydrophobic effect.

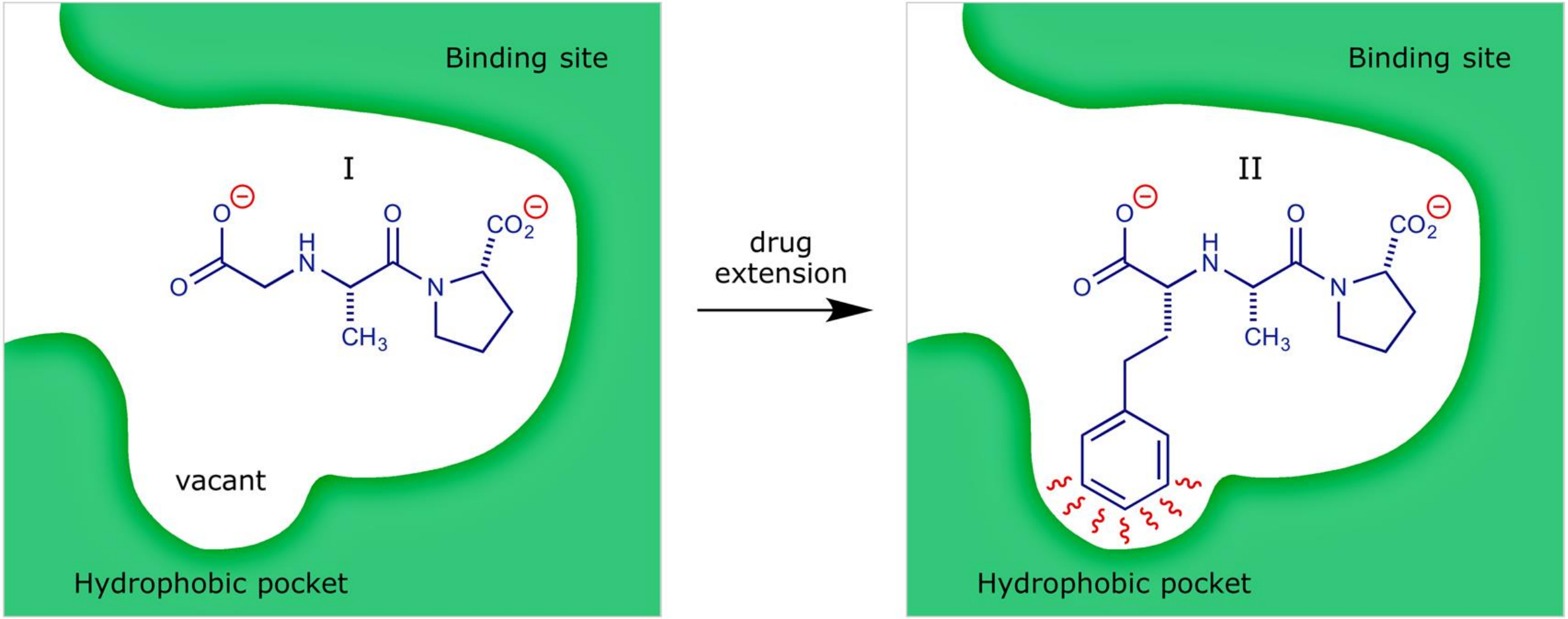






https://www.google.com/imgres?imgurl=https%3A%2F%2Fupload.wikimedia.org%2Fwikipedia%2Fcommons%2Fthumb%2Fc%2Fc6%2FPhospholipids_aqueous_solution_structures.svg%2F1200px-Phospholipids_aqueous_solution_structures.svg.png&imgrefurl=https%3A%2F%2Fen.wikipedia.org%2Fwiki%2FMicelle&tbnid=IxuWMcfHm8DoLM&vet=12ahUKEwj0gIzZvbz2AhXLPM0KHZUhBXkQMygAegUIARDZAQ..i&docid=nPCQd4EaFsOaXM&w=1200&h=1476&q=formaiotion%20of%20micelles&client=opera-gx&ved=2ahUKEwj0gIzZvbz2AhXLPM0KHZUhBXkQMygAegUIARDZAQ

Hydrophobicity of binding sites



https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.stereoelectronics.org%2FwebDD%2FDD_04.html&psig=AOvVaw2iQZ1fFnfos2tQ4IF72BM7&ust=1647033787525000&source=images&cd=vfe&ved=0CAsQjRxqFwoTCJDVrpi9vPYCFQAAAAAdAAAAABAD

Enthalpy of a binding interaction

The formation of an H-bond between the drug and protein may have a reaction similar to the one below…

$$ProteinNH \cdots OH_2 + HOH \cdots ODrug \rightarrow ProteinNH \cdots ODrug + 2HOH$$

In the above reaction, hydrogen bonds between the solvent and protein/ligand are broken, so hydrogen bonds between the protein and drug can form.

Energy is required (enthalpy is positive) upon breakage of bonds

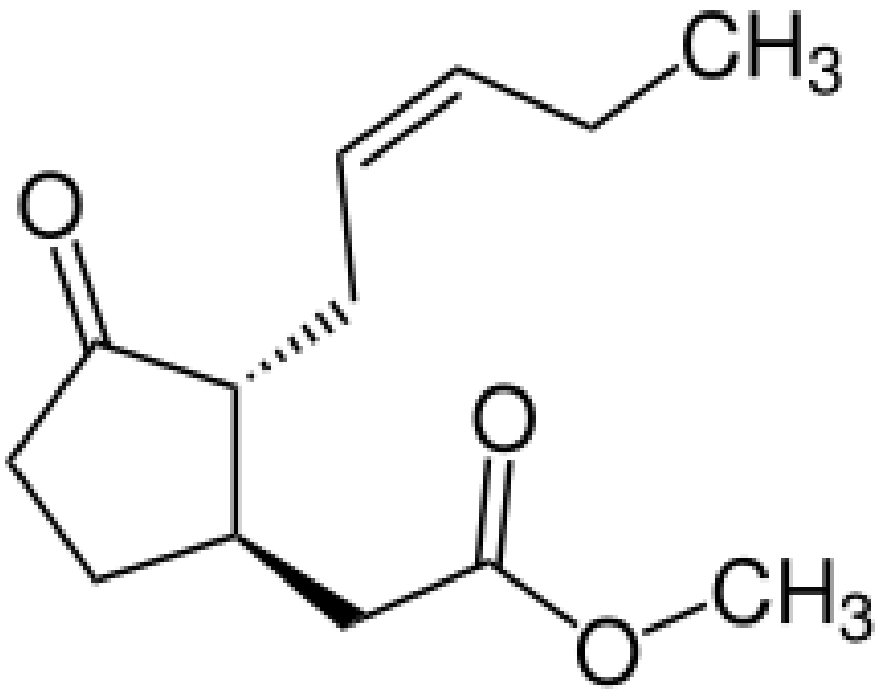
Energy is liberated (enthalpy is negative) upon formation of bonds

https://www.google.com/imgres?imgurl=https%3A%2F%2Fupload.wikimedia.org%2Fwikipedia%2Fcommons%2Fthumb%2Fc%2Fc6%2FPhospholipids_aqueous_solution_structures.svg%2F1200px-Phospholipids_aqueous_solution_structures.svg.png&imgrefurl=https%3A%2F%2Fen.wikipedia.org%2Fwiki%2FMicelle&tbnid=IxuWMcfHm8DoLM&vet=12ahUKEwj0gIzZvbz2AhXLPM0KHZUhBXkQMygAegUIARDZAQ..i&docid=nPCQd4EaFsOaXM&w=1200&h=1476&q=formaiotion%20of%20micelles&client=opera-gx&ved=2ahUKEwj0gIzZvbz2AhXLPM0KHZUhBXkQMygAegUIARDZAQ

Enthalpy and Entropy of Binding – Short Quiz

What do you think that the signs of $\Delta G, \Delta H, \Delta S$ are for the binding reaction between this drug and a protein?

$$\boldsymbol{Drug_{aq} + Protein_{aq} \leftrightarrow Complex_{aq}}$$



What parts of the drug (predominantly) effect:

ΔH (Enthalpy)?

ΔS (Entropy)?

Short Review #1 – Discuss then answer

How is **binding free energy** related to **binding affinity and selectivity**?

What factors contribute to the **Enthalpy** of a binding reaction?

What factors contribute to the **Entropy** of a binding reaction?

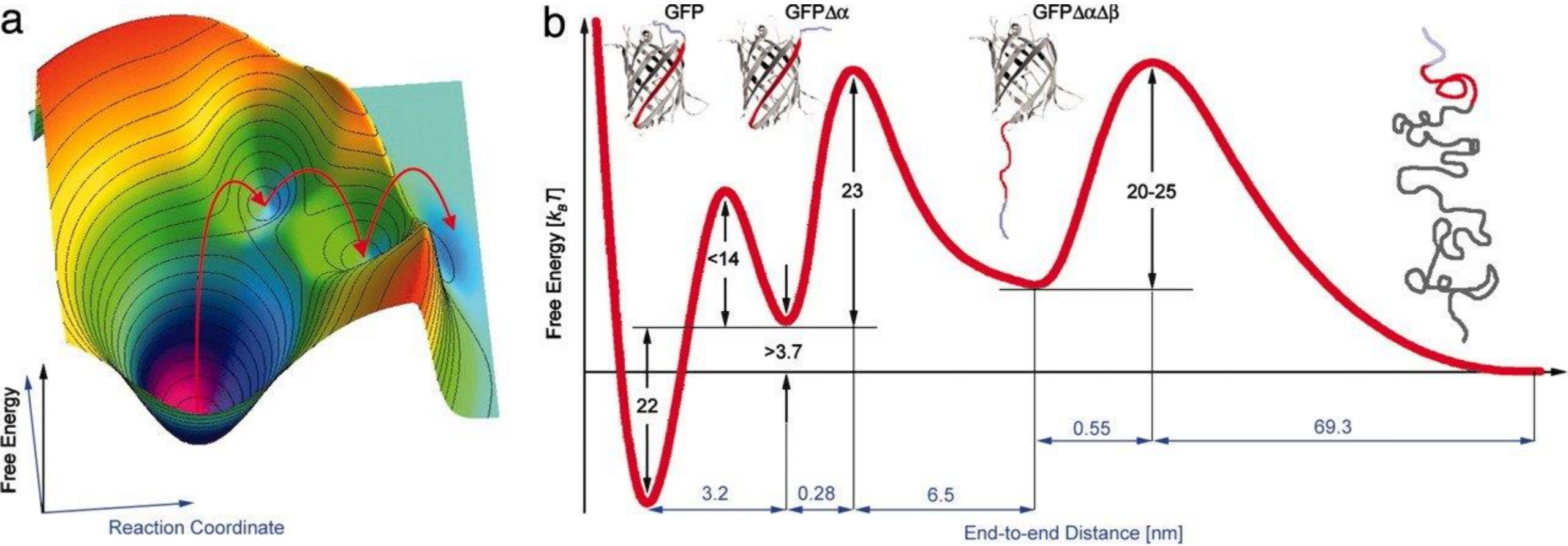
Why predict binding free energy?

Binding free energy is **mathematically related to binding affinity**, and therefore **ideally suited for ranking potential drugs' affinity.**

Binding free energy is **observable in an experimental laboratory,** via techniques such as **Isothermal Titration Calorimetry**.

Binding free energy is **an ensemble property**.

How to predict the free energy differences between states



How to predict the free energy differences between states

End-Point

- Simulate the two states of interest in realistic conditions.
- Intermediate computational expense, compared to docking and alchemical methods.
- Better correlation with experiment than docking alone.

Alchemical

- Simulate realistic states, as well as non-existent intermediates.
- Greatest computational expense.
- Best correlation with experiment.

MMPBSA and MMGBSA – A popular end point method

- The free energy of a state (P, L, PL) is defined as the sum of:
  - MM energy from bonds **(Bonded Interactions)**.
  - Electrostatics and Van der Waals interactions **(Non-Bonded Interactions)**.
  - Polar and non-polar solvation energies.
  - Entropy

$$G = E_{\text{bnd}} + E_{\text{el}} + E_{\text{vdW}} + G_{\text{pol}} + G_{\text{np}} - TS \tag{5}$$

$$\Delta G_{\text{bind}} = \langle G_{\text{PL}} \rangle_{\text{PL}} - \langle G_{\text{P}} \rangle_{\text{P}} - \langle G_{\text{L}} \rangle_{\text{L}} \tag{6}$$

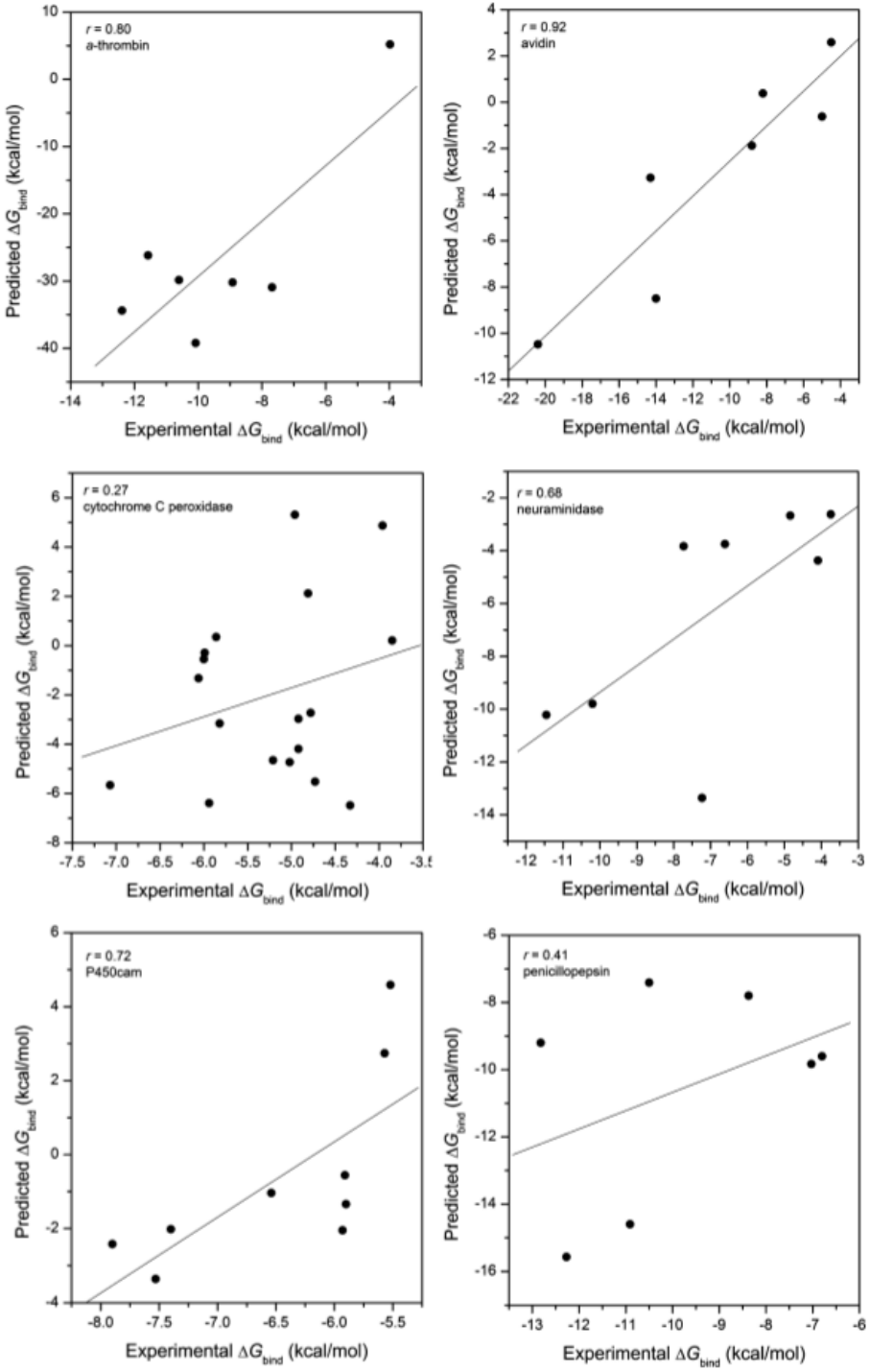
$$\Delta G_{\text{bind}} = \langle G_{\text{PL}} - G_{\text{P}} - G_{\text{L}} \rangle_{\text{PL}} \tag{7}$$

MMPBSA and MMGBSA – How Accurate is it?

At right, the free energy change of 59 ligands binding to:

Alpha-Thrombin	Avidin
Cytochrome C peroxidase	Neuraminidase
P450cam	Penicillopepsin

Is evaluated by MMPBSA and compared to experiment.

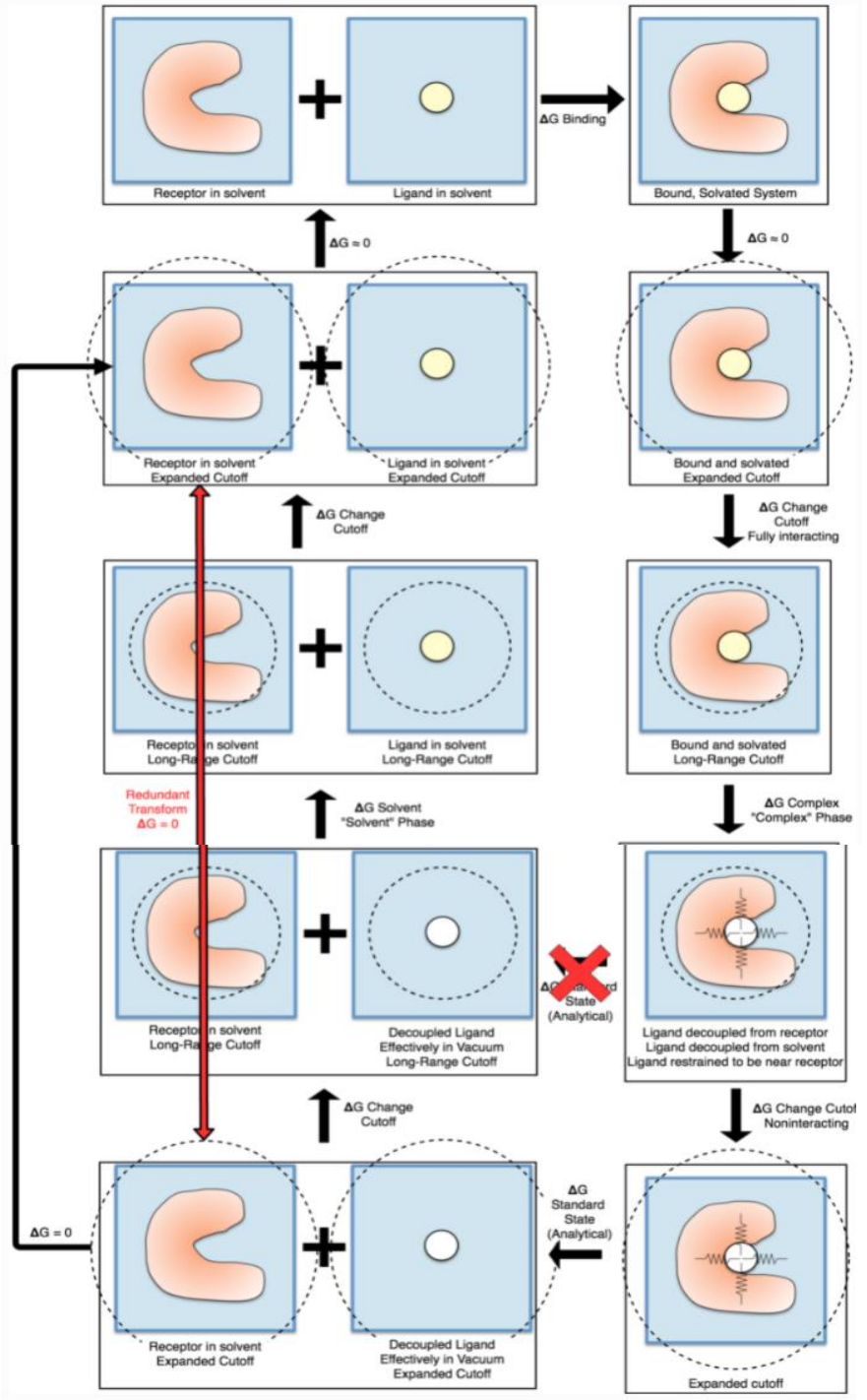


Alchemical Free Energy Methods – Thermodynamic Cycles

What is a **Thermodynamic Cycle?**

Free Energy is a **State Function**

A **state function** has the same result **regardless of the path taken.**



Alchemical Free Energy methods what makes it alchemical?

Artificial Addition and deletion of forces which are not physiologically present.

Restraints

End-to-end elongation

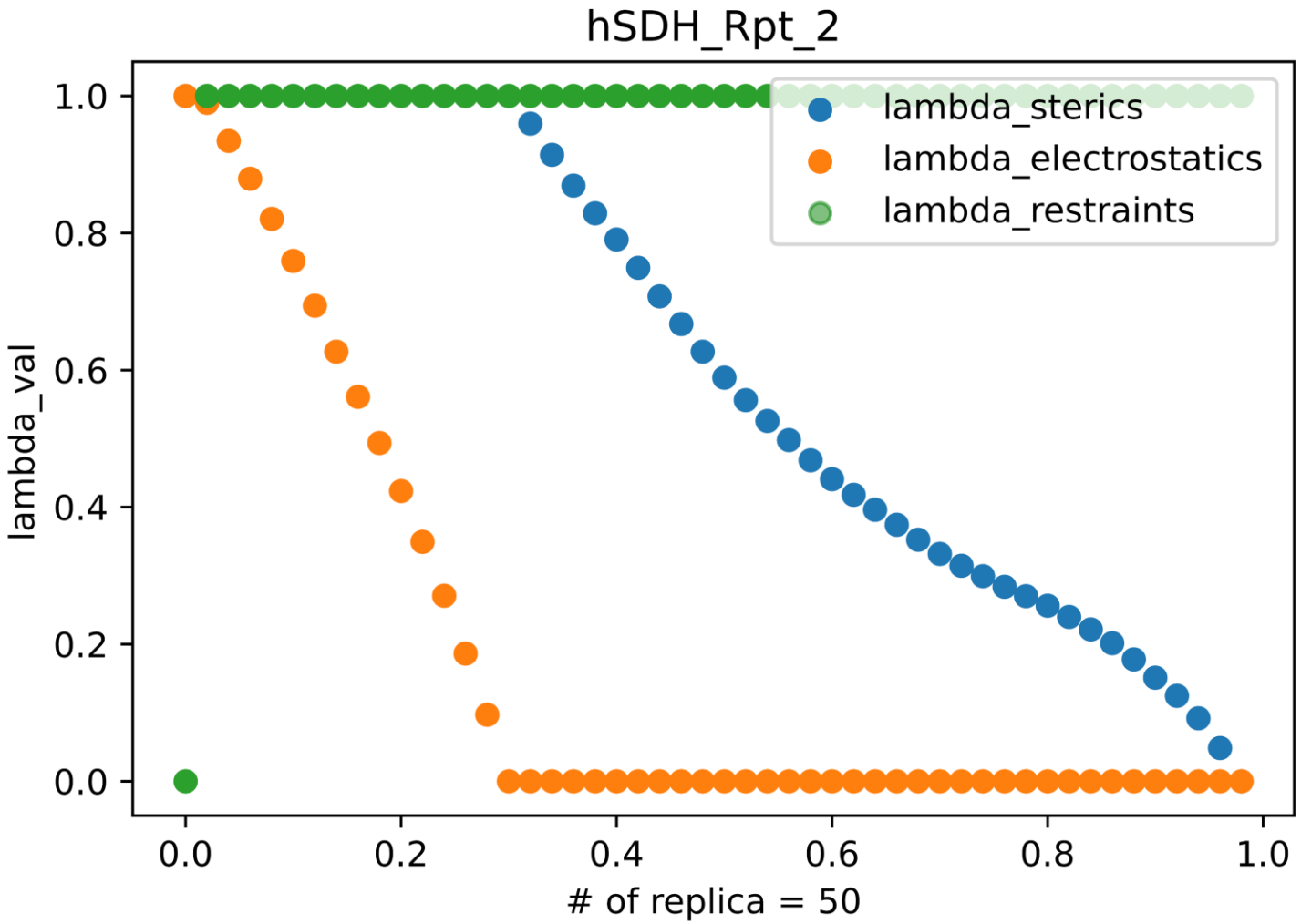
Lambda Nonbonded Interactions

Center of Mass Force

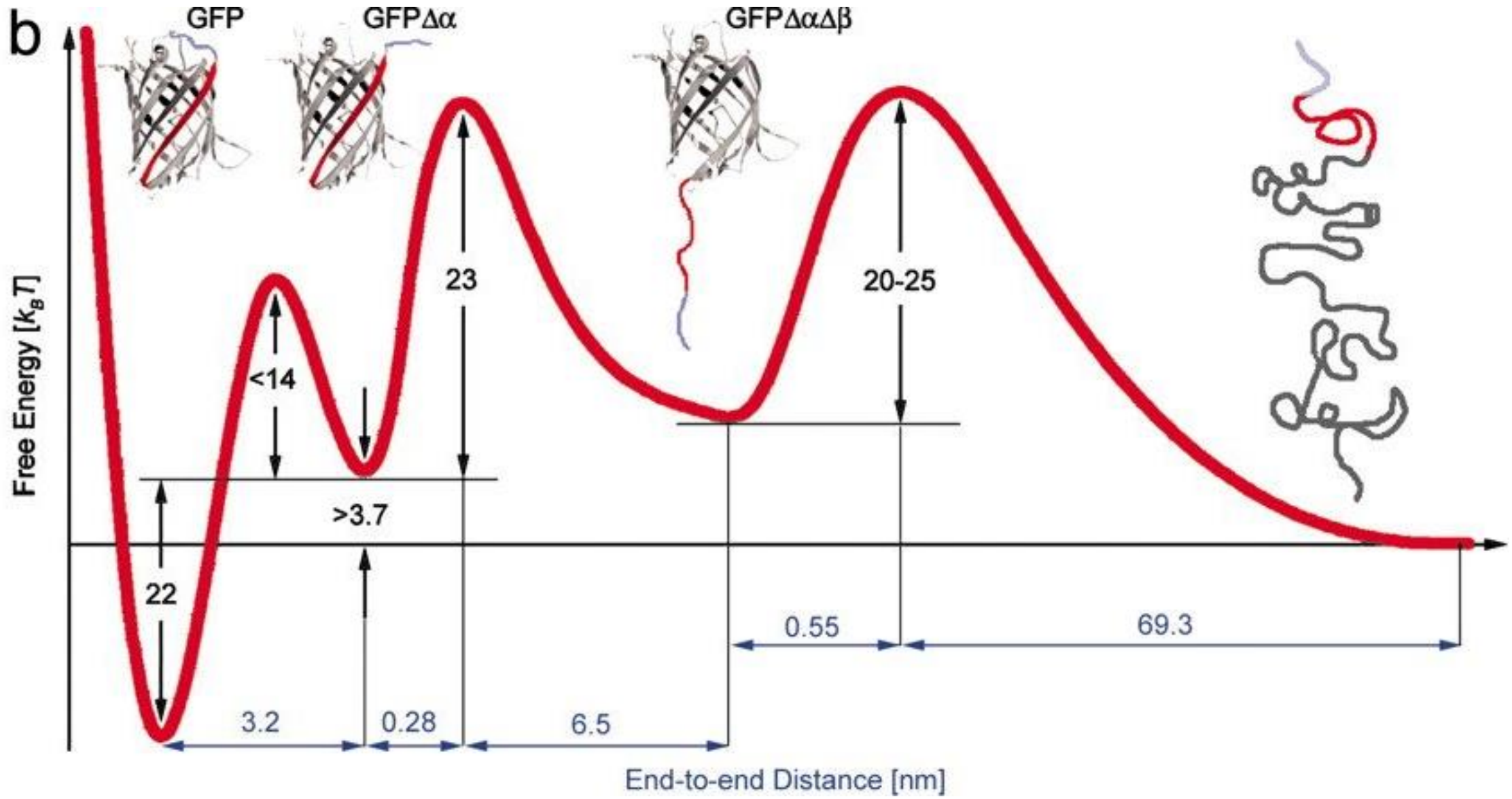
Alchemical Free Energy methods – Lambda Electrostatics and Sterics

One replica exchange package, YANK, utilizes a series of intermediates called **Lambda Windows**.

The value of **Lambda** for restraints, electrostatics, and sterics for one YANK experiment is plotted at right.



Alchemical Free Energy methods



The Final Short Review

Why is it **useful to computationally predict** the binding free energy between a protein and ligand?

What are the benefits and drawbacks of **End-Point BFE Calculations?**

What are the benefits and drawbacks of **Alchemical BFE Calculations?**

Why are alchemical calculations called **'Alchemical'?**