

# BIOC404 Biochemical Methods

## Introduction to Biomolecular Simulations

Dr. Erich Kuechler

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My Office Doesn't Matter Anymore

# Introduction to biomolecular simulation

**Lecture 1:**  
Molecular Dynamics  
& Ensembles

**Lecture 2:**  
Force Fields &  
Solvation Models

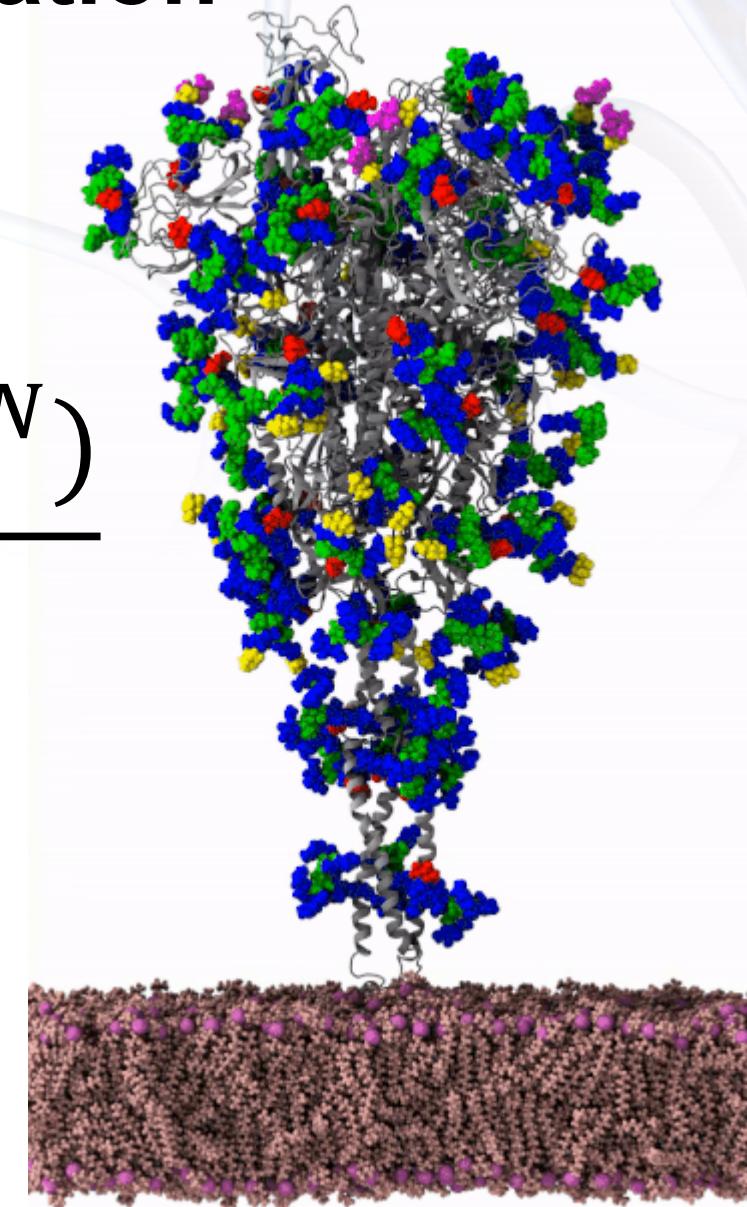
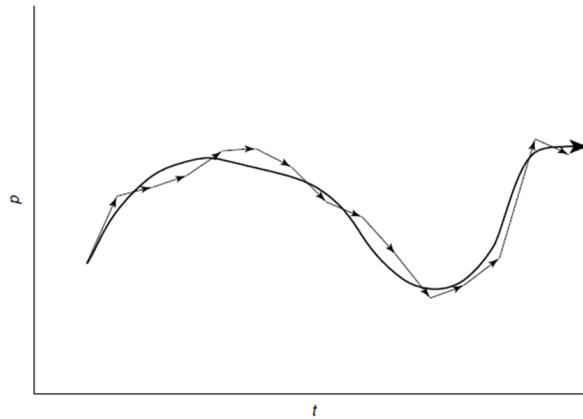
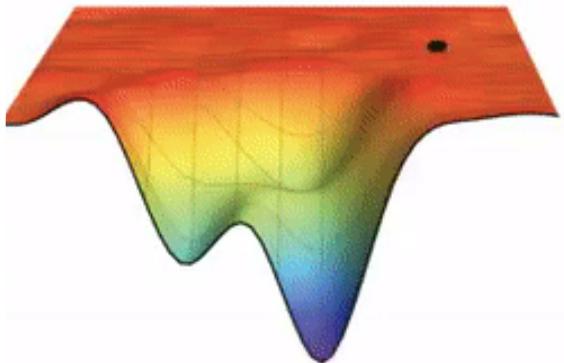
**Lecture 3:**  
Enhanced Sampling  
Methods

**Assignment:**  
Analyze simulation output and relate the findings to concepts introduced by the course.

# Introduction to biomolecular simulation

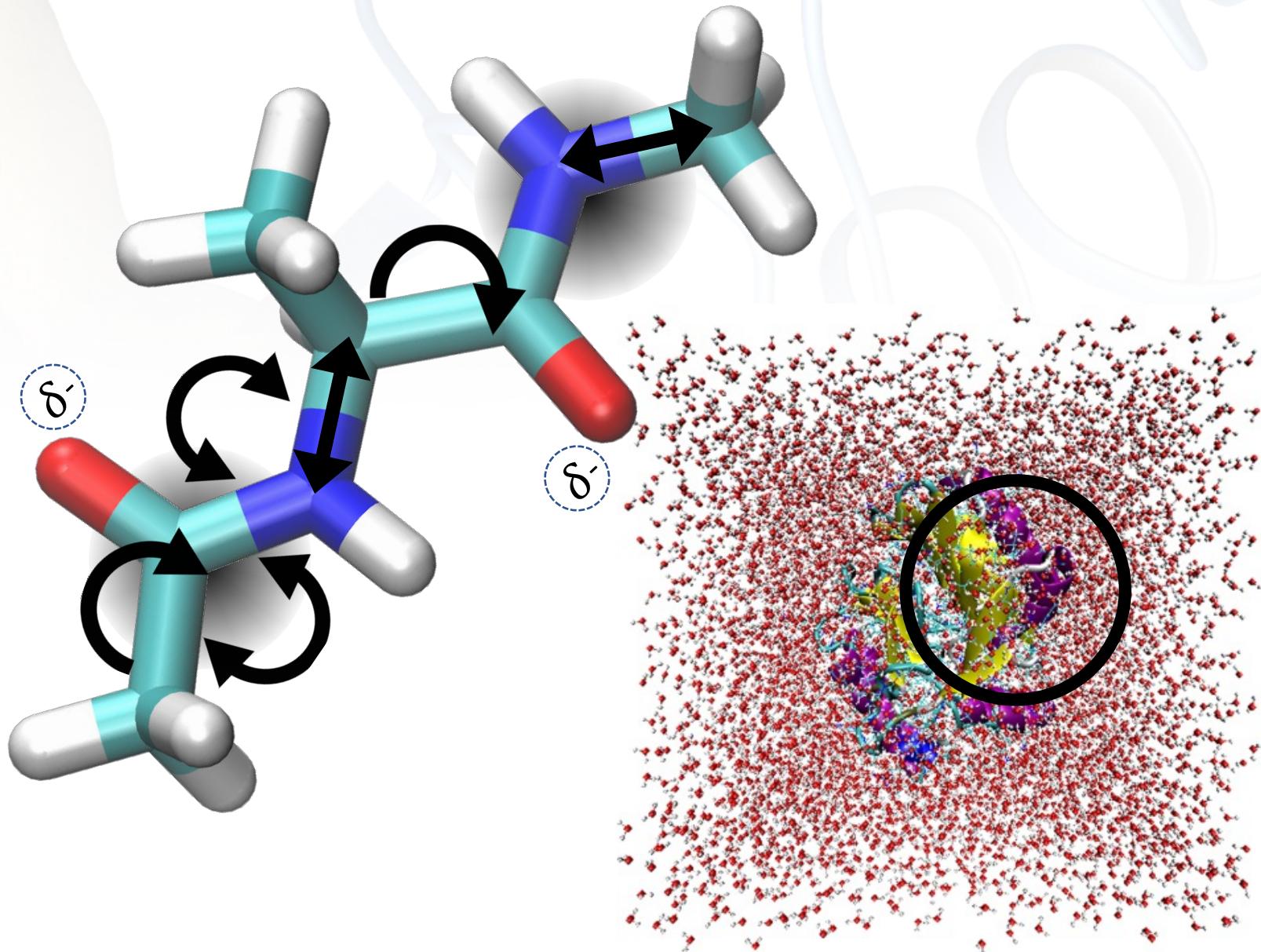
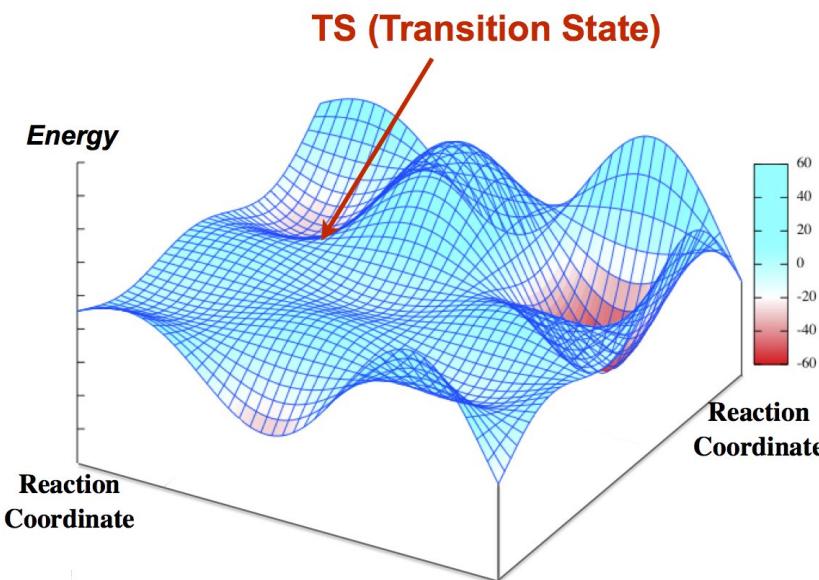
Lecture 1:  
Molecular Dynamics  
& Ensembles

$$\mathbf{F}_i = \dot{\mathbf{p}}_i - \frac{\partial U(\mathbf{r}^N)}{\partial \mathbf{r}_i}$$

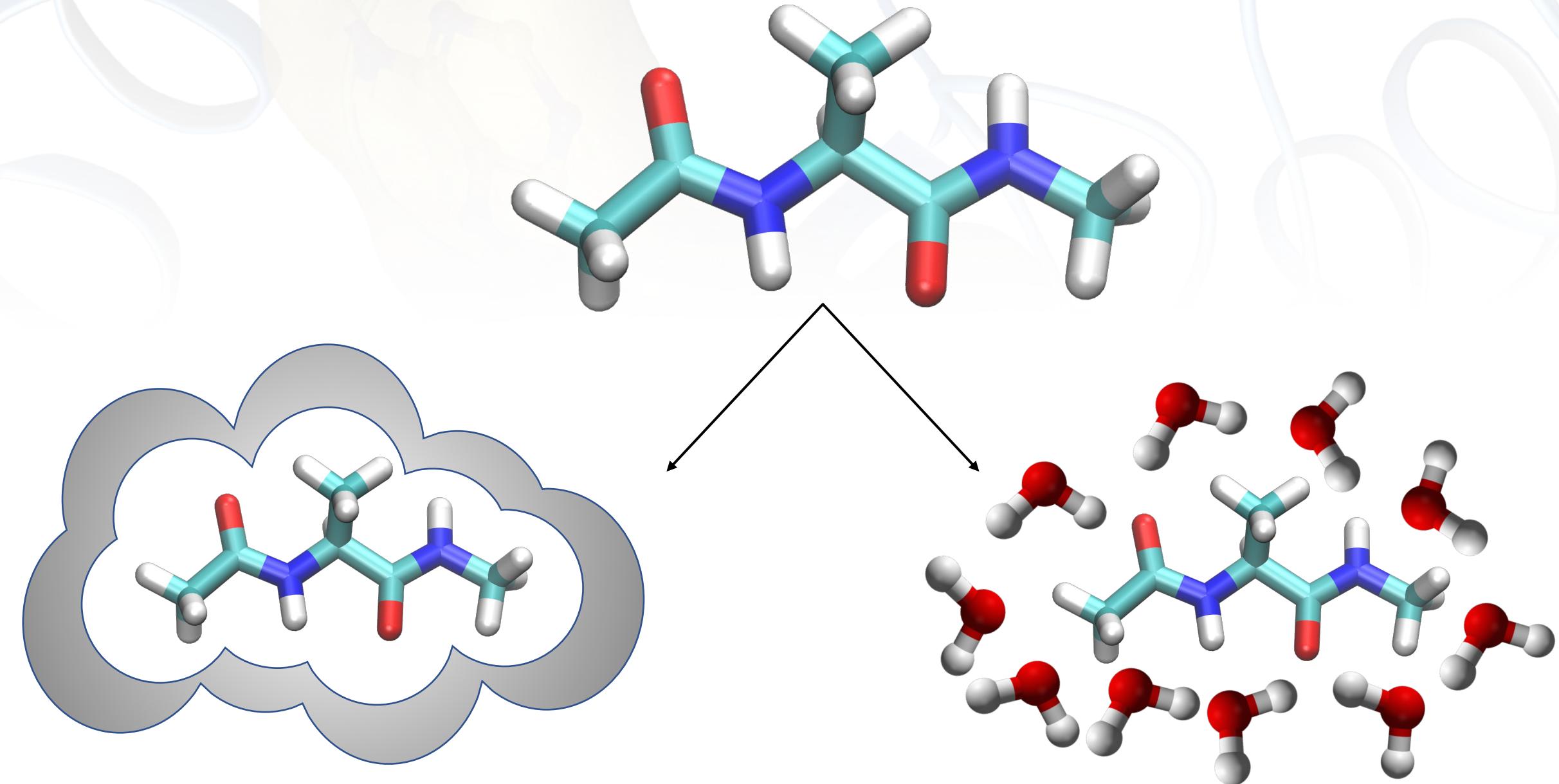


# Introduction to biomolecular simulation

## Lecture 2: Force Fields & Solvation Models



# Molecular Dynamics Solvation



# Molecular Dynamics Solvation

$$\Delta G = \Delta H - T\Delta S$$

$$\Delta G_F = \Delta G_f - \Delta G_u$$



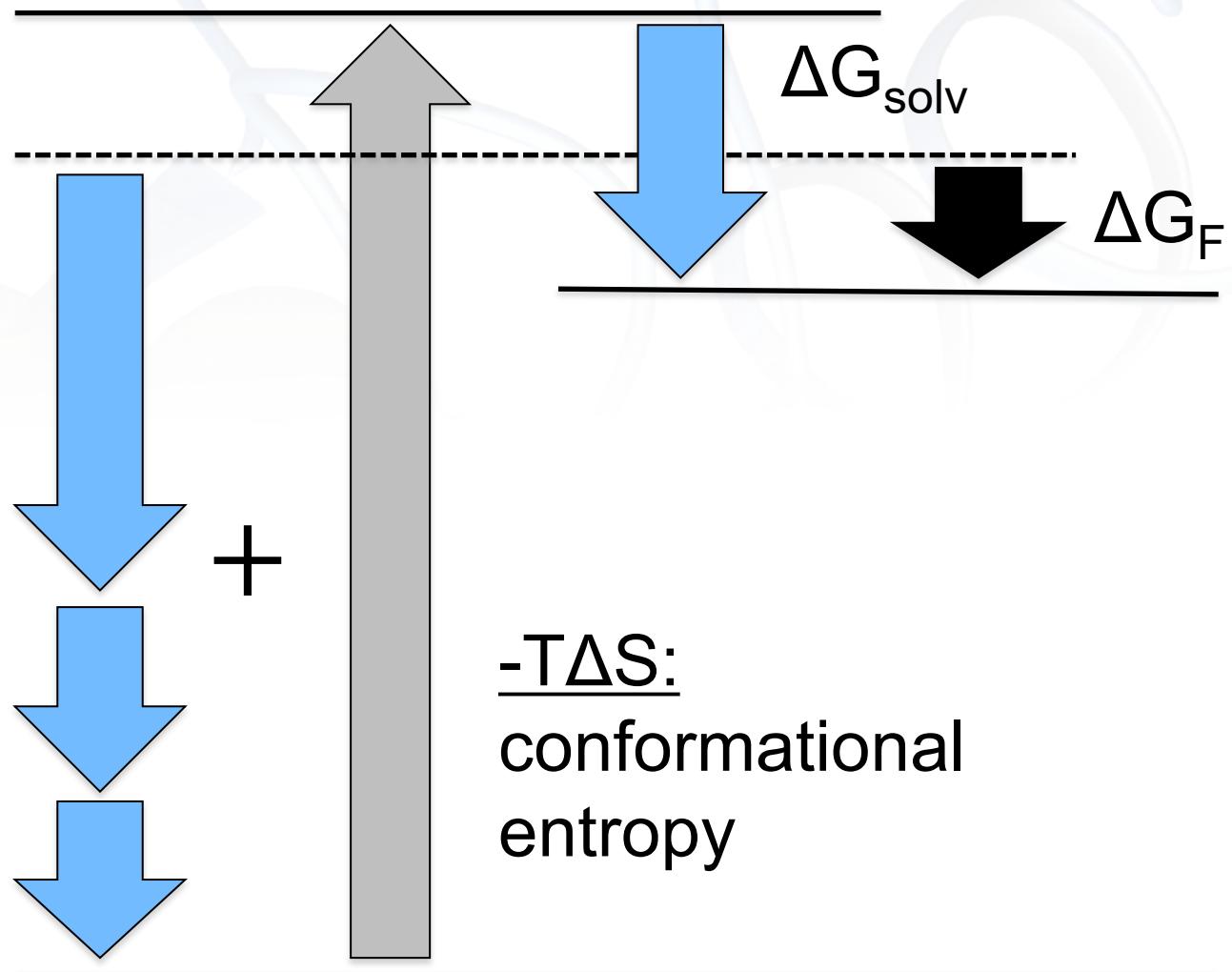
$\Delta H$ :  
hydrogen bonds

van der Waals

electrostatic

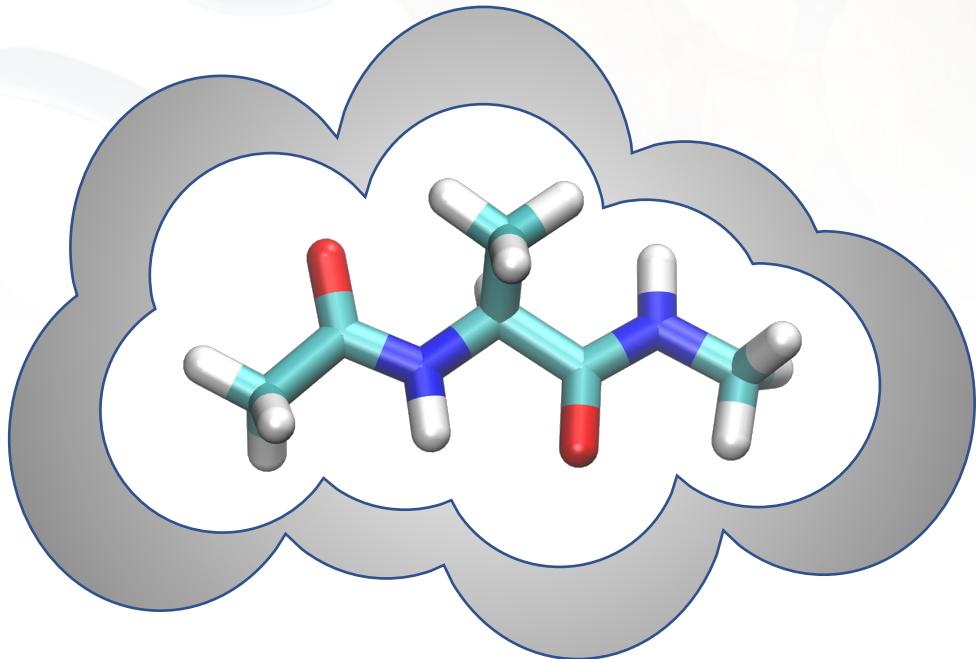
+

$-T\Delta S$ :  
conformational entropy



Protein (solute) in water

# Molecular Dynamics Solvation



Implicit solvation, or **continuum solvent models**, uses a bulk polarizable medium for electrostatic screening and non-bonded interactions.

## Advantages:

- Lower computational cost
- Fast convergence
- Allows for high-level solutes

## Disadvantages:

- Additional terms added to MM FF
- It averages everything out

# Molecular Dynamics Solvation

$$\Delta G = \Delta H - T\Delta S$$

$$\Delta G_F = \Delta G_f - \Delta G_u$$



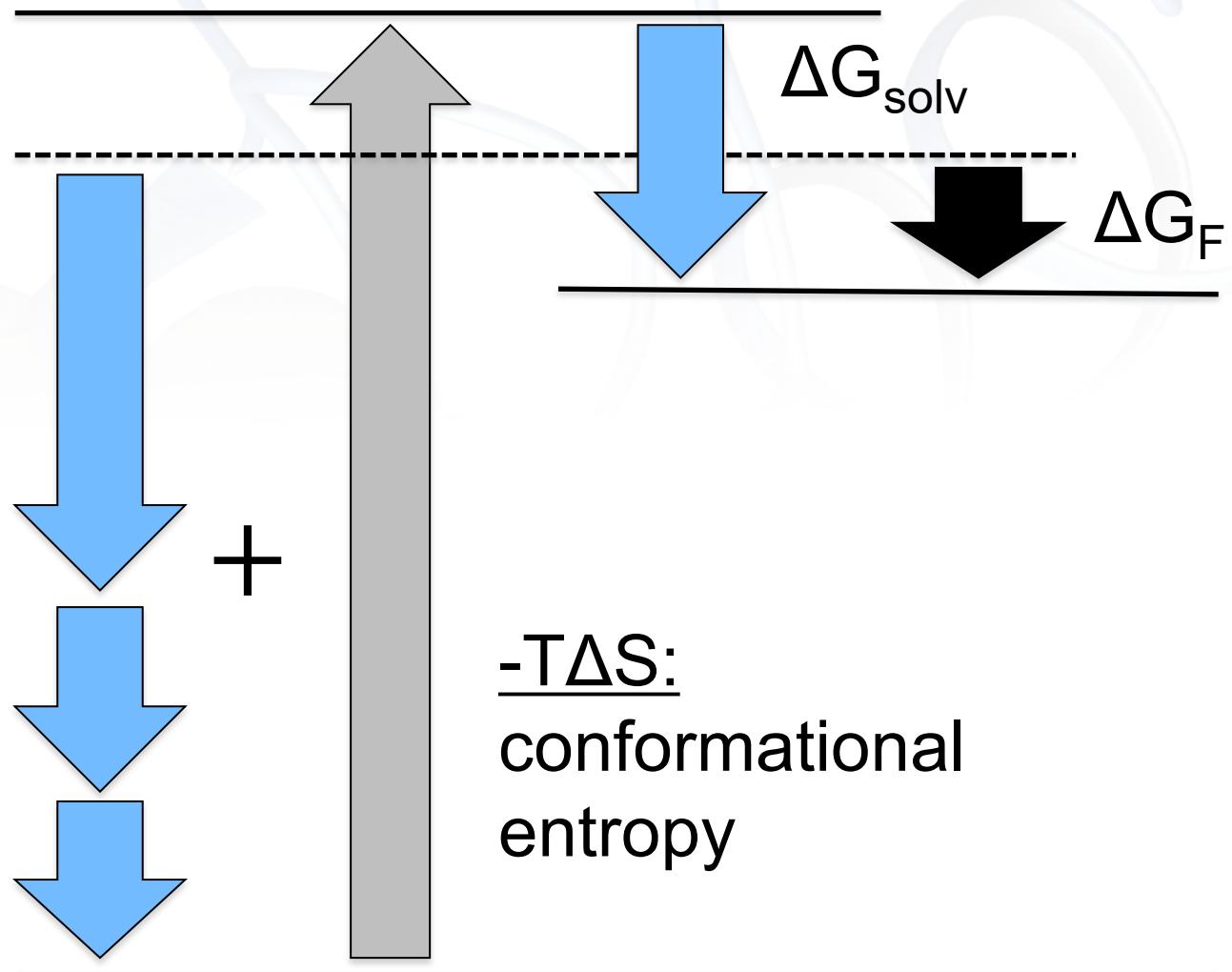
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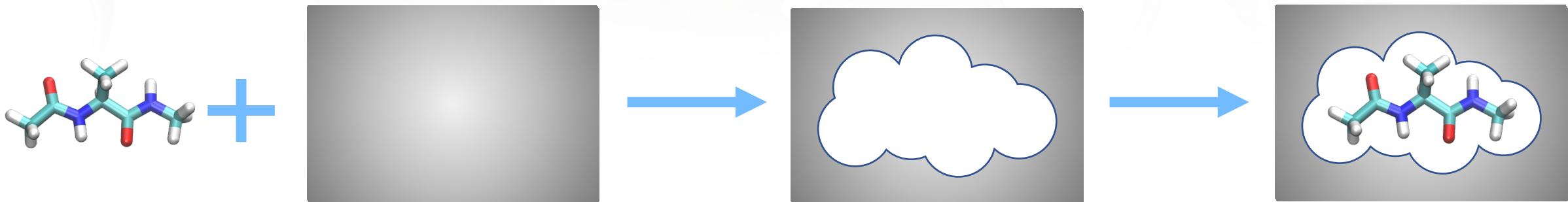
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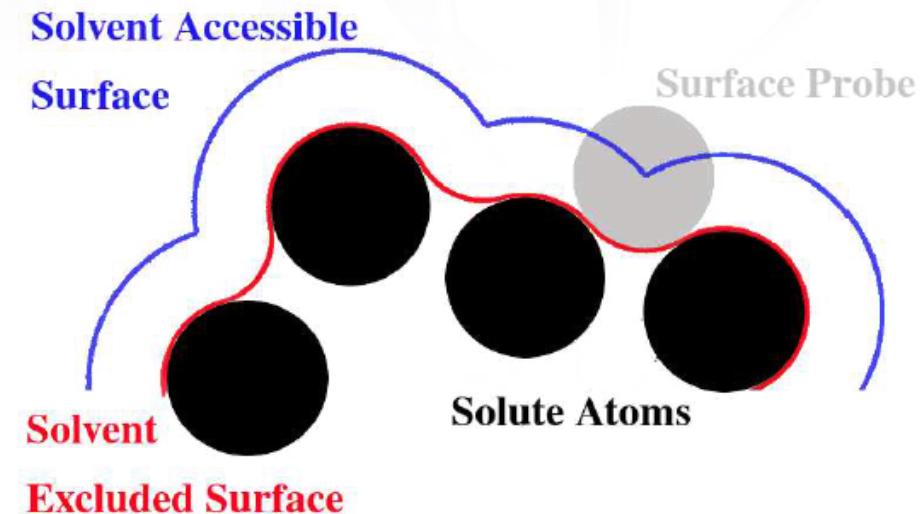
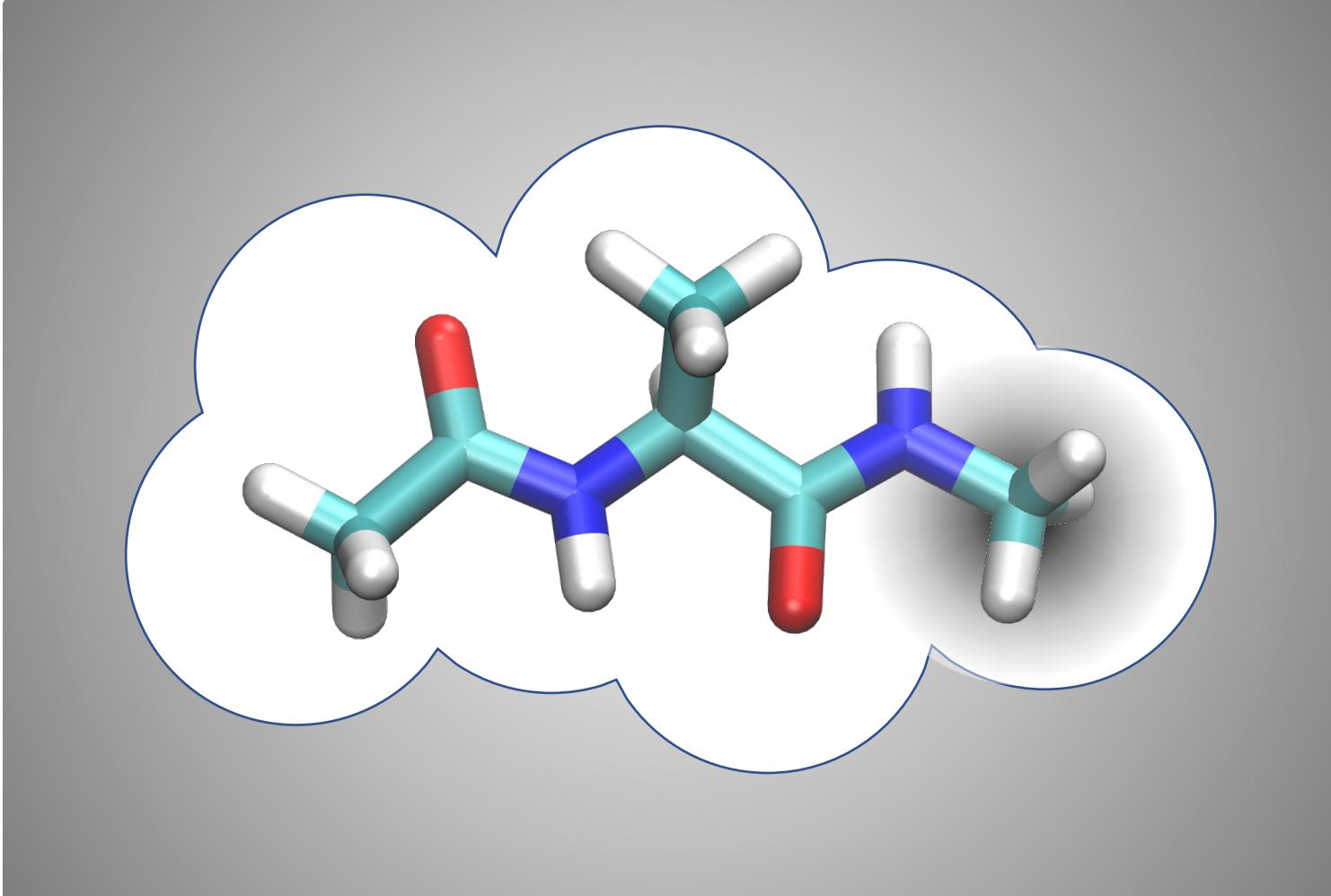
# Molecular Dynamics Solvation

$$\Delta G_{\text{solv}} = \Delta G_{\text{cav}} + \Delta G_{\text{vdw}} + \Delta G_{\text{ele}}$$



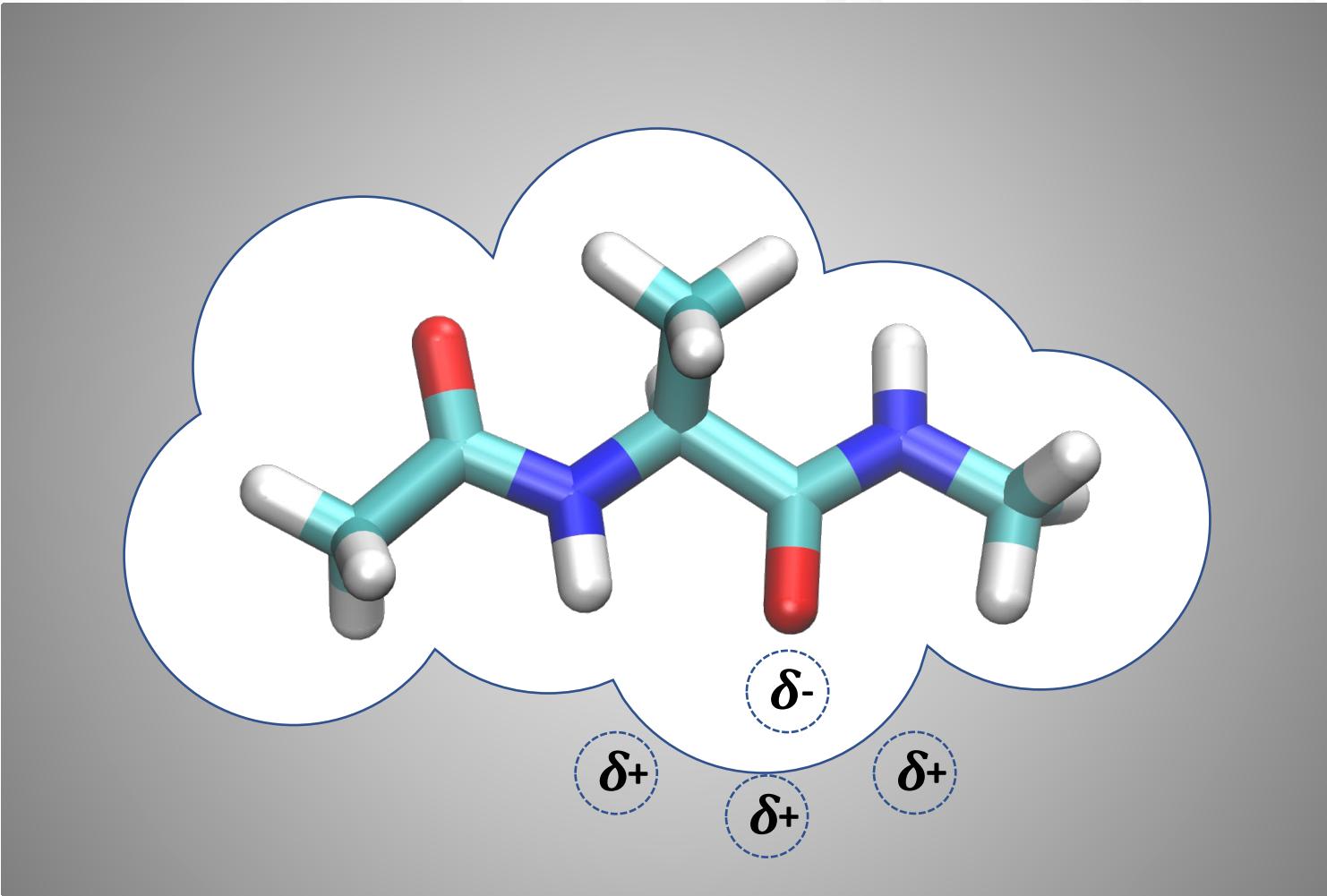
# Molecular Dynamics Solvation

$$\Delta G_{\text{cav}} + \Delta G_{\text{vdW}}$$



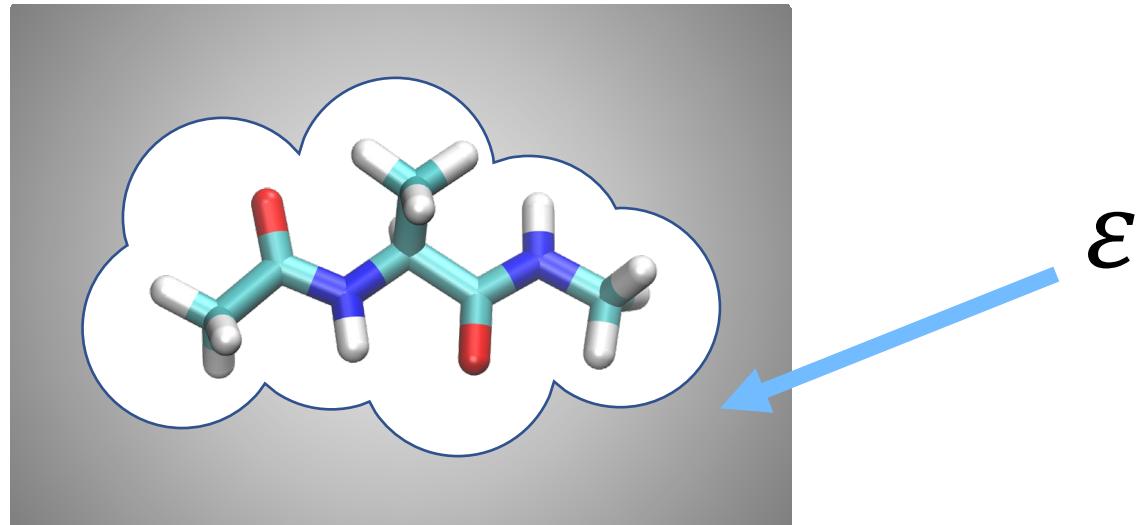
# Molecular Dynamics Solvation

$$\Delta G_{\text{ele}}$$



# Molecular Dynamics Solvation

$$\Delta G_{\text{ele},ij} = \frac{1}{2} \left( 1 - \frac{1}{\epsilon} \right) \sum_{i=1}^N \sum_{j=1}^N \frac{q_i q_j}{f(r_{ij}, a_{ij})}$$

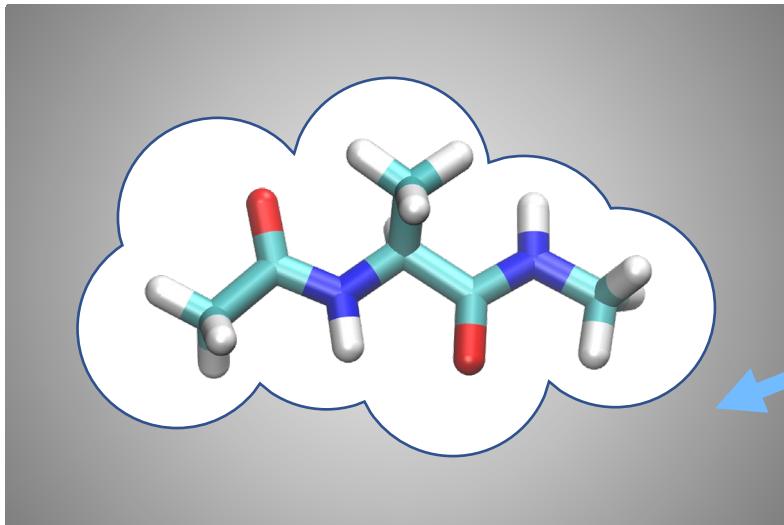


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Material	Dielectric constant $\epsilon$
Vacuum	1.0000
Air (1 atm)	1.0006
Paraffin	2.2
Polystyrene	2.6
Vinyl (plastic)	2–4
Paper	3.7
Quartz	4.3
Oil	4
Glass, Pyrex	5
Rubber, neoprene	6.7
Porcelain	6–8
Mica	7
Water (liquid)	80
Strontium titanate	300

# Molecular Dynamics Solvation

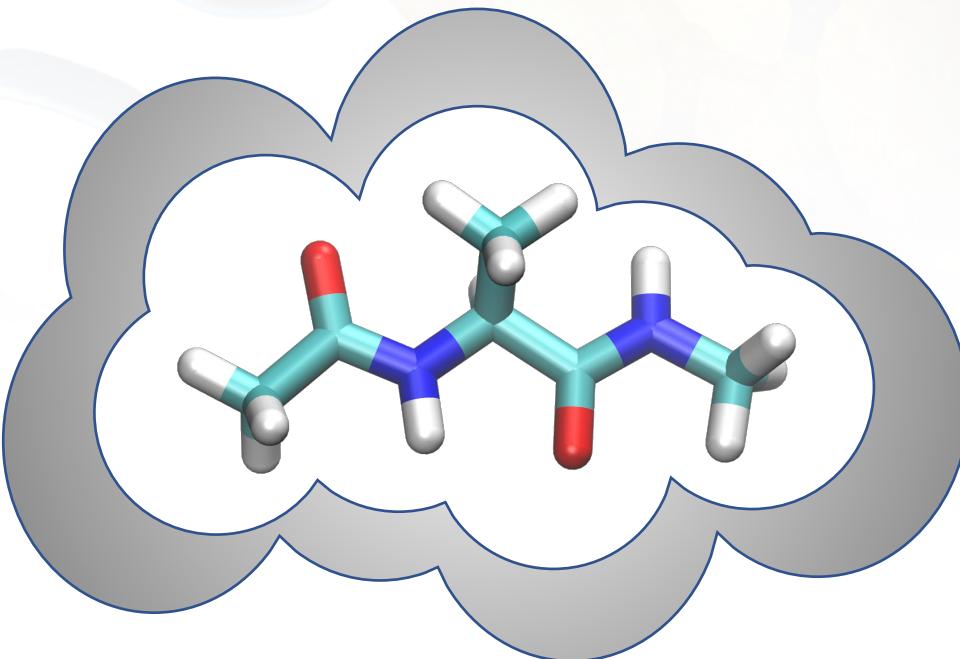
$$\Delta G_{\text{ele}} = \left(1 - \frac{1}{\epsilon}\right) \frac{q^2}{2a}$$



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# Molecular Dynamics Solvation



Implicit solvation: “It’s a big hunk of metal”

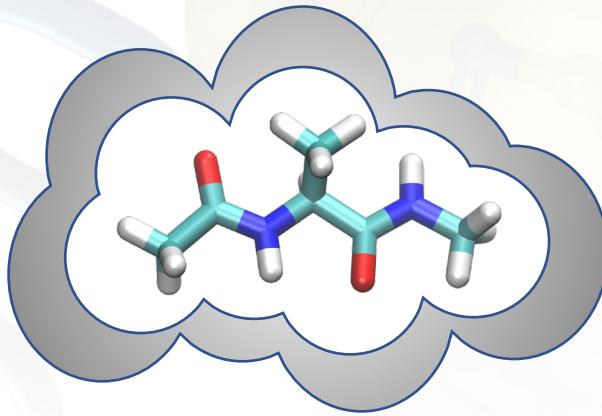
## Advantages:

- Very quick
- Allows for more detailed/larger systems

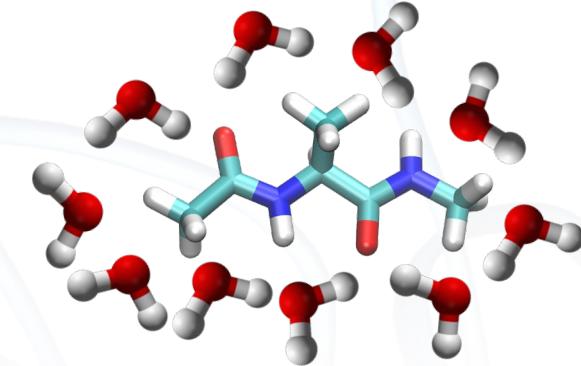
## Disadvantages:

- Only accounts for solvent in an average way
  - No direct solvent interactions
  - No hydrogen bonding
  - No explicit ions/cosolvents
- Problems in cavitation

# Molecular Dynamics Solvation



- Low computational cost
- Fast convergence
- No explicit ions
- No specific interactions
- Infinite dilution
- Cavitation issues
- Screens charge & hydrophobic effect



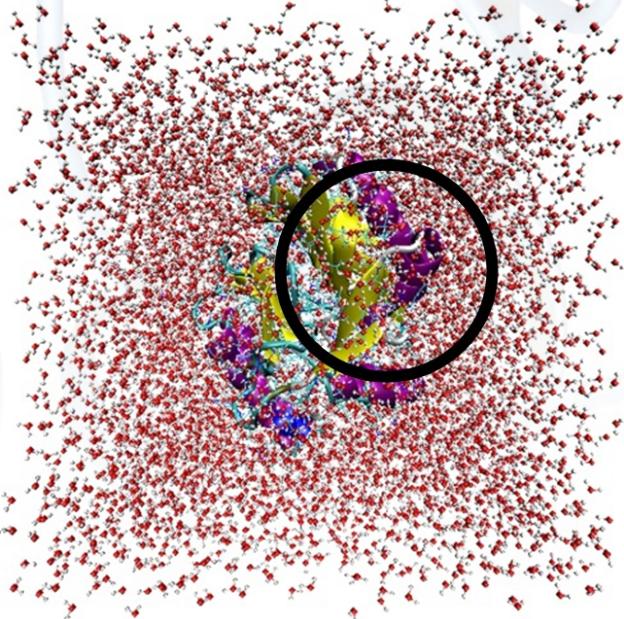
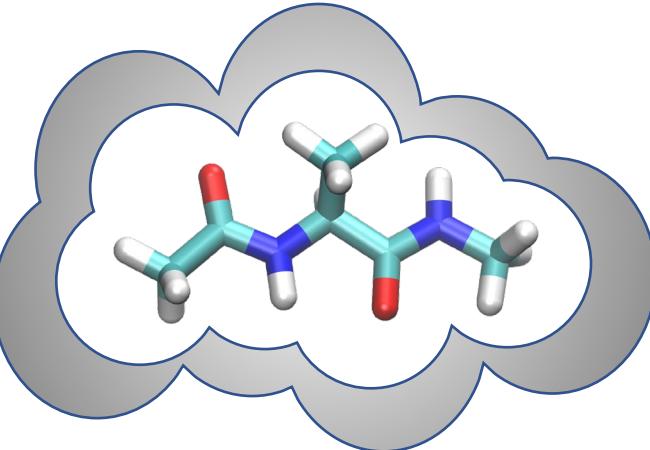
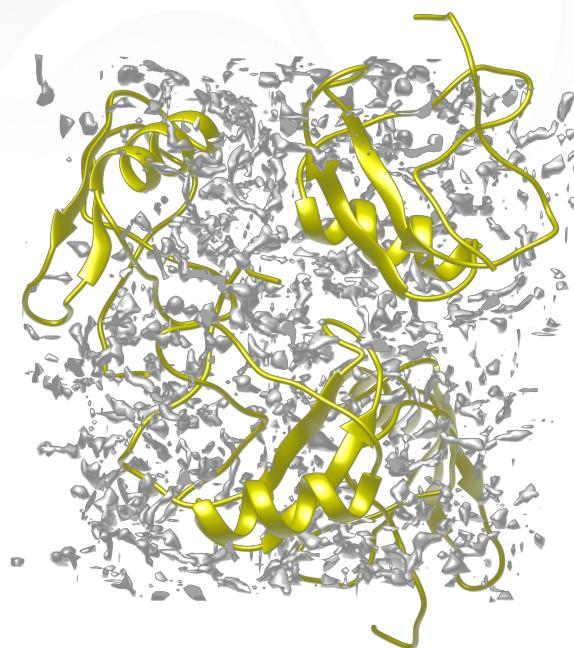
- High computational cost
- Slow convergence
- Explicit ions
- Specific interactions
- Very concentrated
- Periodic boundary issues
- Screens charge & hydrophobic effect

# Molecular Dynamics Solvation

Detail & Computational Cost ↑

## Solvation Model

- Quantum
- Explicit
  - Polarizable
  - **Fixed Charge**
- Integral Equation Models
  - RISM
  - DFT
- Poisson Boltzmann
- SCOSMO
- **General Born**



# Introduction to biomolecular simulation

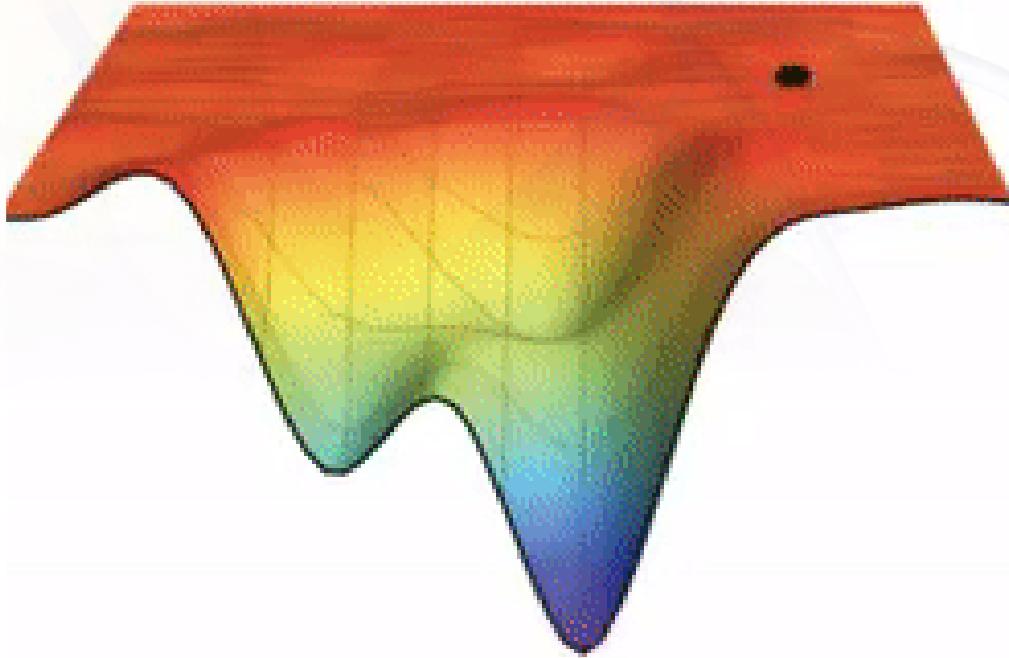
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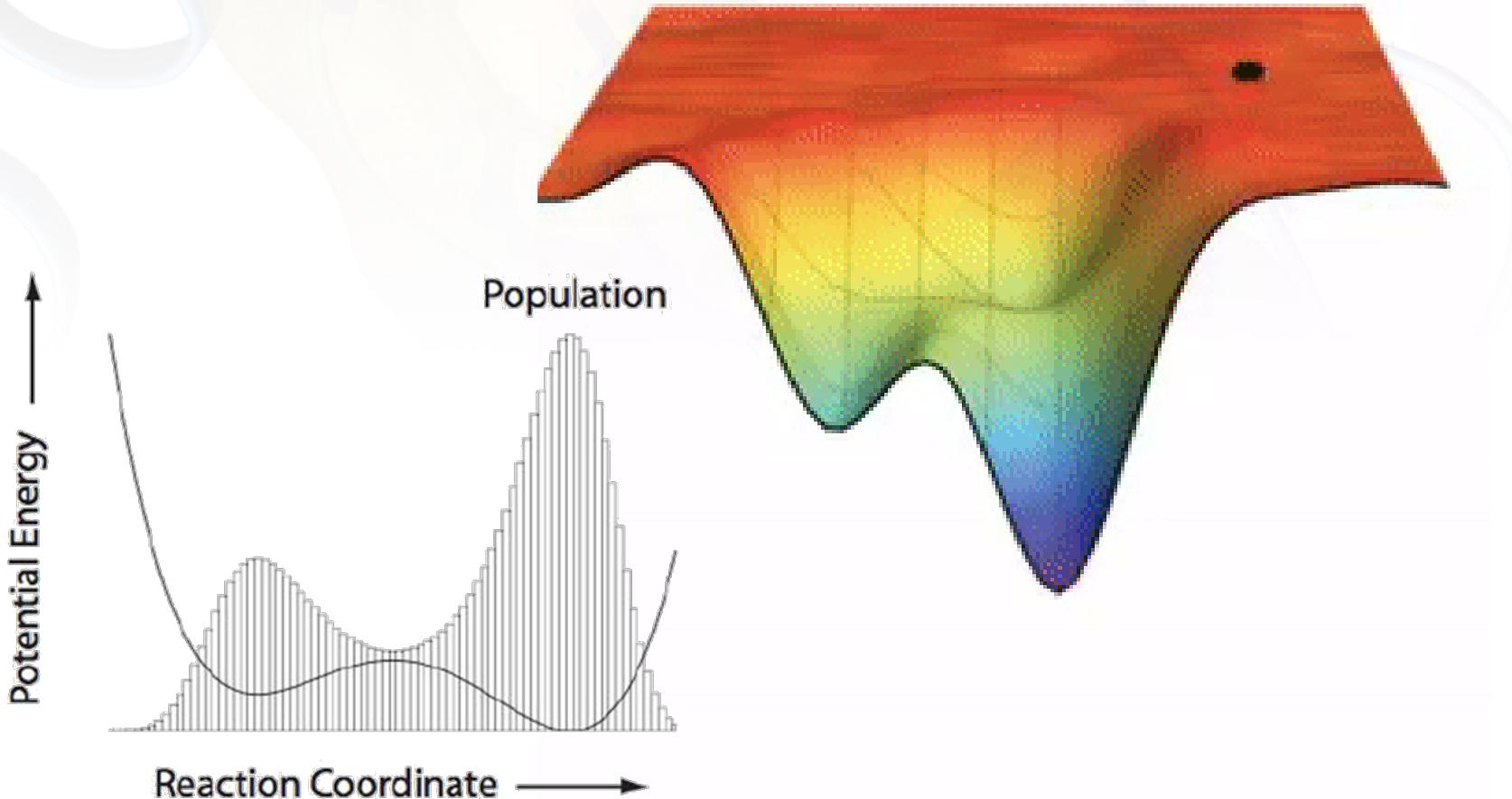
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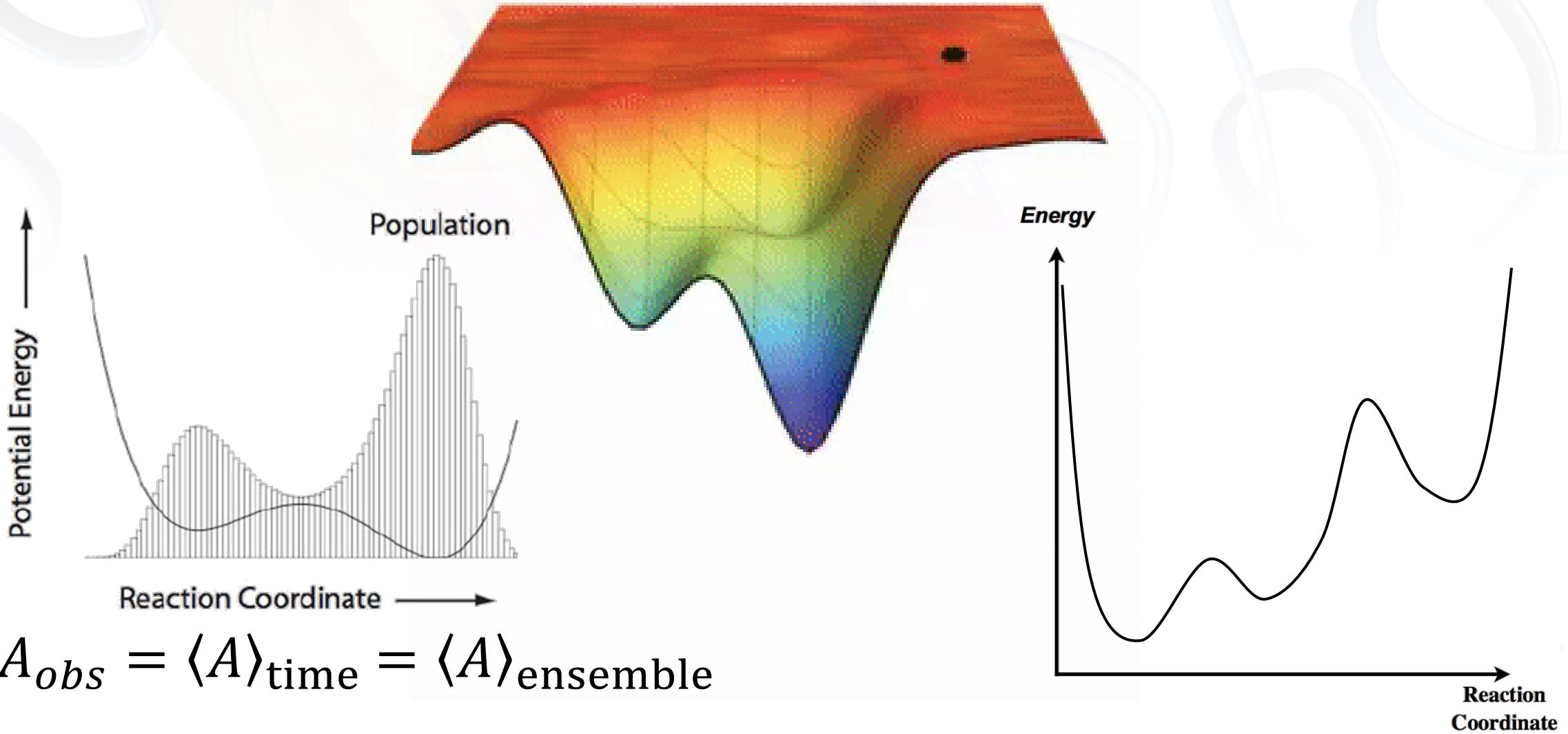


# Introduction to biomolecular simulation

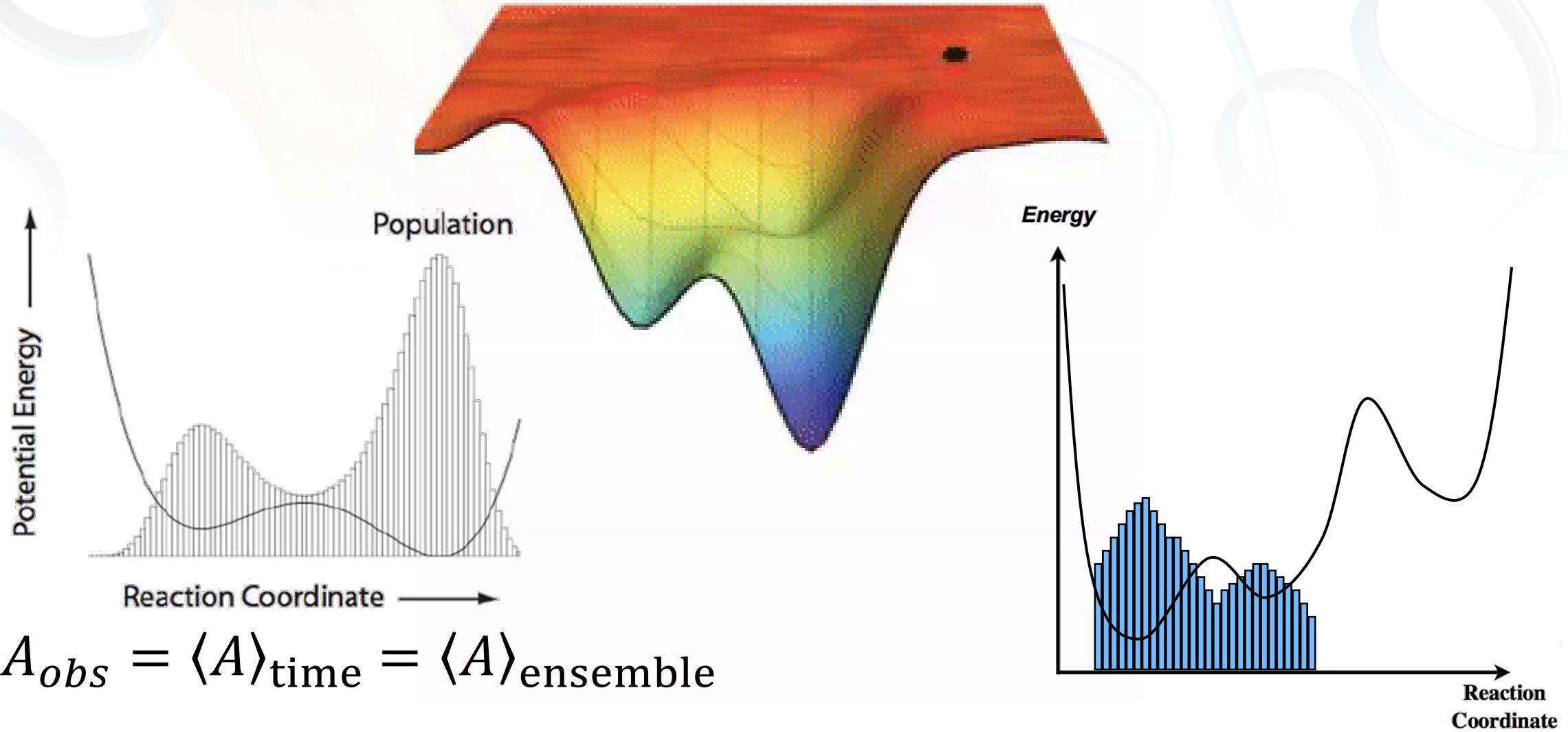


$$A_{obs} = \langle A \rangle_{\text{time}} = \langle A \rangle_{\text{ensemble}}$$

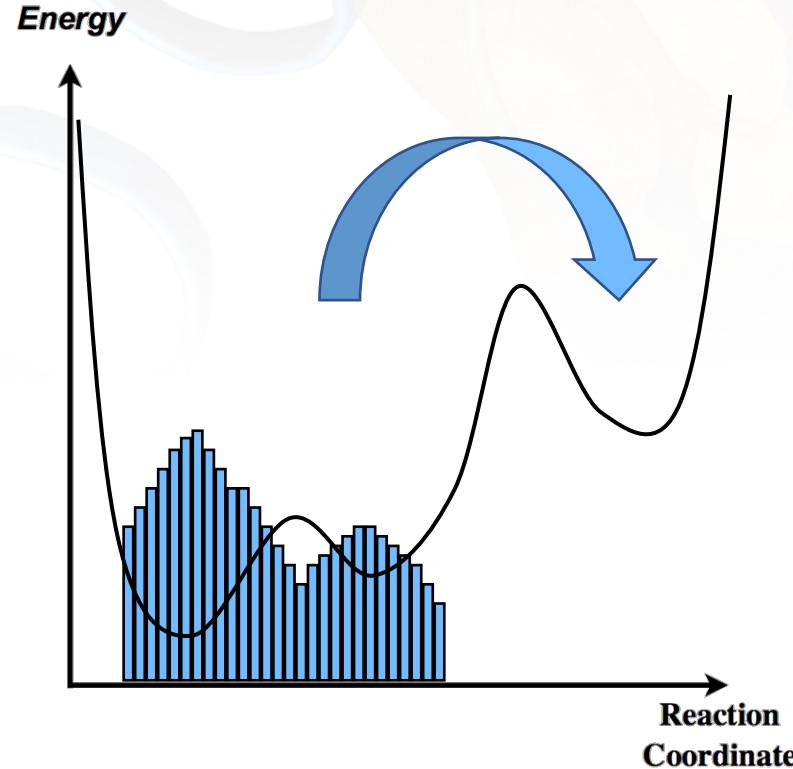
# Introduction to biomolecular simulation



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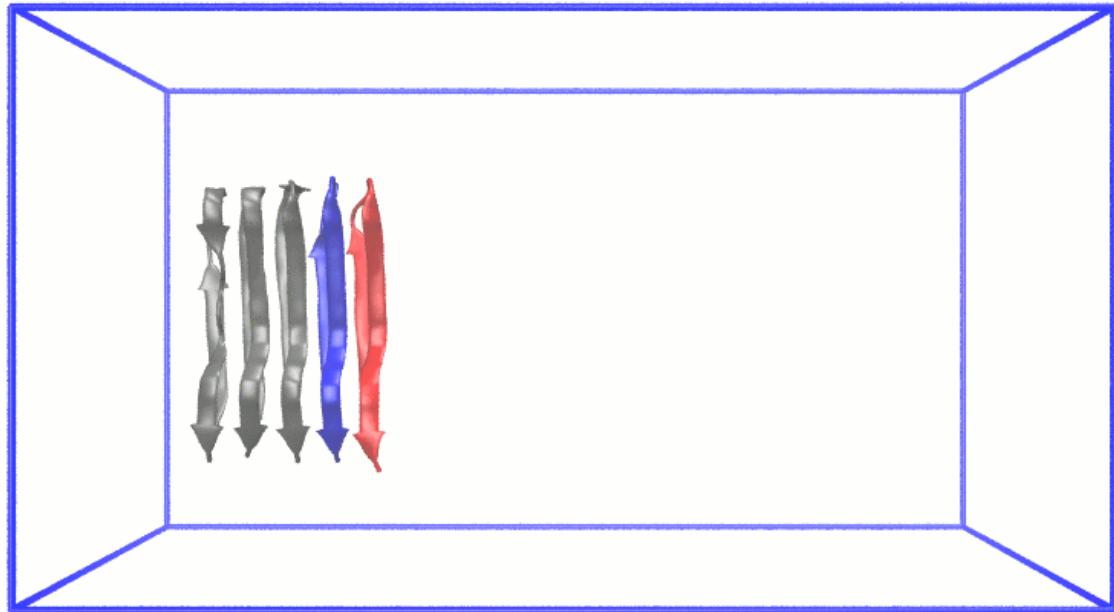
# Introduction to biomolecular simulation



## Enhanced Sampling Techniques

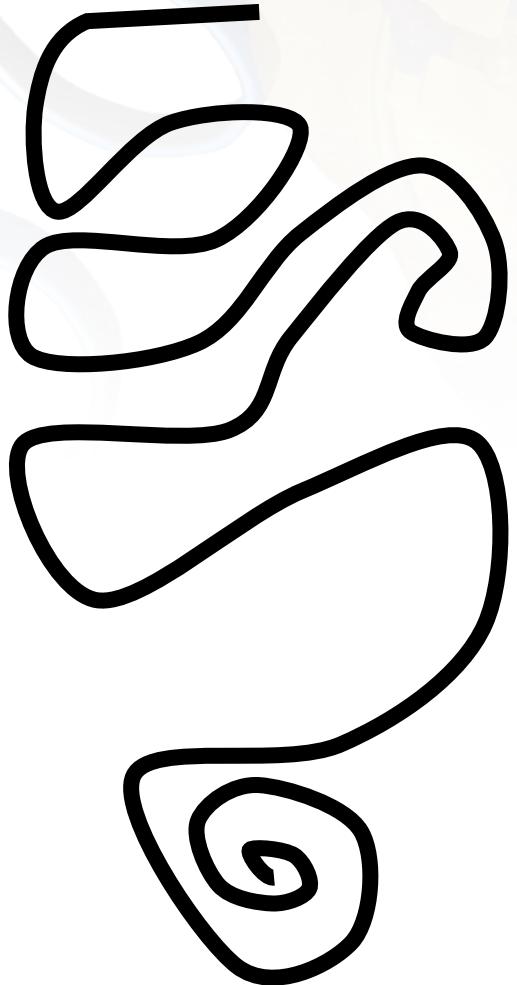
- Umbrella Sampling
- Adaptive Metadynamics
- Replica Exchange Molecular Dynamics

# Umbrella sampling

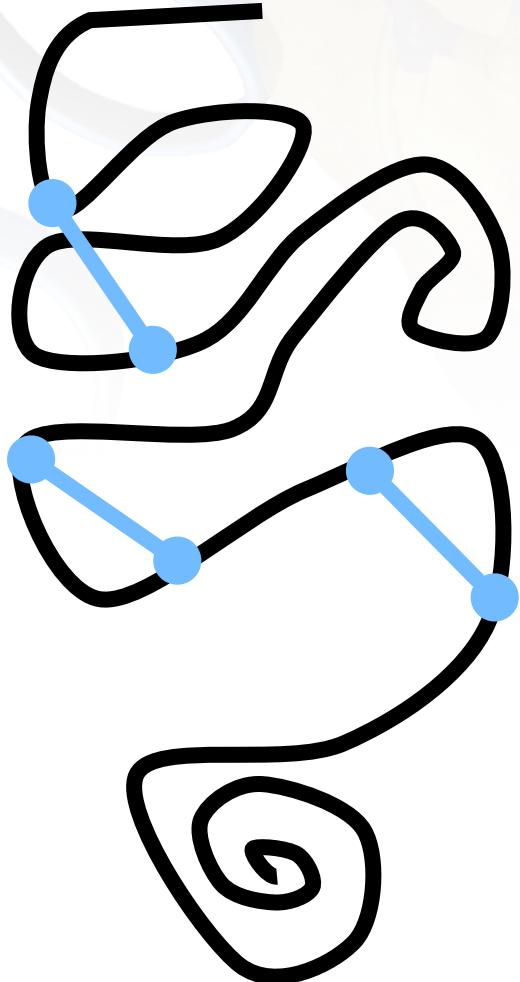


- Restrained Simulation
- Generally uses a collected variable (CV) or reaction coordinate (RC)
- Can overcome PES barriers along the RC

# Restraints vs Constraints

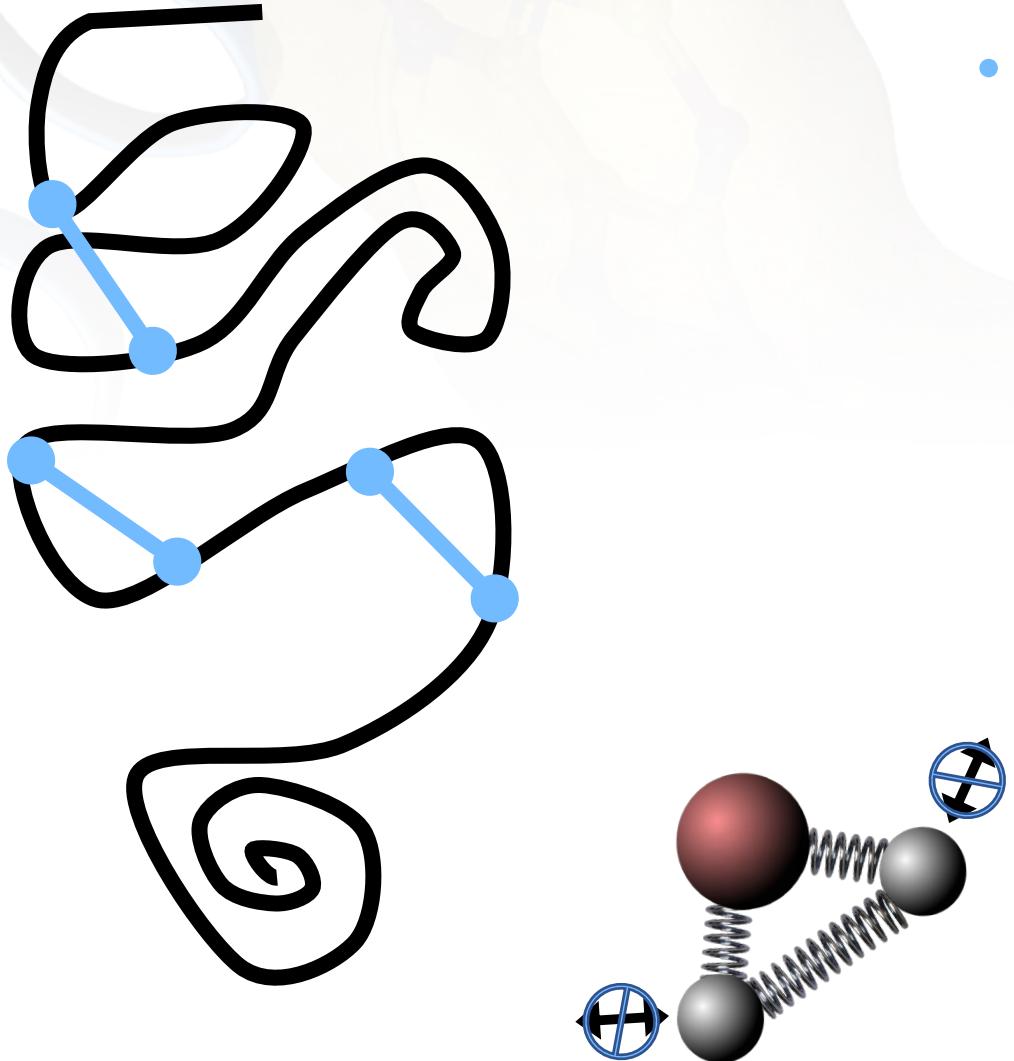


# Restraints vs Constraints



- **Constraints** ‘fix’ atoms at a given position or at set distances
  - Useful in starting delicate or ill-behaved structures
  - Removes degrees of freedom!

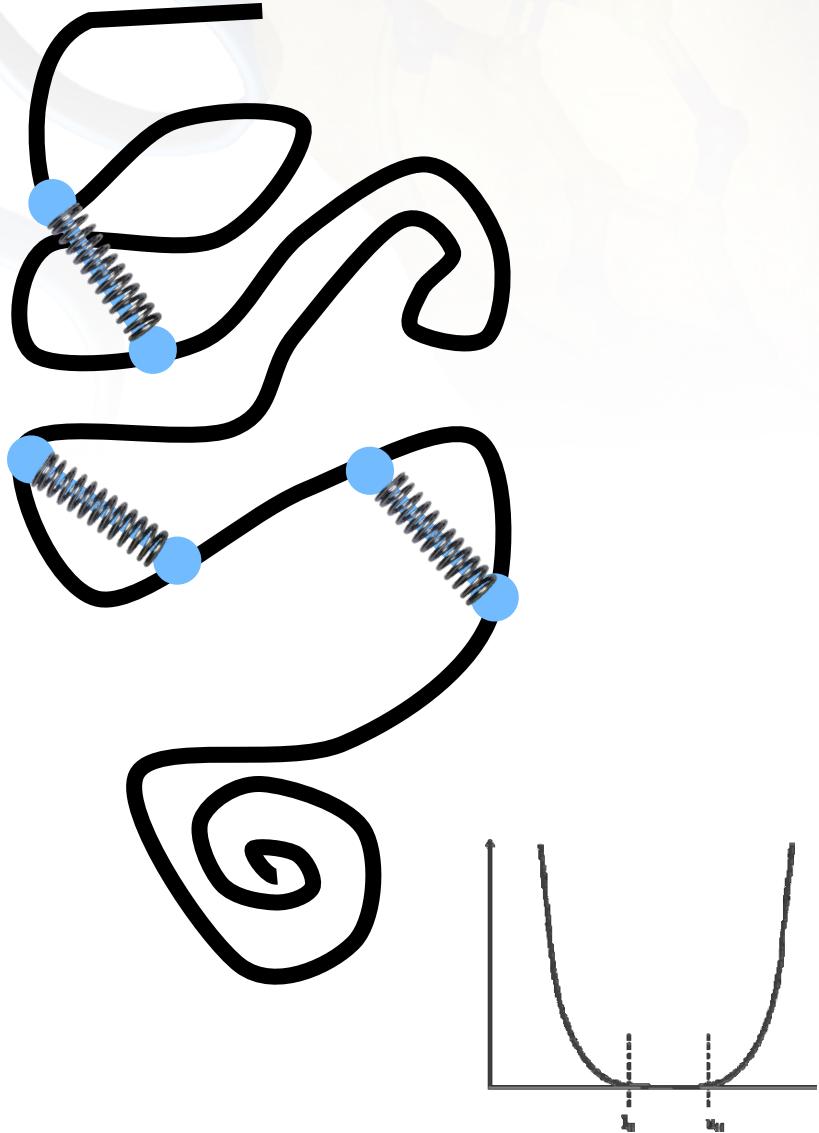
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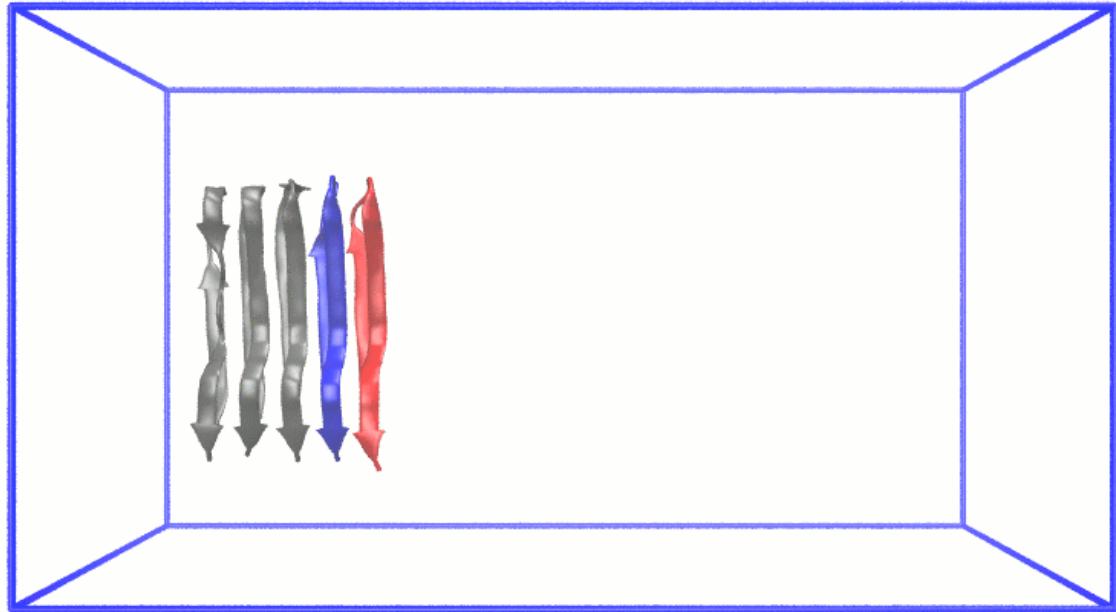
The **SHAKE** algorithm constrains water molecules (and potentially other bonding hydrogen atoms)

# Restraints vs Constraints



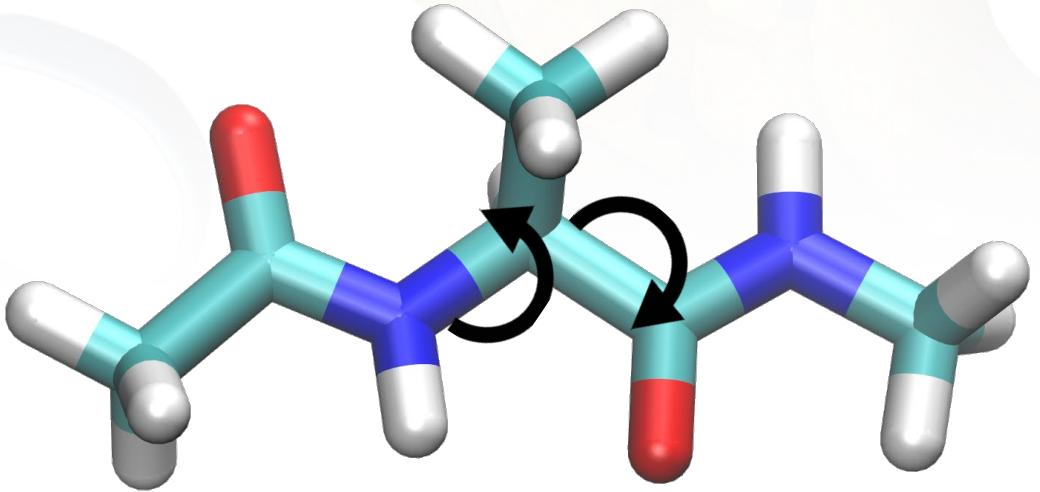
- **Constraints** ‘fix’ atoms at a given position or at set distances
  - Useful in starting delicate or ill-behaved structures
  - Removes degrees of freedom!
- **Restraints** add a restoring force to specific positions or distances
  - Useful for heating, equilibrating, and modeling experiment
  - Sampling a new potential! (But we can fix that...)

# Umbrella sampling



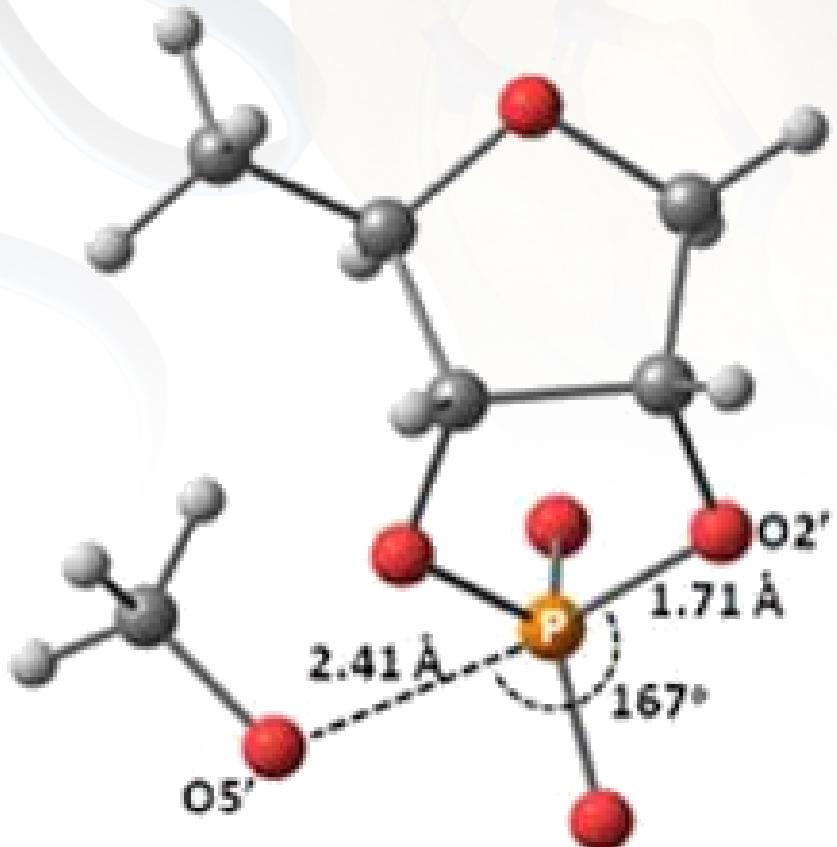
- Restrained Simulation
- Generally uses a collected variable (CV) or reaction coordinate (RC)
  - Runs a number of positions along a given CV
  - Combines simulation outputs using a number of statistical methods
- Can overcome PES barriers along the RC

# Reaction coordinates



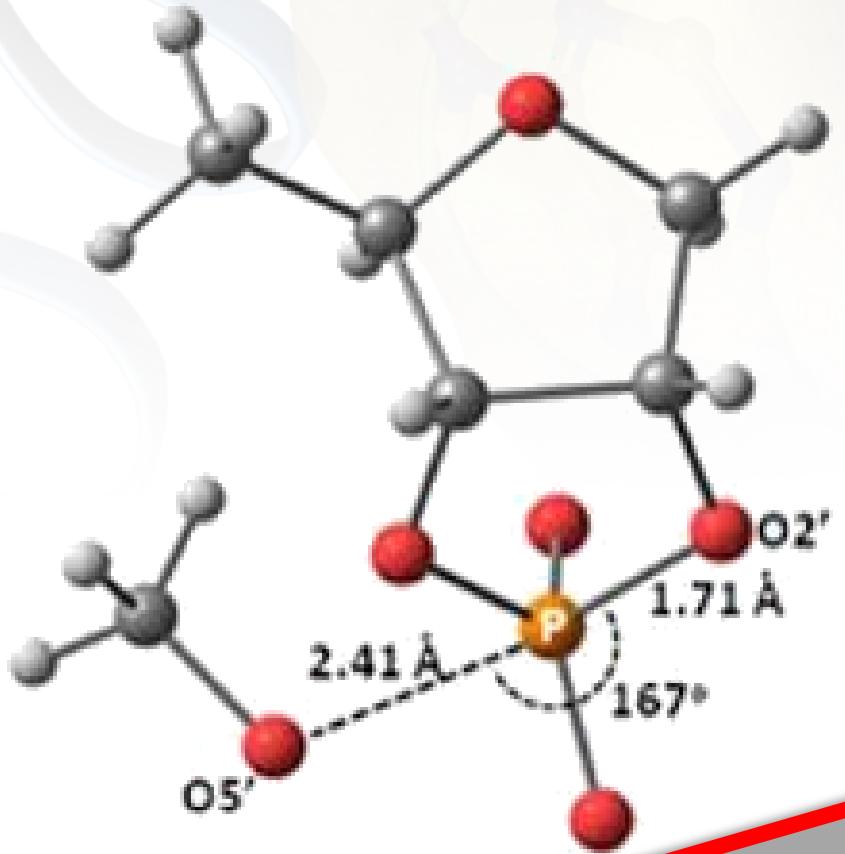
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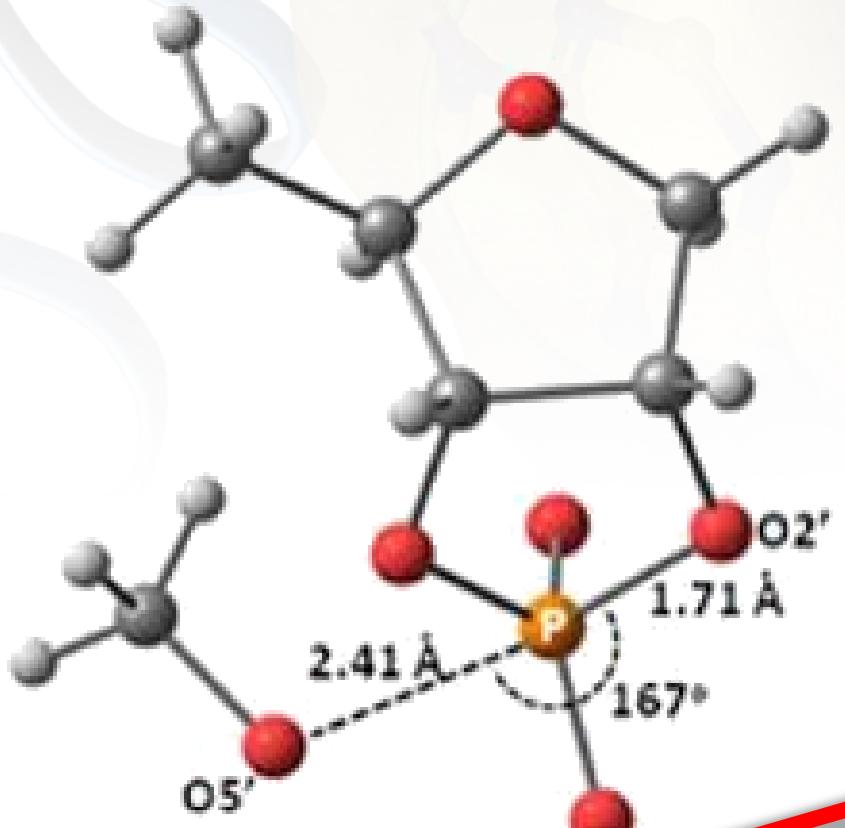
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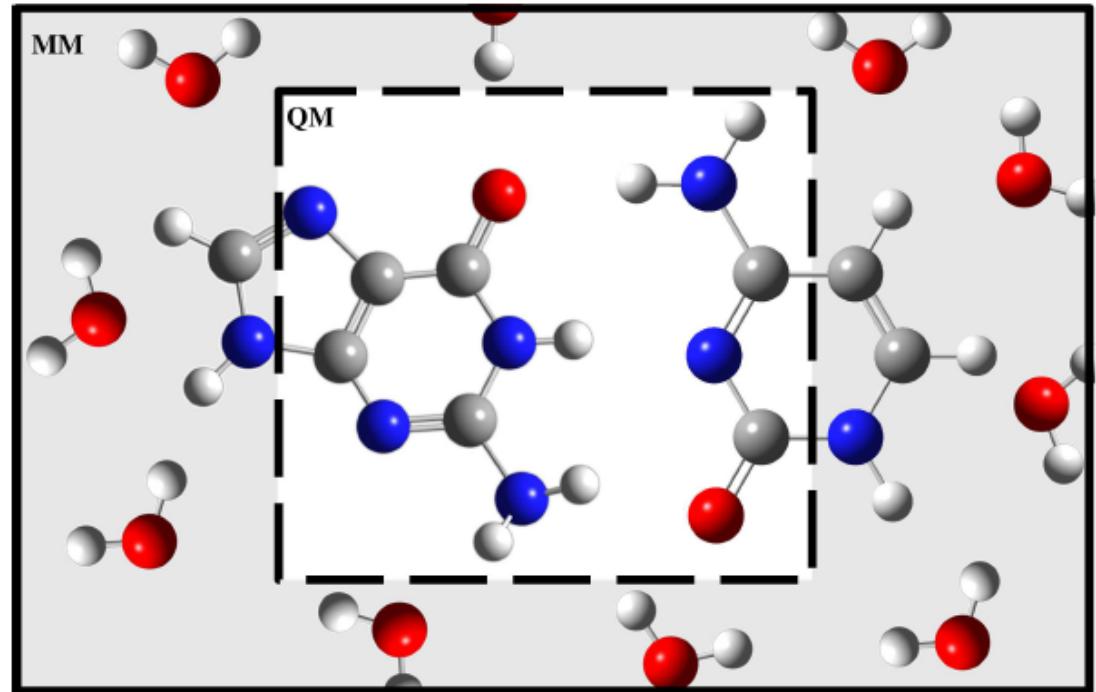
Warning!  
To break and form bonds  
you **MUST** use non-classical  
molecular dynamics

# Reaction coordinates

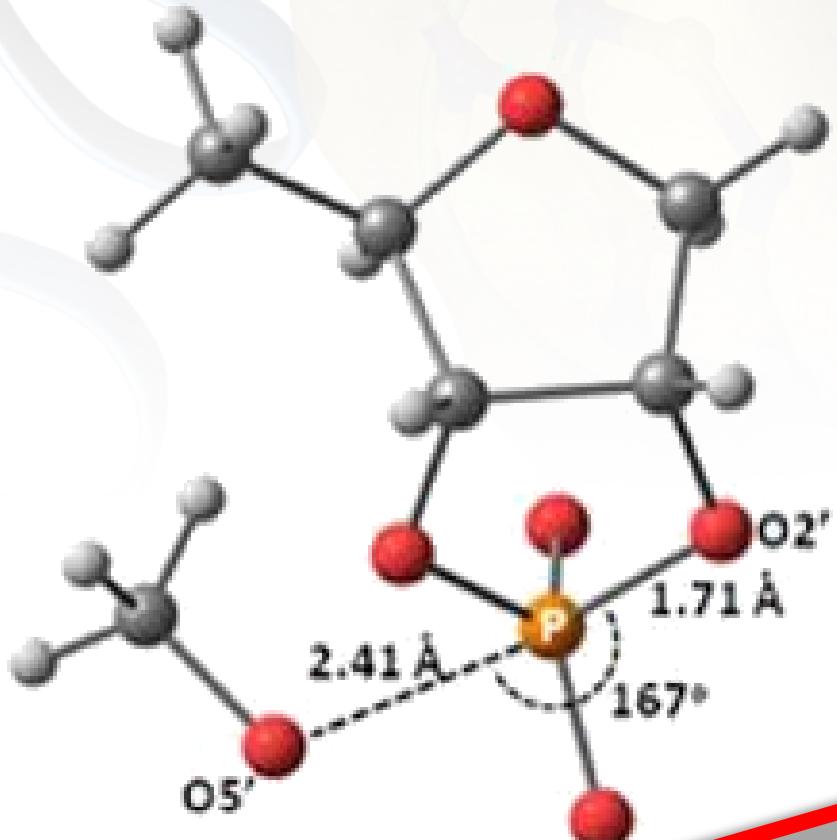


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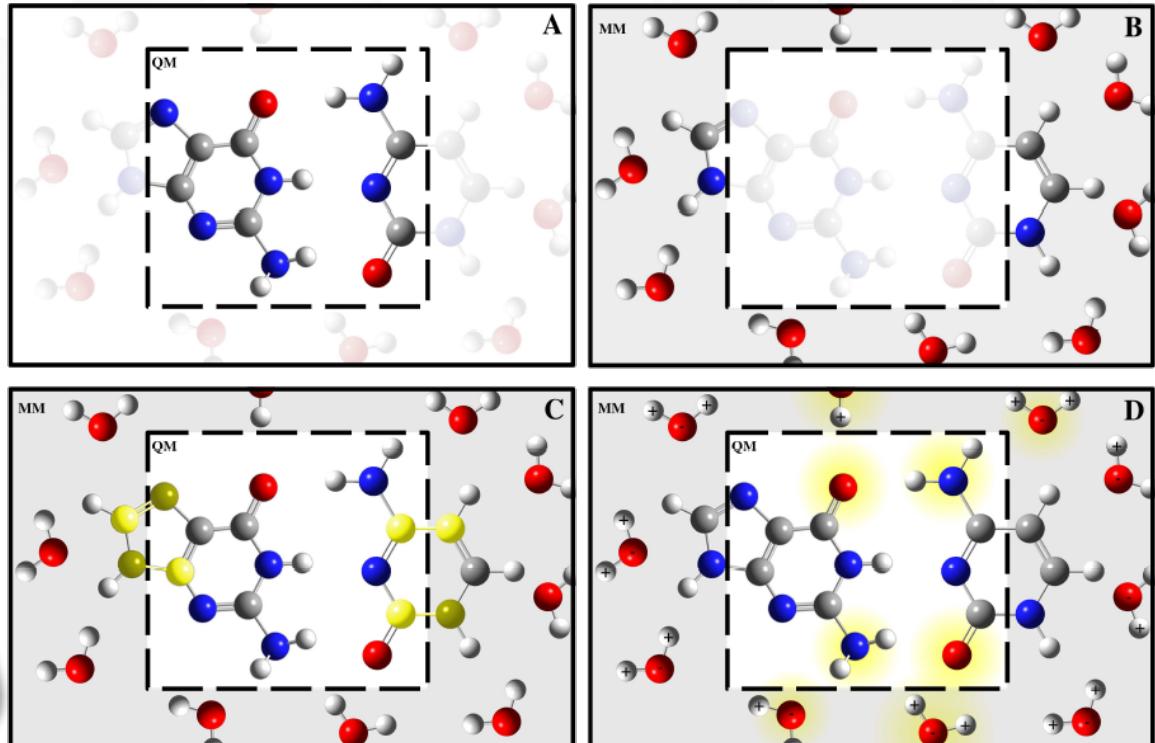


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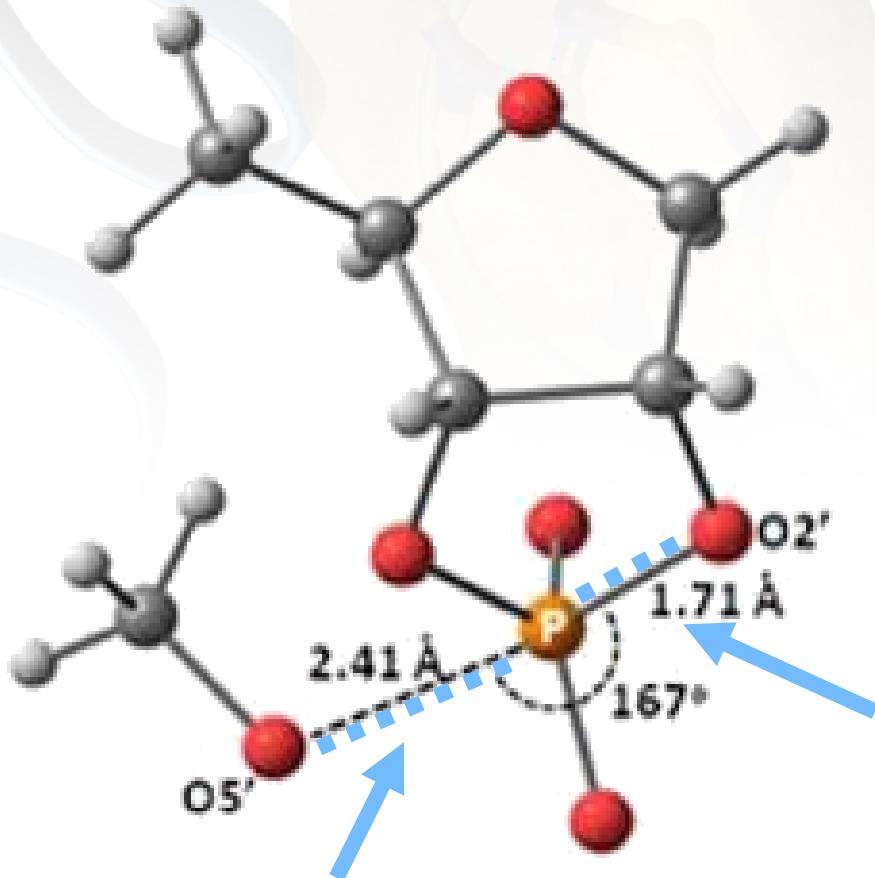


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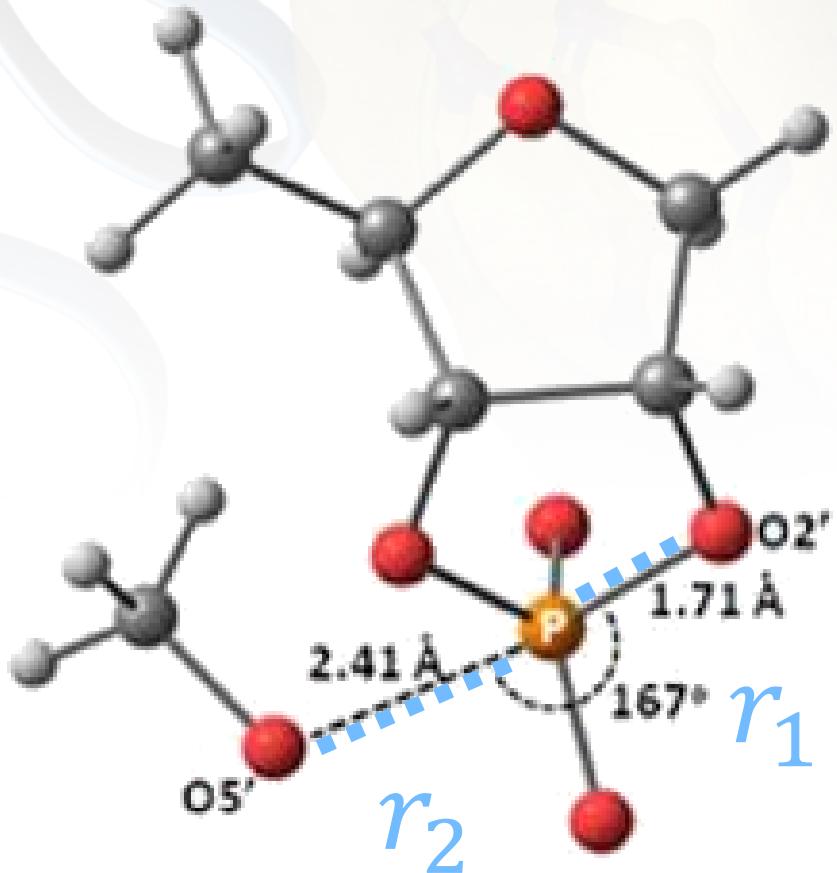


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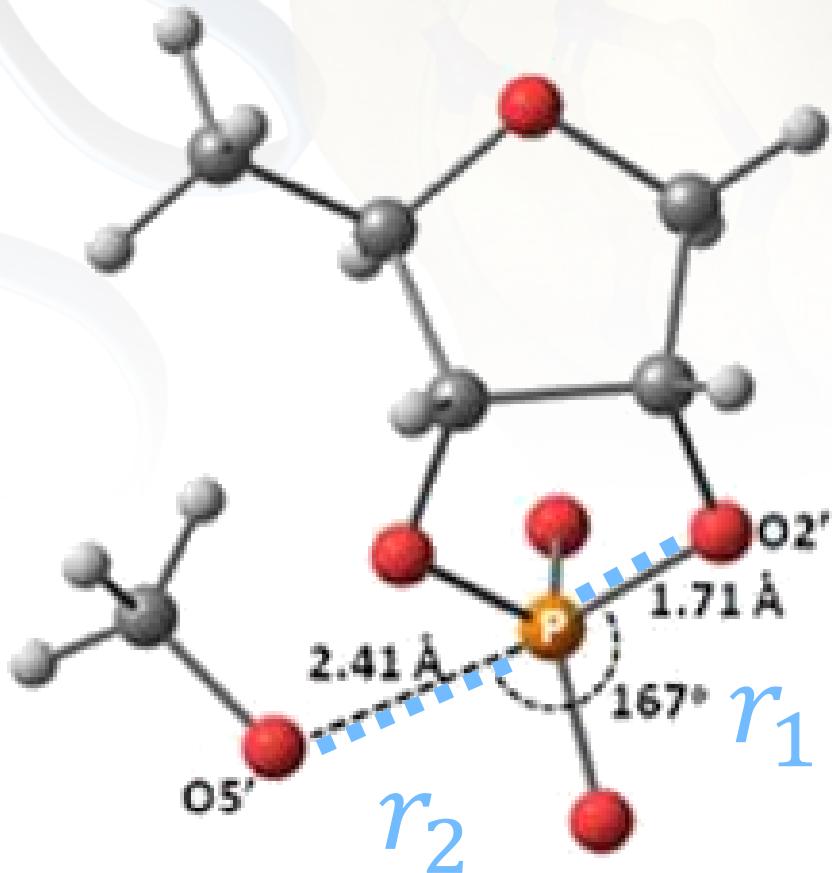
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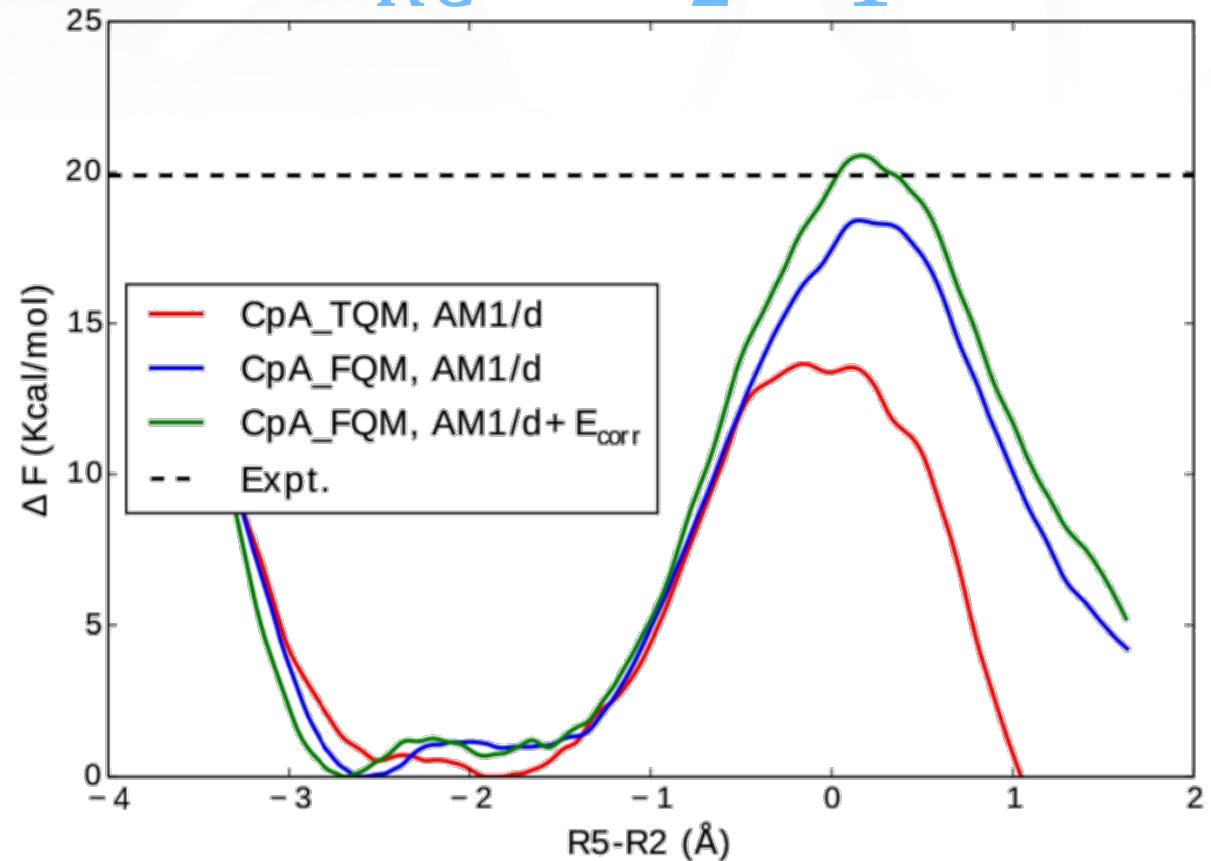
$$r_{RC} = r_2 - r_1$$

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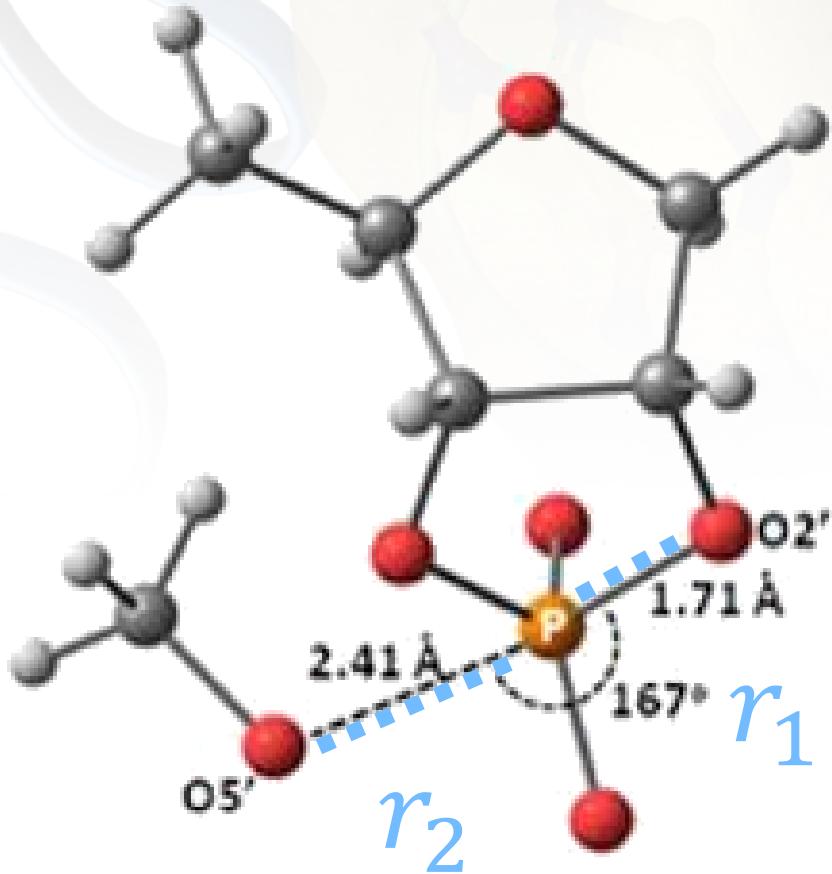


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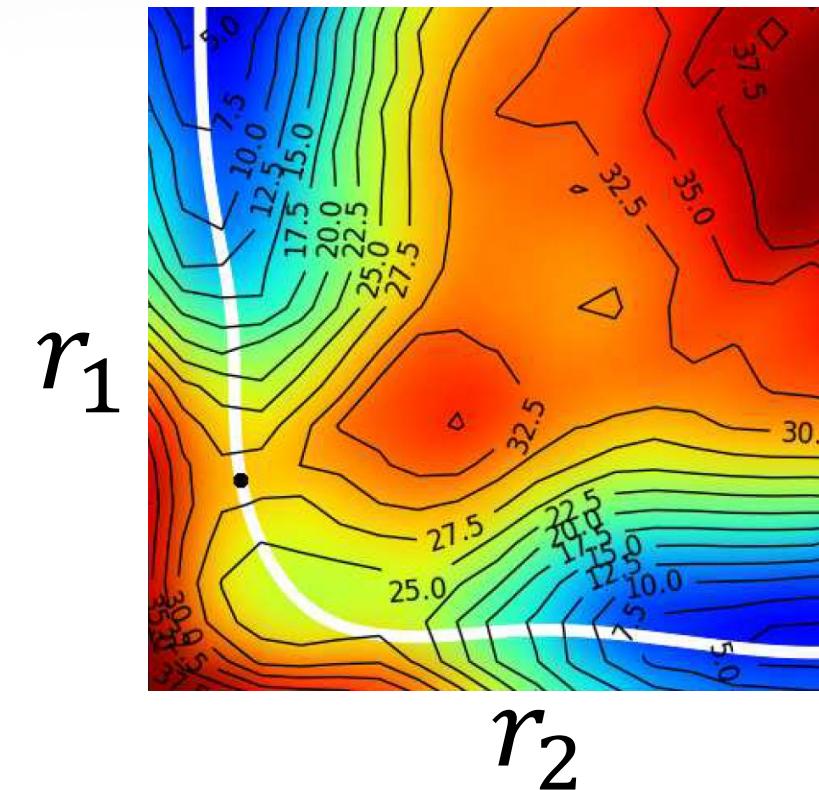


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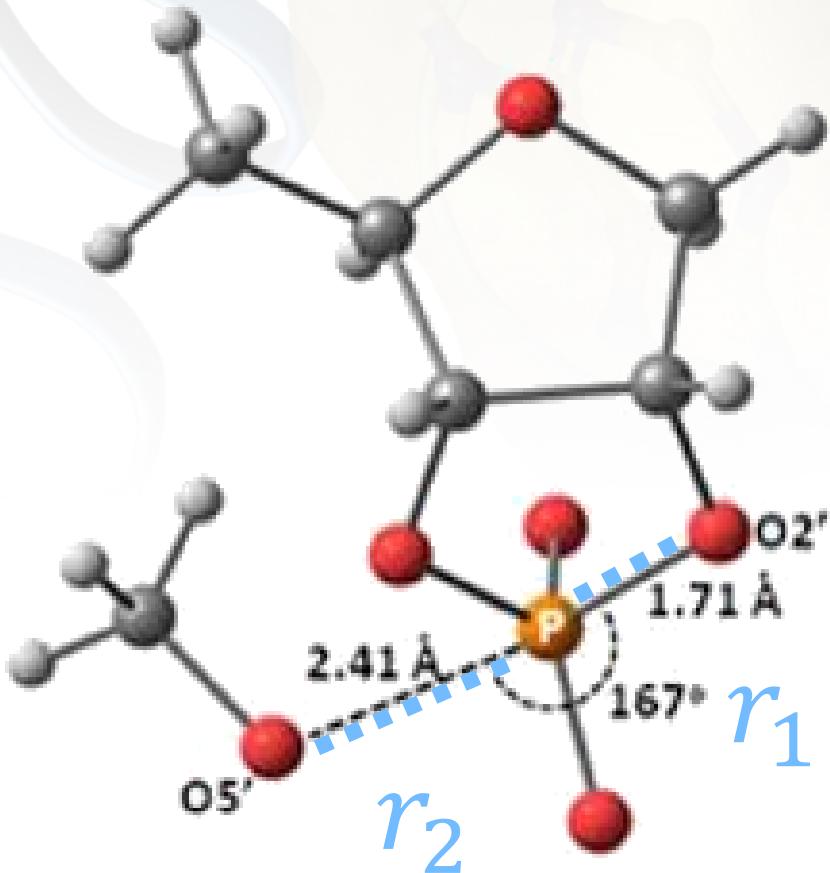


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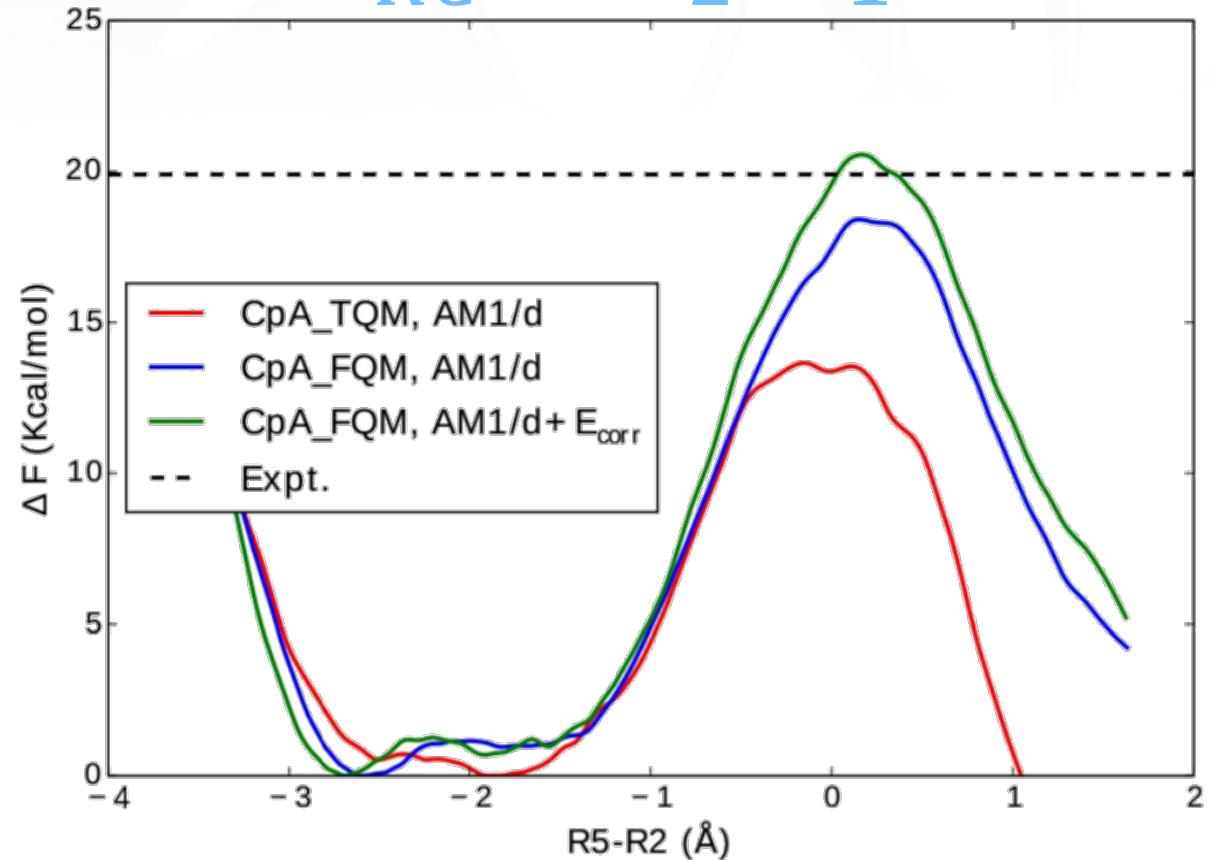


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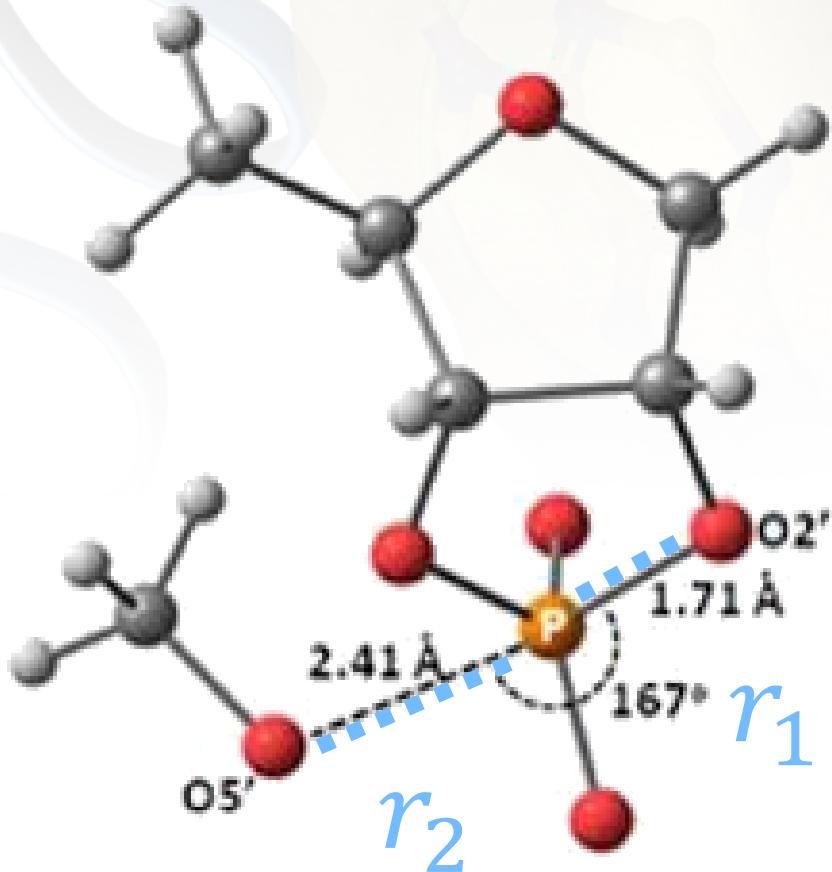


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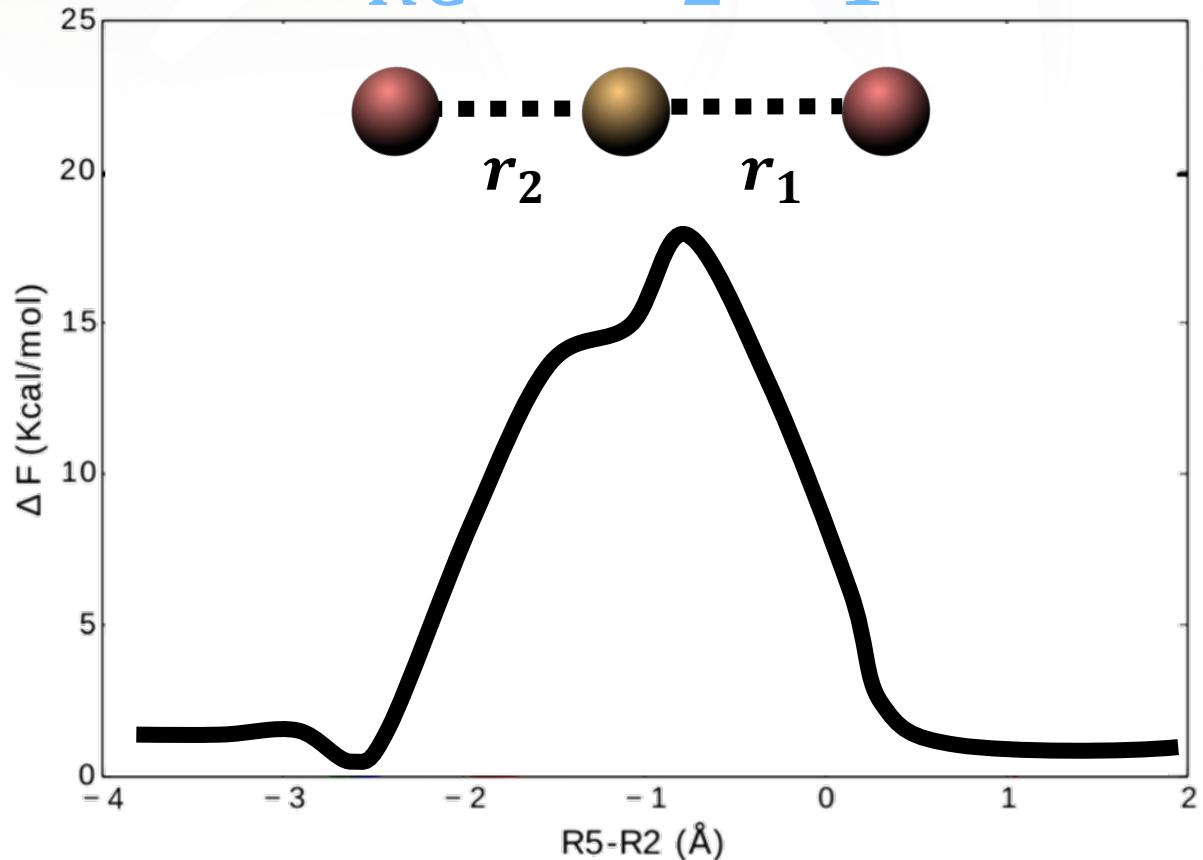


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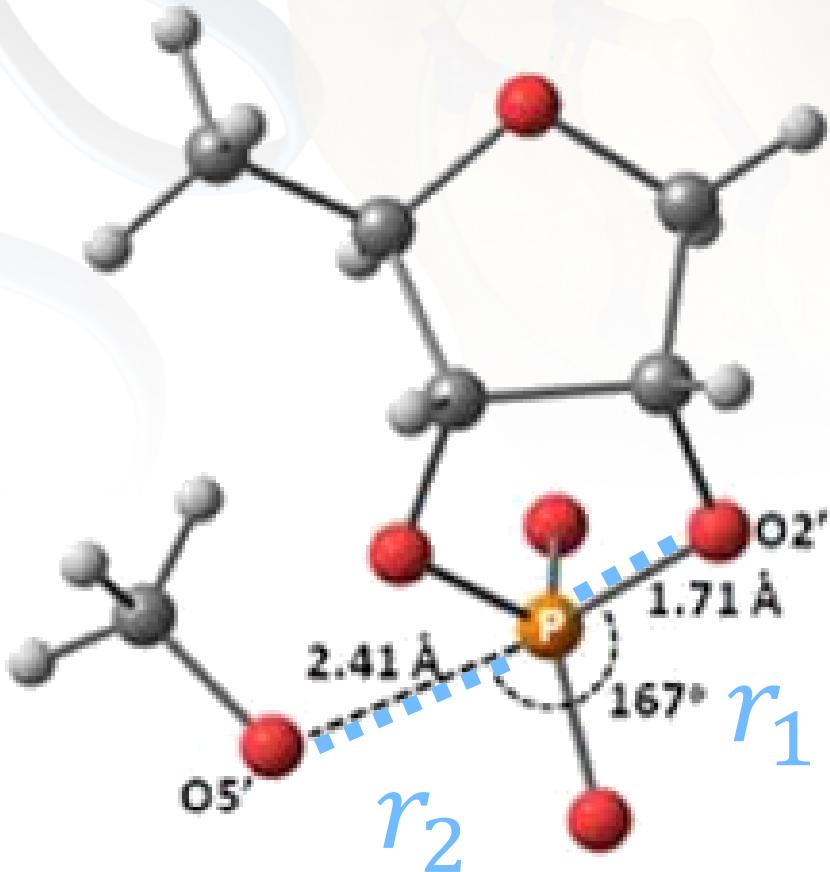


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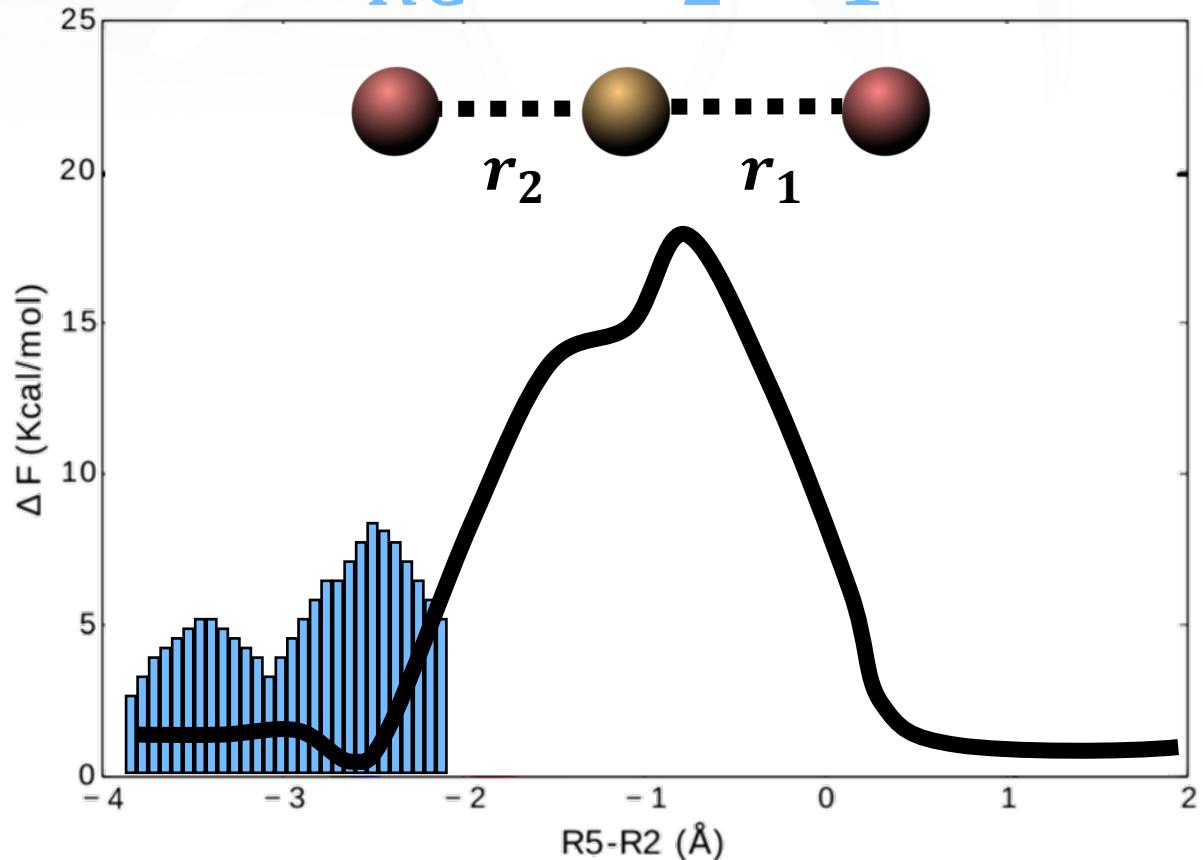


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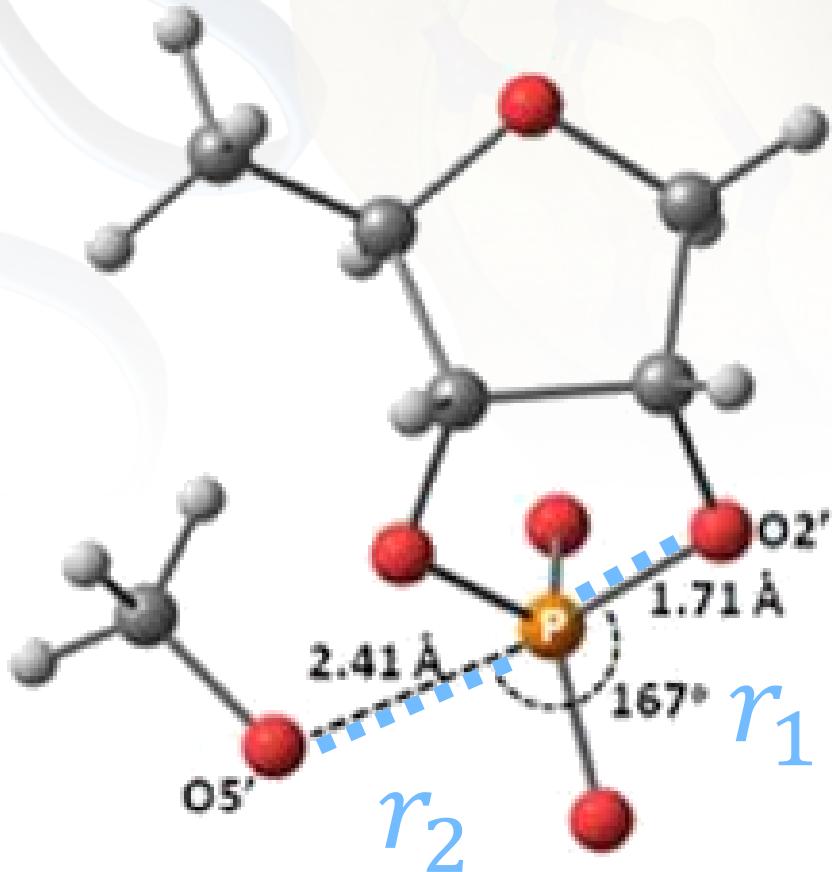


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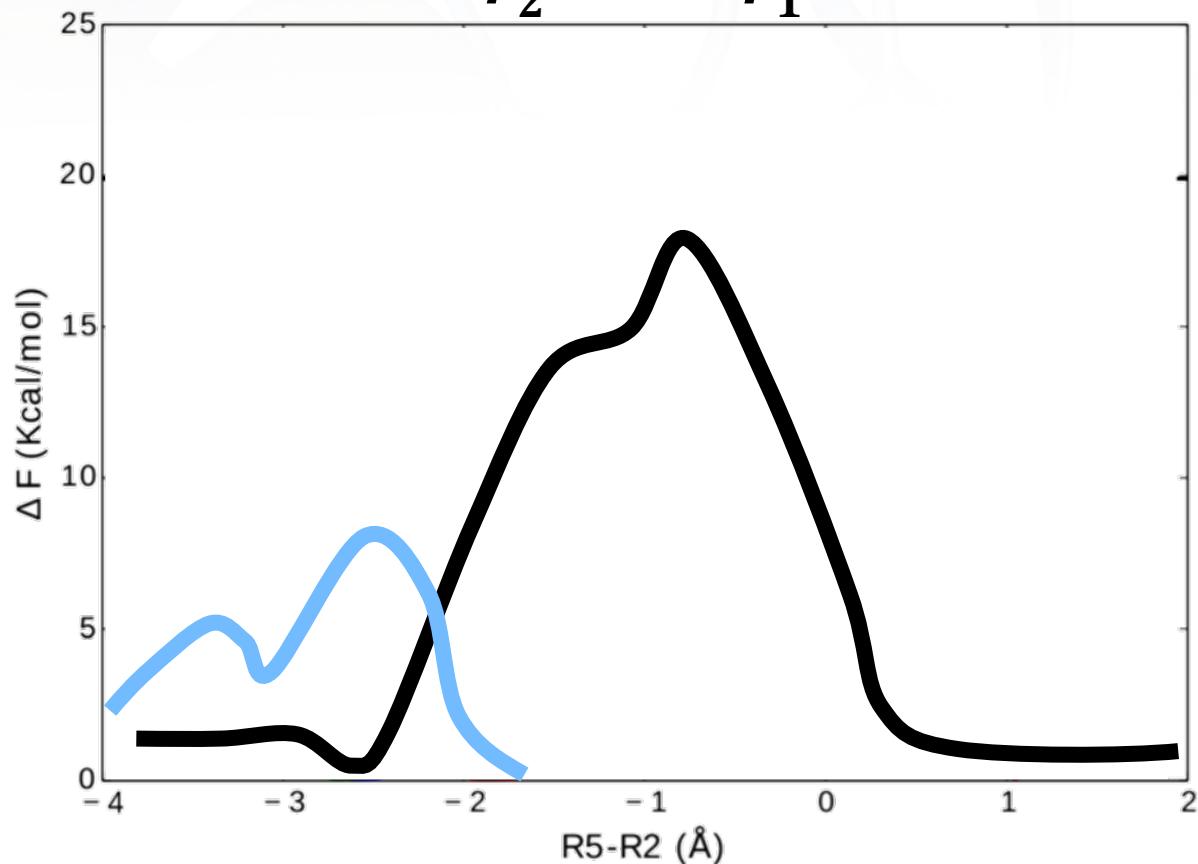
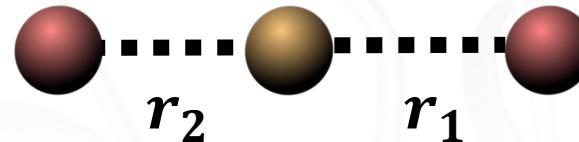


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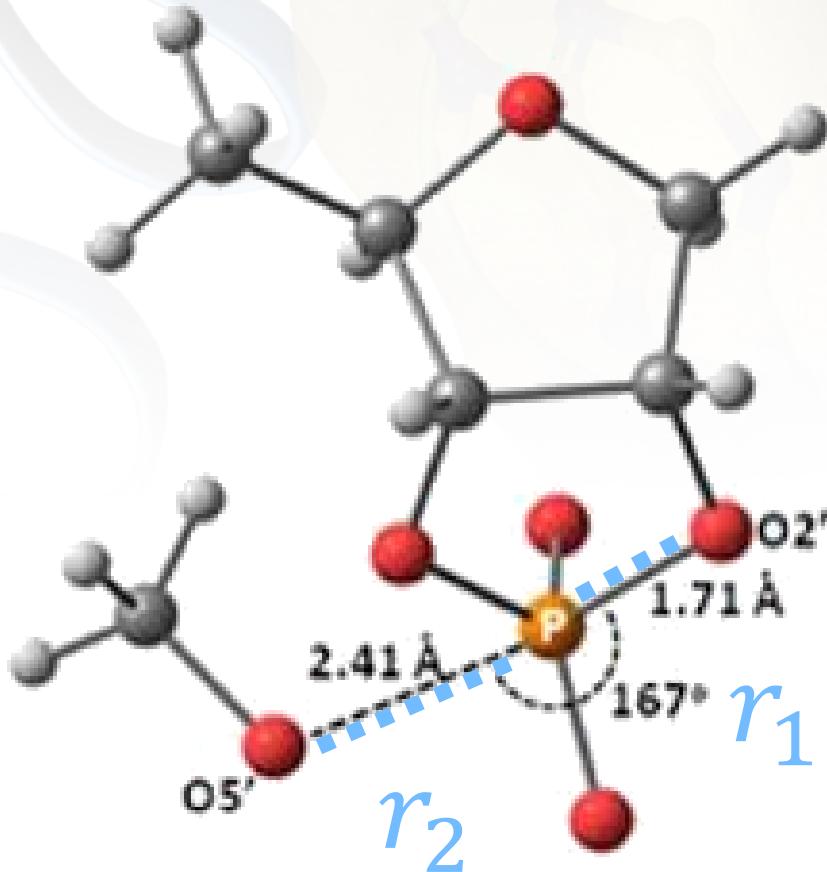


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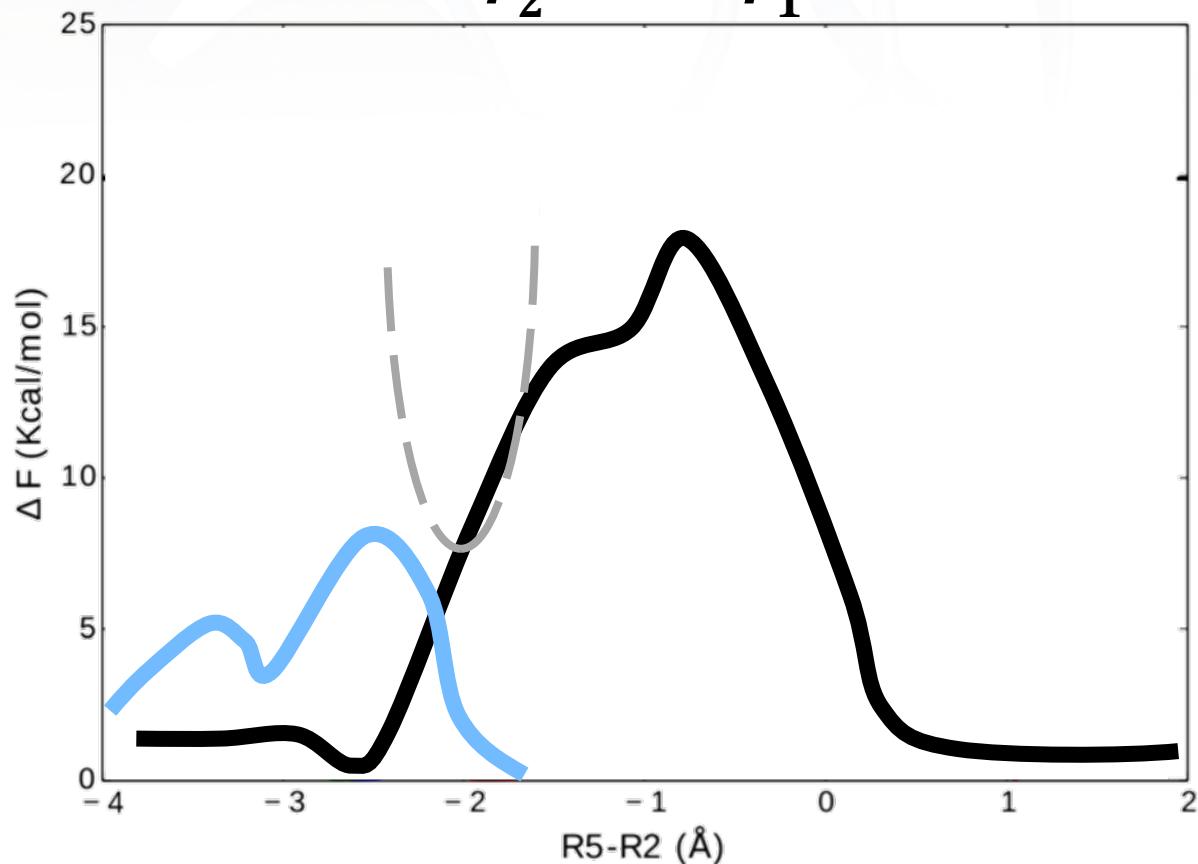


# Umbrella sampling

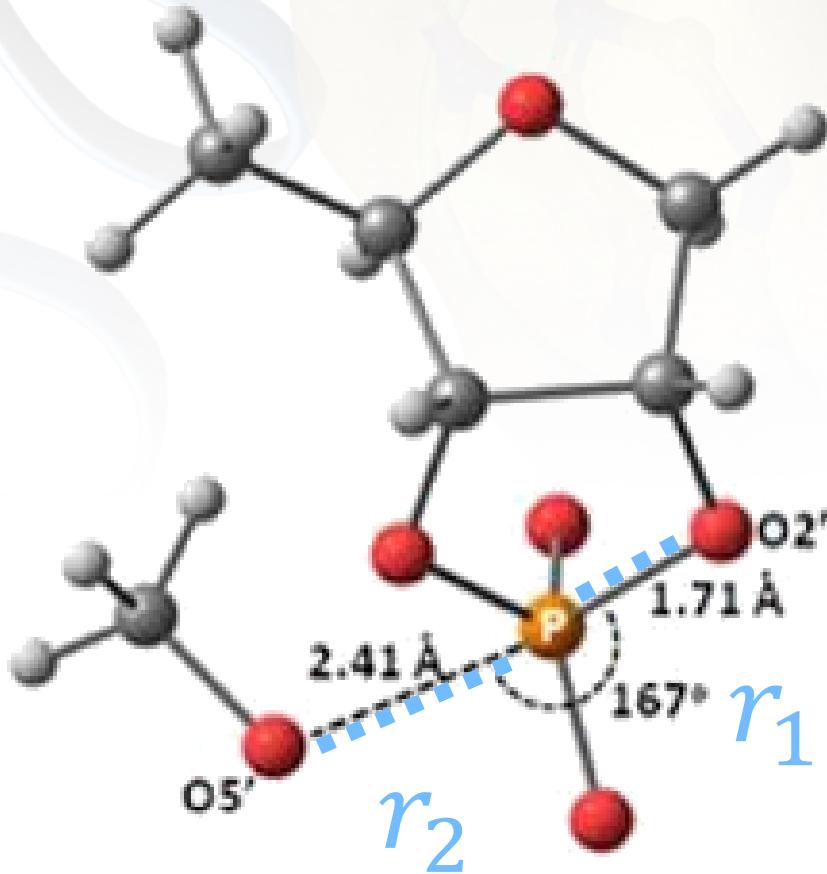


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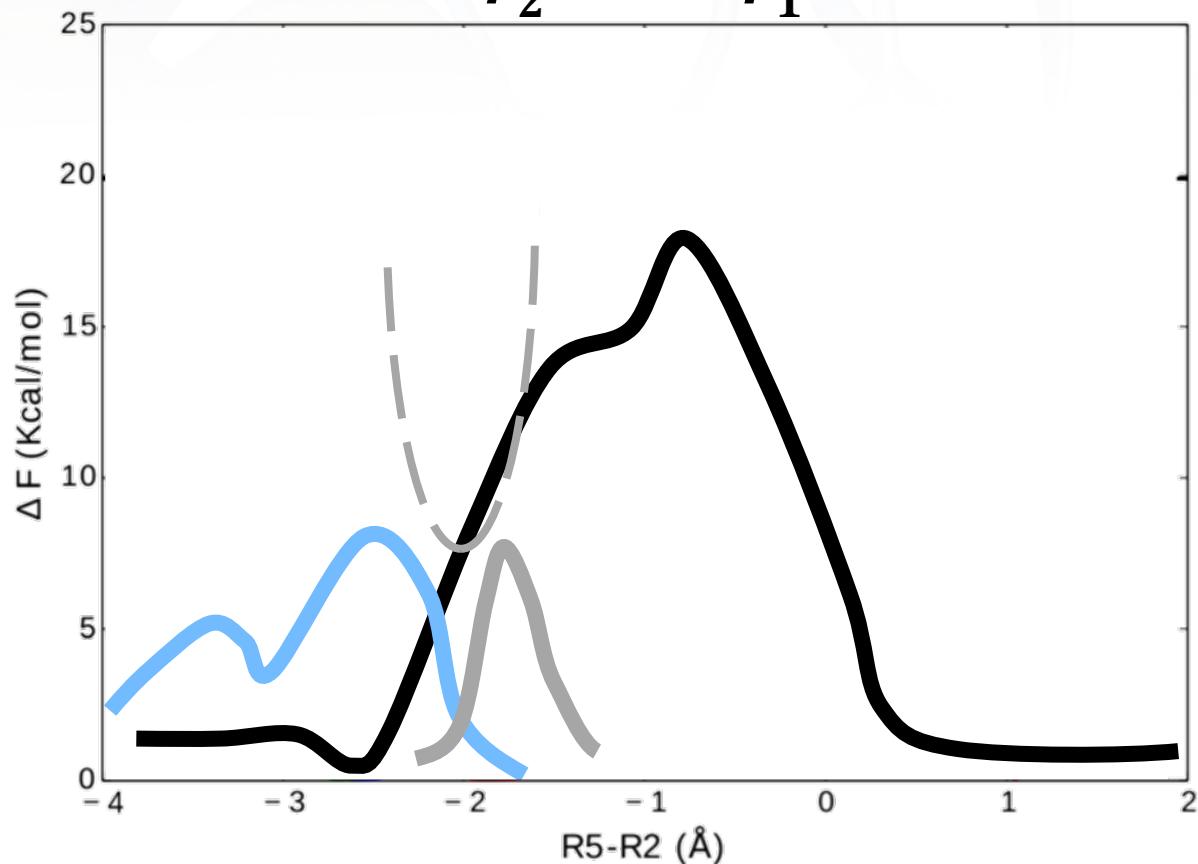


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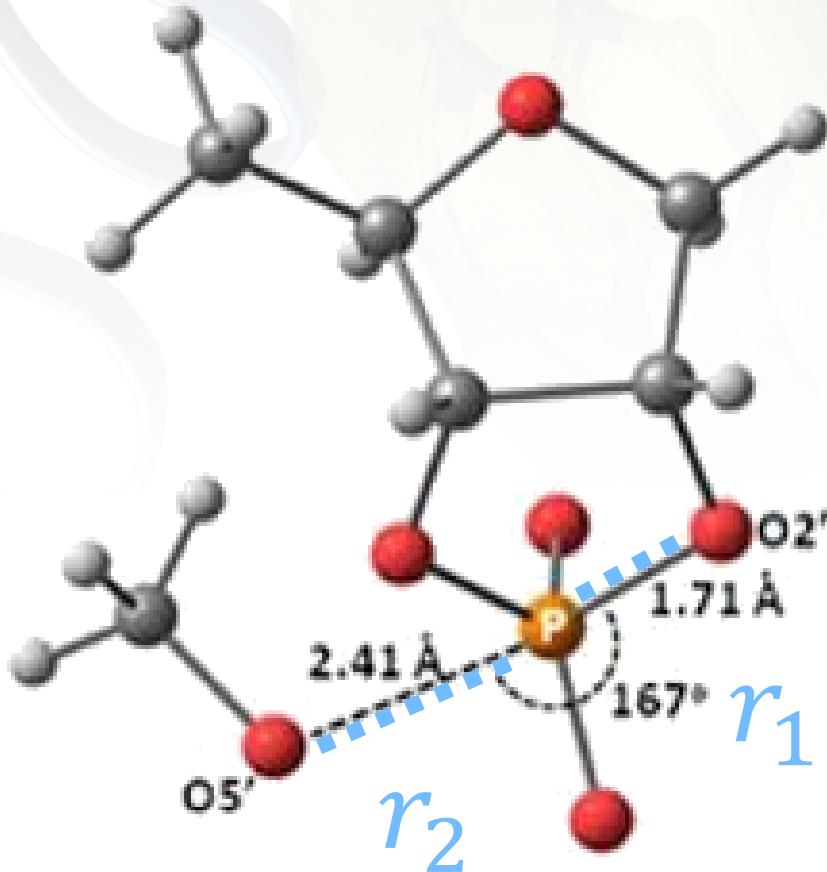


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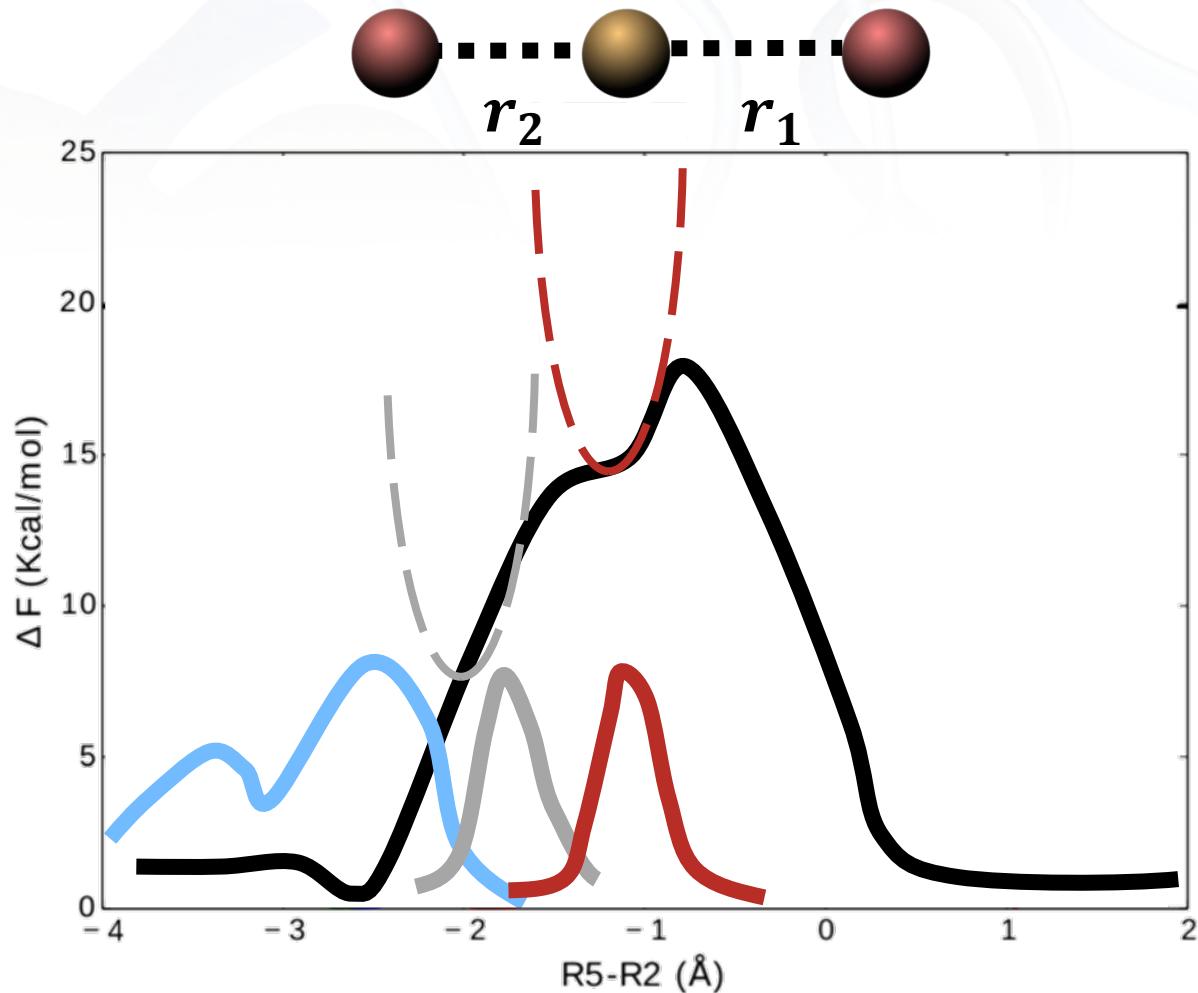


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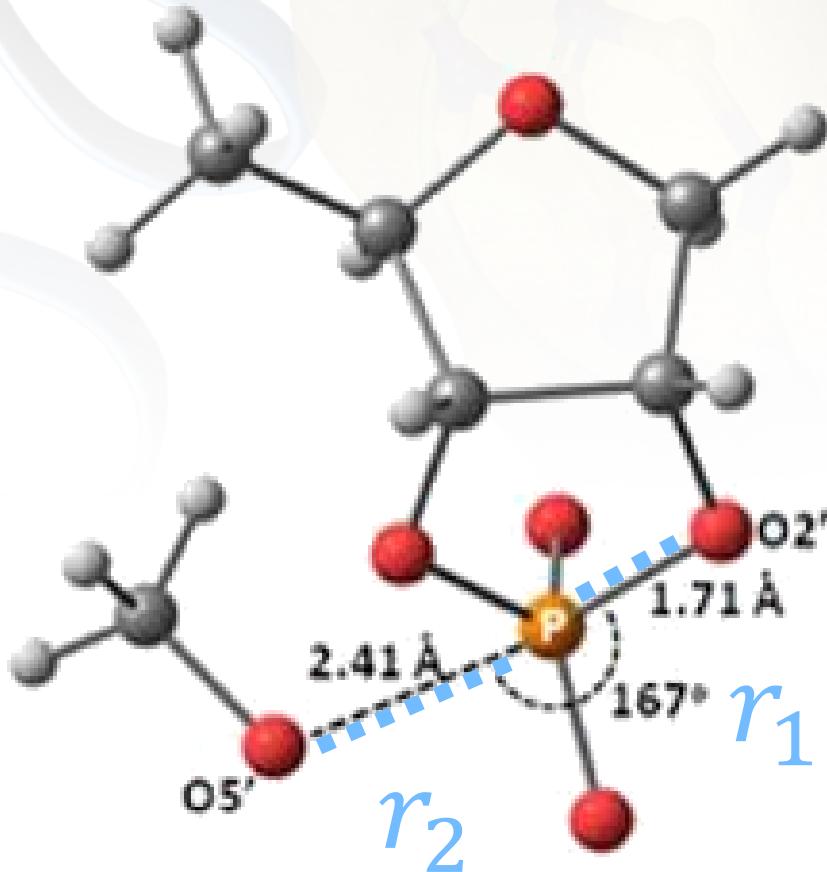


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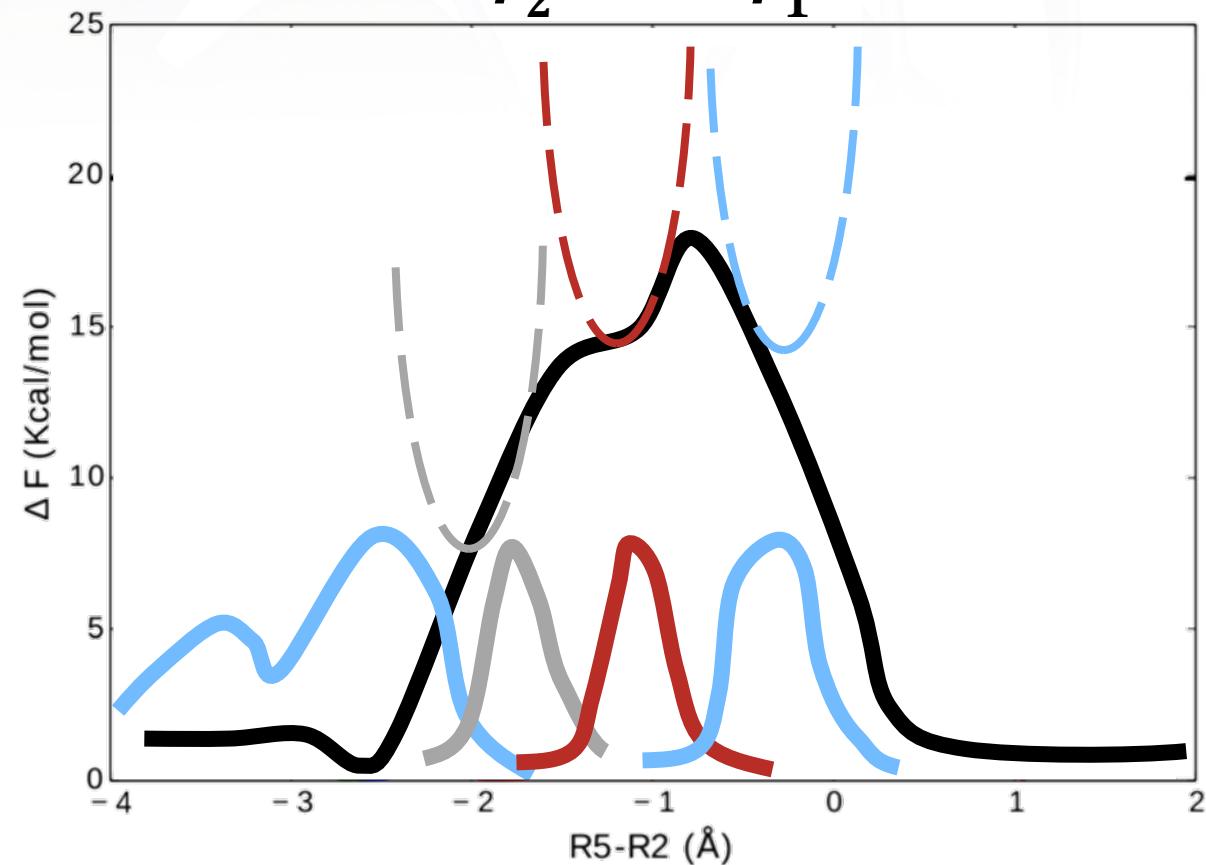


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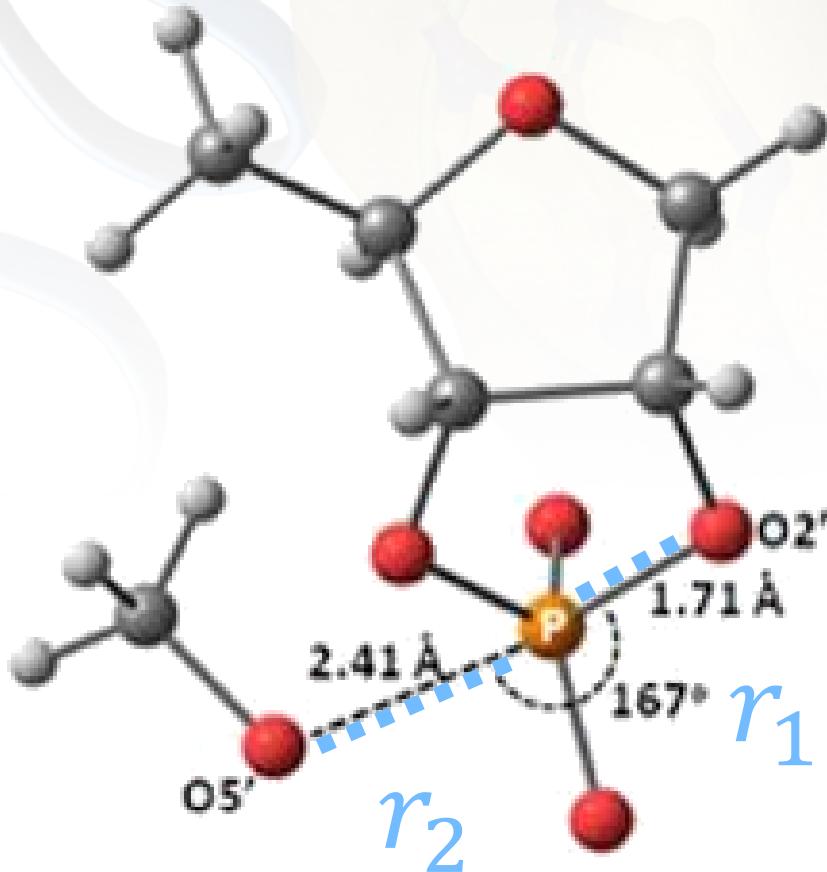


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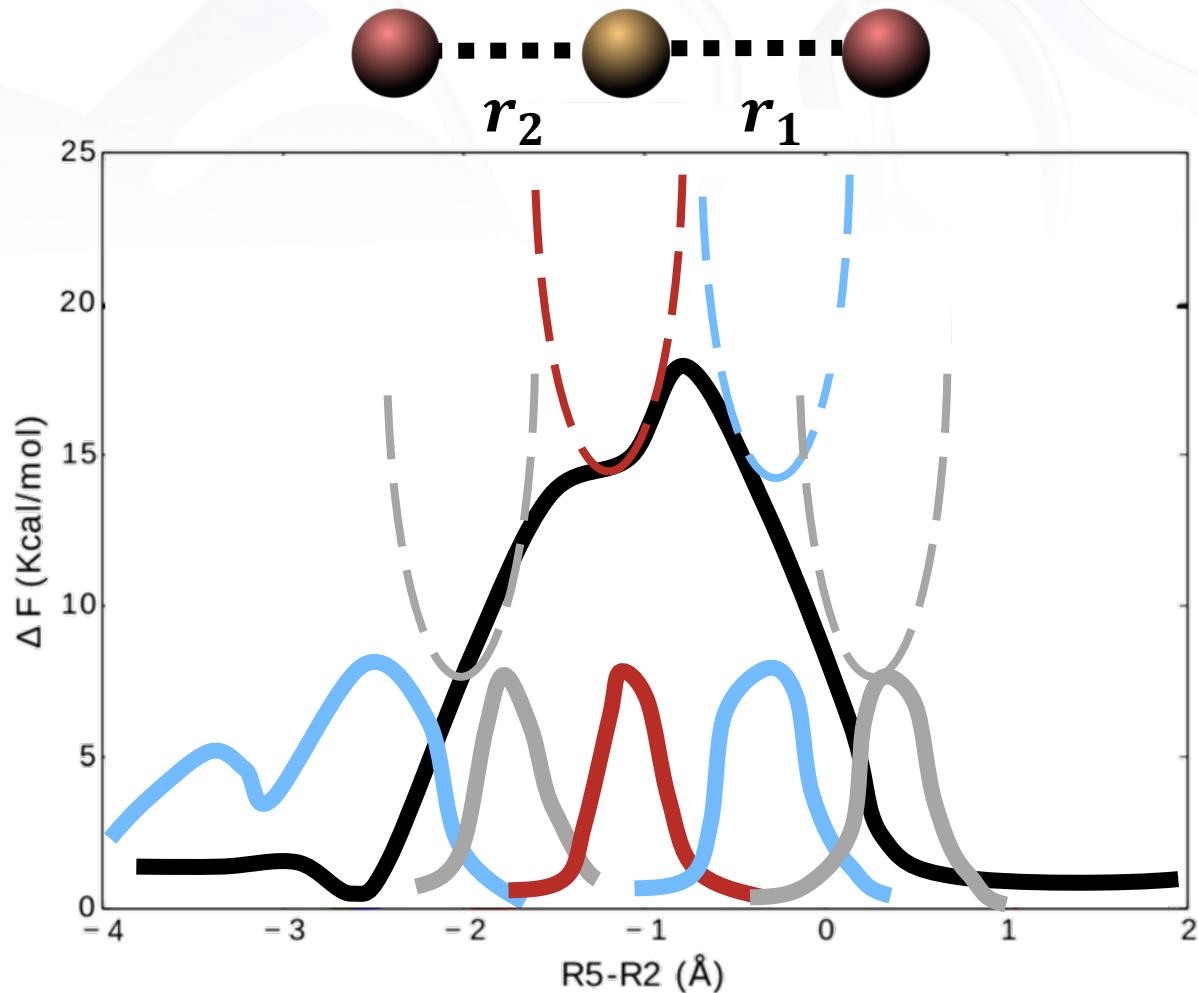


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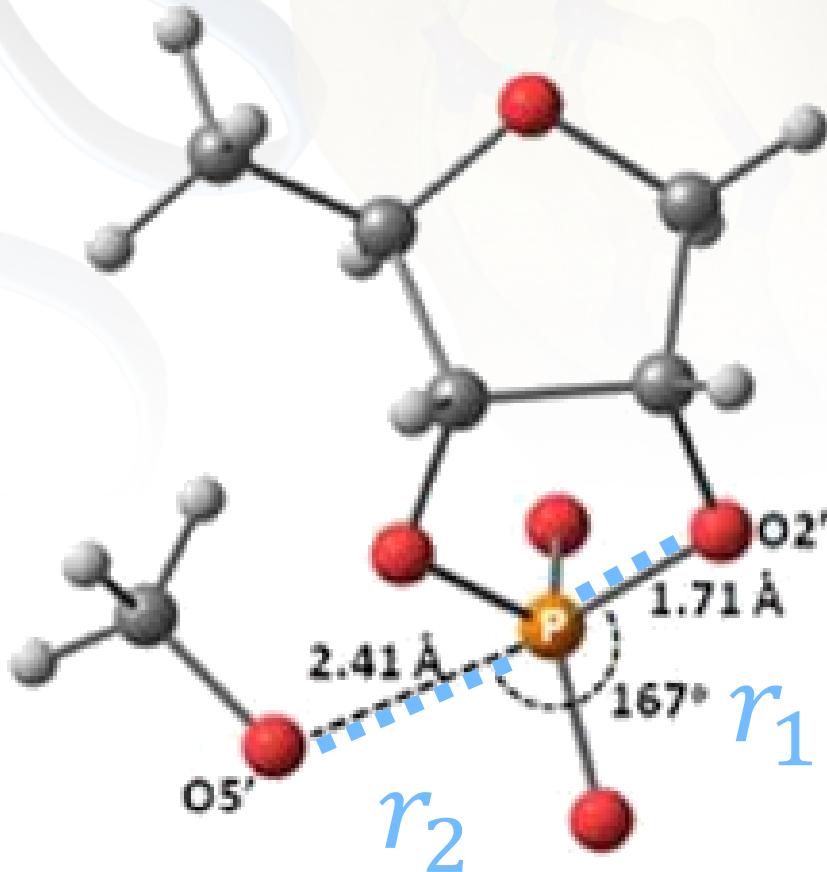


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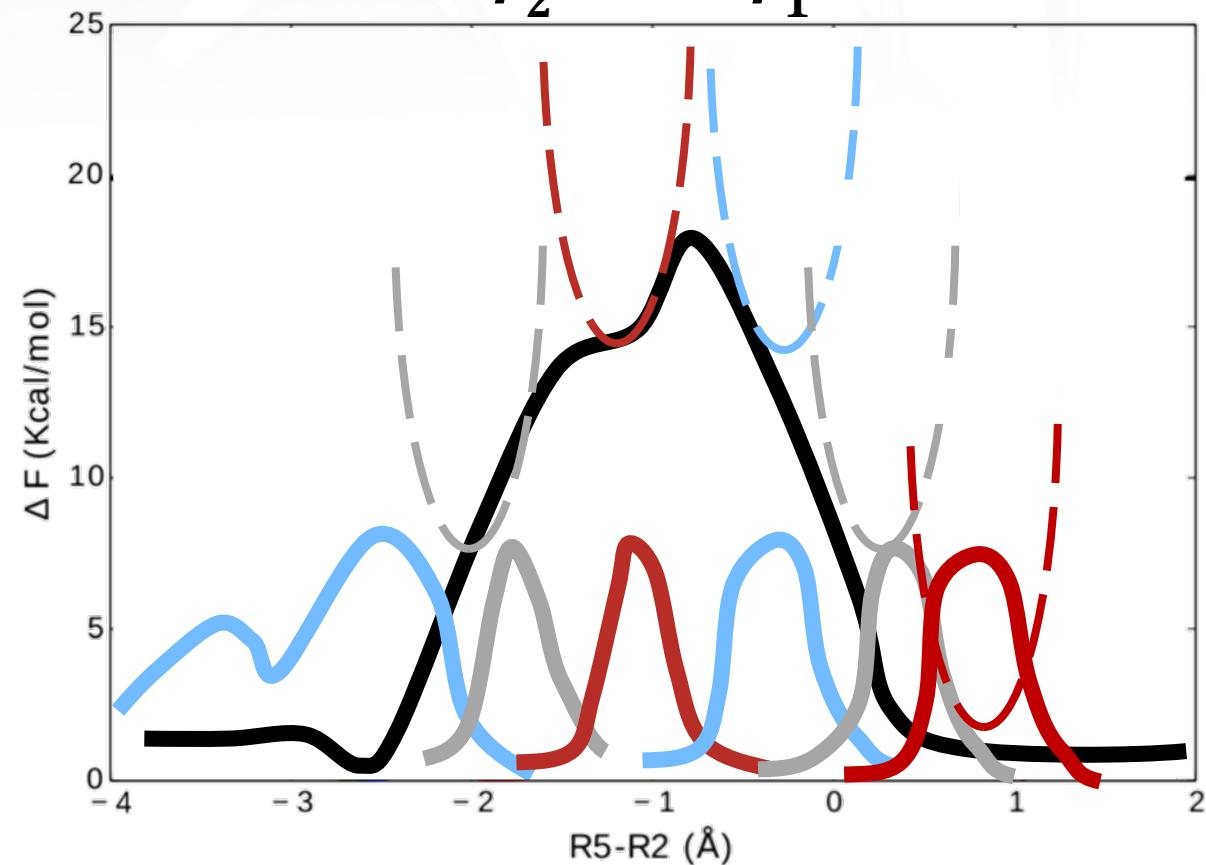


# Umbrella sampling

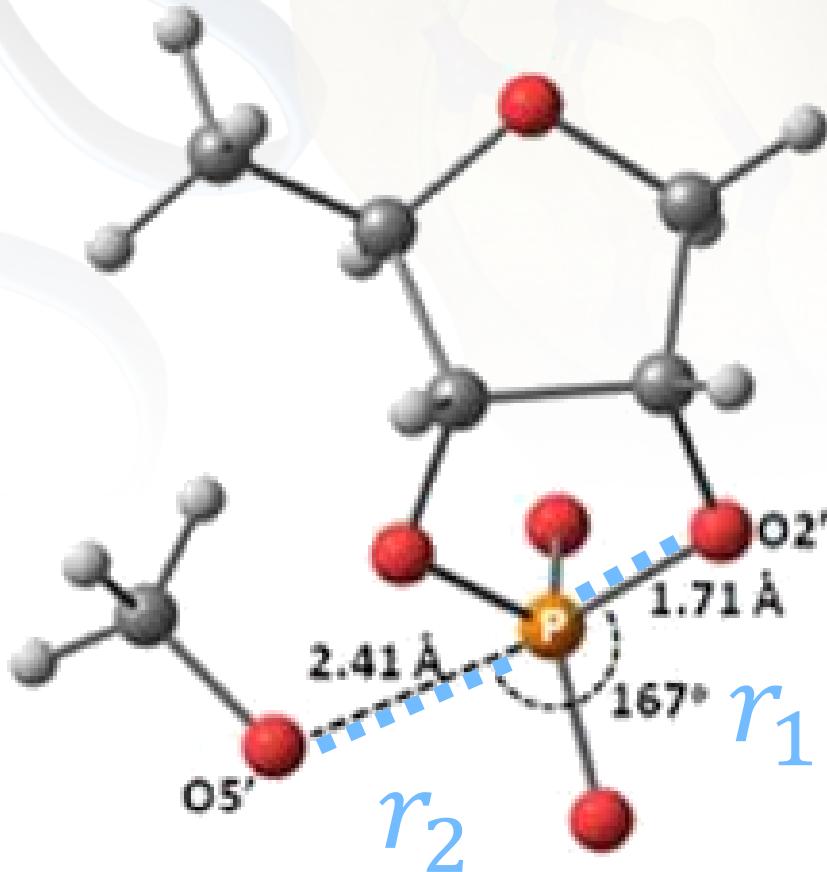


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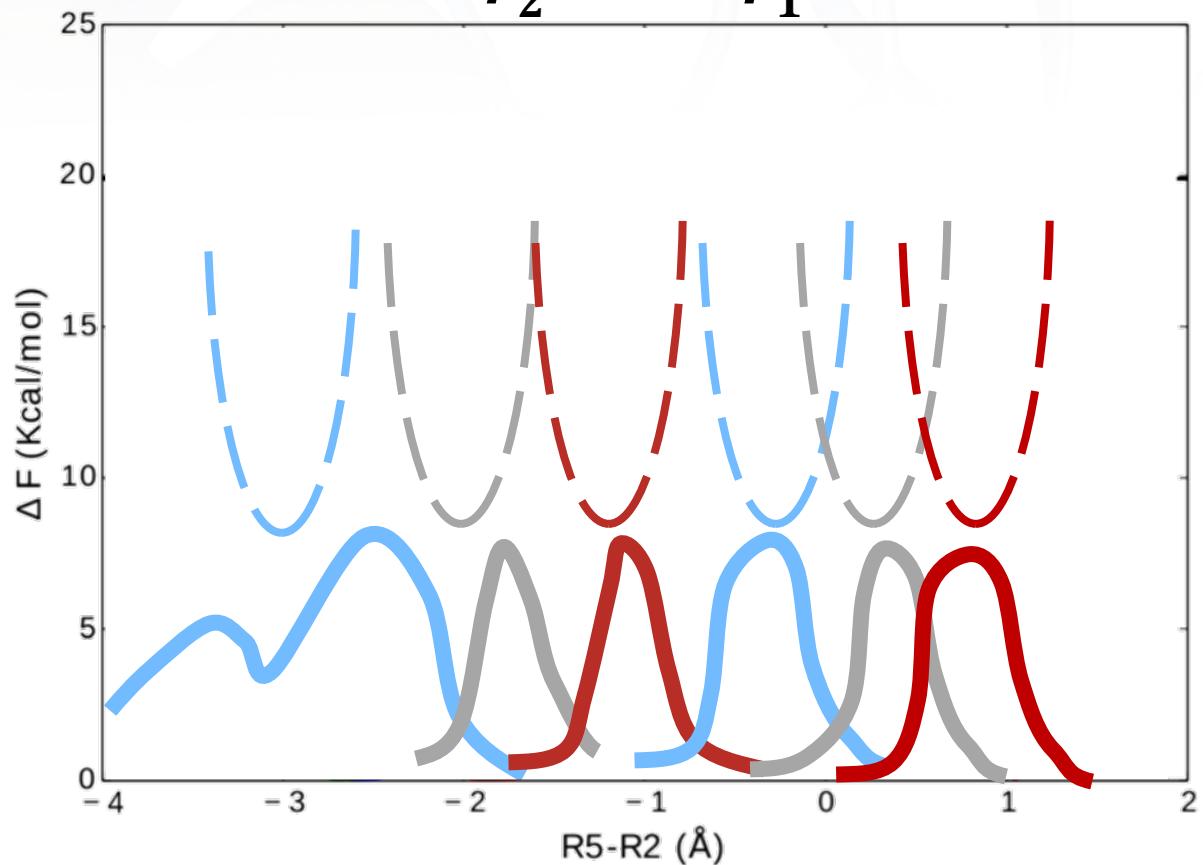
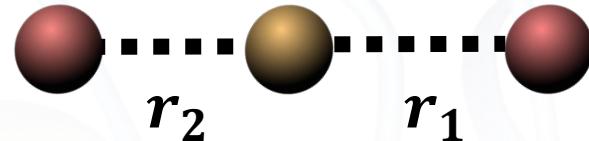


# Umbrella sampling

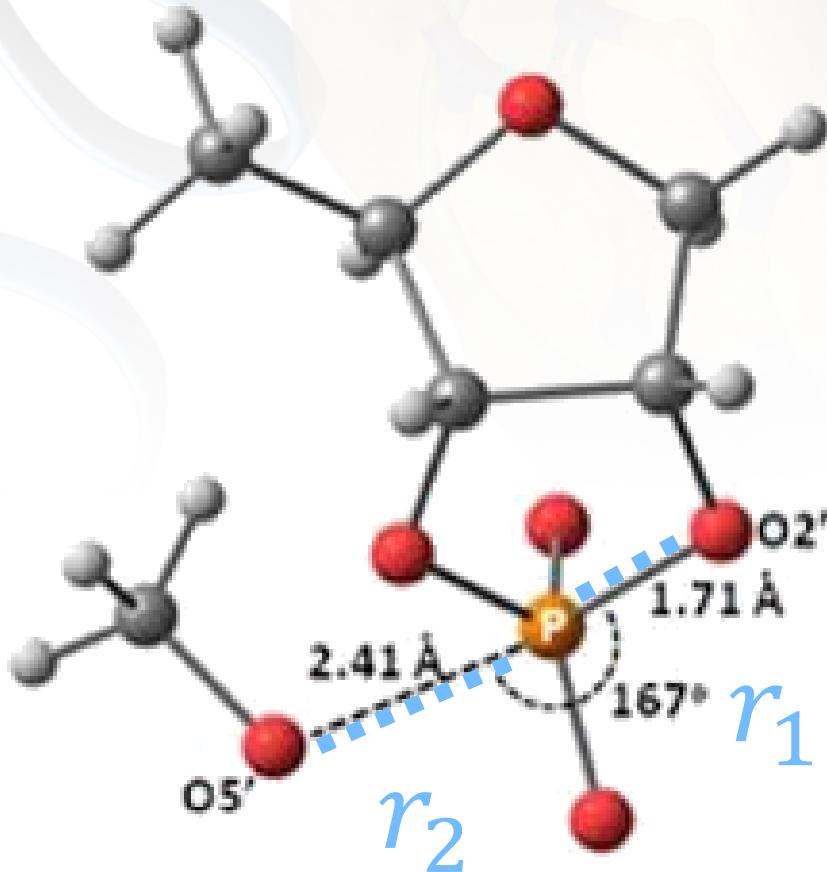


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# Umbrella sampling

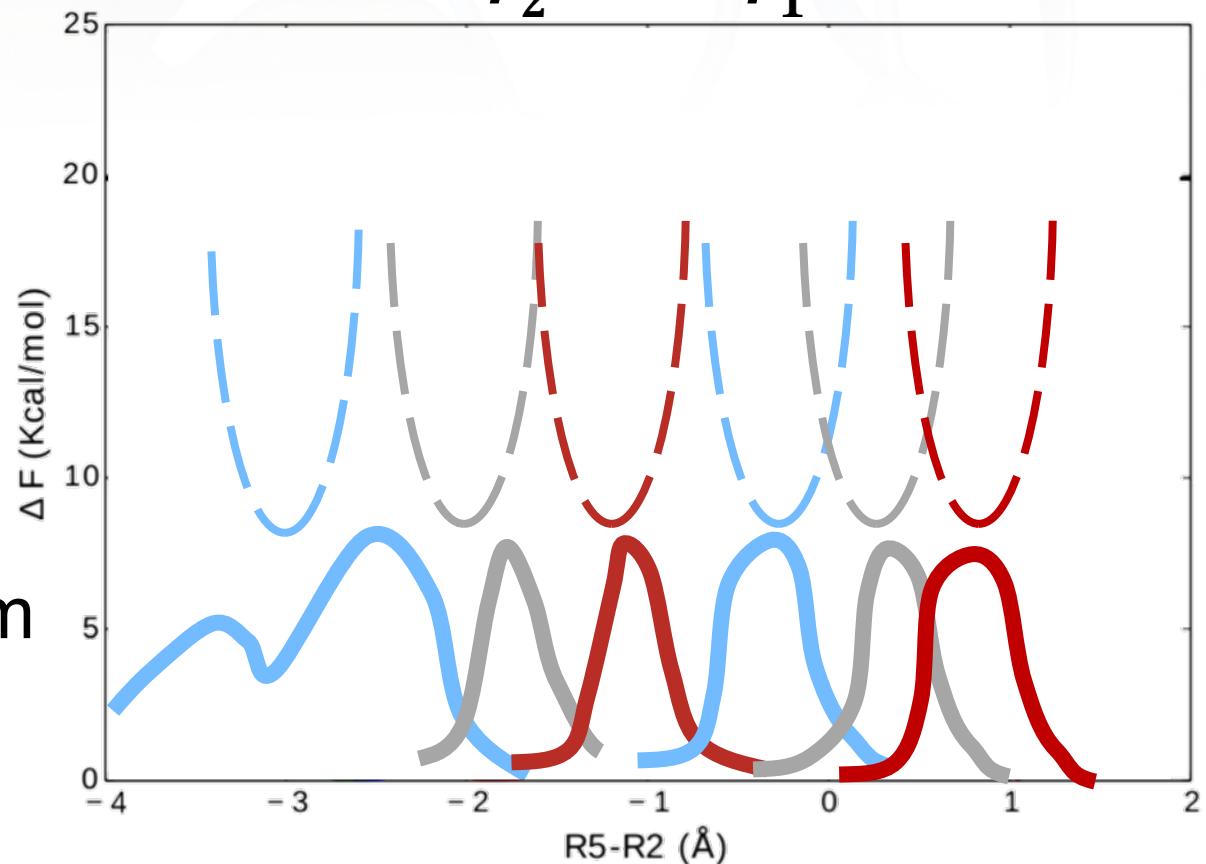


**WHAM:** Weighted Histogram Analysis Method

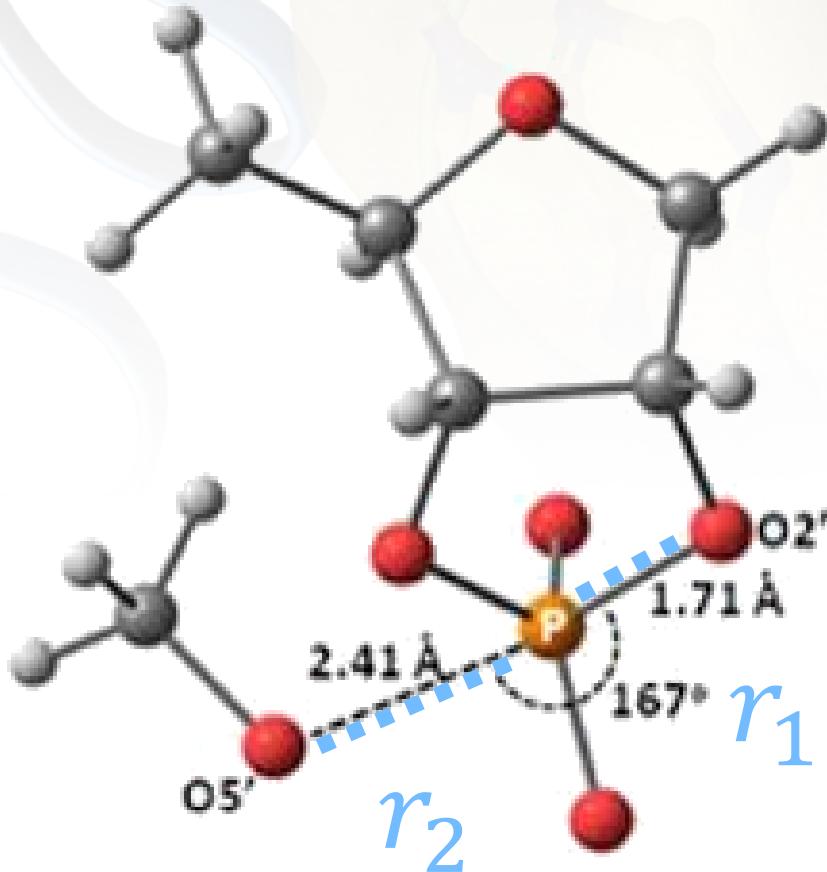
Kumar, et al. J Comput Chem, 13, 1011-1021, 1992

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# Umbrella sampling

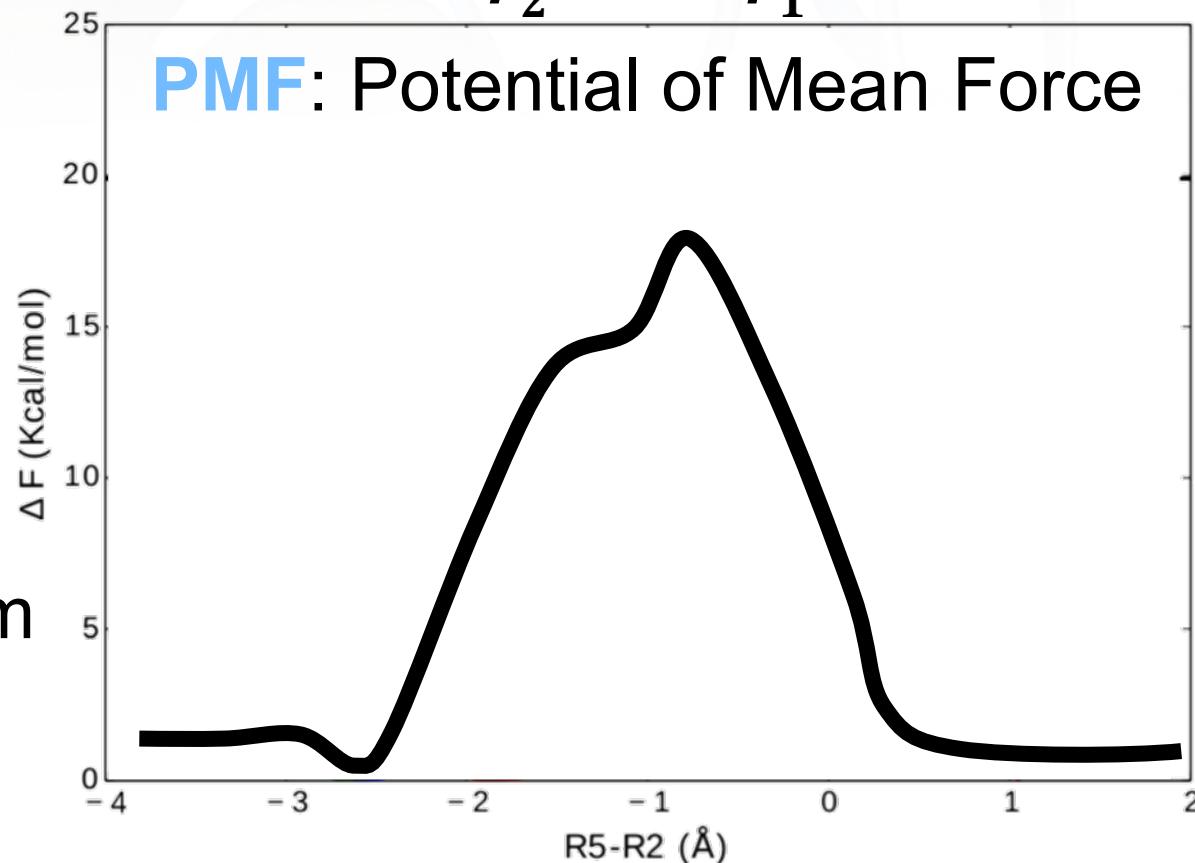
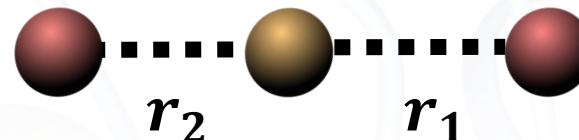


**WHAM:** Weighted Histogram Analysis Method

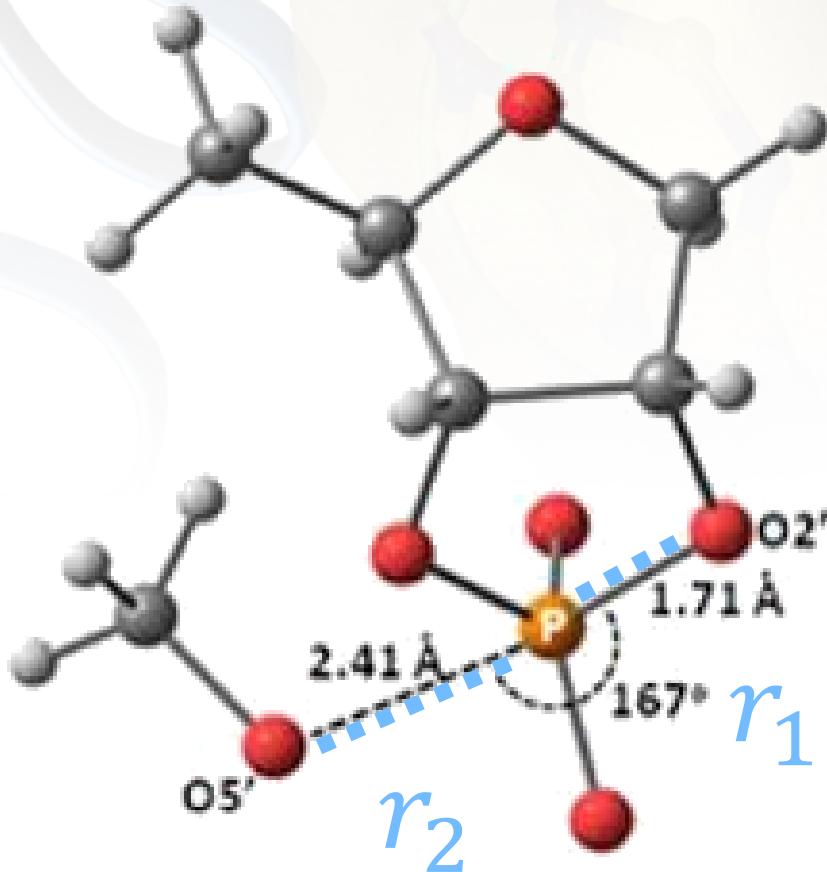
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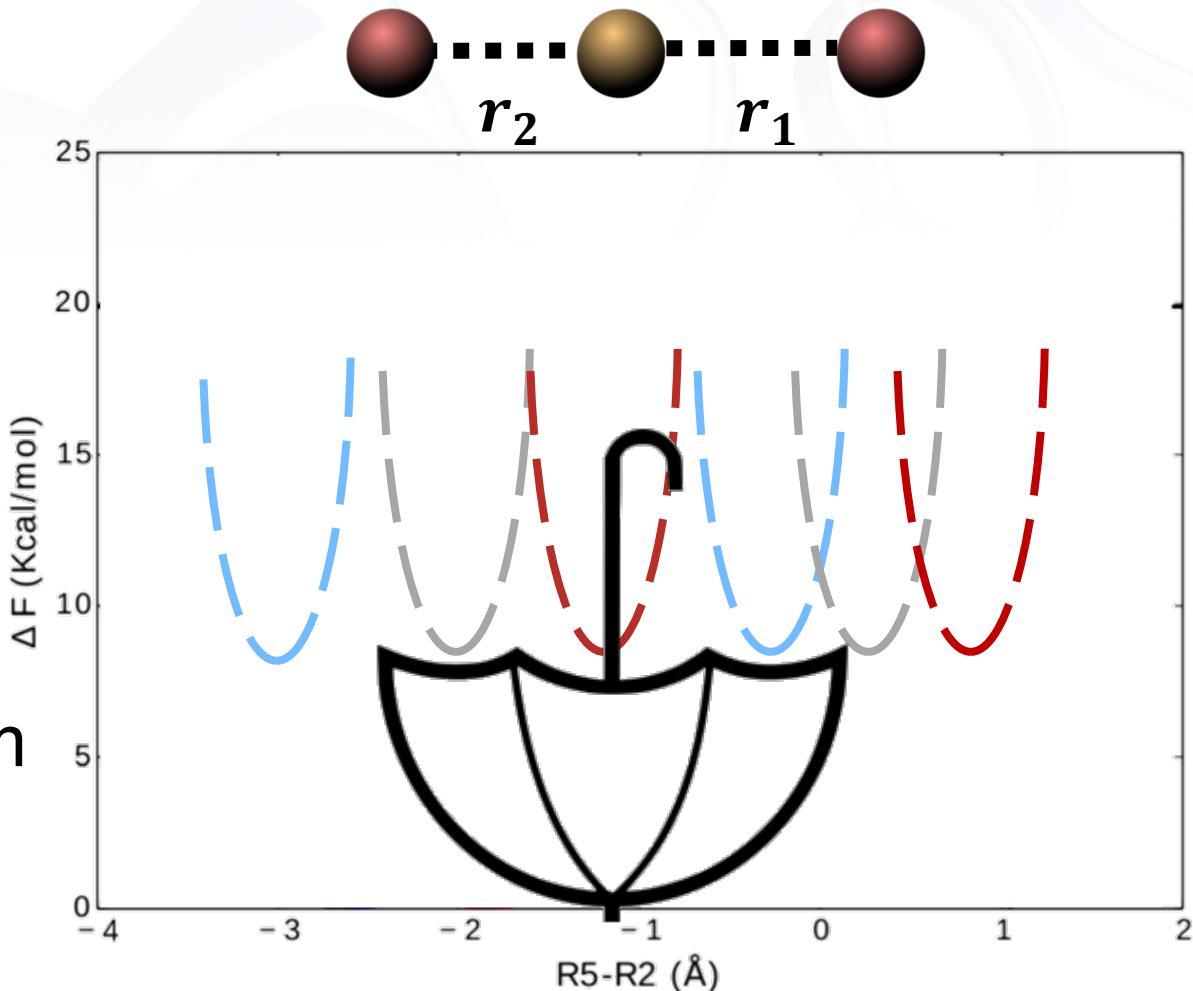


**WHAM:** Weighted Histogram Analysis Method

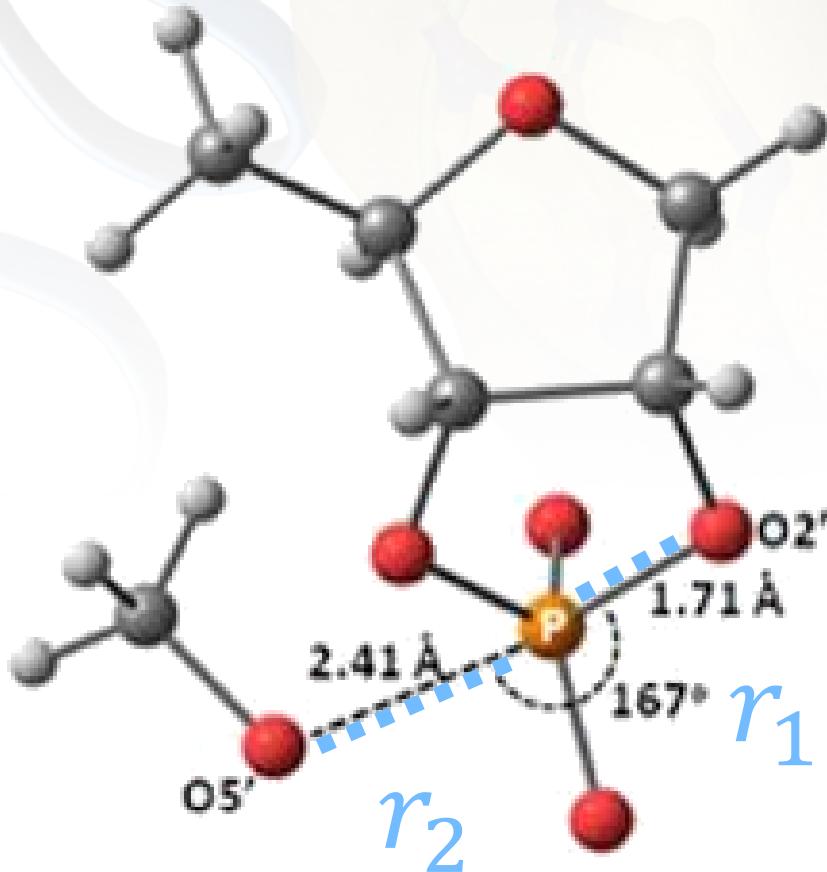
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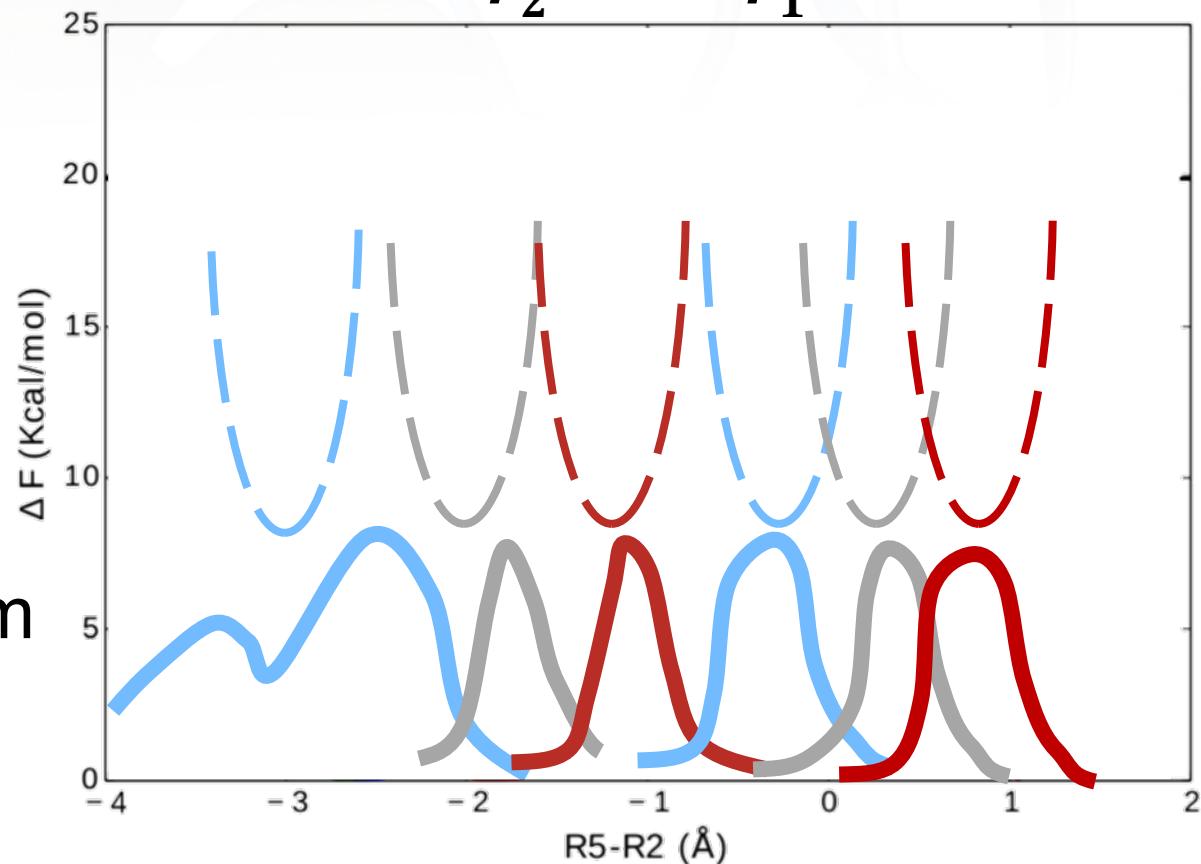


**WHAM:** Weighted Histogram Analysis Method

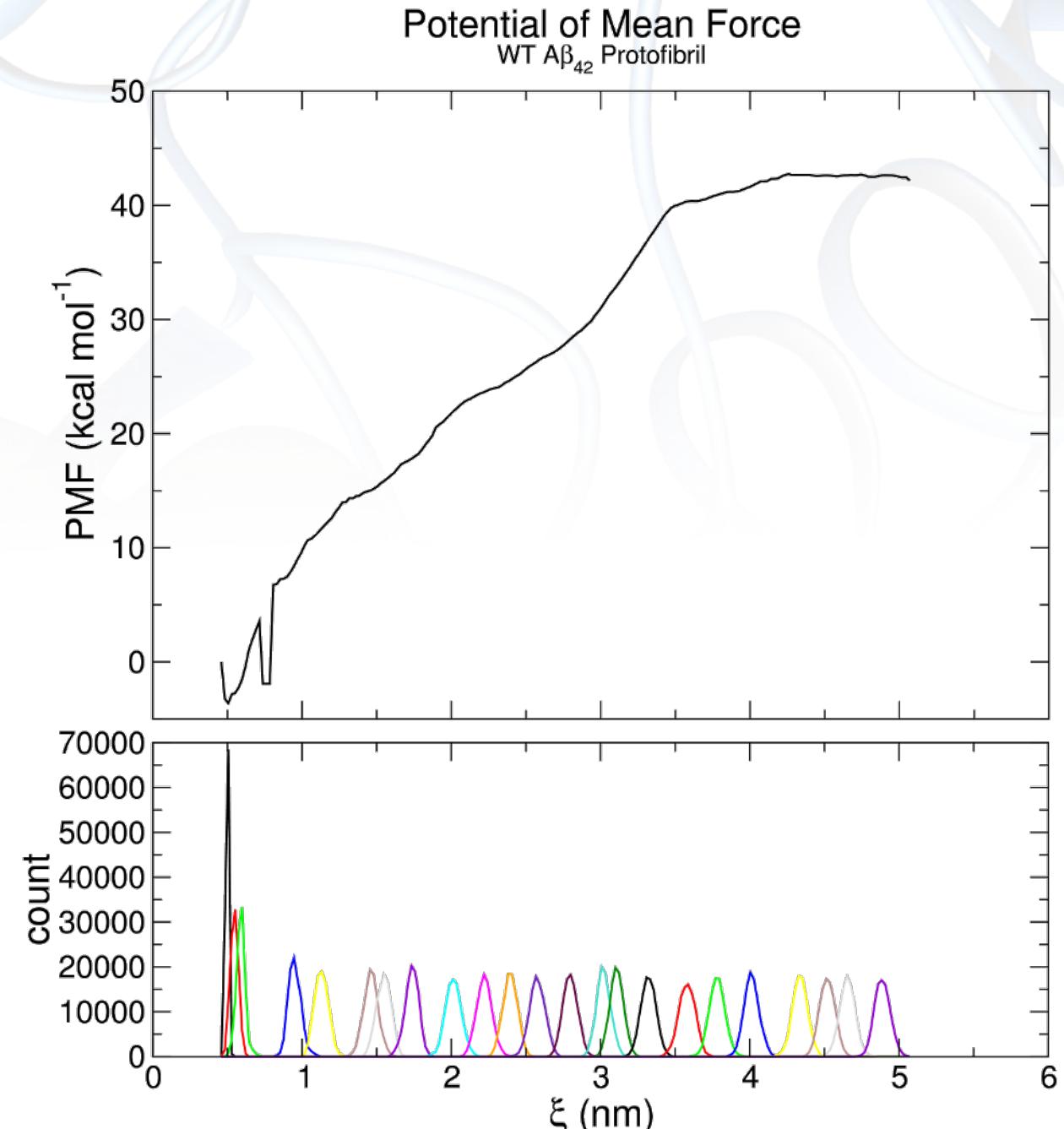
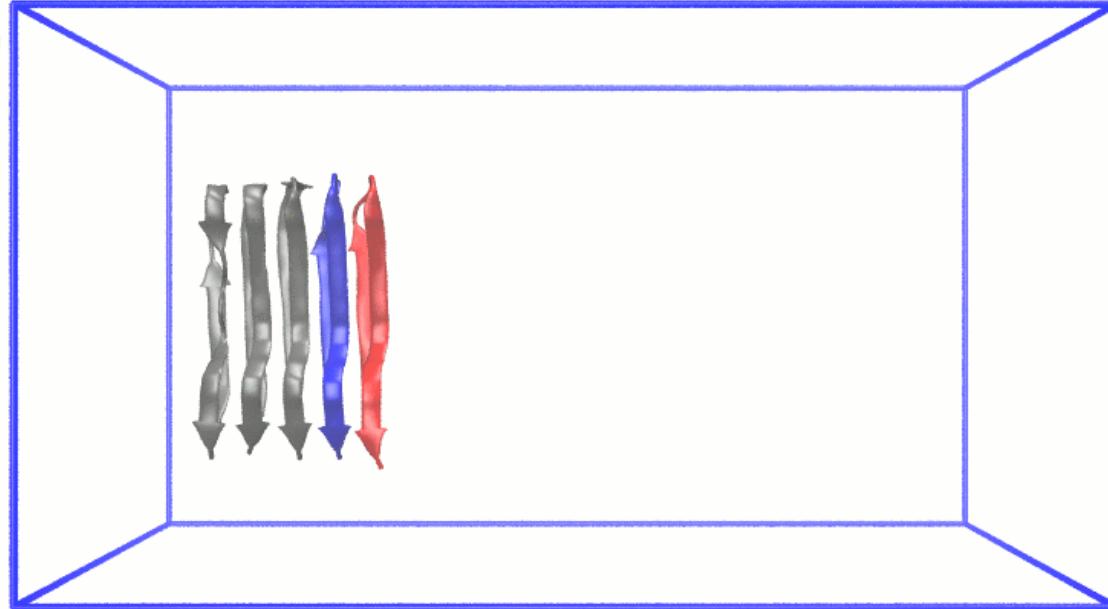
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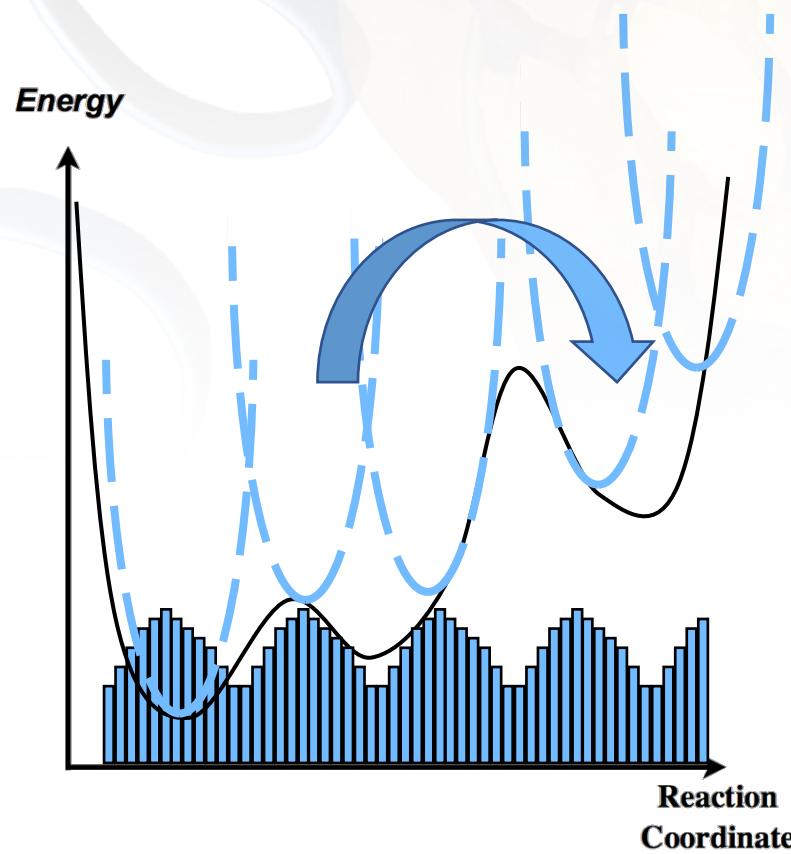
$$r_{RC} = r_2 - r_1$$



# Umbrella sampling



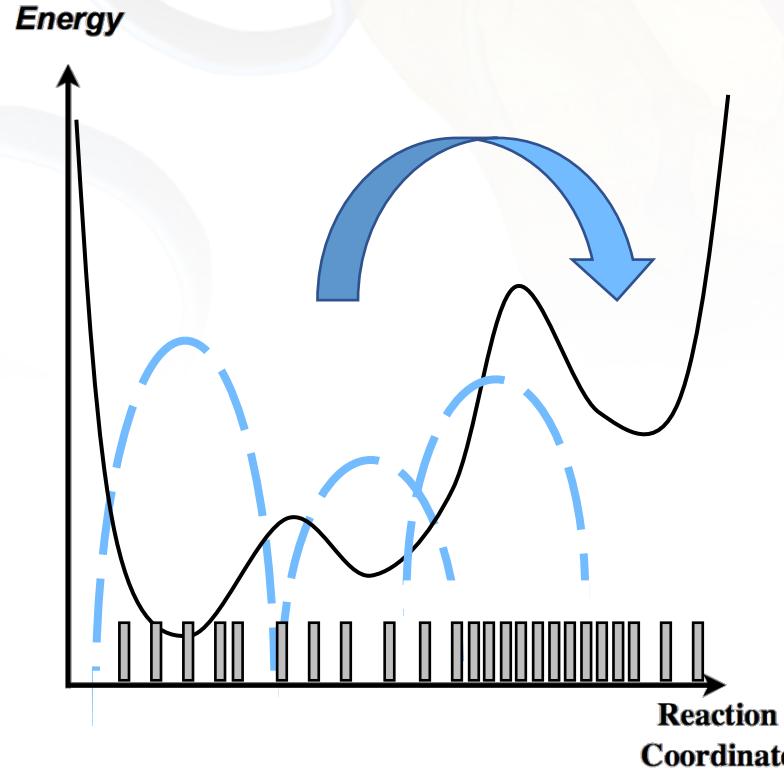
# Enhanced sampling techniques



**Enhanced Sampling Techniques**

- Umbrella Sampling

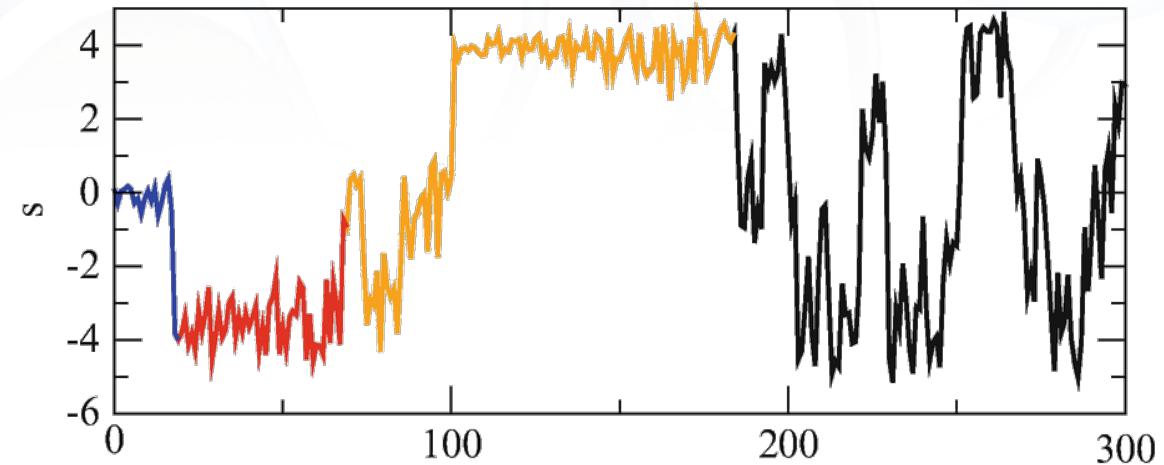
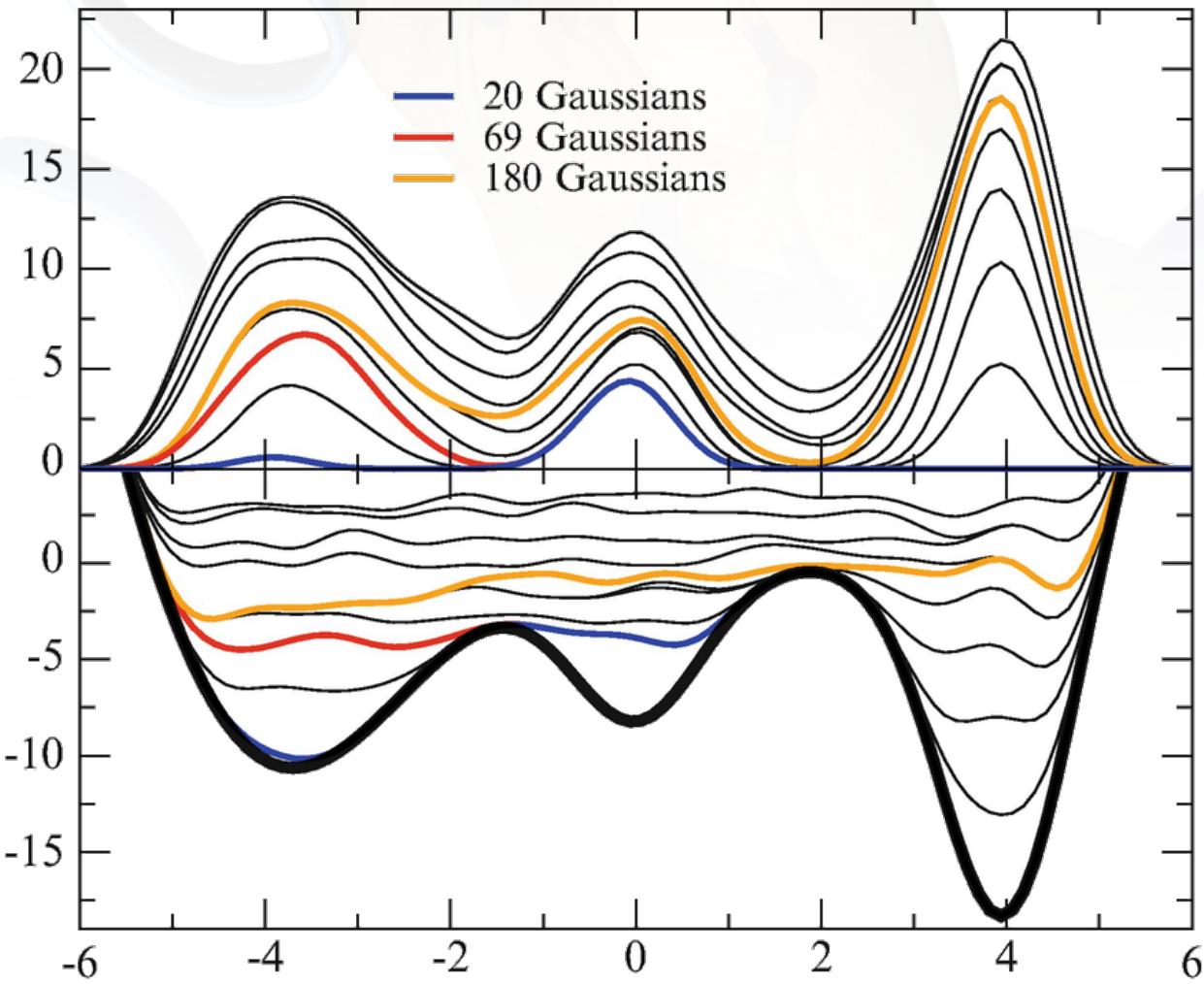
# Enhanced sampling techniques



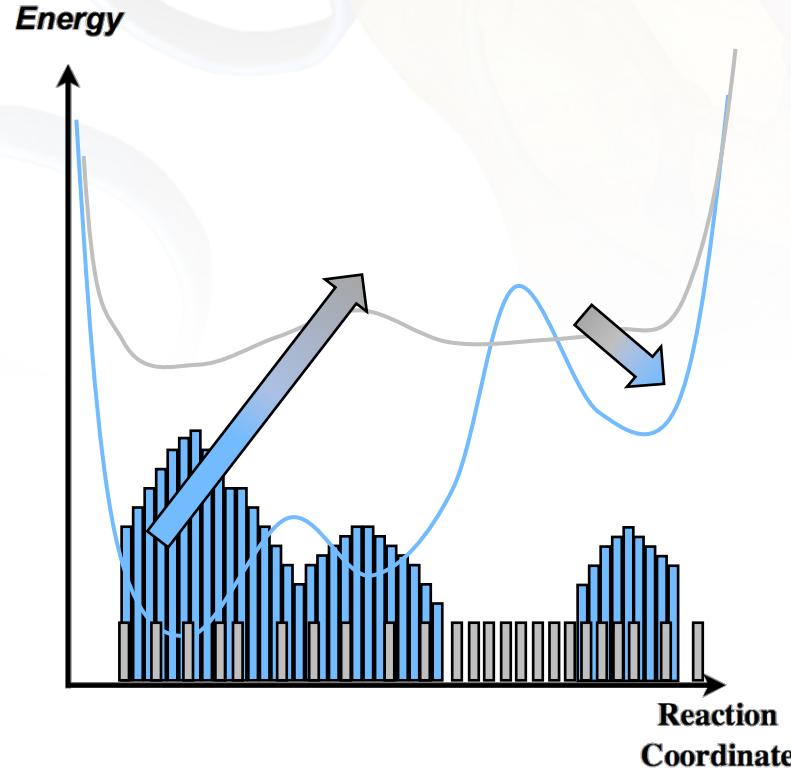
## Enhanced Sampling Techniques

- Umbrella Sampling
- Adaptive Metadynamics

# Enhanced sampling techniques



# Enhanced sampling techniques

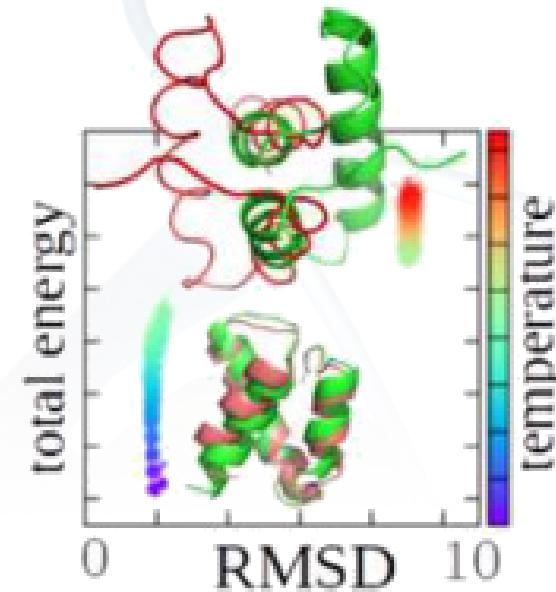
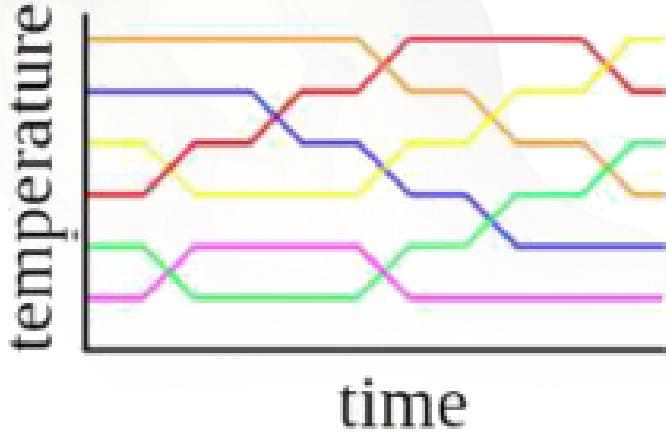


## Enhanced Sampling Techniques

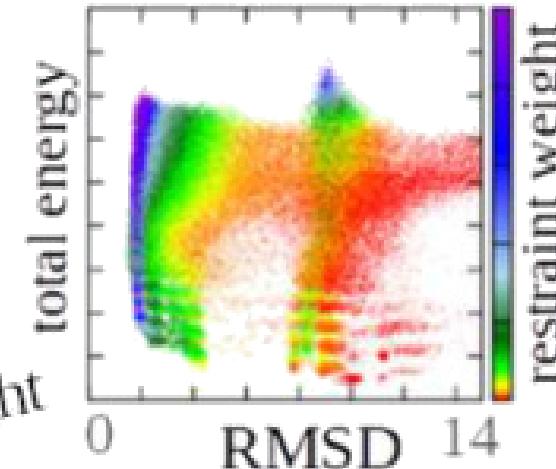
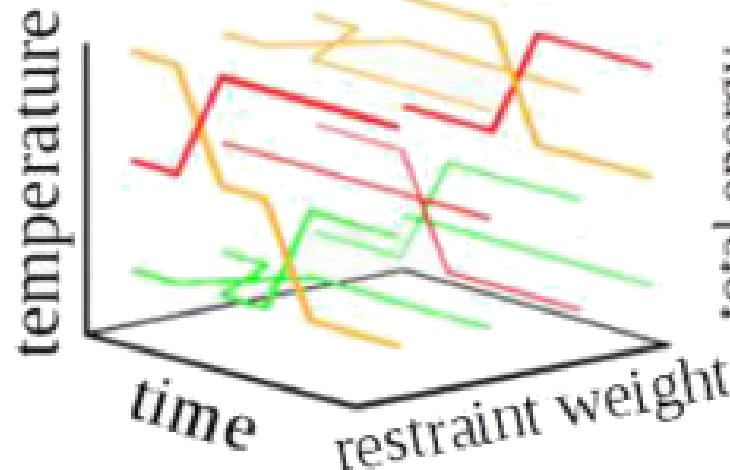
- Umbrella Sampling
- Adaptive Metadynamics
- Replica Exchange Molecular Dynamics

# Enhanced sampling techniques

MREMD

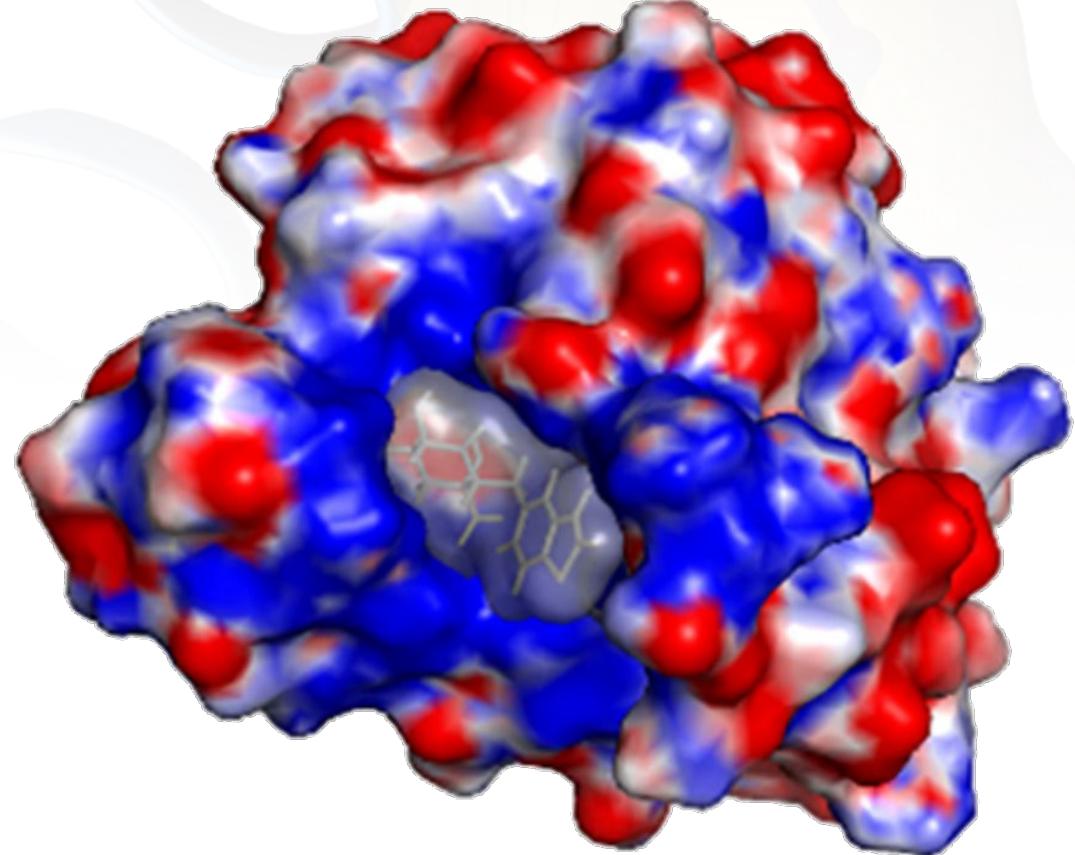


HREMD

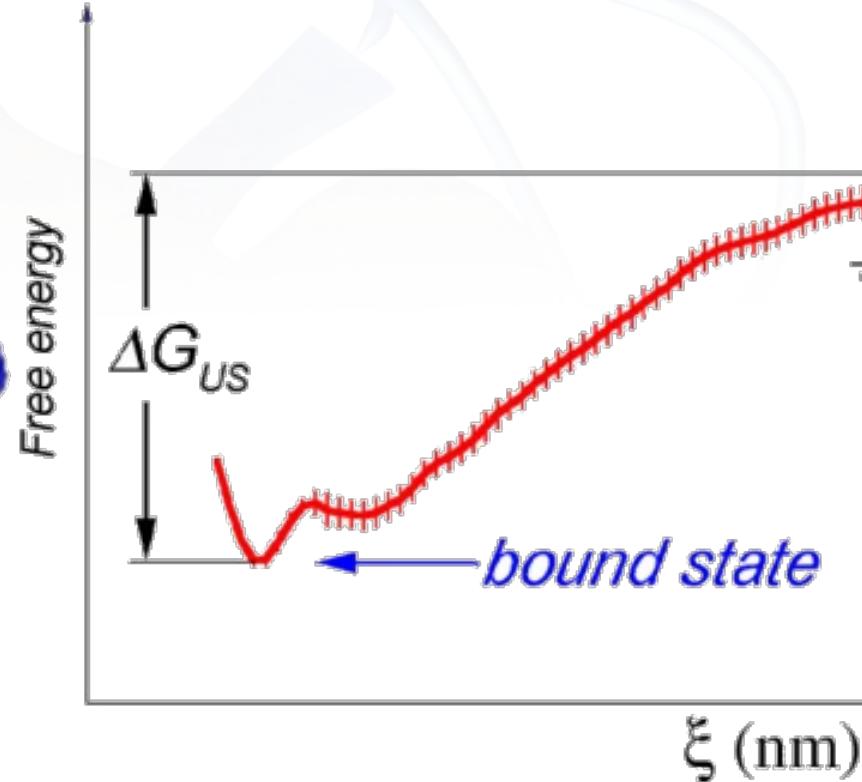
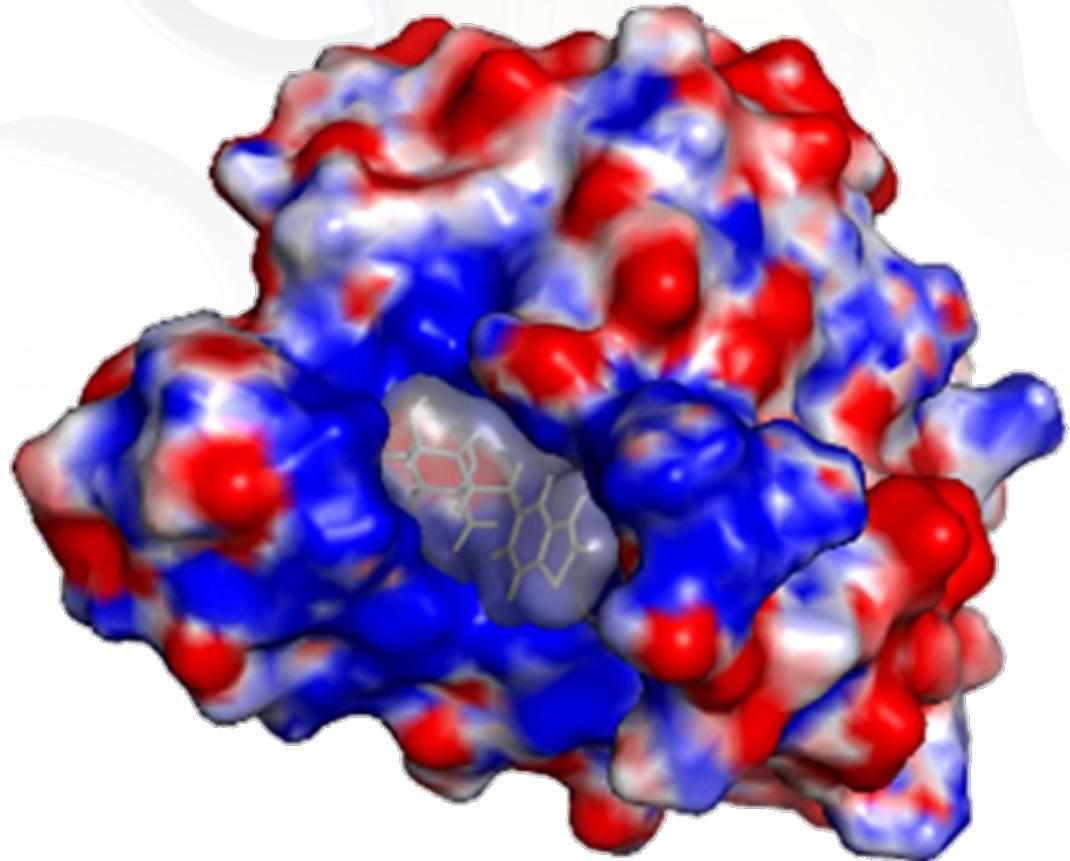


# Questions?

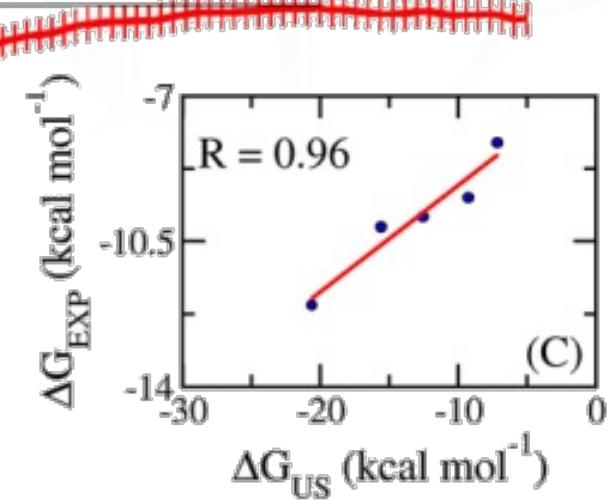
# Thermodynamic integration



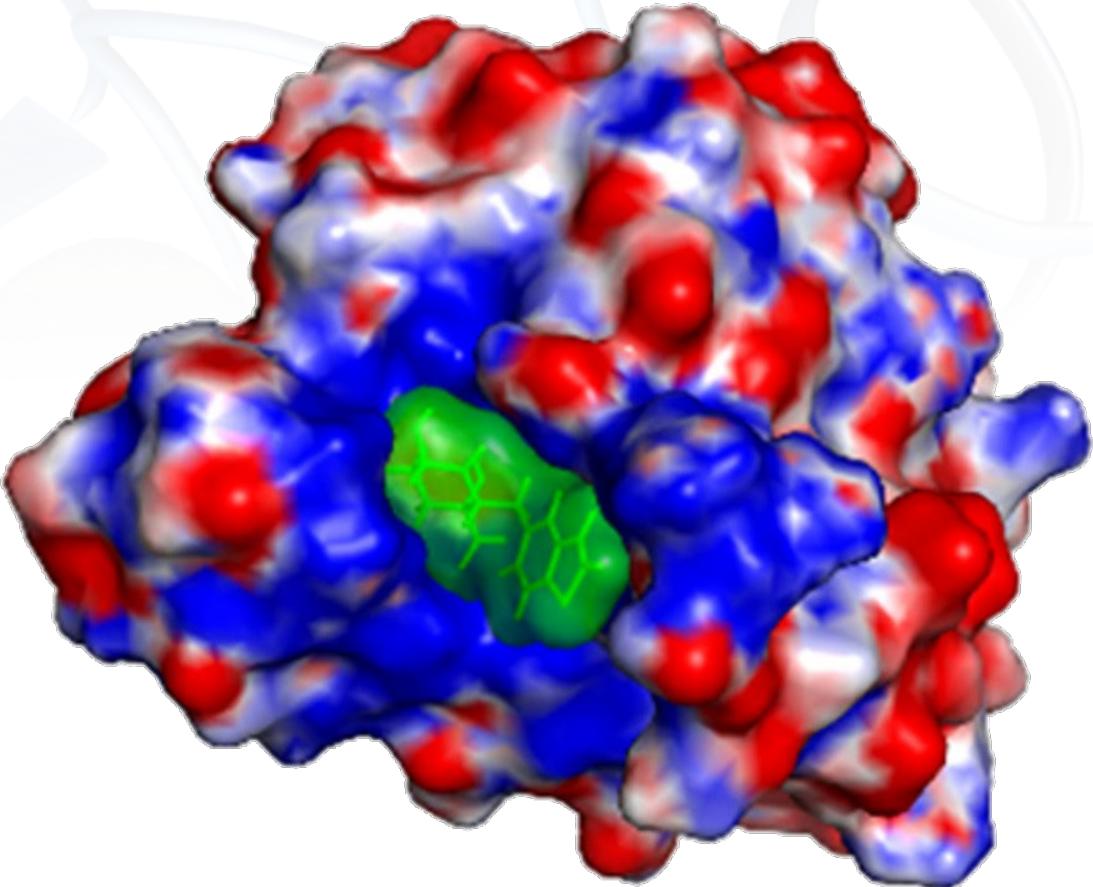
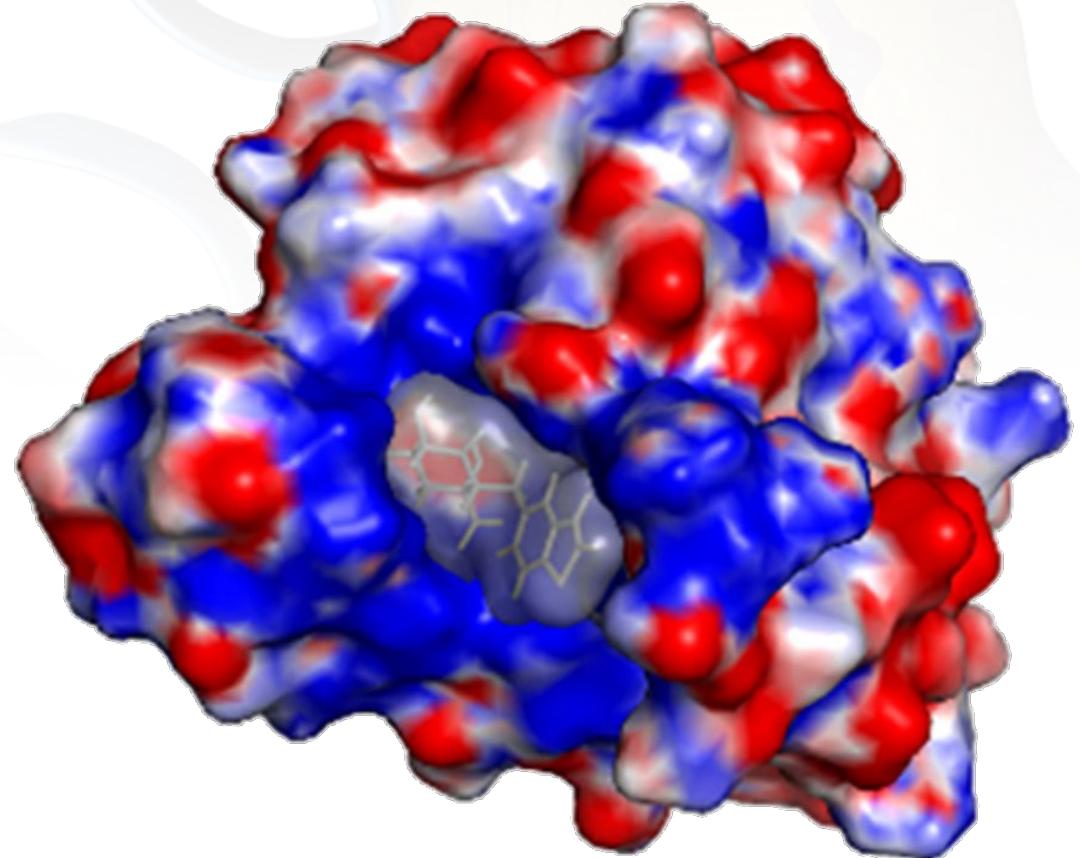
# Thermodynamic integration



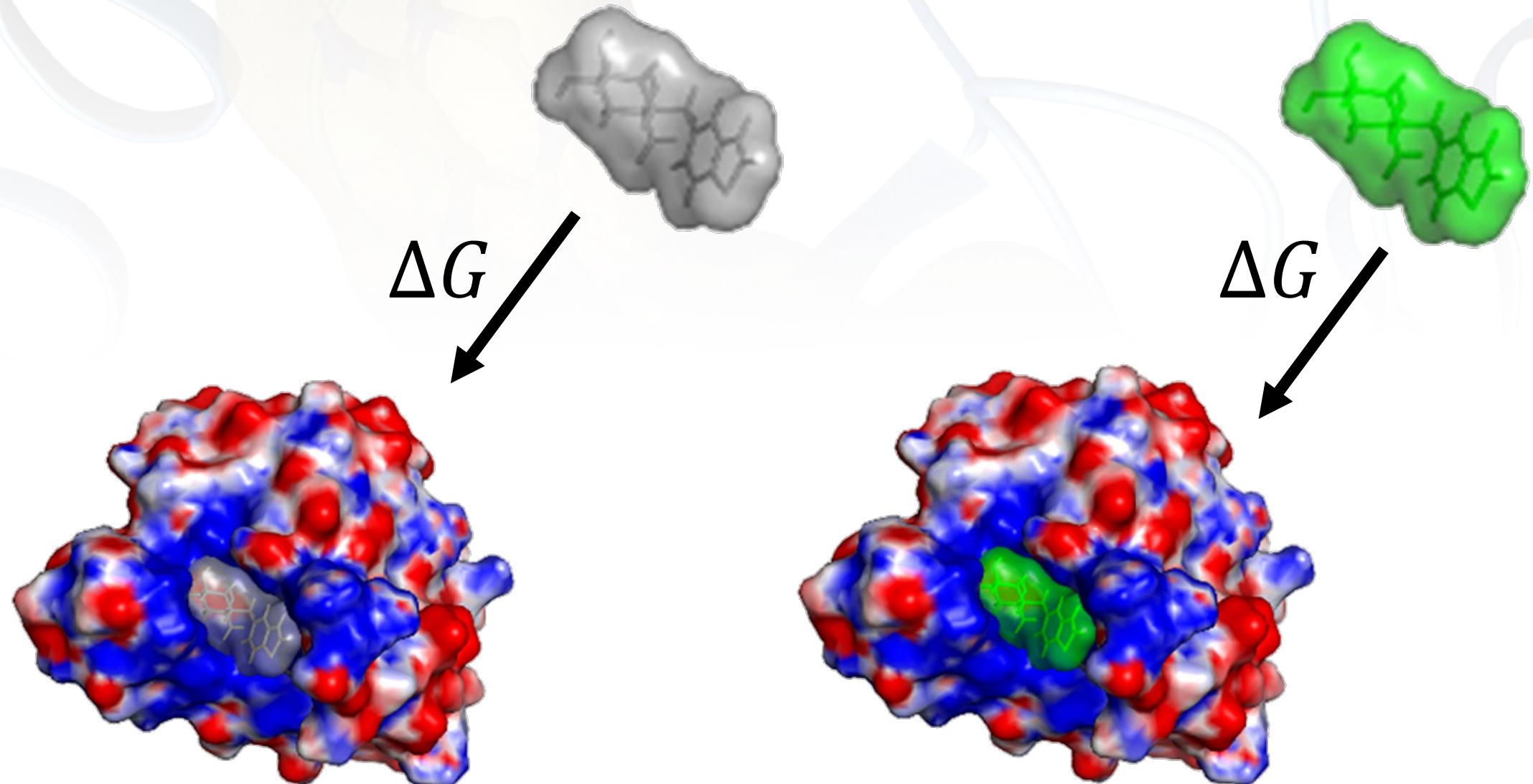
*unbound state*



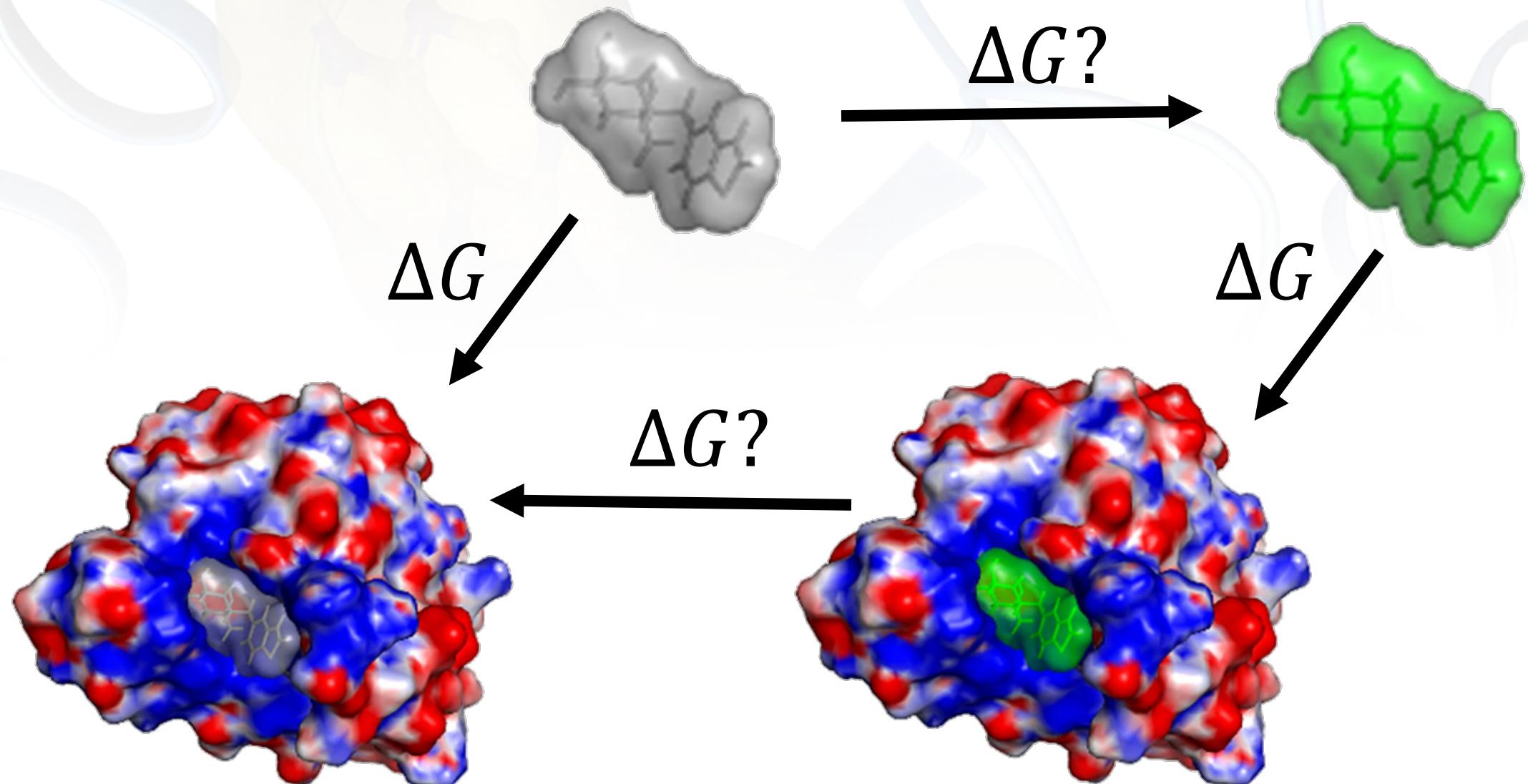
# Thermodynamic integration



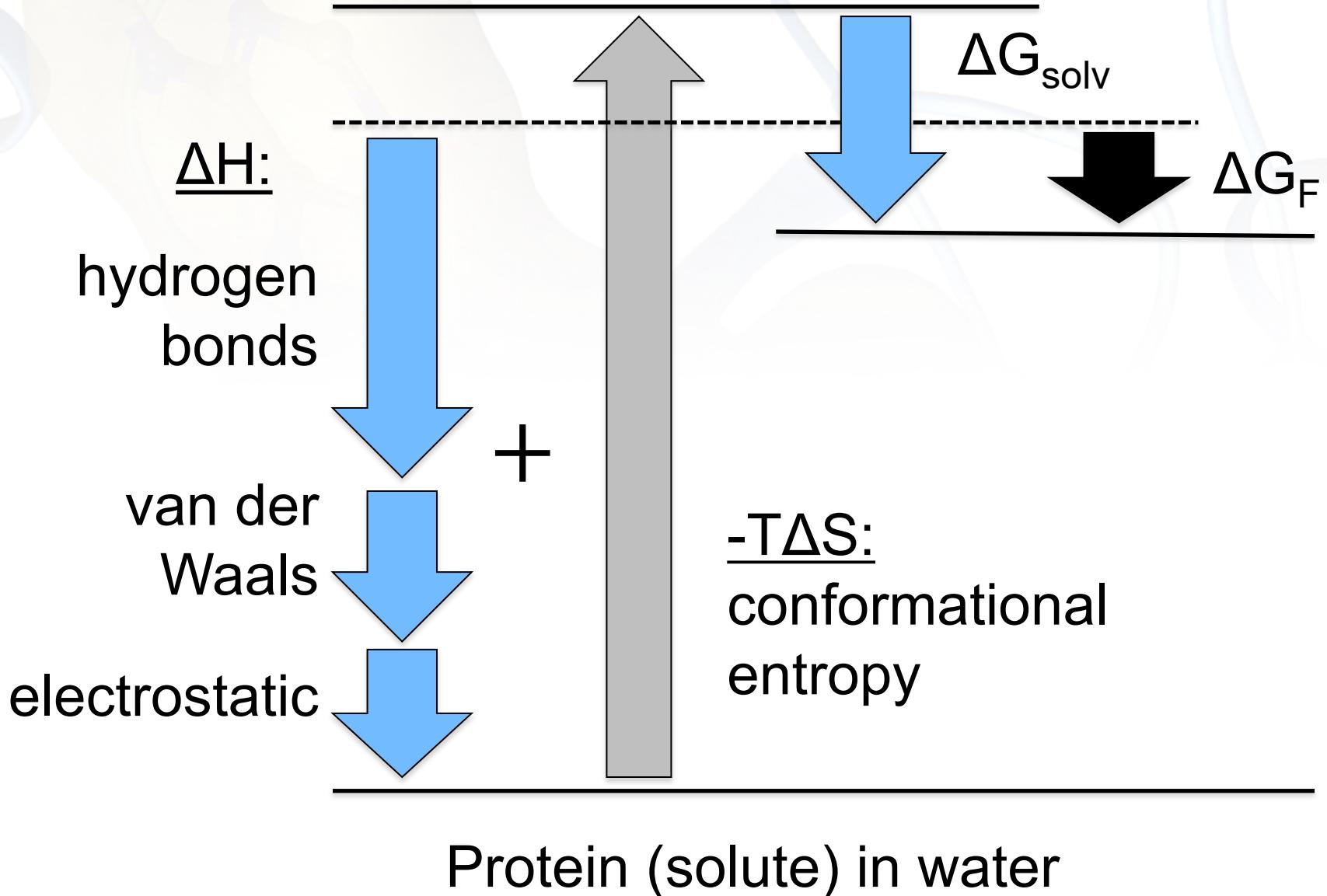
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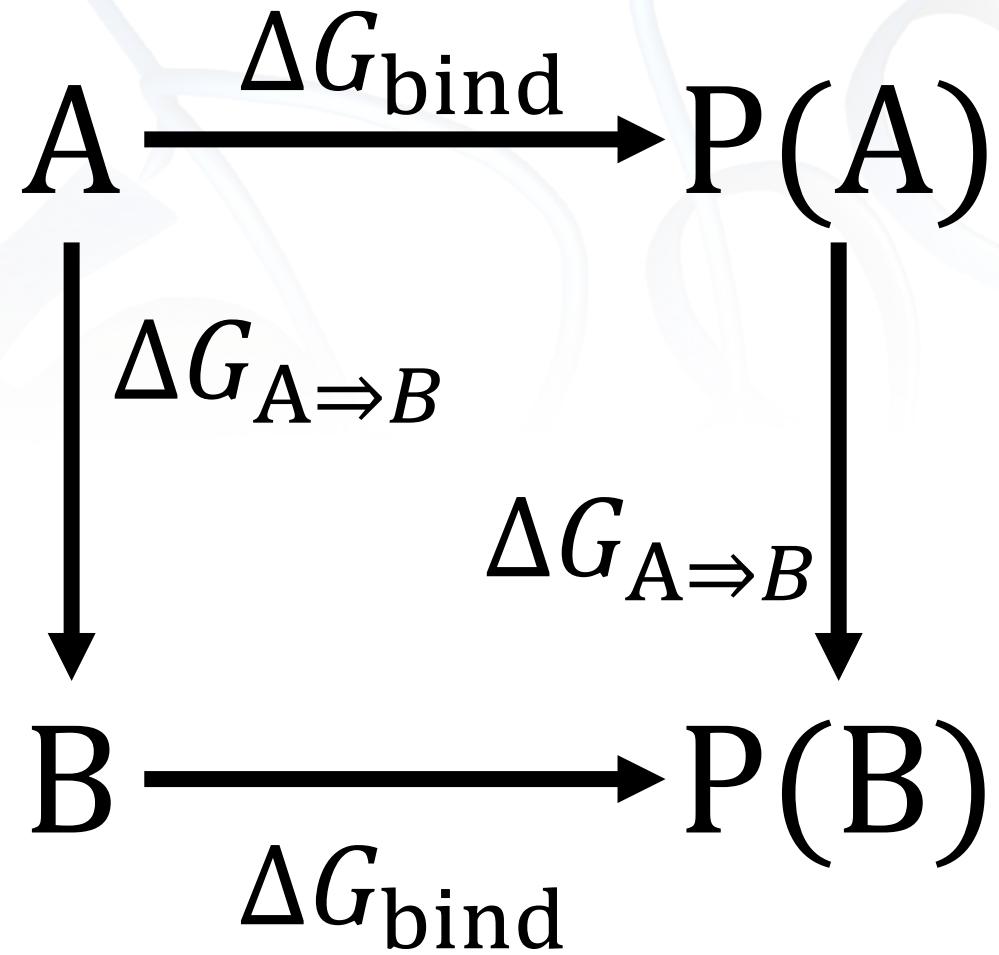
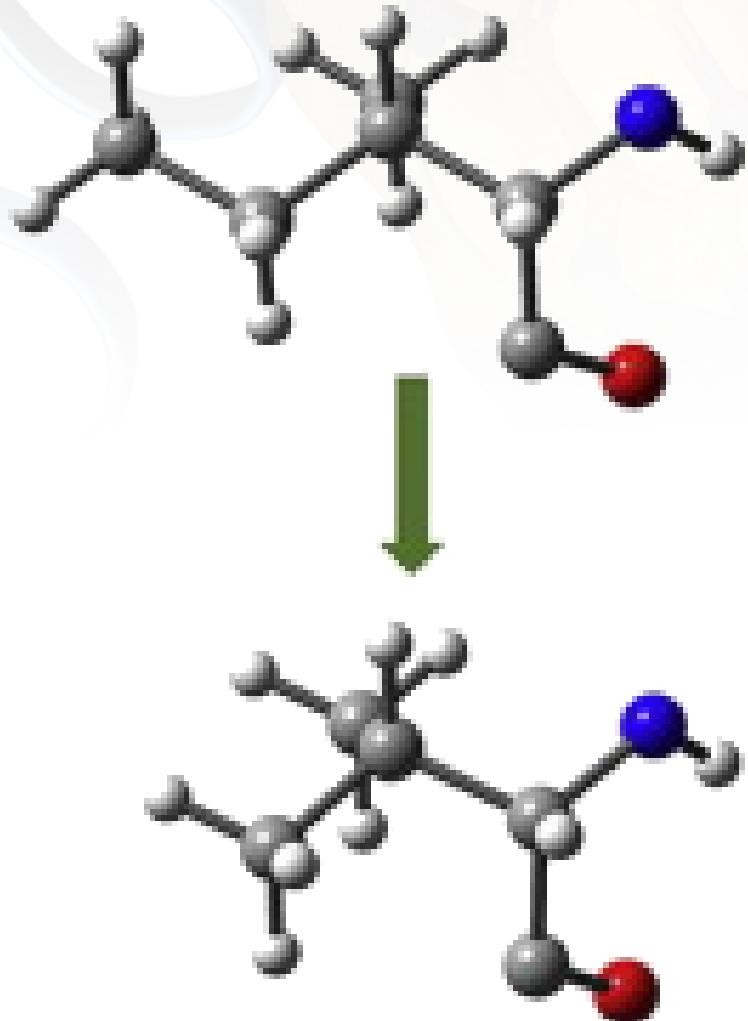
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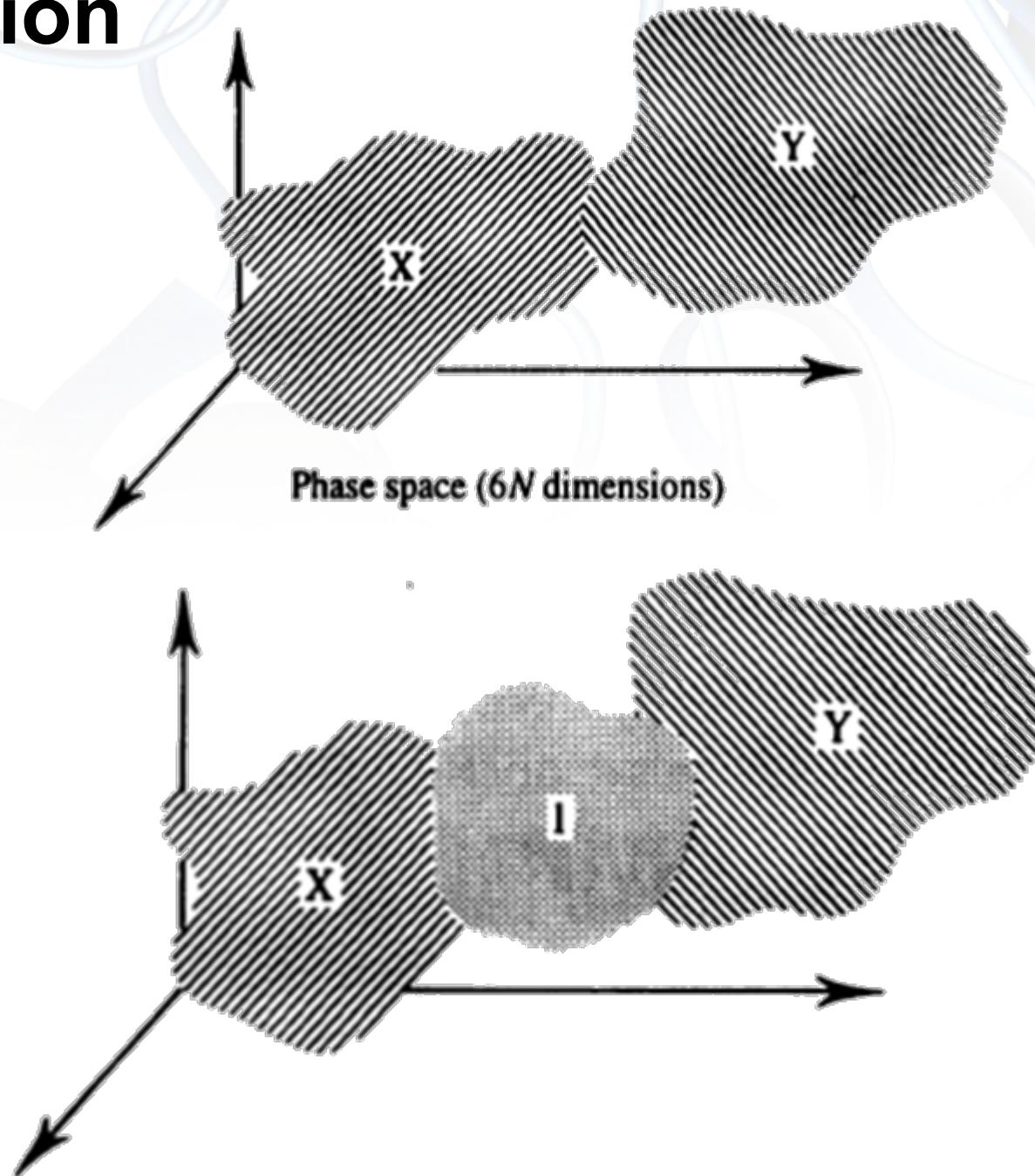
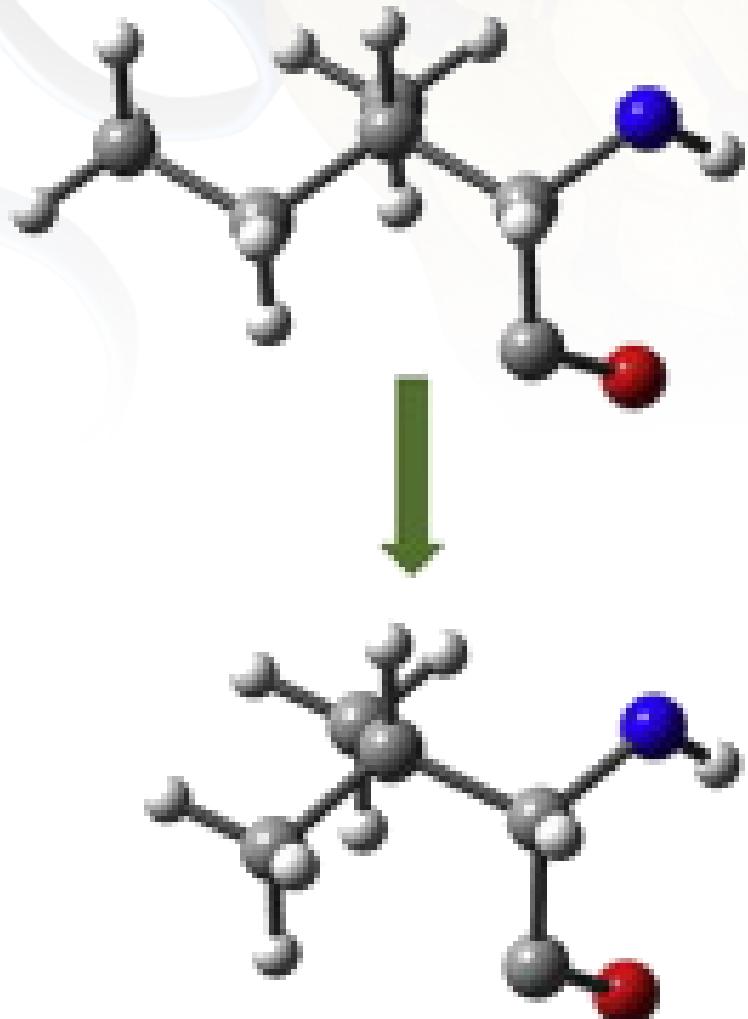
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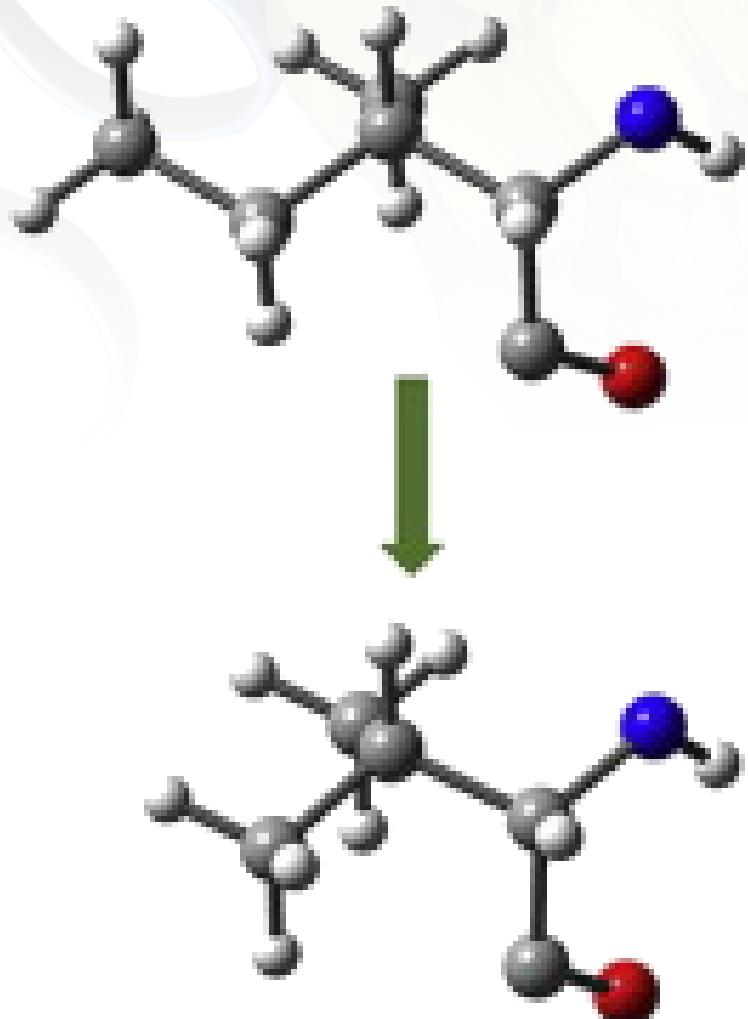
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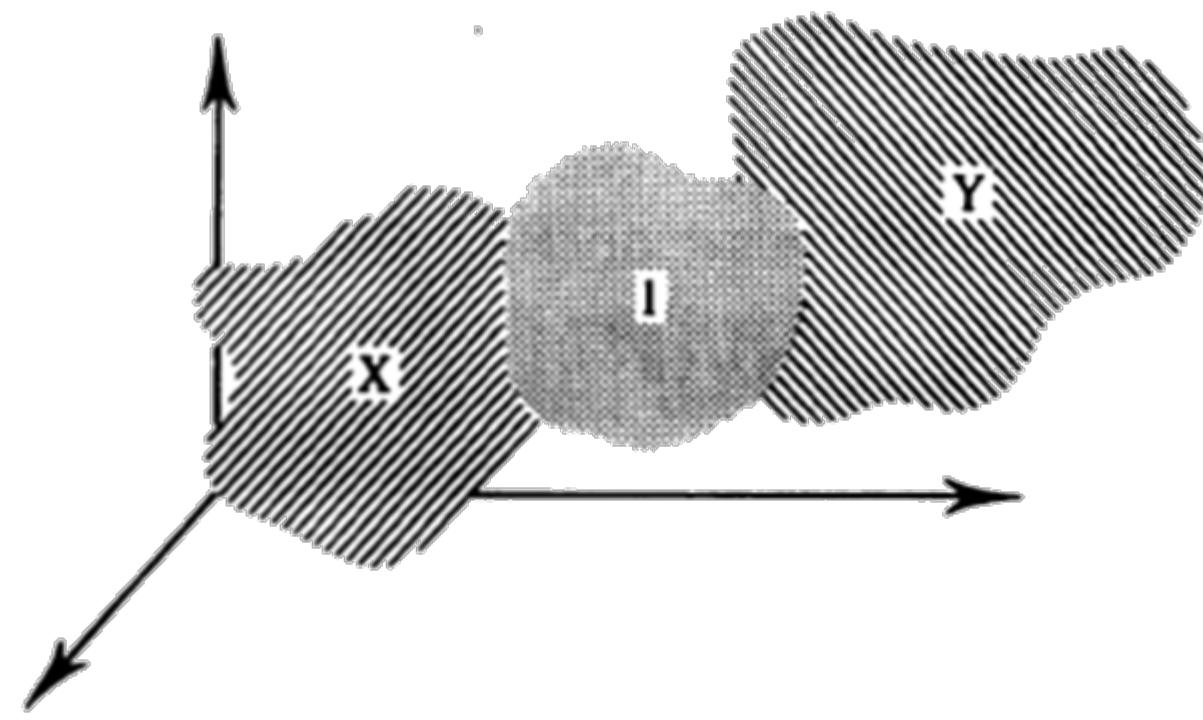
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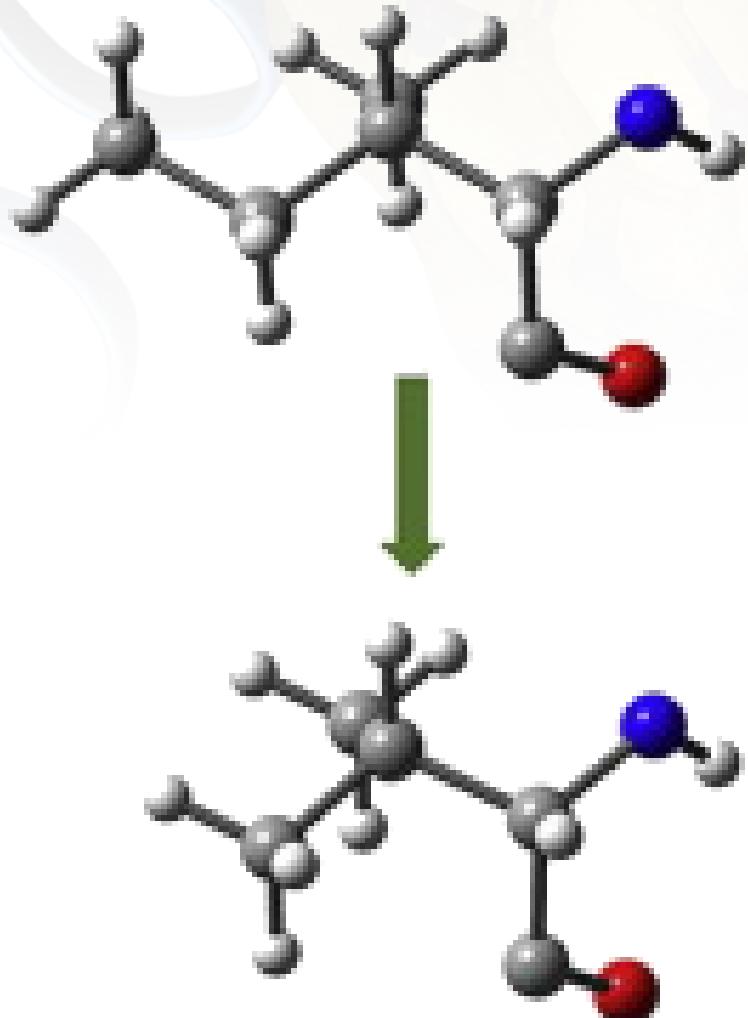
$\lambda=0$

$\lambda=1$

$$\Delta G(\lambda) = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda$$



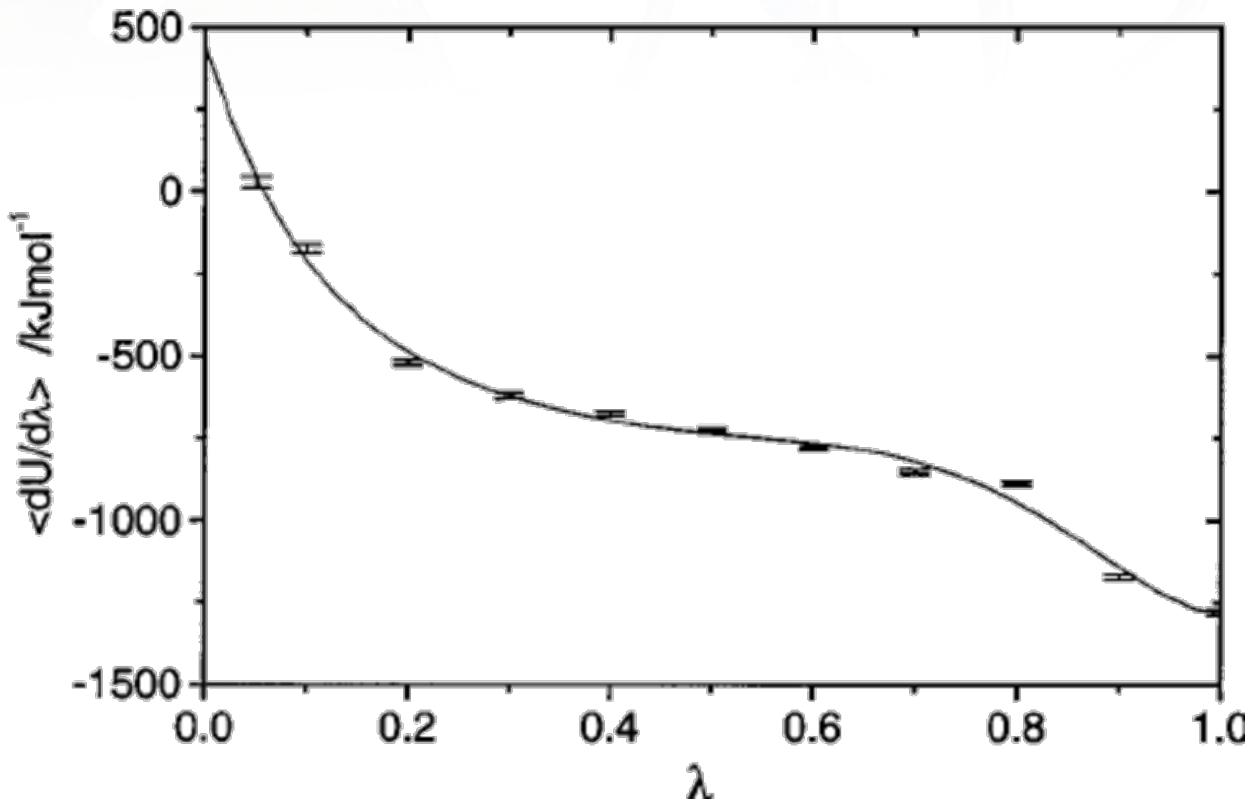
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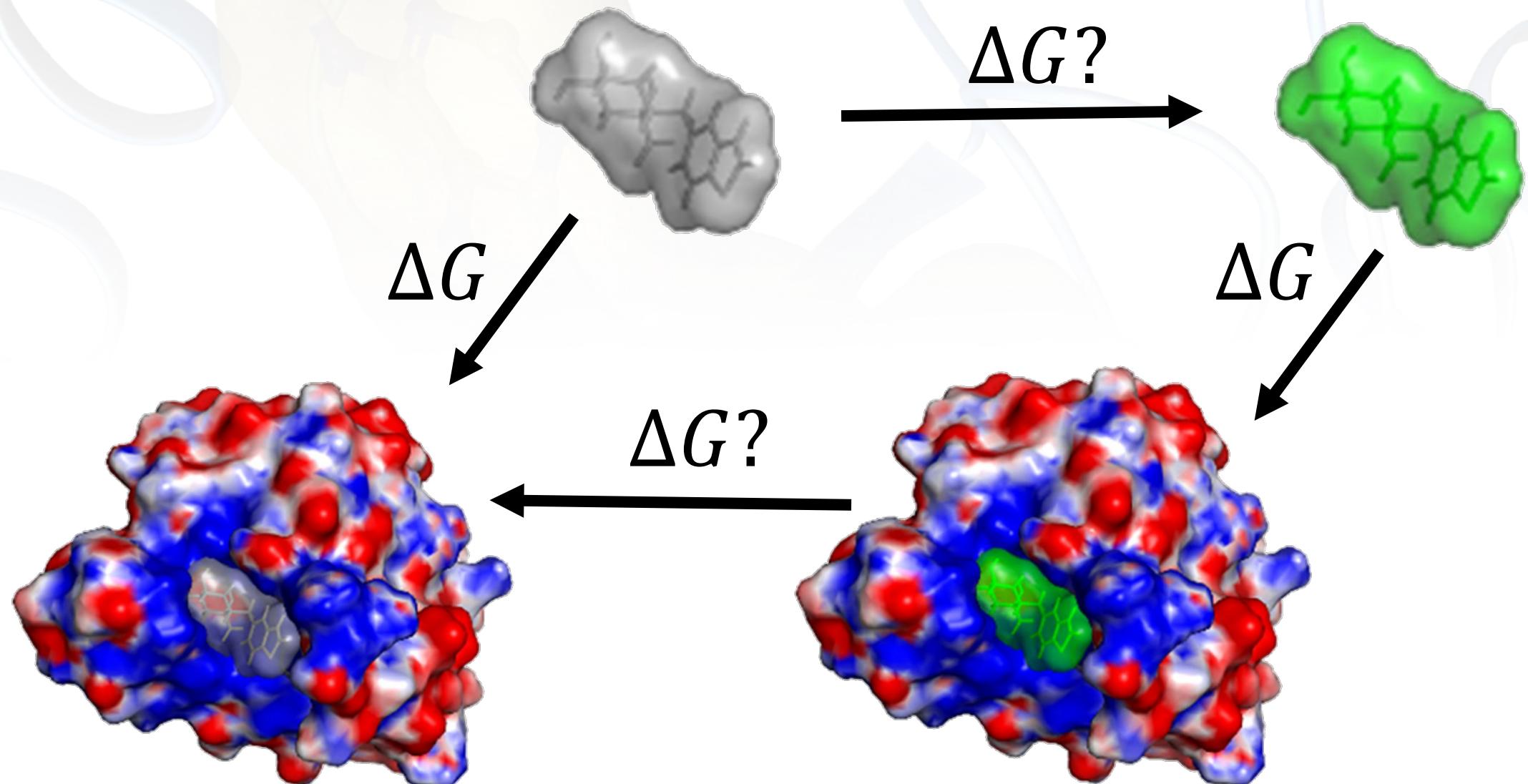
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$$\Delta G(\lambda) = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_{\lambda}$$



# Thermodynamic integration



# Introduction to biomolecular simulation

**Lecture 1:**  
Molecular Dynamics  
& Ensembles

**Lecture 2:**  
Force Fields &  
Solvation Models

**Lecture 3:**  
Enhanced Sampling  
Methods

**Assignment:**  
Analyze simulation output and relate the findings to concepts introduced by the course.