

From JEDI to SITH

A Journey to the Dark Side of Druggability

Joan Clark-Nicolas
ScotCHEM Conference
15th June 2018
University of St Andrews

Contents



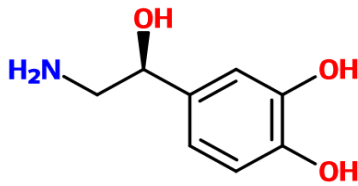
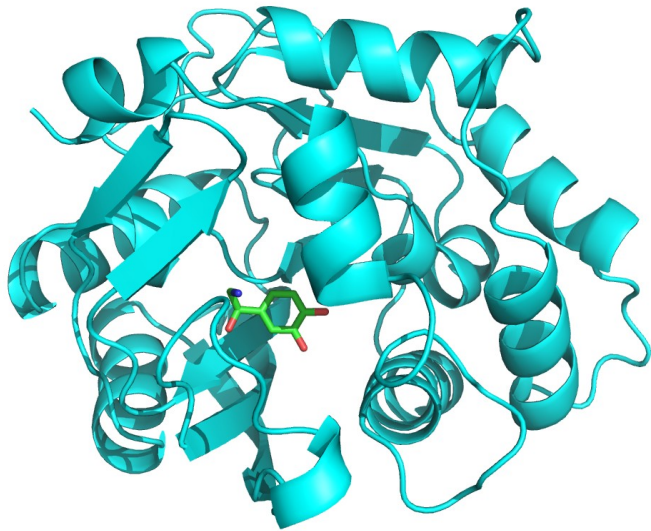
- **Part 1: Druggability of protein cryptic pockets**
- **Part 2: The JEDI approach**
- **Part 3: The SITH sampling protocol**
- **Part 4: Conclusions**

Contents



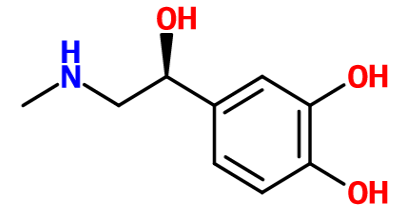
- **Part 1: Druggability of cryptic protein pockets**
- Part 2: The JEDI approach
- Part 3: The SITH sampling protocol
- Part 4: Conclusions

How are diseases related to proteins?



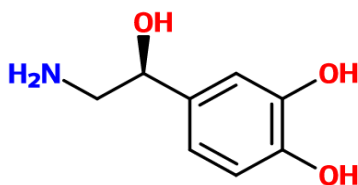
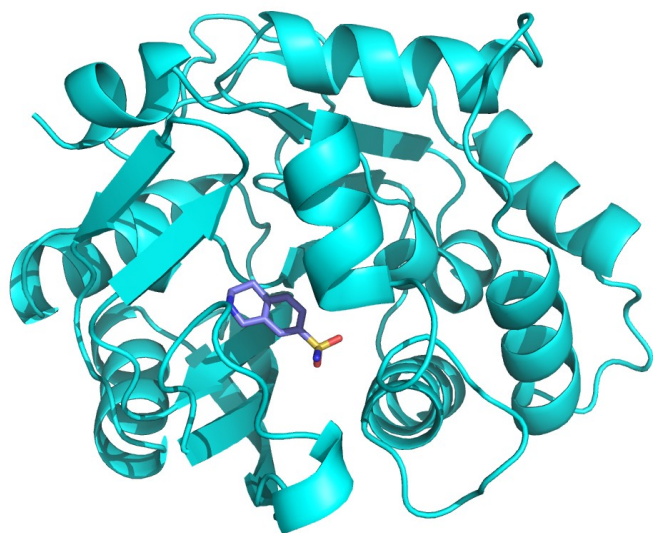
Reactant

Enzyme
→



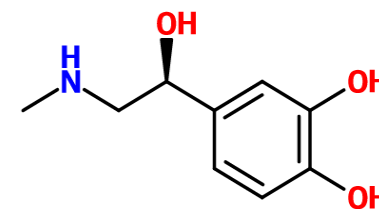
Product

How are diseases related to proteins?

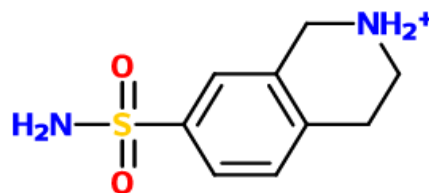


Reactant

Enzyme



Product



Inhibitor

~~Enzyme~~

So how do we cure diseases?



PHASE 1 PHASE 2 PHASE 3

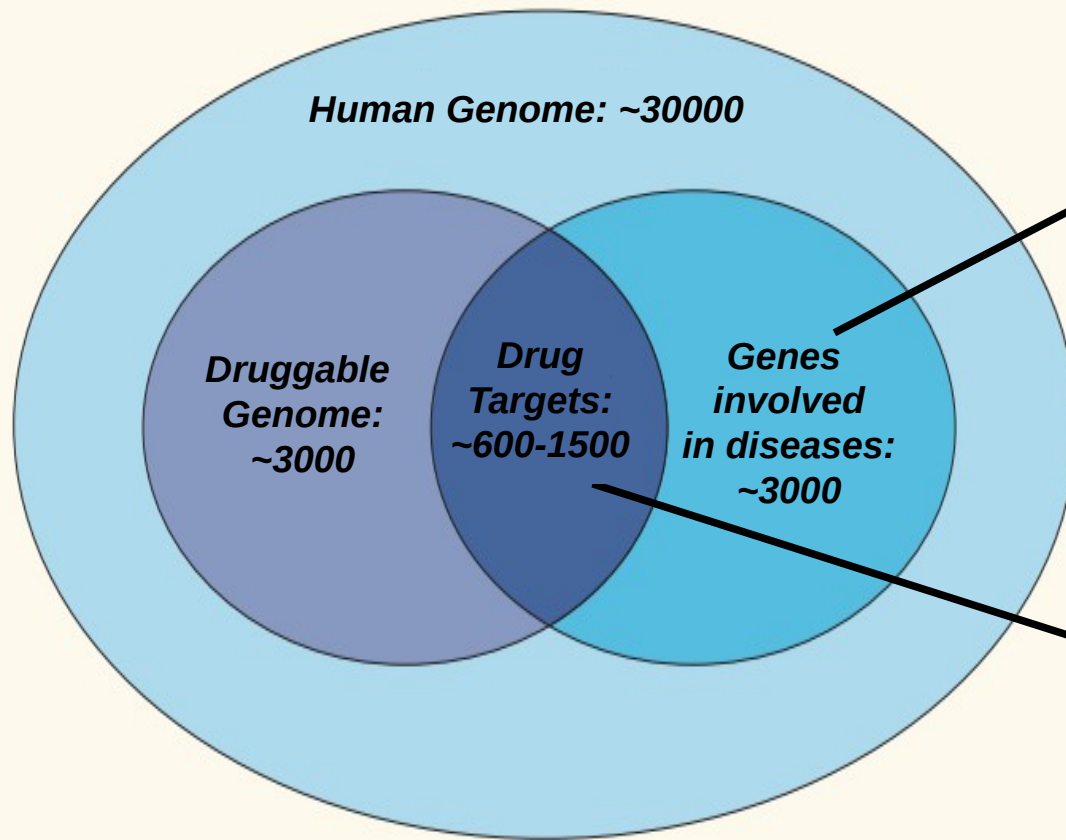
Collect
~~underpants~~
PROTEINS

?

Profit



Not all proteins can bind drugs...



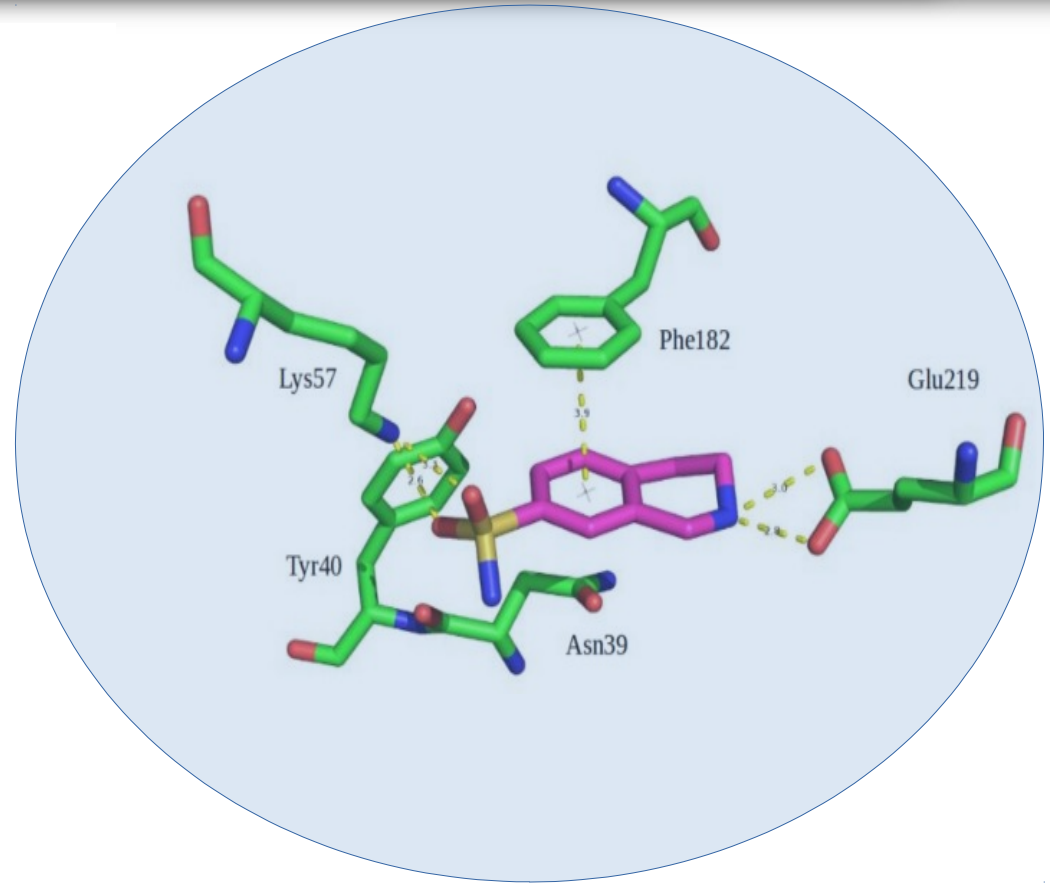
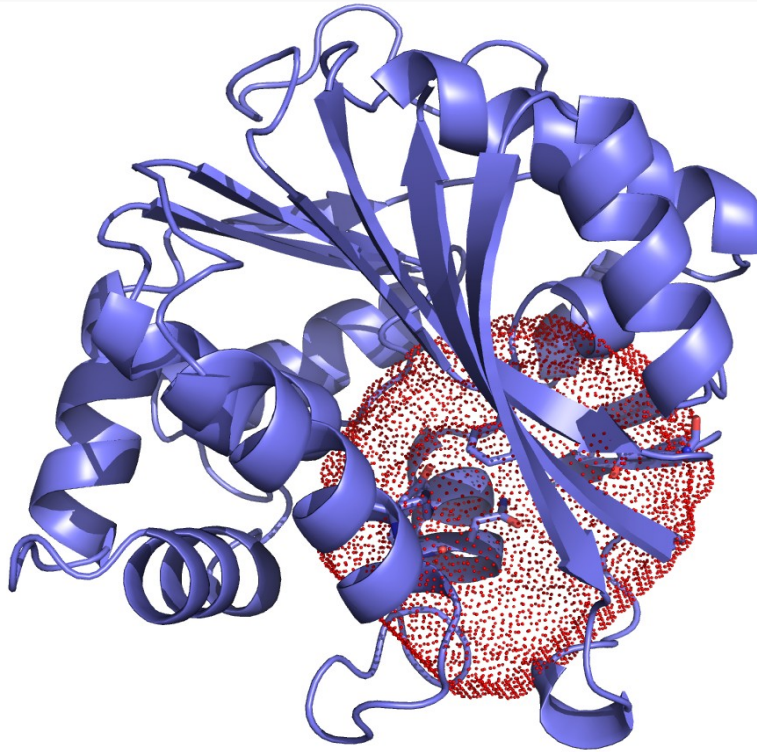
~10% human genome is involved in diseases

~20% - 50% of human genes involved in diseases code proteins targeted by drugs

Hopkins & Groom, Nat. Rev. Drug. Disc. 2002

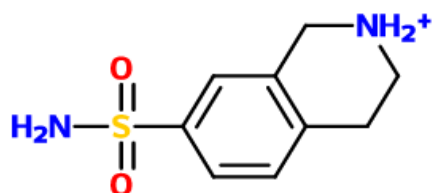
So what does a protein need to be considered a drug target?

Binding pockets



- Volume
- Hydrophobicity
- Enclosure

Binding pockets

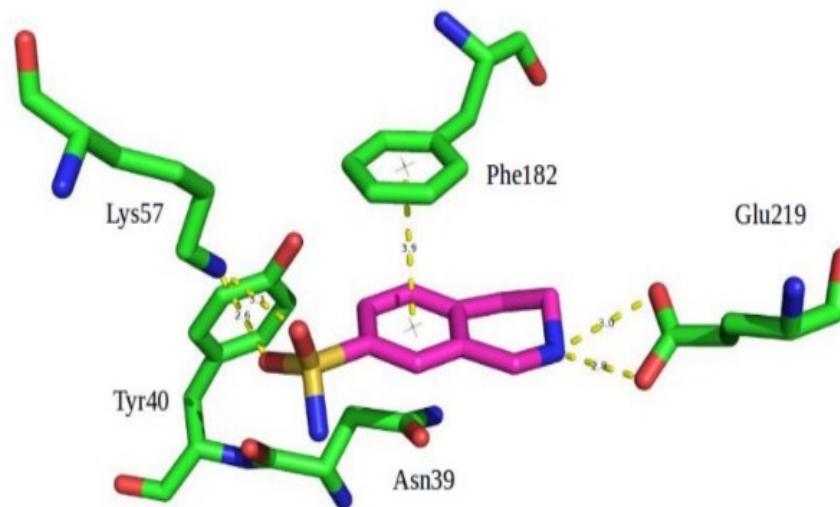


Inhibitor SKF

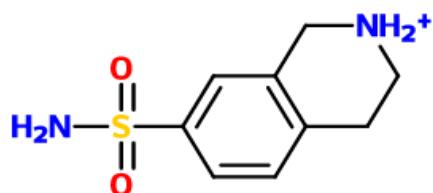
Volume = 258 Å³

K_i = 580 nM

Pocket Volume: 304 Å³



Binding pockets

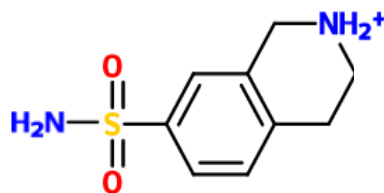


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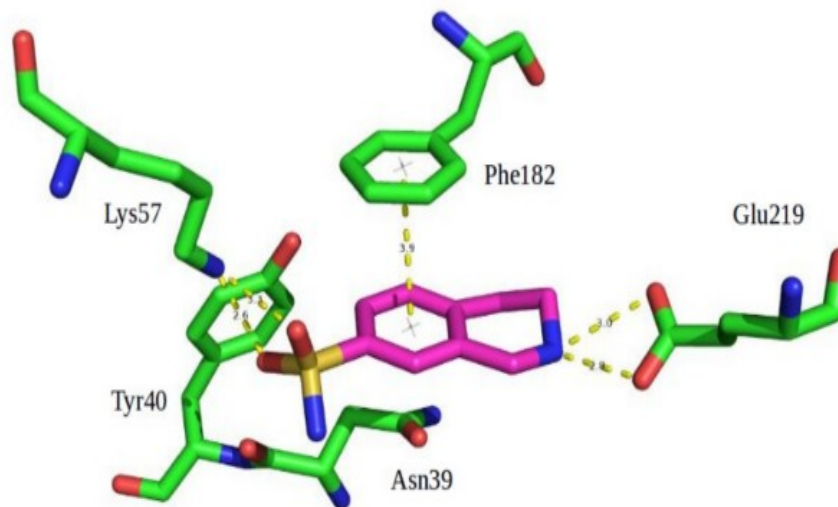
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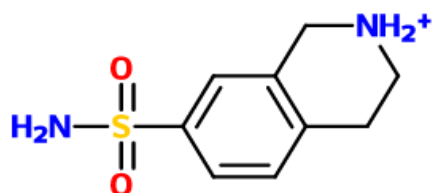
Pocket Volume: 304 Å³



Inhibitor F83



Binding pockets

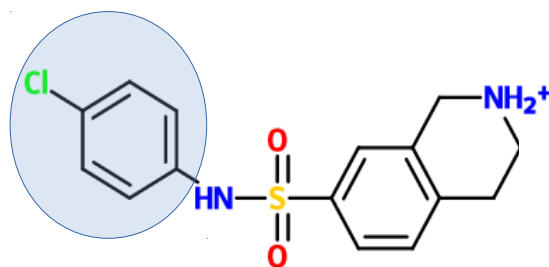


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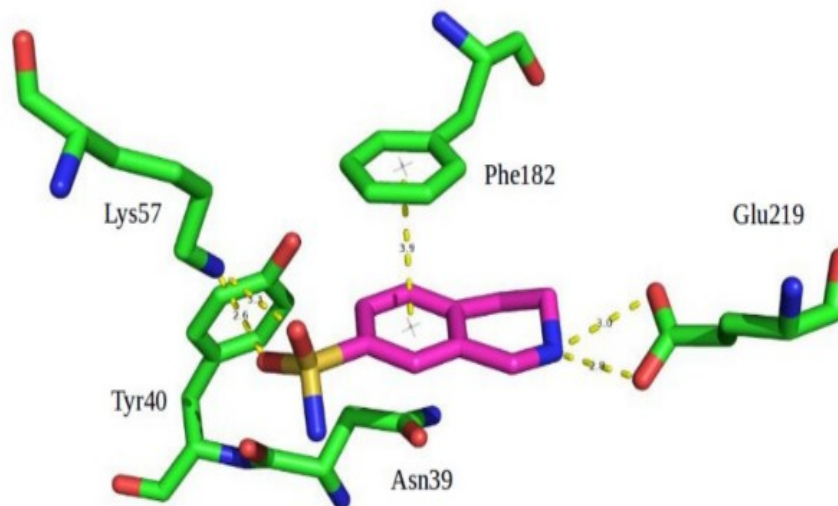
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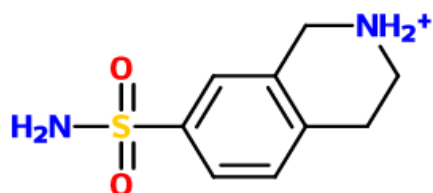
Pocket Volume: 304 Å³



Inhibitor F83



Binding pockets

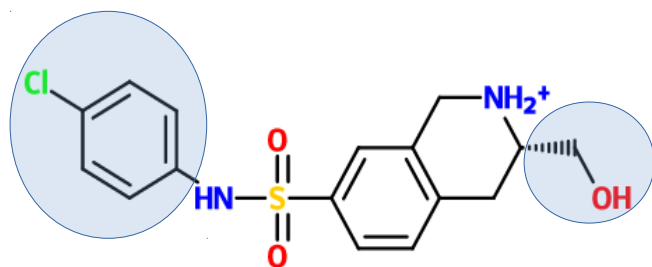


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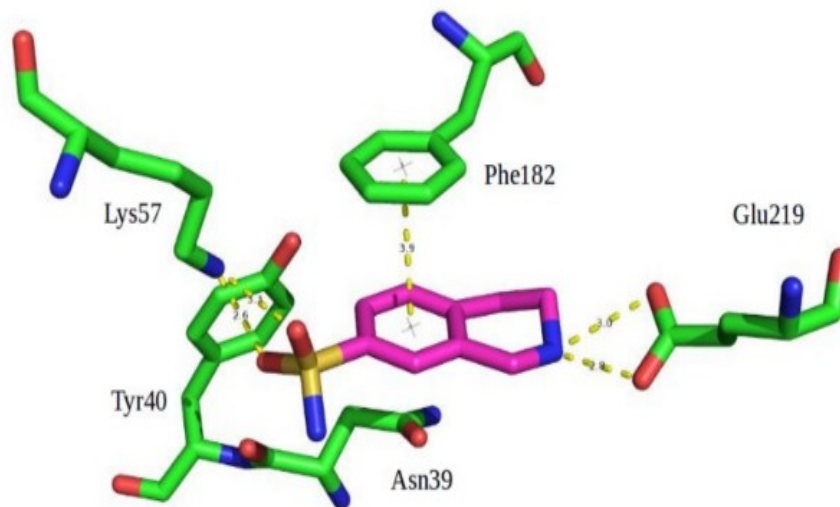
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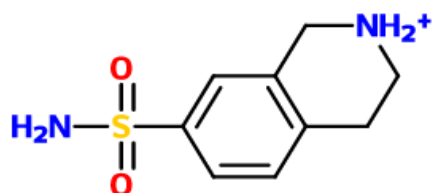
Pocket Volume: 304 \AA^3



Inhibitor F83



Binding pockets

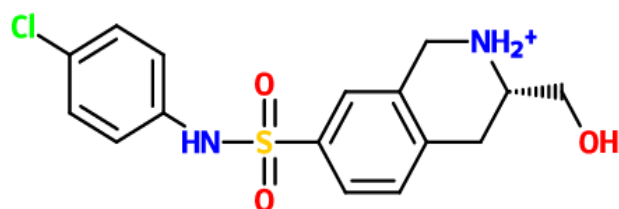
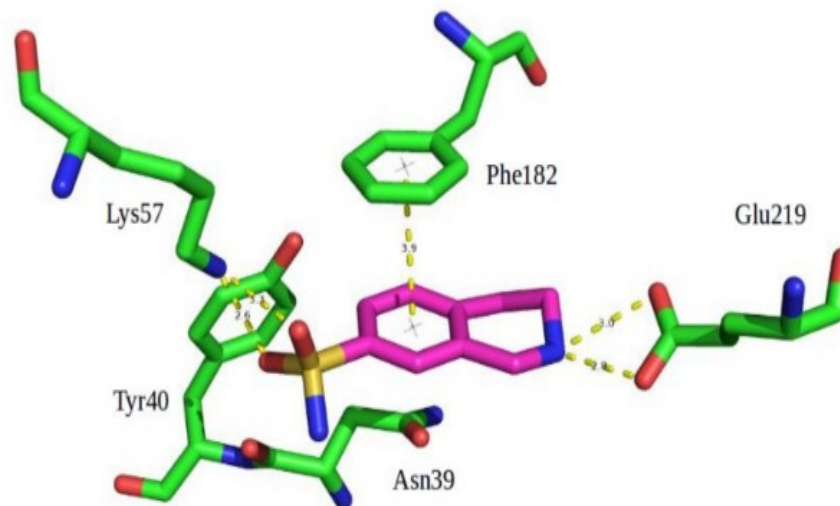


Inhibitor SKF

Volume = 258 Å³

K_i = 580 nM

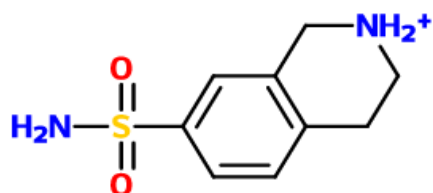
Pocket Volume: 304 Å³



Inhibitor F83

Volume = 422 Å³

Binding pockets

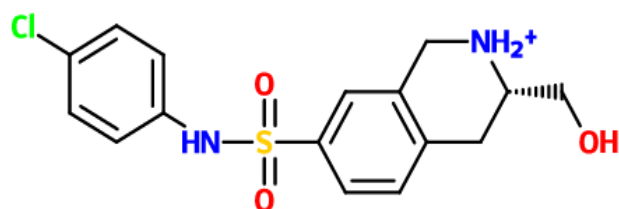
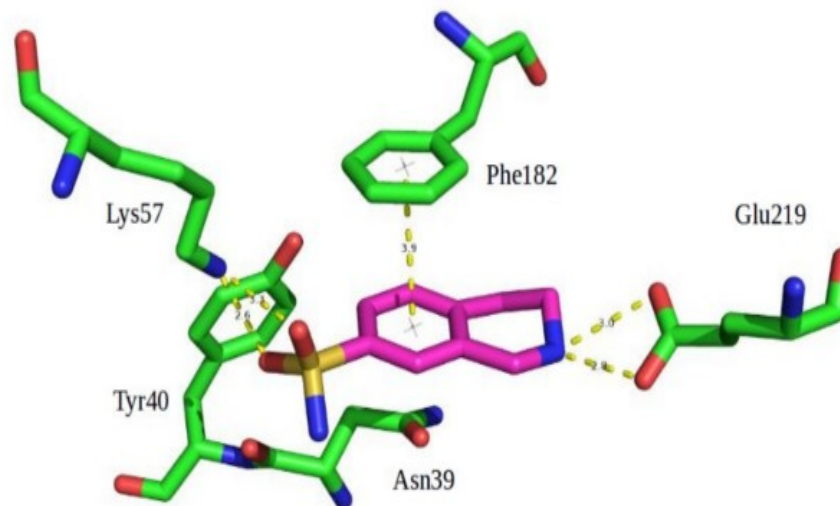


Inhibitor SKF

Volume = 258 Å³

K_i = 580 nM

Pocket Volume: 304 Å³

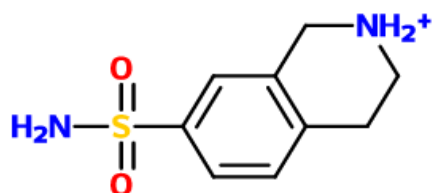


Inhibitor F83

Volume = 422 Å³

K_i = 63 nM

Binding pockets

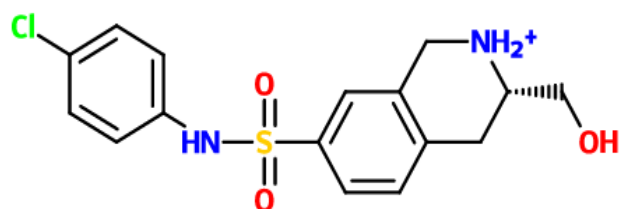
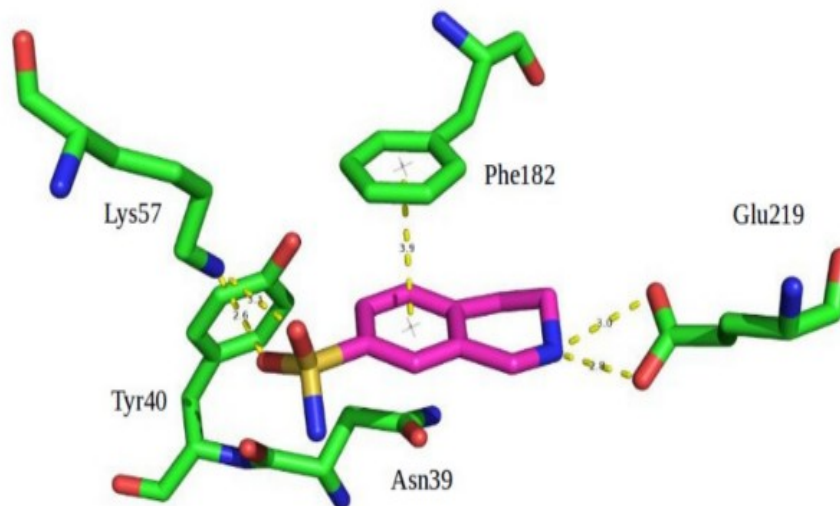


Inhibitor SKF

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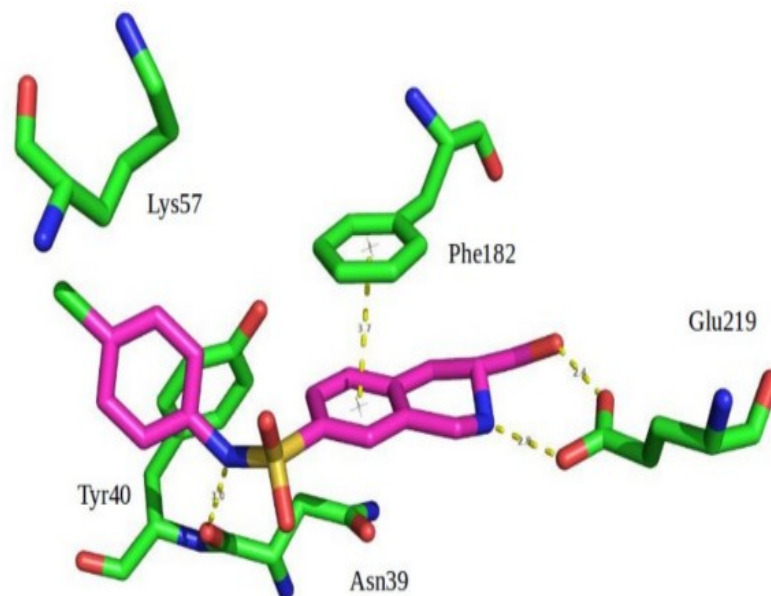
Pocket Volume: 304 Å³



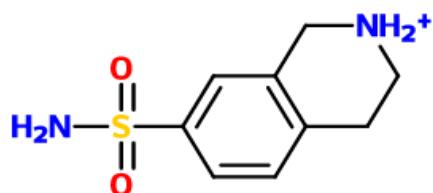
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Binding pockets

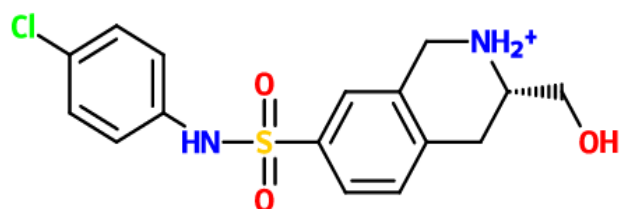
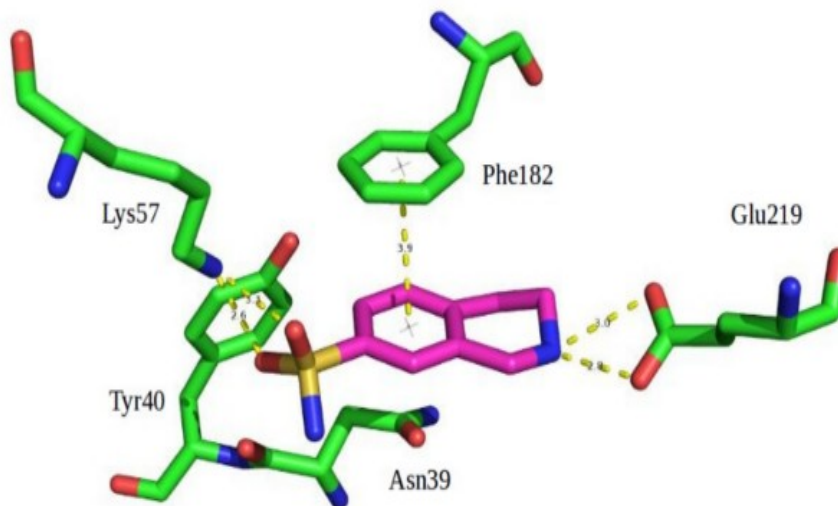


Inhibitor SKF

Volume = 258 Å³

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Pocket Volume: 304 Å³

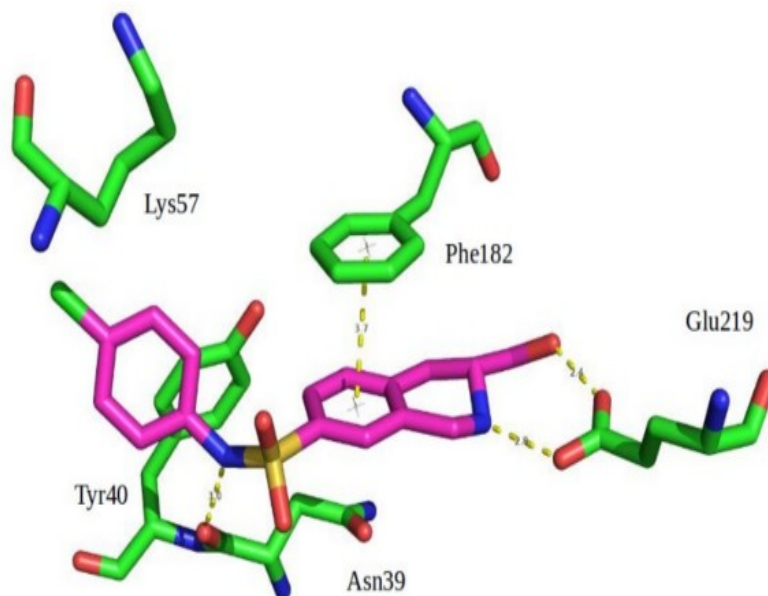


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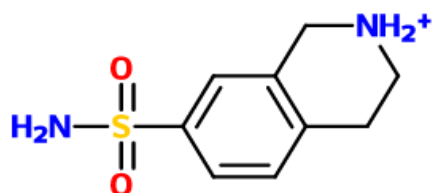
Volume = 422 Å³

K_i = 63 nM

Pocket Volume: 545 Å³



Binding pockets

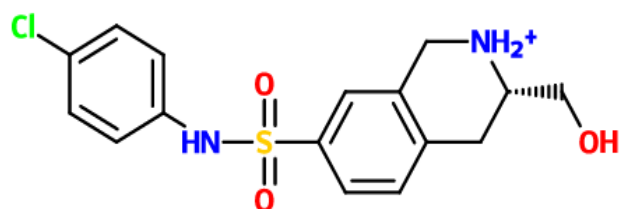
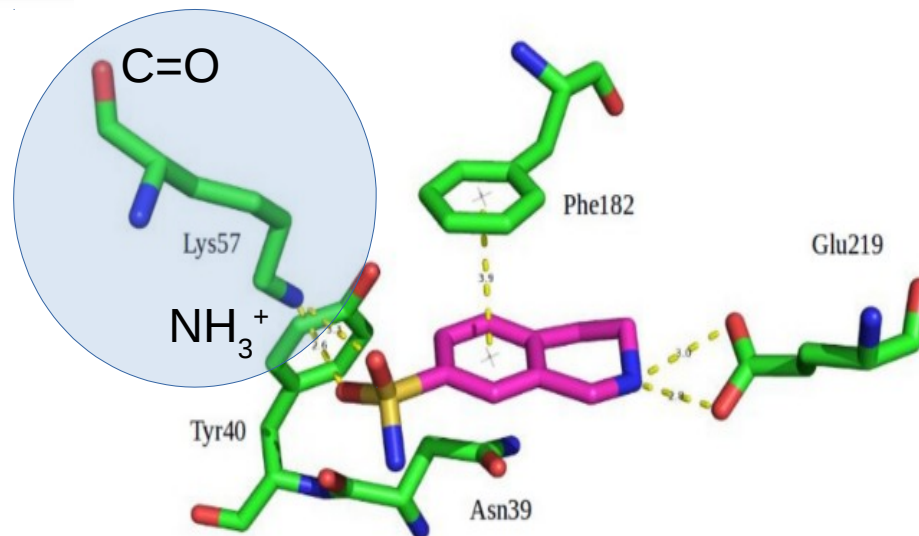


Inhibitor SKF

Volume = 258 Å³

K_i = 580 nM

Pocket Volume: 304 Å³

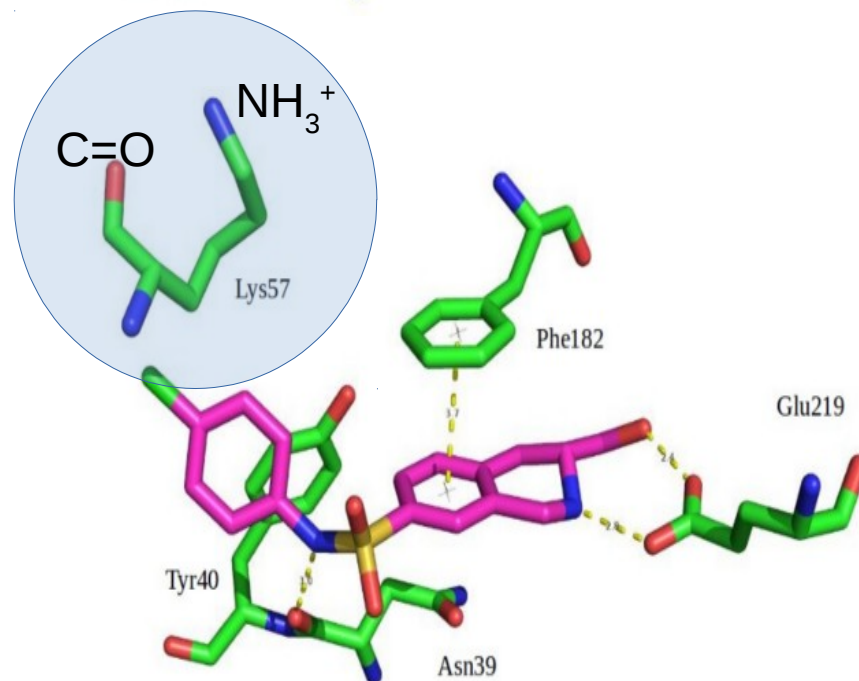


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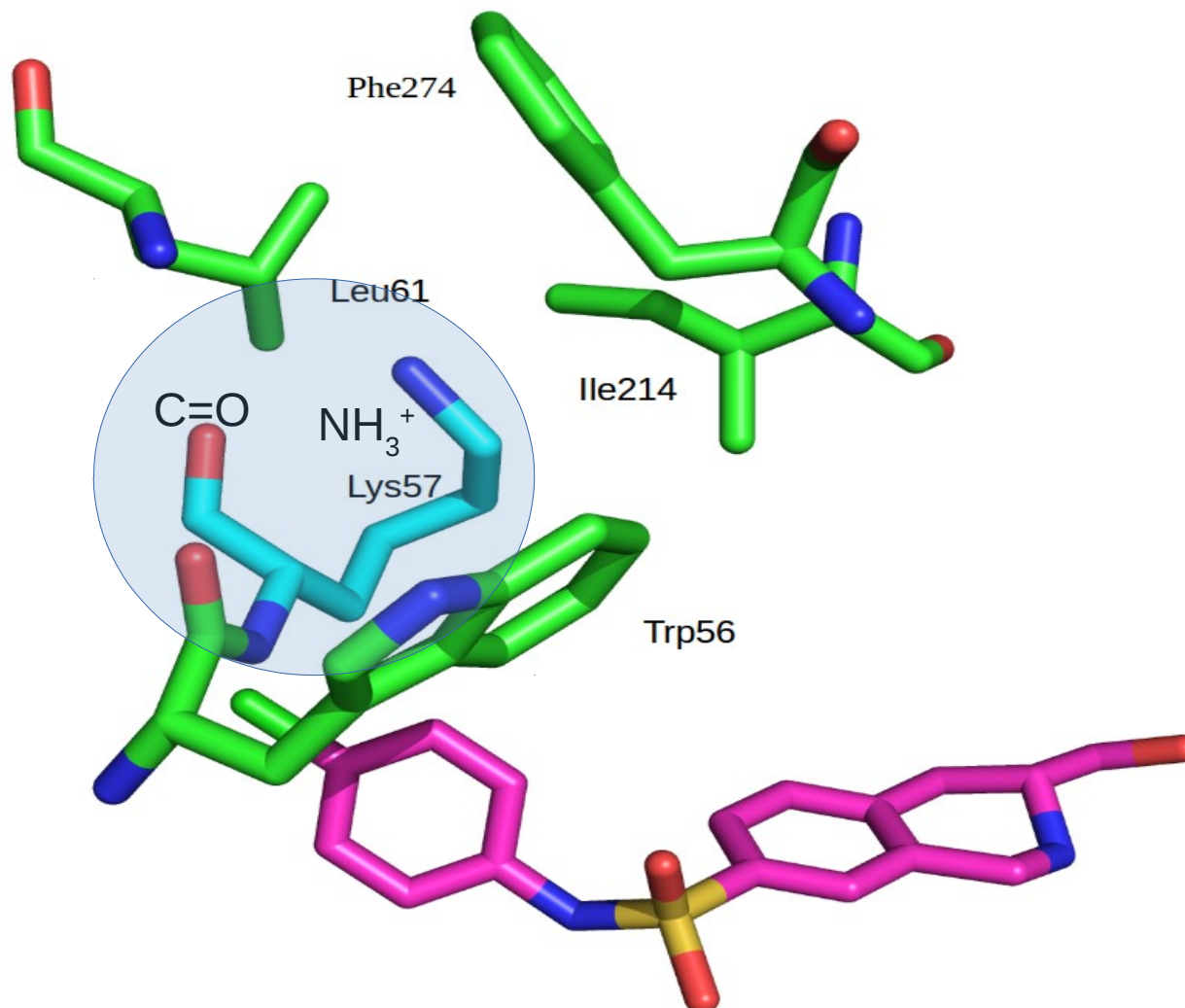
Volume = 422 Å³

K_i = 63 nM

Pocket Volume: 545 Å³



Cryptic Binding pockets



**NOT DETECTED EXPERIMENTALLY
IN THE ABSENCE OF A LIGAND**

Molecular Dynamics

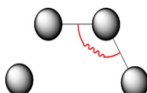


$$\begin{aligned}
 U(R) = & \sum_{\text{bonds}} k_r (r - r_{eq})^2 \\
 & + \sum_{\text{angles}} k_\theta (\theta - \theta_{eq})^2 \\
 & + \sum_{\text{dihedrals}} k_\phi (1 + \cos[n\phi - \gamma]) \\
 & + \sum_{\text{impropers}} k_\omega (\omega - \omega_{eq})^2 \\
 & + \sum_{i < j}^{atoms} \epsilon_{ij} \left[\left(\frac{r_m}{r_{ij}} \right)^{12} - 2 \left(\frac{r_m}{r_{ij}} \right)^6 \right] \\
 & + \sum_{i < j}^{atoms} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}
 \end{aligned}$$

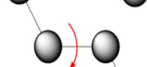
bond



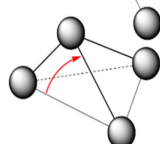
angle



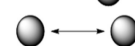
dihedral



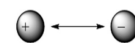
improper



van der Waals



electrostatic



Force field
(Energy function)

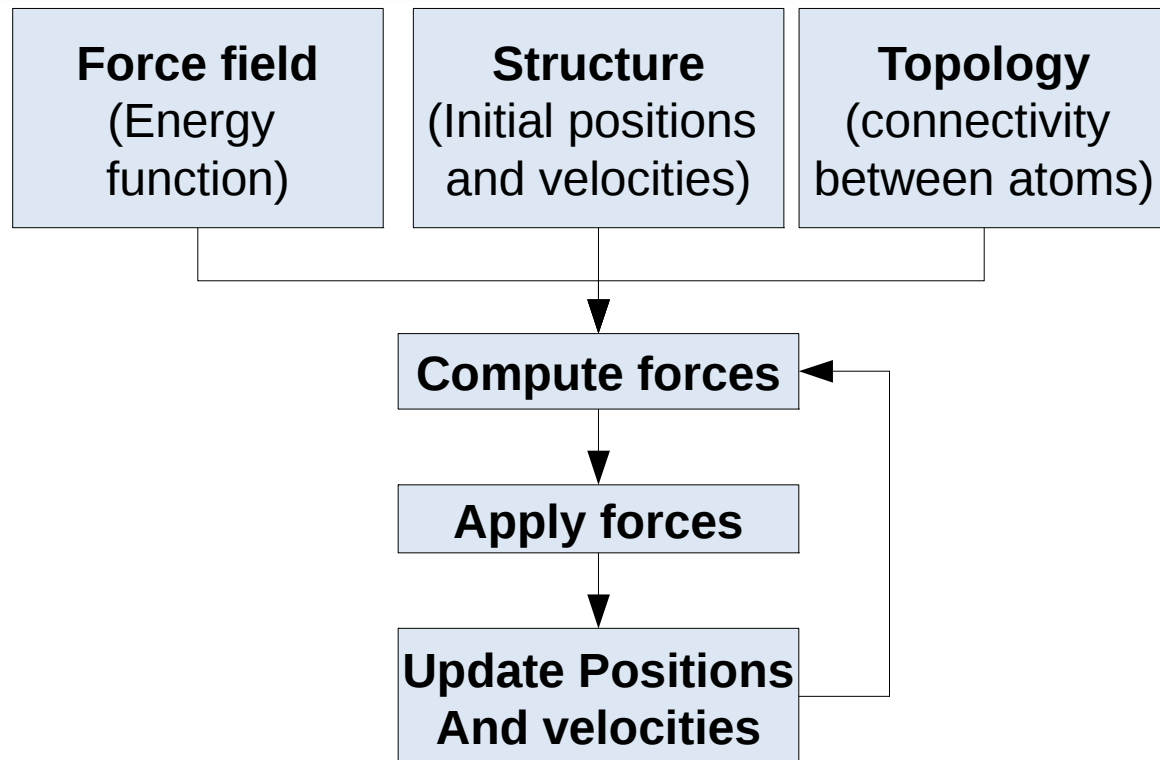
Structure
(Initial positions and velocities)

Topology
(connectivity between atoms)

Compute forces

Apply forces

**Update Positions
And velocities**



Molecular Dynamics

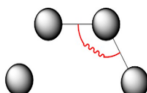


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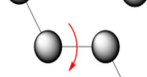
bond



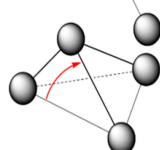
angle



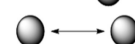
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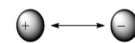
improper



van der Waals



electrostatic



Force field
(Energy function)

Structure
(Initial positions and velocities)

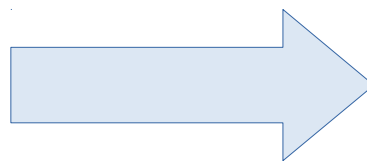
Topology
(connectivity between atoms)

Compute forces

Apply forces

**Update Positions
And velocities**

Naturally occurring forces
Equilibrium Dynamics



**VERY LONG
SIMULATION
TIMES**

Molecular Dynamics

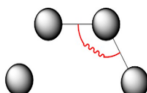


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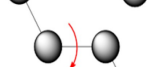
bond



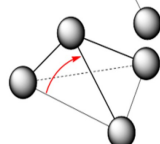
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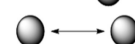
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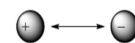
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Force field
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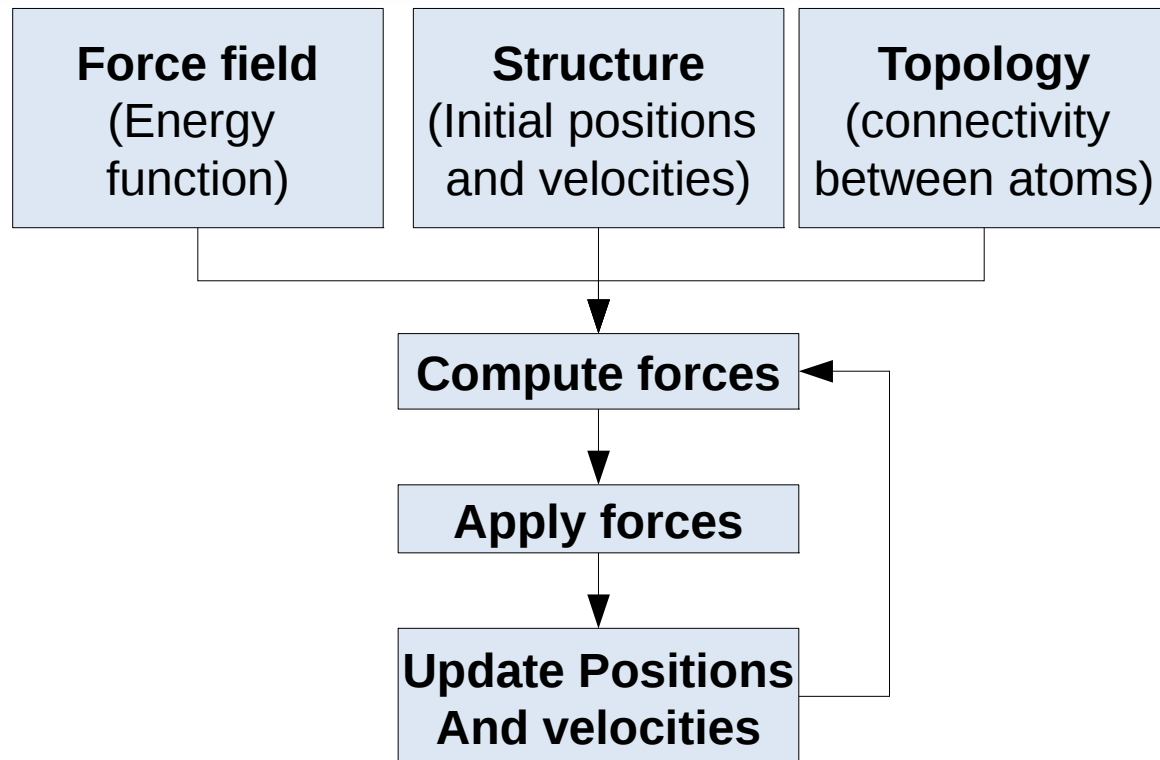
Structure
(Initial positions and velocities)

Topology
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Compute forces

Apply forces

**Update Positions
And velocities**



Molecular Dynamics

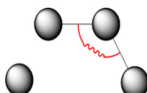


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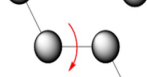
bond



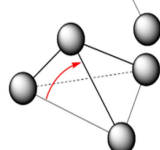
angle



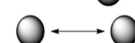
dihedral



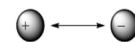
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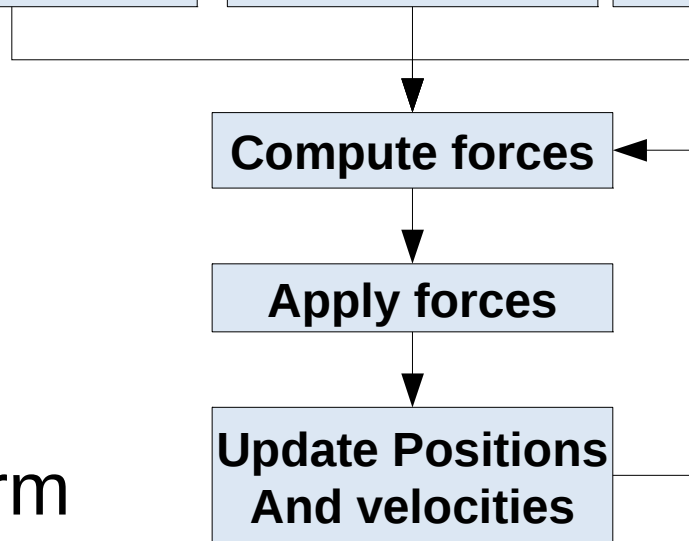
Topology
(connectivity between atoms)

Compute forces

Apply forces

**Update Positions
And velocities**

+U(CV) Additional energy term



Molecular Dynamics

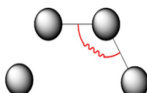


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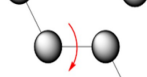
bond



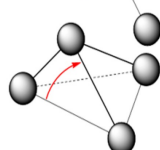
angle



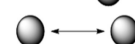
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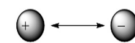
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van der Waals



electrostatic



Force field
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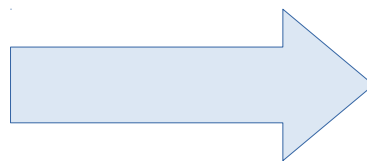
Compute forces

Apply forces

**Update Positions
And velocities**

+U(CV) Additional energy term

**Additional Forces:
Biased Dynamics**



**SPEED UP
RARE EVENT
SAMPLING**

Contents



- Part 1: Druggability of cryptic protein pockets
- **Part 2: The JEDI approach**
- Part 3: The SITH sampling protocol
- Part 4: Conclusions

Quantification of Protein Druggability: JEDI



JCTC

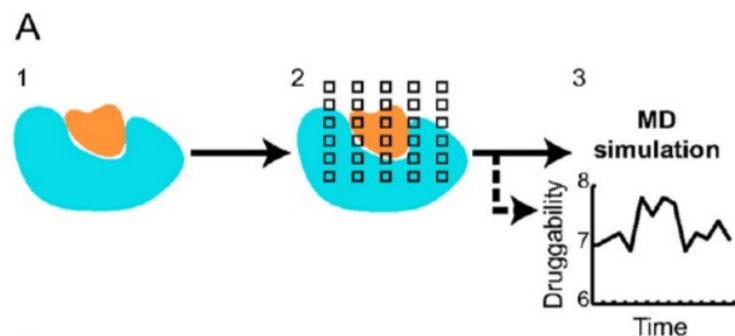
Journal of Chemical Theory and Computation

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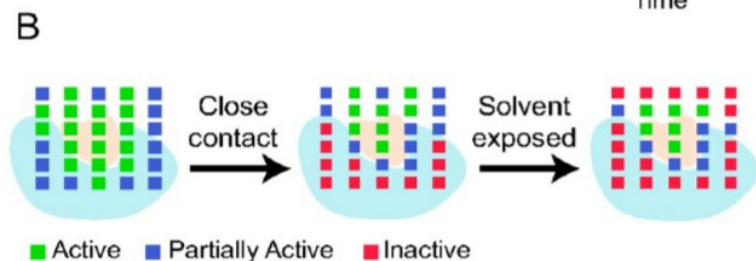
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A Collective Variable for the Rapid Exploration of Protein Druggability

Rémi Cuchillo, Kevin Pinto-Gil, and Julien Michel*



$$a_i = S_{BS_i}^{off}(1.0, BS_{min}, \Delta BS) S_{mind_i}^{on}(1.0, CC_{mind}, \Delta CC) S_{exposure_i}^{on}(1.0, E_{min}, \Delta E)$$



Quantification of Protein Druggability: JEDI



JCTC

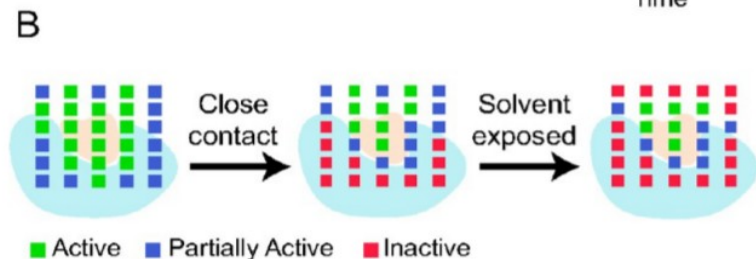
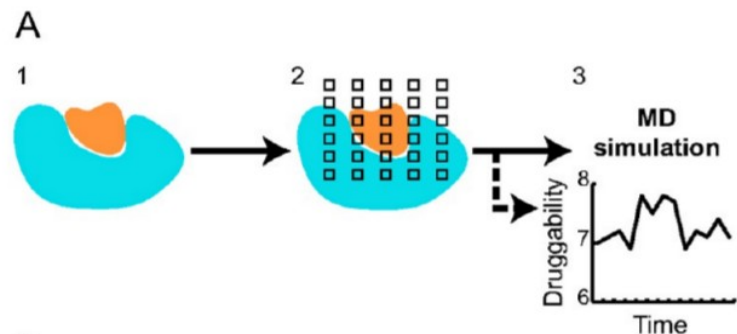
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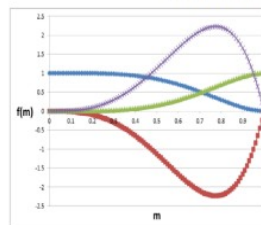
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Kernel Functions



$$S_v^{on}(k, v_{min}, \Delta) = \begin{cases} 0 & \text{if } m < 0 \\ k[1 - (1 - m^2)^2(1 + 2m^2)] & \text{if } 0 \leq m \leq 1 \\ k & \text{if } m > 1 \end{cases}$$

$$S_v^{off}(k, v_{min}, \Delta) = \begin{cases} k & \text{if } m < 0 \\ k[(1 - m^2)^2(1 + 2m^2)] & \text{if } 0 \leq m \leq 1 \\ 0 & \text{if } m > 1 \end{cases}$$

$$m = \frac{v - v_{min}}{\Delta}$$

Michel, J., JEDI Theory, Feb. 2016

Penalize the descriptors with values too big or too low regarding those of the benchmark set

Quantification of Protein Druggability: JEDI



JCTC

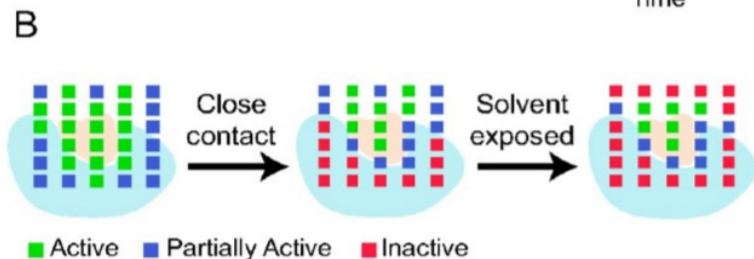
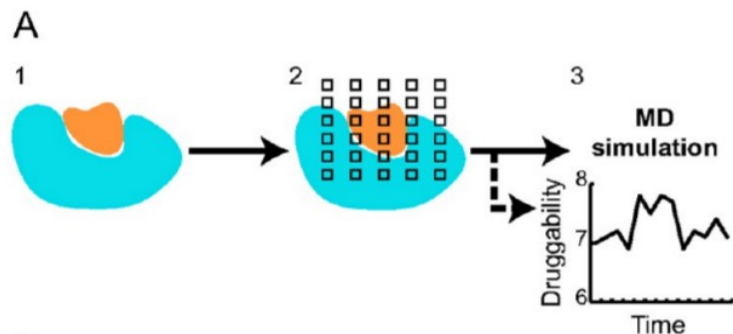
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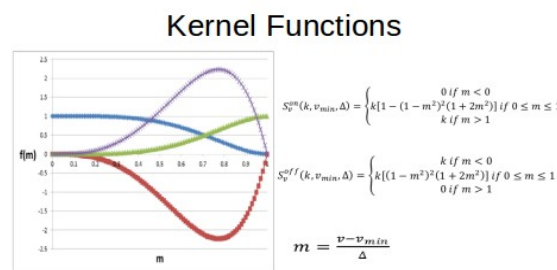
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Michel, J., JEDI Theory, Feb. 2016

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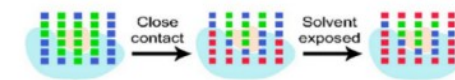
Activity calculation

$$a_i = S_{BS_i}^{off}(1.0, BS_{min}, \Delta BS) S_{mind_i}^{on}(1.0, CC_{mind}, \Delta CC) S_{exposure_i}^{on}(1.0, E_{min}, \Delta E)$$

Distance of grid point i to a known ligand (1 if not defined)

Distance of grid point i to binding site atoms

Exposure of grid point i to the solvent



Quantification of Protein Druggability: JEDI



JCTC

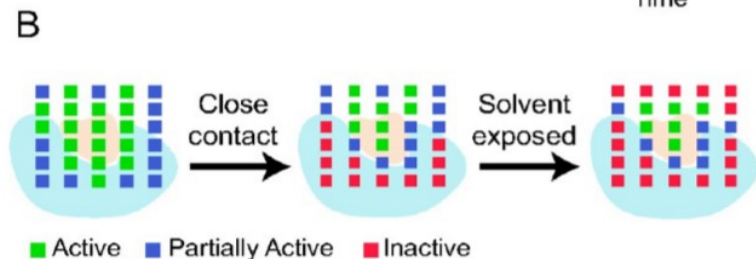
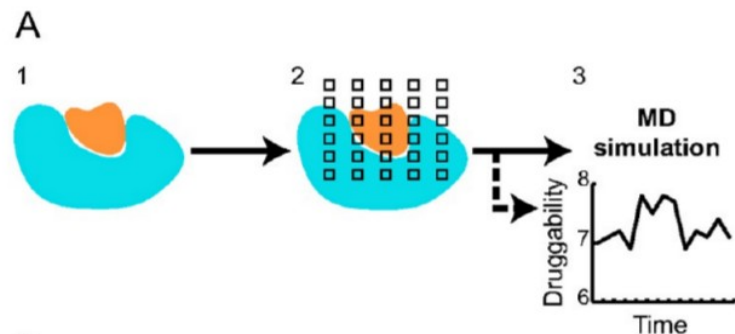
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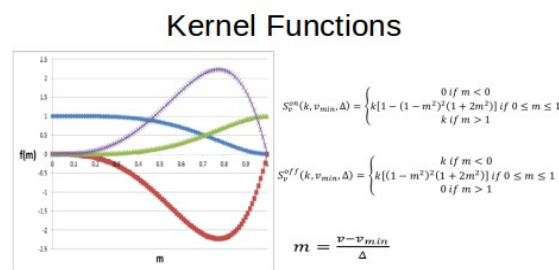
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Distance of grid point i to a known binding site

Distance of grid point i to binding site

Exposure of grid point i to the binding site

Hydrophobicity Descriptor

$$h_i = \frac{apolar_i}{contacts_i}$$

$$contacts_i = \sum_{j=1}^M S_{||r_{ij}||}^{off}(a_i, d_{hydro}, \Delta d_{hydro})$$

$$apolar_i = \sum_{j=1}^M I_{apolar}(j) S_{||r_{ij}||}^{off}(a_i, d_{hydro}, \Delta d_{hydro})$$

$$I_{apolar}(j) = \begin{cases} 1 & \text{if } j \in \text{apolar group} \\ 0 & \text{if } j \in \text{polar group} \end{cases}$$

$$H_a = \sum_{i=1}^N \frac{h_i a_i}{\sum_{i=1}^N a_i}$$

Apolar and polar atoms are defined at the same time as the grid, before the simulation

Quantification of Protein Druggability: JEDI



JCTC

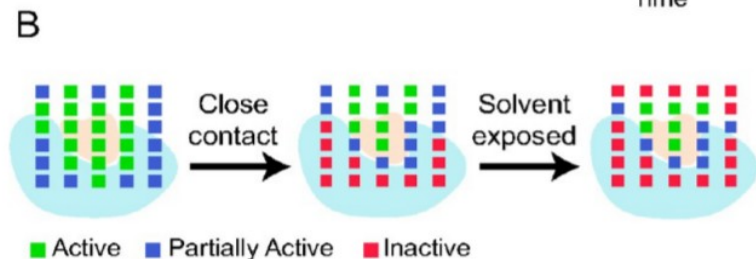
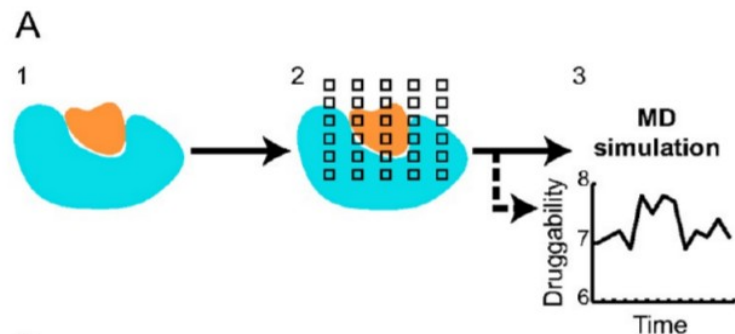
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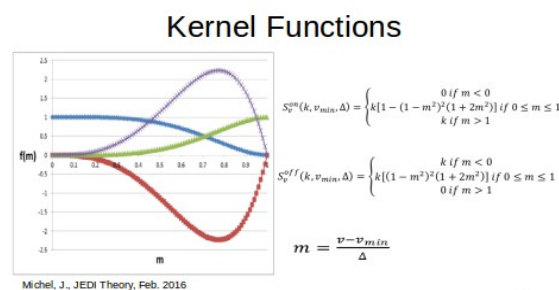
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Active Volume Descriptor

$$V = \sum_{i=1}^N a_i V_g$$

$$V_g = \text{spacing}^3 \longrightarrow \text{ONLY FOR EVENLY SPACED GRIDS!!!!}$$

$$V_a = \frac{V}{V_{max}} \longrightarrow \text{PARAMETER}$$

Activity calculation

$$a_i = S_{BS_i}^{off}(1.0, BS_{min}, \Delta BS) S_{mind_i}^{on}(1.0, CC_{mind}, \Delta CC) S_{exposure_i}^{on}(1.0, E_{min}, \Delta E)$$

Distance of grid point i to a known

Distance of grid point i to binding

Exposure of grid point i to the

Hydrophobicity Descriptor

$$a_i = \frac{apolar_i}{contacts_i}$$

$$tacts_i = \sum_{j=1}^M S_{||r_{ij},z||}^{off}(a_i, d_{hydro}, \Delta d_{hydro})$$

$$|ar_i = \sum_{j=1}^M I_{apolar}(j) S_{||r_{ij},z||}^{off}(a_i, d_{hydro}, \Delta d_{hydro})$$

$$|ar_i(j) = \begin{cases} 1 & \text{if } j \in \text{apolar group} \\ 0 & \text{if } j \in \text{polar group} \end{cases}$$

$$= \sum_{i=1}^N \frac{h_i a_i}{\sum_{i=1}^N a_i}$$

Apolar and polar atoms are defined at the same time as the grid, before the simulation

Quantification of Protein Druggability: JEDI



JCTC

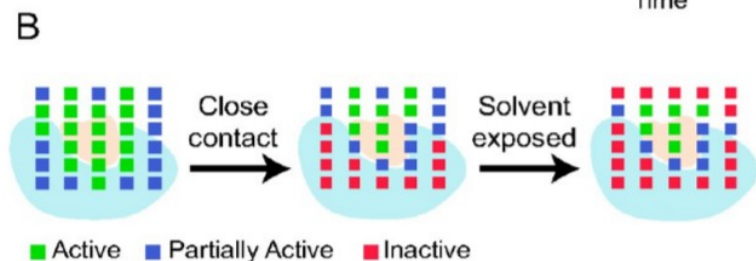
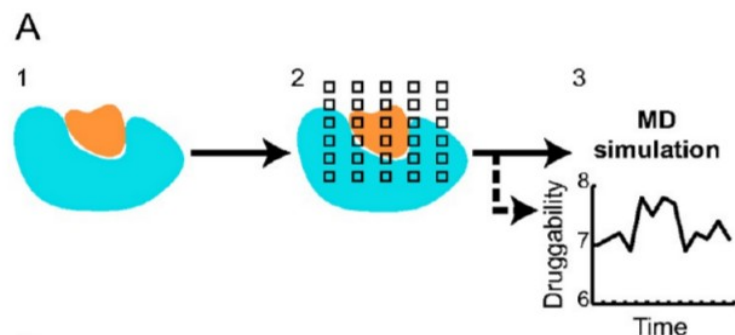
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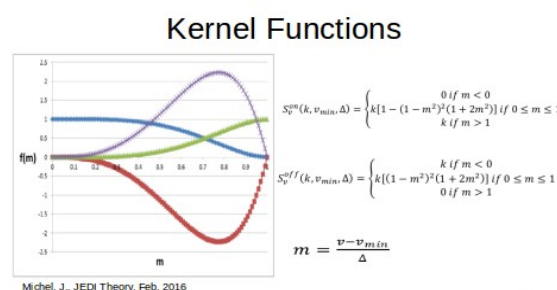
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Activity calculation

$$a_i = S_{BS_i}^{off}(1.0, BS_{min}, \Delta BS) S_{mind_i}^{on}(1.0, CC_{mind}, \Delta CC) S_{exposure_i}^{on}(1.0, E_{min}, \Delta E)$$

Distance of grid point i to a known
Distance of grid point i to binding
Exposure of grid point i to the

Hydrophobicity Descriptor

$$= \frac{apolar_i}{contacts_i}$$

Active Volume Descriptor

$$V = \sum_{i=1}^N a_i V_g$$

$$V_g = spacing^3 \longrightarrow$$

$$V_a = \frac{V}{V_{max}}$$

Druglike Volume Descriptor

$$PAR \quad V_{druglike} = S_V^{off}(1.0, V_{max}, \Delta V_{max}) S_V^{on}(1.0, V_{min}, \Delta V_{min})$$

at the same time as

Penalize pockets that are too big

Penalize pockets that are too small

Quantification of Protein Druggability: JEDI



JCTC

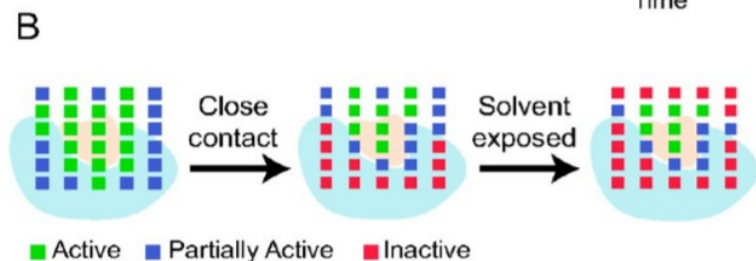
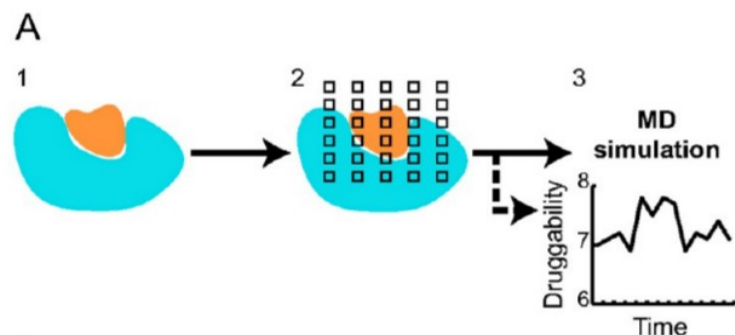
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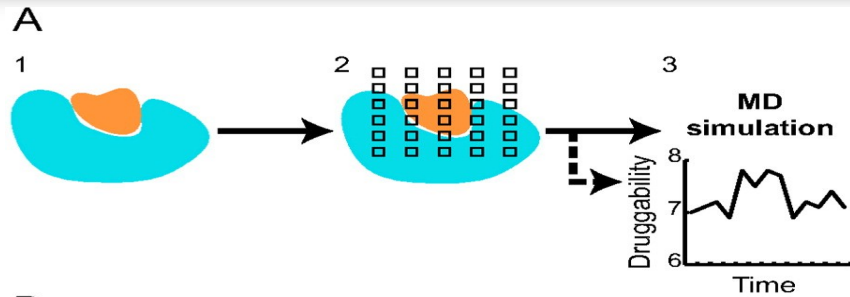
JEDI score

$$JEDI = V_{druglike}(\alpha V_a + \beta H_a + \gamma)$$

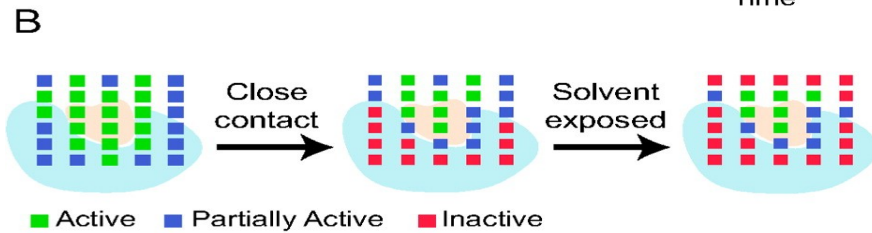
Symbol	Definition	Value
α	PLS derived volume coefficient	5.31
β	PLS derived hydrophobicity coefficient	24.29
γ	PLS derived intercept	-13.39
A_g	grid spacing	0.15 nm
BS_{min}	Minimum distance to <i>ligand group</i> from which the lig_i value starts to decrease	0.2 nm
ΔBS	distance interval over which lig_i decreases to 0	0.6 nm
CC_{mind}	distance below which a grid point is fully in close contact with the <i>binding site group</i>	0.15 nm
ΔCC	distance interval over which a grid point is in partial contact with the <i>binding site group</i>	0.15 nm
E_{min}	minimum exposure value from which a grid point is considered to be partially exposed to the <i>binding site group</i>	10.0
ΔE	interval over which a grid point becomes fully exposed to the <i>binding site group</i>	20.0
$CC2_{min}$	minimum distance below which a grid point is overlapping the binding site group	0.15 nm
$\Delta CC2$	distance interval over which a grid point is in partial contact with the binding site group	0.14 nm

Symbol	Definition	Value
GP_{min}	distance above which a grid point k is considered neighbor of grid point i	0.25 nm
GP_{max}	distance below which a grid point k is considered neighbor of grid point i	0.35 nm
d_{hydro}	distance below which a grid point i is in contact with a binding site atom (for hydrophobicity calculation)	0.40 nm
Δd_{hydro}	distance interval over which a grid point i is in partial contact with a binding site atom (for hydrophobicity calculation)	0.05 nm
V_{max}	volume below which $V_{druglike}$ is equal to 1	0.5 nm ³
ΔV_{max}	volume interval over which $V_{druglike}$ goes from 1 to 0	0.050 nm ³
V_{min}	volume below which $V_{druglike}$ is equal to 0	0.0 nm ³
ΔV_{min}	volume interval over which $V_{druglike}$ goes from 0 to 1	0.050 nm ³

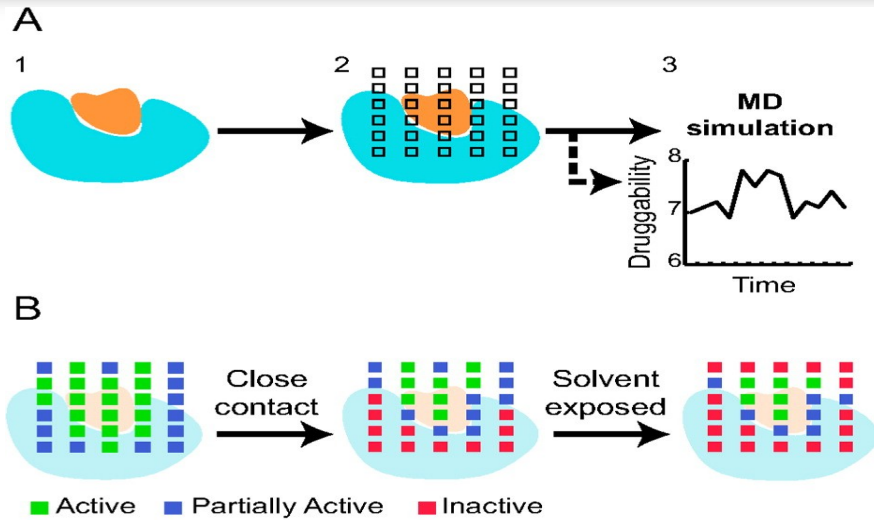
Quantification of Protein Druggability: JEDI



$$JEDI = F(a_{gridpoints})$$



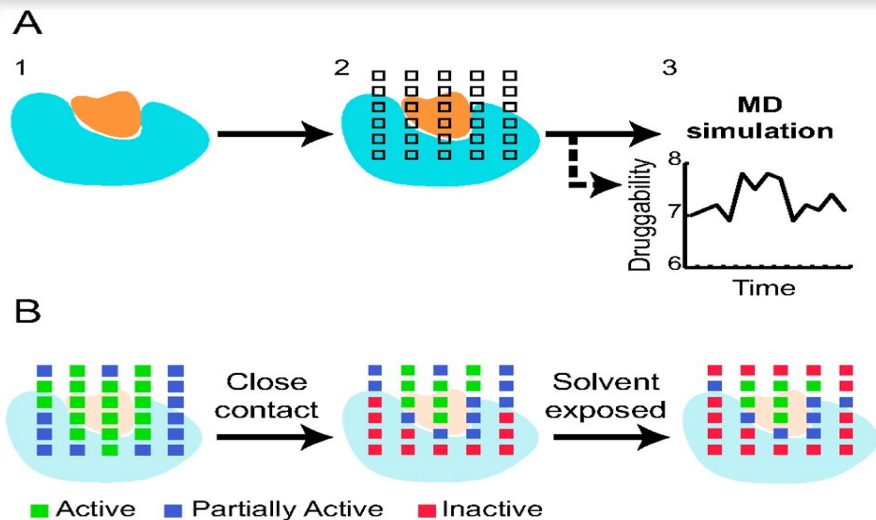
Quantification of Protein Druggability: JEDI



$$JEDI = F(a_{gridpoints})$$

$$a_i = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

Quantification of Protein Druggability: JEDI

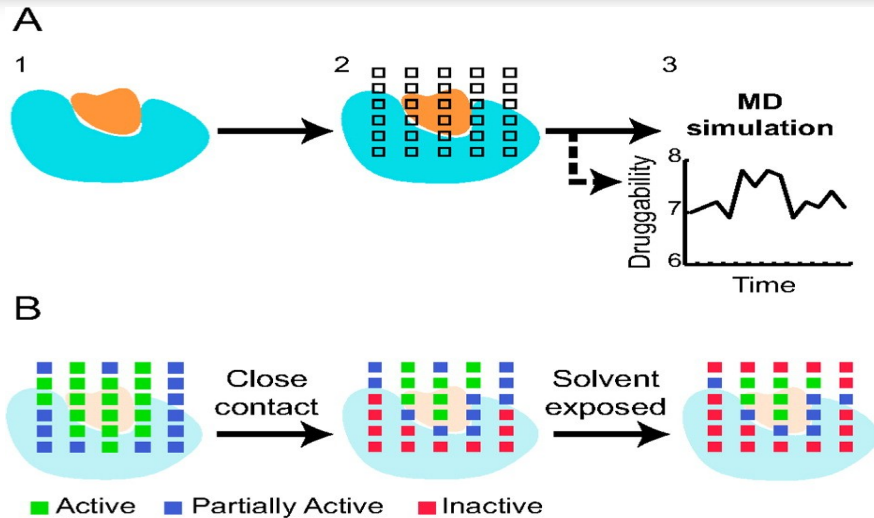


$$JEDI = F(a_{gridpoints})$$

$$a_i = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

$$JEDI = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

Quantification of Protein Druggability: JEDI



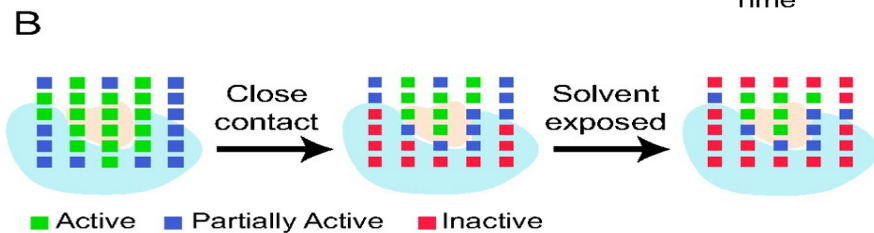
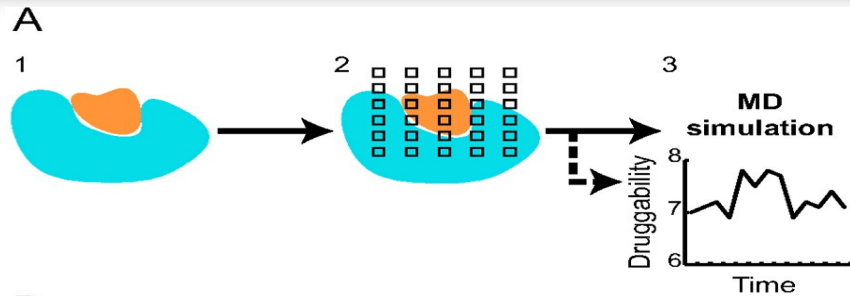
$$JEDI = F(a_{gridpoints})$$

$$a_i = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

$$JEDI = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

$$U_{system} = FF + U_{JEDI}$$

Quantification of Protein Druggability: JEDI



$$JEDI = F(a_{gridpoints})$$

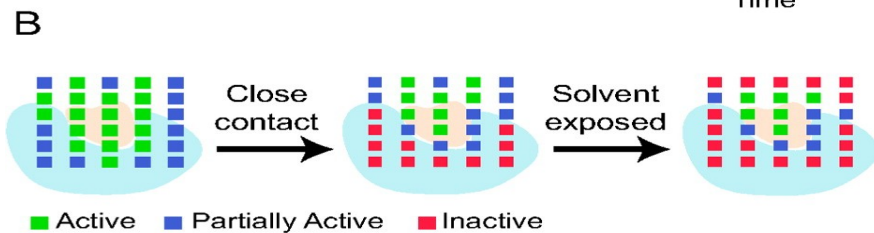
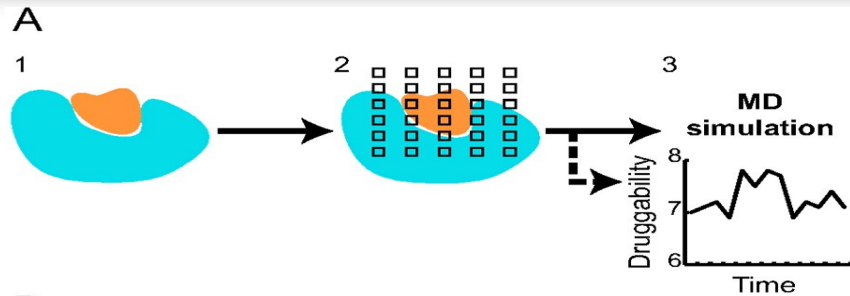
$$a_i = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

$$JEDI = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

$$U_{system} = FF + U_{JEDI}$$

$$\vec{F}_{system} = - \left(\frac{dFF}{d\vec{r}_{system}} + \frac{dU_{JEDI}}{d\vec{r}_{system}} \right)$$

Quantification of Protein Druggability: JEDI



$$JEDI = F(a_{gridpoints})$$

$$a_i = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

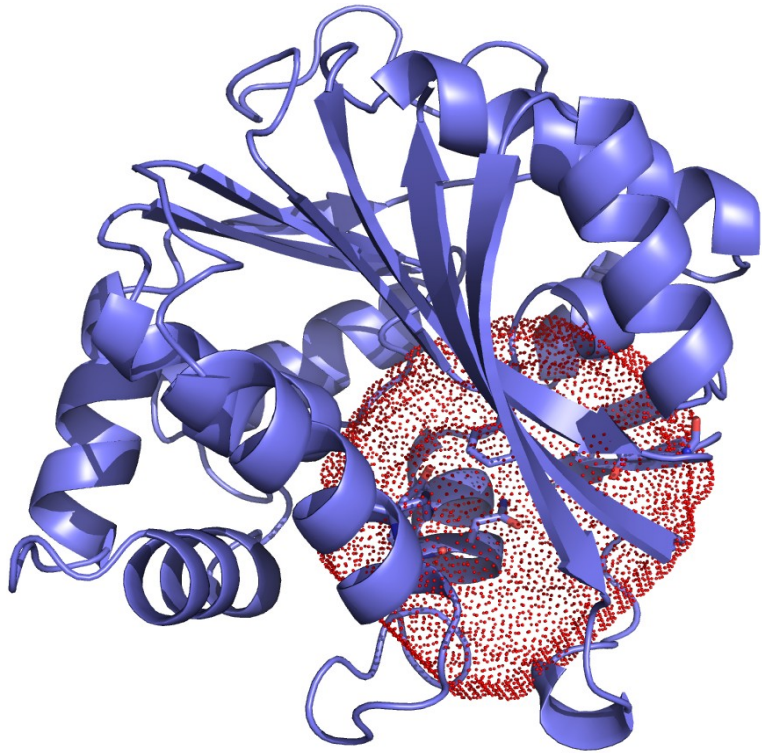
$$JEDI = F(\vec{r}_{gridpoints}, \vec{r}_{atoms})$$

$$U_{system} = FF + U_{JEDI}$$

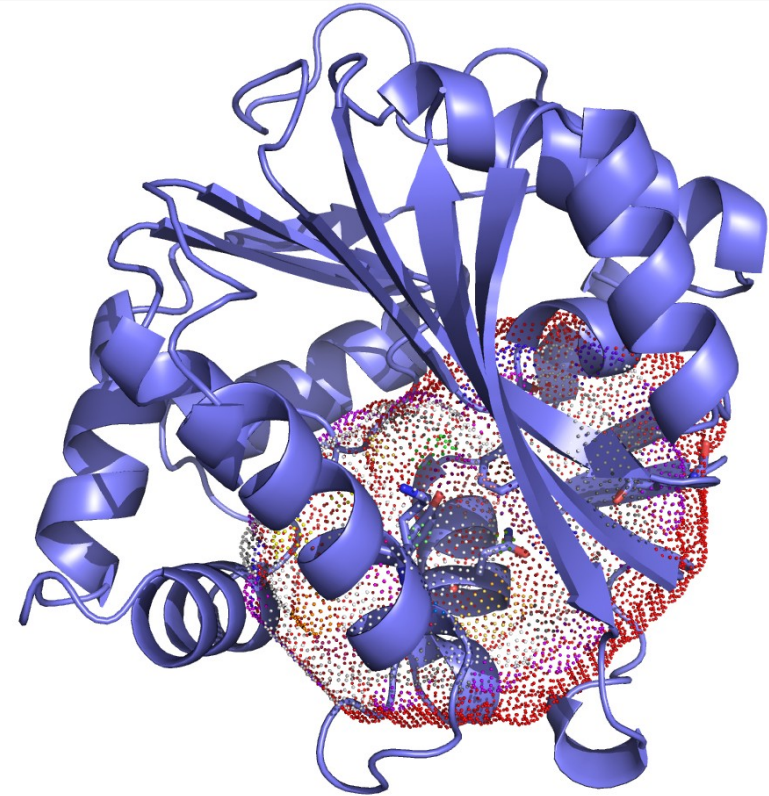
$$\vec{F}_{system} = - \left(\frac{dFF}{d\vec{r}_{system}} + \frac{dU_{JEDI}}{d\vec{r}_{system}} \right)$$

$$\vec{F}_{JEDI} = - \left(\frac{dU_{JEDI}}{dJEDI} \frac{dJEDI}{d\vec{r}_{system}} \right)$$

Can JEDI distinguish protein conformations?



Pocket	Small
LIGAND	SKF (580nM)
JEDI	7.3

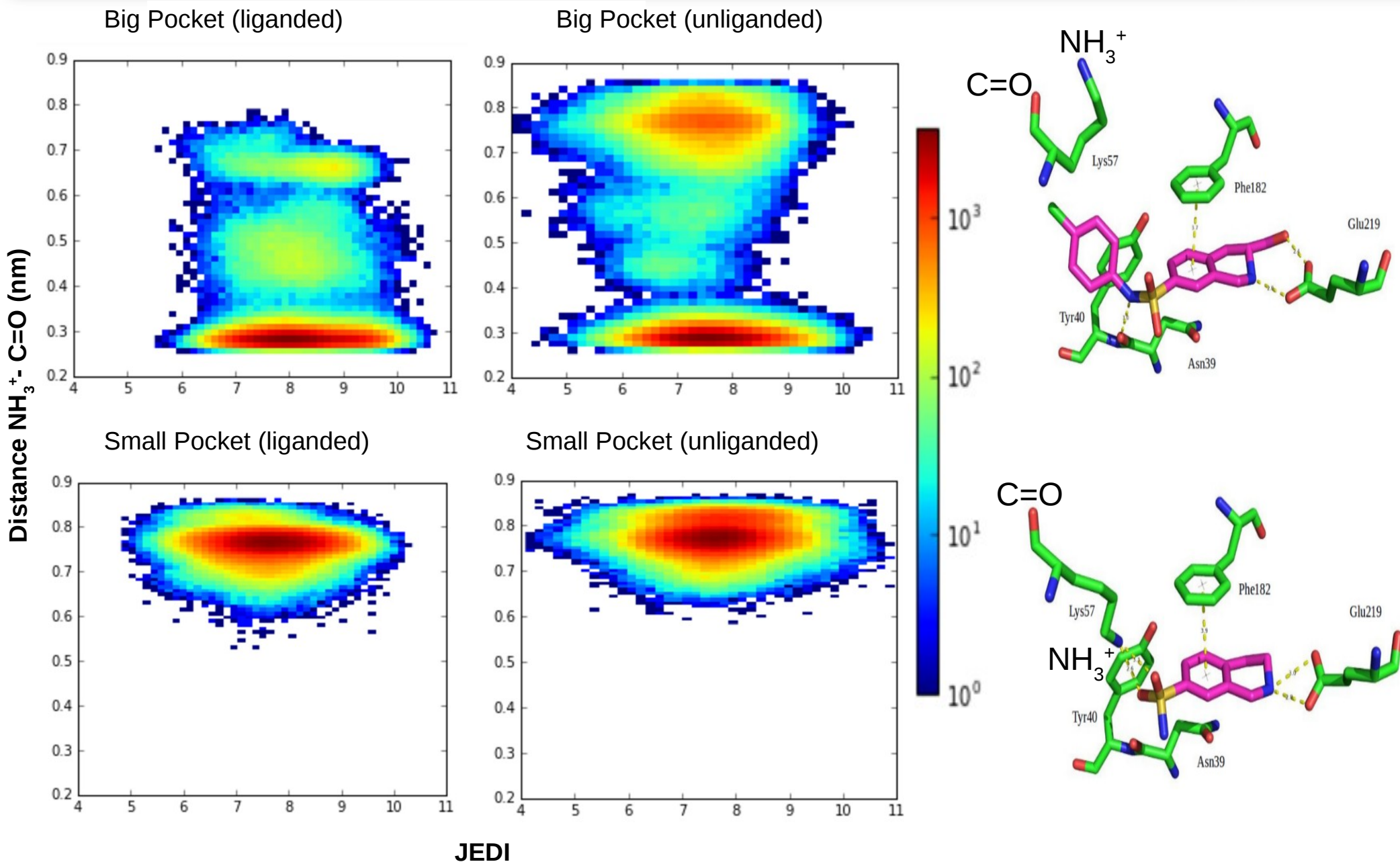


Pocket	Big
LIGAND	F83 (63 nM)
JEDI	9.8

Lower
Druggability

Higher
Druggability

Sampling of protein conformations in microsecond scale MD



How do we sample different conformations?



IS THE DARK SIDE STRONGER?

**NO, NO, NO. EASIER, QUICKER,
MORE SEDUCTIVE.**

Contents



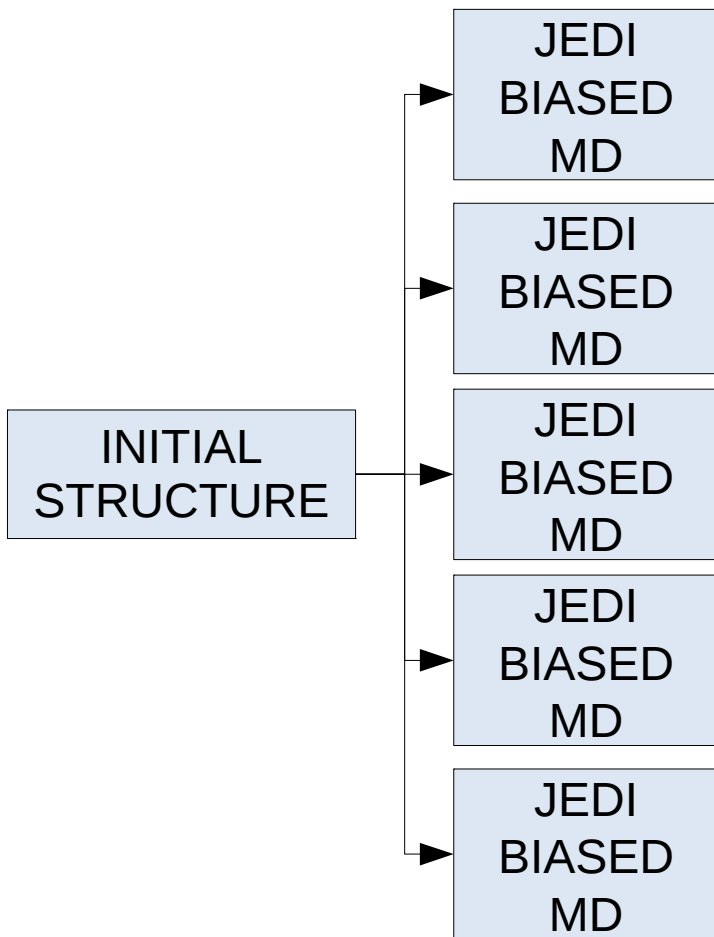
- Part 1: Druggability of cryptic protein pockets
- Part 2: The JEDI approach
- **Part 3: The SITH sampling protocol**
- Part 4: Conclusions

So what is SITH?

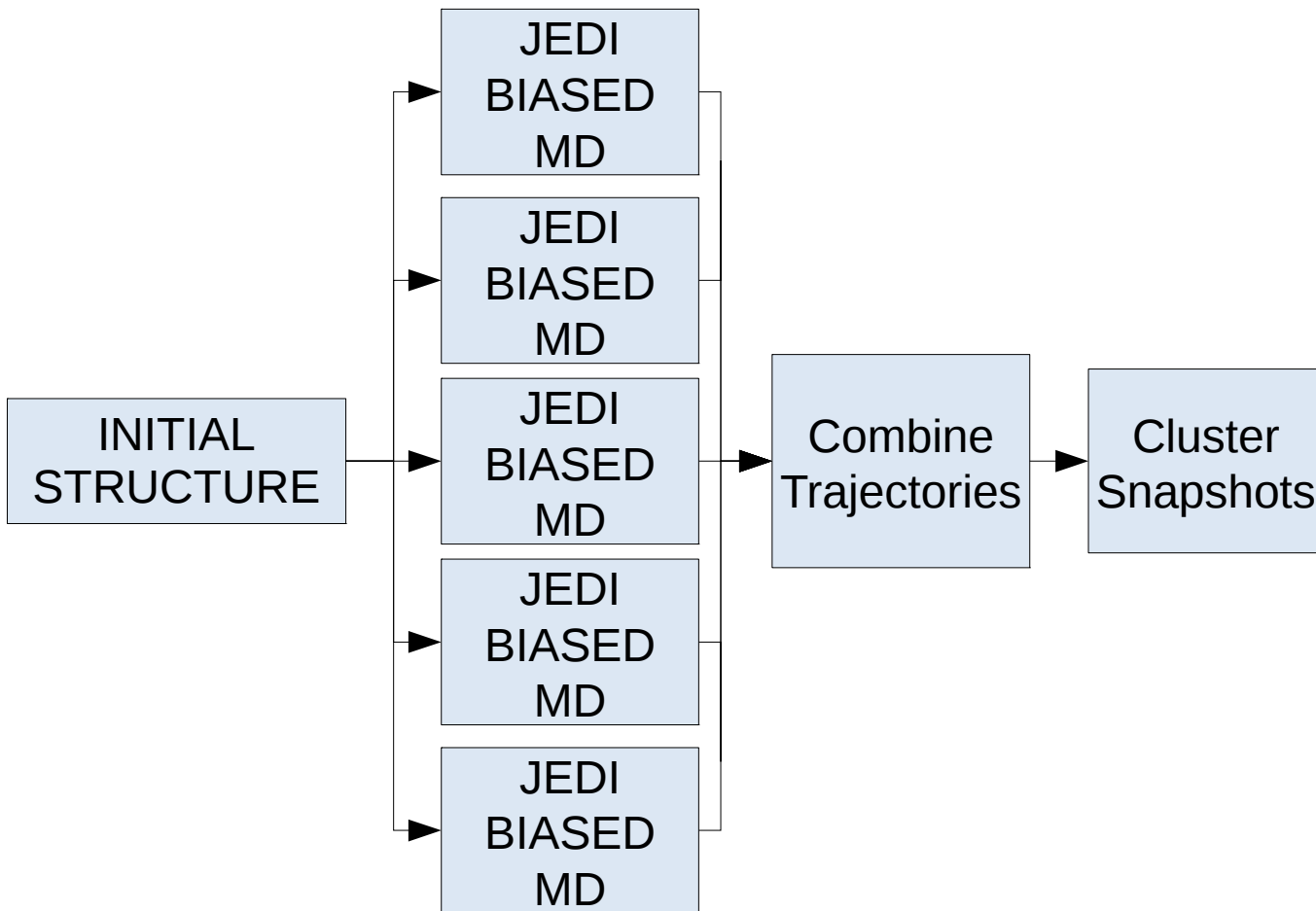


INITIAL
STRUCTURE

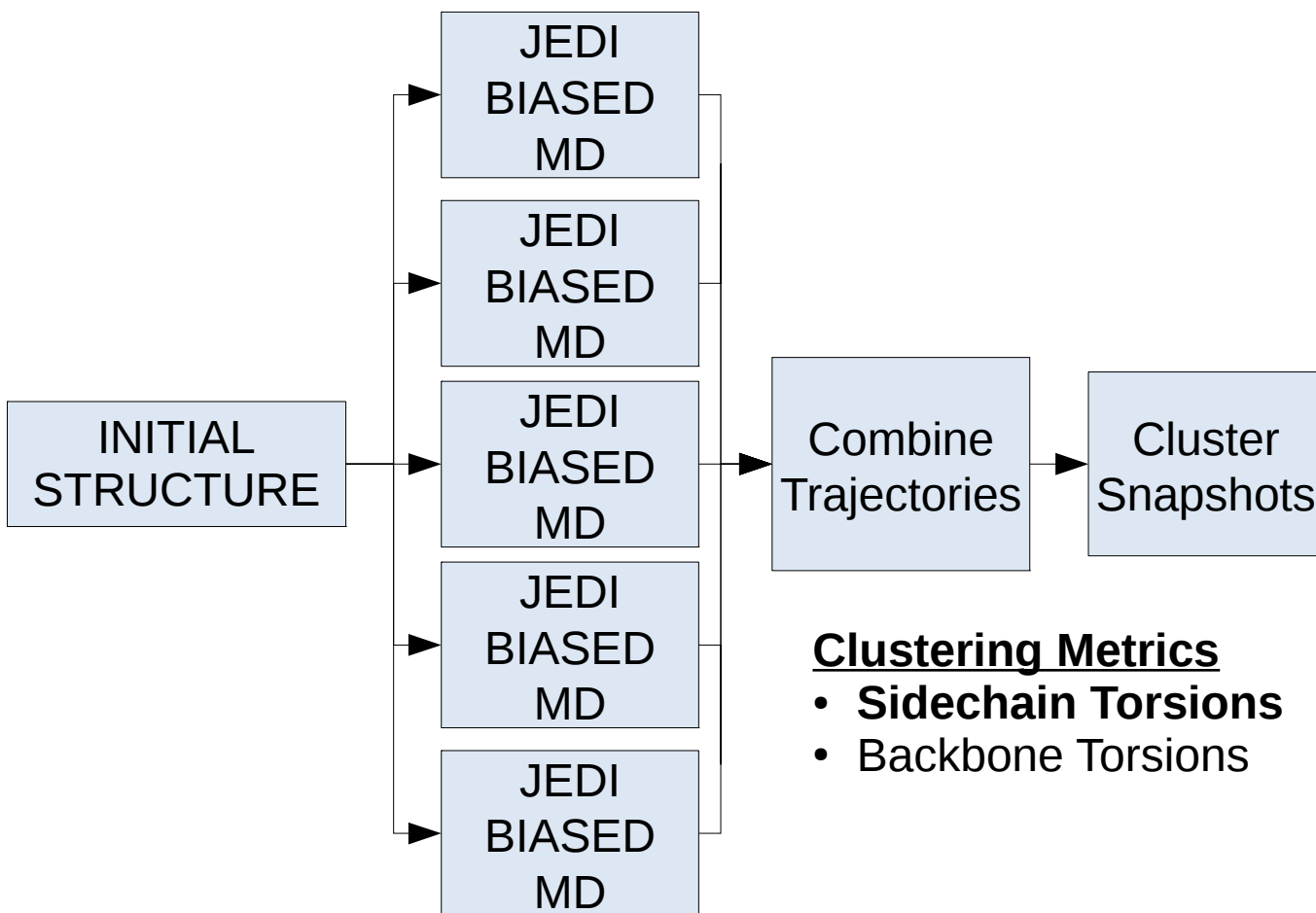
So what is SITH?



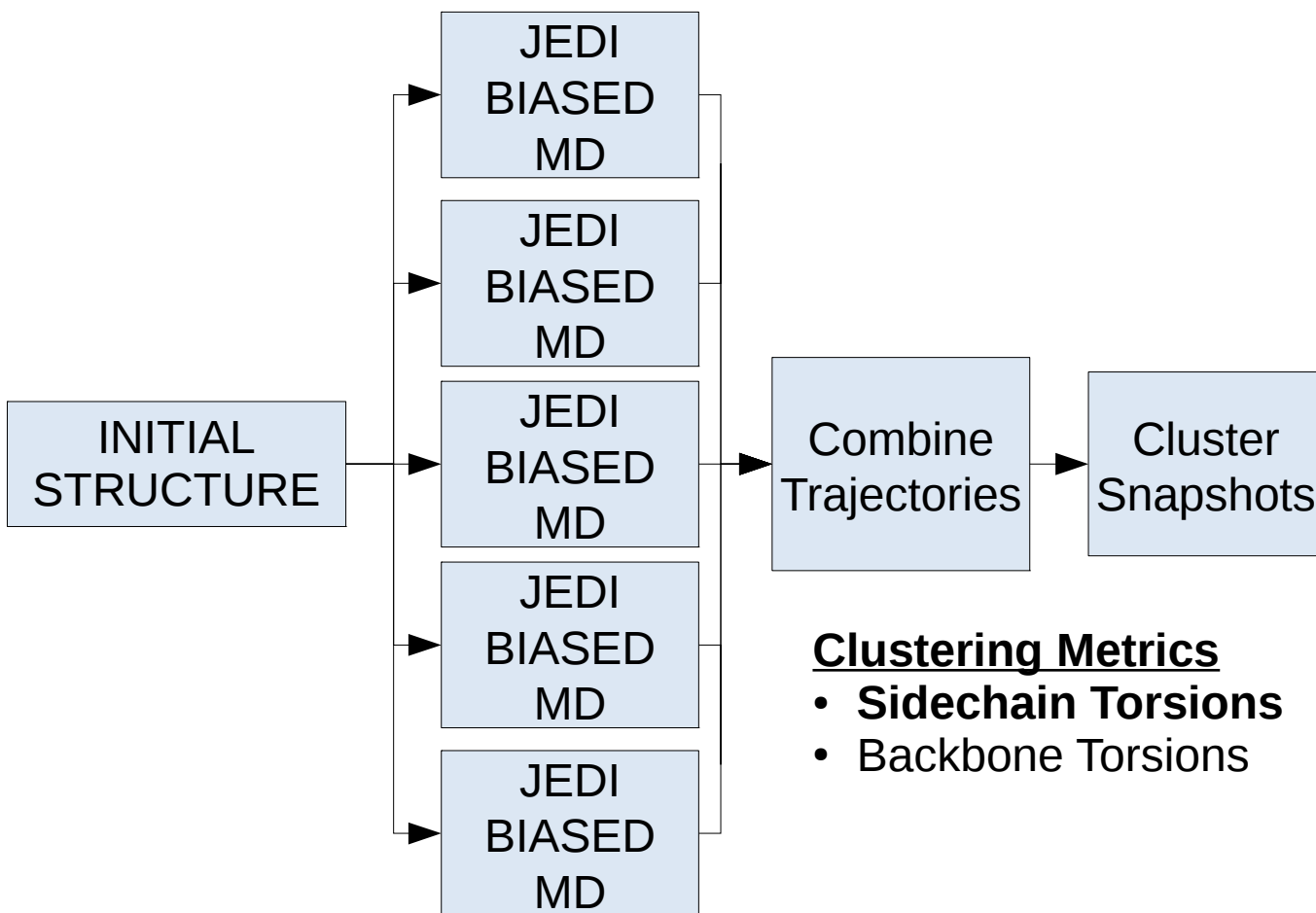
So what is SITH?



So what is SITH?



So what is SITH?



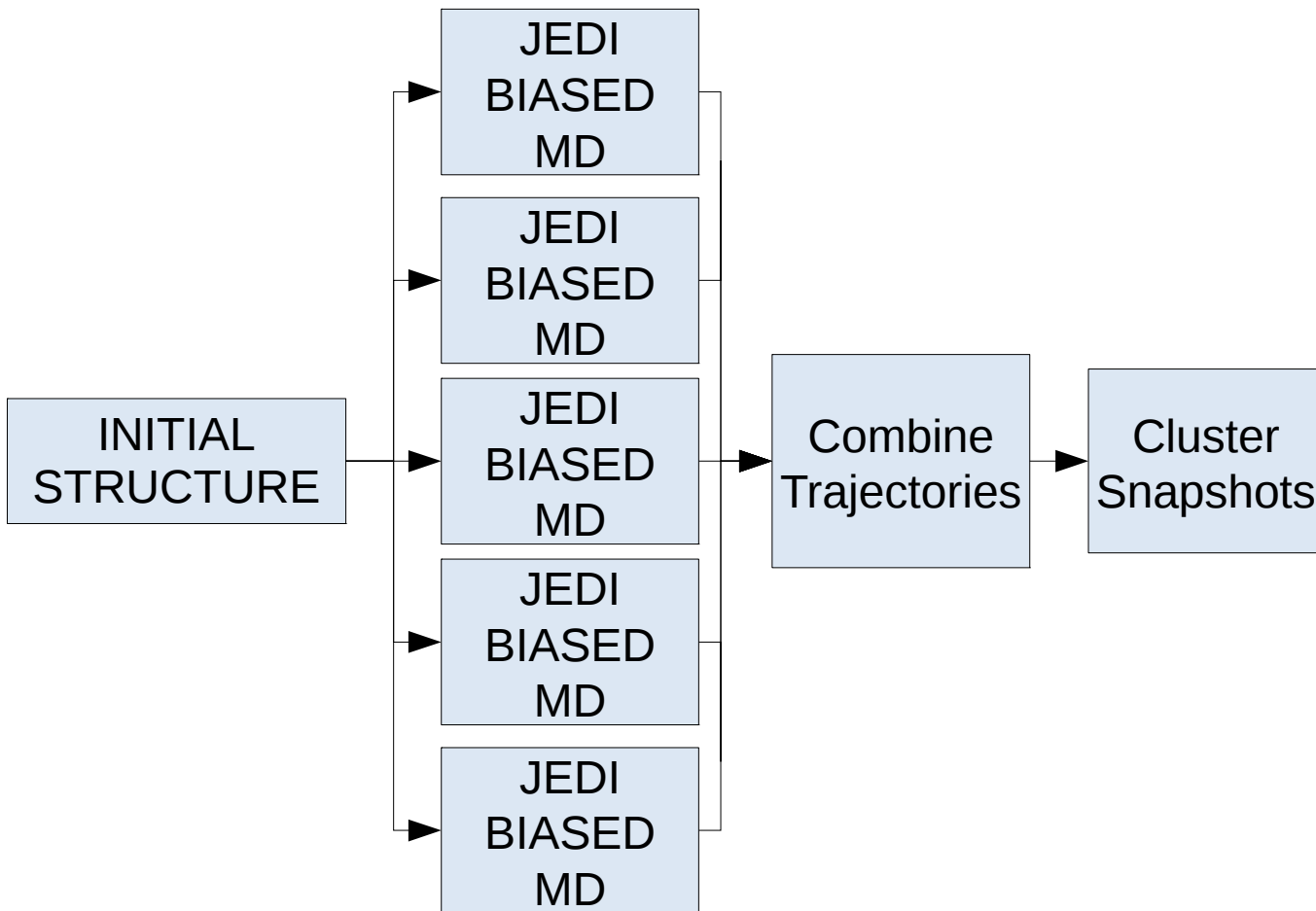
Clustering Metrics

- Sidechain Torsions
- Backbone Torsions

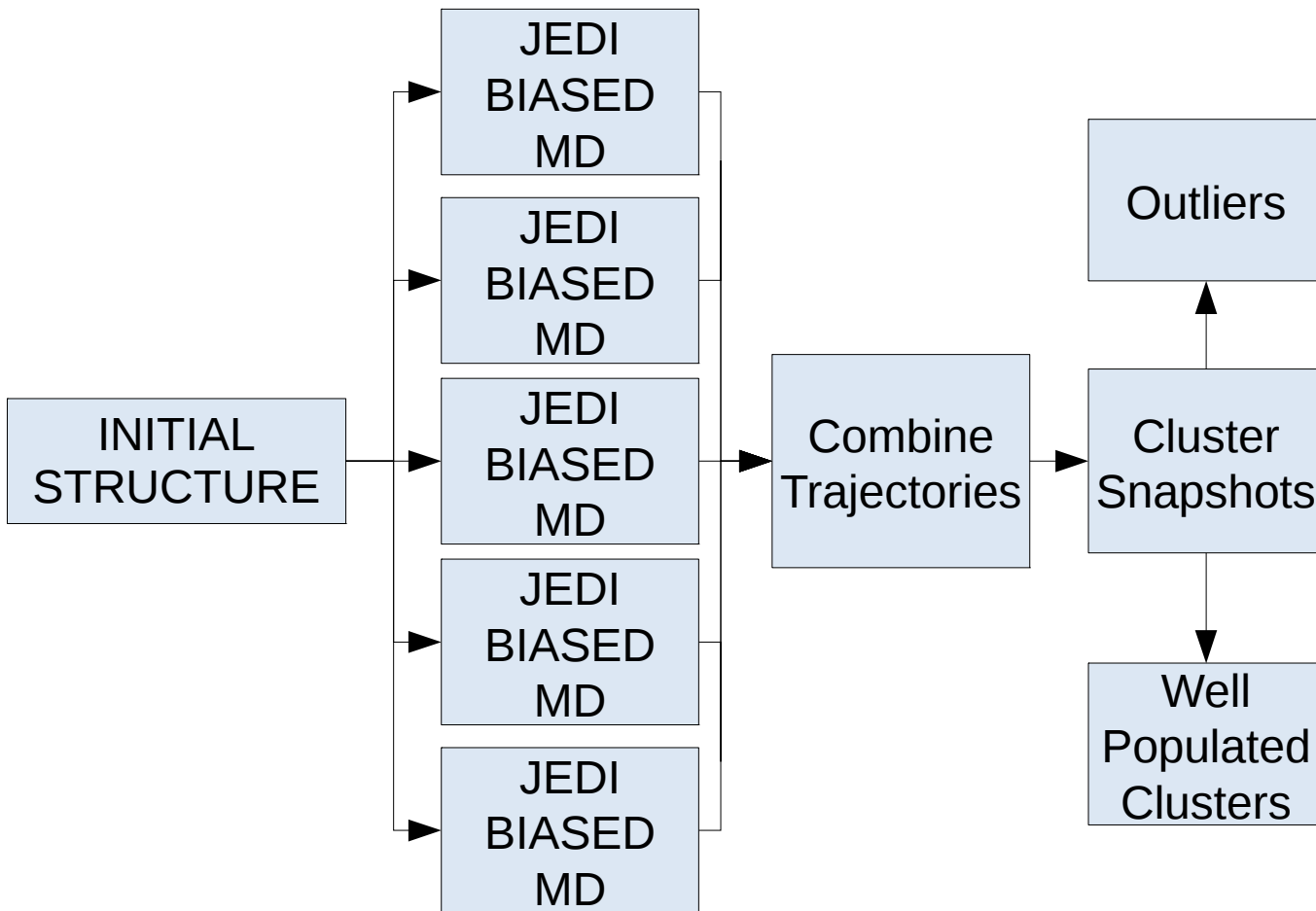
Clustering Algorithms

- Density Peaks
- Distance binning

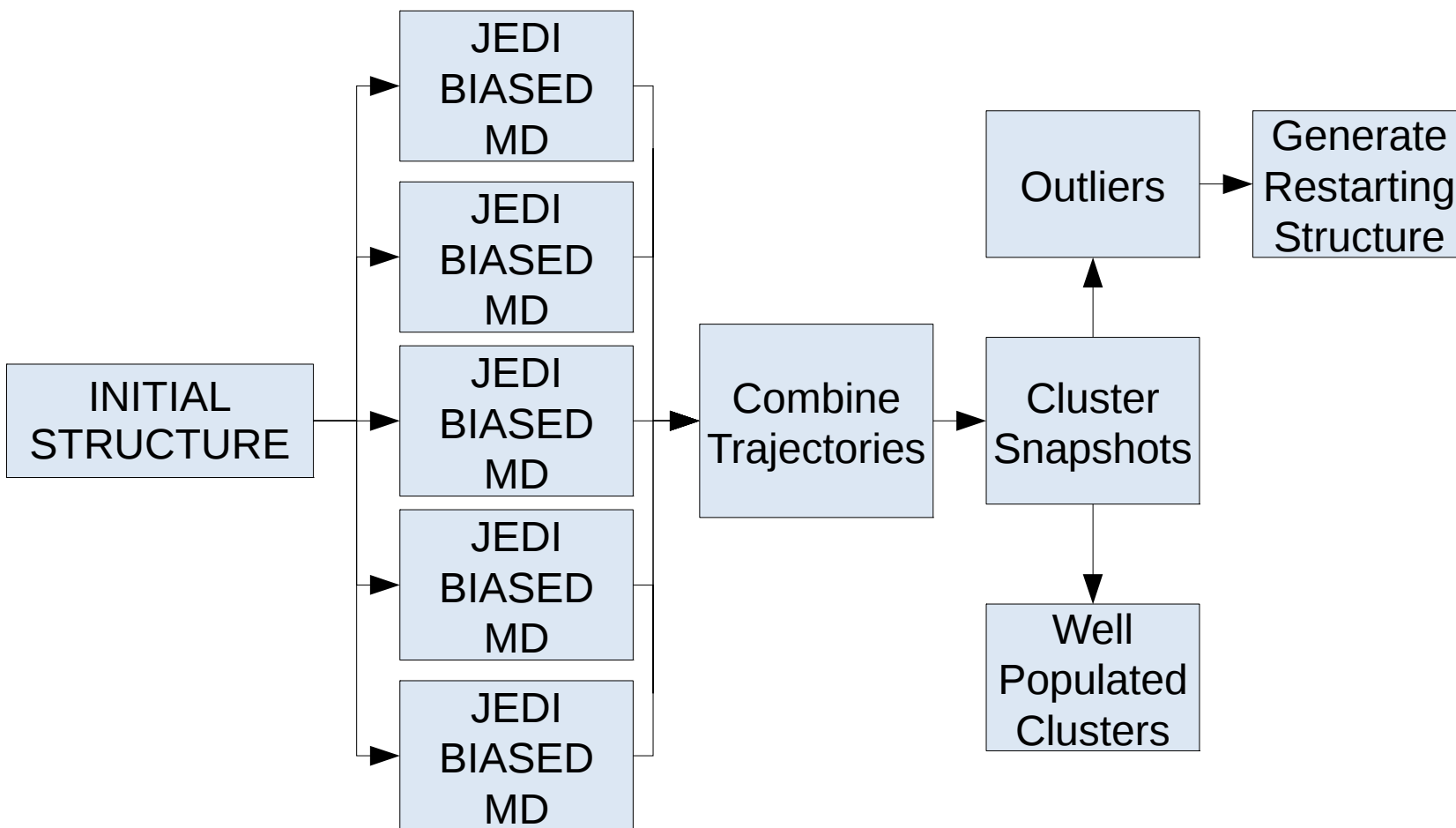
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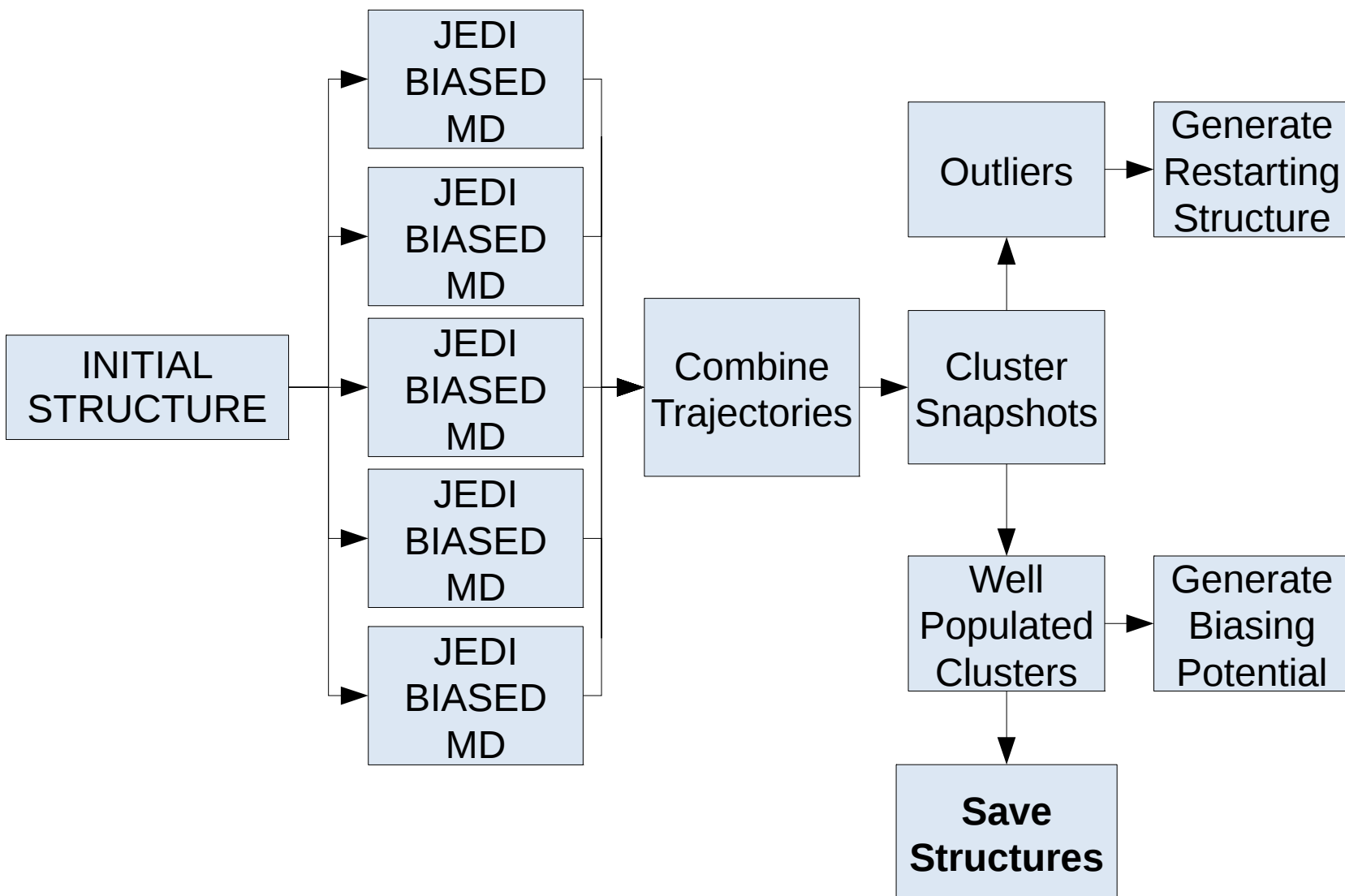
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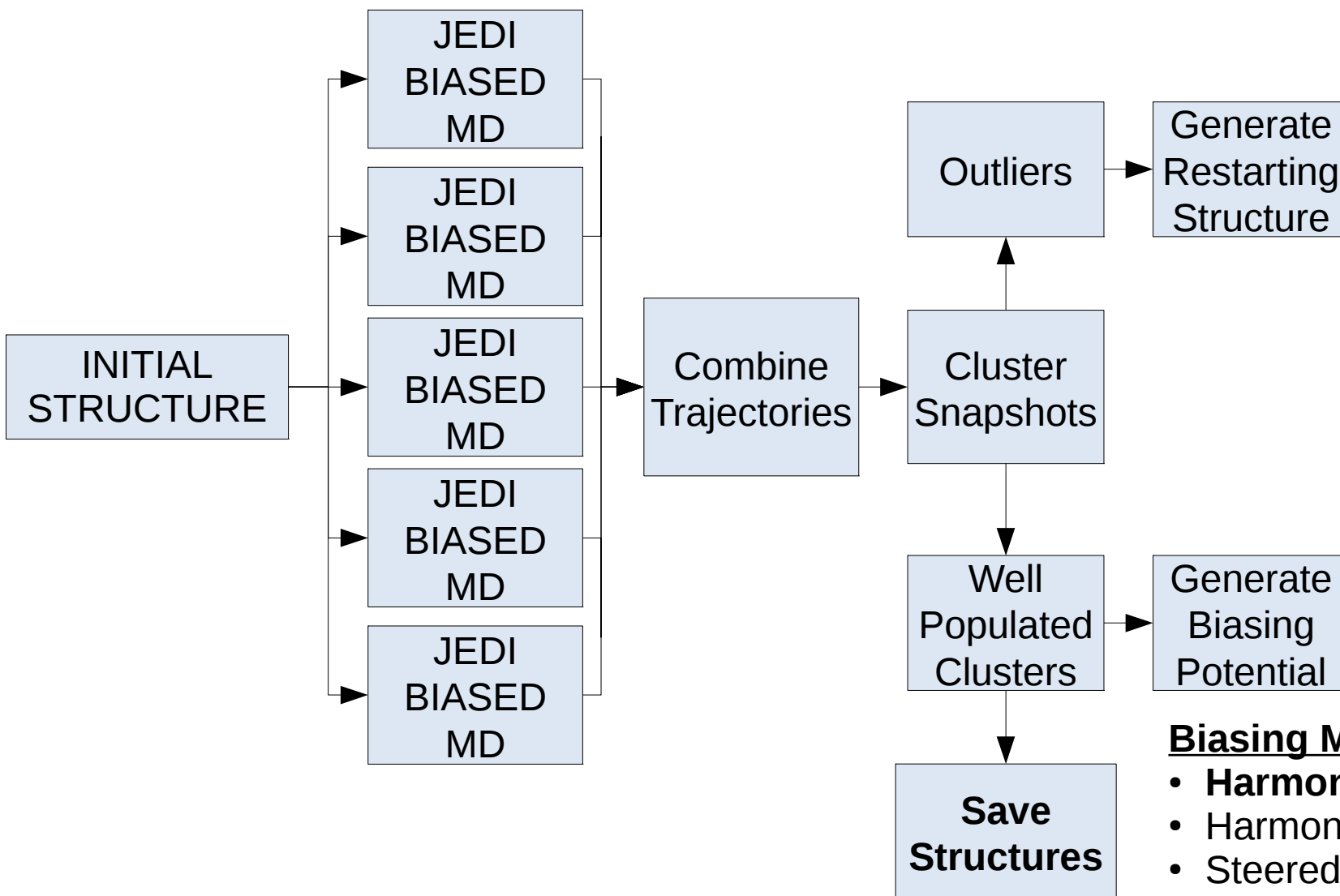
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So what is SITH?



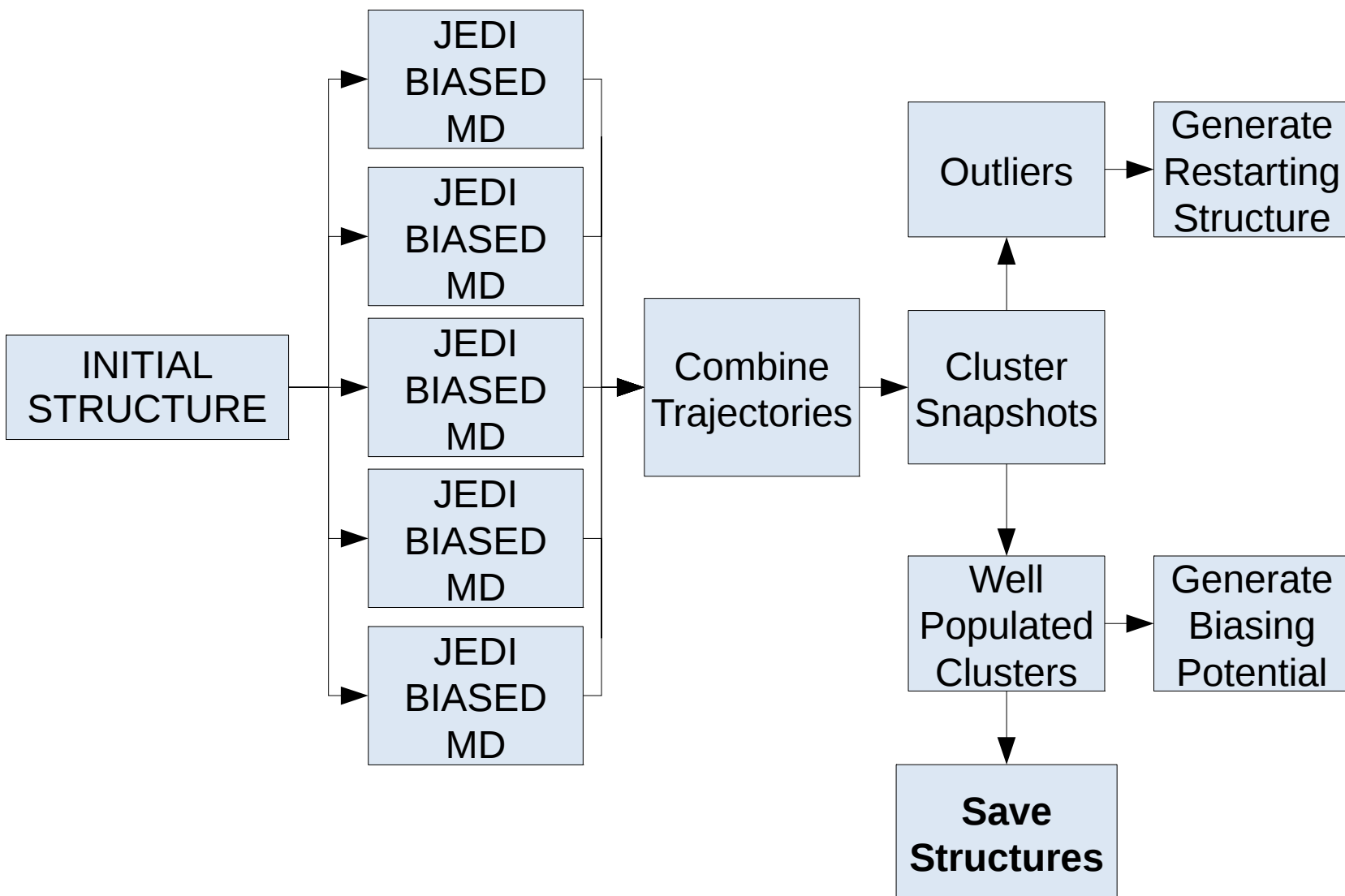
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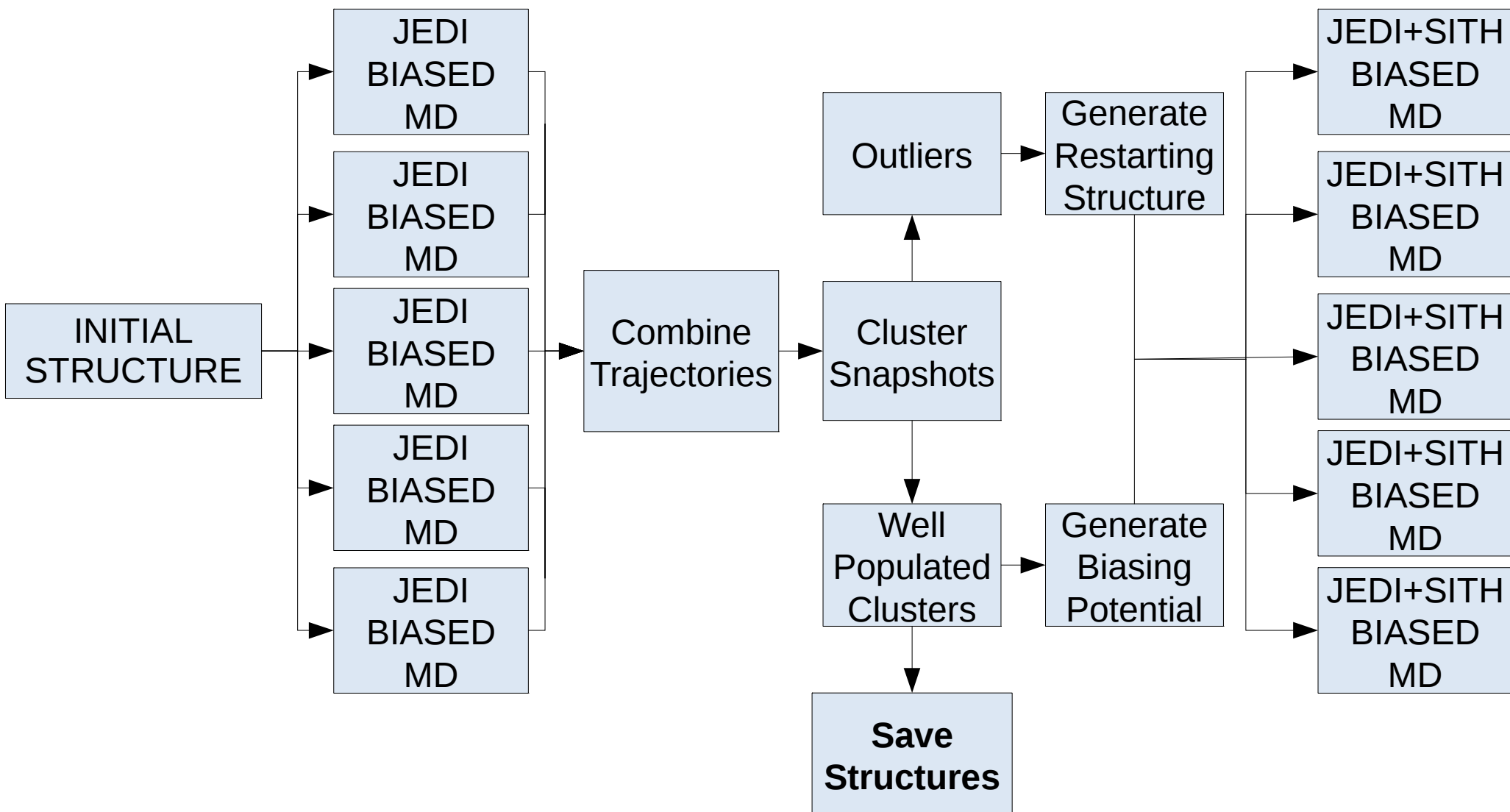
Biasing Methods

- **Harmonic lower wall**
- Harmonic restraint
- Steered MD
- Metadynamics

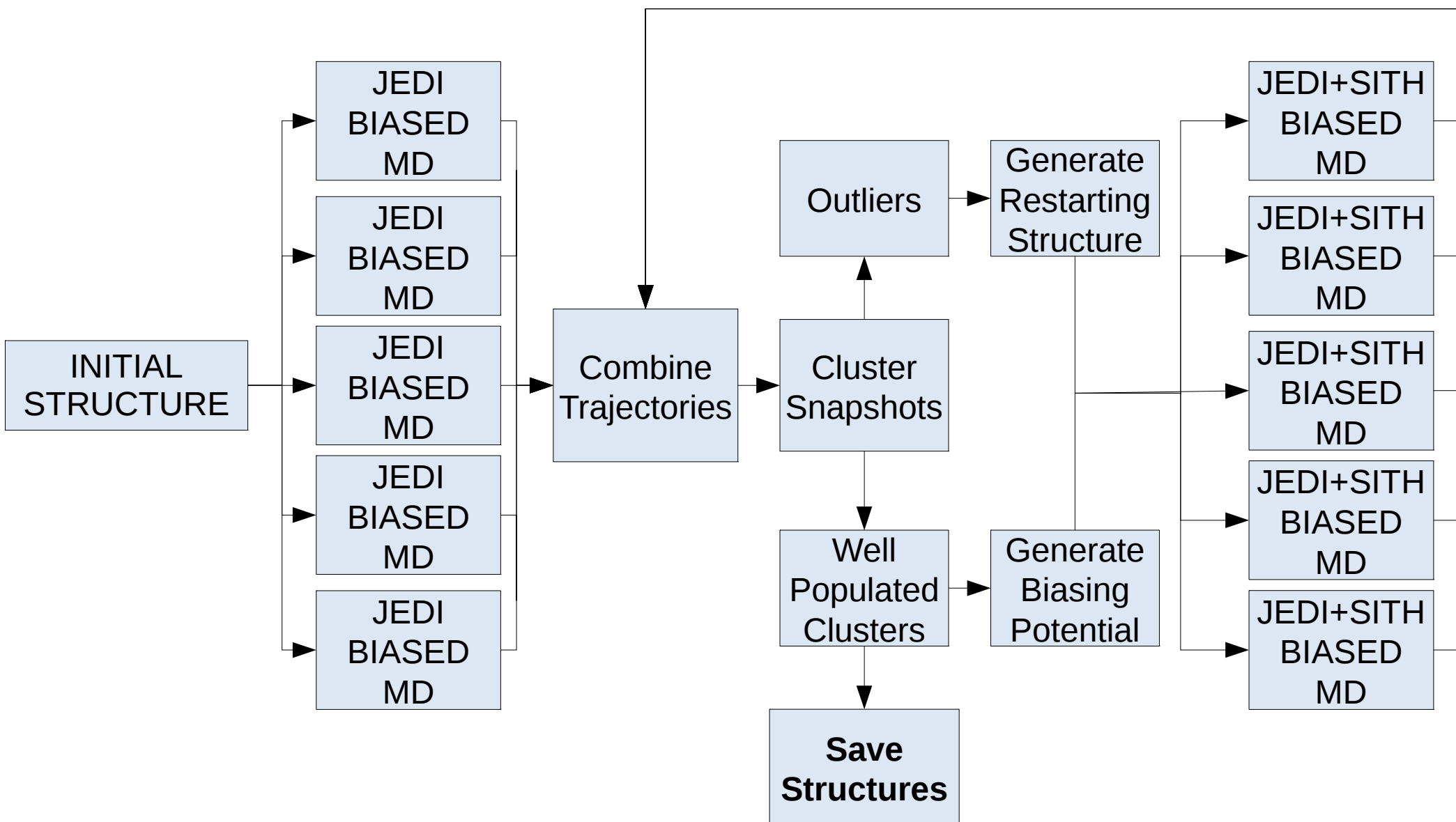
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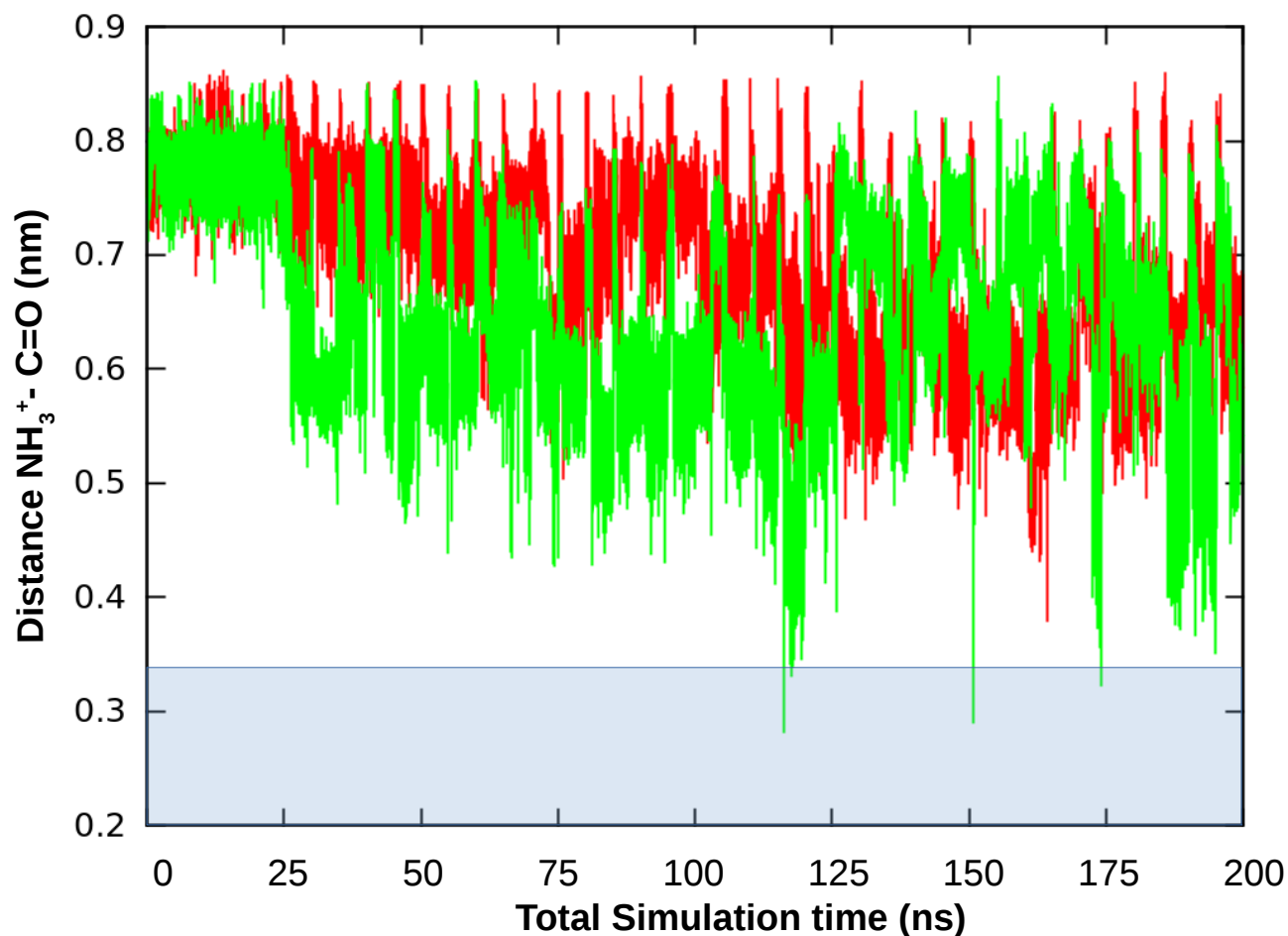
So what is SITH?



So what is SITH?



Results: sampling of Lys57 hydrogen bond



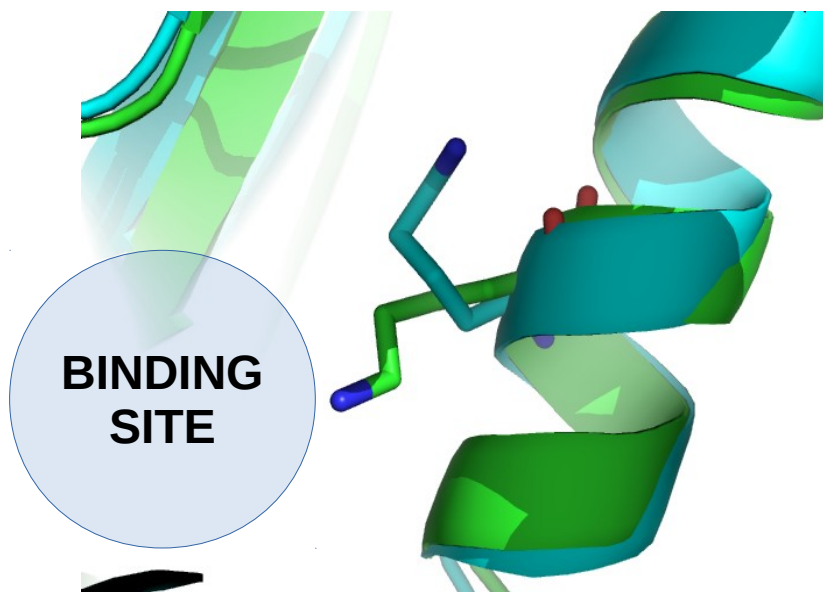
SITH —
SITH+JEDI —

- 8 iterations
- 5 x 5 ns trajectories
- Total = 200 ns
- SITH on Lys57 torsions

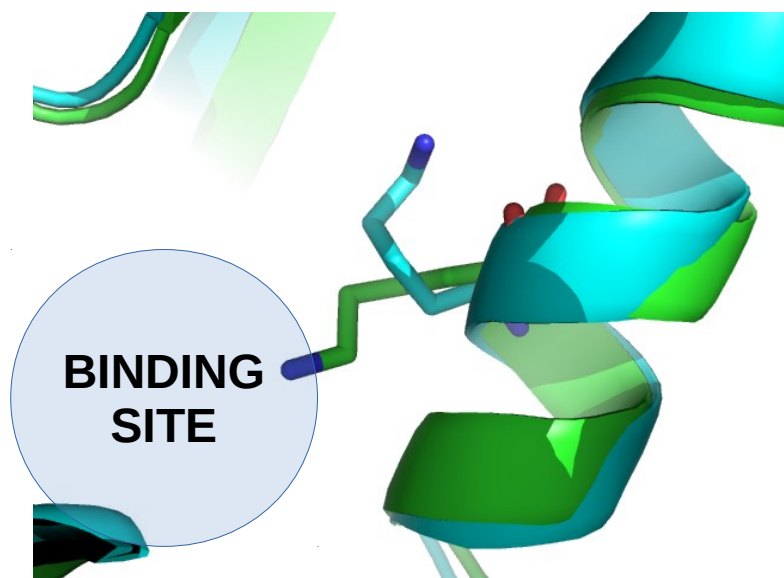
Results: conformations found



SITH without a JEDI bias



SITH with a JEDI bias

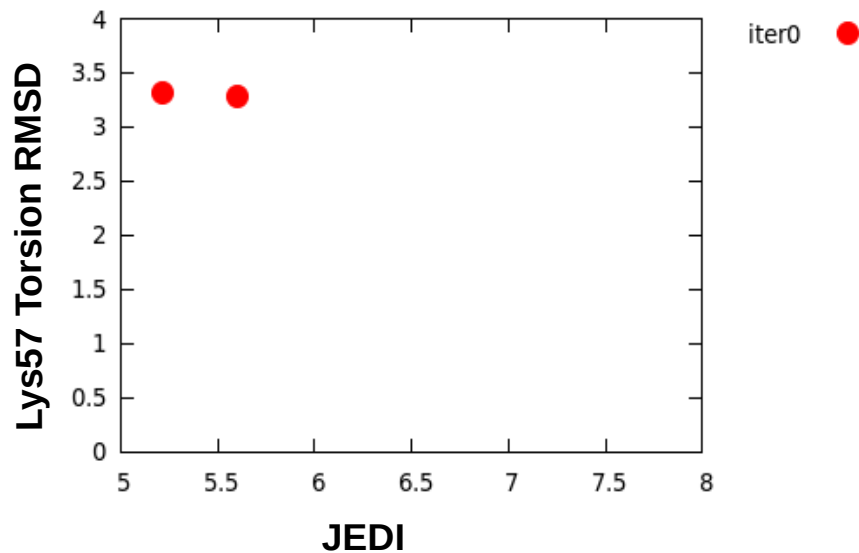
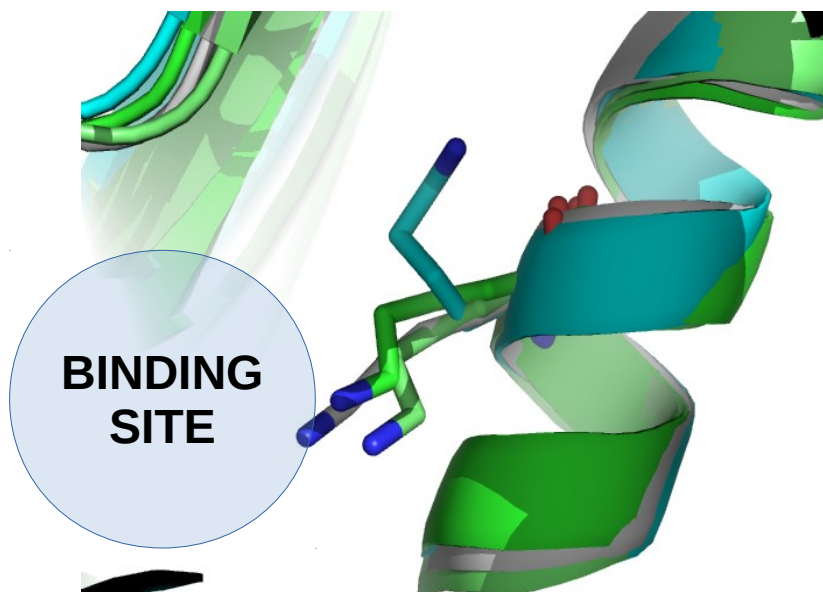


- Start
- Total Simulation Time: 0 ns

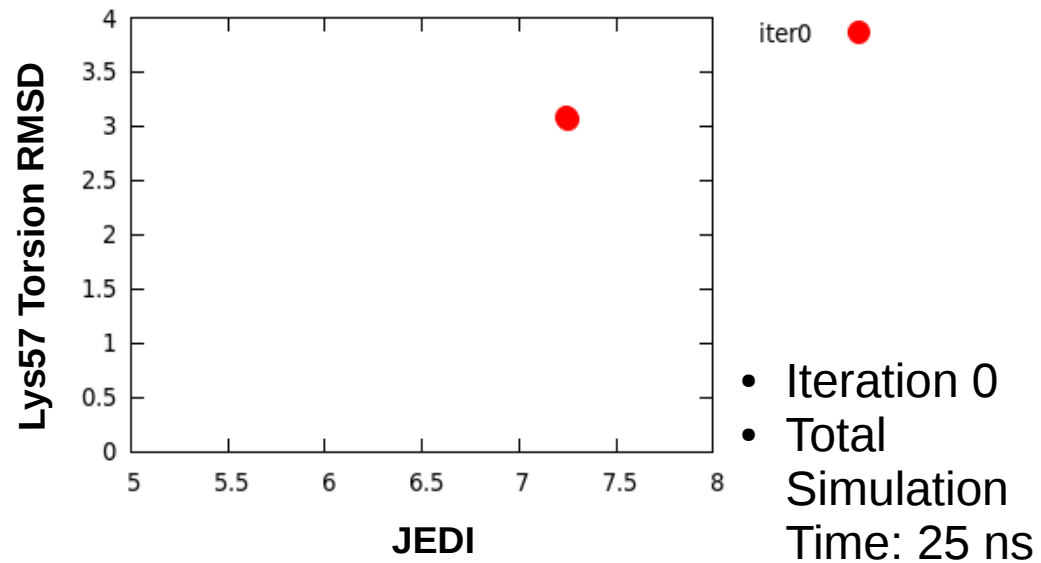
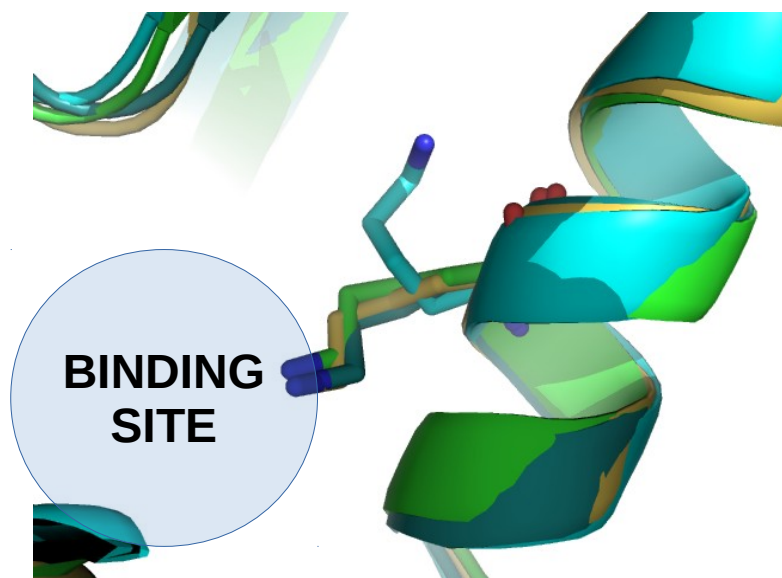
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SITH without a JEDI bias



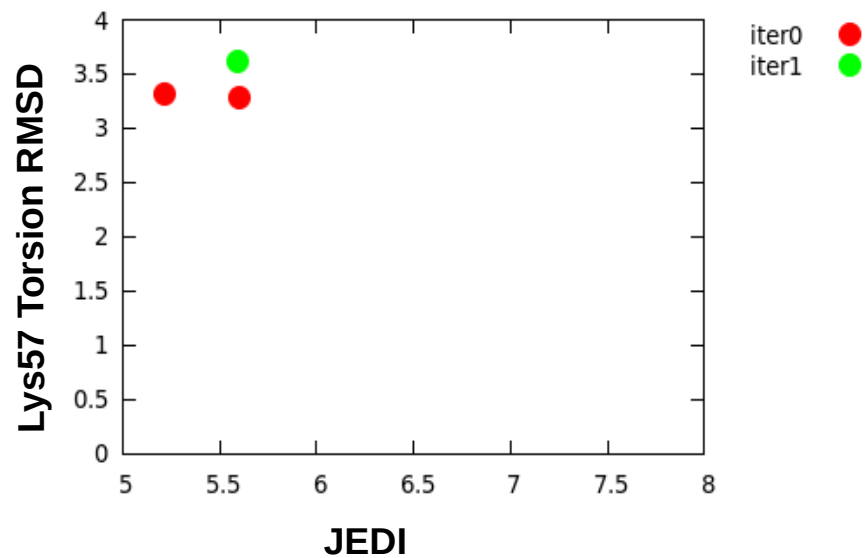
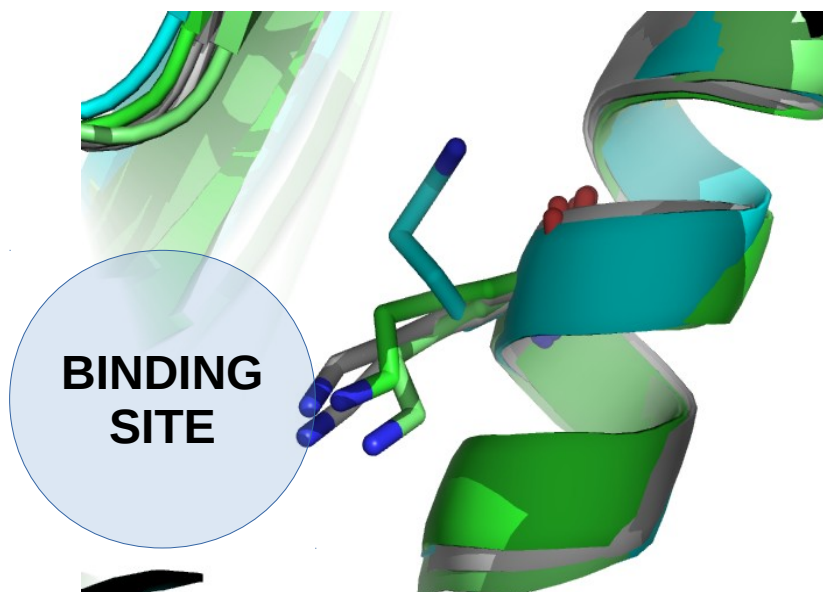
SITH with a JEDI bias



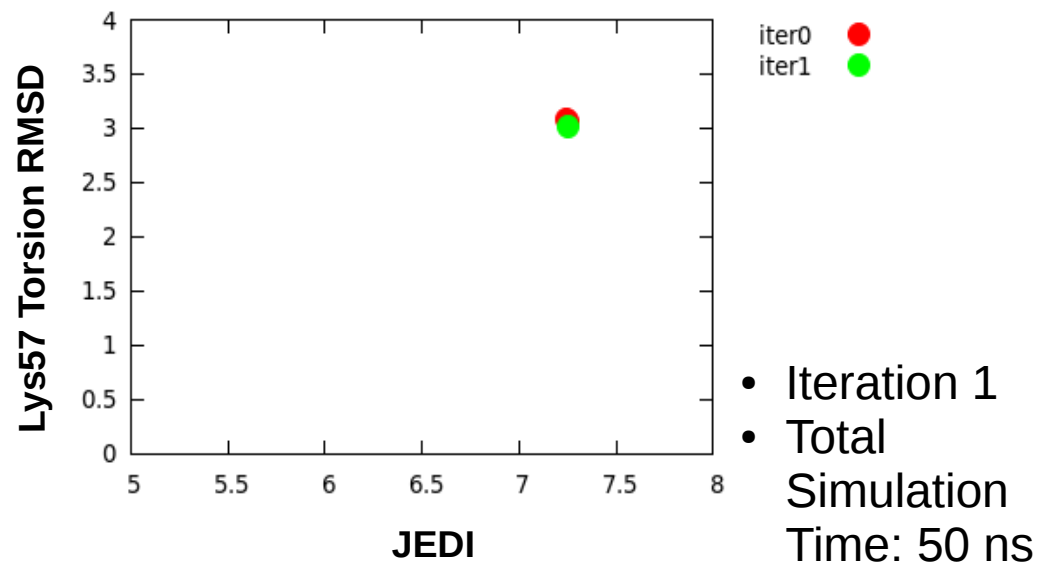
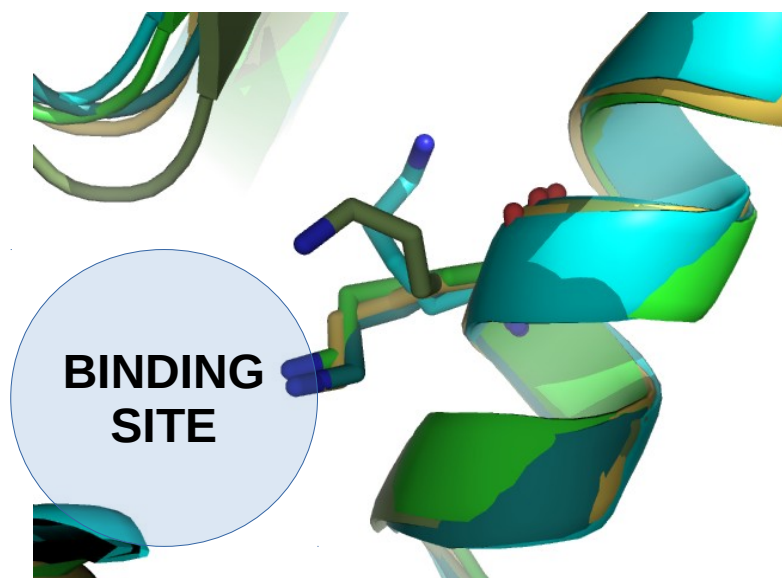
Results: conformations found



SITH without a JEDI bias



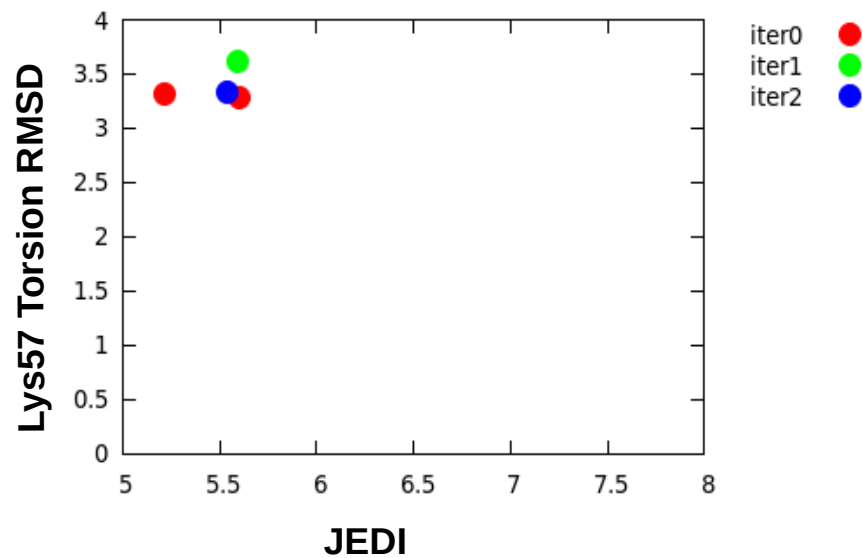
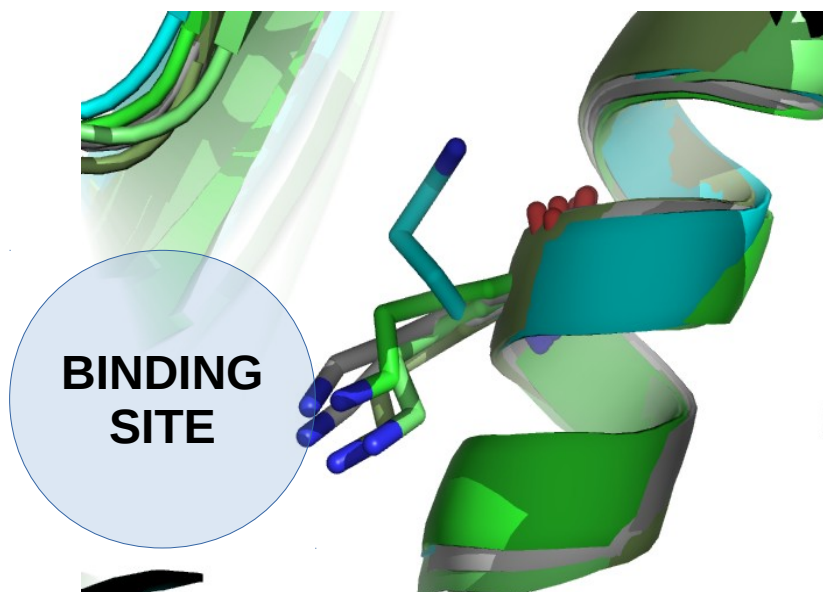
SITH with a JEDI bias



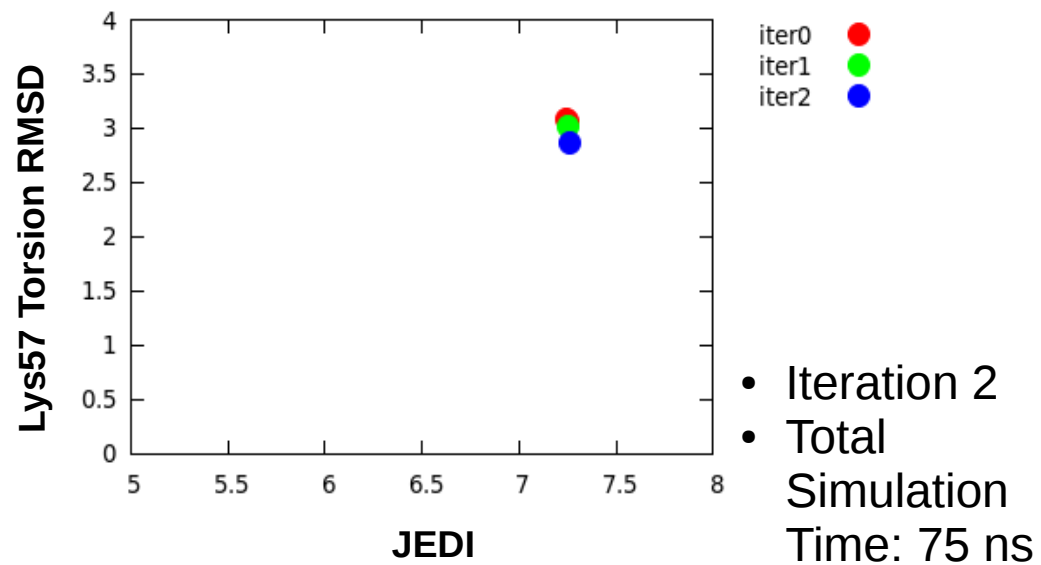
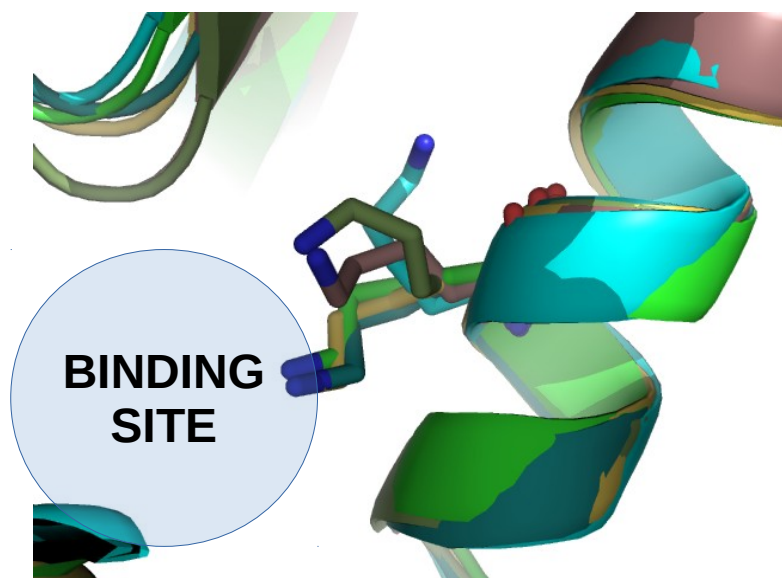
Results: conformations found



SITH without a JEDI bias



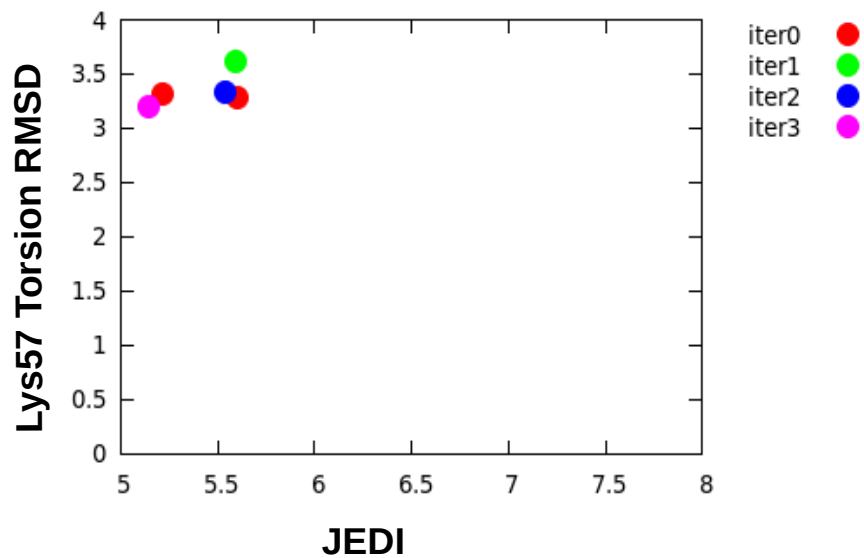
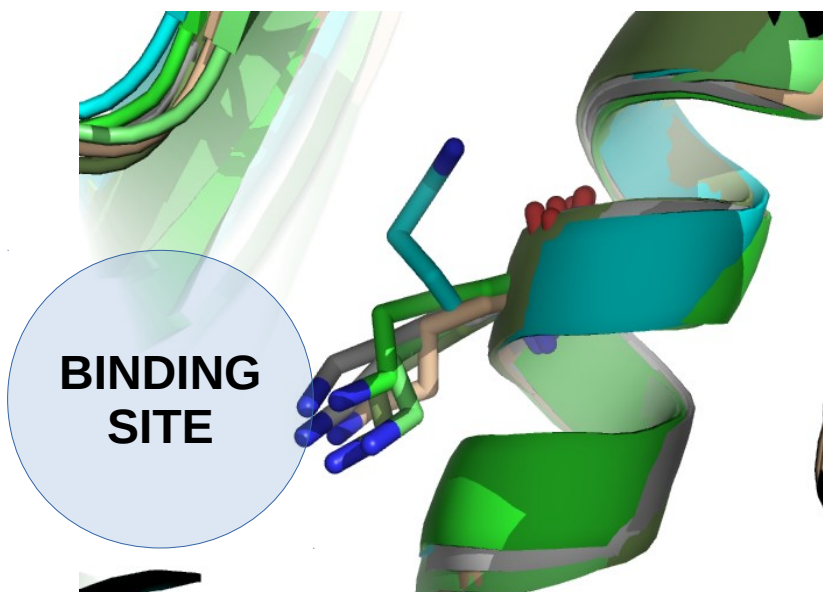
SITH with a JEDI bias



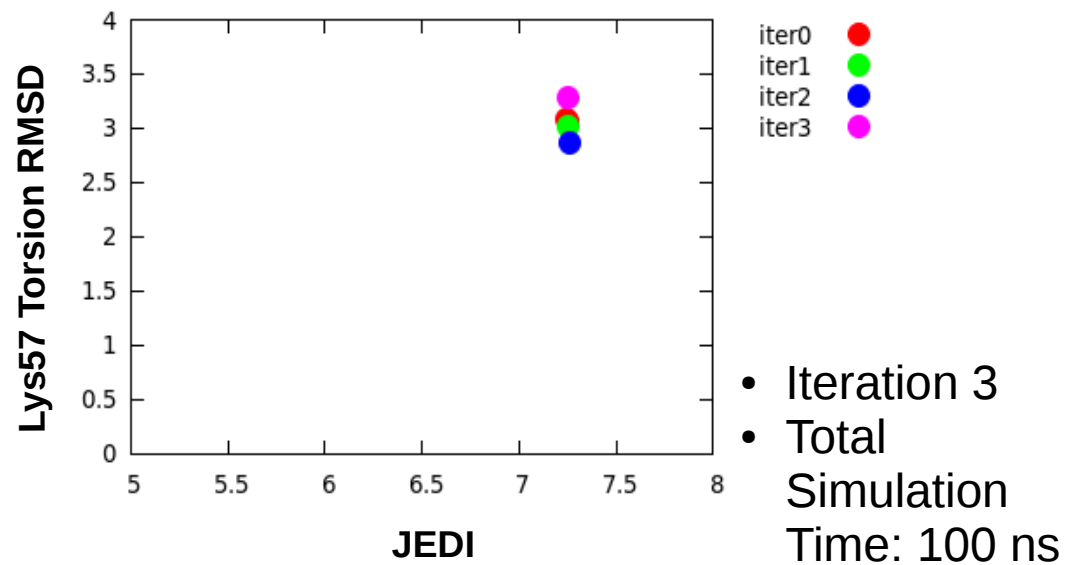
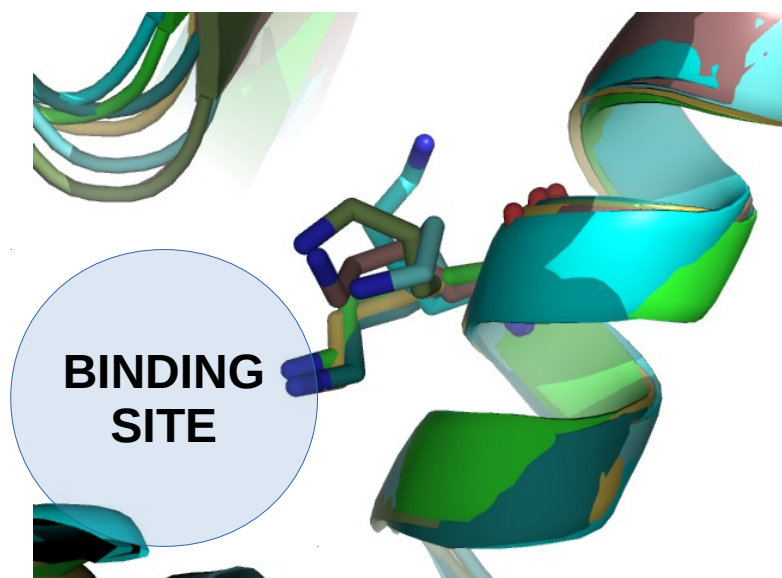
Results: conformations found



SITH without a JEDI bias



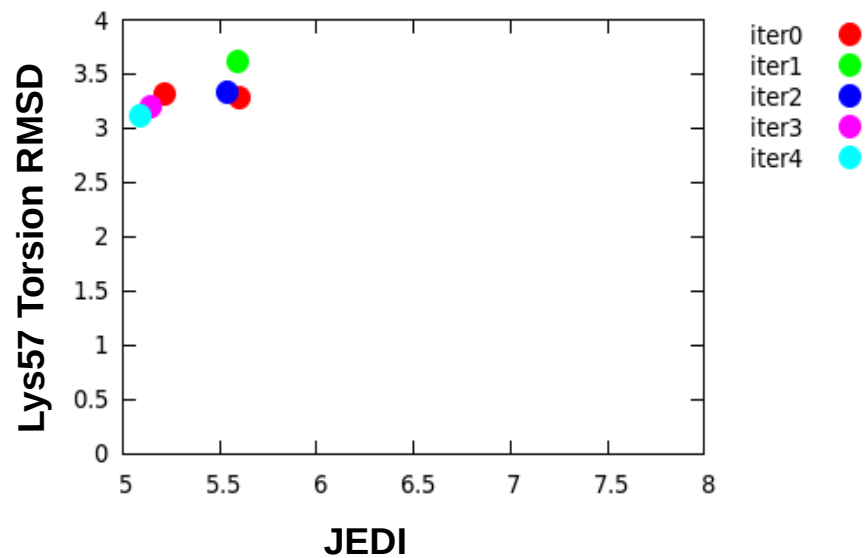
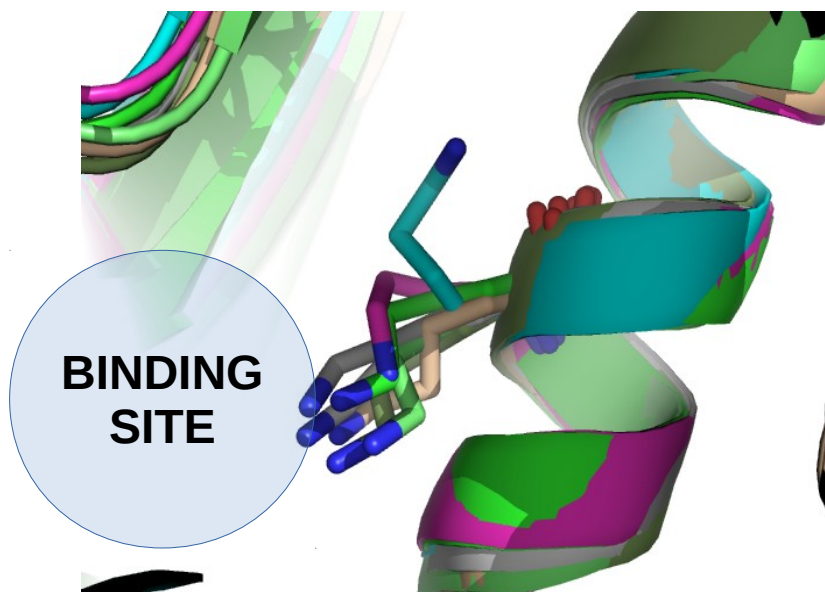
SITH with a JEDI bias



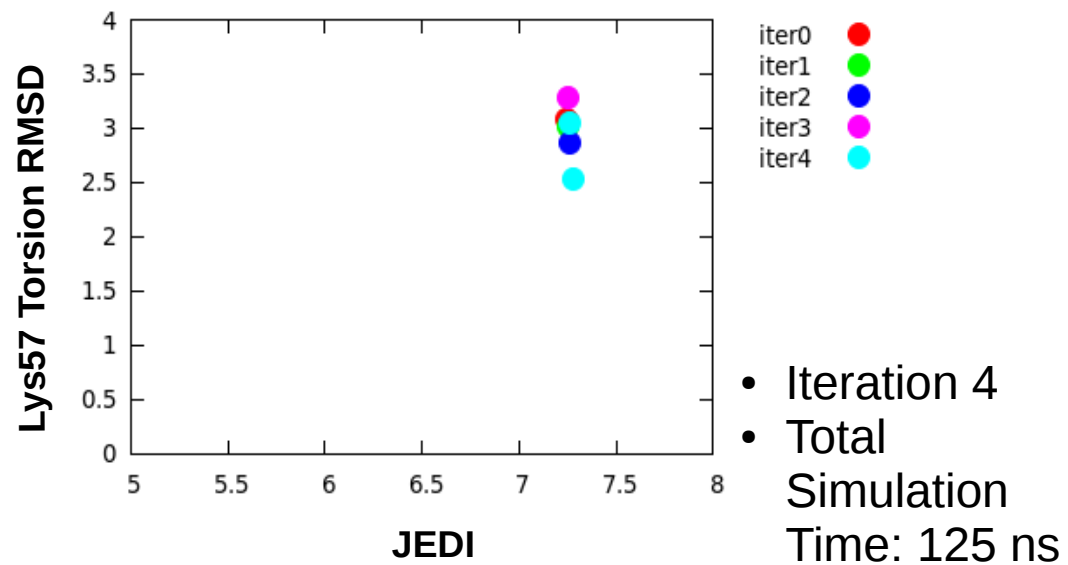
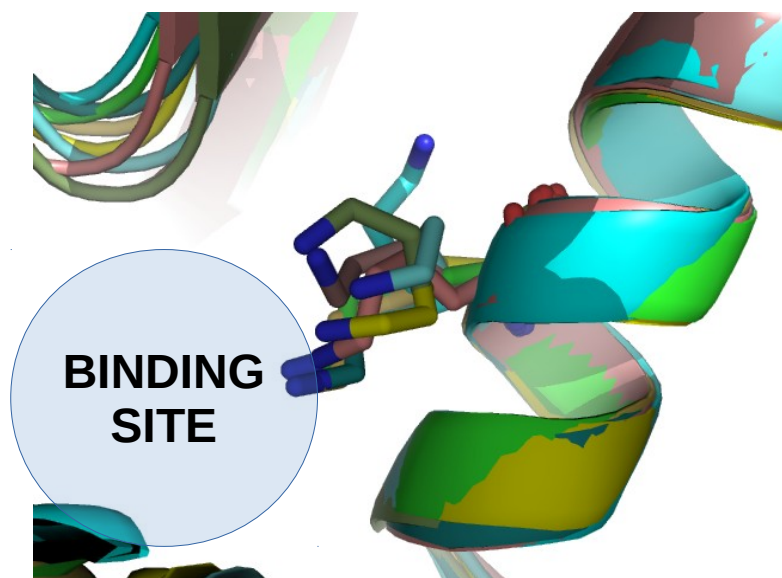
Results: conformations found



SITH without a JEDI bias



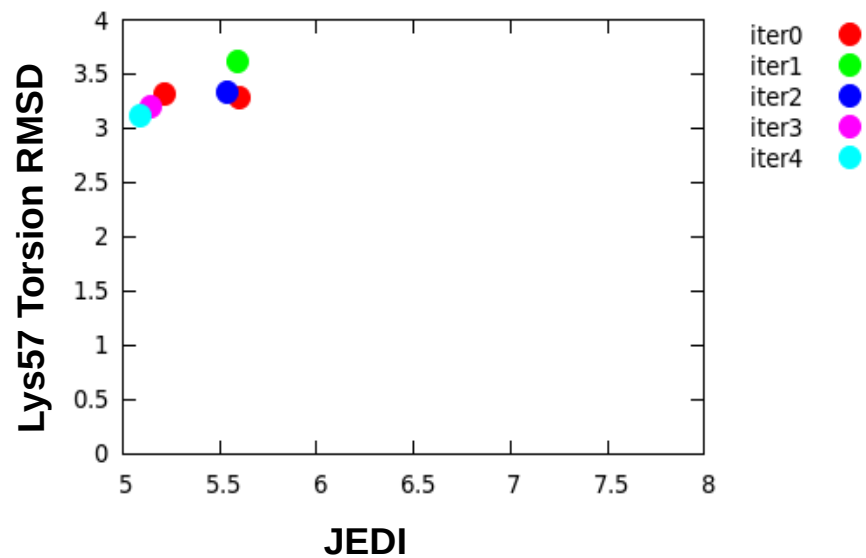
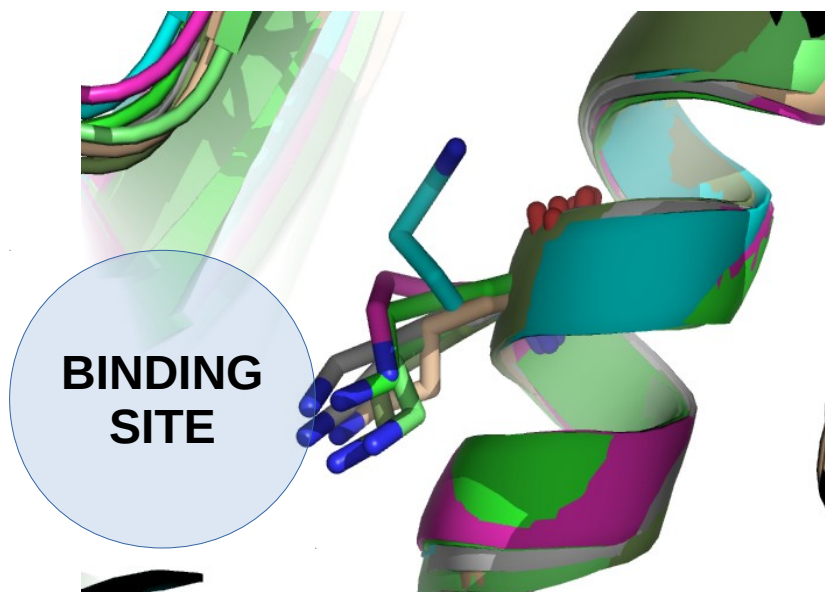
SITH with a JEDI bias



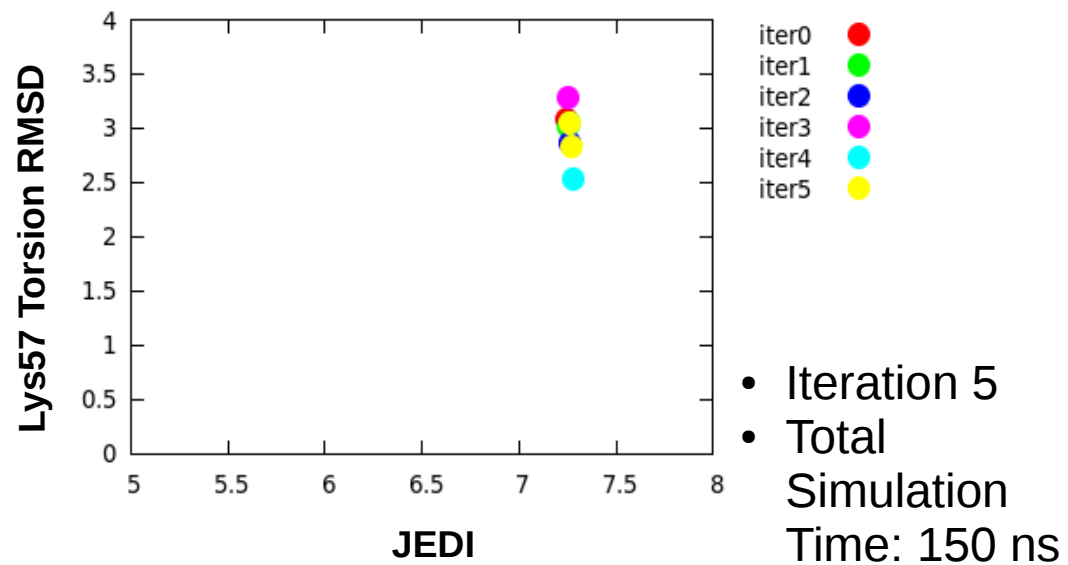
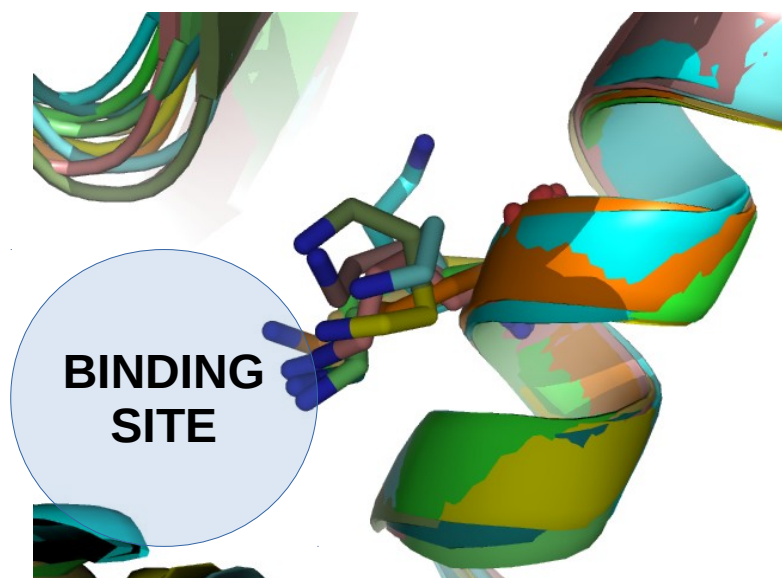
Results: conformations found



SITH without a JEDI bias



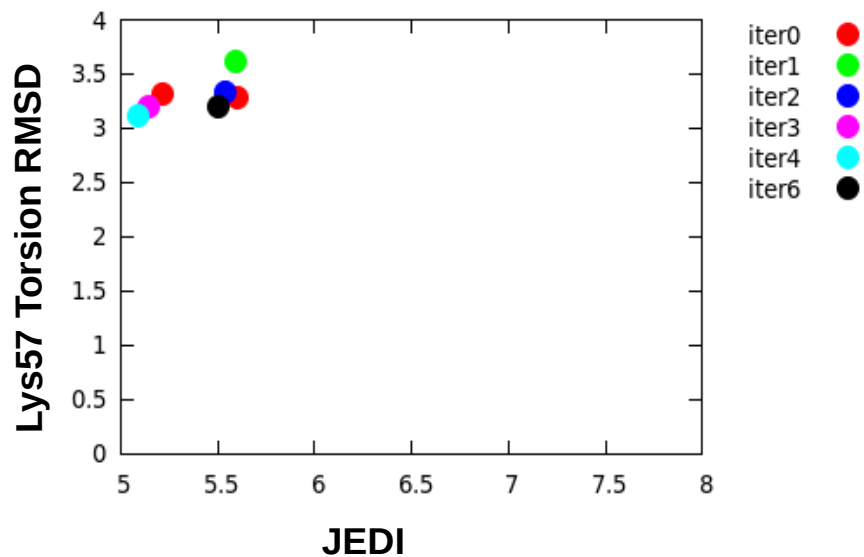
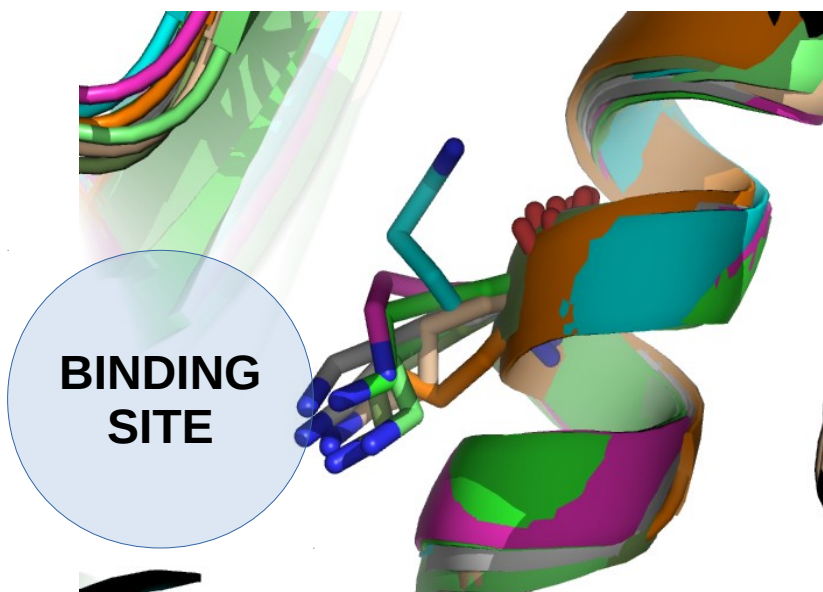
SITH with a JEDI bias



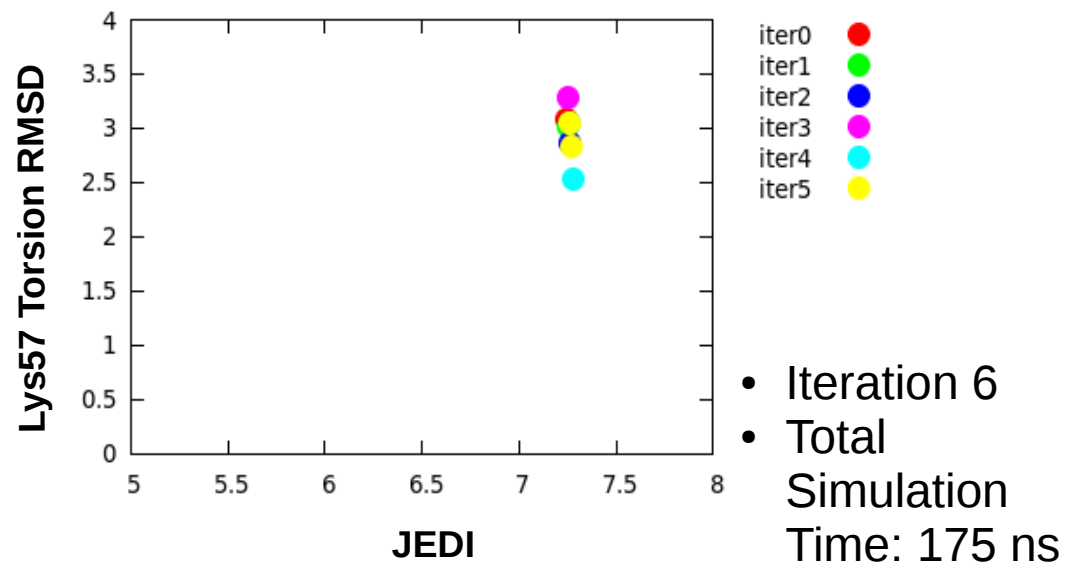
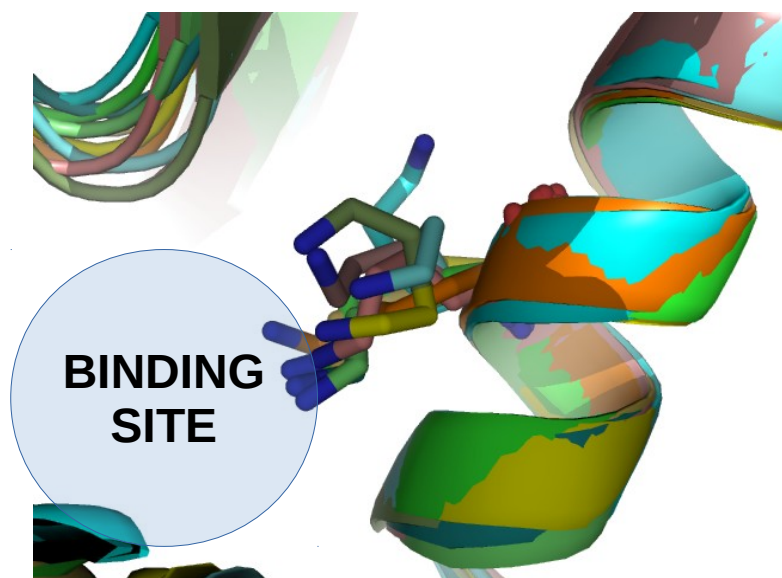
Results: conformations found



SITH without a JEDI bias



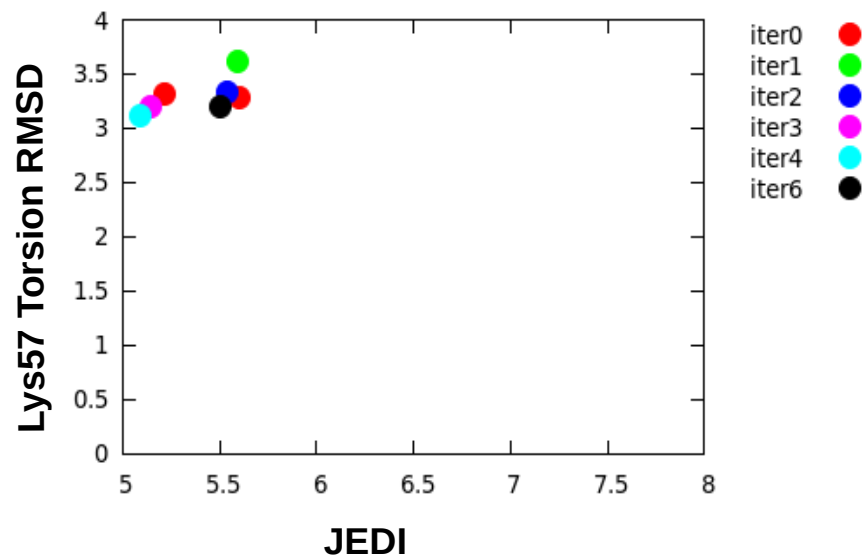
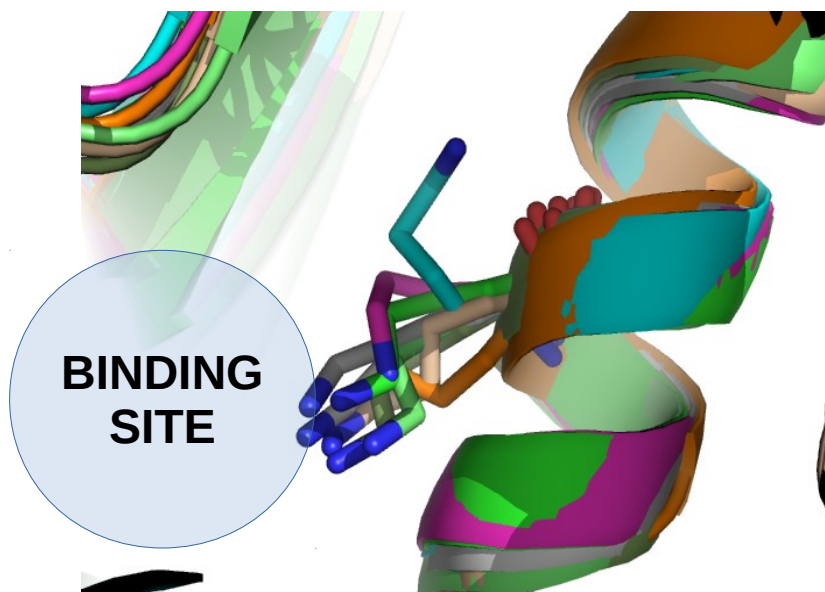
SITH with a JEDI bias



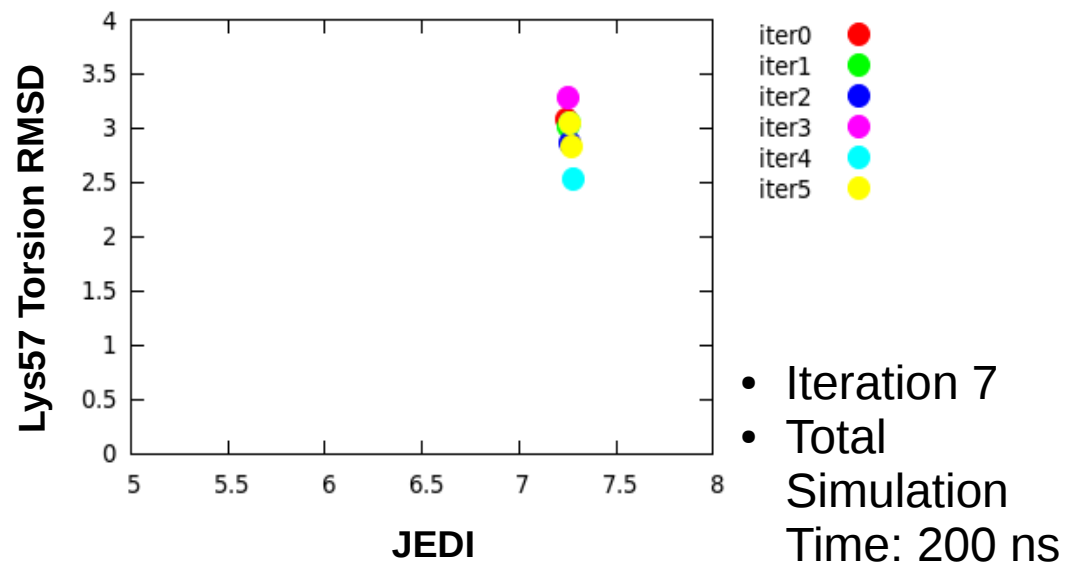
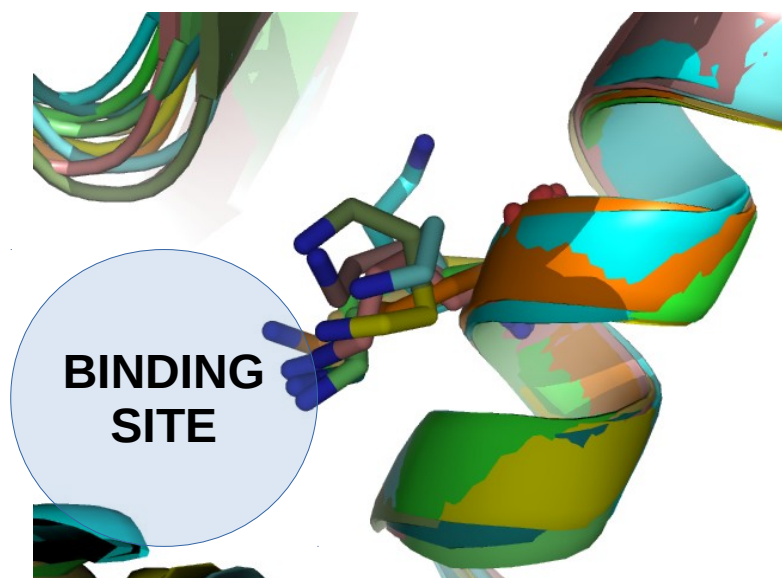
Results: conformations found



SITH without a JEDI bias



SITH with a JEDI bias



Contents



- Part 1: Druggability of cryptic protein pockets
- Part 2: The JEDI approach
- Part 3: The SITH sampling protocol
- **Part 4: Conclusions**

Conclusions

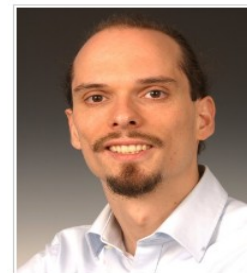


- **Part 1: Druggability of cryptic protein pockets**
 - Exploring druggability could help design drugs for targets currently considered undruggable or improve the efficacy of treating known targets
- **Part 2: The JEDI approach**
 - JEDI is able to distinguish different protein conformations in rigid structures, but the scoring needs to be fixed to work in long MD simulations
- **Part 3: The SITH sampling protocol**
 - The SITH protocol helps generate different conformations and sample the target structure, but the clustering function needs to be optimised in order to identify it as a cluster center.

Acknowledgements



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