From JEDI to SITH

A Journey to the Dark Side of Druggability

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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?

Enzyme

Reactant → Product
How are diseases related to proteins?

Enzyme

Reactant → Product

Inhibitor
So how do we cure diseases?

Phase 1: Collect underpants

Phase 2: Proteins

Phase 3: 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

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

- Volume
- Hydrophobicity
- Enclosure
**Inhibitor SKF**
Volume = 258 Å³
$K_i= 580 \text{ nM}$
Pocket Volume: 304 Å³
Binding pockets

Inhibitor SKF
Volume = 258 Å³
Ki= 580 nM
Pocket Volume: 304 Å³

Inhibitor F83
Binding pockets

**Inhibitor SKF**
- Volume = 258 Å³
- $K_i$ = 580 nM
- Pocket Volume: 304 Å³

**Inhibitor F83**
Binding pockets

Inhibitor SKF
Volume = 258 Å³
Ki= 580 nM
Pocket Volume: 304 Å³

Inhibitor F83
Binding pockets

Inhibitor SKF
Volume = 258 Å³
Ki= 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**
- Volume = 258 Å$^3$
- $K_i$ = 580 nM
- Pocket Volume: 304 Å$^3$

**Inhibitor F83**
- Volume = 422 Å$^3$
- $K_i$ = 63 nM
Binding pockets

**Inhibitor SKF**
Volume = 258 Å³
Ki= 580 nM
Pocket Volume: 304 Å³

**Inhibitor F83**
Volume = 422 Å³
Ki= 63 nM
Pocket Volume: 545 Å³
**Inhibitor SKF**
Volume = 258 Å³
Ki= 580 nM
Pocket Volume: 304 Å³

**Inhibitor F83**
Volume = 422 Å³
Ki= 63 nM
Pocket Volume: 545 Å³
Cryptic Binding pockets

NOT DETECTED EXPERIMENTALLY IN THE ABSENCE OF A LIGAND
Molecular Dynamics

\[ U(R) = \sum_{\text{bonds}} k_b (r - r_{eq})^2 \]
\[ + \sum_{\text{angles}} k_\theta (\theta - \theta_{eq})^2 \]
\[ + \sum_{\text{dihedrals}} k_\phi (1 + \cos[n\phi - \gamma]) \]
\[ + \sum_{\text{impropers}} k_\omega (\omega - \omega_{eq})^2 \]
\[ + \sum_{i<j} \varepsilon_{ij} \left( \frac{r_{ij}}{r_m} \right)^{12} - 2 \left( \frac{r_{ij}}{r_y} \right)^6 \]
\[ + \sum_{i<j} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \]

**Force field** (Energy function)

**Structure** (Initial positions and velocities)

**Topology** (connectivity between atoms)

- **Compute forces**
- **Apply forces**
- **Update Positions And velocities**
Molecular Dynamics

\[ U(R) = \sum_{\text{bonds}} k_b (r - r_{eq})^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} k_\phi (1 + \cos[n\phi - \gamma]) \]

\[ + \sum_{\text{improvers}} k_\omega (\omega - \omega_{eq})^2 \]

\[ + \sum_{\text{atoms}} \varepsilon_{ij} \left[ \left( \frac{r_{ij}}{r_{eq}} \right)^{12} - 2 \left( \frac{r_{ij}}{r_{eq}} \right)^6 \right] \]

\[ + \sum_{i<j} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \]

**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

$U(R) = \sum_{\text{bonds}} k_i (r - r_{eq})^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} k_\phi (1 + \cos[n\phi - \gamma]) + \sum_{\text{improper}} k_\omega (\omega - \omega_{eq})^2$

- **Force field (Energy function)**
- **Structure** (Initial positions and velocities)
- **Topology** (connectivity between atoms)

1. **Compute forces**
2. **Apply forces**
3. **Update Positions And velocities**
Molecular Dynamics

\[ U(R) = \sum_{\text{bonds}} k_b (r - r_{eq})^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} k_\phi (1 + \cos(n\phi - \gamma)) + \sum_{\text{impropers}} k_\omega (\omega - \omega_{eq})^2 \]

\[ + \sum_{i<j} \left[ \frac{(r_m)}{r_{ij}}^{12} - 2 \left( \frac{r_m}{r_{ij}} \right)^6 \right] + \sum_{i<j} \frac{q_i q_j}{4\pi \varepsilon_0 r_{ij}} \]

+ U(CV) Additional energy term

Force field (Energy function)
Structure (Initial positions and velocities)
Topology (connectivity between atoms)

Compute forces
Apply forces
Update Positions And velocities
Molecular Dynamics

\[ U(R) = \sum_{bonds} k_b (r - r_{eq})^2 \]
\[ + \sum_{angles} k_\theta (\theta - \theta_{eq})^2 \]
\[ + \sum_{dihedrals} k_\phi (1 + \cos[n\phi - \gamma]) \]
\[ + \sum_{improppers} k_w (\omega - \omega_{eq})^2 \]
\[ + \sum_{i<j} \varepsilon_{ij} \left( \frac{r_m}{r_{ij}} \right)^{12} - 2 \left( \frac{r_m}{r_{ij}} \right)^{6} \]
\[ + \sum_{i<j} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \]

+U(CV)  Additional energy term

Additional Forces:  
Biased Dynamics

Force field  
(Energy function)

Structure  
(Initial positions and velocities)

Topology  
(connectivity between atoms)

Compute forces

Apply forces

Update Positions And velocities

SPEED UP  
RARE EVENT  
SAMPLING
Contents

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A Collective Variable for the Rapid Exploration of Protein Druggability
Rémi Cuchillo, Kevin Pinto-Gil, and Julien Michel*

\[ a_i = S_{BS}^{off} (1.0, BS_{min}, \Delta BS) S_{mind}^{on} (1.0, CC_{mind}, \Delta CC) S_{exposure}^{on} (1.0, E_{min}, \Delta E) \]
Quantification of Protein Druggability: JEDI

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

Kernel Functions

Penalize the descriptors with values too big or too low regarding those of the benchmark set
Quantification of Protein Druggability: JEDI

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\[ a_t = S_{BS_{t}}^{off}(1.0, BS_{min}, \Delta BS) S_{mind_{t}}^{on}(1.0, CC_{mind}, \Delta CC) S_{exposure_{t}}^{on}(1.0, E_{min}, \Delta E) \]

**Kernel Functions**

**Activity calculation**

Penalize the descriptors with values too big or too low regarding those of the benchmark set.
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\[ a_i = S^\text{off}_{BS}(1.0, BS_{min}, \Delta BS) S^\text{on}_{m_{ind}}(1.0, CC_{m_{ind}}, \Delta CC) S^\text{on}_{\text{exposure}}(1.0, E_{min}, \Delta E) \]

**A**

1. Close contact
2. Solvent exposed

**B**

- Active
- Partially Active
- Inactive

**Kernel Functions**

**Activity calculation**

- Distance of grid point to known
- Distance of grid point to binding

**Hydrophobicity Descriptors**

- Penalty on descriptors with values too big or too low reg.
  - those of the benchmark set

**MD simulation**

- Time

**Hydrophobicity Descriptors**

- Contacts
- Apolar
- Polar

Apolar and polar atoms are defined at the same time as the grid, before the simulation.
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\[ a_i = S_{BS}^{off}(1.0, BS_{min}, \Delta BS) S_{min}^{on}(1.0, CC_{min}, \Delta CC) S_{exposure}^{off}(1.0, E_{min}, \Delta E) \]

**A**

1. **MD simulation**
2. Druggability
3. Time

**B**

- Close contact
- Solvent exposed

**Active**
- Partially Active
- Inactive

**Kernel Functions**

**Activity calculation**

**Hydrophobicity Descriptor**

**Active Volume Descriptor**

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

\[ V_g = \text{spacing}^3 \quad \text{ONLY FOR EVENLY SPACED GRIDS!!!!} \]

\[ V_a = \frac{V}{v_{max}} \quad \text{PARAMETER} \]

Apolar and polar atoms are defined at the same time as the grid, before the simulation.
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\[ a_i = S_{BS}^{off} (1.0, BS_{min}, \Delta BS) S_{CC}^{on} (1.0, CC_{min}, \Delta CC) S_{exposure}^{on} (1.0, E_{min}, \Delta E) \]

---

**Active Volume Descriptor**

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

\[ V_g = \text{spacing}^3 \]

**Druglike Volume Descriptor**

\[ V_d = \frac{V}{v_{max}} \]

**Activity calculation**

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

**Kernel Functions**

\[ \mathcal{K}(x, y) = \begin{cases} \frac{1}{\sigma^2} e^{-\frac{(x-y)^2}{2\sigma^2}} & \text{if } x < \text{threshold} \\ \frac{1}{\sigma^2} e^{-\frac{y^2}{2\sigma^2}} & \text{otherwise} \end{cases} \]

**Hydrophobicity Descriptor**

\[ h(x) = \begin{cases} 1 & \text{if } x \text{ is hydrophobic} \\ 0 & \text{otherwise} \end{cases} \]

---

**Diagram**

- **A**
  - 1: Close contact
  - 2: Solvent exposed
  - 3: MD simulation

- **B**
  - Active
  - Partially Active
  - Inactive

---

**Footnote**

*Corresponding author
Quantification of Protein Druggability: JEDI

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JEDI score

\[ JEDI = V_{\text{druglike}}(\alpha V_a + \beta H_a + \gamma) \]

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>PLS derived volume coefficient</td>
<td>5.31</td>
</tr>
<tr>
<td>( \beta )</td>
<td>PLS derived hydrophobicity coefficient</td>
<td>24.29</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>PLS derived intercept</td>
<td>-13.39</td>
</tr>
<tr>
<td>( A_r )</td>
<td>grid spacing</td>
<td>0.15 nm</td>
</tr>
<tr>
<td>( B_{\text{ligand}} )</td>
<td>minimum distance to ligand group from which the ( bg ) value starts to decrease</td>
<td>0.2 nm</td>
</tr>
<tr>
<td>( \Delta B )</td>
<td>distance interval over which ( bg ) decreases to 0</td>
<td>0.6 nm</td>
</tr>
<tr>
<td>( C_{\text{contact}} )</td>
<td>distance below which a grid point is in close contact with the binding site group</td>
<td>0.15 nm</td>
</tr>
<tr>
<td>( \Delta C )</td>
<td>distance interval over which a grid point is in partial contact with the binding site group</td>
<td>0.15 nm</td>
</tr>
<tr>
<td>( E_{\text{min}} )</td>
<td>minimum distance below which a grid point is considered to be partially exposed to the binding site group</td>
<td>10.0</td>
</tr>
<tr>
<td>( \Delta E )</td>
<td>interval over which a grid point becomes fully exposed to the binding site group</td>
<td>20.0</td>
</tr>
<tr>
<td>( C_{\text{min}} )</td>
<td>distance interval over which a grid point is overlapping the binding site group</td>
<td>0.15 nm</td>
</tr>
<tr>
<td>( \Delta C_{\text{min}} )</td>
<td>distance interval over which a grid point is in partial contact with the binding site group</td>
<td>0.14 nm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( GP_{\text{max}} )</td>
<td>distance above which a grid point ( k ) is considered neighbor of grid point ( l )</td>
<td>0.25 nm</td>
</tr>
<tr>
<td>( GP_{\text{min}} )</td>
<td>distance below which a grid point ( k ) is considered neighbor of grid point ( l )</td>
<td>0.35 nm</td>
</tr>
<tr>
<td>( d_{\text{hydro}} )</td>
<td>distance below which a grid point ( i ) is in contact with a binding site atom (for hydrophobicity calculation)</td>
<td>0.40 nm</td>
</tr>
<tr>
<td>( \Delta d_{\text{hydro}} )</td>
<td>distance interval over which a grid point ( i ) is in partial contact with a binding site atom (for hydrophobicity calculation)</td>
<td>0.05 nm</td>
</tr>
<tr>
<td>( V_{\text{max}} )</td>
<td>volume below which ( V_{\text{druglike}} ) is equal to 1</td>
<td>0.5 ( \text{nm}^3 )</td>
</tr>
<tr>
<td>( \Delta V_{\text{max}} )</td>
<td>volume interval over which ( V_{\text{druglike}} ) goes from 1 to 6</td>
<td>0.050 ( \text{nm}^3 )</td>
</tr>
<tr>
<td>( V_{\text{min}} )</td>
<td>volume below which ( V_{\text{druglike}} ) is equal to 0</td>
<td>0.0 ( \text{nm}^3 )</td>
</tr>
<tr>
<td>( \Delta V_{\text{min}} )</td>
<td>volume interval over which ( V_{\text{druglike}} ) goes from 0 to 1</td>
<td>0.050 ( \text{nm}^3 )</td>
</tr>
</tbody>
</table>
Quantification of Protein Druggability: JEDI

\[ JEDI = F(a_{\text{gridpoints}}) \]
Quantification of Protein Druggability: JEDI

\[ JEDI = F\left( a_{\text{gridpoints}} \right) \]

\[ a_i = F\left( \hat{r}_{\text{gridpoints}}, \hat{r}_{\text{atoms}} \right) \]
Quantification of Protein Druggability: JEDI

\[ JEDI = F(\alpha_{\text{gridpoints}}) \]

\[ a_i = F(\vec{r}_{\text{gridpoints}}, \vec{r}_{\text{atoms}}) \]

\[ JEDI = F(\vec{r}_{\text{gridpoints}}, \vec{r}_{\text{atoms}}) \]
Quantification of Protein Druggability: JEDI

\[ JEDI = F(\alpha_{\text{gridpoints}}) \]

\[ a_i = F(\vec{r}_{\text{gridpoints}}, \vec{r}_{\text{atoms}}) \]

\[ JEDI = F(\vec{r}_{\text{gridpoints}}, \vec{r}_{\text{atoms}}) \]

\[ U_{\text{system}} = FF + U_{JEDI} \]
Quantification of Protein Druggability: JEDI

\[ JEDI = F\left(a_{\text{gridpoints}}\right) \]

\[ a_i = F\left(\vec{r}_{\text{gridpoints}}, \vec{r}_{\text{atoms}}\right) \]

\[ JEDI = F\left(\vec{r}_{\text{gridpoints}}, \vec{r}_{\text{atoms}}\right) \]

\[ U_{\text{system}} = FF + U_{\text{JEDI}} \]

\[ \vec{F}_{\text{system}} = -\left(\frac{dFF}{d\vec{r}_{\text{system}}} + \frac{dU_{\text{JEDI}}}{d\vec{r}_{\text{system}}}\right) \]
Quantification of Protein Druggability: JEDI

\[ JEDI = F \left( a_{\text{gridpoints}} \right) \]

\[ a_i = F \left( \mathbf{r}_{\text{gridpoints}}, \mathbf{r}_{\text{atoms}} \right) \]

\[ JEDI = F \left( \mathbf{r}_{\text{gridpoints}}, \mathbf{r}_{\text{atoms}} \right) \]

\[ U_{\text{system}} = FF + U_{\text{JEDI}} \]

\[ \mathbf{F}_{\text{system}} = - \left( \frac{dFF}{d\mathbf{r}_{\text{system}}} + \frac{dU_{\text{JEDI}}}{d\mathbf{r}_{\text{system}}} \right) \]

\[ \mathbf{F}_{\text{JEDI}} = - \left( \frac{dU_{\text{JEDI}}}{dJEDI} \cdot \frac{dJEDI}{d\mathbf{r}_{\text{system}}} \right) \]
Can JEDI distinguish protein conformations?

<table>
<thead>
<tr>
<th>Pocket</th>
<th>Small</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIGAND</td>
<td>SKF (580nM)</td>
</tr>
<tr>
<td>JEDI</td>
<td>7.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pocket</th>
<th>Big</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIGAND</td>
<td>F83 (63 nM)</td>
</tr>
<tr>
<td>JEDI</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Higher Druggability

Lower 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

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So what is SITH?
So what is SITH?

INITIAL STRUCTURE

JEDI BIASED MD

JEDI BIASED MD

JEDI BIASED MD

JEDI BIASED MD

JEDI BIASED MD
So what is SITH?

INITIAL STRUCTURE

JEDI BIAS MD

JEDI BIAS MD

JEDI BIAS MD

JEDI BIAS MD

Combine Trajectories

Cluster Snapshots
So what is SITH?

- **Initial Structure**
- JEDI BIASED MD
- JEDI BIASED MD
- JEDI BIASED MD
- JEDI BIASED MD

- **Combine Trajectories**
- **Cluster Snapshots**

**Clustering Metrics**
- Sidechain Torsions
- Backbone Torsions
So what is SITH?

INITIAL STRUCTURE

JEDI BIASSED MD

JEDI BIASSED MD

JEDI BIASSED MD

JEDI BIASSED MD

Combine Trajectories

Cluster Snapshots

Clustering Metrics
- Sidechain Torsions
- Backbone Torsions

Clustering Algorithms
- Density Peaks
- Distance binning
So what is SITH?

- Initial Structure
- JEDI Biased MD
- JEDI Biased MD
- JEDI Biased MD
- JEDI Biased MD
- Combine Trajectories
- Cluster Snapshots
So what is SITH?

- INITIAL STRUCTURE
  - JEDI BIASED MD
    - JEDI BIASED MD
      - JEDI BIASED MD
        - JEDI BIASED MD
          - Combine Trajectories
            - Outliers
              - Cluster Snapshots
                - Well Populated Clusters
So what is SITH?

 INITIAL STRUCTURE

 JEDI BIASED MD

 JEDI BIASED MD

 JEDI BIASED MD

 JEDI BIASED MD

 Combine Trajectories

 Outliers

 Generate Restarting Structure

 Cluster Snapshots

 Well Populated Clusters
So what is SITH?

- **INITIAL STRUCTURE**
  - **JEDI BIASED MD**
    - **JEDI BIASED MD**
      - **JEDI BIASED MD**

- **Combine Trajectories**
  - **Outliers**
    - **Generate Restarting Structure**
  - **Cluster Snapshots**
    - **Well Populated Clusters**
      - **Generate Biasing Potential**
  - **Save Structures**
So what is SITH?

- **INITIAL STRUCTURE**
  - JEDI BIASED MD
  - JEDI BIASED MD
  - JEDI BIASED MD
  - JEDI BIASED MD

- **Cluster Snapshots**
  - Combine Trajectories
  - Outliers
    - Generate Restarting Structure
  - Cluster Snapshots
    - Well Populated Clusters
      - Generate Biasing Potential
    - Save Structures

- **Biasing Methods**
  - Harmonic lower wall
  - Harmonic restraint
  - Steered MD
  - Metadynamics
So what is SITH?

INITIAL STRUCTURE

JEDI BIASED MD

Combine Trajectories

Outliers

Generate Restarting Structure

Cluster Snapshots

Well Populated Clusters

Generate Biasing Potential

Save Structures
So what is SITH?

INITIAL STRUCTURE

JEDI BIASED MD

JEDI BIASED MD

JEDI BIASED MD

JEDI BIASED MD

Combine Trajectories

Outliers

Generate Restarting Structure

Generate Biasing Potential

Cluster Snapshots

Well Populated Clusters

Save Structures

JEDI+BIASED MD

JEDI+BIASED MD

JEDI+BIASED MD

JEDI+BIASED MD

JEDI+BIASED MD

JEDI+BIASED MD

JEDI+BIASED MD

JEDI+BIASED MD
So what is SITH?

- INITIAL STRUCTURE
- JEDI BIASED MD
  - JEDI BIASED MD
  - JEDI BIASED MD
  - JEDI BIASED MD

Combine Trajectories
- Outliers
- Cluster Snapshots
- Well Populated Clusters
- Save Structures

Generate Restarting Structure
- JEDI+SITH BIASED MD
  - JEDI+SITH BIASED MD
  - JEDI+SITH BIASED MD
  - JEDI+SITH BIASED MD

Generate Biasing Potential
- JEDI+BIASED MD
  - JEDI+BIASED MD
  - JEDI+BIASED MD
  - JEDI+BIASED MD

Generate Structures
Results: sampling of Lys57 hydrogen bond

- 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
Results: conformations found

SITH without a JEDI bias

SITH with a JEDI bias

BINDING SITE

JEDI

Lys57 Torsion RMSD

Iteration 0
Total Simulation Time: 25 ns
Results: conformations found

SITH without a JEDI bias

SITH with a JEDI bias

- Iteration 1
- Total Simulation Time: 50 ns
Results: conformations found

SITH without a JEDI bias

SITH with a JEDI bias

- Iteration 2
- Total Simulation Time: 75 ns
Results: conformations found

SITH without a JEDI bias

SITH with a JEDI bias

- Iteration 3
- Total Simulation Time: 100 ns
Results: conformations found

SITH without a JEDI bias

SITH with a JEDI bias

- Iteration 4
- Total Simulation Time: 125 ns
Results: conformations found

SITH without a JEDI bias

SITH with a JEDI bias

- Iteration 5
- Total Simulation Time: 150 ns
Results: conformations found

SITH without a JEDI bias

SITH with a JEDI bias

● Iteration 6
● Total Simulation Time: 175 ns
Results: conformations found

SITH without a JEDI bias

SITH with a JEDI bias

- Iteration 7
- Total Simulation Time: 200 ns
Contents

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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.
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