Exploring the function of water molecules in drug discovery

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Wuxi AppTec
The versatile of water

- **Mimic** of the organic molecules (A)
- Hydrogen bond (B-C)
- **occupy void** (D-E)
- Accommodate organic molecules (F)
- Proton transfer, Mediate interactions, work as lubricant…

Incomplete desolvation

Protein

Ligand

Void

Occupied

Energy
what we want to do

Repelling the water
Increase ligand binding **affinity**
Is such water common?

76% in 392 high resolution (<=2Å) PDB structures

Can we repelling the water?

bromodomain (BRD4 BD1 domain)


![Diagram showing the repelling of water with compounds 2 and 3.](image)

**compound 2**
92 nM

**compound 3**
6300 nM

**compound 3**
470 nM
Fundamentals

\[ \Delta G_{\text{PL}} + \Delta G_{\text{hs}} + \Delta G_{\text{other}} \]

\[ \Delta G_{\text{hs}} \text{ is } \text{Favorable} \]

\[ \Delta G_{\text{bulk}} \text{ is } \text{Favorable} \]
Development of the methods


• JAWS (Jorgensen group. J. Am. Chem. Soc. 2009, 131, 15403–15411.)


• SZMAP (Openeye)

• WaterMap (Friesner group, J. Am. Chem. Soc., 2008, 130, 2817-2831)

• STOW (Lazaridis, Kaplus, Michael E. J. Phys. Chem. 1992, 96, 3841-3855)
Mathematical formula

\[ \Delta \Delta G = \Delta G_{hs} - \Delta G_{bulk} \]

\[ \Delta E - T \Delta S - \Delta G_{bulk} \]
Mathematical formula

\[ \Delta E = \Delta E_{vdw} + \Delta E_{ee} \]

\[ \Delta G_{\text{bulk}} \]

\[ T\Delta S \]

- Force field + MD simulations
- Experimental value
- Inhomogeneous fluid theory
Inhomogeneous fluid theory

\[ \Delta S = S_{wp} + \Delta S_{ww} \]

Water-Protein correlation term

\[ S_{wp} = -k \frac{\rho}{\Omega} \int g_{wp}(r, \omega)\ln g_{wp}(r, \omega) \, dr \, d\omega \]

Water-water correlation term

\[ S_{ww} = S_{trans}^{ww} + S_{orient}^{ww} \]

\[ S_{trans}^{ww} = -\frac{1}{2} k p^2 \int g_{wp}^{trans}(r) g_{wp}^{trans}(r') g_{ww}^{bulk}(R) \ln g_{ww}^{bulk}(R) \, dr \, dr' \]

\[ S_{orient}^{ww} = -\frac{1}{2} k p^2 \int g_{wp}^{trans}(r) g_{wp}^{trans}(r') g_{ww}^{bulk}(R) \ln g_{ww}^{bulk}(R) \, dr \, dr' \, d\omega \]
Inhomogeneous fluid theory

Water-Protein correlation term

Separate the relative angle and distance into states $i$

Water-water correlation term

$$S = -k \int p_i \ln p_i$$
Sampling the states and AquaTrace

Amber

Desmond

NAMD

Gromacs

CRD TRAJ

DTR TRAJ

DCD TRAJ

XTC TRAJ

AquTrace

IFT

Water-water entropy

Enthalpy

Water-protein entropy

Side Chain

Pocket Clustering

Volume Calculations

Volume Map
Validation (bulk water)

<table>
<thead>
<tr>
<th></th>
<th>SPC</th>
<th>TIP3P</th>
<th>TIP4P</th>
<th>Experiment</th>
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</thead>
<tbody>
<tr>
<td>Entropy</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
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<tr>
<td>Excess Energy</td>
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<td>-37.5</td>
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<td>-12.5</td>
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<tr>
<td>Enthalpy</td>
<td>-25</td>
<td>-25</td>
<td>-25</td>
<td>-25</td>
</tr>
</tbody>
</table>

With maximum divergence (6 kJ/mol)
Validation (Acetyl-CoA carboxylase)

Fast track for NASH

Validation (Interleukin-1 receptor-associated kinase 4)

\[ \text{Gly195} \]

\[ \text{J. Med. Chem., 2017, 60 (13), pp 5521–5542} \]
Can we repelling the water?

bromodomain (BRD4 BD1 domain)

compound 2
92 nM

compound 3
6300 nM

compound 3
470 nM

Validation (Bromodomain)

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM)</th>
<th>Distances (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>92</td>
<td>W2: 3.0, W5: 3.4, W6: 3.8</td>
</tr>
<tr>
<td>3</td>
<td>6300</td>
<td>W2: 0.7, W5: 2.2, W6: 3.8</td>
</tr>
<tr>
<td>4</td>
<td>470</td>
<td>W2: 2.6, W5: 2.0, W6: 1.2</td>
</tr>
</tbody>
</table>

5 kcal/mol

-5 kcal/mol
Conclusion

Rationally Repelling Water
Gain **Higher** Affinity
(Higher probability)

I appreciated for your time
Q&A