NEW QM/MM IMPLEMENTATION OF THE MOPAC2012 IN THE GROMACS

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2018

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ENZYMES IS LIFE’S KEY MOLECULE

Maltose substrate

Glucose products

https://en.wikipedia.org
\[ E = \frac{k}{2} (b_0 - b)^2 \]

\[ H\psi = E\psi \]

\[ E_{tot} = E_{QM}^{I} + E_{MM}^{II} - E_{MM}^{I} \]  \hspace{1cm} (1)

https://en.wikipedia.org
MM Engine = Gromacs, QM Engine = Mopac
Performance of QM/MM packages for the “small” system on local workstation (left) and supercomputer “Lomonosov-2” with Lustre filesystem (right).
Performance of test systems for the “big” system on local workstation (left) and supercomputer "Lomonosov-2" with Lustre filesystem.
Comparison of energy values for QM subsystem for MOPAC/Gromacs: red circles and ORCA/Gromacs: blue triangles.
· AB has rigid backbone
· AB is burn to be mutated
Medical Importance

Antibody + Antigen → Action

Abzyme + Antigen → Actions
Tyr - OH + O\(\rightarrow\)P - O - NO\(_2\) \(\overset{K_d}{\rightleftharpoons}\) Tyr - OH : O\(\rightarrow\)P - O - NO\(_2\)

Hydrolysis \(\overset{\text{Smirnov et al, PNAS 2011}}{\leftarrow}\) Tyr - O\(\rightarrow\)P - O

\(\overset{\text{H}^+}{\rightarrow}\) Tyr - O\(\rightarrow\)P - O - NO\(_2\)
17 positions = $20^{17}$ mutants
We need to reduce sampling
QM/MM METADYNAMICS

∙ we «warm up» the bond

\[ V(\vec{s}, t) = \sum_{k \tau < t} W(k \tau) \exp \left( - \sum_{i=1}^{d} \frac{(s_i - s_i^{(0)}(k \tau))^2}{2\sigma_i^2} \right) \]

Liao & Parinello, 2002
17 positions = 2 * 10^6 mutants
· 2 * 10^6 mutants
· PyRosseta framework

- Mutate, 10^5 conformations
- top 100
- Optimize
- Sort
- top 3

375 mutants selected (1125 systems) CPU query on Lomonosov-2

375 mutants * 3 replica
Sort on reaction fact
Sort on energy
top 10

- H-bond donor aminoacids won
- 10 mutants was selected on CPU query Lomonosov-2

## EXPERIMENTAL VALIDATION

<table>
<thead>
<tr>
<th>AB</th>
<th>Experiment</th>
<th>Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S35R</td>
<td>229</td>
<td>14</td>
</tr>
<tr>
<td>L47K</td>
<td>333</td>
<td>113</td>
</tr>
<tr>
<td>S35E</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>

WHY MUTANT IS BETTER?

Поиск места для внедрения сайта
ACTIVE CENTER TRANSFER

- 100 ways to accommodate active center
- $5 \times 10^4$ mutants PyRosseta

Active center positions, up to $10^3$

Top 100

Mutate to stabilize, $10^4 \times 10^2$

Sort

Top 1000 QM/MM

15 mutants selected
Authors

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QM/MM Interface improvement was supported by Russian Ministry of Education and Science, project number **RFMEFI57617X0095**
ПОЧЕМУ МУТАНТ ЛУЧШЕ?

METHODS

- Gromacs with Plumed, MOPAC2012 as lib
- PM6-D3H4, Hamiltonian with h-bond corrections or DFTb-D3.
- Metadynamics with 0.2 fs step
- Run multiple replicas with stochastic thermostat