Coupling ReaxFF and DREIDING to Model Enzymatic Reactions

Li Tao, Markus J. Buehler and William A. Goddard
Motivation

- Find efficient computational method to model reactivity in large biological systems

- Existing QM/MM methods can model only a few pre-selected atoms
  - Enzymatic reactions may involve hundreds or thousands of reactive atoms
  - Not feasible with QM/MM schemes

- ReaxFF can model much larger regions involving several thousands of atoms.
  - not practical for entire biological system
    - 80,000 iterations on 280-atom system
      - DREIDING – dynamics took 1h 41m
      - ReaxFF – dynamics took 10h 26m
<table>
<thead>
<tr>
<th>Method</th>
<th>Maximum number of atoms</th>
<th>Estimated Clocktime for 1 ns (max. # atoms)</th>
<th>Able to Model Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM (DREIDING)</td>
<td>100,000</td>
<td>2 days</td>
<td>no</td>
</tr>
<tr>
<td>ReaxFF</td>
<td>3,000</td>
<td>5 days</td>
<td>yes</td>
</tr>
<tr>
<td>QM (DFT)</td>
<td>500</td>
<td>months, years</td>
<td>yes</td>
</tr>
</tbody>
</table>

Compromise: *Hybrid ReaxFF/MM scheme Allows: Large systems (>100,000 atoms with ~3,000 reactive atoms)*
Coupled ReaxFF and DREIDING

- Previous ReaxFF studies on enzymes (subtilisin, lysozyme) fixed non-participating atoms
- This region is important
  - Elasticity, conformational changes, inhibitors
- Treating non-active region with DREIDING allows physical forces to be modeled

Other regions important too?

Localized reaction zone

Active Site

Substrate

Enzyme
Implementation – Coupling of force fields using mixed Hamiltonians

Energy Calculation:

- 100% DREIDING
- 50% ReaxFF, 50% DREIDING
- 100% ReaxFF

- Ghost atoms (0% ReaxFF)
- Calculated with ReaxFF
- Interpolation linearly or smoothly using sine function

- CMDF framework allows to assign weights
- Use transition zone of radius $r_t$
- “Ghost atoms”
The ModMulti Modules

New CMDF Modules for code coupling

- **ModMulti**
  - Functions for selecting atoms, assigning weights (linearly and non-linearly)

- **ModRestraints**
  - Functions for driving reactions using restraints (see next slide)

- **OBtools**
  - Utility functions
  - File output in BGF format
  - Manipulating X OpenBabel objects
Regions selected using python functions

Overlapping weights for bigger regions

Regions can be reassigned as reaction progresses
Implementation - Restraints

Why - Chemical reactions occur slowly at room temperature (biology)
MD currently limited to nanoseconds – Chemical reactions need to be assisted to overcome barrier

- Bond restraints – keep distances between two atoms at specified equilibrium distance
  - Equilibrium distance can change linearly over time to drive reactions
- Angle restraints – control angle between three atoms

\[ f = k_1 \left(1 - e^{k_2 (r - r_{eq})^2}\right) \hat{u} \]
Wave propagation

- Apply sudden jolt to end of C$_{80}$H$_{162}$ chain
- Wave propagated through ReaxFF region
- *Demonstrates seamless coupling*

![Graph showing strain on each carbon as a function of time.](image)
Single molecule tensile test: Stretching a C$_{80}$H$_{162}$ chain

- Apply forces to a hydrocarbon chain to investigate how the chain breaks
  - Relationship between temperature and breaking strain
- Ensure coupling is done correctly
- Same weights as before: 15 carbon atoms in Reax, 10 Å transition zone
Results

Temperature vs. Breaking Strain

- Strain for breakage decreases with temperature
Modeling a Simple Reaction

Number of steps

System Energy (kcal/mol)

Initial State

Transition State

End State

- System energy
- Moving Average
Summary

- Have achieved coupling of ReaxFF and DREIDING
- Demonstrated coupling by propagating waves through the molecule
- Applied this method to modeling breaking strain of single $\text{C}_{80}\text{H}_{162}$ molecule as a function of temperature.
- New method allows coupling $\sim 3,000$ reactive atoms with $100,000$ nonreactive atoms
Modeling Enzymatic Activity of Subtilisin

- Test coupling of force fields on biological system
- Subtilisin is a serine protease from bacteria
- Active site consists of catalytic triad (Ser, His, Asp)
- Entire system of 4,000 atoms
  - Too large for pure ReaxFF

Number of atoms treated by ReaxFF: 1210 (ca. 30%)
Entire: 3933
Procedure for Modeling Enzymatic Activity of Subtilisin

- Minimize energy, then equilibrate system at 300 K
- Model each reaction step using restraints to drive.
  - Our case: First step – Transfer proton from serine to histidine
- Compare energy barriers with pure ReaxFF and QM results

Step 1 – Proton Transfer

Reaction coordinate (Pure ReaxFF)
Conclusion and Outlook

- Possible alternative to QM/MM methods, but simpler to use and much faster
- Coupled calculations are more efficient than pure ReaxFF (tradeoff)
- Possibly useful for quick scanning of reaction pathways
  - Designing enzyme with improved enzymatic activity
  - Understanding biological mechanisms
Acknowledgements

- Markus J. Buehler
- Adri van Duin
- CMDF group
- William A. Goddard
- Caltech SURF program
- DARPA PROM for CMDF funding