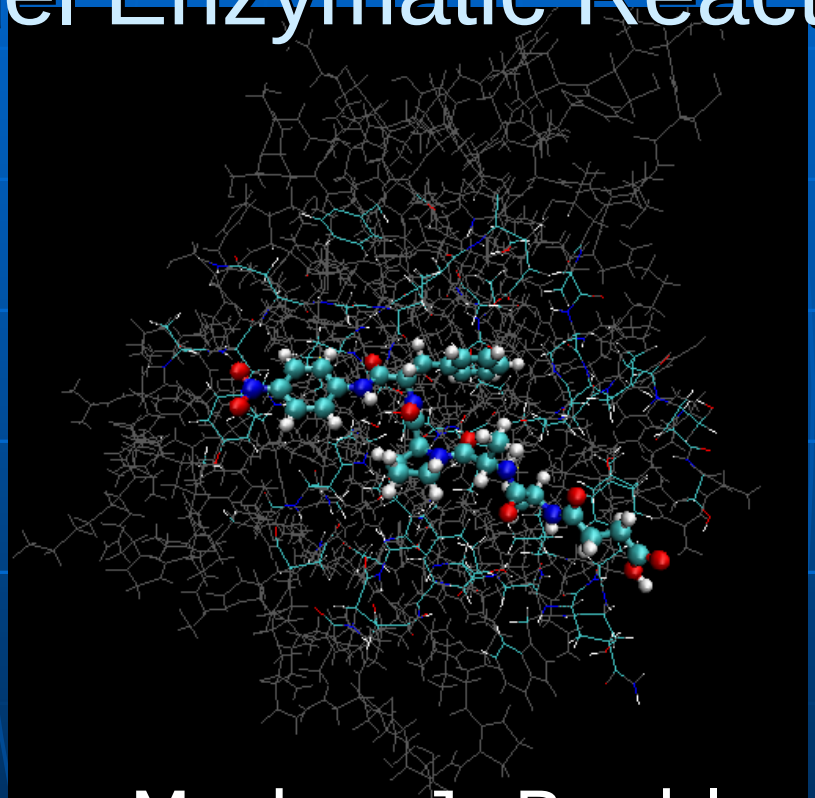
Coupling ReaxFF and DREIDING to Model Enzymatic Reactions



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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

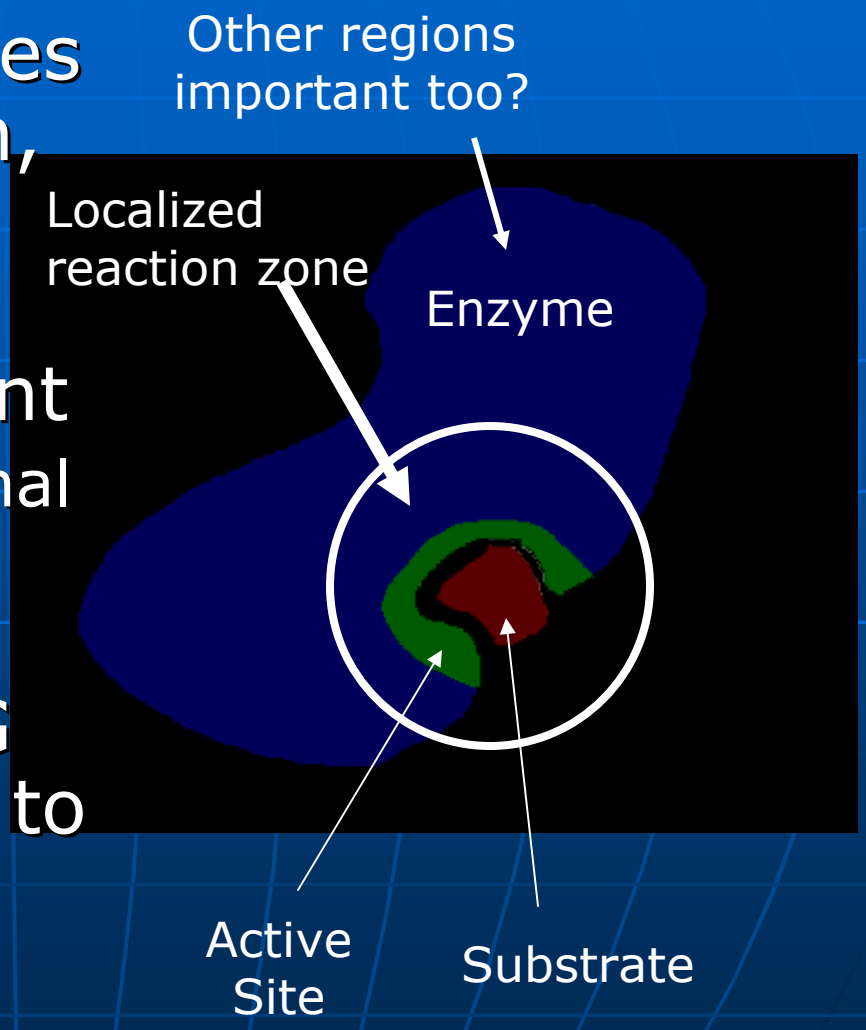
Comparison MM, ReaxFF, QM

	Maximum number of atoms	Estimated Clocktime for 1 ns (max. # atoms)	Able to Model Reactivity
MM (DREIDING)	100,000	2 days	no
ReaxFF	3,000	5 days	yes
QM (DFT)	500	months, years	yes

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

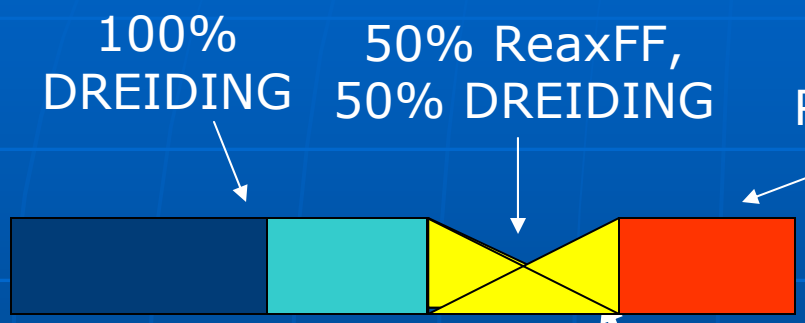
Coupled ReaxFF and DREIDING

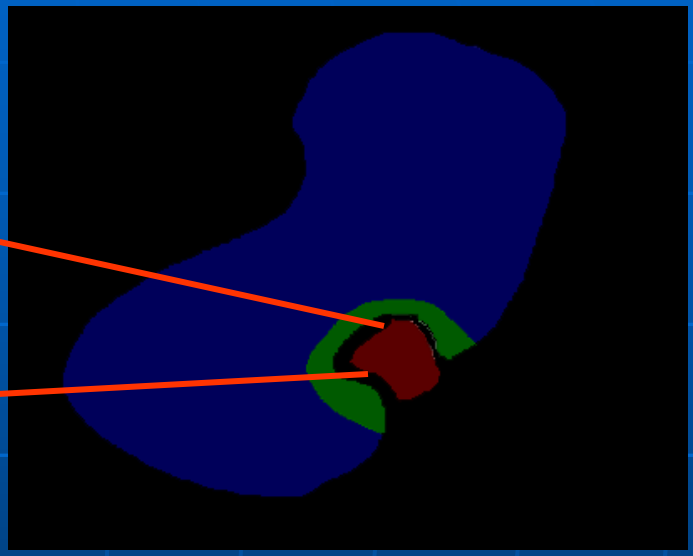
- Previous ReaxFF studies on enzymes (subtilisin, lysozyme) fixed non-participating atoms
- This region is important
  - Elasticity, conformational changes, inhibitors
- Treating non-active region with DREIDING allows physical forces to be modeled



Implementation – Coupling of force fields using mixed Hamiltonians

Energy Calculation:





- CMDF framework allows to assign weights
- Use transition zone of radius r_t
- "Ghost atoms"

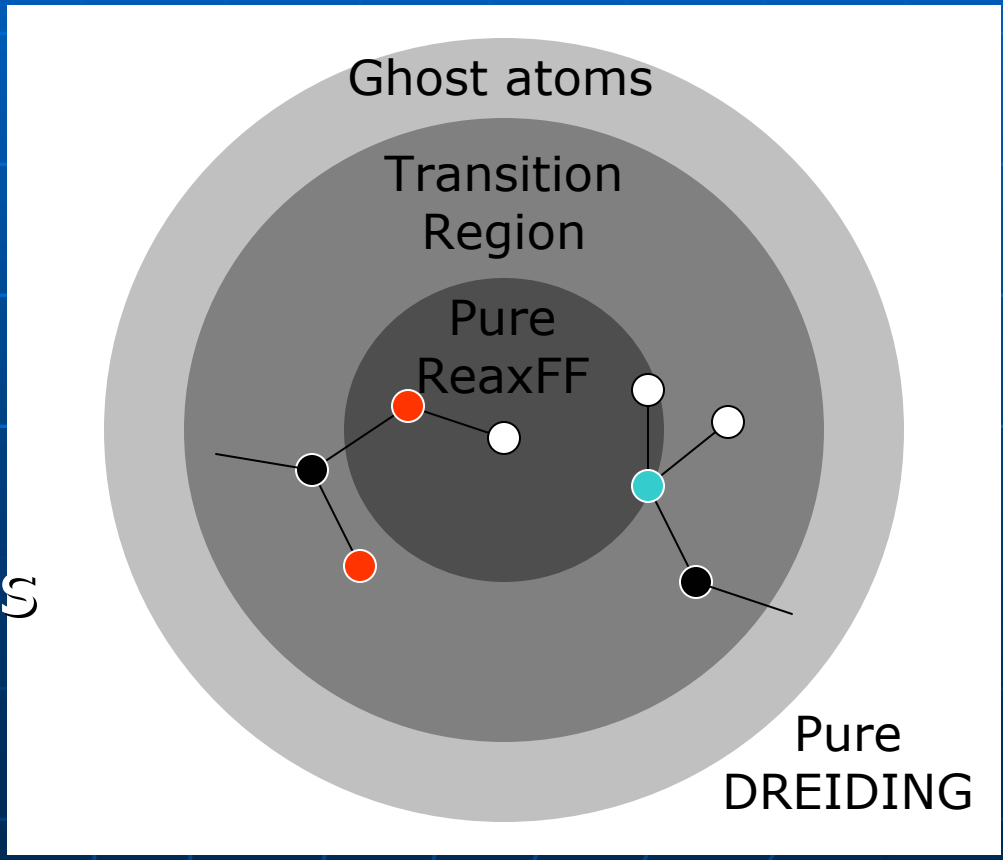
The ModMulti Modules
New CMDF Modules for code coupling

- 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

Implementation - Coupling

- Regions selected using python functions
- Overlapping weights for bigger regions
- Regions can be reassigned as reaction progresses

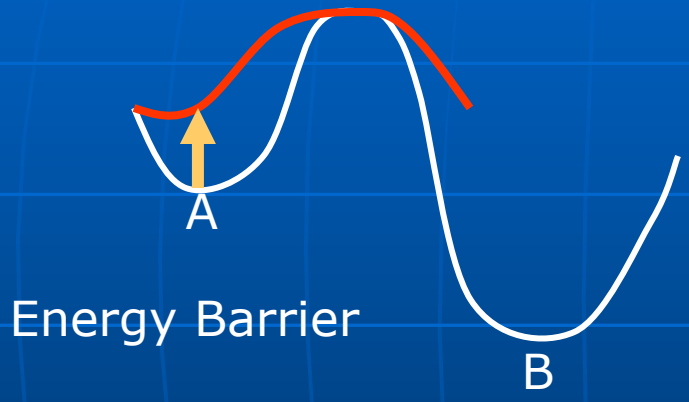
assignsphere_weights() function



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



Energy Barrier

Bond Restraint

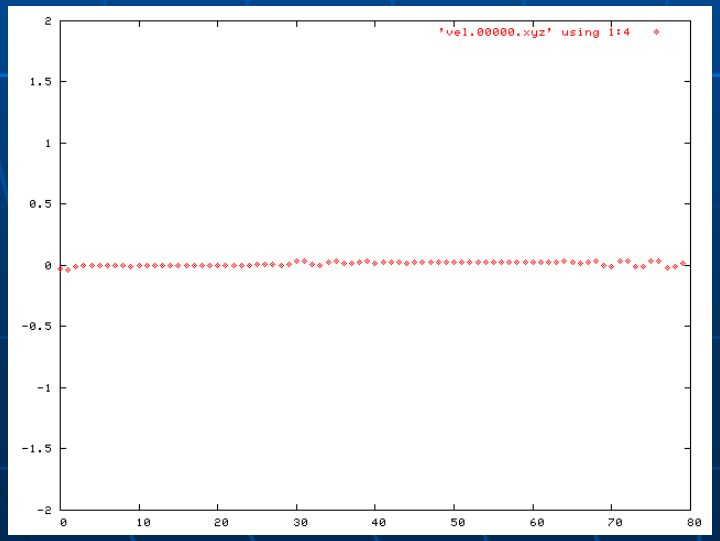
- Bond restraints – keep distances between two atoms at specified equilibrium distance
  - Equilibrium distance can change linearly over time to drive reactions
- Angle restraints – control angle between three atoms

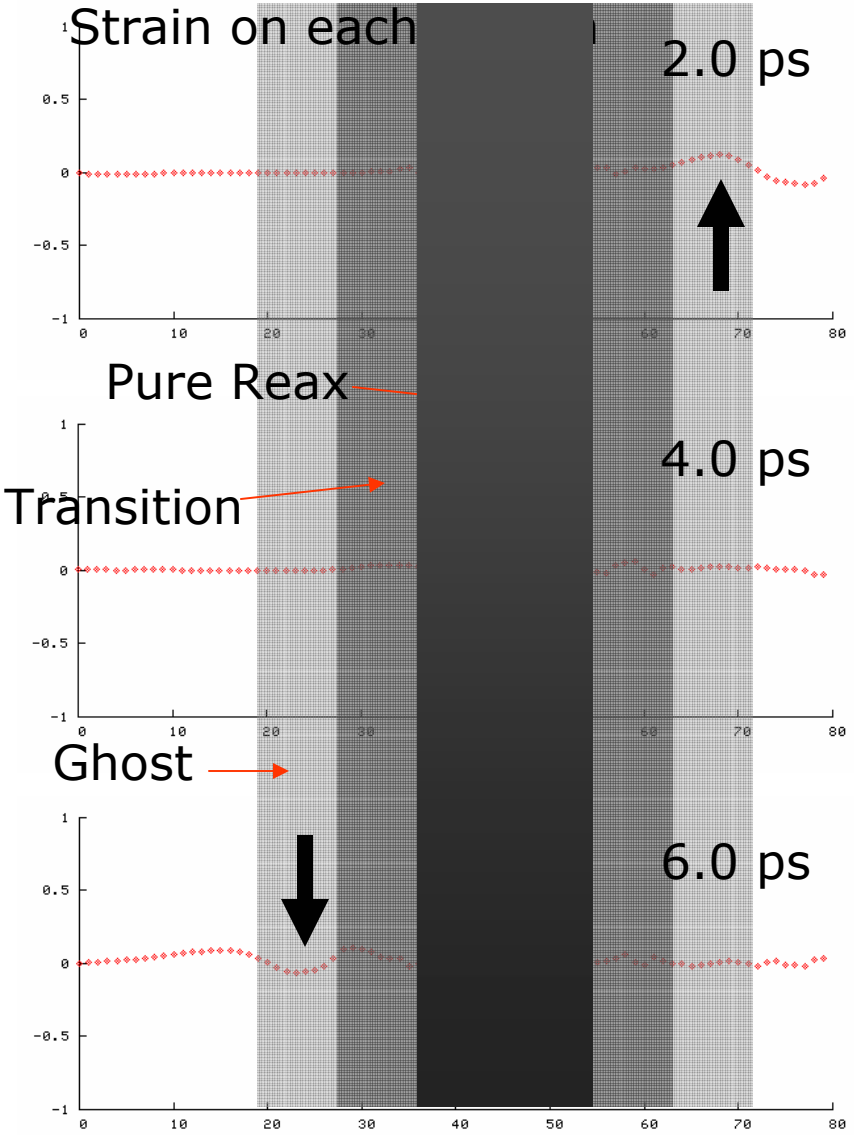
$$f = k_1\left(1 - e^{k_2\left(r - r_{eq}\right)^2}\right)\vec{u}$$

Angular Restraint

Wave propagation

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

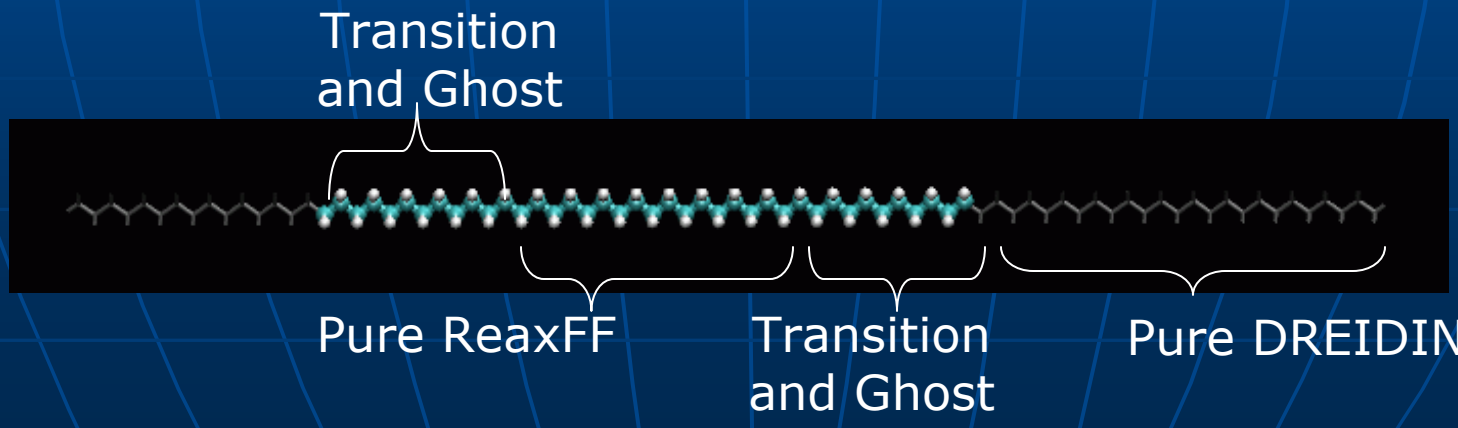




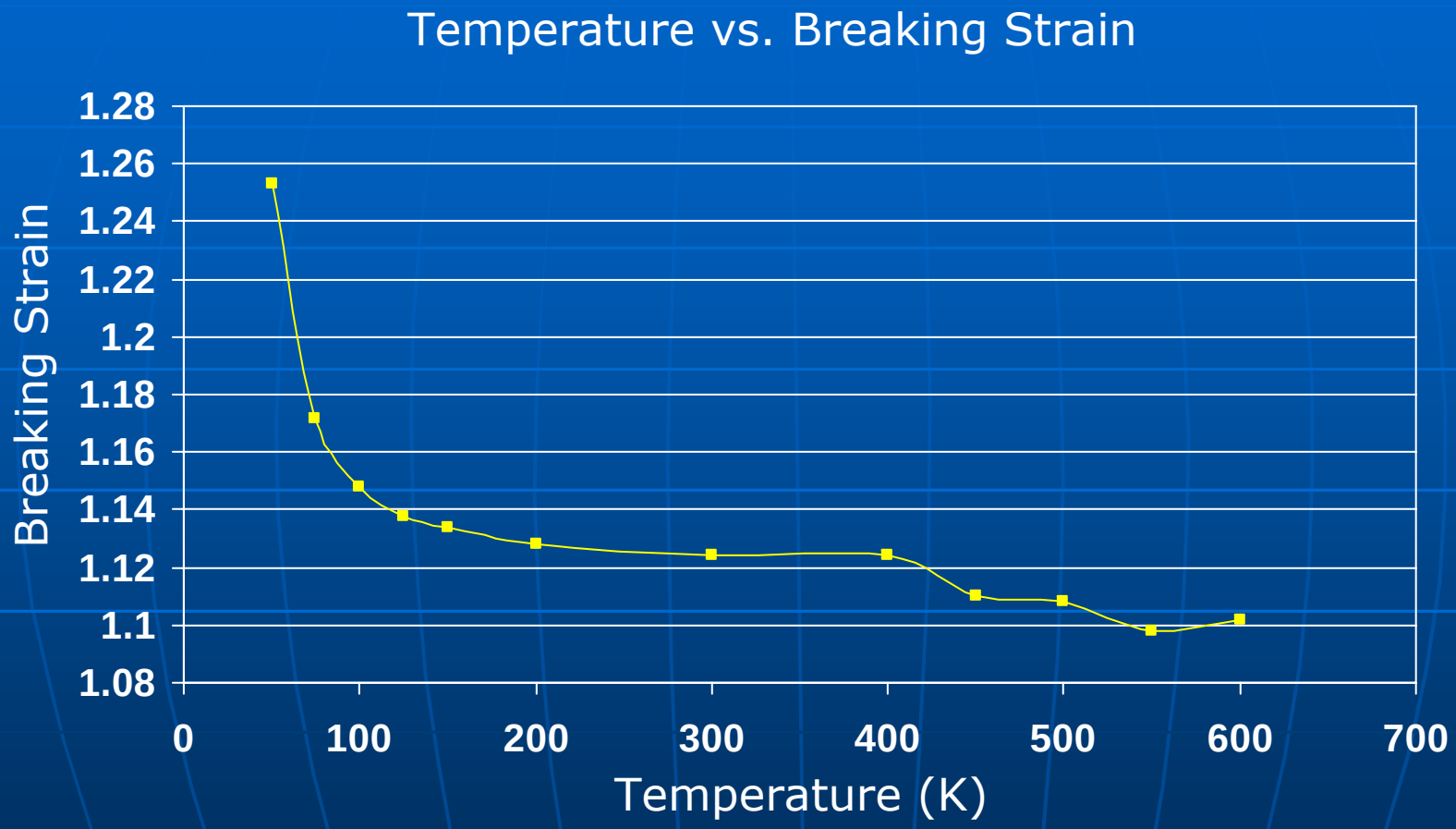
Single molecule tensile test: Stretching a $C_{80}H_{162}$ chain

Atomistic model:

- 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 A transition zone

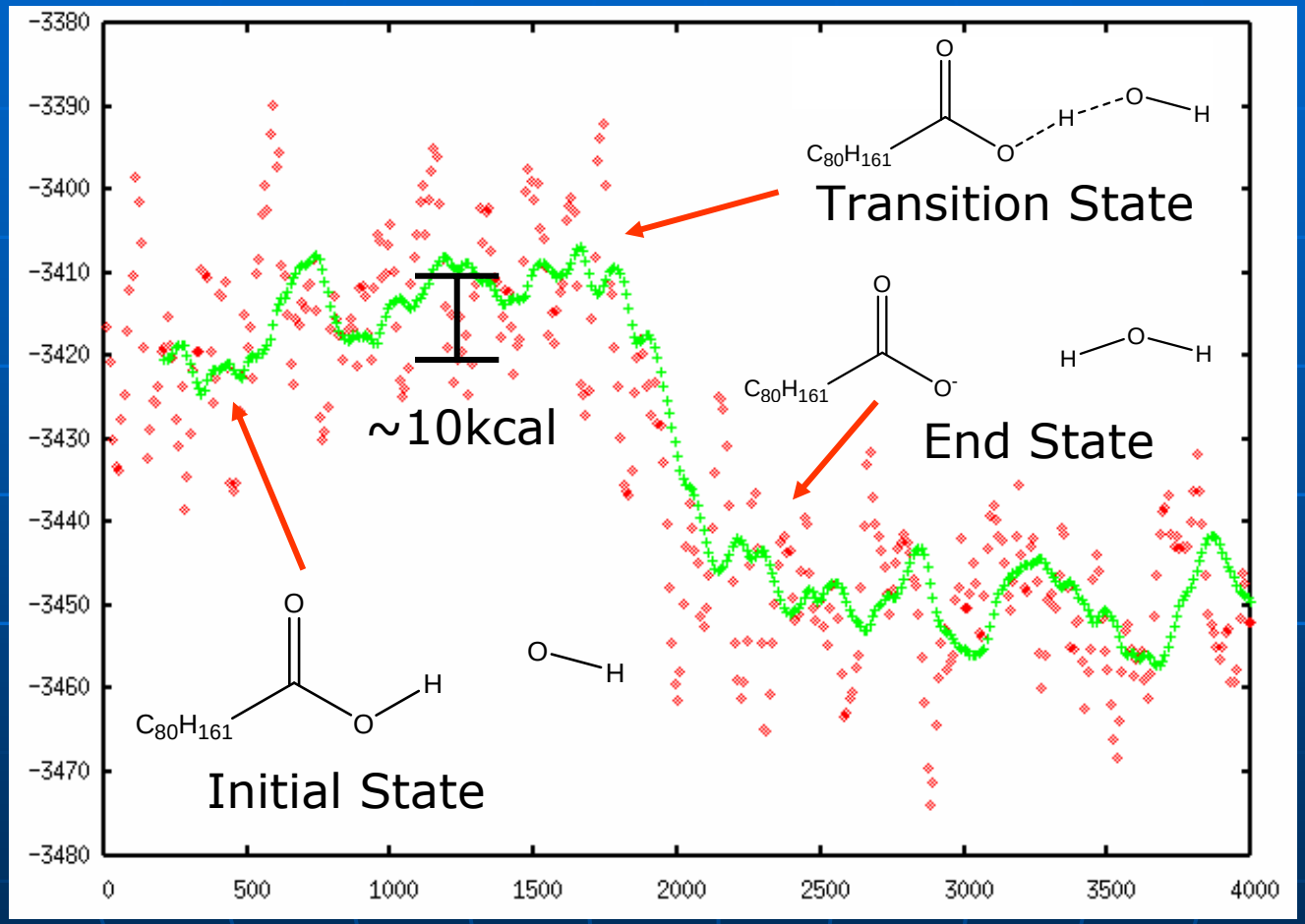


Results



- Strain for breakage decreases with temperature

Modeling a Simple Reaction



- System energy
- Moving Average

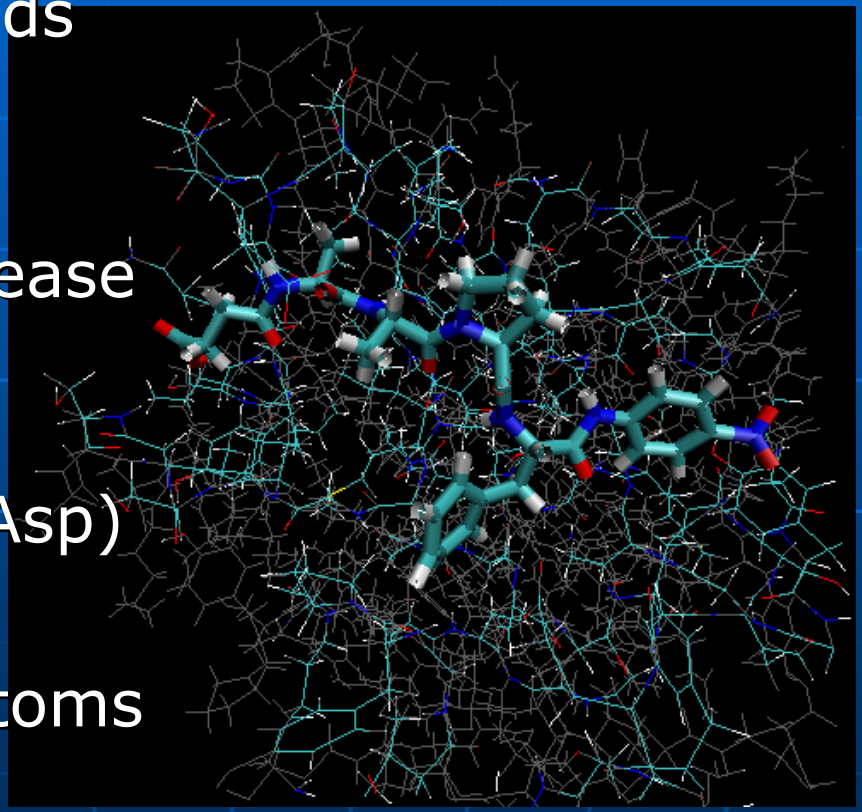
Summary

- Have achieved coupling of ReaxFF and DREIDING
- Demonstrated coupling by propagating waves through the molecule
- Applied this method to modeling breaking strain of single $C_{80}H_{162}$ molecule as a function of temperature.

- *New method allows coupling ~3,000 reactive atoms with 100,000 nonreactive atoms*

Modeling Enzymatic Activity of Subtilisin

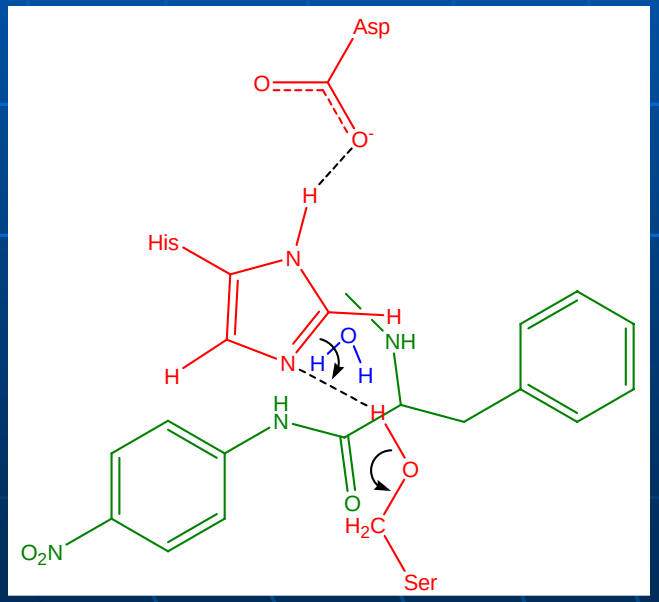
- Test coupling of force fields on biological system
- Subtilisin is a serine protease from bacteria
- Active site consists of catalytic triad (Ser, His, Asp)
- Entire system of 4,000 atoms
  - Too large for pure ReaxFF



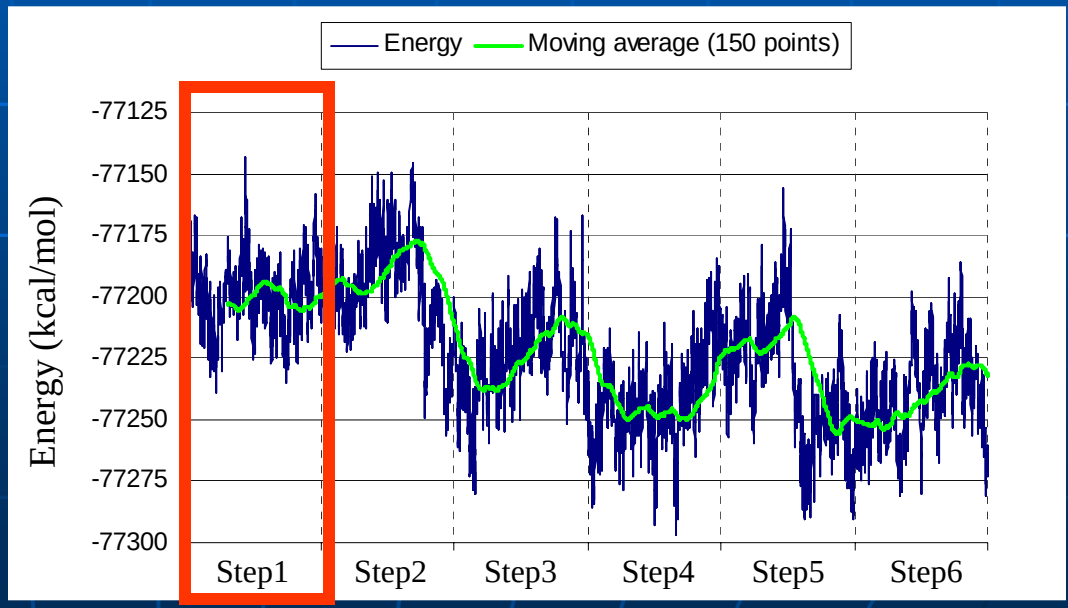
Number of atoms treated by
ReaxFF: 1210 (ca. 30%)
Entire: 3933

Procedure for Modeling Enzymatic Activity of Subtilisin

- Minimize energy, then equilibriate 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