CSSI Element: **Element Software Enabling Millisecond-scale Biomolecular Dynamics**

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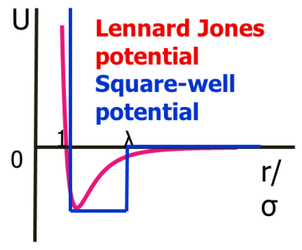
Abstract

The goal of this research is to develop an open-source software framework to enable multi-millisecond dynamic simulations of peptides and peptidomimetic polymers. This will allow us to study very long time-scale biomolecular phenomena such as biopolymer folding, aggregation and inhibition of aggregation, fibril formation and protein binding. The goal will be achieved by implementing a parallel discontinuous molecular dynamics (DMD) package, developing a suite of DMD interaction potentials, and providing tools for translating continuous atomistic models into DMD models.

Background information

Discontinuous Molecular Dynamics

- Follows particle trajectories by analytically calculating new velocities whenever collision, capture, or bounce occur

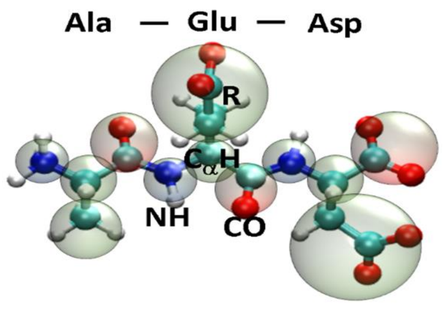


Coarse-grained Peptide Model

- 4-sphere-per-residue representation

  NH, C_αH, CO, R

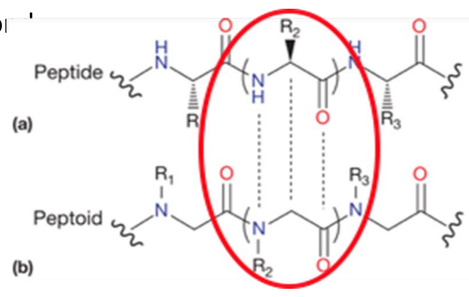
- Directional backbone hydrogen bonding between NH and C=O
- Parameters for 20 different sidechains (hydrophobic, polar, charge-charge interactions)
- Reduced temperature $T^*=k_BT/\varepsilon_{hydrogen\text{-}bo}$



Cheon M. et al. *Protein.* 2010

Peptoids vs Peptides

- Sidechain moved to backbone N atom
- No chiral α carbon
- No backbone H-bonding
- Protease resistant and thermally stable



Seo et. al. *Comp. Biomat.* 2011

1) Parallel DMD package

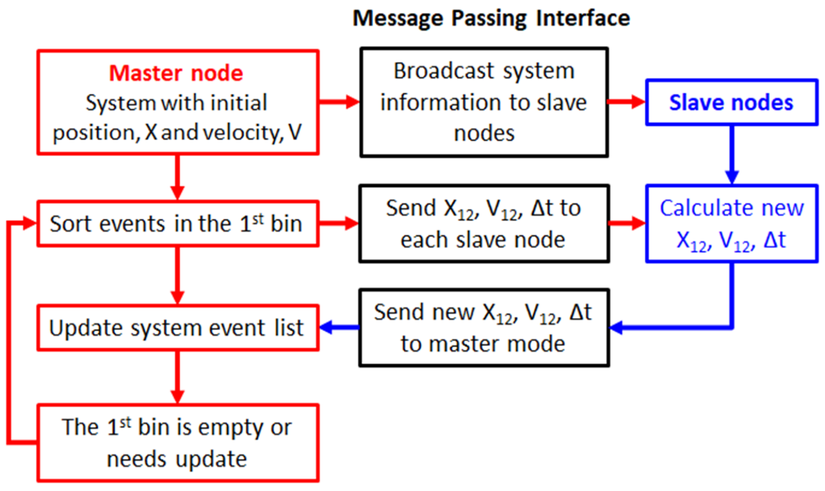
- **Goal: Develop a parallel version of the existing serial DMD/ PRIME20 code that will enable the leap from hundreds of microseconds to multiple milliseconds**

- **Current progress: Parallelizing simplified version of DMD/ PRIME20 code which omits the sidechain bead for each amino acid and turns off the directional hydrogen bonding between backbone NH and CO beads**

- **Current results:**
  - Multiple collision events are processed by multiple slave nodes
  - Simulation can be performed for NVE and NVT ensemble

- **Plan of work:**

1. **Optimize event scheduling algorithm and offload collision dynamic calculation from master node to slave nodes to improve computing efficiency**
2. **Extend simplified PRIME20 to full PRIME20 model**



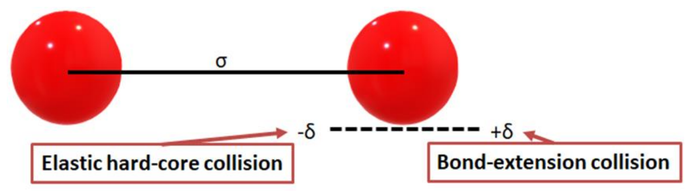
2) Improve PRIME20 model

- **Goal: Improve the accuracy and efficiency of the current PRIME20 model**

- **Plan of work:**

1. Improve efficiency

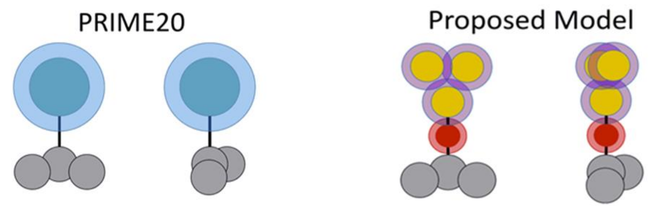
- Reduce the number of collisions needed to achieve 1μs by reducing the frequency of intramolecular collisions
- Intramolecular collision happens when bonding bead reaches bond length tolerance, δ



- Increase bond length tolerance to force two neighbor beads to travel longer distance before collision while maintaining realistic Φ-Ψ angles from Ramachandran plots

2. Improve geometry and energetics for better aromatic amino acid representation

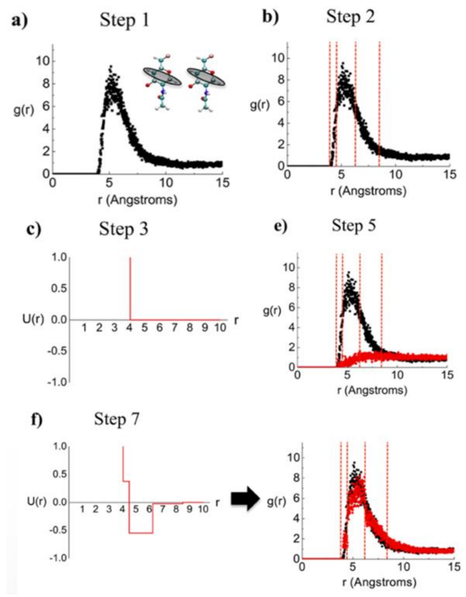
- Determine additional set of parameters to describe the geometries and energies of multi-bead side chain model



Latshaw. *Thesis Dissertation*. 2015

3. Develop a library of new coarse-grained parameters from atomistic simulations

- Allow collection of parameters for natural peptides, non-natural peptides and peptoids
- Enable users to customize suitable interaction potentials to their target molecules
- Use modified iterative Boltzmann inversion method by Benner and Hall



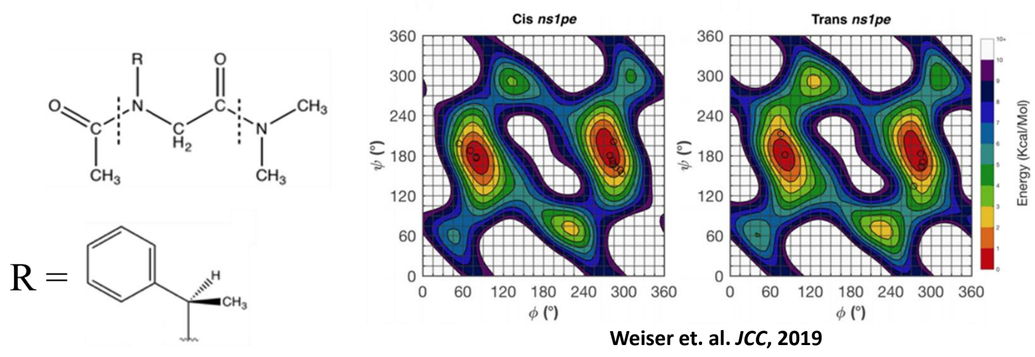
Benner, S. W., and Hall, C. K. *J. Phys. Chem. B*. 2016

3) Coarse Grained forcefield for peptoids

- **Goal: Use top down (SAFT-VR) and bottom up (Relative Entropy) coarse graining to develop a DMD simulation forcefield for peptoids**

- **Current Progress:**
  - Developed and validated a CGenFF-based atomistic force field for peptoids (atom type NTOID)
  - Developed a general purpose DMD code for analyzing any kind of polymer chain

- **Current Results: Development of an atomistic forcefield**



Weiser et. al. *JCC*, 2019

- Reproduced Ramachandran plots for different peptoid chains
- Predicted helical propensity in solution

- **Plan of work:**

1. **Implement the developed NTOID forcefield with relative entropy method to generate intramolecular potential parameters**
2. **Utilize available thermodynamic properties with SAFT-VR to obtain intermolecular potential parameters**