Coarse Grained MD Parametrization and Application to Peptide Nanotube Formation

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Motivation for CMM Model

- Coarse grain MD focuses on inter-object structure => NOT A FOLDING MODEL!
- Parametrization strategy different from all-atom
- Antimicrobial Peptide/Lipid Interactions
  - Large number of peptides
  - Membrane curvature => large system sizes
  - Large timescales
- Peptide Aggregation
- Protein Drug Interactions
Existing CG Models

I. Simple model (phenomenological)  
   e.g. Marrink et al. JPCB (2004)

II. Inverse Boltzmann (radial distribution function)  
    e.g. Shelley et al. JPCB (2001)

III. Force matching method (from all-atom MD)  
    e.g. Izvanov and Voth, JPCB (2005)

<table>
<thead>
<tr>
<th>Model</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>??</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Transferability</td>
<td>Yes</td>
<td>No</td>
<td>No?</td>
<td>Yes</td>
</tr>
<tr>
<td>Systematic</td>
<td>No</td>
<td>Yes?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Parameterization Philosophy

- **Systematic**
  - Consistent addition of new CG-site for parametrizing new molecules
- **Reduced all-atom dependence**
  - Option to confirm/compare with AA
- **Practical Implementation**
  - Implement in current and well performing MD codes as systems are large and trajectories long (so far: LAMMPS, Gromacs)
Coarse Grain Mapping

- 3 – 4 heavy atoms per coarse grain site
- Conservation of mass
- Trying to preserve chemical nature

ARG side chain
Potential Forms

- **Non-bonded**
  - Lennard-Jones type
    - LJ 9-6, LJ 12-4

- **Bonded**
  - Harmonic Potentials
    - Bonds, Bends and Torsions
  - Multi-minimum Potentials
    - Torsions??

\[
V(r) = \frac{27}{4} \varepsilon \left( \frac{\sigma^9}{r^9} - \frac{\sigma^6}{r^6} \right)
\]

\[
V(r) = \frac{3\sqrt{3}}{2} \varepsilon \left( \frac{\sigma^{12}}{r^{12}} - \frac{\sigma^4}{r^4} \right)
\]

\[
V_{bond}(r) = K_b(r - r_0)^2
\]

\[
V_{angle}(\theta) = K_a(\theta - \theta_0)^2
\]

Shinoda et.al., Mol. Sim. 33, 27 (2007)
Non-Bonded Parameterization

Self Interaction:

$LJ \ (\varepsilon, \sigma)$ \rightarrow \text{Surface Tension Density}

Cross Interactions:

Option a: repeat above procedure (if possible)

Option b: assume a combination rule
Non-bonded Parameterization (2)

Water Interaction:

Thermodynamic Integration

$\varepsilon_{BW} \sigma_{BW}$

Solvation
Free Energy

Evaluation and fine tuning:

- Octanol-water partitioning coefficients
- Useful for assembled peptides
- Check cross interactions
Bonded Parameterization

- Two Options:
  - static data (PDB database)
  - dynamic data (all atom simulation)

- Reproduce average (equilibrium) bond length/angles

- Reproduce distributions
  - can be done interactively
  - more sophisticated means are possible
Water CG Parametrization

- 3 water molecules per CG site
- Nonpolar (no charges/dipoles)
- LJ 12-4 Nonbonded Interaction (peptides etc. are LJ 9-6)

Shinoda et al., Mol. Sim. 33, 27 (2007)
Protein Backbone

- Two CG backbone bead types:
  - Glycine style (non-ALA residues)
  - Alanine style
- Single backbone CG bead per residue
- Non-polar

Glycine

Alanine
Side Chains

- **Single Bead**
  - Val, Leu, Ile, Pro, Met, Ser, Thr, Cys, Asn, Gln, Asp, Glu
- **Double Bead**
  - Phe, Tyr, Lys, Arg, His
- **Triple Bead**
  - Trp
- **Charged Residues**
  - Asp, Glu, Lys, Arg, His, Unit charge
Computational Demand

Implementation in LAMMPS MD code

361260 CG Particles

1003500 CG Particles
Cyclic D,L-α-Peptides

- Cyclic peptide rings of alternating D- and L- amino acid residues adopt a β-sheet like conformation
- Antimicrobial Agents
  - Self assemble into nanotubes, stabilized by hydrogen bonds
  - Believed to introduce membrane leakage

Mechanism of self-assembly in lipid bilayer?

- Water
- Polar head groups
- Non-polar tails

Mode of action as antibacterial agents?

- Intramolecular pore
- Barrel stave
- Carpet-like
CG Model for D,L-Ring System

- One CG-bead for backbone, one bead for side chain => 172 AA sites to 16 CG-sites
- Intra-molecular parameters from AA-simulation
- Nonane represented by 3 CG-beads
Peptide-Peptide Interaction

- Experiments:
  - Association in nonane
  - Dissociation in water
Partitioning

- Independent of initial setup
  - Peptide in nonane or water
System Setup

- 220 Peptide Rings in Nonane/Water
- ~29000 Coarse Grain Beads
- 5 fs time step, Velocity Verlet
- LAMMPS MD code
- > 2µs trajectory

E. Khurana, R.H. DeVane, A. Kohlmeyer, M.L. Klein, Biophysical Letters (submitted)
Self-Assembly of Rings

Number of monomers, dimers, and trimers/tetramers over simulation time.

Graph showing the number of monomers, dimers, and trimers/tetramers over simulation time. The graph indicates a decrease in the number of monomers and an increase in the number of dimers and trimers/tetramers as simulation time progresses.
Conclusions

- CG-MD helpful to study peptide self-assembly mechanisms
- Peptide rings assemble at the water-nonane interfaces
- Two mechanisms:
  - Monomers form dimers and trimers by sliding on top of each other at very high monomer concentration
  - Larger stacks tilt and then connect at monomer saturated interface
- “Carpet-like” function plausible
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