An efficient hybrid method for modeling lipid membranes with molecular resolution

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Outline

✓ Motivation
✓ Hybrid CG modeling (ongoing, conceptual)
✓ Enhanced sampling (quick)
✓ Conclusions/outlook
Motivation

Using/adapting dynamic mesoscopic methodology for block copolymers to simulate life-mimicking (biomematic) structures and structure formation

- Veterinarian
- Biologist
- Physicist
- Mathematician?
Motivation

“Cell membrane dynamics essentially lipidic” (100+ simulation papers)

VW Project 2009-2012 ‘Multiscale hybrid modeling of (bio)membranes’ (Schmid, Zvelindovsky, Böker, AS)

Aim: **Realistic** computational modeling of liposome formation, dynamics and (assisted) fusion
Motivation: intriguing experiments in Leiden

Vesicle fusion induced by coiled-coil motif (short peptide fragments)

General issues: length and time scales

Nm and mm: model for complete vesicle and/or vesicle fusion requires considerable coarse graining.

Efficient, realistic, dynamic

The DNA of simulation

Based on SDSC Blue Horizon (SP3)
512-1024 processors
1.728 Tflops peak performance
CPU time = 1 week / processor

Methods

Thermodynamics
Average, collective

Statistical physics
Specific, detail

Monte Carlo molecular dynamics

Atomistic Simulation Methods

Semi-empirical methods
Ab initio methods

Monte Carlo molecular dynamics

Specific, detail

Mappings

Based on SDSC Blue Horizon (SP3)
512-1024 processors
1.728 Tflops peak performance
CPU time = 1 week / processor

Japan, 2010
Vesicle formation and fusion (2005)

METHOD: DDFT= mean-field
       SCFT+diffusion

20% $A_2B_2$ in a selective bad solvent

Movie

Beyond block copolymers:

- How to realistically represent lipids?
- Increasing complexity?

- ‘Floppy’ Gaussian chains: onion vesicles
- Mean-field: concentrated systems
Hybrid particle-field model

Aim: flexibility, efficient and realistic liposome simulation
(ongoing work)
DDFT: pattern formation dynamics in concentrated BCP

\[ F[\rho_I] = F^{ideal}[\rho_I, U_I] + F^{cohesive}[\rho_I] + \frac{1}{2} \kappa_H \int_V \left( \sum_I \rho_I \right)^2 \]

- Entropic: Gaussian chains in self-consistent field \( U \)
- Enthalpic: mean-field interactions (FH)
- Pressure term, incompressible
- Local kinetic model
- Processing conditions
- \((\text{quasi})\text{equilibrium behavior, AB, ABC, branched}\)
- Phase transition under external fields (confinement, shear, \( E \), etc)
Synergetic validation: flat polymeric ‘membrane’

Structural transition due to thickness reduction: top view

Experiment

\[ \Delta t^{sim} \sim \text{sec} \]

Calculation

nucleation  annihilation  splitting

High-speed SFM measurements of membrane dynamics: \( \sim \text{sec ptf} \)
Different representations of constituents

**DDFT:** Underlying harmonic spring, calculations and interactions
field-based

**Particles (DPD):** Harmonic spring, angle and torsion
potentials, soft core repulsive pair potentials

\[ a_{ij} = a_{ij}^0 + \Delta a_{ij} \]

Liquid incompressibility

\[ f_{\text{repulsive}} \]
Hybrid model

\[ F_{\text{hybrid}}[\rho_I, \vec{r}_k] = F^{DDFT}[\rho_I] + U^{\text{particles}}[\vec{r}_k] + F^{\text{coupling}}[\rho_I, \vec{r}_k] \]

\[ \sum_{l,k} c_{lk} \int V K(\vec{r} - \vec{r}_k) \rho_I(\vec{r}) d\vec{r} \]

\[ \partial_t r_k = D_k [f_k^{\text{conserv}} - \int V \sum_l c_{lk} K(\vec{r} - \vec{r}_k) \nabla \rho_I(\vec{r}) d\vec{r}] \partial t + r_k^{\text{random}}(t) \]

\[ \frac{d\rho_I(\vec{r})}{dt} = M \nabla \cdot \rho_I(\vec{r}) \nabla [\mu^{DDFT}(\vec{r}) + \sum_k c_{lk} K(\vec{r} - \vec{r}_k)] + \eta_I \]

Diffusion, timescales are more or less comparative (coupled update)
Positive $c$

**Coupling force:** away from high density field values  
**Coupling chemical potential:** field diffuses away from regions with many particles

Advantage is possibility to mix different representations on CG level for same or different constituents: sparse (particles) + abundant (field)

Mapping: besides FH parameter ($\chi$)/interaction strengths ($a$) we need compressibility ($\kappa$) and coupling ($C_{Ik}$).
Determine ‘free’ parameters by requiring thermodynamic consistency for single bead solvent in both representations.

\[ \kappa : \text{match either pressure or excess chemical potential} \]

\[ C_{Ik} : \text{use field partitioning to determine FH } \chi \text{ and Groot} \]

\& Warren to convert to soft-core potential strength

\[ \rightarrow c_{Ik} = c_{Ik}(\alpha) \]

Note: both particles and fields adapt dynamically
Hybrid vs DPD lipid membrane simulation

Use these values and realistic DPD lipid parameters \( (16^3) \)

DPD, Shillcock and Lipowky 2002
(realistic)

Hybrid calculation where the solvent is replaced by a field, with the same S&L parameters for the lipid
Hybrid membrane simulation

Averaging over many initial condition and time frames
Additional benefits: implicit solvent

Preliminary: analytical equilibrium solution for solvent (field) can be converted into an additional potential in particle description

\[ (\vec{r}_{sol}^k, \vec{r}_{lipid}^k) \xrightarrow{\text{mapping}} (\rho_{sol}^k, \vec{r}_{lipid}^k) \xrightarrow{\text{analytic}} \vec{r}_{lipid}^k \]

\[ V \rightarrow A \]

CGMD, implicit solvent

Vesicle formation pathway following quench

Diffusion is patient (DPD – O(20000))
Experiments: slow process!

Solution? S-QN: accelerating collective modes
Enhanced sampling:

Accelerating collective modes in a CG particle description
Stochastic Quasi-Newton method

 Optimization in numerical mathematics (objective function)

\[ \Delta x_k = x_{k+1} - x_k = -\alpha_k \nabla \Phi \]
Steepest descent

\[ \Delta x_k = x_{k+1} - x_k = -\alpha_k H^{-1} \nabla \Phi \]
Newton method

\[ \dot{B}_k \rightarrow H^{-1} \]
Quasi-Newton method

 Diffusion in statistical mechanics (potential function)

\[ \Delta x_k = -M \nabla \Phi(x_k) \Delta t + \sqrt{2 M k_B T \Delta t \Delta W_k} \]

\[ M(x) \]
Fluctuation-dissipation

\[ \sqrt{M(x)} \]
Curvature-dependent mobility

\[ M(x) = (\nabla^2 \Phi(x))^{-1} \]
+ spurious drift
Stochastic Quasi-Newton method

Illustration: 1-D Harmonic oscillator

\[ \Phi(x) \sim \frac{k}{2} x^2 \]

\[ dx = -kxdt + \sqrt{2k_B T}dW(t) \quad \text{for } M = 1 \]

\[ dx = -xdt + \sqrt{\frac{k_B T}{k}}dW(t) \quad \text{for } M = k^{-1} = (\nabla^2 \Phi)^{-1} \]

Drift term noise term \( \sim k^{-1} \)

Stability analysis: \( \Delta t^{\text{max}} \) independent of \( k \)

Sparse sampling

Dense sampling

k<1 \hspace{1cm} \text{slow modes} \hspace{1cm} k>1 \hspace{1cm} \text{fast modes}
Stochastic Quasi-Newton method

\[ M(x) = M_k(x_k) = M_k(x_k, \ldots, x_0) \text{ approximate of } H(x_k)^{-1} \]

New factorized update method (equivalent to DFP) for \( M_{k+1} \):

- Hereditary: minimal \( \left\| M_{k+1} - M_k \right\|_F \)
- If \( M_0 \) positive definite, \( M_{k+1} \) positive definite (\( \sqrt{M} \) exists!)
- \( M_{k+1} \) is approximate of inverse Hessian (secant condition)
- Efficiency: \( M_{k+1} = J_{k+1}J_{k+1}^T \quad \rightarrow \quad \text{update } J_{k+1} \)

Rouse chain

\[ M_k \rightarrow H^- \]

Additional costs per timestep but \( \Delta t^{SQN} \gg \Delta t^{LD} \)
Stochastic Quasi-Newton method

Analysis for quadratic potential (Rouse chain): *all* modes evolve equally fast (real-space Fourier acceleration)

Minimal model of a protein

\[ \Phi = \frac{1}{2} \Phi_{bond} + \frac{1}{2} \Phi_{bending} + \Phi_{dihedral} + \Phi_{LJ} \]

Bead=amino acid (either neutral, hydrophobic or hydrophilic)

Conclusions (S-QN):
✓ Enhanced sampling of energy landscape (many inherent states)
✓ Hierarchical optimization (bond length, angles, torsions, non bonded)

**Generic S-QN method**: accelerated but no ’realistic’ dynamics
Conclusions and outlook

Conclusions:
✓ New hybrid model for particle/field mixtures
✓ Reuse DPD parameters for CG lipids
✓ Possibility of implicit solvent (analytic)
✓ Additional sparse constituents can be added as CG particle chains
✓ New S-QN method to speed up formation kinetics

To do:
✓ Validate membrane material parameters in hybrid model
✓ Concise derivation of implicit solvent
✓ Implementation and parameterization of SNARE-like CG proteins

Outlook:
✓ Large scale simulations
✓ Vesicle fusion
✓ …
Thank you for your attention

Questions?
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Minimal model of a protein (3D): sampling efficiency

Standard LD (SLD)

\[ T > T_{\text{collapse}} \]

One basin

Several basins

Principles of SQN

‘native state’

Our FSU method
Minimal model of a protein (3D): mode analysis

$T <\ll T^{fold}$

**Native state:** left, turn and right sub-domains

$\text{LB}_8\text{B(NL)}_2\text{NBLB}_3\text{LB}$

**Equilibration order:** bonds, angles, torsions, LJ (even for reduced spring constants)

$\Phi = \frac{1}{2} \Phi_{bond} + \frac{1}{2} \Phi_{bending} + \Phi_{dihedral} + \Phi_{LJ}$

Principles of SQN 30