Frontiers of Coarse-Graining

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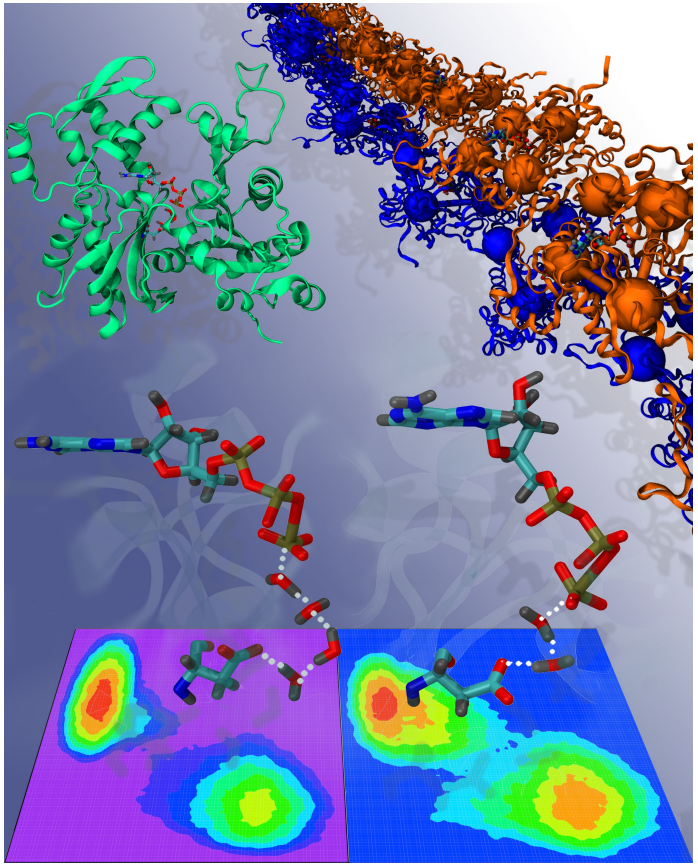

Outline of Today's Talk

- **Brief background on "bottom-up" coarse-graining**
- **Ultra-Coarse-Graining (UCG): Exciting new capability**
- **Coarse-grained Directed Simulation**
- **Mesoscopic Coarse-graining**

Acknowledgements

James Dama (Simons Jr Fellow)
Anton Sinitskiy (Stanford Postdoc)

Jaehyeok Jin
Alek Durumeric
Yining Han
Glen Hocky
Thomas Dannenhofer-Lafage
John Grime
Aram Davtyan
Martin McCullagh (CSU Faculty)
Sergei Izvekov (ARL)
Will Noid (Penn State)
Lanyuan Lu (NTU Singapore)
Zhih-Wei Chu (NCTU Taiwan)

Collaborators

Hans Andersen (Stanford)
Aaron Dinner (UofC)
Benoit Roux (UofC)
Jonathan Weare (UofC)

Funding

National Science Foundation
National Institutes of Health

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The Concept of "Bottom-up" Coarse-graining

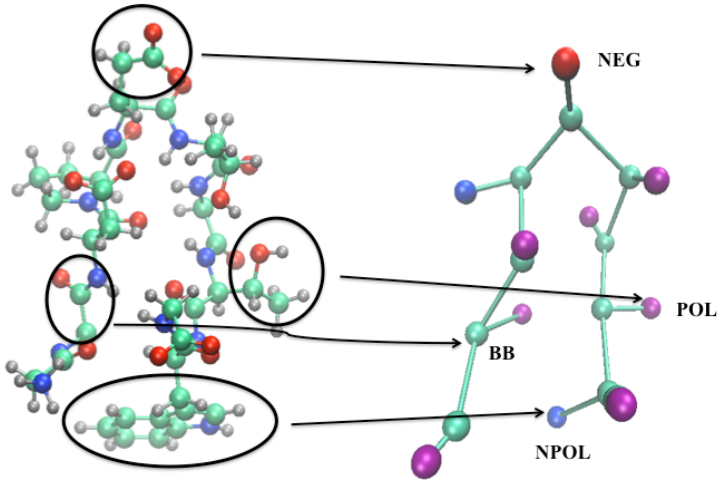
Coarse-Graining can be based on Statistical Mechanics

$$\exp(-\beta F) \propto \int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \qquad (\beta = 1/k_B T)$$

$$\int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \equiv \int d\mathbf{R}_{CG} \exp[-\beta V_{CG}(\mathbf{R}_{CG})] \qquad \left(N_{\mathbf{R}_{CG}} << N_{\mathbf{r}}\right)$$

How best to define $\mathbf{R}_{CG}$?

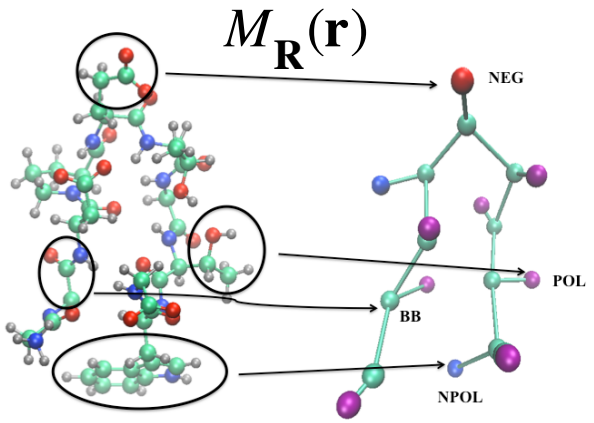
How to determine $V_{CG}(\mathbf{R}_{CG})$?



Shown here is a "high resolution" CG model having some number of CG sites or "beads" per each amino acid residue in the peptide.

Coarse-Graining Consistent with Statistical Mechanics: Mathematical Details

$$\left(N_{\mathbf{R}_{CG}} << N_{\mathbf{r}}\right)$$



For a given $\mathbf{R}_{CG}$:

How to determine $V_{CG}(\mathbf{R}_{CG})$?

$$\int d\mathbf{R}_{CG} \exp[-\beta V_{CG}(\mathbf{R}_{CG})] = \int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \qquad (\beta = 1/k_B T)$$

$$\int d\mathbf{r} \exp[-\beta V(\mathbf{r})] = \int d\mathbf{r} \overbrace{\int d\mathbf{R}_{CG} \delta(M_{\mathbf{R}}(\mathbf{r}) - \mathbf{R}_{CG})}^{=1} \exp[-\beta V(\mathbf{r})]$$

$\rightleftarrows$

Switch Integration Order, Substitute and Subtract RHS

$$\int d\mathbf{R}_{CG} \left[\exp[-\beta V_{CG}(\mathbf{R}_{CG})] - \int d\mathbf{r} \delta(M_{\mathbf{R}}(\mathbf{r}) - \mathbf{R}_{CG}) \exp[-\beta V(\mathbf{r})] \right] = 0$$

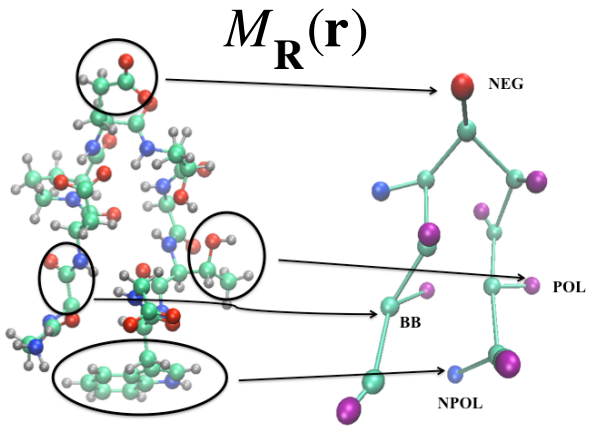
For integral to be *strictly zero* for arbitratry $V(\mathbf{r})$, it follows that...

(Stat Mech Consistency)

$\downarrow$

$$\exp[-\beta V_{CG}(\mathbf{R}_{CG})] \equiv \int d\mathbf{r} \delta(M_{\mathbf{R}}(\mathbf{r}) - \mathbf{R}_{CG}) \exp[-\beta V(\mathbf{r})]$$

Coarse-Graining Consistent with Statistical Mechanics: Mathematical Details



For a given $\mathbf{R}_{CG}$:

How to determine $V_{CG}(\mathbf{R}_{CG})$ **?**

$$\int d\mathbf{R}_{CG} \exp[-\beta V_{CG}(\mathbf{R}_{CG})] = \int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \qquad (\beta = 1/k_B T)$$

$$\int d\mathbf{r} \exp[-\beta V(\mathbf{r})] = \int d\mathbf{r} \overbrace{\int d\mathbf{R}_{CG} \delta(M_{\mathbf{R}}(\mathbf{r}) - \mathbf{R}_{CG})}^{=1} \exp[-\beta V(\mathbf{r})]$$

$\rightleftarrows$

Switch Integration Order, Substitute and Subtract Right Hand Side

$$\int d\mathbf{R}_{CG} \left[\exp[-\beta V_{CG}(\mathbf{R}_{CG})] - \int d\mathbf{r} \delta(M_{\mathbf{R}}(\mathbf{r}) - \mathbf{R}_{CG}) \exp[-\beta V(\mathbf{r})] \right] = 0$$

For integral to be strictly zero for arbitratry $V(\mathbf{r})$, it follows that...

(Stat Mech Consistency)

$$\exp[-\beta V_{CG}(\mathbf{R}_{CG})] \equiv \int d\mathbf{r} \delta(M_{\mathbf{R}}(\mathbf{r}) - \mathbf{R}_{CG}) \exp[-\beta V(\mathbf{r})]$$

The Multiscale Coarse-Graining (MS-CG) Variational "Force-Matching" Approach*

$\vec{\mathbf{r}}$: **Atomic coordinates**

$\vec{\mathbf{R}}$: **CG site coordinates**

$\vec{F}_\alpha^{CG}$: **Exact CG force**

V_{CG} : **Exact CG potential**

$\vec{F}_\alpha$: **Instantaneous sum of atomic forces acting on the CG site**

M : **Total number of CG sites**

χ^2 : **The residual**

$\langle \ldots \rangle$ **average over configurations**

$$\chi^2\left[\vec{F}^{CG}\right] = \frac{1}{3M}\left\langle \sum_{\alpha=1}^{N_{CG}} \left| \vec{F}_\alpha^{CG}\left(\vec{\boldsymbol{R}}\right) - \vec{F}_\alpha\left(\vec{\boldsymbol{r}}\right) \right|^2 \right\rangle$$

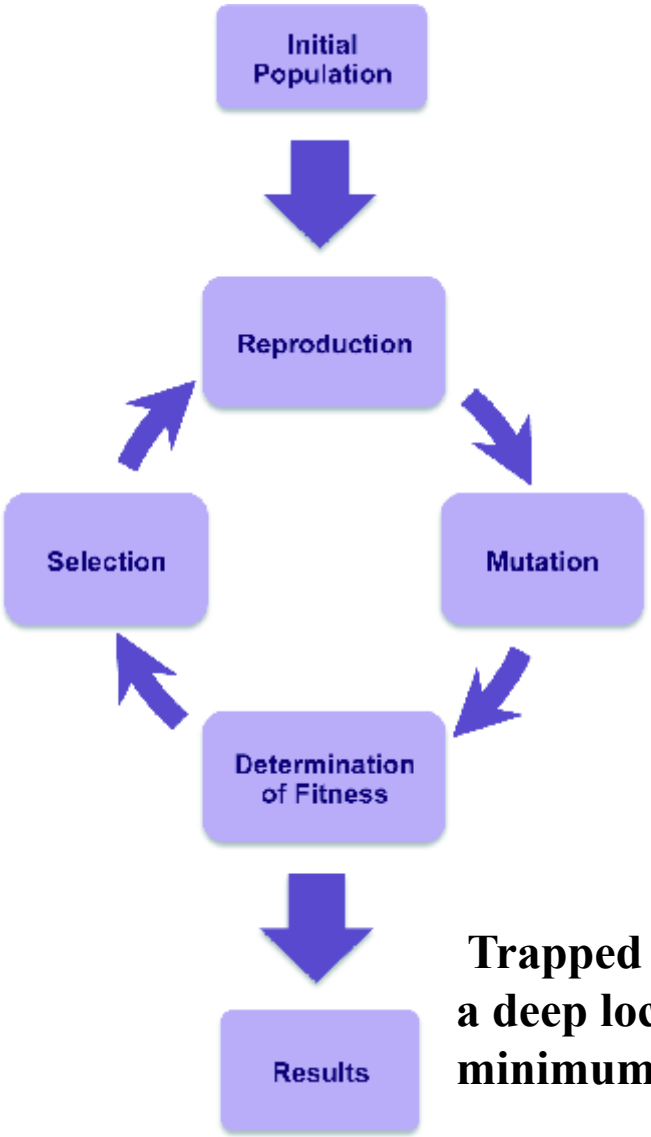
Find $\vec{F}_\alpha^{CG}\left(\vec{\boldsymbol{R}}\right)$ **from** $\dfrac{\delta\chi^2\left[\vec{F}^{CG}\right]}{\delta\vec{F}_\alpha^{CG}} = 0$

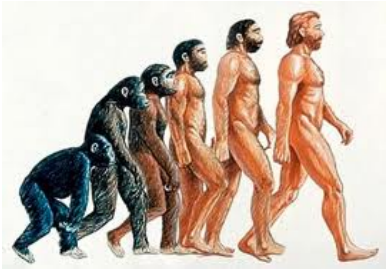
Proven That: $\vec{F}_\alpha^{CG}\left(\vec{\boldsymbol{R}}\right) = -\dfrac{\partial V_{CG}\left(\vec{\boldsymbol{R}}\right)}{\partial\vec{R}_\alpha}$

*S. Izvekov and GAV, J. Phys. Chem. B 109, 2469 (2005); J. Chem. Phys. 123, 134105 (2005); W. G. Noid, et al., J. Chem. Phys. 128, 244114 (1-11) (2008); 128, 244115 (1-20) (2008).

Force Matching: Genetic Algorithm (aka "Machine Learning")

$$\chi^2 = \left\langle \sum_{j=1}^{N_{CG}} \left| \mathbf{F}_j^{CG} - \mathbf{F}_j^{AA} \right|^2 \right\rangle$$





Trapped in a deep local minimum?

??

The MS-CG Algorithm ("Machine Learning")

(1) Assume pair wise decomposable radial non-bonded forces:

$$\vec{F}_\alpha^{CG} \xrightarrow[with]{approximate} \vec{F}_\alpha^{MS} \qquad \vec{F}_\alpha^{MS} = \sum_{\beta\neq\alpha}^{\mathrm{M}} F_{\alpha\beta}^{MS}\left(R_{\alpha\beta};\phi\right)\vec{u}_{\alpha\beta}$$

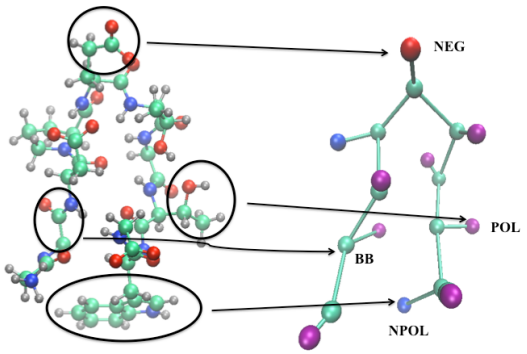
(2) Expand all types of interactions as a *linear expansion of basis functions*:

$$F_{\alpha\beta}^{MS}\left(R_{\alpha\beta};\phi\right) = \sum_{d=1}^{N_d}\phi_d f\left(R_{\alpha\beta},\left\{R_1,\ldots R_{N_d}\right\}\right)$$

(3) Force matching becomes a linear least squares problem:

$$\chi^2\left[\phi\right] = \frac{1}{3M}\left\langle\sum_{\alpha=1}^{M}\left|\vec{F}_\alpha^{MS}\left(\vec{\boldsymbol{R}};\phi\right) - \vec{F}_\alpha\left(\vec{\boldsymbol{r}}\right)\right|^2\right\rangle$$

$$\frac{\delta\chi^2\left[\phi\right]}{\delta\phi_{d'}} = 0$$



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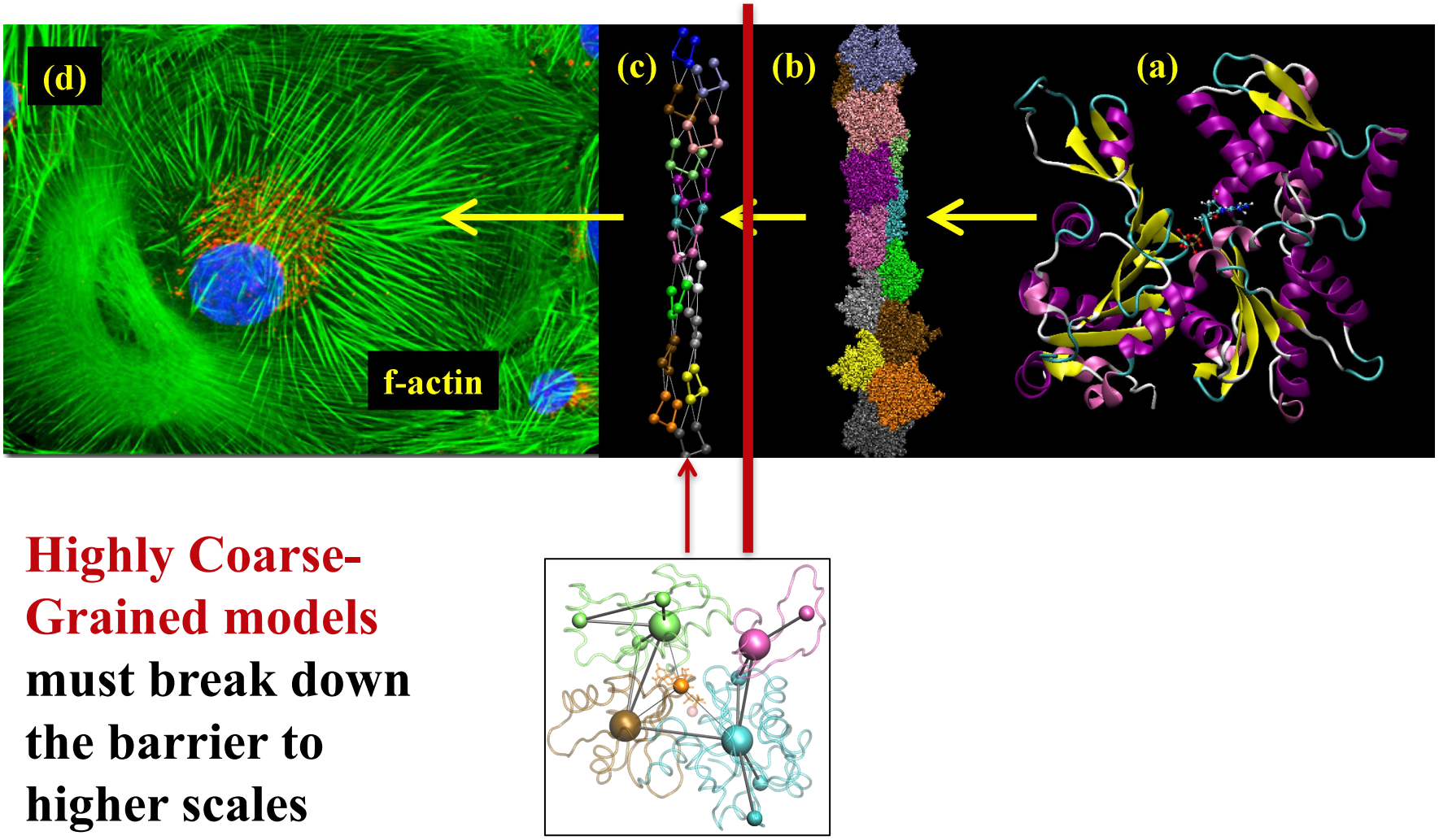
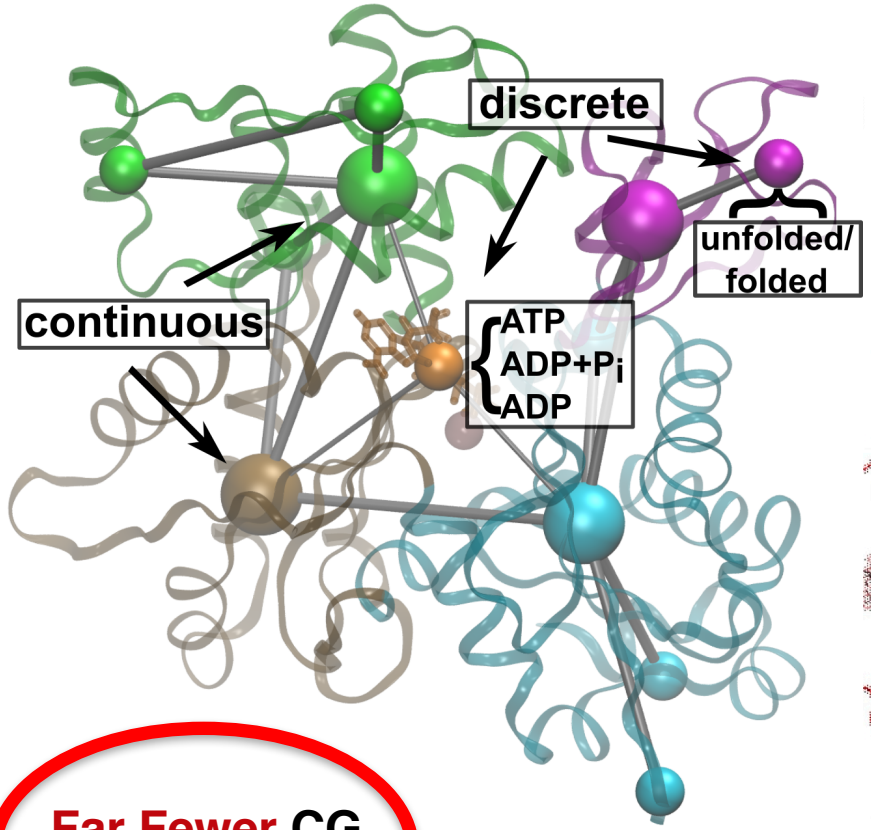
The Multiscale Challenge

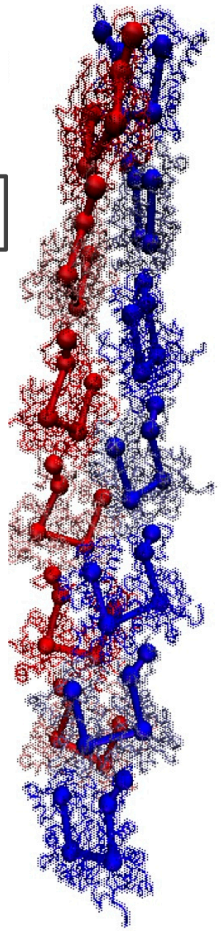
Physics-based Computer Simulation at the Scales of Cellular Biology



Highly Coarse-Grained models must break down the barrier to higher scales

A Step Further and Something Very Different!
Ultra-Coarse-Graining (UCG)*





Continuous kinematic movement of CG particles is there *but not enough*

CG Particles must have internal "states"

Dynamic state change *within* the CG particles modulates interactions *between* CG particles

Far Fewer CG "Particles"

*J. F. Dama, A. V. Sinitskiy, M. McCullagh, J. Weare, B. Roux, A. R. Dinner, and G. A. Voth, "Theory of Ultra Coarse-Graining. I. General Principles", J. Chem. Theor. Comp. **9**, 2466–2480 (2013).

UCG Advantage ⇒

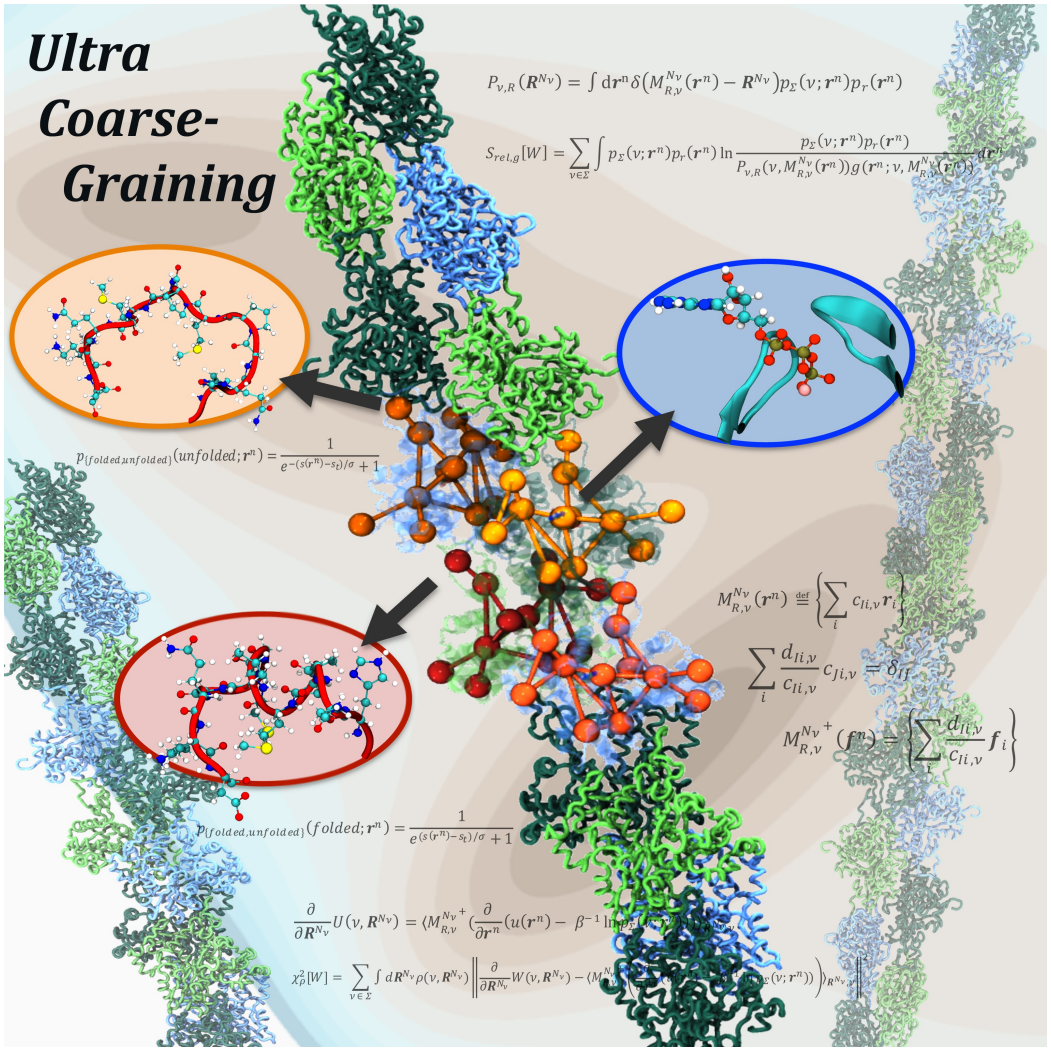
$$(\#\text{UCG States}) \times (\#\text{UCG Sites}) \ll (\#\text{Higher Res CG Sites}) < (\#\text{Atomic Sites})$$

Origins of Possible "States" in the UCG Sites

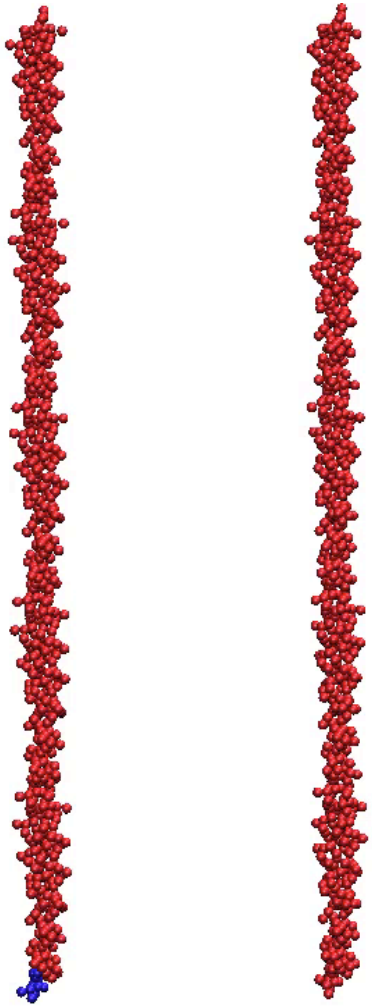
States within UCG "beads"

— physical —
disorder transition
ligand binding
loop folding/unfolding

— chemical —
nucleotide hydrolysis
redox reaction
protonation

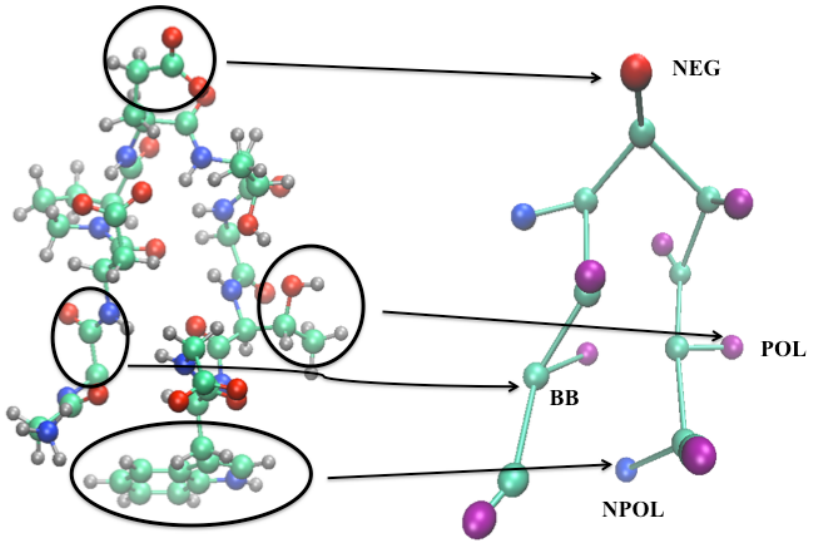


Cooperative versus Random ATP Hydrolysis in Actin Filaments



Depending on the UCG site conformations and the correlations between their motions, once can witness these two limits. The real case is of course in between and affected by polymerization dynamics.

UCG: Also New Life for "Higher Resolution" Coarse-graining?



Shown here is a "high resolution" CG model having some number of CG sites or "beads" per each amino acid residue in the peptide.

Ultra Coarse-Graining: Variational Equations

Refactor the Multiple State Metrics

Simple sums of metrics reference biased simulations:

$$\chi(\{U_\nu\}, u_p) = \chi_\nu + \sum_\nu \chi_f(U_\nu, u_p + u_{b,\nu})$$

$$\chi_{FM}(\{U_\nu\}, u_p) = \chi_\nu + \sum_\nu \frac{c_\nu}{T_\nu} \sum_{t_\nu=0}^{T_\nu} ||(\nabla U_\nu|_{t_\nu} - (\mathcal{F}_{p,t_\nu} + \mathcal{F}_{b,\nu,t_\nu}))||^2$$

But can be cast in terms of a single unbiased simulation:

$$\chi_{FM}(\{U_\nu\}, u_p) = \chi_\nu + \frac{1}{T} \sum_{t=0}^{T} \sum_\nu c_\nu p_{\nu,t} ||(\nabla U_\nu|_t - (\mathcal{F}_{p,t} + \mathcal{F}_{b,\nu,t}))||^2$$

Allows use of existing simulations and MS-CG software

What is the Influence on the UCG Distributions from the Internal States?

- There should be some sort of **isomorphism to mixed quantum-classical evolution of nuclear motion on multiple potential energy surfaces**
  - But are there too many states?? *In principle*:

$$\text{Total \# of states} = M^{N_{CG}} \text{ (Yikes!!)}$$

where M is # internal states, N_{CG} is total # of UCG sites

- **No! Dynamics will be in the "decoherence" limit**; No-off diagonal density matrix elements: simpler equations for the remaining diagonal elements
- **Mean field-like solutions:** $\text{Total \# of states} \sim M \times N_{CG}$

Two Limits of UCG State Dynamics

$$\text{UCG Payoff} \Rightarrow (\#\,\text{UCG States}) \times (\#\,\text{UCG Sites}) \ll (\#\text{Higher Res CG Sites}) < (\#\text{All-Atom Sites})$$

- **Limit I**: States can **change infrequently**, leading to a **surface-hopping style dynamics**
  - Use a **local ansatz** for **rates**:

$$\text{Rate of state switch for } i = k(\{neighs\}_i)$$
$$\text{where } \{neighs\}_i \text{ is local configuration, } k \text{ is UCG rate}$$

- **Limit II**: States can **change frequently**, leading to an **adiabatic and Ehrenfest style dynamics**
  - Use a **local** ansatz for **populations**:

$$\text{Prob of state } \alpha \text{ for site } i = p_{i,\alpha}(\{neighs\}_i)$$
$$\text{where } \{neighs\}_i \text{ is local configuration, } p_{i,\alpha} \text{ is UCG occupation}$$

UCG Limit II: Rapid Local Equilibrium*

Consider a mix between two pairwise force fields

- Use two states per particle and separable probabilities

General Free Energy Over All States

$$U(\vec{R}^N) = \sum_{\sigma} p_{\sigma}(\vec{R}^N)\left(U_{\sigma}(\vec{R}^N) + k_B T \log p_{\sigma}(\vec{R}^N)\right)$$

Separable State Populations *Ansatz*

$$p_{\sigma}(\vec{R}^N) = \prod_{i} p_{i,\alpha_i \in \sigma}(\vec{R}^N)$$

Simplify for State-wise Pair Potentials

$$U(\vec{R}^N) = \sum_{i}\sum_{\alpha_i} p_{i,\alpha_i} k_B T \log(p_{i,\alpha_i}) + \sum_{ij}\sum_{\alpha_i,\beta_j} p_{i,\alpha_i} p_{j,\beta_j} u_{\alpha_i\beta_j}(r_{ij})$$

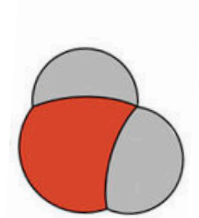
Forces from chain rule are *always* local *if* the p are local

*J. F. Dama, J. Jin, and G. A. Voth, "The Theory of Ultra-Coarse-Graining. 3. Coarse-grained Sites with Rapid Local Equilibrium of Internal States", J. Chem. Theory Comp. **13**, 1010 (2017).

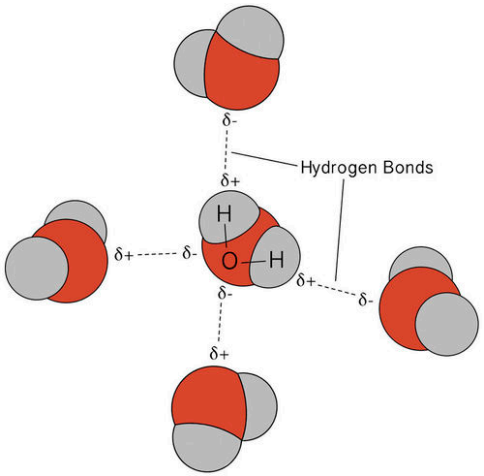
UCG Limit II Example : Cooperative Interactions

Phase coexistence is an excellent target application for UCG

Gas Phase



Liquid Phase



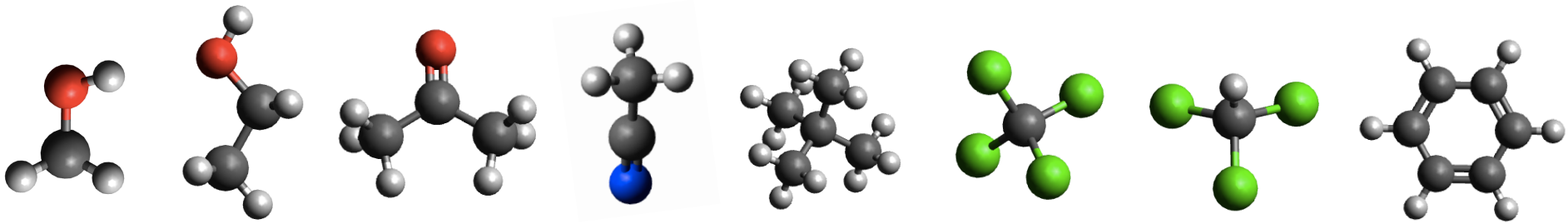
UCG "Bead" with two internal states

Mean Molecular Interactions Differ by Phase

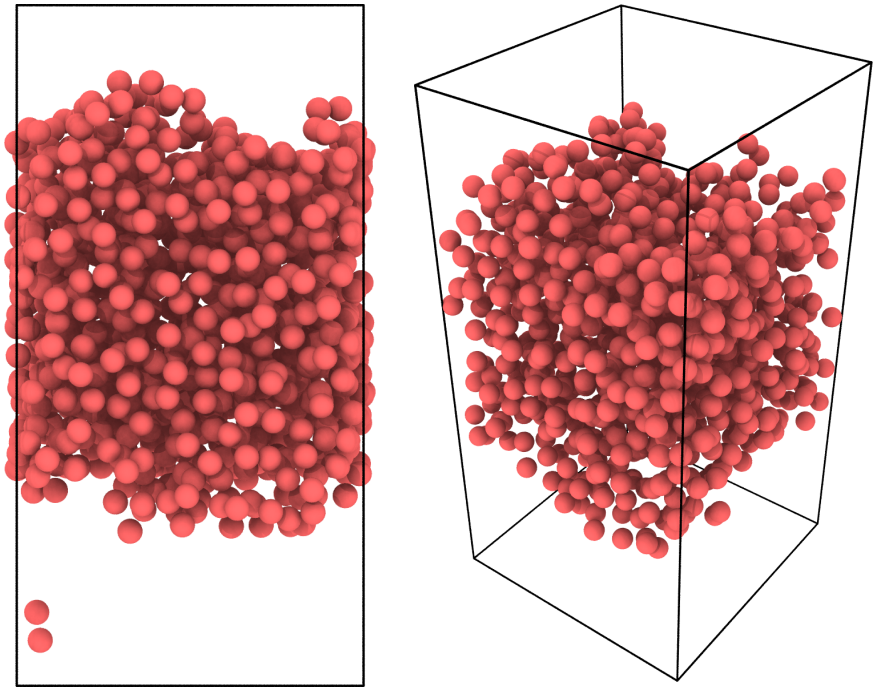
Representability Problem:
Standard CG force fields can generally only match one phase at a time

UCG Model for Liquid/Vapor Interfaces

Target system: Include different intermolecular interactions and molecular symmetry between molecules



Methanol Ethanol Acetone Acetonitrile Neopentane CCl_4 CCl_3H Benzene

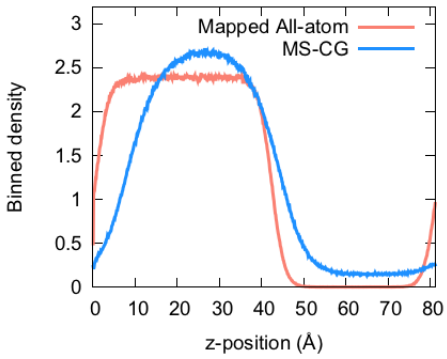


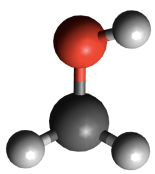
J. Jin, G. A. Voth. In preparation

- **All-atom simulation** is from OPLS/AA for 1,000 molecules
- **Coarse-grained simulation** is from one-site CG model (center-of-mass)

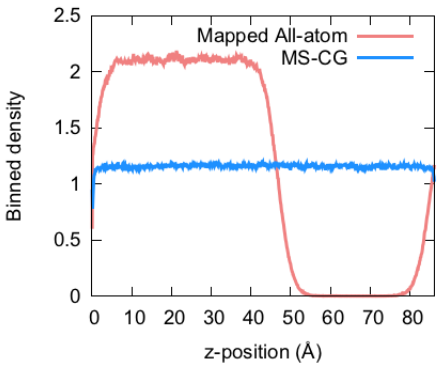
Slab Density Profiles: All-atom and MS-CG

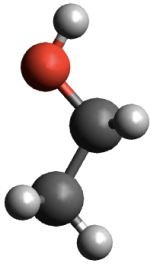
(a) Methanol



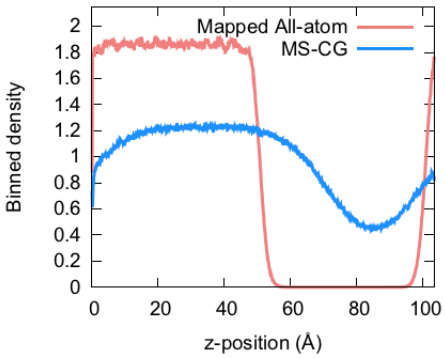


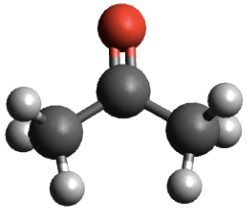
(b) Ethanol



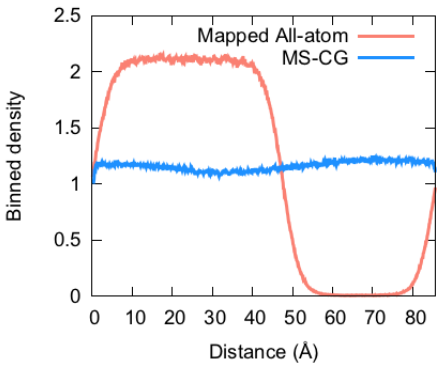


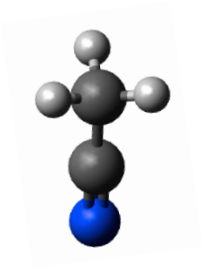
(c) Acetone





(d) Acetonitrile





Longer chain

Linear chain

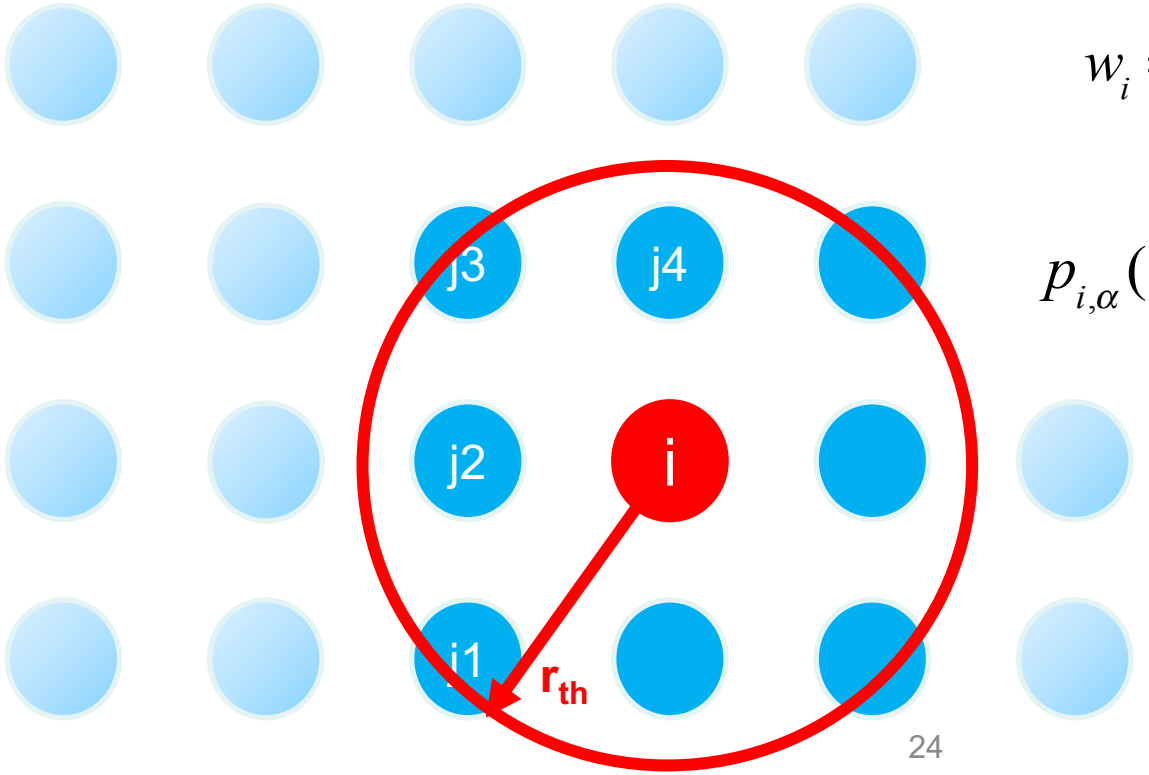
MS-CG theory generally fails to describe the interface system

J. Jin, G. A. Voth. In preparation

UCG Limit II Example: Density-Based States

Phase membership via a density order parameter:

- Track number of sites within a set radius of each site
- Mix states based on whether that exceeds a threshold



$$w_i = \sum_{j \in 2r_{th}} \frac{1}{2}\left(1 - \tanh\left(\frac{r_{ij} - r_{th}}{0.1 r_{th}}\right)\right)$$

$$p_{i,\alpha}(w_i) = \frac{1}{2}\left(1 + \tanh\left(\frac{w_i - w_{th}}{0.1 w_{th}}\right)\right)$$

The α state is the **locally dense** state

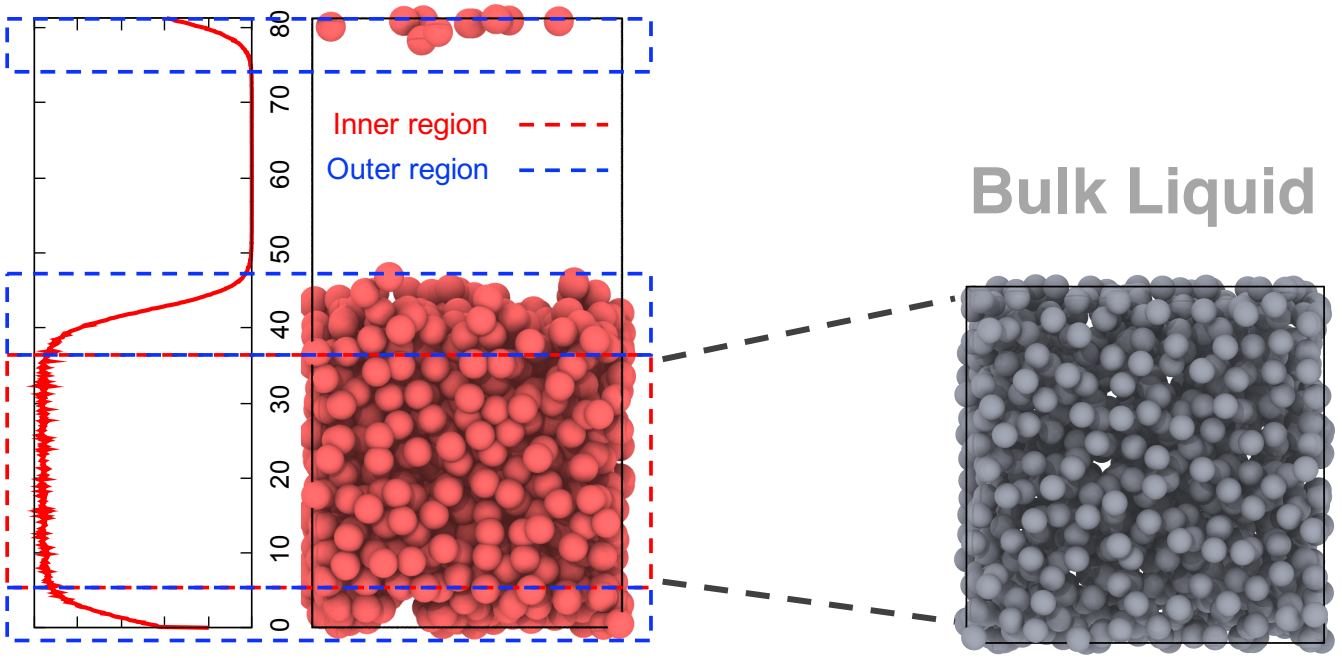
UCG Model Design: Inner/Outer Regions

Define inner and outer regions based on liquid phase and phase boundary of the system

Vapor Phase

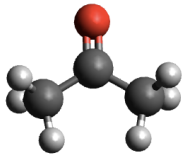
Phase Boundary

Liquid Phase

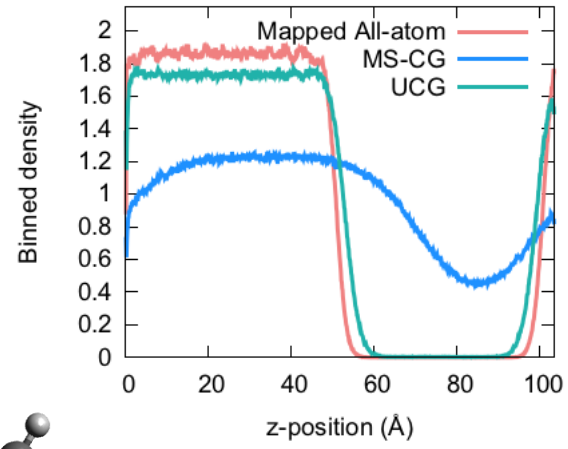


UCG internal states are designed to distinguish denser (inner region) and less dense (outer region) local environment

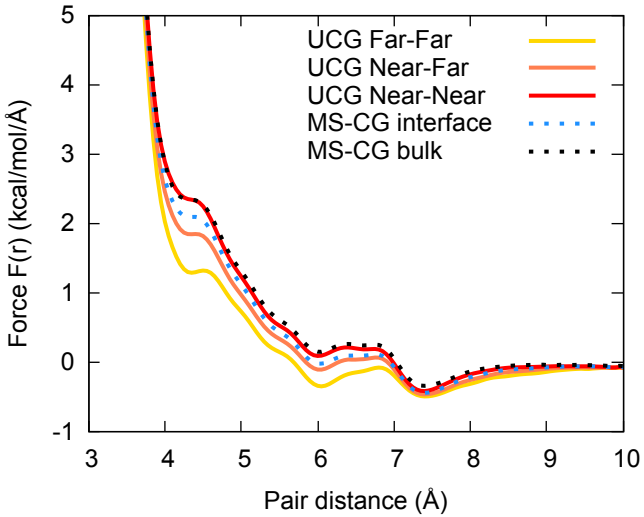
Liquid/Vapor One Bead UCG Model Results



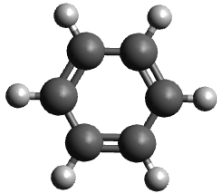
Density Profile



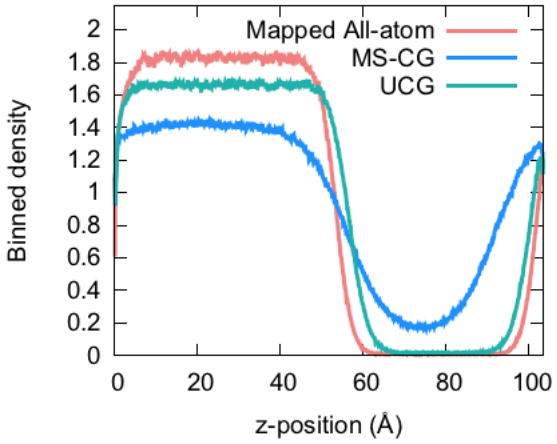
CG Pair Interaction



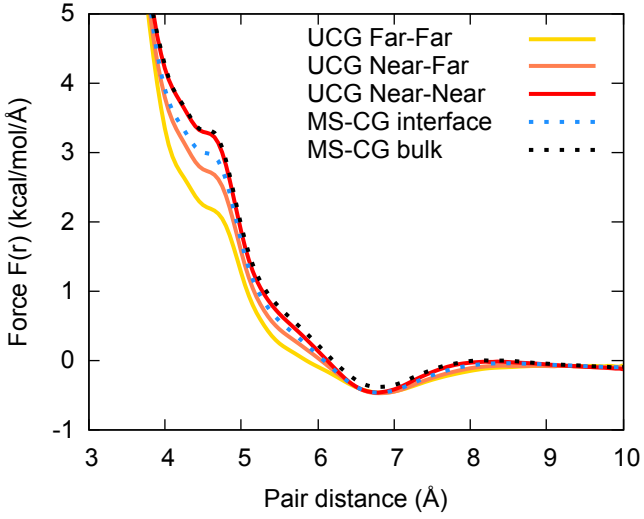
UCG models provide better density profile



Density Profile



CG Pair Interaction

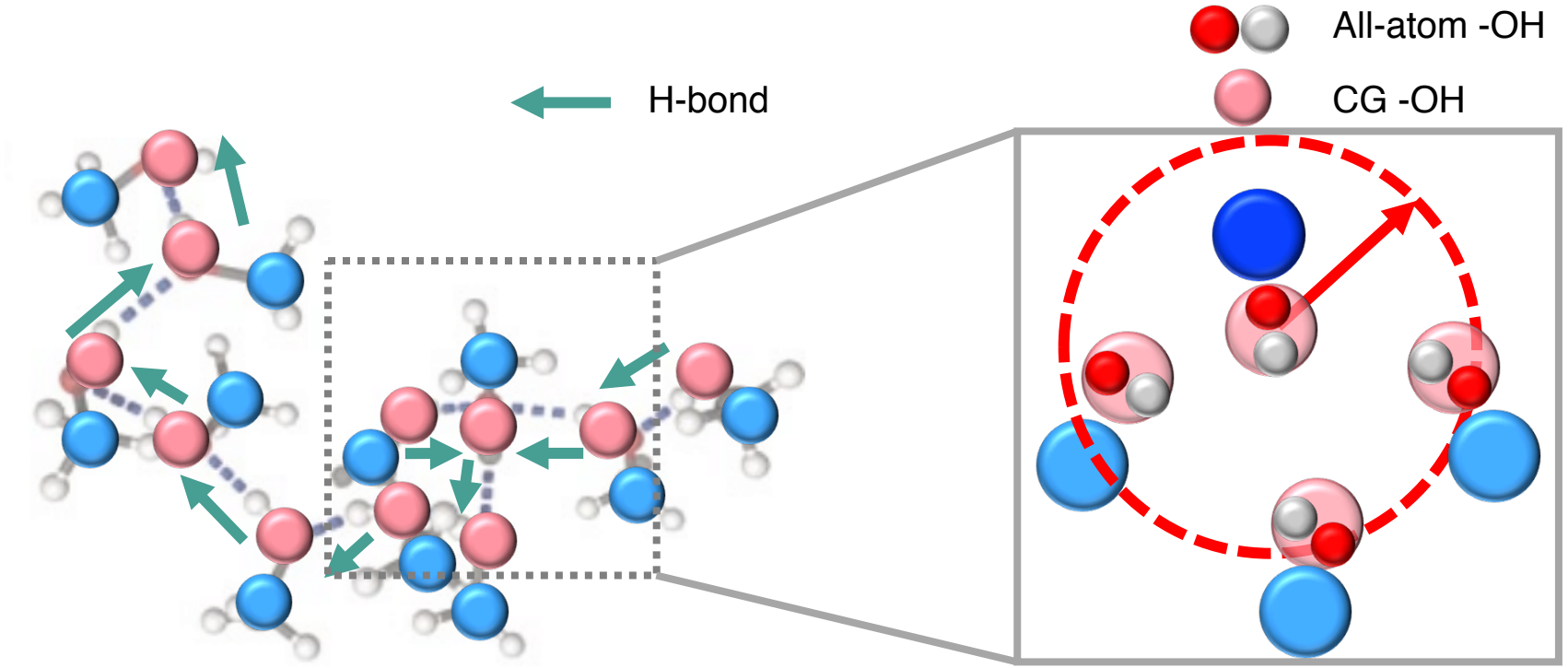


UCG Near-Near (liquid phase) interaction is transferable to bulk interaction (**MS-CG bulk**)

Direct MS-CG to interface (**MS-CG interface**) fails to distinguish interactions between states

J. Jin, G. A. Voth. In preparation

H-bond topology can be modeled via UCG



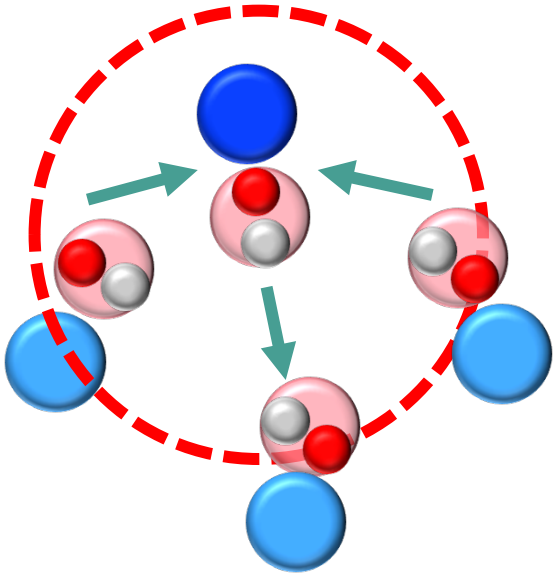
- Important **H-bond topology** is lost during coarse-graining: acceptor/donor pairs, differences in direction and interaction.
- **UCG model** is designed to capture these configurations by imposing “acceptor” and “donor” states

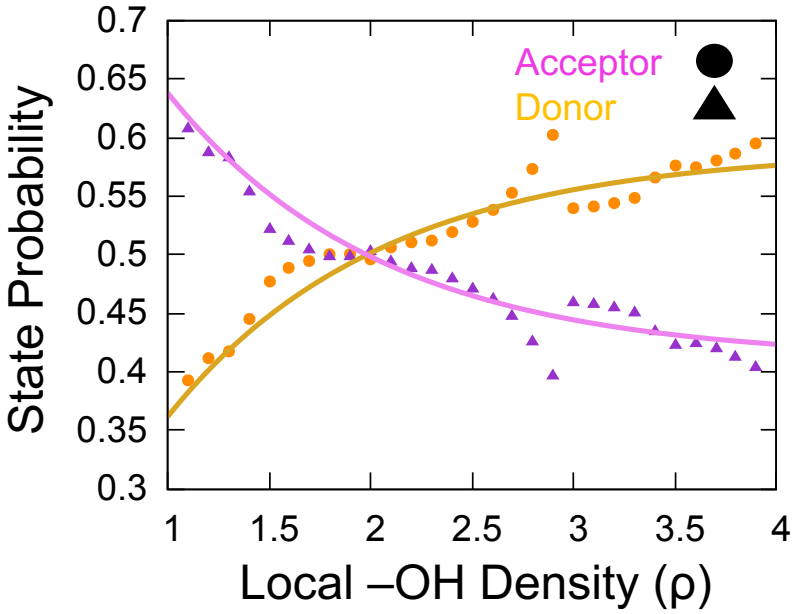
H-bond topology can be modeled via UCG

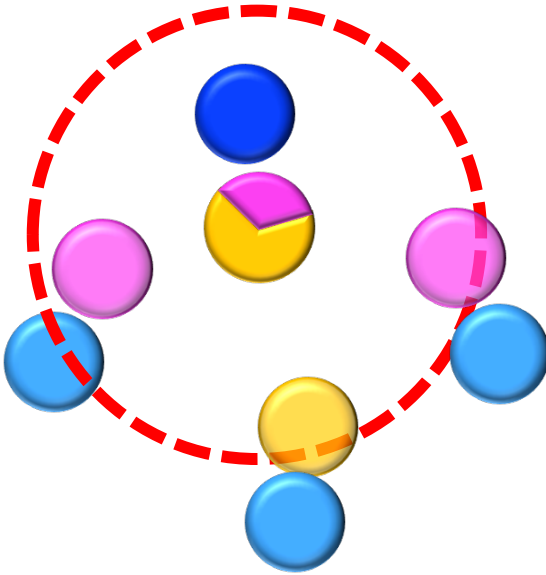
Collect H-bond topology from FG

Calculate histogram and fit substate probability

Construct the UCG model

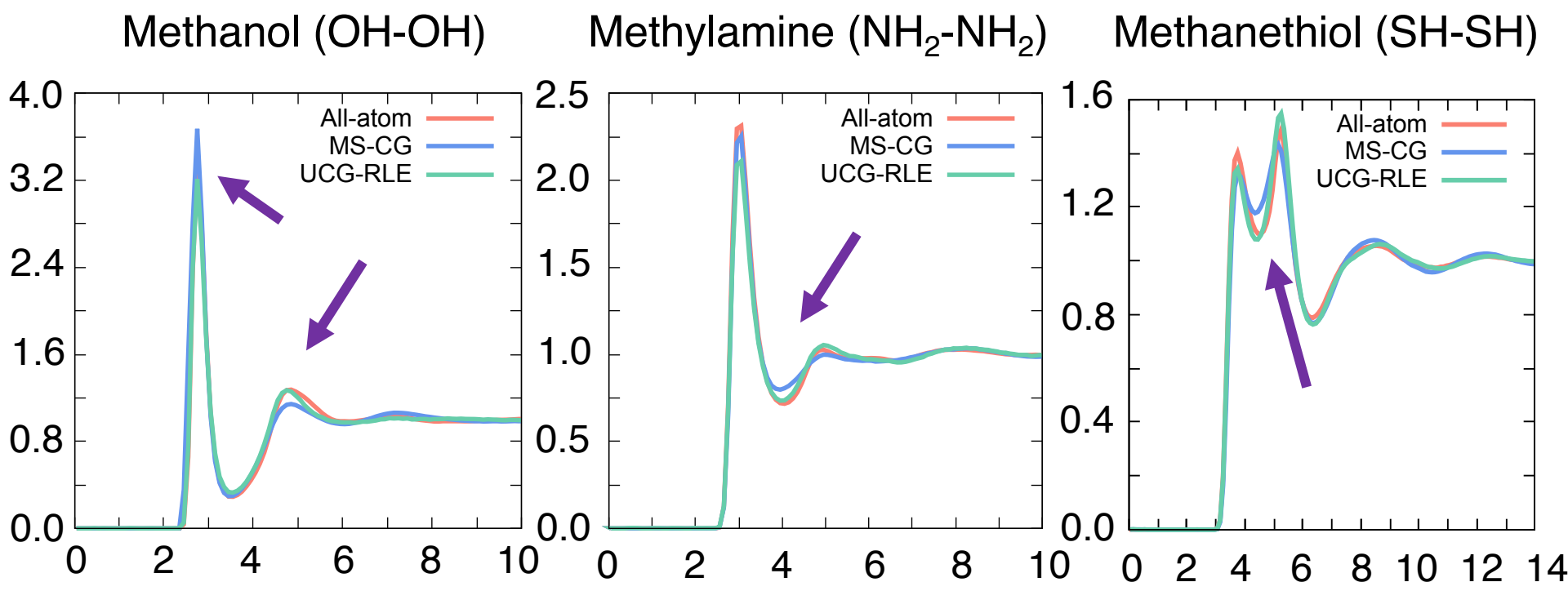






UCG model provides mean-field description of H-bond topology at the specific local density

UCG H-bond model improves pair structure



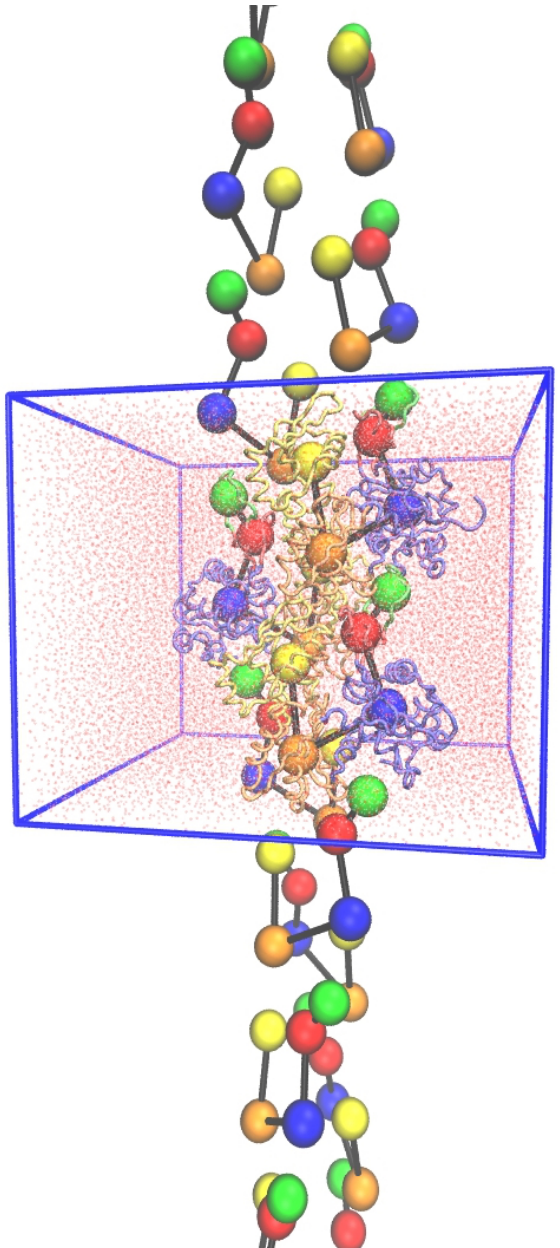
Improved pair structures can be seen from RDF:

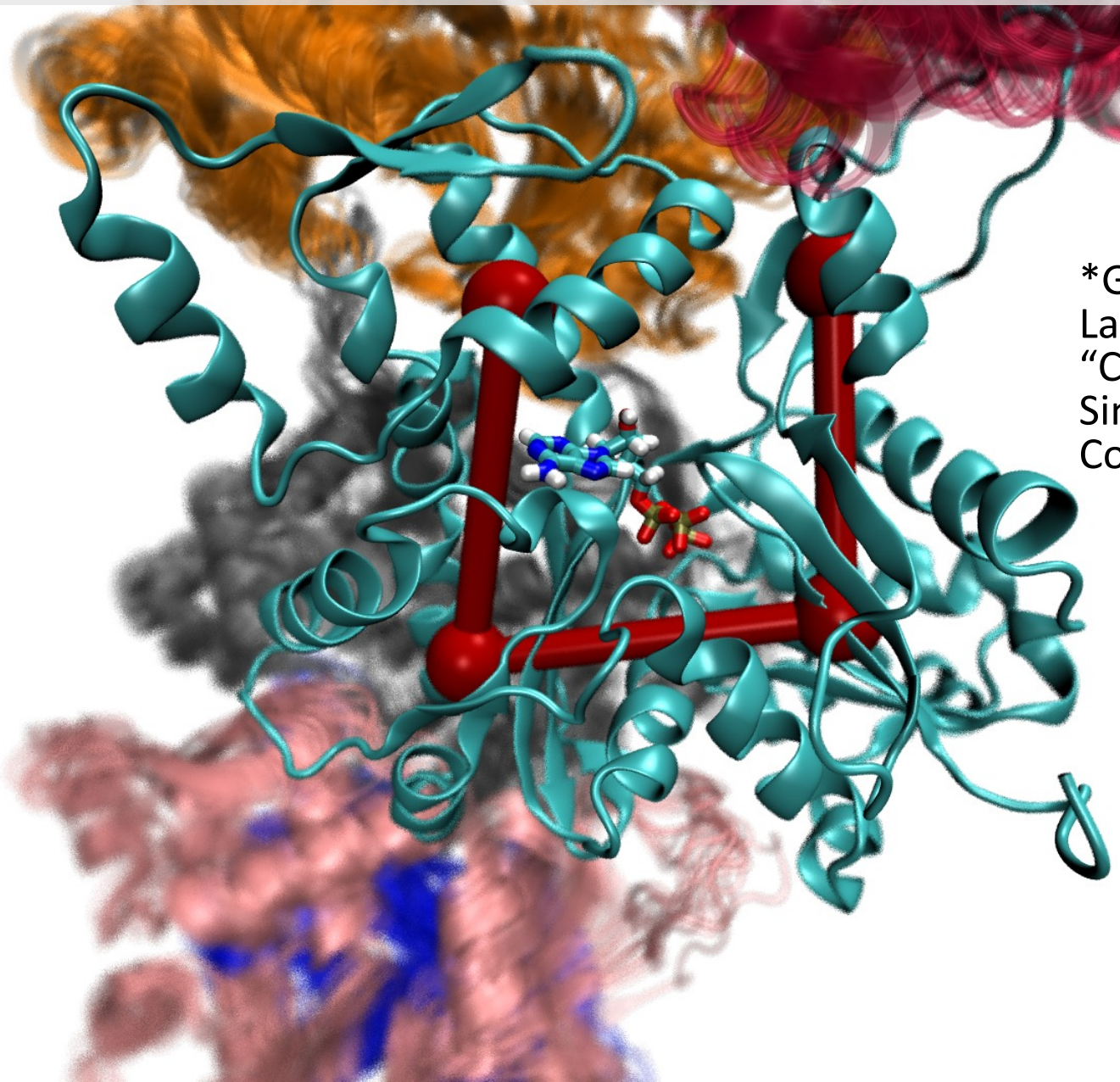
- Enhancements are observed at 2-4 Å compared to MS-CG (**effective H-bond range**)
- UCG statewise interactions differentiate H-bond topology

Outline of Today's Talk

- **Brief background on "bottom-up" coarse-graining**
- **Ultra-Coarse-Graining (UCG): Exciting new capability**
- **Coarse-grained Directed Simulation**
- **Mesoscopic Coarse-graining**

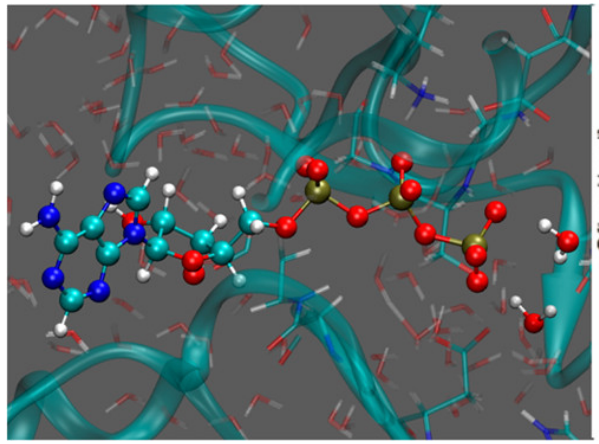
COARSE-GRAINED DIRECTED SIMULATION*

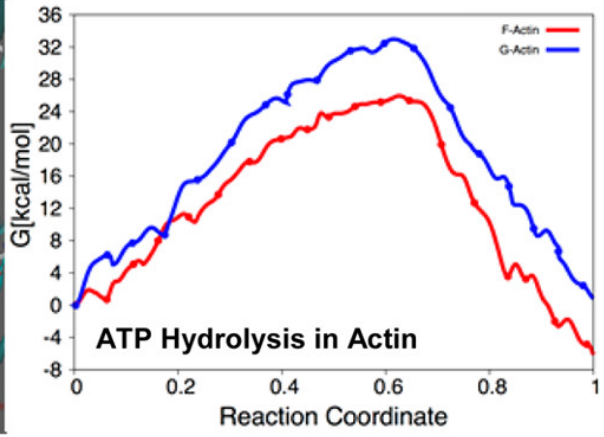




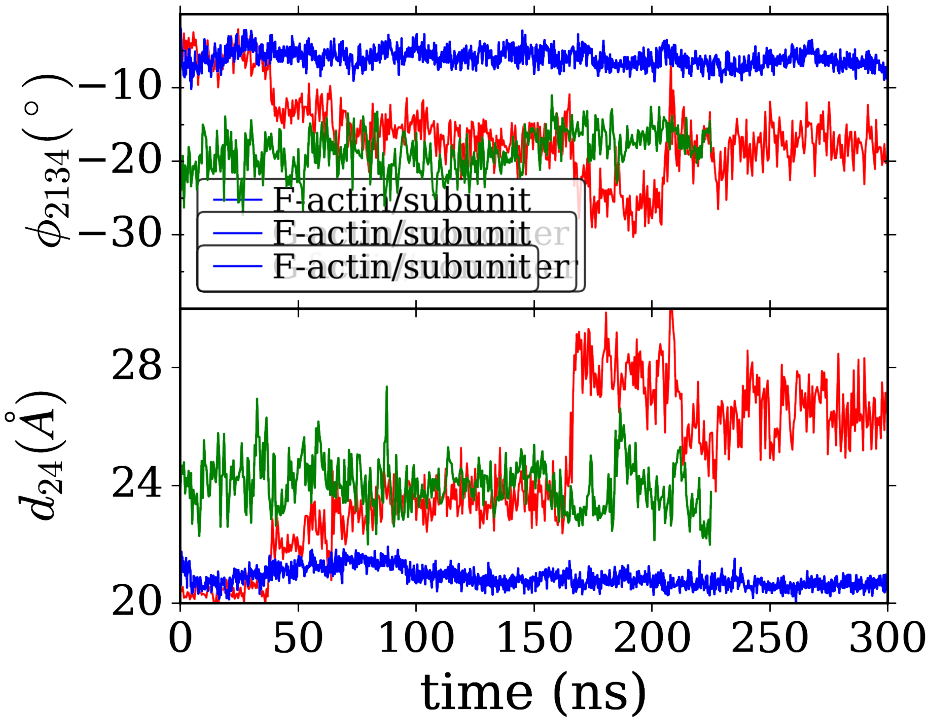
*G. M. Hocky, T. Dannenhoffer-Lafage, and G. A. Voth, "Coarse-grained Directed Simulation", J. Chem. Theory Comp. **13**, 4593-4603 (2017).

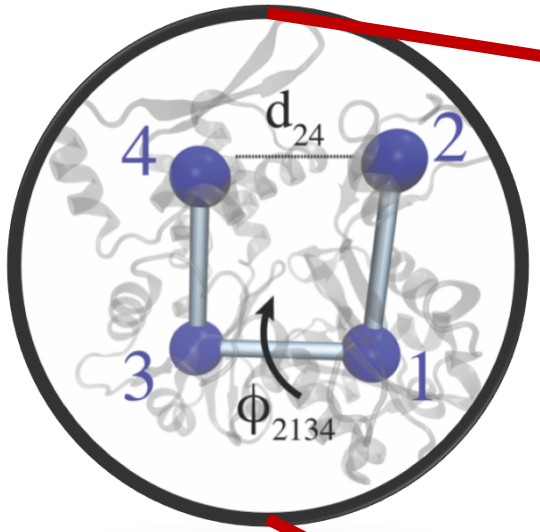
Actin-Catalyzed ATP Hydrolysis

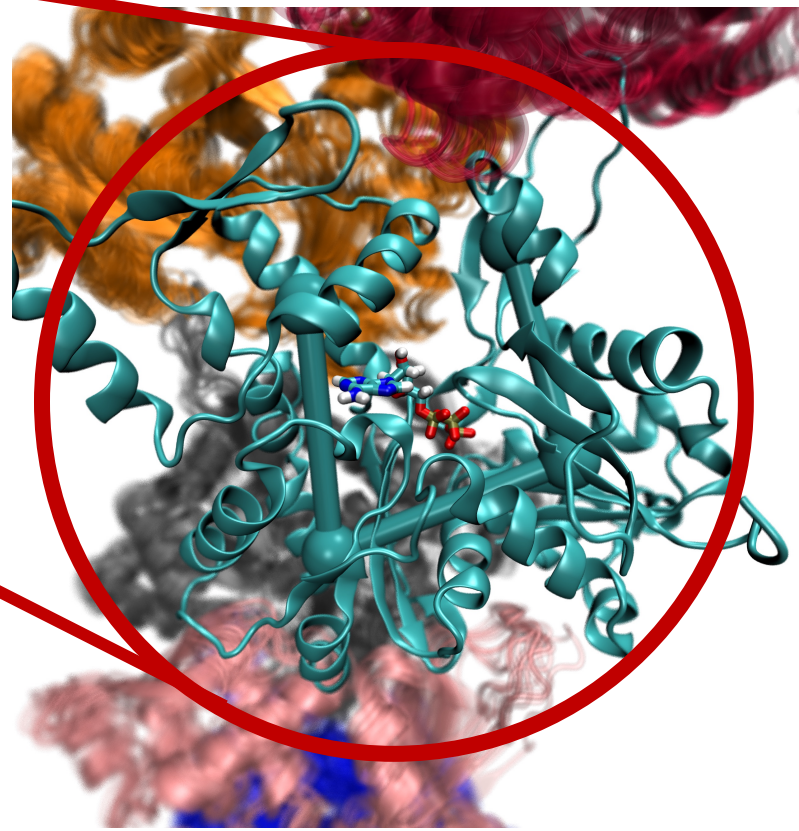




R. Sun, O. O. Sode, J. F. Dama, G.A. Voth. JCTC (2017)



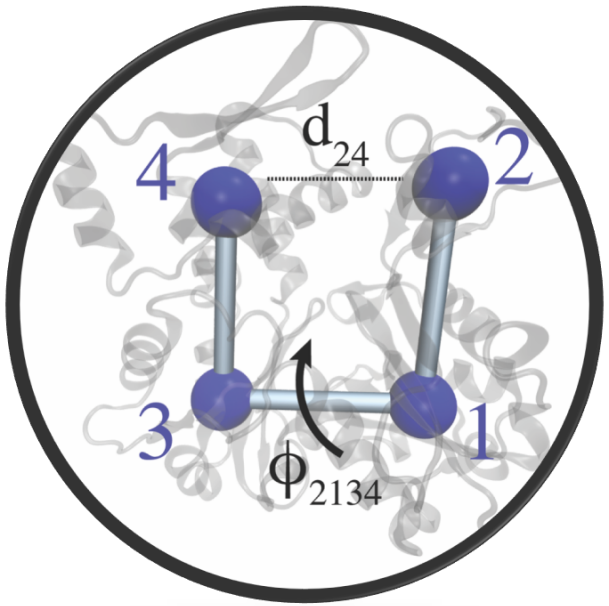


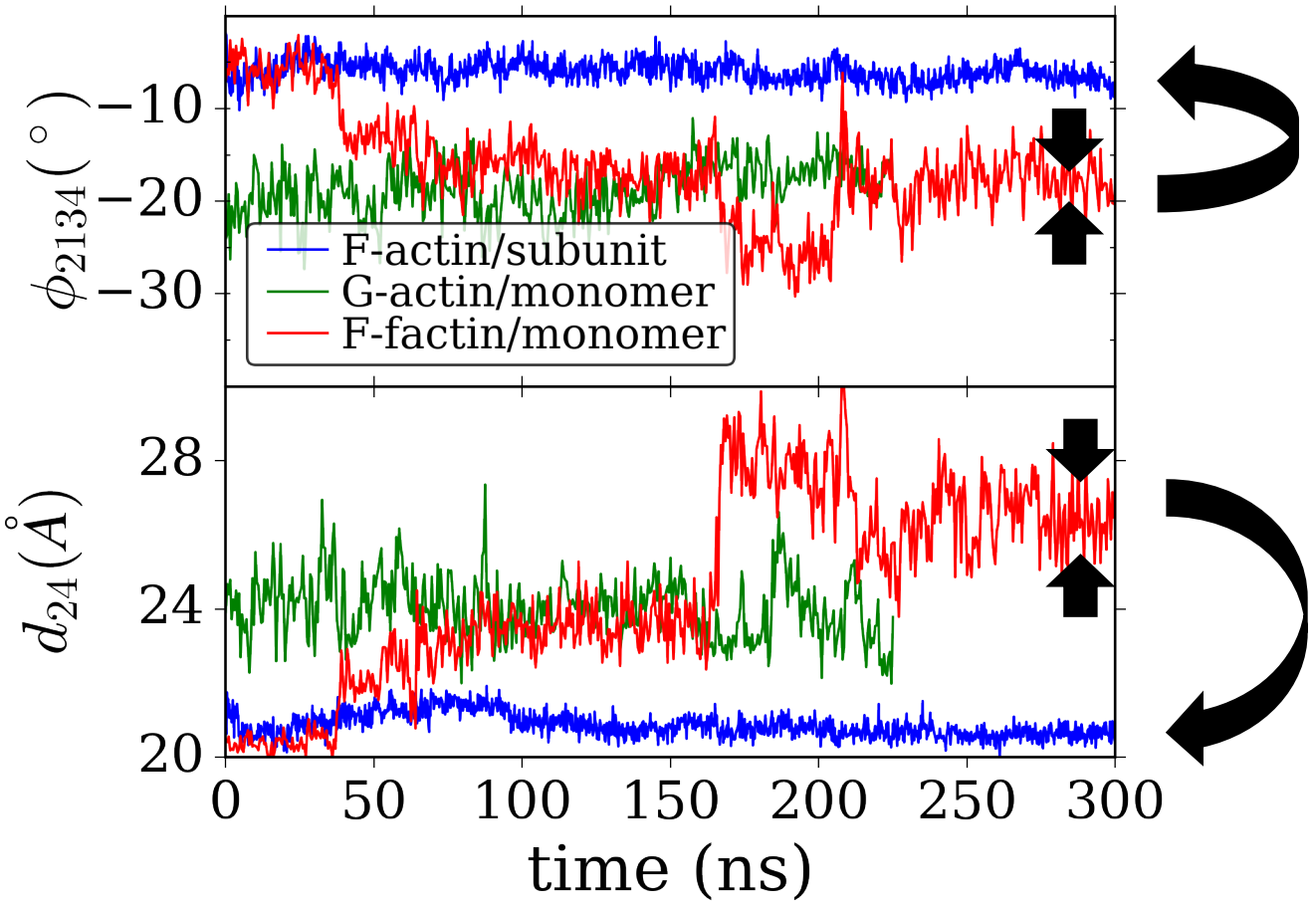


- **Result**: Twist in actin structure accelerates ATP hydrolysis by > 10^4
- **Problem:** have to restrain actin monomer to get these results

CHALLENGE – SAMPLE CORRECT MEAN AND FLUCS

In general: want a method to restrain a subsystem and have it behave as if it is still part of a complex





IDEA – USE "MINIMAL BIAS" METHODS

Goal: modify simulation forcefield such to match known observations (see Pitera and Chodera, JCTC 2012)

Observations are defined as averages from simulation, which are expected to converge to:

$$f_0 = \langle f(X) \rangle = \frac{\int dX f(X) e^{-\beta H(X)}}{\int dX e^{-\beta H(X)}}$$

IDEA – USE "MINIMAL BIAS" METHODS

Goal: modify simulation forcefield such to match known observations (see Pitera and Chodera, JCTC 2012)

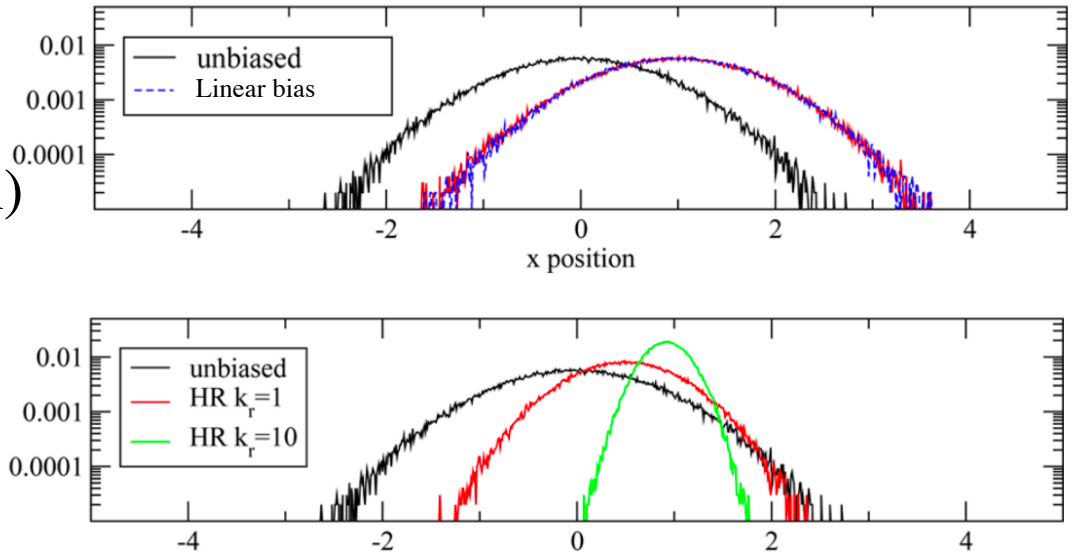
Minimize *I*, difference between new distribution *P* and distribution from *H*, P_0 (e.g. normal Boltzmann distribution)

$$I = \int dX P(X) \log(P(X)/P_0(X))$$

…subject to constraints

$$\int dX P(X) = 1 \text{ and } \hat{f}_i = \int dX f_i(X) P(X)$$

$$\Rightarrow P(X) = \frac{e^{-\beta(H(X)+H'(X))}}{\int dX e^{-\beta(H(X)+H'(x))}} \quad \boxed{H'(x) = \lambda f(x)}$$

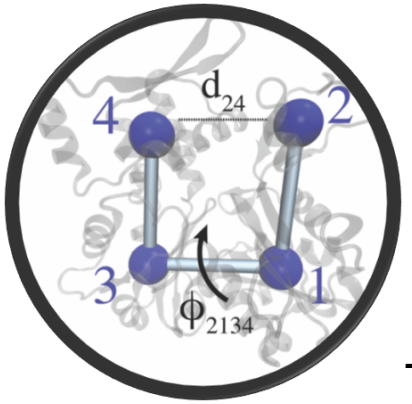


Contrast to:

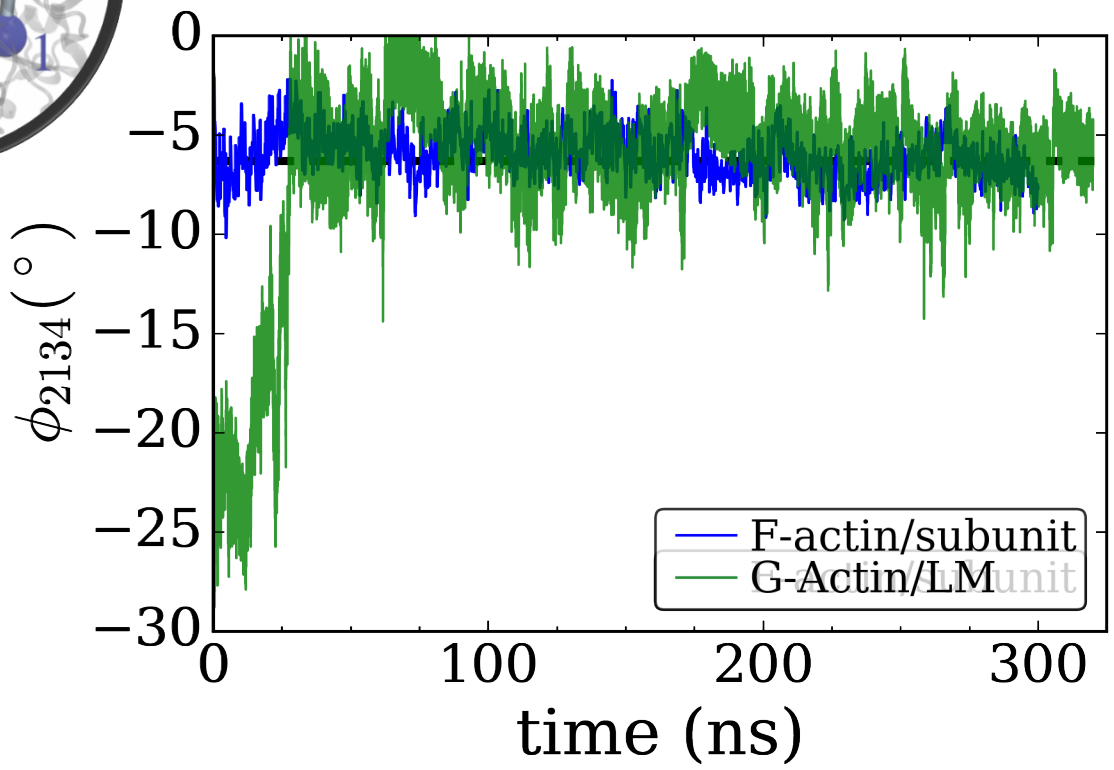
$$H'(X) = \frac{1}{2}\kappa(f(X) - f_t)^2$$

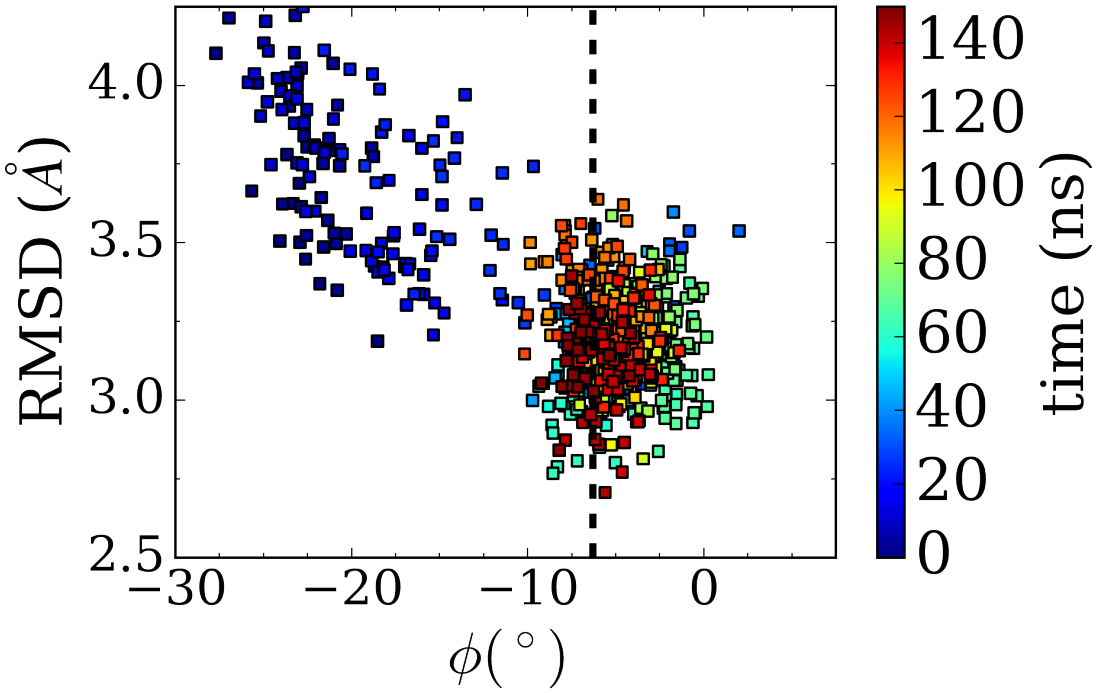
$$f_t = \lim_{\kappa \to \infty} f_b(\kappa)$$

RESULTS FOR FULLY ATOMISTIC SYSTEM



Biasing $\phi, \delta\phi^2, d, \delta d^2$, without optimizing τ

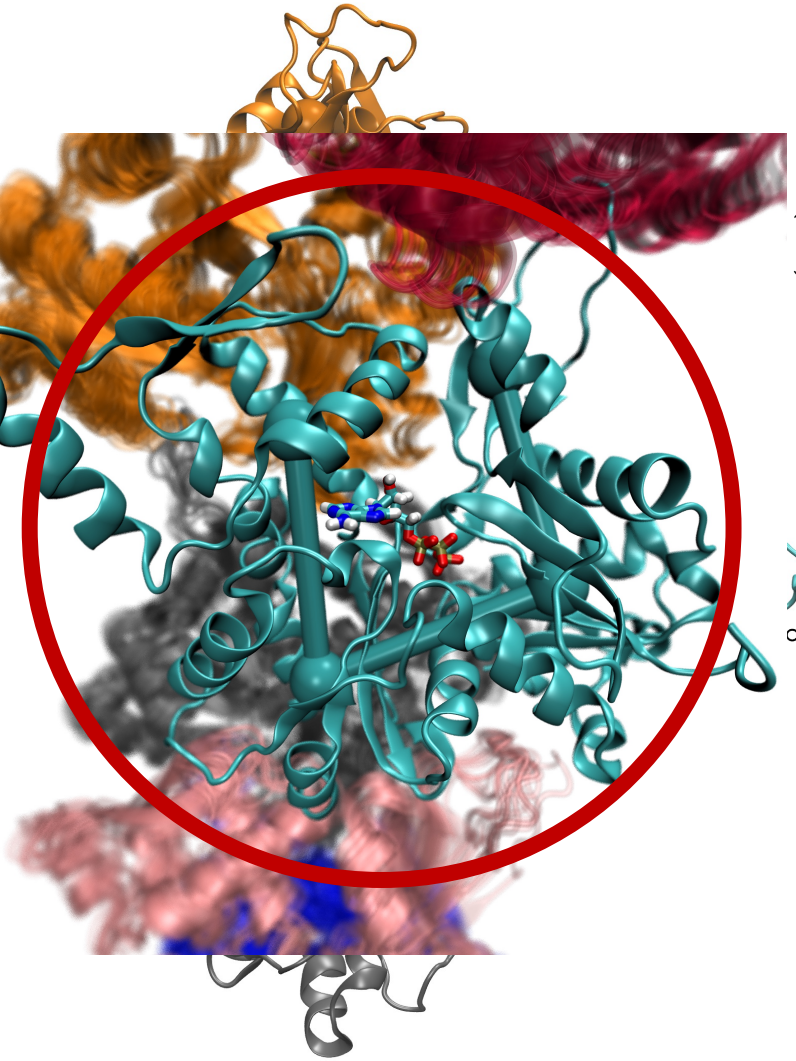


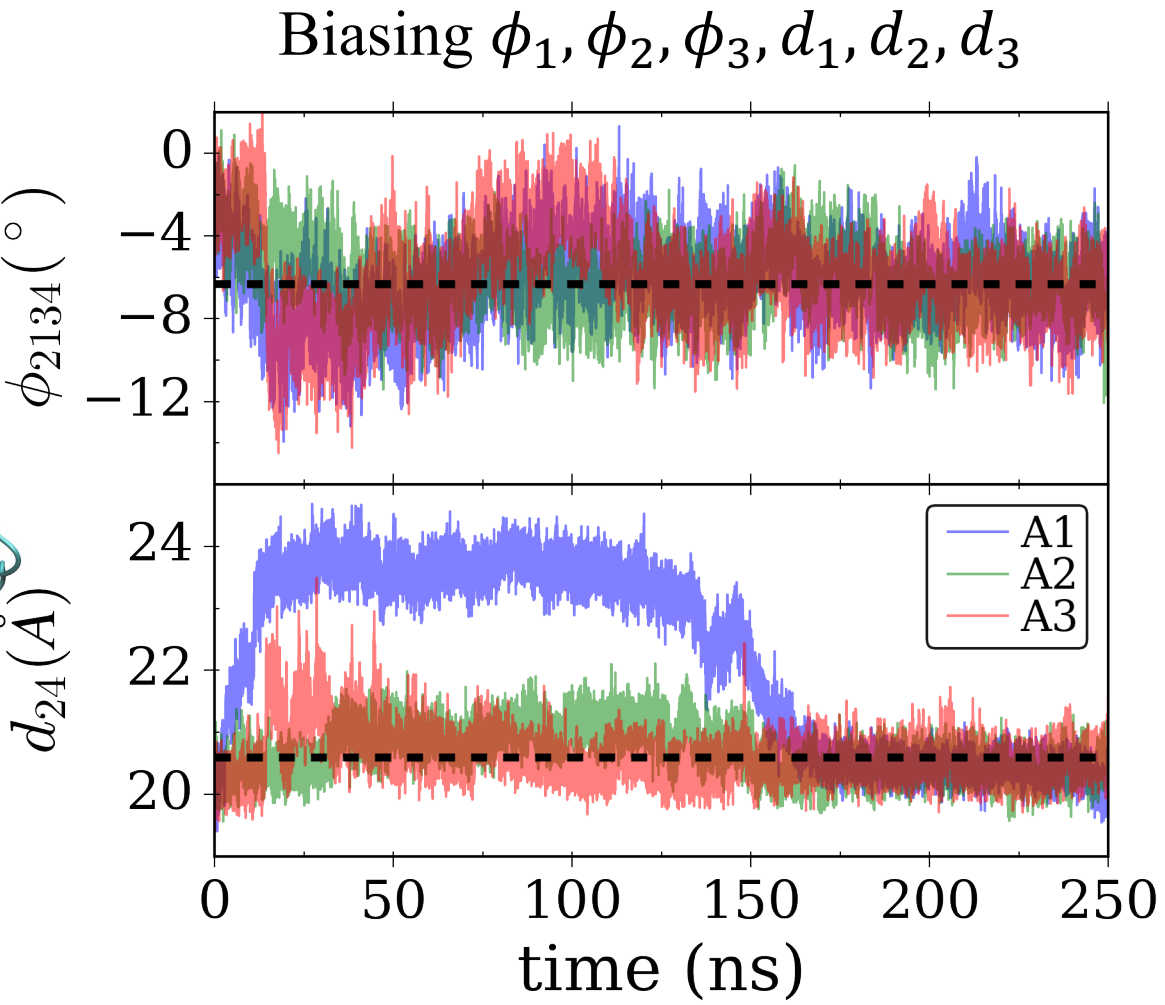


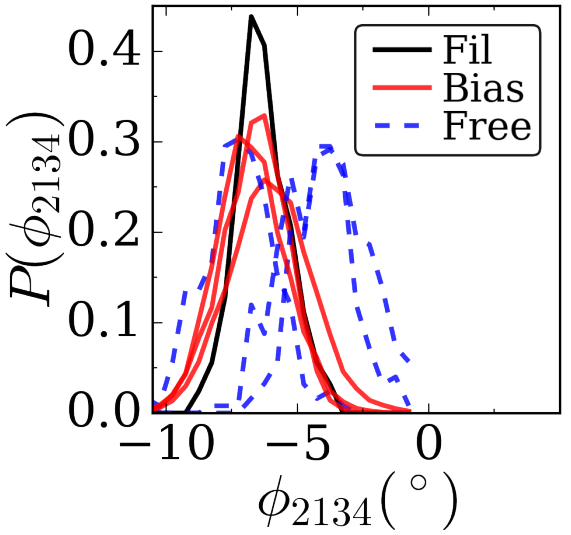
ALTERNATIVE SUBSYSTEMS

In general: want to simulate smallest possible sub-system

However: larger subsystem contains extra context



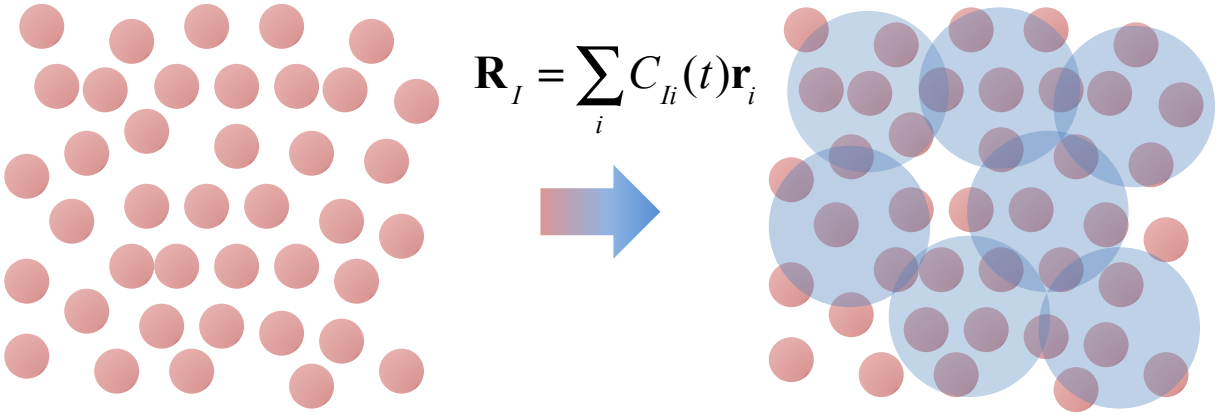




Outline of Today's Talk

- **Brief background on "bottom-up" coarse-graining**
- **Ultra-Coarse-Graining (UCG): Exciting new capability**
- **Coarse-grained Directed Simulation**
- **Mesoscopic Coarse-graining**

Dynamic Mapping Operator For Supramolecular Mesoscopic Coarse Graining of Liquids

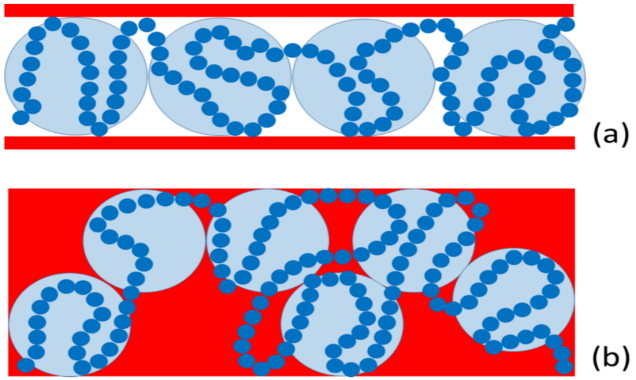


Models at Mesoscale

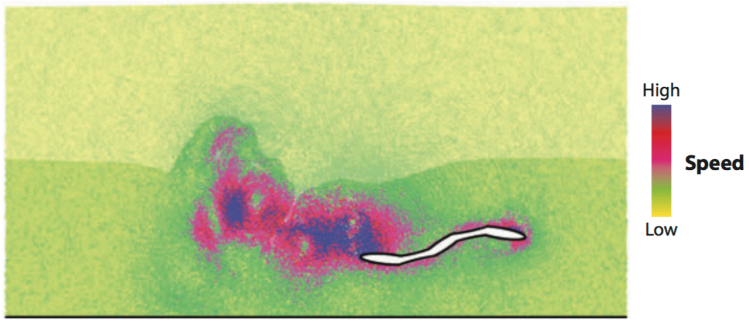
Phenomenological models have done very well in modeling universal mesoscale behavior

- De Gennes polymer blobs: DPD
- Hydrodynamic models: Smoothed Particle Hydrodynamics (SPH)
- EM2 membrane models (Developed in our group)

Blob Model

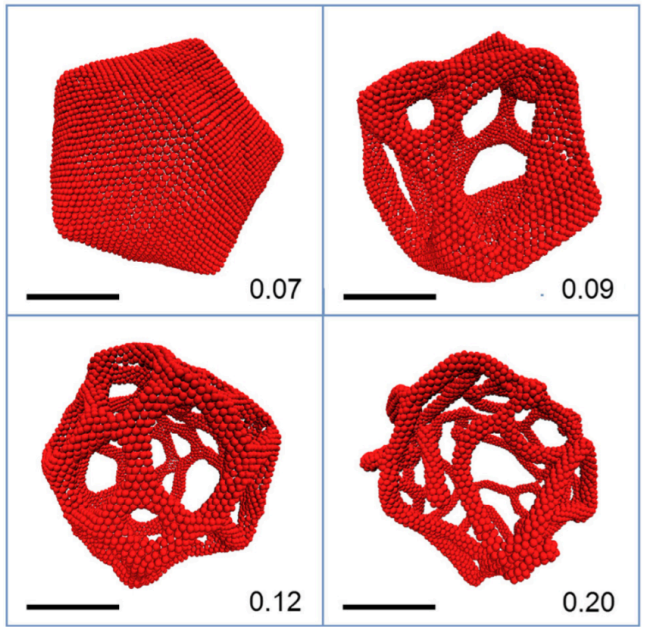


SPH



J. J. Monaghan, Annu. Rev. Fluid Mech. 44, 323, 2012

EM2



A. Davtyan, M. Simunovic and G. A. Voth, J. Struct. Biol., 196, 2016, 57

Bottom-Up Challenge at Mesoscale

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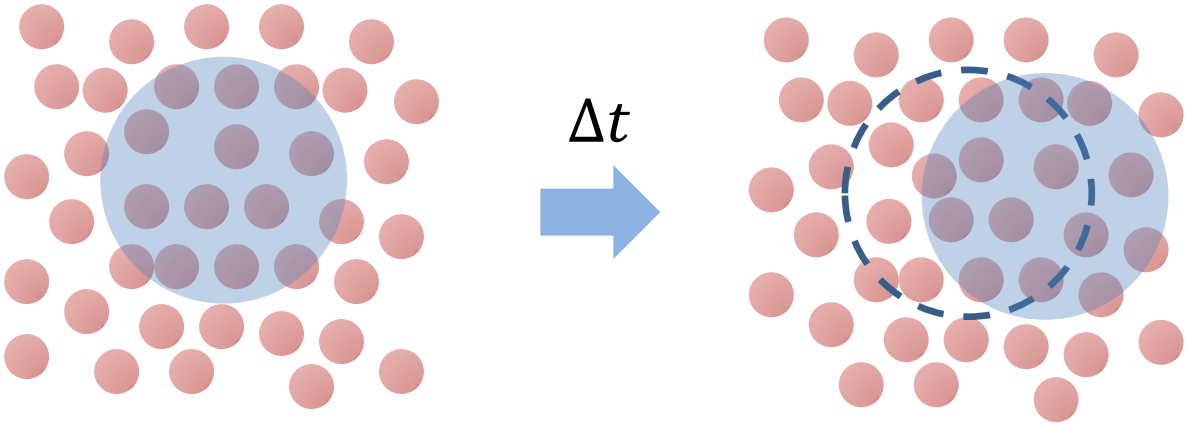
Lagrangian mesoscale CG is difficult because it is inherently supramolecular

- De Gennes polymer blobs contain solvent
- SPH beads expand and contract
- EM2 membrane beads trade lipids

The CG entities are therefore difficult to define formally in terms of molecular entities

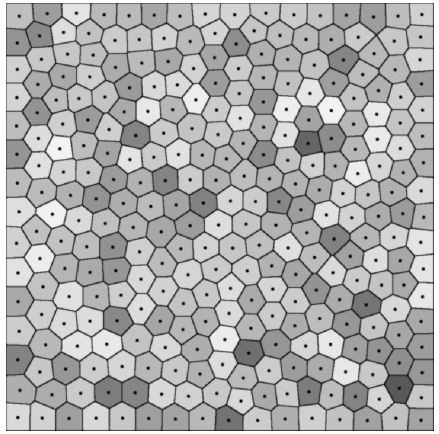
Each coarse-graining map must be **time dependent**



Our First Target: Proximity Mapping

Lagrangian mesoscopic models have one thing in common: beads represent spatial chunks of material

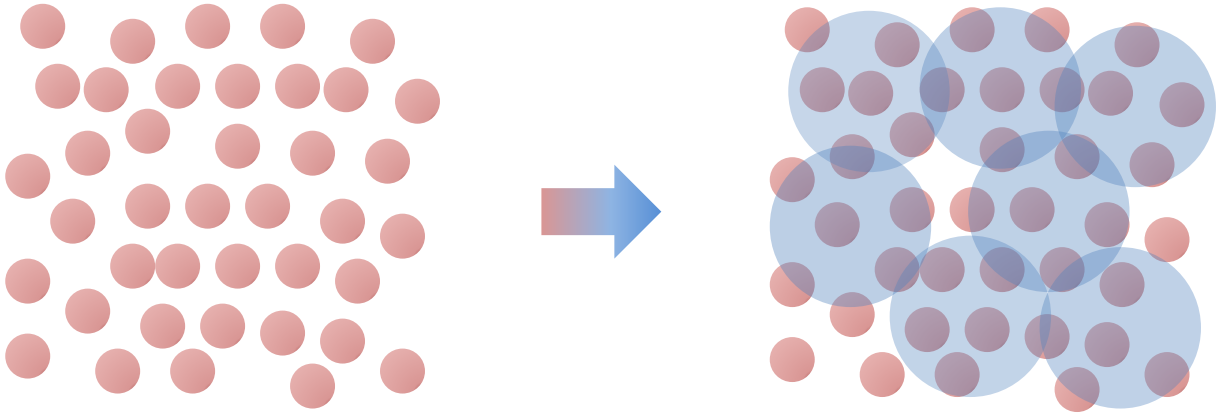
- The bead owns the molecules near it
- The molecules determine the bead position
- To be self-consistent, both must match
- Mapping should be translationally and rotationally invariant



"Centroidal Voronoi tesselation."

$$\mathbf{R}_I = \sum_i C_{Ii}(t)\mathbf{r}_i$$

$$C_{Ii} = \frac{w(|R_I - r_i|) / \sum_J w(|R_J - r_i|)}{\sum_j w(|R_I - r_j|) / \sum_J w(|R_J - r_j|)}$$



Dynamics of CG beads

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$$\mathbf{R}_I = \sum_i C_{Ii}(t)\mathbf{r}_i$$

$$C_{Ii} = \frac{w_{Ii} / \sum_J w_{Ji}}{\sum_k w_{Ik} / \sum_J w_{Jk}} \equiv \frac{f_{Ii}}{F_I}$$

$$f_{Ii} = w_{Ii} / \sum_J w_{Ji}$$

$$F_I = \sum_k f_{Ik}$$

In Dynamic Mapping Approach,
The change of mapping operator matters!

$$\dot{\mathbf{R}}_I = \sum_i \left(\frac{\partial C_{Ii}(t)}{\partial t}\mathbf{r}_i + C_{Ii}(t)\frac{\partial \mathbf{r}_i}{\partial t} \right)$$

$$V_{In} - V_{In}^{map} = \sum_j \sum_m N_{Ij}^{nm} v_{jm} + \sum_J \sum_m M_{IJ}^{nm} V_{Jm}$$

$$V_{In}^{map} = \sum_i C_{Ii} v_{in}$$

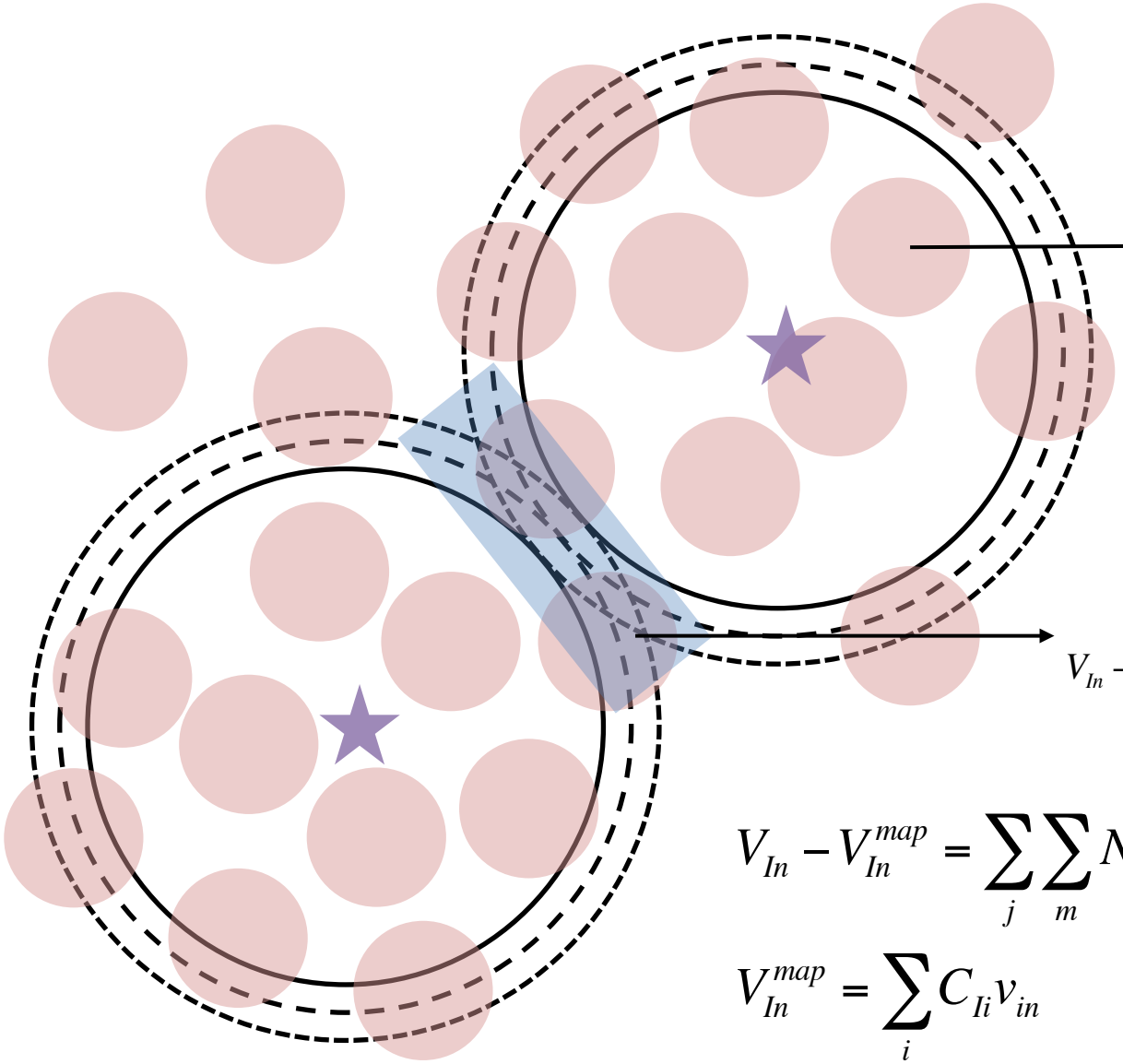
Exchange

Overlap

$$(\mathbf{I} - \mathbf{M})\mathbf{V} = (\mathbf{C} + \mathbf{N})\mathbf{v}$$

For each frame of **Fine Grained Trajectory**, we **map** the CG **velocities**, then **propagate** their **positions**

Illustration of the Physics



Langevin Fluctuations

$$V_{In}^{map} = \sum_i C_{Ii} v_{in}$$

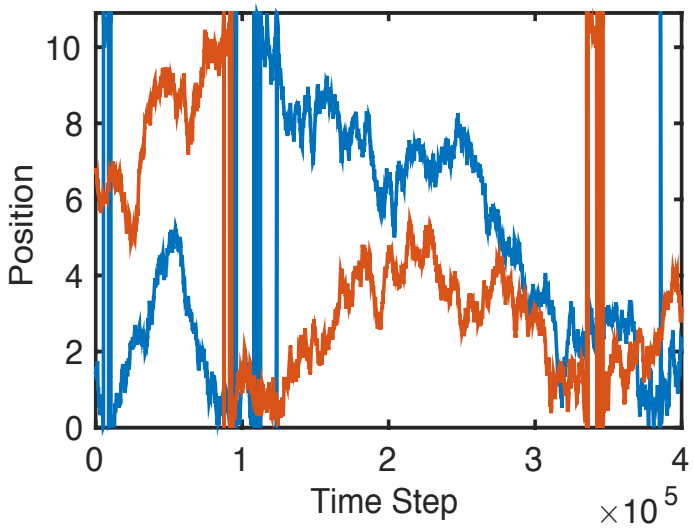
DPD like interactions

$$V_{In} - V_{In}^{map} = \sum_j \sum_m N_{Ij}^{nm} v_{jm} + \sum_J \sum_m M_{IJ}^{nm} V_{Jm}$$

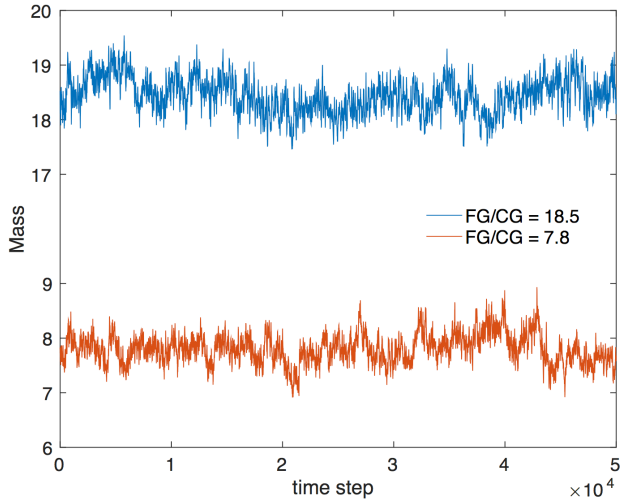
$$V_{In} - V_{In}^{map} = \sum_j \sum_m N_{Ij}^{nm} v_{jm} + \sum_J \sum_m M_{IJ}^{nm} V_{Jm}$$

$$V_{In}^{map} = \sum_i C_{Ii} v_{in}$$

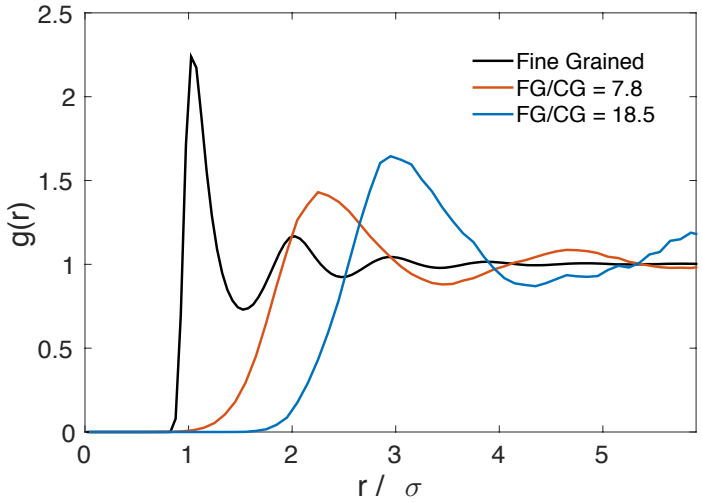
Features of Mapped Trajectory



Ergodicity



Stable Mass Partitioning



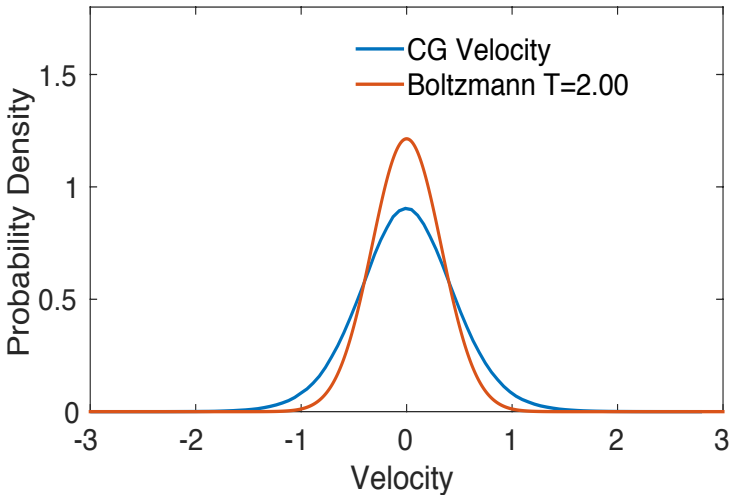
Softness

Features of Mapped Trajectory

- CG trajectory is ergodic
- Size of CG bead fluctuates but stable
- CG bead behaves like soft, deformable blobs

Based on CG-ing simple quiescent Lennar-Jones fluid

Momentum Space



Assuming

$$M_{CG} = m \cdot \frac{N_{CG}}{N_{FG}}$$

The CG particle velocity distribution does not follow the Maxwell-Boltzmann distribution at the certain temperature of fine grained system

CG beads overlap!

Velocity Mapping Equation: $\mathbf{V} = (\mathbf{I} - \mathbf{M})^{-1}(\mathbf{C} + \mathbf{N})\mathbf{v} = \mathbf{B}(\mathbf{R}, \mathbf{r})\mathbf{v}$

Ensemble Average of CG Bead velocity:

$$\left\langle V_I^2 \right\rangle = \frac{k_B T}{m} \left\langle \sum_i B_{Ii}^2 \right\rangle_R$$

$$M_{Maxwell} = m \cdot \left\langle \sum_i B_{Ii}^2 \right\rangle_R^{-1}$$

We can redefine the CG Mass (We call it Maxwell Mass) to match the fine-grained temperature

Minimum Size of CG Beads

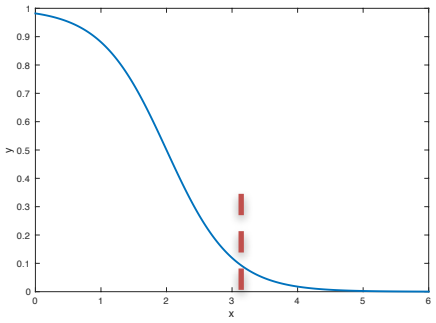
The current algorithm is only stable when the CG bead is larger than 7-8 fine-grained particles.

- Higher CG resolution leads to stronger overlaps between CG beads, the overlapping matrix M and exchange matrix N could dominate the mapping equations of motion, which causes numerical instabilities.

$$V_{In} - V_{In}^{map} = \sum_{j}\sum_{m} N_{Ij}^{nm} v_{jm} + \sum_{J}\sum_{m} M_{IJ}^{nm} V_{Jm}$$

$$V_{In}^{map} = \sum_{i} C_{Ii} v_{in}$$

- The numerical stability depends on the form of weighting functions. The hyperbolic tangent function with a cut-off is showing the best stability among several candidates.

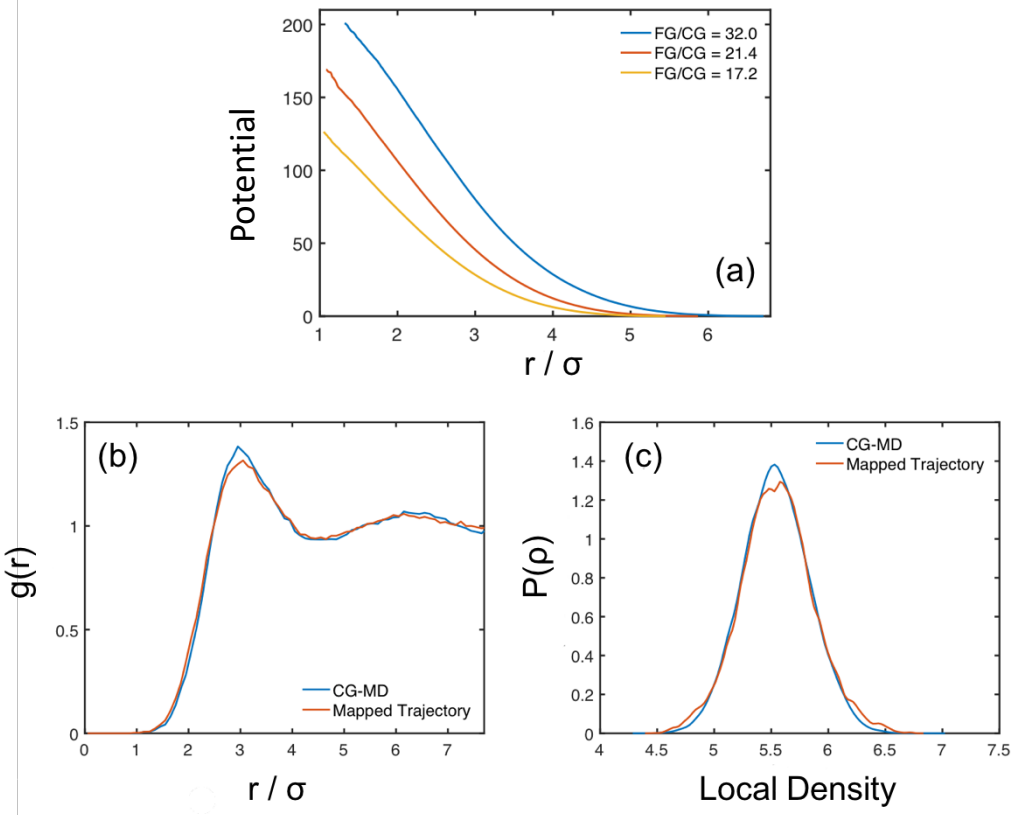


Model Parameterization - Structure

- We parameterize the conservative interactions using MS-CG (Force Matching) method
- Instantaneous CG forces are approximated by accelerations

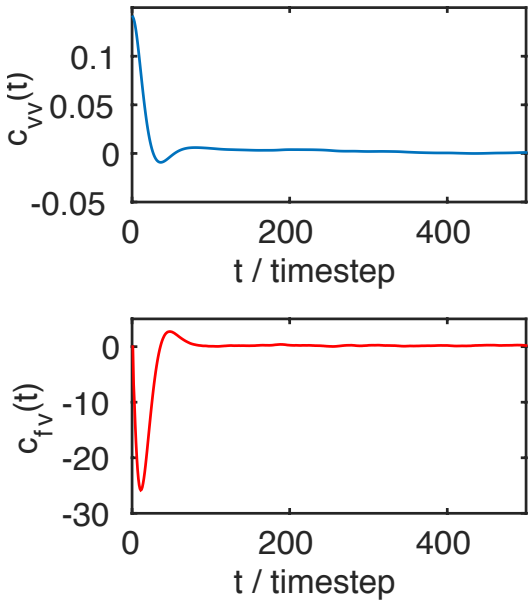
$$F_I(t) \approx M_I \frac{V_I(t+\Delta t) - V(t-\Delta t)}{2\Delta t}$$

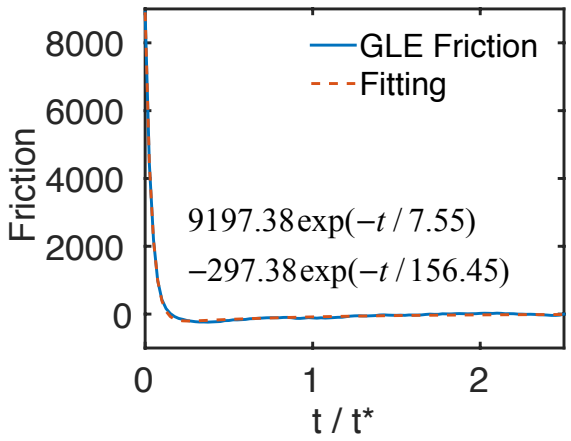
- The Linear-Decaying forces, which is well adopted in DPD models, is obtained



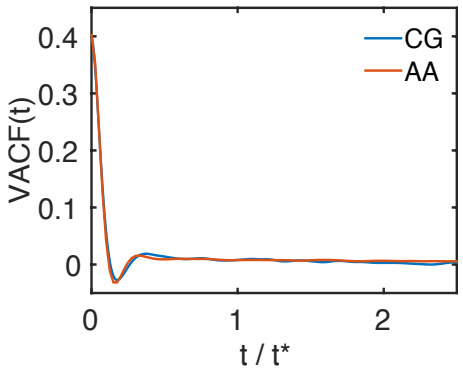
Inferred interactions preserves the mesoscale structure – RDF and local density distribution

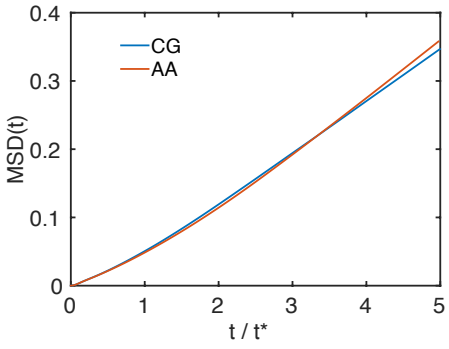
Model Parameterization - Dynamics





- A Generalized Langevin Equation was parameterized from bottom up, based on the mapped CG Dynamics
- A friction with separable time scales
- Both the short term and long term dynamics could be reproduced
- A parameterization algorithm of DPD type equations of motion is under development





Conclusion

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We proposed a **dynamic** mapping approach that extends coarse graining into supramolecular scale.

- A new type of CG mapping based on the mathematical concept of flow.
- The mapped CG beads trajectory is continuous, smooth and ergodic, keeps all of the dynamical information.
- CG beads behave like soft, deformable blobs
- The mass partition of fine grained atoms to coarse grained beads is uniform and stable
- Bottom up parameterization of both conservative and non-conservative interactions
- Powerful tool for constructing highly coarse-grained models for soft matter, like polymer and lipid bilayers, from bottom up.

Summary: For the Future

- **Ultra-Coarse-Graining (UCG): Exciting new capability, lots to do**
- **Coarse-grained Directed Simulation: Closing "top to bottom" loop**
- **Mesoscopic "non-molecular frame" coarse-graining**

- **Reactive and multi-configurational CG models (in prep)**
- **Rigorous "bottom-up" theory for "QM/CG-MM" (submitted)**
- **"On the fly" coarse-graining with quantum electronic structure**
- **Coarse-graining in quantum statistical mechanics (submitted)**
- **Coarse-graining of the quantum statistical mechanics (published)**

Thank you!