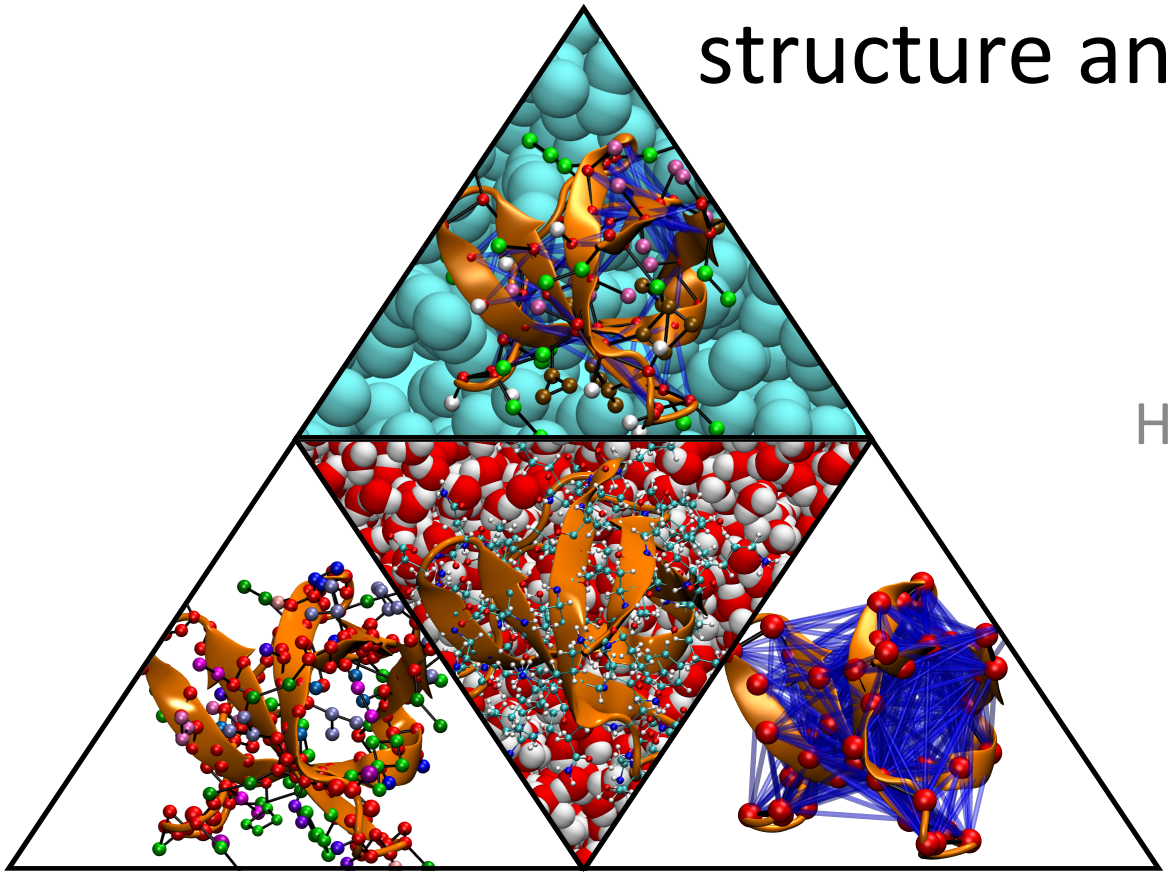
PENNSTATE

1855

Low resolution models for mesoscale structure and thermodynamics of soft materials



W. G. Noid

High Performance Computing Working Group

Interagency Modeling and Analysis Group

April 10, 2015

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National Science Foundation
WHERE DISCOVERIES BEGIN

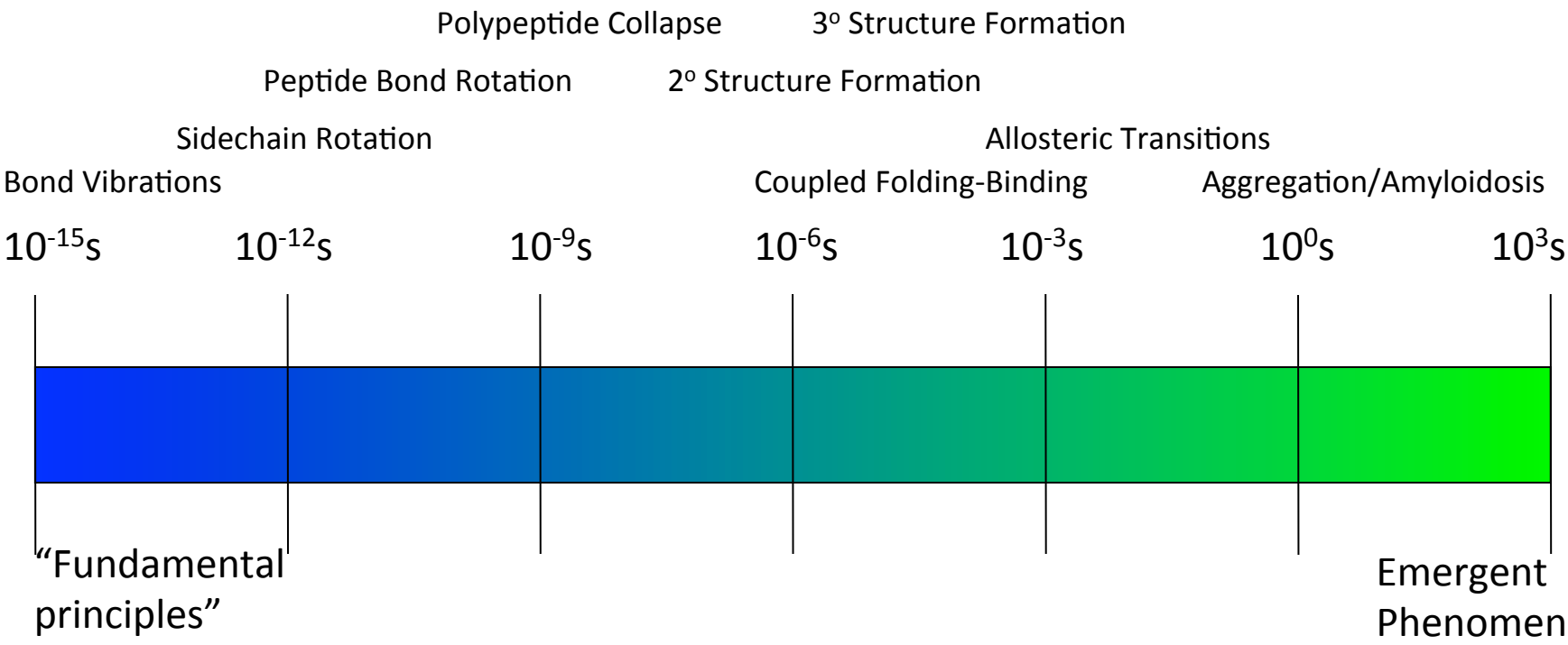
2011 Sloan Research Fellows

The Camille & Henry Dreyfus Foundation, Inc.
dedicated to the advancement of the chemical sciences

ACS PRF New Directions Award

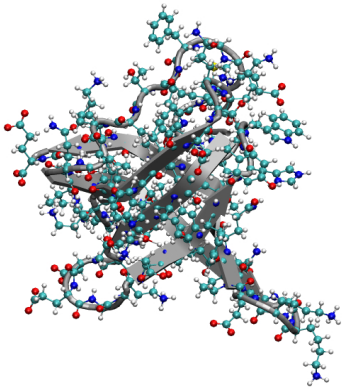
Penn State Institute for Cyberscience

Multiscale Nature of Soft Materials

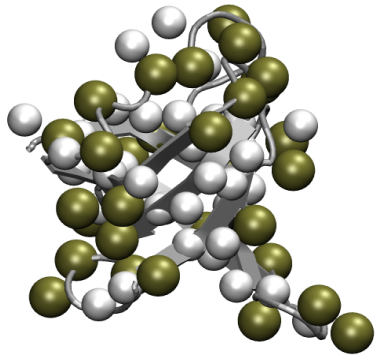


"Fundamental principles"

Emergent Phenomena



Separation in time scales between atomistic vibrations and emergent phenomena of interest motivate coarse-grained models.



Inspiration

Computer simulation of protein folding

Michael Levitt* & Arieh Warshel*

Department of Chemical Physics, Weizmann Institute of Science, Rehovoth, Israel

Nature Vol. 253 February 27 1975

"Here we tackle the [protein folding] problem differently. First, we simplify the representation of a protein by averaging over fine details. This is done both to make the calculations much more efficient and also to avoid having to distinguish between many conformations that differ only in these finer details. Second, we simulate the folding of this simple structure …"

"Our method … is based on two assumptions: (1) that much of the protein's fine structure can be eliminated by averaging, and (2) that the overall chain folding can be obtained by considering only the most effective variables (those that vary most slowly yet cause the greatest changes in conformation)."

Nature Vol. 267 16 June 1977 585

articles

Dynamics of folded proteins

J. Andrew McCammon, Bruce R. Gelin & Martin Karplus

A Warning

On the formation of protein tertiary structure on a computer

(protein folding/computer simulation/protein evolution/role of glycines)

ARNOLD T. HAGLER* AND BARRY HONIG†

"[Previous studies] have used extremely simplified representations of PTI, which, upon energy minimization, fold into globular structures that in some way resemble the native protein. … The impression generated by these various simulations is that major progress has been made … i.e., the folding problem may be far more tractable than generally been considered. …

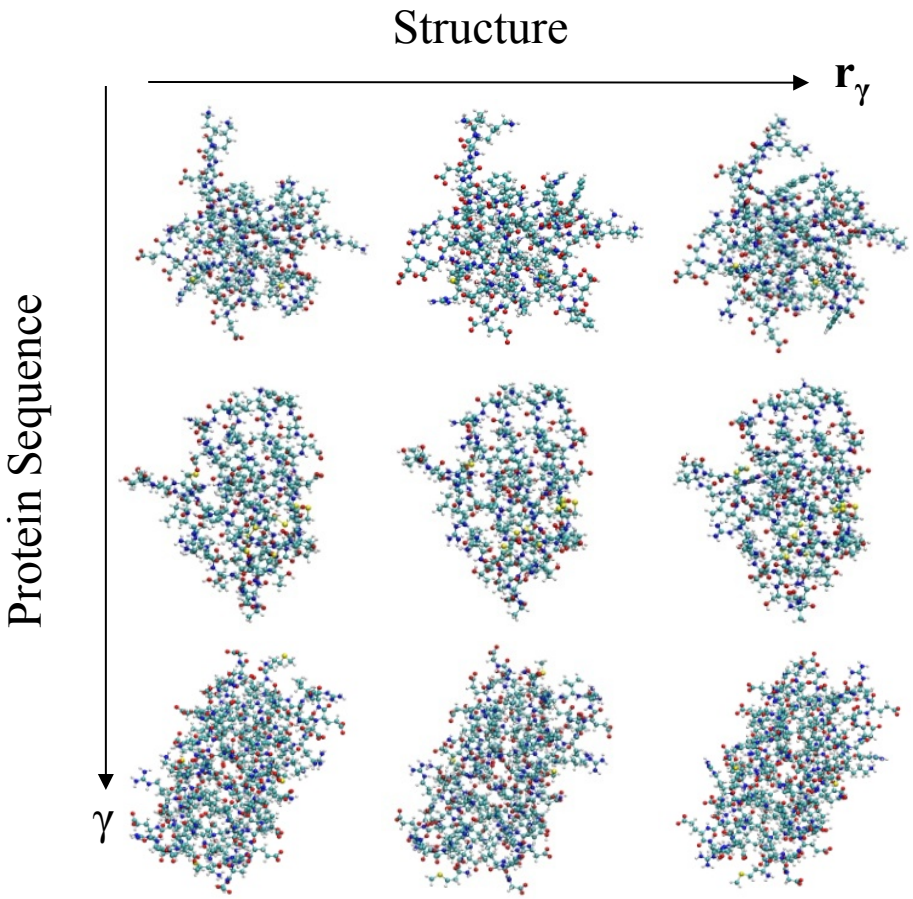
One of the major conclusions of this study is that the criteria that have been used to evaluate the success of most folding simulations has been overly permissive. … First, we show that it is possible to obtain a computed structure of PTI that satisfies all of the criteria that have been used previously to define successful folding simulations, from a sequence that would certainly not yield PTI-like conformation … Many of the positive results that have been reported are due entirely to [built-in features of the models] and may thus be regarded as artifacts.

A careful examination reveals that despite superficial similarities to the native protein, all computed structures have fundamental flaws … they fail to reproduce … important features characteristic of the tertiary structure … [and] appear sterically inaccessible from the native conformation. … "

Proc. Natl. Acad. Sci. USA
Vol. 75, No. 2, pp. 554–558, February 1978

The derailment at Gare Montparnasse, Paris, 1895.
http://phys.columbia.edu/~tutorial/

A Very Good Question



Tanaka and Scheraga (1976):

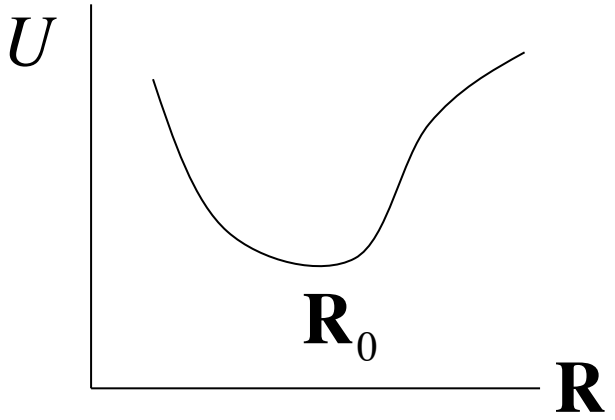
What interactions generated the PDB structures?

(At a Coarse-grained level.)

Knowledge-based approaches

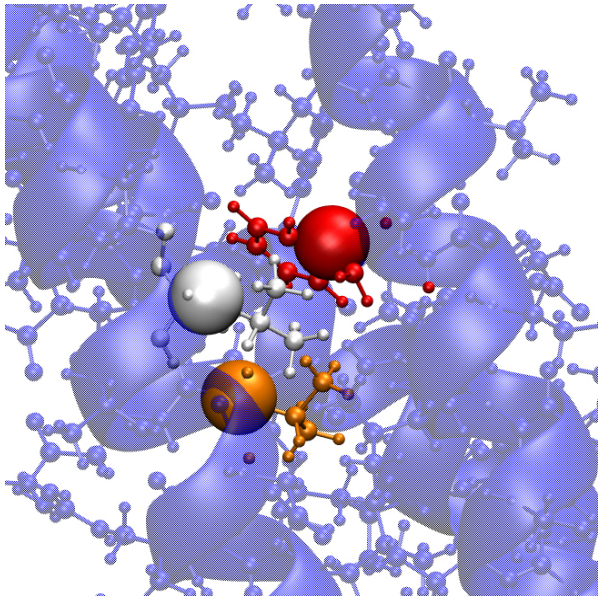
Foldability Criterion: given $\mathbf{R}_0$ for each protein

$$U(\mathbf{R}_0) = \min U(\mathbf{R})$$



Crippen, Wolynes, Scheraga, Shakhnovich, Banavar, Elber, …

Boltzmann hypothesis:



Reference State

$$U(\mathbf{R}) = U_0(\mathbf{R}) + \sum_{\zeta} U_\zeta(r_\zeta)$$

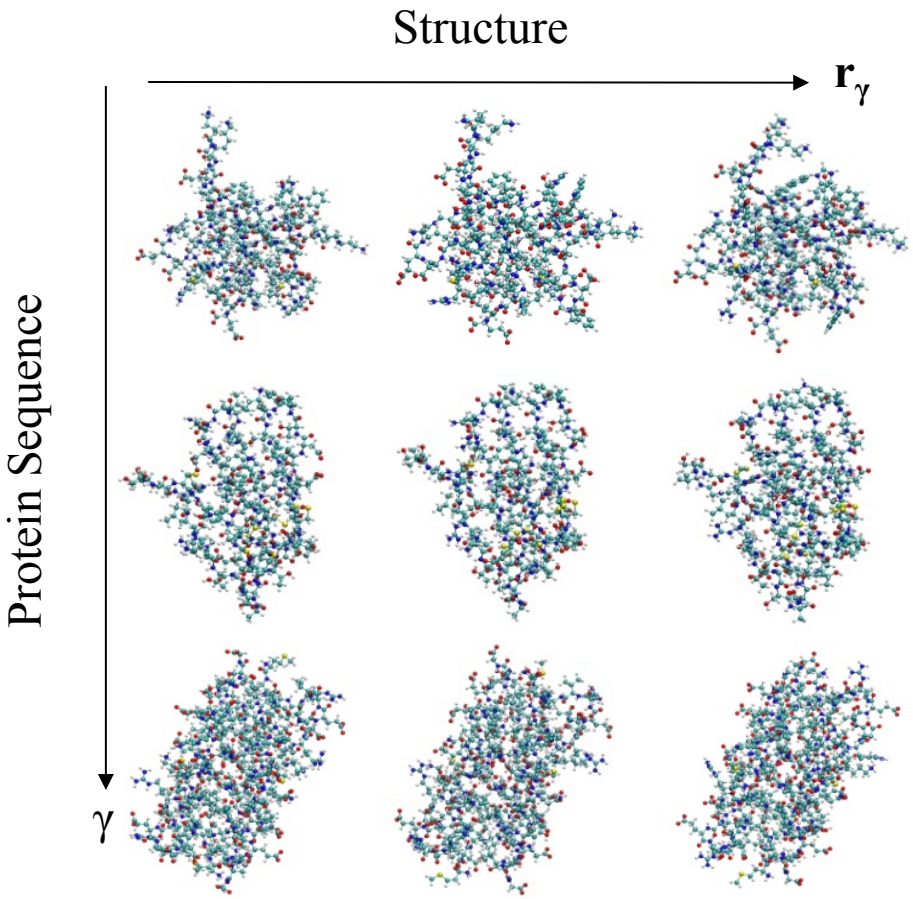
Interaction

$$p(\mathbf{R}) = p_0(\mathbf{R}) \prod_{\zeta} p_\zeta(r_\zeta)$$

$$\exp[-U_\zeta(r) / kT] = p_\zeta(r) / p_{\zeta 0}(r)$$

Scheraga, Jernigan, Sippl, Baker, Skolnick, Dill, Thirumalai, Straub …

Motivating Questions



What interactions generated the PDB structures? (Tanaka and Scheraga 1976)

1. Given a collection of structures, what was the underlying potential?

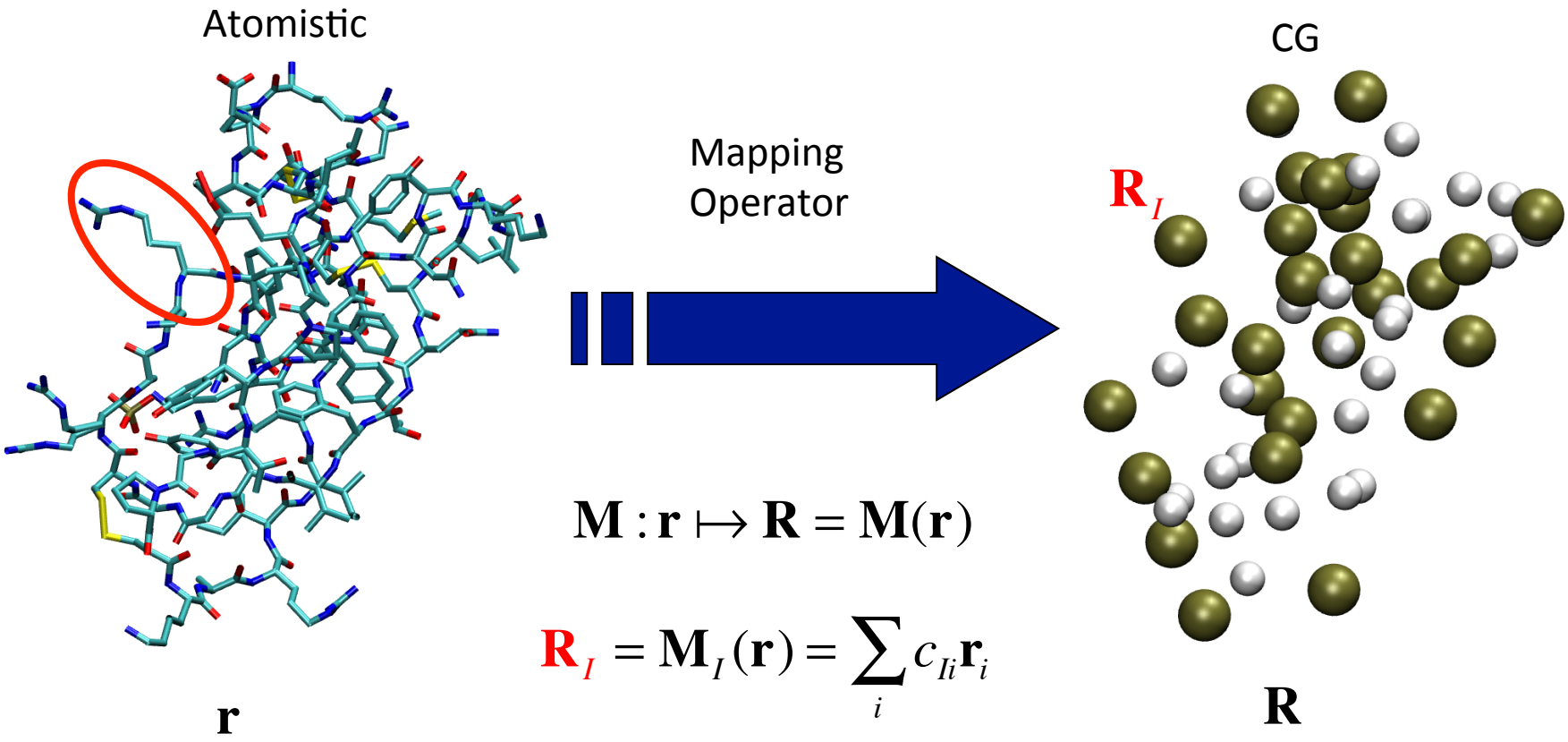
2. How can one determine a transferable Coarse-Grained (CG) potential that accurately models structure for multiple proteins?

Outline

The derailment at Gare Montparnasse, Paris, 1895.
http://phys.columbia.edu/~tutorial/

- Motivating questions
- The many-body Potential of Mean Force:
  The exact potential for structure-based coarse-graining
- The generalized-Yvon-Born-Green Theory:
  A rigorous variational approach
  - Exact results
  - Accurate approximations
  - Less accurate approximations
- The many-body Potential of Mean Force:
  - Thermodynamic properties
  - Information loss
- Variational approach for transferable models
- Conclusions

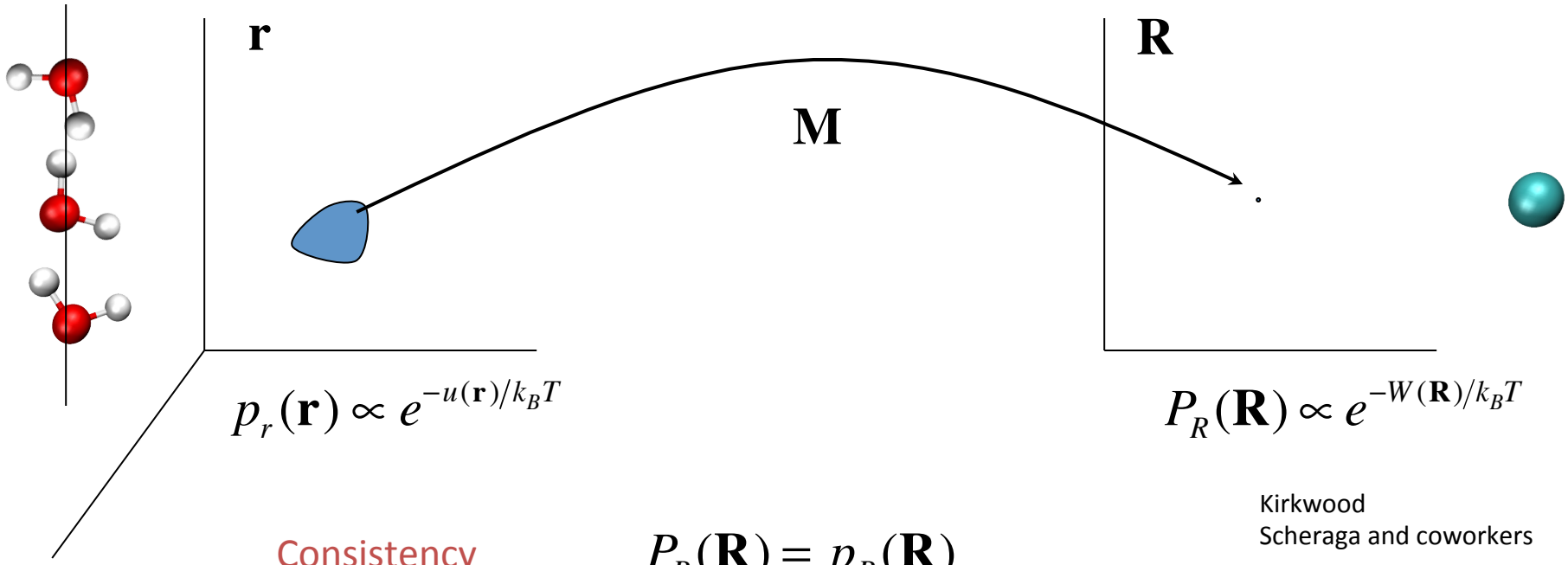
Coarse-grained (CG) Mapping



The mapping operator transforms an atomistic configuration onto a CG configuration by defining the coordinates of each site as a linear combination of the coordinates defining each site.

Noid, Chu, …, Voth, Andersen
J Chem Phys (2008)

The PMF: Structurally Consistent CG Models



Consistency $P_R(\mathbf{R}) = p_R(\mathbf{R})$

$$e^{-W(\mathbf{R})/k_BT} \propto \int d\mathbf{r}\; p_r(\mathbf{r})\,\delta\big(\mathbf{M}(\mathbf{r}) - \mathbf{R}\big)$$

Kirkwood
Scheraga and coworkers

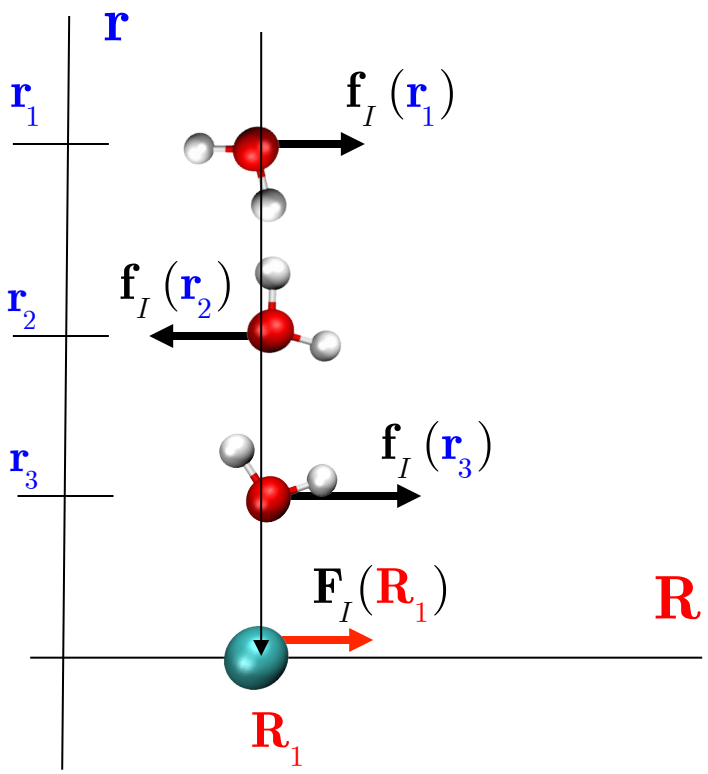
Noid, Chu, …, Voth, Andersen
J Chem Phys (2008)

Noid *J Chem Phys* (2013)

For a consistent CG model reproducing the distribution of structures generated by the atomistic model, the appropriate CG potential is a many-body potential of mean force (PMF).

Mean Force Field

$$\mathbf{F}_I(\mathbf{R}) = \frac{-\partial W(\mathbf{R})}{\partial \mathbf{R}_I} = \left\langle \mathbf{f}_I(\mathbf{r}) \right\rangle_{\mathbf{R}}$$



Atomistic FF:

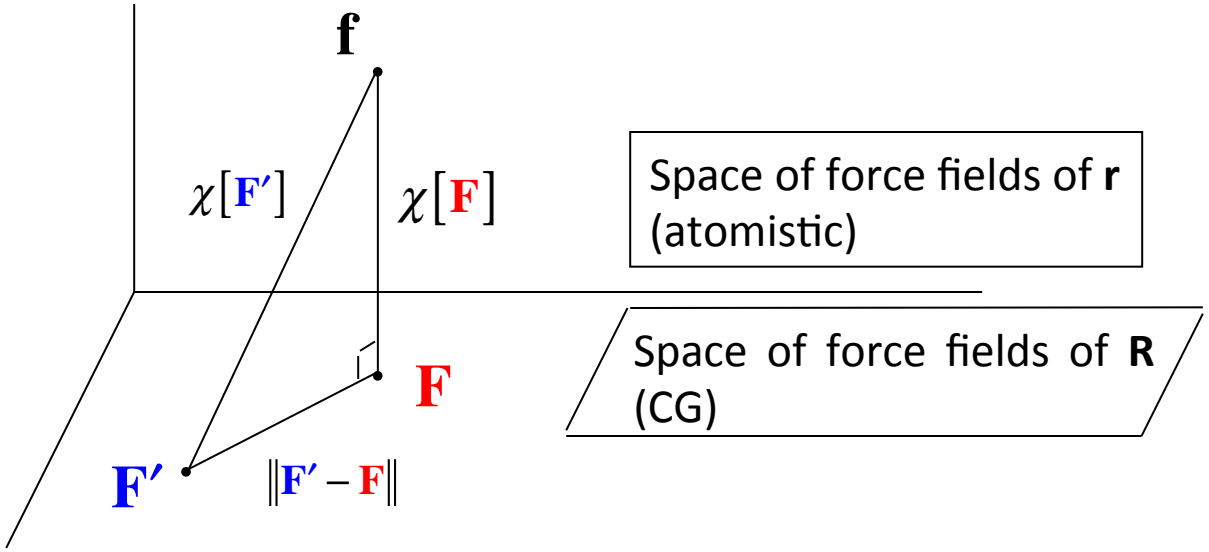
$$\mathbf{f}_I(\mathbf{r}) = \sum_{i \in I} \mathbf{f}_i(\mathbf{r})$$

$$\mathbf{R}_1 = \mathbf{M}(\mathbf{r}_1) = \mathbf{M}(\mathbf{r}_2) = \cdots$$

In a structurally consistent model, the CG force field is the conditioned average of the atomistic force field. The mean force field is sufficient for a consistent CG model.

Variational Principle for Multiscale Coarse-graining

$$\chi^2[\mathbf{F}'] = \frac{1}{3N}\left\langle \sum_{I=1}^{N} \left| \mathbf{F}'_I(\mathbf{M}(\mathbf{r})) - \mathbf{f}_I(\mathbf{r}) \right|^2 \right\rangle$$
$$= \chi^2[\mathbf{F}] + \|\mathbf{F}' - \mathbf{F}\|^2$$



$$\mathbf{F} = -\nabla W \quad \text{MF}$$
$$\chi[\mathbf{F}] = \|\mathbf{F} - \mathbf{f}\|$$
$$\chi[\mathbf{F}'] = \|\mathbf{F}' - \mathbf{f}\|$$

Izvekov and Voth.
J Phys Chem B (2005)
J Chem Phys (2005)

Noid, Chu, Ayton, Voth
J Phys Chem B (2007)
Noid, Chu, …, Voth, Andersen
J Chem Phys (2008)

See also
Ercolessi and Adams 1994
Chorin 2003, 2006

The Multiscale Coarse-graining (MS-CG) variational principle determines the many-body PMF through a geometric optimization problem in the space of CG force fields.

Molecular Mechanics Basis Set

Approx. CG Potential

$$U(\mathbf{R}) = \sum_{I-J>4}^{pairs} U_{IJ}^{nb}(R_{IJ}) + \sum_{i}^{bonds} U_i^b(d_i) + \sum_{i}^{angles} U_i^\theta(\theta_i) + \sum_{i}^{dihedrals} U_i^\psi(\psi_i) + \cdots$$

Approx. CG Force field

$$\mathbf{F}_I(\mathbf{R}) = \sum_{I-J>4}^{pairs} F_{IJ}^{nb}(R_{IJ}) \frac{\partial R_{IJ}}{\partial \mathbf{R}_I} + \sum_{i}^{bonds} F_i^b(d_i) \frac{\partial d_i}{\partial \mathbf{R}_I} + \sum_{i}^{angles} F_i^\theta(\theta_i) \frac{\partial \theta_i}{\partial \mathbf{R}_I} + \cdots$$

Basis expansion

$$\mathbf{F} = \sum_{\zeta} \int dz \, F_\zeta(z) \mathbf{G}_\zeta(z)$$

Force function $F_\zeta(z) = -dU_\zeta(z)/dz$

Basis vector $\mathbf{G}_\zeta(z) = \left(\frac{\partial \psi_\zeta(\mathbf{R})}{\partial \mathbf{R}_I} \right) \delta\left(\psi_\zeta(\mathbf{R}) - z \right)$

Interactions ζ

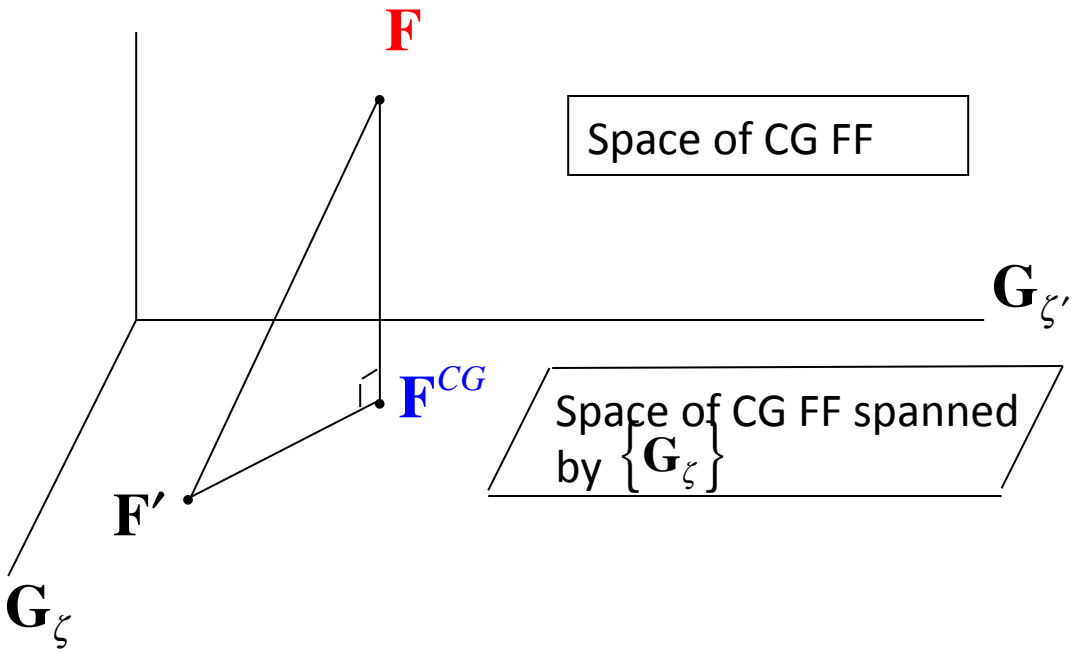
Noid, …, Andersen, Voth
J Chem Phys (2008)

An approximate CG potential determines a set of force field basis vectors

Linear Least Squares Problem

$$\mathbf{F}^{CG}(\mathbf{R}) = \sum_{\zeta} \int dz\, F_{\zeta}(z)\, \mathbf{G}_{\zeta}(\mathbf{R}; z)$$

$$\chi^2[F] = \frac{1}{3N} \left\langle \sum_{I=1}^{N} \left| \sum_{\zeta} \int dz\, F_{\zeta}(z)\, \mathbf{G}_{I;\zeta}\left(\mathbf{M}(\mathbf{r}); z\right) - \mathbf{f}_I(\mathbf{r}) \right|^2 \right\rangle$$



$\mathbf{F}^{CG}(\mathbf{R})$ CG FF

F_{ζ} Force functions

$\mathbf{G}_{\zeta}(\mathbf{R})$ FF basis fcns

The MS-CG variational principle determines F_{ζ} by projecting the PMF onto the space of CG force fields spanned by the given basis.

Geometric Projection

Basis expansion:

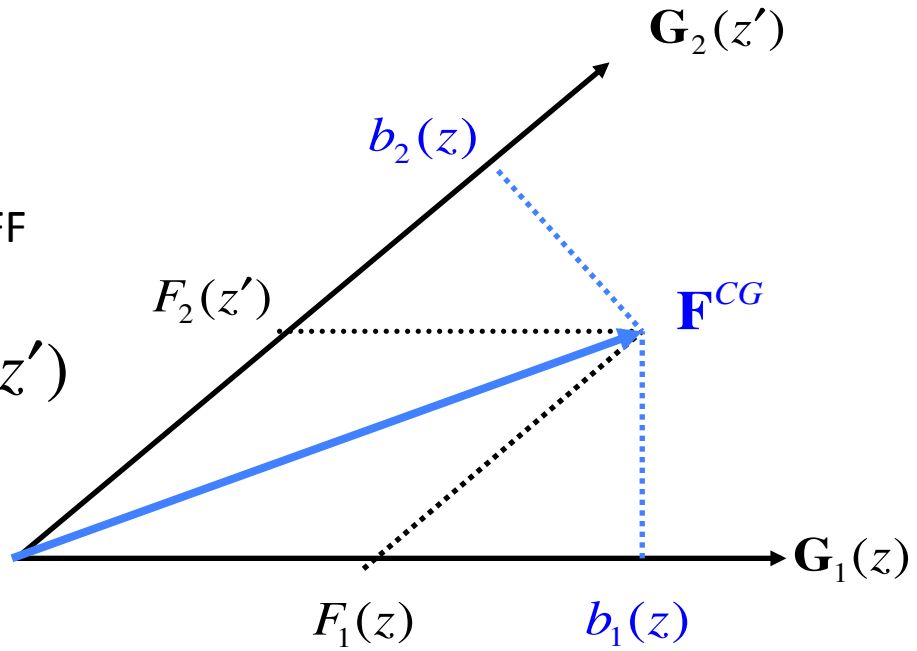
$$\mathbf{F}^{CG} = \sum_{\zeta} \int dz\, F_{\zeta}(z) \mathbf{G}_{\zeta}(z)$$

Projections:

$$b_{\zeta}(z) = \mathbf{G}_{\zeta}(z) \cdot \mathbf{F} \qquad \text{MF}$$

$$= \mathbf{G}_{\zeta}(z) \cdot \mathbf{F}^{CG} \qquad \text{Approx FF}$$

$$= \sum_{\zeta'} \int dz' G_{\zeta\zeta'}(z,z') F_{\zeta'}(z')$$



Gram Matrix:

$$G_{\zeta\zeta'}(z,z') = \mathbf{G}_{\zeta}(z) \cdot \mathbf{G}_{\zeta'}(z')$$

$$= \left\langle \sum_{I} \mathbf{G}_{I;\zeta}(\mathbf{M}(\mathbf{r});z) \cdot \mathbf{G}_{I;\zeta'}(\mathbf{M}(\mathbf{r});z') \right\rangle$$

Noid, …, Andersen, Voth. *J Chem Phys* (2008)
Mullinax and Noid. *J Phys Chem C* (2010)
Mullinax and Noid *J Chem Phys* (2010)

The PMF is approximated by projecting the MF onto each basis vector, while treating the metric tensor resulting from many-body correlations.

Generalized Yvon-Born-Green Equation

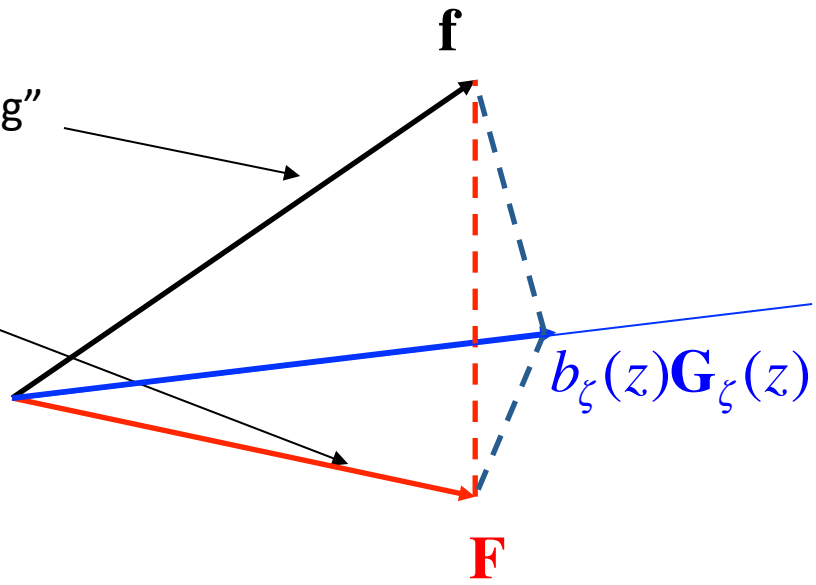
Integral Eq $$b_\zeta(z) = \mathbf{G}_\zeta(z)\cdot\mathbf{F} = \mathbf{G}_\zeta(z)\cdot\mathbf{F}^{CG} = \sum_{\zeta'}\int dz' G_{\zeta\zeta'}(z,z')F_{\zeta'}(z')$$

$$b_\zeta(z) = \mathbf{G}_\zeta(z)\cdot\mathbf{f}$$ MS-CG "Force-Matching"

$$= \mathbf{G}_\zeta(z)\cdot\mathbf{F}$$ MF

$$= \mathbf{G}_\zeta(z)\cdot\nabla\left(-k_BT\ln p_R(\mathbf{R})\right)$$

$$= k_BT\, d\overline{g}_\zeta(z)/dz$$



$$k_BT\, d\overline{g}_\zeta(z)/dz = \sum_{\zeta'}\int dz' G_{\zeta\zeta'}(z,z')F_{\zeta'}(z')$$

Mullinax and Noid.
Phys Rev Lett **103** 198104 (2009)
J Phys Chem C **114** 5661 (2010)

The generalized-YBG Equation determines the MS-CG potentials directly from structures!

Relative Entropy

$\Phi(\mathbf{R})$ Information content in configuration **R** for distinguishing atomistic and CG distributions

$$\Phi(\mathbf{R}|U) = \ln\left[\frac{p_R(\mathbf{R})}{P_R(\mathbf{R}|U)}\right]$$

Atomistic

CG

$$0 \quad \text{if} \quad p_R(\mathbf{R}) = P_R(\mathbf{R}|U)$$

$$\pm\infty \quad \text{if} \quad p_R(\mathbf{R})/P_R(\mathbf{R}|U) \to \infty \text{ or } 0$$

Relative Entropy:
(Kullback-Leibler divergence)

$$S_{\mathrm{Rel}}[U] = \int d\mathbf{R}\; p_R(\mathbf{R})\Phi(\mathbf{R}|U) \geq 0$$

$$\delta S_{\mathrm{Rel}}[U]/\delta U_\zeta(z) = \left(p_\zeta(z) - P_\zeta(z|U)\right)/k_BT$$

Considering variations w.r.t. CG potential $U_\zeta(z)$

1. The Relative Entropy is minimized when the conjugate distribution is reproduced
2. Minimizing the Relative entropy via Newton's method leads to IMC equations

References: Kullback & Leibler *Ann Math Stat* (**1951**); Shell *JCP* (**2008,2010**); Murtola et al. *JCP* (**2009**)

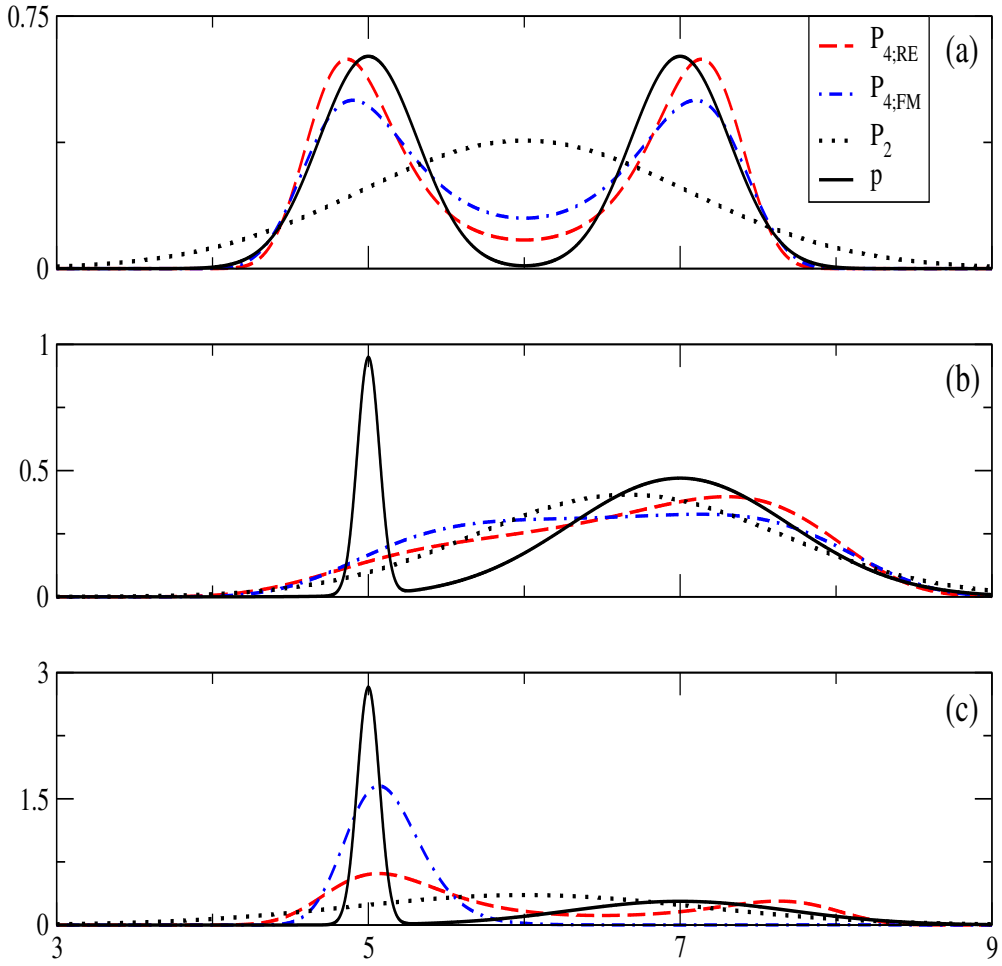
Relation to the Relative Entropy

Inverse Monte Carlo/Molecular RG (Relative Entropy) functional:

$$S_{\mathrm{Rel}}[U] = k_B \int d\mathbf{R}\; p_R(\mathbf{R})\Phi(\mathbf{R}|U)$$

Multiscale Coarse-graining "force-matching" functional

$$\chi^2[U] = \frac{1}{3N}\left\langle \sum_{I=1}^{N} \left|\mathbf{F}'_I(\mathbf{M}(\mathbf{r})) - \mathbf{f}_I(\mathbf{r})\right|^2 \right\rangle$$
$$= \chi^2\left[U^0\right]$$
$$+ \frac{(k_B T)^2}{3N} \int d\mathbf{R}\; p_R(\mathbf{R}) \left|\nabla\Phi(\mathbf{R}|U)\right|^2$$



Both the MS-CG/g-YBG "force-matching" and iterative structure-based methods can be derived from the Kullback-Leibler information function.

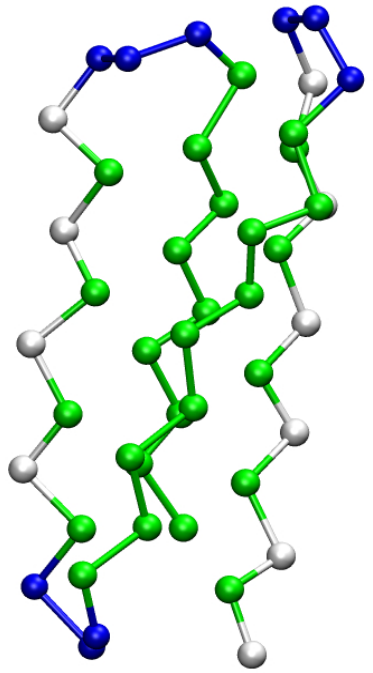
Rudzinski and Noid *JCP* **2011**
Noid *Methods Mol Biol* **2013**

Honeycutt-Thirumalai (HT) Model

Green: hydrophobic (B)

White: hydrophilic (L)

Blue: neutral (N)

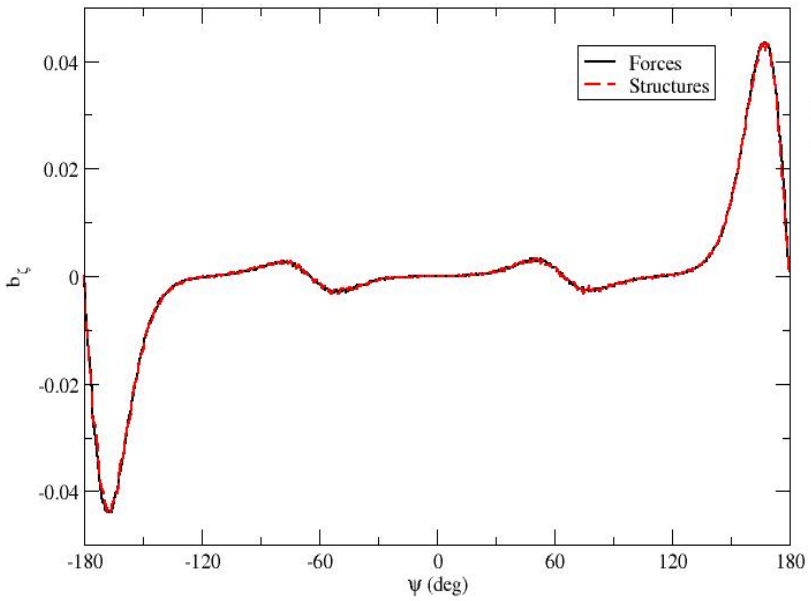


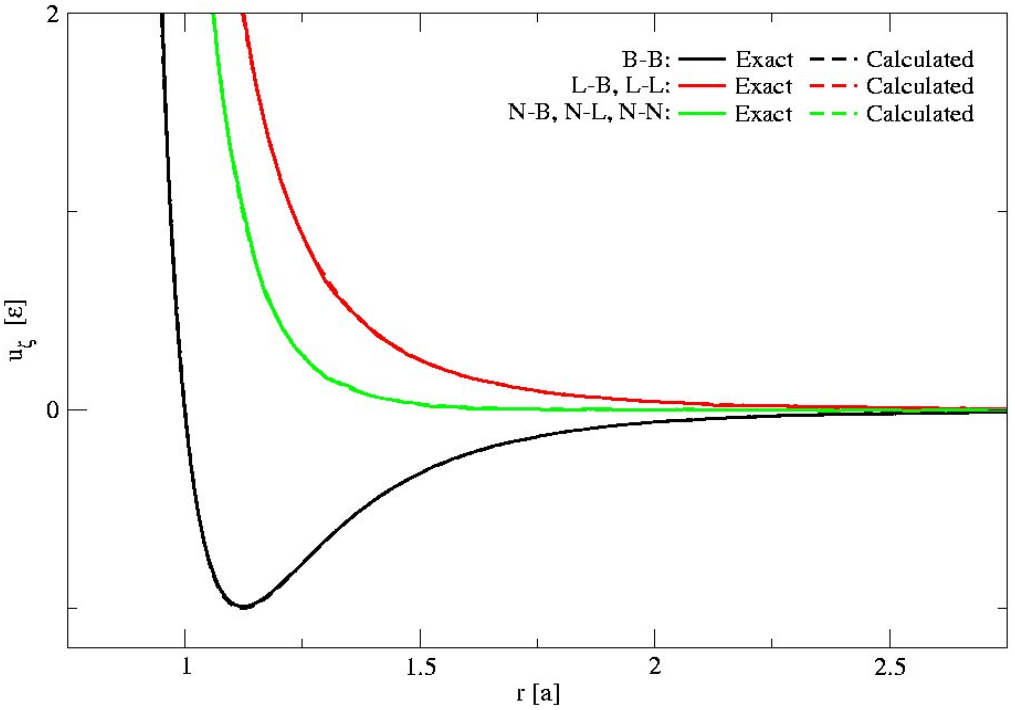
$$U(\mathbf{R}) = \sum_{I-J>4}^{pairs} U_{IJ}^{nb}(R_{IJ}) + \sum_{i}^{bonds} U_i^b(d_i) + \sum_{i}^{angles} U_i^\theta(\theta_i) + \sum_{i}^{dihedrals} U_i^\psi(\psi_i)$$

Honeycutt and Thirumalai *Biopolymers* (1992) **32**, 695

HT Results 1

$$b_\zeta(z) = k_B T \, d\overline{g}_\zeta(z)/dz$$

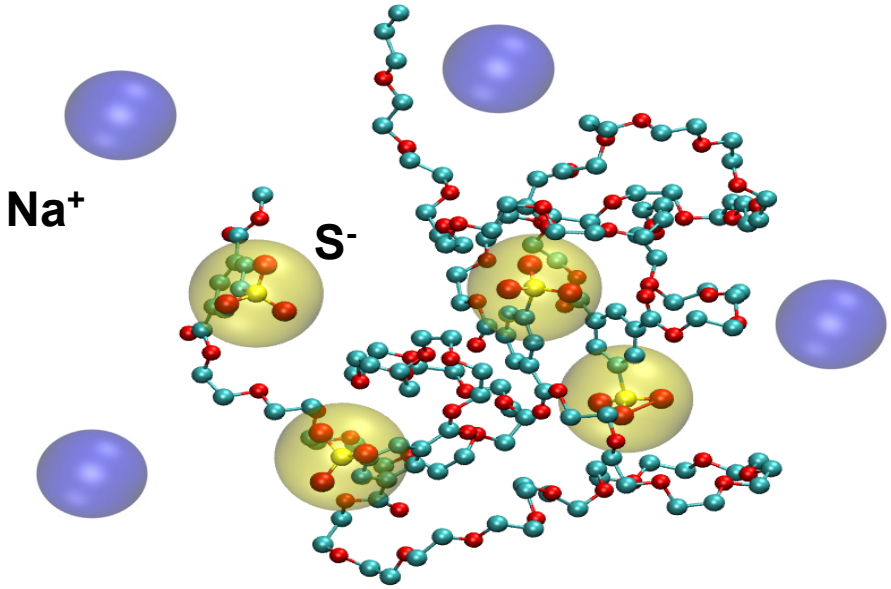


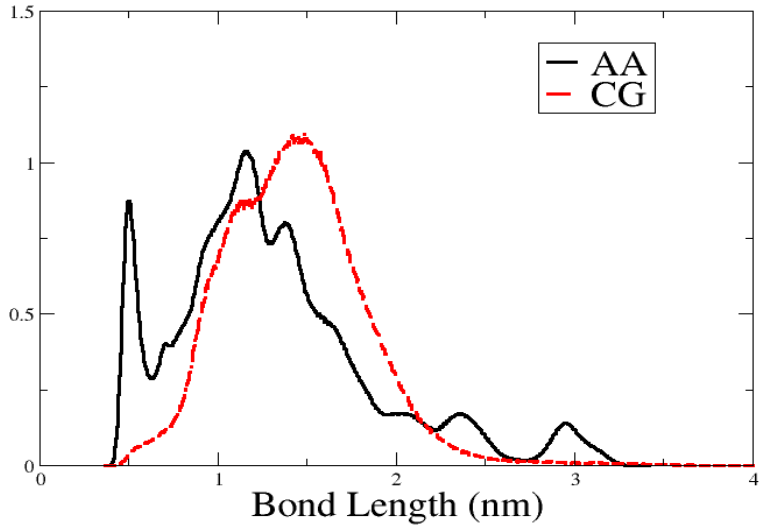


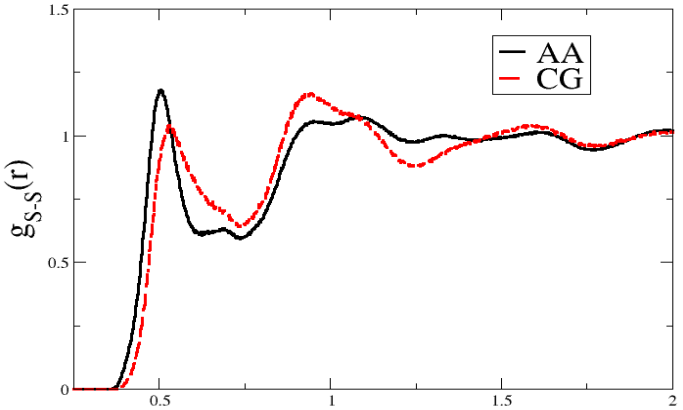
Mullinax and Noid
Phys Rev Lett **131** 198104 (2009)

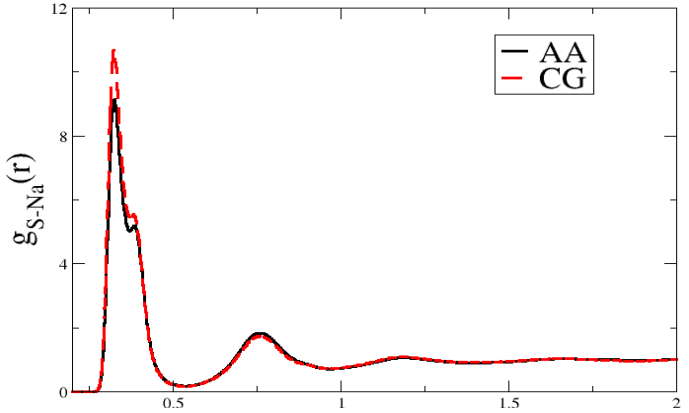
First generalization of the YBG theory for proteins with many-body, e.g., torsional and angle, interactions.

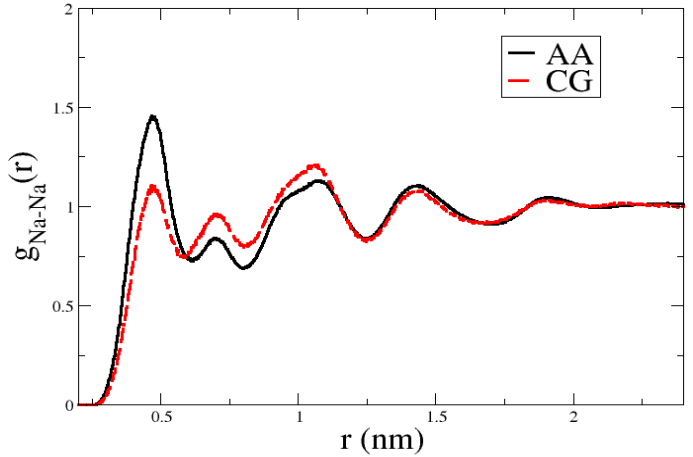
Ionomer model





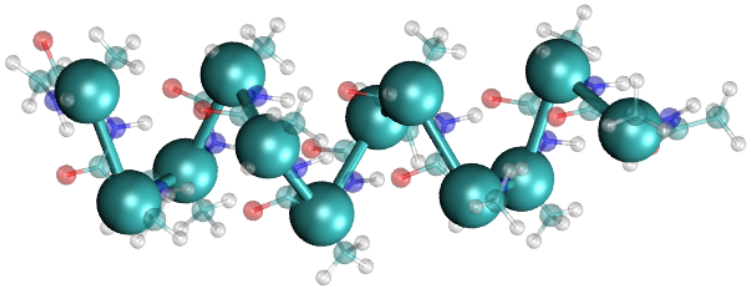


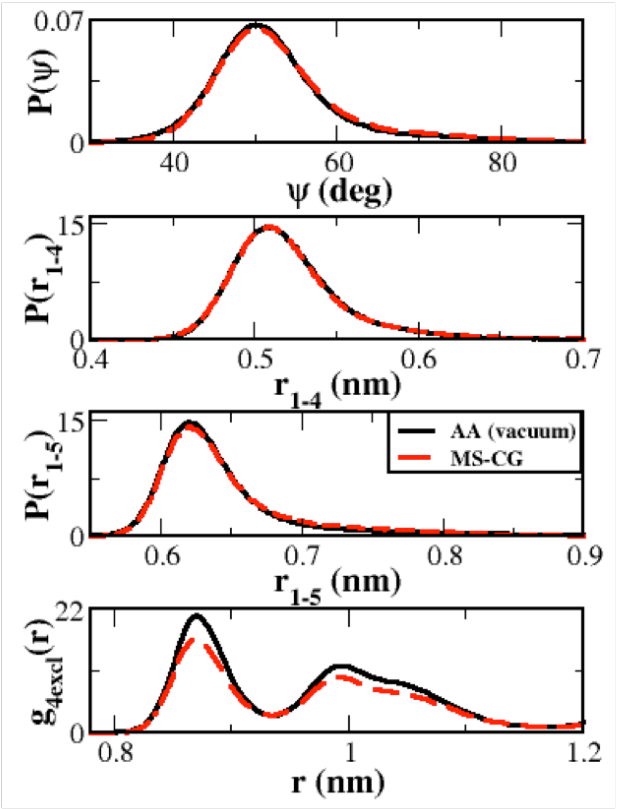


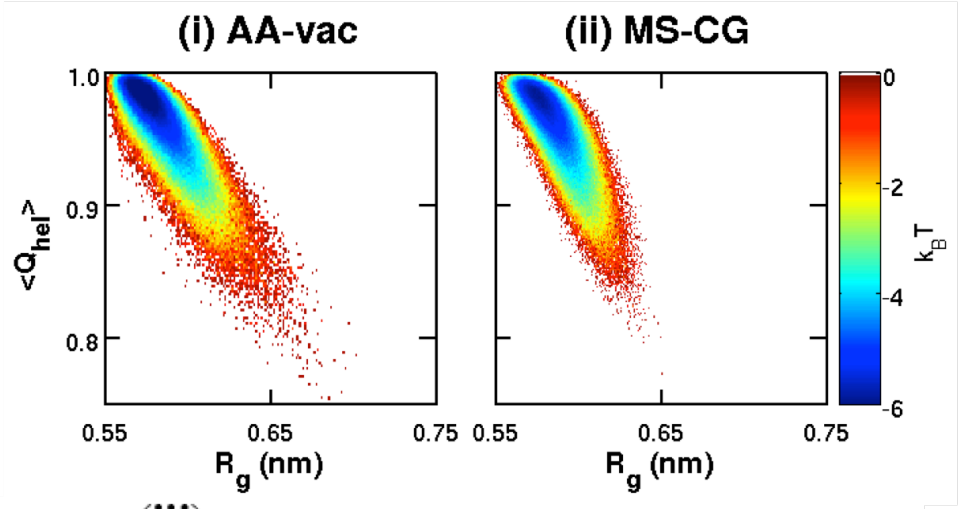


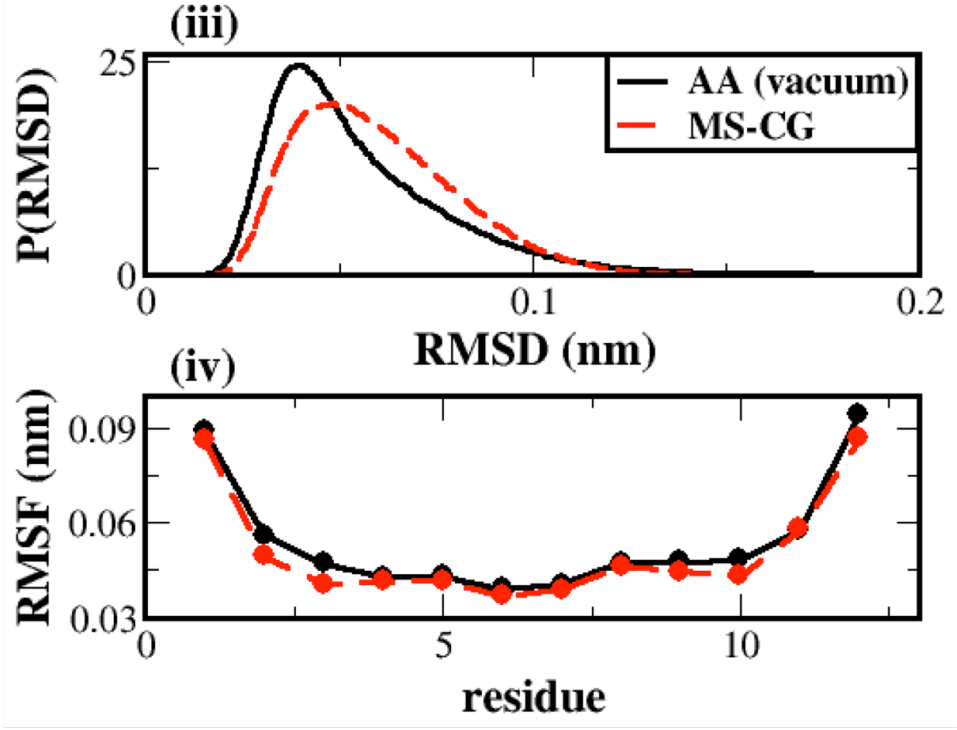
Lu, Rudzinski, Noid, Milner, Maranas. *Soft Matter* **2014**

Helical peptides



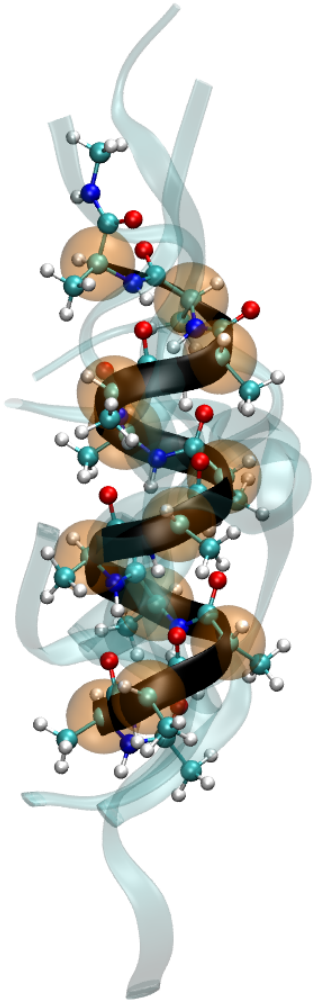






Rudzinski and Noid JCTC **2015**

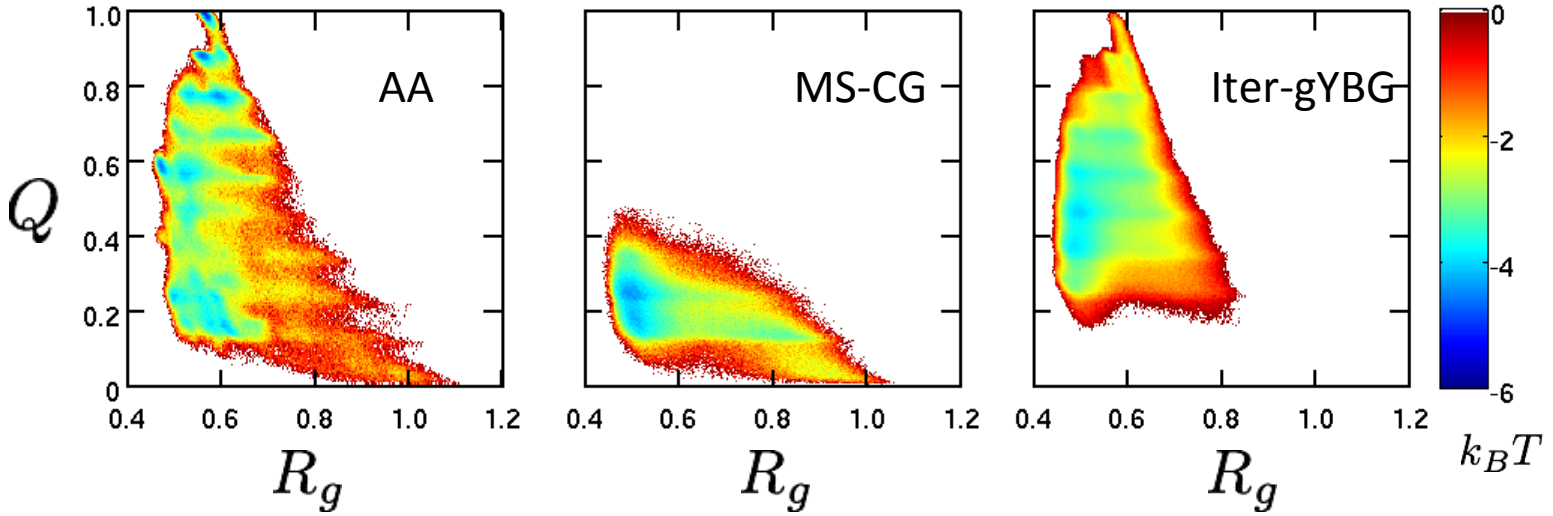
Realistic/Disordered Peptides



$$b_\zeta(z|\mathbf{F}) \equiv \mathbf{G}_\zeta(z)\cdot\mathbf{F}$$ Projection of MF (Atomistic structure)

$$= \sum_{\zeta'}\int dz' G_{\zeta\zeta'}(z,z'|\mathbf{F})F_{\zeta'}(z')$$ Projection of approx F

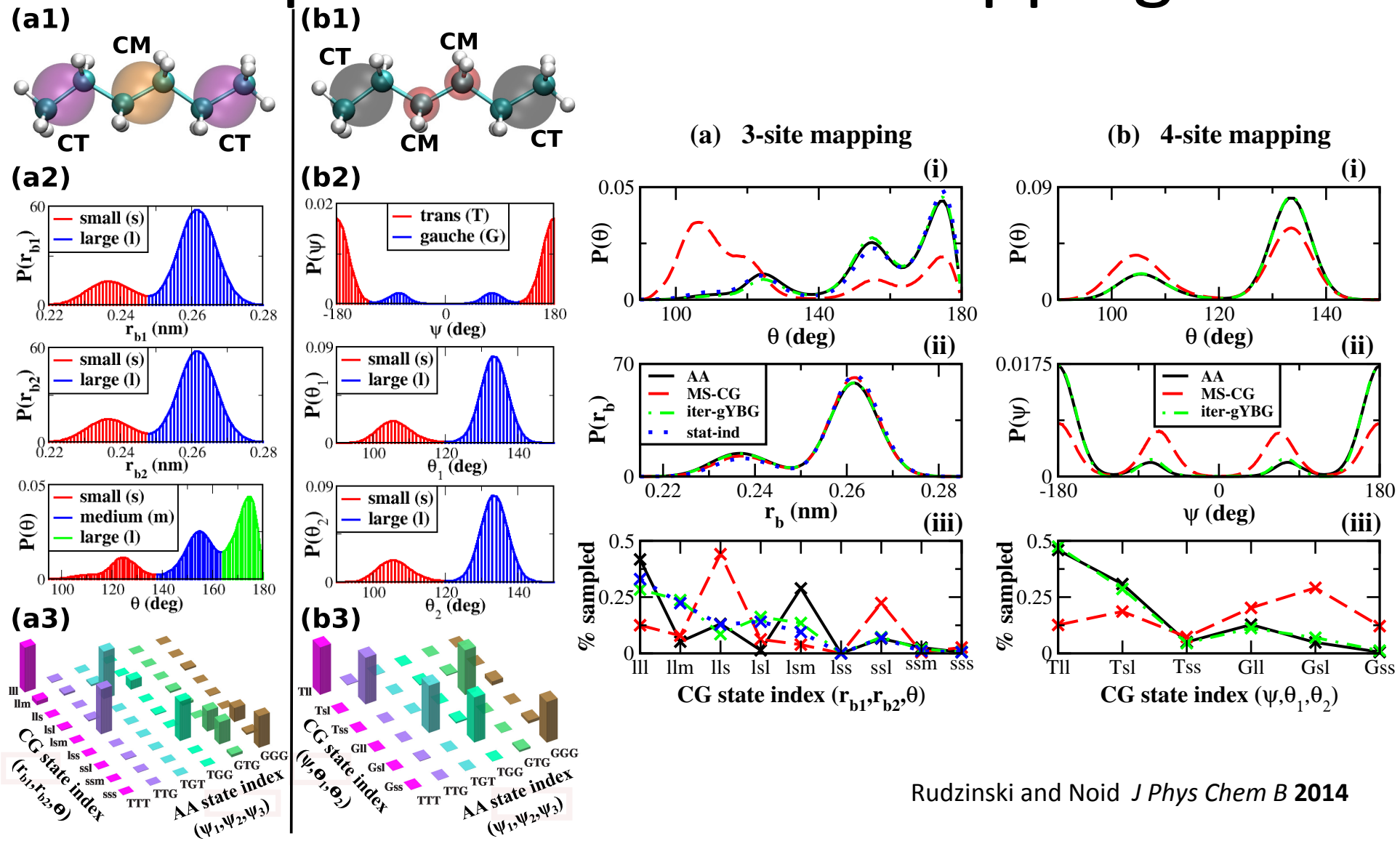
$$= \sum_{\zeta'}\int dz' G_{\zeta\zeta'}(z,z'|\mathbf{F})F_{\zeta'}(z')$$ Self-consistent F



A self-consistent g-YBG approach accurately models the free energy surface of a disordered peptide.

Cho and Chu JCP **2009**
Dama, Lu, and Voth JCP **2013**
Rudzinski and WGN JPCB **2014**, JCTC **2015**

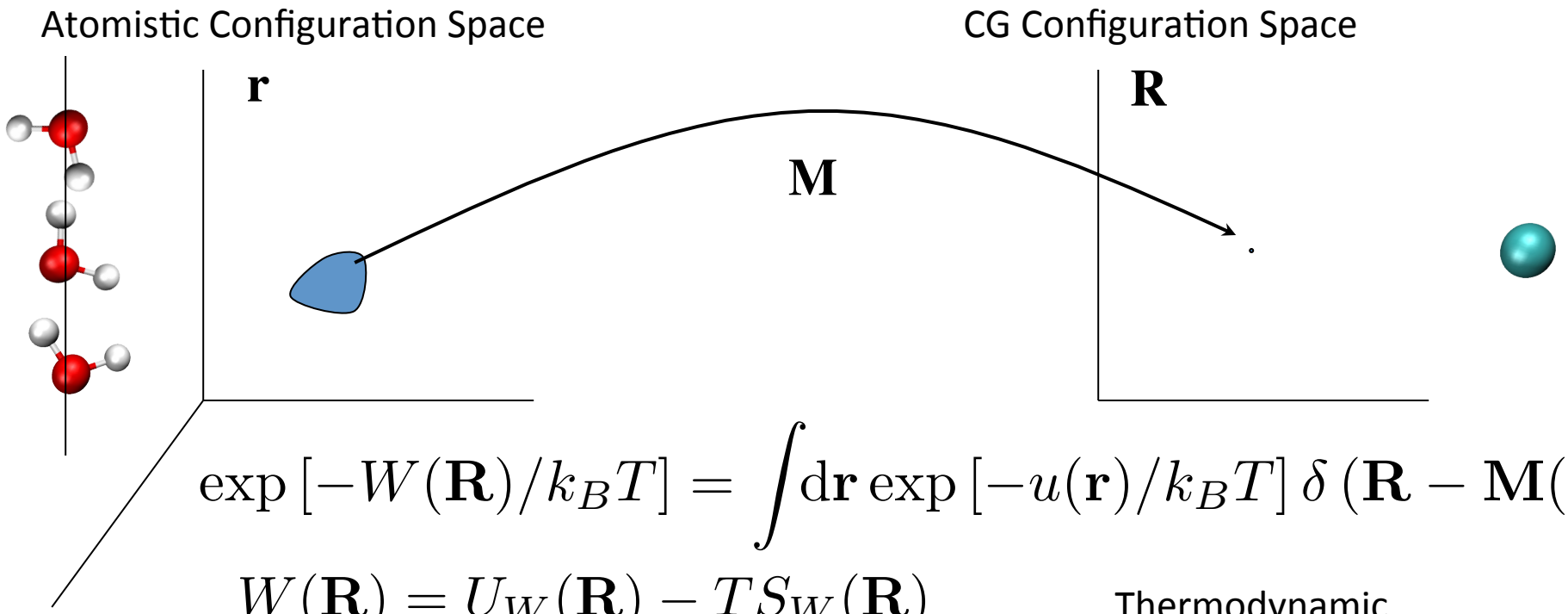
Implications for CG mappings



Rudzinski and Noid *J Phys Chem B* **2014**

Bad maps introduce complex cross-correlations and forbidden conformations, such that 1D distributions are reproduced at the expense of distorting cross-correlations.

The PMF: Thermodynamic Content



$$\exp\left[-W(\mathbf{R})/k_BT\right] = \int \mathrm{d}\mathbf{r} \exp\left[-u(\mathbf{r})/k_BT\right] \delta\left(\mathbf{R} - \mathbf{M}(\mathbf{r})\right)$$

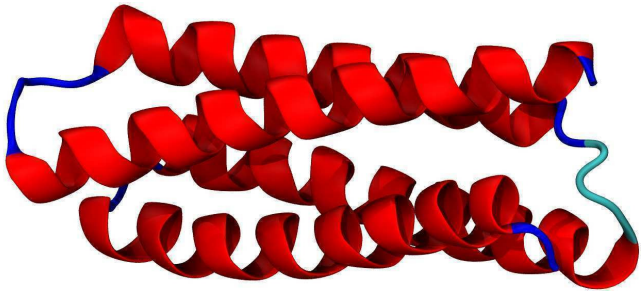
$$W(\mathbf{R}) = U_W(\mathbf{R}) - TS_W(\mathbf{R})$$ Thermodynamic

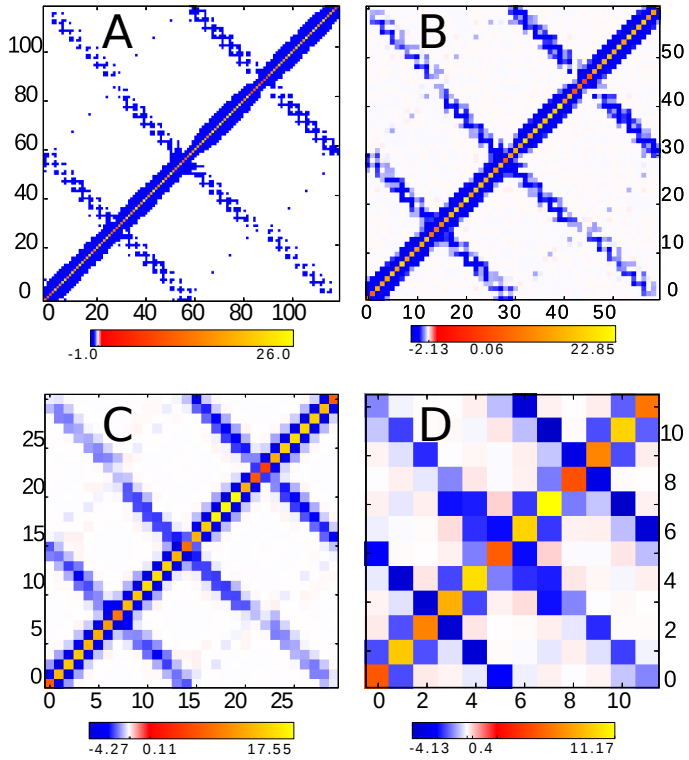
$$U_W(\mathbf{R}) = \langle u(\mathbf{r}) \rangle_{\mathbf{R}}$$ Energy

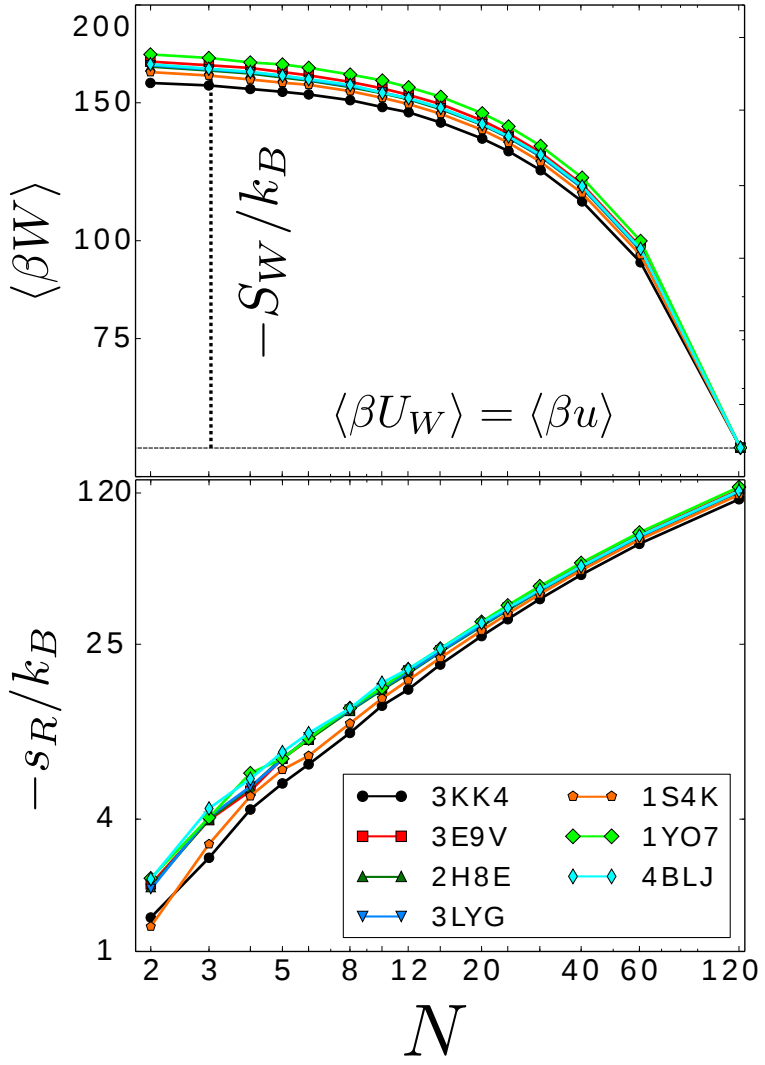
$$S_W(\mathbf{R}) = k_B \left\langle \ln \left[\frac{V^N p_R(\mathbf{R})}{V^n p_r(\mathbf{r})} \right] \right\rangle_{\mathbf{R}}$$ Entropy

- Temp dependence
- Information loss
- Mapping

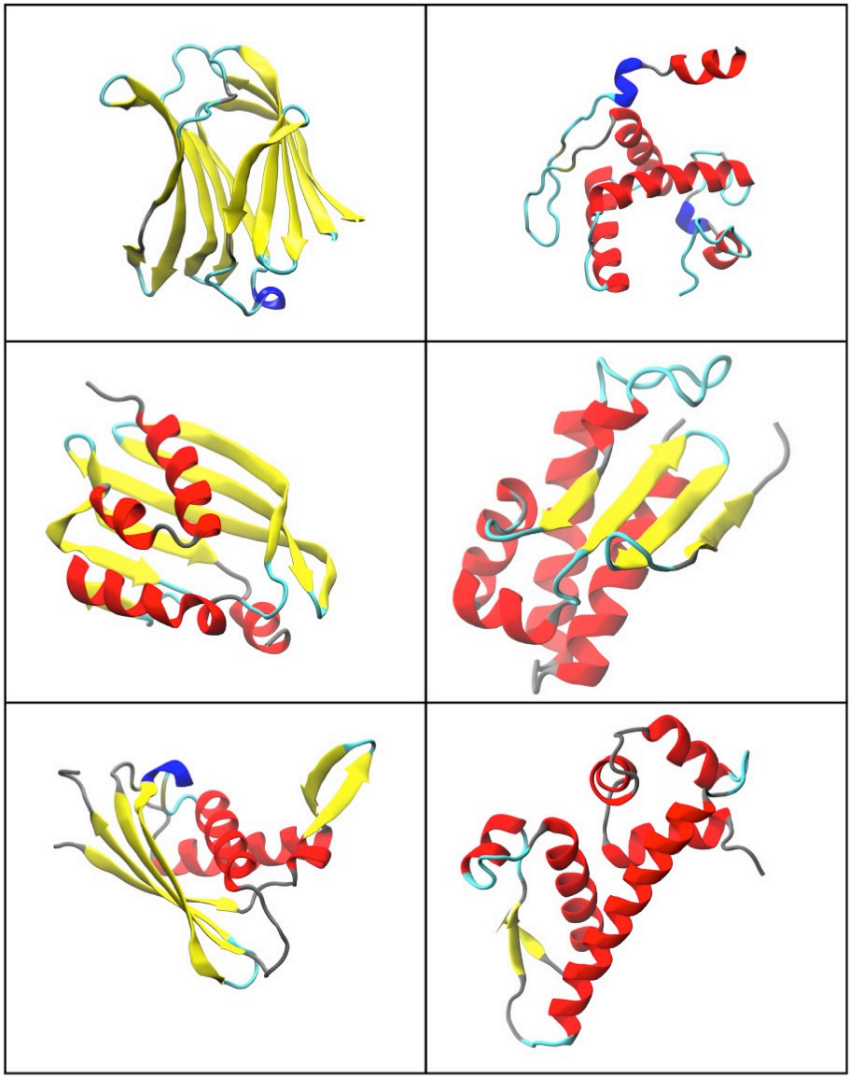
A simple analytic model

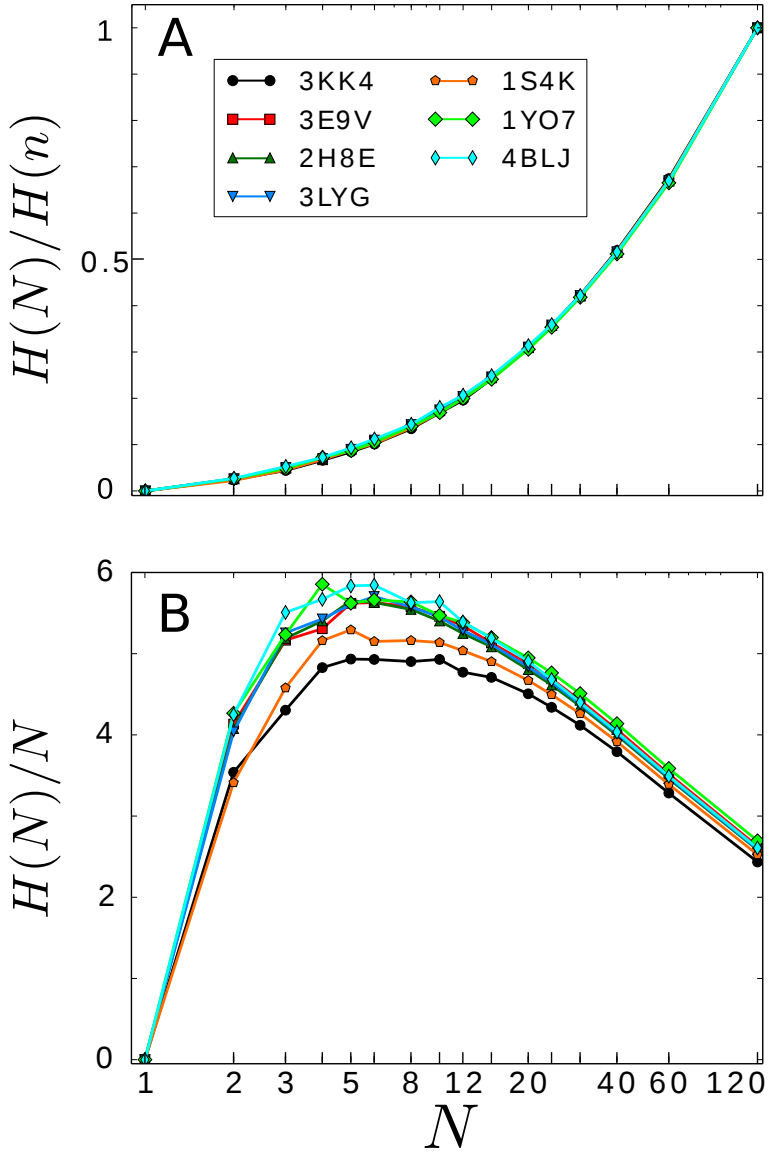






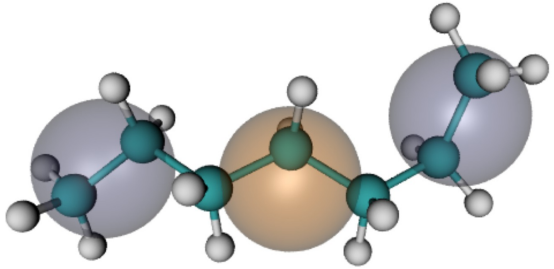
Optimally efficient representations



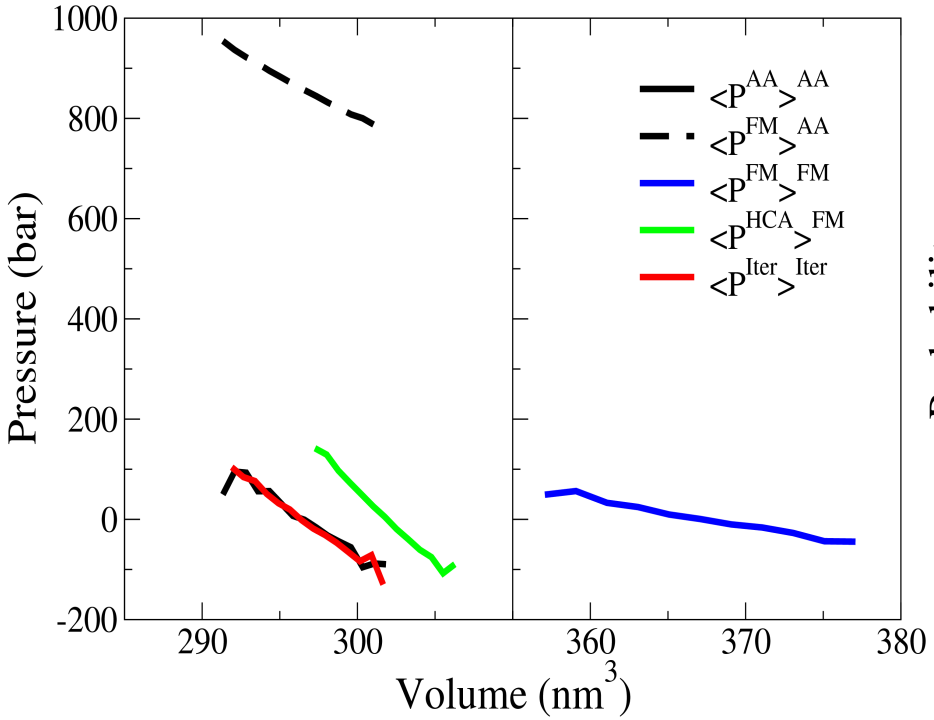


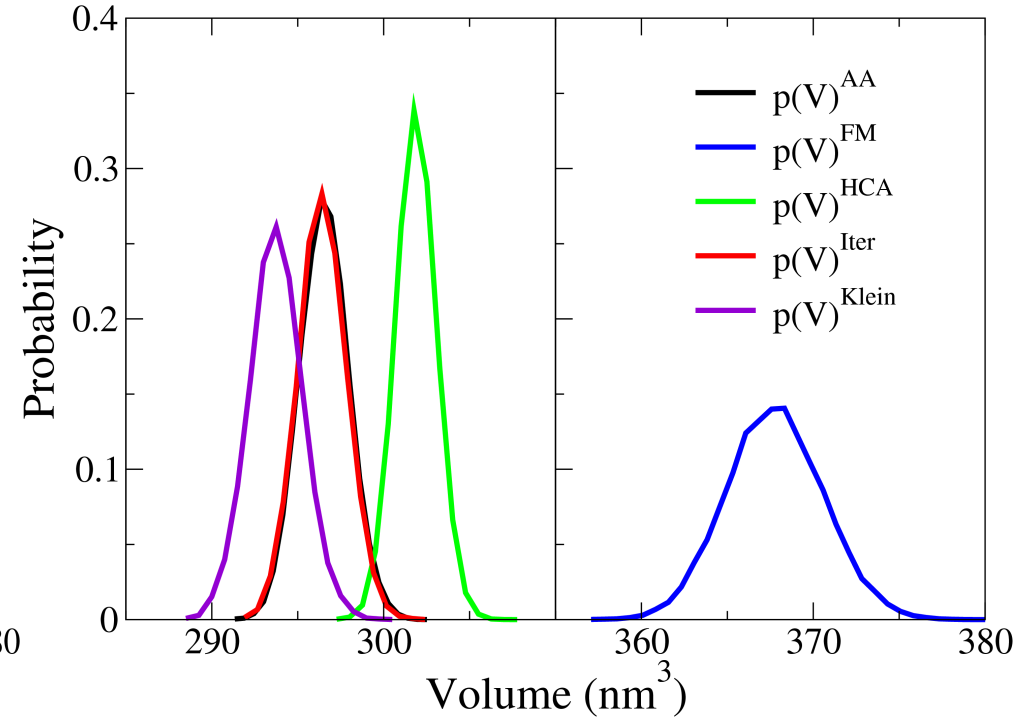
Volume dependence of the PMF

"Pressure Matching"
Das, Andersen *JCP* 2010



$$\chi^2[F_V] = \left\langle |\mathcal{P}_{AA}(\mathbf{r};V) - \mathcal{P}_{CG}(\mathbf{M}(\mathbf{r});V) - F_V(V)|^2 \right\rangle_{\mathrm{PT}}$$





Dunn, Noid In progress 2015
Cf Muller-Plathe, Izvekov and Voth

W(V) determines the effective force on the walls.

Precise Definition of Transferability

Model:

(1) Topology
- Particles and bonds used to describe system

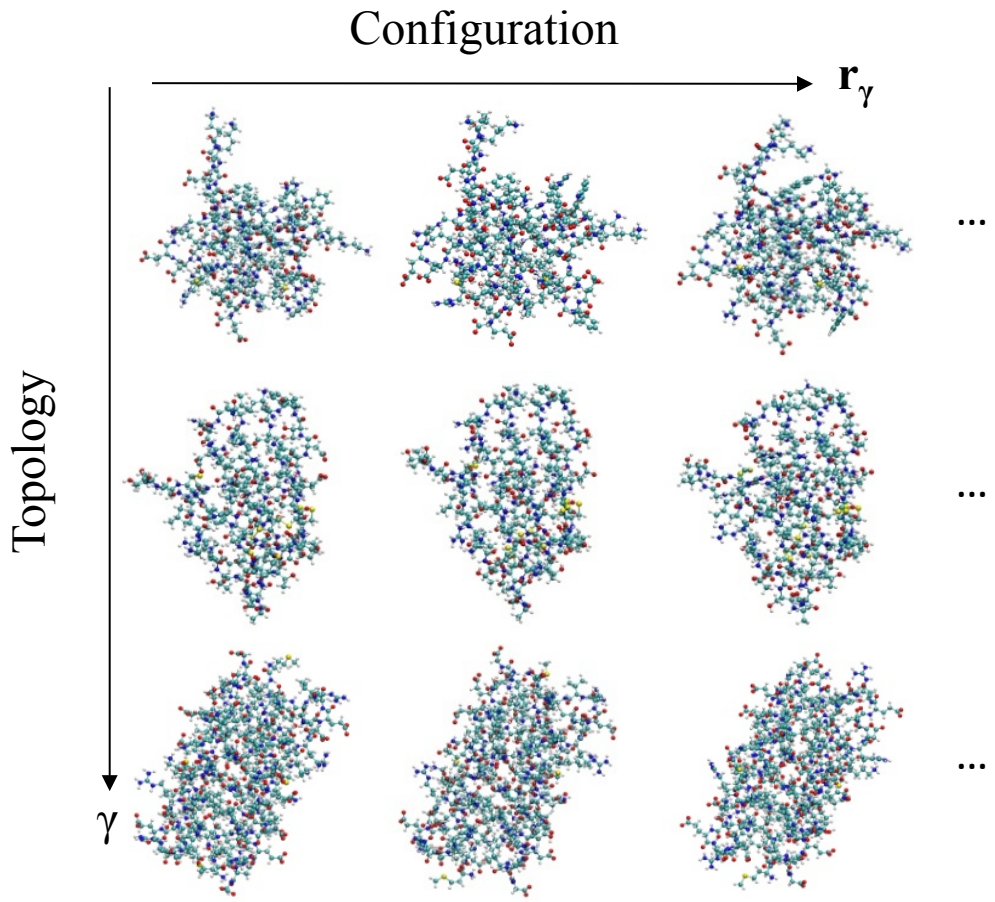
(2) Potential
- Interactions among those particles

atomistic	CG
γ	Γ
$u_\gamma(\mathbf{r}_\gamma)$	$U_\Gamma(\mathbf{R}_\Gamma)$

A potential is transferable if it can be used for describing multiple topologies.

Mullinax and Noid. *J Chem Phys* 2009.

Extended Ensemble



An **extended ensemble** is a collection of equilibrium ensembles for different **topologies.**

Distributions:

p_γ	topology
$p_{r\|\gamma}(\mathbf{r}_\gamma)$	configuration

Averages: $$\left\langle a_\gamma(\mathbf{r}_\gamma)\right\rangle = \sum_\gamma p_\gamma \int d\mathbf{r}_\gamma\, p_{r|\gamma}(\mathbf{r}_\gamma) a_\gamma(\mathbf{r}_\gamma)$$

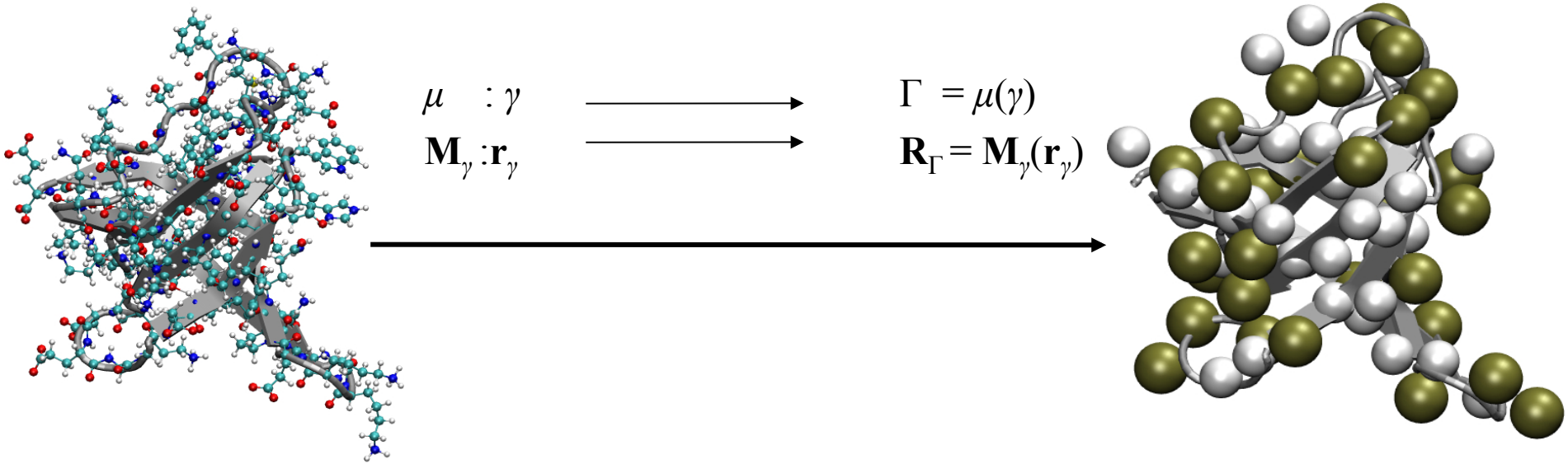
Mullinax and Noid. *J Chem Phys* 2009.

Mappings

Constructing a CG model requires **two** maps:

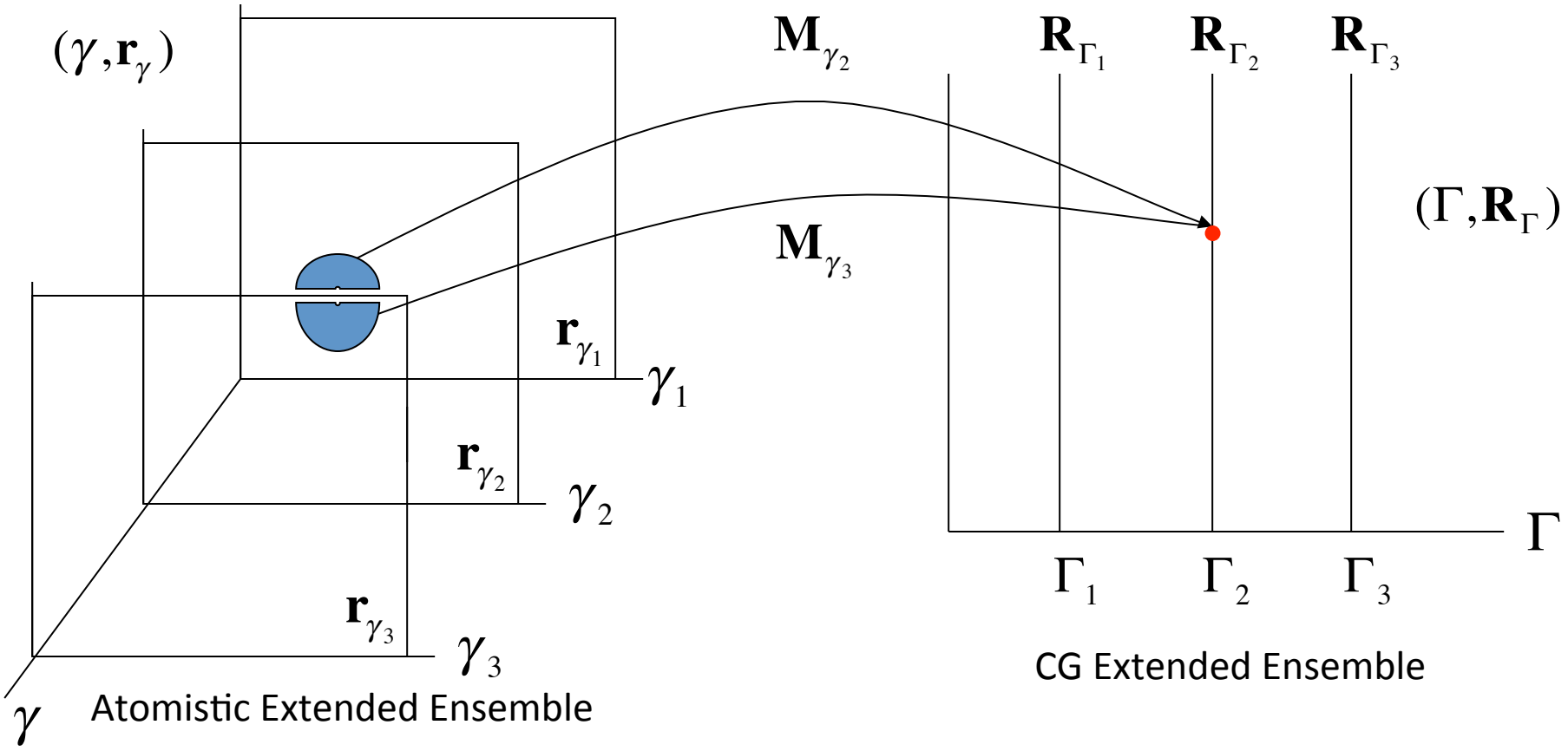
(1) Topology map - specifying site types and bonds

(2) Configuration map - specifying site coordinates



Then the remaining challenge is to determine $U_\Gamma(\mathbf{R}_\Gamma)$

Consistency between extended ensembles



Consistency:

$$P_\Gamma = \left\langle \delta_{\Gamma,\mu(\gamma)} \right\rangle$$

Generalized PMF

$$\exp[-U_\Gamma(\mathbf{R}_\Gamma)/k_B T] \propto \left\langle \delta_{\Gamma,\mu(\gamma)} \delta\left(\mathbf{R}_\Gamma - \mathbf{M}_\gamma(\mathbf{r}_\gamma)\right) \right\rangle$$

Mullinax and Noid. *J Chem Phys* 2009.

Variational Principle for the generalized PMF

$$\chi^2\left[\mathbf{F}'\right] = \left\langle \sum_{I=1}^{N_{\mu(\gamma)}} \left| \mathbf{F}'_{\mu(\gamma);I}\left(\mathbf{M}_\gamma(\mathbf{r}_\gamma)\right) - \mathbf{f}_{\gamma;I}(\mathbf{r}_\gamma) \right|^2 \right\rangle$$

$$= \chi^2\left[\mathbf{F}\right] + \left\|\mathbf{F}' - \mathbf{F}\right\|^2$$

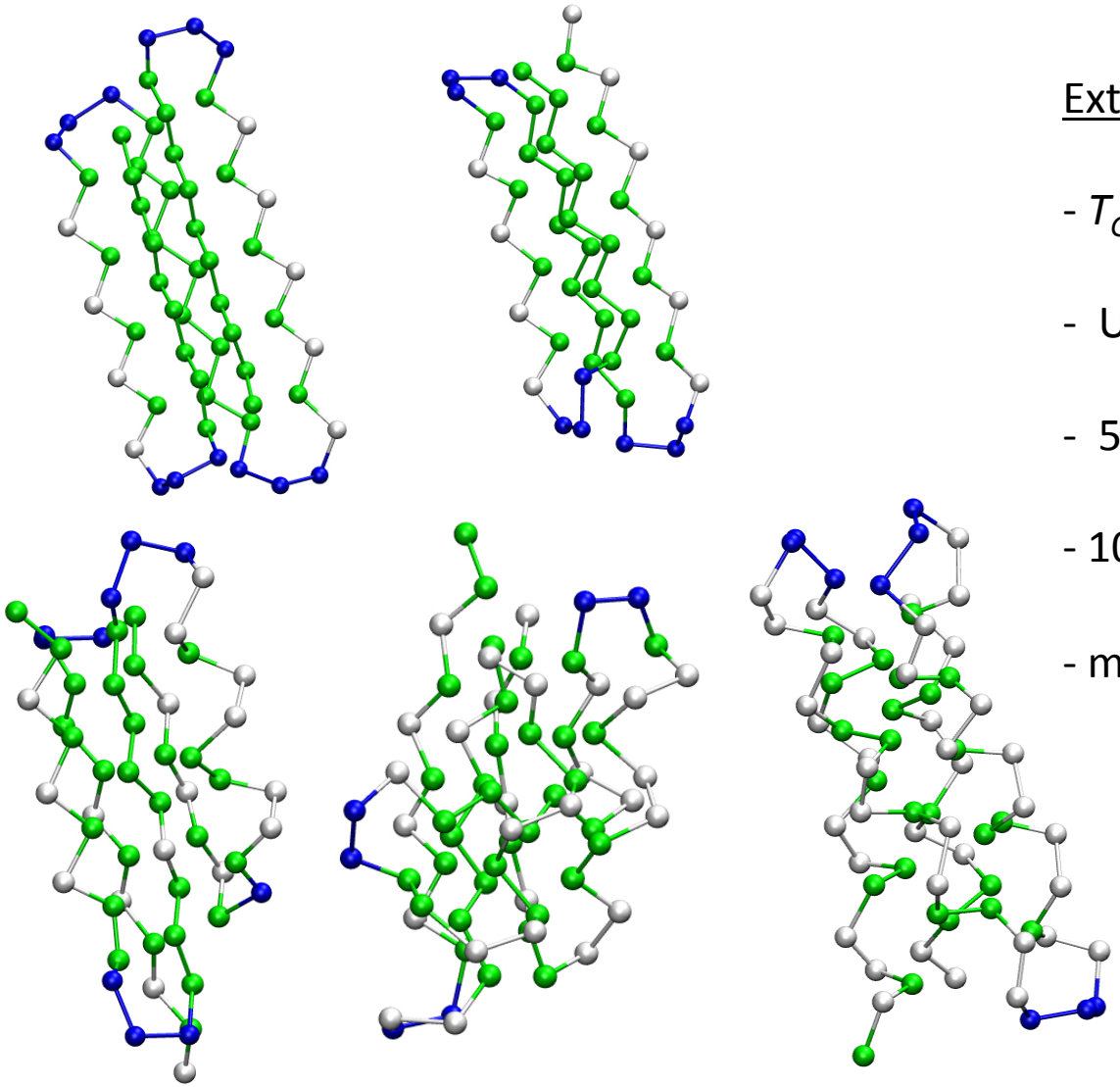
where $\mathbf{F}_{\Gamma I}(\mathbf{R}_\Gamma) = -\nabla_{\Gamma I} U_\Gamma(\mathbf{R}_\Gamma)$ is a mean force field

Key approximation

$$U_\Gamma(\mathbf{R}_\Gamma) \approx \sum_{\zeta \in \Gamma} U_\zeta\left(\psi_\zeta(\mathbf{R}_\Gamma)\right)$$

Determine optimal transferable approximation to the PMF

Model Protein Databank



Extended Ensemble

- $T_G < T < T_F$

- Uniform topology distribution

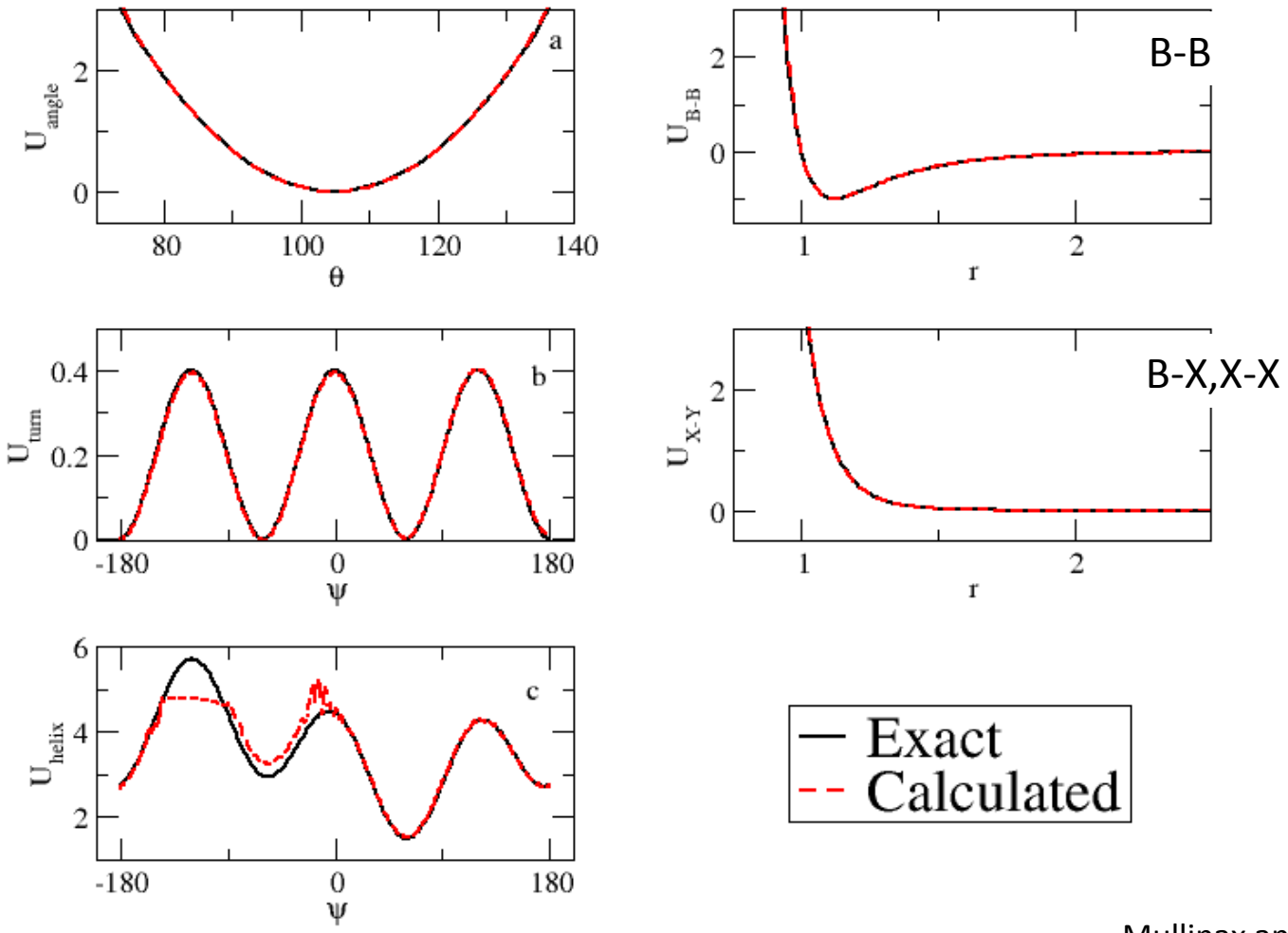
- 5 sequences

- 10^5 structures / sequence

- modified HT potential

Honeycutt and Thirumalai
Biopolymers (1992) **32**, 695

Validation

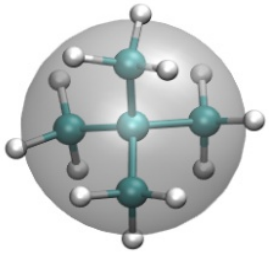


The generalized-YBG theory quantitatively determines the underlying potentials for a model extended ensemble of folded protein structures.

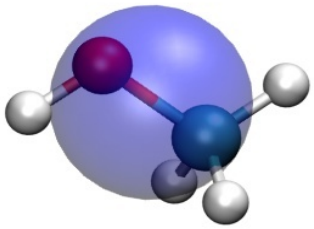
Mullinax and Noid.
JCP **131** 104110 (2009)
PRL **103** 198104 (2009)
PNAS **107** 19867 (2010)

Methanol-Neopentane Test System

M1N1

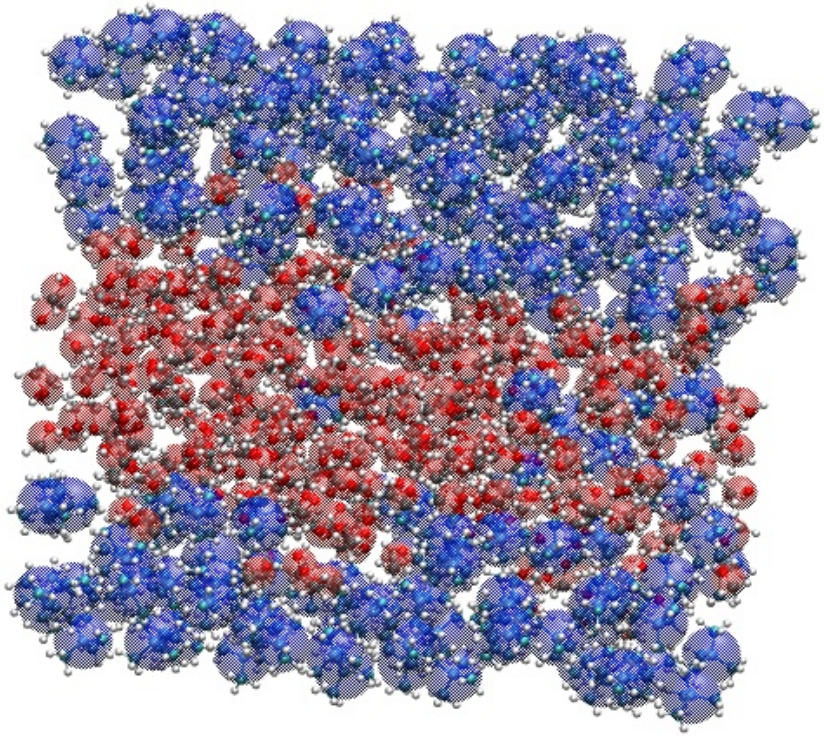


neopentane



methanol

Percent methanol (%)	Methanol	Neopentane
100	968	0
80	574	144
60	342	228
50	259	259
40	189	284
20	81	323
0	0	353



CG Potential

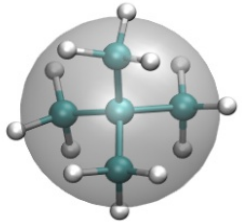
$$U_{\Gamma}(\mathbf{R}_{\Gamma}) = \sum_{\{I,J\}\in\Gamma} U^{(2)}_{\zeta(I,J)}(R_{IJ})$$

Mullinax and Noid. *J Chem Phys* 2009.

M-N: Results 1

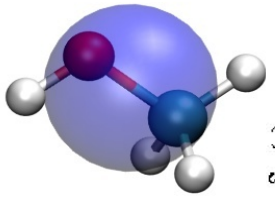
M1N1

N

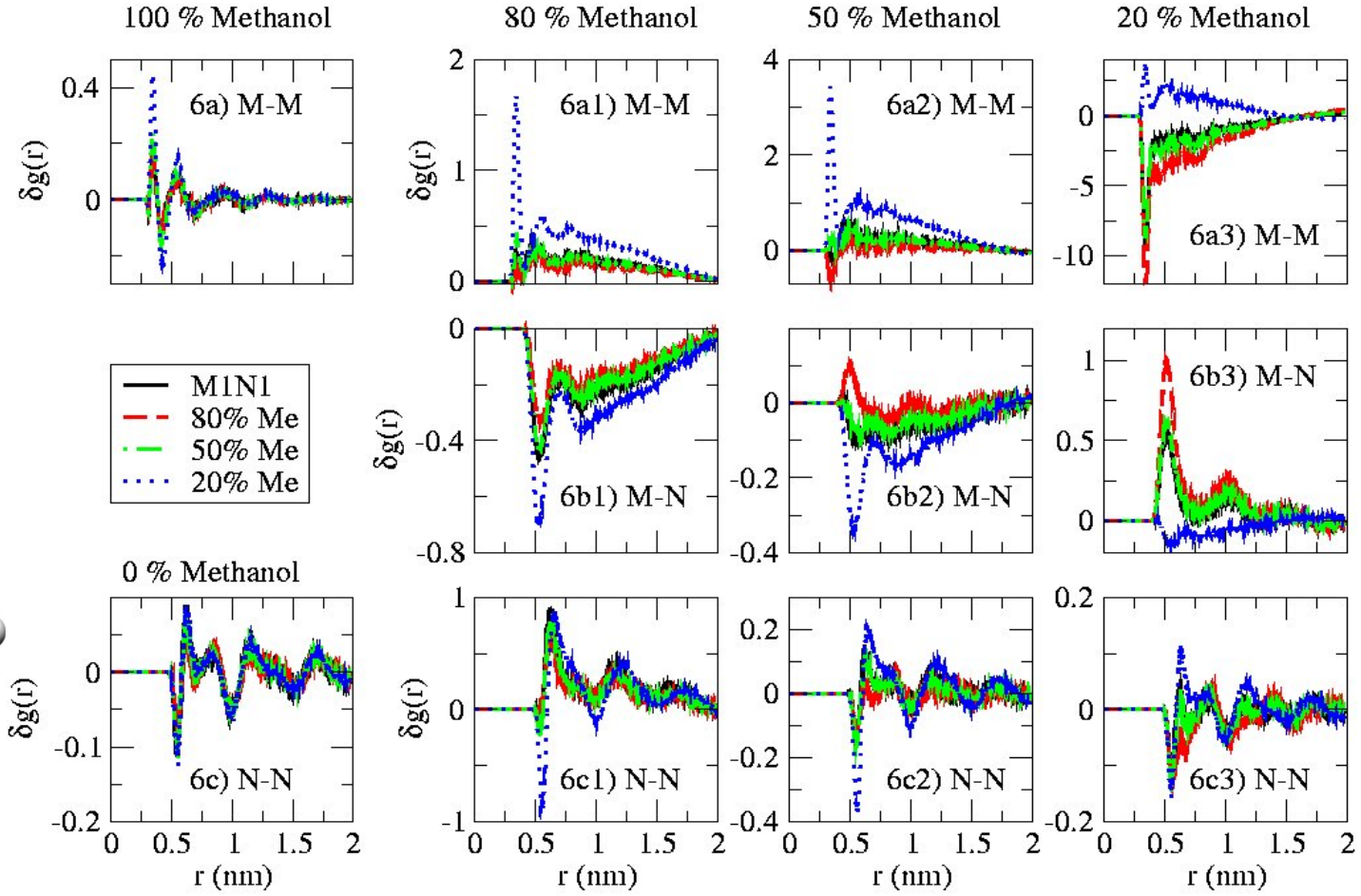


neopentane

M



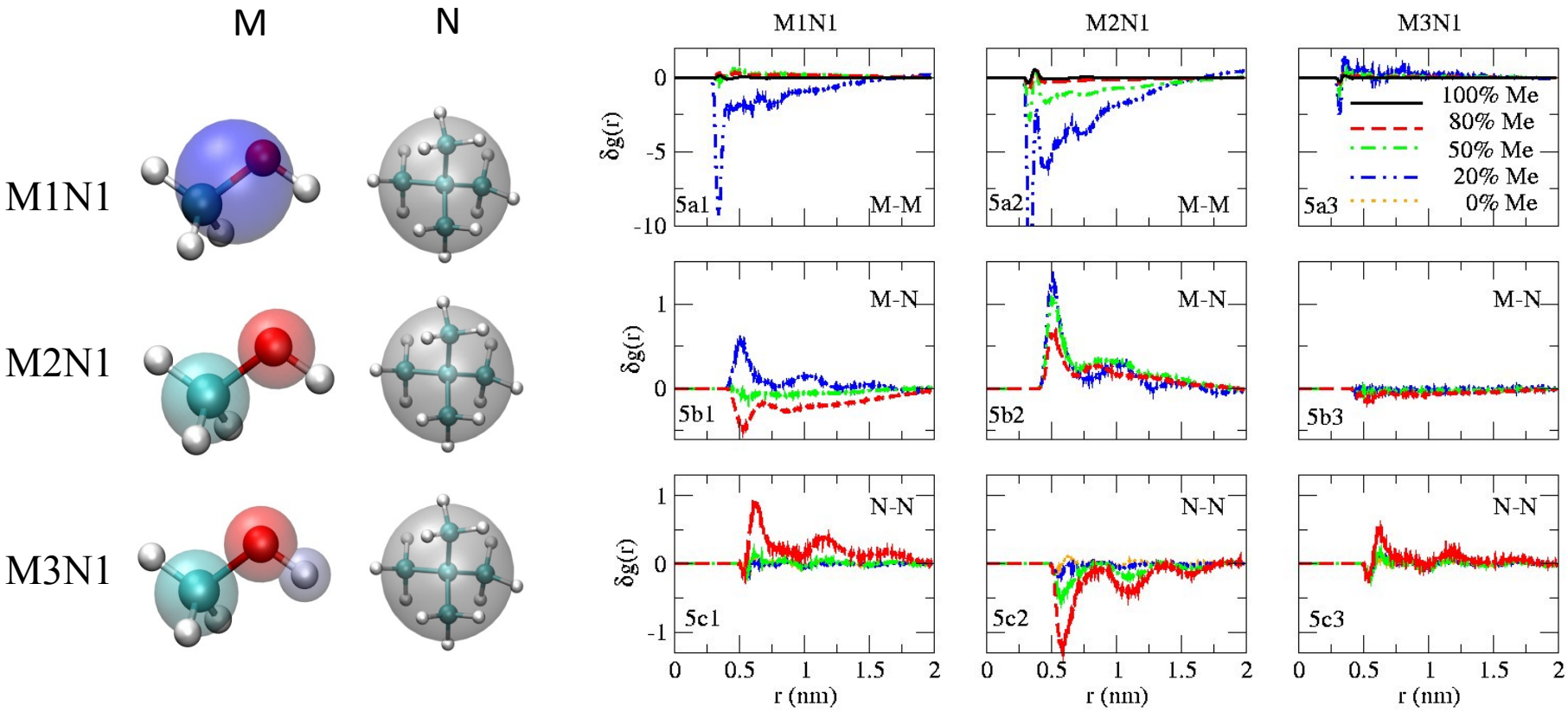
methanol



Mullinax and Noid. *J Chem Phys* 2009.

Extended ensemble potentials provide improved transferability.

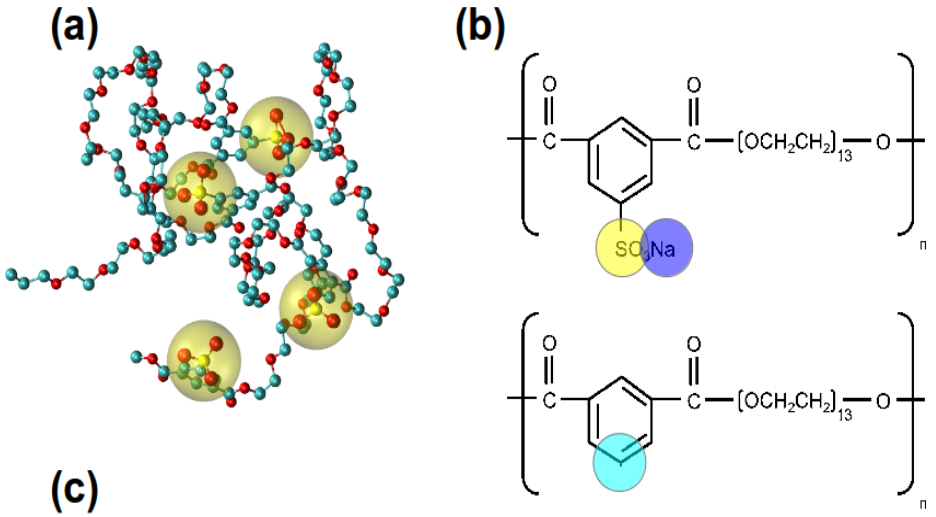
M-N: Results 2



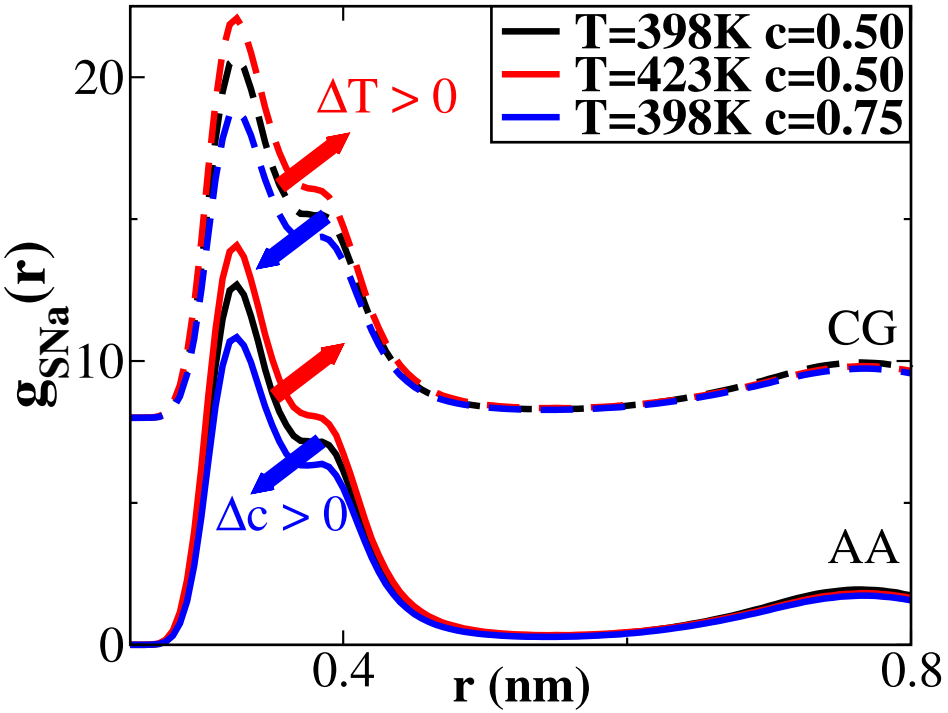
Mullinax and Noid. *J Chem Phys* 2009.

The accuracy and transferability of the potentials are sensitive to the topology mapping.

Towards Transferable Ionomer Models



T / %S	25	38	50	63	75	83	100
343K							
373K							
398K							
423K							



J. Rudzinski, K. Lu, S. Milner, J. Maranas, W.G. Noid In progress 2015

Conclusions

I. The generalized-YBG theory (g-YBG) determines variationally optimal approximations to the PMF directly (i.e., noniteratively) from structures. This theory also

A. Establishes surprising connections to information theory and liquid state theory.
B. Quantifies the role of many-body correlations in determining CG potentials.
C. Determines accurate models for complex polymers and biomolecules with well-defined structure
D. Iterative self-consistent framework

II. The PMF
A. Contains all structural and thermodynamic properties of the atomic model
B. Provides a framework for determining optimal representations

III. The extended ensemble framework systematically and quantitatively improves the transferability of CG potentials for accurately modeling multiple chemically distinct systems.

A. Exact in complete basis limit
B. Systematically improves transferability of liquid mixtures
C. Progress towards a transferable ionomer model as a function of temperature and composition

IV. Challenges:

A. Optimized mappings and basis sets
B. Improved metrics
C. Representing thermodynamics and transferability
D. Propagating dynamics
E. Phase transitions and aggregation in complex mixtures
F. Lunch theorems – What **can** we get and how much does it **cost**?

http://www.greendiary.com/entry/futuristic-trains-change-face-public-transportation/