How Structure Determines Coarse-grained Potentials and Vice Versa

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WHERE DISCOVERIES BEGIN

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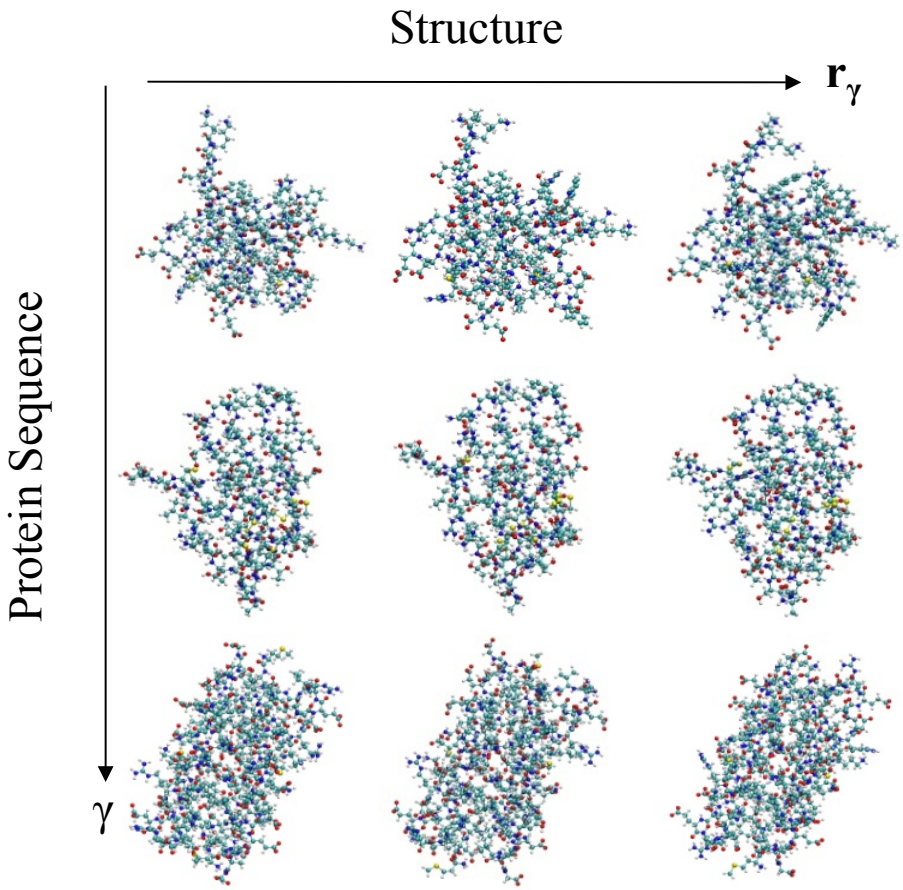
Motivating Questions



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

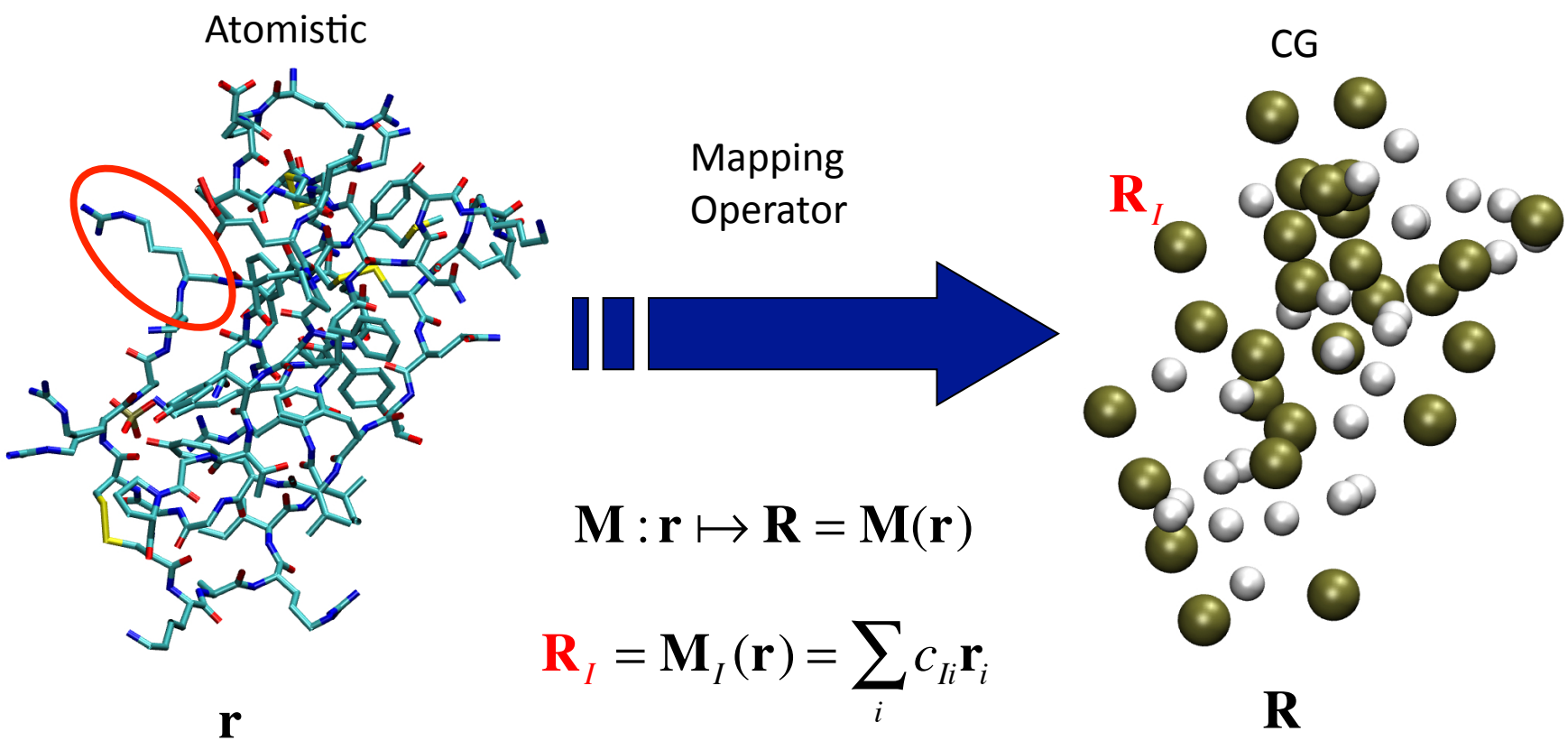
1. Given a collection of structures, what was the underlying potential?

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

Outline

1. Introduction: Basic theory of force-matching
2. Force-matching without forces: Generalized Yvon-Born-Green Theory
3. New directions:
    1. Information theoretic formulation of force-matching
    2. Mean forces as a unifying framework for understanding structure-potential relations
4. Outstanding challenges

Coarse-grained (CG) Mapping



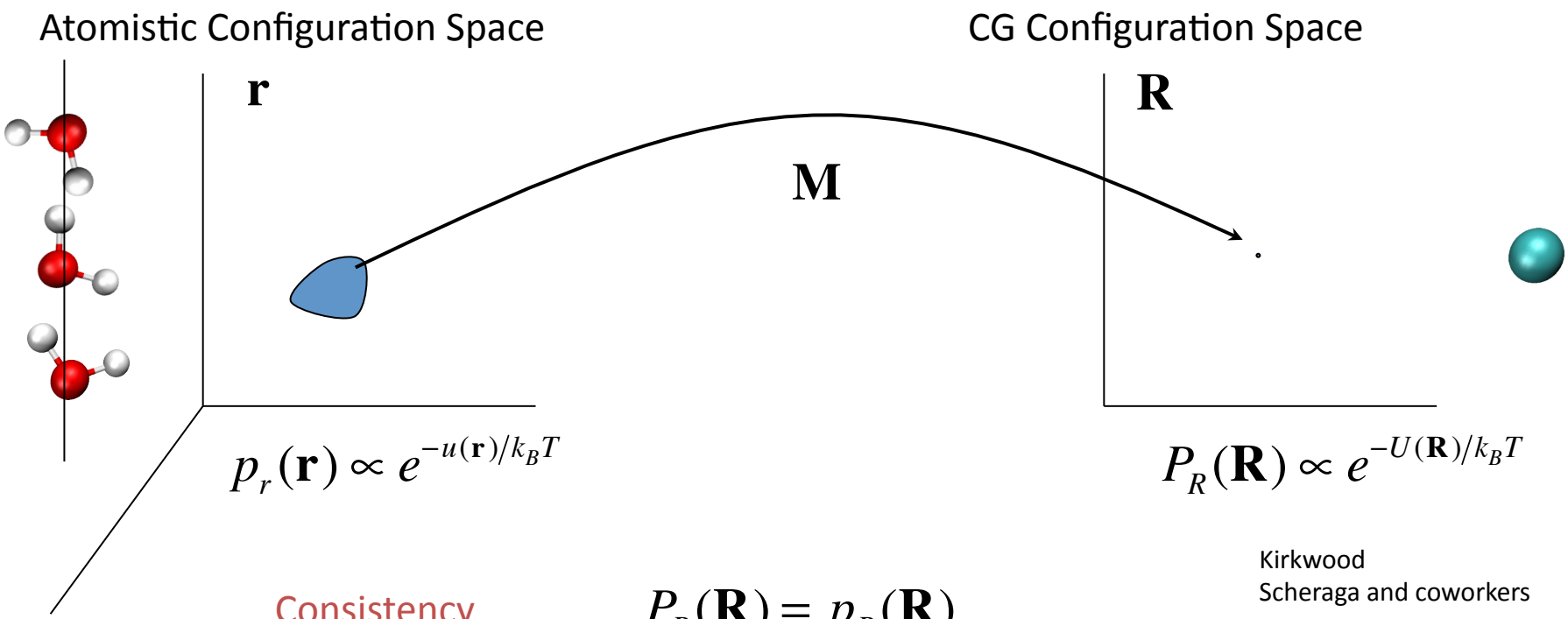
$$\mathbf{M} : \mathbf{r} \mapsto \mathbf{R} = \mathbf{M}(\mathbf{r})$$

$$\mathbf{R}_I = \mathbf{M}_I(\mathbf{r}) = \sum_i c_{Ii}\mathbf{r}_i$$

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



Kirkwood
Scheraga and coworkers

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

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

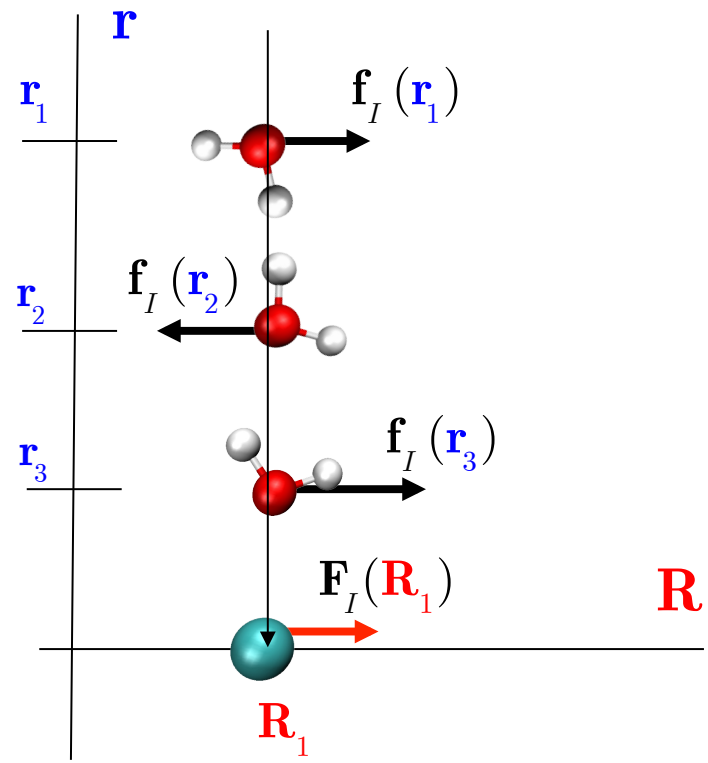
$$e^{-U(\mathbf{R})/k_B T} \propto \int d\mathbf{r}\; p_r(\mathbf{r})\, \delta\big(\mathbf{M}(\mathbf{r}) - \mathbf{R}\big)$$

For a consistent CG model that reproduces the distribution of structures generated by the atomistic model, the appropriate CG potential is a many-body PMF.

Mean Force Field

$$\mathbf{F}_I(\mathbf{R}) = \frac{-\partial U(\mathbf{R})}{\partial \mathbf{R}_I}$$

$$= \left\langle \mathbf{f}_I(\mathbf{r}) \right\rangle_{\mathbf{M}(\mathbf{r})=\mathbf{R}}$$



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

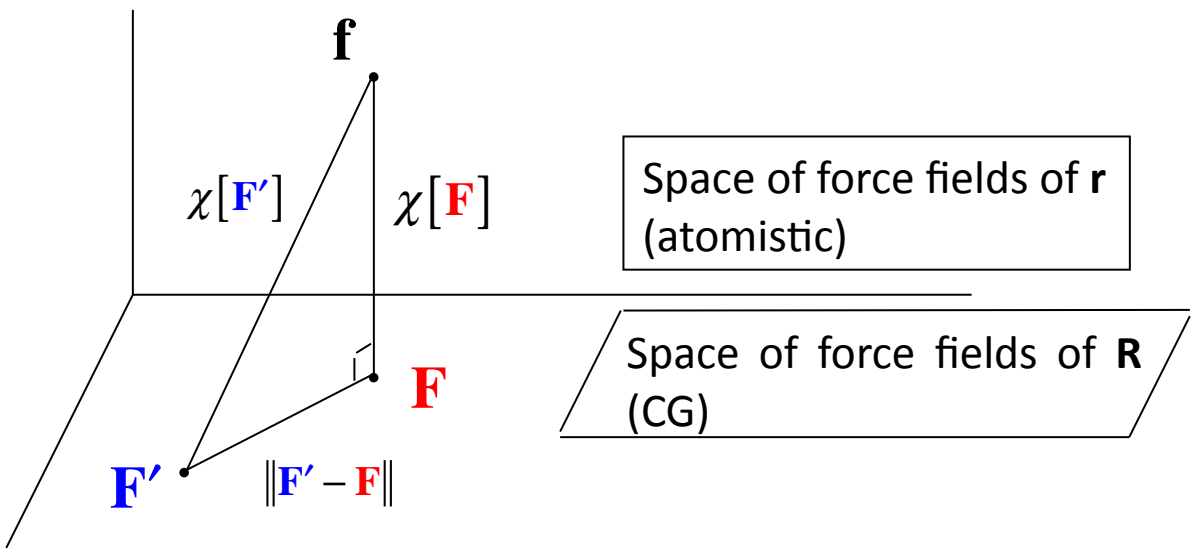
Atomistic FF:

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

In a consistent model, the CG force field is the conditioned average of the atomistic force field (I.e., the mean force field). The mean force field is sufficient for a consistent CG model.

Variational Principle for Multiscale Coarse-graining

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



$$\chi[\mathbf{F}] = \|\mathbf{F} - \mathbf{f}\|$$
$$\chi[\mathbf{F}'] = \|\mathbf{F}' - \mathbf{f}\|$$

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 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

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

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

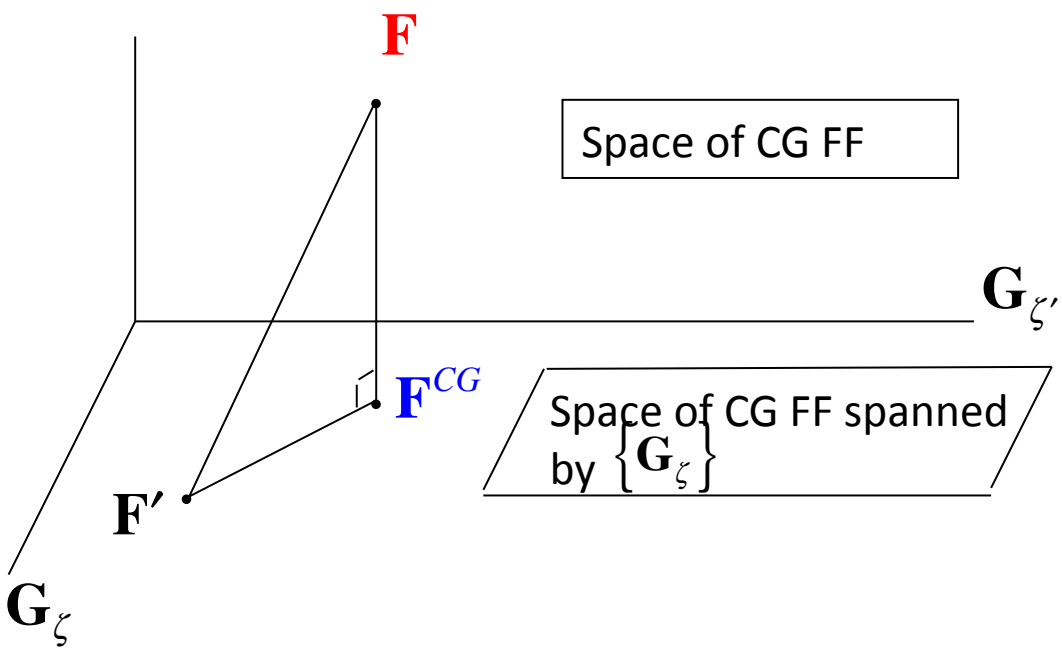
Noid, …, Chu, …, Andersen, Voth
J Chem Phys (2008)

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

Linear Least Squares Problem

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

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



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

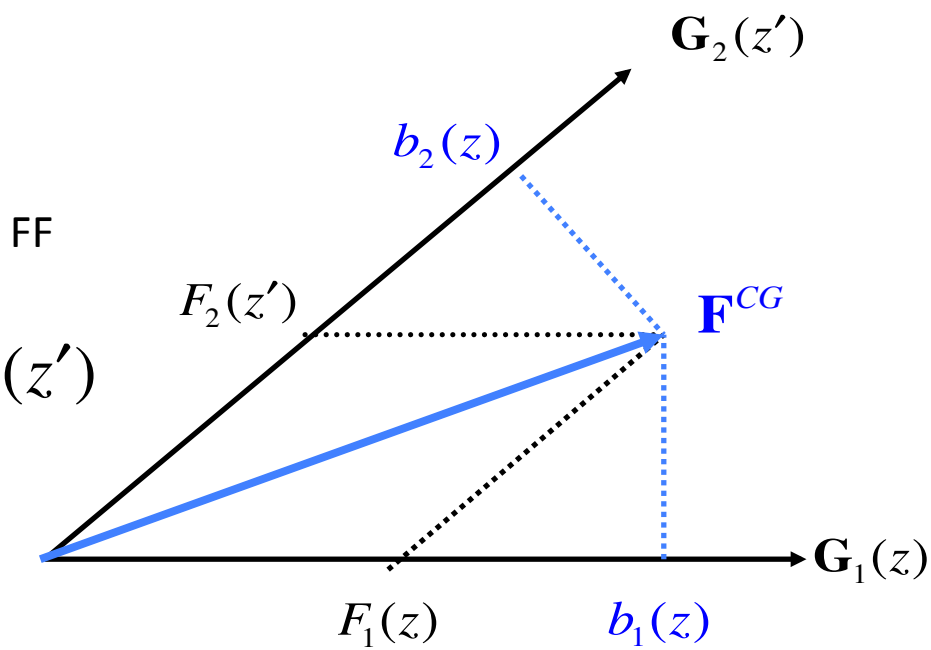
$$\boxed{\mathbf{F}^{CG} = \sum_{\zeta} \int dz\, F_{\zeta}(z)\mathbf{G}_{\zeta}(z)}$$

Projections:

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

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

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



Metric Tensor:

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

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

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

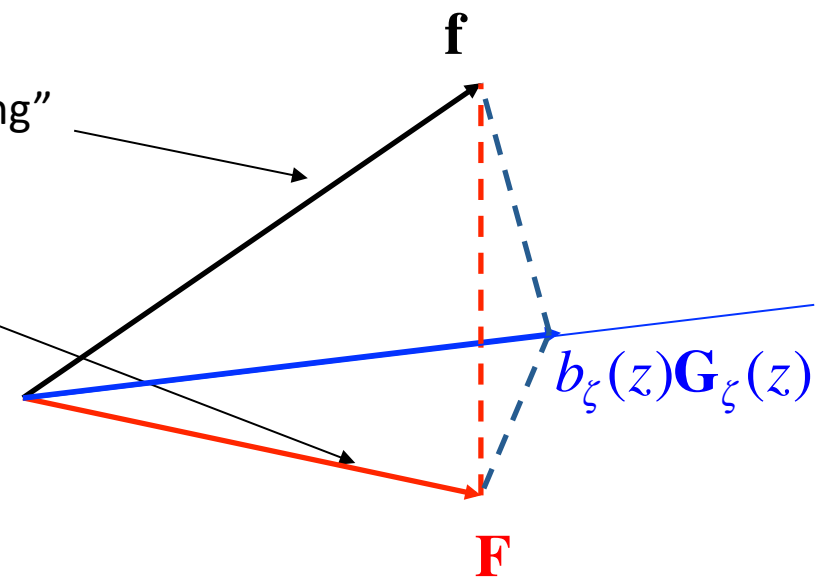
Integral Eq $$b_\zeta(z) = \mathbf{G}_\zeta(z)\cdot\mathbf{F} = \mathbf{G}_\zeta(z)\cdot\mathbf{F}^{CG} = \sum_{\zeta'}\int dz' G_{\zeta\zeta'}(z,z')F_{\zeta'}(z')$$

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

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

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

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

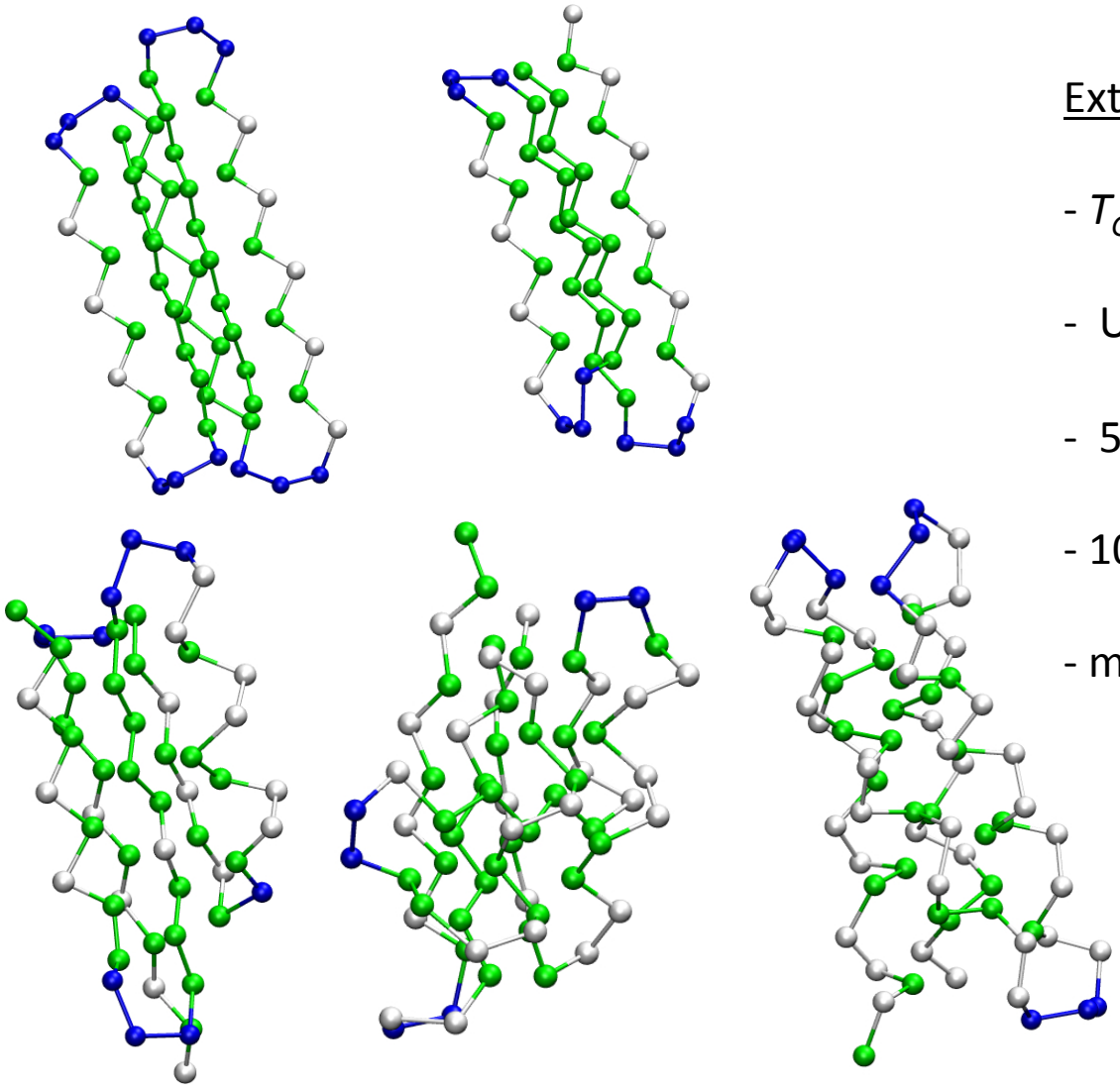


$$\boxed{k_B T\, d\bar{g}_\zeta(z)/dz = \sum_{\zeta'}\int dz' G_{\zeta\zeta'}(z,z')F_{\zeta'}(z')}$$

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!

Model Protein Databank



<u>Extended Ensemble</u>

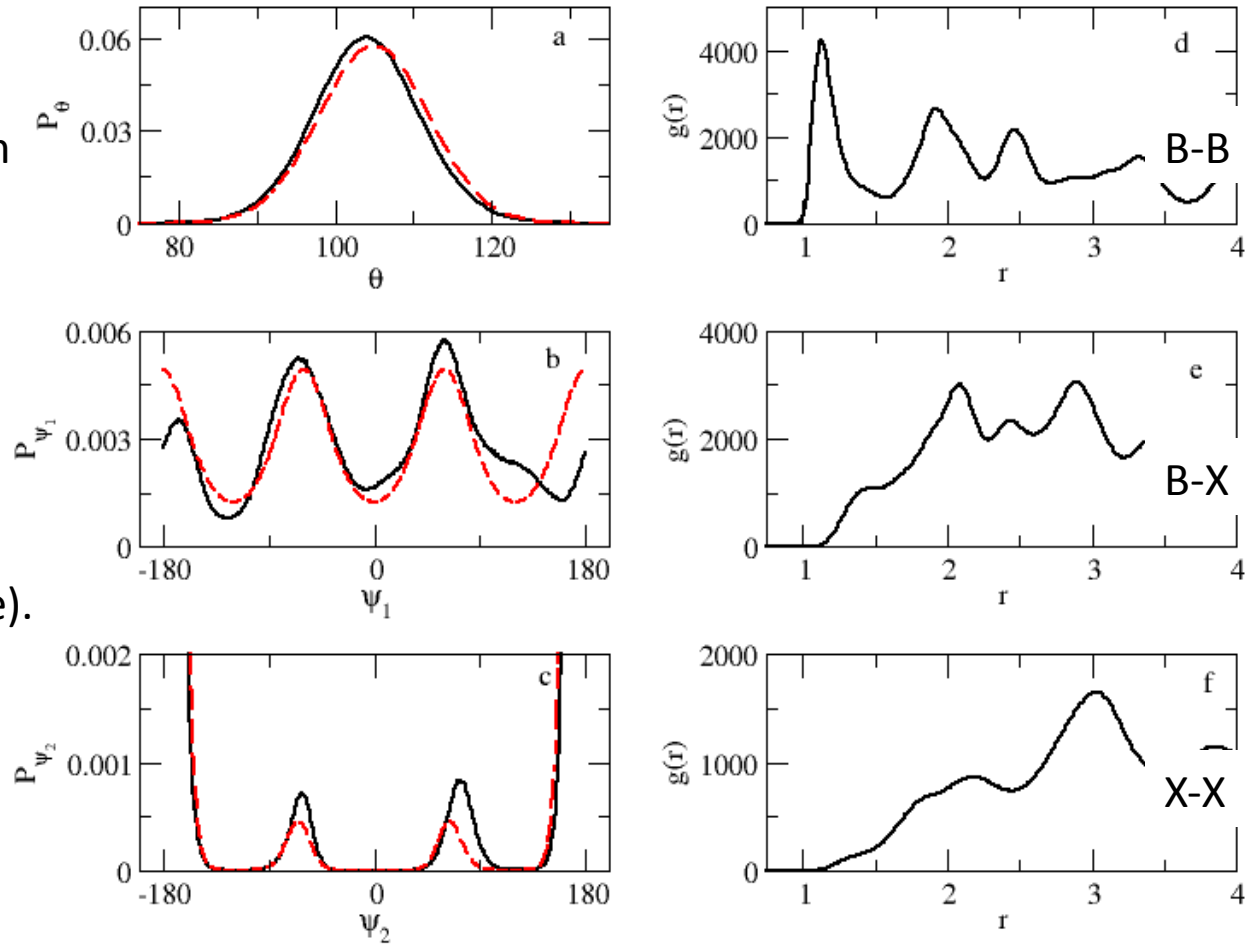
- $T_G < T < T_F$
- Uniform topology distribution
- 5 sequences
- 10^5 structures / sequence
- modified HT potential

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

Distributions from Model PDB

1. Soft degrees of freedom couple to other degrees of freedom.

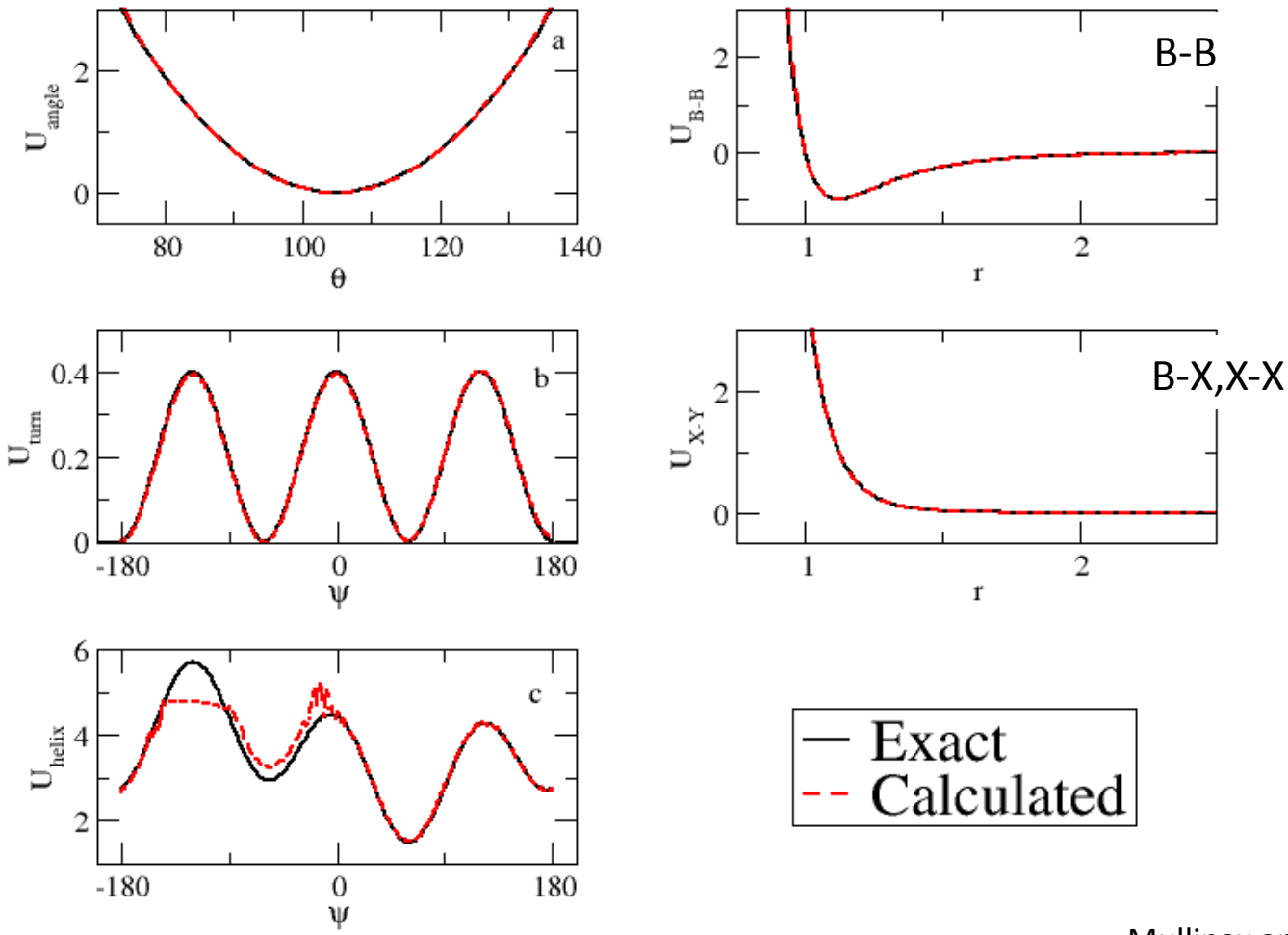
2. Chain connectivity generates long-ranged effective interactions between B-X and X-X pairs (which are purely repulsive).



Mullinax and Noid. *PNAS* **107** 19867 (2010)

Soft degrees of freedom are strongly coupled and cannot be treated independently.

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)

Relative Entropy

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

Atomistic

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

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)

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

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

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**)

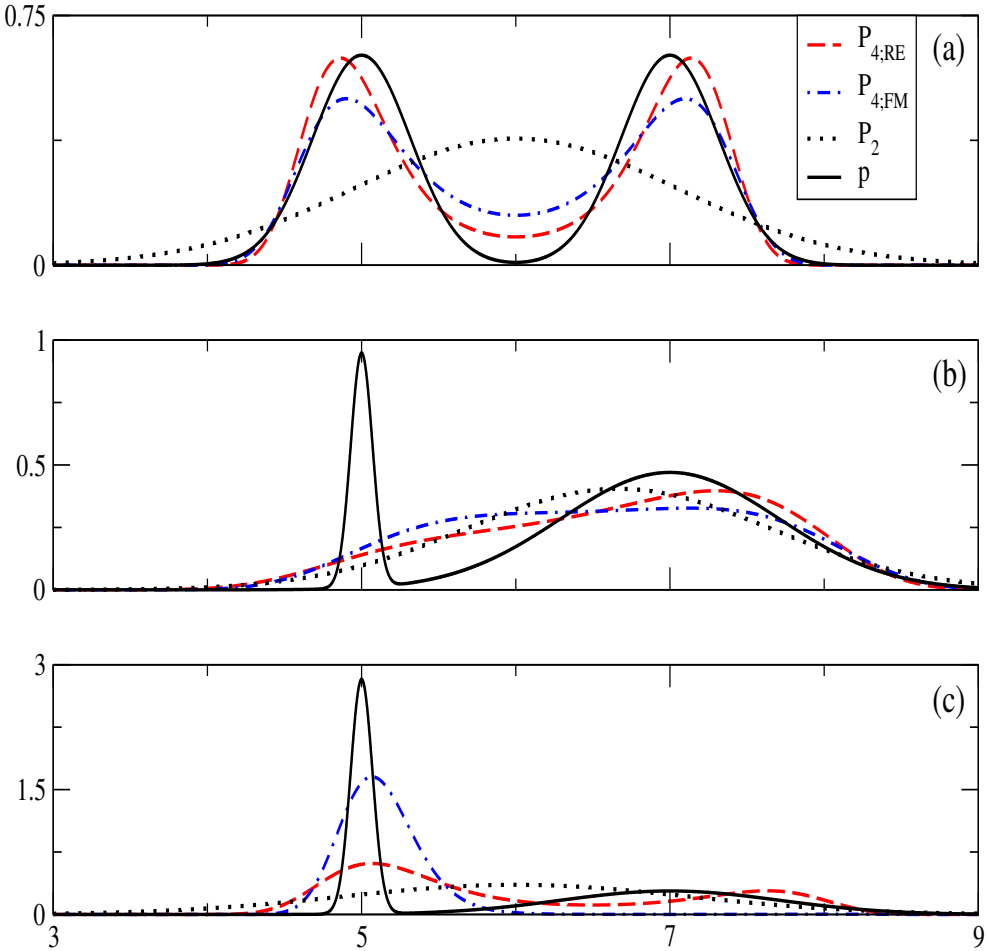
Relation to the Relative Entropy

Inverse Monte Carlo (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 "force-matching" and Inverse Monte Carlo approaches can be expressed in terms of the Kullback-Leibler information function.

Rudzinski and Noid *JCP* **2011**

Incidental results

1. Equivalence of Force- and Structure-based potentials for quadratic potentials

2. Remarkable parallels in formulation:
   Variational problems in linear space with bases that are related by differentiation

3. Generalization of Henderson's uniqueness theorem

   1. Conditions – Linear independence of conjugate density operators
   2. Relation to force-matching uniqueness:
      Uniqueness of force-matching implies uniqueness of structure-based potential

4. Generalization of force-matching and g-YBG theory for arbitrary potentials

5. Entropy changes in coarse-graining:

$$s_{\mathbf{r}} = -k_B \int d\mathbf{r}\ p_r(\mathbf{r}) \ln\left[V^n p_r(\mathbf{r})\right]$$

$$s_{\mathbf{R}} = -k_B \int d\mathbf{R}\ p_R(\mathbf{R}) \ln\left[V^N p_R(\mathbf{R})\right]$$

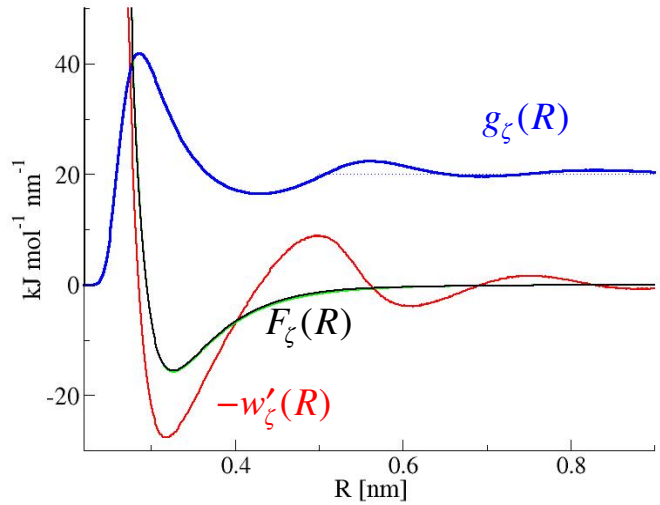
$$s_{\mathbf{r}} - s_{\mathbf{R}} \leq k_B \left\langle \ln\left[\frac{V^N}{V^n}\Omega_1\left(\mathbf{M}(\mathbf{r})\right)\right]\right\rangle$$

Rudzinski and Noid *JCP* **2011**

Mean forces

Generalized YBG theory:

$$b_\zeta(z) = k_B T \, d\bar{g}_\zeta(z)/dz = \sum_{\zeta'} \int dz' G_{\zeta\zeta'}(z,z') F_{\zeta'}(z')$$



$$-w'_\zeta(R) = F_\zeta(R) + \sum_{\zeta'} \int dz' \, F_{\zeta'}(z') \, \bar{G}_{\zeta\zeta'}(R,z')/\bar{g}_\zeta(R)$$

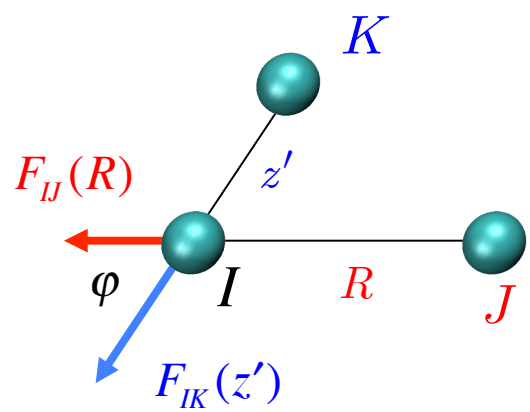
pair MF

direct

indirect

CG pair force

conditioned
3-particle density



The generalized Yvon-Born-Green equation determines the CG potential that reproduces the mean force (when using atomistic configurations).

Ellis, Rudzinski, and Noid
Macromol Sim Theory (2011)

Iterative Boltzmann Inversion

First estimate:

$$i = 0 \quad U_\zeta^0(z) = w_\zeta(z) = -k_B T \ln\left(p_\zeta(z) / J_\zeta(z)\right)$$

Corresponding pmf

CG MD

$$P_\zeta(z \mid U^i) \neq p_\zeta(z)$$

Error in distribution

Error in pmf:

$$w_\zeta(z) - W_\zeta^i(z) = -k_B T \ln\left[p_\zeta(z) / P_\zeta(z \mid U^i)\right]$$

Improve pmf:

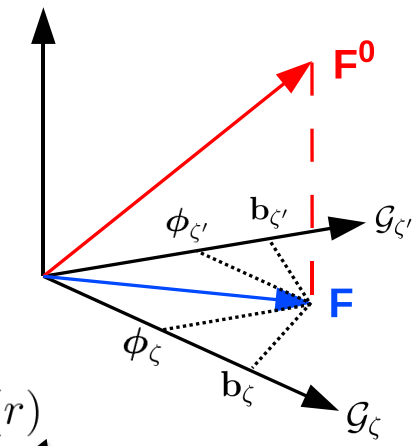
$$i = 0, \ldots \quad U_\zeta^{i+1}(z) = U_\zeta^i(z) - k_B T \ln\left[p_\zeta(z) / P_\zeta(z \mid U^i)\right]$$

Iterate to convergence !

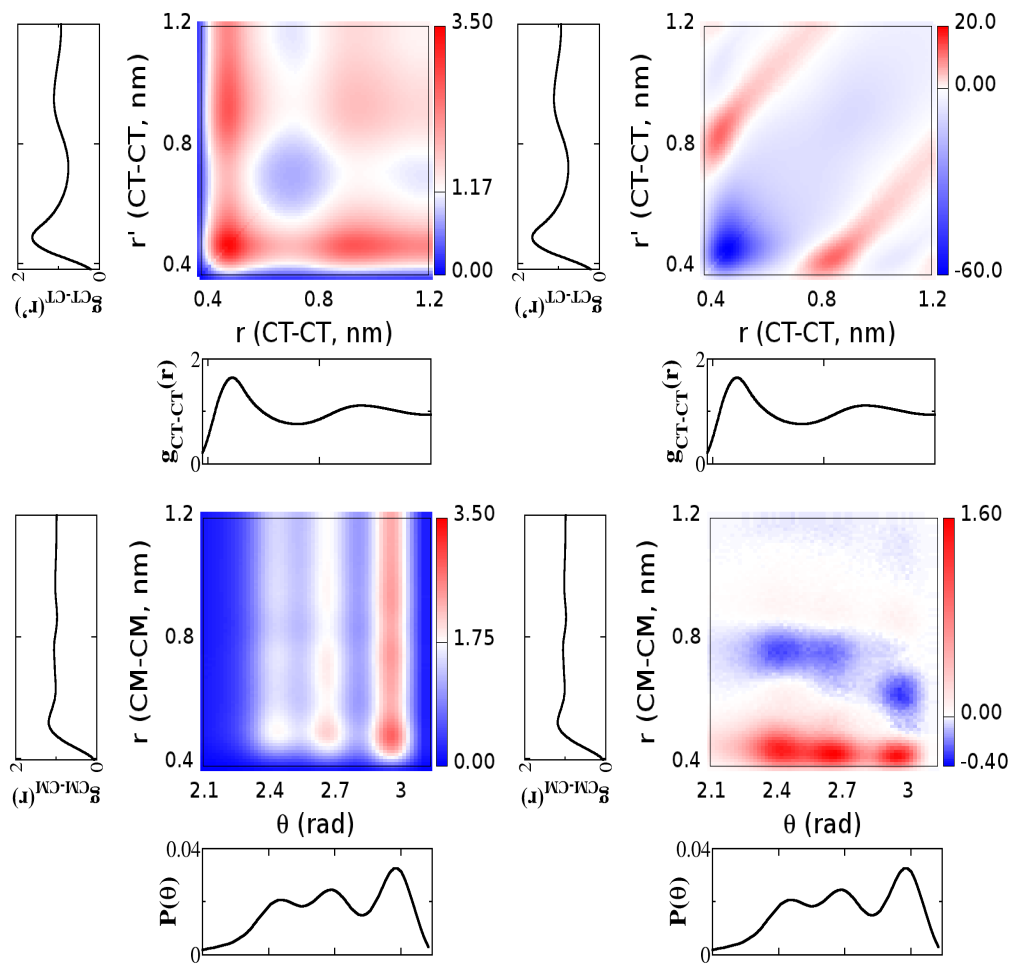
References:

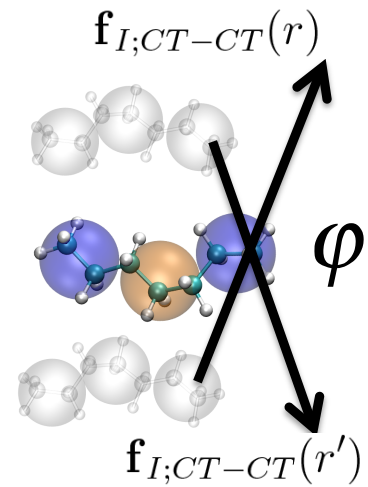
- Schommers *Phys Rev A* (1983) **28** 3599
- Soper *Chem Phys* (1996) **202** 295
- Muller-Plathe *ChemPhysChem* (2002) **9** 754
- Faller, and others
- Majek and Elber *Proteins* (2009) **76** 930

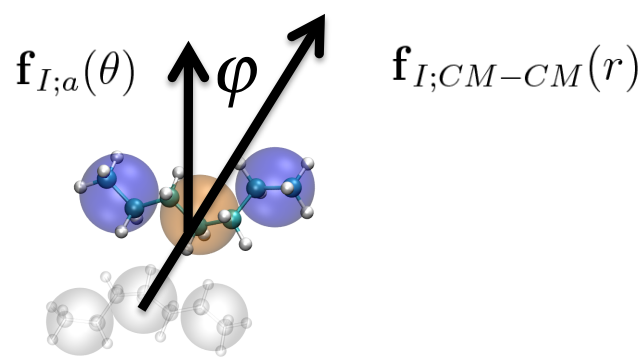
Understanding the Metric Tensor



$$P_{\zeta\zeta'}(r,r') \qquad \bar{G}_{\zeta\zeta'}(r,r') = \langle \cos\varphi \rangle_{r,r'}$$





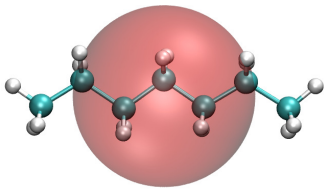


Rudzinski and Noid *JPCB* **2012**

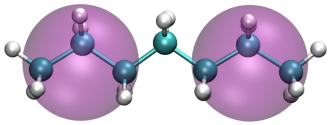
Robust features

$$\bar{G}_{\zeta\zeta'}(r,r') = \langle \cos\varphi \rangle_{r,r'}$$

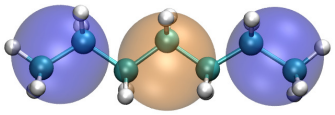
(a) CC

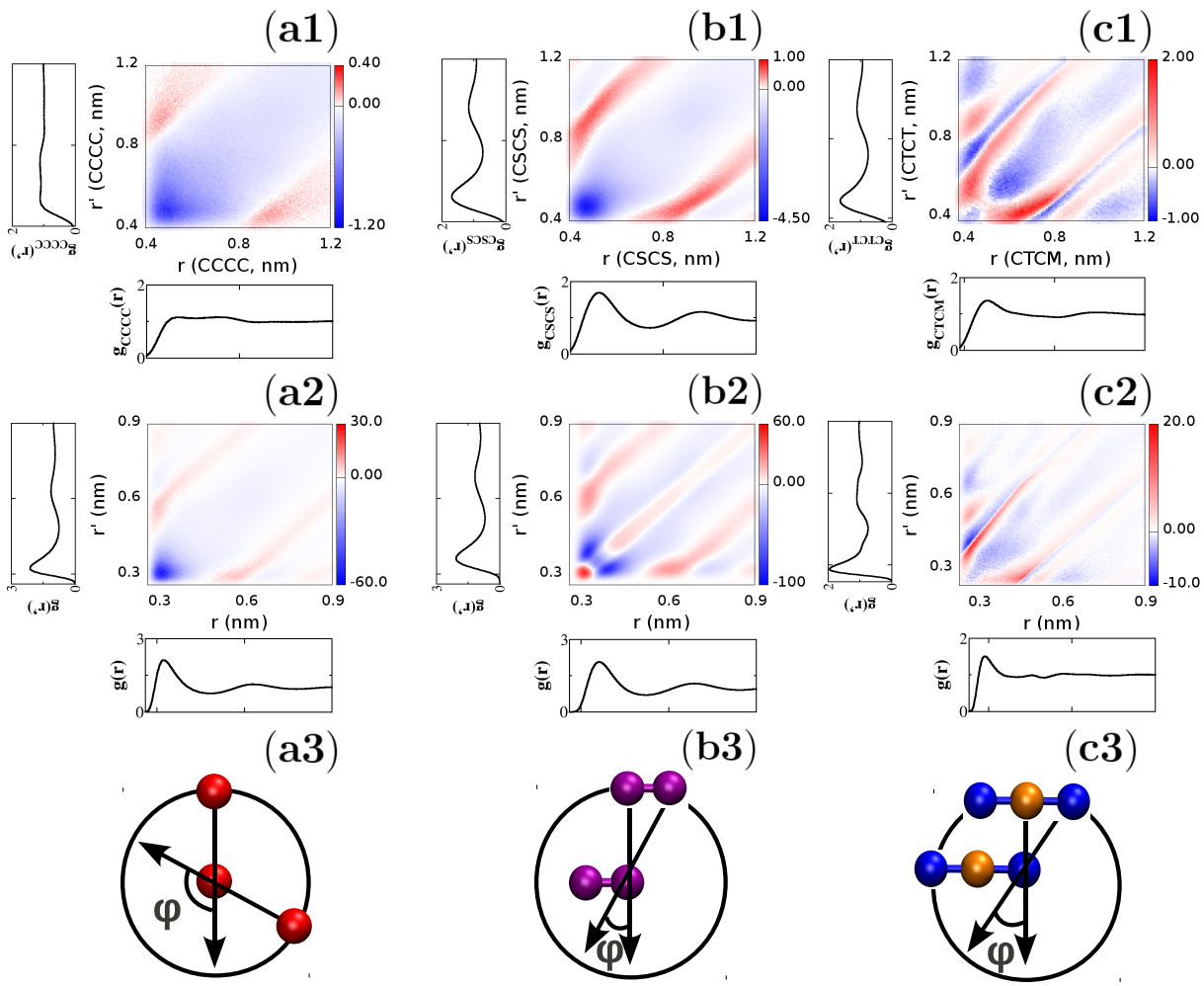


(b) CS-CS



(c) CT-CM-CT





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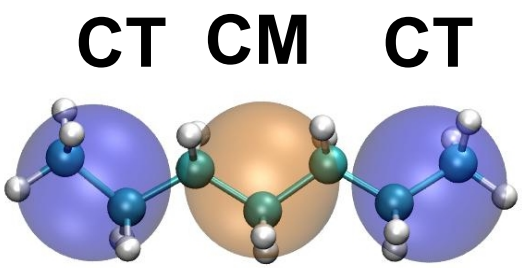
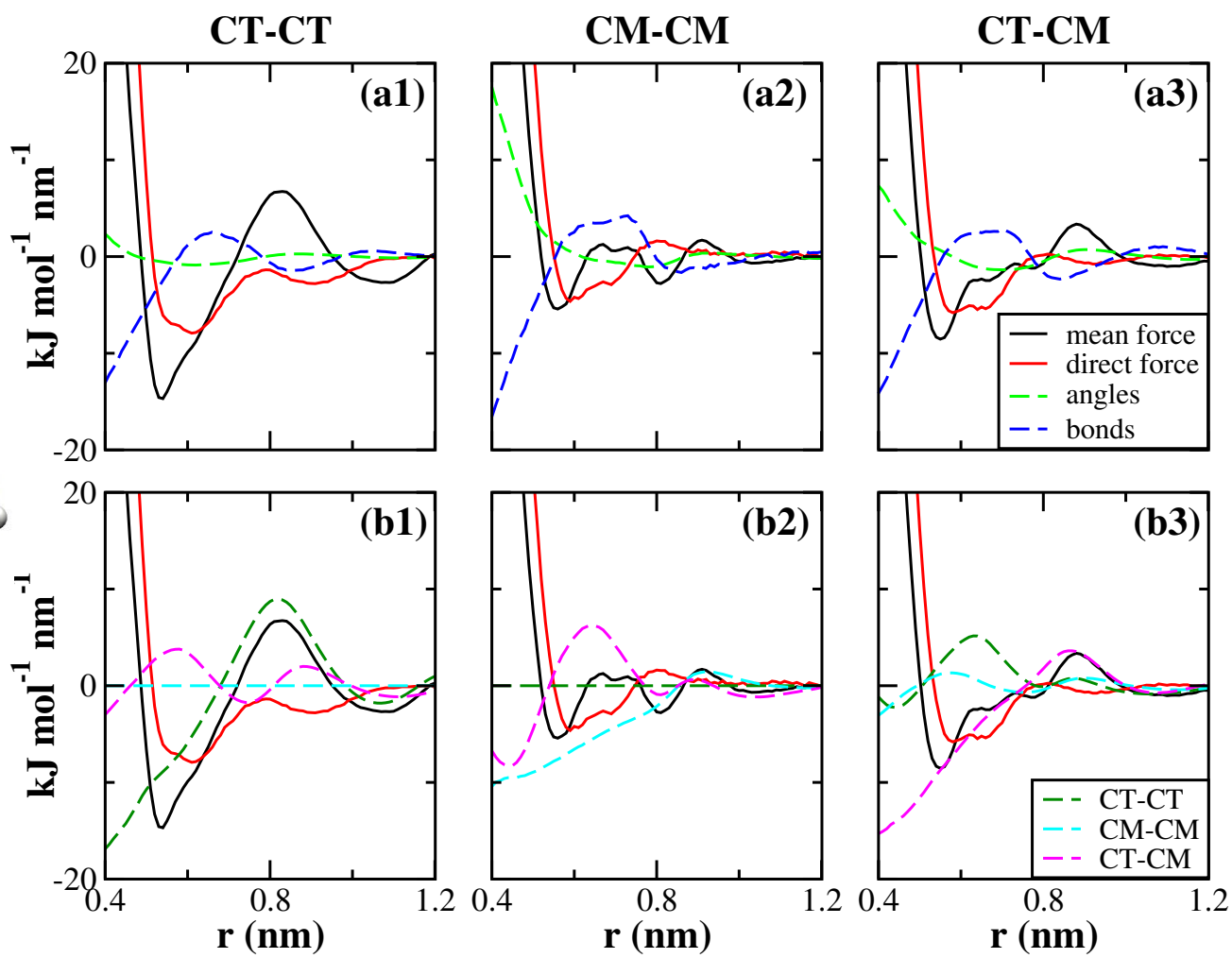
Decomposition of mean forces





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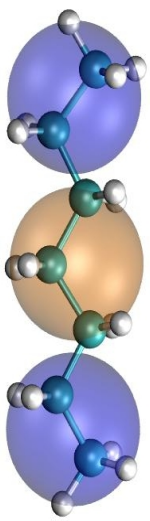
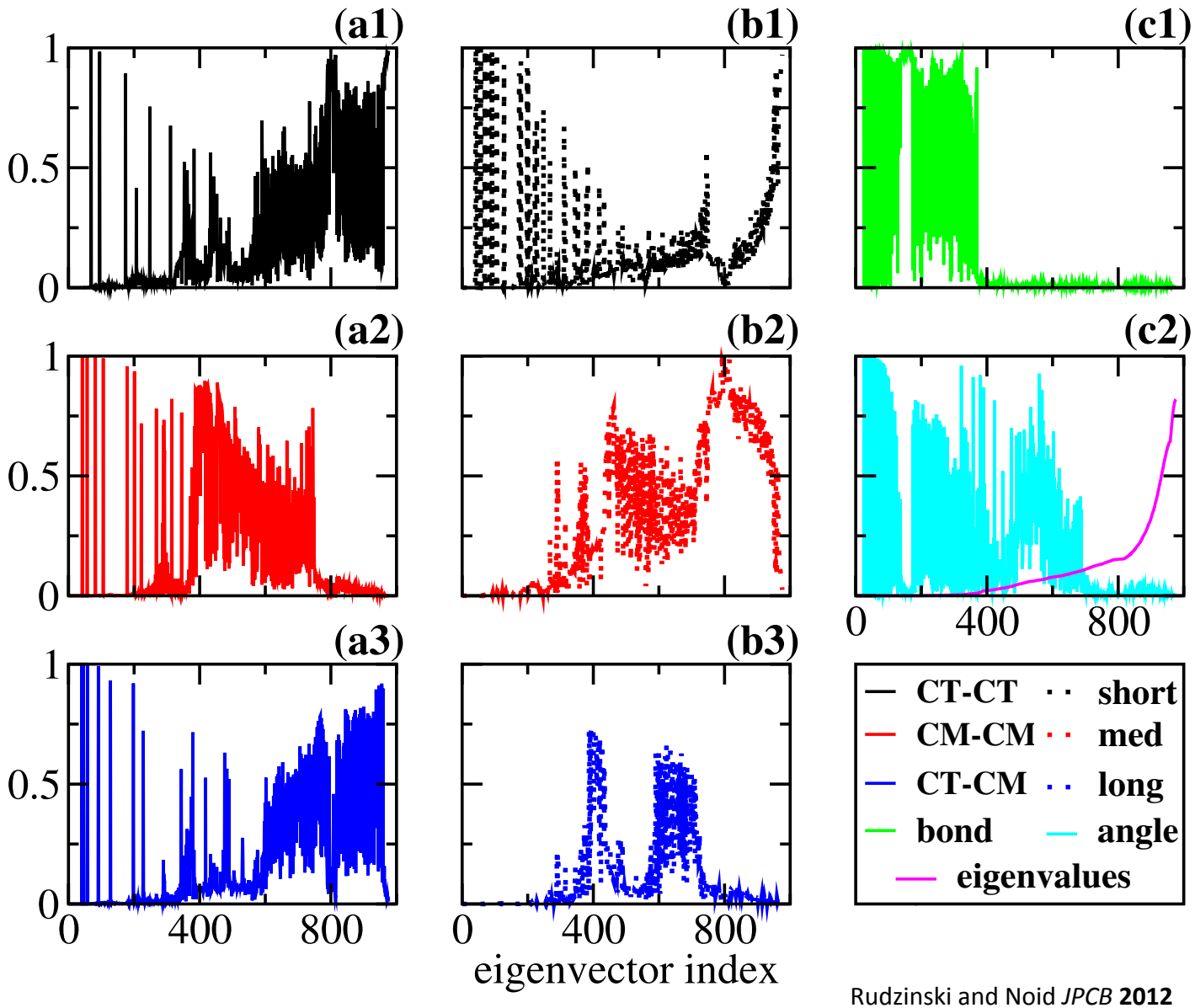
Eigenspectrum of metric tensor



CT

CM

CT



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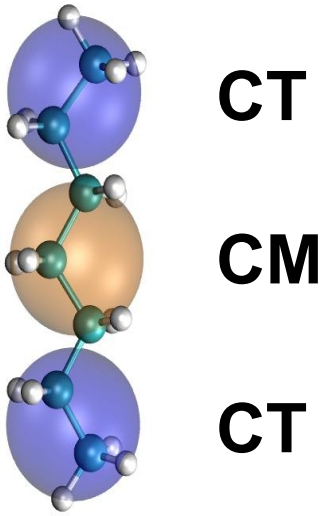
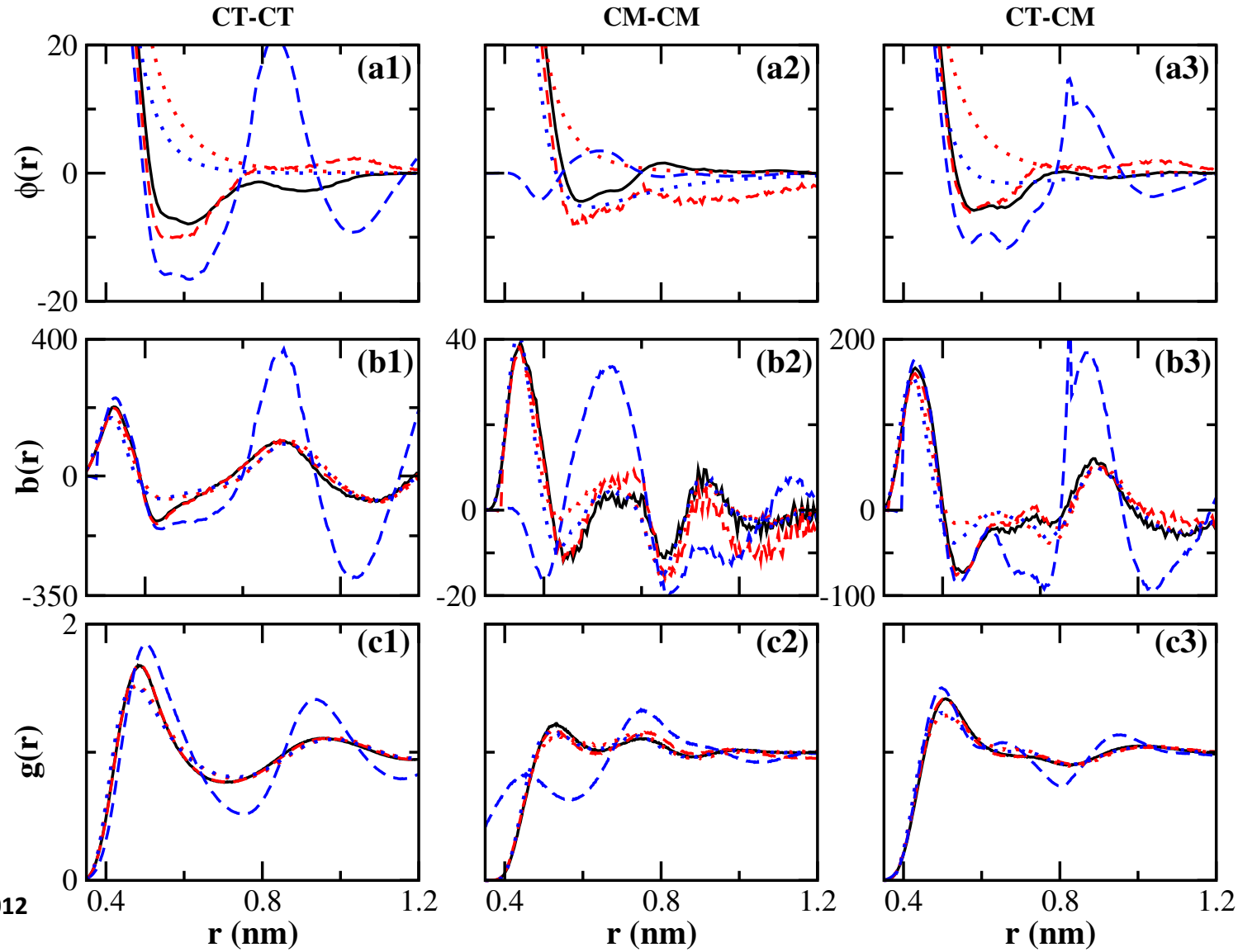
Impact upon CG structure





Rudzinski and Noid *JPCB* **2012**

Outstanding Challenges for Structure-Motivated Coarse-graining

1. Better metrics? – Are rdfs good enough?
2. Expanded basis sets?
3. Optimized mappings?
4. Transferability? – State Point, Systems,
5. Thermodynamics? – Pressure, Phase transitions?
6. Explicit solvent?
7. Explicit simulations? – Experimental data or theory?
8. Predictiveness and error bounds? – CG Amber?
9. Lunch theorems? - What do we want and is it possible?
    1. Does lunch exist?
    2. How much does it cost?

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

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