A Novel Coarse-Grained Force Field for Unbiased Protein-Membrane Simulations

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KITP program on
"Modeling Soft Matter: Linking Multiple Length and Time Scales"

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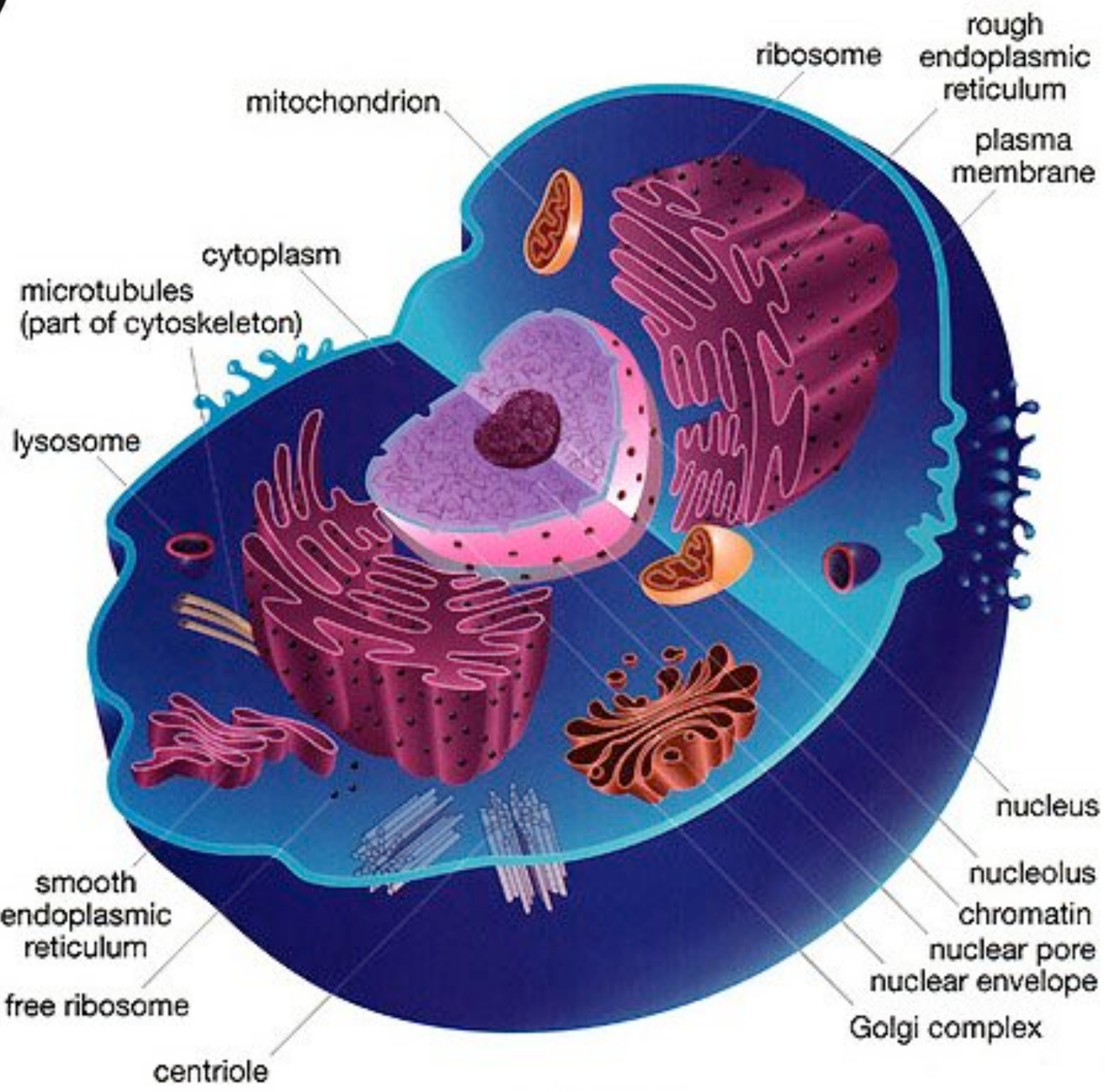
Introduction



http://www.animalport.com/img/Animal-Cell.jpg

Membranes are crucial for the functioning of cells.

Proteins do the work. They also help shaping membranes.

Things often happen on large length- and time-scales.

Protein structure not always known and not always fixed.

Are there any generic principles at work?

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Introduction

We would like to look into this, using tools of the following ilk:

chemically realistic but coarse-grained modeling of both membranes and proteins

no bias on secondary structure

a modicum of transferability

implicit solvent

Introduction

We think we have accomplished a little bit of that tall order. Let me thus talk about:

1. Our membrane model
2. Our peptide model
3. Our method of cross-parametrizing them
4. Some examples of what we can do

1. Our membrane model

Z.-J. Wang and M. Deserno, J. Phys. Chem. B **114**, 11207 (2010).

Z.-J. Wang and M. Deserno, New J. Phys. **12**, 095004 (2010).

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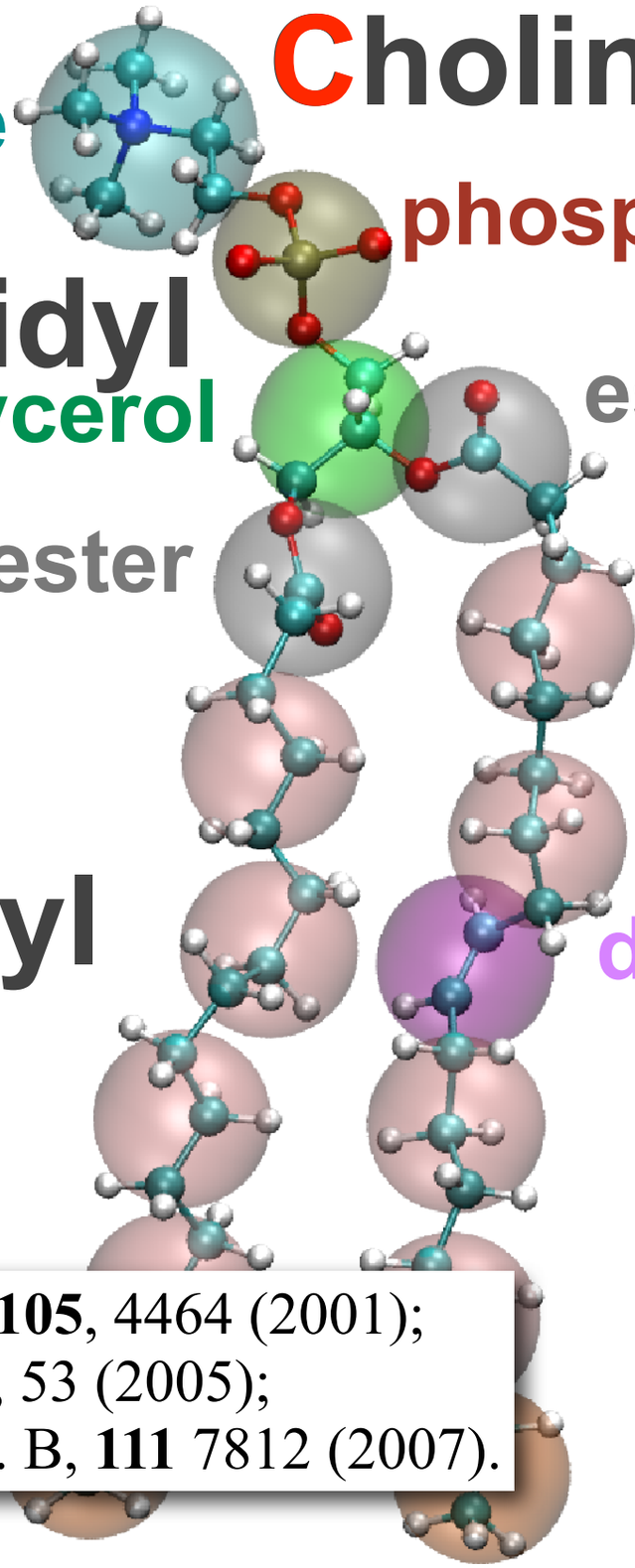
Mapping



16 beads,
7 distinct

J. Shelley *et al*., J. Phys. Chem. B **105**, 4464 (2001);
A. Lyubartsev, Eur. Biophys. J. **35**, 53 (2005);
S.-J. Marrink *et al*., J. Phys. Chem. B, **111** 7812 (2007).

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Construction principles:

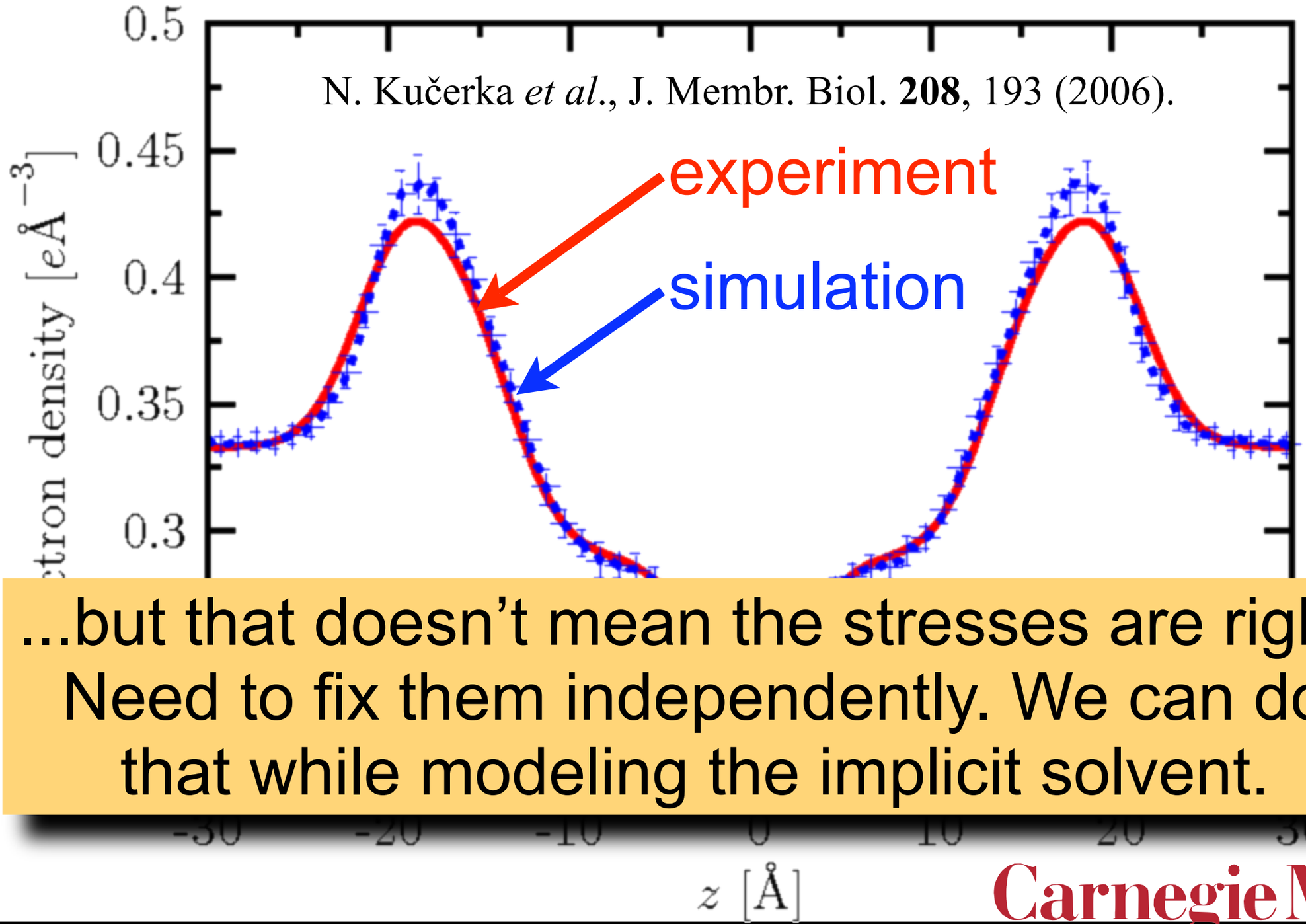
Structure-based coarse-graining
(for most non-bonded interactions)

density and pressure profiles
(from experiment and simulation)

area per lipid
(from experiment)

Area per lipid

The electron density at an area-per-lipid fixed to the correct value is reproduced very well!



...but that doesn't mean the stresses are right. Need to fix them independently. We can do that while modeling the implicit solvent.

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Strategy:

Use aa simulations at the correct area to infer structure

Introduce phenomenological cohesion in CG model to drive aggregation

Choose value of that cohesion to fix the zero-tension area per lipid.

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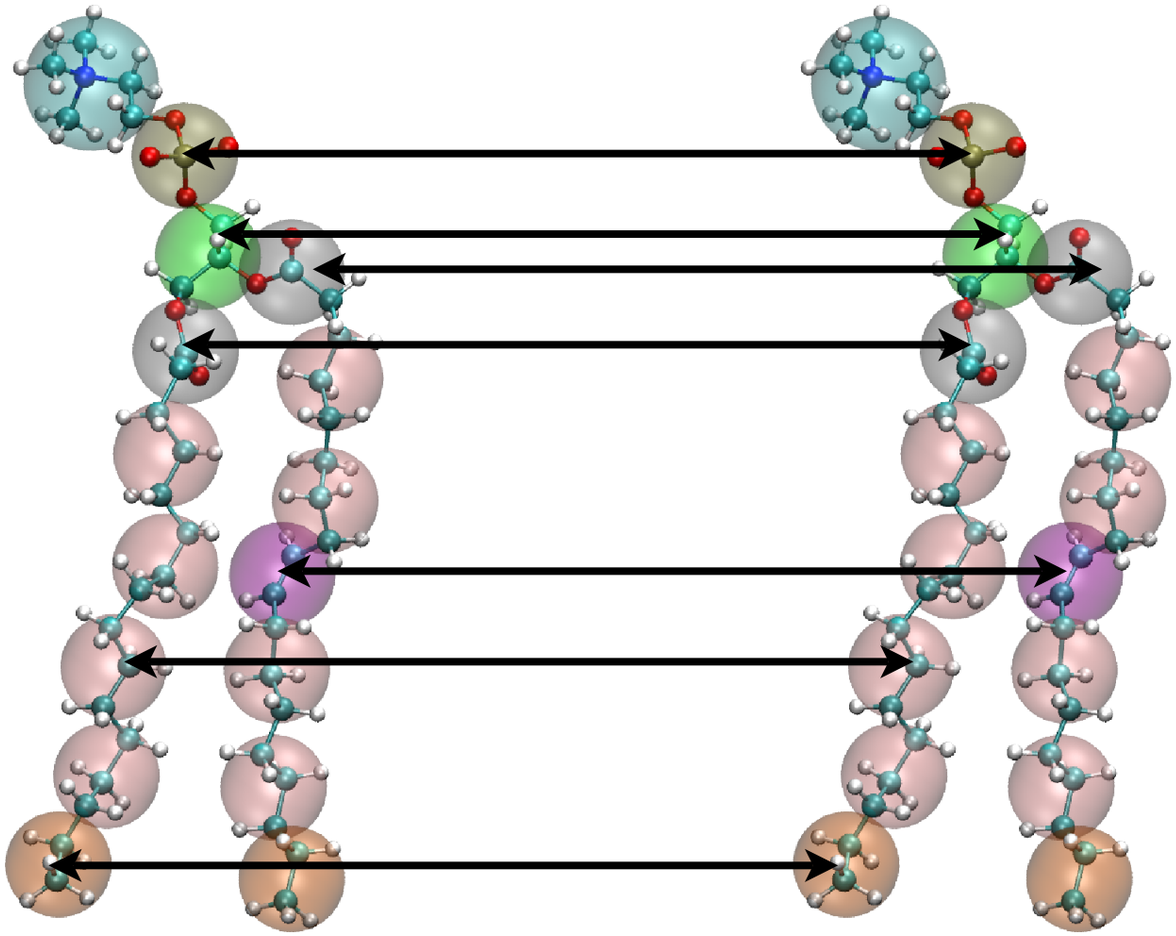
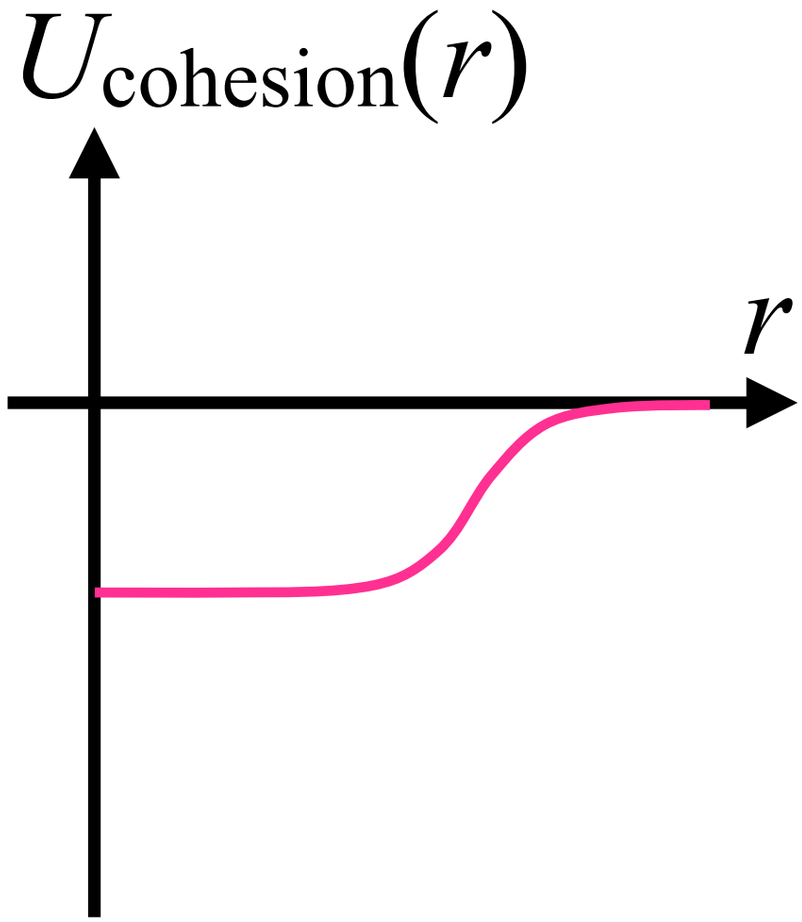
Strategy:





Range and amplitude can vary between different bead types.
This is optimized to reproduce the pressure profile.

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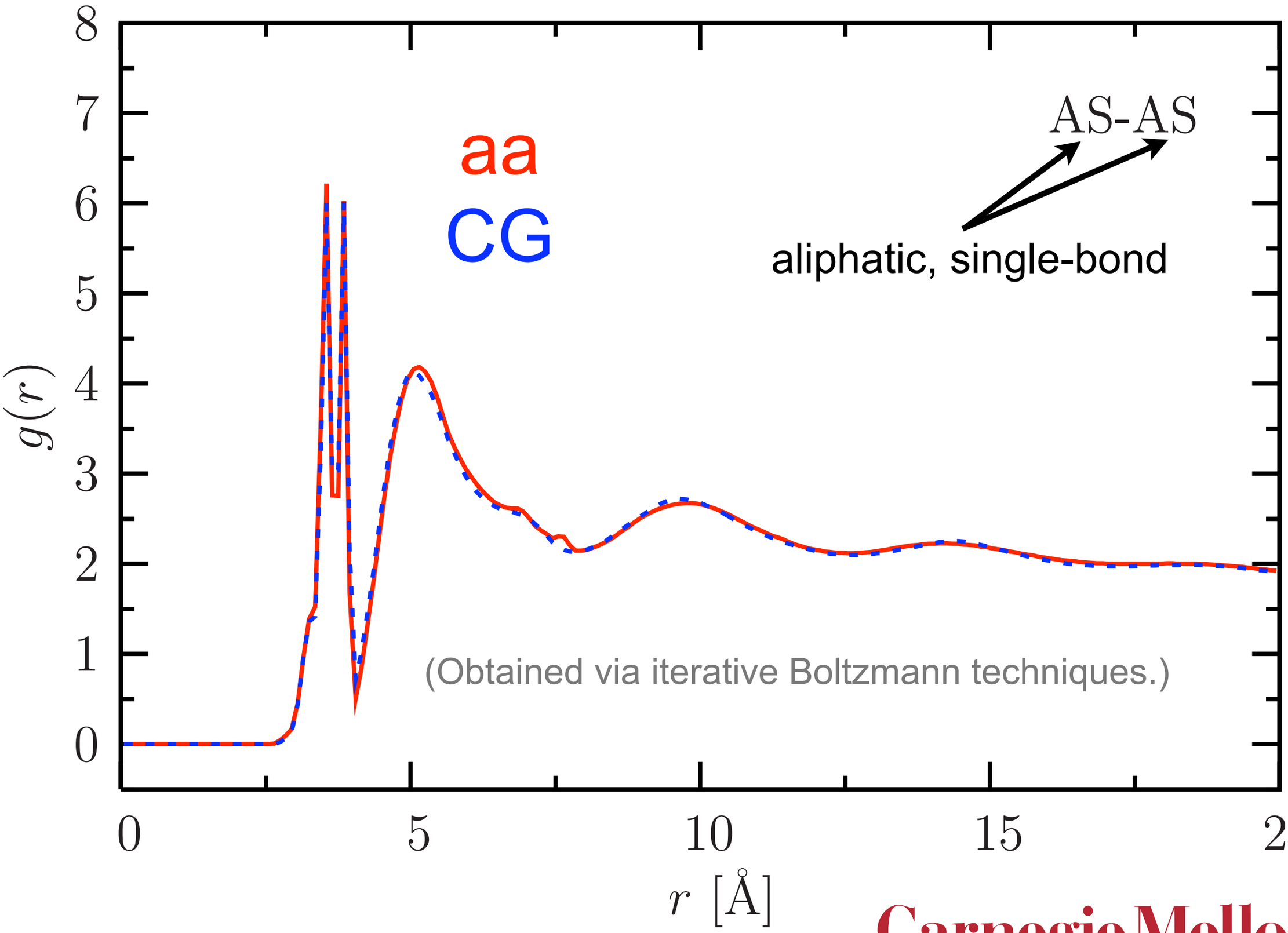
Example for structure



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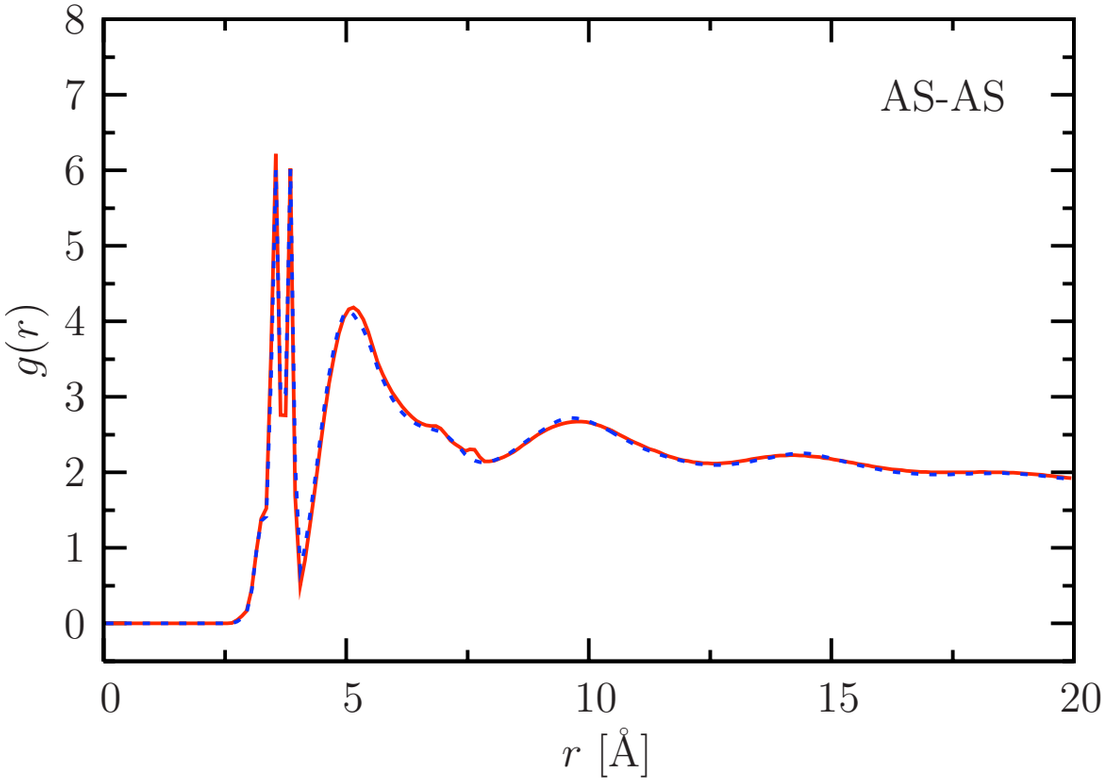
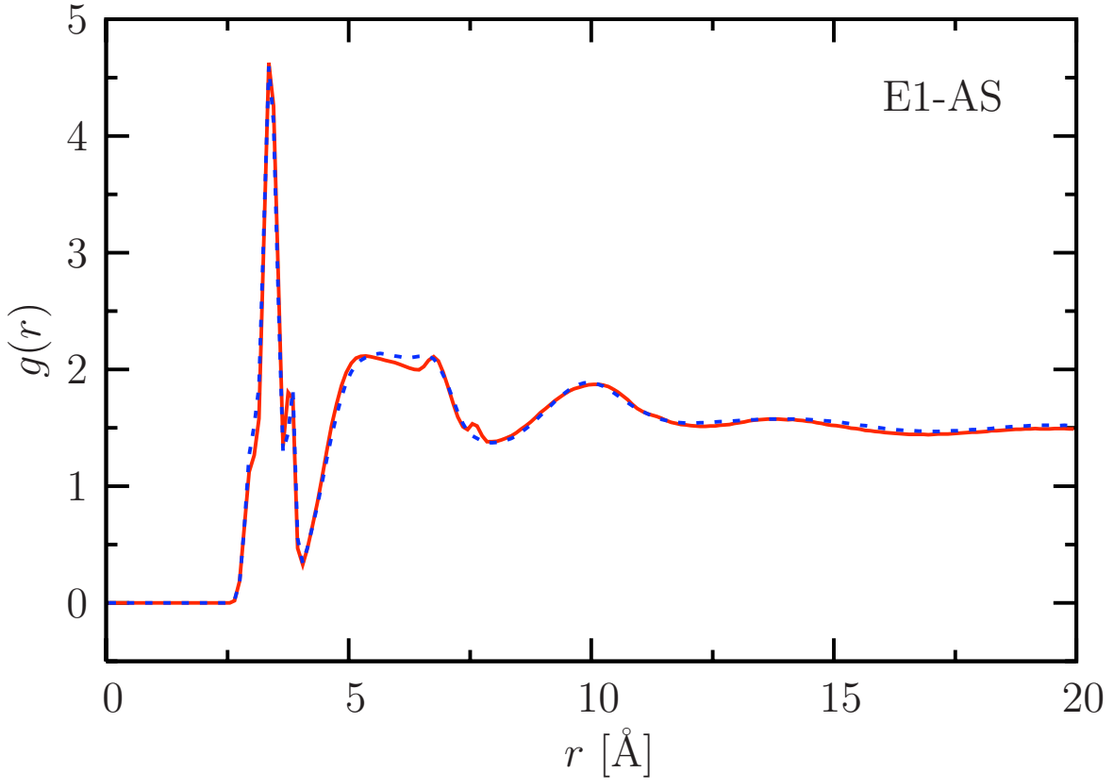
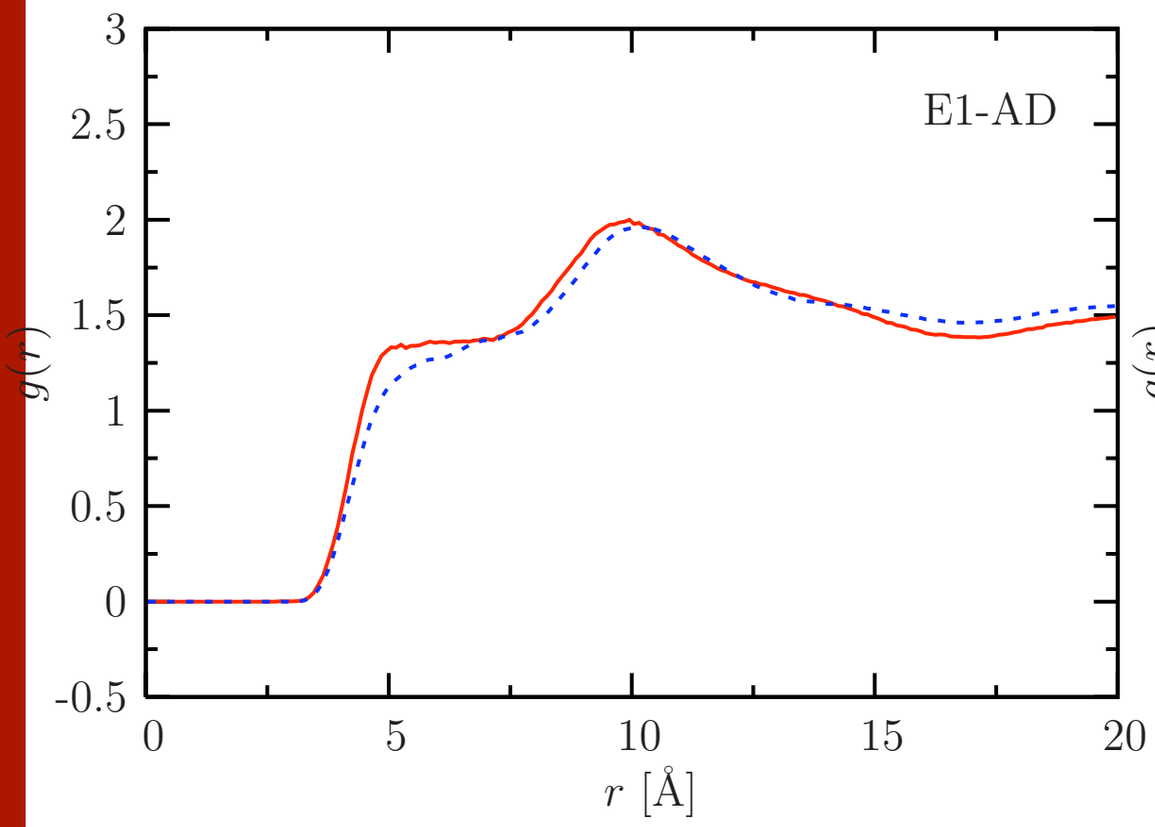
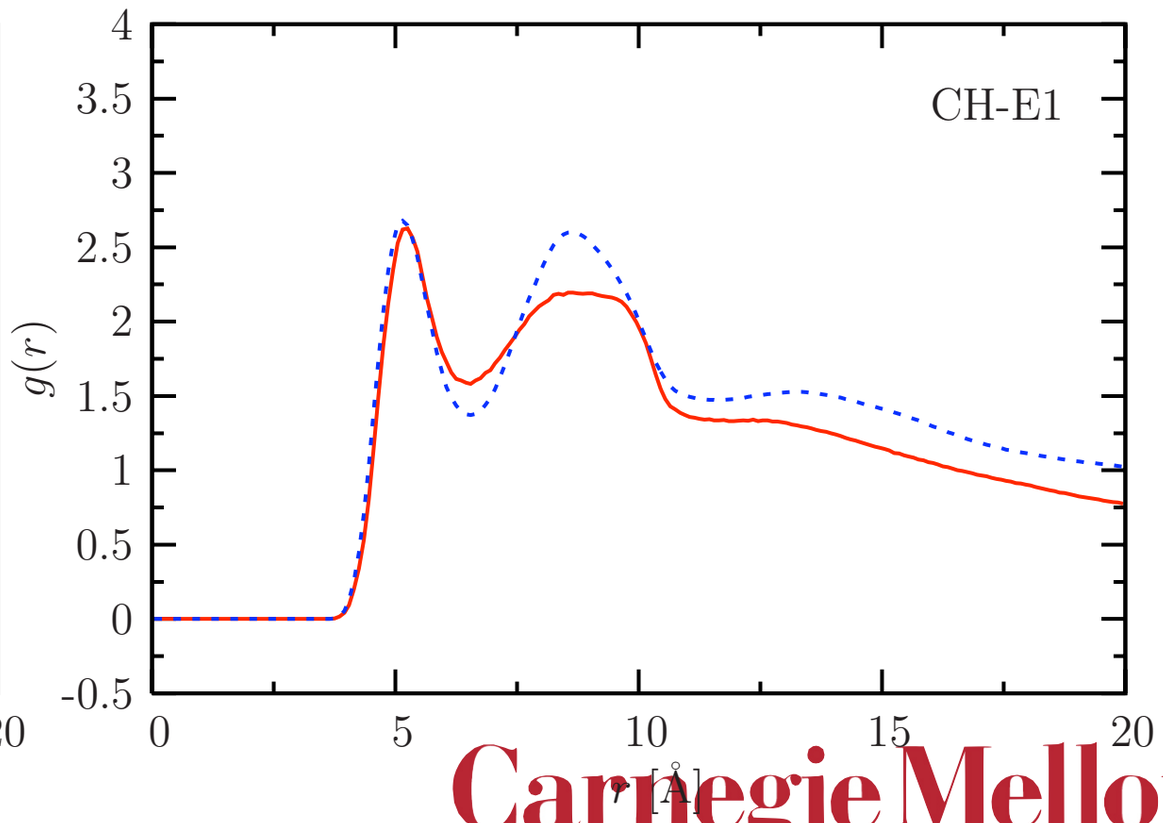
Example for structure aa CG









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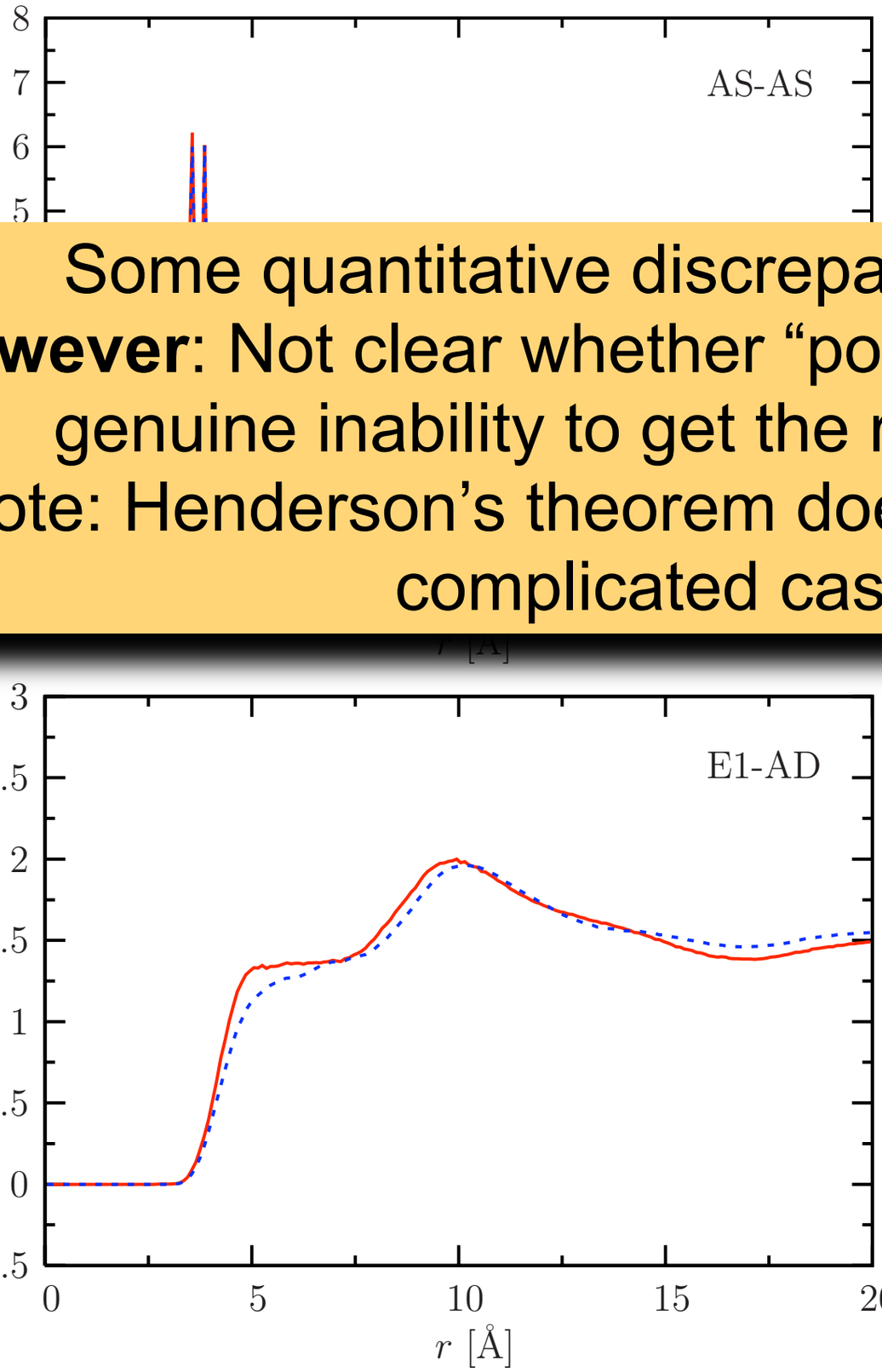
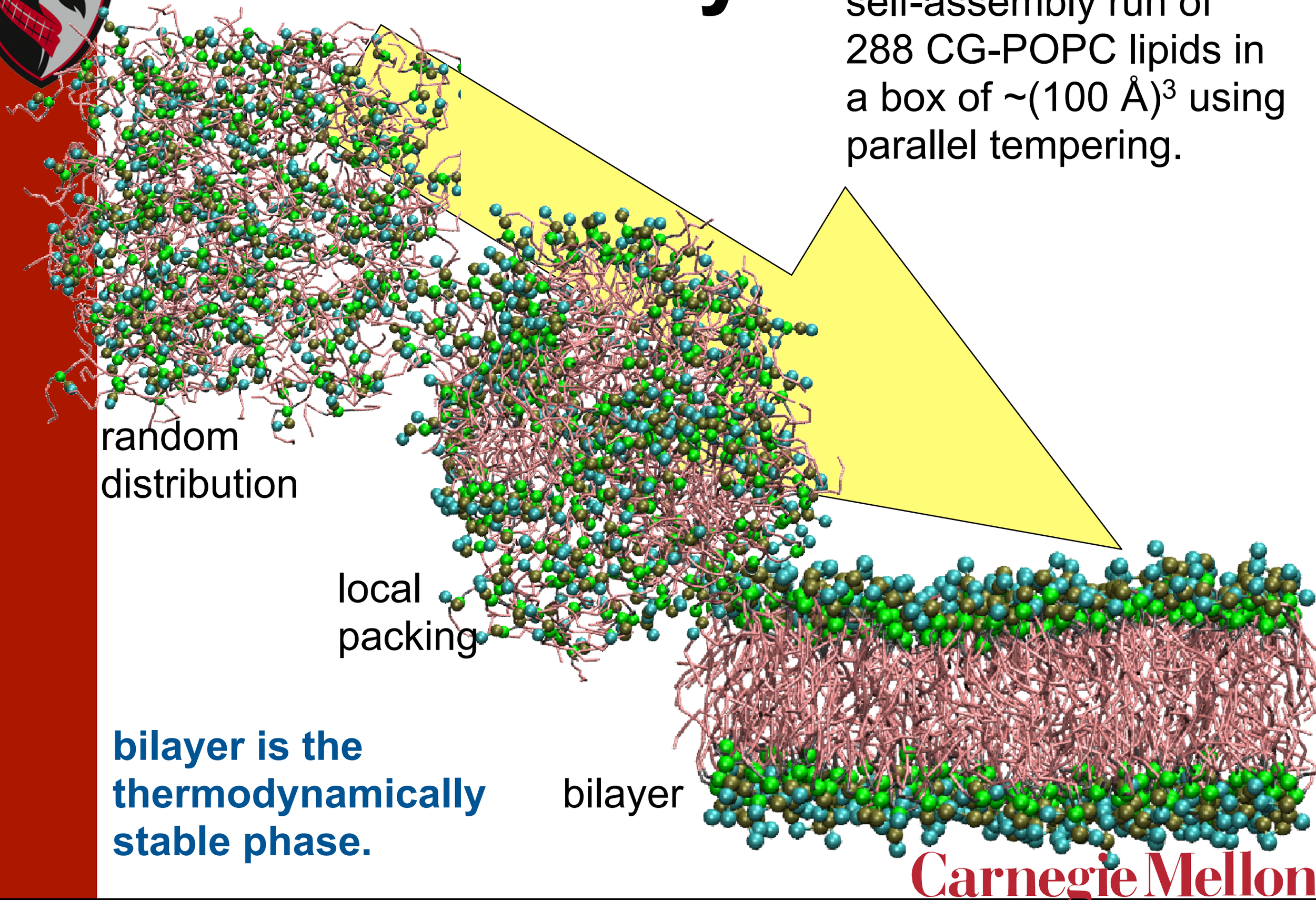
Example for structure aa CG



Some quantitative discrepancies remain.
However: Not clear whether “poor convergence” or genuine inability to get the right structure.
(Note: Henderson’s theorem does *not* apply to this complicated case!)

Self-assembly

self-assembly run of 288 CG-POPC lipids in a box of ~(100 Å)^3 using parallel tempering.



random distribution

local packing

bilayer

bilayer is the thermodynamically stable phase.

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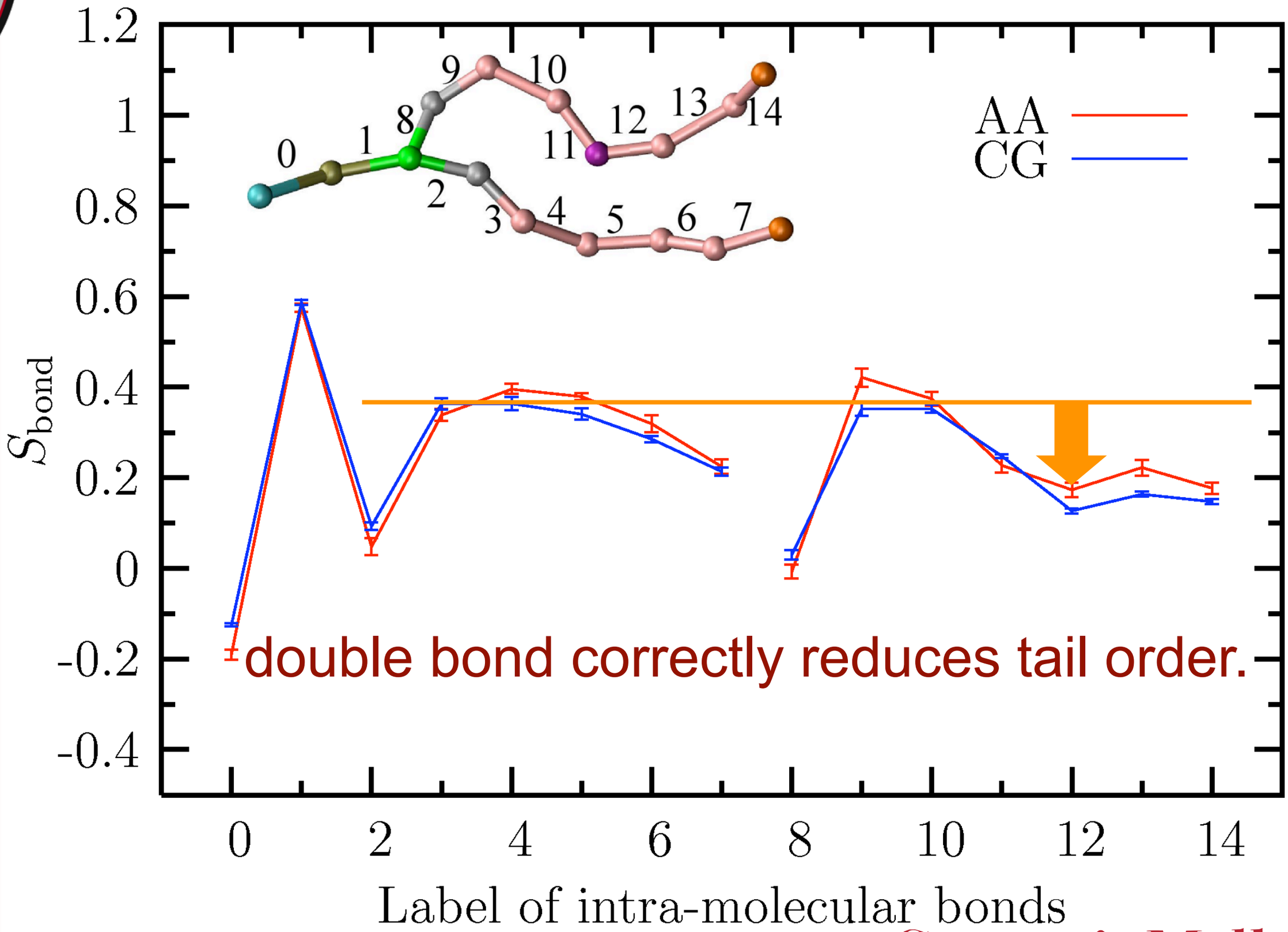
Tail order



double bond correctly reduces tail order.

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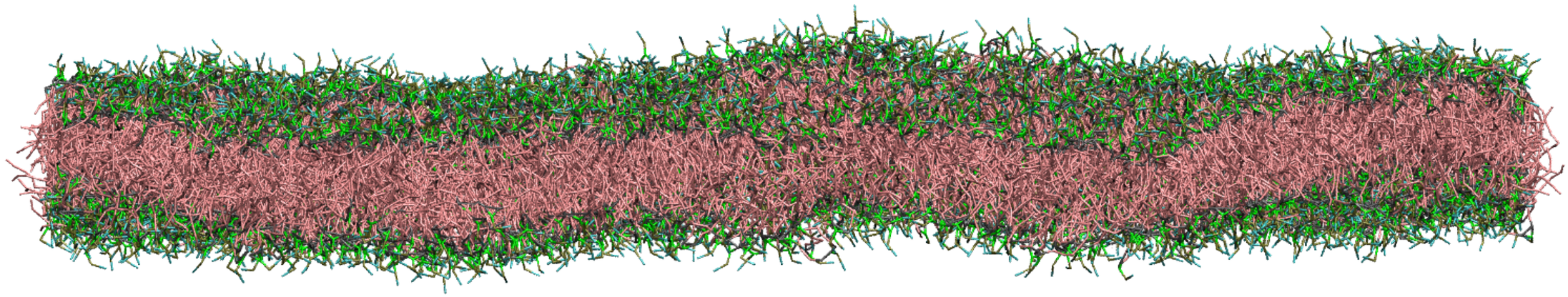
Elastic properties

Bending modulus κ

4608 lipids, (~40nm)^2 box, several μs



from fluctuations: $\kappa = \dfrac{k_B T}{L^2 q^4 \left\langle \left| h_q \right|^2 \right\rangle}$ $(8...10)\times10^{-20}$ J

experimentally, it's about: 8.5×10^{-20} mN/m

N. Kučerka, S. Tristram-Nagle & J.F. Nagle, J. Mem. Biol. **208**, *193* (2005).

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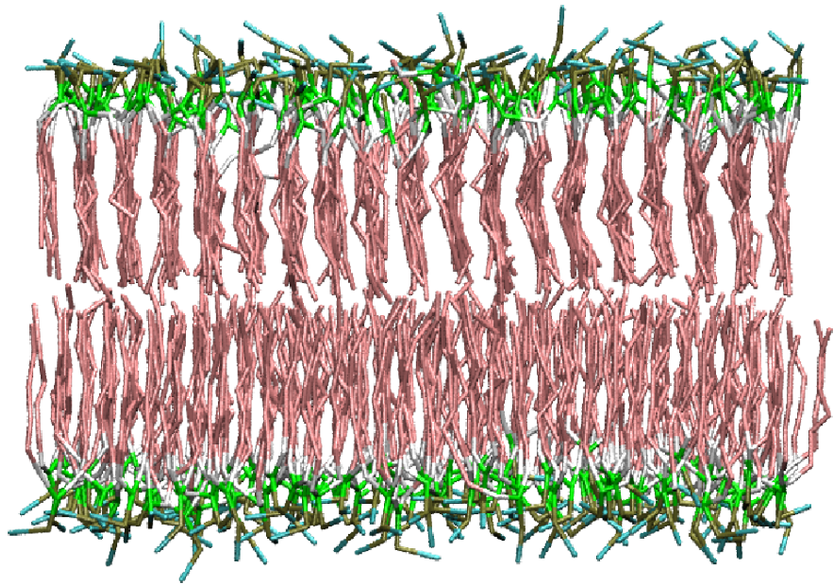
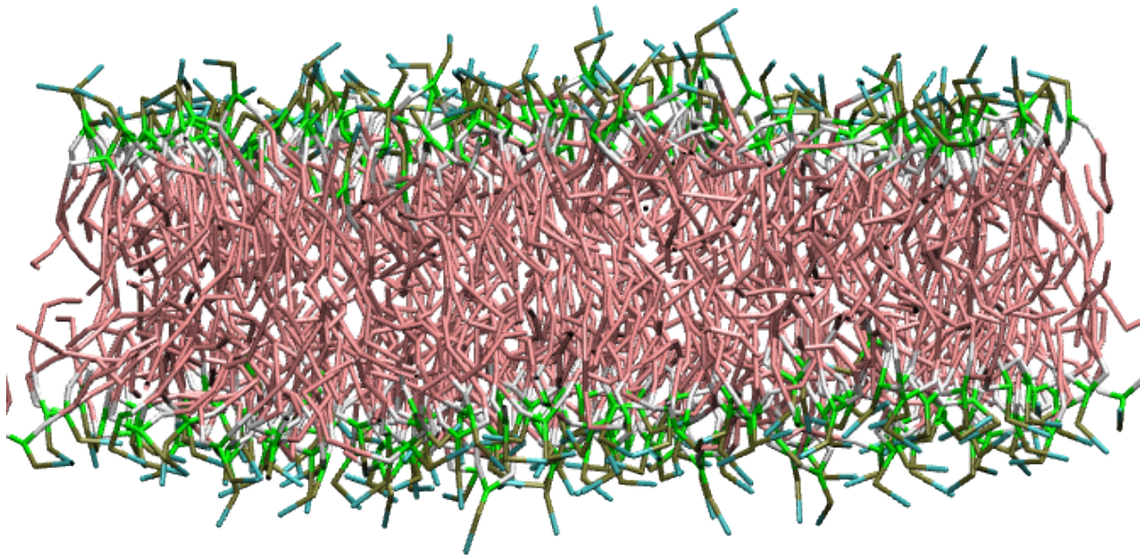
Phase behavior

Our bilayer shows a liquid-gel transition.



T=279 K



T=310 K

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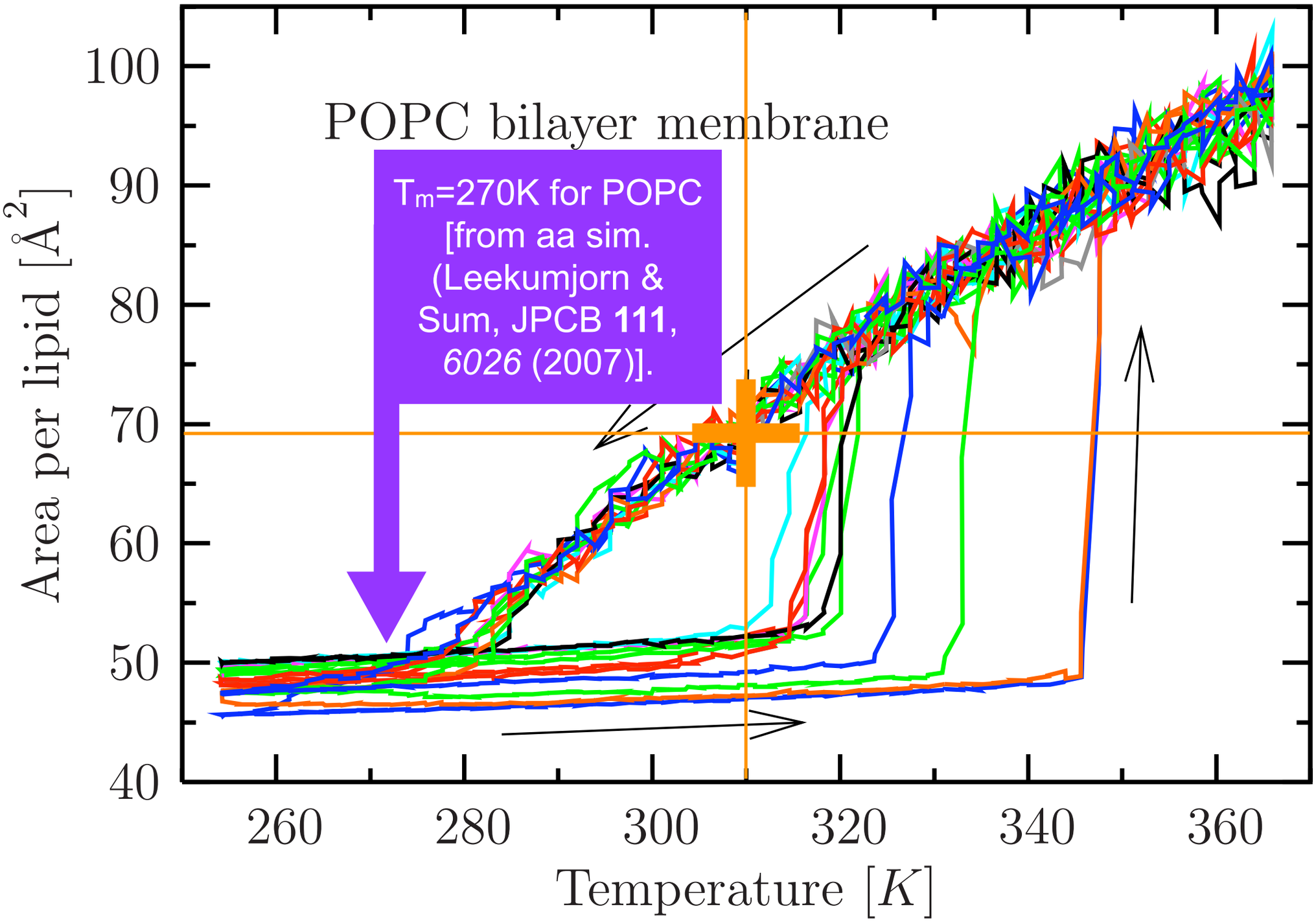
Phase behavior



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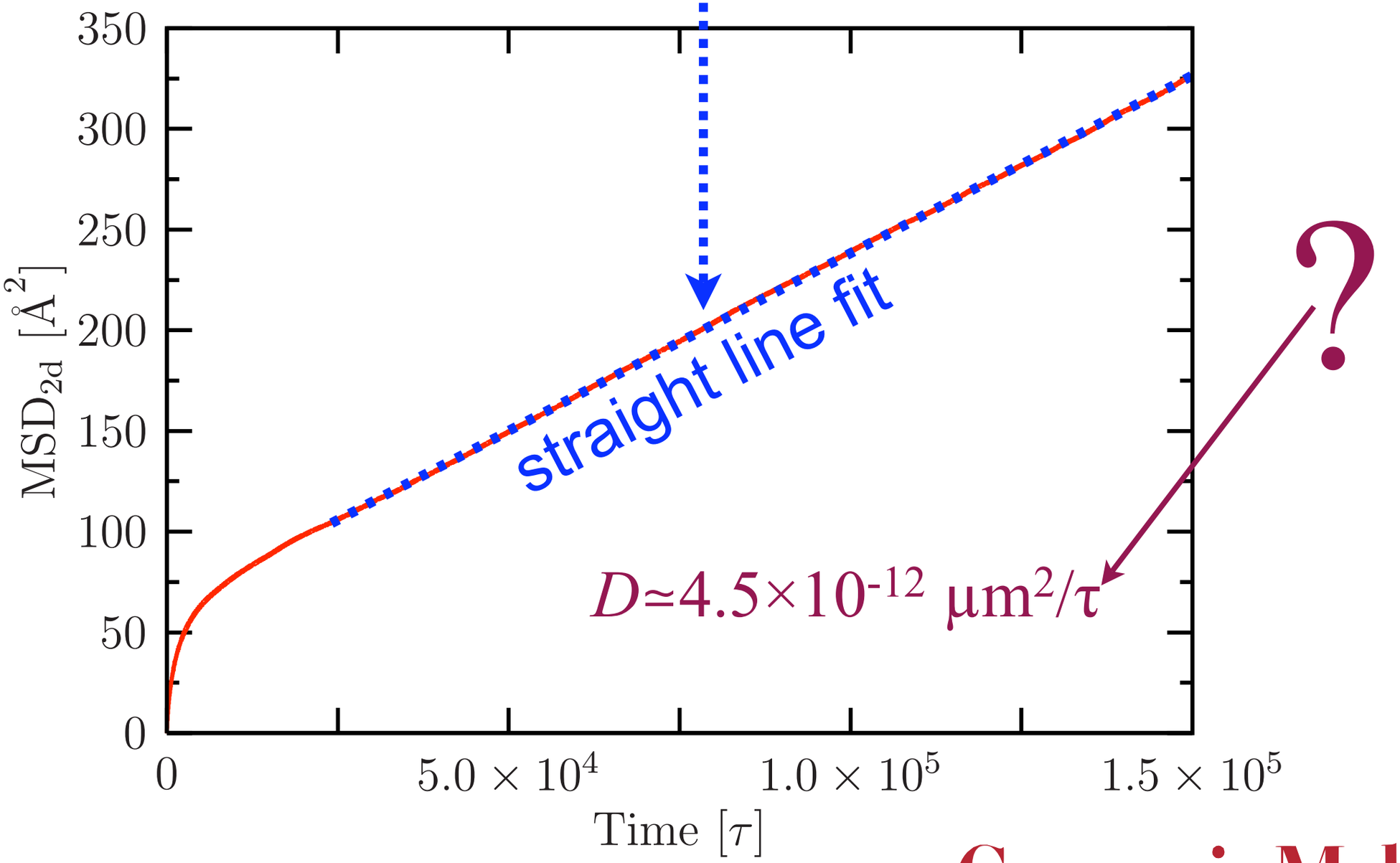
Diffusion

Diffusion constant from: $D = \lim_{t\to\infty}\left\{\frac{1}{4N}\frac{\mathrm{d}}{\mathrm{d}t}\left\langle\sum_{i=1}^{N}\Delta r_i^2\right\rangle\right\}$



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Time mapping

intrinsic computer time: $\tau = \sigma\sqrt{m/\varepsilon} = 0.062\,\mathrm{ps}$

Using this to translate times gives

$D \simeq 4.5\times10^{-12}\ \mu m^2/(0.062\ ps) \simeq 73\ \mu m^2/s$

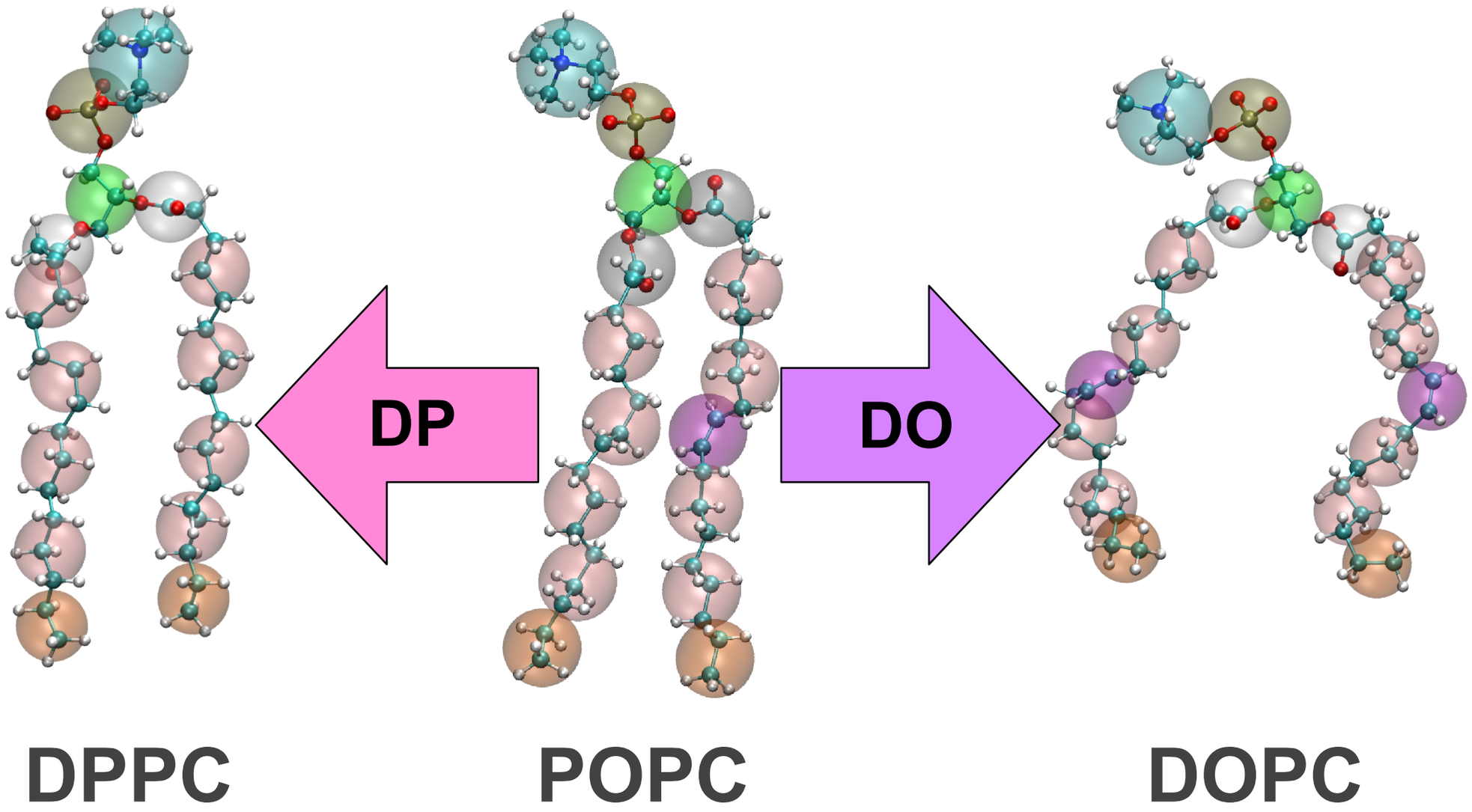
Experimentally, more like $D \simeq (1...10)\ \mu m^2/s$

However:

Reduced CG resolution implies reduced friction and thus an *expected* speed-up!
(Here, between one and two orders of magnitude)

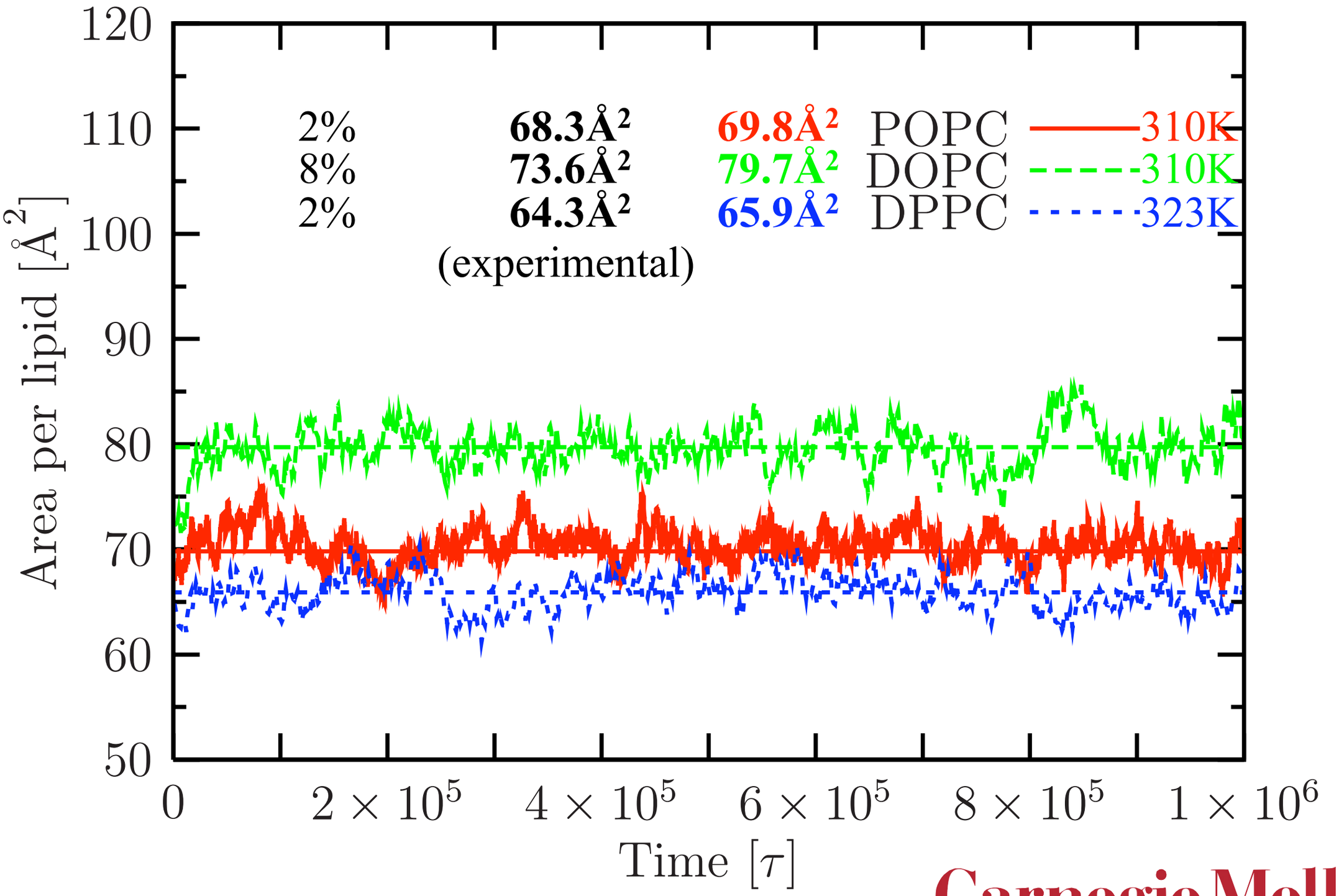
Transferability

Example: “tail swapping”



Transferability

Area per lipid



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2. Our peptide model

T. Bereau and M. Deserno, J. Chem. Phys. **130**, 235106 (2009);
T. Bereau, M. Bachmann, and M. Deserno, J. Am. Chem. Soc. **132**, 13129 (2010);
T. Bereau, M. Deserno, and M. Bachmann, Biophys. J. **100**, 2764 (2011);
T. Bereau, C. Globisch, M. Deserno, and C. Peter, J. Chem. Theo. Comput. ASAP (2012).

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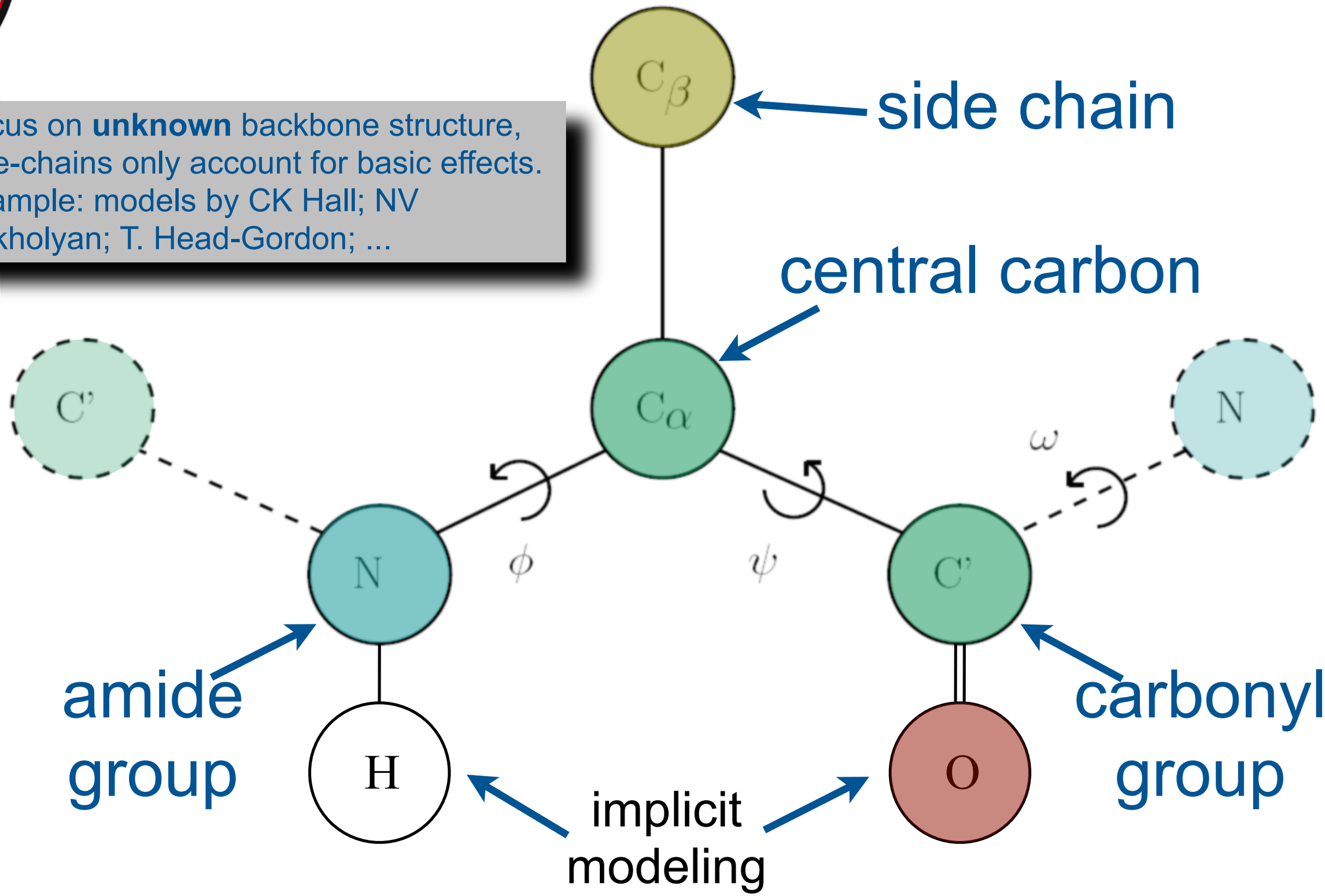
Our model

Focus on **unknown** backbone structure, side-chains only account for basic effects. Example: models by CK Hall; NV Dokholyan; T. Head-Gordon; ...



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Interactions

bonded

- harmonic bonds
- harmonic angles
- dihedrals: simple cosine

improper dihedrals
fix chirality at C_α

non-bonded

- excluded volume ← Ramachandran plot
- hydrophobic interactions
- hydrogen bonds
- peptide dipoles

} folding characteristics

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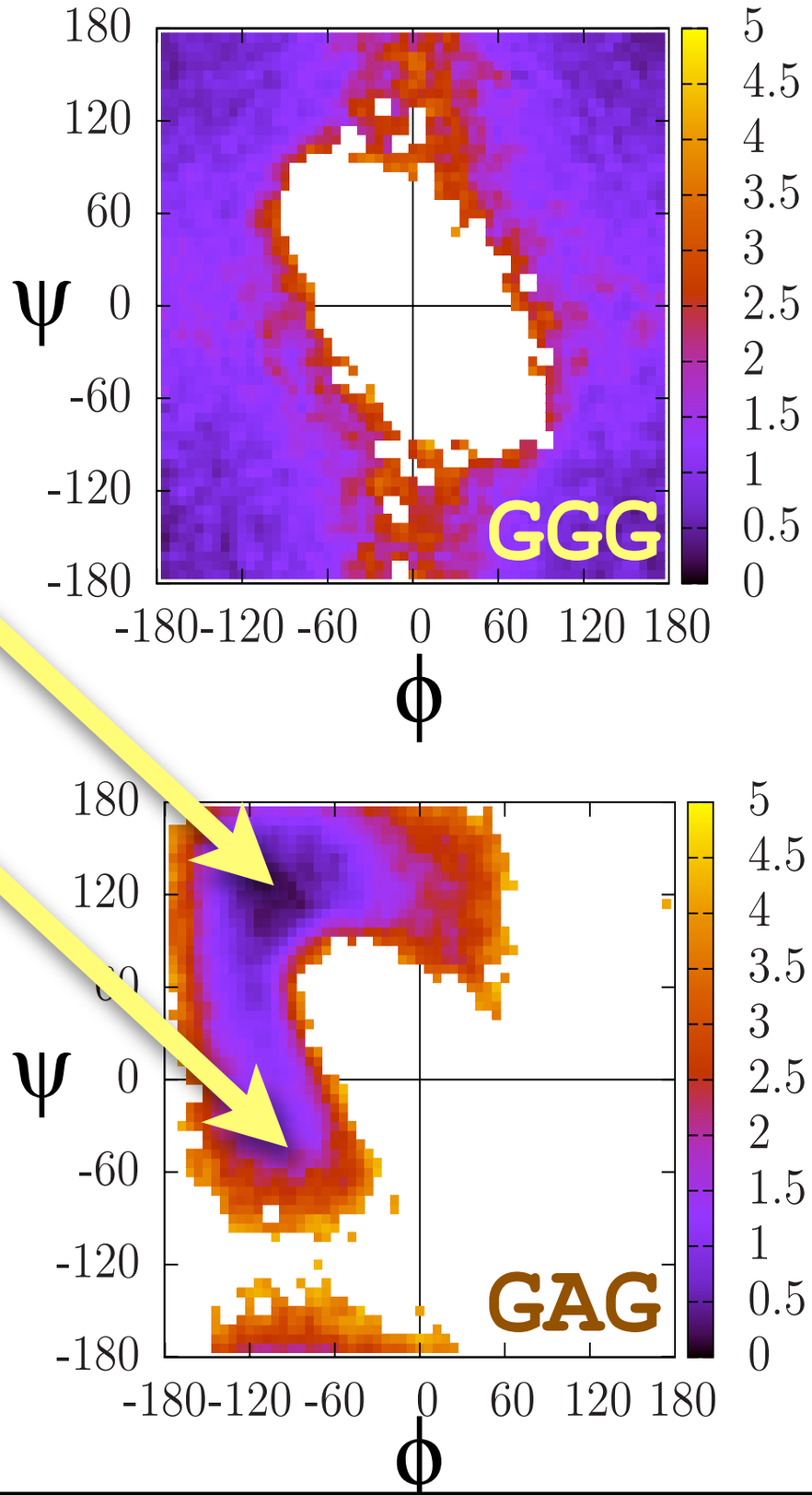
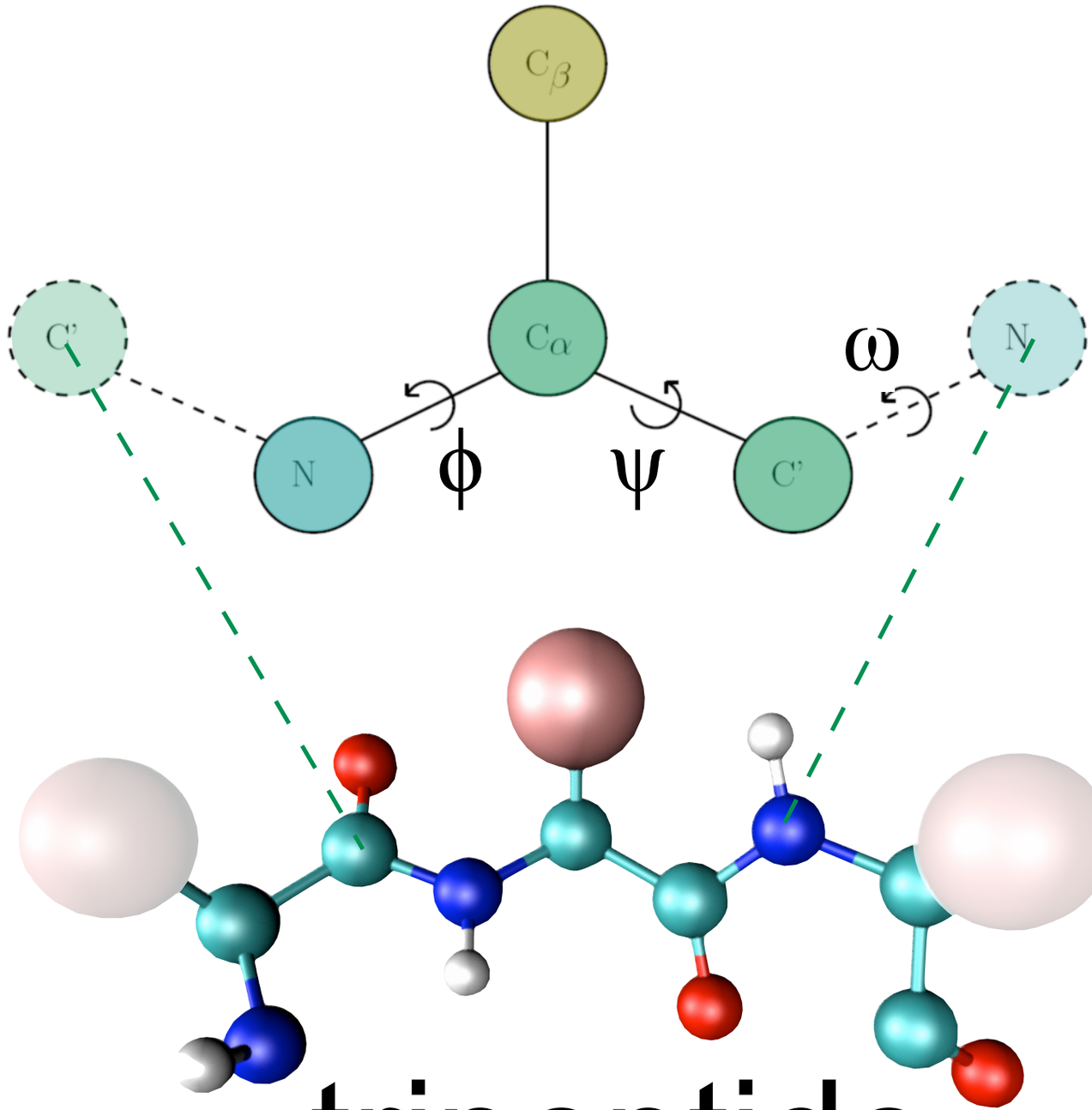
Ramachandran plots



β

α



tripeptide

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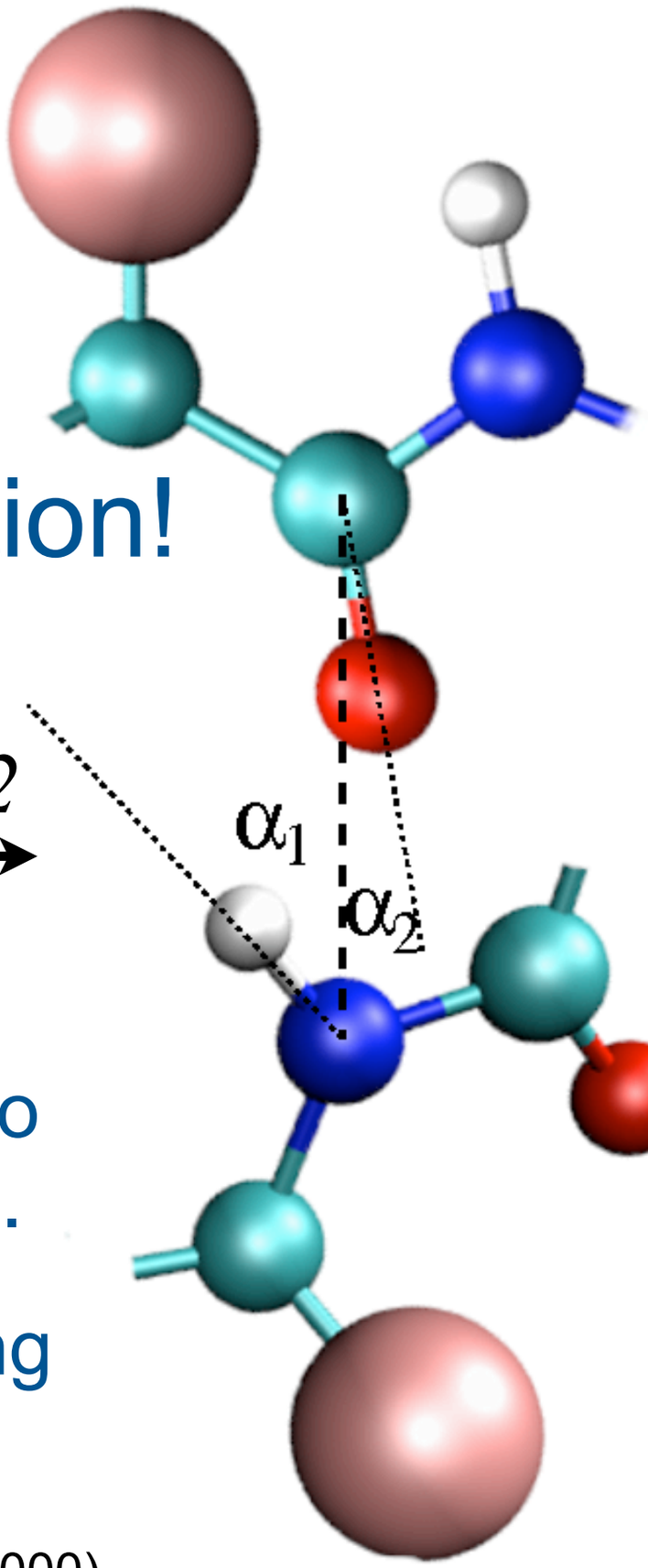
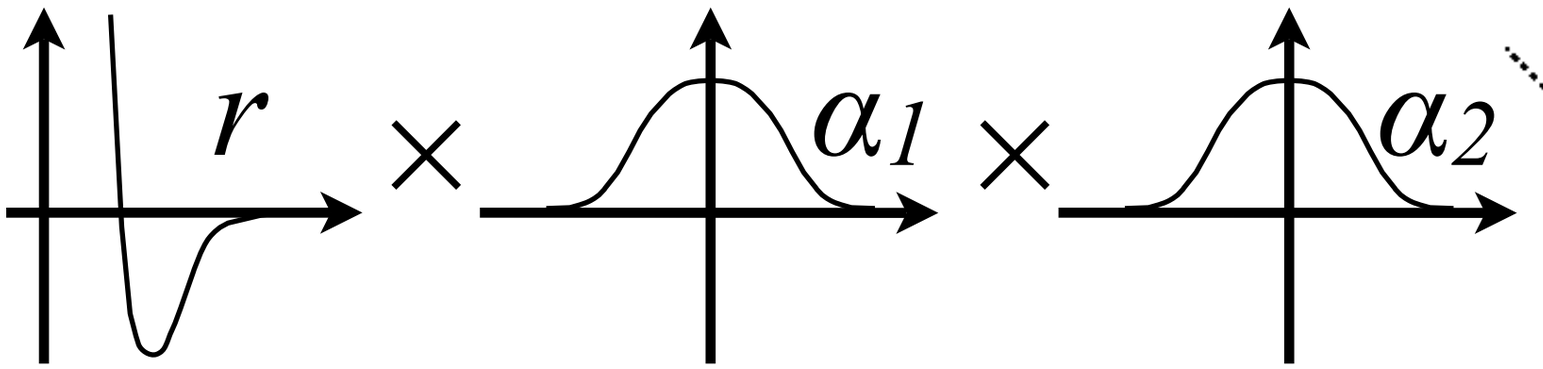
Hydrogen bonds



extremely important for secondary structure formation!

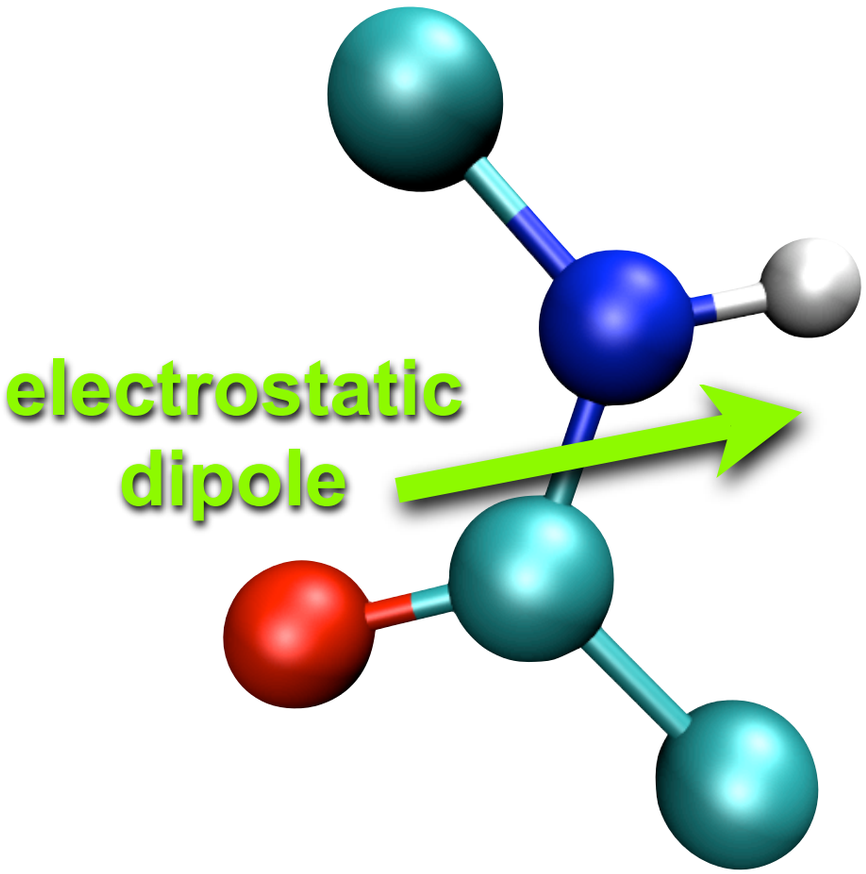


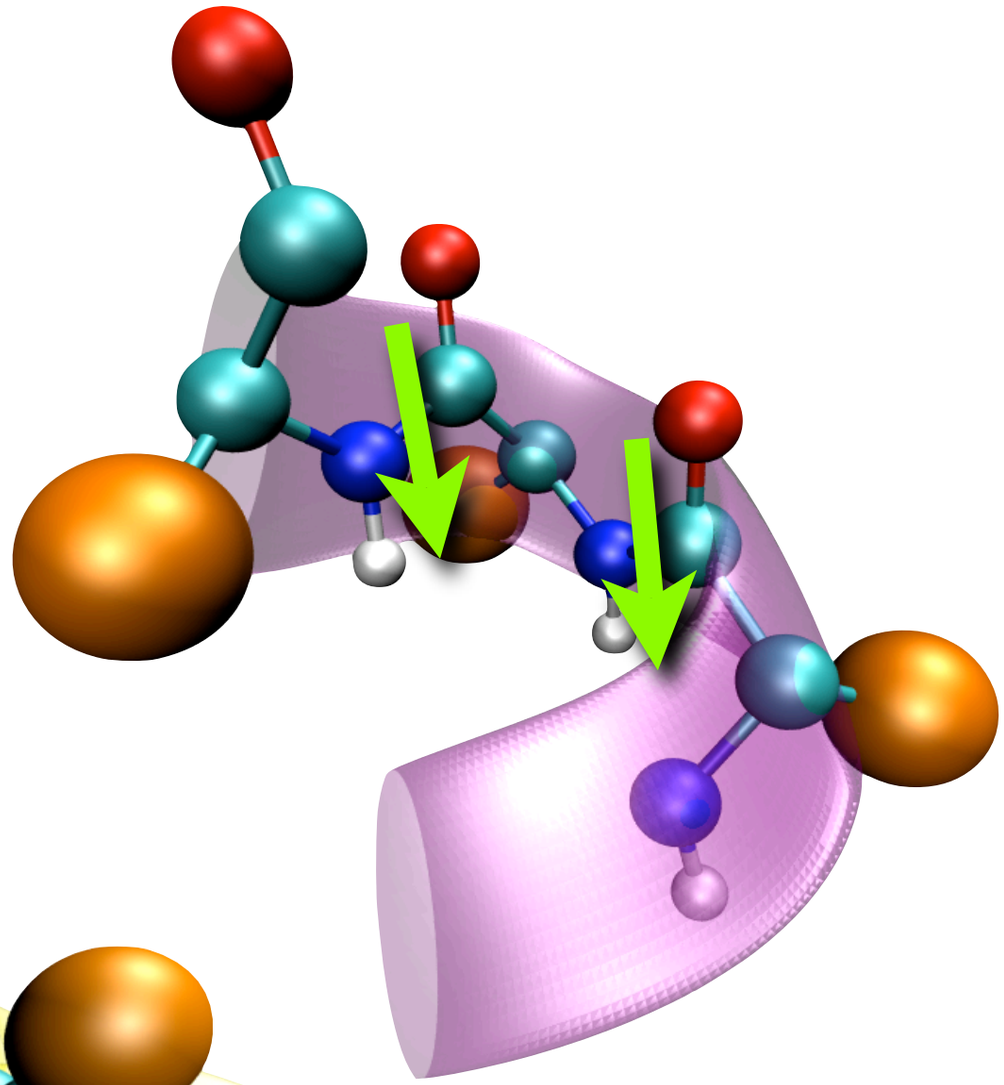
Potential ***range*** adjusted according to known properties of hydrogen bonds.

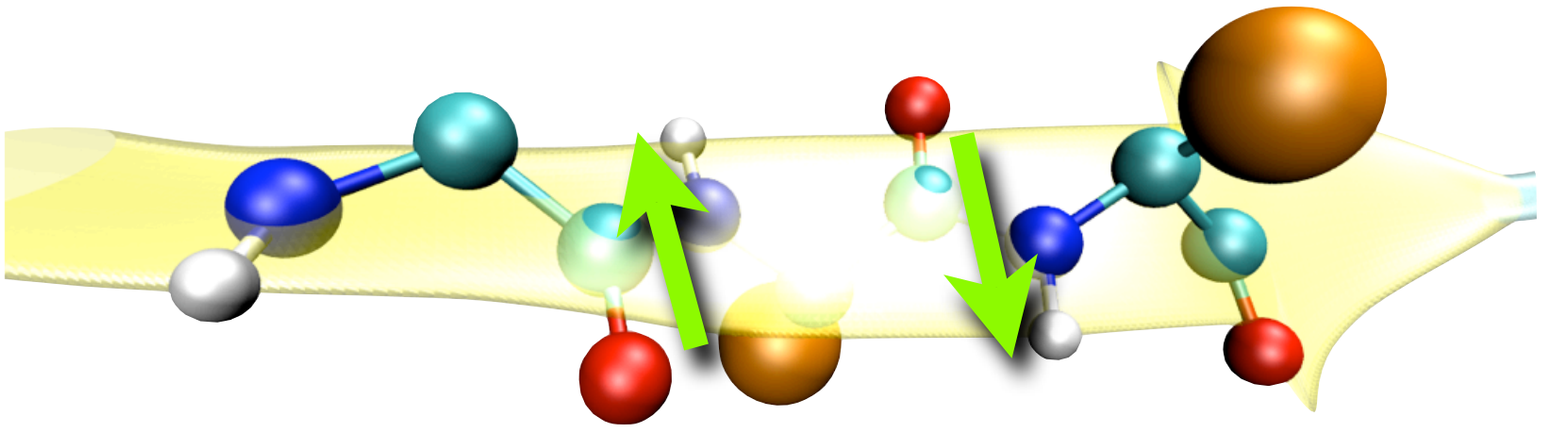
Potential ***strength*** adjusted according to folding properties of the model.

A. Irbäck, F. Sjunneson, and S. Wallin, PNAS 97, 13614 (2000)

Peptide bond dipoles







N.Y. Chen, Z.Y. Su, and C.Y. Mou, Phys. Rev. Lett. **96**, *078103* (2006)

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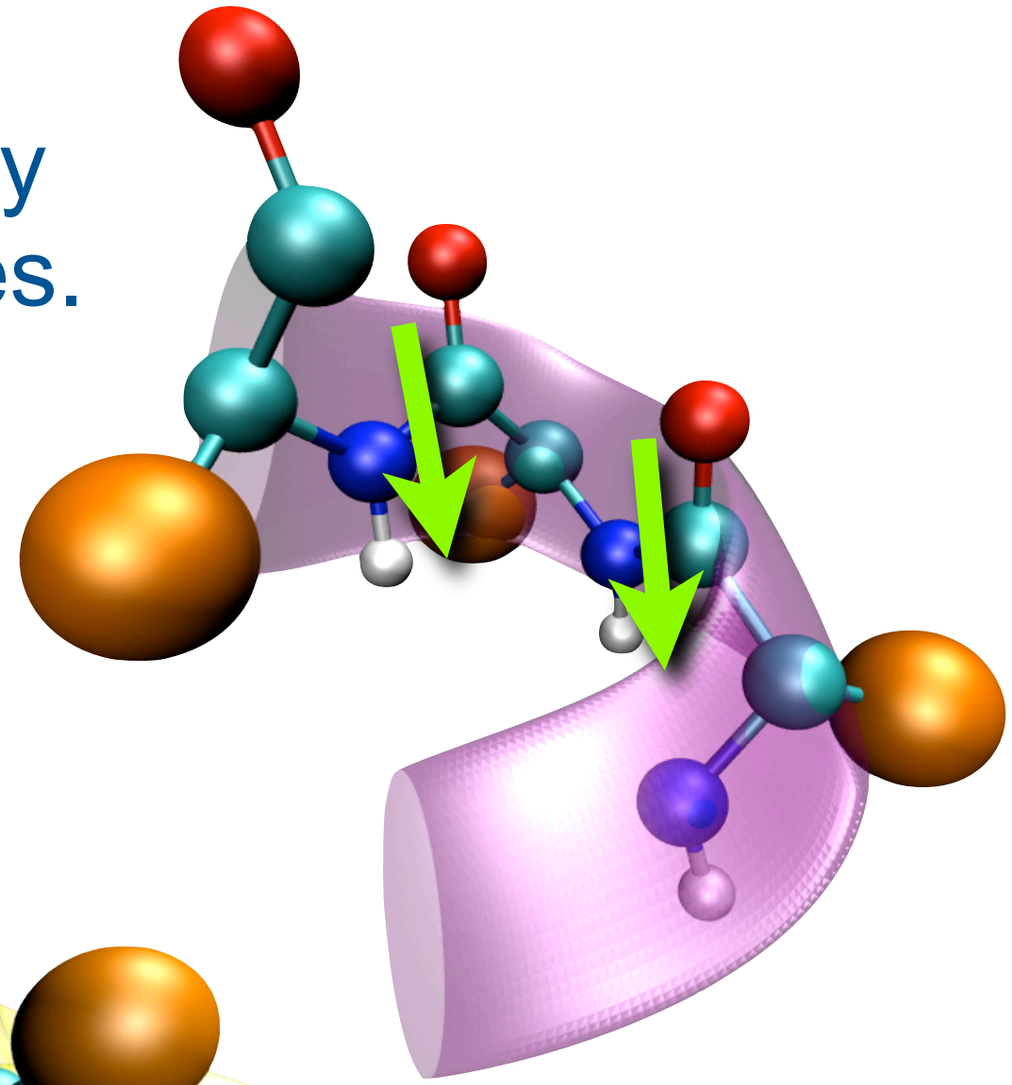
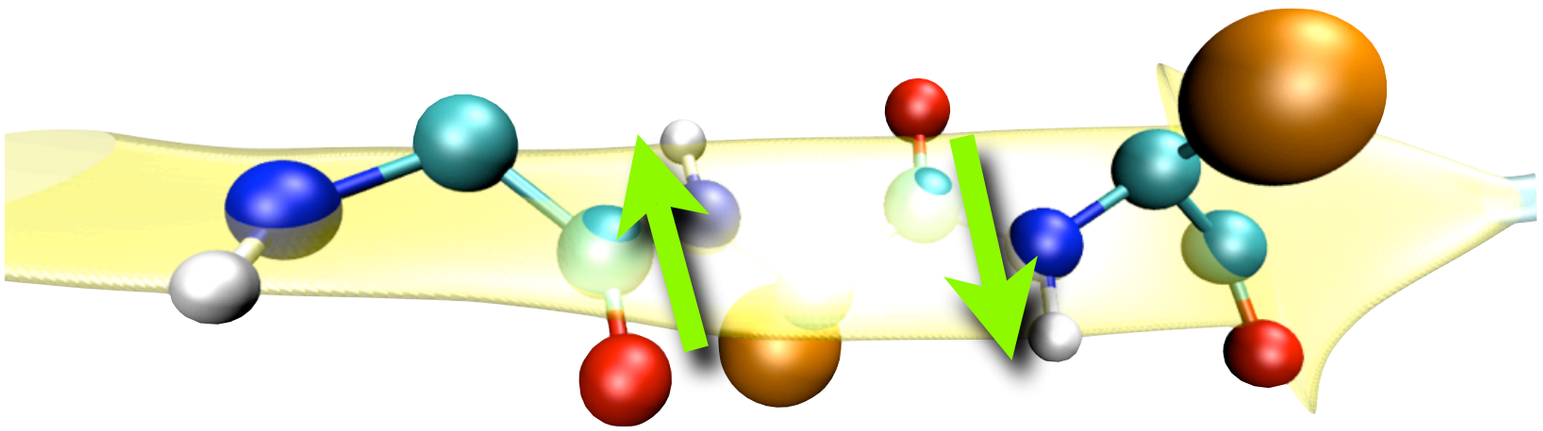
Peptide bond dipoles

β-sheets are electrostatically more favorable than α-helices.

Incorporate this effect in the (ϕ,ψ)-dihedrals!





N.Y. Chen, Z.Y. Su, and C.Y. Mou, Phys. Rev. Lett. **96**, *078103* (2006)

Y. Mu and Y.Q. Gao, J. Chem. Phys. **127**, *105102* (2007)

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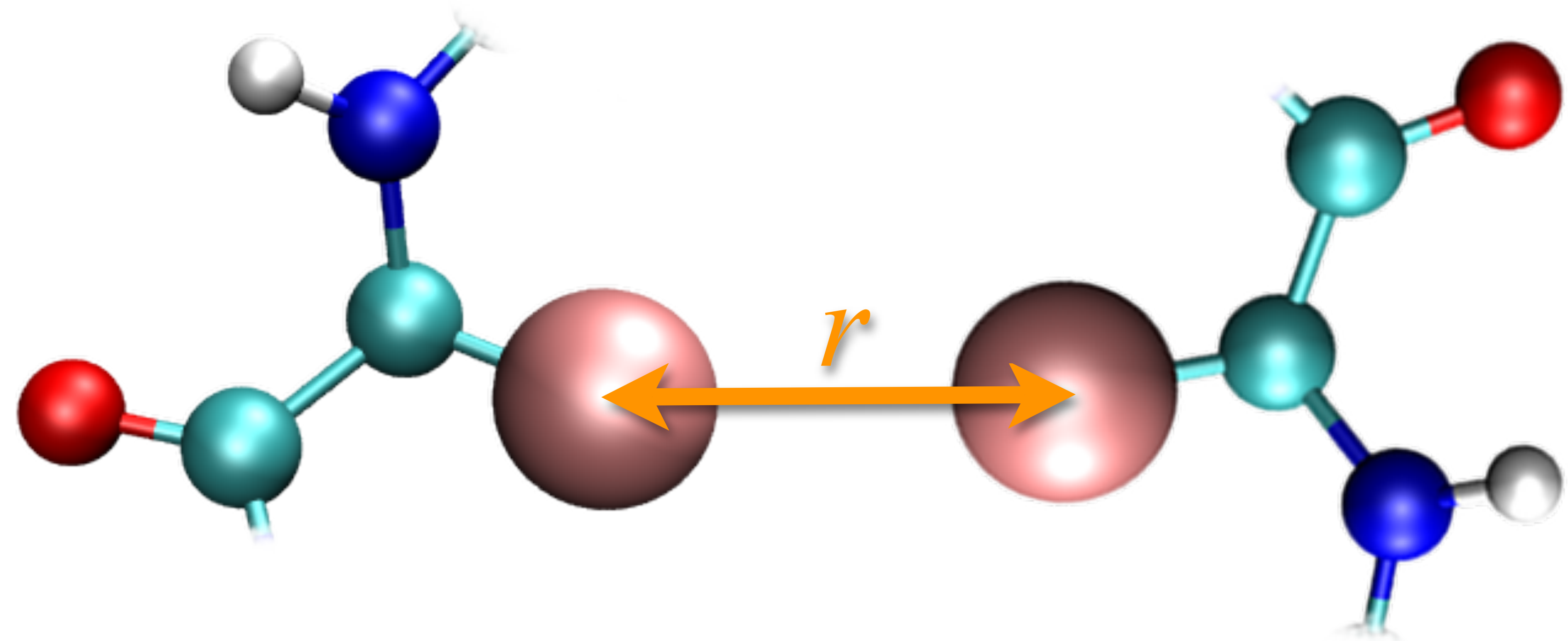
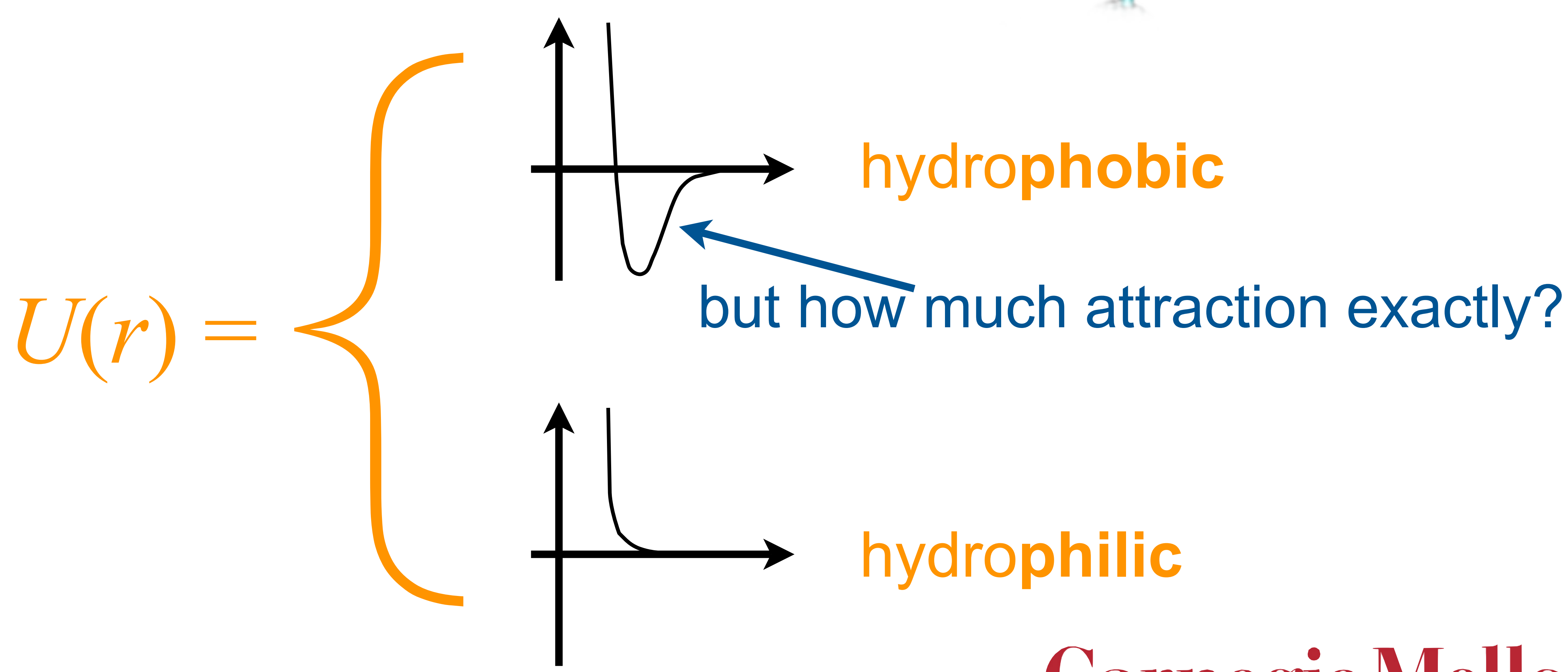
Hydrophobic interactions





Miyazawa-Jernigan matrix

$$\epsilon_{ij}^{\mathrm{MJ}}$$

	Ser	Gly	Phe	
Ser	**-1.67**	**-1.82**	**-4.02**	• • •
Gly	**-1.82**	**-2.24**	**-4.13**	• • •
Phe	**-4.02**	**-4.13**	**-7.26**	• • •

S. Miyazawa and R.L. Jernigan, J. Mol. Biol. **256**, *623* (1996)

Miyazawa-Jernigan matrix

$$\epsilon_{ij}^{\mathrm{MJ}} \approx \varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$$ (Lorentz-Berthelot)

normalize: $0 \longleftrightarrow 1$

$$\varepsilon_i' = \frac{\varepsilon_i - \min\ \varepsilon_k}{\max\ \varepsilon_k - \min\ \varepsilon_k}$$

correlation between $\epsilon_{ij}^{\mathrm{MJ}}$ and ε_{ij} : 98%

correlation between ε_i' and ϵ_i : 87%

hydrophobicity scale by Fauchere and Pliska

J.L. Fauchere and V. Pliska, Eur. J. Med. Chem. **18**, *369* (1983).

S. Miyazawa and R.L. Jernigan, J. Mol. Biol. **256**, *623* (1996)

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Miyazawa-Jernigan matrix

$$\epsilon_{ij}^{\mathrm{MJ}} \approx \varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$$ (Lorentz-Berthelot)

normalize: $\varepsilon_i' = \dfrac{\varepsilon_i - \min\ \varepsilon_k}{\max\ \varepsilon_k - \min\ \varepsilon_k}$

$0 \longleftrightarrow 1$

Use $\varepsilon_{\mathrm{overall}} \times \varepsilon_i'$ as the strength in a Lennard-Jones potential.

S. Miyazawa and R.L. Jernigan, J. Mol. Biol. **256**, *623* (1996)

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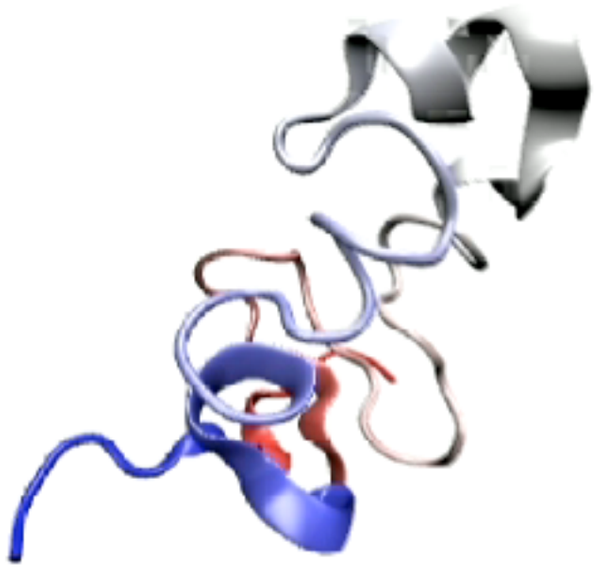
Folding of a 3-helix bundle

73 aa

2A3D MGSWAEFKQRLAAIKTRLQALGGSEAELAAFEKEIAA···
···FESELQAYKGKGNPEVEALRKEAAAIRDELQAYRHN



Parallel tempering at 8 temperatures;
shown: configuration in lowest replica.
Total simulation time: ~10 hours.

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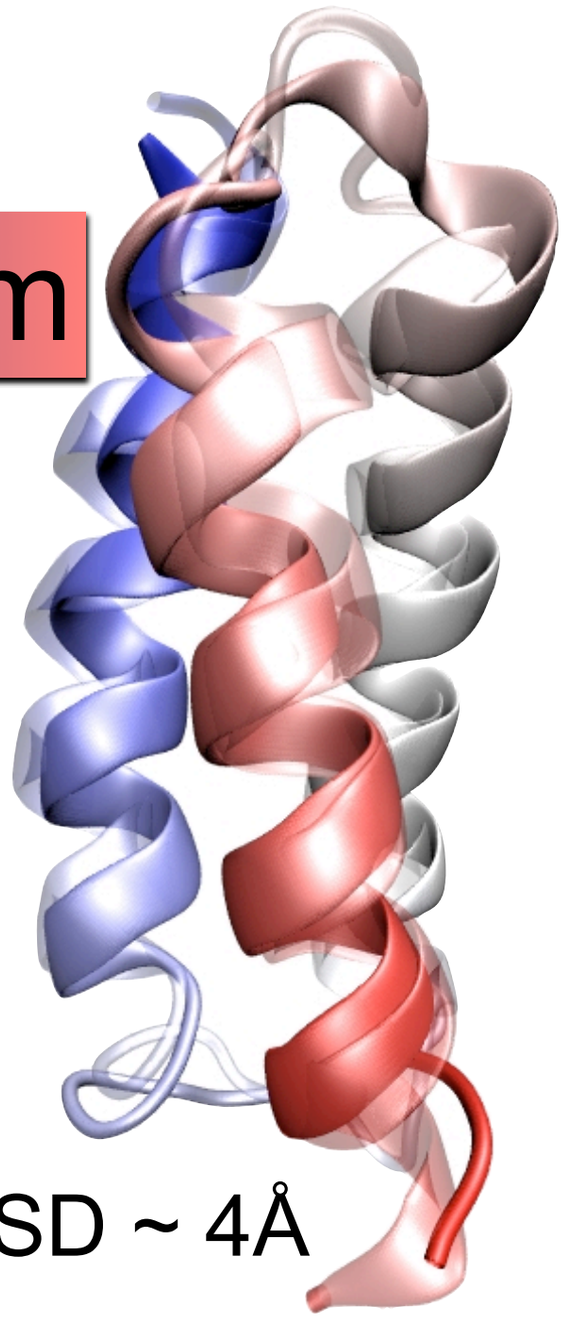
Folding of a 3-helix bundle

73 aa

2A3D `MGSWAEFKQRLAAIKTRLQALGGSEAELAAFEKEIAA···`
`···FESELQAYKGKGNPEVEALRKEAAAIRDELQAYRHN`

CG sim

NMR



RMSD ~ 4Å

hydrophobicity:

proper helix-alignment,
but not a collapsed globule

hydrogen bond:

secondary structure formation,
but not just one long α-helix.

dipole term:

β-sheets maximally stable
without disabling α-helices.

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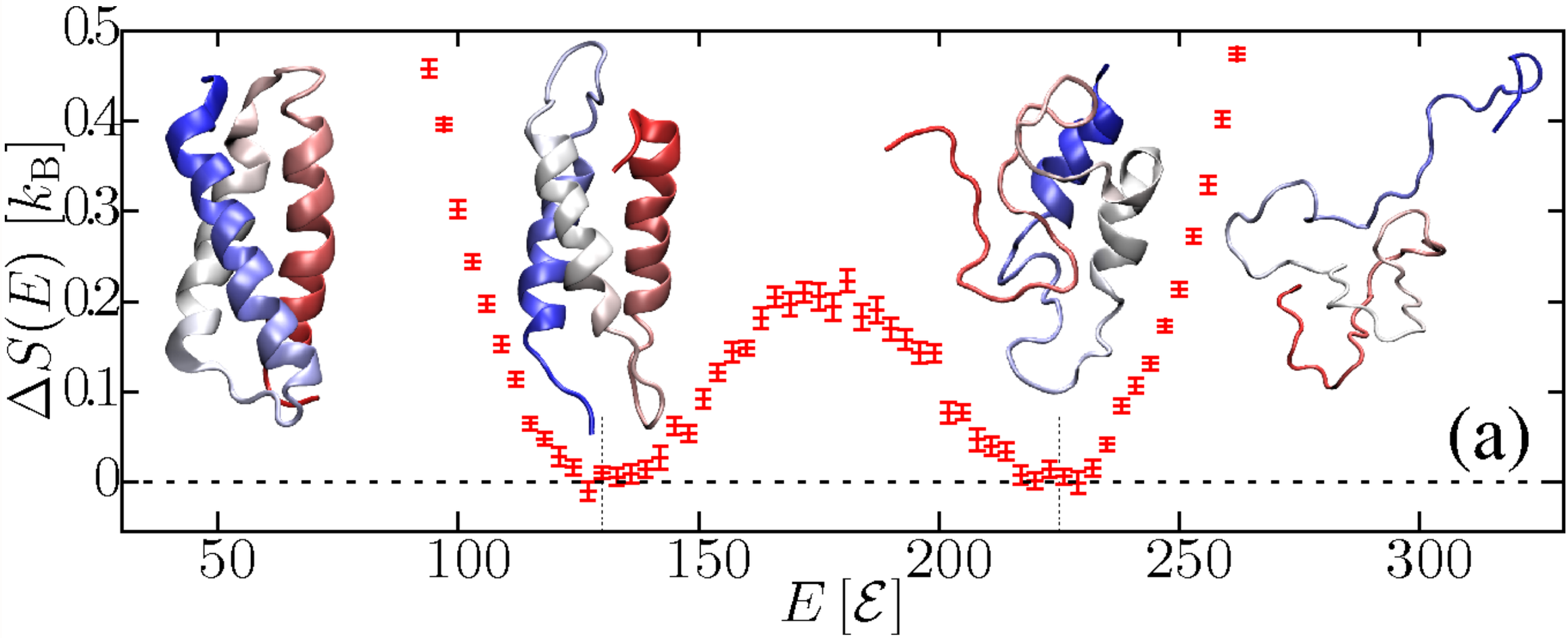
Example application

Microcanonical folding analysis of this 3-helix bundle.



T. Bereau, M. Bachmann, and M. Deserno, J. Am. Chem. Soc. **132**, 13129 (2010);
T. Bereau, M. Deserno, and M. Bachmann, Biophys. J. **100**, 2764 (2011);

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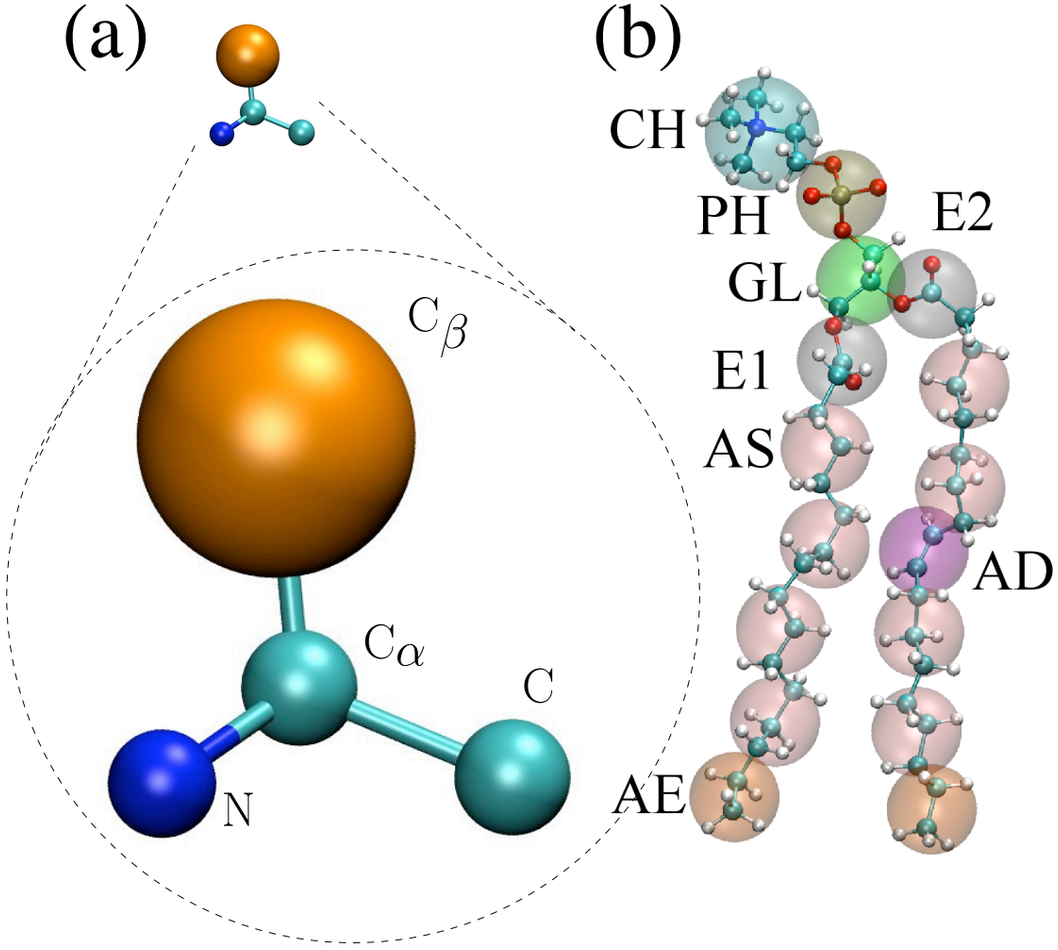
3. Cross-parametrization

Aim: Reproduce *free energy of insertion* of individual amino acids into the bilayer.

Target data for this:

J. L. MacCallum, W. F. D. Bennett, and D. P. Tieleman, Biophys. J. **94**, 3393 (2008).



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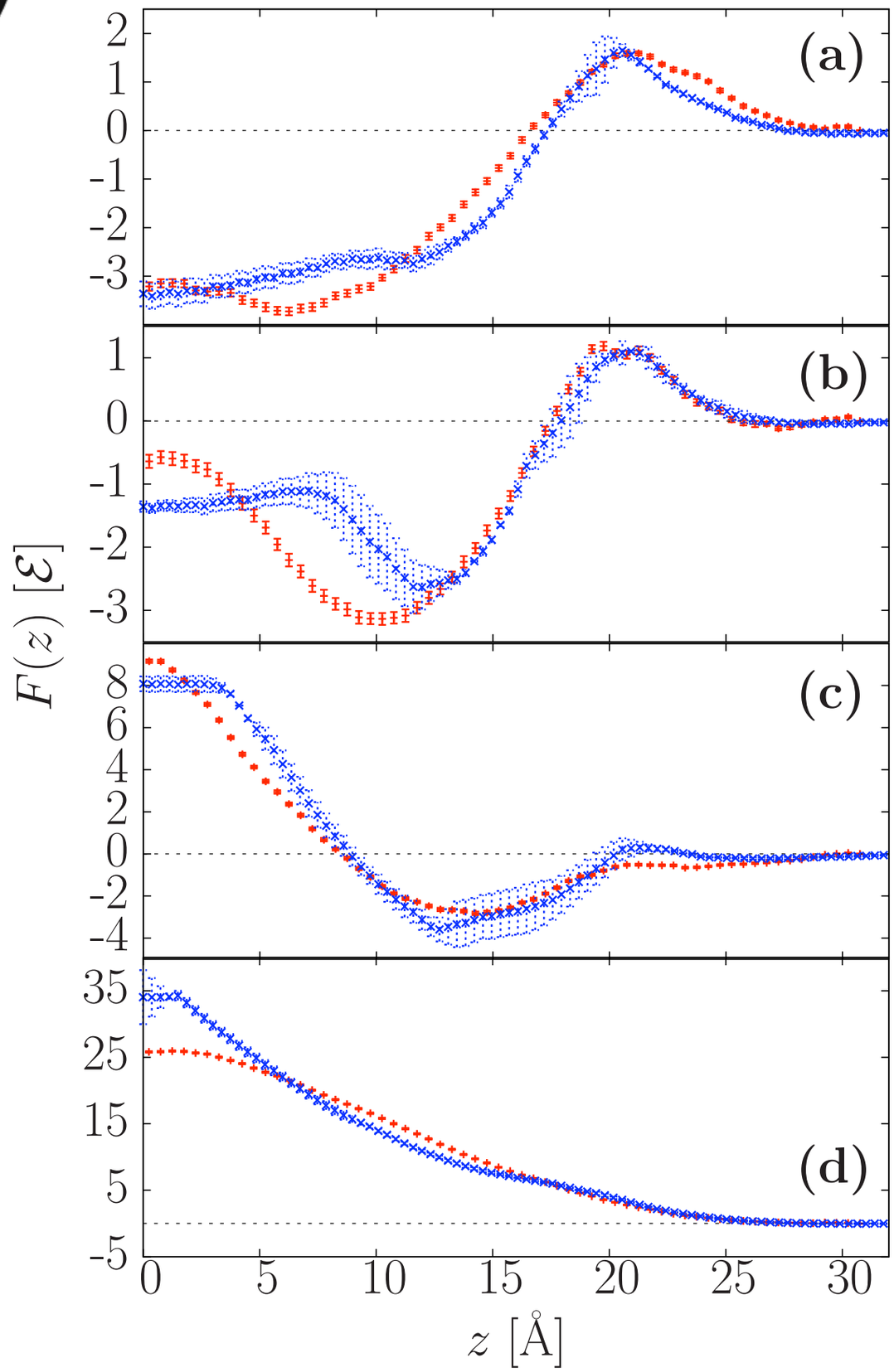
Free energy of insertion



Ala — atomistic / CG

Cys — Generic features captured semi-quantitatively.

Gln — "Sharp" features difficult to match with low-resolution model.

Glu^- — Final interaction potentials likely not unique, but this is not a problem.

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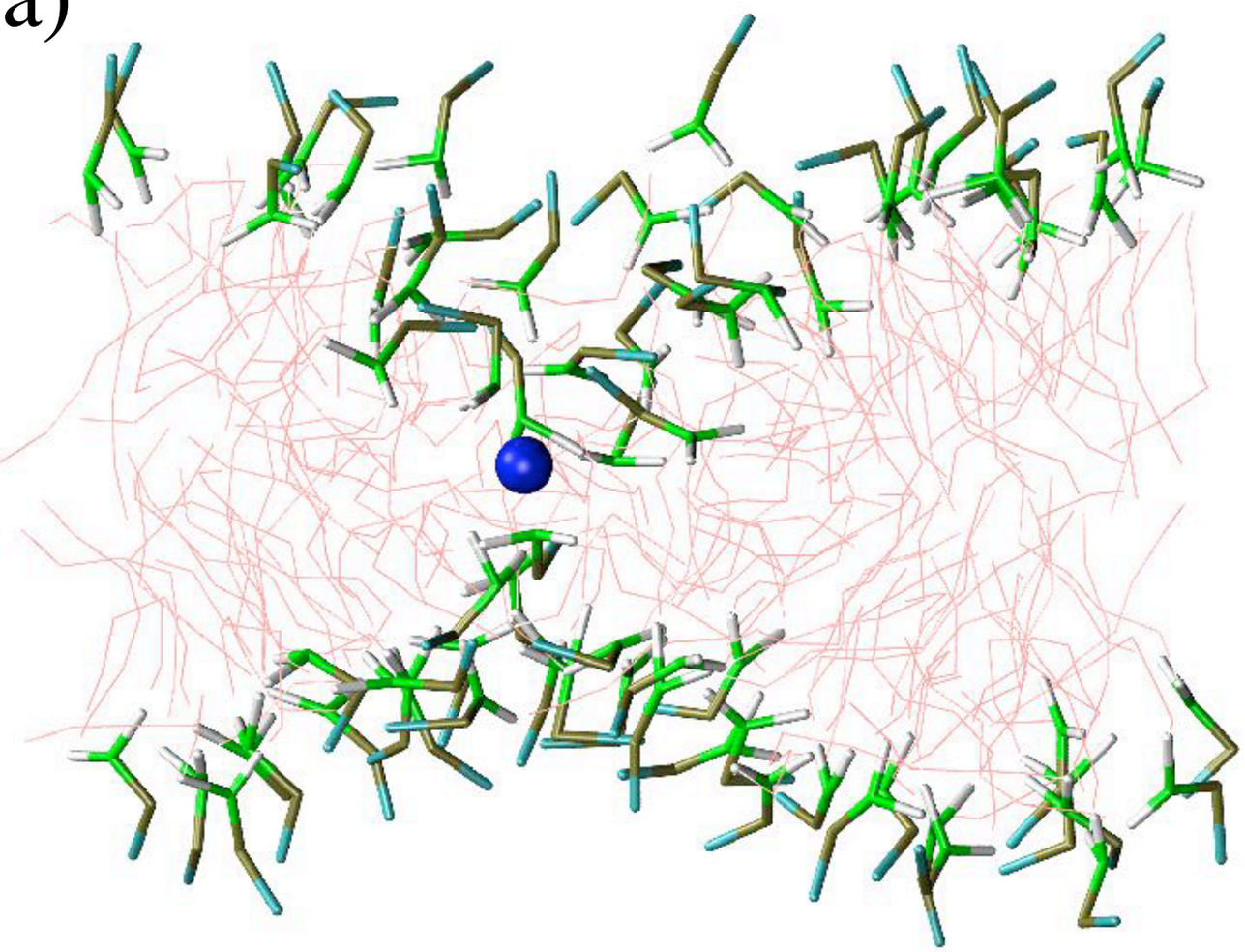
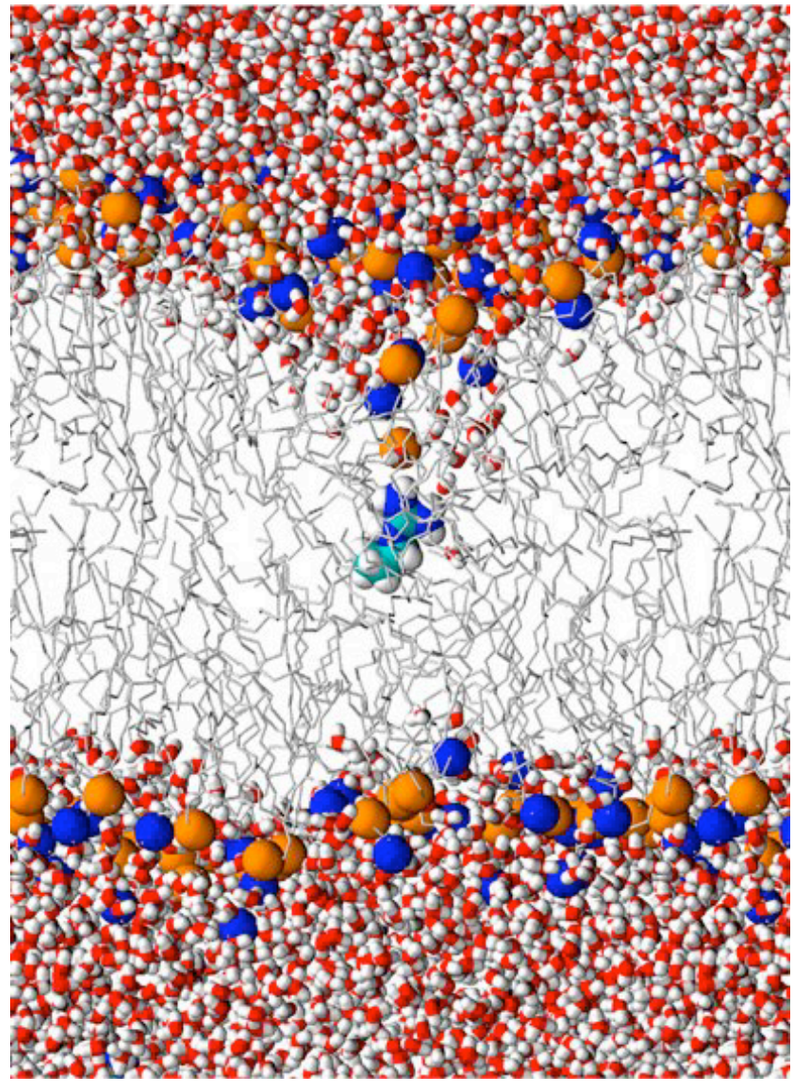
Arg^+ in a DOPC bilayer

(a)



(b)



coarse grained

atomistic

can observe “water defects” (without water)

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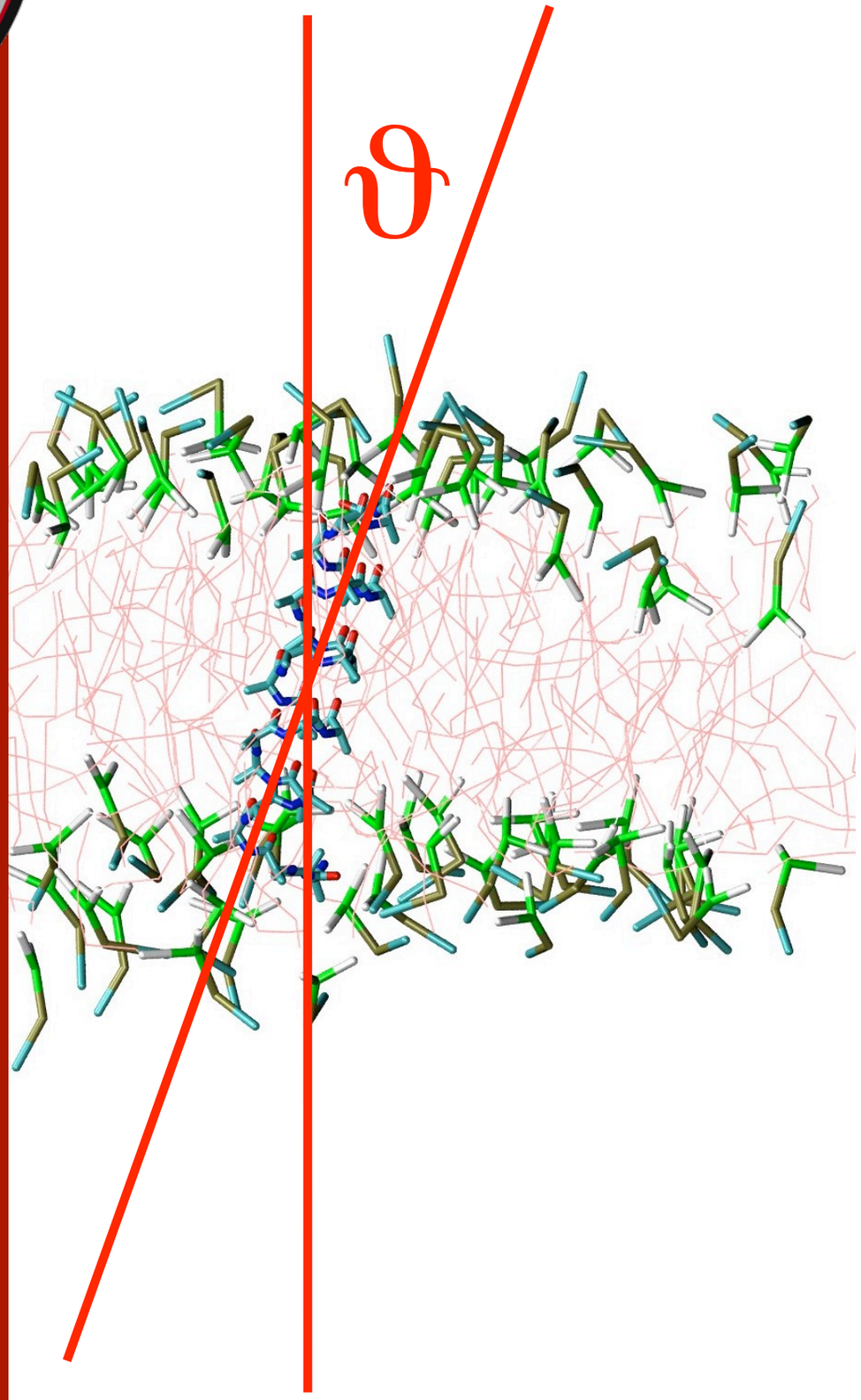
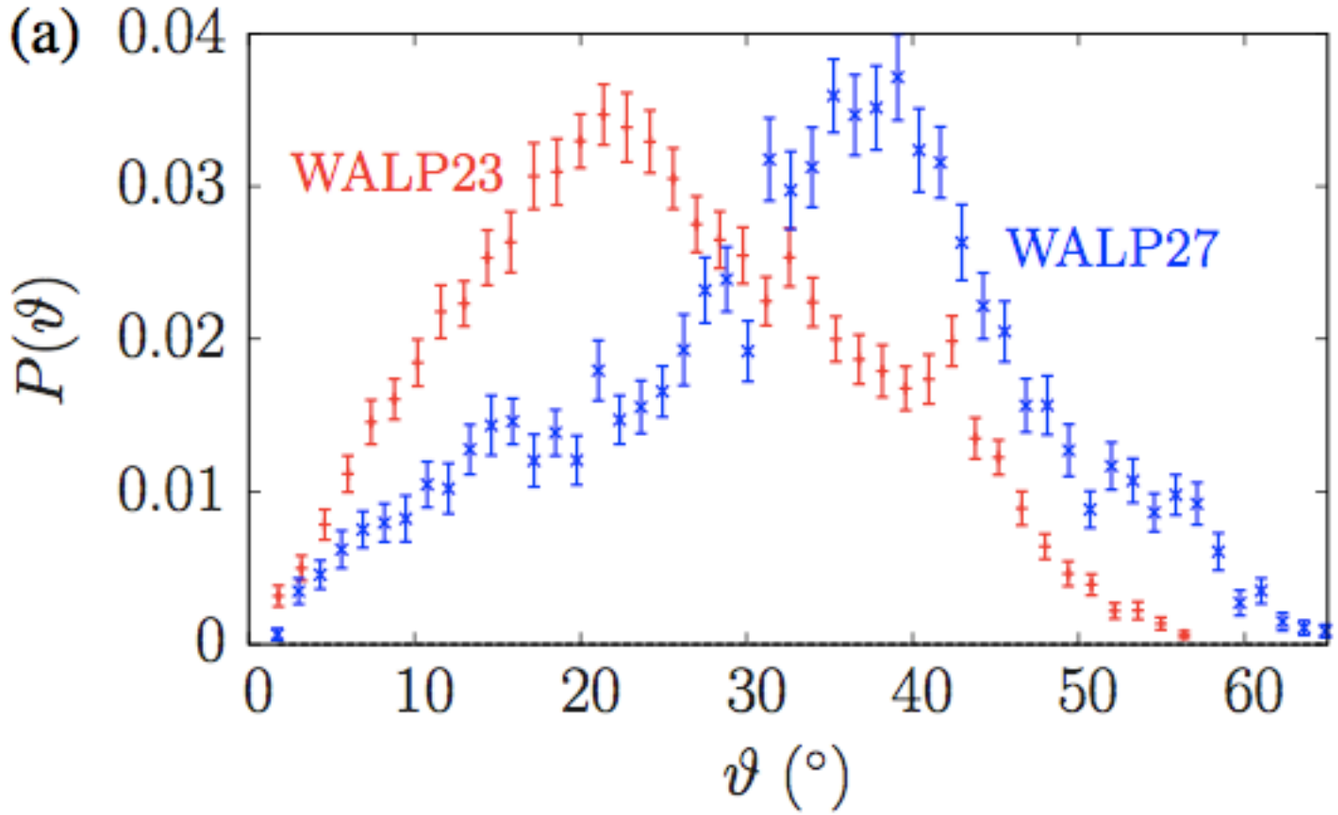
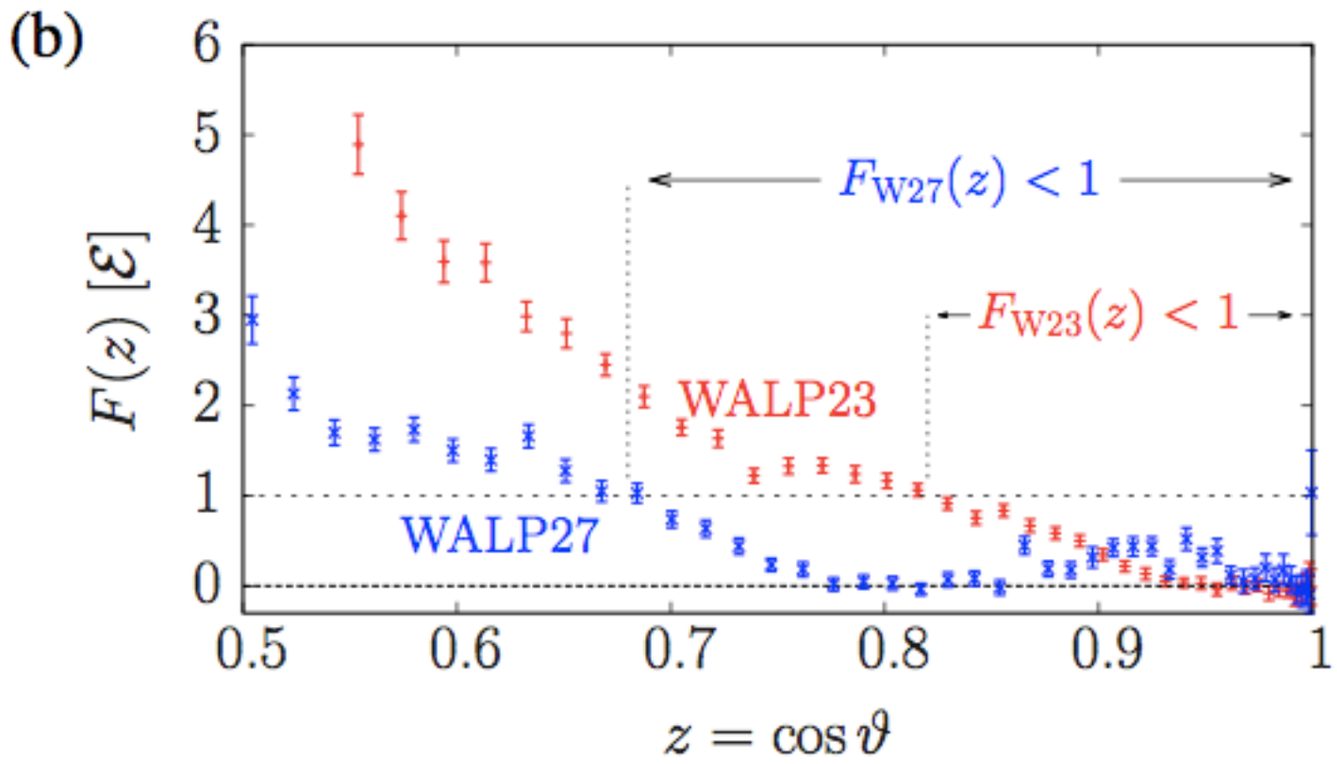
Helix tilt fluctuations







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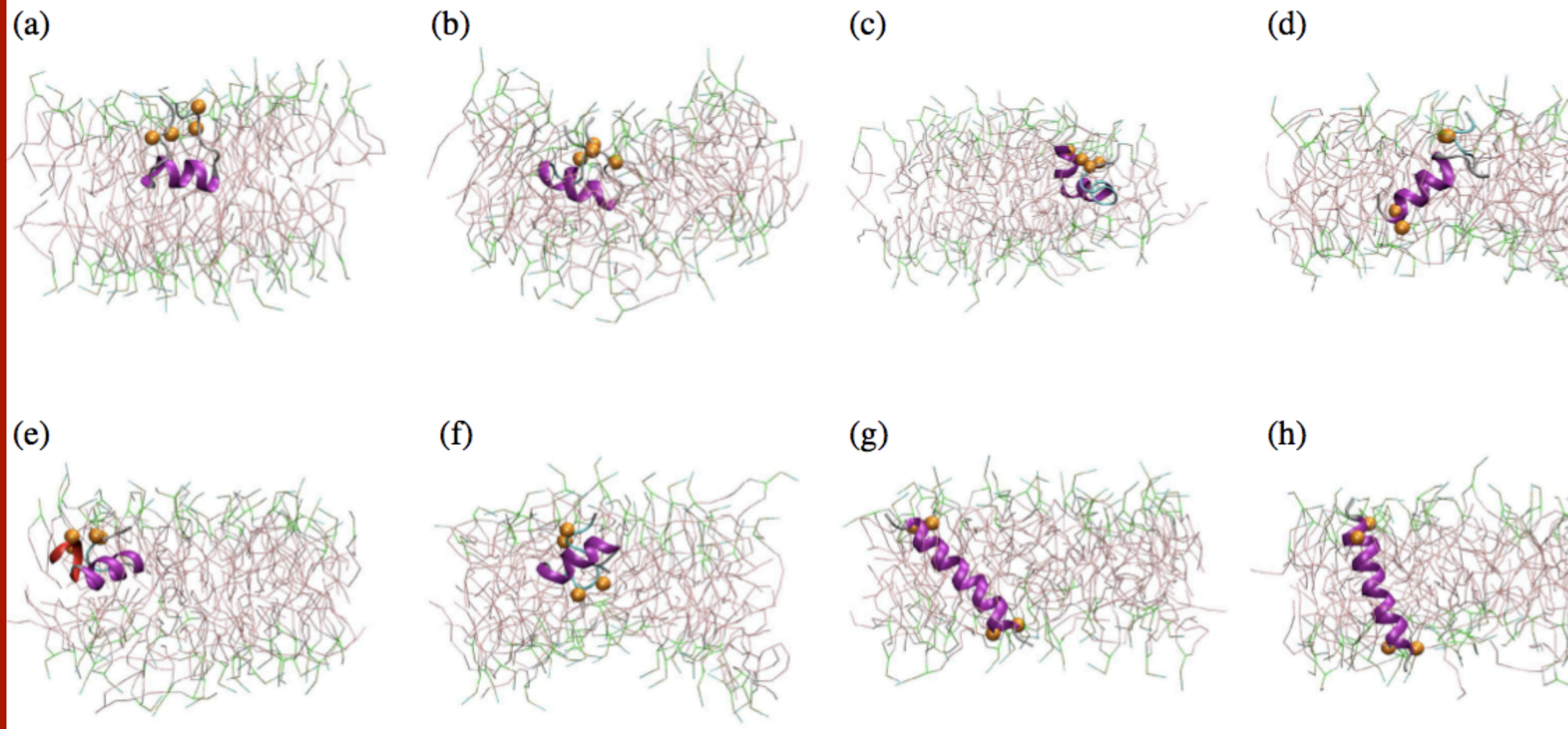
Folding of WALP23 in membrane environment



WALP23 in 62 lipid POPC bilayer at T=356K.
CG REMD, total time ~ 10^6 τ (~~8μs)

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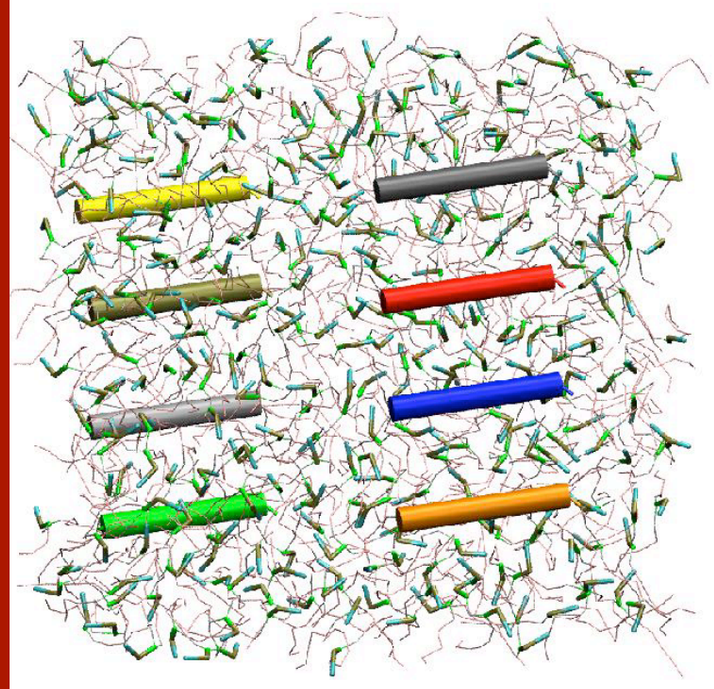
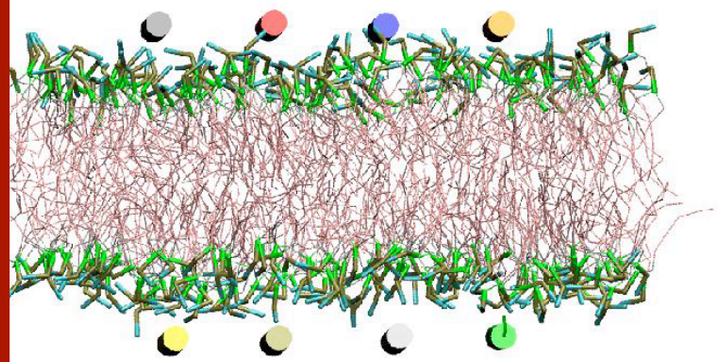
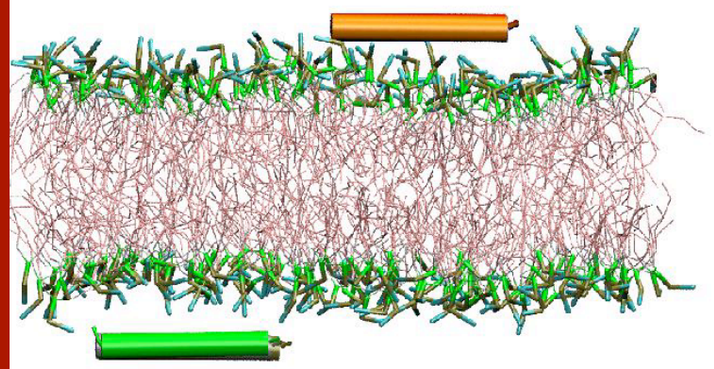
Pore formation by APs

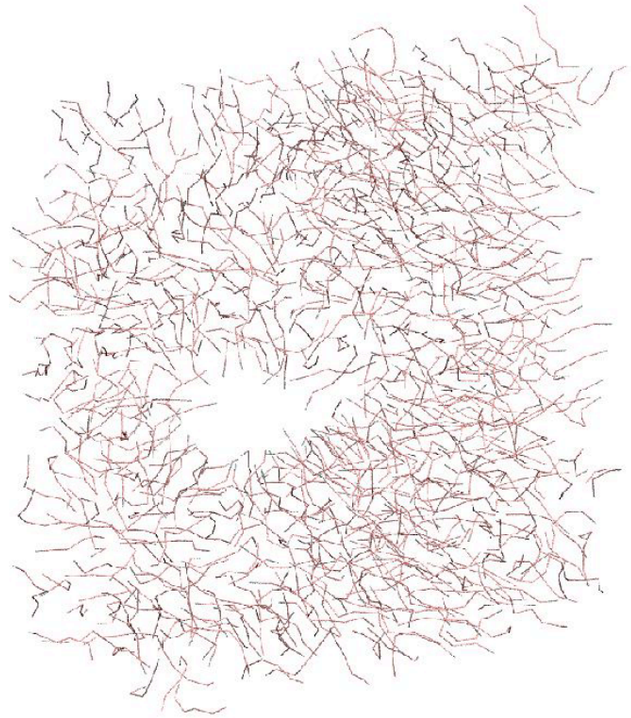
$t = 0\,\tau$

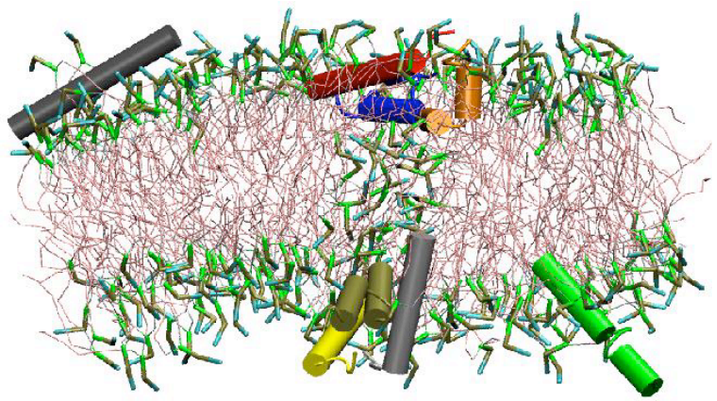


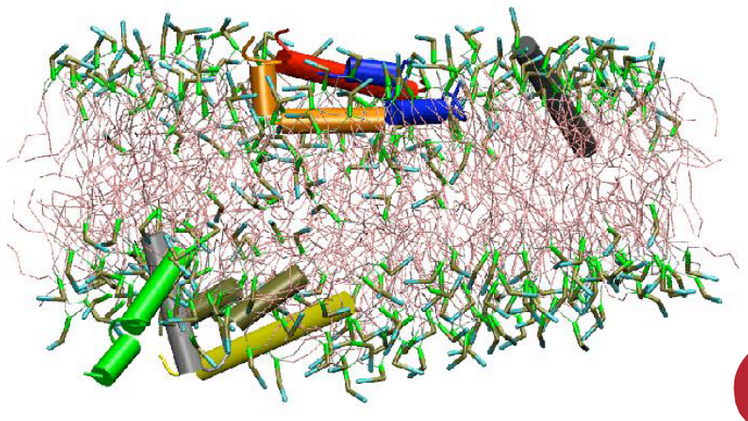




$t = 291\,000\,\tau$







8 magainin, 288 POPC, T=308K. CG REMD. Total time ~~2μs

Pore is created without even one AP actually spanning it. Helices break.

Results secondary at this point. But notice the kinds of problems you could treat in this way.

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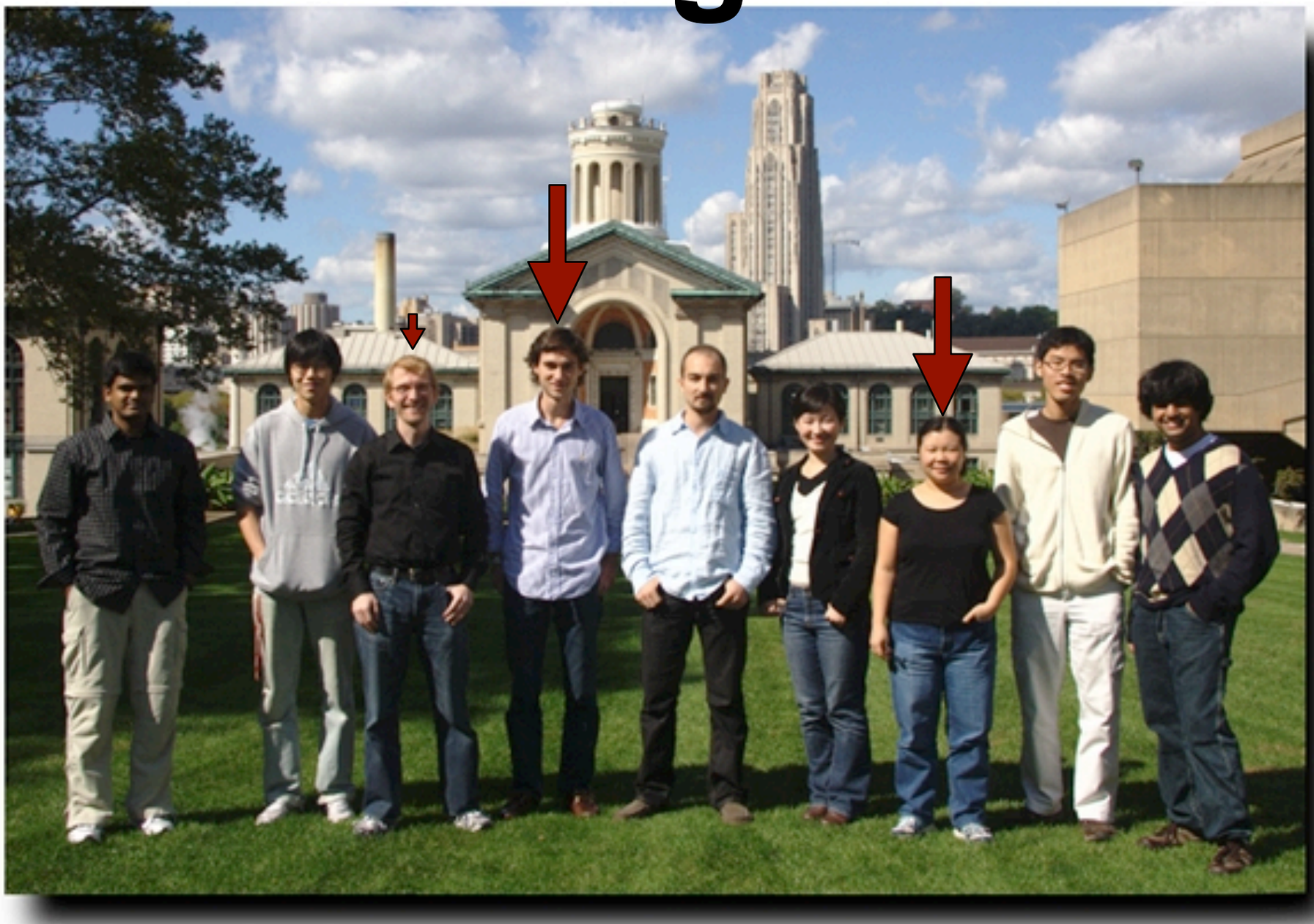
Acknowledgements



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