

Modelos Coarse-Grained

(MARTINI ...)

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Hubert Stassen

`gullit@iq.ufrgs.br`

Grupo de Química Teórica
Instituto de Química - UFRGS

The Nobel Prize in Chemistry 2013



Photo: A. Mahmoud

Martin Karplus

Prize share: 1/3



Photo: A. Mahmoud

Michael Levitt

Prize share: 1/3



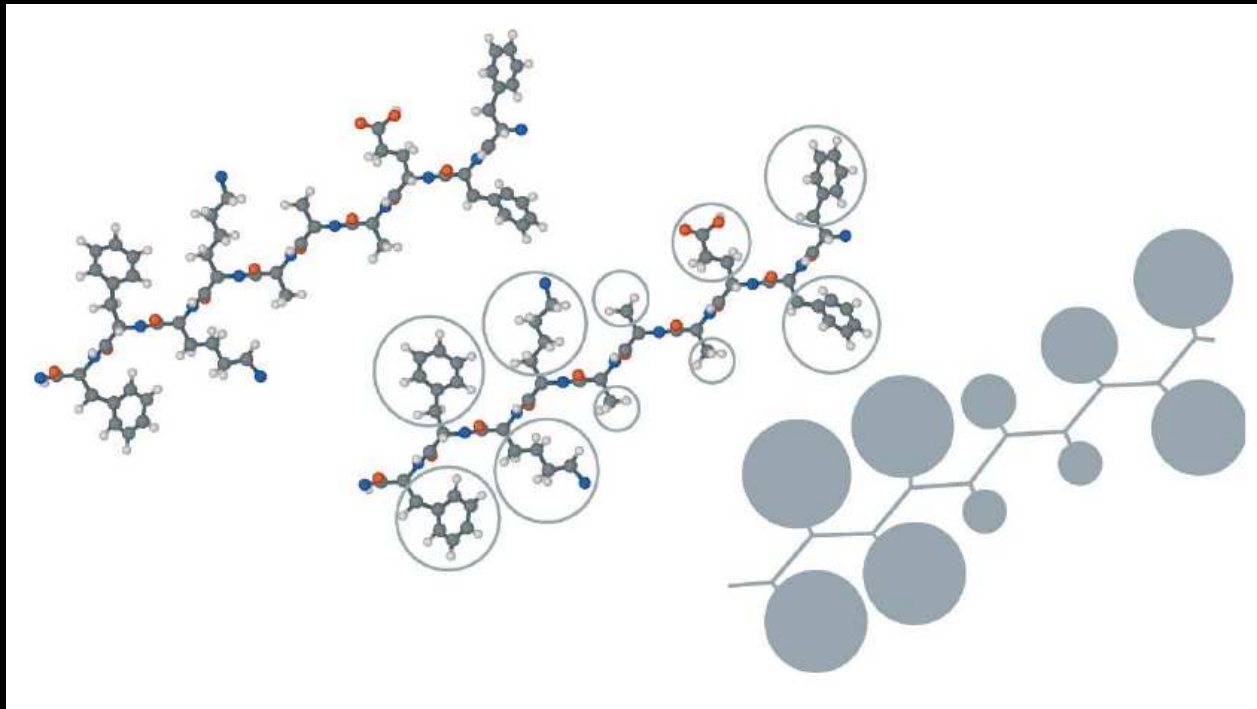
Photo: A. Mahmoud

Arieh Warshel

Prize share: 1/3

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

Photos: Copyright © The Nobel Foundation



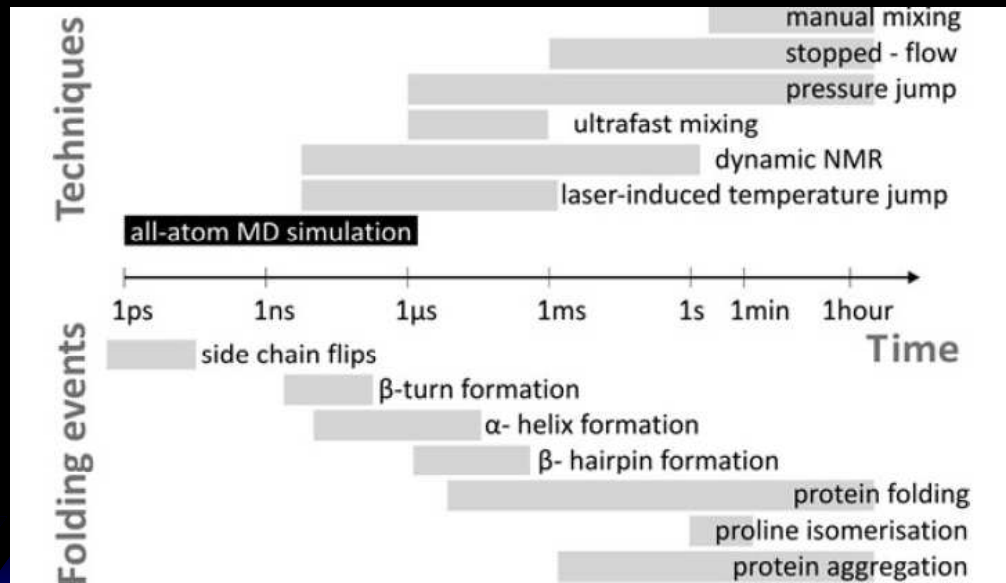
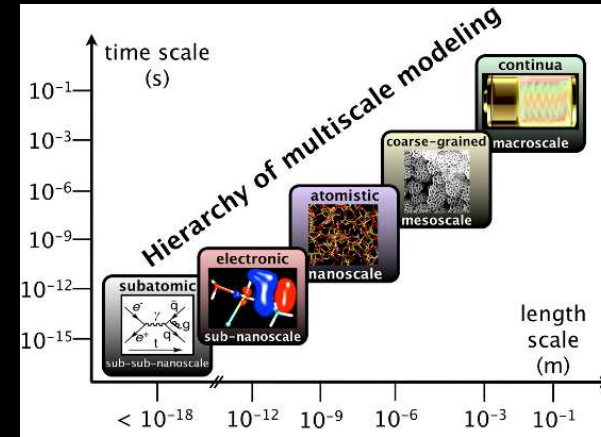
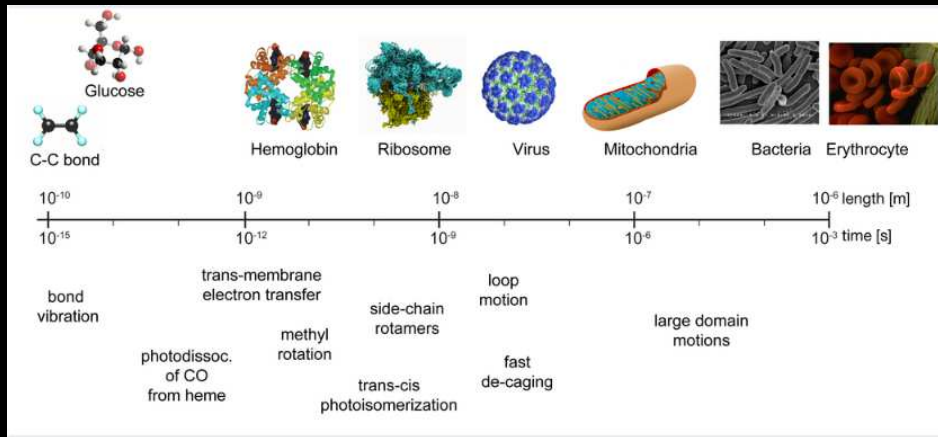
Simulated annealing of a "CG" Bovine Pancreas Trypsin Inhibitor

M. Levitt, A. Warshel, Nature 253 (1975), 694

Outline

1. Time and Length Scales
2. Molecular Dynamics
3. Coarse-Grained Models
 - (a) Non-Martini
 - (b) Martini
4. Protein Membrane Interaction
5. Jumping between Scales

Time and Length Scales



Molecular Dynamics

Numerical solution of equations of motion -
classical case

$$\mathbf{r}_i(\Delta t) = \frac{\mathbf{F}_i}{2m_i}\Delta t^2 + \mathbf{v}_i(0)\Delta t + \mathbf{r}_i(0)$$

$$\mathbf{v}_i(\Delta t) = \frac{\mathbf{F}_i}{m_i}\Delta t + \mathbf{v}_i(0)$$

$$\mathbf{F}_i = -\frac{d}{d\mathbf{r}_i}V(\mathbf{r})$$

with $i = 1, 2, \dots, N$

based on a force field (here: AMBER)

$$\begin{aligned} V(\mathbf{r}) = & \sum_{i=1}^{bonds} k_{b,i} (\mathbf{r}_i - \mathbf{r}_{o,i})^2 + \sum_{i=1}^{angles} k_{\theta,i} (\theta_i - \theta_{o,i})^2 \\ & + \sum_{i=1}^{dihed.} \frac{V_{o,i}}{2} [1 + \cos(n_i \phi_i - \gamma_i)] \\ & + \alpha \sum_{i,j>i}^N 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] \\ & + \beta \sum_{i,j>i}^N \frac{q_i q_j}{4\pi\epsilon_o r_{ij}} \end{aligned}$$

$$\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j} \quad \sigma_{ij} = \frac{\sigma_i + \sigma_j}{2}$$

Time step Δt

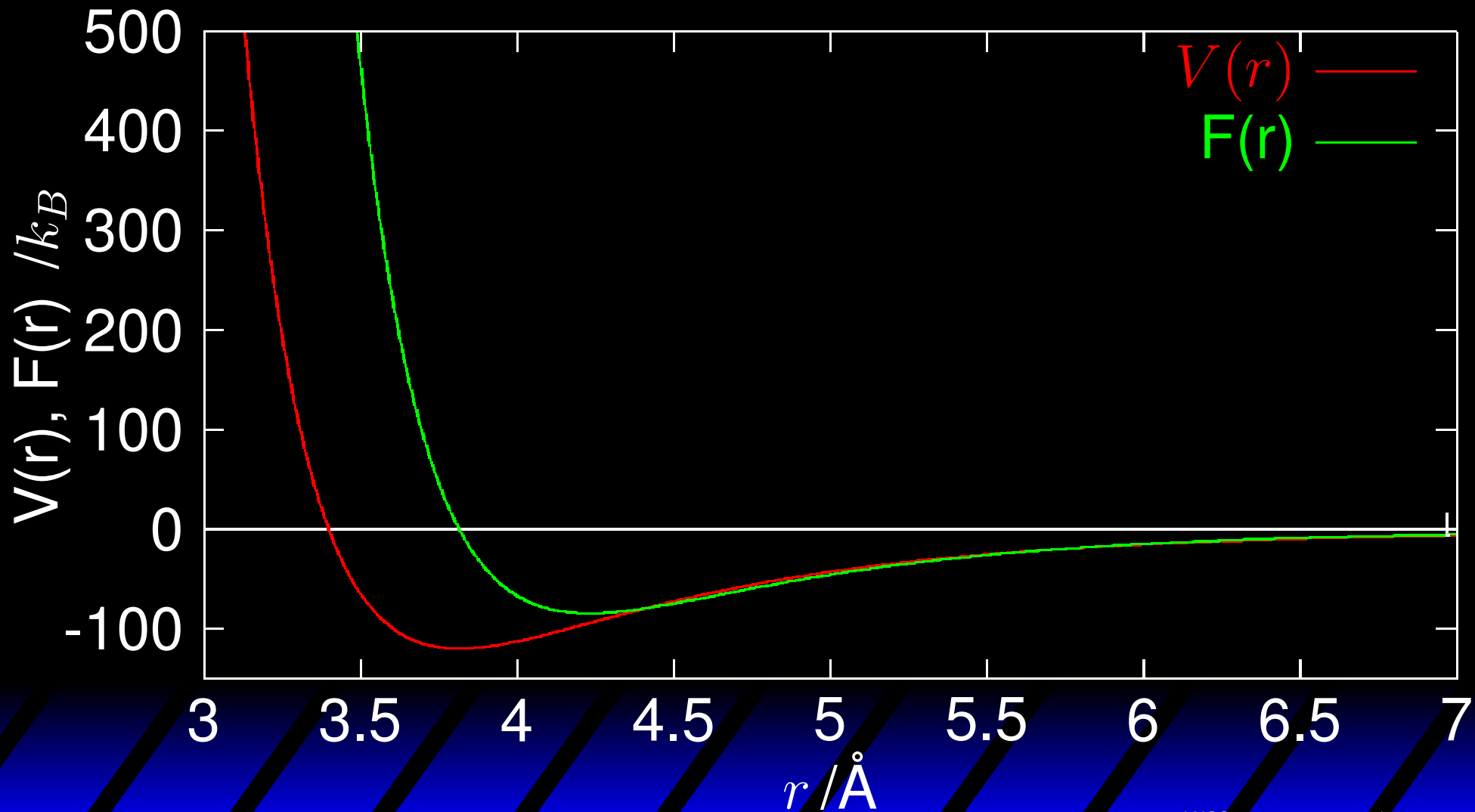
- as large as possible
- resolve the dynamical process



- flexible atomistic simulations: $\Delta t \simeq 1 \cdot 10^{-15}$ s (fs)

- we need constant forces during Δt

(12/6)-Lennard-Jones Potential



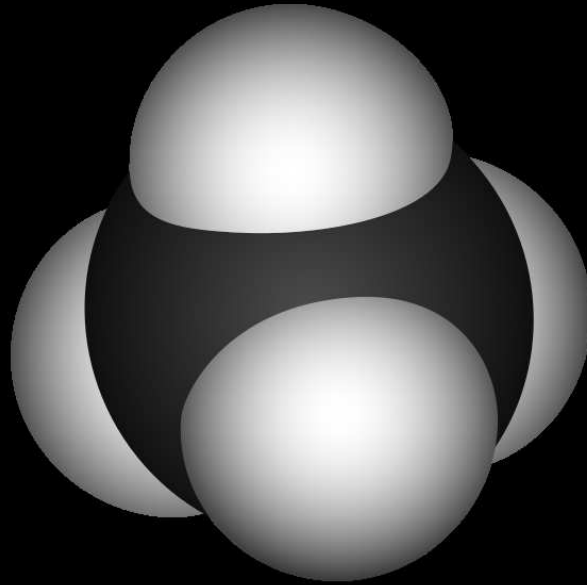
Increasing the time step Δt

- remove the fastest processes (constraints)
 $\implies \Delta t \simeq 2 \text{ fs}$
- smooth potentials
- Maxwell-Boltzmann

$$\langle v \rangle = \sqrt{\frac{8k_B T}{\pi m}}$$

\implies increase the mass

Case study: methane

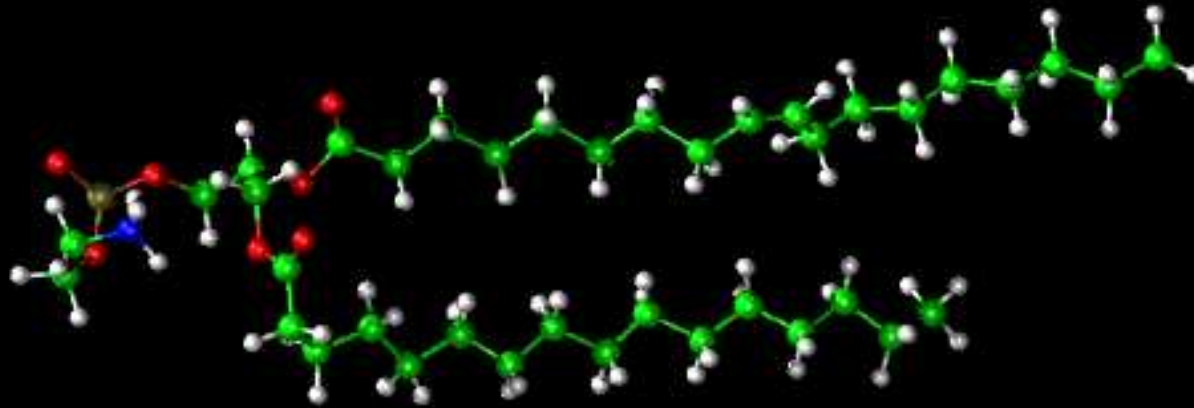


- OPLS-AA: C (opls138), H (opls140)
⇒ 25 pair interactions and electrostatics
- OPLS-UA: CH₄ (opls066)
⇒ 1 pair interaction without electrostatics

- Vibrational dephasing: all-atom, flexible
- Rotational dynamics, neutron scattering, . . . : all-atom, constraints
- Liquid density, diffusion constant, vaporization enthalpy, . . . : united-atom

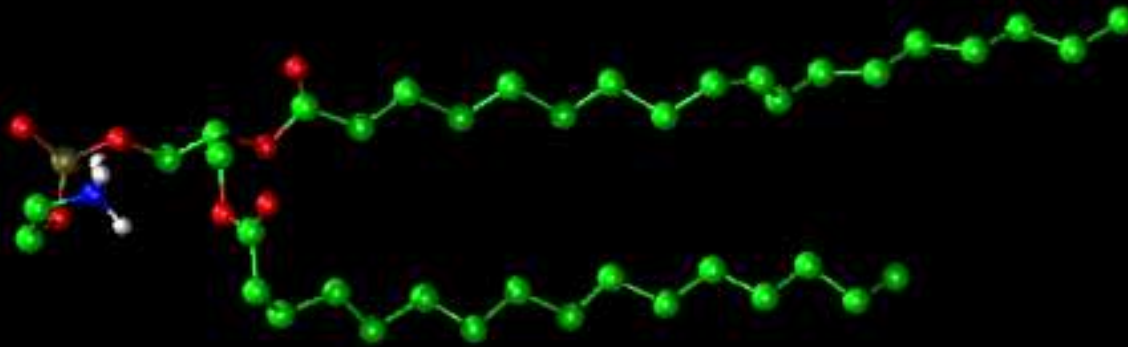
⇒ we are already scaling on time and length scales

Case study: POPE all-atom (1-Palmitoyl-2-oleoylphosphatidylethanolamine)



125 atoms
⇒ 15625 pair interactions
constraints for membrane simulations: $\Delta t \simeq 2$ fs

Case study: POPE united-atom, but polar hydrogens



52 atoms

⇒ 2704 pair interactions

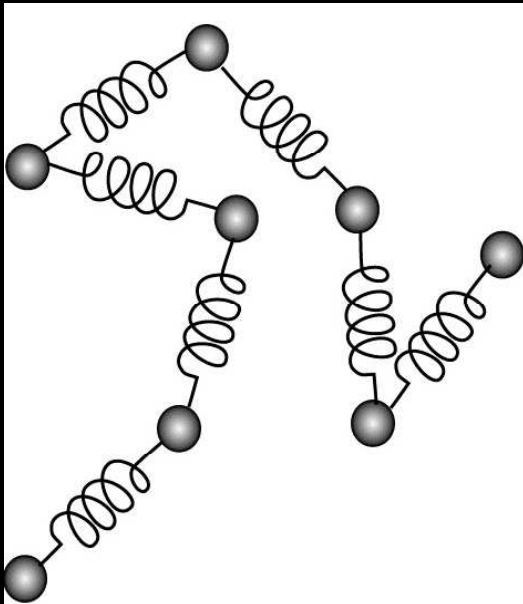
constraints for membrane simulations: $\Delta t \simeq 2$ fs

Coarse-Graining

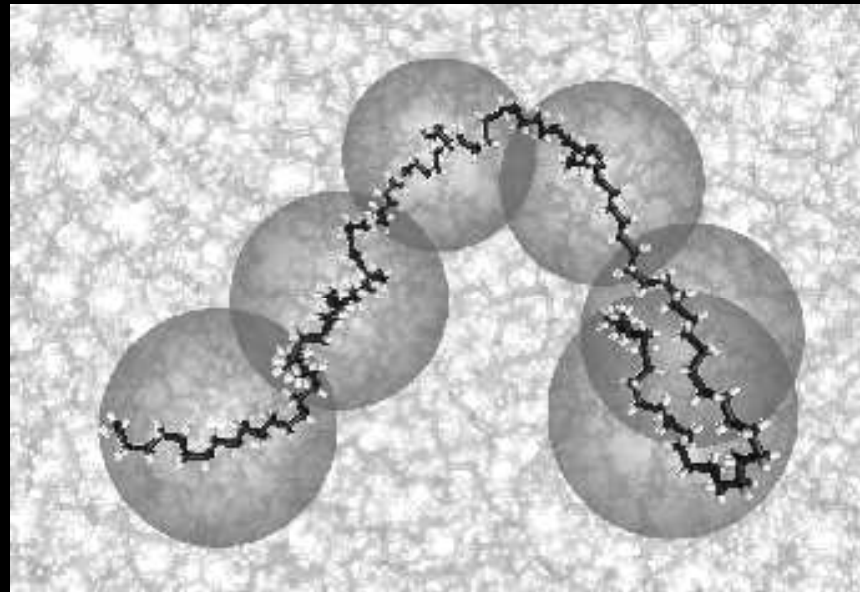
- Goal: realistic simulation of large complex systems for a long time by
 - reduction of interaction sites (MD CPU time $\propto N^2$)
 - elimination of very fast dynamical processes (small masses, large force constants)
 - Maintaining the essential physics of the system

Polymer physics

Rouse-Zimm
spring-bead



de Gennes
blob



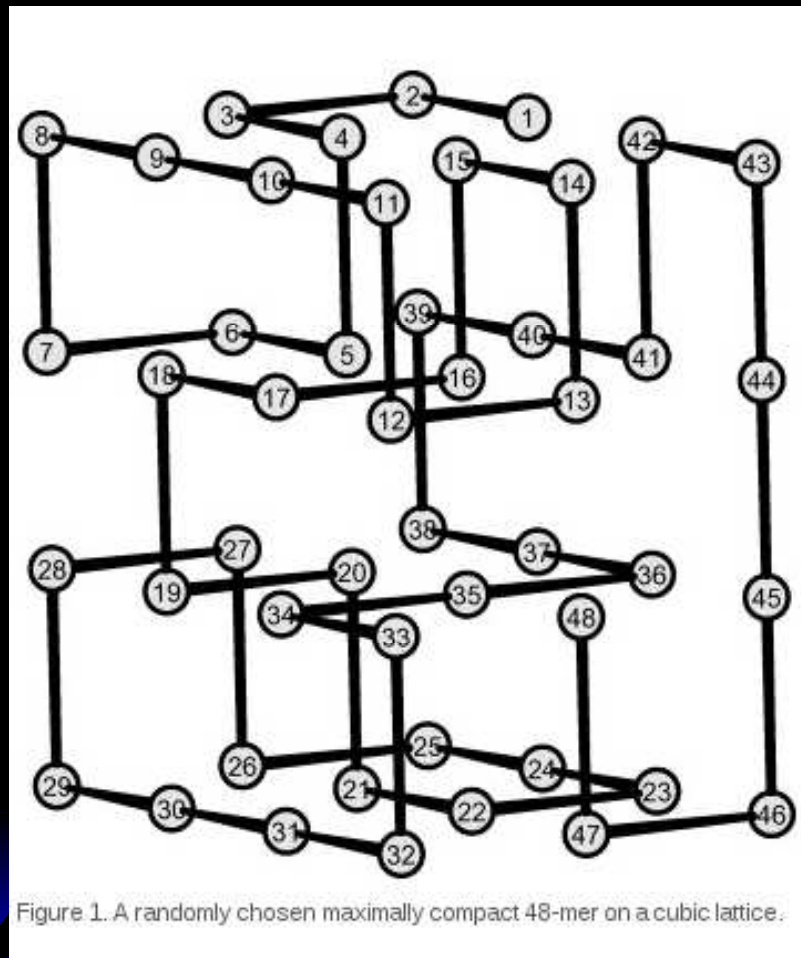
Protein folding

- M. Levitt, A. Warshel, Nature 253 (1975), 694

- Go models

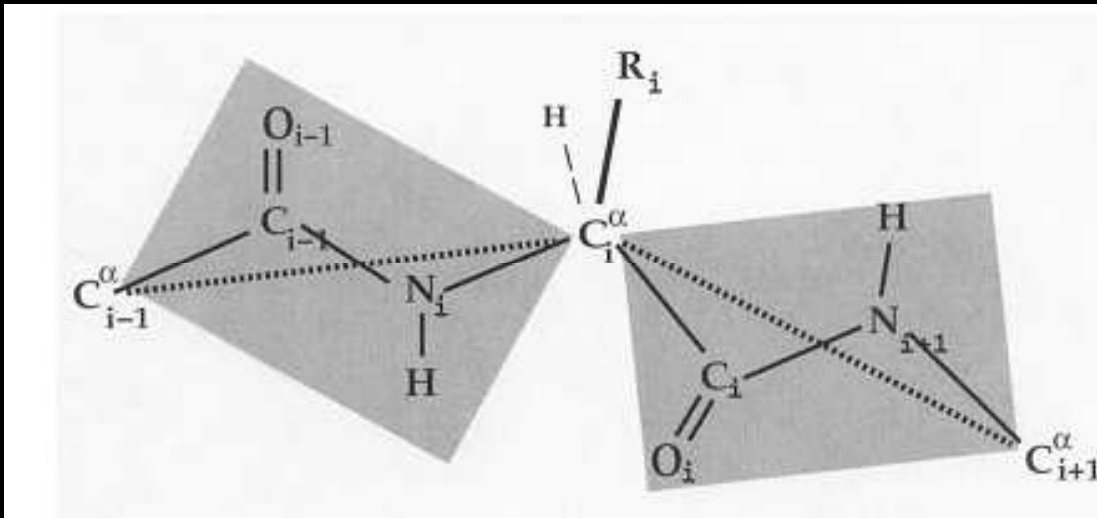
2-D: H. Taketomi et al., Int. J. Pept. Res. 7 (1975), 445.

3-D Example: V.I. Abkevich et al., Folding and Design 1 (1996), 221



Creating a CG model: Mapping

- Physical/chemical intuition: polar/non-polar, hydrogen bond donor/acceptor, charged/neutral, attractive/repulsive, ...
- Bead at the center of mass of the atoms to be joined (proteins: center at C_α)



Parameters for the CG force field

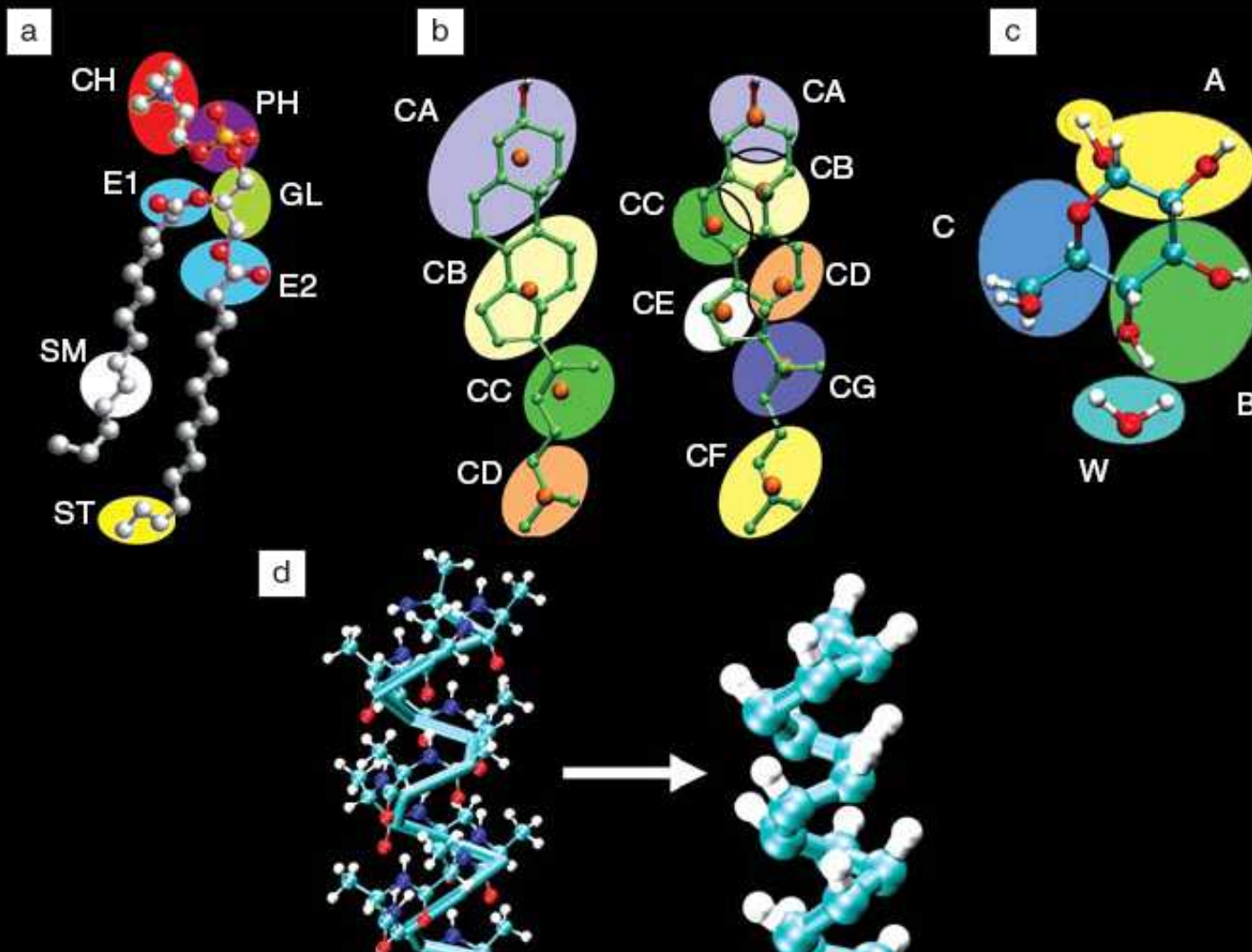
- Boltzmann factor:
 - Reverse Monte Carlo applied to radial distributions functions of atomistic simulations

T. Murtola et al., JCP **121** (2004), 9156; **126** (2007), 075101; **131** (2009), 055101; PCCP **11** (2009), 1869
 - Force matching of atomistic systems

S. Izvekov e G.A. Voth, JPCB **109** (2005), 2469; JCP **123** (2005), 134105; JCTC **2** (2006), 637
- Experimental properties (density, partition coefficients, membrane properties, solvation energies)

Non-Martini Models

MS-CG: G.S. Ayton et al, MRS Bulletin 32 (2007), 929.

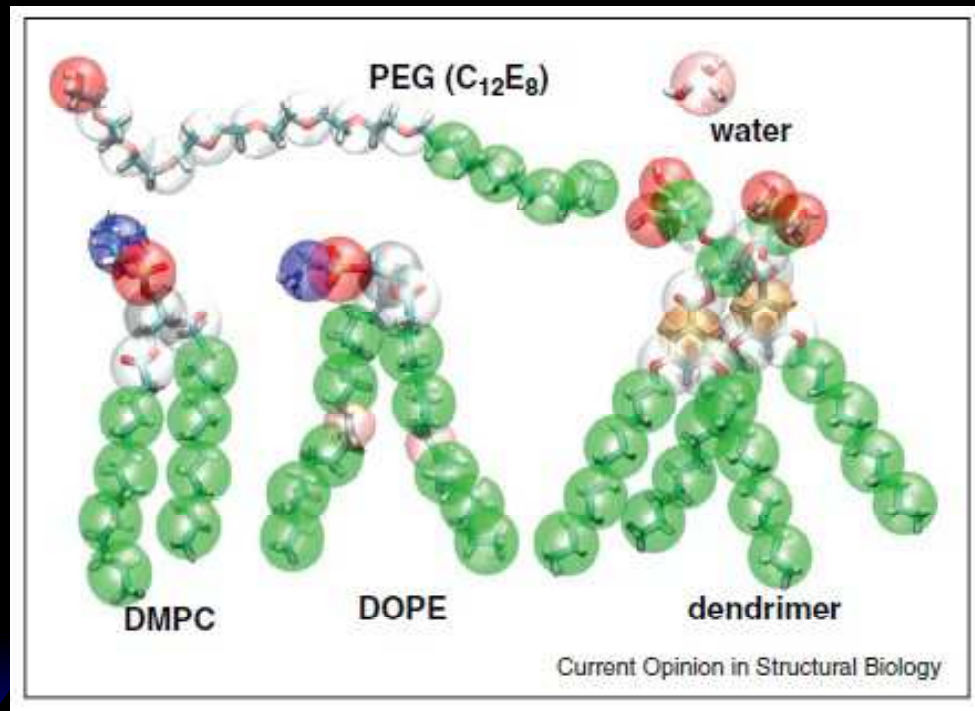


Amphiphilic Molecules

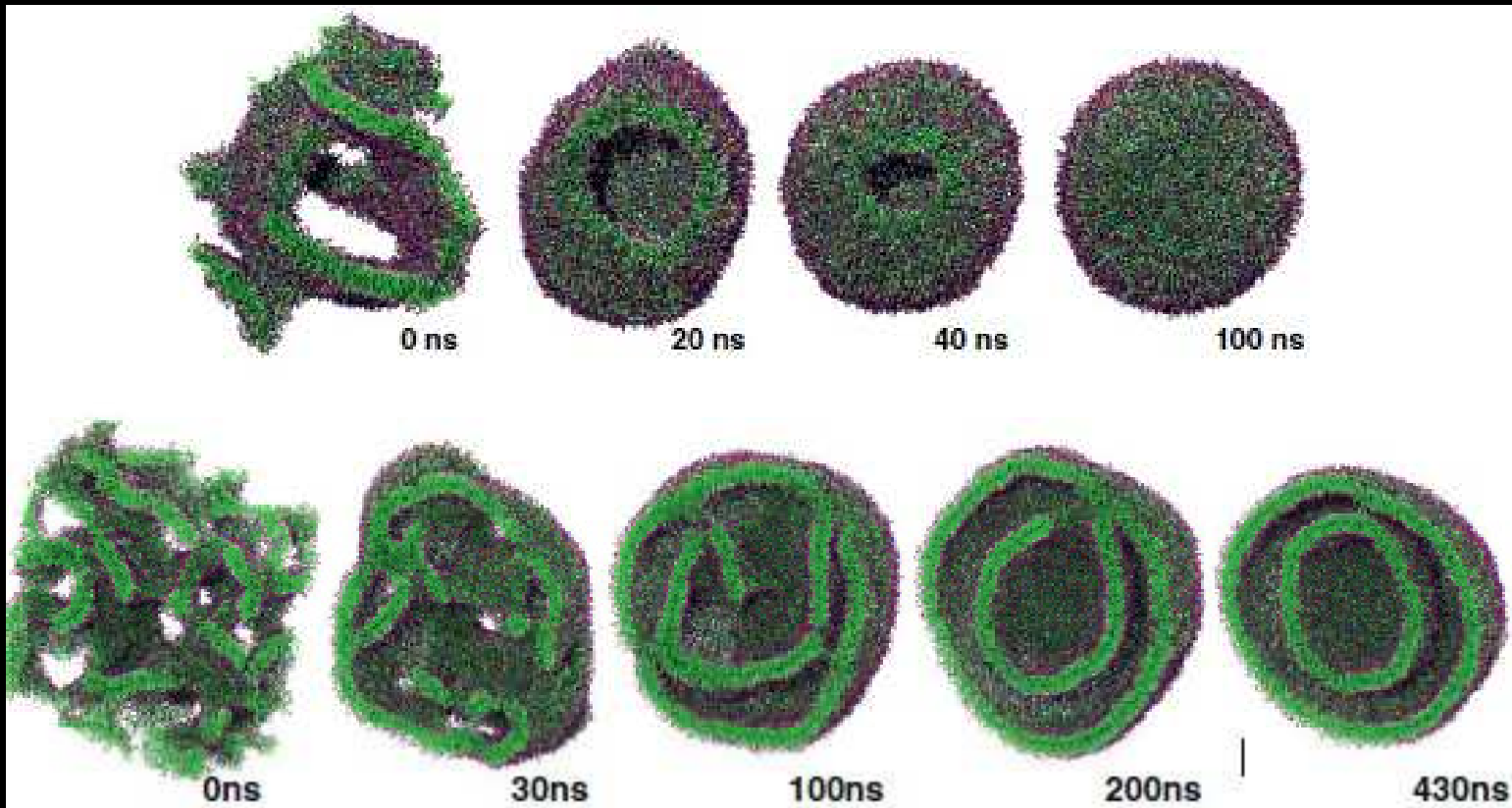
- SDK: Shinoda, de Vane, Klein

Parameterization against experimental data

Mapping:

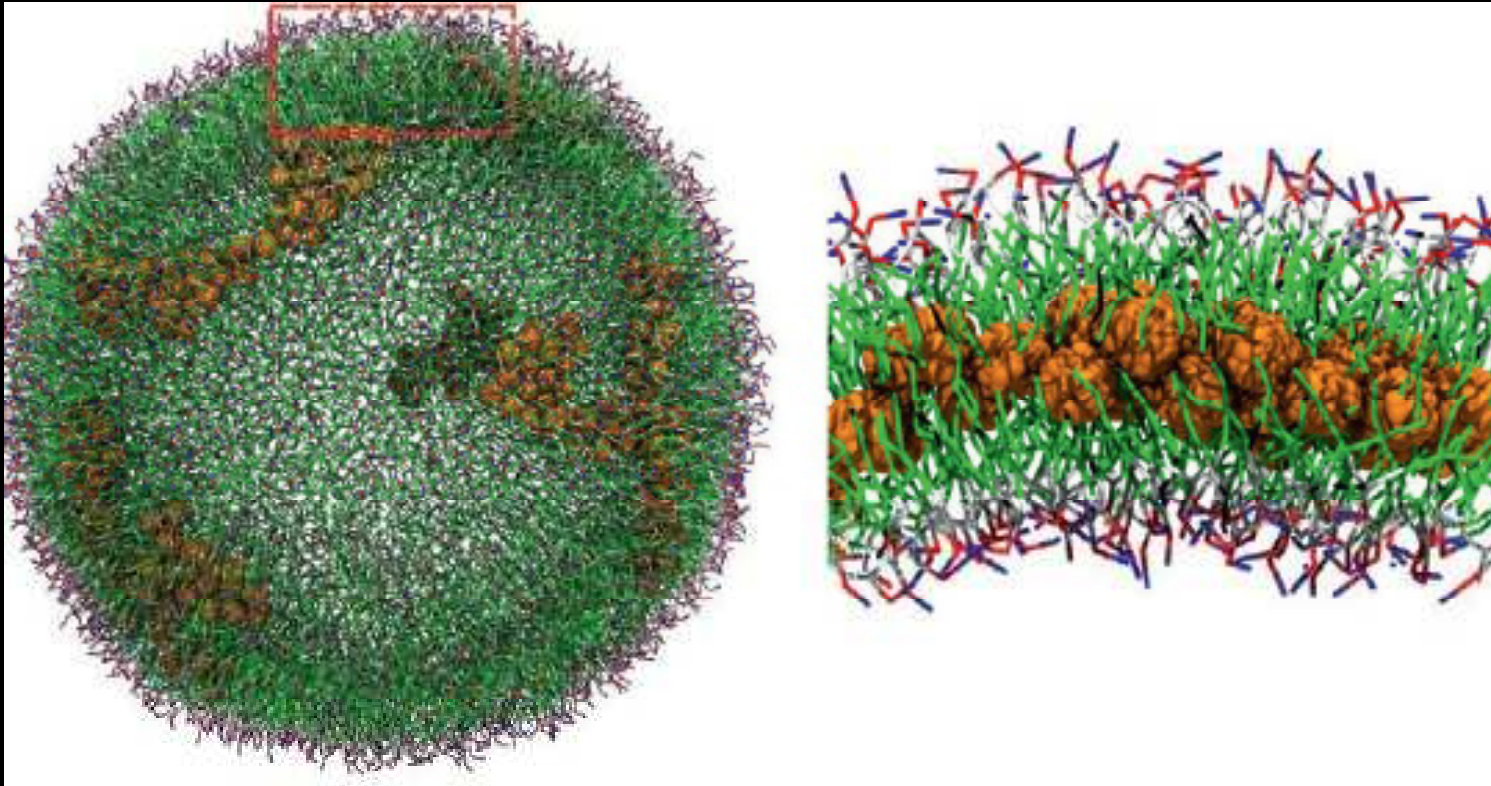


Simulation of 5000 (vesicle) and 20000 DMPC (multilamellar vesicle) in water

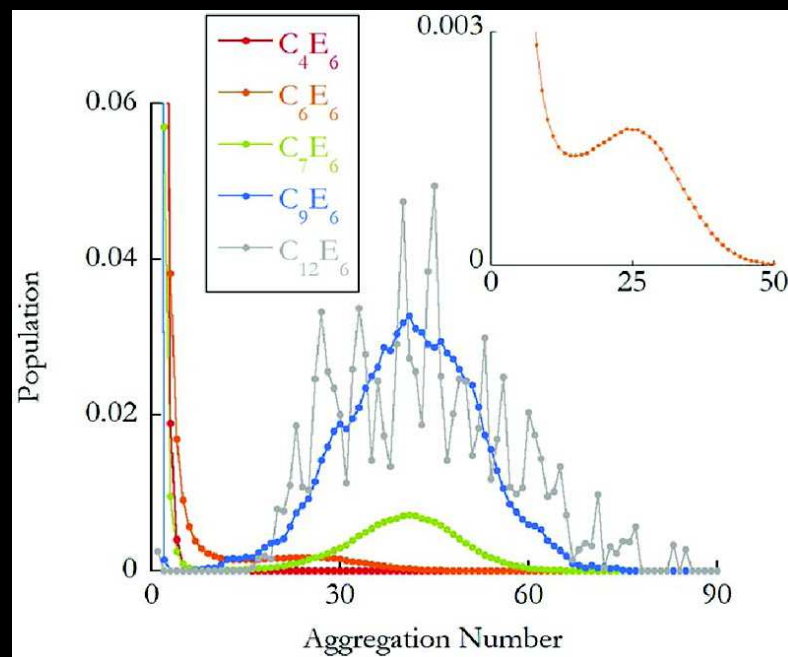
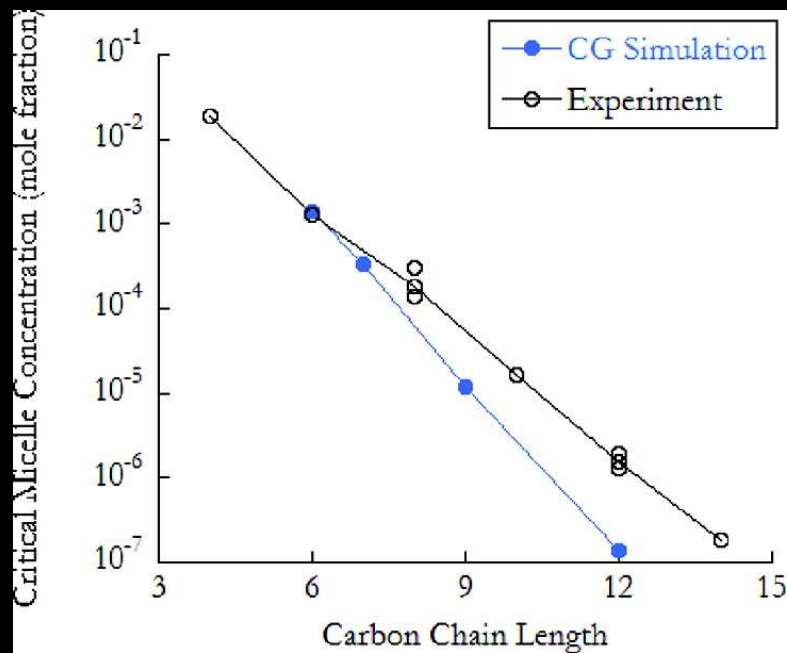


W. Shinoda et al., Curr. Opin. Struct. Biol. 22 (2012), 175.

5000 DMPC with 330 C₆₀ in water after 1.7 μ s



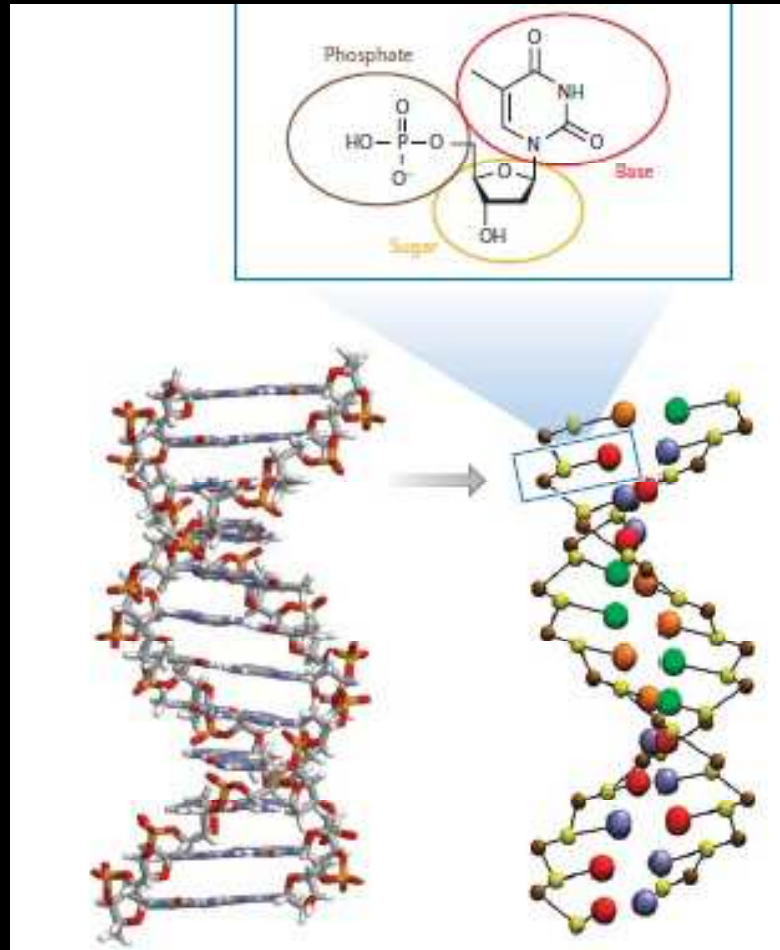
Micellization of C_nE_6



B.G. Levine et al., JCTC 7 (2011), 4135

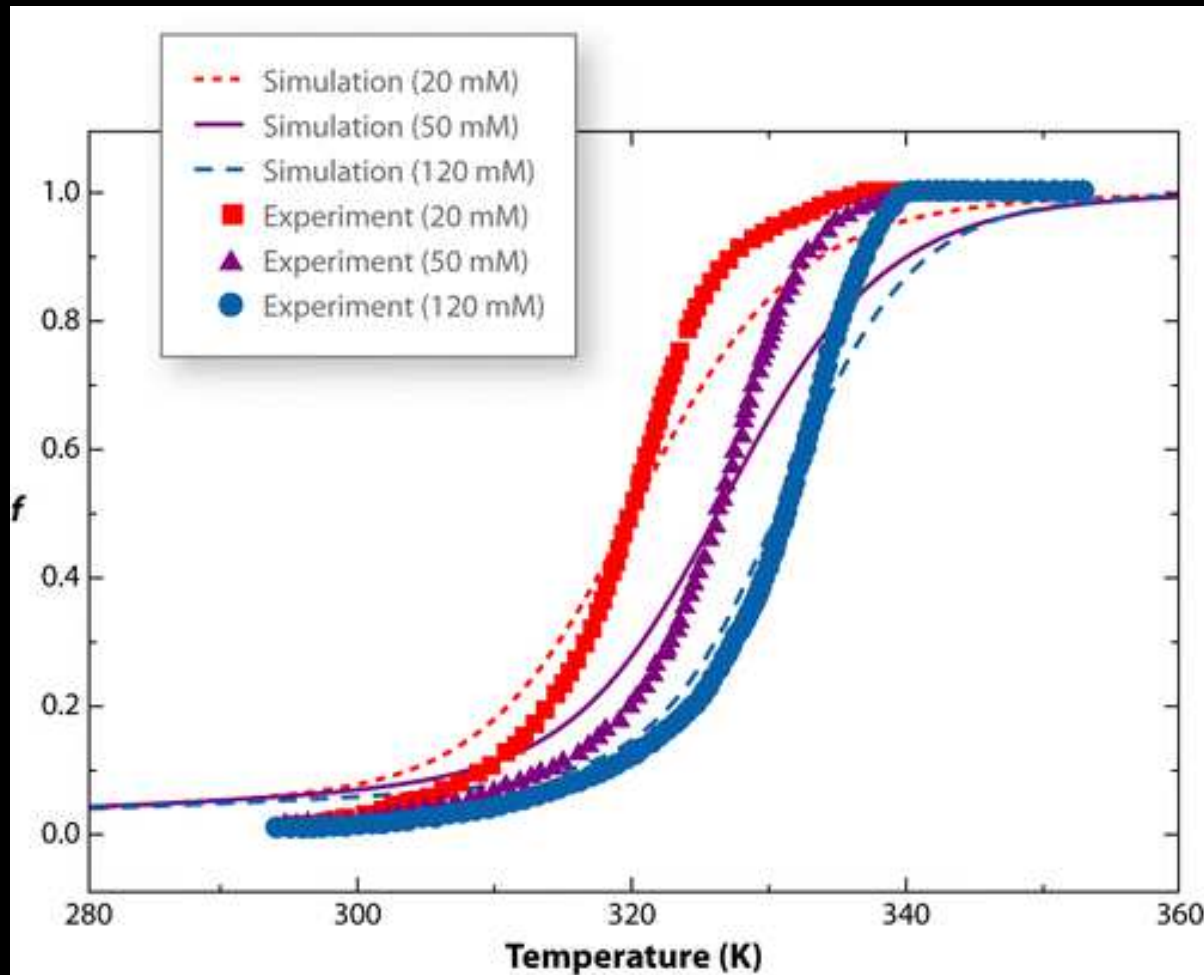
DNA, RNA

- 3SPN (three sites per nucleotide)



J.J. de Pablo, Annu. Rev. Phys. Chem. 62 (2011), 555.

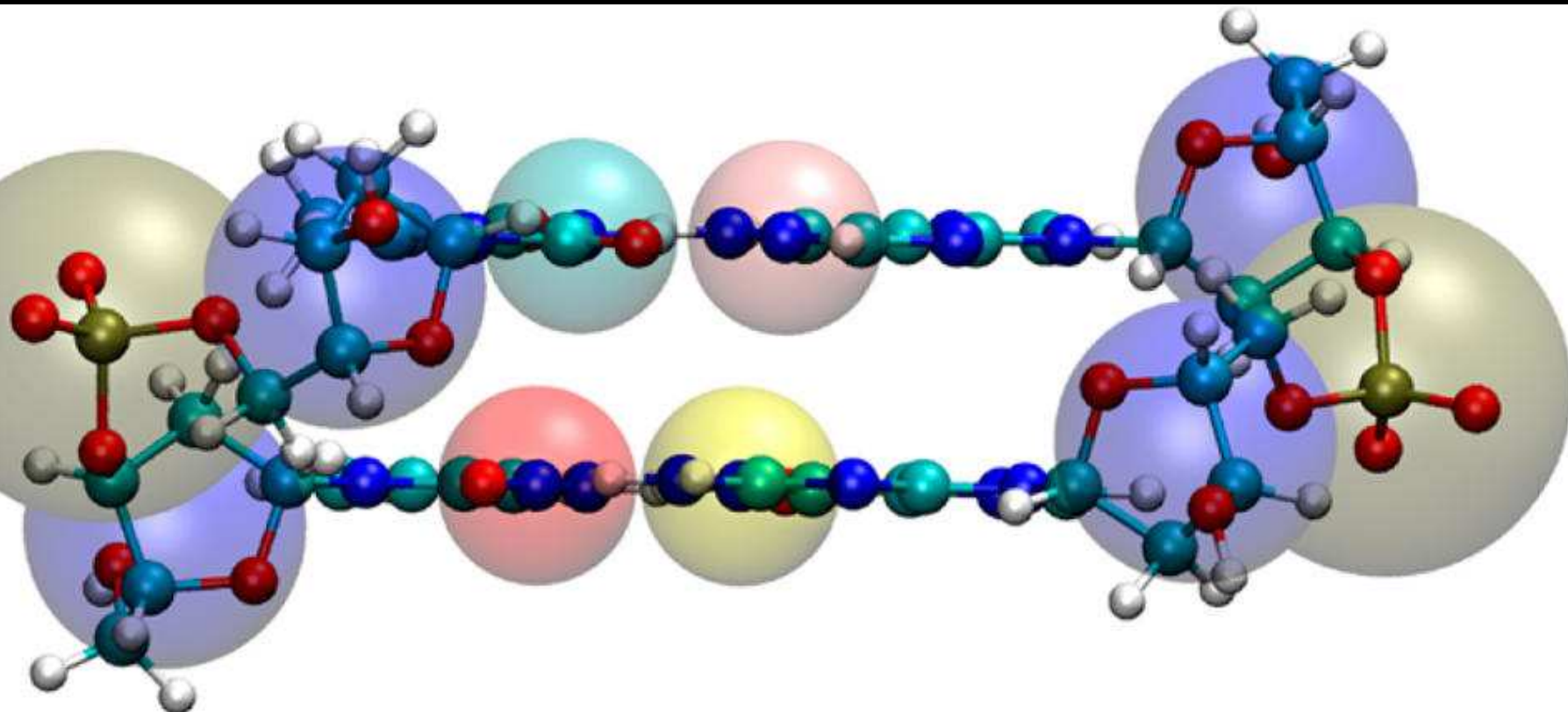
Melting curves: shape of curves and concentration effects



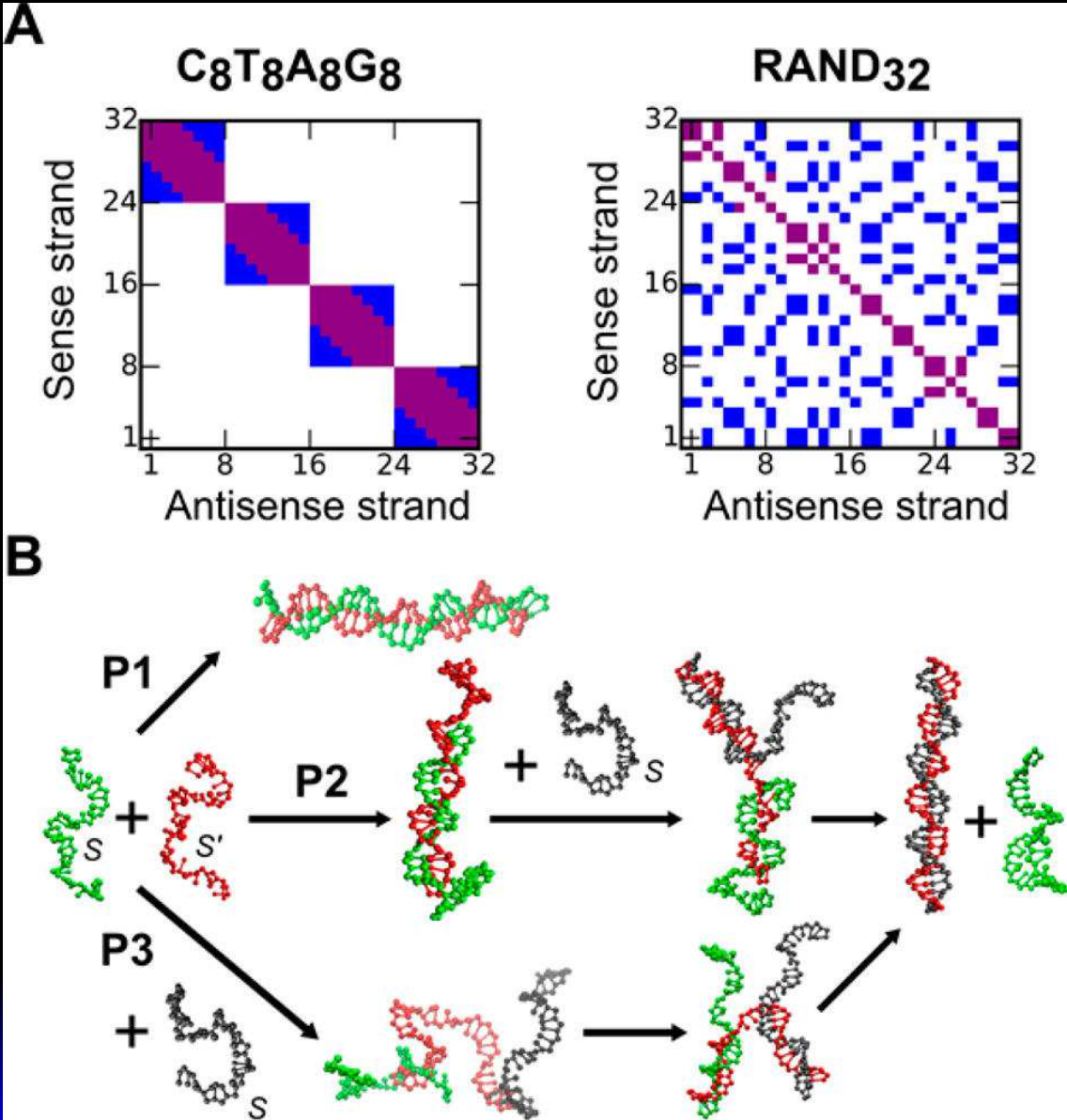
de Pablo JJ. 2011.

Annu. Rev. Phys. Chem. 62:555–74

- **BioModi:** C.B. Markegard et al., J. Phys. Chem. B 120 (2016), 7795.

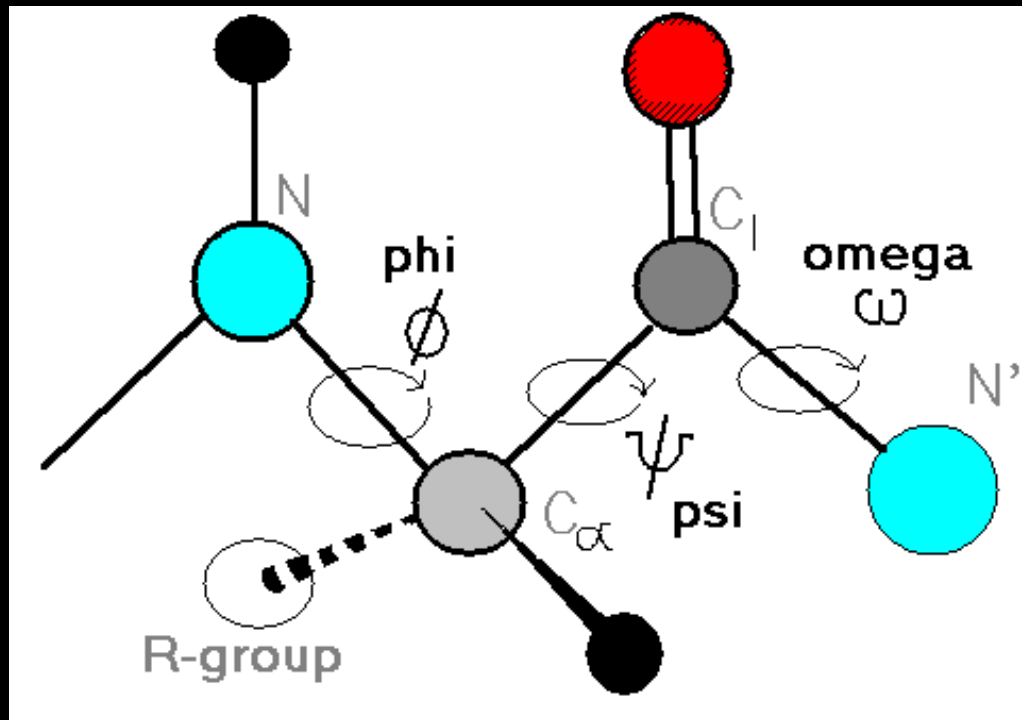


Kinetics of self-assembly



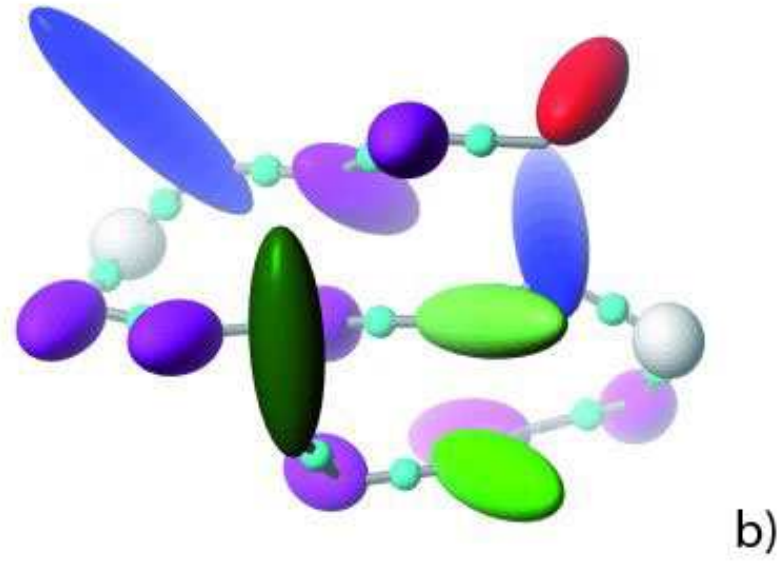
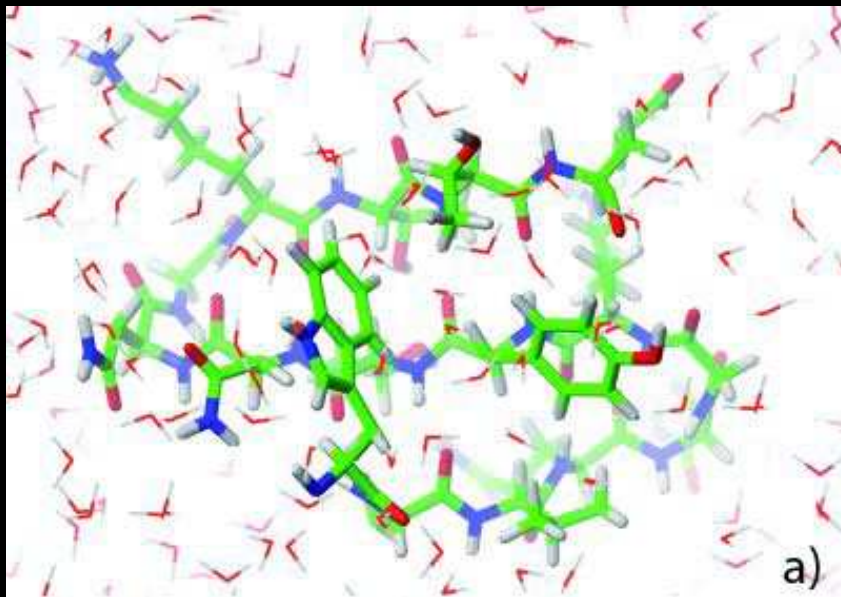
Proteins

- Secondary structure



<http://www.bioinf.org.uk/teaching/bbk/molstruc/practical2/peptide.html>

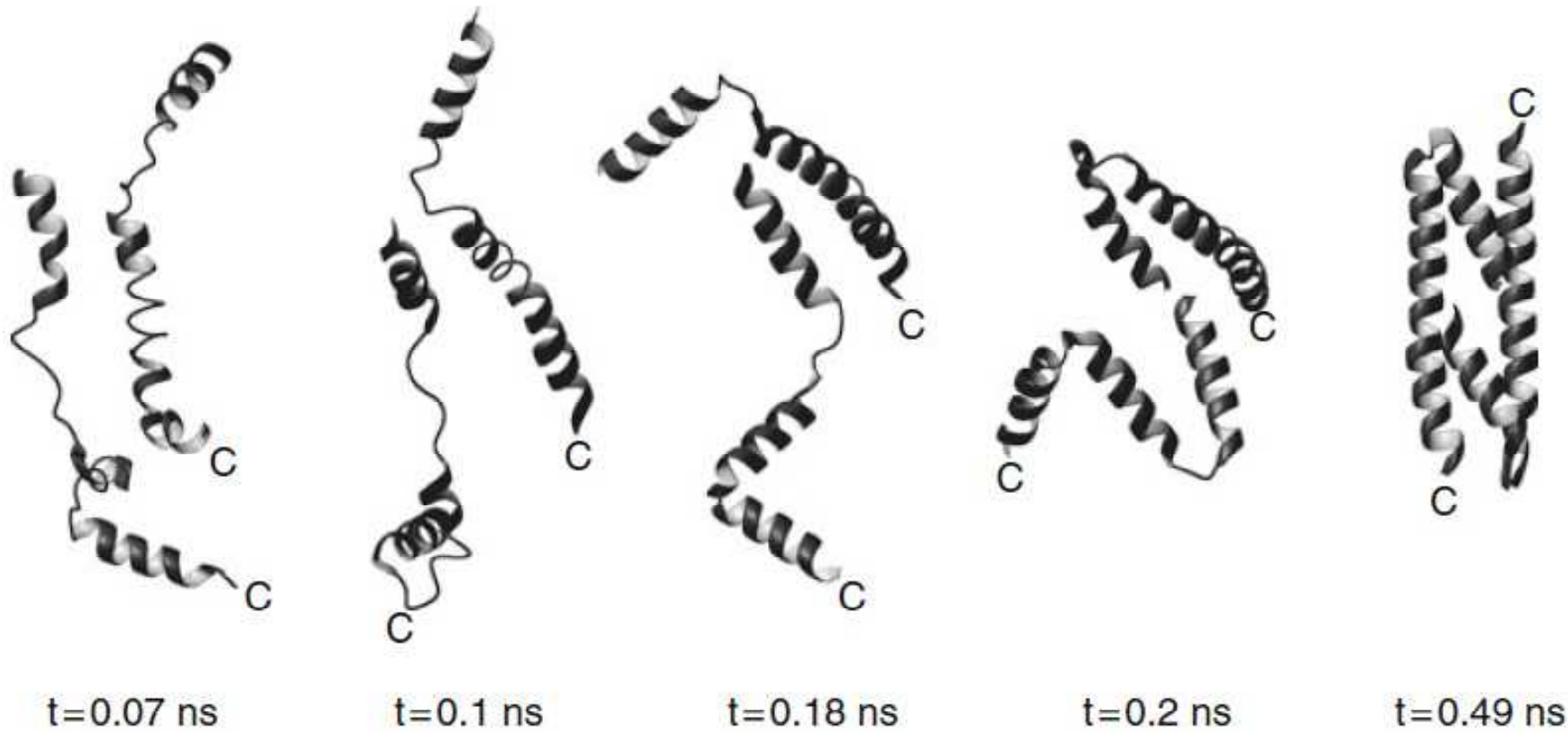
- UNRES proposal (H.A. Scheraga group): beads at C_α , side chains, and in the middle between the C_α 's



www.unres.pl

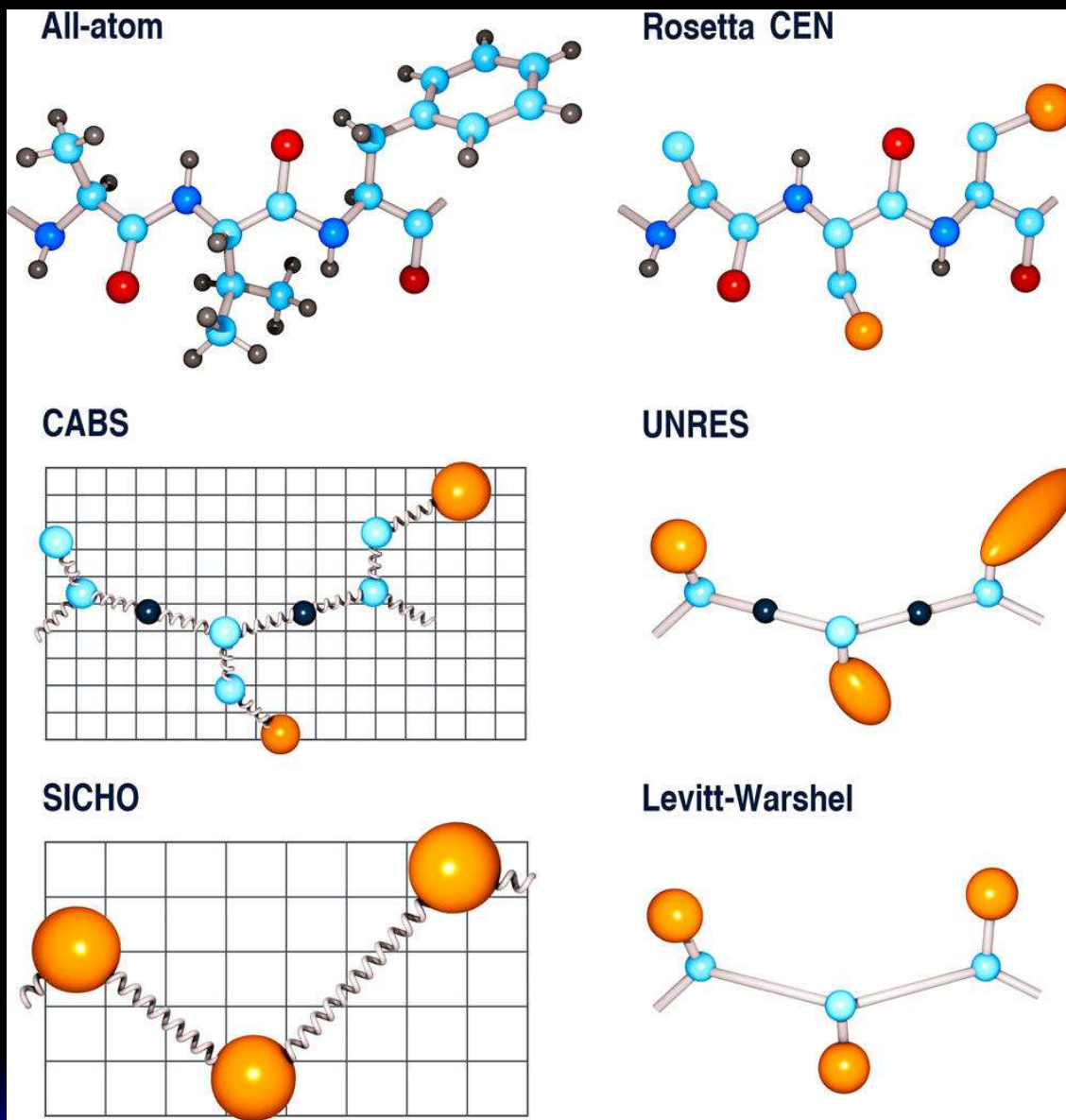
not potential, but free energy based

rather successful in CASP competition



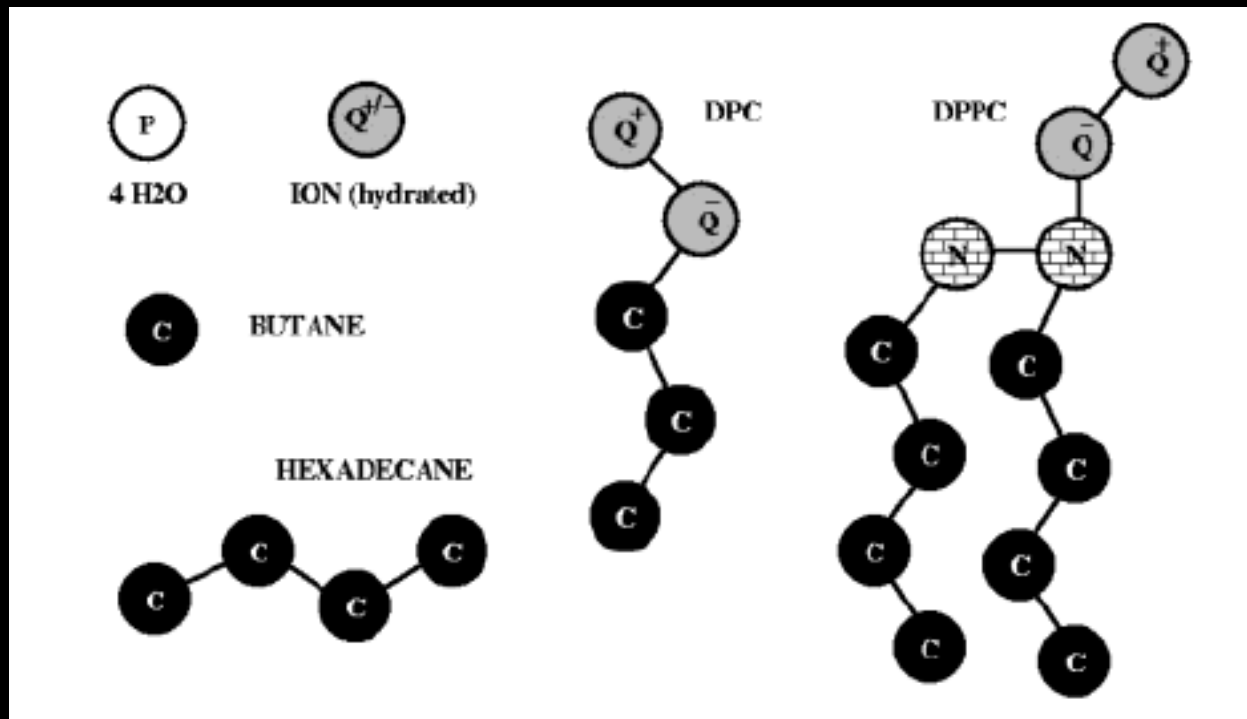
1G6U (dimer): A.V. Rojas et al., JPCB 111 (2007), 293.

- **Very recent review:** S. Kmiecik et al., Chem. Rev. 116 (2016), 7898.



MARTINI

Mapping scheme 4-1: S.J.Marrink et al., JPCB 108 (2004), 750.



- LJ + Coulomb (reaction field with dielectric constant of 20) + springs (bonds) + harmonic cosines (angles)

system	CG model	density, ^b g cm ⁻³	compressibility, ^c 10 ⁻⁵ bar ⁻¹	diffusion, ^d 10 ⁻⁵ cm ² s ⁻¹
water	P	0.99 (0.99)	6 (4.5)	2.0 (2.3)
butane	C	0.68 (0.58)	28 (> 17)	1.9 (> 5)
hexane	C-C	0.58 (0.66)	14 (17)	0.7 (4)
octane	C-C	0.77 (0.70)	14 (13)	0.6 (2)
decane	C-C-C	0.67 (0.73)	12 (11)	0.35 (1)
dodecane	C-C-C	0.80 (0.75)	12 (10)	0.3 (-)
tetradecane	C-C-C-C	0.71 (0.76)	12 (9)	0.25 (-)
hexadecane	C-C-C-C	0.81 (0.77)	12 (9)	0.2 (-)
octadecane	C-C-C-C-C	0.74 (0.78)	11 (-)	0.2 (0.3)
eicosane	C-C-C-C-C	0.82 (0.79)	11 (-)	0.15 (-)

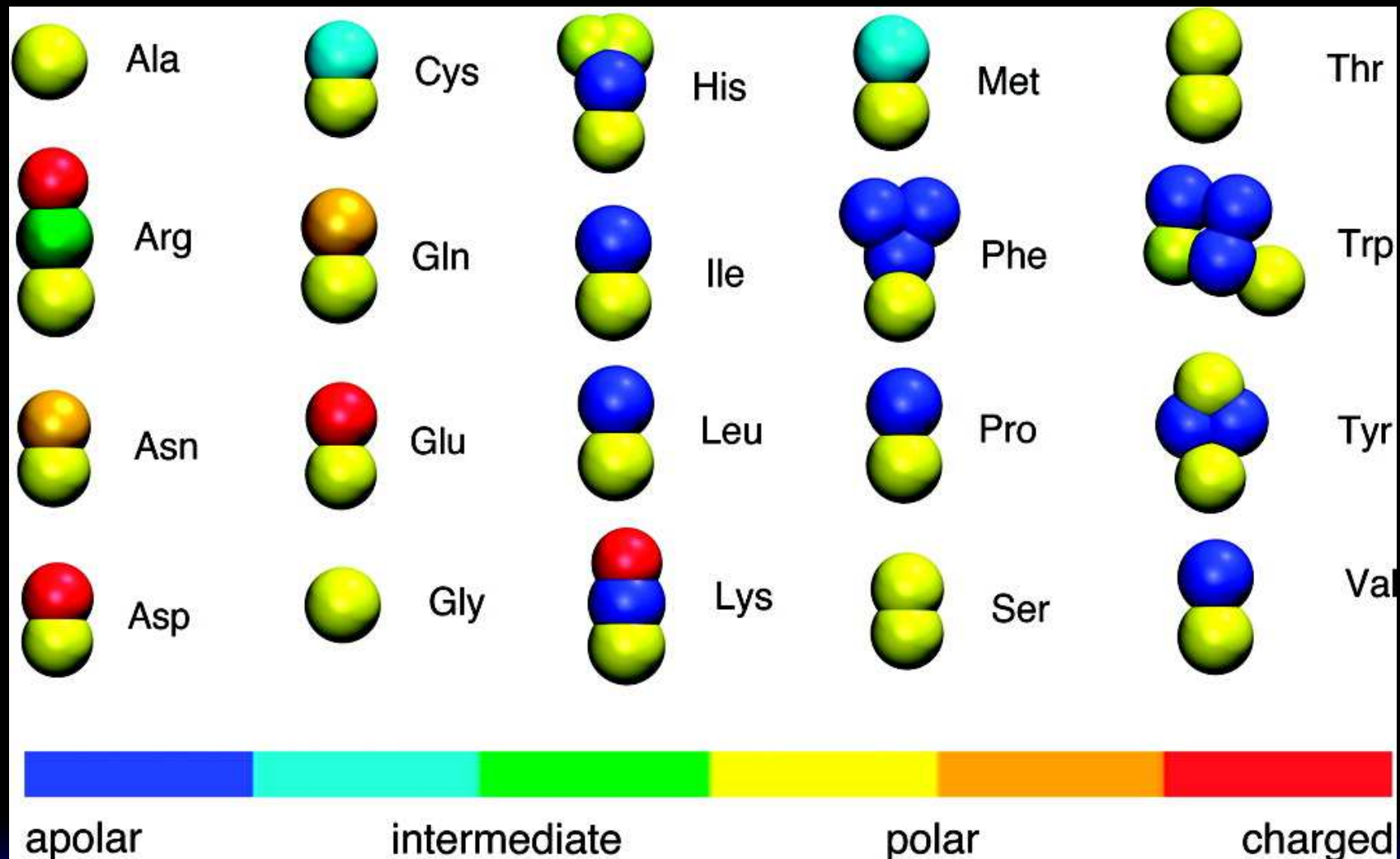
- Membrane properties

system	simulated area, ^a nm ²	experimental area, ^a nm ²
DPPC	0.47 ^b (283 K)	0.46 ^b (273 K), 0.48 ^c (293 K)
DPPC	0.59 (300 K)	
DPPC	0.64 (323 K)	0.64 (323 K)
DPPC	0.66 (338 K)	0.64–0.67 ^d (333 K), 0.67 (338 K)
DLPC	0.60 (300 K)	0.57 (293 K), 0.63 (303 K)
DLPC	0.66 (338 K)	0.64–0.68 ^d (333 K), 0.71 (338 K)
DSPC	0.66 (338 K)	0.65 (333 K), 0.66 (338 K)
DOPC	0.67 (300 K)	0.72 (303 K)
DPPE	0.62 (338 K)	0.61 (342 K)
DOPE	0.61 (273 K)	0.65 (271 K)
DLPE	0.55 (300 K)	0.51 (308 K)
POPE	0.59 (300 K)	0.57 (303 K)

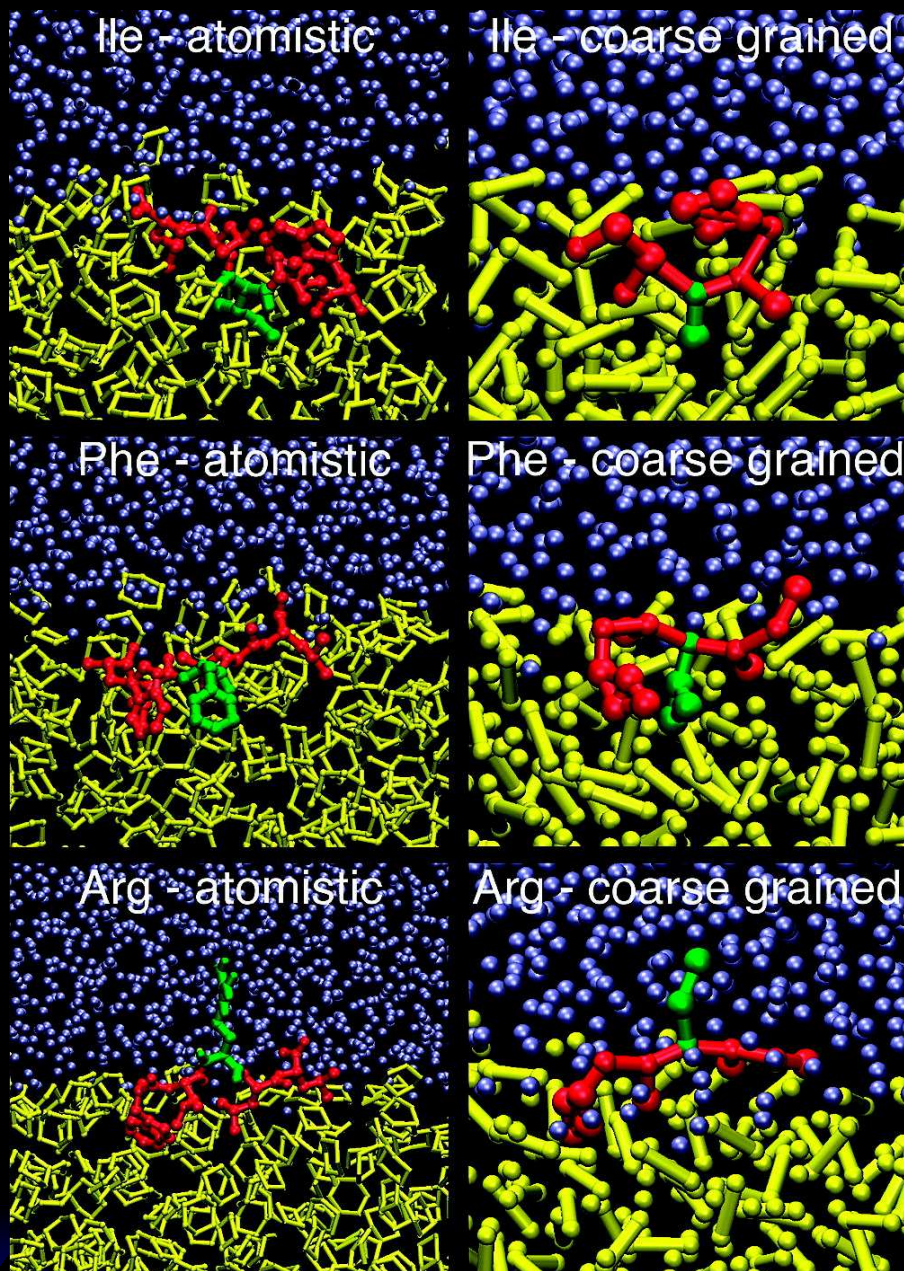
- Refinement (water/octanol partition) and inclusion of benzene and cholesterol
 \Rightarrow improper dihedrals

S.J.Marrink et al., JPCB 111 (2007), 7812.

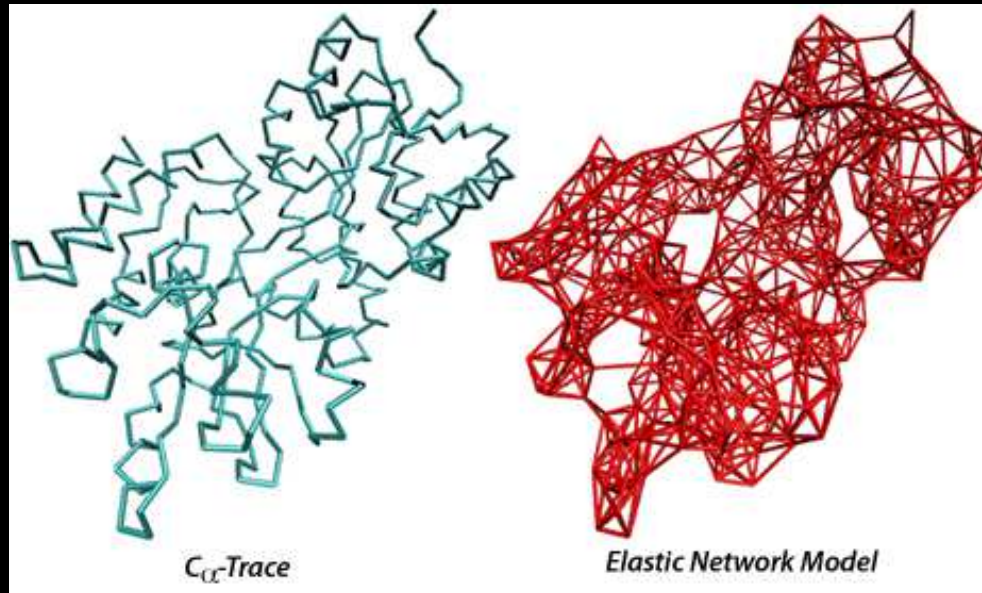
- Amino acids: beads at C_{α} (main chain) with different lateral groups (side chain)



L. Monticelli et al., JCTC 4 (2008), 819.



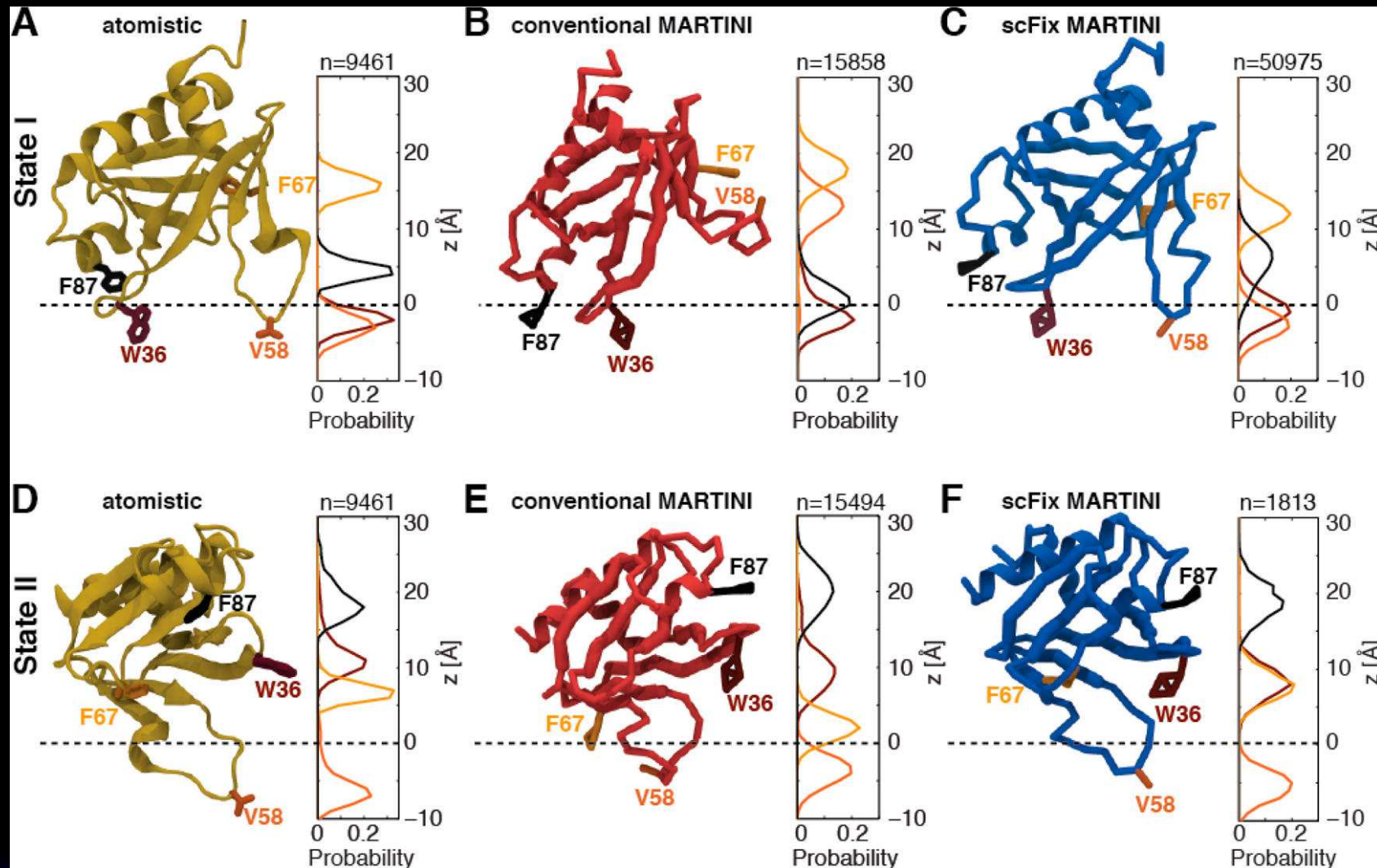
with elastic network



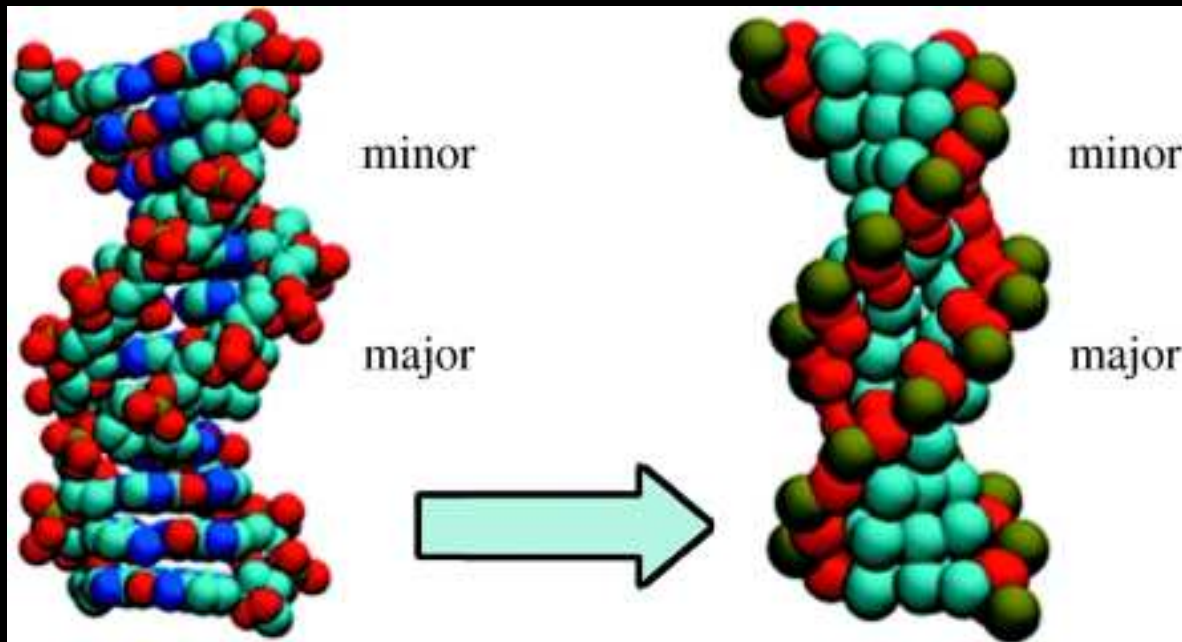
<http://lorentz.immstr.pasteur.fr/nma>

\Rightarrow conserved secondary structure during the simulation

- Fixed side chains F.A. Herzog et al., JCTC 12 (2016), 2446.

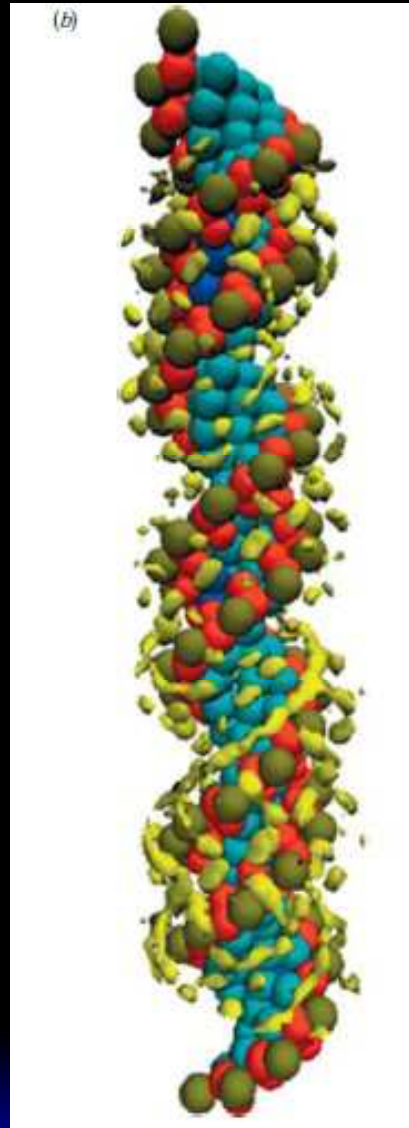


- DNA (early version)
12 base pairs (1BNA.pdb)

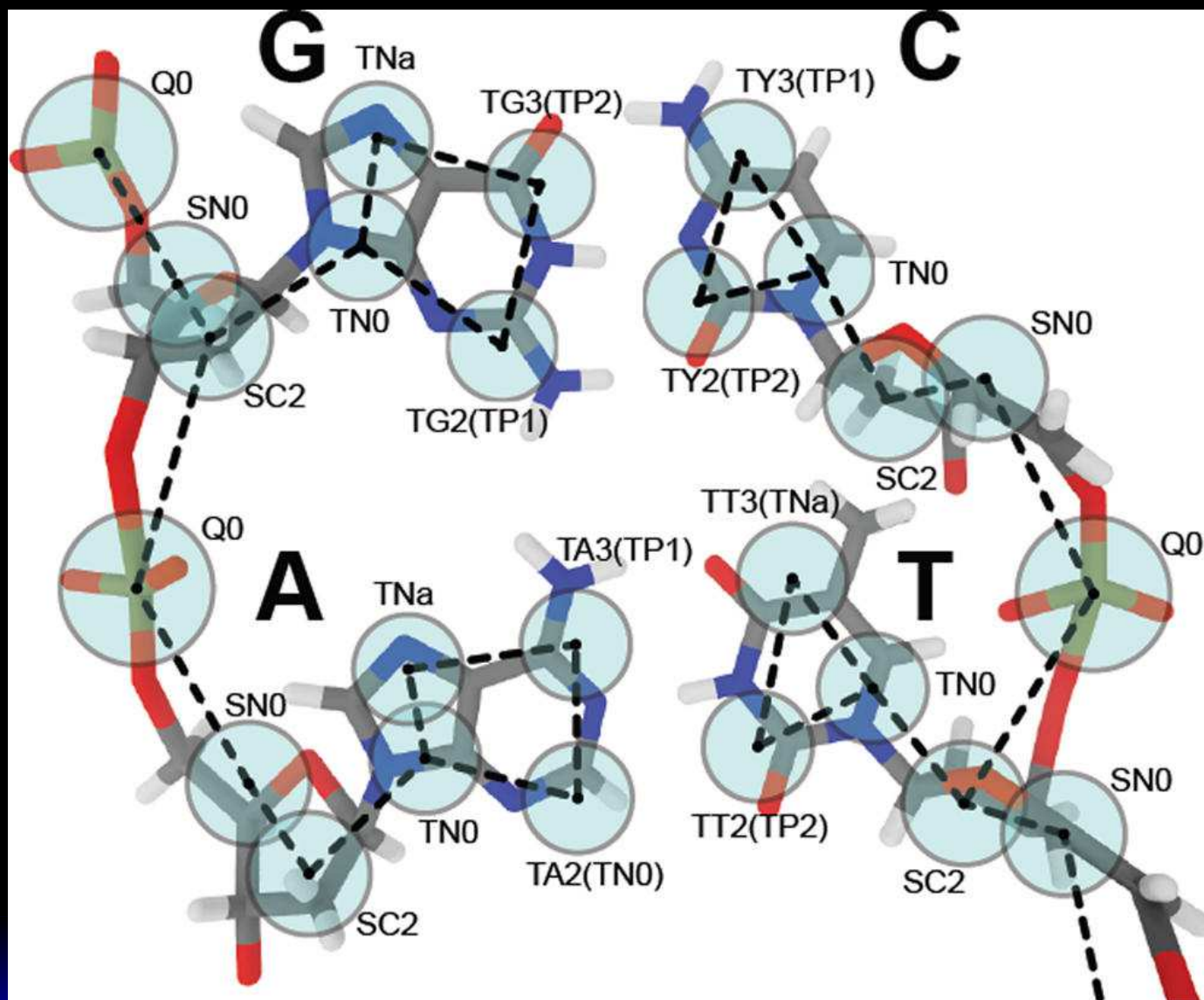


S. Khalid et al., J. R. Soc. Interface 5 (2008), 241.

Density of Na^+ around the 12 base pairs

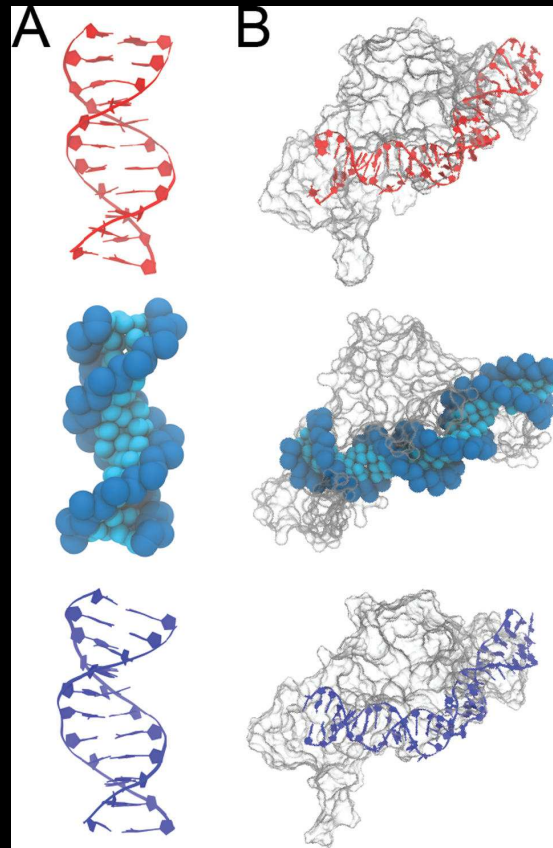
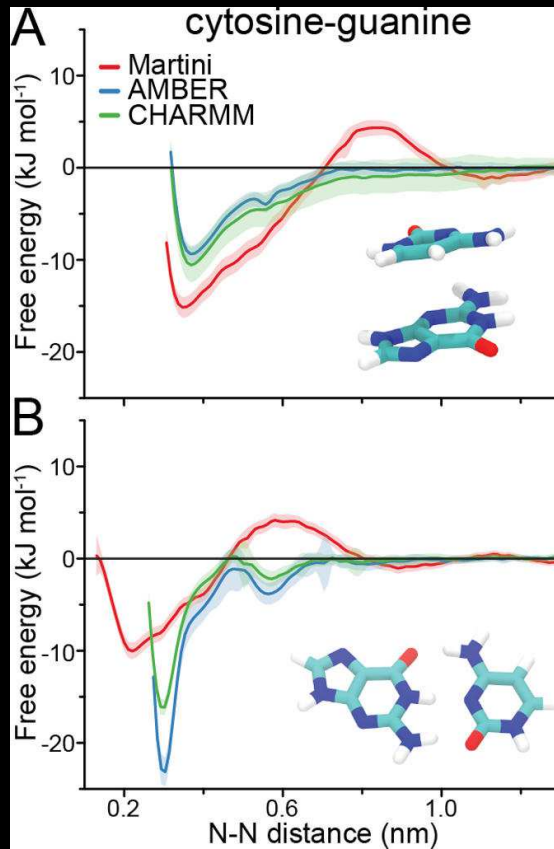


- DNA (new version): J.J. Uusitalo et al., JCTC 11 (2015), 3932.

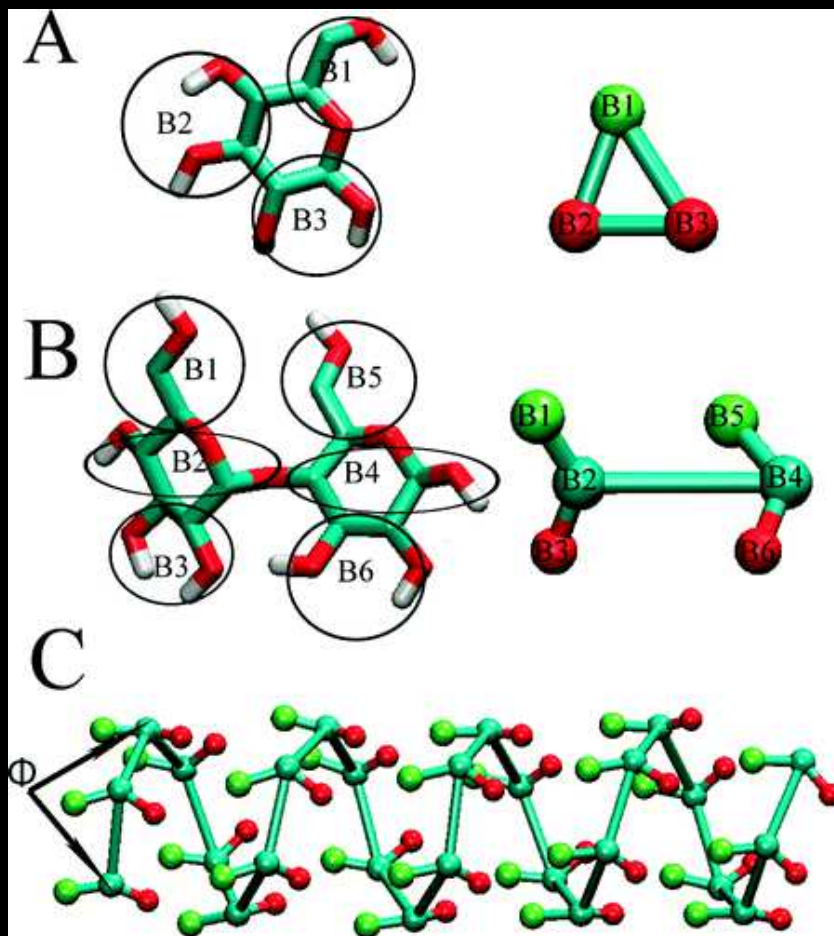


PMF (stack, in plane)

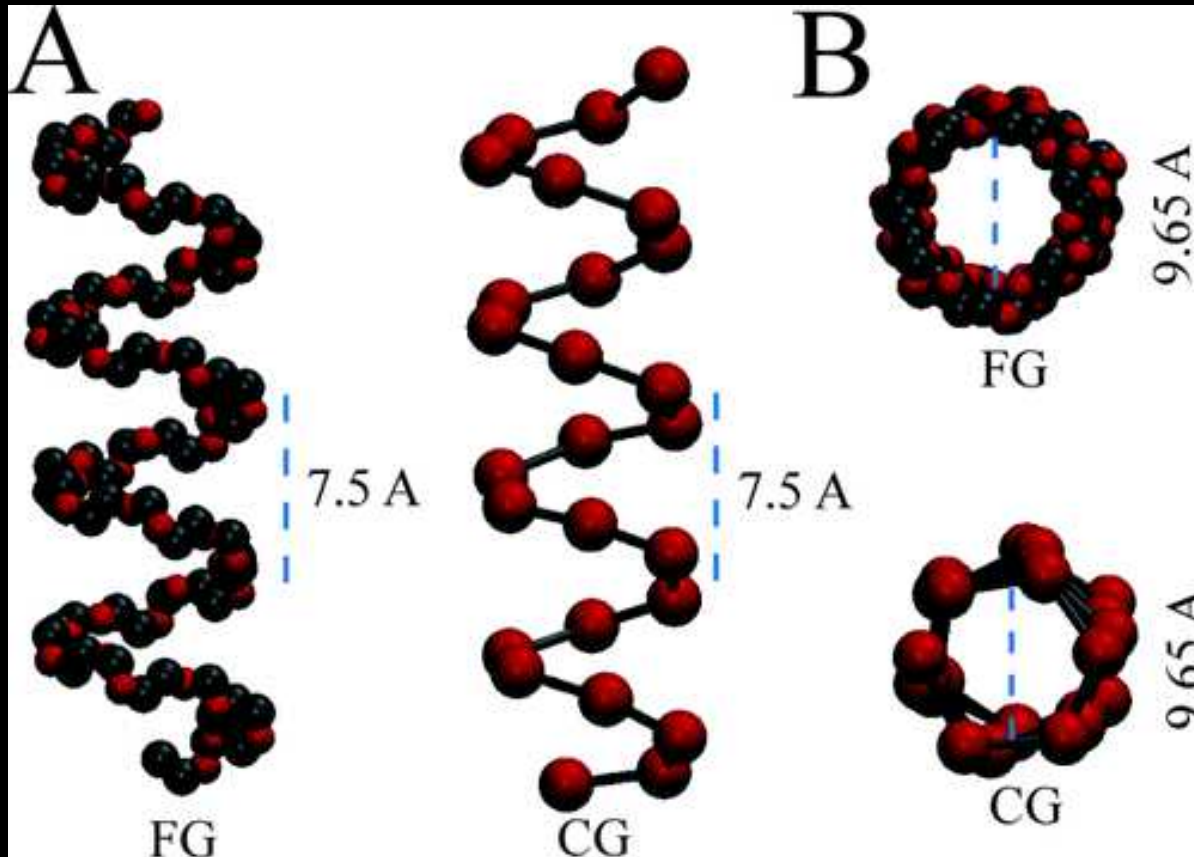
AA-CG-AA



- Sugars (Sweet MARTINI) C.A. López et al., JCTC 5 (2009), 3195.

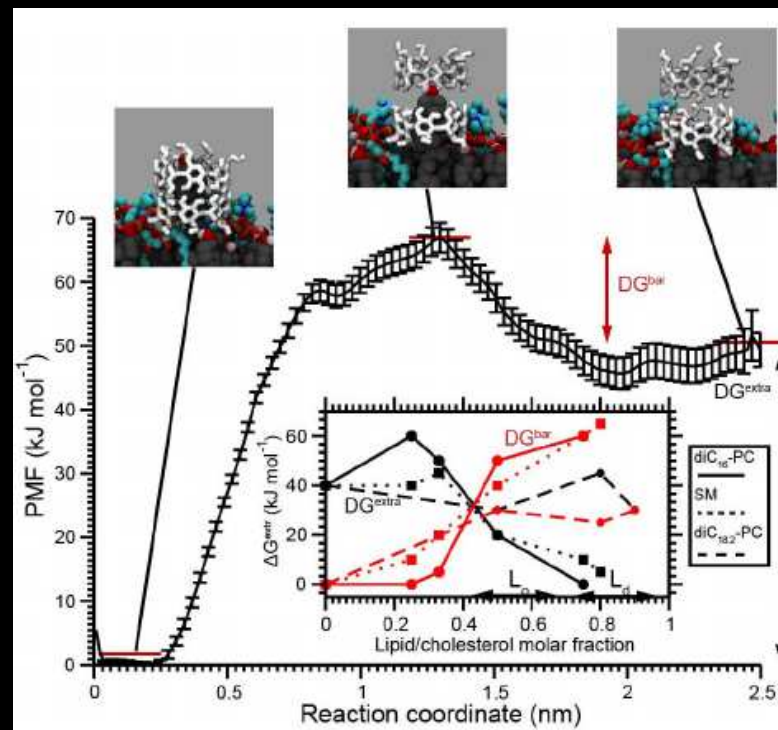
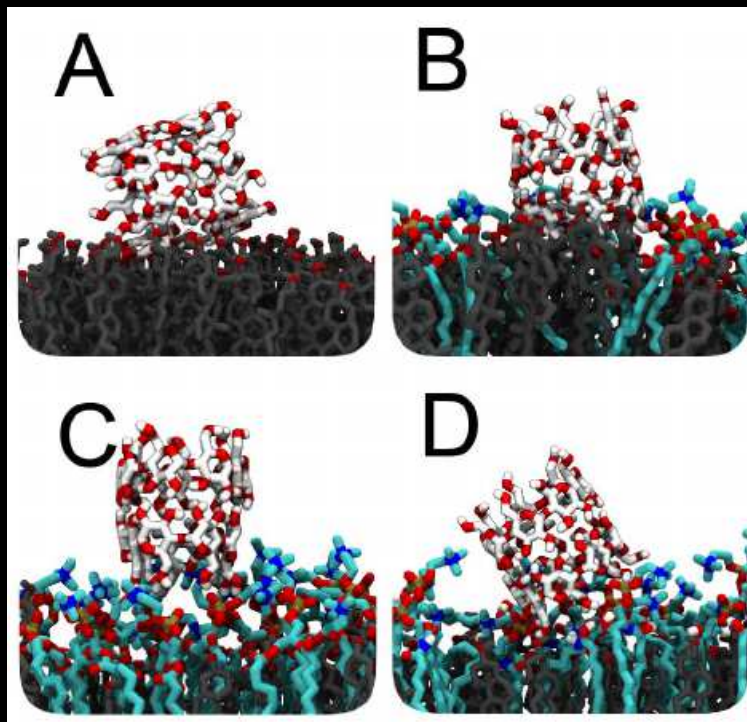


Amylose in nonane (atomistic vs. CG)

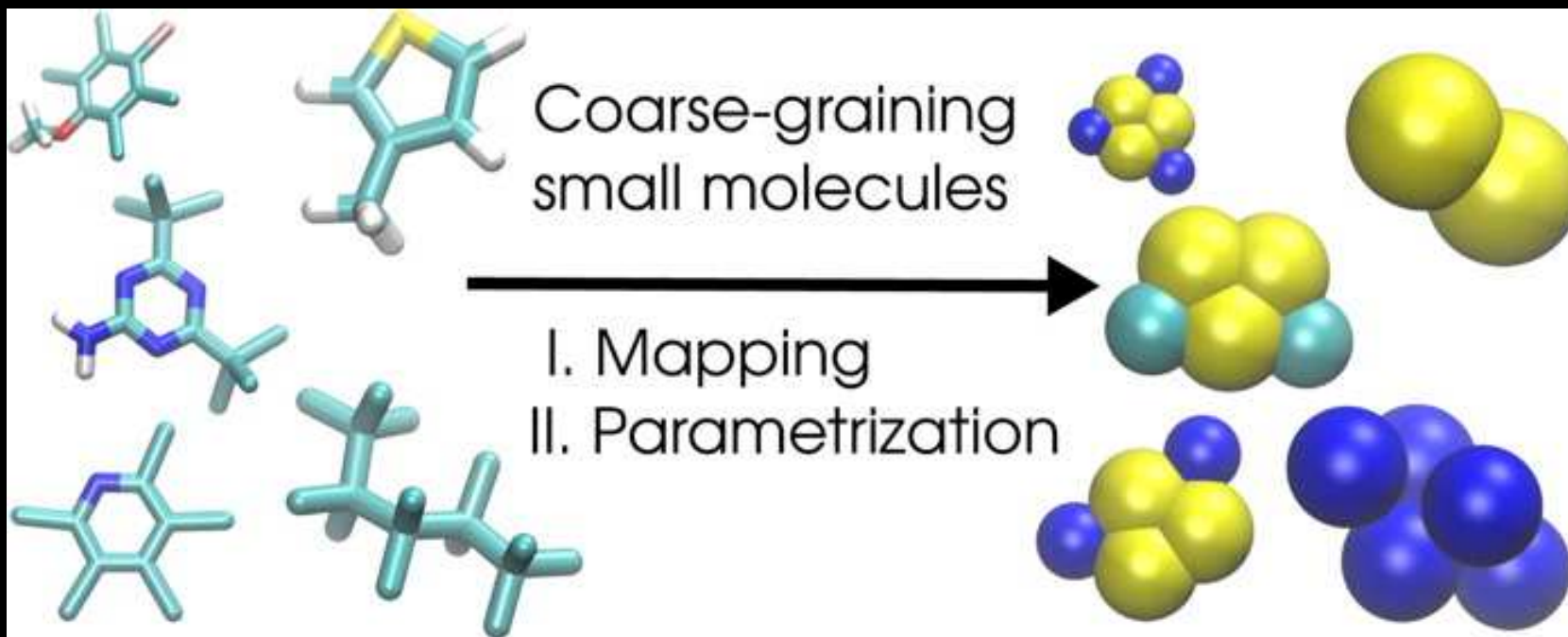


Cholesterol extraction by β -Cyclodextrin:

C.A. López et al., Sci. Rep. 3 (2013), 2071.



- **Automartini:** T. Bereau, K. Kremer, JCTC 11 (2015), 2783.



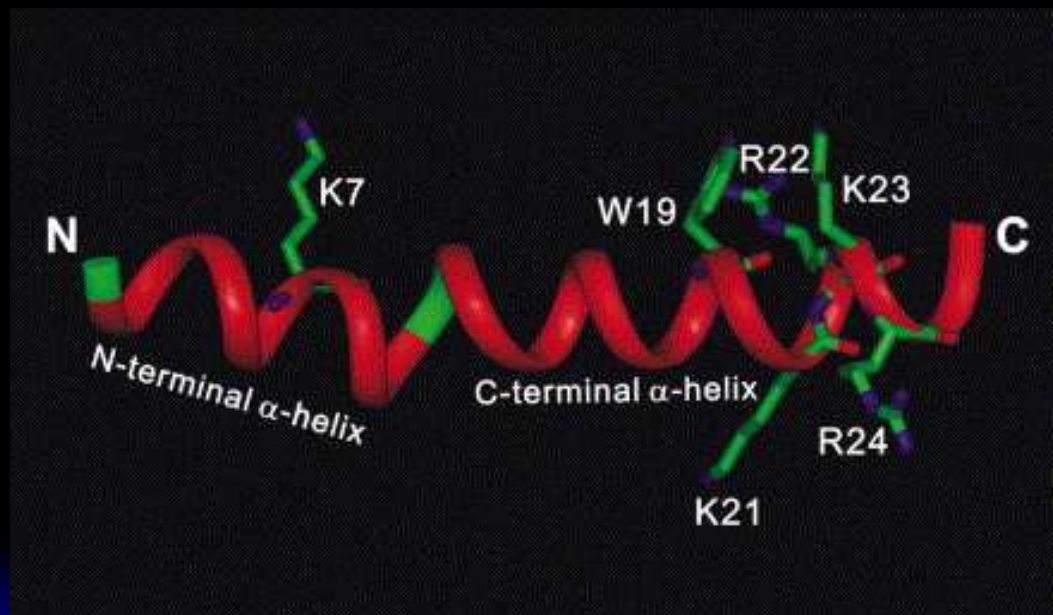
Test: free energy of solvation and partitioning

Protein Membrane Interaction

- AMPs:

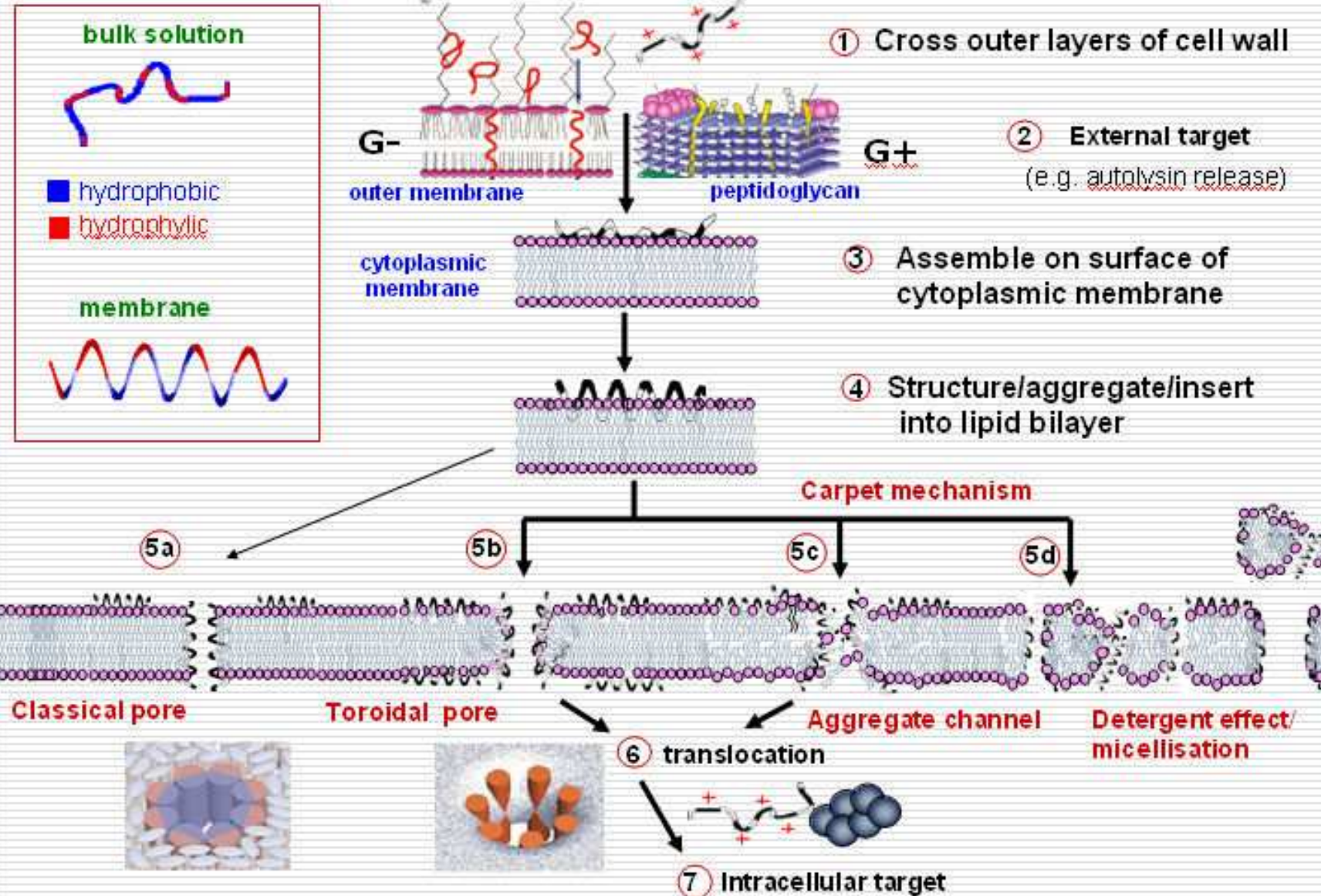
Magainin-H2 (23aa, +3)

Melittin (26aa, +6)

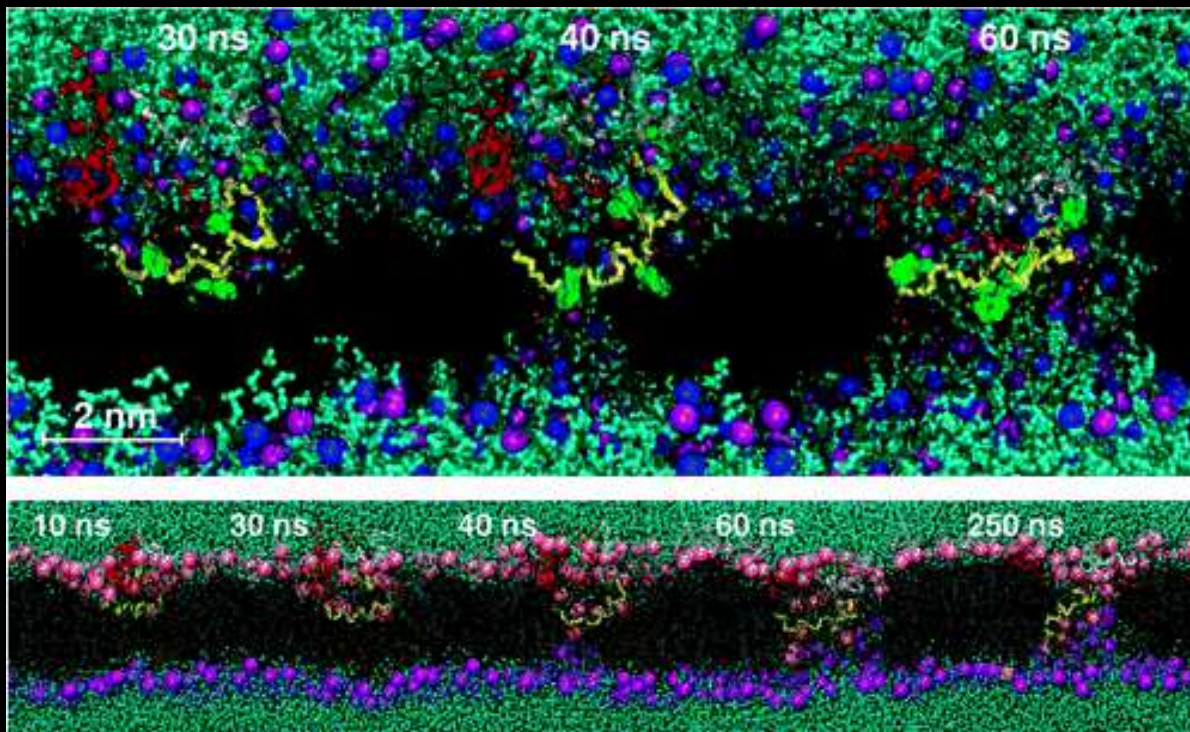


H.L. Liu, C.M. Hsu, CPL 375 (2003), 119.

Mode of action of α -helical AMPs



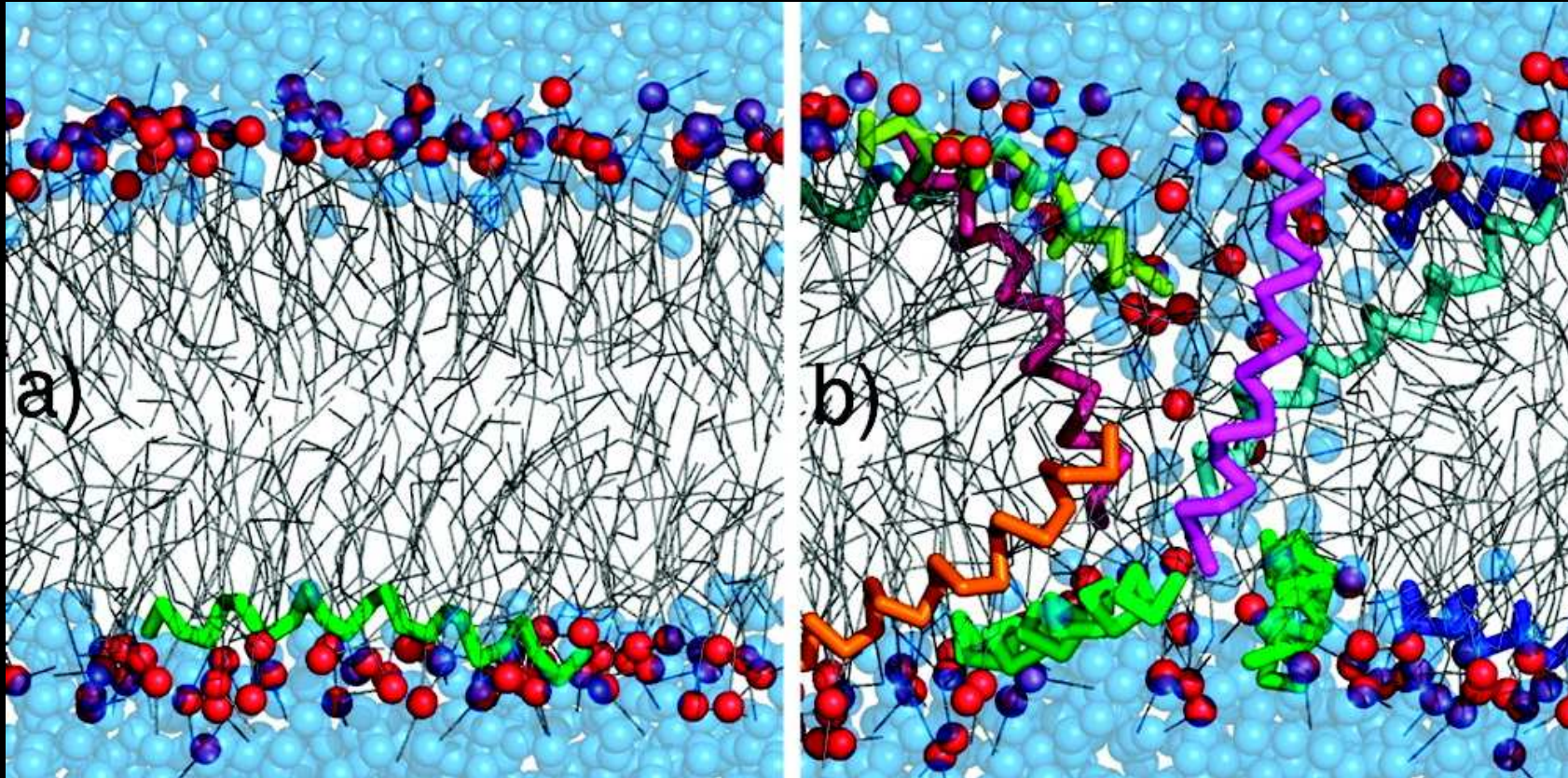
Magainin-H2: atomistic simulation of 4 polypeptides at a DPPC bilayer



H. Leontiadou et al., JACS 128 (2006), 12156.

disordered toroidal pore

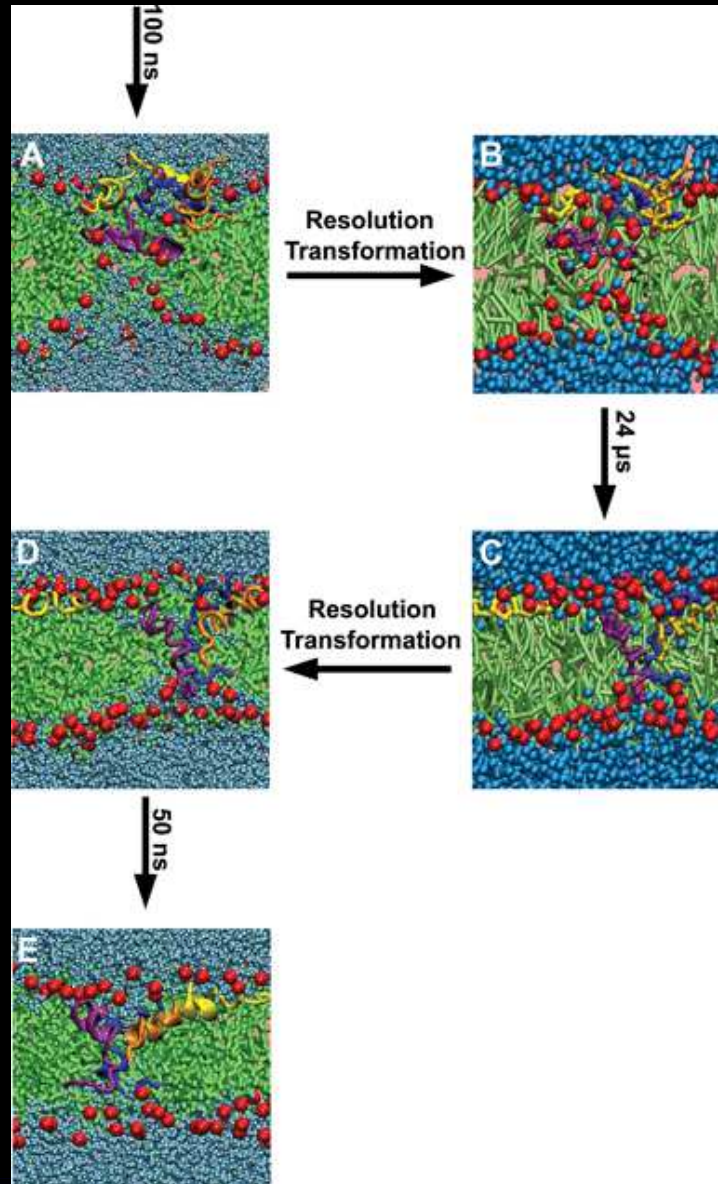
CG self-aggregation of polypeptides with DPPC in water



L. Monticelli et al., JCTC 4 (2008), 819.

disordered toroidal pore with two magainins in the center and others at the edge of the pore

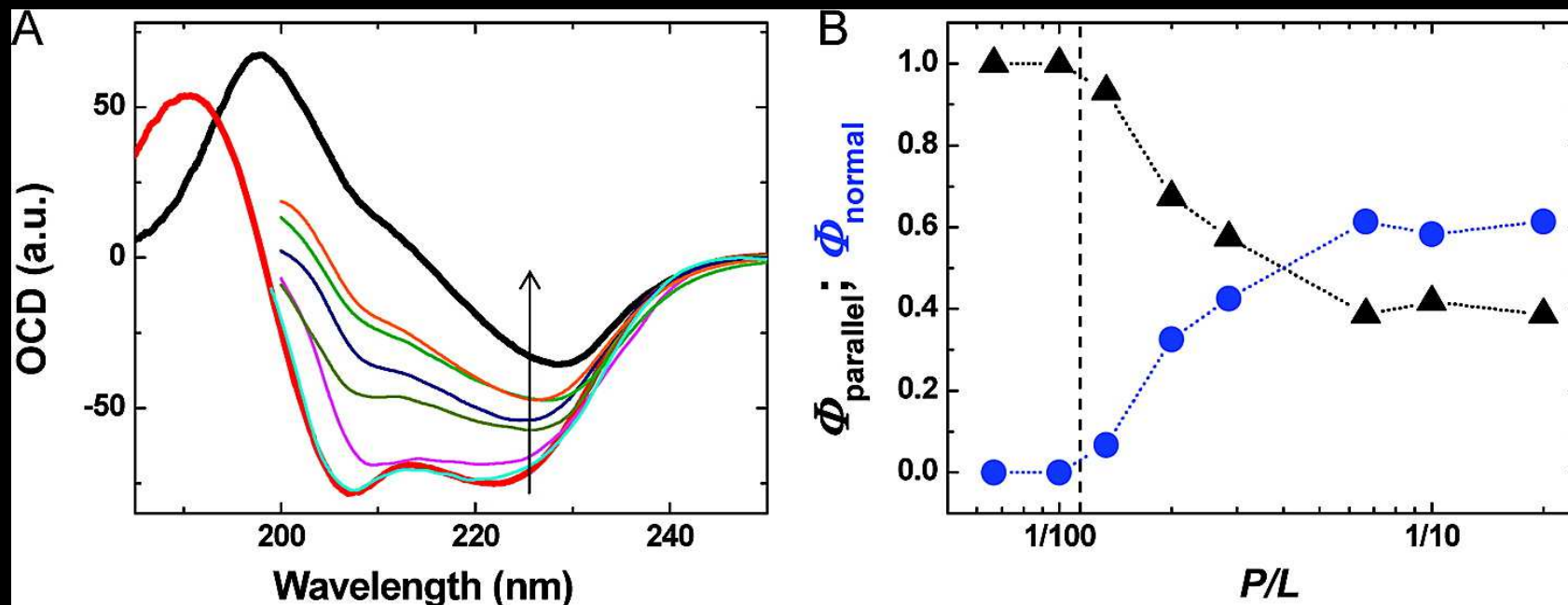
"multiscaling" of 4 polypeptides in a DPPC bilayer



A.J. Rzepiela et al., Faraday Discuss. 144 (2010), 431.

- different orientations and transitions of the polypeptides
- flip-flop of DPPC in the pore region
- water content within the center of the pore depends on the helicity (max. for 65 % helicity; pore closes for complete α -helical polypeptides)

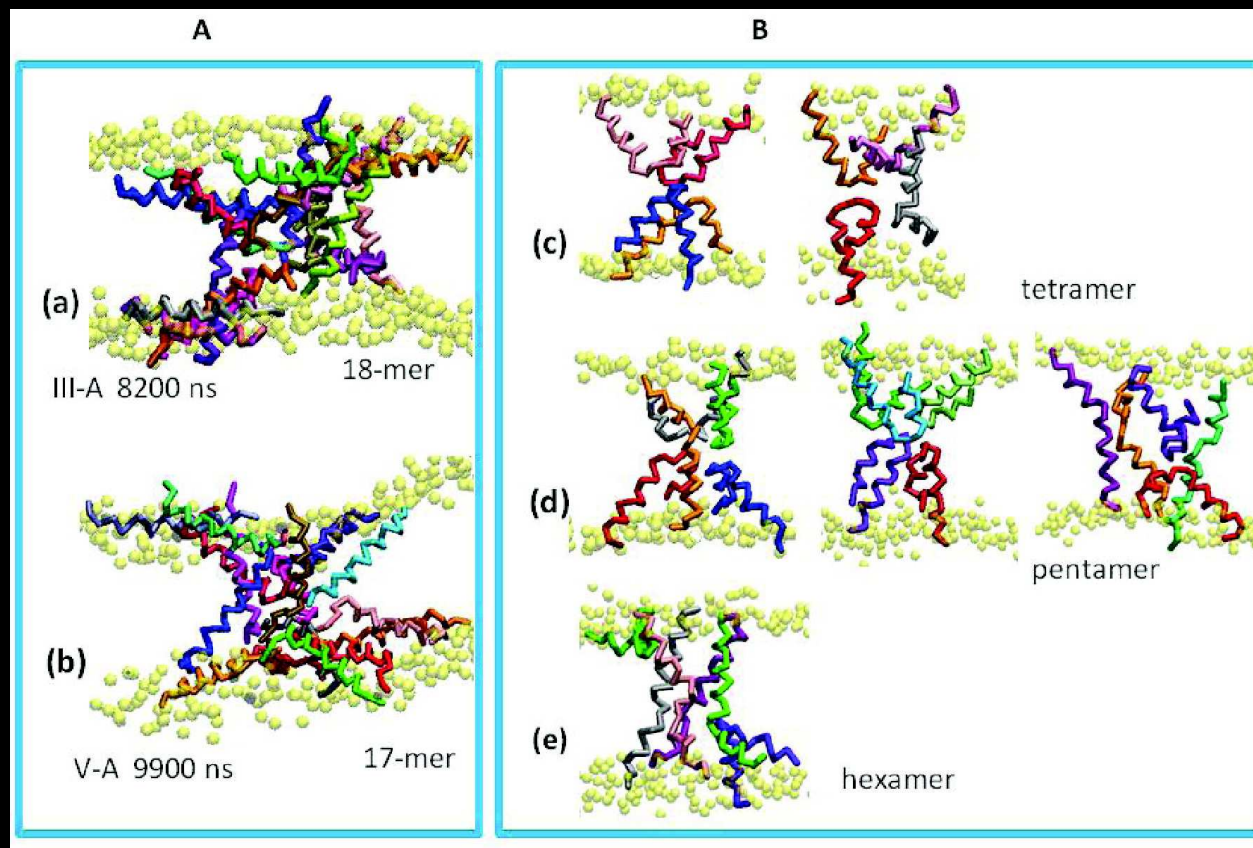
Melittin: recent experimental observations (POPC/DPPC)



Y. Yu et al., JACS 132 (2010), 195.

⇒ transmembrane orientation for concentrations above 1 melittin per 40 lipid molecules

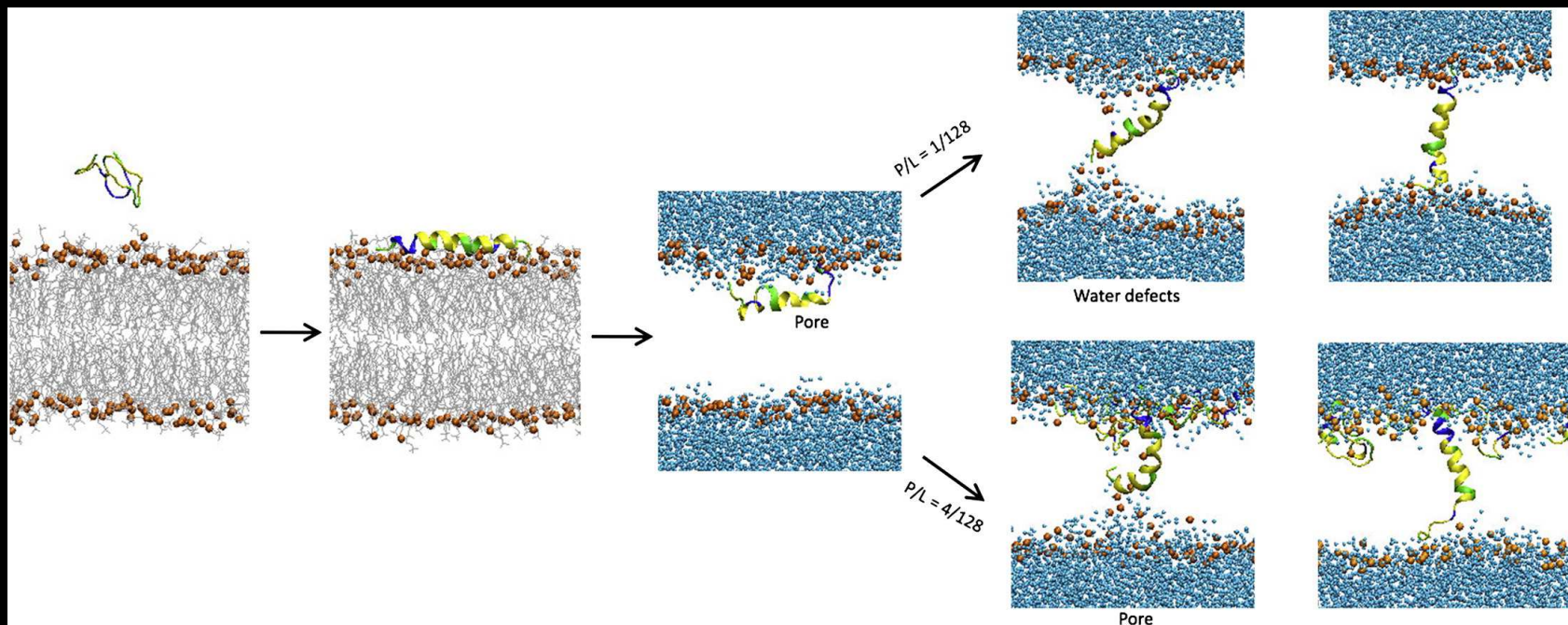
CG of 24 magainins (A) and melittins (B) at a DPPC bilayer (512 molecules)



K. Santo and M.L. Berkowitz, JPCB 116 (2012), 3021.

Melittin: Pore formation only for initial configurations with melittins at both interfaces

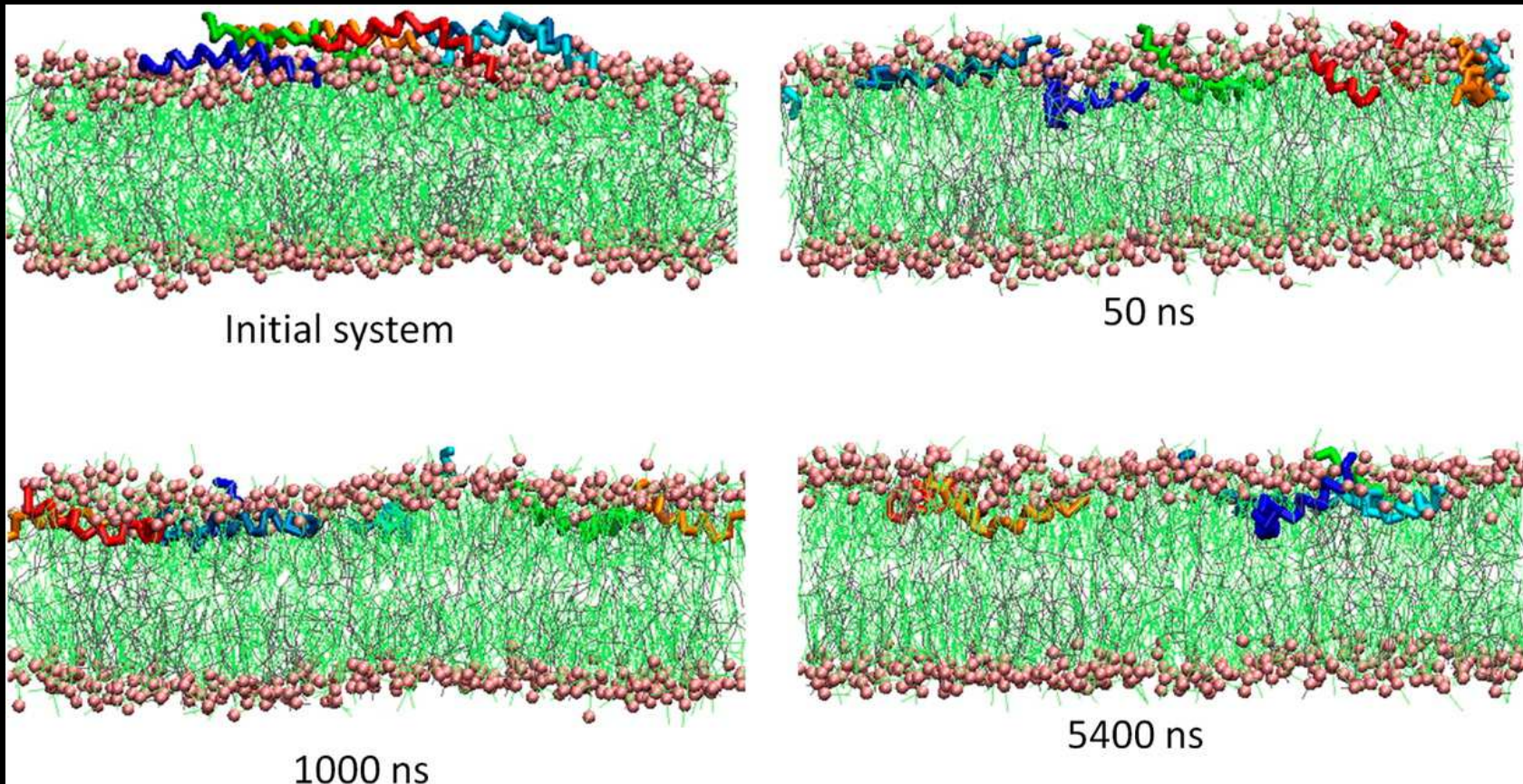
Pulled atomistic molecular dynamics of melittin at a POPC bilayer



S.J. Irudayam and M.L. Berkowitz, BBA 1818 (2012), 2975.

⇒ higher melittin concentrations for reorientation process

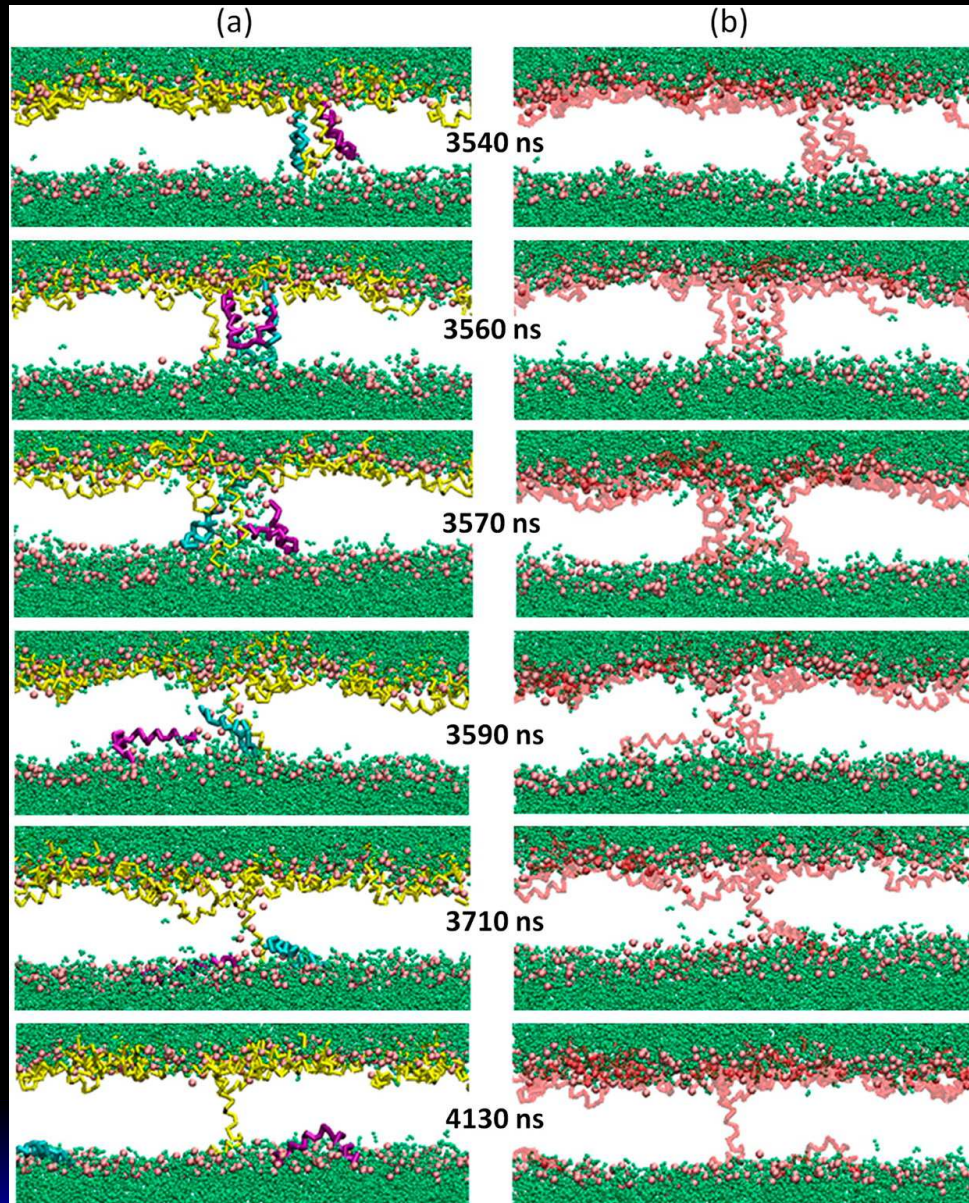
CG of melittin at DPPC/POPG (7:3) bilayer (melittin/lipid=1/100)



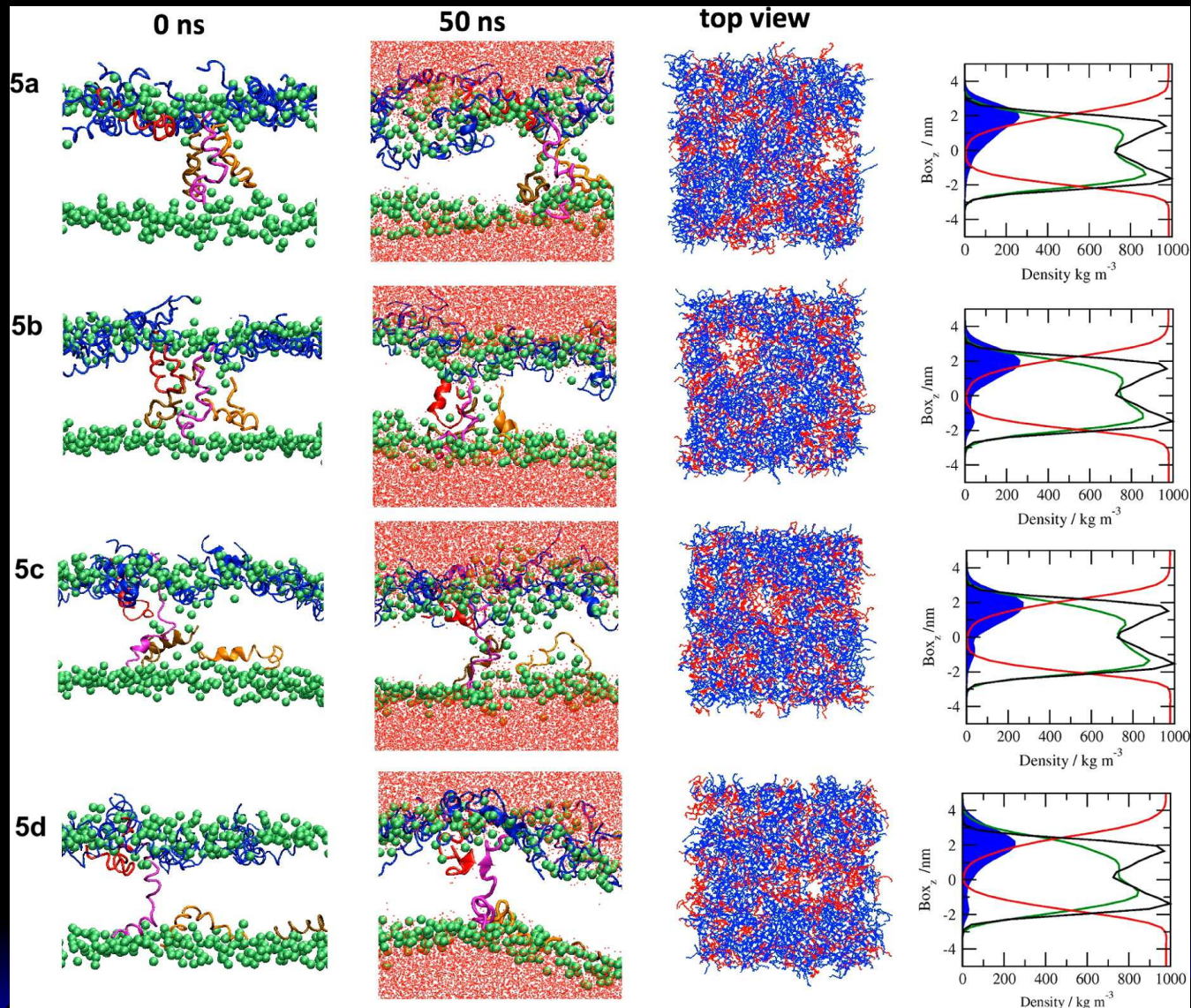
K.P. Santo et al., JPCB 117 (2013), 5031.

⇒ no melittin reorientation

melittin/lipid=1/21: transient pore

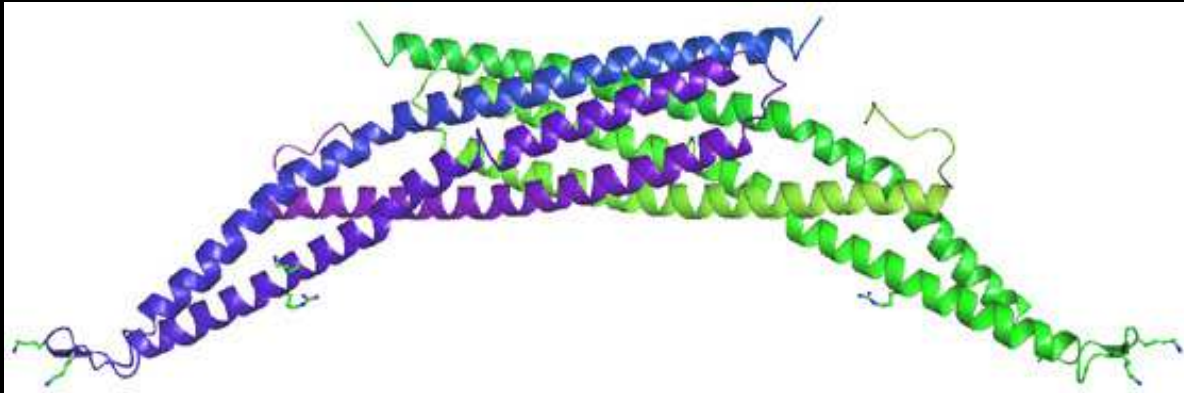


continuation by atomistic simulations



K.P. Santo et al., JPCB **117** (2013), 5031.

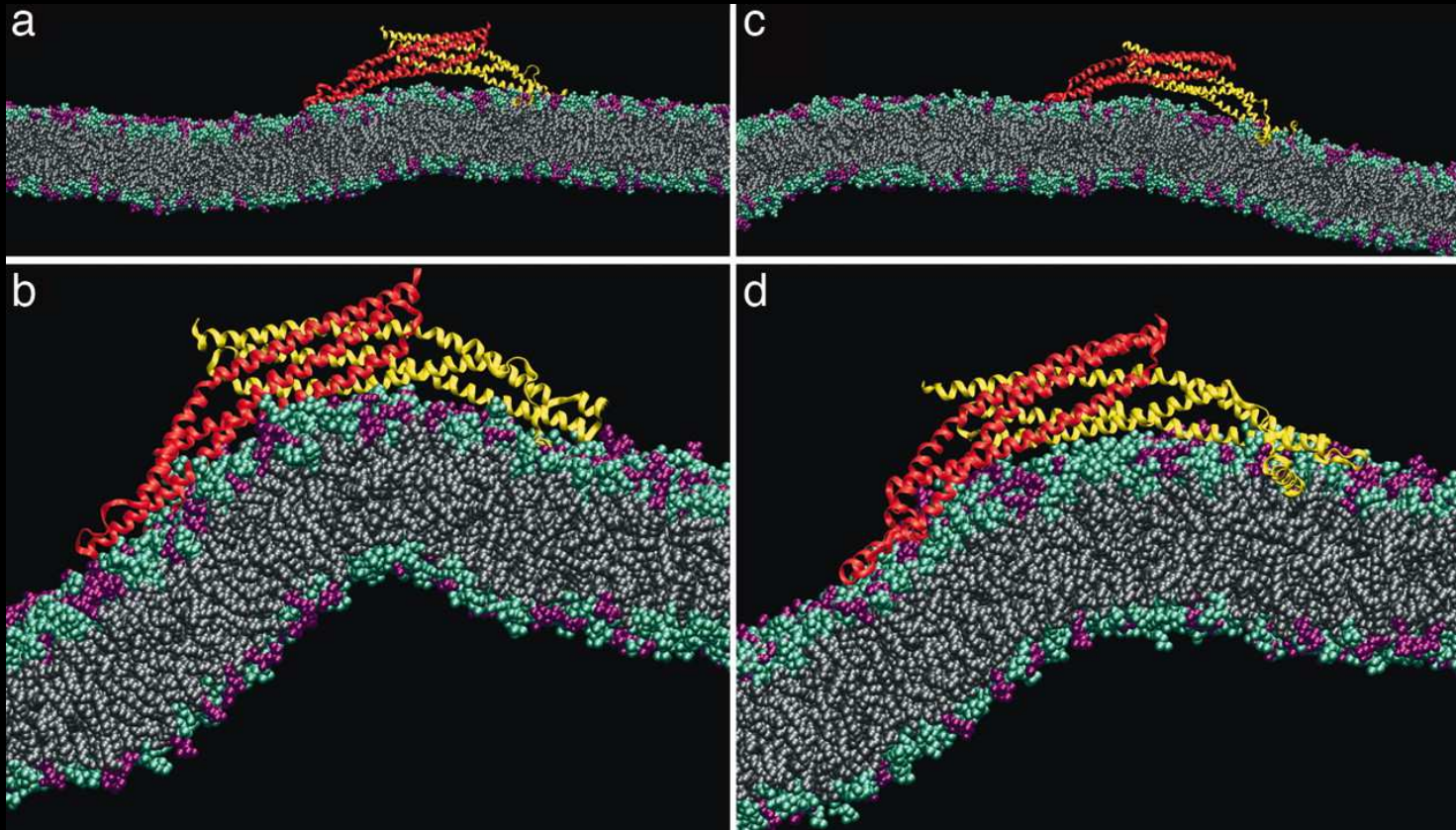
- BAR (bin/amphiphysin/rvs)



<http://www.endocytosis.org/BARdomains/BARs.html>

banana shaped (concave) α -helical dimer
induces/recognizes membrane curvature
N-BAR domain: amphiphilic N-terminals

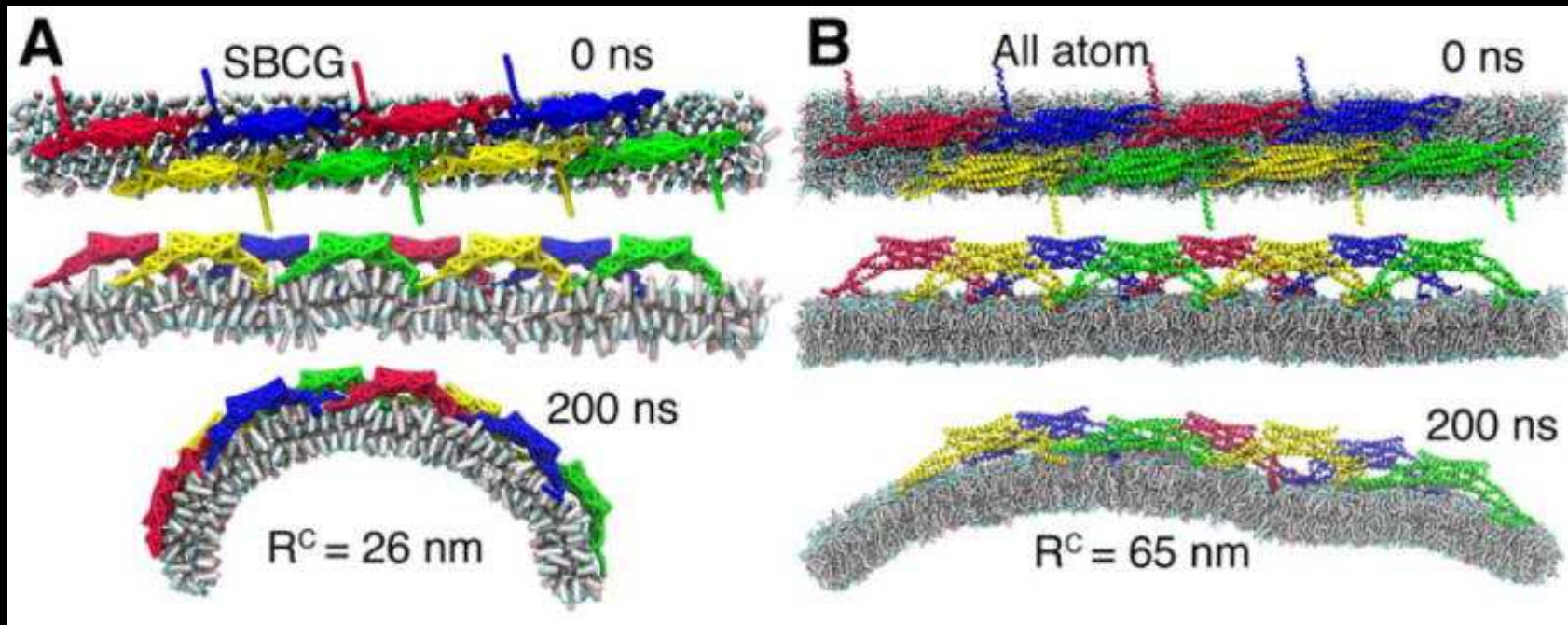
Atomistic simulations at DOPC/DOPS (7/3)



P.D. Blood, G.A. Voth, PNAS 103 (2006), 15068.

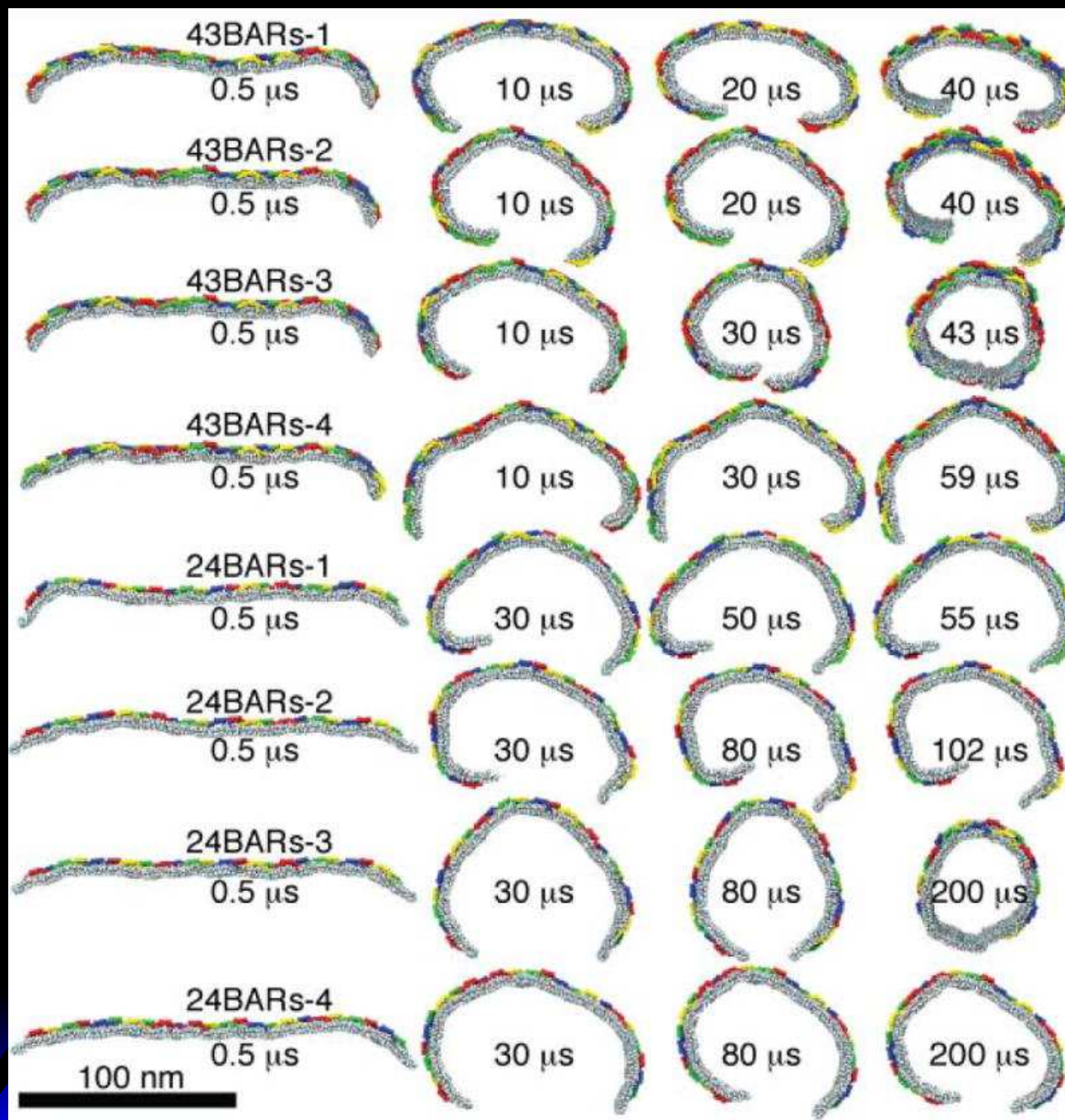
snapshots at 10 and 27 ns

Shape-based CG



Y. Yin et al., Structure 17 (2009), 882.

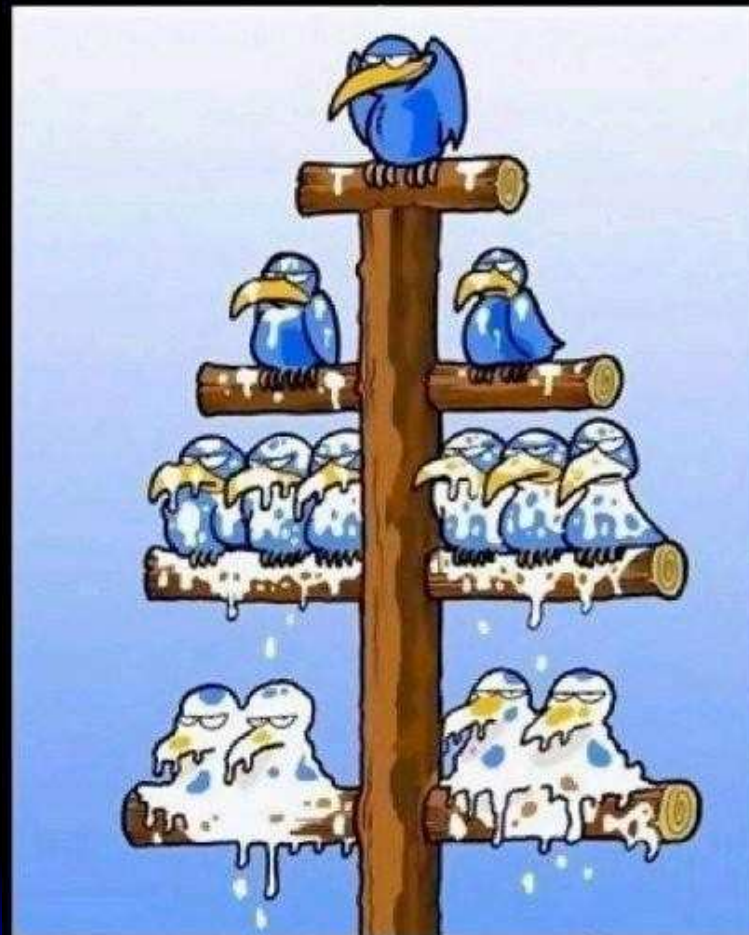
⇒ tubulation



Jumping between Scales

- bottom-up and top-down

When top level guys look down
they see only shit.



When bottom level guys look up
they see only assholes.

- MARTINI: bottom-up

Rules: bead at the center of mass (C_{α} for proteins)

flowchart at <http://www.cgmartini.nl/cgmartini/index.php/flowchartfile>
indicating utilities for the transformation

pdb file

Proteins: sequence and secondary structure

⇒ that was easy

Automartini for small molecules

- MARTINI: top-down (the old version)

A.J. Rzepiela et al., J. Comput. Chem. 31 (2010), 1333.

Defining randomly AA positions around the CG bead ($r_{CG} = 0.3 \text{ nm}$)

Restraining the AA to the corresponding CG bead

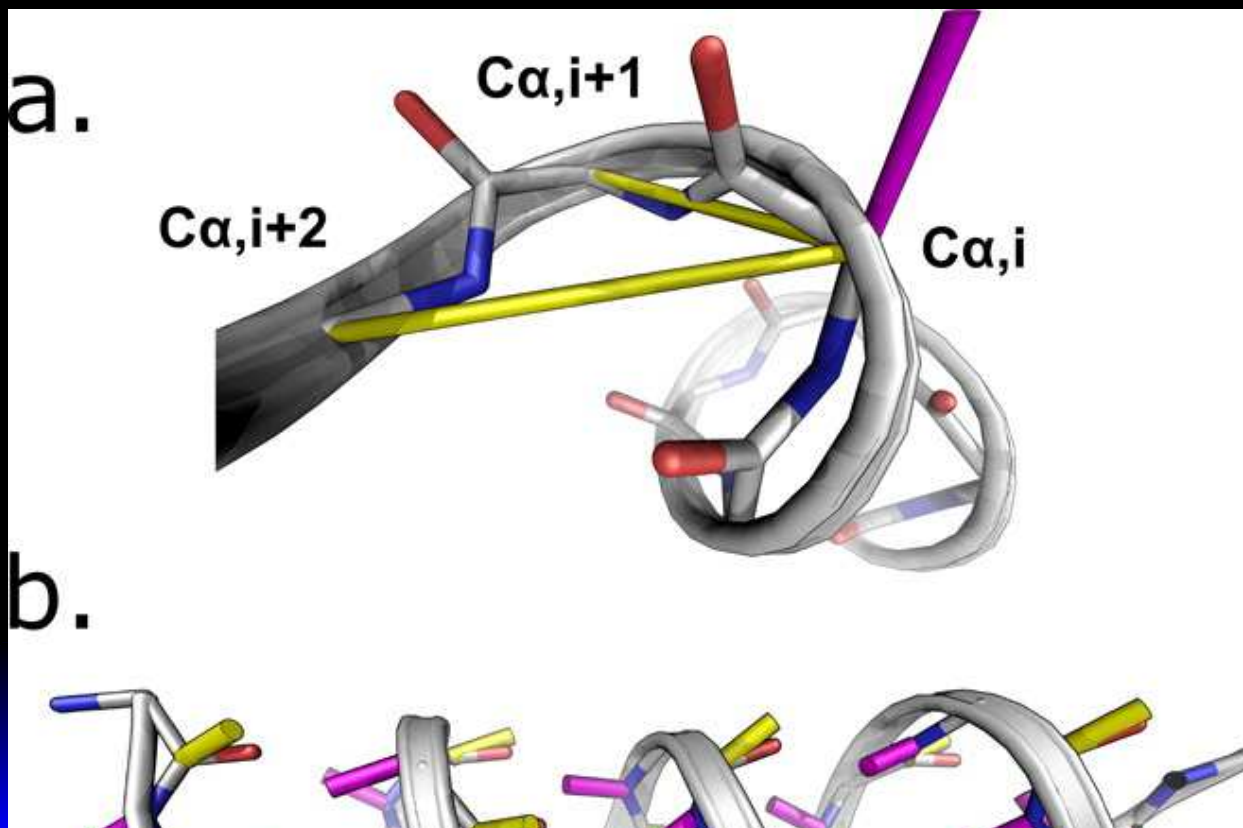
$$U_{restr} = \sum_{i=1}^n \frac{k}{2} \left(\mathbf{r}_i^{CG} - \mathbf{r}_i^{AA,com} \right)^2$$

Performing simulated anealing starting at high temperature (1300 K) with a small cooling rate

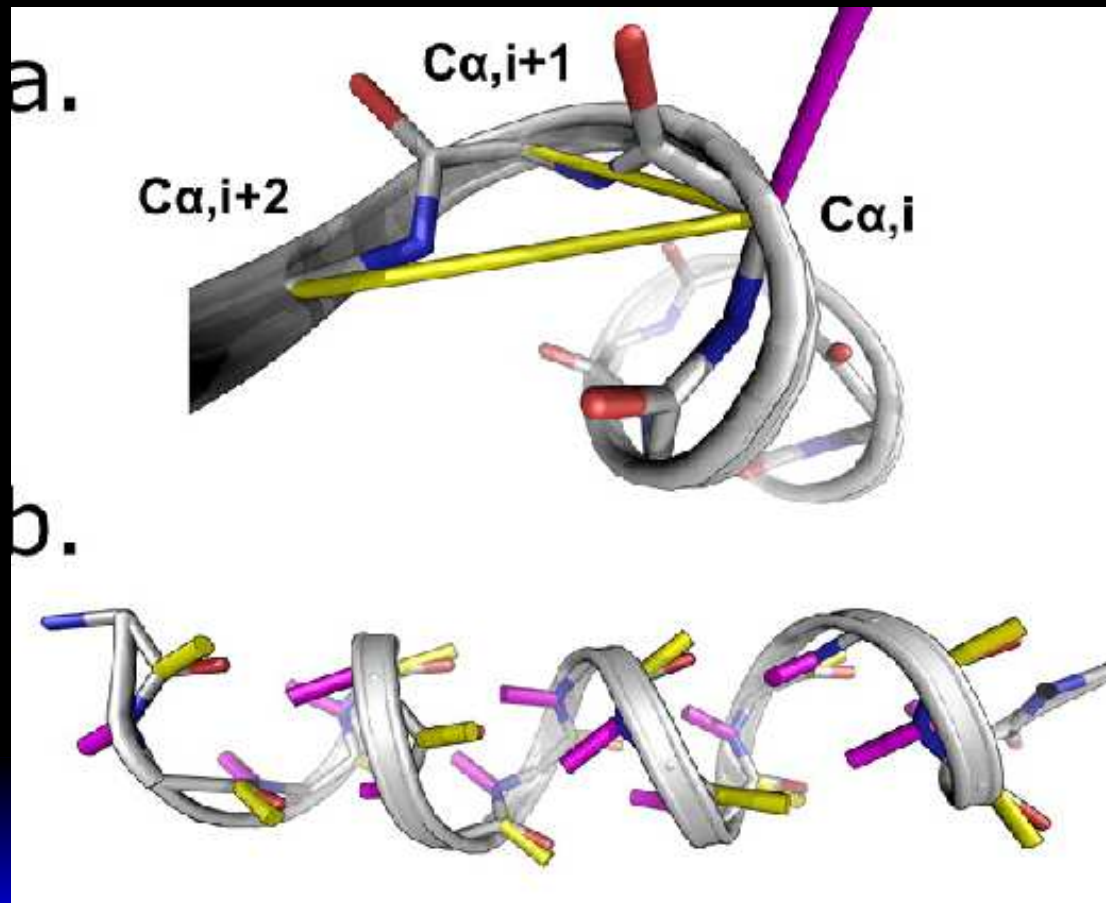
- MARTINI: top-down (the new version)

T.A. Wassenaar et al., JCTC 10 (2014), 676.

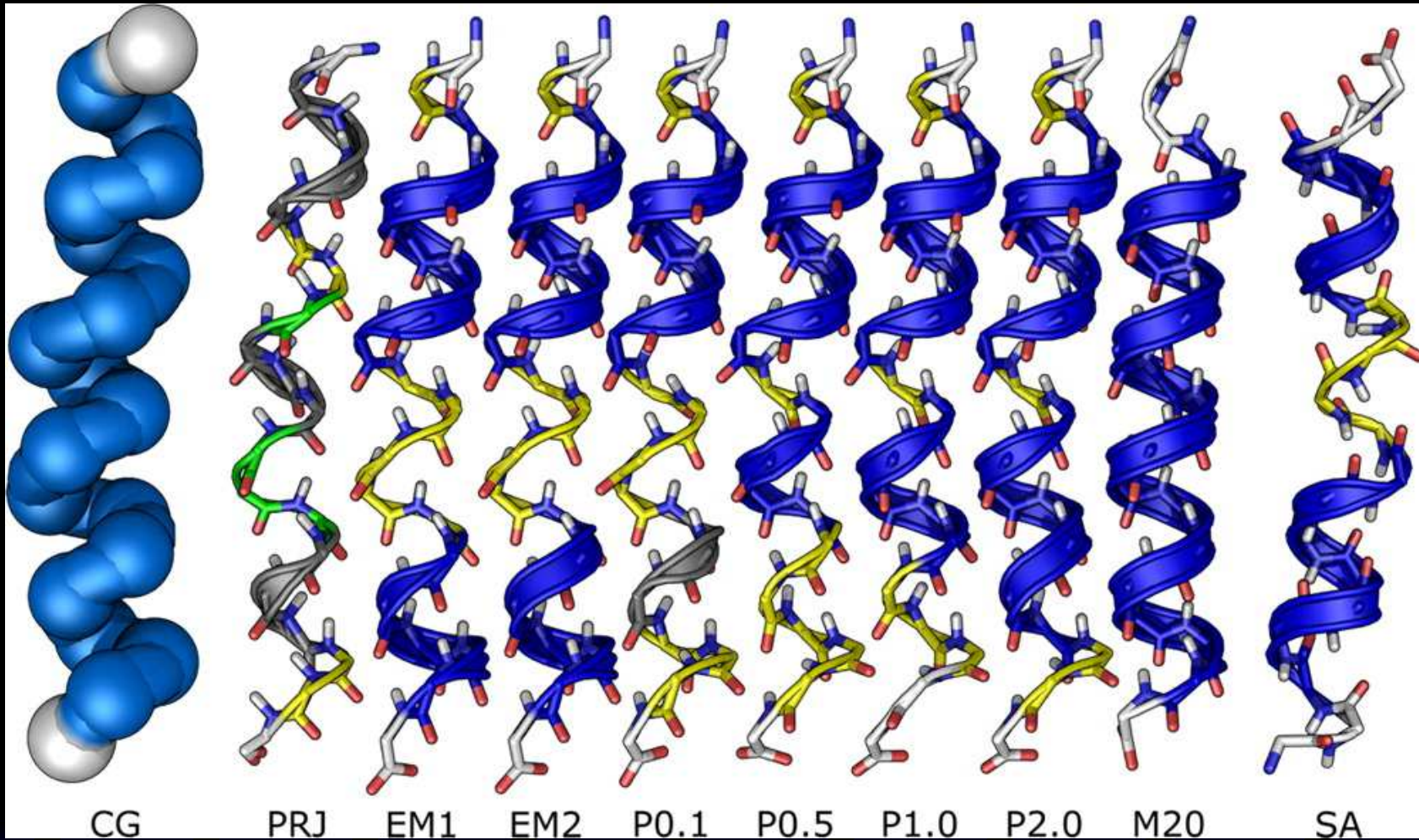
Observation: vector cross product of $\mathbf{C}_{\alpha,i+1} - \mathbf{C}_{\alpha,i}$ and $\mathbf{C}_{\alpha,i+2} - \mathbf{C}_{\alpha,i}$ approximates the direction of C=O at $\mathbf{C}_{\alpha,i}$



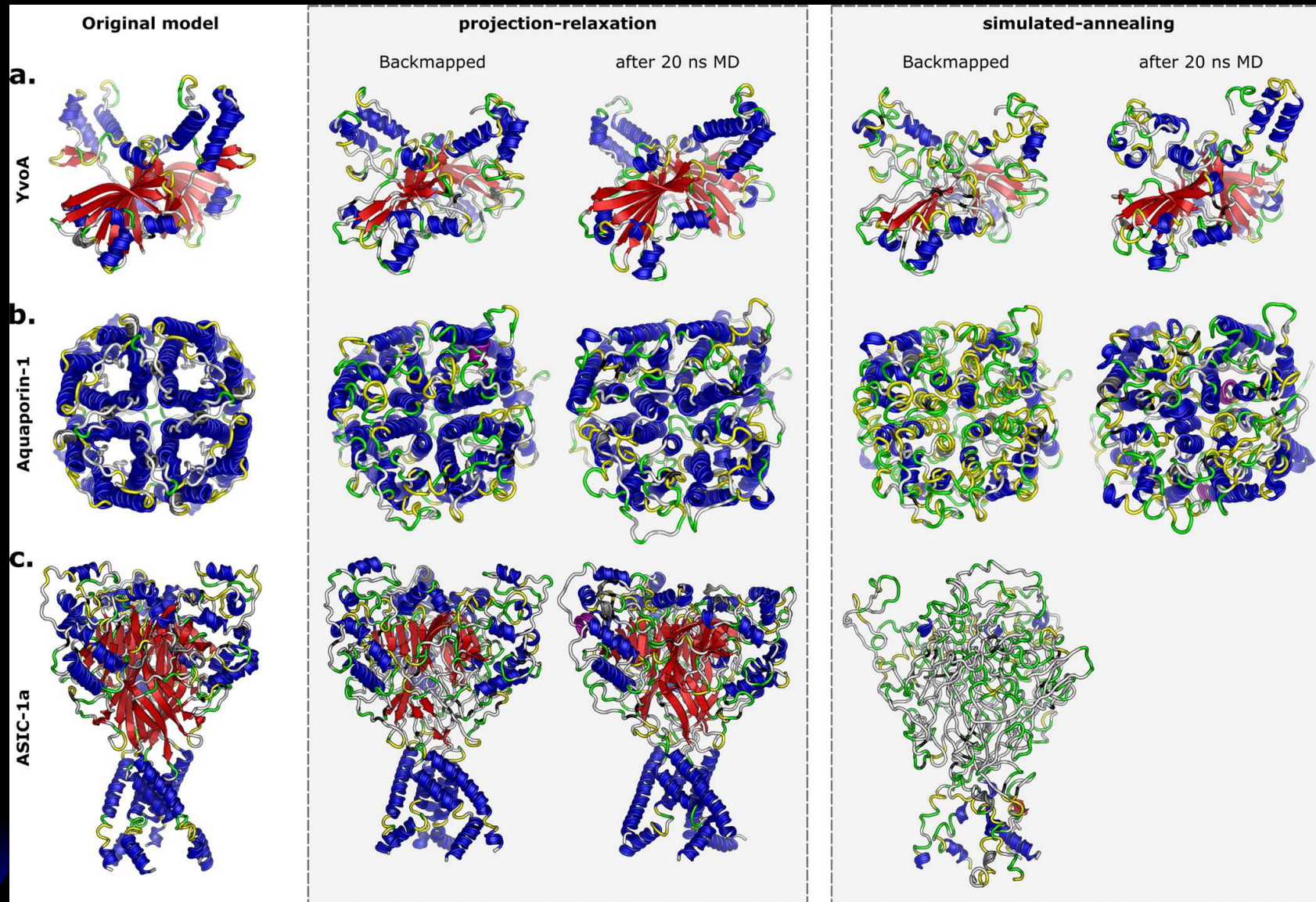
C=O at $1/3$ of the distance from $C_{\alpha,i}$ to $C_{\alpha,i+1}$
N-H at $2/3$ of this distance in opposite
direction



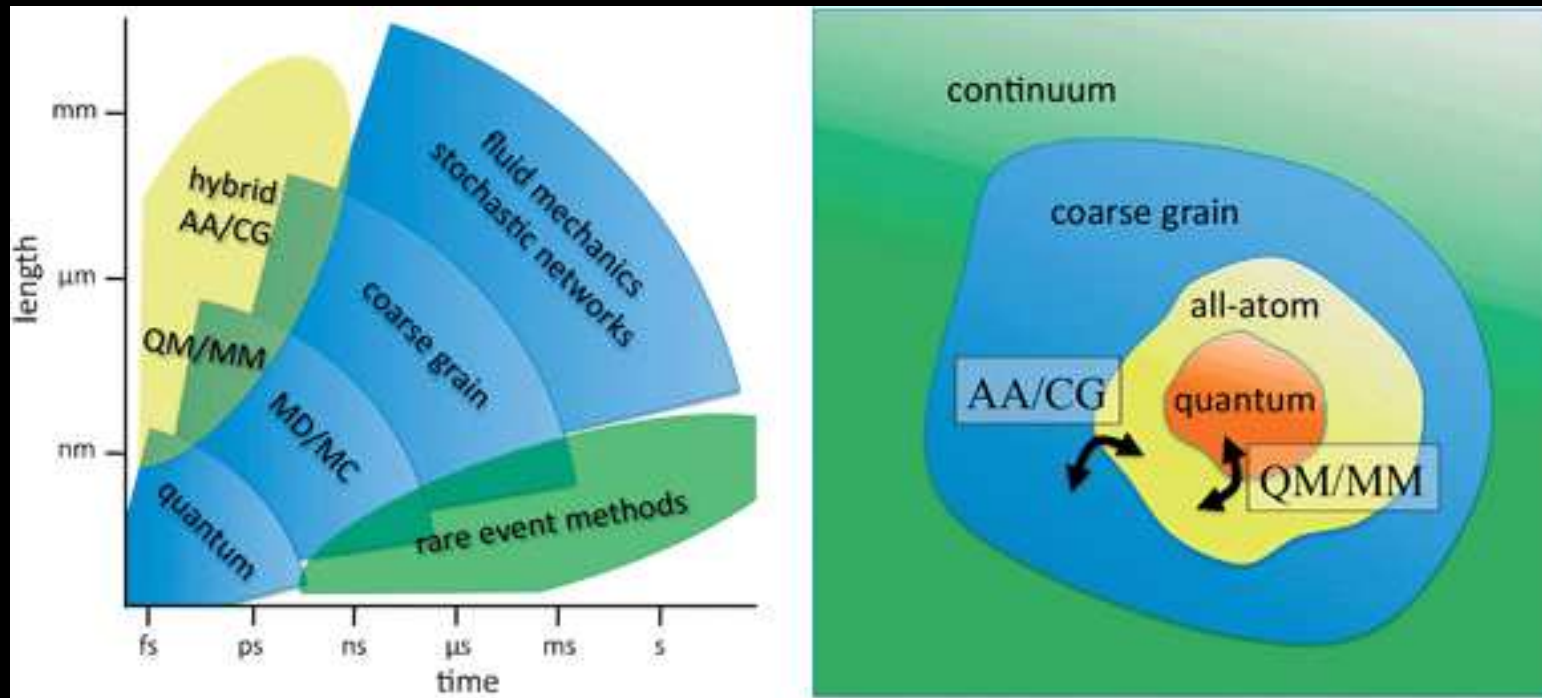
Example: WALP20 (helical)



Other examples



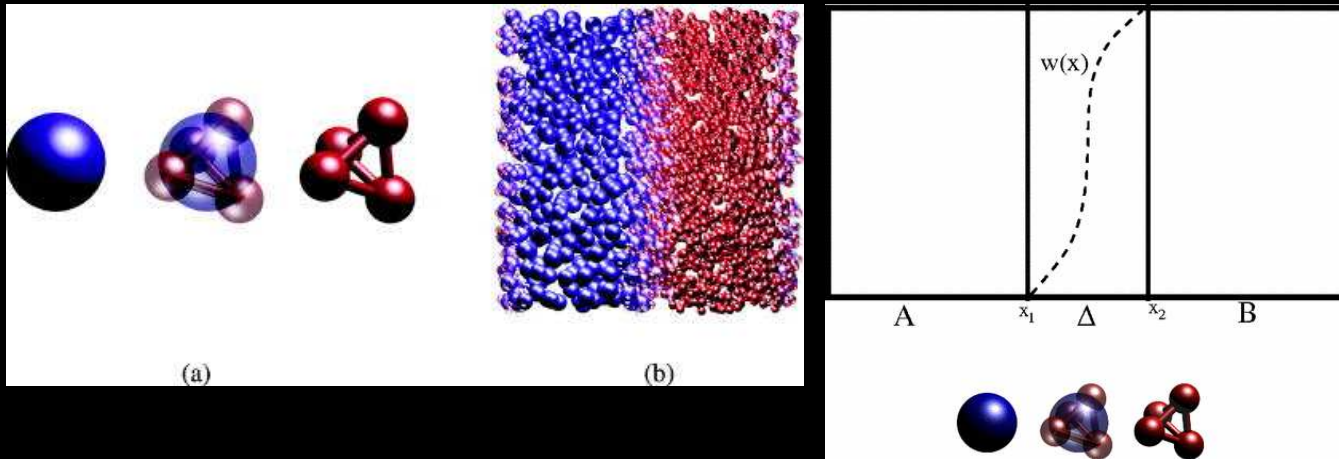
- Real Multiscaling



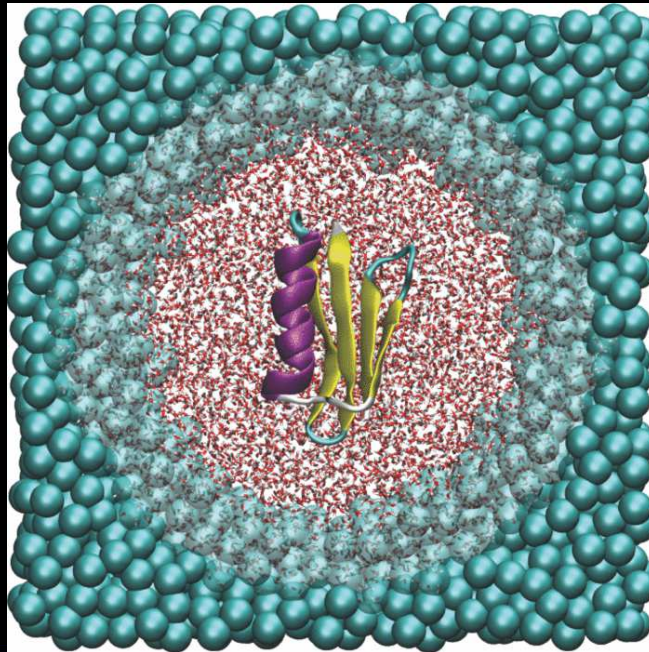
S.O. Nielsen et al., PCCP 12 (2010), 12401.

need for multiple time step algorithms

- Adaptive Resolution

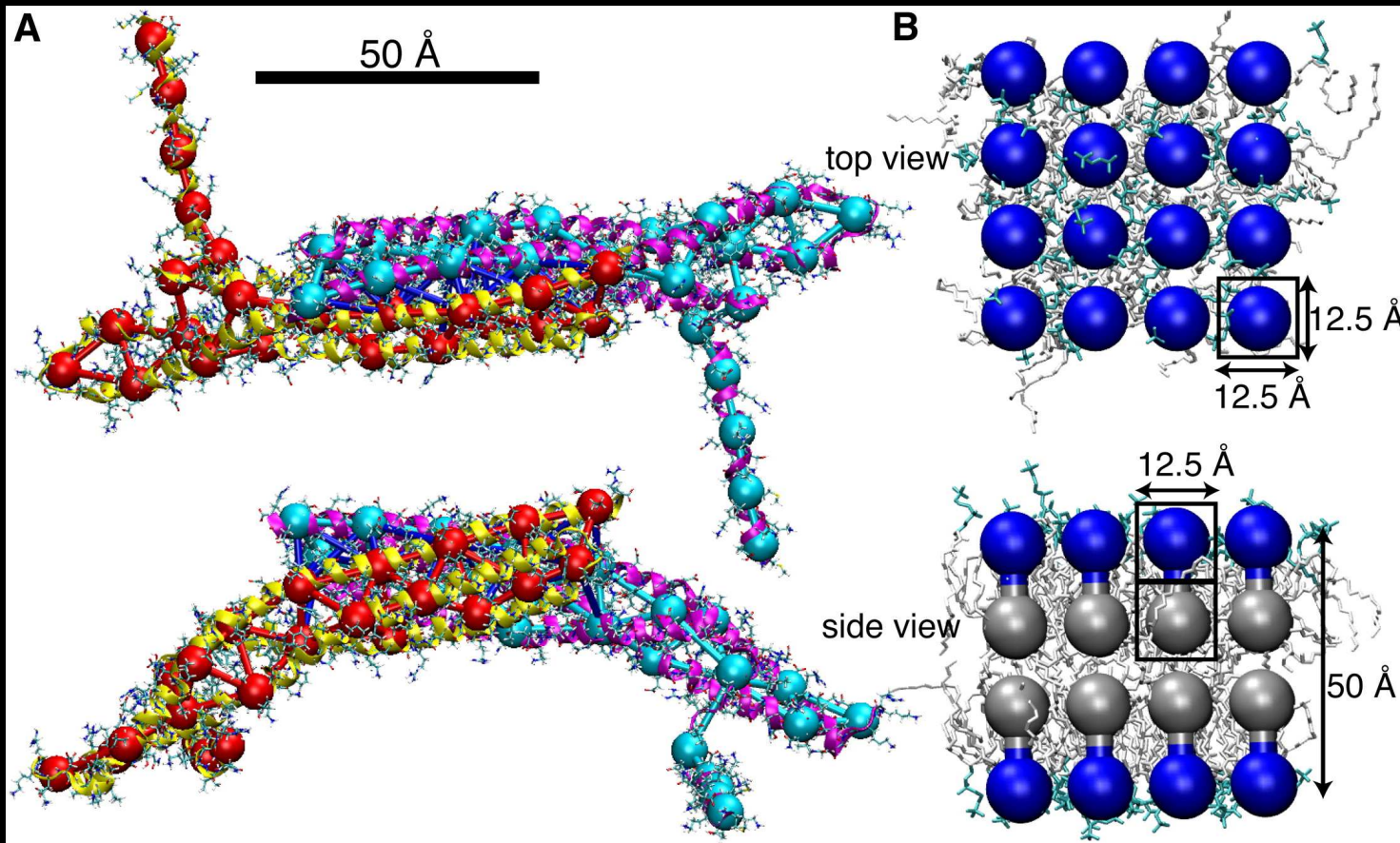


M. Praprotnik et al., JCP 123 (2005), 224106.



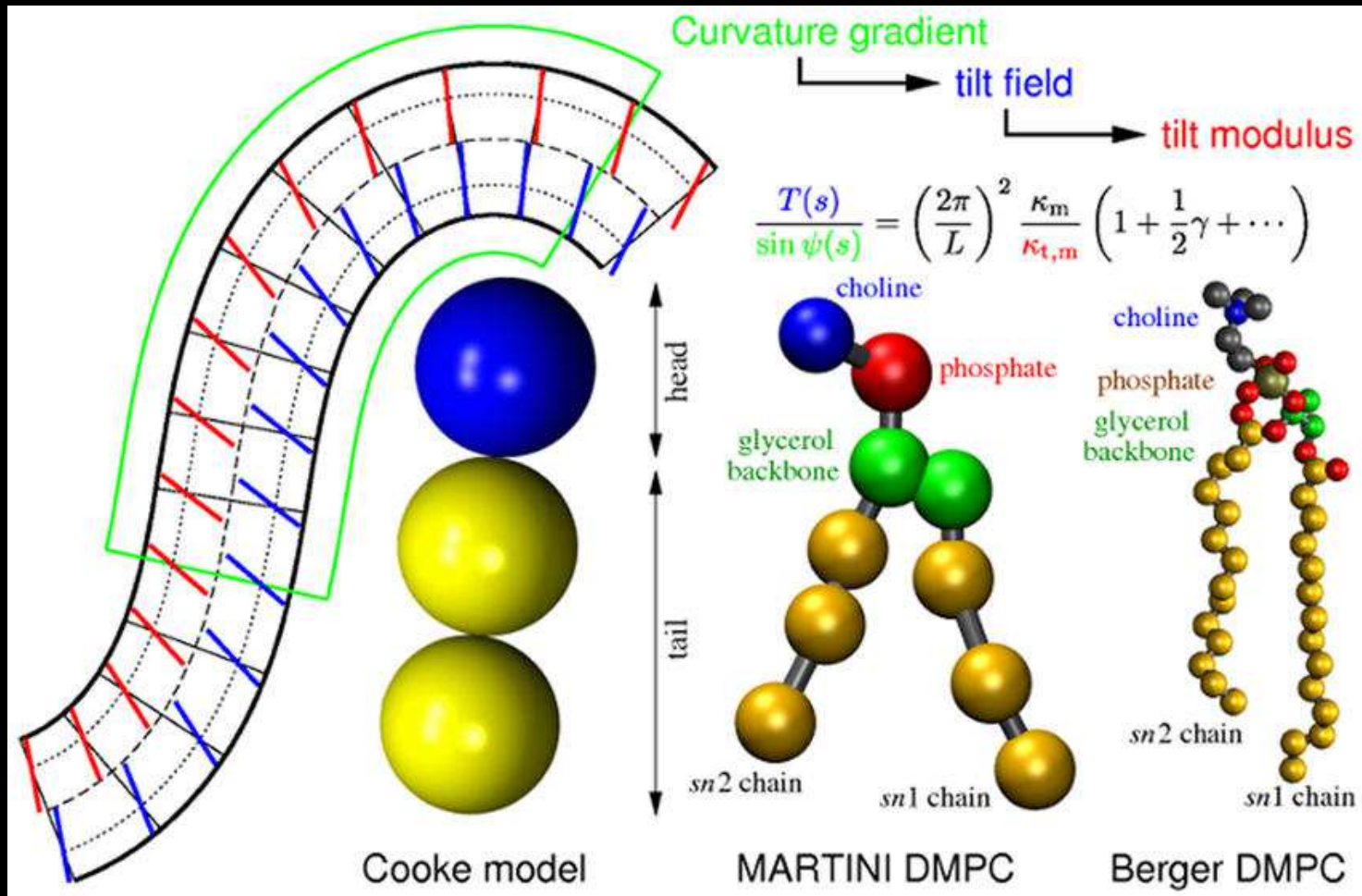
G-protein: J. Zavadlav et al., JCP 140 (2014), 054114.

- Ultra-CG (shape-based CG)
BAR domain

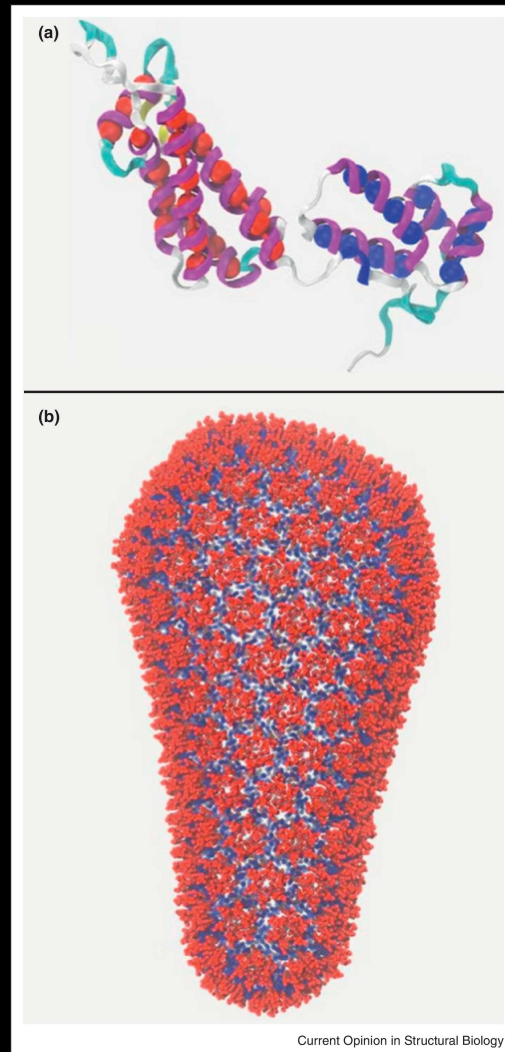


Y. Yin et al., Structure 17 (2009), 882.

- **Cooke lipids:** X. Wang, M. Deserno, J. Phys. Chem. B 120 (2016), 6061.



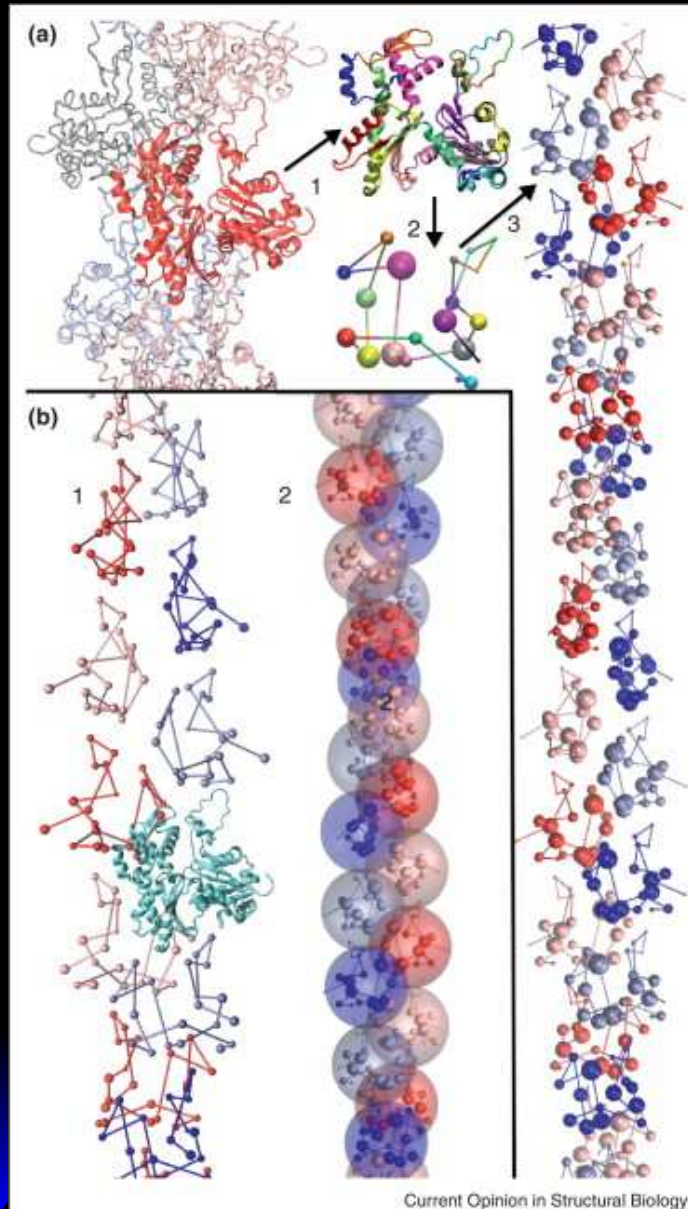
HIV capsid protein: shape based CG



M.G. Saunders, G.A. Voth, Curr. Opin. Struct. Biol., 22 (2012), 144.

- Bridging: Actin filament (muscle)

M.G. Saunders, G.A. Voth, Curr. Opin. Struct. Biol., 22 (2012), 144.



“Everything should be made
as simple as possible,
but not simpler.”

Albert Einstein

