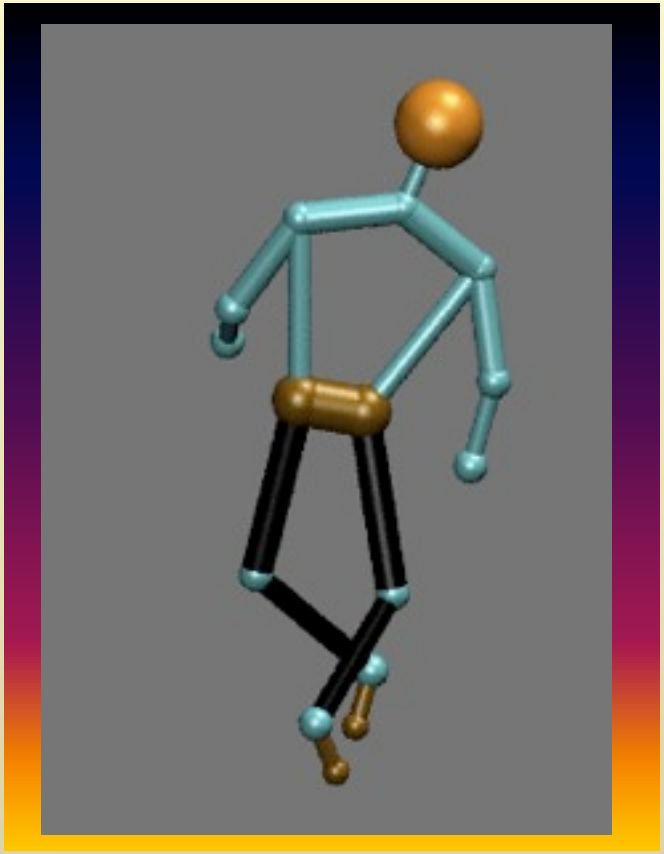
The Art of Coarse Graining



How to become a CG master

Coarse-grained (CG) biomolecular simulations

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- Basic CGing philosophy
- Parameterization
- Applications

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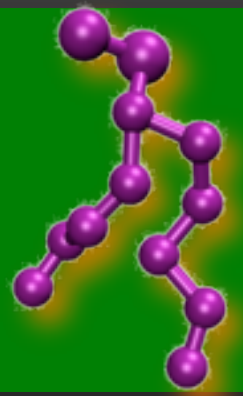

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- Parameterization
- Elastic networks
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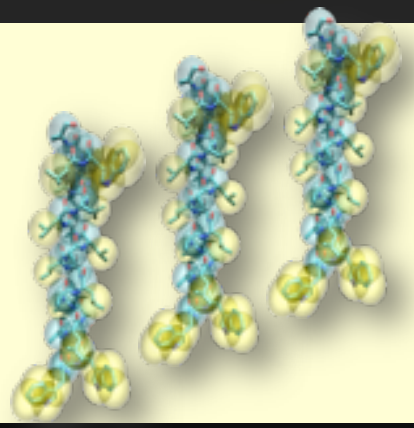

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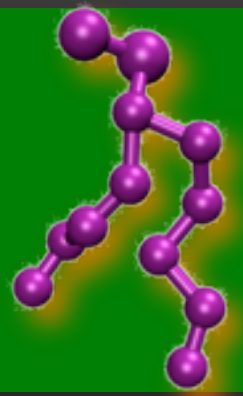

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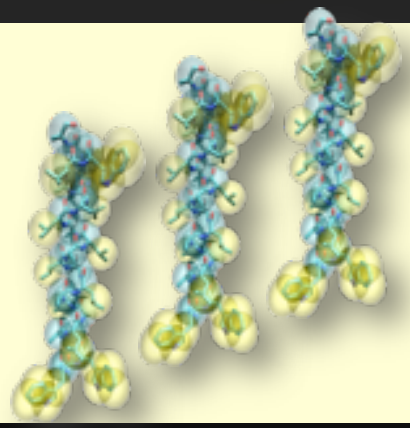


III Future

- Hybrid models
- Polarizable CG

Multiscale Modelling

mean field level

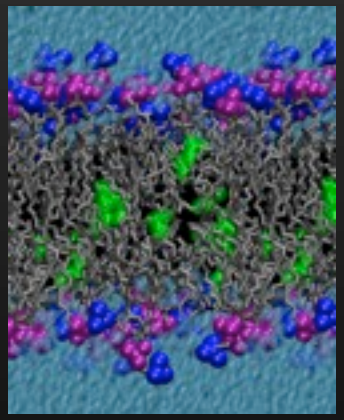
COARSENING

all atom level

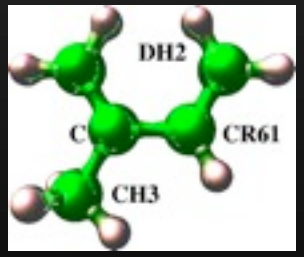
Continuum

Coarse-Grained

Atomistic



Quantum



pico nano micro milli

SCALE

Multiscale Modelling

mean field level

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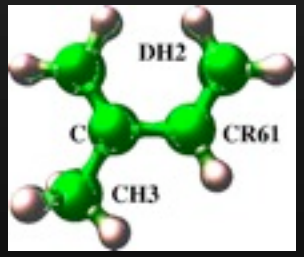

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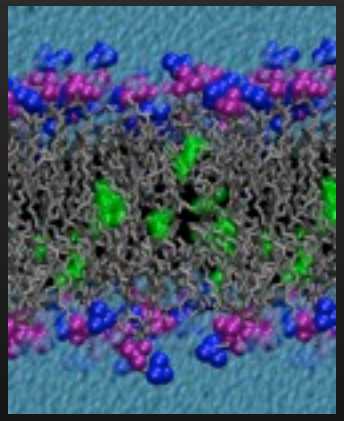

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What are the ingredients for a computational model?

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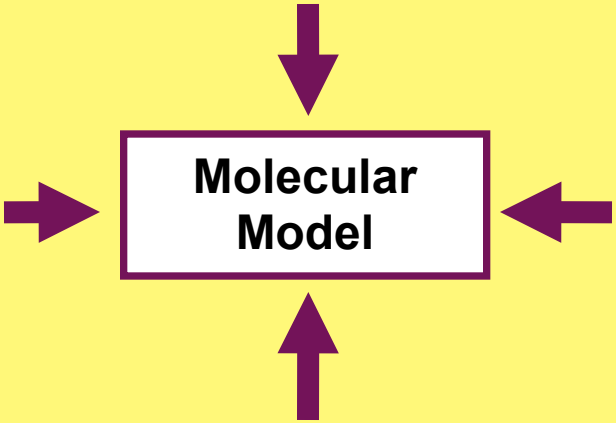


Van Gunsteren et al.
Angew. Chem. Int. Ed. **45**, 4064 (2006)

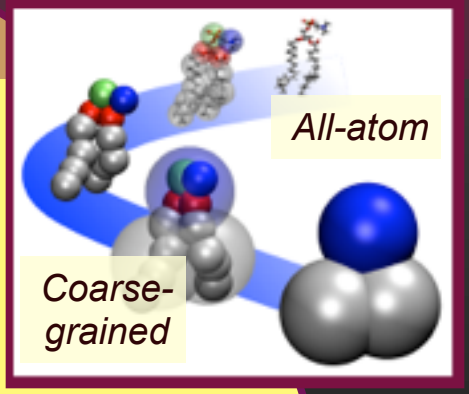
Molecular Modelling

What are the ingredients for a computational model?

Degrees of freedom:

All-atom?
Coarse-grained?
Implicit solvent?

Molecular Model



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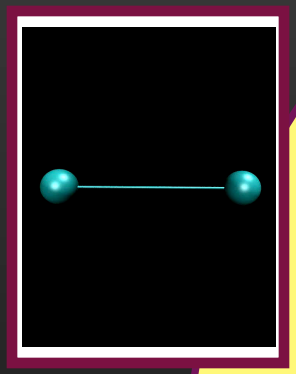

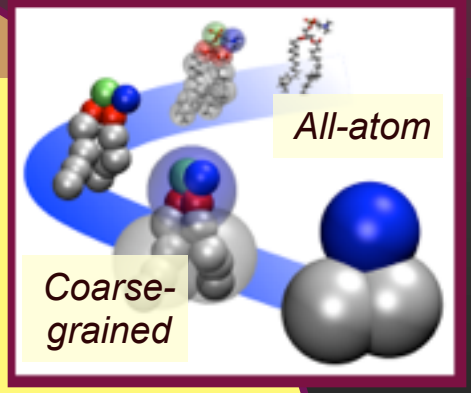

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Force field:

Bonded, Electrostatic, VanderWaals interactions

(calibrated on experimental data)

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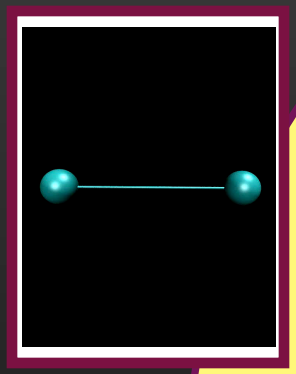

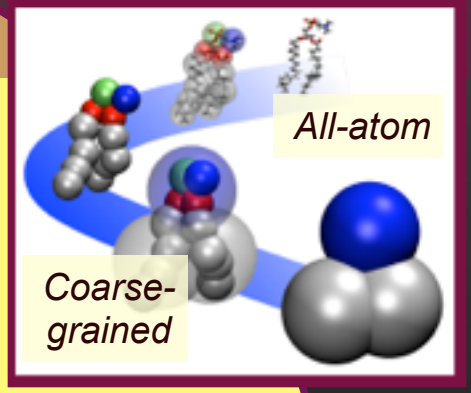

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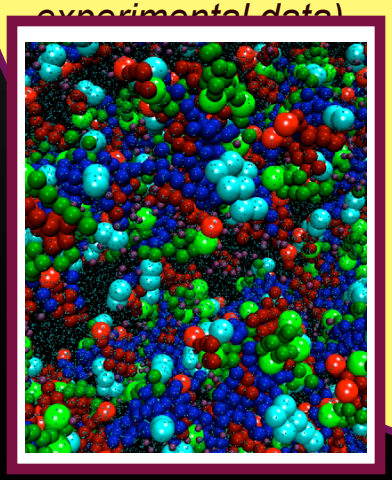

Simulation technique:

Molecular Dynamics,
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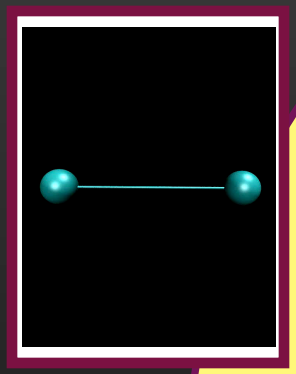

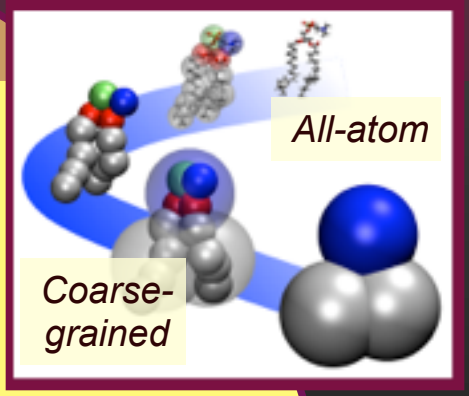

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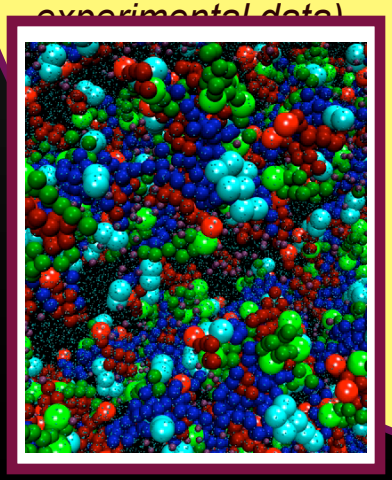
Molecular Model

Boundary conditions:

Periodic or fixed

Pressure,
Temperature



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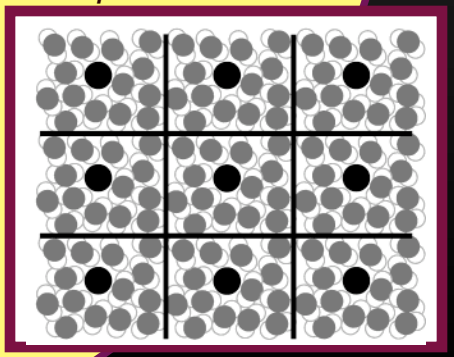

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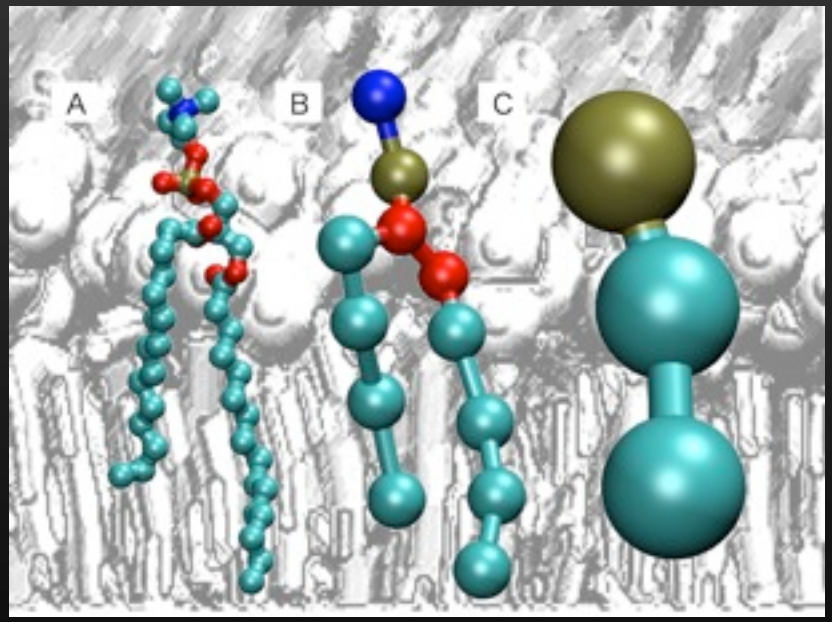

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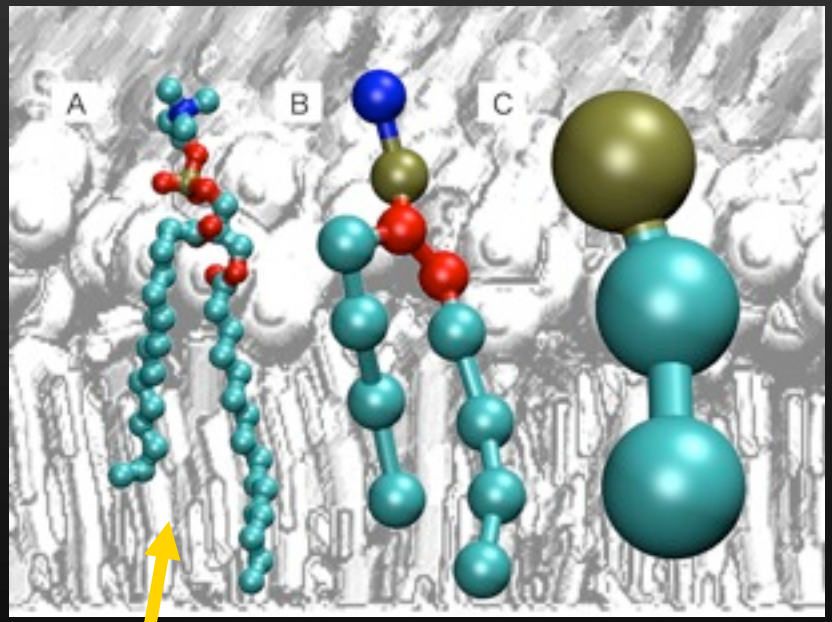

United atom

CG models

Generic

- Lipid head/tail, cylindrical peptides

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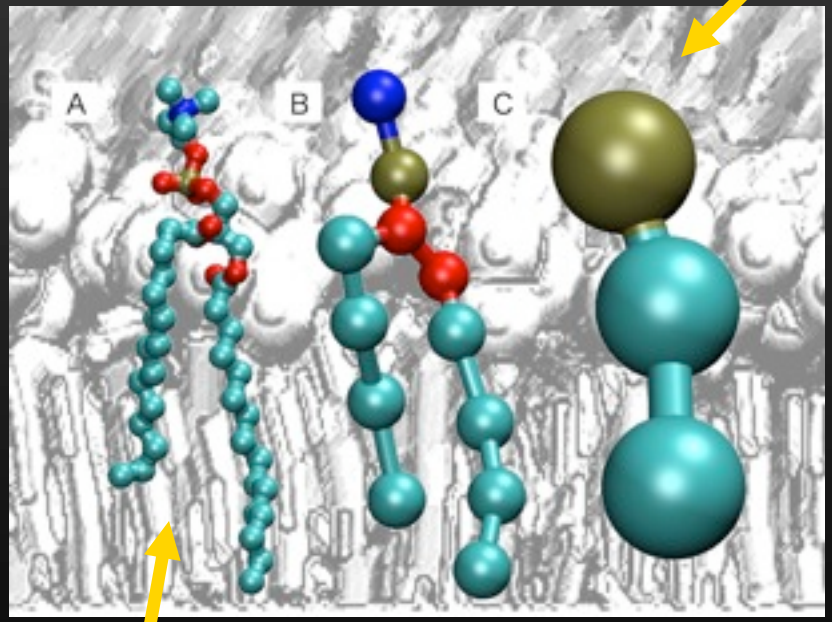

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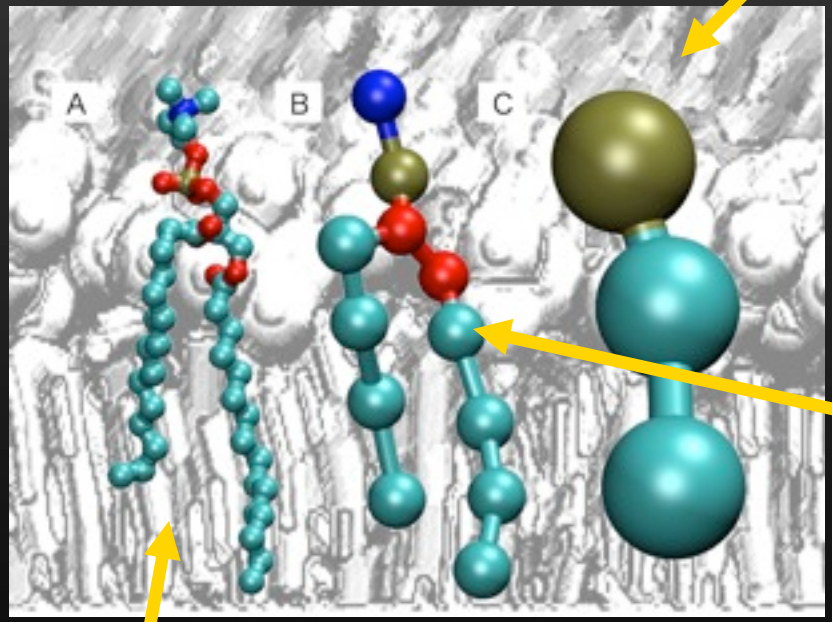

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Specific

- Mapping to real residues, specific lipids, 3-5 to 1 mapping

- Optimized potential energy functions

- Real physical units (nm, K, kJ/mol)

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Smit, Deserno, Kumar, Brown, Shillcock, ...

Simple interaction potentials:

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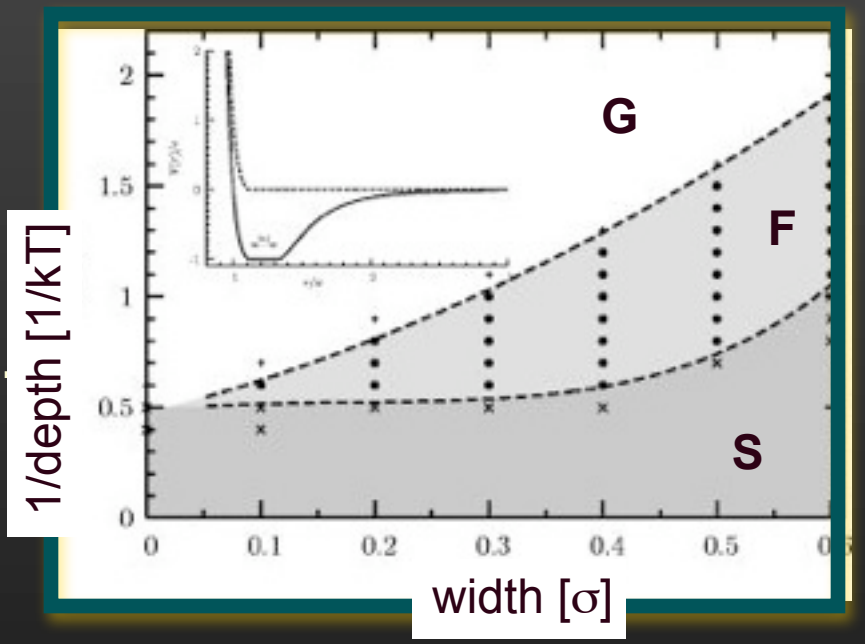

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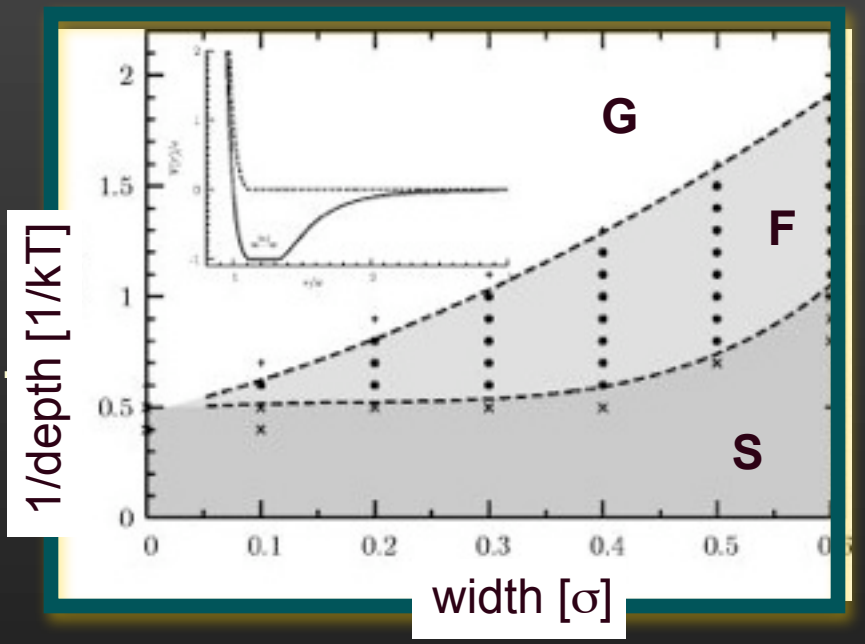

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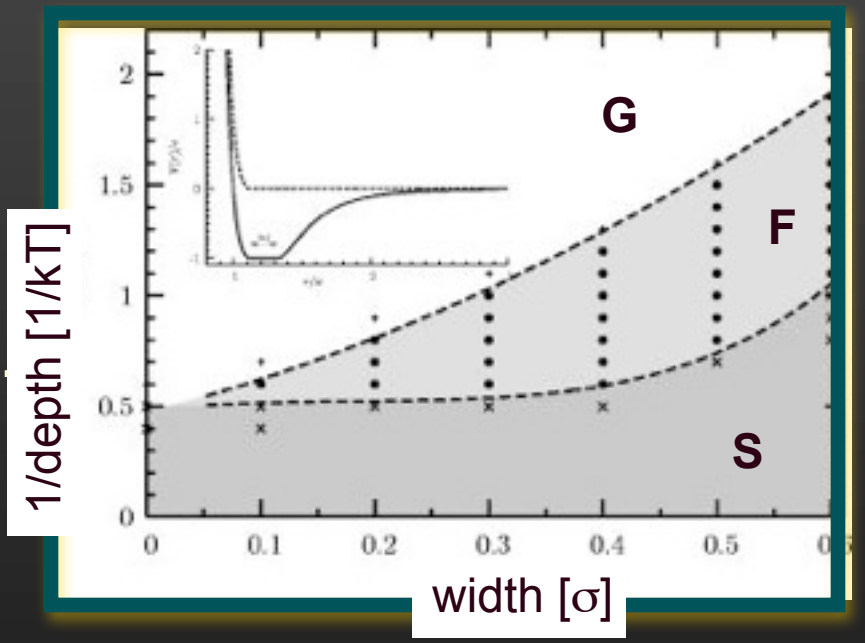

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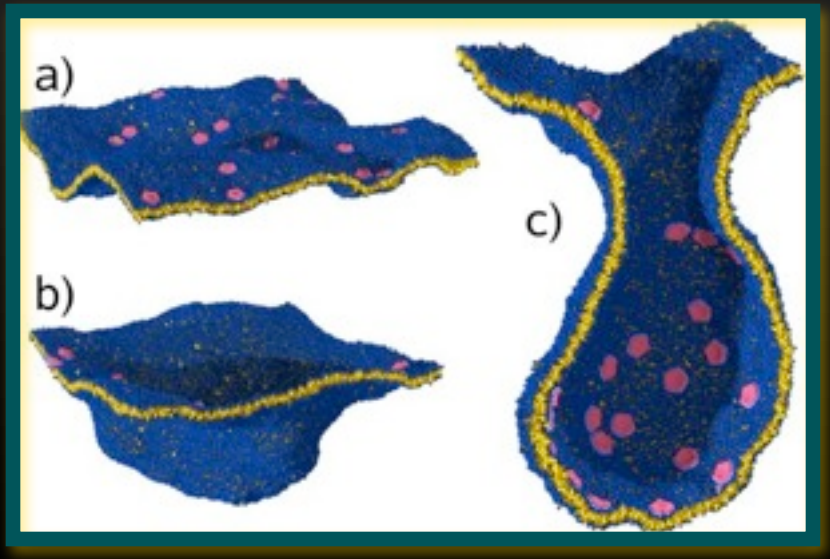

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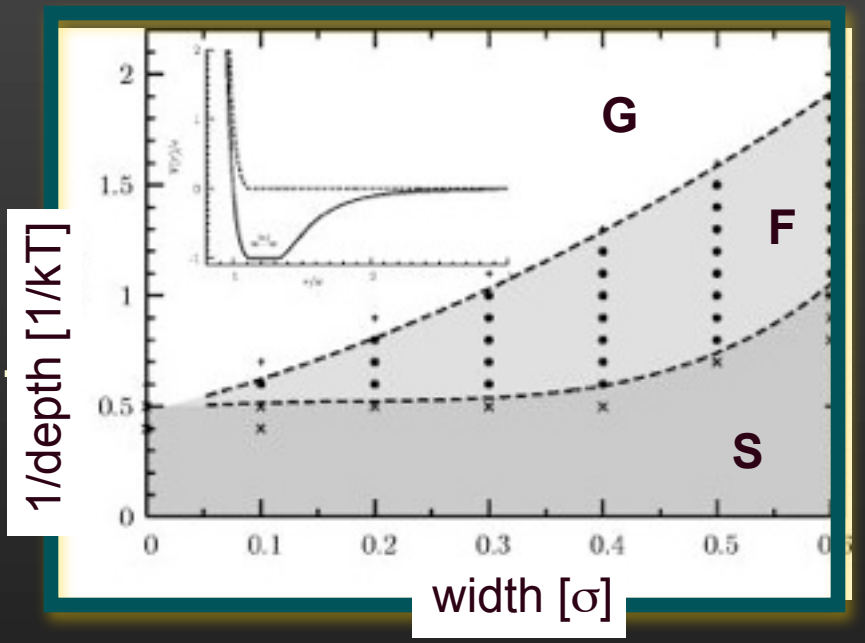

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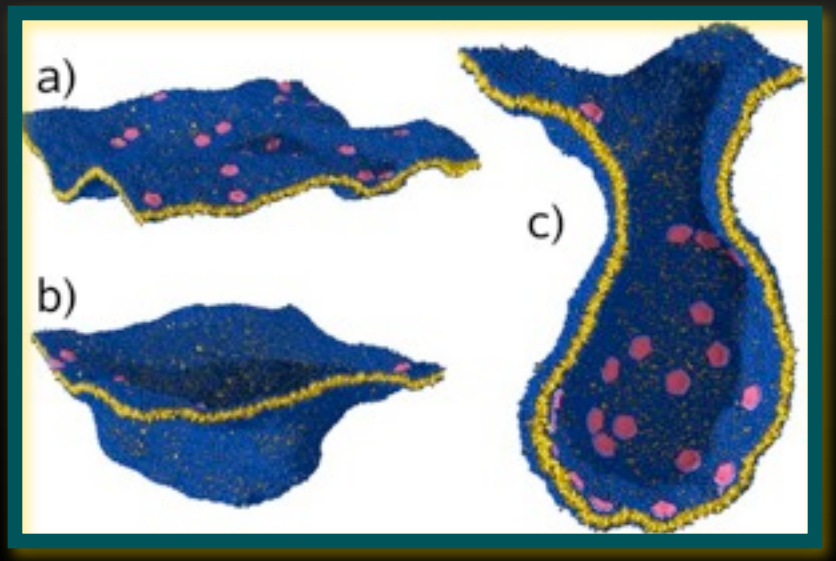

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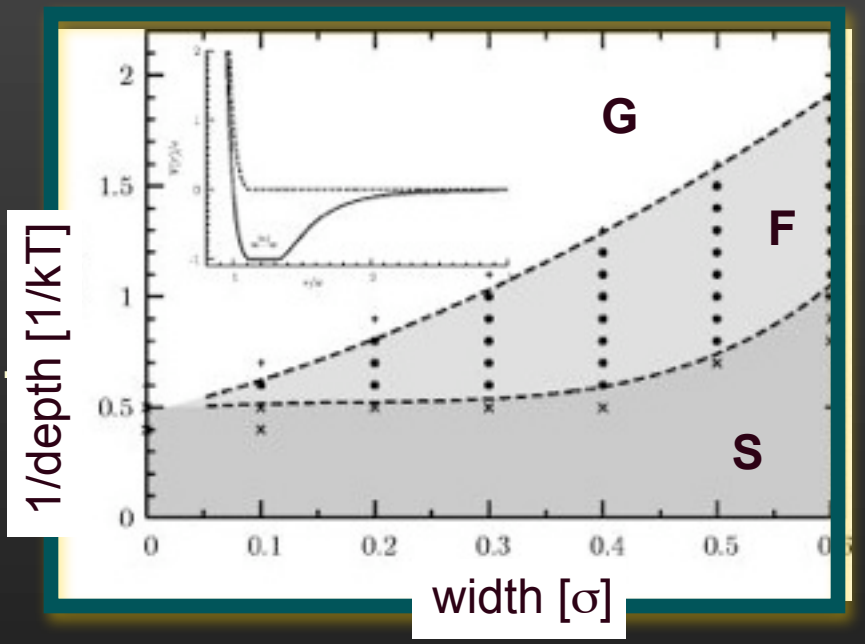
Head-Gordon ?



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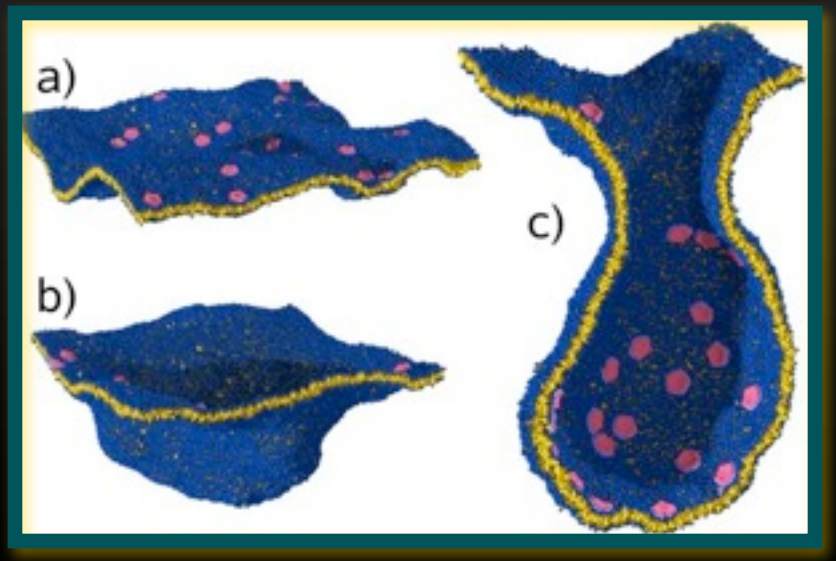

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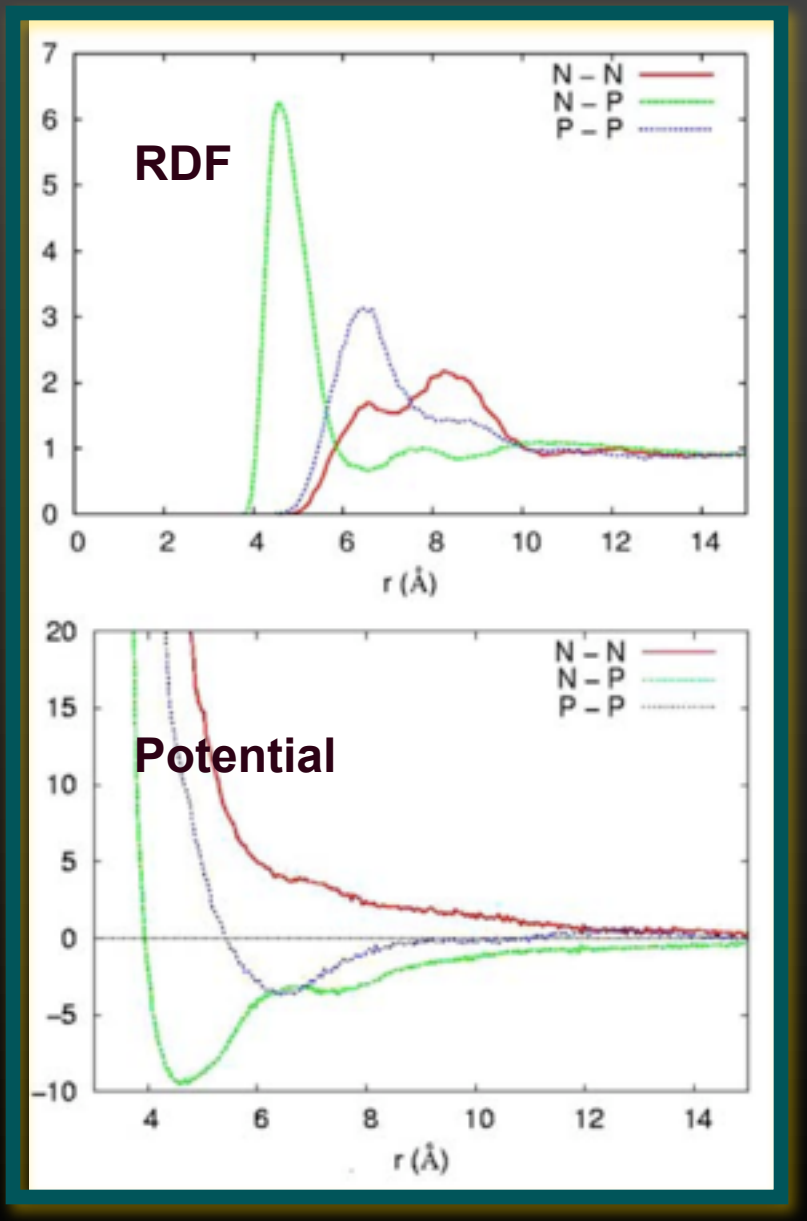

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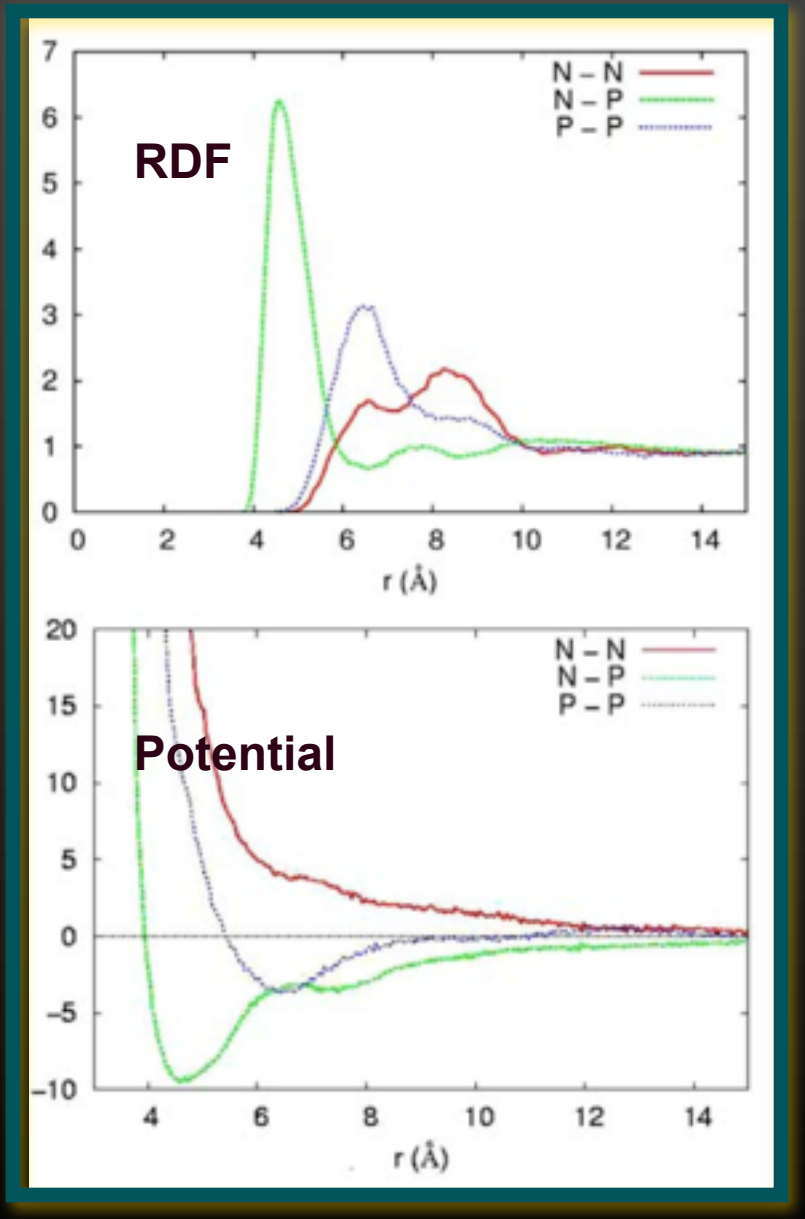

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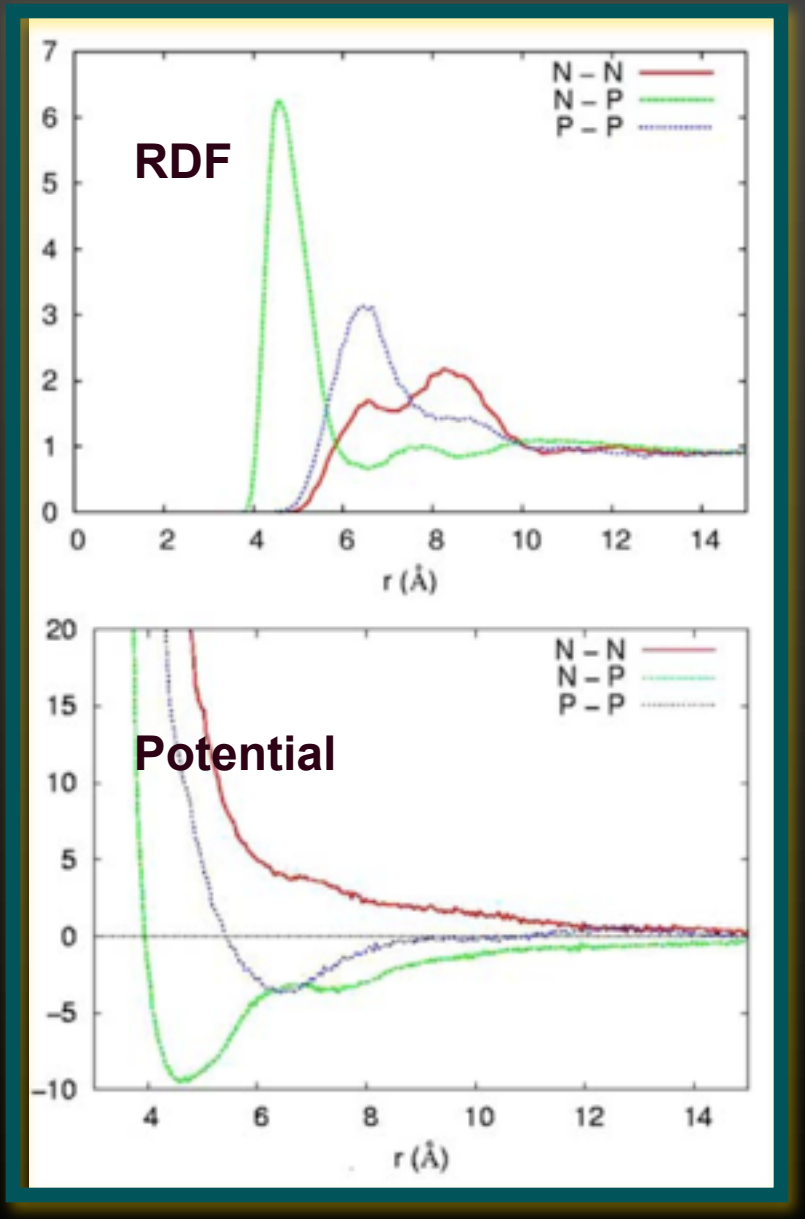

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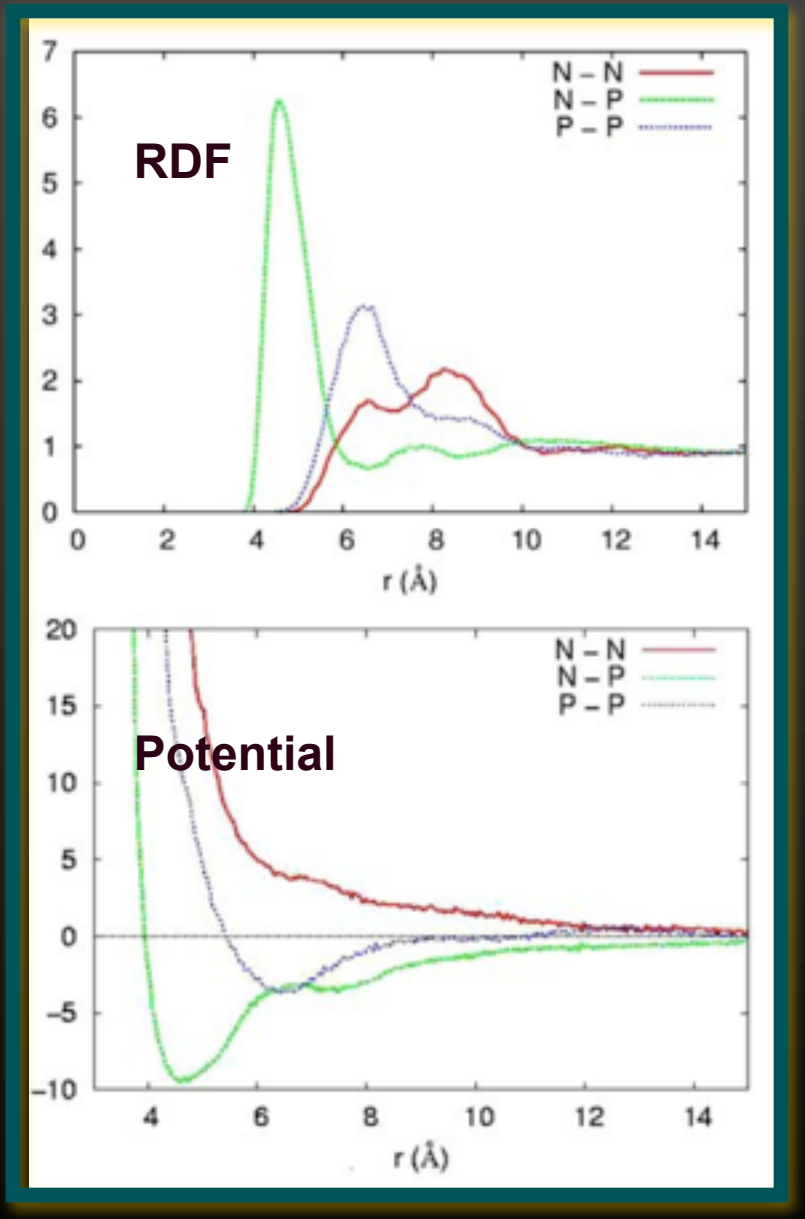

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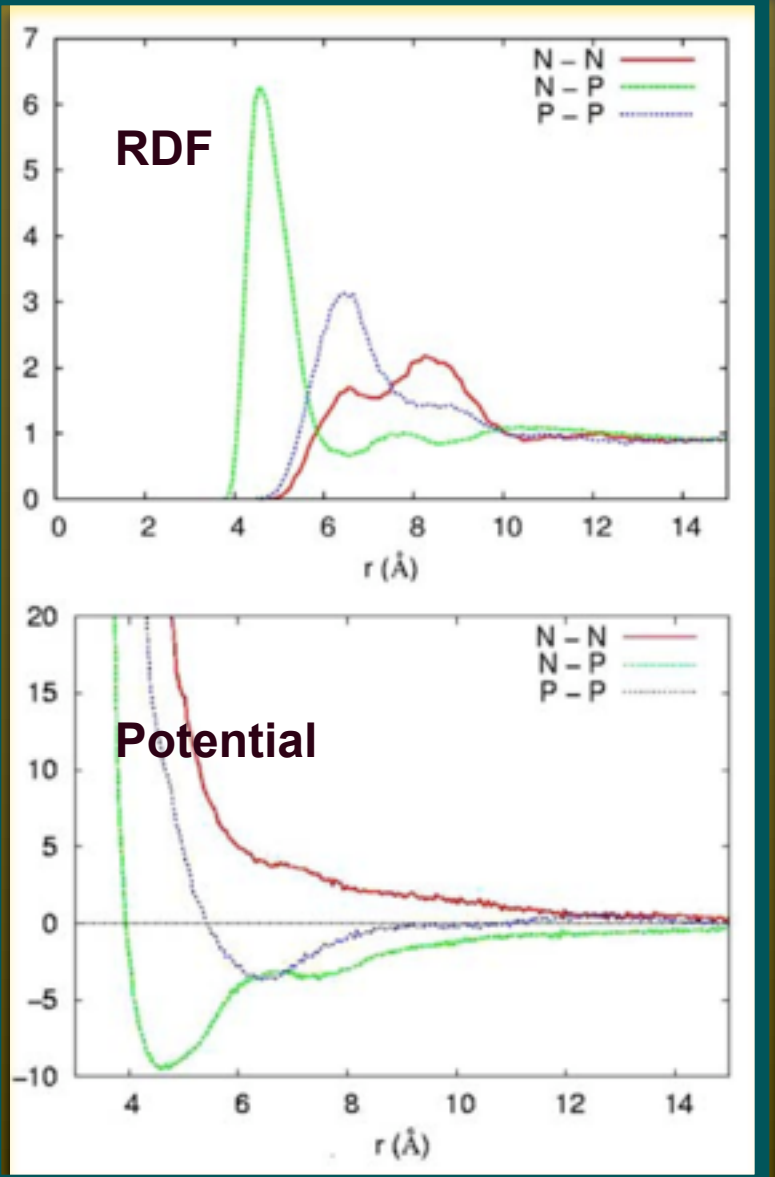

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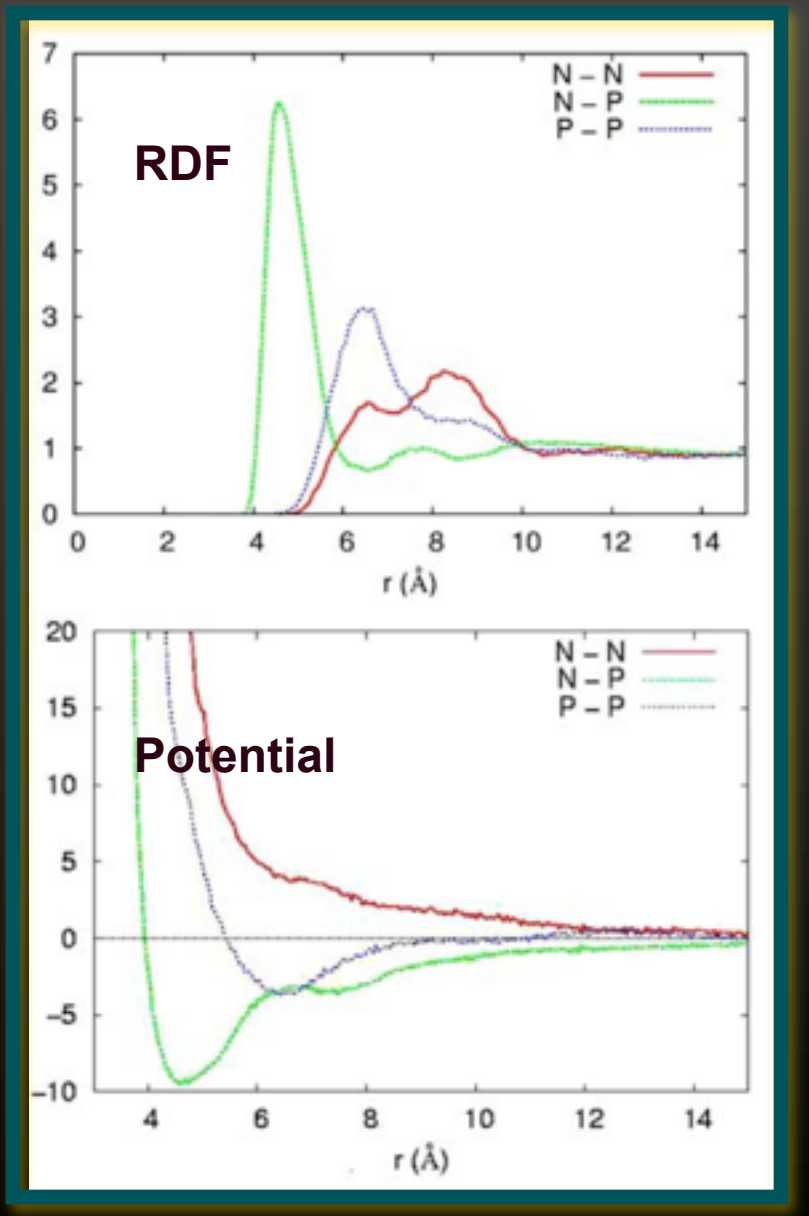

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Coarse-Grained Forcefield for Biomolecular Simulations

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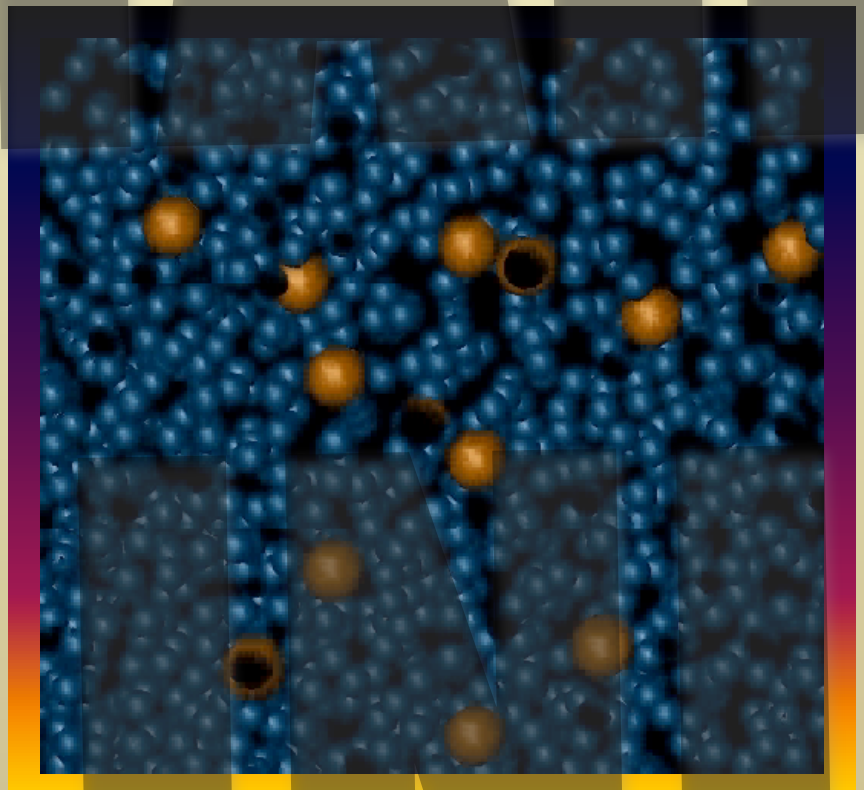
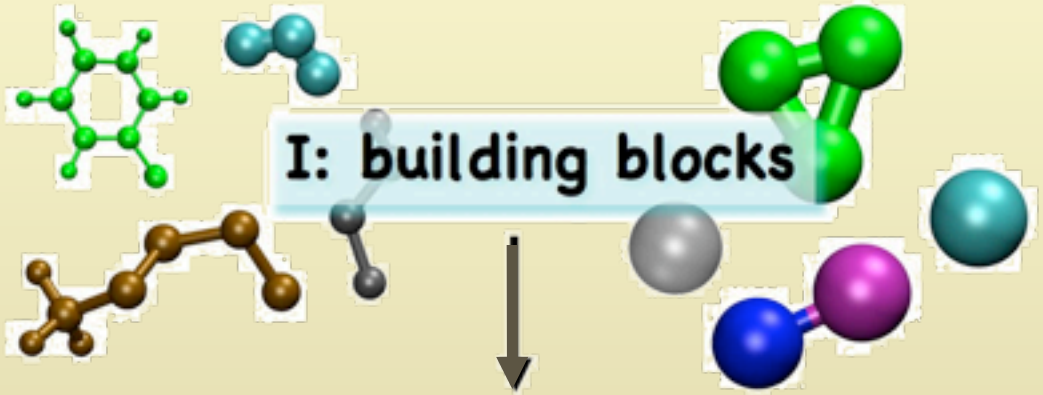


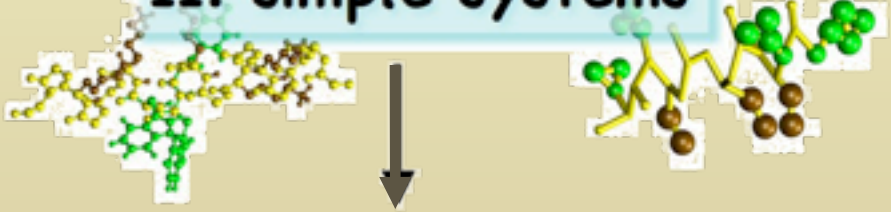
systematic framework for hierarchical modeling

fine grained ⇄ *coarse grained*

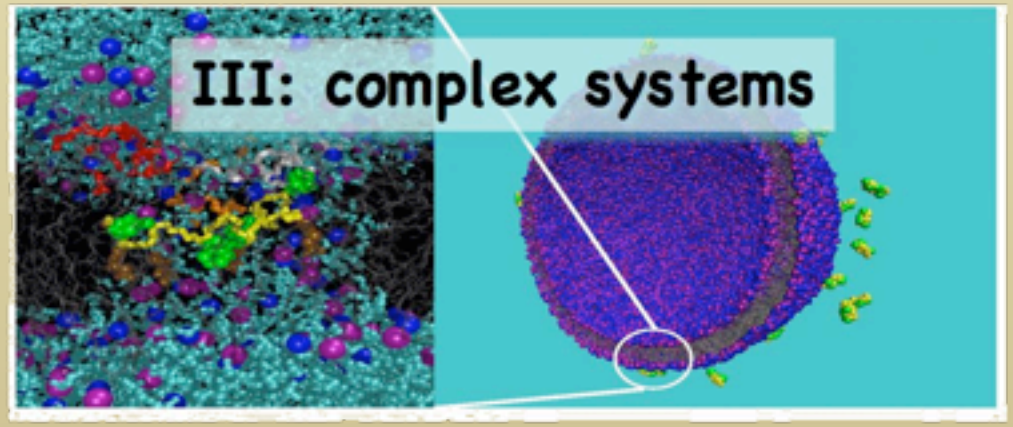
calibration using thermodynamic & structural data



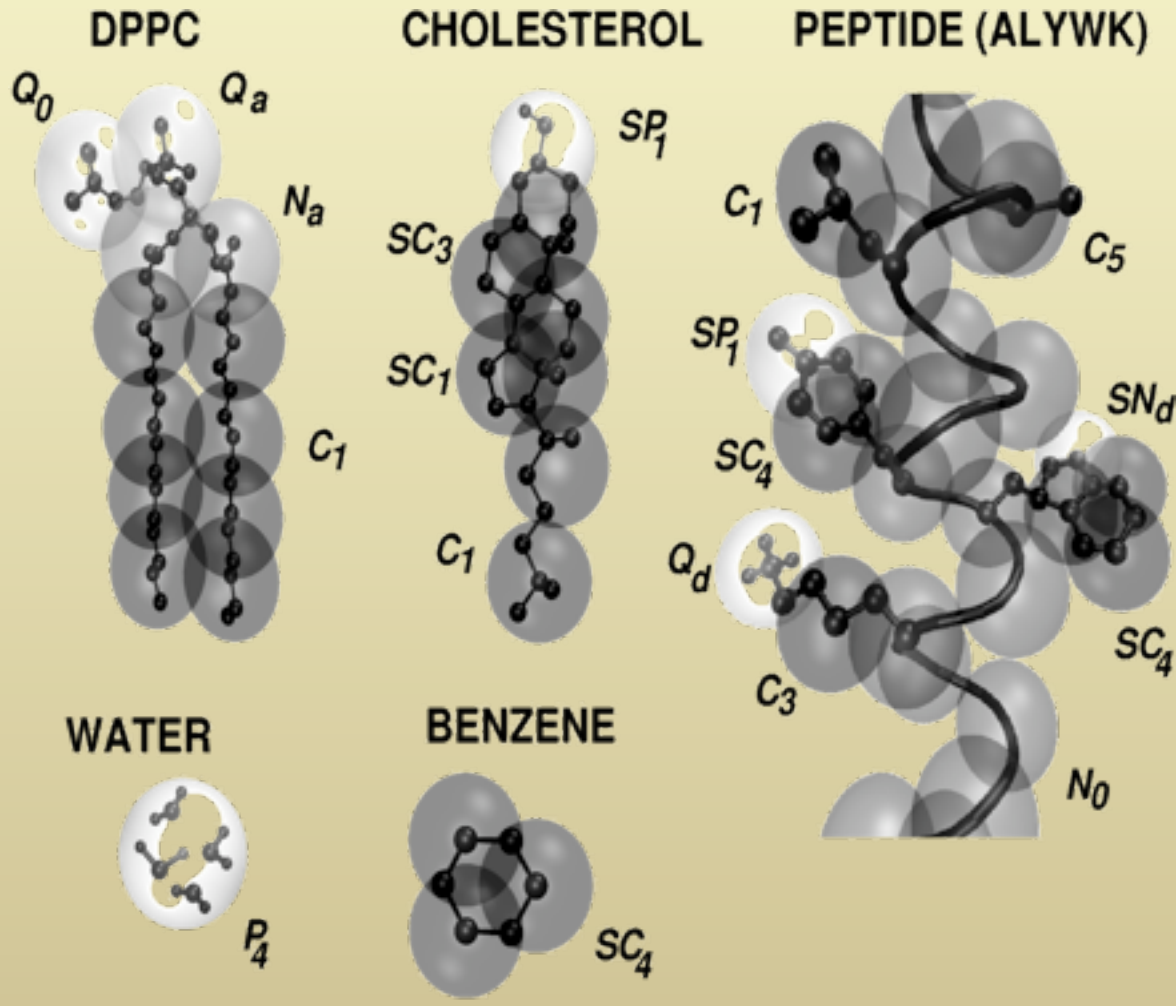
extensive testing on model systems



fundamental insight of collective processes at (near) atomic resolution

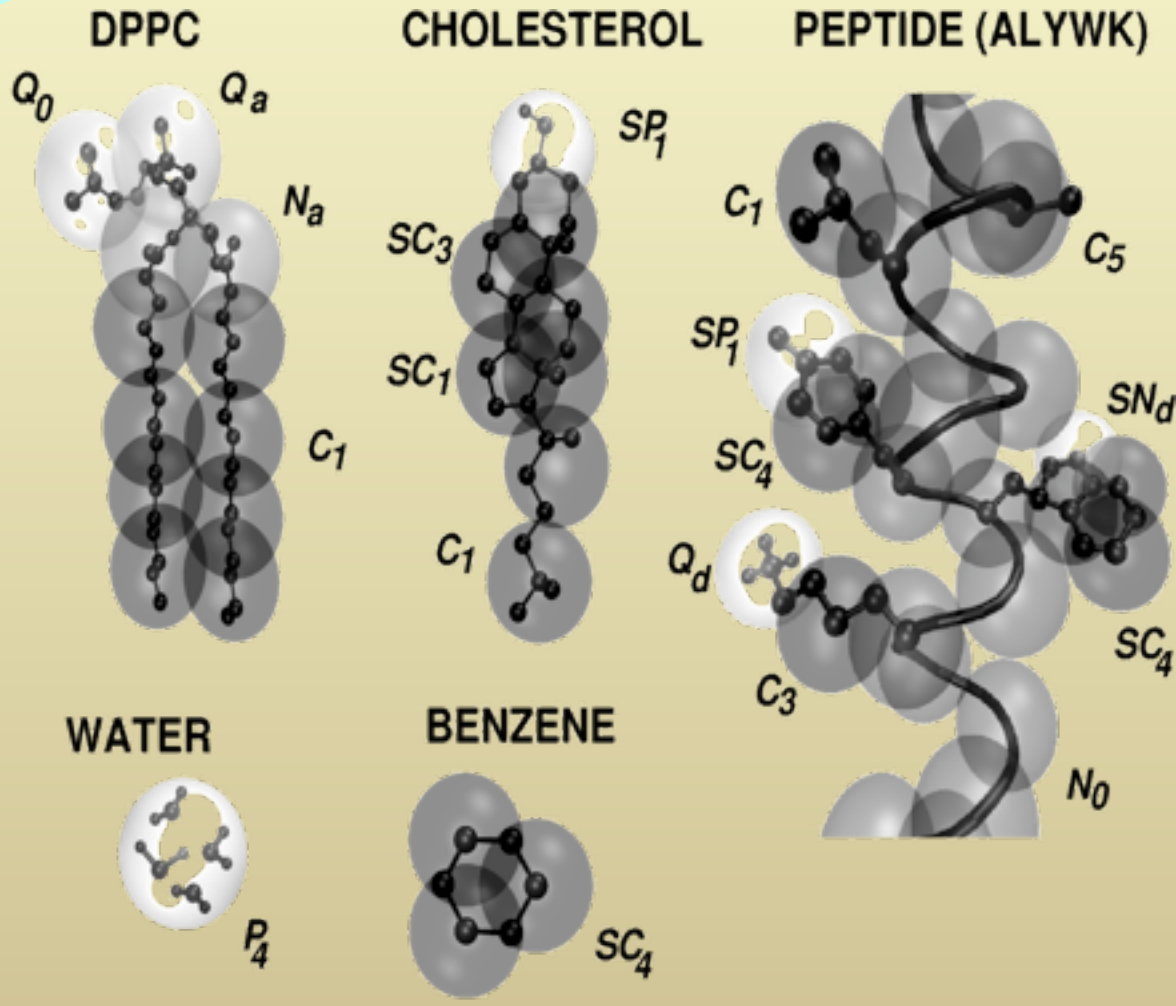


The MARTINI CG Model



The MARTINI CG Model

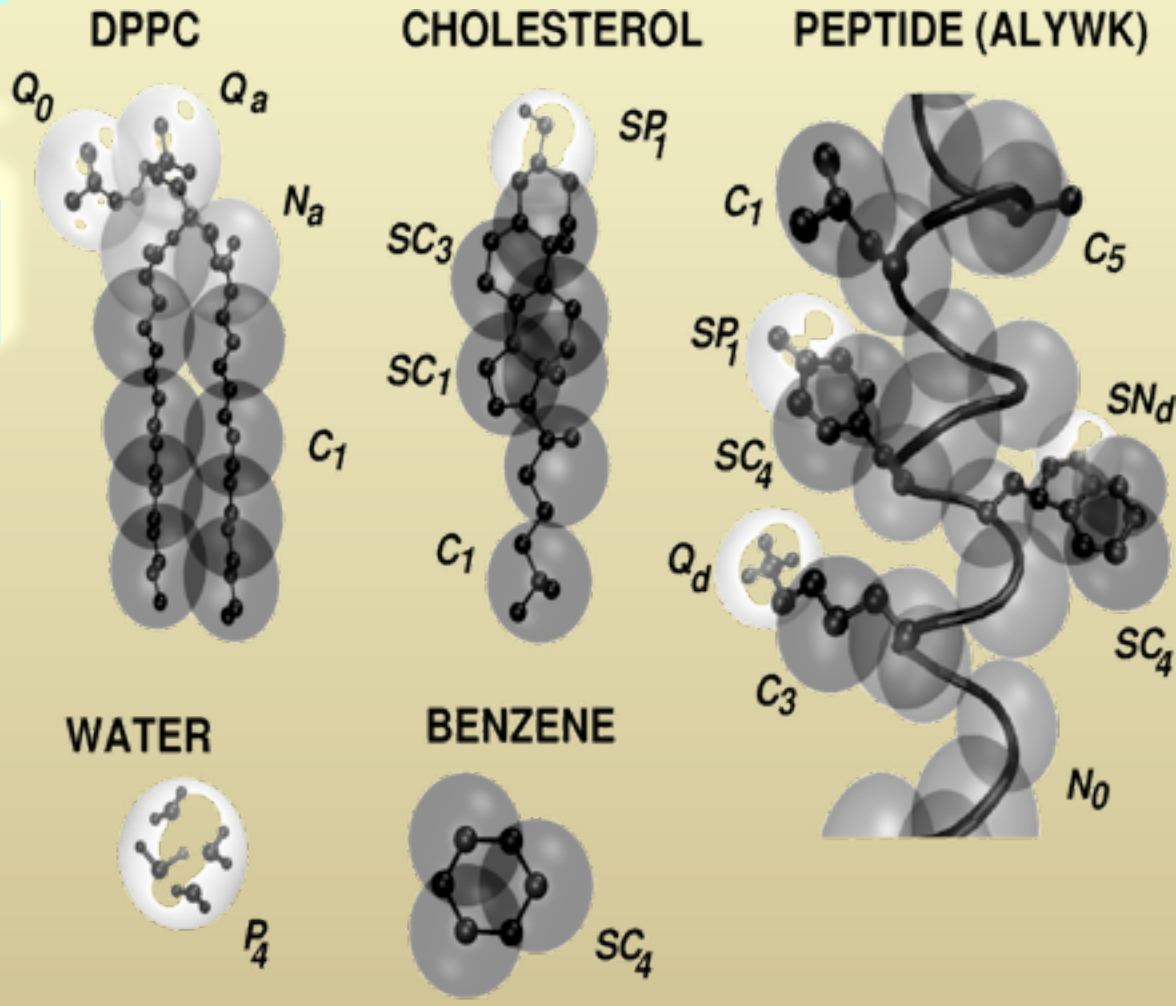
Speed:
Short range
Large timestep
Few particles



The MARTINI CG Model

Speed:
Short range
Large timestep
Few particles

General:
Biomolecular systems
Consistent modeling

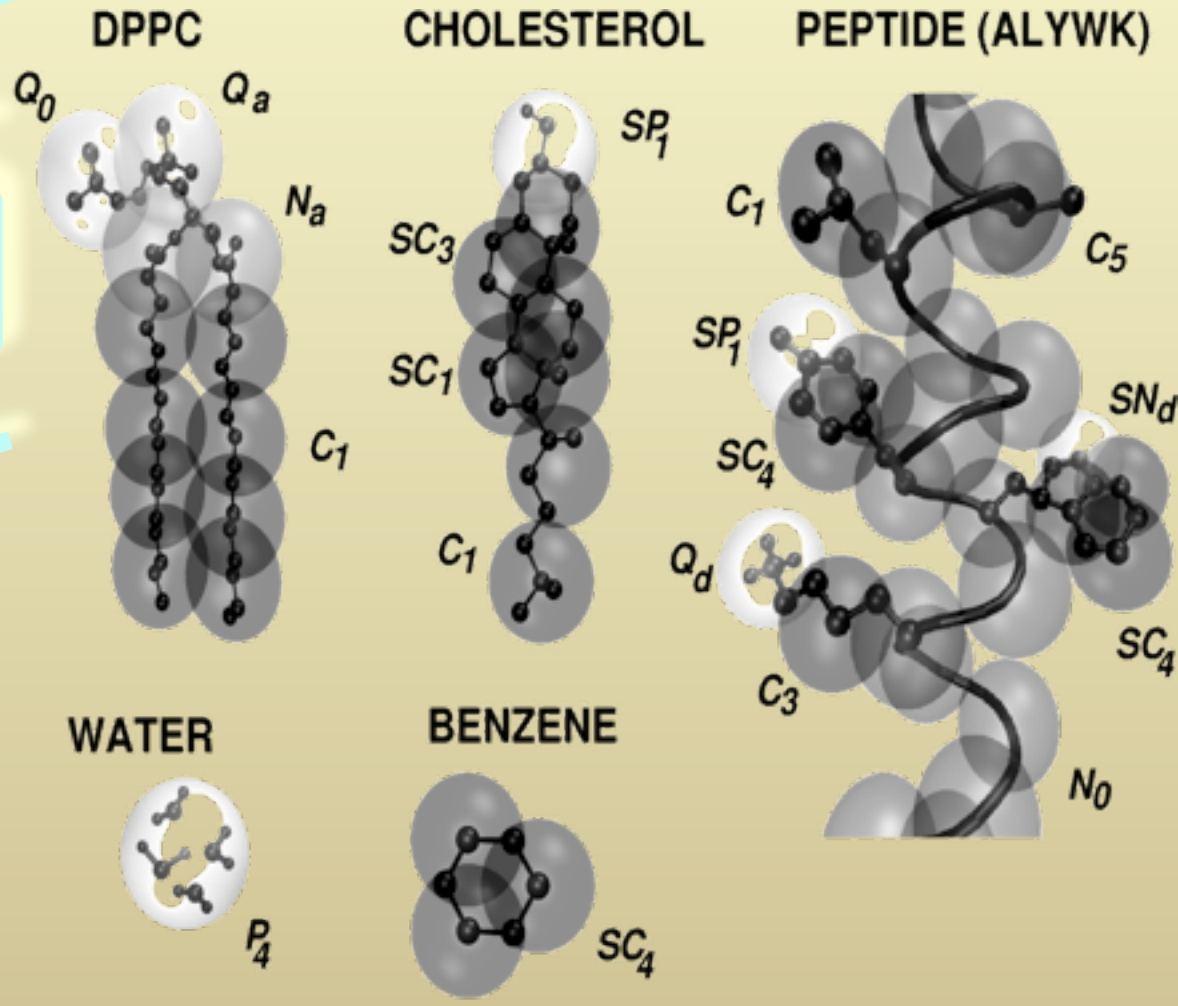


The MARTINI CG Model

Speed:
Short range
Large timestep
Few particles

General:
Biomolecular systems
Consistent modeling

Easy2Use:
Buildingblock approach
Limited # particle types



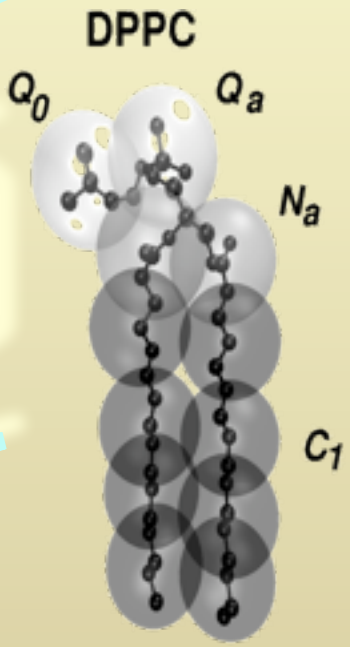
The MARTINI CG Model

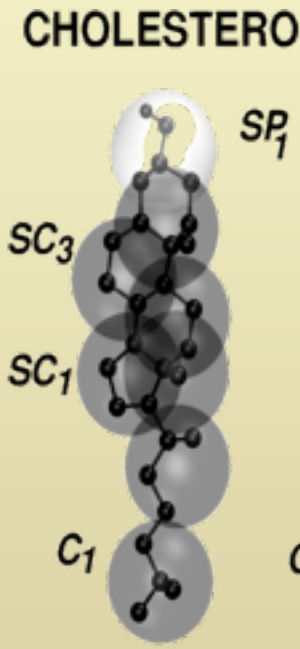
Speed:
Short range
Large timestep
Few particles

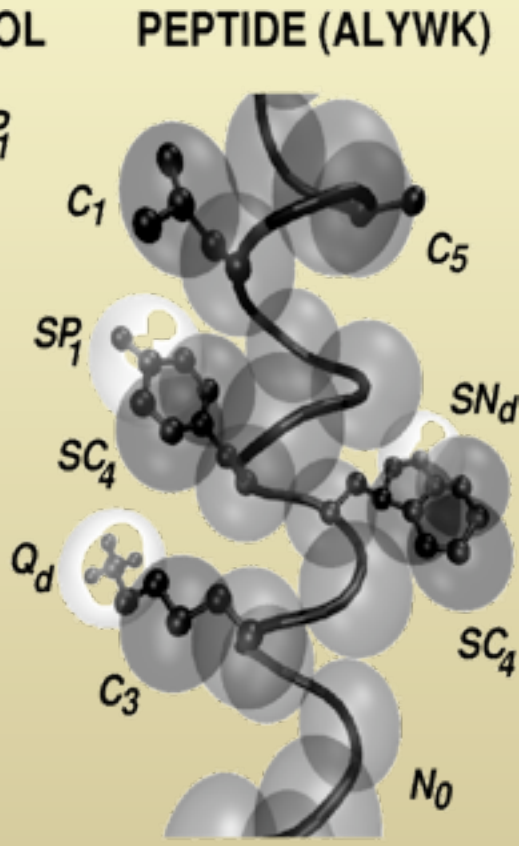
General:
Biomolecular systems
Consistent modeling

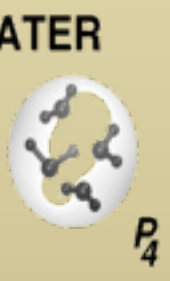
Easy2Use:
Buildingblock approach
Limited # particle types

Accuracy:
Multi level optimization
Parameterization based on thermodynamic data



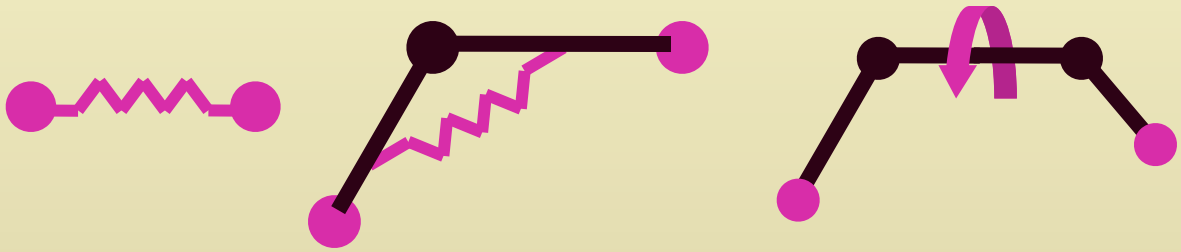






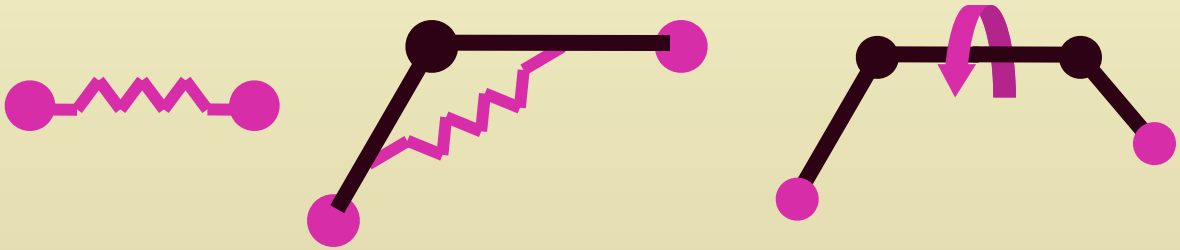
THE LOOKS: bonded

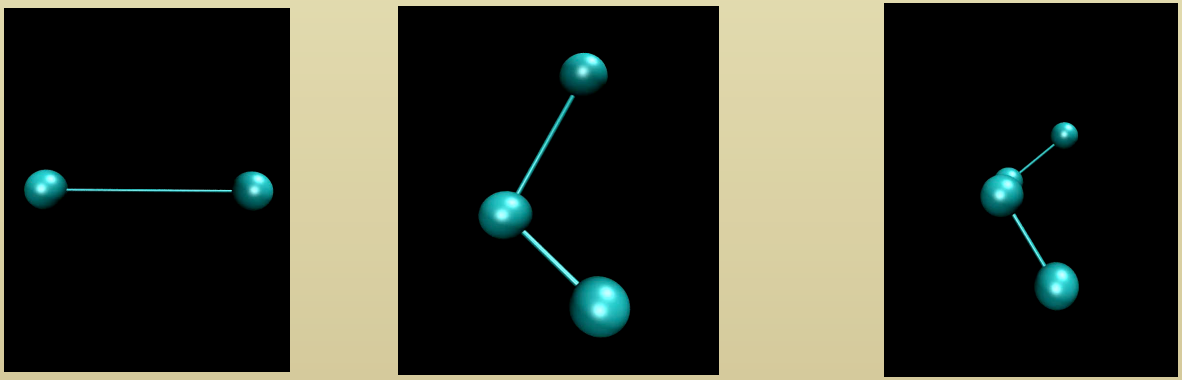
Bonded interactions described by standard harmonic potential energy functions



THE LOOKS: bonded

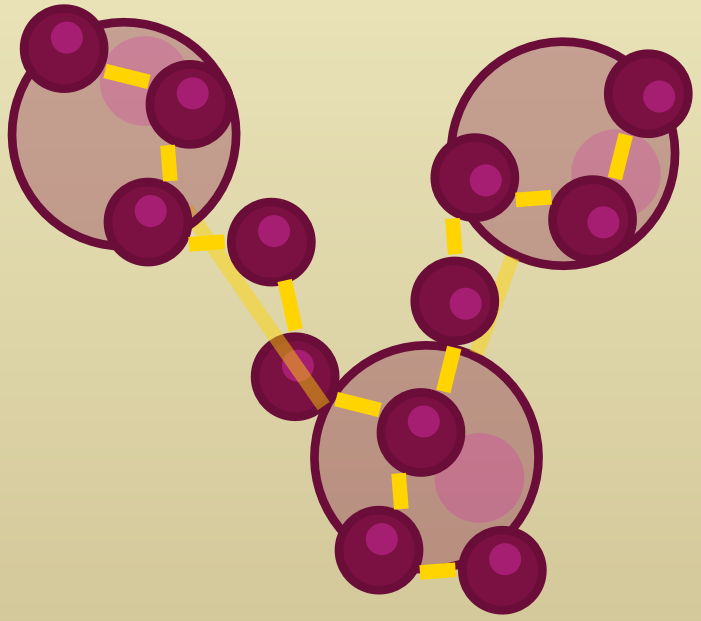
Bonded interactions described by standard harmonic potential energy functions

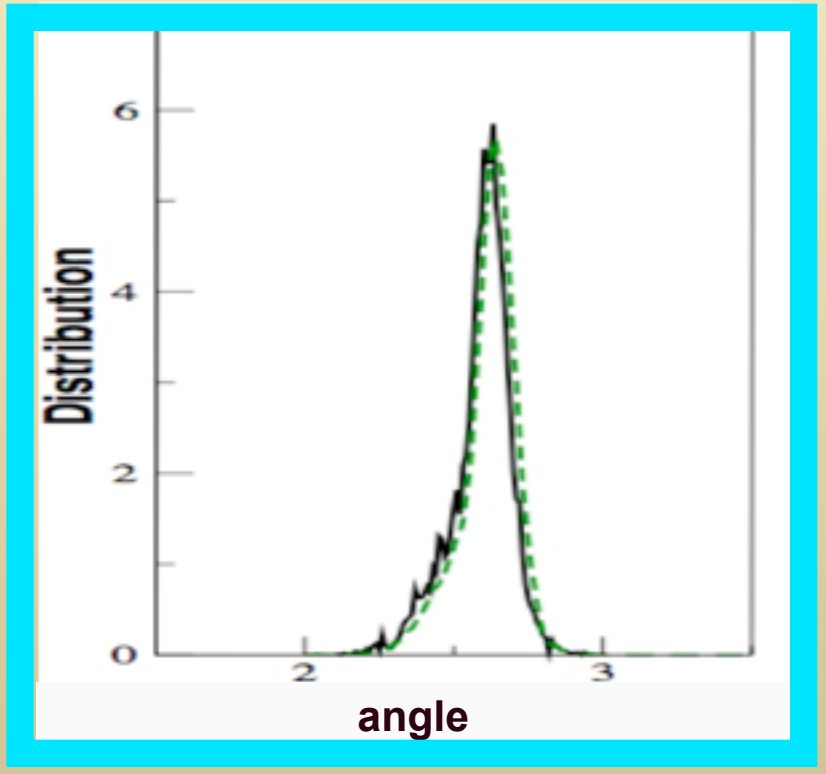




THE PARAMETRIZATION: bonded

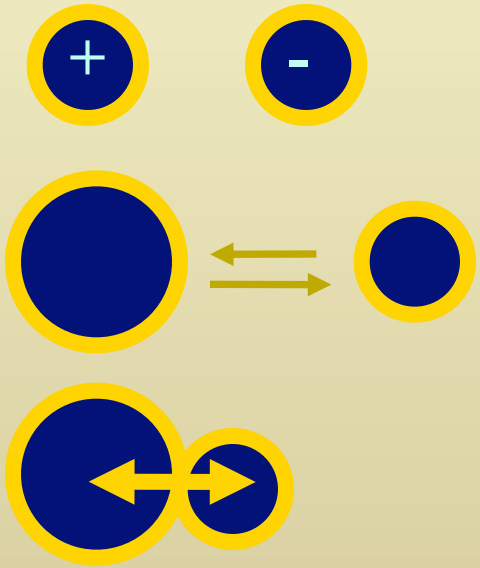
Bonded interactions are parameterized by mapping to all-atom simulations





THE LOOKS: non-bonded

Non-bonded interactions described by standard LJ and Coulombic energy functions



electrostatic

dispersion

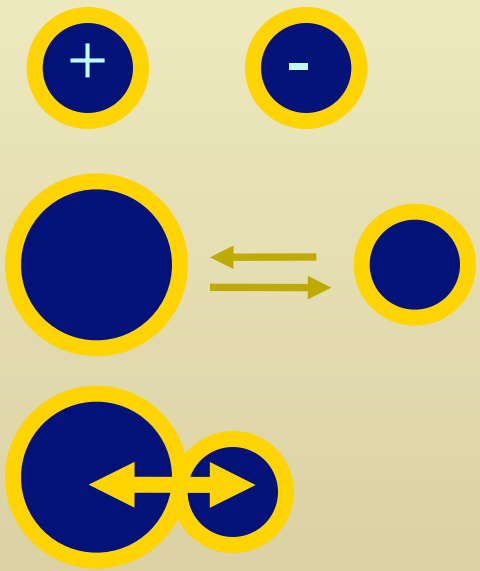
overlap

Coulomb

} *Lennard-Jones*

THE LOOKS: non-bonded

Non-bonded interactions described by standard LJ and Coulombic energy functions



electrostatic — *Coulomb*

dispersion

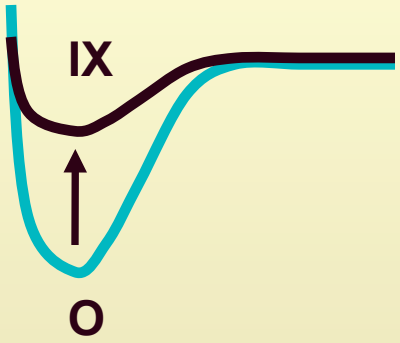
overlap

} *Lennard-Jones*

.... however: short-ranged by use of shifted functions
(cut-off 1.2 nm, 2-3 neighbors)

THE LOOKS: non-bonded

LJ interactions depend on hydrophilicity of CG particle type
2.0 < ε < 5.6 kJ/mol ; σ = 0.47 nm

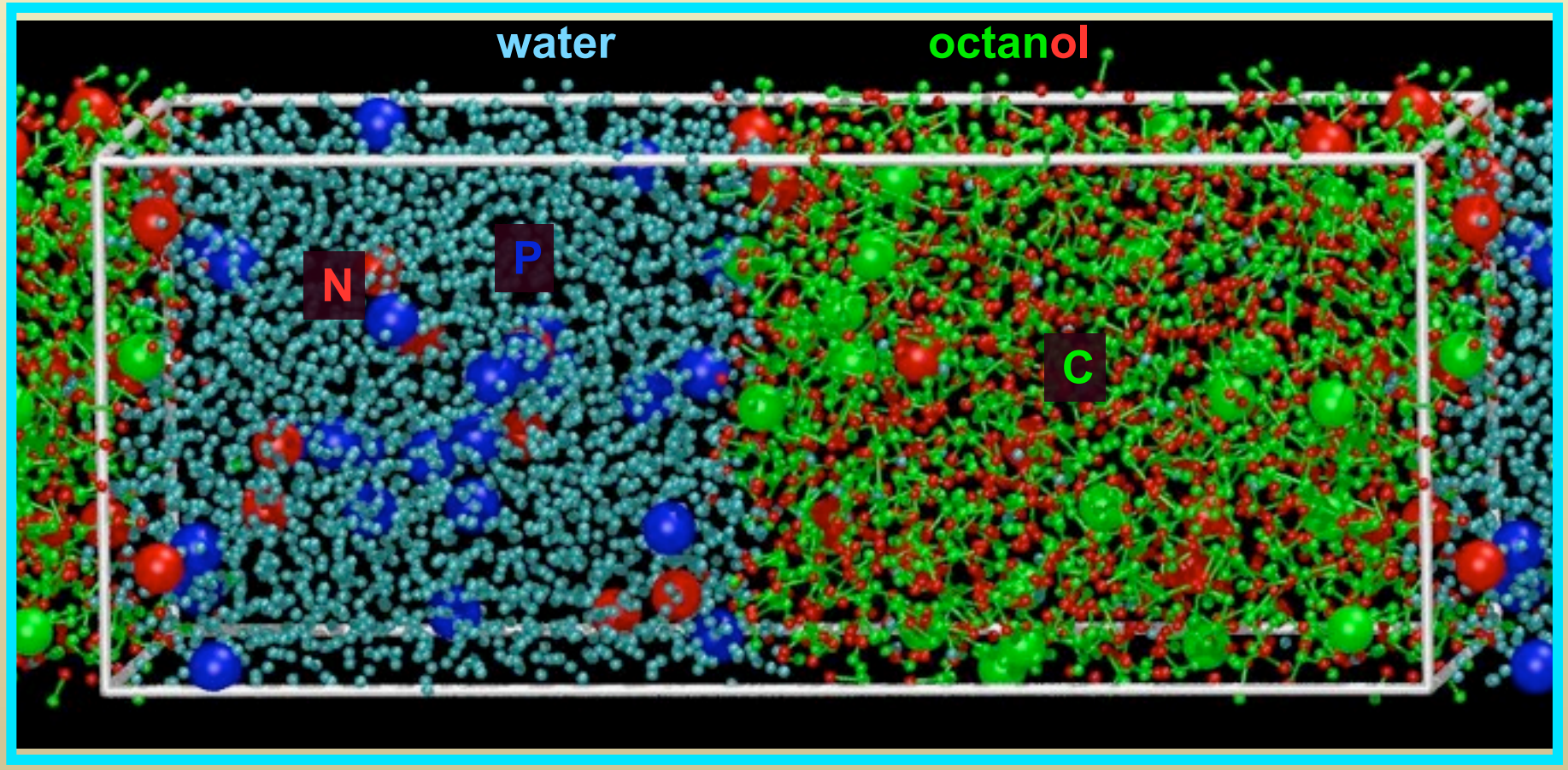


charged polar intermediate apolar

Type		Q				P					N				C				
	sub	*da*	*d*	*a*	0	5	4	3	2	1	*da*	*d*	*a*	0	5	4	3	2	1
Q	*da*	O	O	O	II	O	O	O	I	I	I	I	I	IV	V	VI	VII	IX	IX
	d	O	I	O	II	O	O	O	I	I	I	III	I	IV	V	VI	VII	IX	IX
	a	O	O	I	II	O	O	O	I	I	I	I	III	IV	V	VI	VII	IX	IX
	0	II	II	II	IV	I	O	I	II	III	III	III	III	IV	V	VI	VII	IX	IX
P	5	O	O	O	I	O	O	O	O	O	I	I	I	IV	V	VI	VI	VII	VIII
	4	O	O	O	O	O	I	I	II	II	III	III	III	IV	V	VI	VI	VII	VIII
	3	O	O	O	I	O	I	I	II	II	II	II	II	IV	IV	V	V	VI	VII
	2	I	I	I	II	O	II	II	II	II	II	II	II	III	IV	IV	V	VI	VII
	1	I	I	I	III	O	II	II	II	II	II	II	II	III	IV	IV	IV	V	VI
N	*da*	I	I	I	III	I	III	II	II	II	II	II	II	IV	IV	V	VI	VI	VI
	d	I	III	I	III	I	III	II	II	II	II	III	II	IV	IV	V	VI	VI	VI
	a	I	I	III	III	I	III	II	II	II	II	II	III	IV	IV	V	VI	VI	VI
	0	IV	IV	IV	IV	IV	IV	IV	III	III	IV	IV	IV	IV	IV	IV	IV	V	VI
C	5	V	V	V	V	V	V	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	V	V
	4	VI	VI	VI	VI	VI	VI	V	IV	IV	V	V	V	IV	IV	IV	IV	V	V
	3	VII	VII	VII	VII	VI	VI	V	V	IV	VI	VI	VI	IV	IV	IV	IV	IV	IV
	2	IX	IX	IX	IX	VII	VII	VI	VI	V	VI	VI	VI	V	V	V	IV	IV	IV
	1	IX	IX	IX	IX	VIII	VIII	VII	VII	VI	VI	VI	VI	VI	V	V	IV	IV	IV

THE PARAMETRIZATION: non-bonded

LJ interactions are parameterized based on experimental partitioning free energies (and densities)



THE PARAMETRIZATION: non-bonded

Type	Building Block	Examples	ΔG^{vap} Exp	ΔG^{vap} CG	ΔG^{hyd} Exp	ΔG^{hyd} CG	ΔG^{part}_{HW} Exp	ΔG^{part}_{HW} CG	ΔG^{part}_{EW} Exp	ΔG^{part}_{EW} CG	ΔG^{part}_{OW} Exp	ΔG^{part}_{OW} CG
			water						octanol			
Q_{da}	H_3N^+-C_2-OH	Ethanolamine (protonated)				-25		≤-30		-18		-13		-18
Q_d	H_3N^+-C_3	1-Propylamine (protonated)				-25		≤-30		-18		-13		-18
	NA^+ OH	Sodium (hydrated)				-25		≤-30		-18		-13		-18
Q_a	PO_4^-	Phosphate				-25		≤-30		-18		-13		-18
	CL^- HO	Chloride (hydrated)				-25		≤-30		-18		-13		-18
Q_0	C_3N^+	Choline				-25		≤-30		-18		-13		-18
P_5	H_2N-C_2=O	Acetamide	sol	sol	-40	-25	-27	-28	(-20)	-18	-15	-13	-8	-10
P_4	HOH (×4)	Water	-27	-18	-27	-18	-25	-23		-14	-10	-7	-8	-9
	HO-C_2-OH	Ethanediol	-35	-18	-33	-18	-21	-23		-14		-7	-8	-9
P_3	HO-C_2=O	Aceticacid	-31	-18	-29	-18	-19	-21	-9	-10	-2	-6	-1	-7
	C-NH-C=O	Methylformamide	-35	-18		-18		-21		-10		-6	-5	-7
P_2	C_2-OH	Ethanol	-22	-16	-21	-14	-13	-17	-5	-2	-3	1	-2	-2
P_1	C_3-OH	1-Propanol	-23	-16	-21	-14	-9	-11	-2	-2	0	1	1	-1
		2-Propanol	-22	-16	-20	-14	-10	-11	-2	-2	-1	1	0	-1
N_{da}	C_4-OH	1-Butanol	-25	-16	-20	-9	-5	-7	2	0	4	2	4	3
N_d	H_2N-C_3	1-Propylamine	-17	-13	-18	-9	(-6)	-7	(1)	0	(-3)	2	(3)	3
N_a	C_3=O	2-Propanone	-17	-13	-16	-9	-6	-7	1	0	-1	2	-1	3
	C-NO_2	Nitromethane	-23	-13	-17	-9	-6	-7		0		2	-2	3
	C_3≡N	Proprionitril	-22	-13	-17	-9	-5	-7		0		2	1	3
	C-O-C=O	Methylformate	-16	-13	-12	-9	(-6)	-7	(4)	0	(-1)	2	(0)	3
	C_2HC=O	Propanal		-13	-15	-9	-4	-7		0	2	2	3	3
N_0	C-O-C_2	Methoxyethane	-13	-10	(-8)	-2	(1)	-2		6	(3)	6	(3)	5
C_5	C_3-SH	1-Propanethiol	-17	-10		1		5		10		10		6
	C-S-C_2	Methylethylsulfide	-17	-10	-6	1	(7)	5		10		10	(9)	6
C_4	C_2≡C_2	2-Butyne	-15	-10	-1	5		9		13		13	9	9
	C=C-C=C	1,3-Butadiene		-10	2	5	11	9		13		13	11	9
	C-X_4	Chloroform	-18	-10	-4	5	(7)	9	14	13		13	11	9
C_3	C_2=C_2	2-Butene		-10		5		13		13		13	13	14
	C_3-X	1-Chloropropane	-16	-10	-1	5	12	13		13		13	12	14
		2-Bromopropane	-16	-10	-2	5		13		13		13	12	14
C_2	C_3	Propane	gas	-10	8	10		16		15		14	14	16
C_1	C_4	Butane	-11[a]	-10	9	14	18	18		18		14	16	17
		Isopropane	gas	-10	10	14		18		18		14	16	17

THE PARAMETRIZATION: non-bonded

type	chemical building block	example	vap. EXP	vap. CG	hydration EXP	hydration CG	partitioning free energy (kJ/mol) water/hexadecane EXP	water/hexadecane CG	water/chloroform EXP	water/chloroform CG	water/ether EXP	water/ether CG	water/octanol EXP	water/octanol CG
Q_{da}	H_3N^+-C_2-OH	Ethanolamine (protonated)				-25		≤-30		-18		-13		-18
Q_d	H_3N^+-C_3	1-Propylamine (protonated)				-25		≤-30		-18		-13		-18
	NA^+ OH	Sodium (hydrated)				-25		≤-30		-18		-13		-18
Q_a	PO_4^-	Phosphate				-25		≤-30		-18		-13		-18
	CL^- HO	Chloride (hydrated)				-25		≤-30		-18		-13		-18
Q_0	C_3N^+	Choline				-25		≤-30		-18		-13		-18
P_5	H_2N-C_2=O	Acetamide	sol	sol	-40	-25	-27	-28	(-20)	-18	-15	-13	-8	-10
P_4	HOH (×4)	Water	-27	-18	-27	-18	-25	-23		-14	-10	-7	-8	-9
	HO-C_2-OH	Ethanediol	-35	-18	-33	-18	-21	-23		-14		-7	-8	-9
P_3	HO-C_2=O	Aceticacid	-31	-18	-29	-18	-19	-21	-9	-10	-2	-6	-1	-7
	C-NH-C=O	Methylformamide	-35	-18		-18		-21		-10		-6	-5	-7
P_2	C_2-OH	Ethanol	-22	-16	-21	-14	-13	-17	-5	-2	-3	1	-2	-2
P_1	C_3-OH	1-Propanol	-23	-16	-21	-14	-9	-11	-2	-2	0	1	1	-1
		2-Propanol	-22	-16	-20	-14	-10	-11	-2	-2	-1	1	0	-1
N_{da}	C_4-OH	1-Butanol	-25	-16	-20	-9	-5	-7	2	0	4	2	4	3
N_d	H_2N-C_3	1-Propylamine	-17	-13	-18	-9	(-6)	-7	(1)	0	(-3)	2	(3)	3
N_a	C_3=O	2-Propanone	-17	-13	-16	-9	-6	-7	1	0	-1	2	-1	3
	C-NO_2	Nitromethane	-23	-13	-17	-9	-6	-7		0		2	-2	3
	C_3≡N	Proprionitril	-22	-13	-17	-9	-5	-7		0		2	1	3
	C-O-C=O	Methylformate	-16	-13	-12	-9	(-6)	-7	(4)	0	(-1)	2	(0)	3
	C_2HC=O	Propanal		-13	-15	-9	-4	-7		0	2	2	3	3
N_0	C-O-C_2	Methoxyethane	-13	-10	(-8)	-2	(1)	-2		6	(3)	6	(3)	5
C_5	C_3-SH	1-Propanethiol	-17	-10		1		5		10		10		6
	C-S-C_2	Methylethylsulfide	-17	-10	-6	1	(7)	5		10		10	(9)	6
C_4	C_2≡C_2	2-Butyne	-15	-10	-1	5		9		13		13	9	9
	C=C-C=C	1,3-Butadiene		-10	2	5	11	9		13		13	11	9
	C-X_4	Chloroform	-18	-10	-4	5	(7)	9	14	13		13	11	9
C_3	C_2=C_2	2-Butene		-10		5		13		13		13	13	14
	C_3-X	1-Chloropropane	-16	-10	-1	5	12	13		13		13	12	14
		2-Bromopropane	-16	-10	-2	5		13		13		13	12	14
C_2	C_3	Propane	gas	-10	8	10		16		15		14	14	16
C_1	C_4	Butane	-11[a]	-10	9	14	18	18		18		14	16	17
		Isopropane	gas	-10	10	14		18		18		14	16	17

THE PARAMETRIZATION: non-bonded

type	chemical building block	example	vap. EXP	vap. CG	hydration EXP	hydration CG	partitioning free energy (kJ/mol) water/ hexadecane EXP	hexadecane CG	chloroform EXP	chloroform CG	ether EXP	ether CG	octanol EXP	octanol CG
Q_{da}	H_3N^+-C_2-OH	Ethanolamine (protonated)				-25		≤-30		-18		-13		-18
Q_d	H_3N^+-C_3	1-Propylamine (protonated)				-25		≤-30		-18		-13		-18
	NA^+ OH	Sodium (hydrated)				-25		≤-30		-18		-13		-18
Q_a	PO_4^-	Phosphate				-25		≤-30		-18		-13		-18
	CL^- HO	Chloride (hydrated)				-25		≤-30		-18		-13		-18
Q_0	C_3N^+	Choline				-25		≤-30		-18		-13		-18
P_5	H_2N-C_2=O	Acetamide	sol	sol	-40	-25	-27	-28	(-20)	-18	-15	-13	-8	-10
P_4	HOH (×4)	Water	-27	-18	-27	-18	-25	-23		-14	-10	-7	-8	-9
	HO-C_2-OH	Ethanediol	-35	-18	-33	-18	-21	-23		-14		-7	-8	-9
P_3	HO-C_2=O	Aceticacid	-31	-18	-29	-18	-19	-21	-9	-10	-2	-6	-1	-7
	C-NH-C=O	Methylformamide	-35	-18		-18		-21		-10		-6	-5	-7
P_2	C_2-OH	Ethanol	-22	-16	-21	-14	-13	-17	-5	-2	-3	1	-2	-2
P_1	C_3-OH	1-Propanol	-23	-16	-21	-14	-9	-11	-2	-2	0	1	1	-1
		2-Propanol	-22	-16	-20	-14	-10	-11	-2	-2	-1	1	0	-1
N_{da}	C_4-OH	1-Butanol	-25	-16	-20	-9	-5	-7	2	0	4	2	4	3
N_d	H_2N-C_3	1-Propylamine	-17	-13	-18	-9	(-6)	-7	(1)	0	(-3)	2	(3)	3
N_a	C_3=O	2-Propanone	-17	-13	-16	-9	-6	-7	1	0	-1	2	-1	3
	C-NO_2	Nitromethane	-23	-13	-17	-9	-6	-7		0		2	-2	3
	C_3≡N	Proprionitril	-22	-13	-17	-9	-5	-7		0		2	1	3
	C-O-C=O	Methylformate	-16	-13	-12	-9	(-6)	-7	(4)	0	(-1)	2	(0)	3
	C_2HC=O	Propanal		-13	-15	-9	-4	-7		0	2	2	3	3
N_0	C-O-C_2	Methoxyethane	-13	-10	(-8)	-2	(1)	-2		6	(3)	6	(3)	5
C_5	C_3-SH	1-Propanethiol	-17	-10		1		5		10		10		6
	C-S-C_2	Methylethylsulfide	-17	-10	-6	1	(7)	5		10		10	(9)	6
C_4	C_2≡C_2	2-Butyne	-15	-10	-1	5		9		13		13	8	9
	C=C-C=C	1,3-Butadiene		-10	2	5	11	9		13		13	11	9
	CX_4	Chloroform	-18	-10	-4	5	(7)	9	14	13		13	11	9
C_3	C_2=C_2	2-Butene		-10		5		13		13		13	13	14
	C_3-X	1-Chloropropane	-16	-10	-1	5	12	13		13		13	12	14
		2-Bromopropane	-16	-10	-2	5		13		13		13	12	14
C_2	C_3	Propane	gas	-10	8	10		16		15		14	14	16
C_1	C_4	Butane	-11[a]	-10	9	14	18	18		18		14	16	17
		Isopropane	gas	-10	10	14		18		18		14	16	17

SIMULATION PARAMETERS

SIMULATION PARAMETERS

Simulation parameters are considered to be part of the force-field!

- Cut-off 1.2 nm (using shifted potentials)
- Relative dielectric constant = 15 for implicit screening
- Time step ~20-30 fs

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Reality

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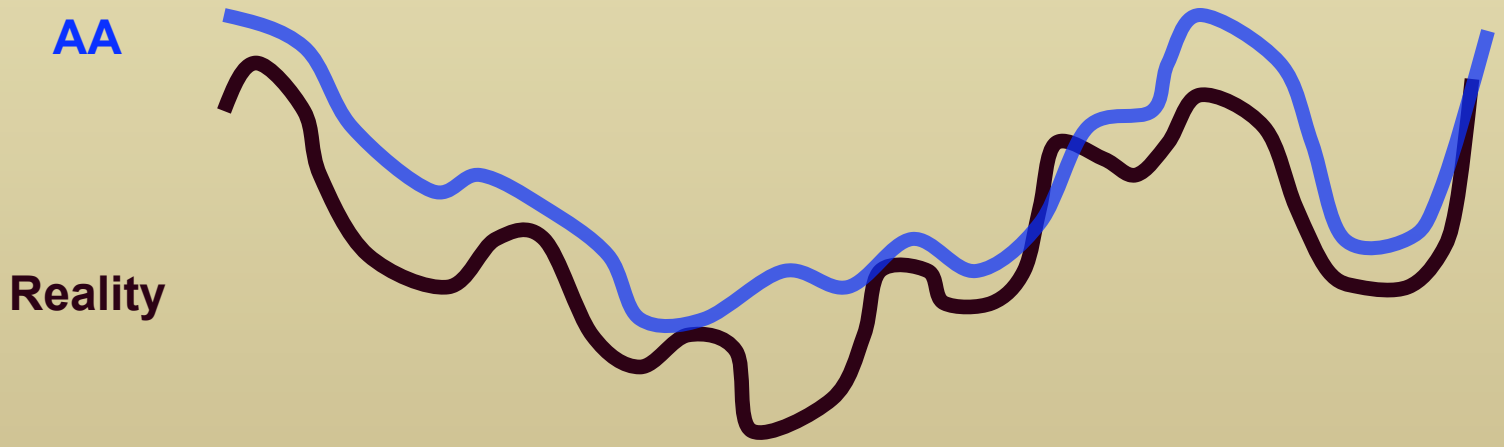

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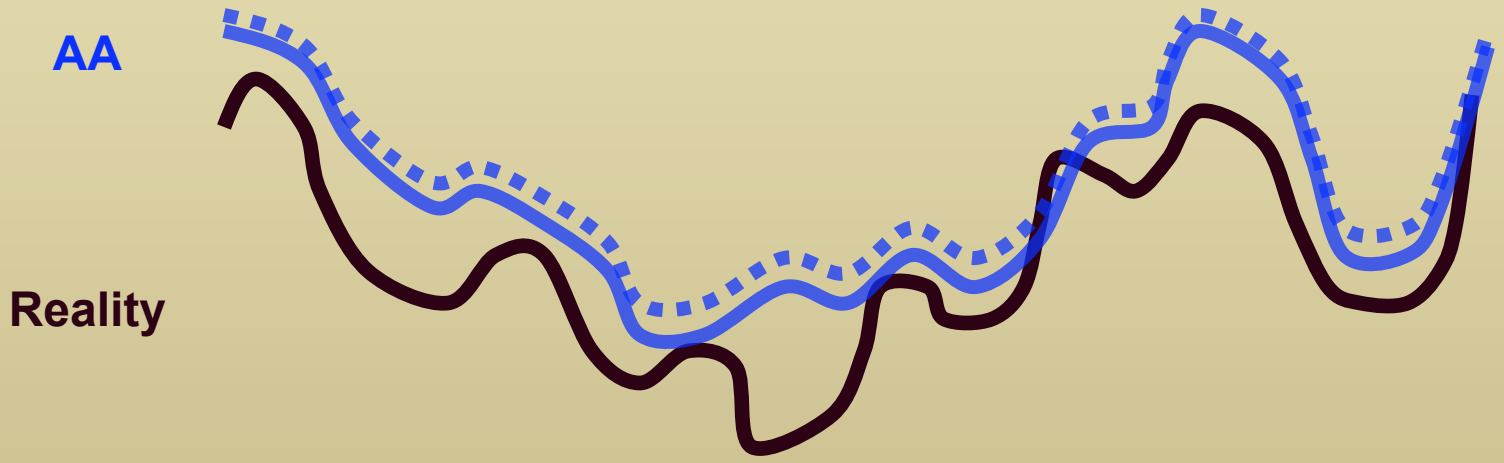

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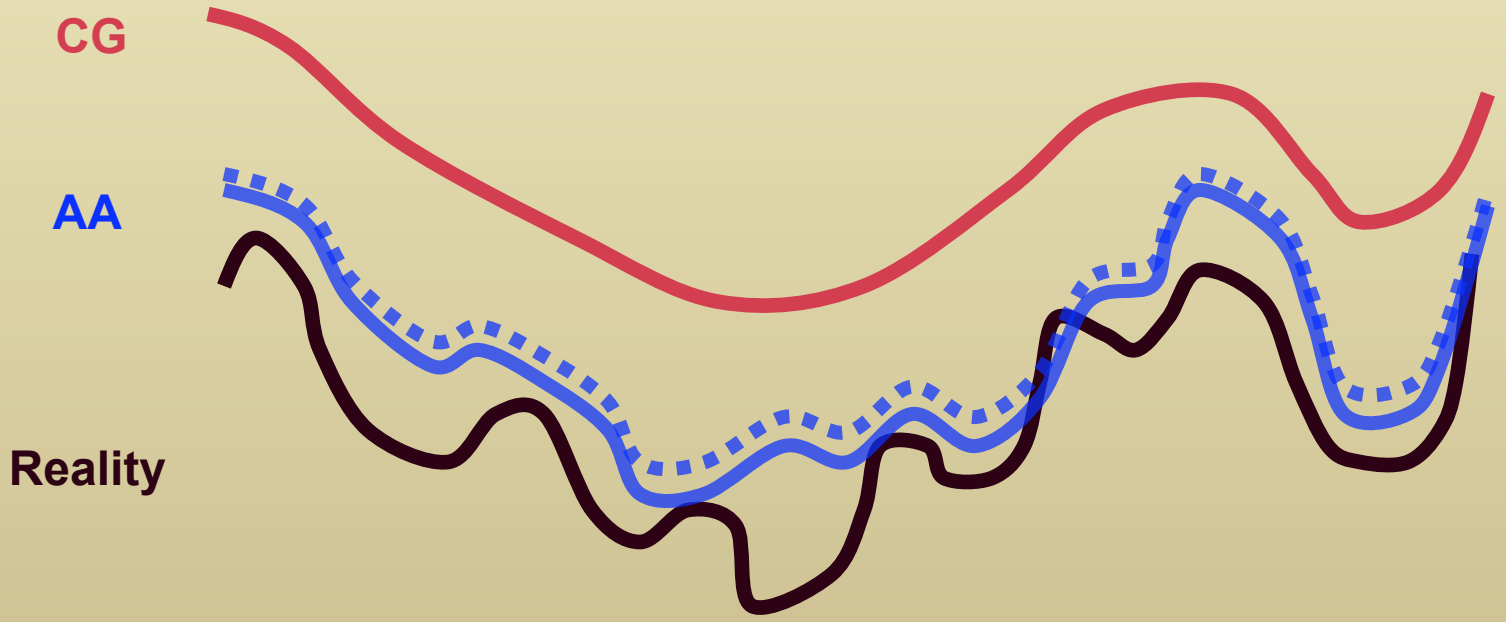

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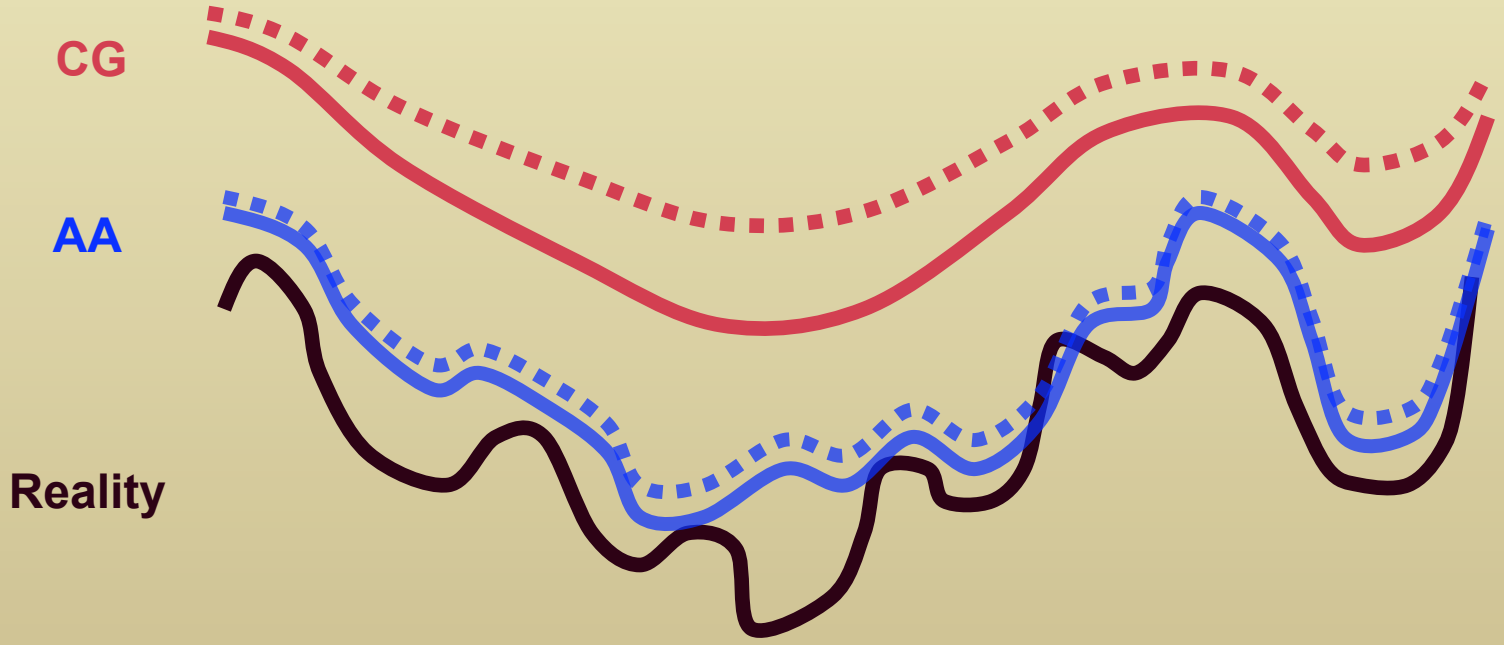
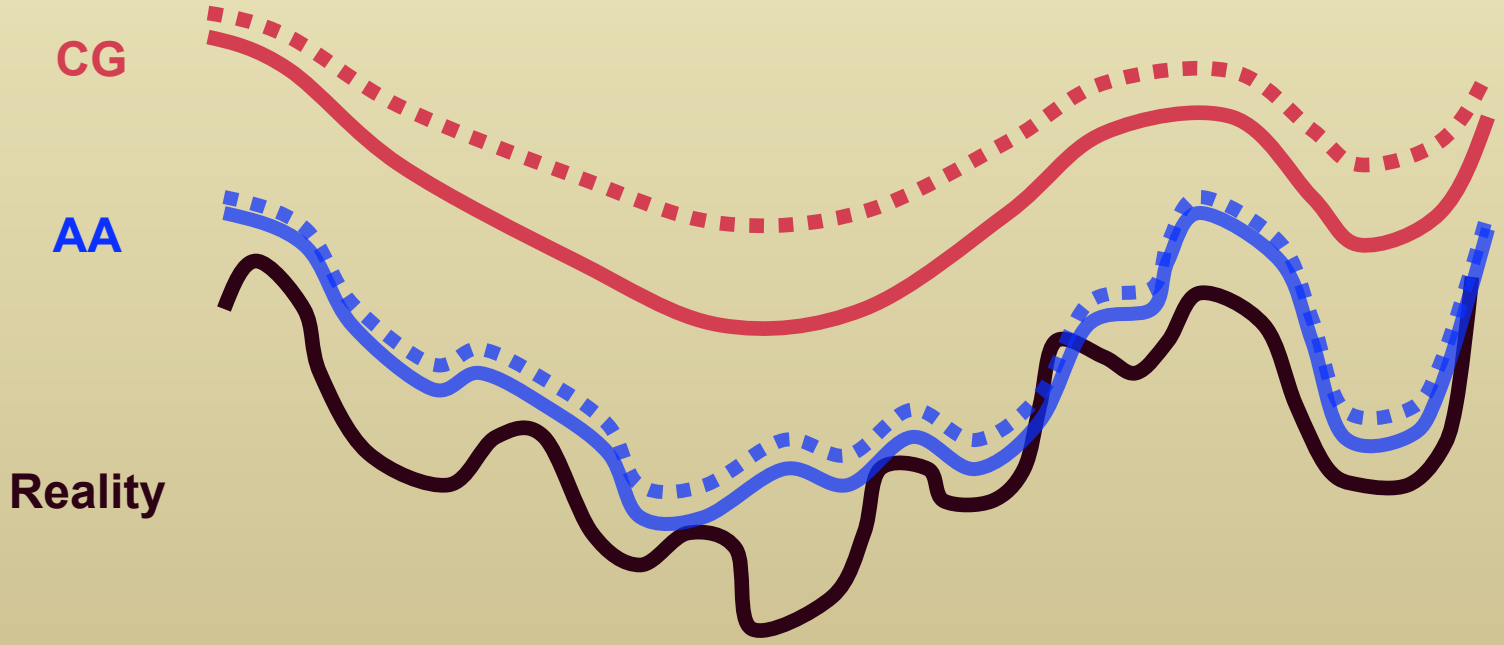


SIMULATION PARAMETERS

Kinetics need to be mapped on real time

- A mapping factor of 4 reproduces self-diffusion of water, and describes friction dominated processes in general (e.g. lipid diffusion, water permeation)

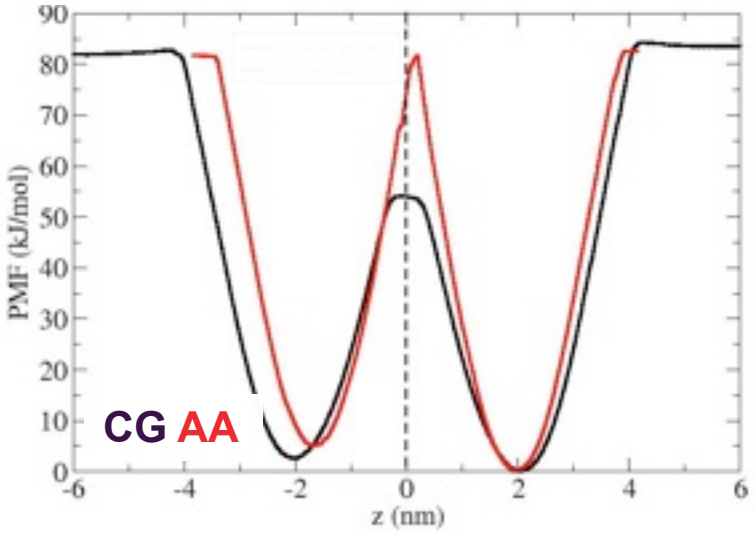
- Kinetics of more complex processes depend on energy barriers



THE VALIDATION

comparing to atomistic level simulations

Free energy of a lipid inside a bilayer



Tieleman & Marrink, JACS, 2006

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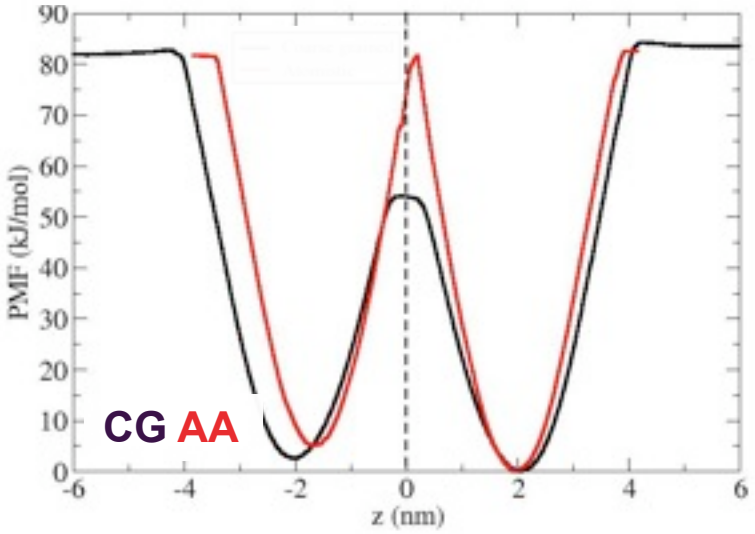

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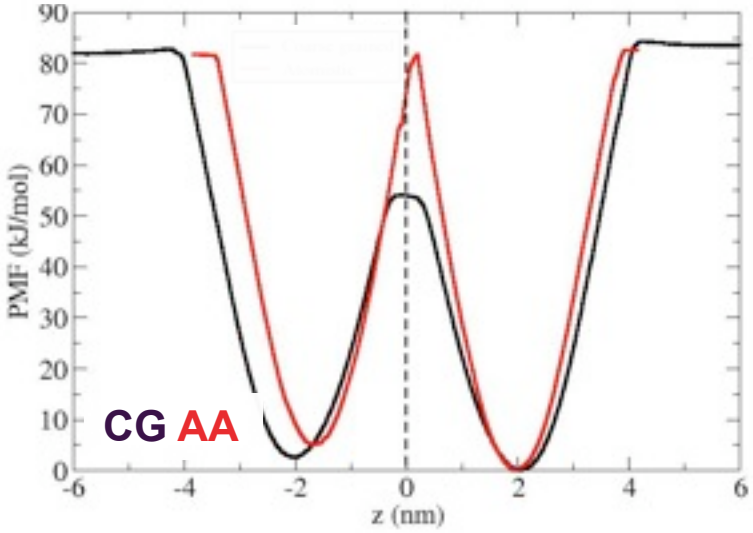

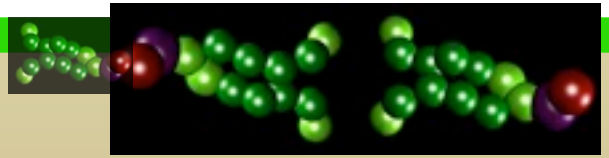

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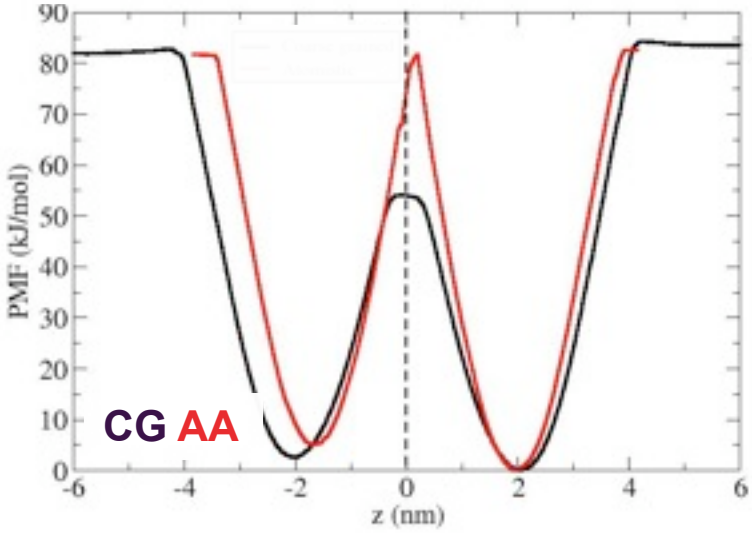
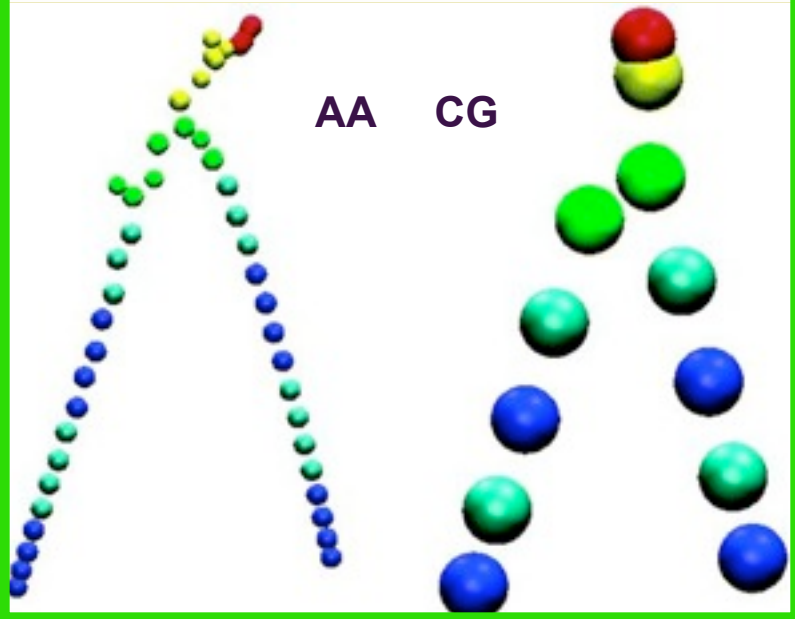


Tieleman & Marrink, JACS, 2006

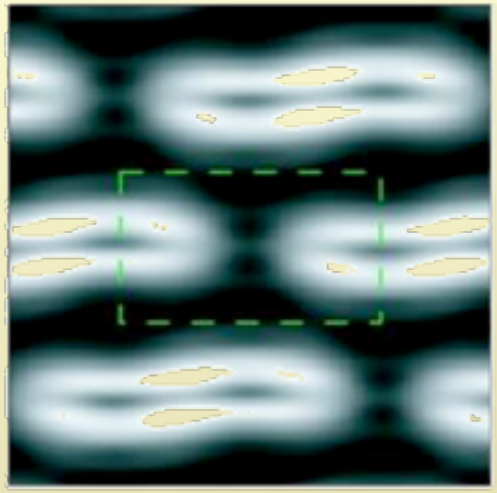
Averaged configurational space

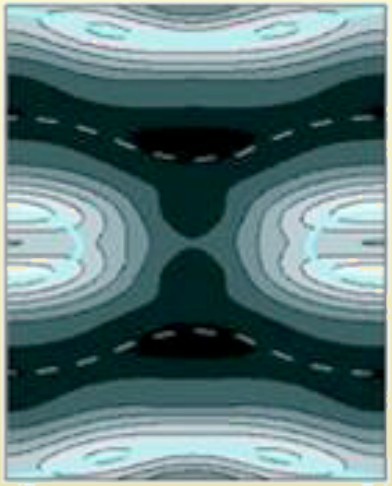


Baron & van Gunsteren, JPC-B, 2006

THE VALIDATION

comparing to experimental measurements

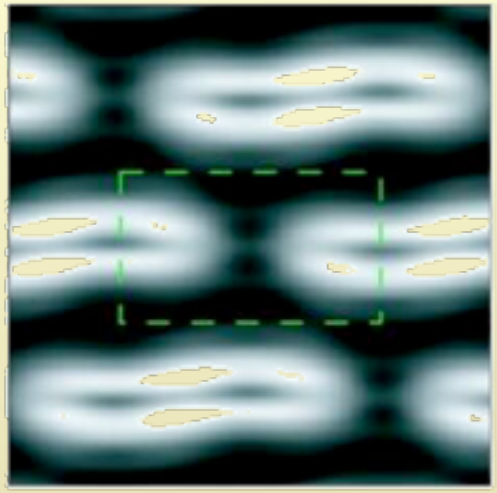


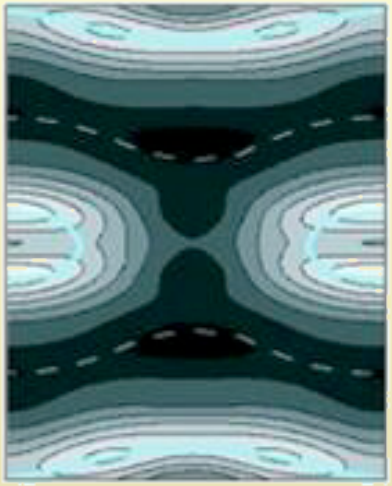


Rhombohedral phase (experimentally observed for DOPC/DOPE 3:1 and 2:1 *Lyan & Huang, 2002)*

THE VALIDATION

comparing to experimental measurements





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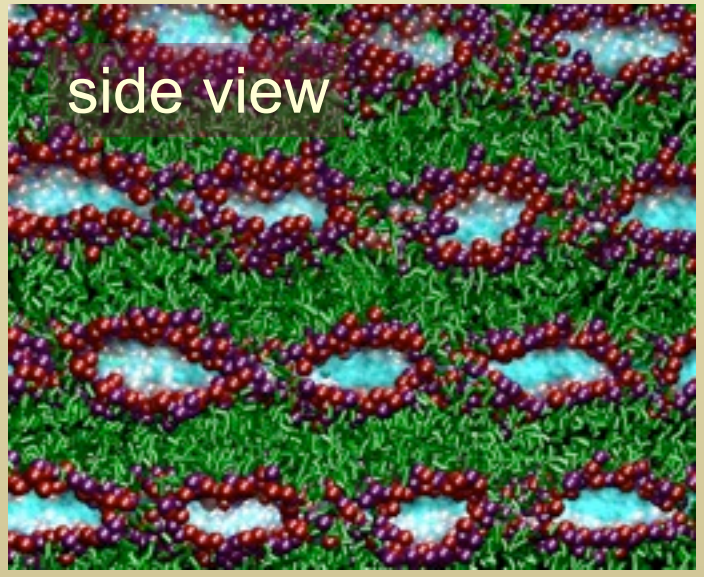
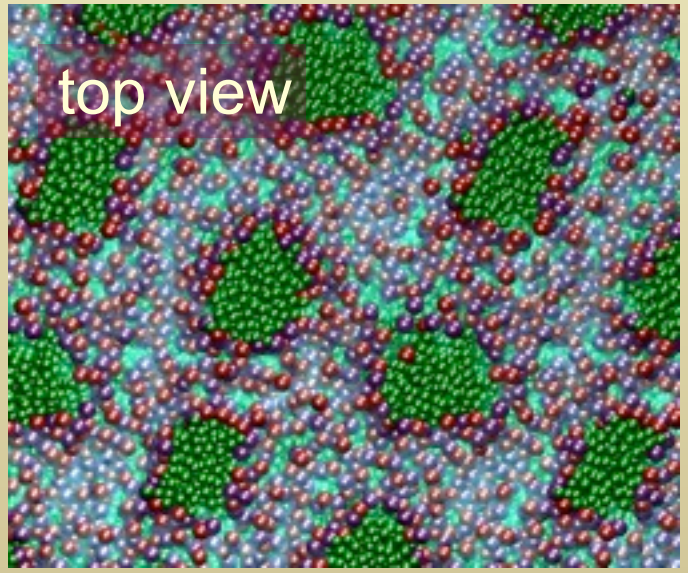
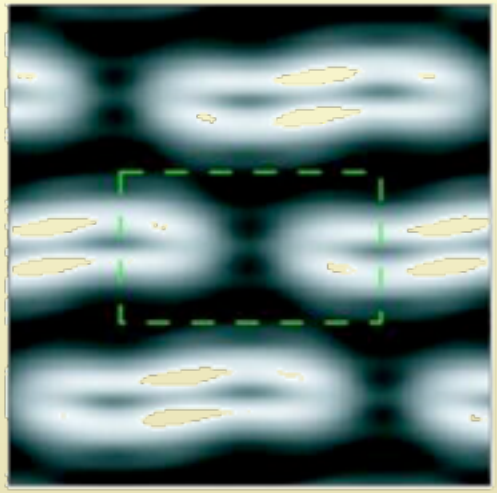


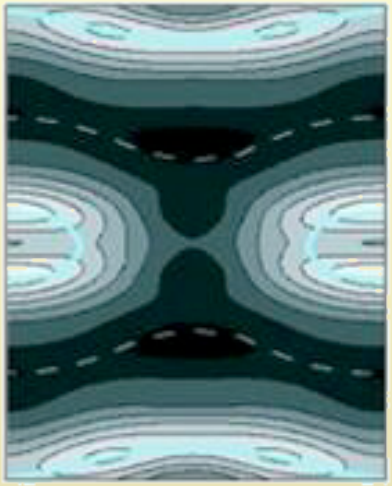


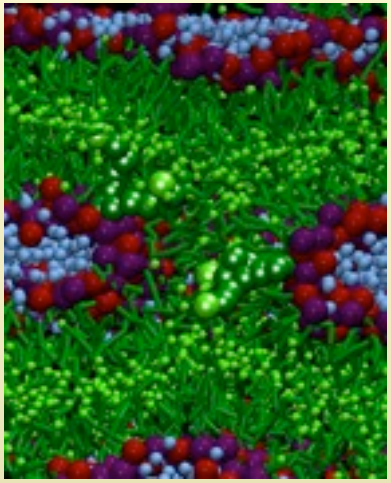
Reproduced in CG simulation *(Marrink & Mark, Biophys. J., 2004)*

THE VALIDATION

comparing to experimental measurements







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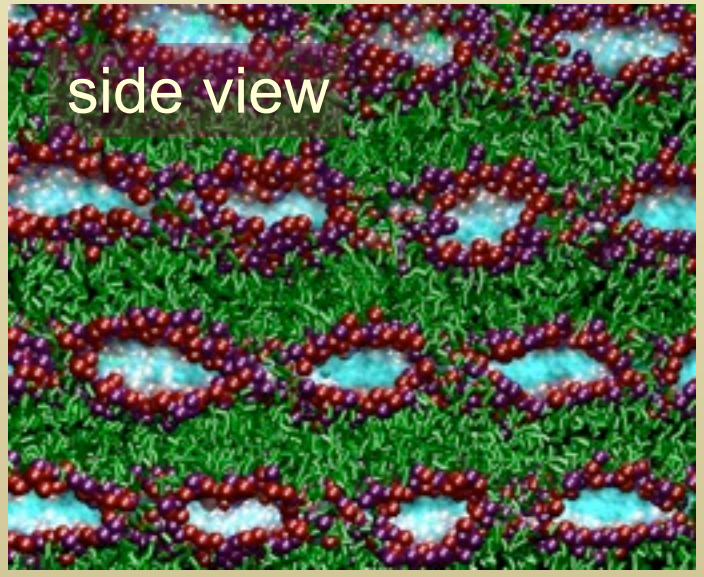

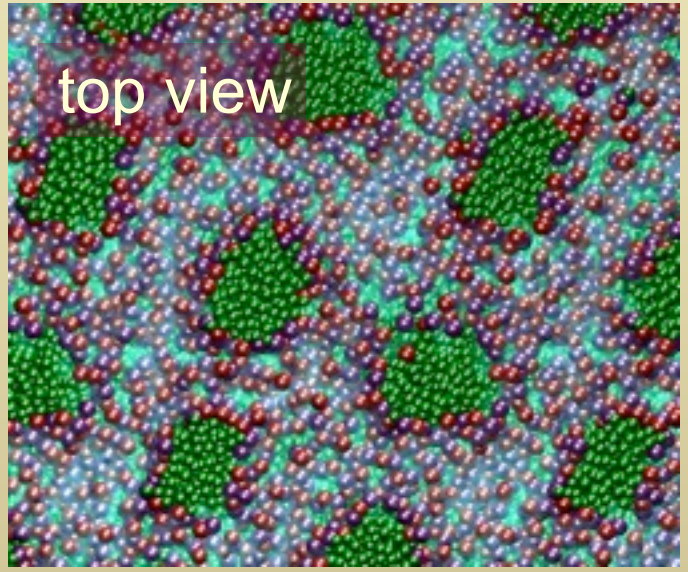

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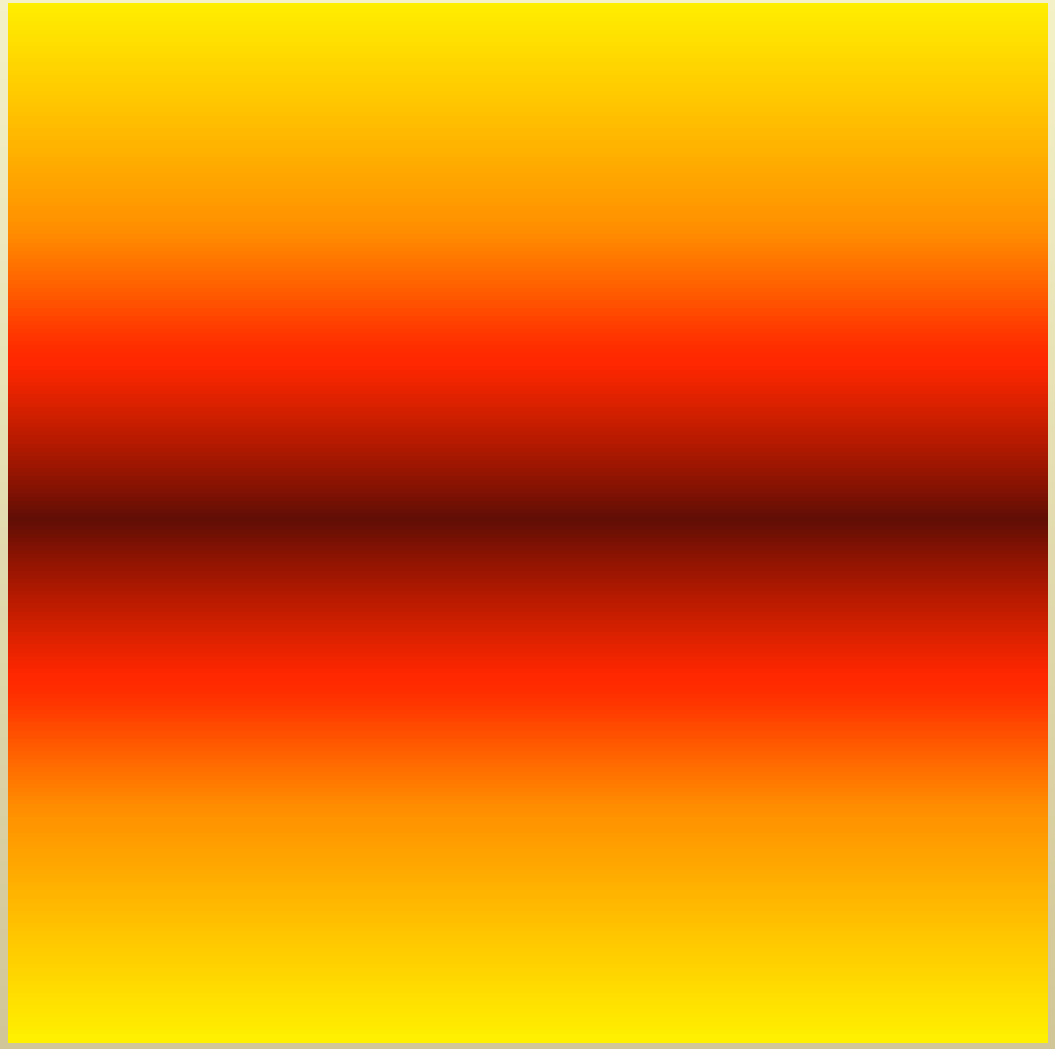
THE VALIDATION

Properties of bilayers



THE VALIDATION

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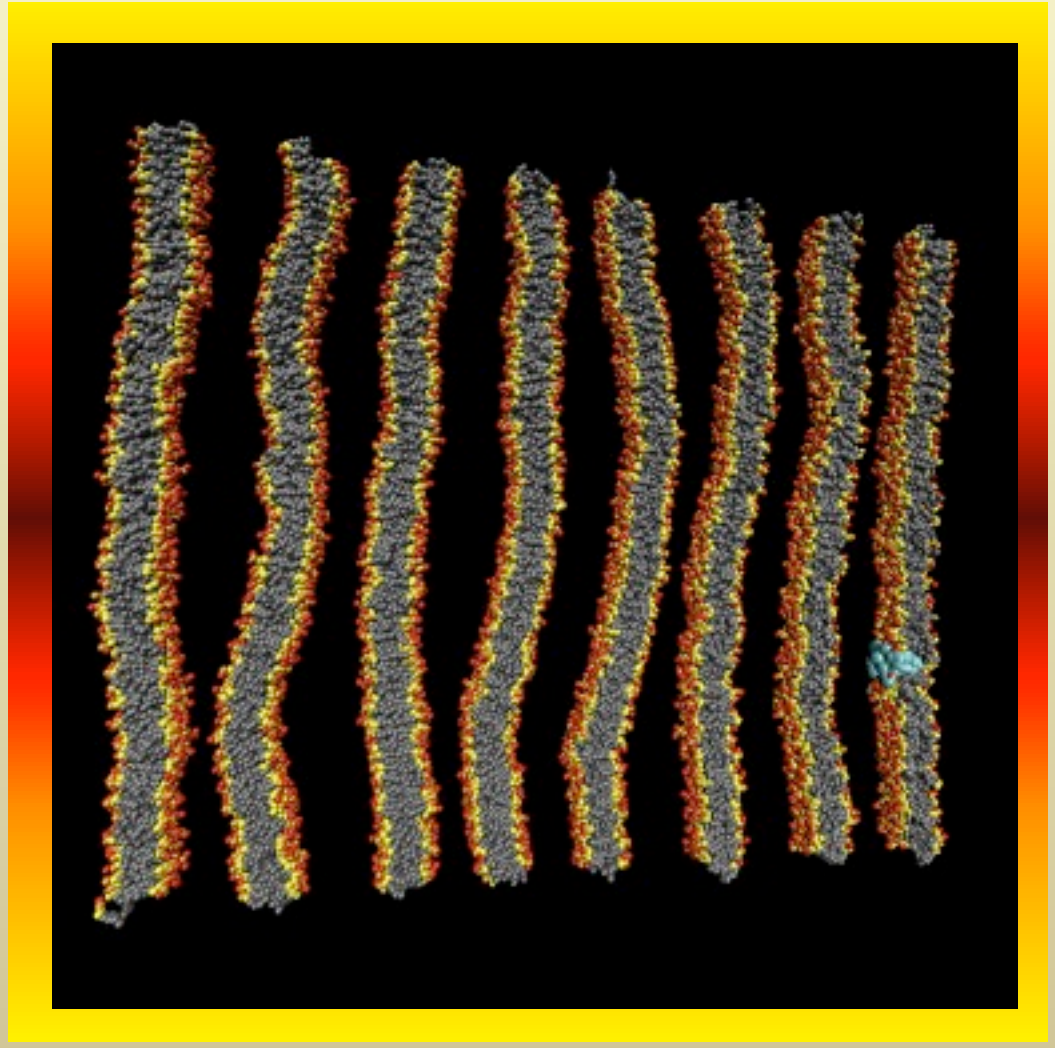
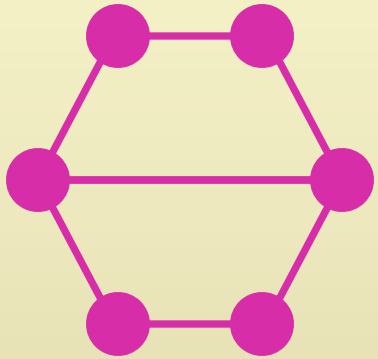


THE VALIDATION

Bilayer properties in semi-quantitative agreement with experiments

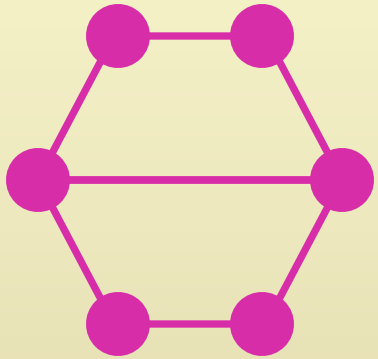
		Martini CG	Experimental
Structural			
	Area/lipid (nm^2)		
	DPPC	0.66	0.64
	DPPE	0.62	0.60
	DSPC	0.66	0.65
Elastic			
	Bending rigidity (J)	8×10^{-20}	6×10^{-20}
	Area compress. ($mN\ m^{-1}$)	260	230
Thermodynamical			
	Phase transition T (K)	300	315
	Line tension (pN)	30	10-20
Dynamical			
	Lipid diffusion coeff. ($cm^2\ s^{-1}$)	2.5×10^{-7}	10^{-7}-10^{-8}
	Water permeation rate ($cm\ s^{-1}$)	1.5×10^{-3}	~ 10^{-3}

LORD OF THE RINGS



LORD OF THE RINGS

Rings: Four-to-one mapping inadequate



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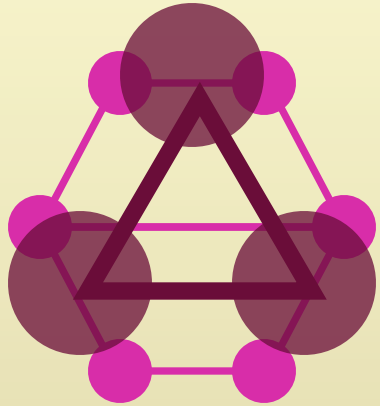
- Two/three-to-one mapping



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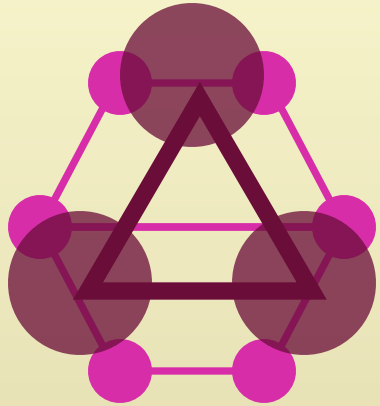

- Two/three-to-one mapping
- Reduction of interaction size and strength

$$\sigma = 0.7 * \sigma_{standard}$$

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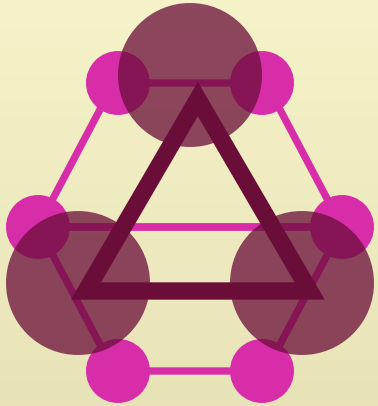

- Two/three-to-one mapping
- Reduction of interaction size and strength

$$\sigma = 0.7 * \sigma_{standard}$$
$$\varepsilon = 0.75 * \varepsilon_{standard}$$

- Reproduction of
  liquid densities & partitioning free energies

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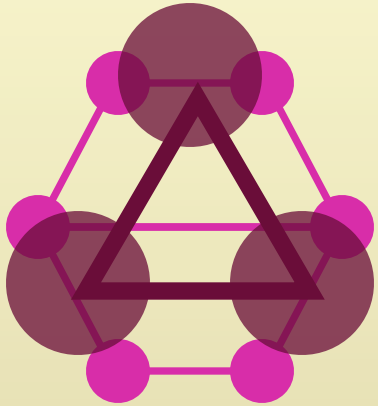

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- Reproduction of
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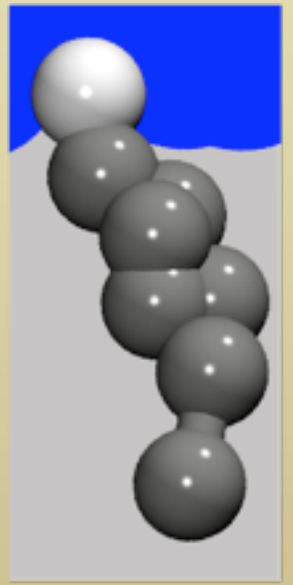
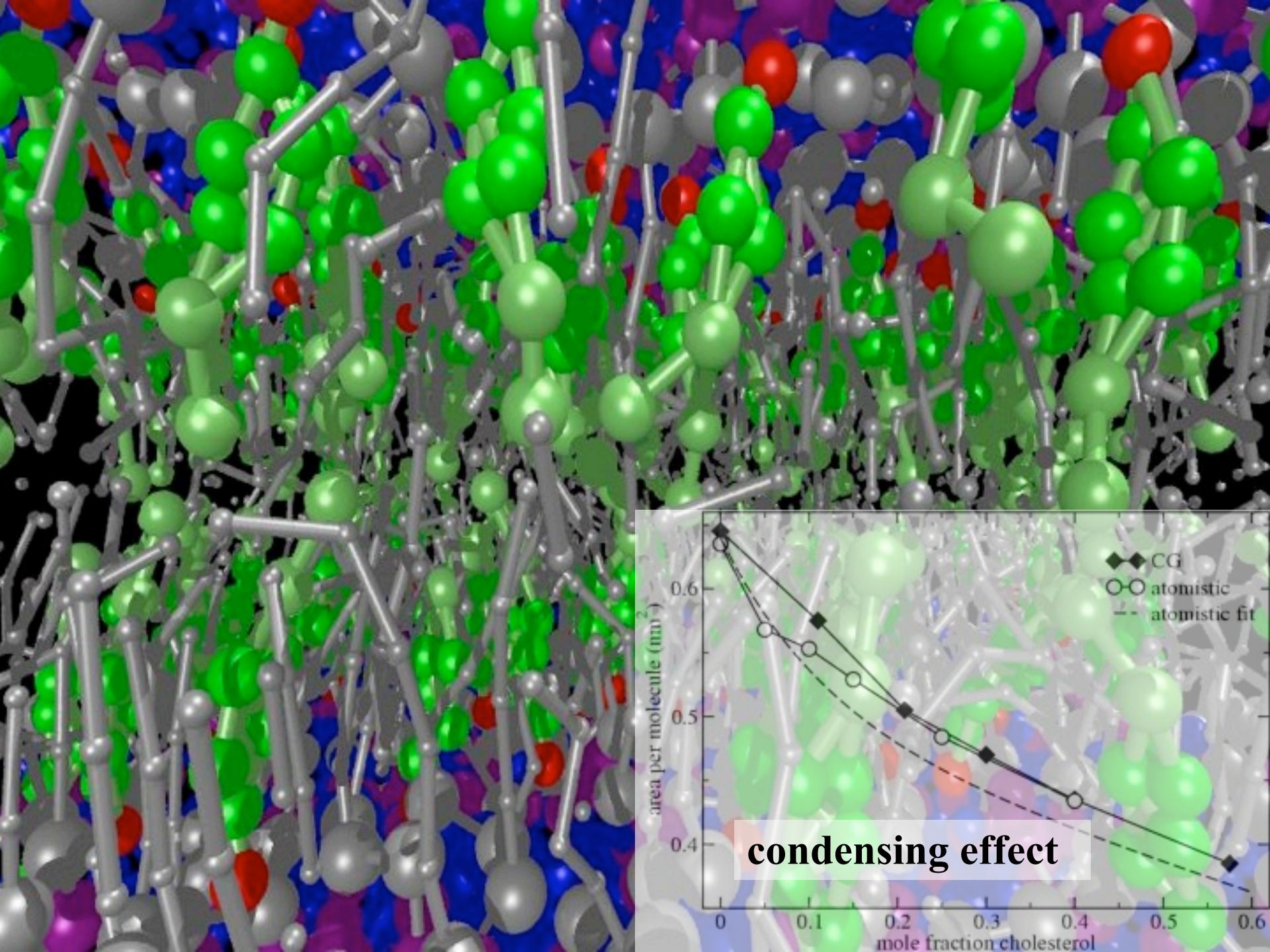
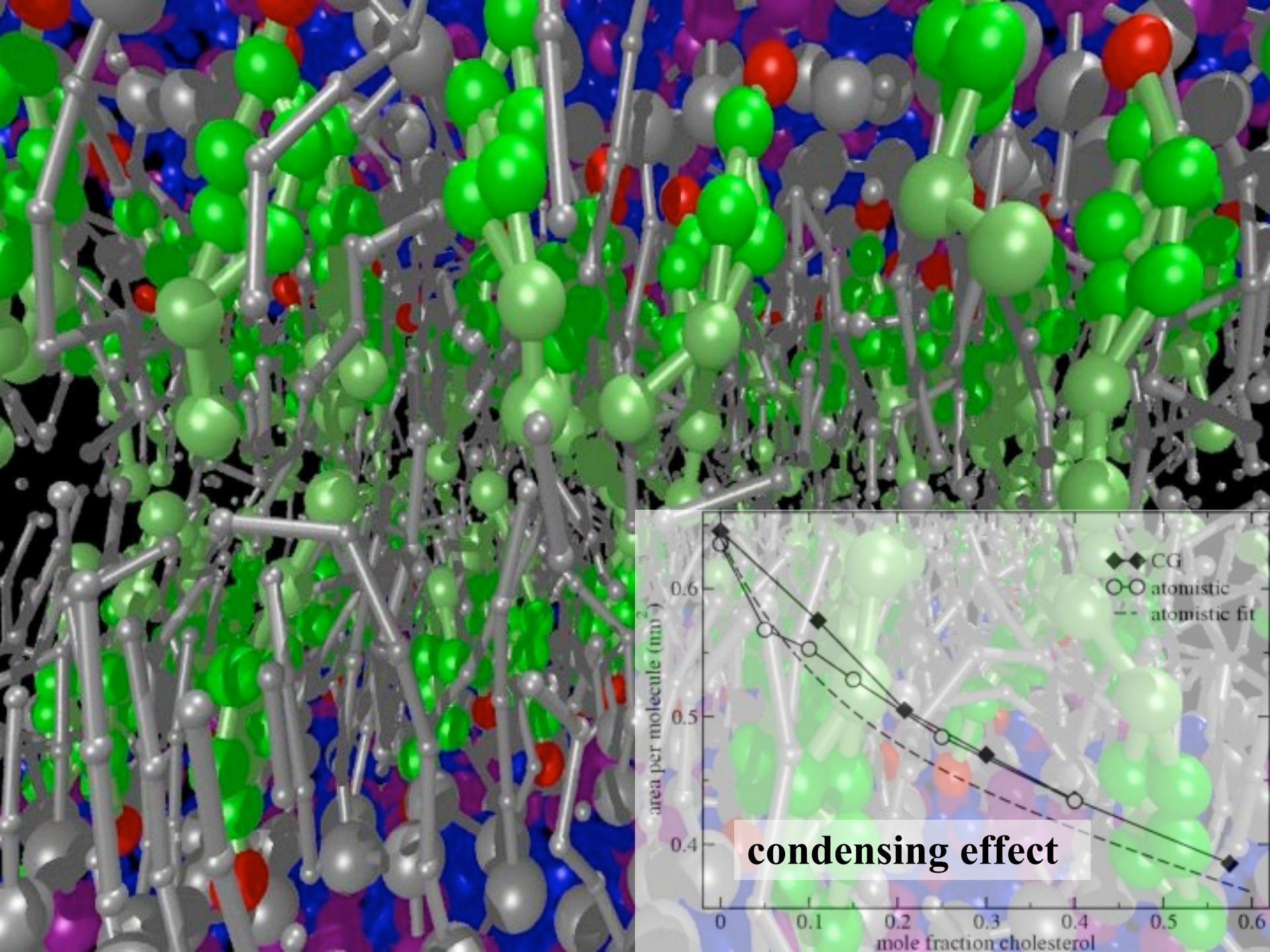
  for benzene and cyclohexane
- Behavior of cholesterol in membranes




CG
atomistic
atomistic fit
area per molecule (nm^2)
0.6
0.5
0.4
0
0.1
0.2
0.3
0.4
0.5
0.6
mole fraction cholesterol
condensing effect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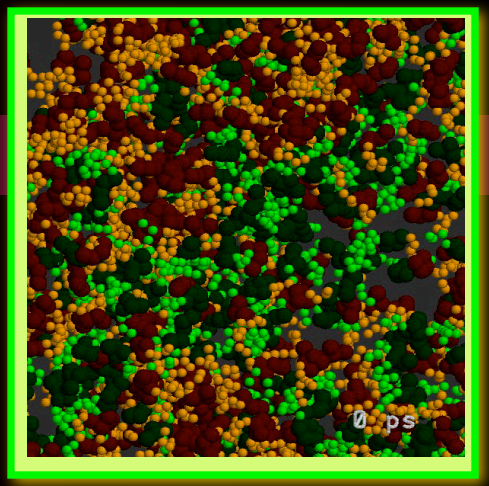
The art of liposome modeling

How to simulate lipid vesicles?

The art of liposome modeling

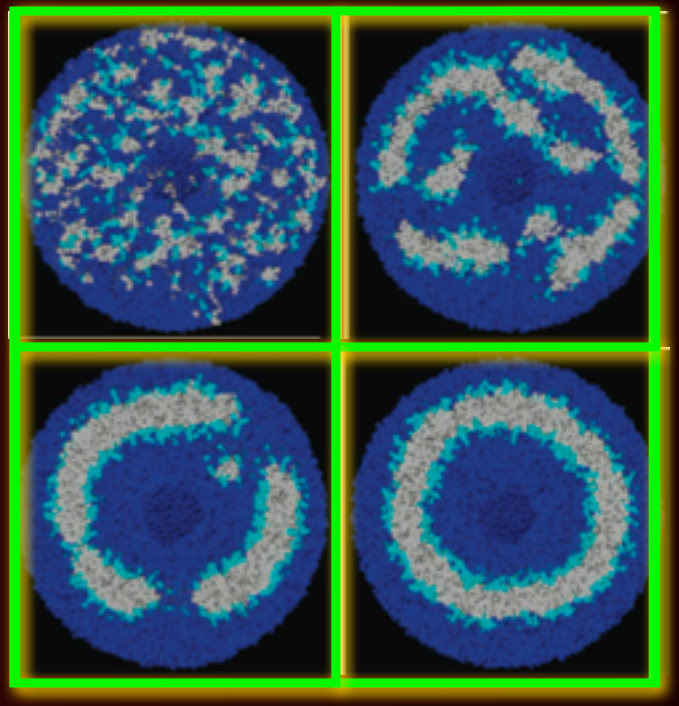
How to simulate lipid vesicles?

Vesicle self-assembly



The art of liposome modeling

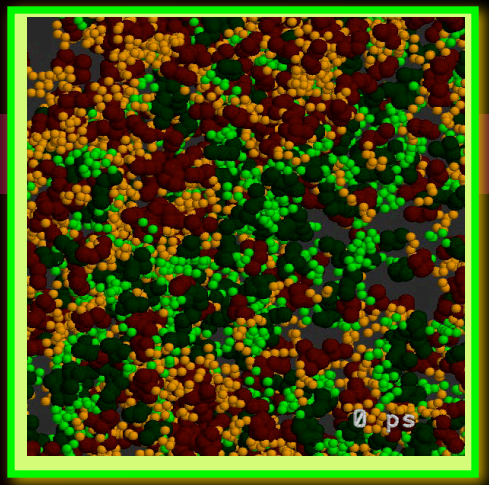
How to simulate lipid vesicles?



Vesicle self-assembly

Mean field potentials save time ...

Risselada & Marrink, JPC-B (2008)



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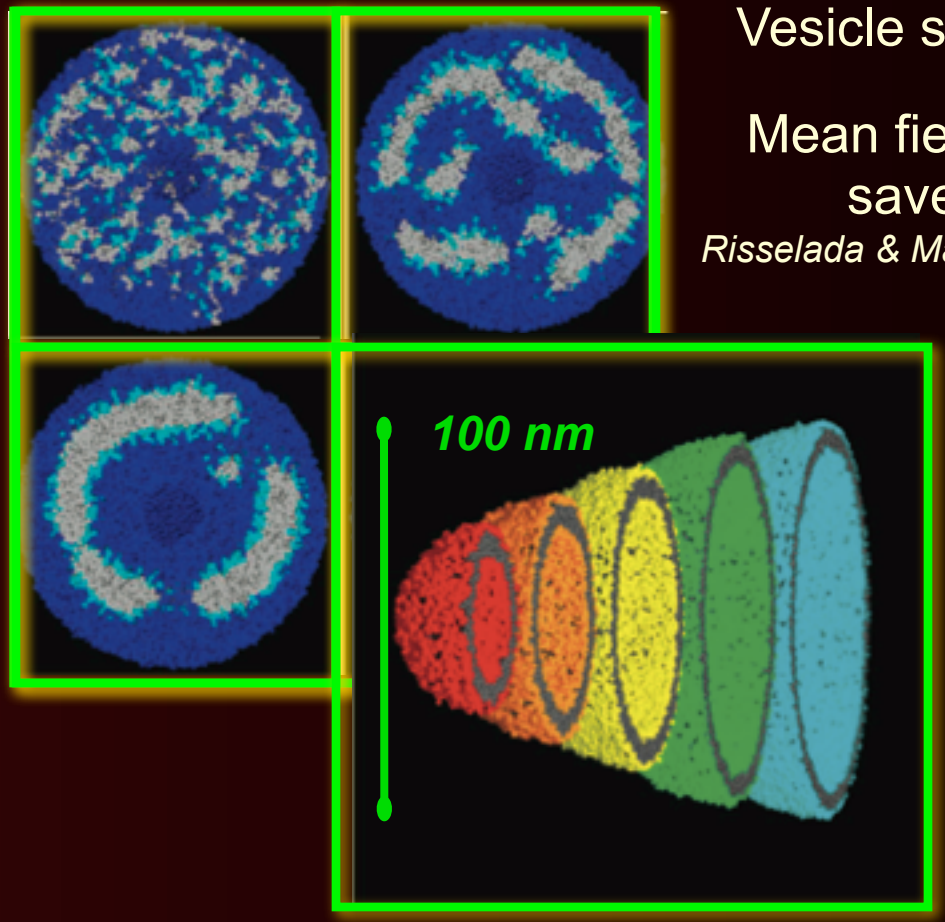

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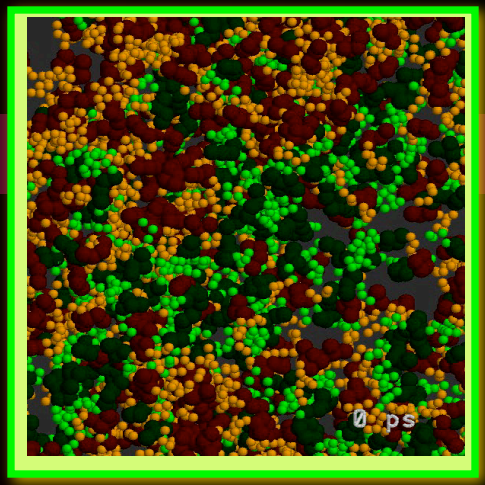
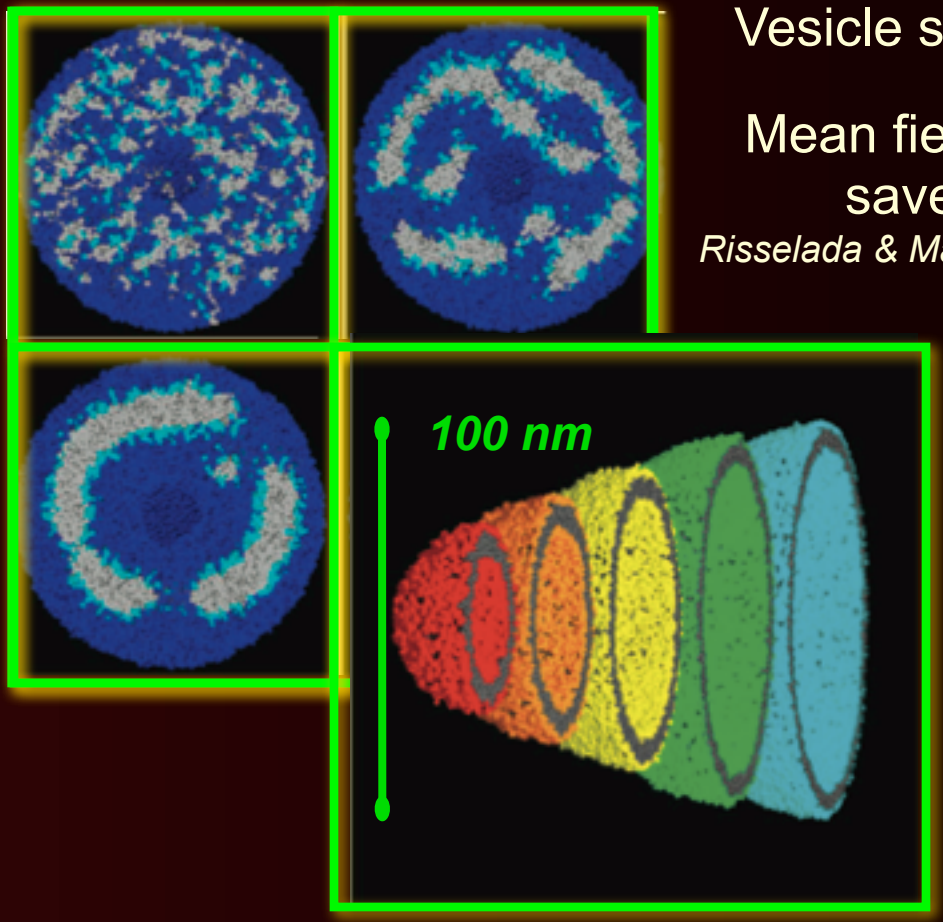


The art of liposome modeling

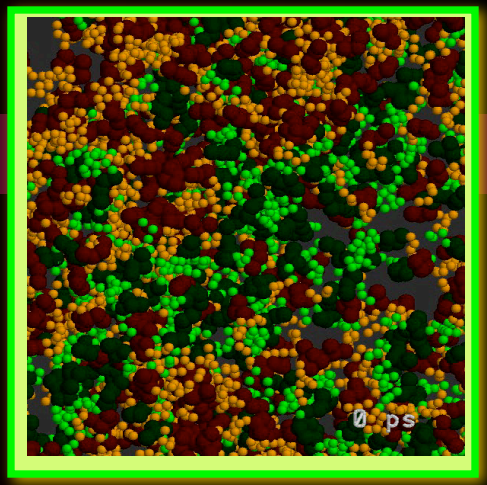
How to simulate lipid vesicles?



Vesicle self-assembly

Mean field potentials save time ...

Risselada & Marrink, JPC-B (2008)



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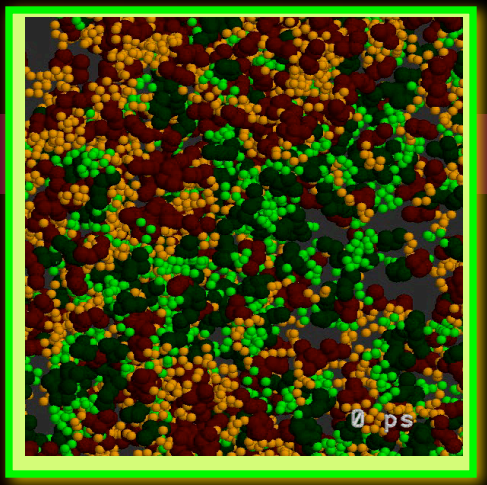

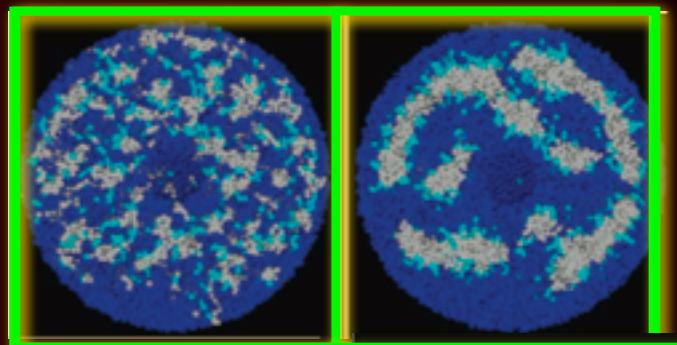

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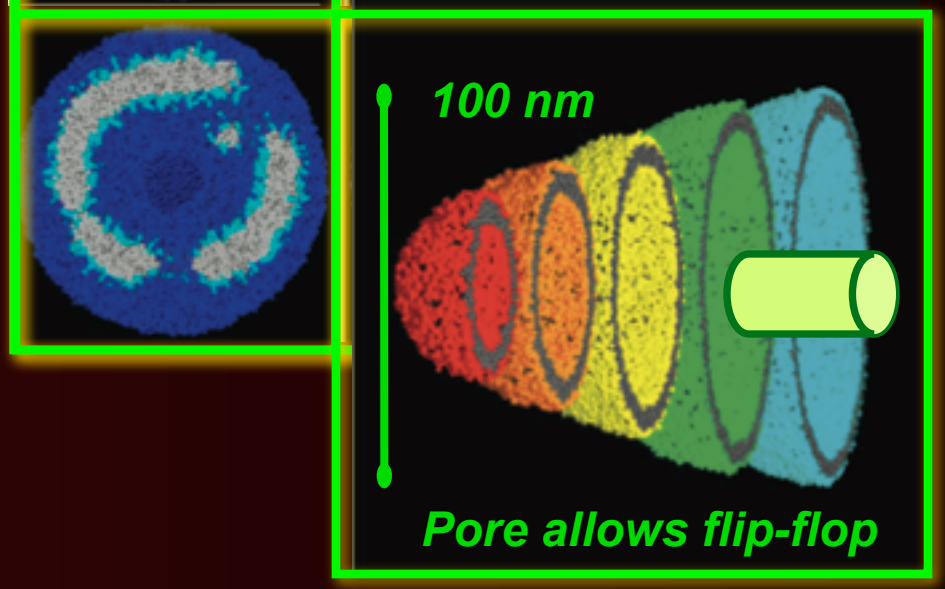

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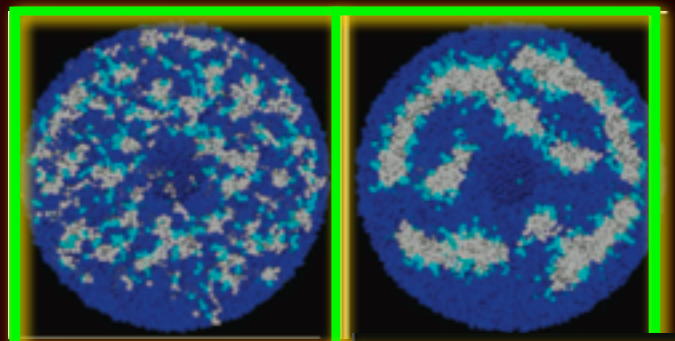

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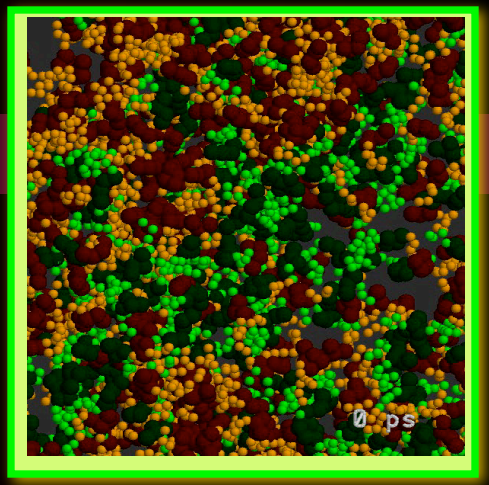

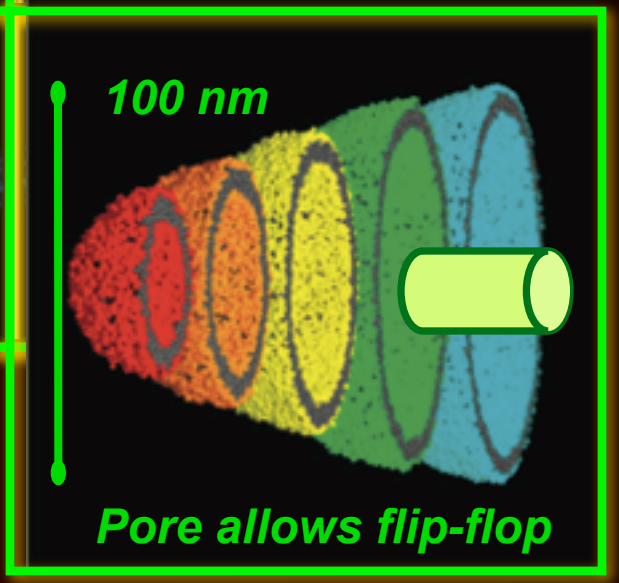

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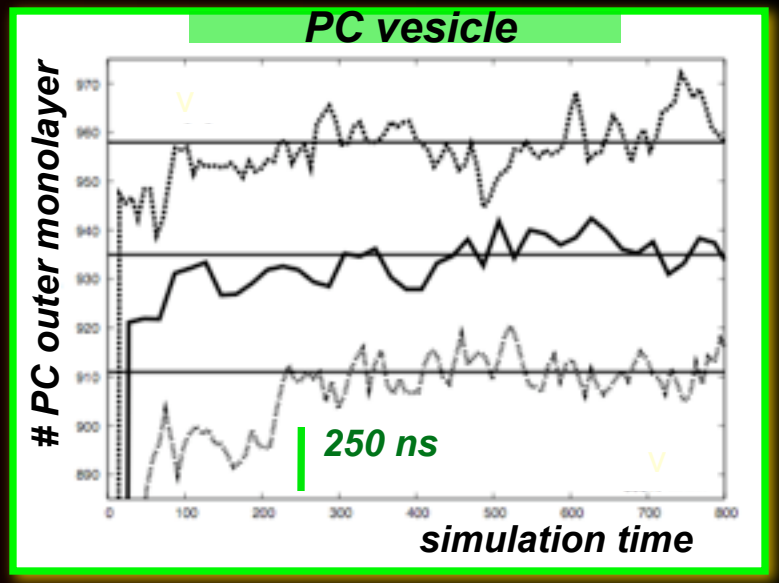

No! Equilibration takes 100s of ns

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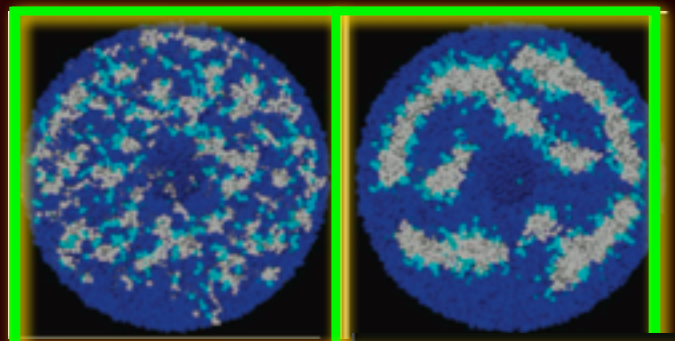

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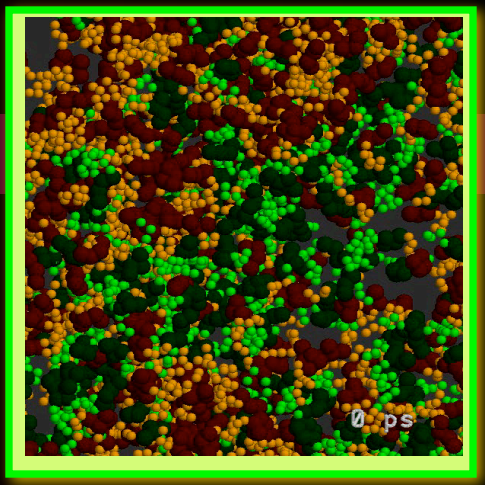

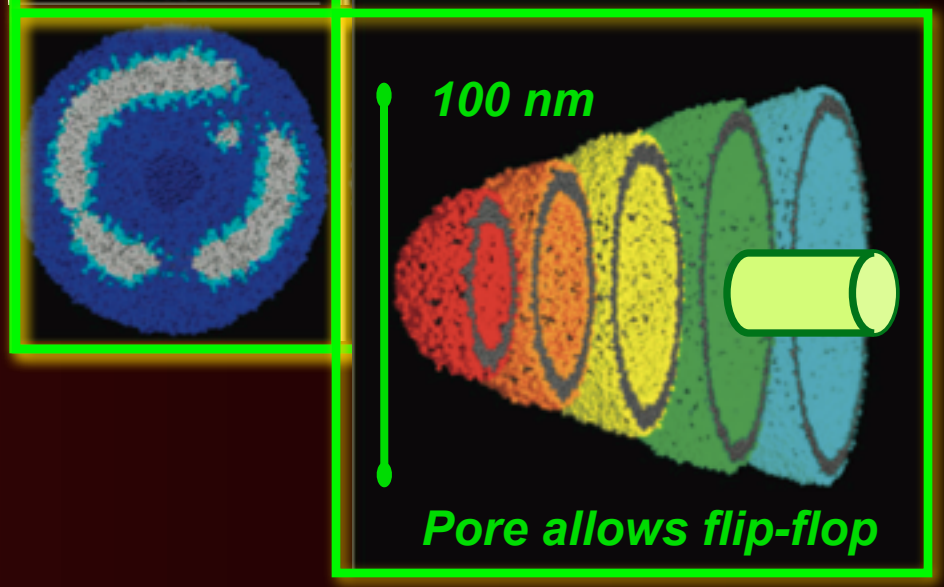

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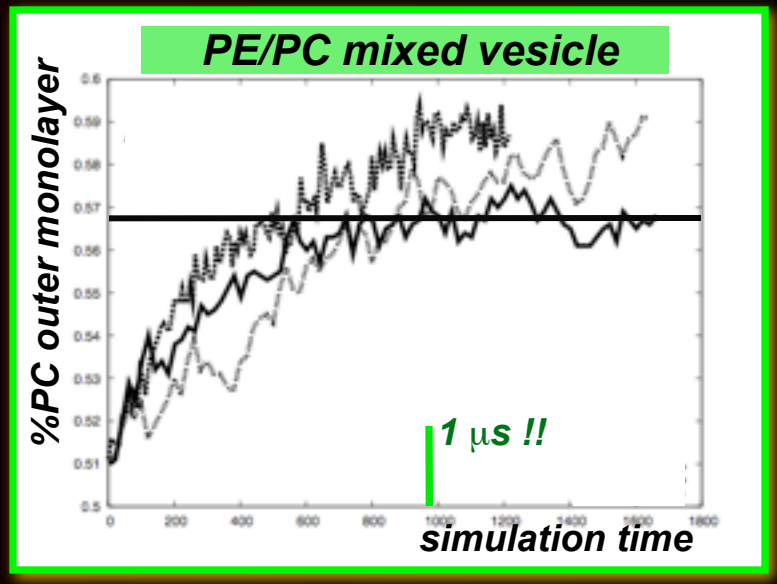

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The Martini forcefield

What you can do and what you should be careful of

DO's **(but be careful)**

DO-NOTs **(or be very careful)**

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(undulations, flip-flops)

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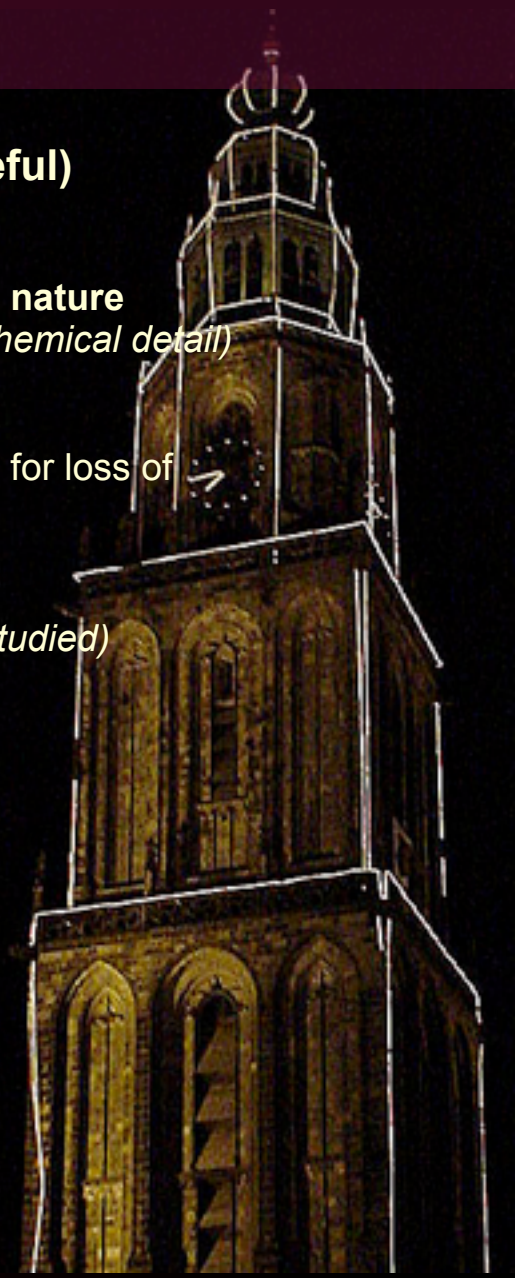

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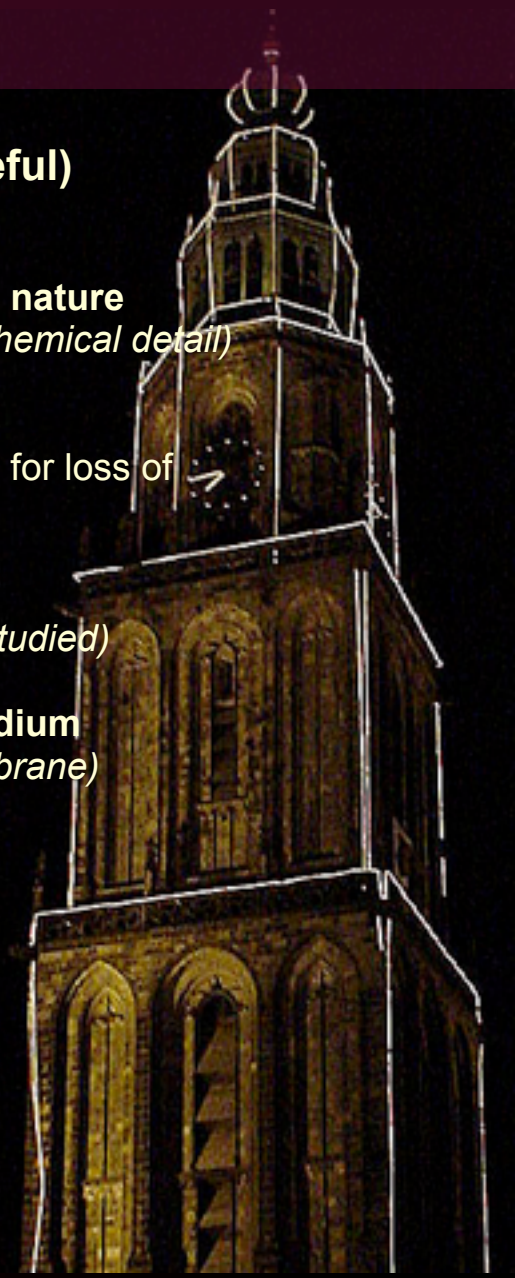

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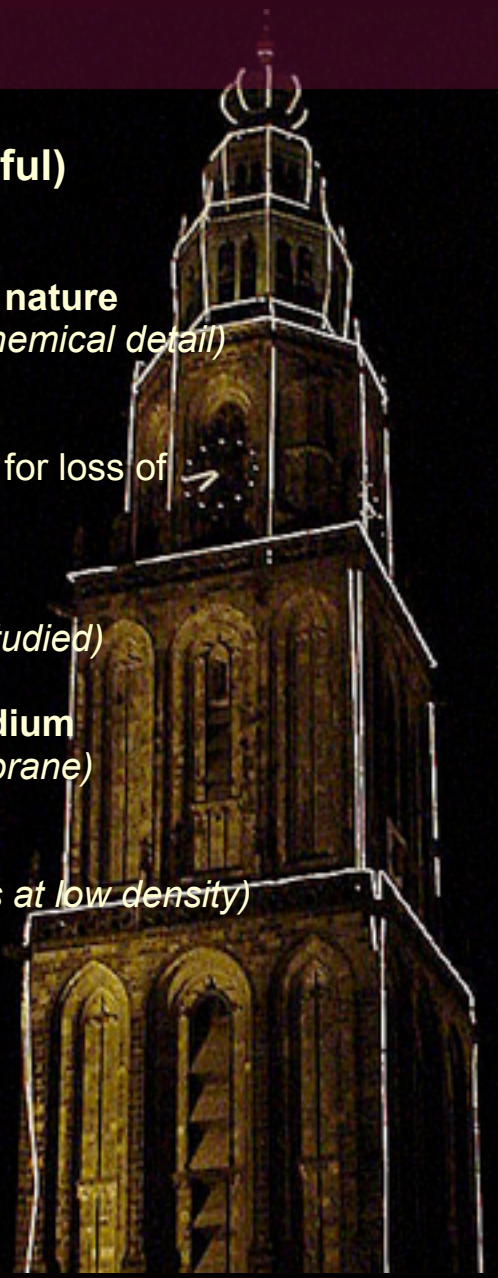

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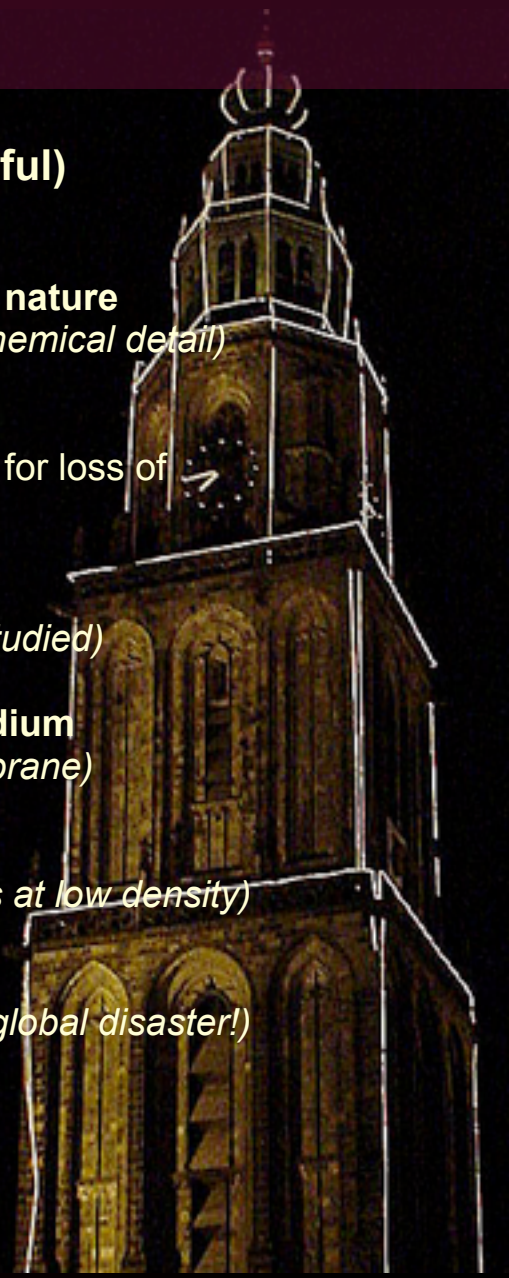

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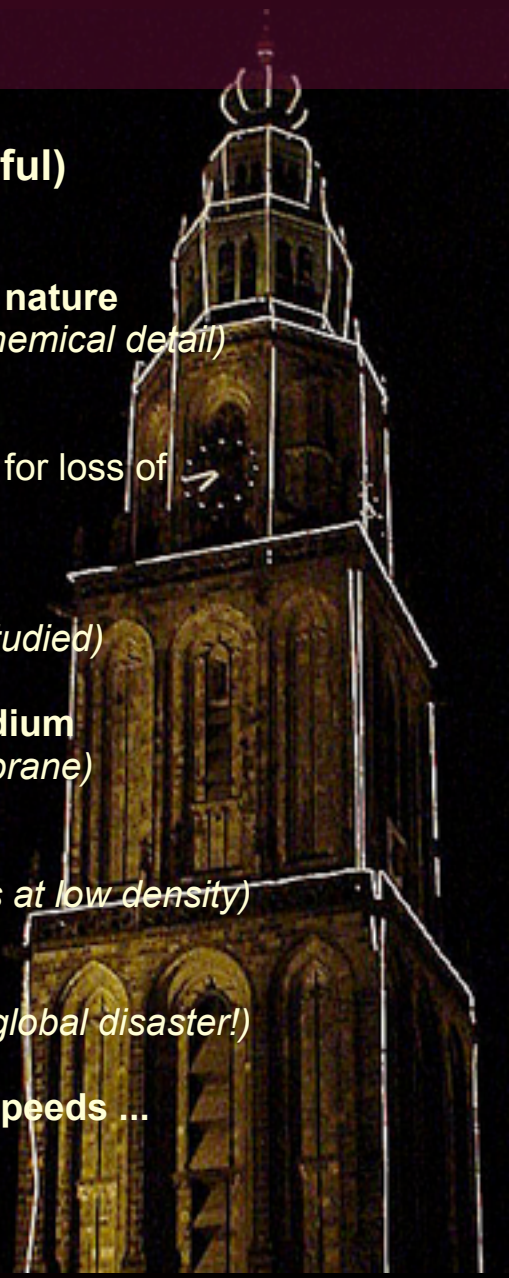
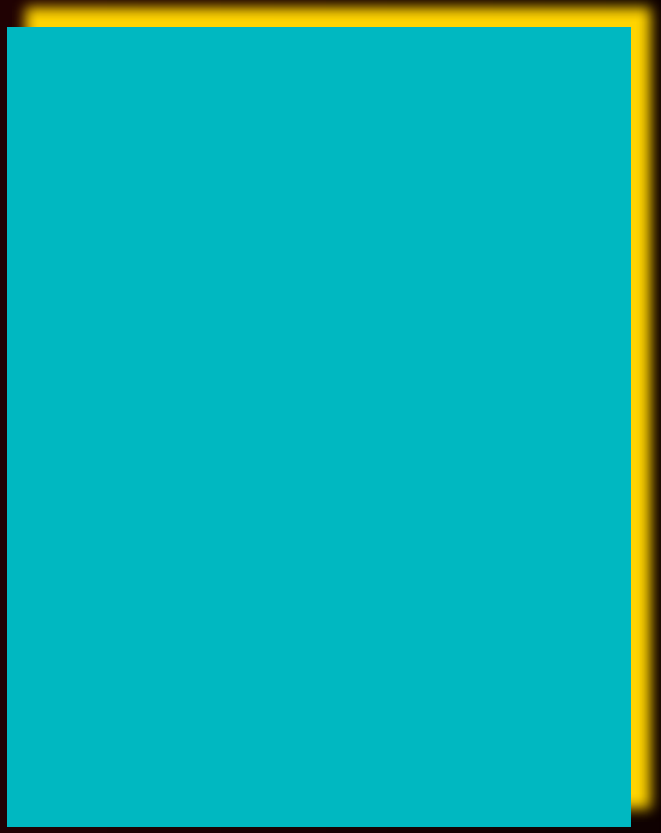
Applications using relativistic speeds ...





Don’t try this at home:
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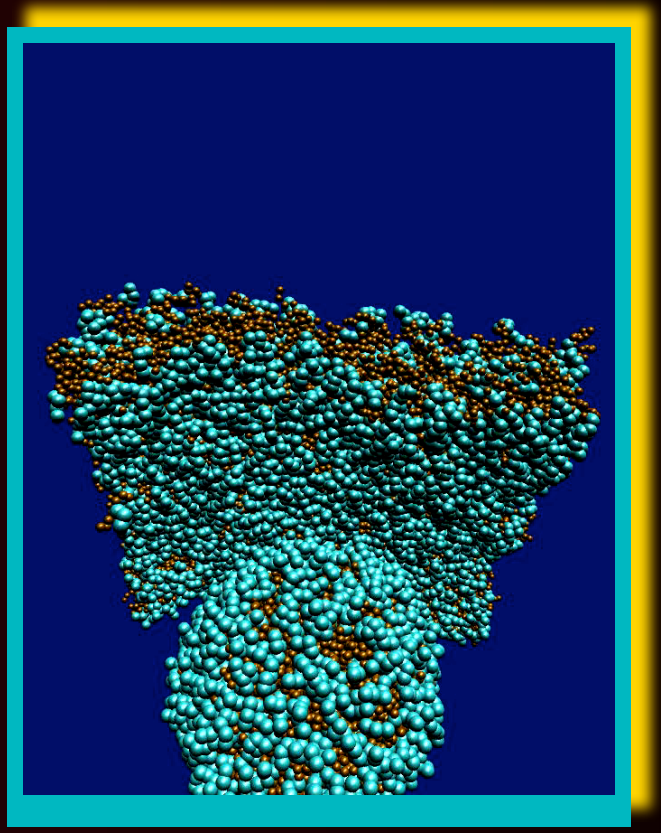

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