Lateral Organization in Mixed Lipid Bilayers: Atomistic and Coarse-grained Simulation

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Topics

- Atomistic simulations of binary and ternary mixtures of DOPC, Sphingomyelin and Cholesterol
- Mean field-based Langevin Dynamics: A coarse-grained approach

Gandhavadi et al, BJ 82, 1469 (2002)

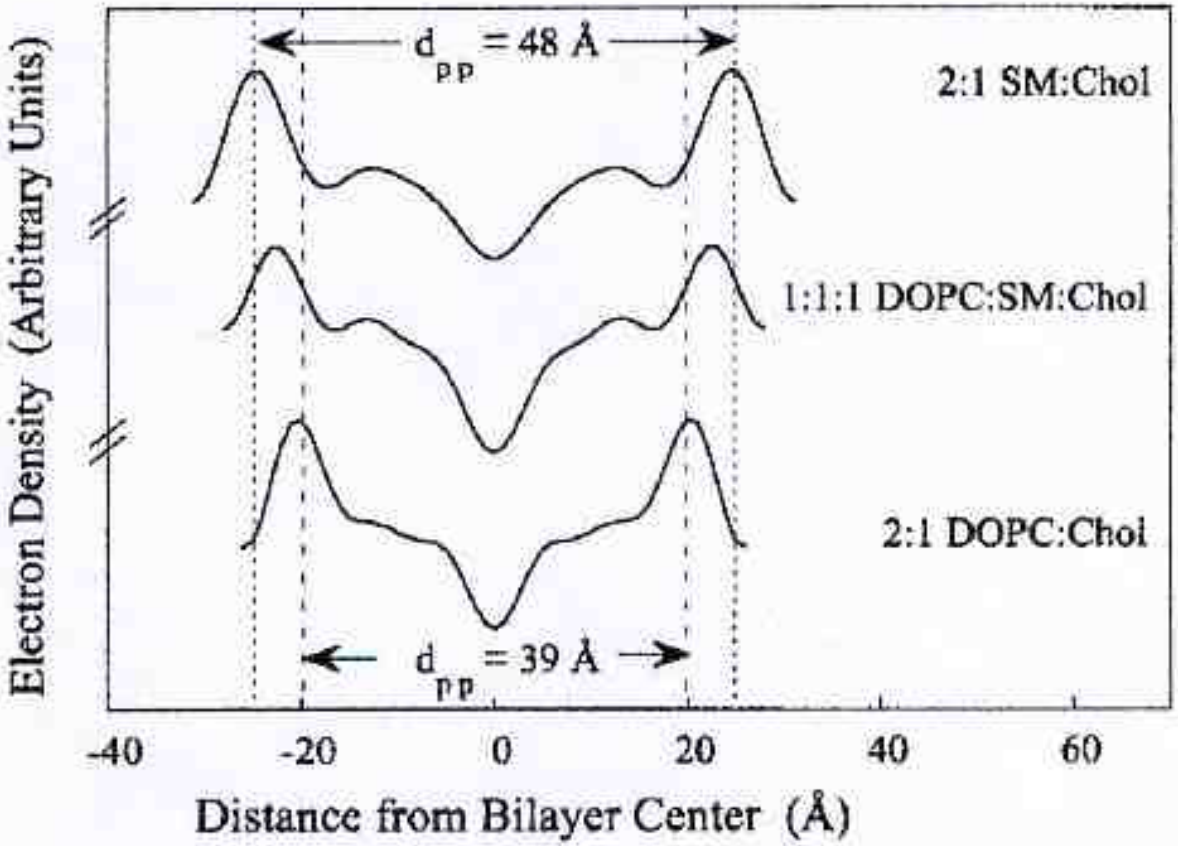
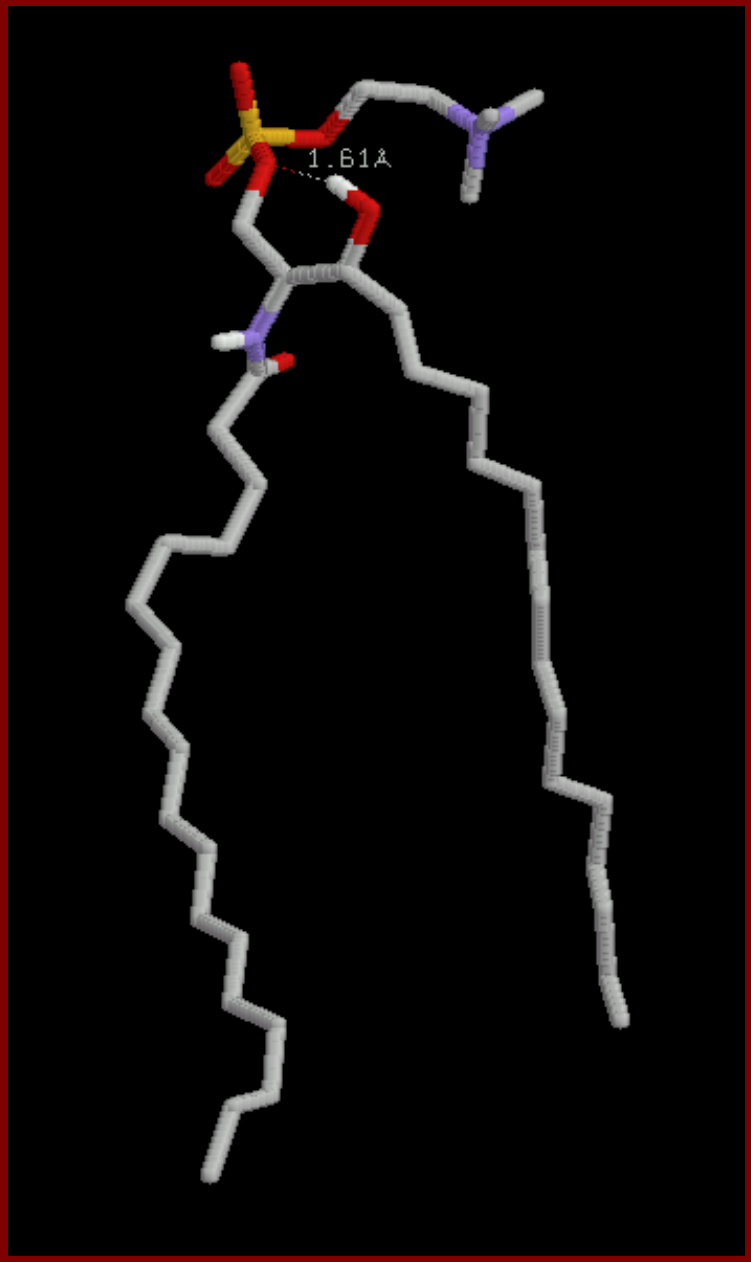


FIGURE 7 Electron density profiles (resolution of $d/2h_{max} \approx 4.5$ Å) for 2:1 SM:cholesterol, 1:1:1 DOPC:SM:cholesterol, and 2:1 DOPC:cholesterol. For each profile, the center of the bilayer is at the origin and the high-density peaks correspond to the lipid head groups. The headgroup peaks are noted with vertical dotted lines for 2:1 SM:cholesterol and with dashed lines for 2:1 DOPC:cholesterol.

Unique properties of SM from simulation

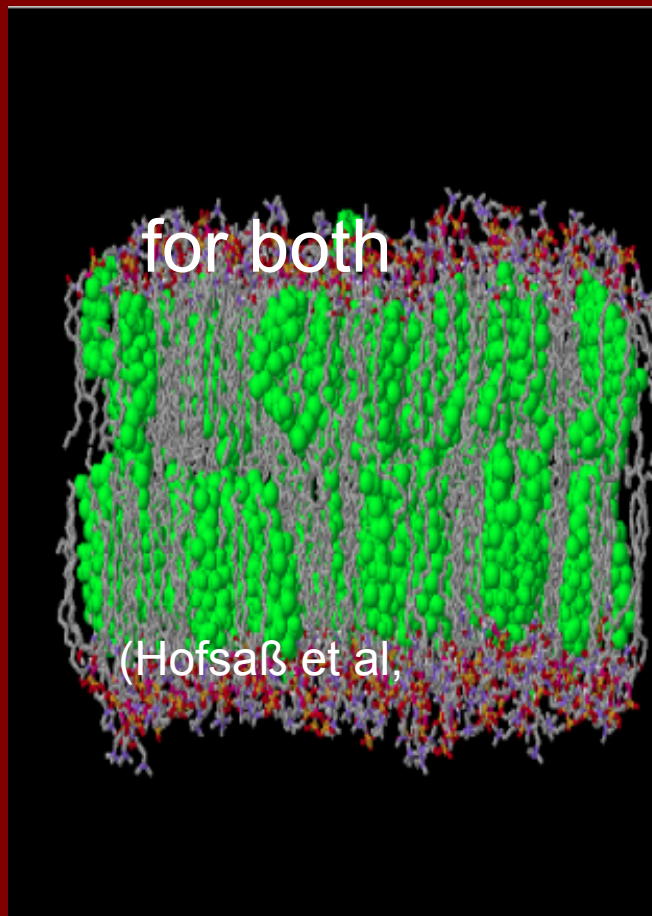
- Area/ molecule 52.7 A^2
- high degree of order @
- intra-molecular hydrogen bonding
- decreased hydration of region (vs DPPC)
- ~8 x larger bending DPPC

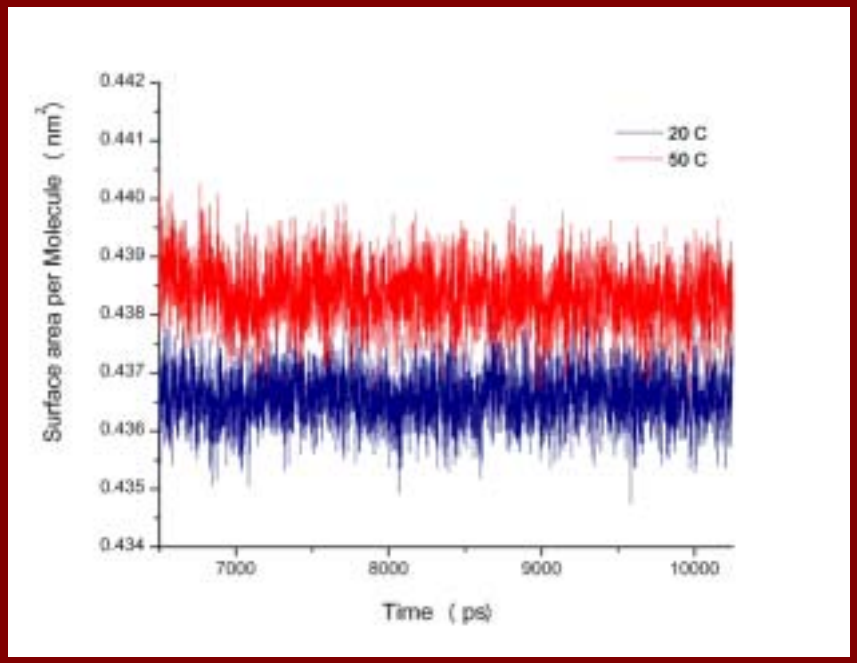


Simulation studies of lipid-cholesterol binary mixtures: 18:0 SM-Cholesterol

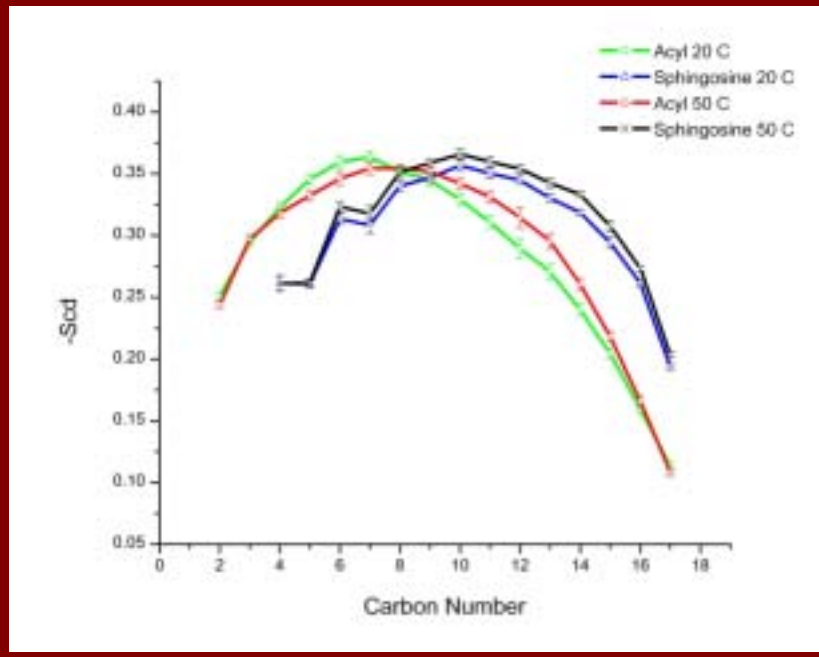
- 266 18:0 SM, 122 Chol, 11,861 waters
- 10 ns runs @ 20 C and 50 C
- Area per molecule ~ 43.8 A^2 for both temperatures
- Area per SM: 51.3 A^2
- Area per Chol: 27.2 A^2

(Hofsaß et al, BJ 84, 2192)



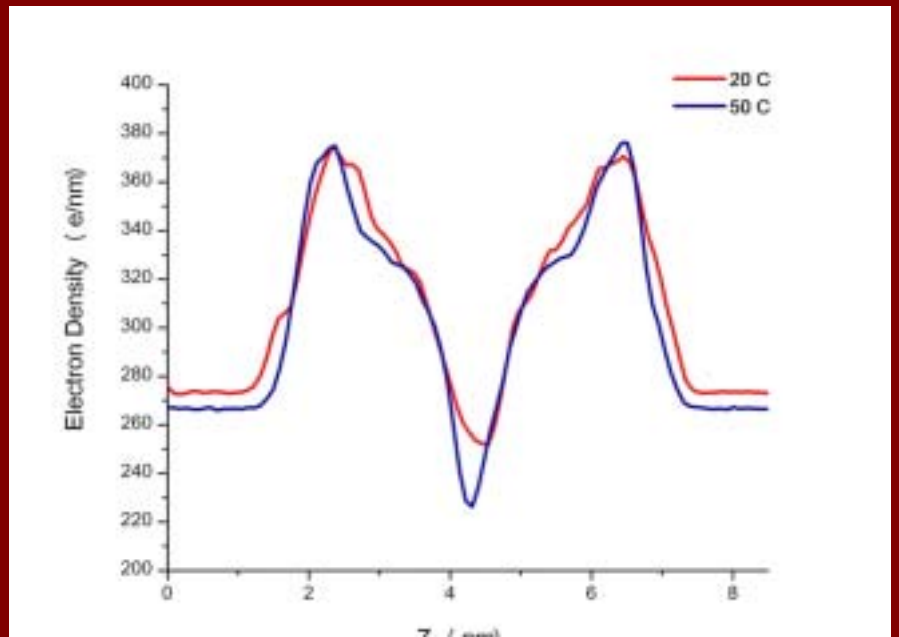


area per molecule



order parameter profiles

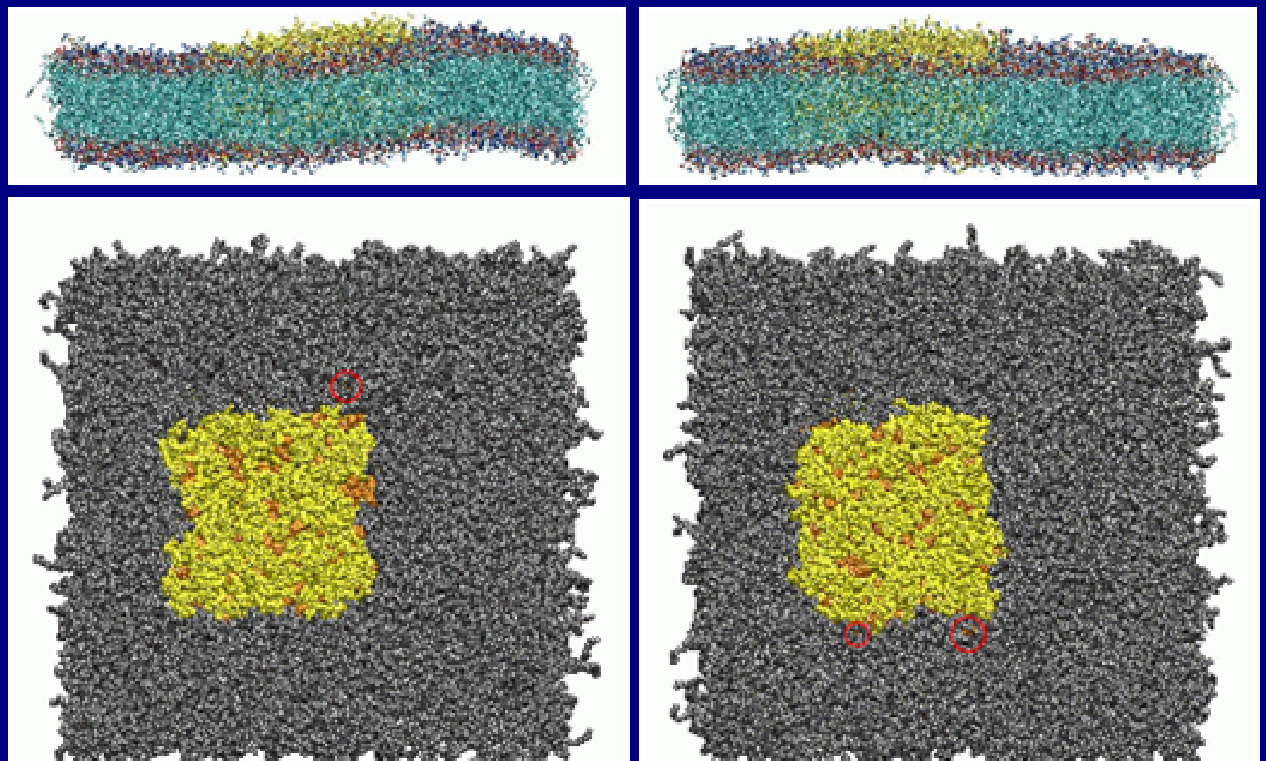
electron density profiles



peak-to-peak ~ 41 A

Ternary mixture with pre-formed aggregate

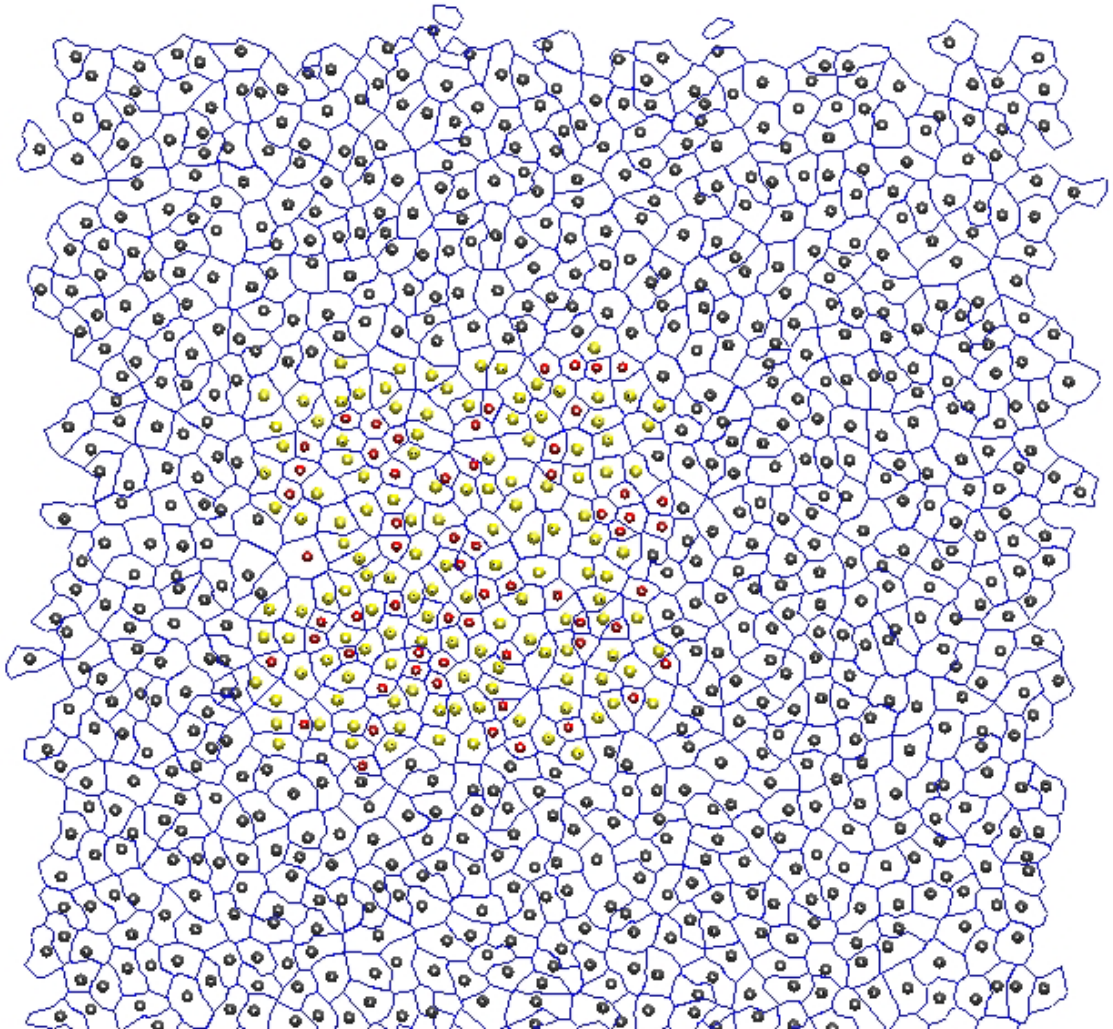
- System: 1424 DOPC, 266 18:0 Sm, 122 CHOL @ 293 K
- total simulation: 20 ns (12 ns equilibration, 8 ns with PME and revised forcefield)



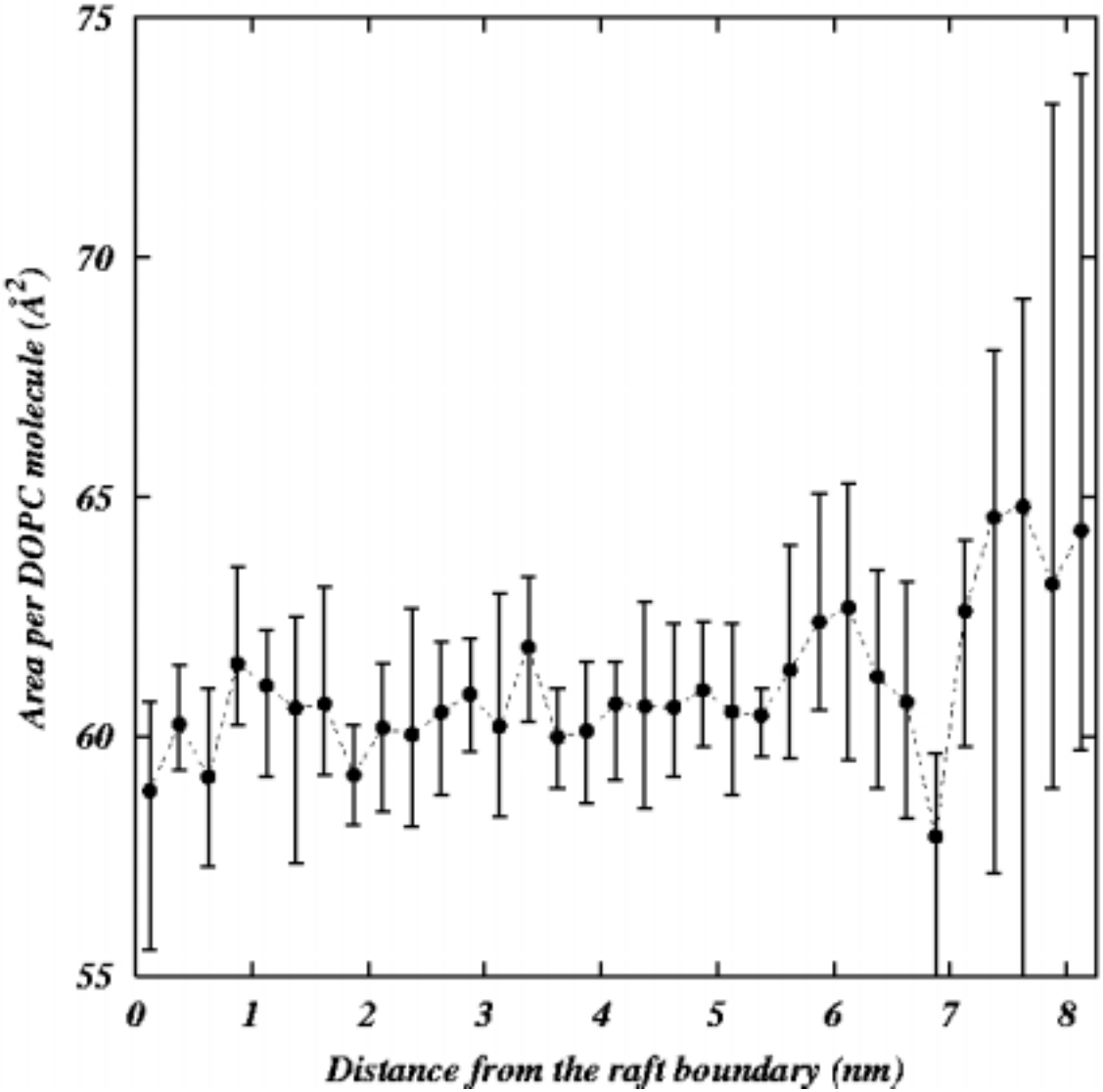
Area per Sphingomyelin: 46.5 A**2 /mol

Area per DOPC: 61.0 A**2 /mol

Area per Cholesterol: 29.6 A**2 /mol



Area/molecule of DOPC vs distance from SM-cholesterol domain



DOPC molecular area affected by the ordered domain out to 8 nm

Summary

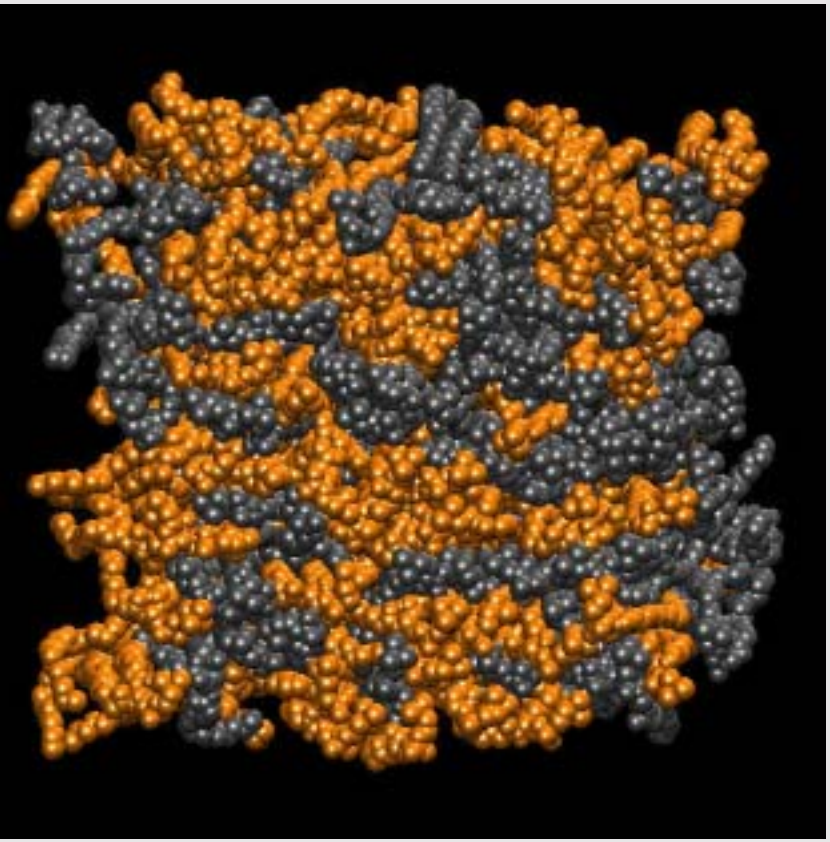
- In ~ 20 ns 3 cholesterols became solvated by DOPC
- No sphingomyelins became solvated by DOPC
- the SM-CHOL domain affects DOPC order over entire simulation box
- thickness profile is consistent with AFM data but less than X-ray data for bovine brain SM

Binary and Ternary mixture simulations starting from random distribution

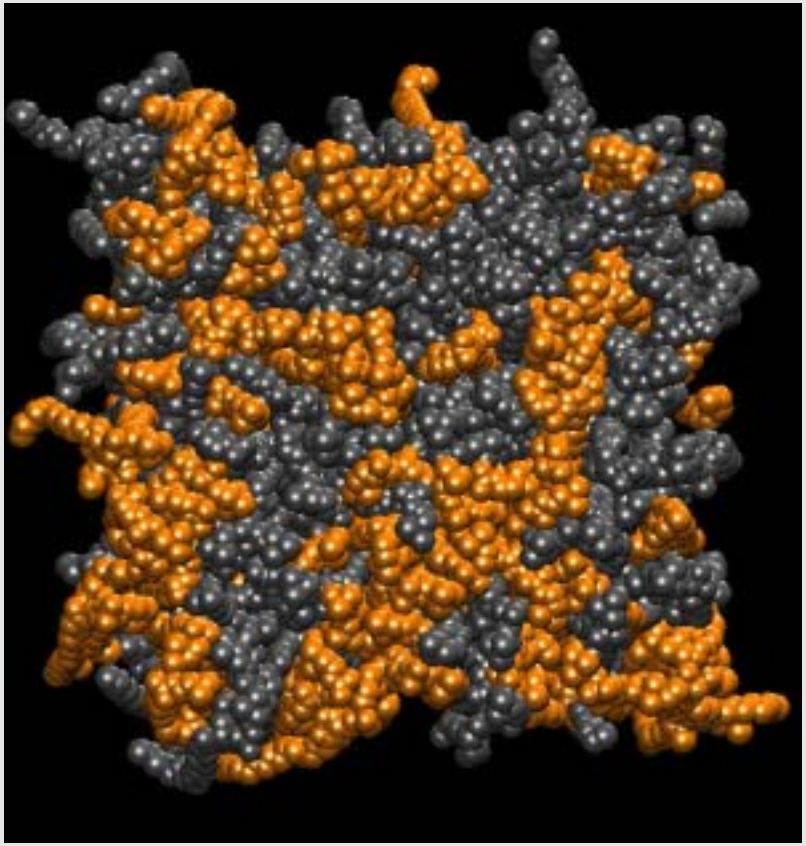
- 1:1 DOPC:SM 200 ns
- 1:1:1 DOPC:SM:CHOL 200 ns
- 4:1:1 DOPC:SM:CHOL 50 ns
- all runs: NPT ensemble; PME for electrostatics w/ 9.5 A cutoff, 18 A cutoff for 6-12's

Binary mixture: 100 DOPC, 100 18:0 SM, 7000 water (31600 atoms)

0 ns

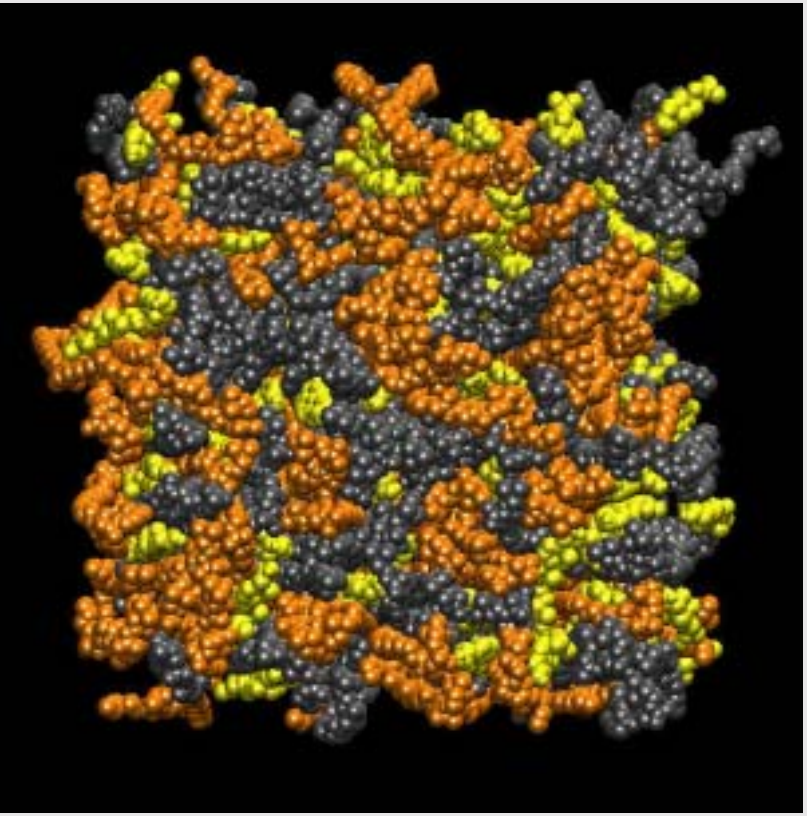


200 ns

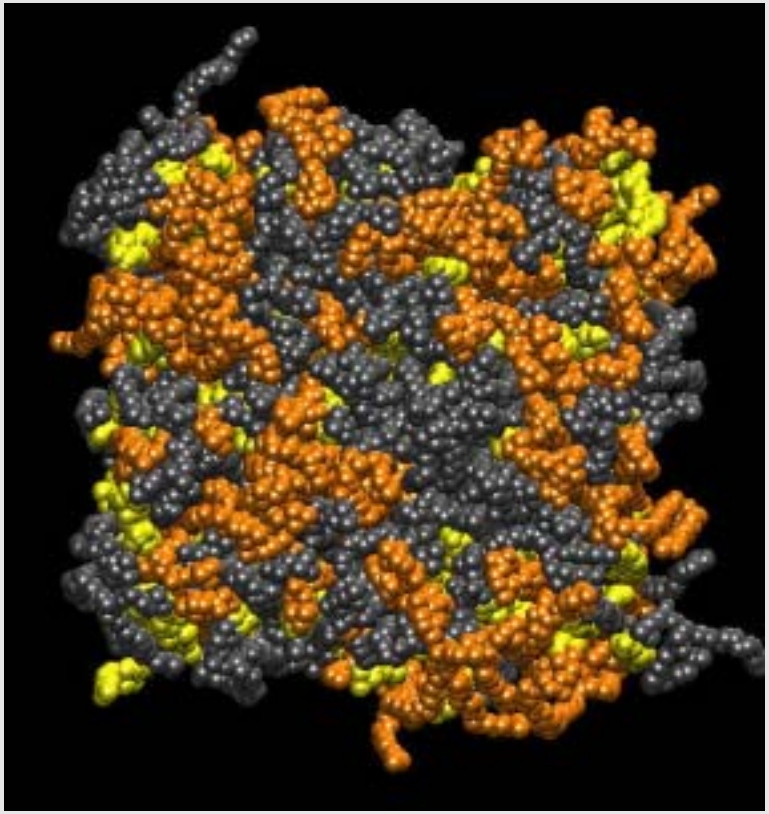


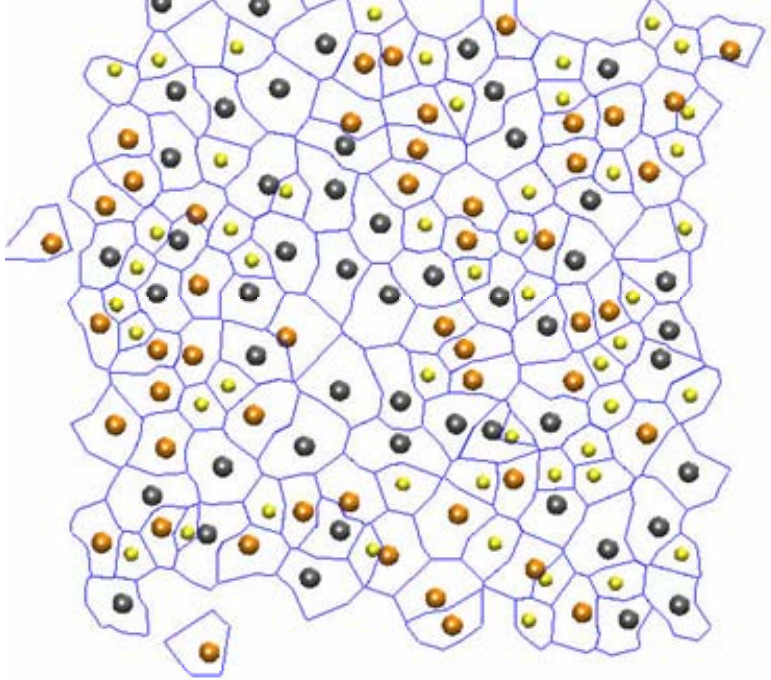
ernary mixture: 100 DOPC, 100 18:0 SM, 100 CHOL, 10000 water (43500 atoms)

0 ns

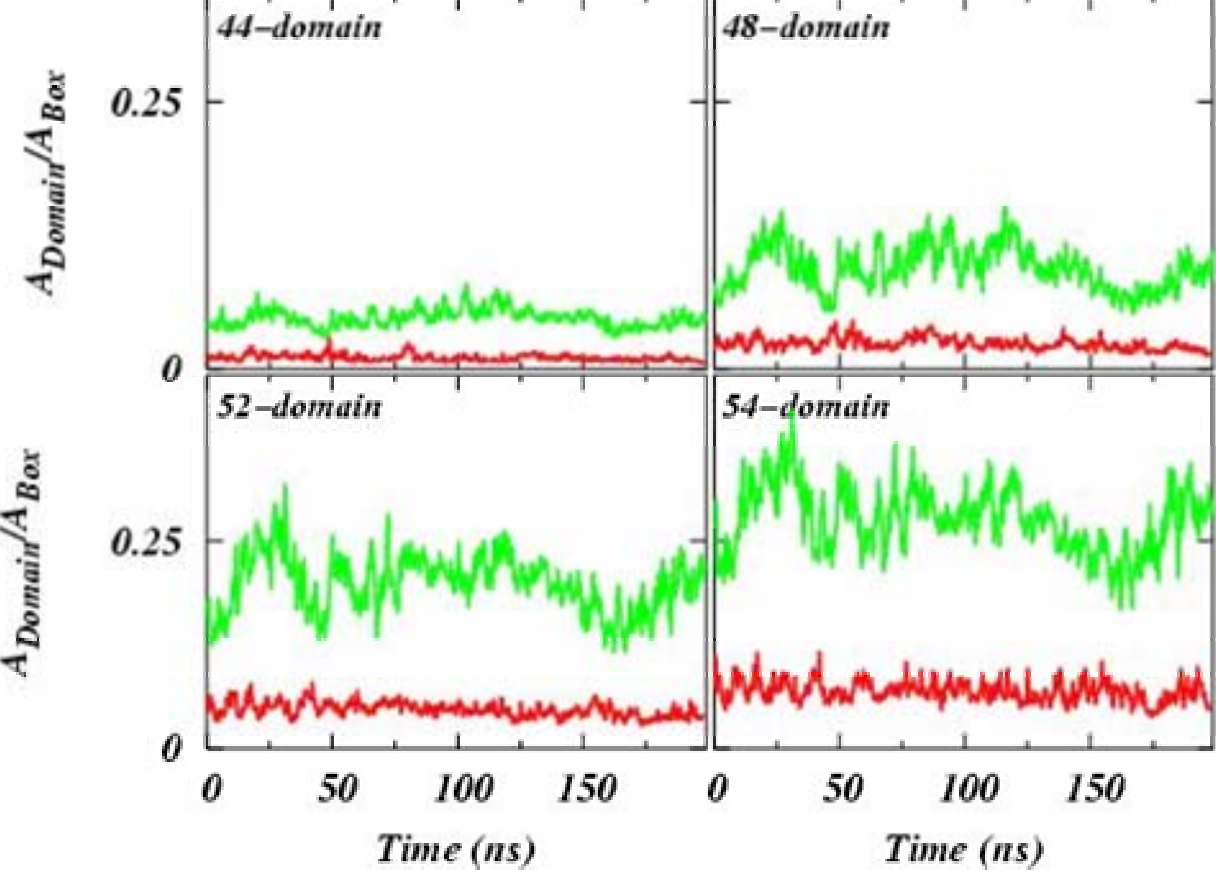


200 ns





Area	Binary Mixture ($Å^2$/molecule)	Ternary Mixture ($Å^2$/molecule)
DOPC	67	69
SM	54	53
CHOL	-	29

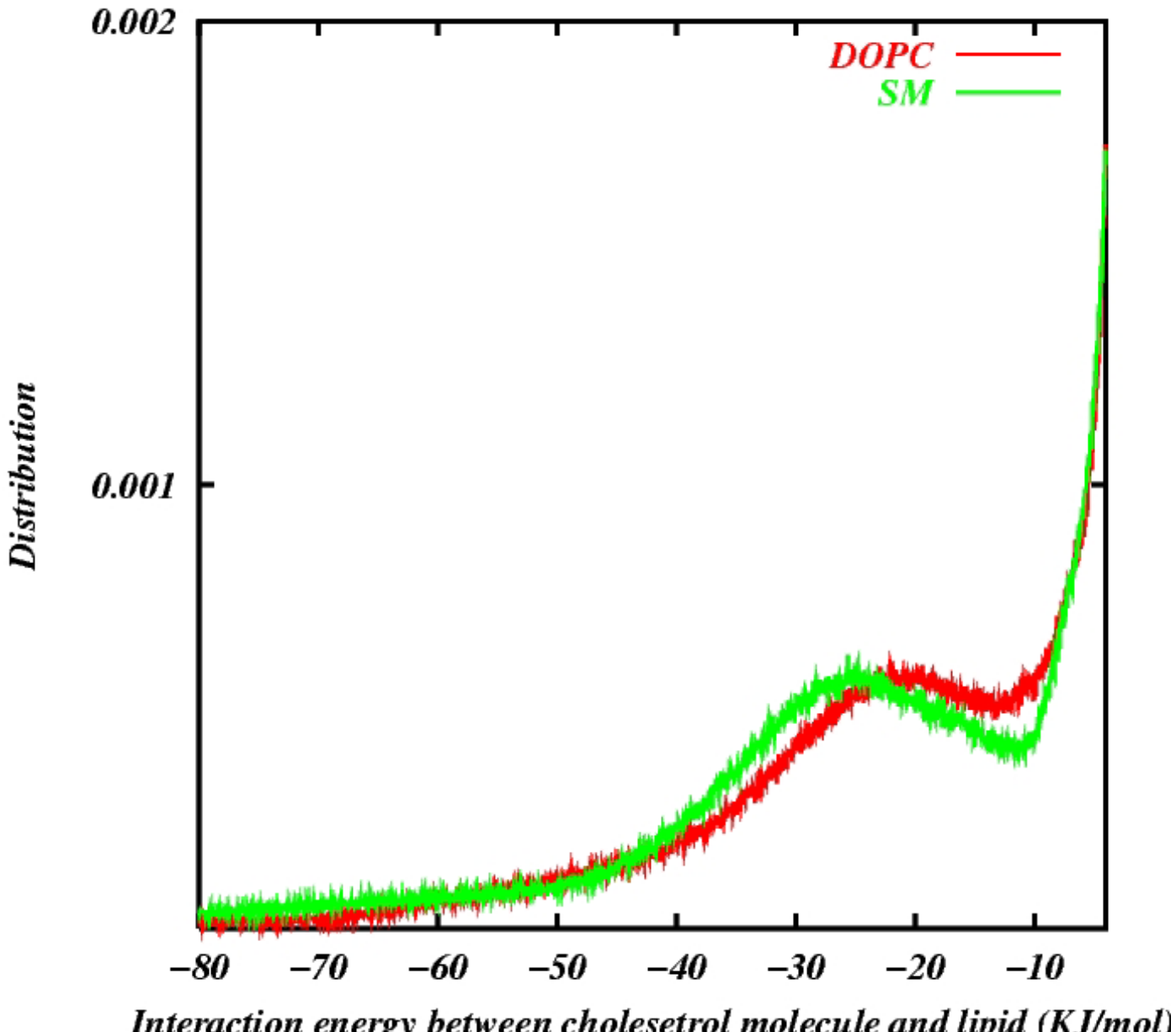


green: DOPC-SM-CHOL

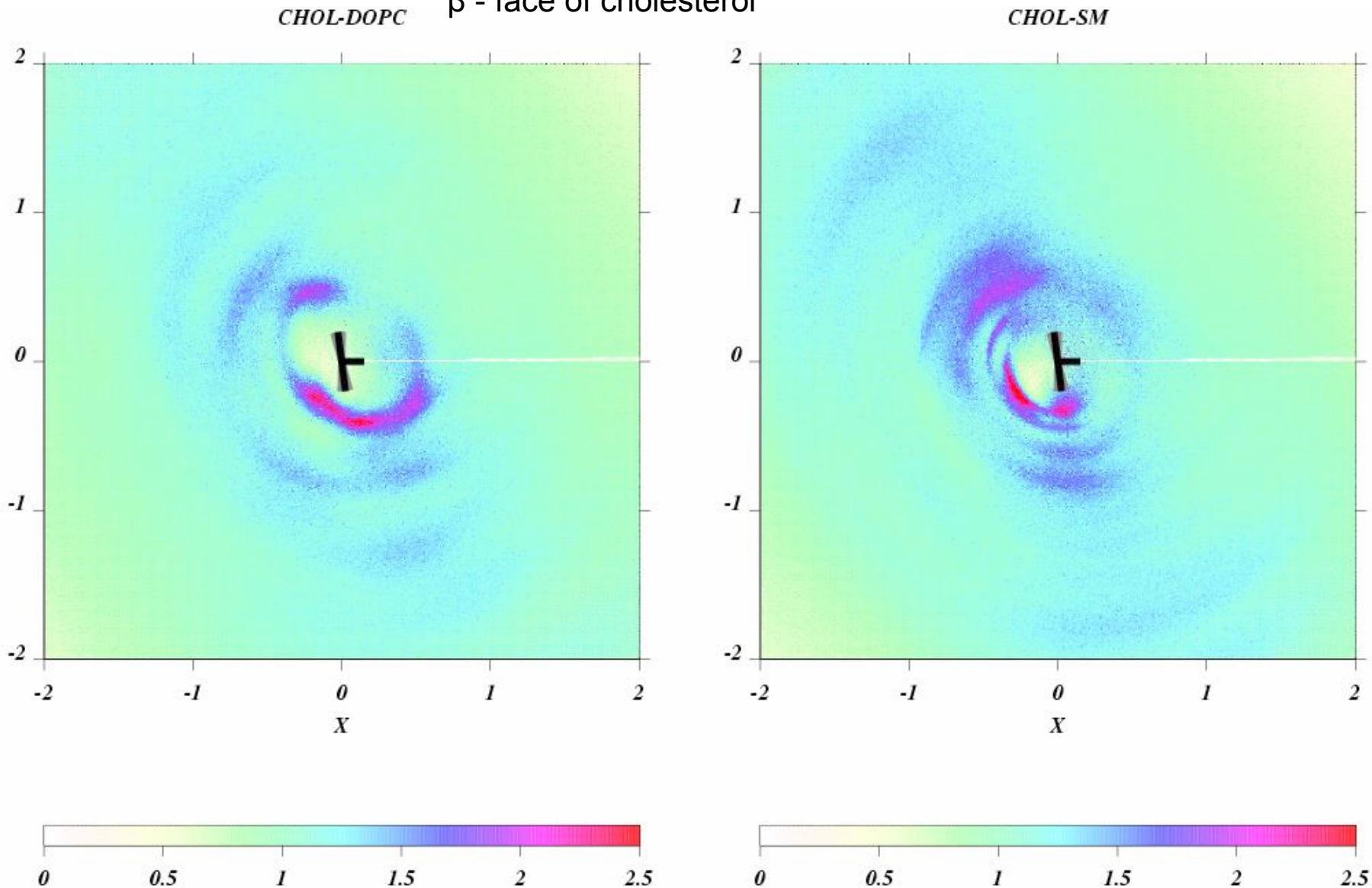
red: DOPC-SM

Cholesterol promotes domain formation

Energies of interaction with cholesterol are nearly identical for SM and DOPC!

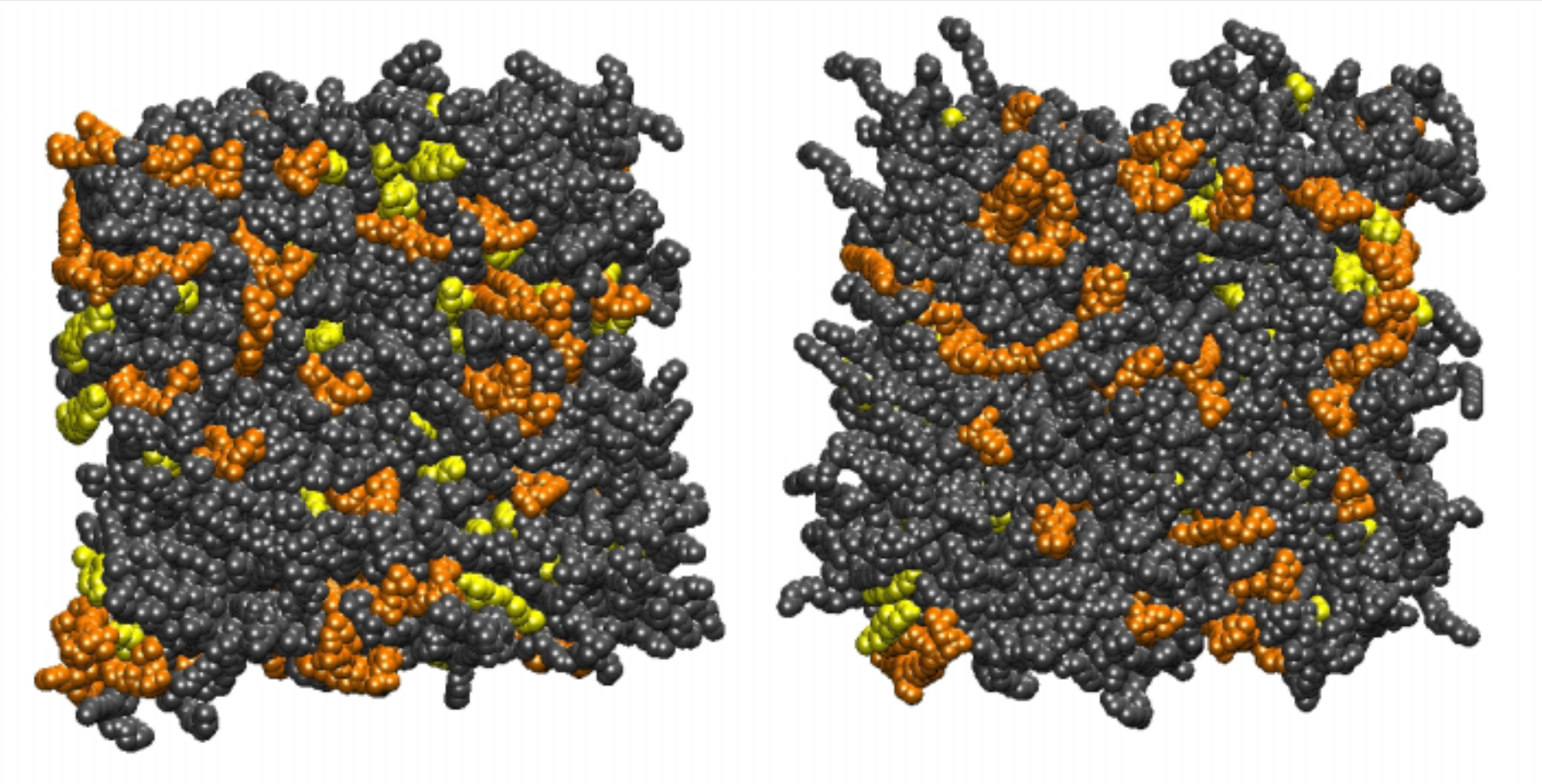


β - face of cholesterol



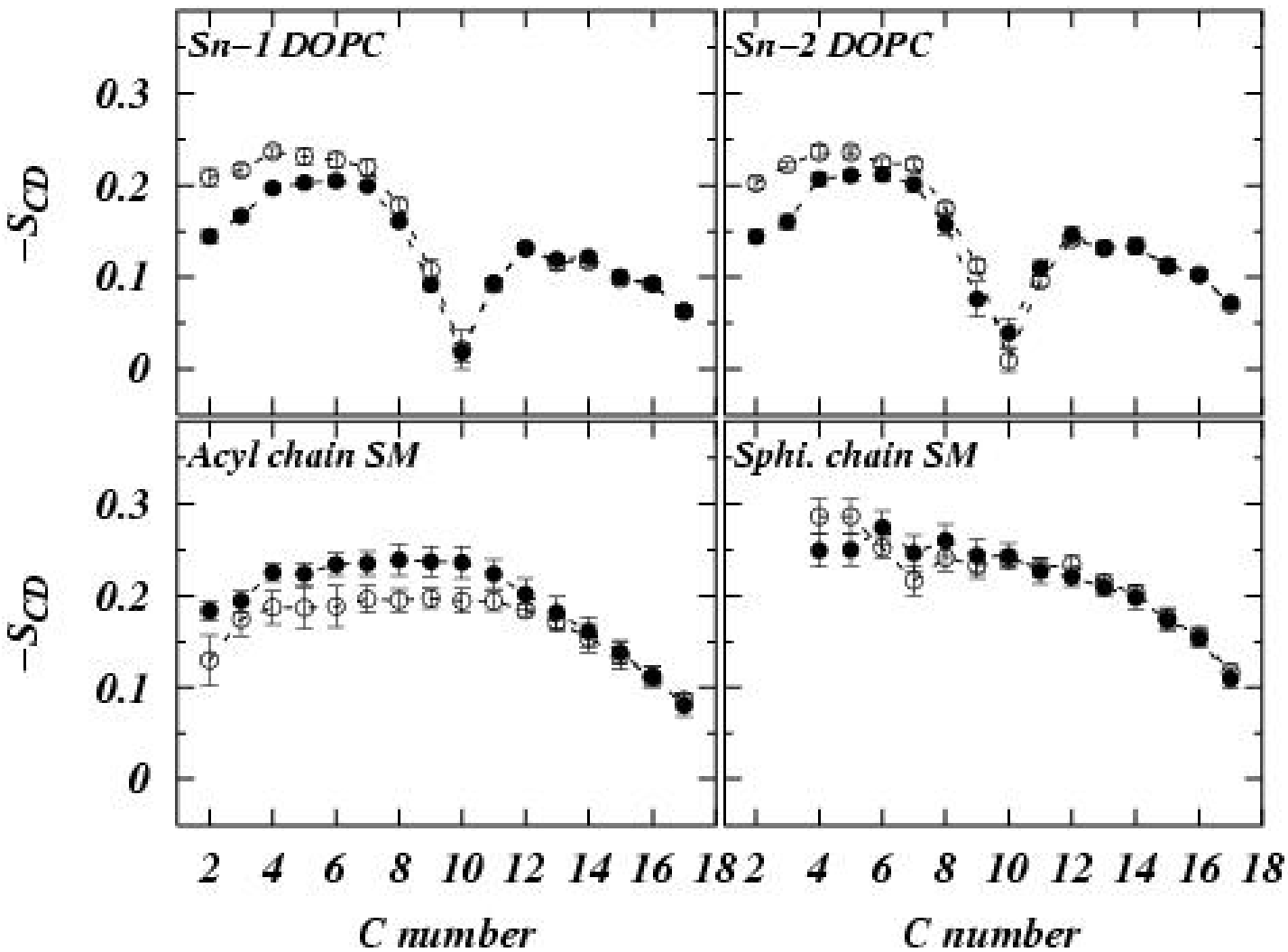
SM packs preferentially at the α - face of cholesterol

Ternary mixture: 200 DOPC, 50 18:0 SM, 50 CHOL, 10000 water (44850 atoms)



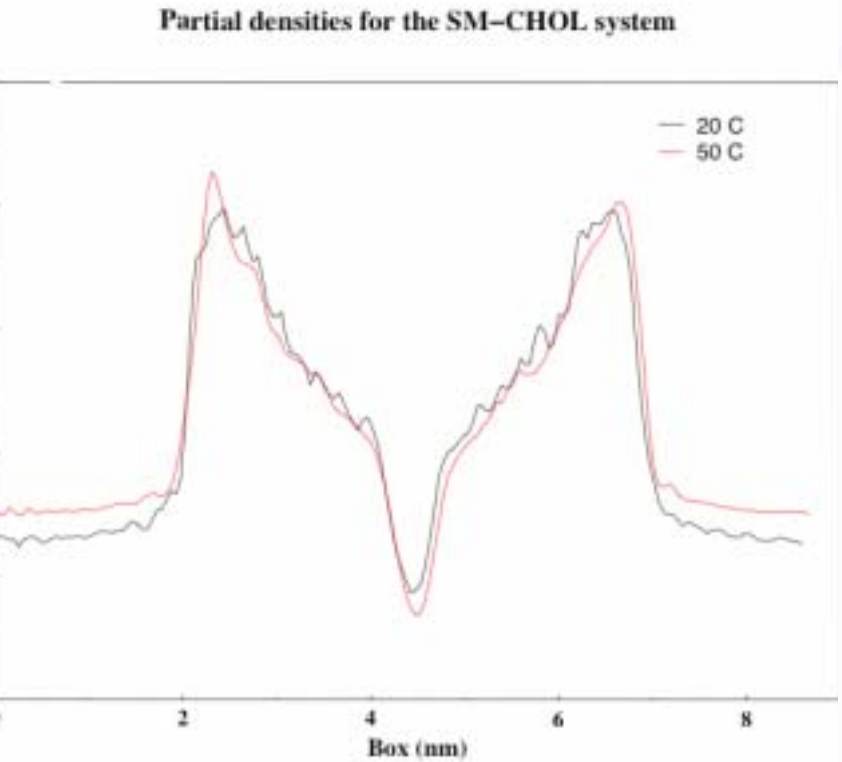
t = 0 ns

t = 75 ns



Order parameters for 4:1:1 simulation at t = 0 ns (open symbols) & t = 75 ns(filled symbols)

2-1 SM-Chol: experiment & simulation



d = 41 Å

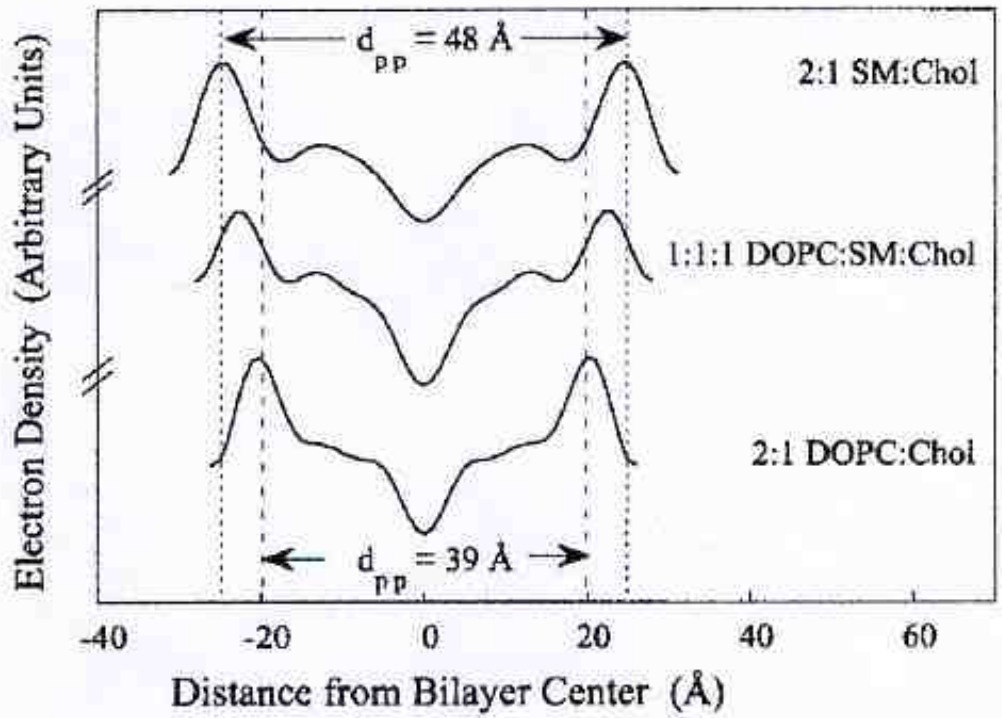
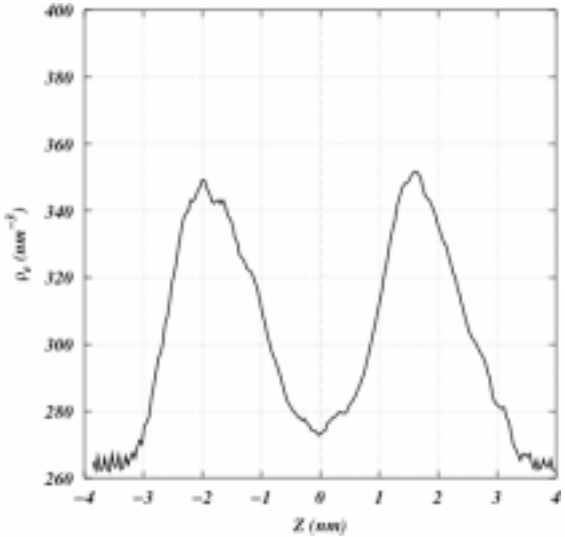
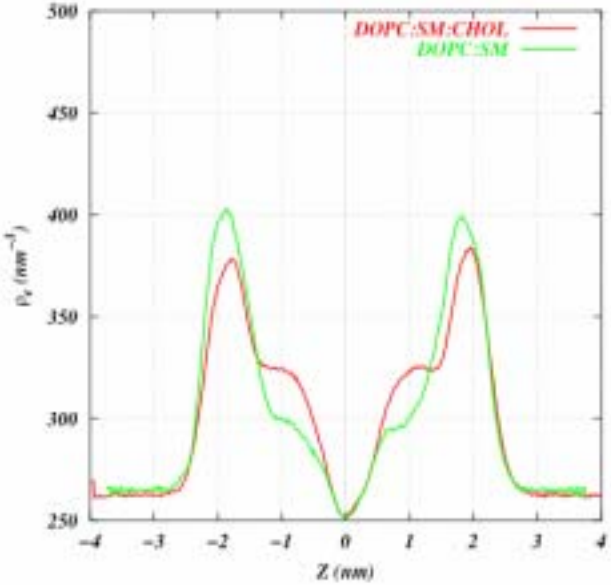


FIGURE 7 Electron density profiles (resolution of $d/2h_{max} \approx 4.5$ Å) for 2:1 SM:cholesterol, 1:1:1 DOPC:SM:cholesterol, and 2:1 DOPC:cholesterol. For each profile, the center of the bilayer is at the origin and the high-density peaks correspond to the lipid head groups. The headgroup peaks are noted with vertical dotted lines for 2:1 SM:cholesterol and with dashed lines for 2:1 DOPC:cholesterol.

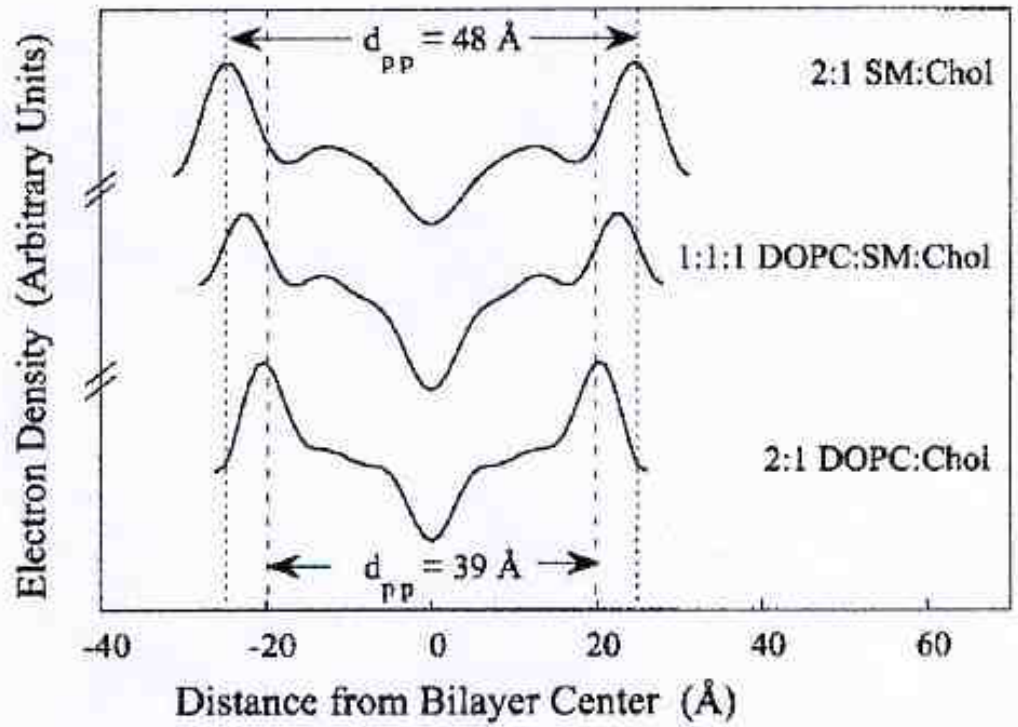
1-1-1 DOPC-SM-Chol: experiment & simulation



Built-in domain: d = 36 Å



Random mixture: d = 38 Å



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Coarse-grain-dynamical Mean Field model :

di-palmitoyl phosphatidylcholine-cholesterol bilayer leaflet

- goal: to use input from atomistic simulations to predict lateral organization over meseoscopic scales of length & time

- statistical mechanical basis: gradient in Free Energy due to inhomogeneities drives lateral motions of lipids and cholesterol

Time Dependent Ginzburg-Landau model

- project lipid chains onto sites of 2-D lattice
- lipid chains interact according to self-consistent Mean Field theory of Marcelja (Biochim Biophys Acta 367, 165, 1974)
- cholesterol molecules are hard rods of length 1.1 lattice constant
- cholesterols translate & rotate in time
- lipid chain order changes in time

Time evolution of the system: Time-dependent Ginzburg-Landau equation plus Langevin equations

chain order parameter evolution

$$\partial\psi_i/\partial t = -\Gamma\partial F(\psi_i)/\partial\psi_i + \zeta$$

cholesterol position & orientation evolution

$$\partial\theta_i/\partial t = -M_\theta\partial F/\partial\theta_i + \xi_i$$

$$\partial\vec{r_i}/\partial t = -M_r\partial F/\partial\vec{r_i} + \vec{\eta_i}$$

Simulation Procedure:

1. initialize: construct N x N lattice, distribute desired number of cholesterols over sites randomly

2. Solve SCMFT equation for initial chain order

3. Evolve system by 1 timestep

4. Re-equilibrate chains by solving SCMFT

5. go to step 3

arameters that control the evolution of the system:

$$D \approx 5 \times 10^{-12} m^2/s \text{ (experiment)}$$

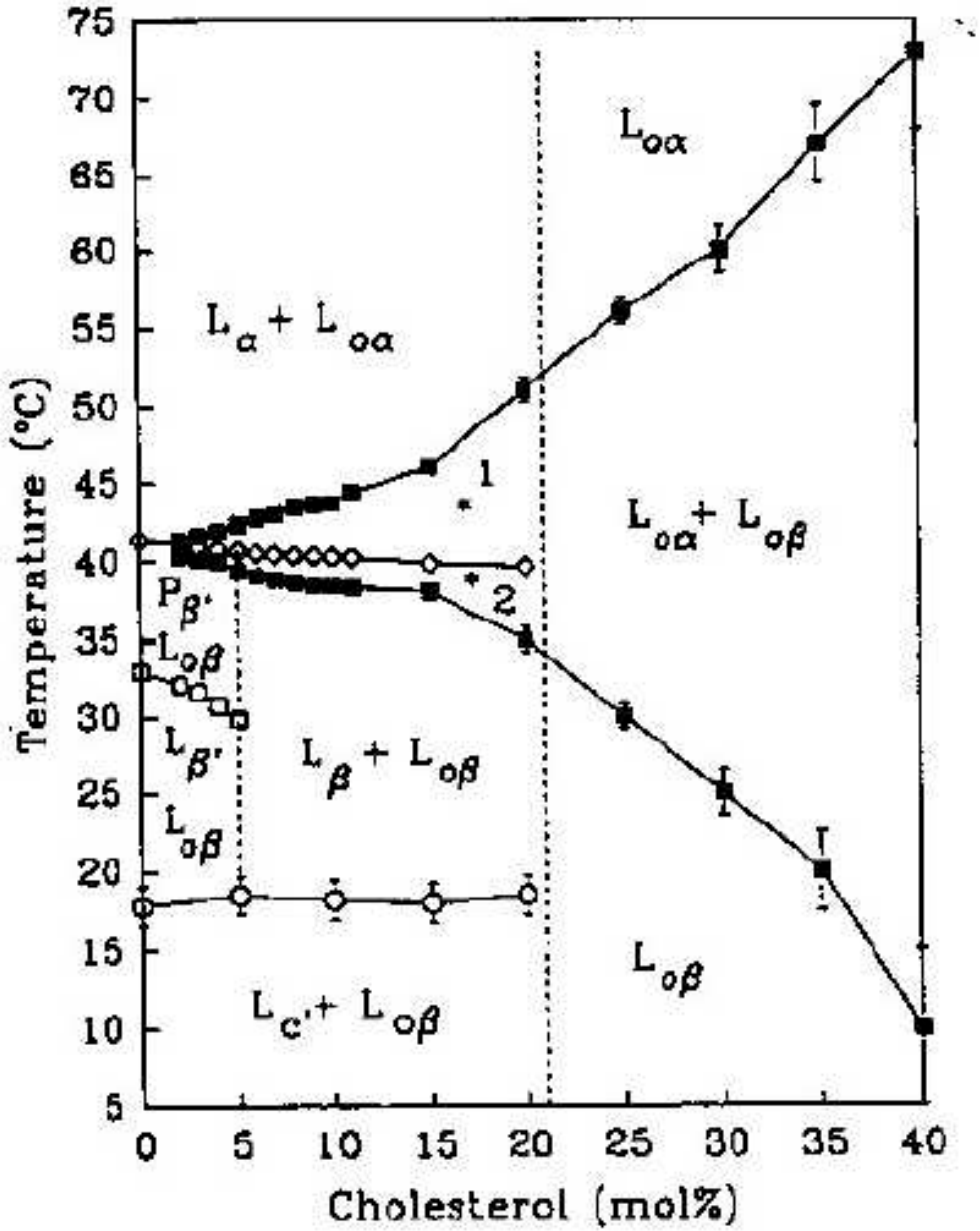
$$M_r = D/k_b T \qquad M_\theta = (10 - 100) \times M_r$$

$$\Gamma = 10 M_r$$

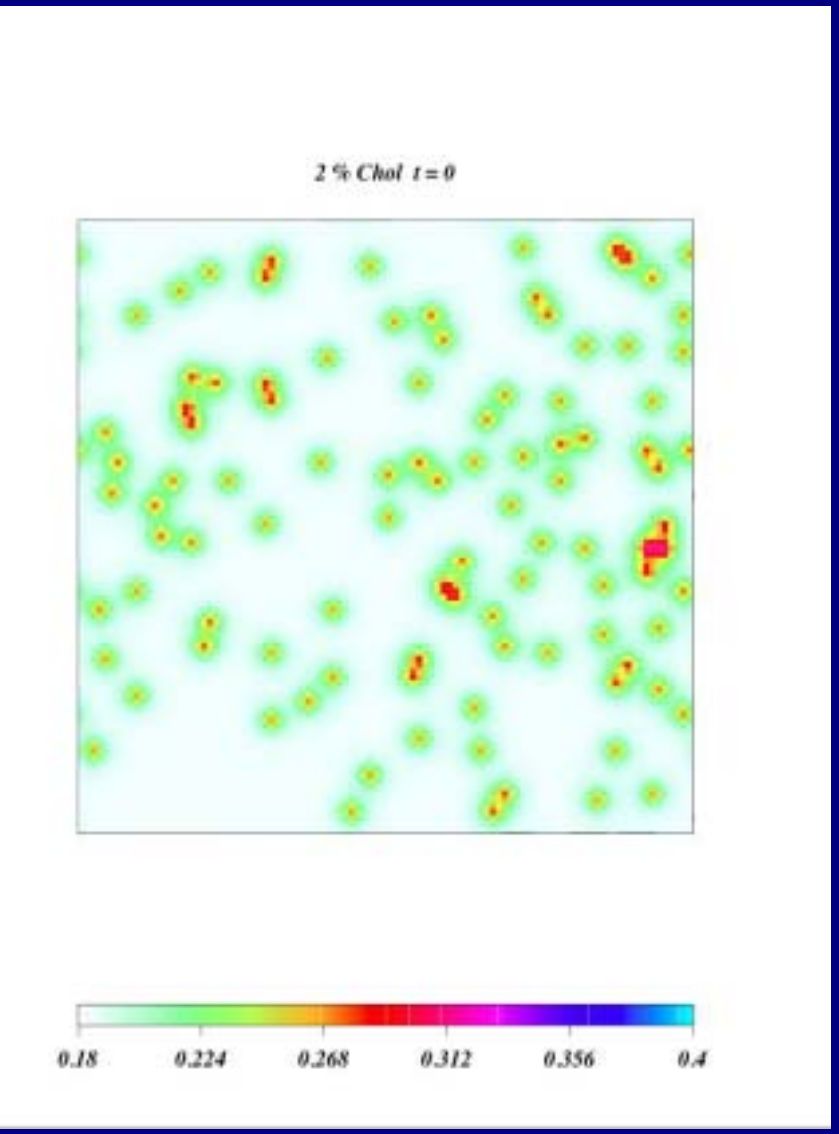
$$\Delta t_{sim} = \frac{D}{\ell^2} \Delta t \approx 10^7 \Delta t \qquad \ell = 0.65 nm$$

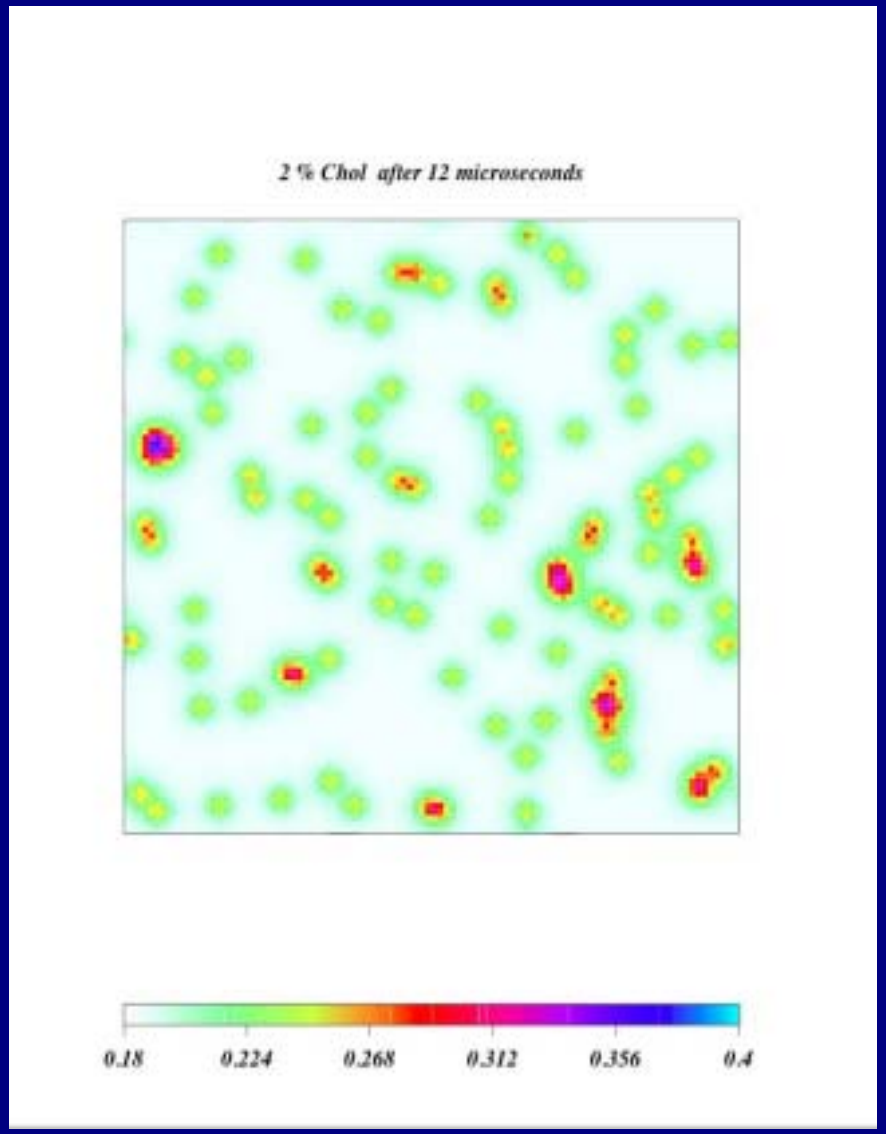
DPPC-cholesterol phase diagram

McMullen & McElhaney, BBA 1234, 90-98, 1995



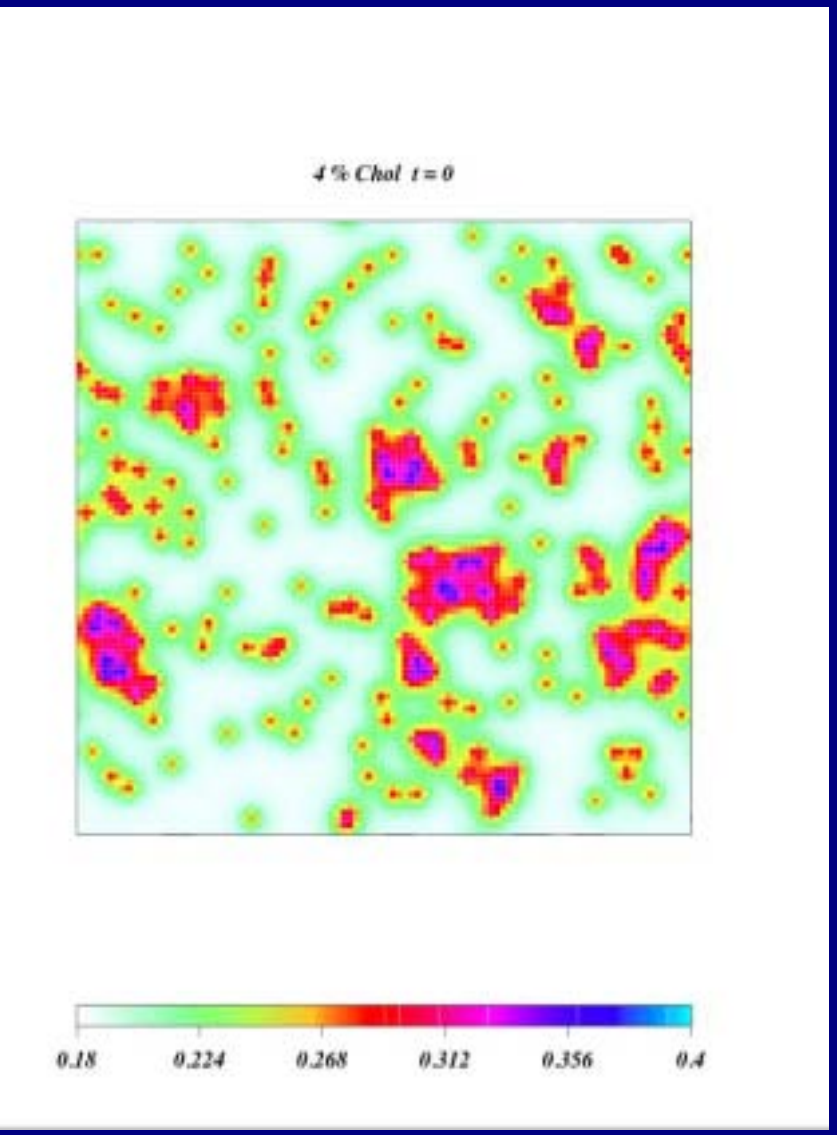
2% Chol

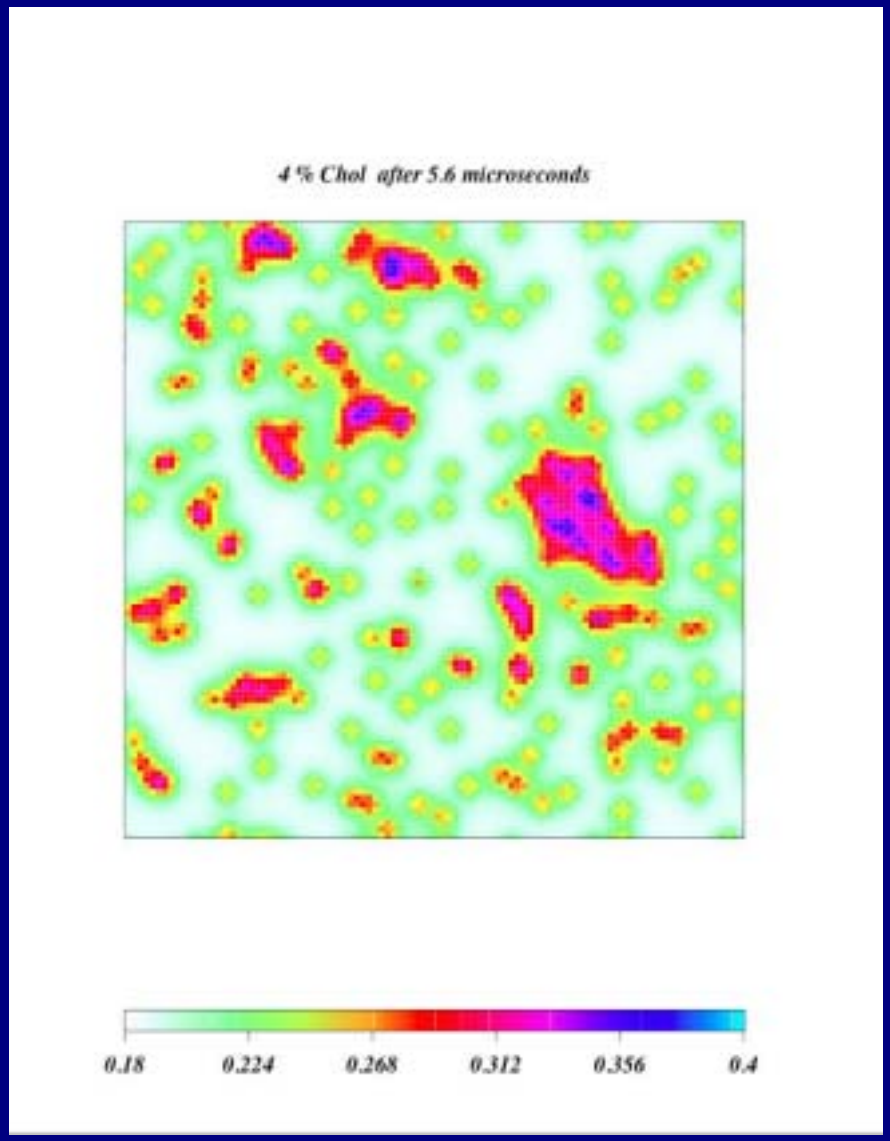




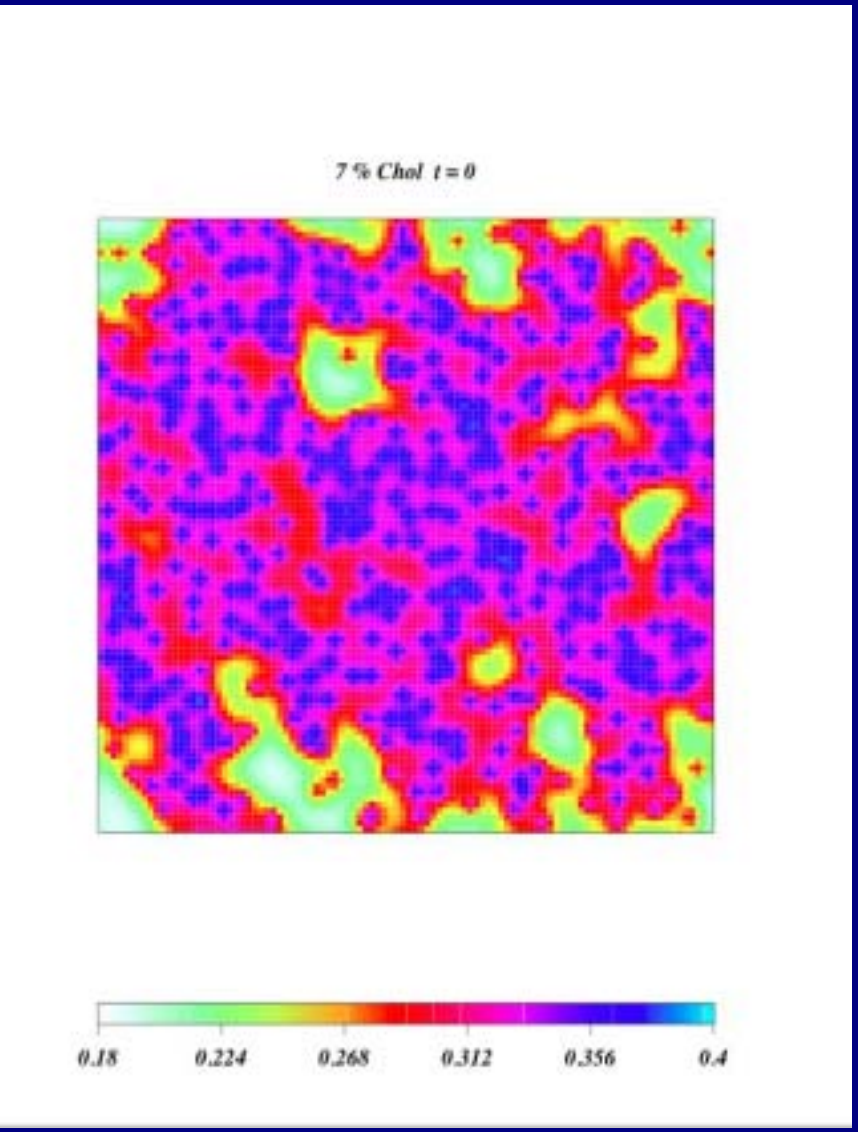
Khelashvili, Pandit and Scott, (preprint).

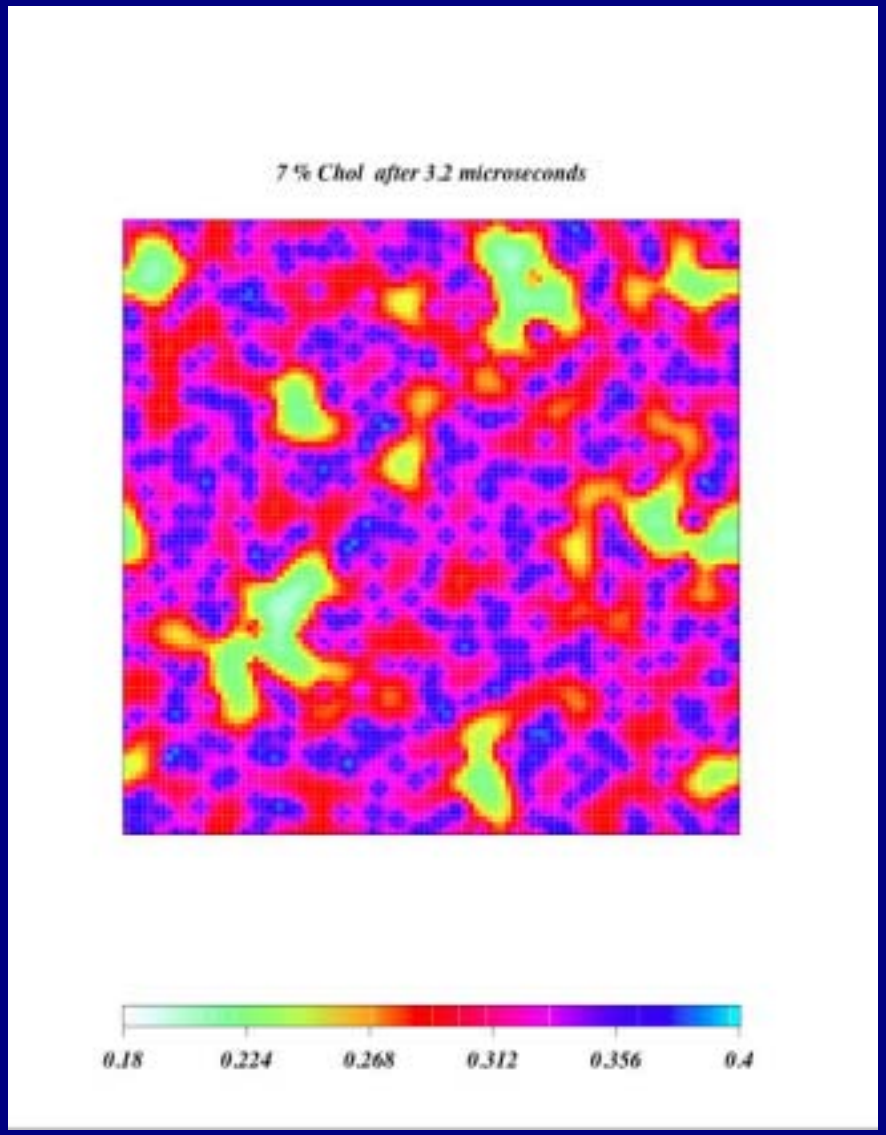
4 % Chol


4 % Chol t = 0
0.18
0.224
0.268
0.312
0.356
0.4

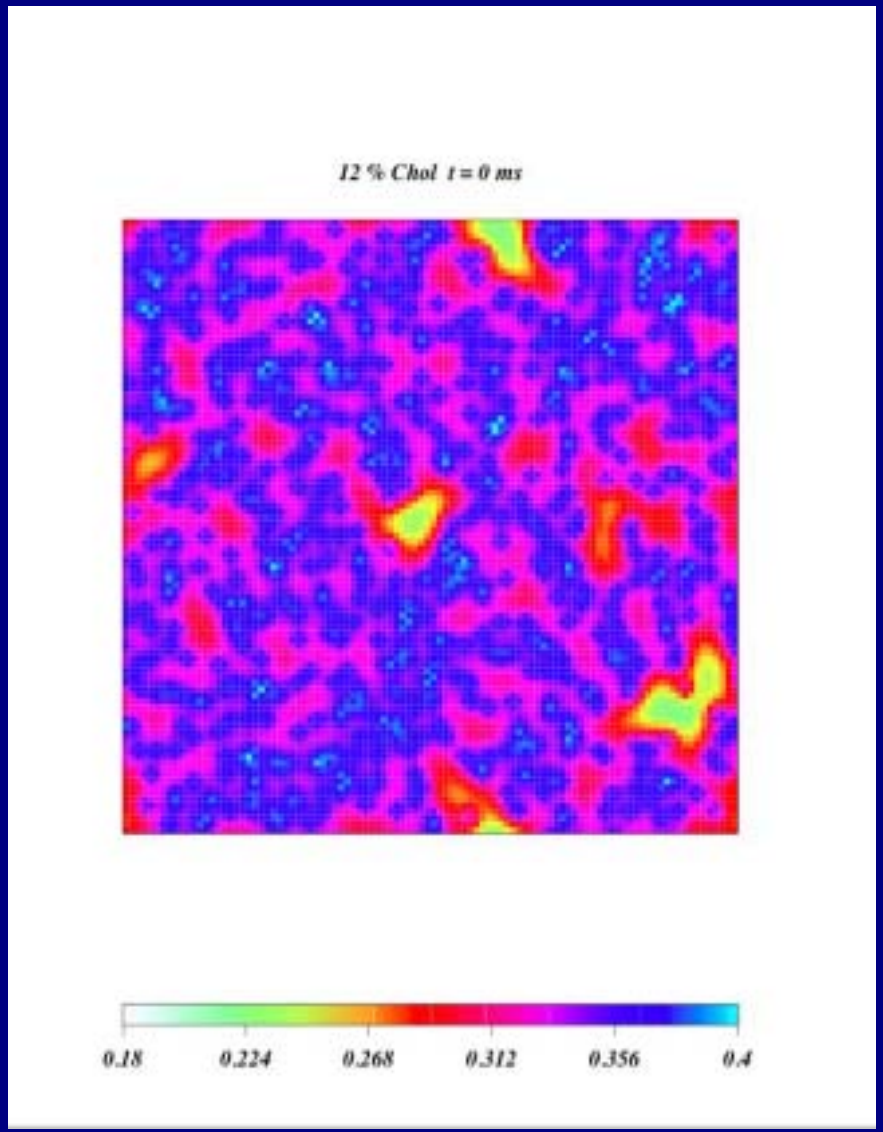

4 % Chol after 5.6 microseconds
0.18
0.224
0.268
0.312
0.356
0.4

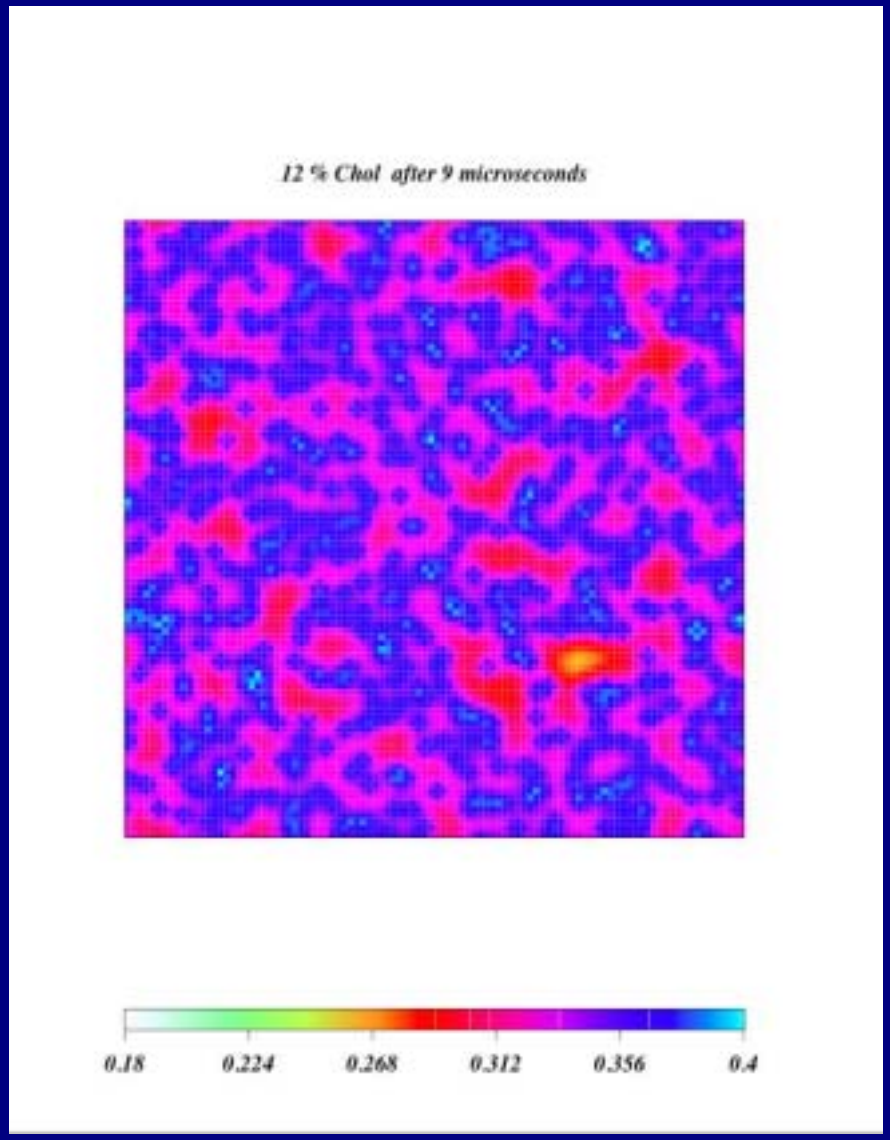
7% Chol


7 % Chol t = 0
0.18
0.224
0.268
0.312
0.356
0.4

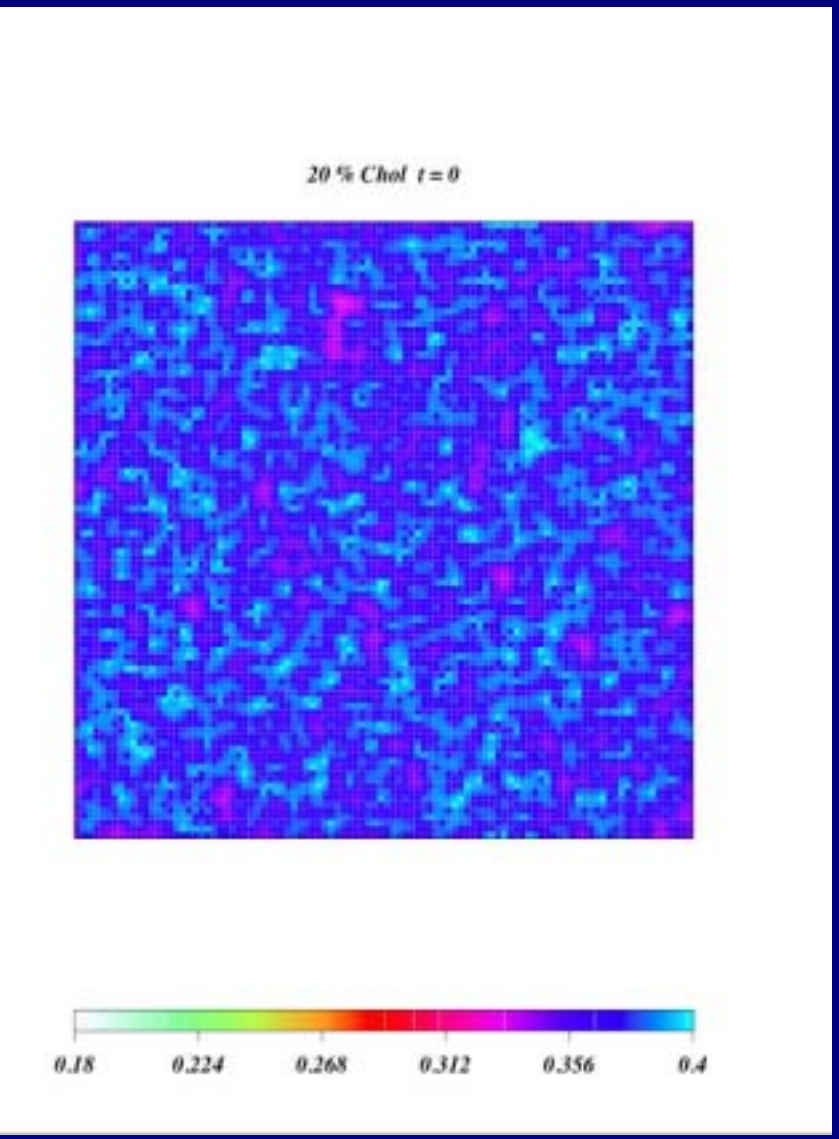

7 % Chol after 3.2 microseconds
0.18
0.224
0.268
0.312
0.356
0.4

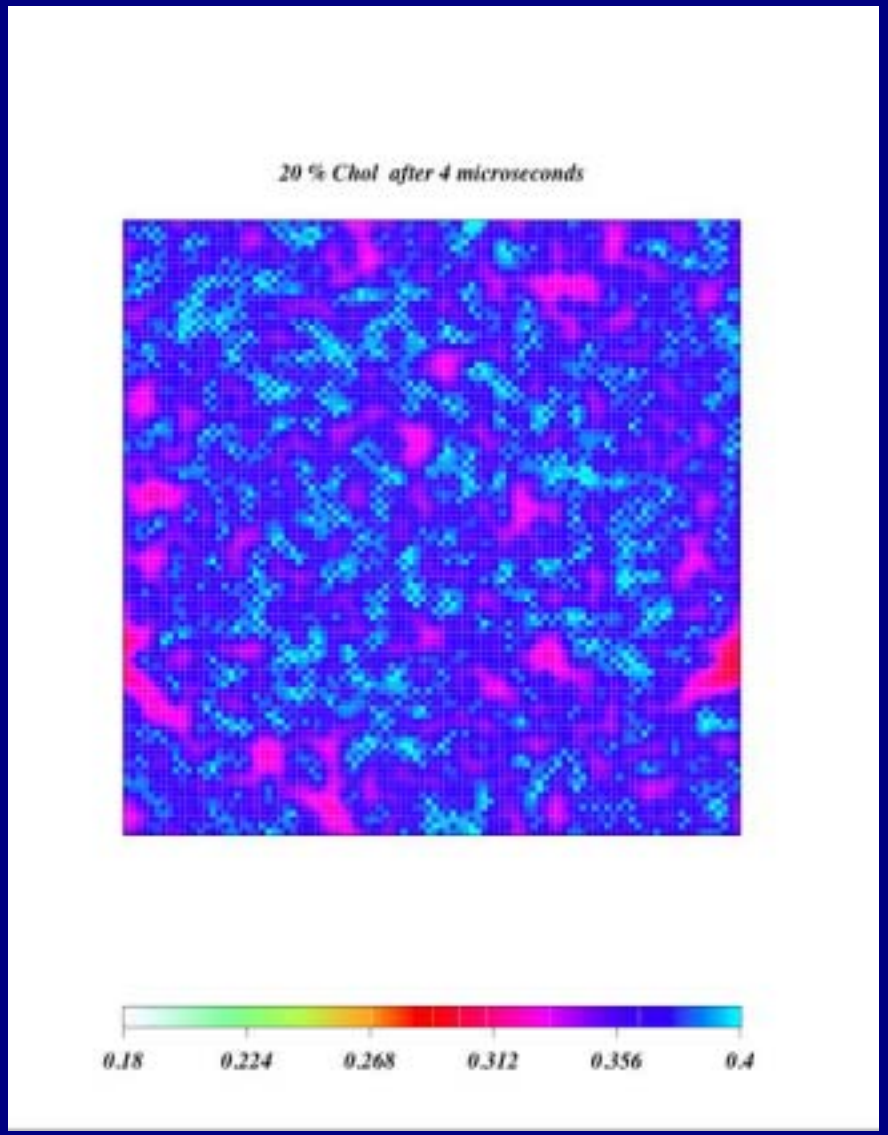
12% Chol


12 % Chol t = 0 ms
0.18
0.224
0.268
0.312
0.356
0.4

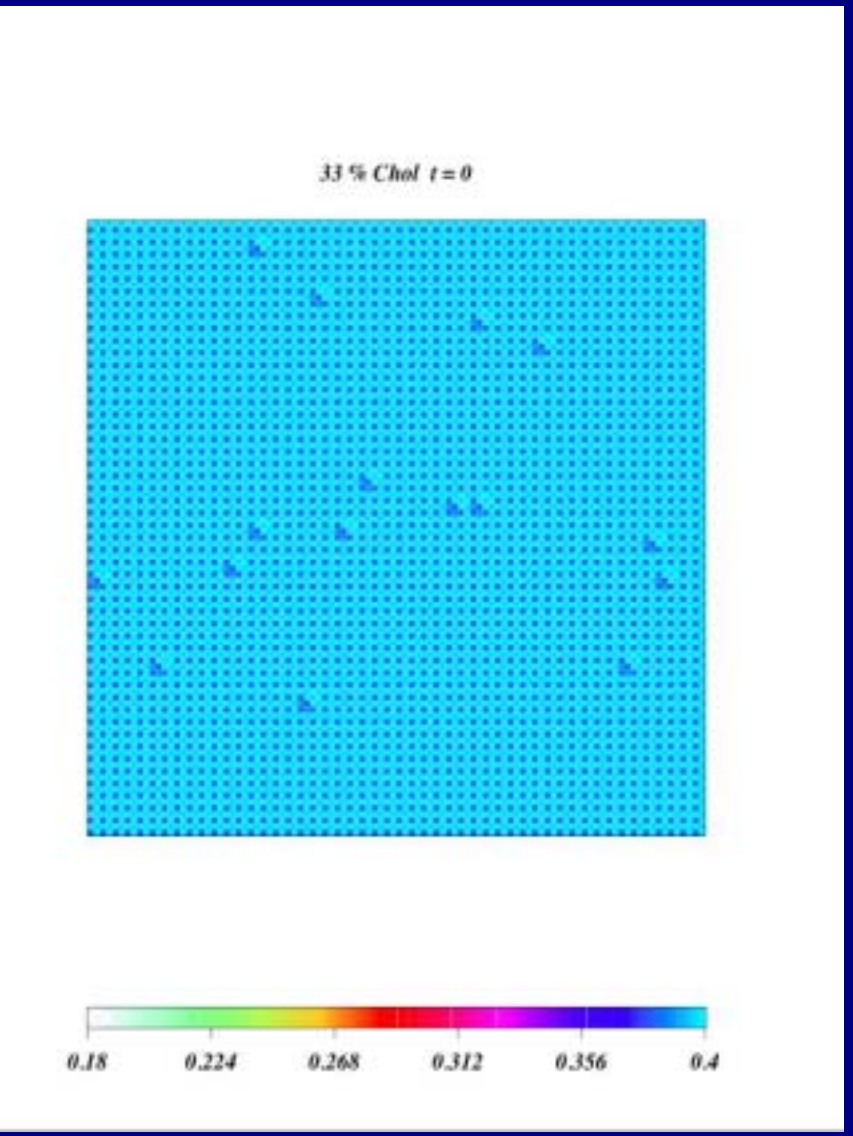

12 % Chol after 9 microseconds
0.18
0.224
0.268
0.312
0.356
0.4

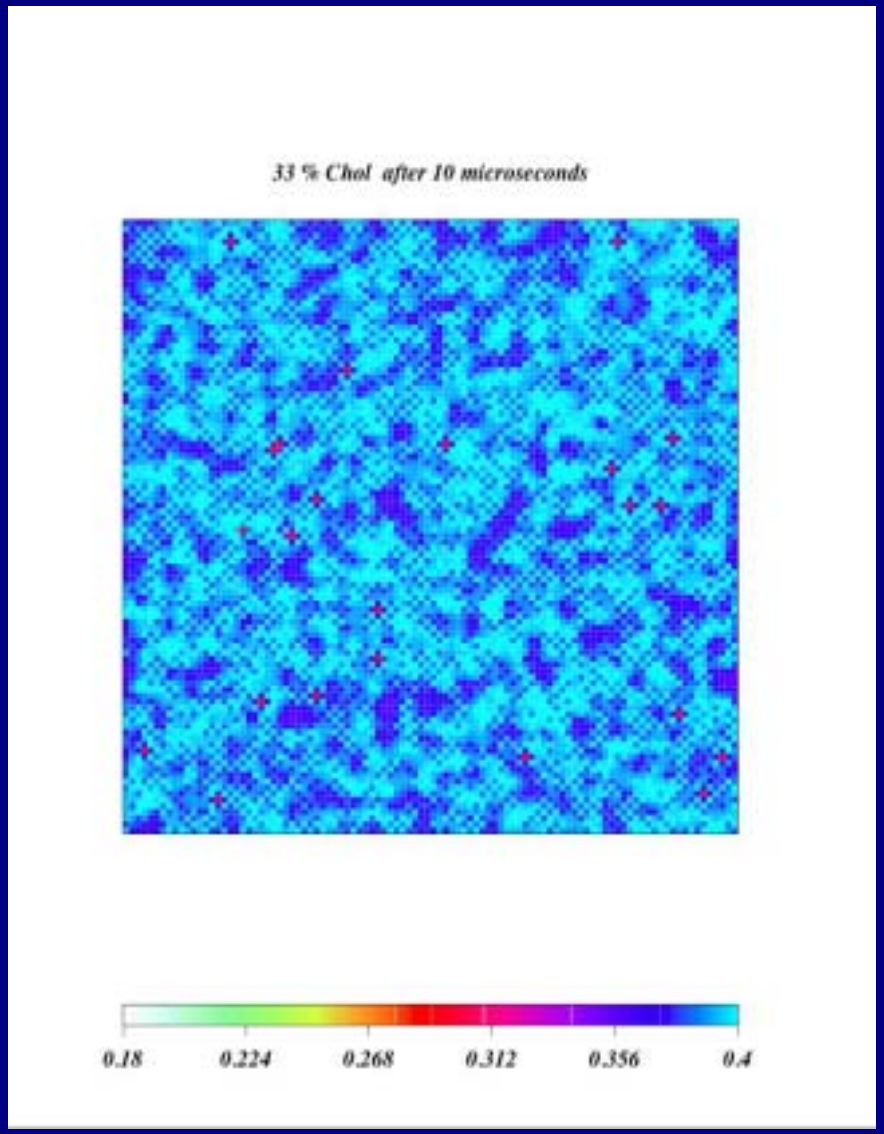
20% Chol


20 % Chol t = 0
0.18
0.224
0.268
0.312
0.356
0.4


20 % Chol after 4 microseconds
0.18
0.224
0.268
0.312
0.356
0.4

33% Chol


33 % Chol t = 0
0.18
0.224
0.268
0.312
0.356
0.4

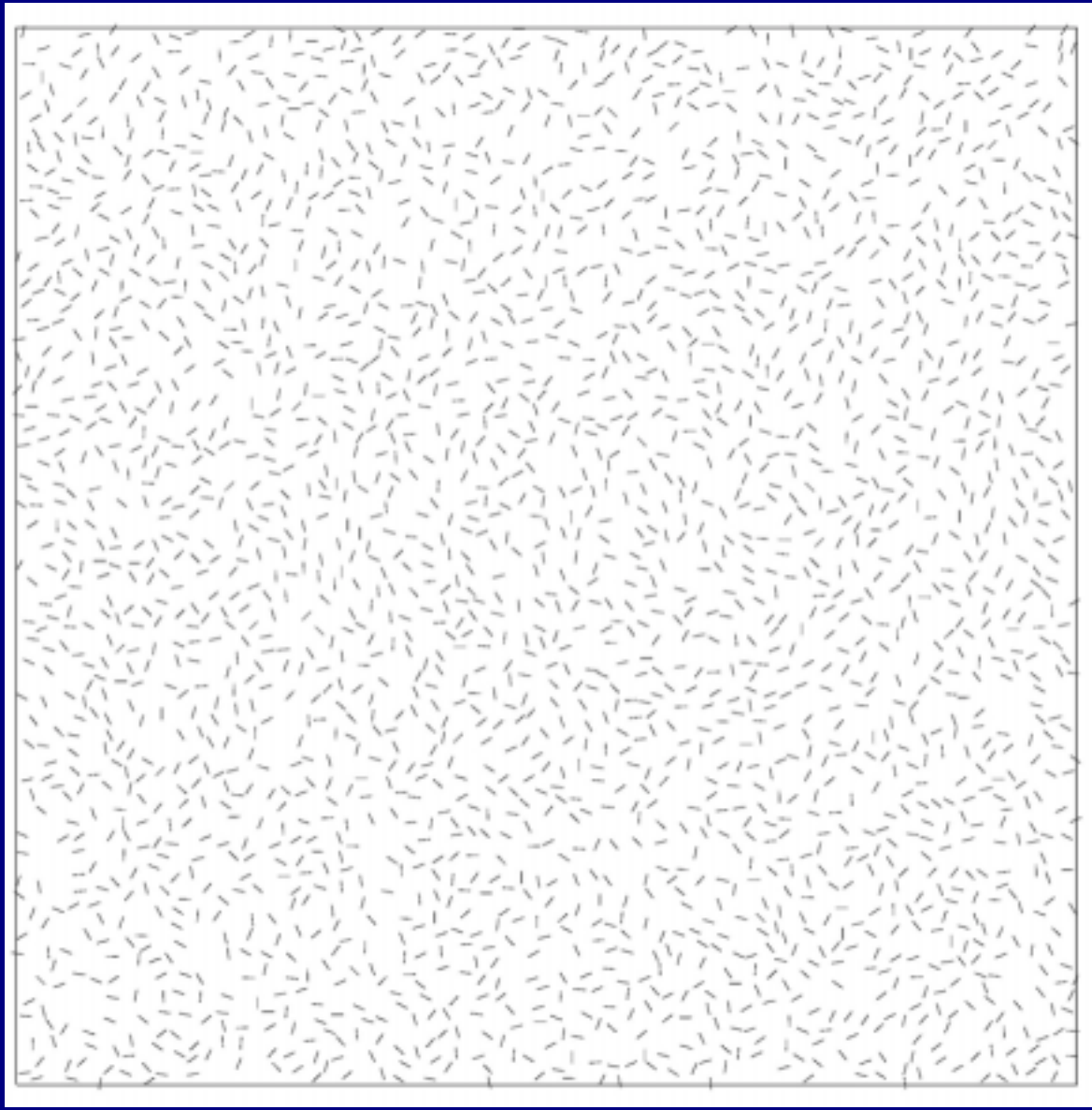

33 % Chol after 10 microseconds
0.18
0.224
0.268
0.312
0.356
0.4

@ IIT
Sagar Pandit
George Khelashvili

@ UIUC
Eric Jakobsson
R. Jay Mashl
See-Wing Chiu

Thanks to NIH, NCSA for support

cholesterol distribution @ 33% after 3 μ s



Mean Field Model for Lipid Bilayer

(Marcelja, BBA 367, 156-176, 1974)

chain order parameter

$$\psi_i = (\frac{n_{tr}}{n}) \sum_j (\frac{3}{2} \cos^2 \theta_{i,j} - \frac{1}{2})/n$$

Chain energy in mean field approximation

$$E_{MF}(i) = -\psi_i \left[\sum_{nn:l} V_o < \psi_{nn} > + \sum_{nn:c} V_{lc} \right]$$

molecular field at lipid chain site i

$$\Phi_i = \sum_{nn:l} V_0 < \psi_{nn} > + n_c V_{lc}$$

lipid-cholesterol interaction (from simulations)

Self Consistent equation at site i

$$< \psi_i >= \frac{1}{Z_i} \Sigma \psi(i) e^{-(\psi_i \Phi_i / kT)}$$

$$Z_i = \Sigma e^{-(\psi_i \Phi_i / kT)}$$

Sum is over all chain configurations from a simulation of 1600 DPPC in water