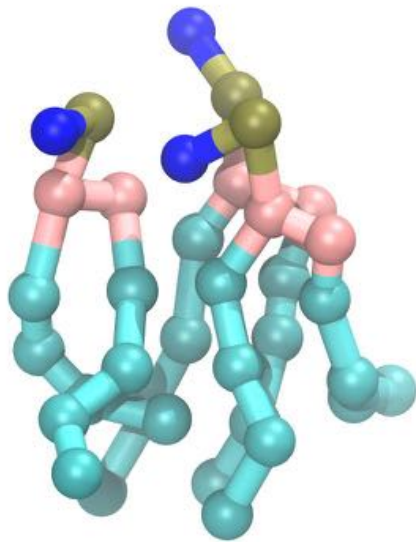


# Lipid biophysics with the Martini model



2017 Martini Workshop, Groningen  
August 21<sup>st</sup> 2017

**Helgi I. Ingólfsson**

# Overview

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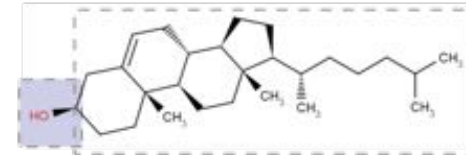
- Lipids – the what and the why
- The Martini lipidome
  - available lipids types
  - naming standard
  - overall properties
- Building bilayers
- Calculating lipids properties
- Examples of Martini lipid projects
- The plasma membrane project
  - setup
  - results
  - analysis
- The Brain plasma membrane
- Future Martini lipids and projects

# Lipids – definition



- Naturally occurring fats or fat-like compounds
- Insoluble in water
- Soluble in organic solvents
- Hydrophobic/amphipathic molecules

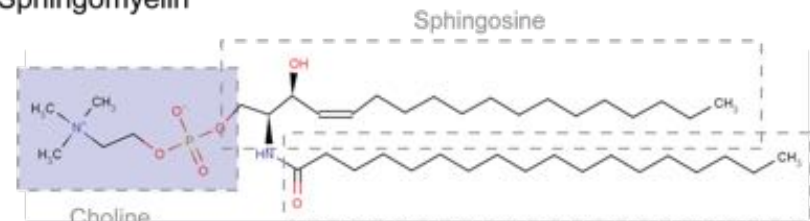
Cholesterol



Head group

Tail

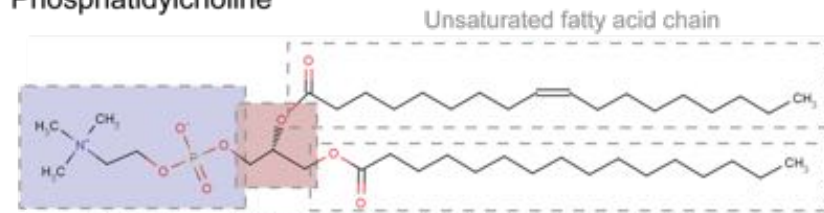
Sphingomyelin



Choline head group

Saturated fatty acid chain

Phosphatidylcholine

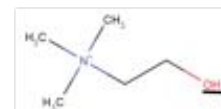


Choline head group

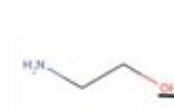
Glycerol linker

Saturated fatty acid chain

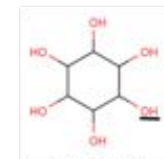
Examples of lipid head groups



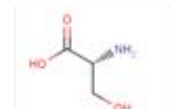
Choline



Ethanolamine



Inositol



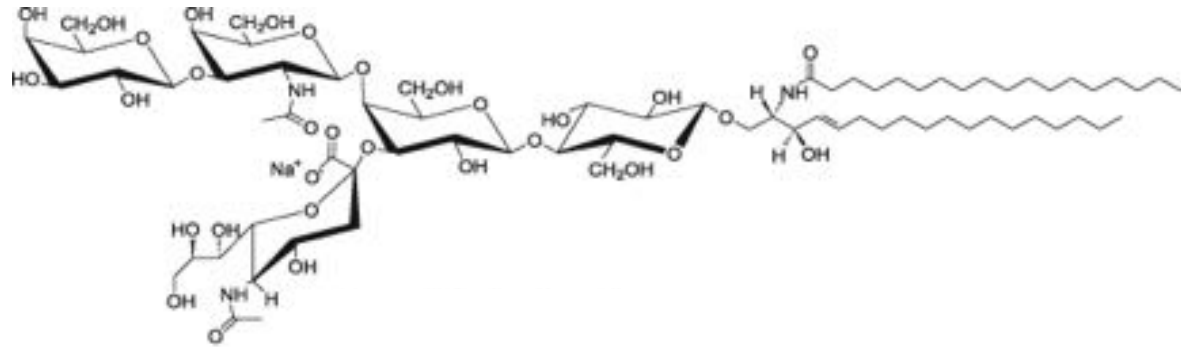
Serine

# Lipids – definition

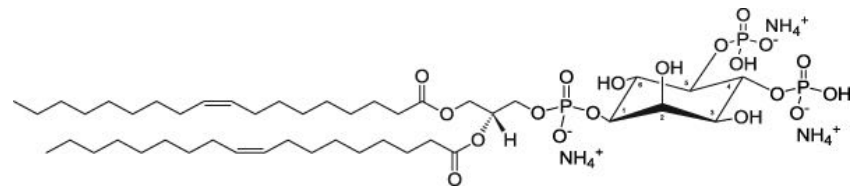


- Naturally occurring fats or fat-like compounds
- Insoluble in water
- Soluble in organic solvents
- Hydrophobic/amphipathic molecules

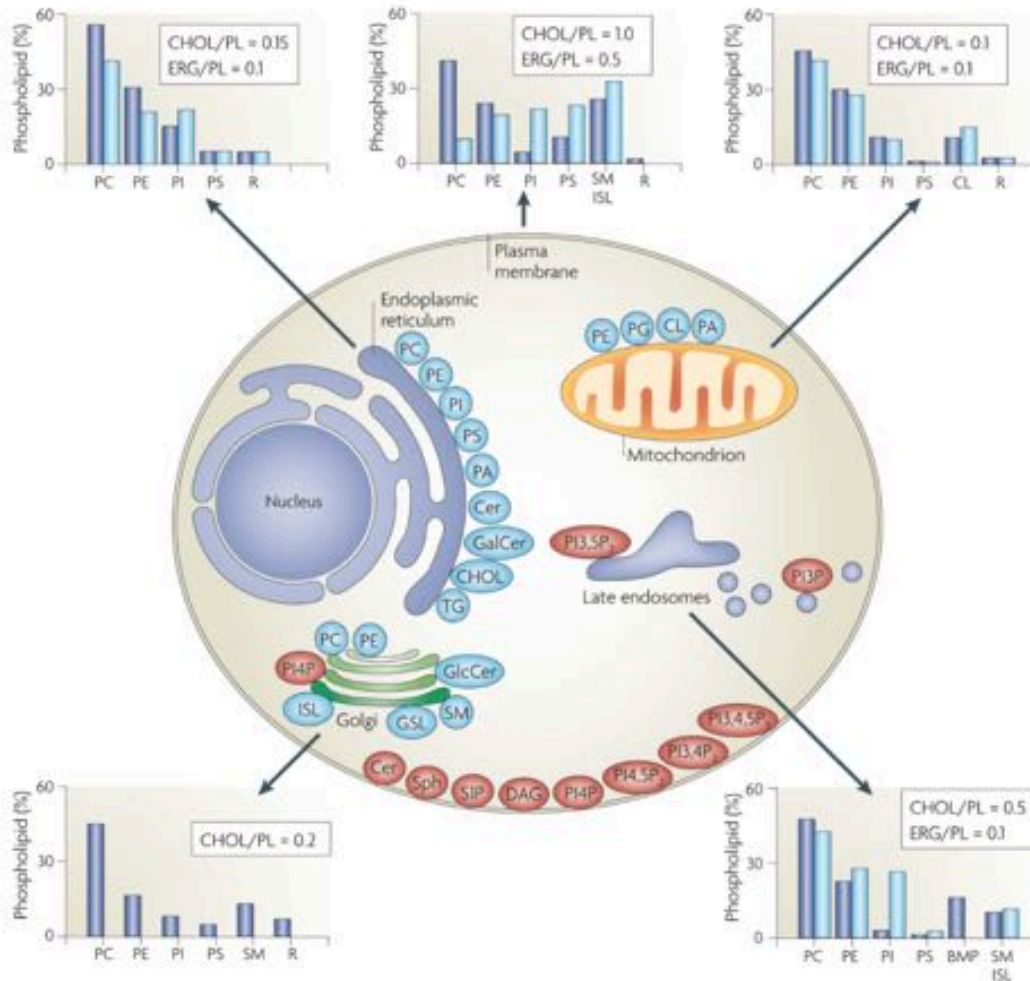
GM1



PIP<sub>2</sub>(4,5)



# Lipids – diversity

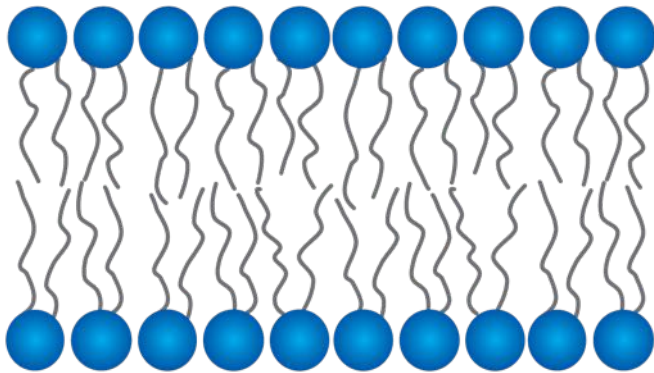


- Membranes contain 100s of different lipid types
- Cells have 1000s
- Currently [www.lipidmaps.org](http://www.lipidmaps.org) has >40.000 unique lipid structures

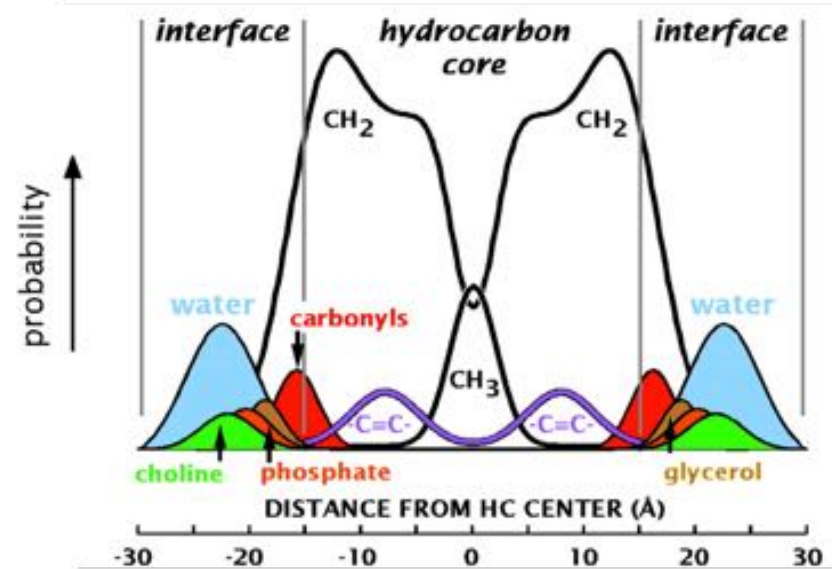
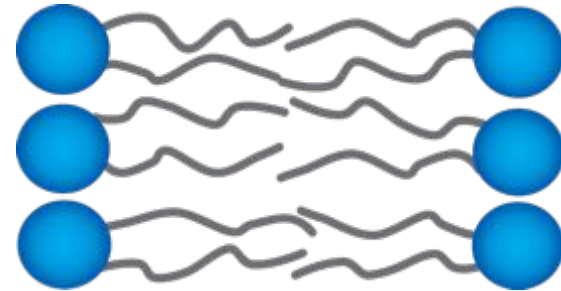
van Meer GJ, Voelker DR, Feigenson GW. (2008) Membrane lipids: where they are and how they behave. *Nat Rev Mol Cell Biol.* 9:112-24.

# Lipids – bilayers

**Lipid bilayer** refers to the physical bulk of the membrane, or the “hydrophobic continuum”, and the associated interfacial polar groups



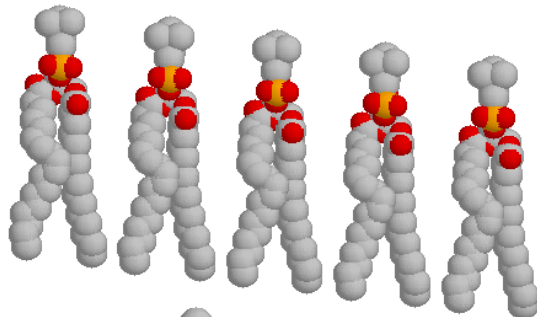
- Lipids
- Other amphiphiles
- Membrane proteins



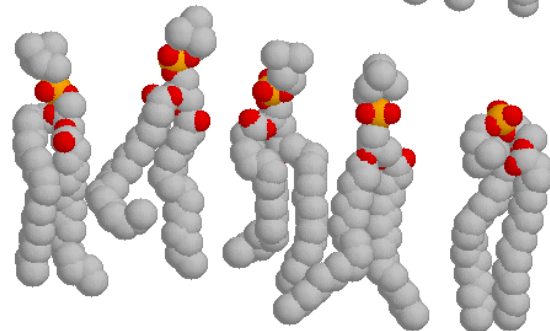
White, S. H., Ladokhin, A. S., Jayasinghe, S., & Hristova, K. (2001). How membranes shape protein structure. *Journal of Biological Chemistry*, 276(35), 32395–32398

# Lipids – bilayers

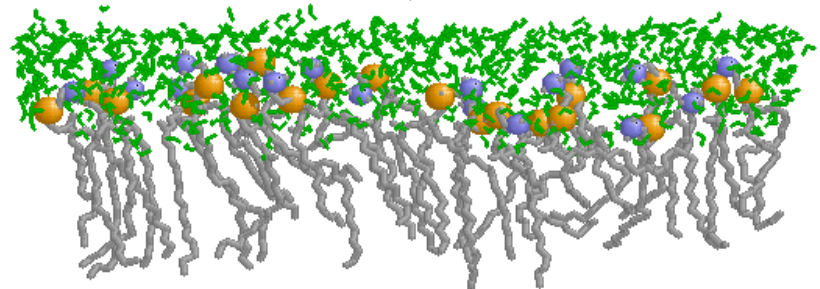
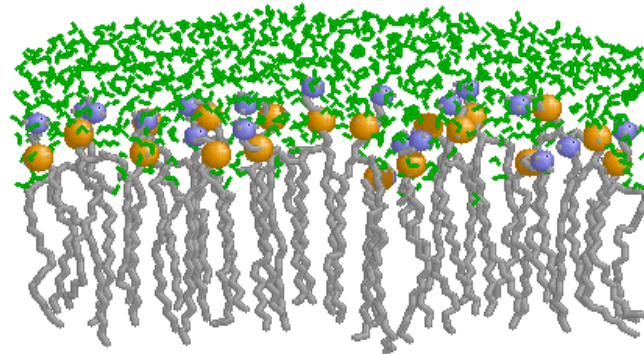
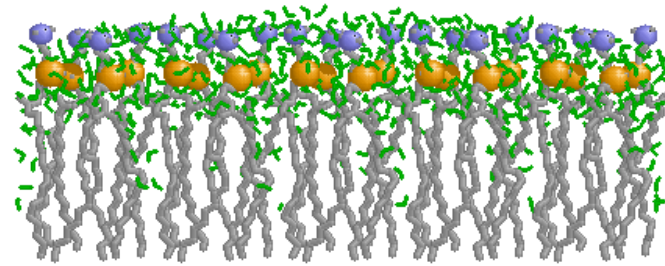
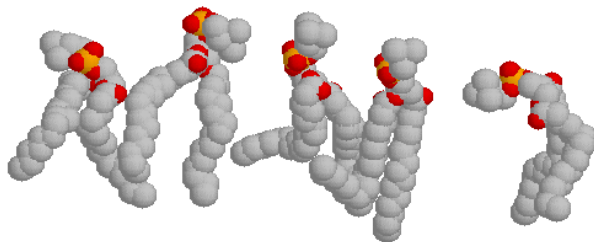
Crystal



Gel



Fluid

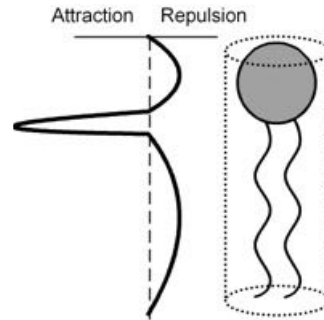
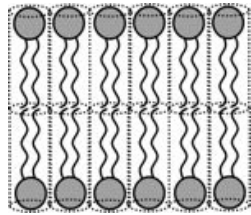


Water Nitrogen Phosphorus  
Other phospholipid atoms

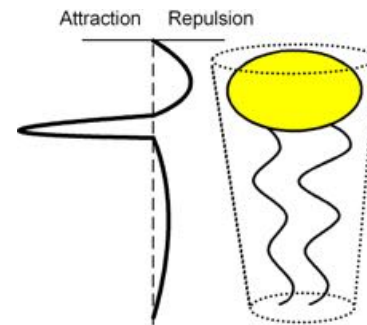
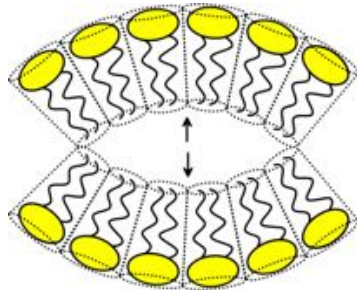
Images from Eric Martz using RasMol, structures from:  
Heller et al. 1993. *J Phys Chem* 97:8343-8360

LLNL-PRES-737105

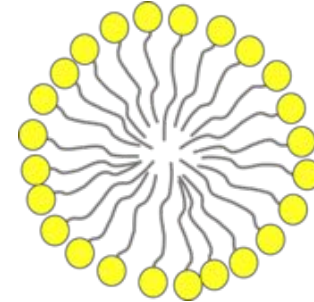
# Lipids – shape



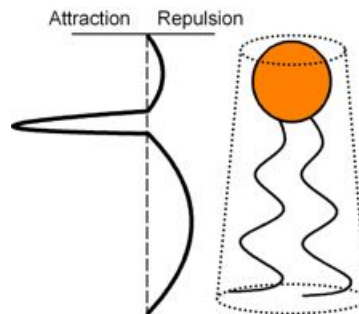
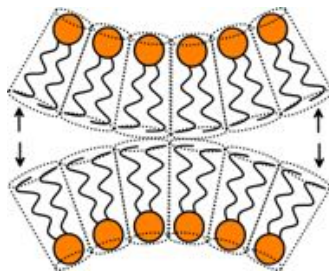
Positive intrinsic curvature



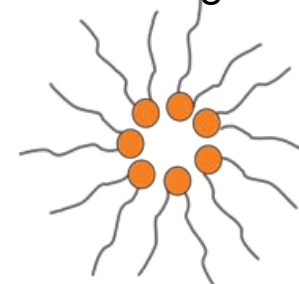
Micelle



Negative intrinsic curvature

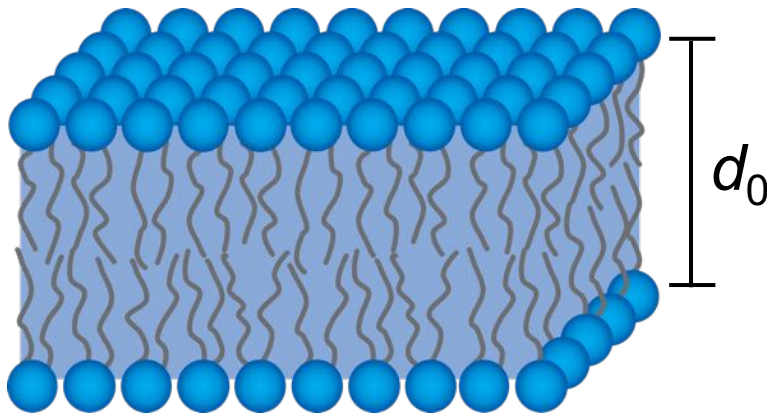
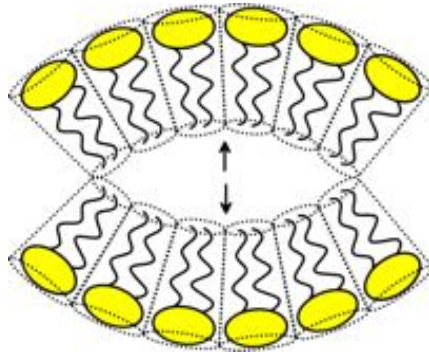


Inverted hexagonal phase



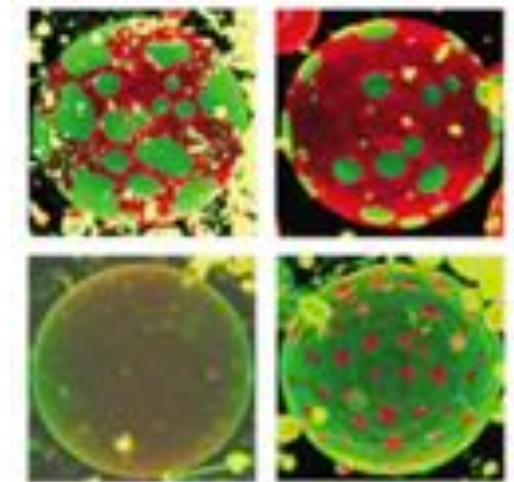
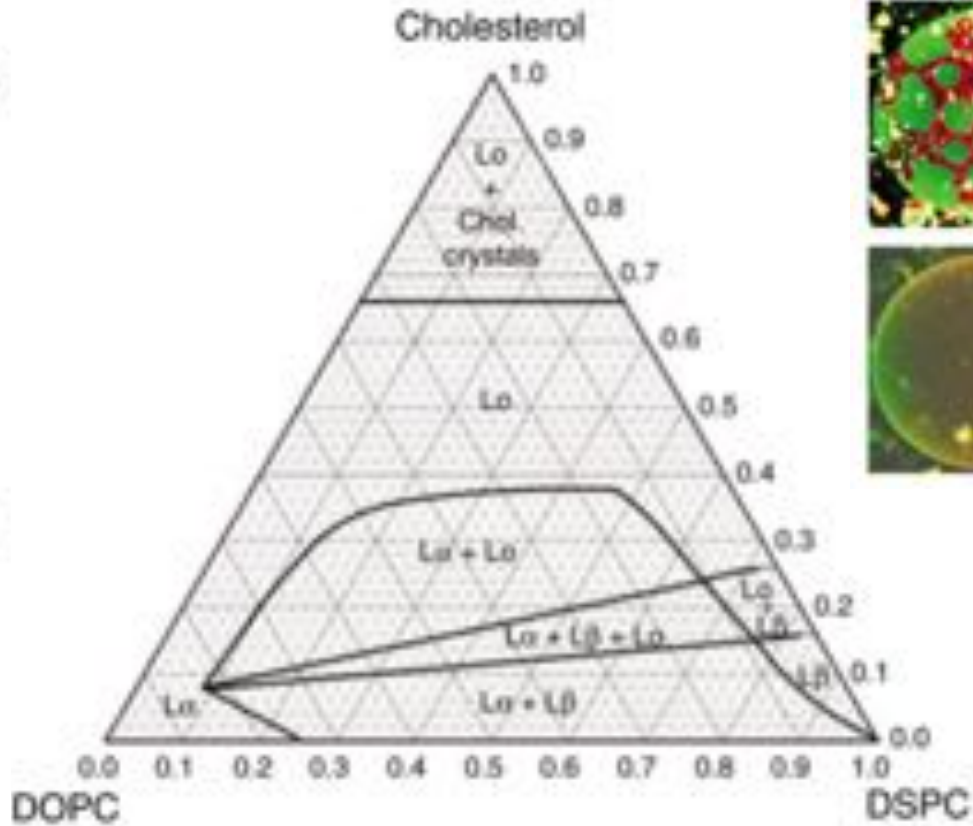
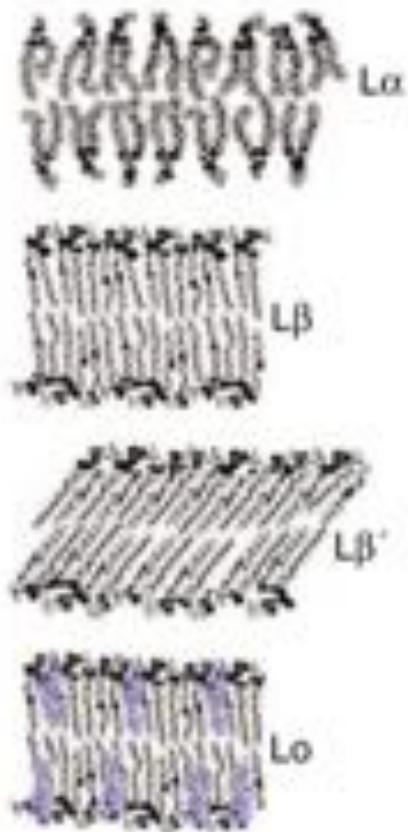


# Lipids – properties



- Intrinsic lipid curvature ( $c_0$ )
- Actual curvature ( $c$ )
- Hydrophobic thickness ( $d_0$ )
- Area compression-expansion modulus ( $K_a$ )
- Splay-distortion modulus ( $K_c$ )
- Fluidity
- Diffusion
- Area per lipid
- Order parameter
- Surface tension
- Acyl chain packing
- Lateral pressure profile
- Lipid packing stress
- Bilayer stiffness

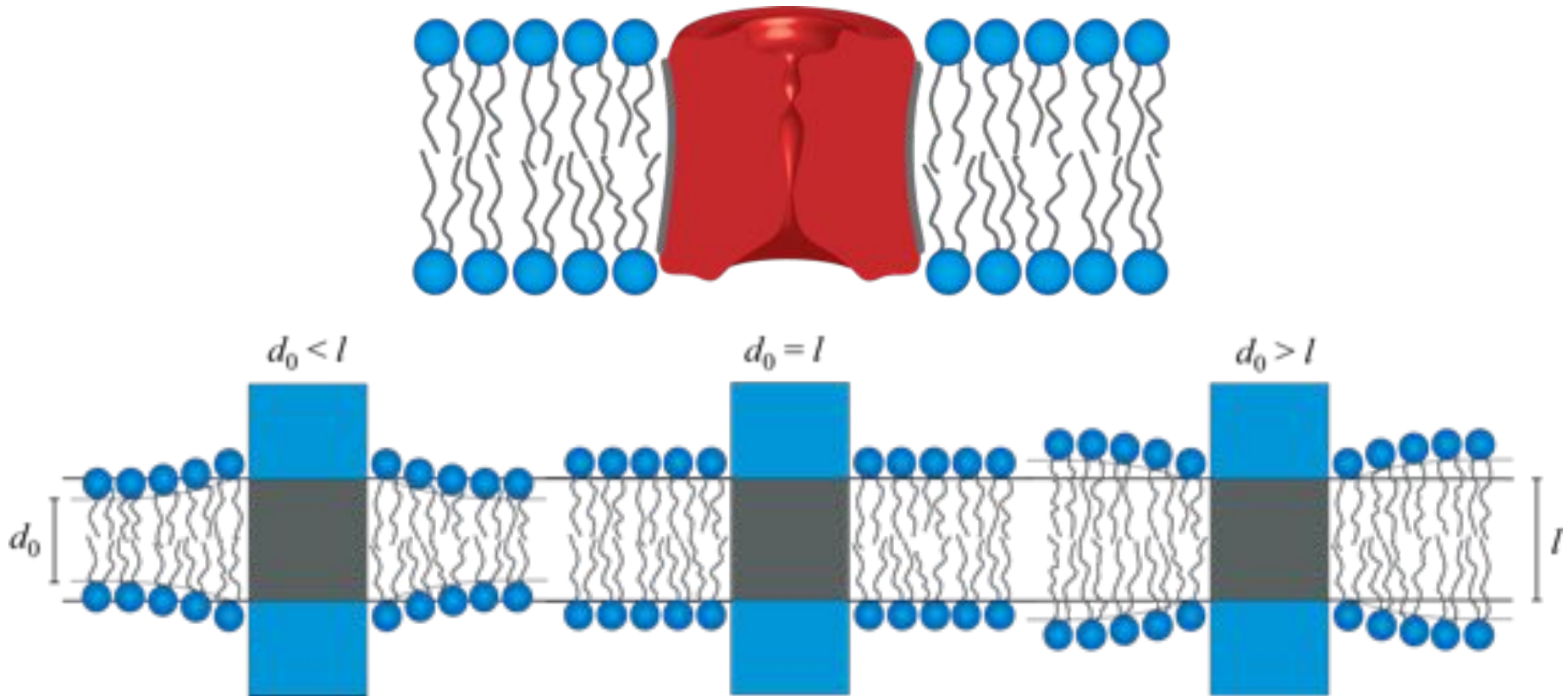
# Lipids – “rafts” / domains / phases



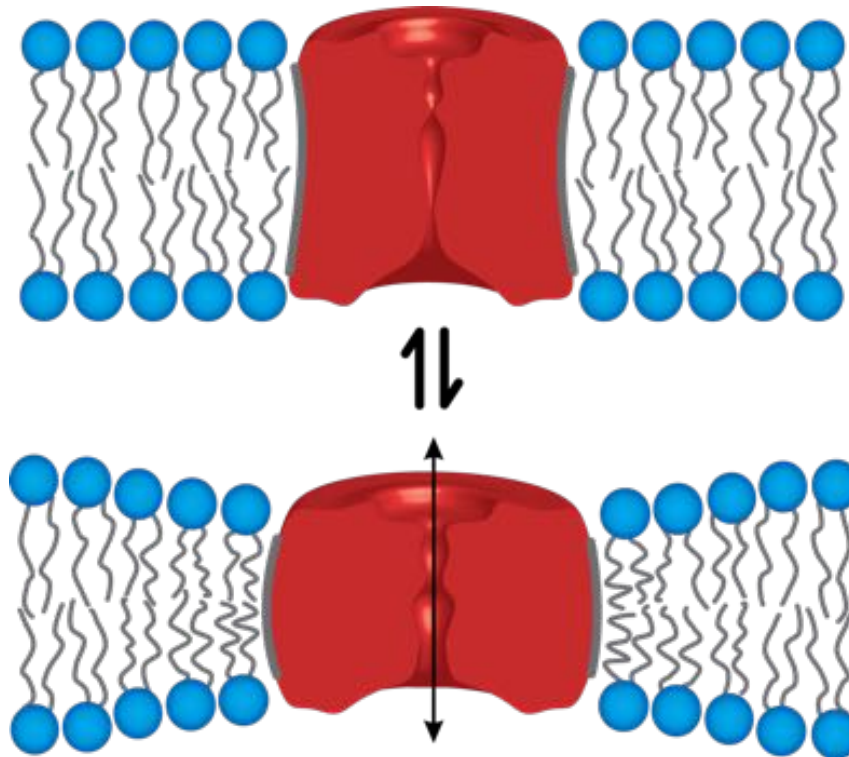
Feigenson, G.W. 2006. Phase behavior of lipid mixtures. Nat. Chem. Biol. 2: 560–563.

## Lipids – bilayer/protein interactions

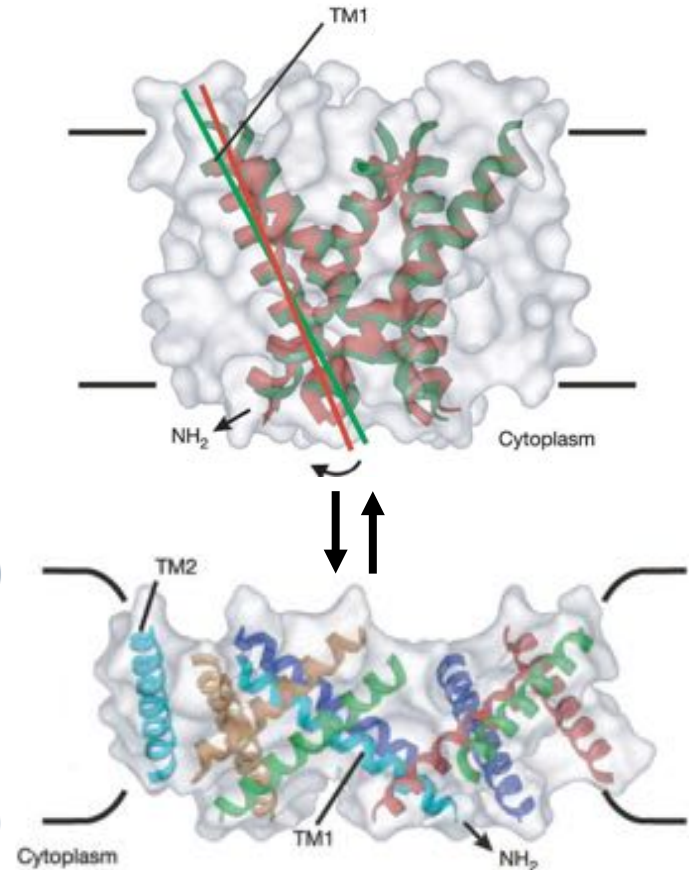
**Hydrophobic matching:** to minimize exposure to water, a membrane protein's hydrophobic domain is embedded in the bilayer hydrophobic core.



# Lipids – bilayer/protein interactions



## MscL channel

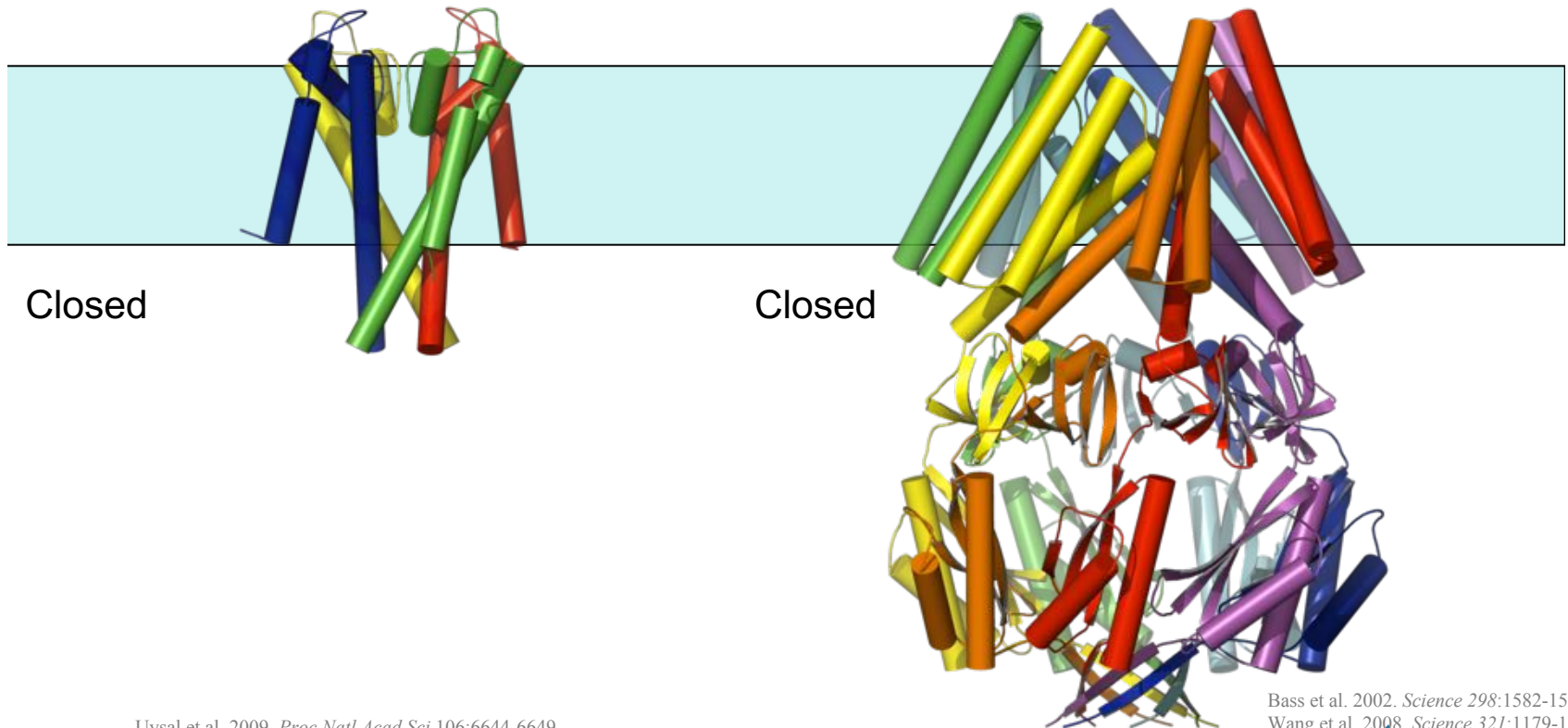


Chang et al. 1998. *Science* 282:2220-2226 and  
Perozo et al. 2002. *Nature* 418:942-948

# Lipids – bilayer/protein interactions

## KcsA channel

## MscS channel



Closed

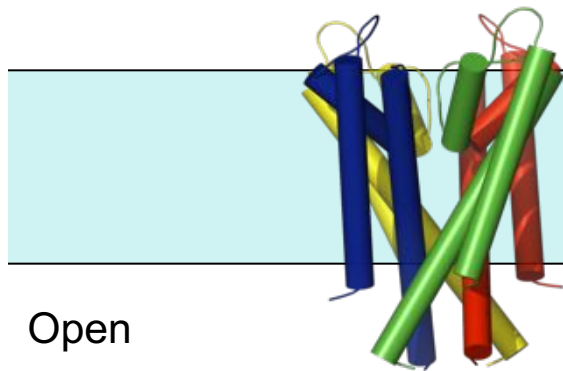
Closed

Uysal et al. 2009. *Proc Natl Acad Sci* 106:6644-6649

Bass et al. 2002. *Science* 298:1582-1587  
Wang et al. 2008. *Science* 321:1179-1183

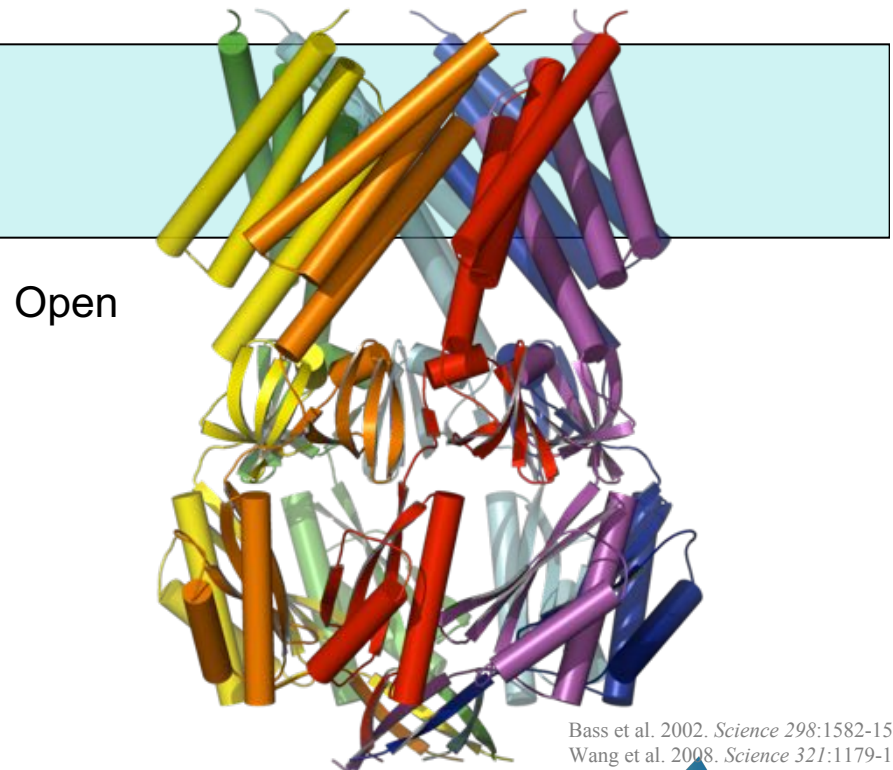
# Lipids – bilayer/protein interactions

## KcsA channel



Open

## MscS channel



Open

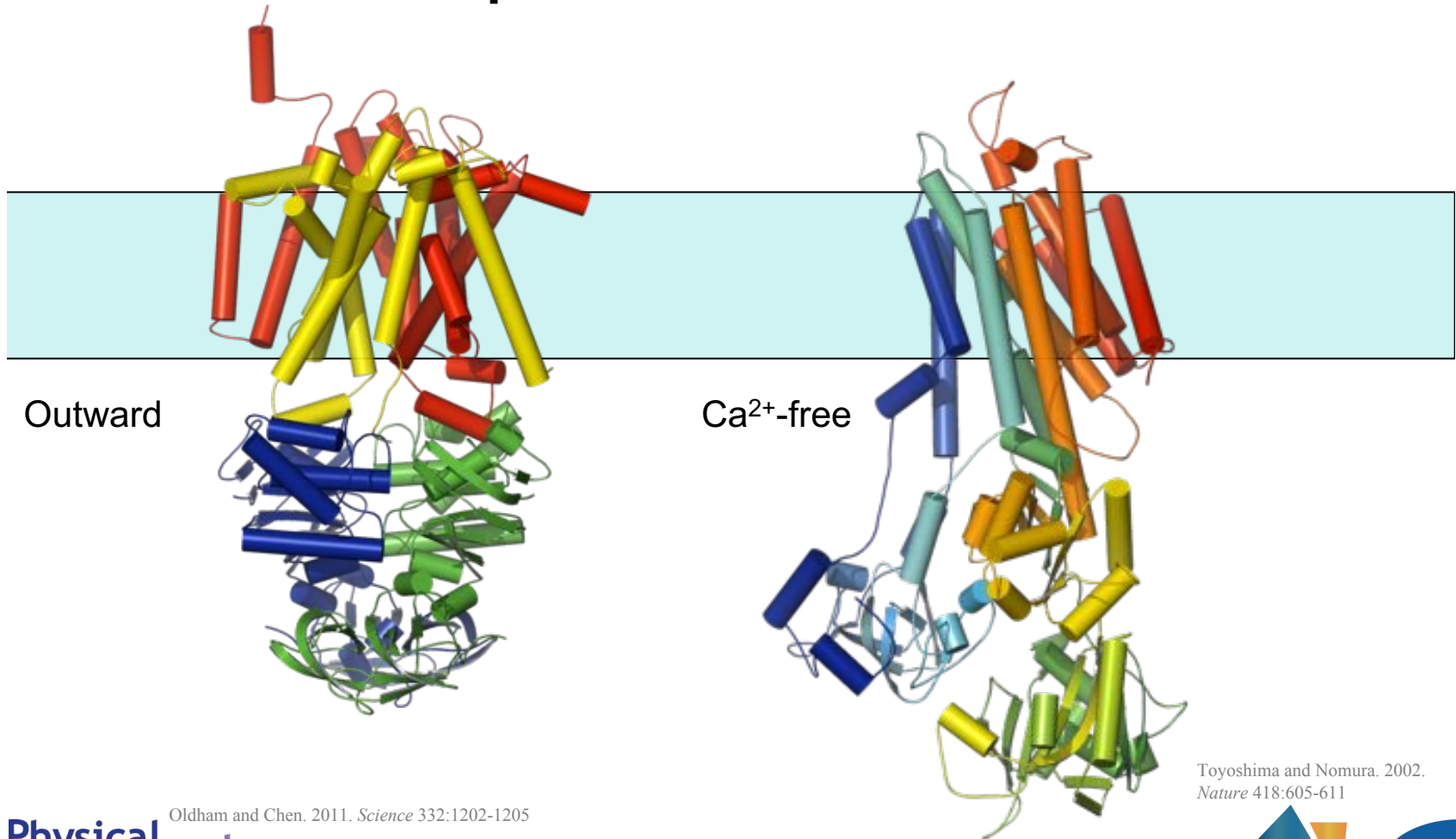
Morais-Cabral et al. 2001. *Nature* 414:37-42

Bass et al. 2002. *Science* 298:1582-1587  
Wang et al. 2008. *Science* 321:1179-1183

# Lipids – bilayer/protein interactions

## Maltose transporter

## Ca<sup>2+</sup>-ATPase

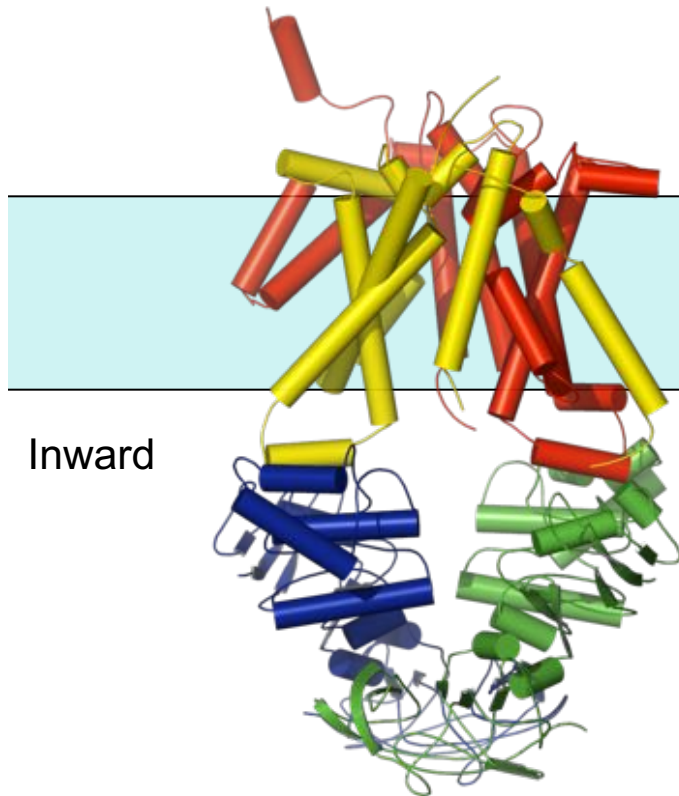


Oldham and Chen. 2011. *Science* 332:1202-1205

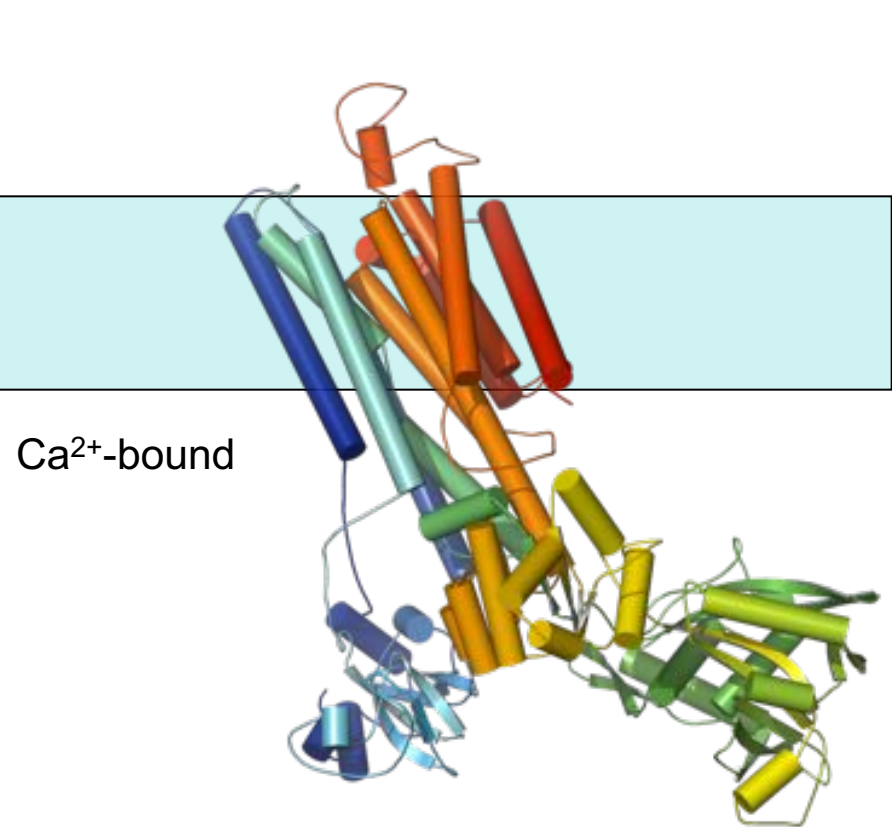
Toyoshima and Nomura. 2002.  
*Nature* 418:605-611

# Lipids – bilayer/protein interactions

## Maltose transporter



## Ca<sup>2+</sup>-ATPase



Chen, Oldham, Davidson, and Chen. 2013. *Nature* 499:364-368

Toyoshima and Nomura. 2002.  
*Nature* 418:605-611

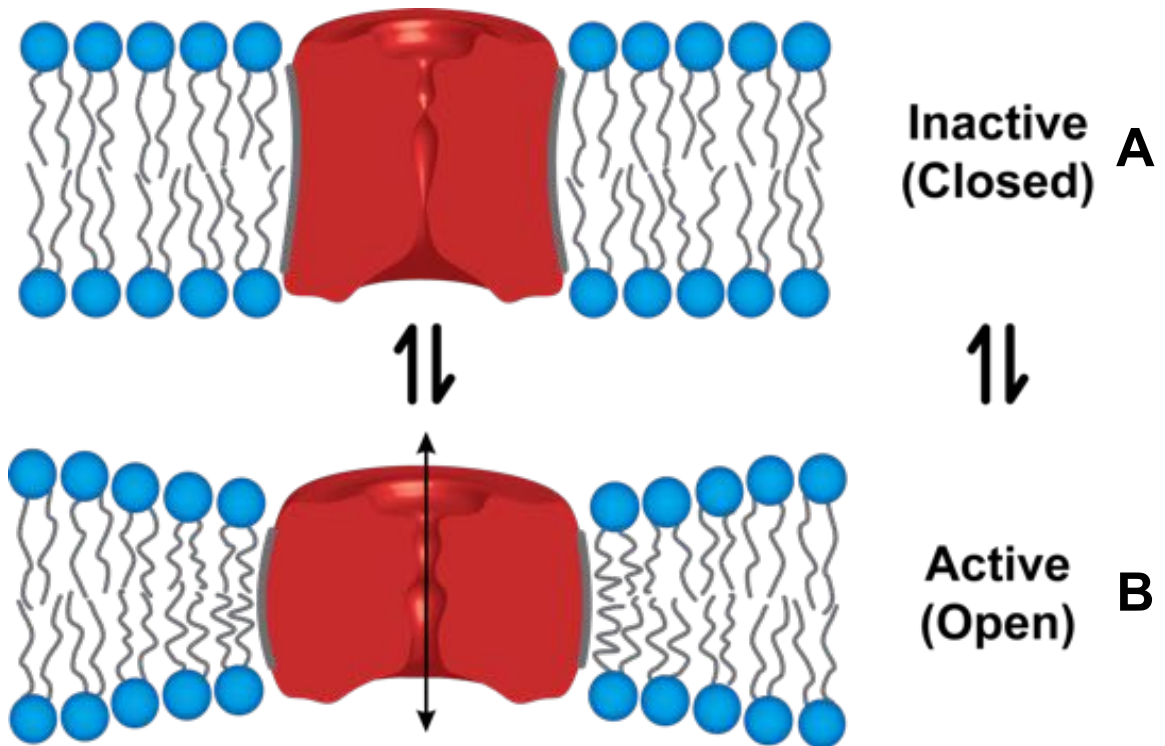


# Lipids – bilayer/protein interactions

**Protein conformational** changes involving the protein hydrophobic area are energetically coupled to the lipid bilayer.

$$\frac{n_B}{n_A} = \exp \left\{ \frac{-\Delta G_{\text{tot}}^{A \rightarrow B}}{k_B T} \right\}$$

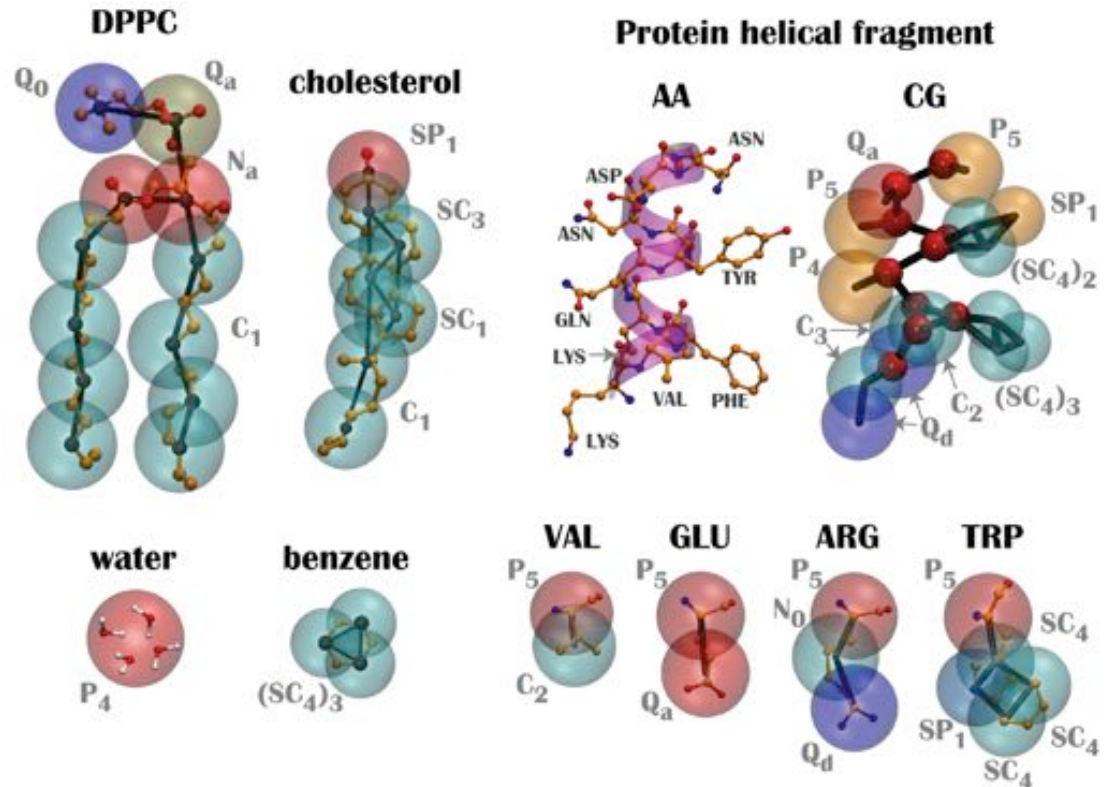
$$\Delta G_{\text{tot}}^{A \rightarrow B} = \Delta G_{\text{prot}}^{A \rightarrow B} + \Delta G_{\text{bilayer}}^{A \rightarrow B}$$



# Martini - coarse-grained (CG) MD simulations

## The Martini CG force field

- Approximately 4:1 mapping of heavy atoms
- A 2-3 orders of magnitude speedup compared to atomistic simulations
- A large number of parameterized lipids
- Easy backmapping to AA



X. Periole and S.J. Marrink. The Martini coarse-grained force field. In "Methods in molecular biology", Vol 924, L. Monticelli & E. Salonen Eds., Springer, 2013, pp 533-565.

# Martini - coarse-grained (CG) MD simulations

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TABLE 1: Interaction Matrix<sup>a</sup>

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

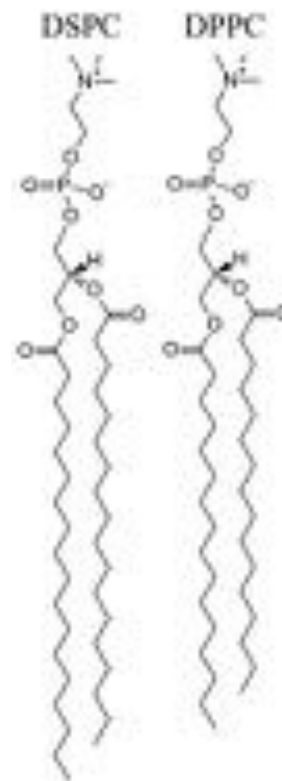
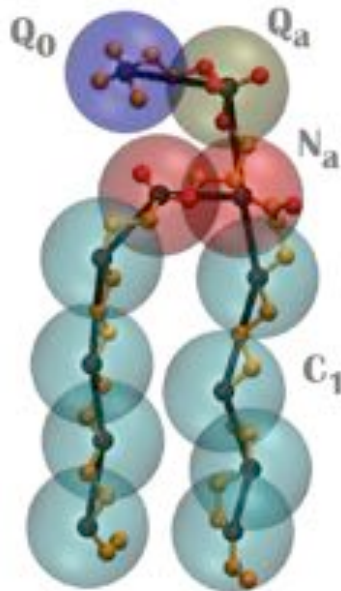
LJ interactions depend on hydrophilicity of CG bead  
*nine levels with  $2.0 < \epsilon < 5.6$  kJ/mol;  $\sigma = 0.47$  nm*

Marrink, S.J., H.J. Risselada, S. Yefimov, D.P. Tieleman, and A.H. De Vries. 2007. The MARTINI force field: coarse grained model for biomolecular simulations. *J. Phys. Chem. B.* 111: 7812–7824.

# Martini - coarse-grained (CG) MD simulations

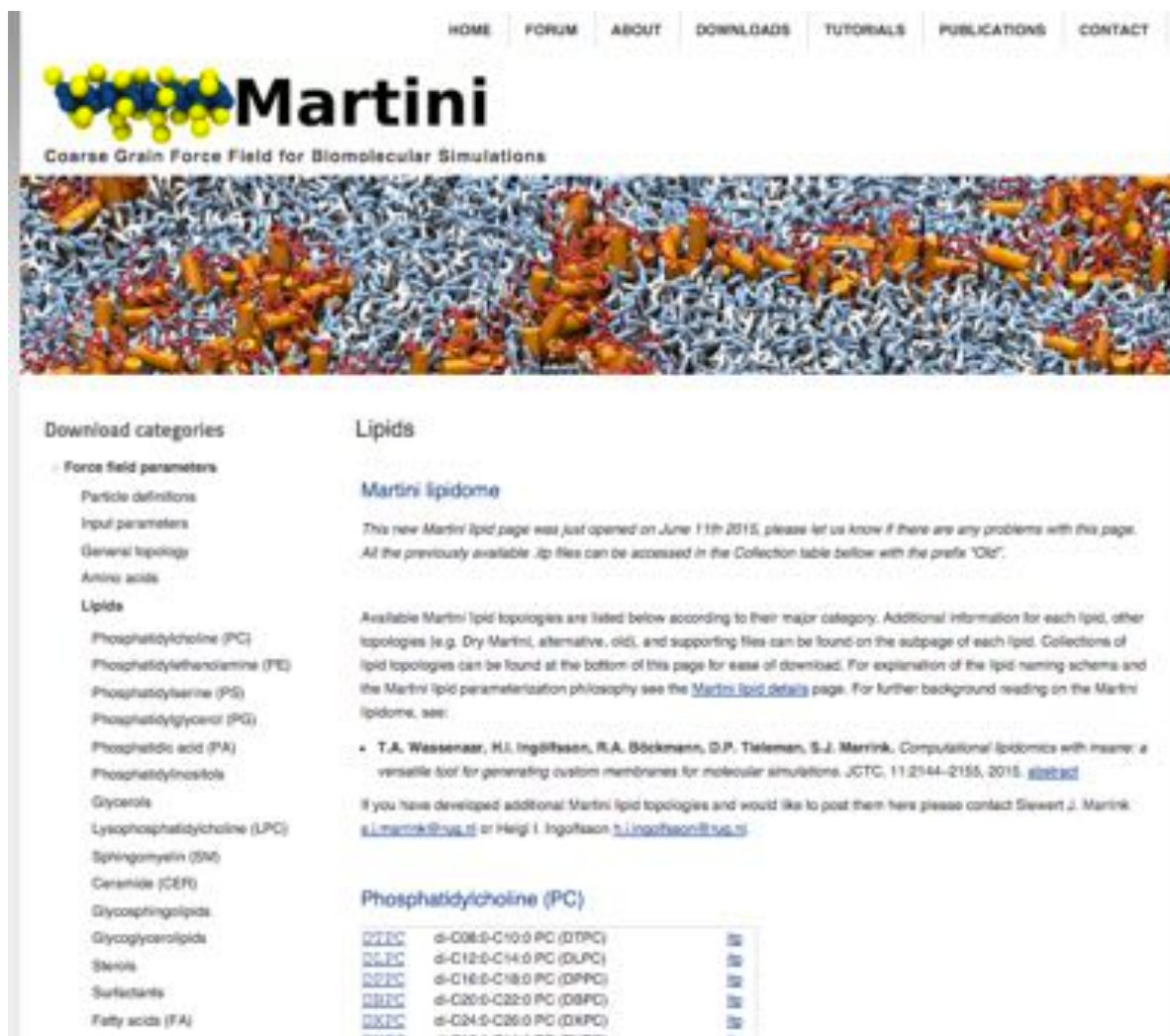
## The Martini CG force field

- Approximately 4:1 mapping of heavy atoms
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- A large number of parameterized lipids
- Easy backmapping to AA



DPPC, di-C16:0 palmitic tails  
DSPC, di-C18:0 stearoyl tails

# Lipidome – the Martini lipids website



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## Martini

Coarse Grain Force Field for Biomolecular Simulations

Download categories

- Force field parameters
  - Particle definitions
  - Input parameters
  - General topology
  - Amino acids
- Lipids
  - Phosphatidylcholine (PC)
  - Phosphatidylethanolamine (PE)
  - Phosphatidylserine (PS)
  - Phosphatidylglycerol (PG)
  - Phosphatidic acid (PA)
  - Phosphatidylinositol
  - Glycerols
  - Lysophosphatidylcholine (LPC)
  - Sphingomyelin (SM)
  - Ceramide (CE)
  - Glycosphingolipids
  - Glycoglycerolipids
  - Sterols
  - Surfactants
  - Fatty acids (FA)

### Lipids

#### Martini lipidome

This new Martini lipid page was just opened on June 11th 2015, please let us know if there are any problems with this page. All the previously available .zip files can be accessed in the Collection table below with the prefix "Old".

Available Martini lipid topologies are listed below according to their major category. Additional information for each lipid, other topologies (e.g. Dry Martini, alternative, old), and supporting files can be found on the subpage of each lipid. Collections of lipid topologies can be found at the bottom of this page for ease of download. For explanation of the lipid naming scheme and the Martini lipid parameterization philosophy see the [Martini lipid details](#) page. For further background reading on the Martini lipidome, see:

- T.A. Wassenaar, H.I. Ingólfsson, R.A. Böckmann, D.P. Teleman, S.J. Marrink. Computational lipidomics with mearns: a versatile tool for generating custom membranes for molecular simulations. JCTC, 11:2144–2155, 2015. [abstract](#)

If you have developed additional Martini lipid topologies and would like to post them here please contact Siewert J. Marrink [s.j.marrink@vup.nl](mailto:s.j.marrink@vup.nl) or Heig I. Ingólfsson [h.i.ingolfsen@vup.nl](mailto:h.i.ingolfsen@vup.nl)

#### Phosphatidylcholine (PC)

<a href="#">DTPC</a>	d-C08:0-C10:0 PC (DTPC)	<a href="#">DTPC</a>
<a href="#">DLPC</a>	d-C12:0-C14:0 PC (DLPC)	<a href="#">DLPC</a>
<a href="#">DPPC</a>	d-C16:0-C18:0 PC (DPPC)	<a href="#">DPPC</a>
<a href="#">DOPC</a>	d-C20:0-C22:0 PC (DOPC)	<a href="#">DOPC</a>
<a href="#">DOPX</a>	d-C24:0-C26:0 PC (DOPX)	<a href="#">DOPX</a>

<http://cgmartini.nl/index.php/force-field-parameters/lipids>

# Lipidome – the Martini lipids website



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## Martini

Coarse Grain Force Field for Biomolecular Simulations



**Download categories**

- Force field parameters
  - Particle definitions
  - Input parameters
  - General topology
  - Amino acids
  - Lipids
  - Solvents
  - Ions
  - Sugars
  - Polymers
  - Others
  - Dry Martini
  - ChA
- Example applications
- Tools

**Login Form**

User Name:

Password:

Remember me:

### Martini topology

Lipids -> PC -> DPPC

**Description:**  
A general model phosphatidylcholine (PC) lipid corresponding to atoms: e.g. C18:1(9c), C18:1(9c) dioleoyl (DOPC) tails.

**Parameterization:**  
This topology follows the standard Martini 2.0 lipid definitions and building block rules.

**Reference(s):**

- S.J. Marrink, A.H. de Vries, A.E. Mark. Coarse grained model for semi-quantitative lipid simulations. *JPC-B*, 108:750-760,2004. doi:10.1021/jp036908g
- S.J. Marrink, H.J. Risselada, S. Yefimov, D.P. Tieleman, A.H. de Vries. The MARTINI force field: coarse grained model for biomolecular simulations. *JPC-B*, 111:7812-7824, 2007. doi:10.1021/jp071897f
- T.A. Wassenaar, H.J. Ingólfsson, R.A. Bokkann, D.P. Tieleman, S.J. Marrink. Computational lipidomics with inerte: a versatile tool for generating custom membranes for molecular simulations. *JCTC*, 15(4):1215-12604, 2015. doi:10.1021/acs.jctc.5b00209



**Topology files:**

[martini\\_v2.2\\_DPPC\\_02.itp](#) current  
[martini\\_v2.2\\_DPPC\\_01.itp](#) old v5 head-steryl tail model

**Mapping files:**

<http://cgmartini.nl/index.php/force-field-parameters/lipids>

# Lipidome – the Martini lipid tail naming schema

One letter names	Bead assignment	Corresponding to atomistic tails	Examples of corresponding fatty acid names
C	C	C04:0-C06:0	C04:0 butyryl - C06:0 hexanoyl
T	CC	C08:0-C10:0	C08:0 octanoyl - C10:0 decanoyl
L	CCC	C12:0-C14:0	C12:0 lauric acid - C14:0 myristoyl
P	CCCC	C16:0-C18:0	C16:0 palmitic acid - C18:0 stearoyl
B	CCCCC	C20:0-C22:0	C20:0 arachidoyl - C22:0 behenoyl
X	CCCCCC	C24:0-C26:0	C24:0 lignoceroyl - C26:0 hexacosanoyl
Y	CDC	C12:1-C14:1(9c)	C14:1(9c) myristoleoyl
O	CDCC	C16:1-C18:1(9c)	C16:1(9c) palmitoleic acid, C18:1(9c) oleic acid
V	CCDC	C16:1-C18:1(11c)	C16:1(11c), C18:1(11c) cis-vaccenic acid, C18:1(12c)
G	CCDCC	C20:1-C22:1(11c)	C20:1(11c) gondoic acid, C22:1(11c), C22:1(13c) erucoyl
N	CCCDCC	C24:1-C26:1(9c)	C24:1(9c) nervonic acid, C26:1(9c)
I	CDDC	C16:2-C18:2(9-12c)	C18:2(9c,12c) linoleic acid
F	CDDD	C16:3-C18:3(9-15c)	C18:3(9c,12c,15c) octadecatrienoyl
E	CCDDC	C20:2-C22:2(11-16c)	C20:2(11c,14c) eicosadienoic acid, C22:2(13c,16c) docosadienoic acid
Q	CDDDC	C20:3-C22:3(5-14c)	C20:3(5c,8c,11c) mead acid, C20:3(8c,11c,14c) dihomo-gamma-linolenic acid
A	DDDDC	C20:4-C22:5(4-16c)	C20:4(5c,8c,11c,14c) arachidonic acid, C22:5(4c,7c,10c,13c,16c) docosapentaenoic acid
U	DDDDD	C20:5-C22:6(4-19c)	C22:6(4c,7c,10c,13c,16c,19c) docosahexaenoic acid
R	DDDDDD	C24:6-C26:6(6-21c)	C24:6(6c,9c,12c,15c,18c,21c) nisinic acid
J	TCCC	C16:1-C18:1(3t)	C16:1(3t) trans-3-hexadecanoic acid
Pa	TCC	C(d16:1)-C(d18:1)	Sphingosine C16 palmitic acid - C18 stearoyl with a trans double bond
B <sup>a</sup>	TCCC	C(d20:1)-C(d22:1)	Sphingosine C20 arachidoyl - C22 behenoyl with a trans double bond
X <sup>a</sup>	TCCCC	C(d24:1)-C(d26:1)	Sphingosine C24 lignoceroyl - C26 hexacosanoyl with a trans double bond

<sup>a</sup>Sphingosine lipids and have one C bead less as a few of the first carbons of the tail are part of the AM1 linker bead.

# Lipidome – recent lipid improvements

- **Improved Cholesterol**

Reparameterized using virtual sites, a middle hinge and extended plane extrusions.

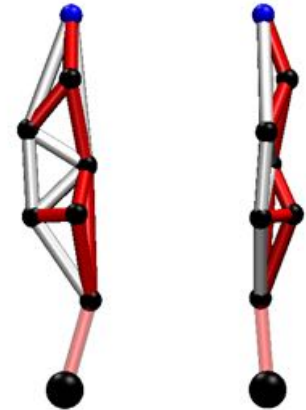
- **Gangliosides**

GM1 was stabilized using virtual sites and altered headgroup linking. GM3 created and less “sticky” alt. parameters developed.

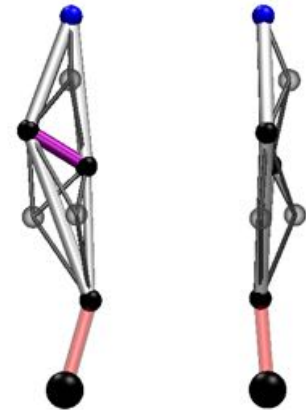
- **Phosphatidylinositol**

Stability of PI and PIP2 improved and PIP1 and PIP3 added. Further improved geometry and all variants of POP1 and PIP2 phosphates on their way

Old cholesterol



New cholesterol



Manuel

Melo, M. N., Ingólfsson, H. I., & Marrink, S. J. (2015). Parameters for Martini sterols and hopanoids based on a virtual-site description. *The Journal of Chemical Physics*, 143(24), 243152.



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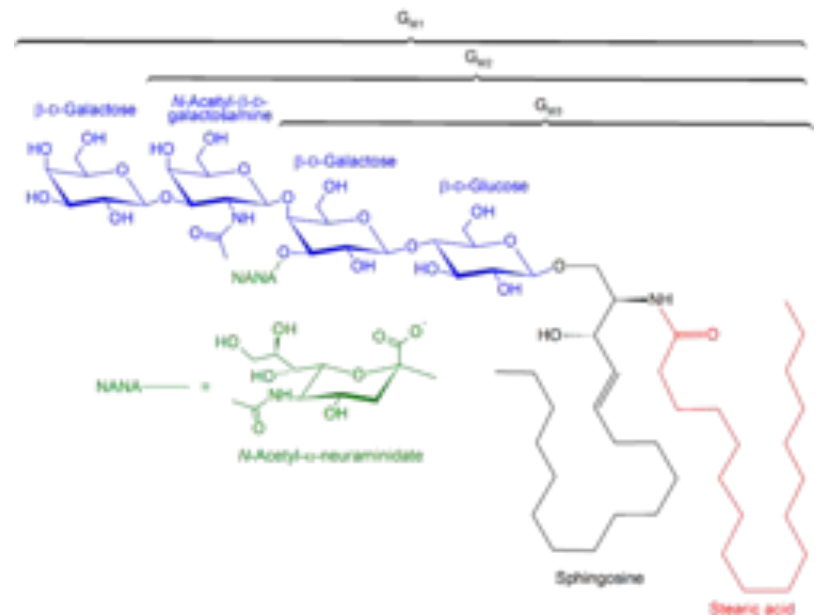
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<http://en.wikipedia.org/wiki/GM3>

Ruo-Xu Gu

Gu, R.-X., Ingólfsson, H. I., De Vries, A. H., Marrink, S. J., & Tieleman, D. P. (2017). Ganglioside-Lipid and Ganglioside-Protein Interactions Revealed by Coarse-Grained and Atomistic Molecular Dynamics Simulations. *The Journal of Physical Chemistry B*, 121(15), 3262–3275.

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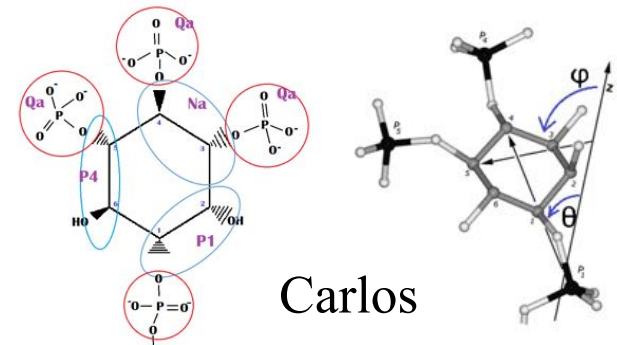
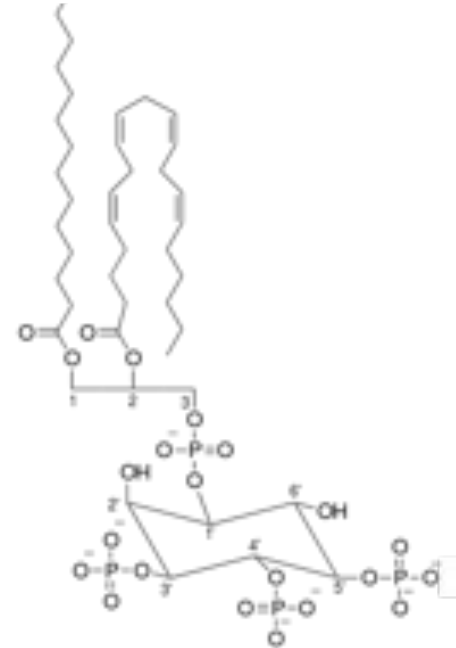
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Carlos

[http://en.wikipedia.org/wiki/Phosphatidylinositol\\_\(3,4,5\)-trisphosphate](http://en.wikipedia.org/wiki/Phosphatidylinositol_(3,4,5)-trisphosphate)

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# Lipidome – recent lipid improvements

- **Lipopolysaccharides (LPS)**

More than on set of Martini parameters

- **More sterols**

Using the same backbone as the improved cholesterol

- **Plant galactolipids**

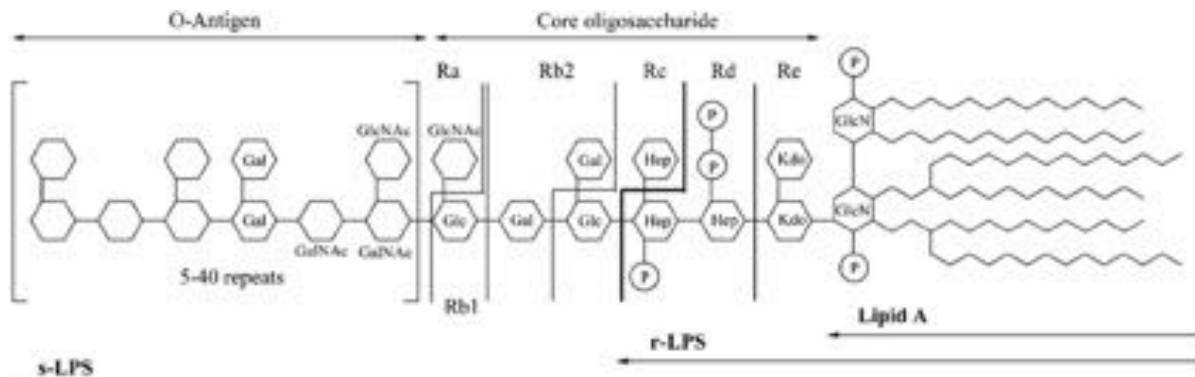
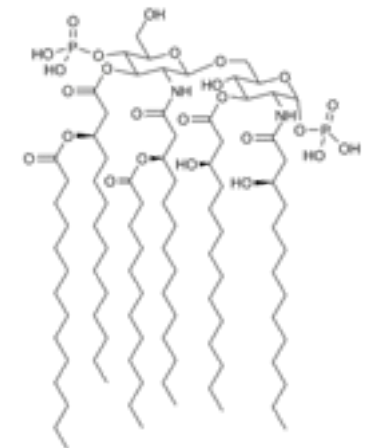
Slightly modified parameters compared to the previous glycolipid headgroups

P.C. Hsu, D. Jefferies, and S. Khalid (2016) Molecular Dynamics Simulations Predict the Pathways via Which Pristine Fullerenes Penetrate Bacterial Membranes. *J. Phys. Chem. B* 120:11170-11179

Brad Van Osten and Thad Harroun. A MARTINI extension for Pseudomonas aeruginosa PAO1 lipopolysaccharide, *J. Mol. Graph Model* 63:125-133, 2016

Ma H, Irudayanathan FJ, Jiang W, Nangia S. Simulating Gram-Negative Bacterial Outer Membrane: A Coarse Grain Model. *J Phys Chem B*. 2015 Nov 19;119(46):14668-82.

## Lipid A



[www.researchgate.net/figure/49629406\\_fig2\\_FIG-2-General-structure-of-E-coli-LPS-The-sugar-moieties-in-the-core-region-and-the](http://www.researchgate.net/figure/49629406_fig2_FIG-2-General-structure-of-E-coli-LPS-The-sugar-moieties-in-the-core-region-and-the)

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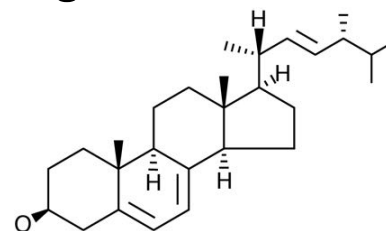
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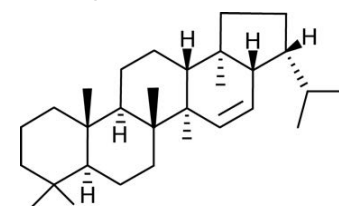
- **Plant galactolipids**

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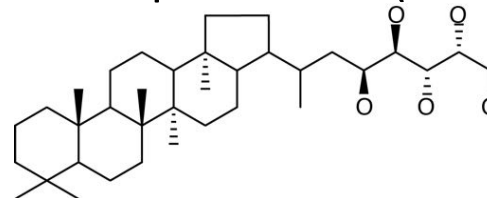
Ergosterol



Hopananes



Bacteriohopanetetrol (BHT)



## Manuel

Melo, M. N., Ingólfsson, H. I., & Marrink, S. J. (2015). Parameters for Martini sterols and hopanoids based on a virtual-site description. *The Journal of Chemical Physics*, 143(24), 243152.

# Lipidome – recent lipid improvements

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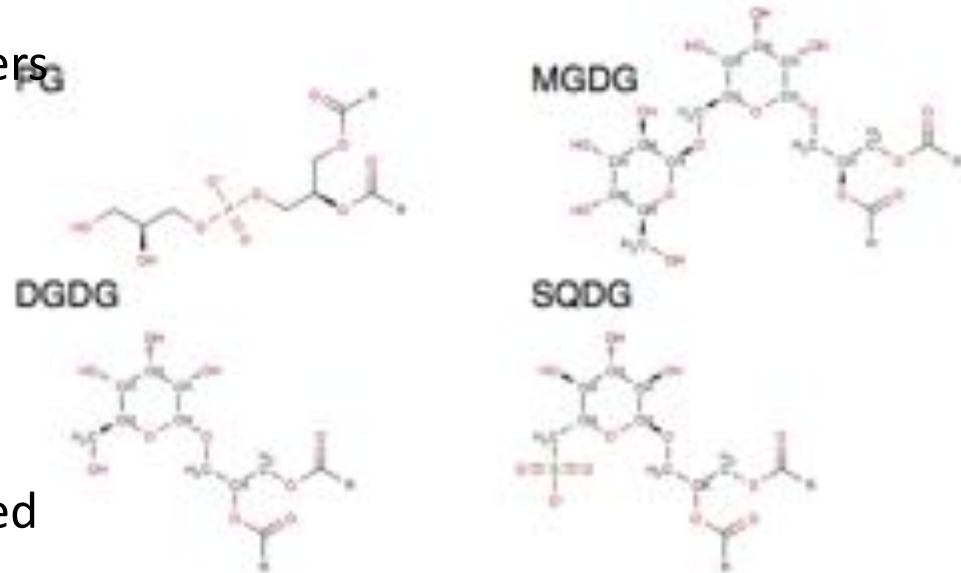
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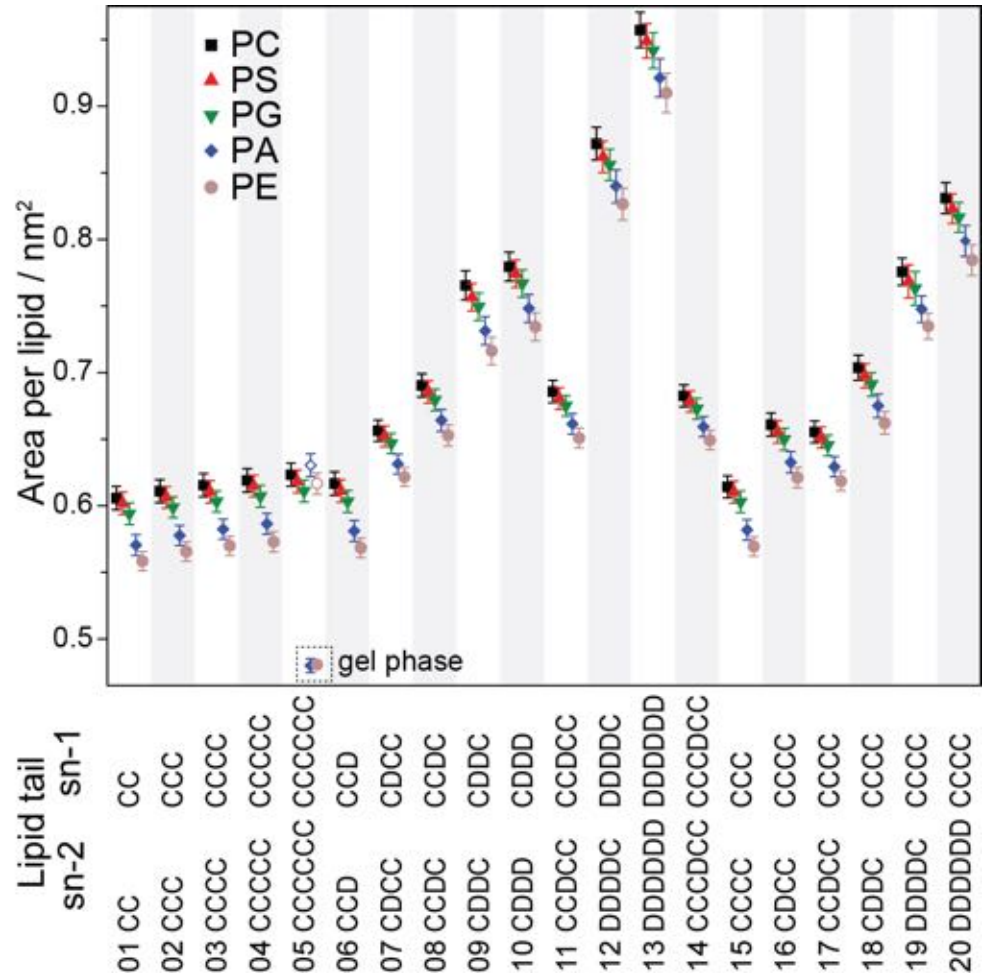
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van Eerden, F.J., D.H. de Jong, A.H. de Vries, T.A. Wassenaar, and S.J. Marrink. 2015. Characterization of thylakoid lipid membranes from cyanobacteria and higher plants by molecular dynamics simulations. *BBA - Biomembranes*. 1848: 1319–1330.

# Lipidome – Martini lipidomics

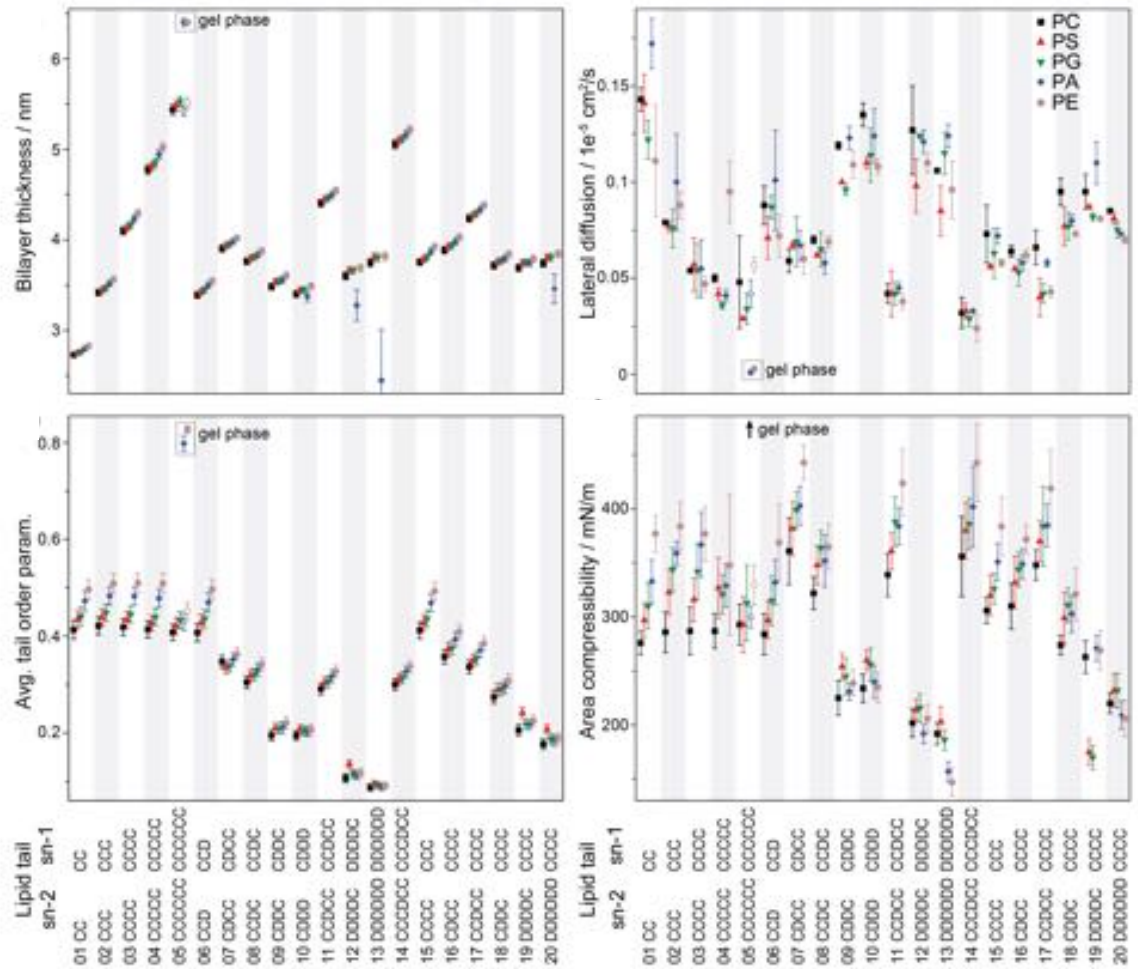
Using the *insane* membrane builder and the Martini 2.0 building blocks we created and characterized 100 different lipid types, combining 5 headgroups (PC, PS, PG, PA, PE) and 20 tails.



Wassenaar T.A., Ingólfsson H.I., Böckmann R.A., Tieleman D.P. and Marrink S.J. Computational lipidomics with insane: a versatile tool for generating custom membranes for molecular simulations. *JCTC*, 2015, 11, 2144–2155.

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# Building bilayers – CHARMM-GUI Martini Maker

**CHARMM-GUI**  
Effective Simulation Input-Generator and Files

CHARMM is a versatile program for atomic-level simulation of many-particle systems, particularly macromolecules of biological interest - M. Karplus

about us :: input generator :: archive :: charmm docs :: MD lectures :: movie gallery :: video demos :: citations :: update log

CHARMM-GUI has updated. See our [update log](#) to see what is changed. Contact us ([E-mail](#)) or [ChatRoom Forum](#) if you have any problem/question/comment.

**Input Generator**

- POB Reader
- Glycan Reader
- Solver
- Quick MD Simulator
- Drude Prepper
- Membrane Builder
- Martini Maker
- FACE CG Builder
- Boundary Potential
- PBEG Solver
- Implicit Solvent Modeler
- Free Energy Calculator
- GCN/BD Ion Simulator

### Martini Bilayer Maker

The Martini Bilayer Maker is designed to provide coarse-grained simulation systems and inputs in bilayer using the Martini force field.

The Martini force fields available in CHARMM-GUI are:

- martini22: Martini 2.2 amino acid, Martini 2.0 lipids and non-polarizable water.
- martini22p: Martini 2.2 polar amino acids, Martini 2.0 lipids and polarizable water.
- albedyn: Elastic Network in Dynamics. An elastic network is used for the protein/Martini 2.0 lipids and non-polarizable water.
- albedynp: Polar albedyn protein, Martini 2.0 lipids and polarizable water.
- dry Martini: Martini without water beads. Only lipids are available.

Notes for Martini Maker:

- Only GROMACS input files are provided for simulations.
- The available molecules include protein, lipids, water, and ions. DNA, sugar, and polymer are not currently supported.
- Double precision GROMACS is **STRONGLY** recommended for minimization.
- The GROMACS input files are compatible with version 4.5.x. If GROMACS 5.0 is used, add `cut-off-scheme=group` in `mdp` files.
- For membrane systems, the protein must be oriented with respect to a membrane bilayer whose normal is parallel to the Z-axis and whose center is located at Z=0. RCSB PDB structures are **NOT** pre-oriented, but can be oriented in site 2 (see below). CPM (<http://comp.phar.umich.edu/>) provides pre-oriented protein coordinates with respect to the membrane normal.
- For glycol tails, a new x1 bead model from a [recent development](#) is used. The new model provides consistent mapping between CG beads and atomic representations, and gives slightly better bilayer thickness. The topology of the new model is defined in `glycma-v01-pa2.itp`. The old x5 bead model is commented out in `martini_v2.0_lipids.itp`. The x5 bead model is still used in Dry Martini.

References for Martini Maker:

S. Jo, T. Kim, V.G. Iyer, and W. Im (2008). CHARMM-GUI: A Web-based Graphical User Interface for CHARMM. *J. Comput. Chem.* **29**:1350-1365

Y. Qi, H.J. Ingólfsson, X. Cheng, J. Lee, S.J. Marrink, and W. Im. CHARMM-GUI Martini Maker for Coarse Grained Simulations with the Martini Force Fields. submitted.

**Protein/Membrane System**

Select Martini Models:

Download PDB File:  Download Source:

Upload PDB File:  No file chosen  
PDB Format:  RCSB  CHARMM

**Membrane Only System**

Next Step  
Select Model/Chain

**Solution,  
Micelle,  
Vesicle,  
and Bilayer  
Builders for Martini**

Yifei Qi,  
Xi Cheng,  
Jumin Lee, and  
Wonpil Im

Qi Y., H.I. Ingólfsson, X. Cheng, J. Lee, S.J. Marrink and W. Im. CHARMM-GUI Martini Maker for coarse-grained simulations with the Martini force field. *JCTC*, 2015

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# Building bilayers – CHARMM-GUI Martini Maker

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about us :: input generator :: archive :: charmm docs :: MD lectures :: movie gallery :: video demos :: citations :: update log

CHARMM-GUI has updated. See our [update log](#) to see what is changed. Contact us ([E-mail](#)) or [CHARMM-GUI user](#) if you have any problem/question/comment.

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- POB Reader
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Notes for Martini Maker:

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Next Step: Select Model Chain

**Now supports  
Lipopolysaccharides (LPS)**

Bart and Paulo

P.-C. Hsu, B.M.H. Bruininks, D. Jefferies, P.C.T. Souza, J. Lee, D.S. Patel, S.J. Marrink, Y. Qi, S. Khalid, and W. Im. CHARMM-GUI Martini Maker for Modeling and Simulation of Complex Bacterial Membranes with Lipopolysaccharides. *J. Comput. Chem.* 2017.

**Solution,  
Micelle,  
Vesicle,  
and Bilayer  
Builders for Martini**

Yifei Qi,  
Xi Cheng,  
Jumin Lee, and  
Wonpil Im

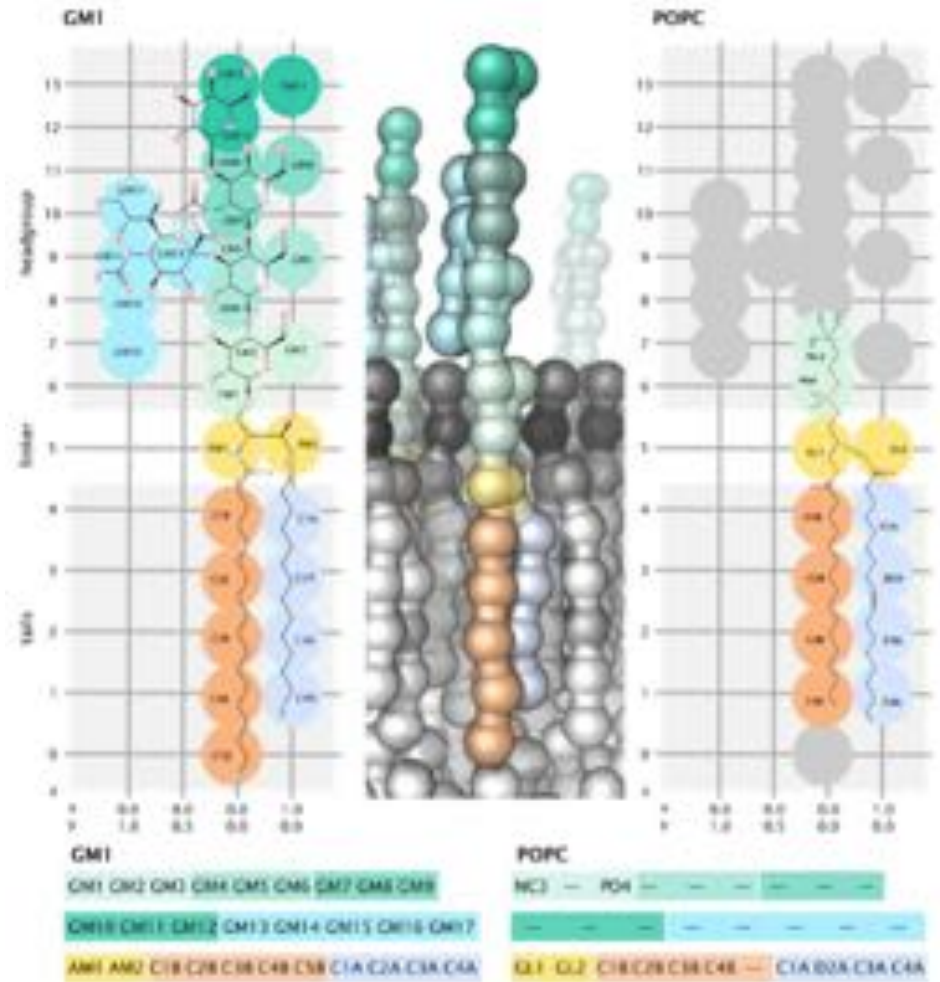
Qi Y., H.I. Ingólfsson, X. Cheng, J. Lee, S.J. Marrink and W. Im. CHARMM-GUI Martini Maker for coarse-grained simulations with the Martini force field. *JCTC*, 2015

LLNL-PRES-737105

# Building bilayers – *insane*

## INSert membrANE

A flexible CG bilayer builder that supports both complex lipid templates and on the fly lipid definitions.



Tsjerk

Wassenaar T.A., Ingólfsson H.I., Böckmann R.A., Tieleman D.P. and Marrink S.J. Computational lipidomics with insane: a versatile tool for generating custom membranes for molecular simulations. *JCTC*, 2015, 11, 2144–2155.

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# Building bilayers – *insane*

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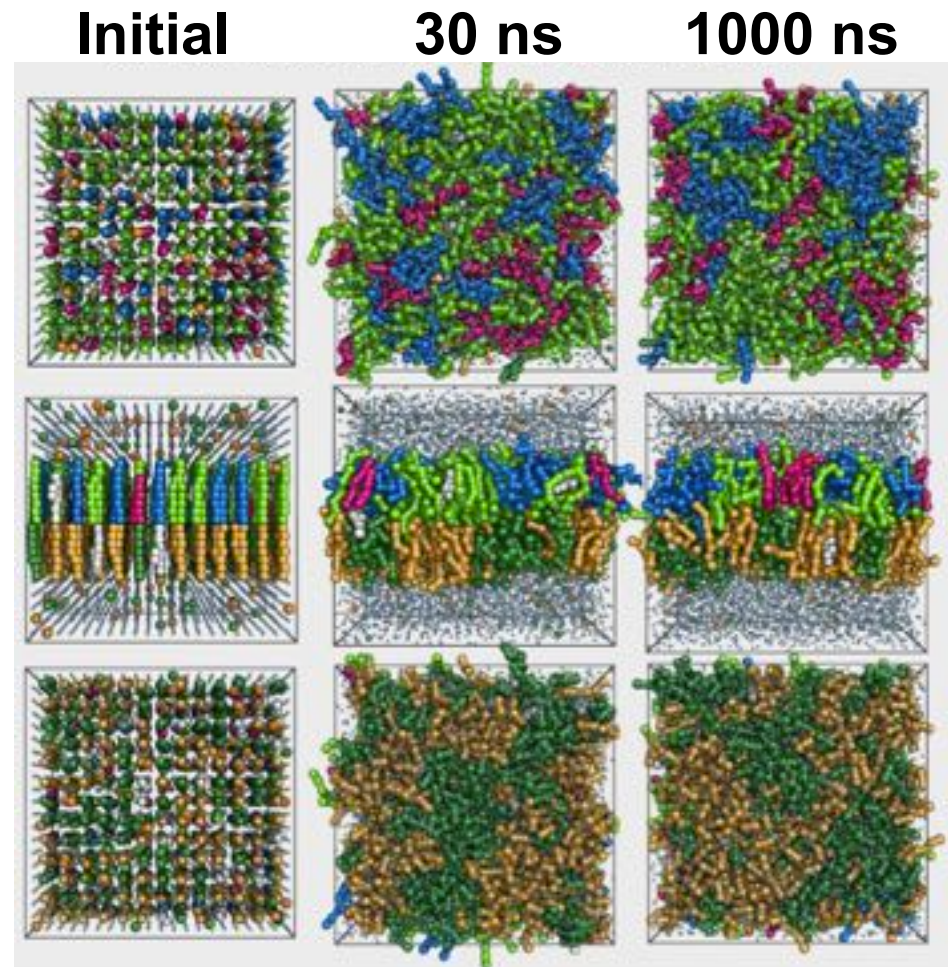
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Asymmetric

DAPC:DOPC:DLPC:cholesterol

DPPC:DIPC:cholesterol

Tsjerk



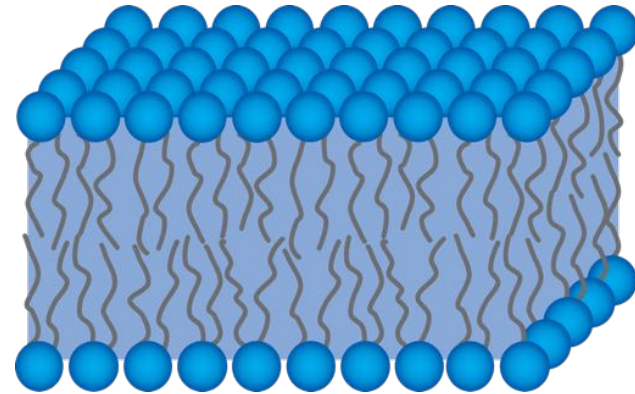
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LLNL-PRES-737105



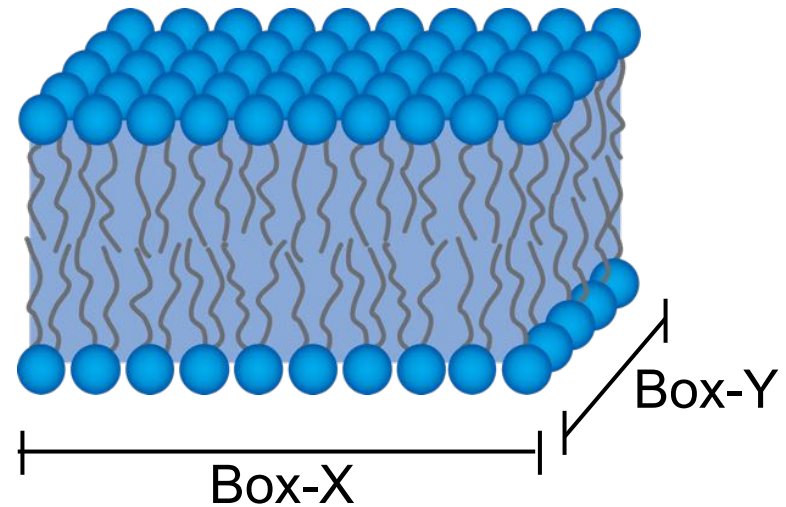
# Calculating bilayer properties

- Intrinsic lipid curvature ( $c_0$ )
- Actual curvature ( $c$ )
- Hydrophobic thickness ( $d_0$ )
- Area compression-expansion modulus ( $K_a$ )
- Splay-distortion modulus ( $K_c$ )
- Fluidity
- Diffusion
- Area per lipid
- Order parameter
- Surface tension
- Acyl chain packing
- Lateral pressure profile
- Lipid packing stress
- Bilayer stiffness



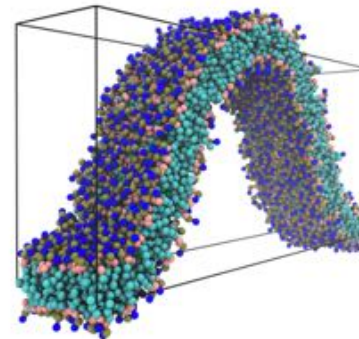
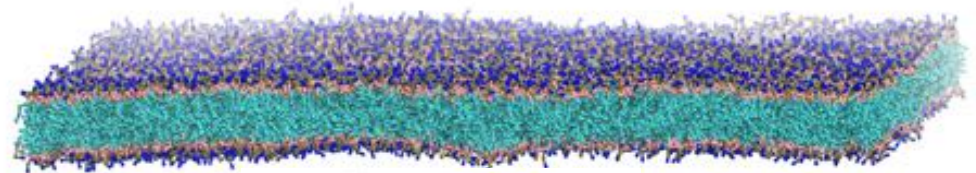
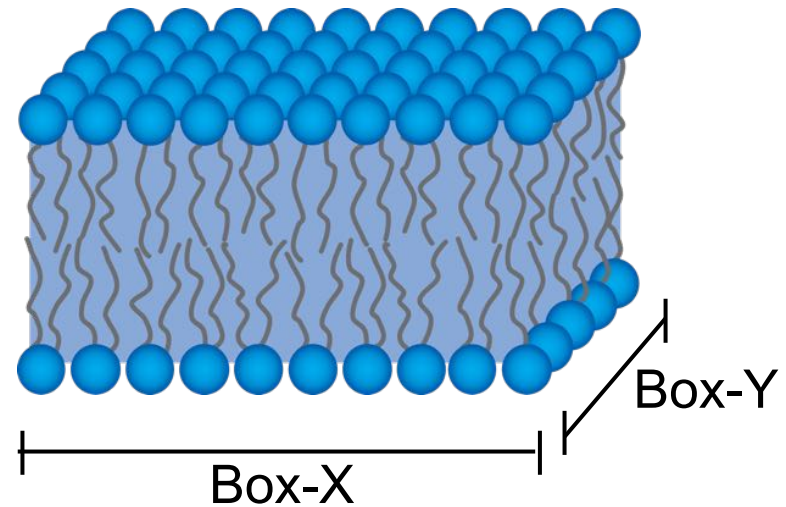
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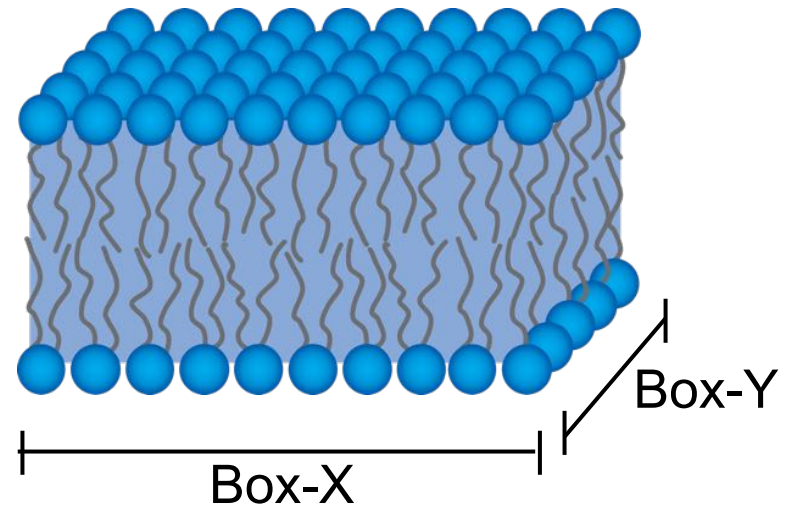
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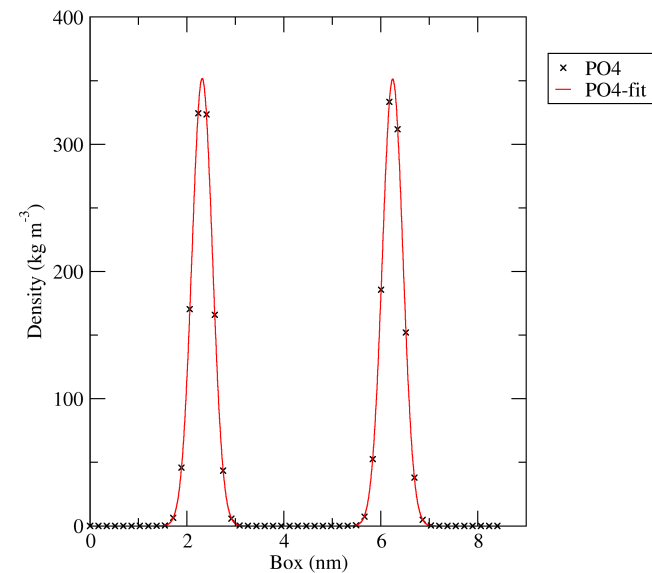
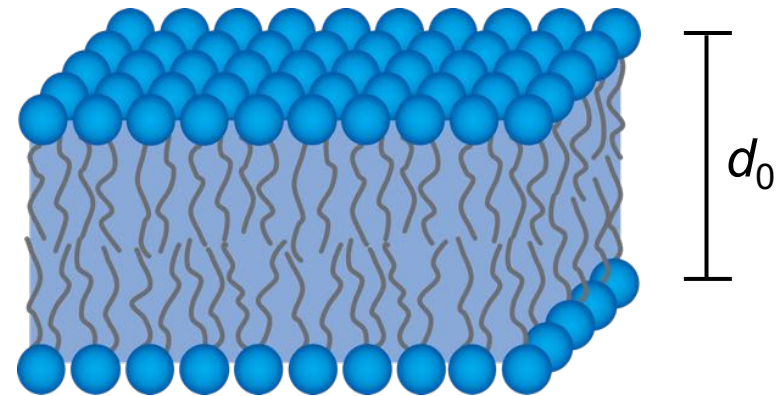
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$$K_A = k_B T \frac{\langle A \rangle}{N \langle (A - A_0)^2 \rangle}$$

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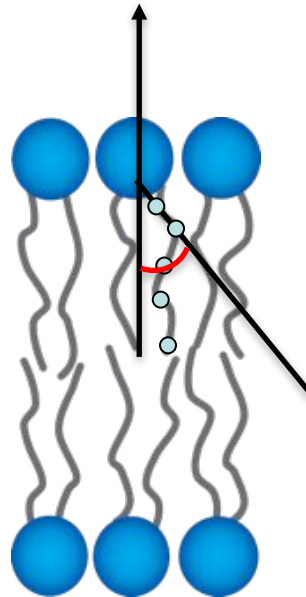
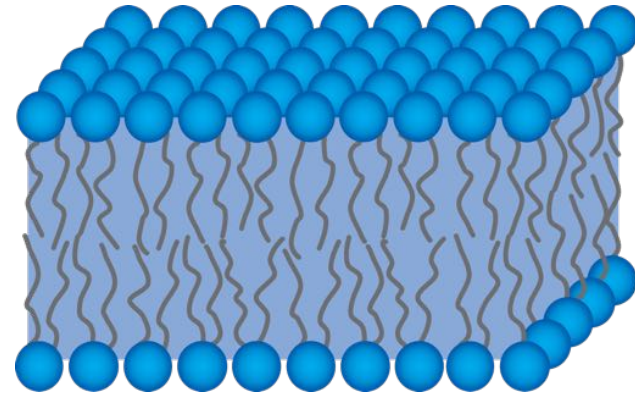
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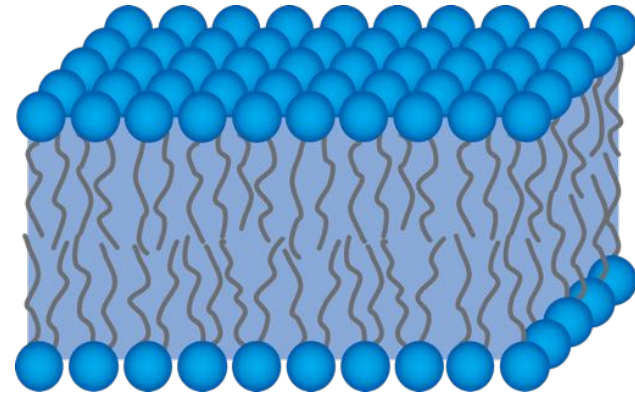
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$$S_{\text{seg}} = \frac{1}{2}(3\langle \cos^2 \theta \rangle - 1)$$

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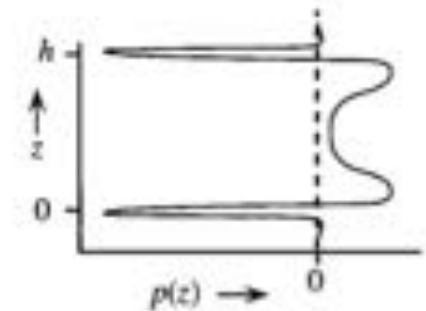
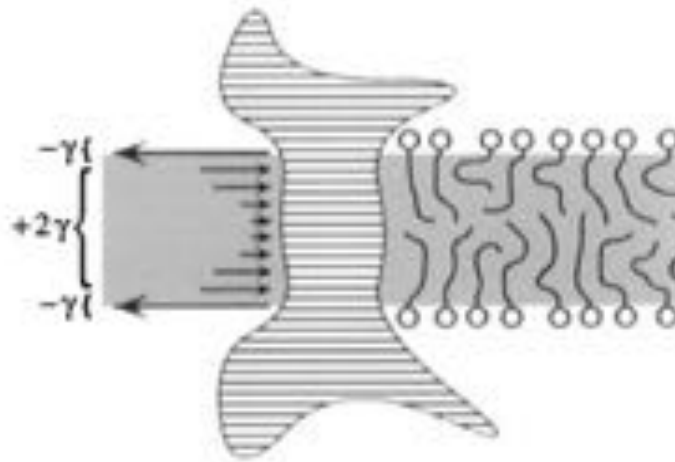
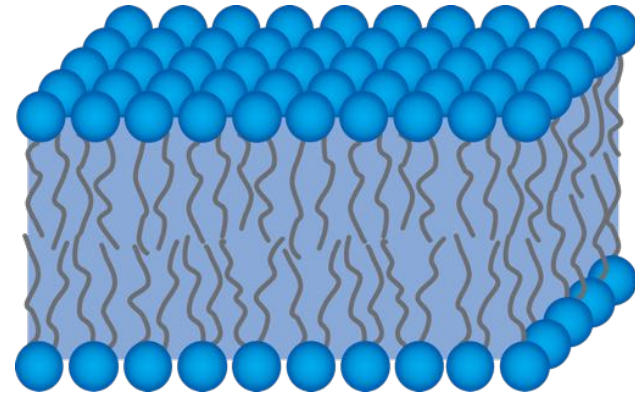
## Bending modulus ( $K$ )

$$S_u(q) = \frac{k_B T}{A_l \kappa q^4}$$

Brandt, E.G., A.R. Braun, J.N. Sachs, J.F. Nagle, and O. Edholm. 2011. Interpretation of fluctuation spectra in lipid bilayer simulations. *Biophys. J.* 100: 2104–2111.

# Calculating bilayer properties

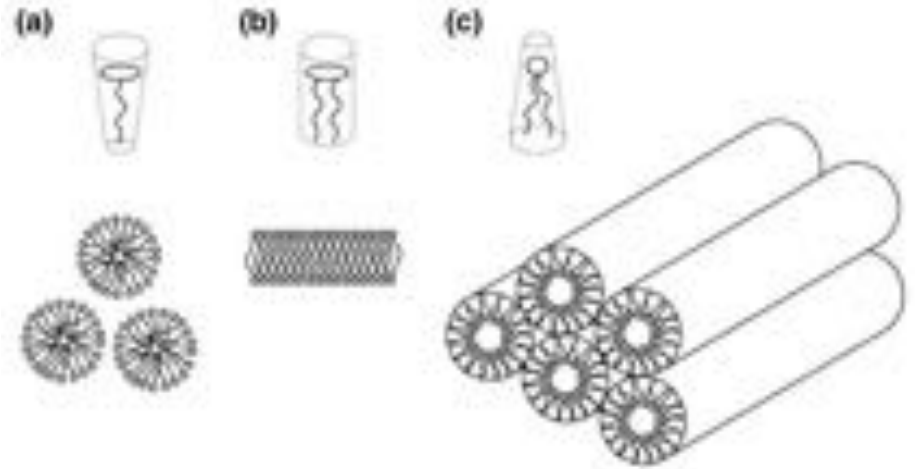
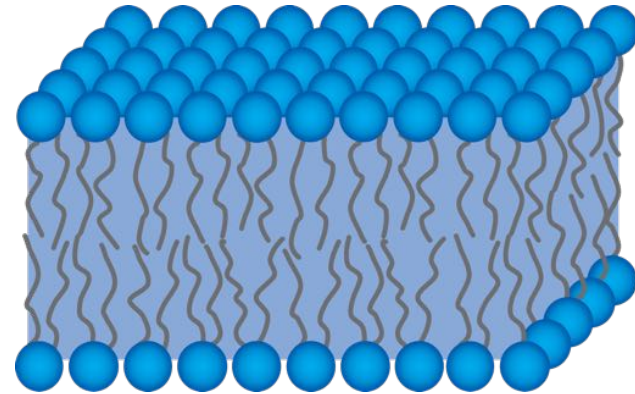
- Intrinsic lipid curvature ( $c_0$ )
- Actual curvature ( $c$ )
- Hydrophobic thickness ( $d_0$ )
- Area compression-expansion modulus ( $K_a$ )
- Splay-distortion modulus ( $K_c$ )
- Fluidity
- Diffusion
- Area per lipid
- Order parameter
- Surface tension
- Acyl chain packing
- **Lateral pressure profile**
- Lipid packing stress
- Bilayer stiffness



Cantor, R.S. 1997. Lateral Pressures in Cell Membranes: A Mechanism for Modulation of Protein Function. *J. Phys. Chem. B.* 101: 1723–1725.

# Calculating bilayer properties

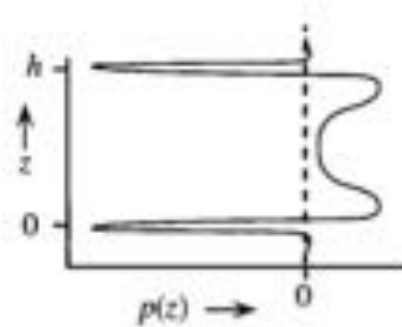
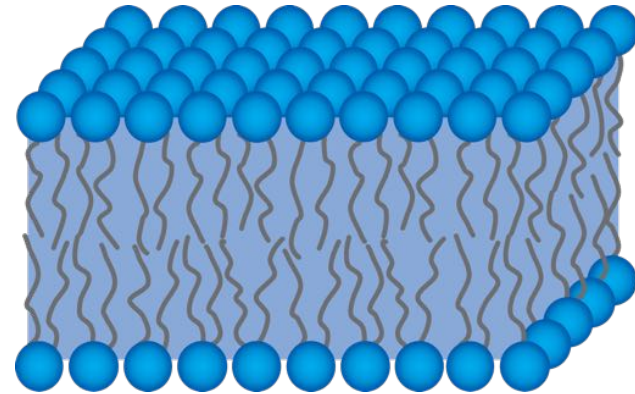
- **Intrinsic lipid curvature ( $c_0$ )**
- Actual curvature ( $c$ )
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- Area compression-expansion modulus ( $K_a$ )
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FRENDS in Cell Biology

# Calculating bilayer properties

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- Actual curvature ( $c$ )
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$$\frac{1}{2}\Sigma = \int_0^{\infty} dz \sigma_0(z) ,$$

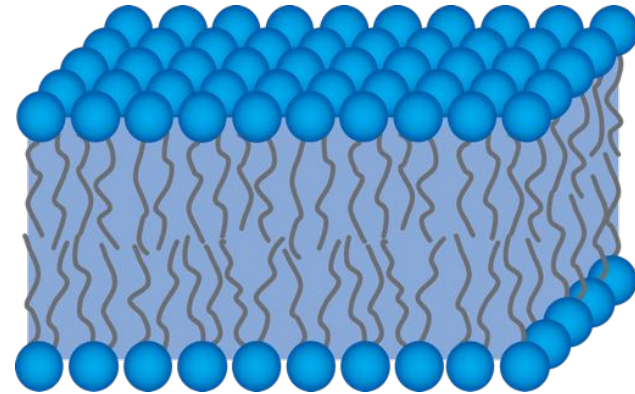
$$-\kappa_m K_{0m} = \int_0^{\infty} dz \sigma_0(z)(z - z_0) ,$$

$$\bar{\kappa}_m = \int_0^{\infty} dz \sigma_0(z)(z - z_0)^2 .$$

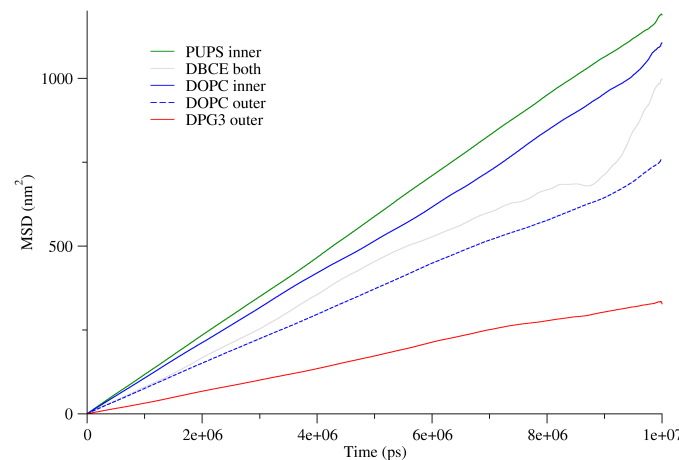
Hu, M., D.H. de Jong, S.J. Marrink, and M. Deserno. 2013. Gaussian curvature elasticity determined from global shape transformations and local stress distributions: a comparative study using the MARTINI model. *Faraday Discuss.* 161: 365–82– discussion 419–59.

# Calculating bilayer properties

- Intrinsic lipid curvature ( $c_0$ )
- Actual curvature ( $c$ )
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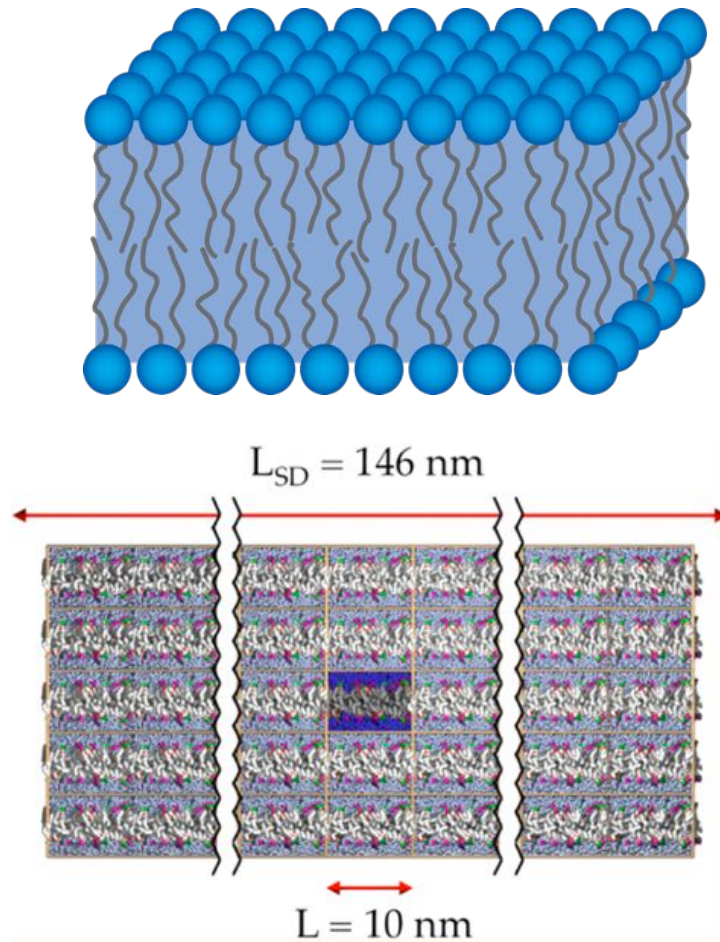


Mean square displacement (MSD) with time  
Einstein relation  $(D*t + c) t$



# Calculating bilayer properties

- Intrinsic lipid curvature ( $c_0$ )
- Actual curvature ( $c$ )
- Hydrophobic thickness ( $d_0$ )
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- Surface tension
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- Lateral pressure profile
- Lipid packing stress
- Bilayer stiffness



Venable, R. M., Ingólfsson, H. I., Lerner, M. G., Perrin, B. S., Camley, B. A., Marrink, S. J., et al. (2017). Lipid and Peptide Diffusion in Bilayers: The Saffman-Delbrück Model and Periodic Boundary Conditions. *The Journal of Physical Chemistry B*, 121(15), 3443–3457.

LLNL-PRES-737105

# Martini Examples

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# Martini Examples – lipid domains

## Disaccharides Impact the Lateral Organization of Lipid Membranes

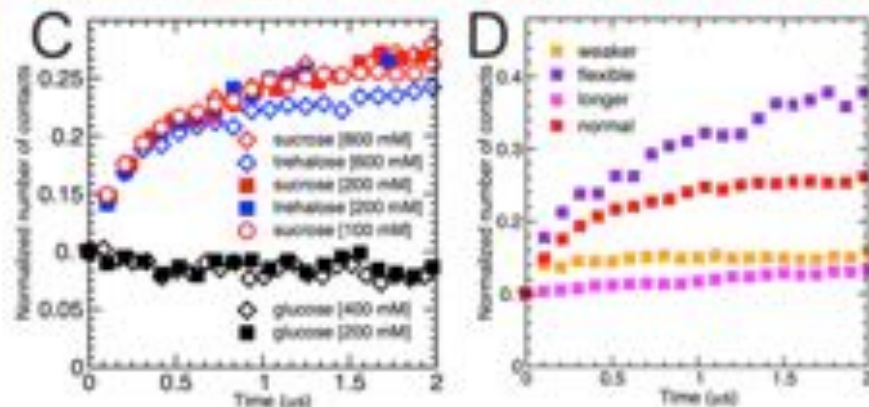
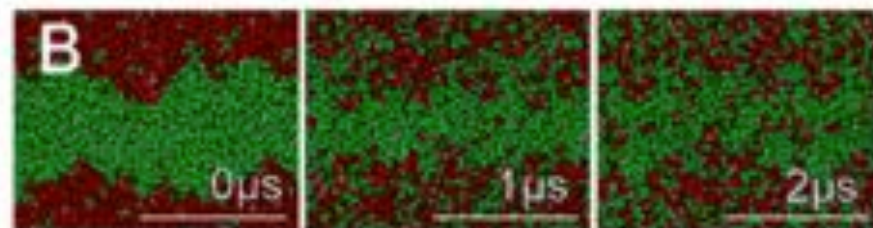
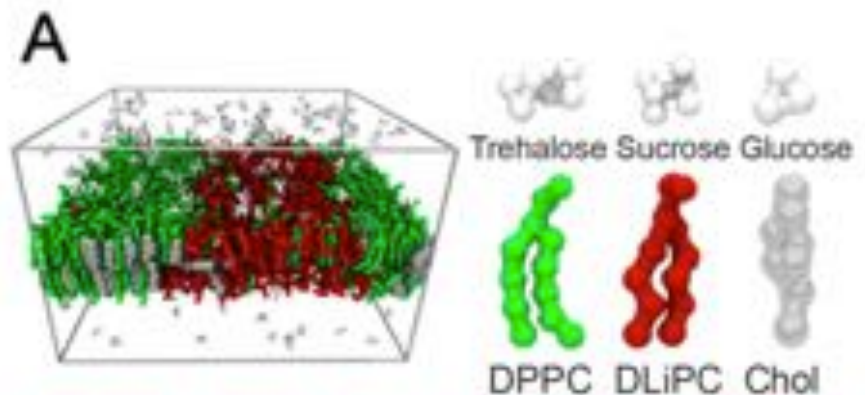
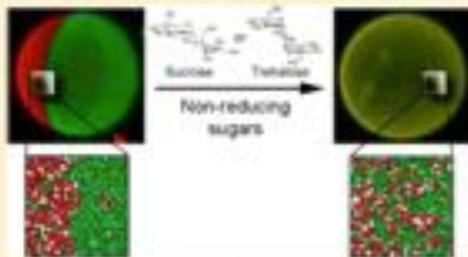
Gemma Moiset,<sup>1</sup> Cesar A. López,<sup>1</sup> Rianne Bartelds,<sup>1</sup> Lukasz Syga,<sup>1</sup> Egon Rijkema,<sup>2</sup> Abhishek Cukkemane,<sup>2</sup> Marc Baldus,<sup>2</sup> Bert Poolman,<sup>1,2</sup> and Siewert J. Marrink<sup>1\*</sup>

<sup>1</sup>Groningen Biomolecular Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands

<sup>2</sup>NMR Spectroscopy, Bijvoet Center for Biomolecular Research Department of Chemistry, Faculty of Science, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

Supporting Information

**ABSTRACT:** Disaccharides are well-known for their membrane protective ability. Interaction between sugars and multicomponent membranes, however, remains largely unexplored. Here, we combine molecular dynamics simulations and fluorescence microscopy to study the effect of mono- and disaccharides on membranes that phase separate into  $L_1$  and  $L_2$  domains. We find that nonreducing disaccharides, sucrose and trehalose, strongly destabilize the phase separation leading to uniformly mixed membranes as opposed to monosaccharides and reducing disaccharides. To unveil the driving force for this process, simulations were performed in which the sugar linkage was artificially modified. The availability of accessible interfacial binding sites that can accommodate the non-reducing disaccharides is key for their strong impact on lateral membrane organization. These exclusive interactions between the nonreducing sugars and the membranes may rationalize why organisms such as yeasts, tardigrades, nematodes, bacteria and



Moiset, G., C.A. Lopez, R. Bartelds, L. Syga, E. Rijkema, A. Cukkemane, M. Baldus, B. Poolman, and S.J. Marrink. 2014. Disaccharides impact the lateral organization of lipid membranes. *J. Am. Chem. Soc.* 136: 16167–16175.

# Martini Examples – lipid domains

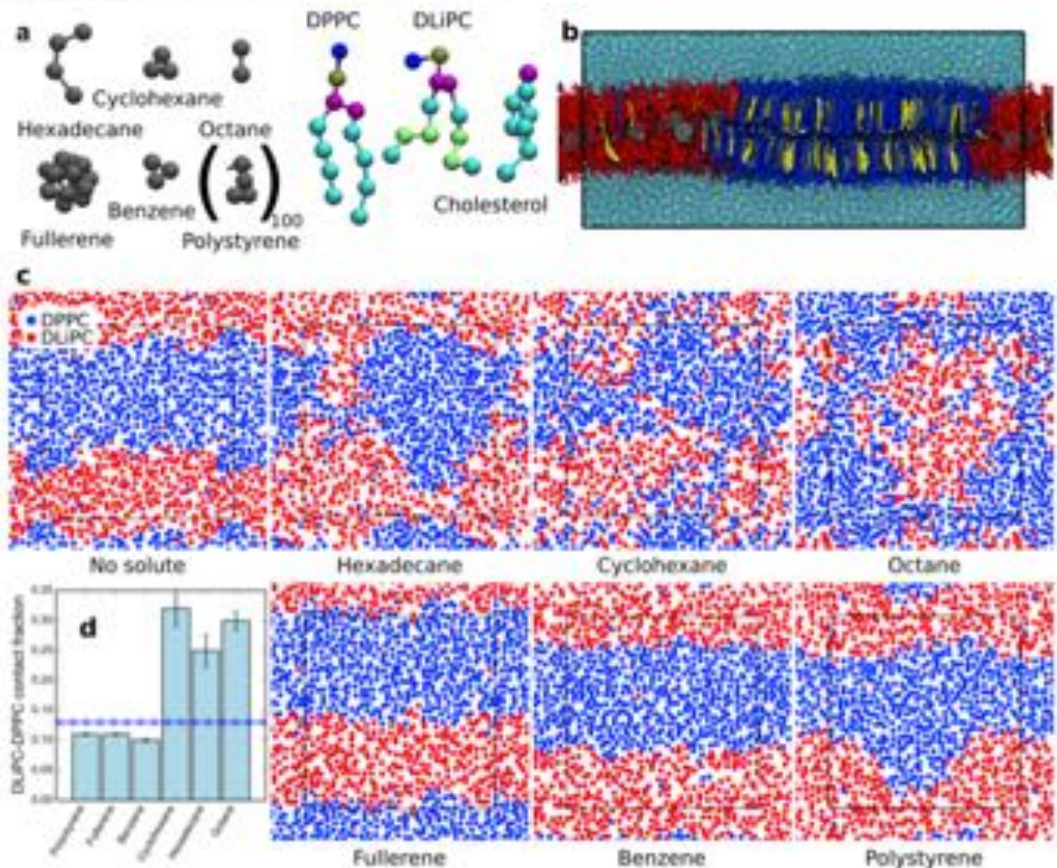
## Hydrophobic Compounds Reshape Membrane Domains

Jonathan Barnoud<sup>1,2</sup>, Giulia Rossi<sup>3</sup>, Siewert J. Marrink<sup>4</sup>, Luca Monticelli<sup>1,2\*</sup>

<sup>1</sup>IBCP, CNRS UMR 5086, Lyon, France, <sup>2</sup>Université Claude Bernard Lyon 1, Lyon, France, <sup>3</sup>Dept of Physical Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Groningen, Groningen, The Netherlands, <sup>4</sup>Department of Chemistry, University of Groningen, Groningen, The Netherlands

### Abstract

Cell membranes have a complex lateral organization featuring domains which play an essential role in cellular processes such as signal transduction. Membrane domains (e.g., by drugs or lipophilic compounds) have major



Barnoud, J., G. Rossi, S.J. Marrink, and L. Monticelli. 2014. Hydrophobic compounds reshape membrane domains. PLoS Comput. Biol. 10: e1003873.

# Martini Examples – lipid domains

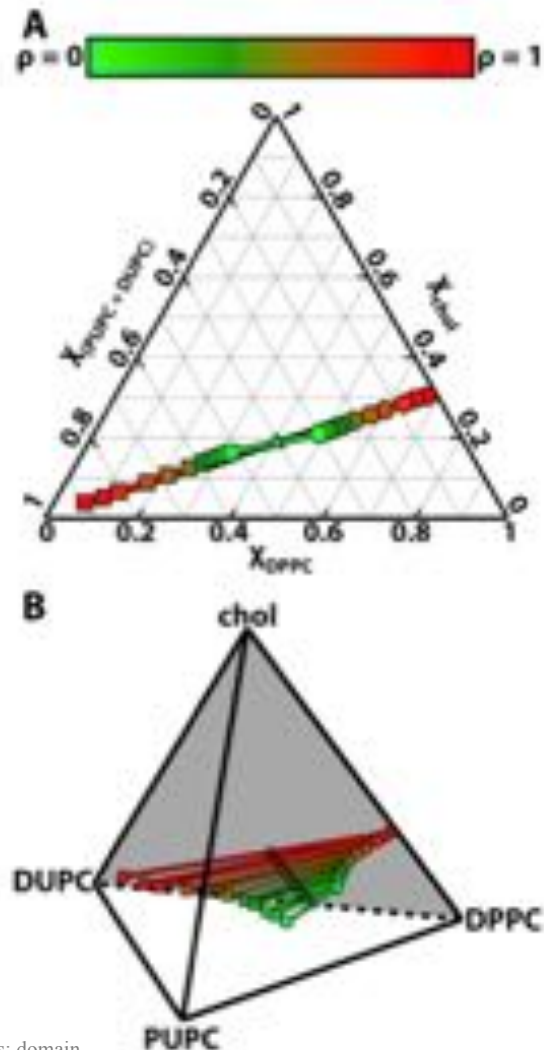
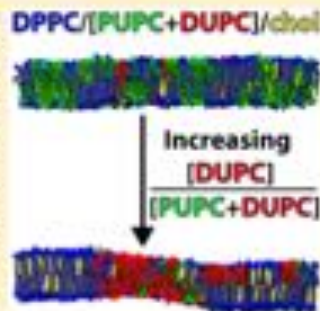
## Multiscale Modeling of Four-Component Lipid Mixtures: Domain Composition, Size, Alignment, and Properties of the Phase Interface

David G. Ackerman and Gerald W. Feigenson\*

Department of Molecular Biology and Genetics, Cornell University, Ithaca, New York 14853, United States

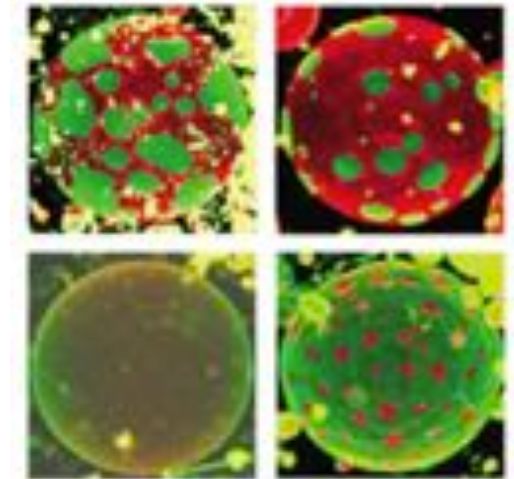
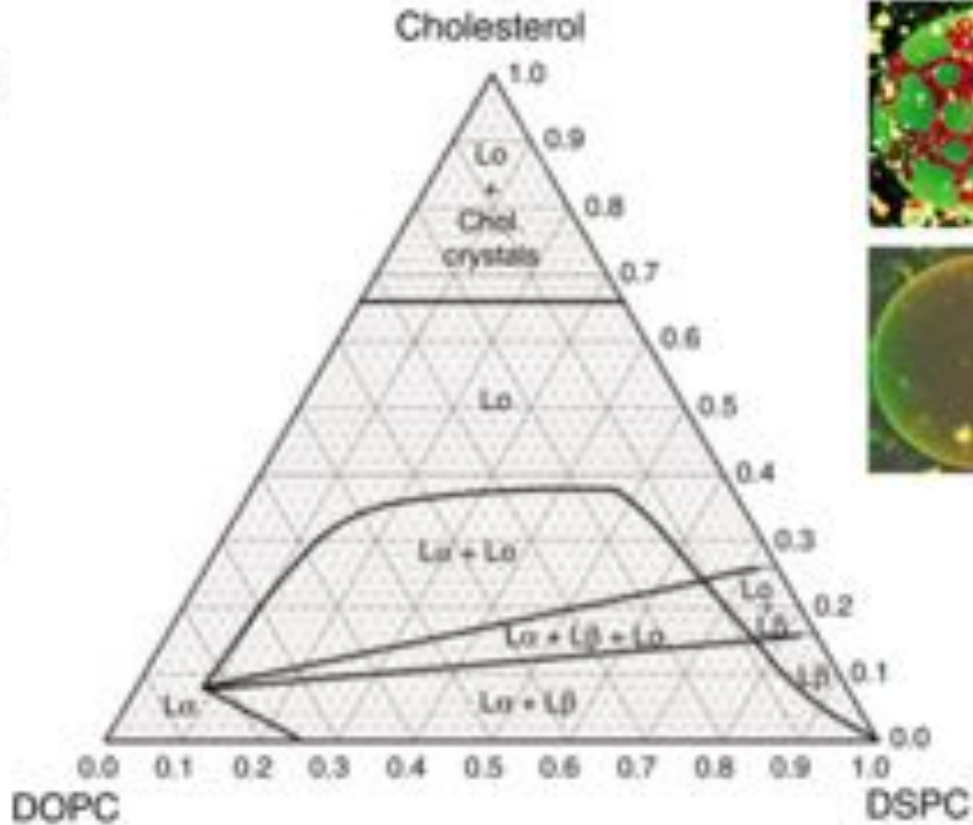
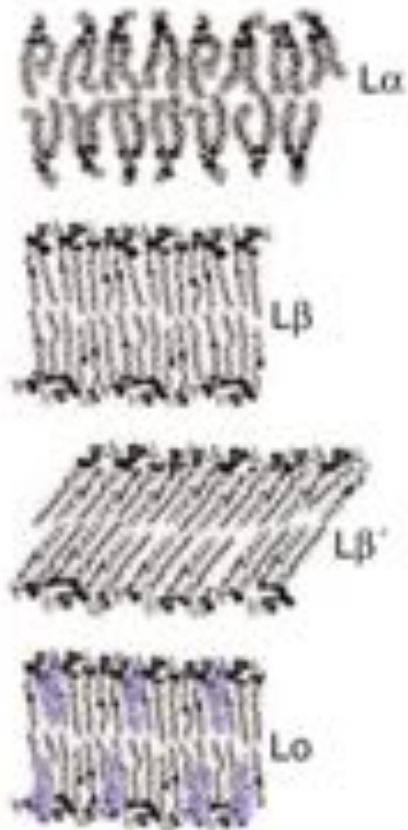
Supporting Information

**ABSTRACT:** Simplified lipid mixtures are often used to model the complex behavior of the cell plasma membrane. Indeed, as few as four components—a high-melting lipid, a nanodomain-inducing low-melting lipid, a macrodomain-inducing low-melting lipid, and cholesterol (chol)—can give rise to a wide range of domain sizes and patterns that are highly sensitive to lipid compositions. Although these systems are studied extensively with experiments, the molecular-level details governing their phase behavior are not yet known. We address this issue by using molecular dynamics simulations to analyze how phase separation evolves in a four-component system as it transitions from small domains to large domains. To do so, we fix concentrations of the high-melting lipid 16:0,16:0-phosphatidylcholine (DPPC) and chol, and incrementally replace the nanodomain-inducing low-melting lipid 16:0,18:2-PC (PUPC) by the macrodomain-inducing low-melting lipid 18:2,18:2-PC (DUPC). Coarse-grained simulations of this four-component system reveal that lipid demixing increases as the amount of DUPC increases.



Ackerman, D.G., and G.W. Feigenson. 2015. Multiscale modeling of four-component lipid mixtures: domain composition, size, alignment, and properties of the phase interface. *J. Phys. Chem. B.* 119: 4240–4250.

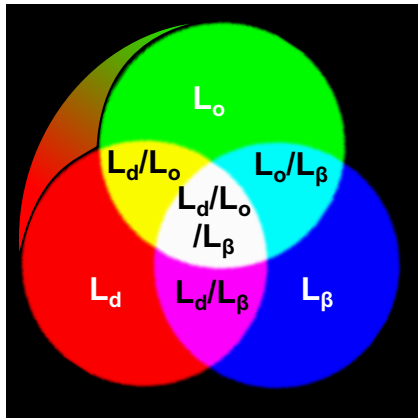
# Martini Examples – phases separation



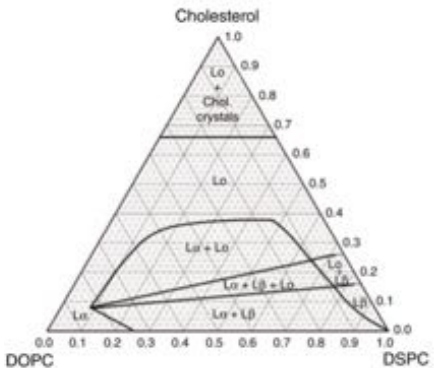
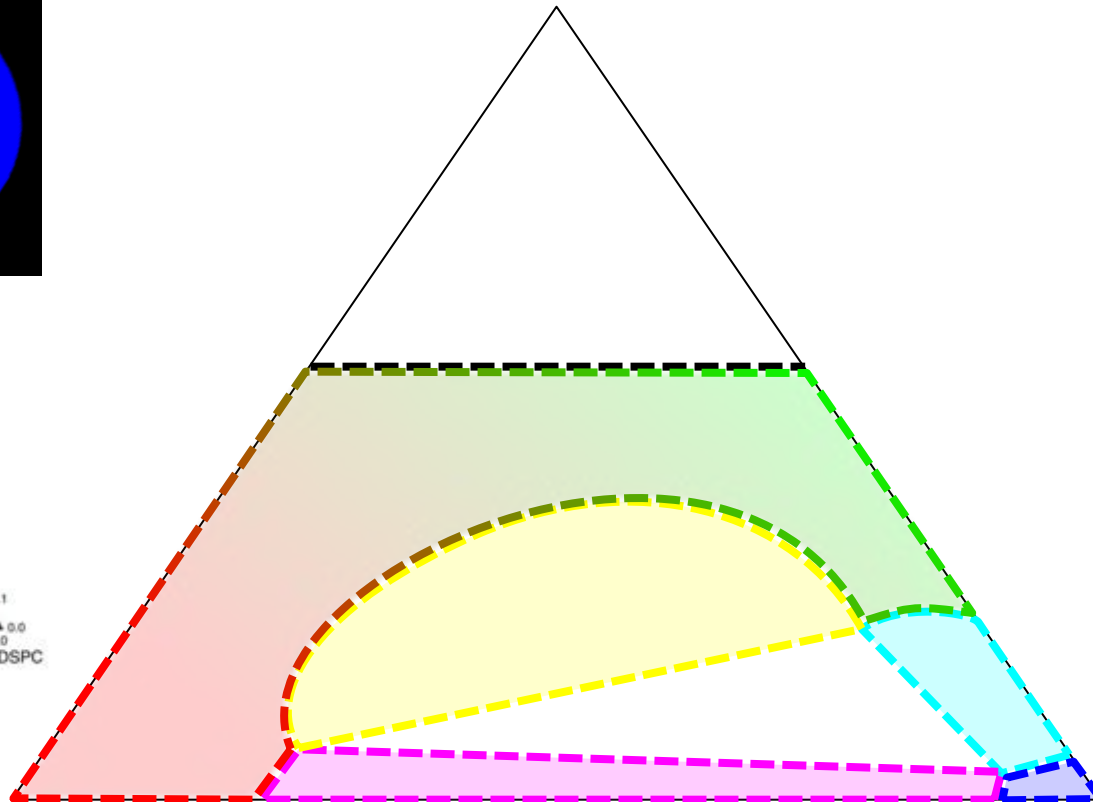
Feigenson, G.W. 2006. Phase behavior of lipid mixtures. Nat. Chem. Biol. 2: 560–563.

# Martini Examples – phases separation

Tim Carpenter



CHOL



DOPC

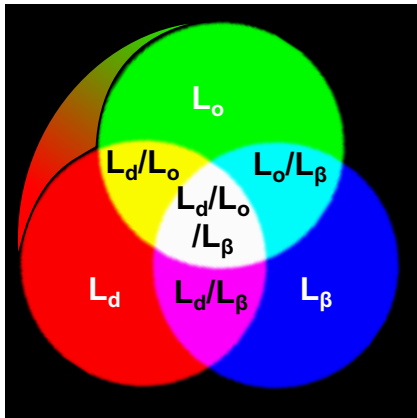
DPPC

John F. Nagle. Faraday Discuss., 2013,161, 11-29

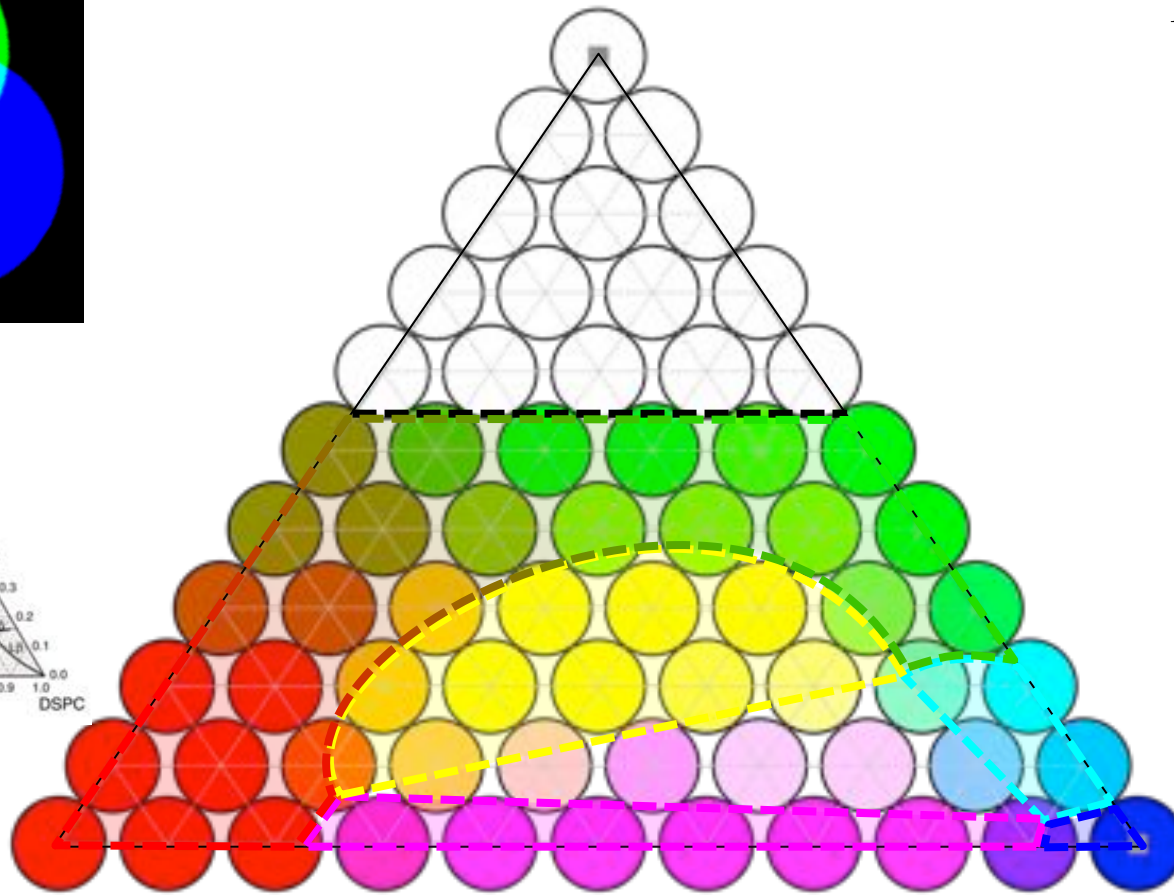
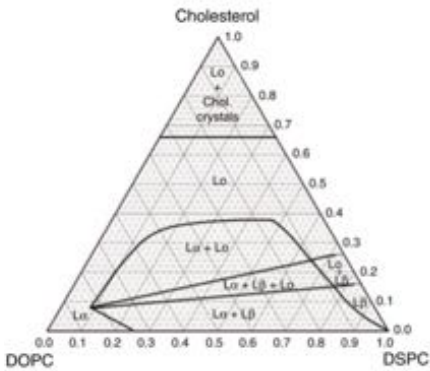
LLNL-PRES-737105

# Martini Examples – phases separation

Tim Carpenter



CHOL



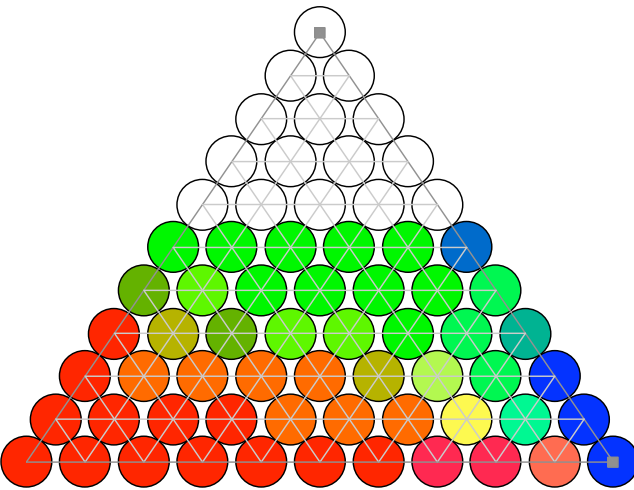
DOPC

DPPC

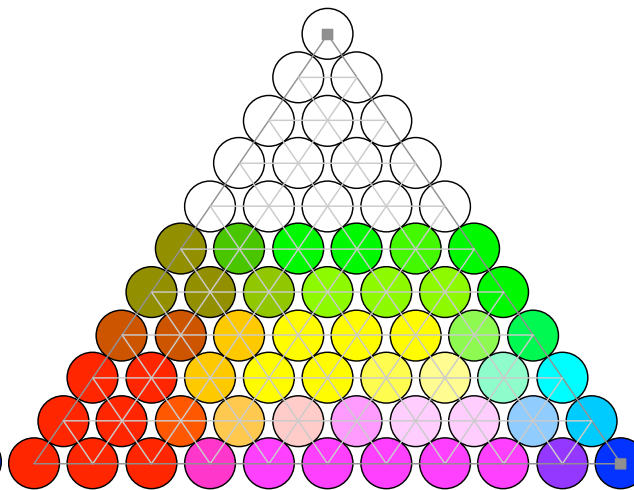
# Martini Examples – phases separation

Tim Carpenter

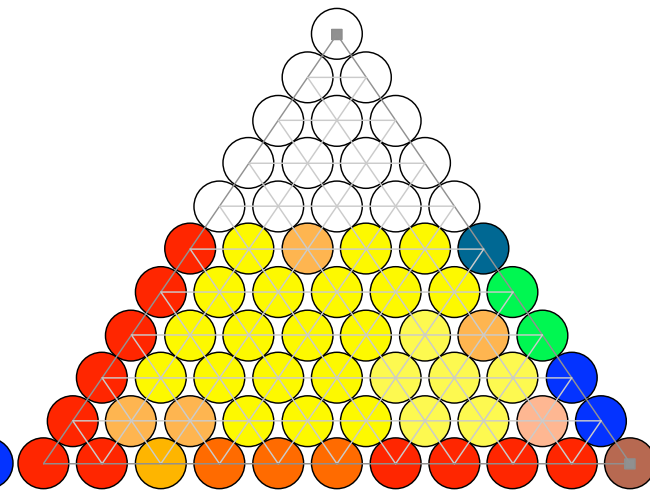
DPPC-DOPC-CHOL



Experimental average



DPPC-DIPC-CHOL



# Martini Examples – tethers

1866

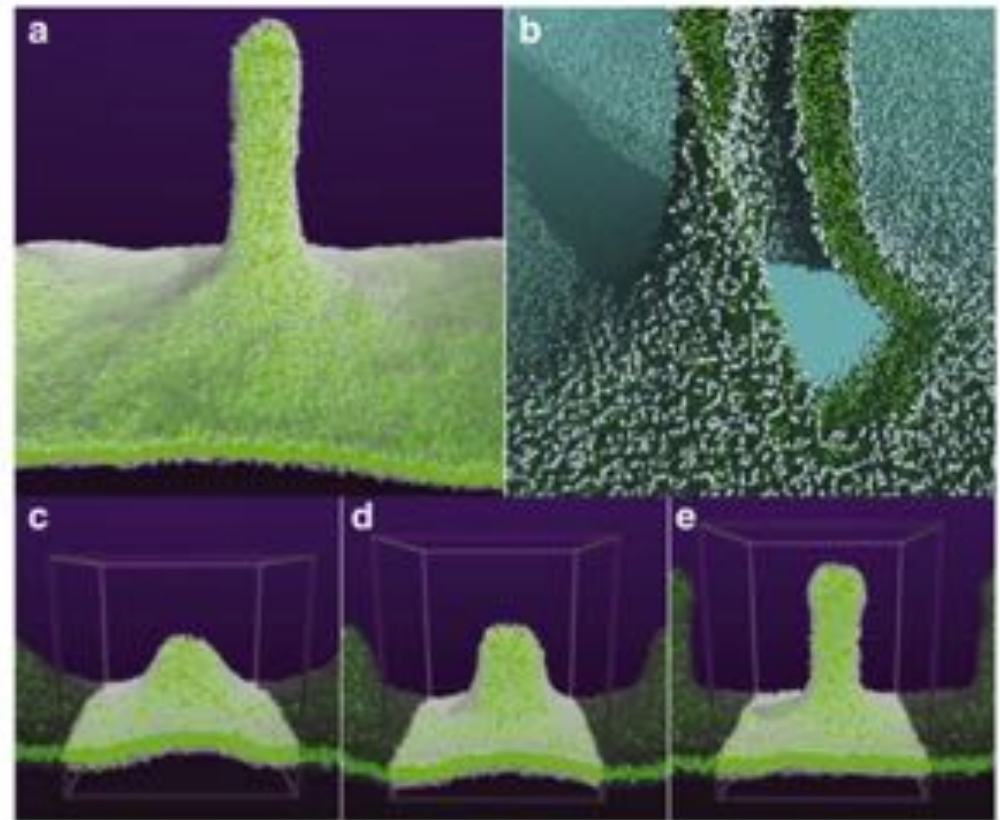
Biophysical Journal Volume 102 April 2012 1866–1871

## Molecular Structure of Membrane Tethers

Svetlana Baoukina,<sup>1†</sup> Siewert J. Marrink,<sup>2\*</sup> and D. Peter Tieleman<sup>1,3\*</sup>

<sup>1</sup>Department of Biological Sciences and <sup>2</sup>Institute for Biocomplexity and Info  
<sup>3</sup>Groningen Biomolecular Sciences and Biotechnology Institute and <sup>4</sup>Zernike  
Groningen, The Netherlands

**ABSTRACT** Membrane tethers are nanotubes formed by a lipid bilayer. They provide an experimental window on lipid properties. Tethers have been studied in theoretical models, but their molecular structure remains unknown. We used molecular dynamics simulations to obtain molecular-level insight into the structure of lipid bilayers by application of an external force to a lipid



Baoukina, S., S.J. Marrink, and D.P. Tieleman. 2012. Molecular structure of membrane tethers. *Biophys. J.* 102: 1866–1871.



# Martini Examples – complex membrane

Biochimica et Biophysica Acta 1848 (2015) 1319–1330



Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: [www.elsevier.com/locate/bbamem](http://www.elsevier.com/locate/bbamem)



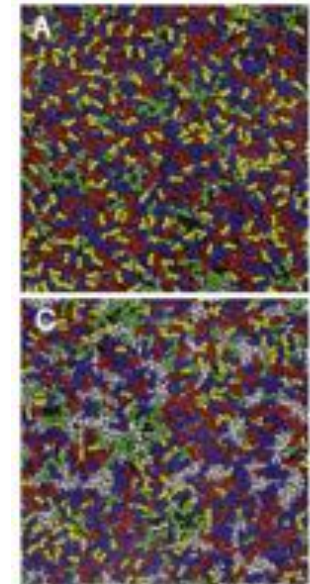
## Characterization of thylakoid lipid membranes from cyanobacteria and higher plants by molecular dynamics simulations



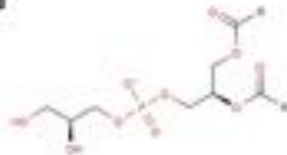
Floris J. van Eerden <sup>a,\*</sup>, Djurre H. de Jong <sup>b</sup>, Alex H. de Vries <sup>a</sup>, Tsjerk A. Wassenaar <sup>c</sup>, Siewert J. Marrink <sup>a</sup>

<sup>a</sup> Groningen Centre  
<sup>b</sup> Institute for Physics  
<sup>c</sup> Computational R

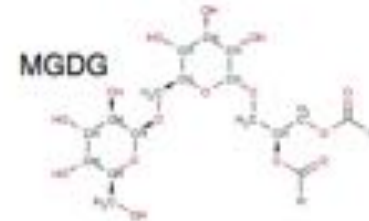
Groningen, the Netherlands



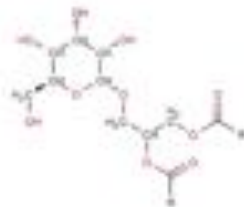
PG



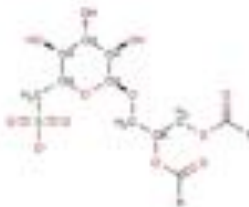
MGDG



DGDG



SQDG



Tail : Head →	Cyanobacterial membrane				Plant membrane			
	PG	DGDG	MGDG	SQDG	PG	DGDG	MGDG	SQDG
16:0	47.9	43.6	45.1	62.0	15.6	6.7	3.1	49.2
18:0	8.9	2.5	3.9	8.0	0.4	0.6	0.6	2.3
saturated	(50)	(50)	(50)	(80)	(16)	(8)	(6)	(50)
16:1(7)	nd	nd	nd	nd	nd	0.2	0.3	1.4
16:1(9)	10.7	15.1	15.5	3.9	nd	nd	nd	nd
18:1(9)	26.3	28.1	27.9	20.9	nd	1.7	1.1	2.9
18:1(11)	6.2	10.7	7.6	5.2	nd	nd	nd	nd
unsaturated	(50)	(50)	(50)	(20)				
16:1(3c)	nd	nd	nd	nd	46.8	nd	nd	nd
trans-unsaturated					(50)			
16:3(7,10,13)	nd	nd	nd	nd	nd	4.1	13.6	1.0
18:2(9,12)	nd	nd	nd	nd	2.2	2.4	3.1	6.3
18:3(9,12,15)	nd	nd	nd	nd	35.0	84.3	78.2	36.9
poly-unsaturated					(34)	(92)	(94)	(56)
total	6.1	25.6	43.5	24.8	12.6	25.1	40.1	15.2
	(10)	(25)	(40)	(25)	(13)	(30)	(40)	(15)

van Eerden, F.J., D.H. de Jong, A.H. de Vries, T.A. Wassenaar, and S.J. Marrink. 2015. Characterization of thylakoid lipid membranes from cyanobacteria and higher plants by molecular dynamics simulations. BBA - Biomembranes. 1848: 1319–1330.

# Martini Examples – complex membrane

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PLOS COMPUTATIONAL BIOLOGY

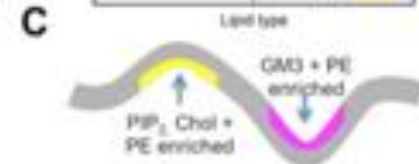
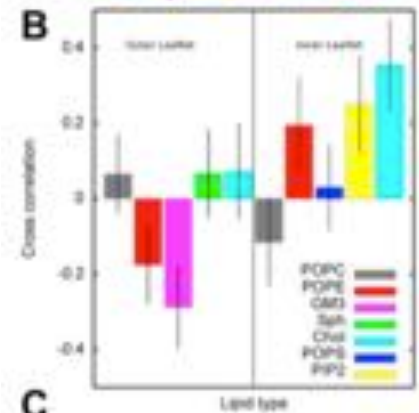
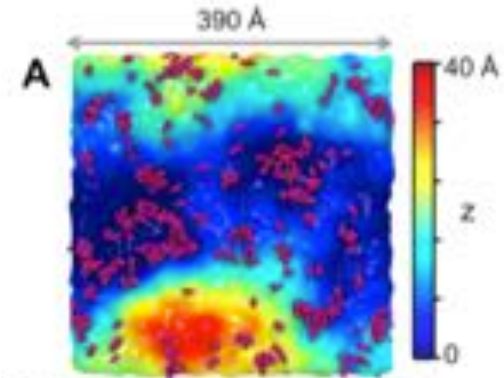
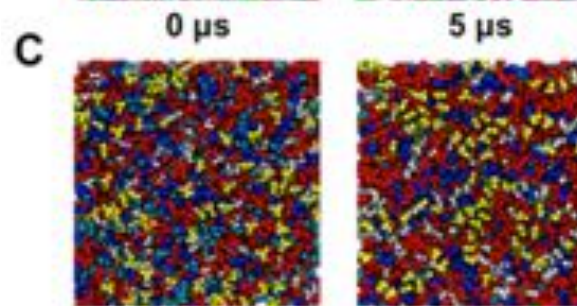
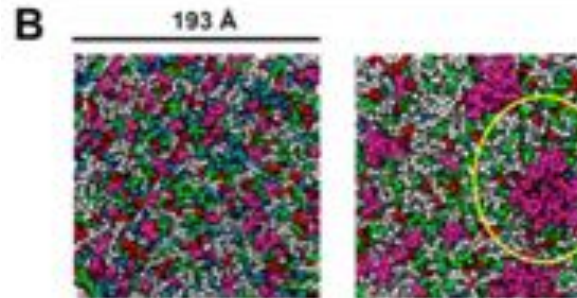
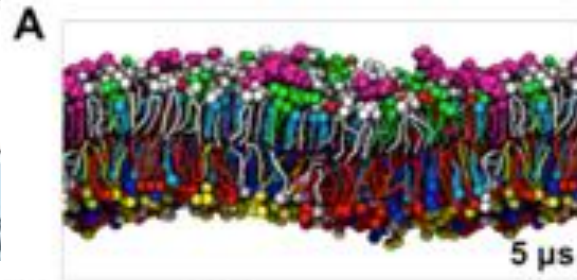
## Lipid Clustering Correlates with Membrane Curvature as Revealed by Molecular Simulations of Complex Lipid Bilayers

Heidi Koldsø, David Shorthouse, Jean Hélié, Mark S. P. Sansom\*

Department of Biochemistry, University of Oxford, Oxford, United Kingdom

### Abstract

Cell membranes are complex multicomponent systems, which are highly heterogeneous in composition. To date, most molecular simulations have focussed on relatively simple



Koldsø, H., D. Shorthouse, J. Hélié, and M.S.P. Sansom. 2014. Lipid clustering correlates with membrane curvature as revealed by molecular simulations of complex lipid bilayers. PLoS Comput. Biol. 10: e1003911.

# PM – plasma membrane

## Lipid Organization of the Plasma Membrane

Helgi I. Ingólfsson,<sup>†</sup> Manuel N. Melo,<sup>†</sup> Floris J. van Eerden,<sup>†</sup> Clément Arnarez,<sup>†</sup> Cesar A. Lopez,<sup>†</sup> Tsjerk A. Wassenaar,<sup>†,‡</sup> Xavier Periole,<sup>†</sup> Alex H. de Vries,<sup>†</sup> D. Peter Tieleman,<sup>§</sup> and Siewert J. Marrink<sup>\*†</sup>

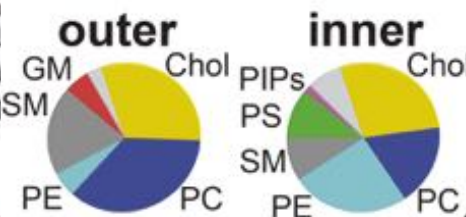
<sup>†</sup>Groningen Biomolecular Sciences and Biotechnology Institute, Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands

<sup>‡</sup>Computational Biology, Department of Biology, University of Alberta, Edmonton, Alberta T6G 2G1, Canada

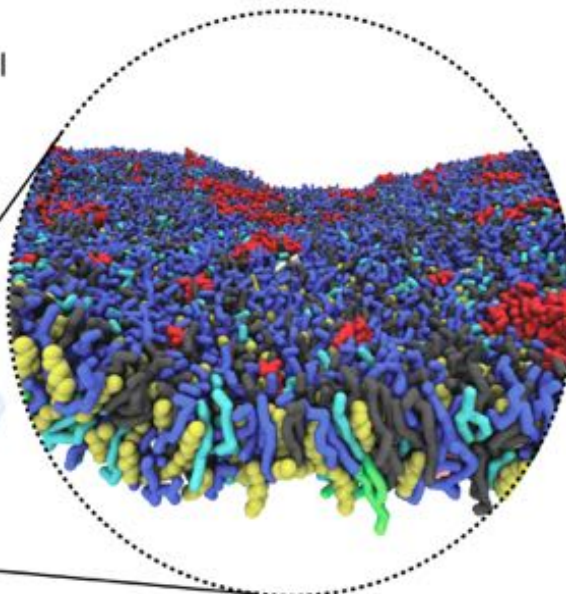
<sup>§</sup>Centre for Molecular Simulation and Department of Biochemistry, University of Alberta, Edmonton, Alberta T6G 2G1, Canada

Supporting Information

**ABSTRACT:** The detailed organization of cellular membranes remains rather elusive. Based on large-scale molecular simulations, we provide a high-resolution view of the lipid organization of a plasma membrane at an unprecedented level of complexity. Our plasma membrane model consists of 63 different lipids, combining 14 types of headgroups and 11 types of tails, distributed across the two leaflets, closely mirroring mammalian plasma membrane. We observe an enrichment of cholesterol in the outer leaflet and a general non-ideal distribution of the different lipid species. Transient domains with characteristic form and disappear on the microsecond time scale. Domains are coupled across the two membrane leaflets. Distinct nanodomains consisting of gangliosides are observed in the outer leaflet. Our data provide a key view on the lateral organization of lipids in one of life's fundamental structures, the cell membrane.

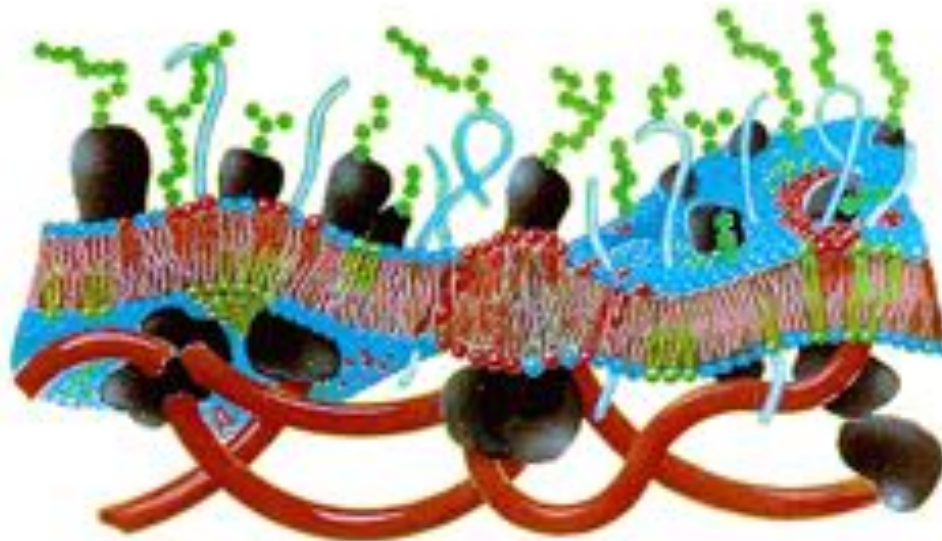


>60 lipid types

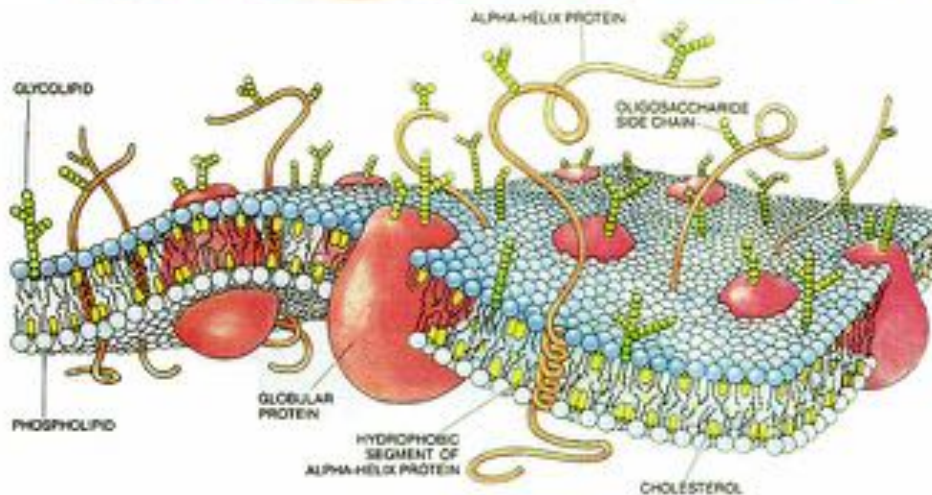


Ingólfsson, H. I., Melo, M. N., van Eerden, F. J., Arnarez, C., Lopez, C. A., Wassenaar, T. A., et al. (2014). Lipid Organization of the Plasma Membrane. *JACS*, 136, 14554–14559.

# PM – cell envelopes / plasma membranes



- Hundreds of different lipid species
- Asymmetric leaflet distribution
- Lateral inhomogeneity

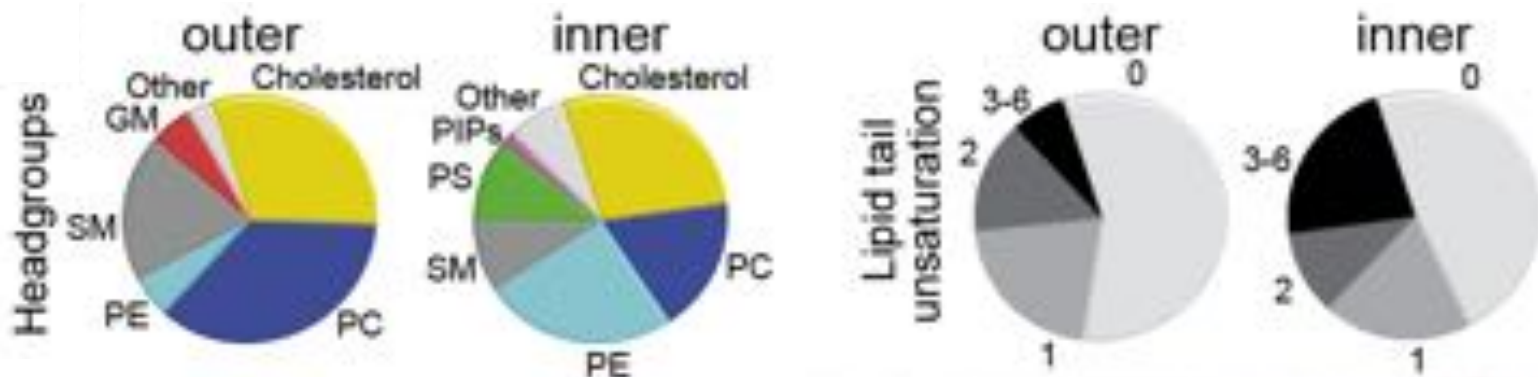


Mouritsen OG, Anersen OS (1998) Biologiske Skrifter, Danish Royal Science Society 49:7–12.

[http://en.wikibooks.org/wiki/Biochemistry/Membranes\\_and\\_Lipids](http://en.wikibooks.org/wiki/Biochemistry/Membranes_and_Lipids)

# PM – Idealized mammalian plasma membrane

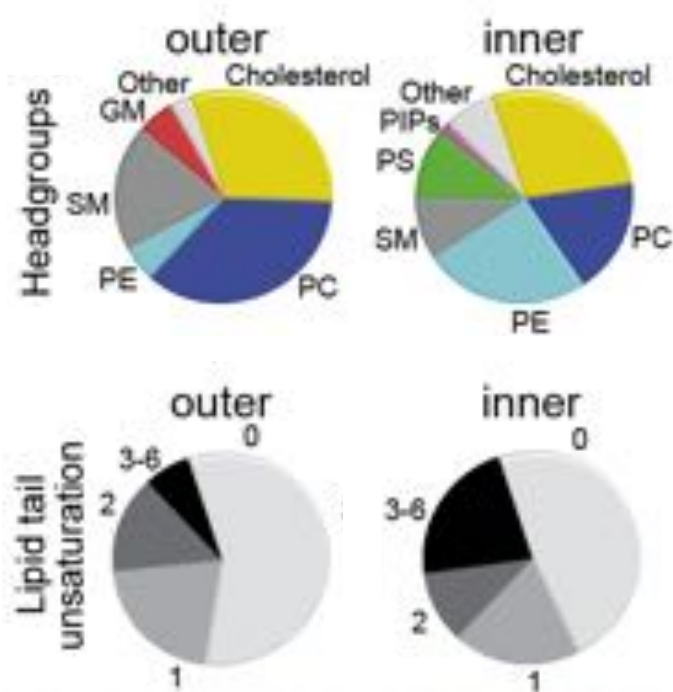
Lipids	mol %	16:0-18:0 4bead	20:0-22:0 5bead	24:0-26:0 6bead	16:1-18:1 4bead	20:1-22:1 5bead	24:1,2-26:1 6bead	18:2 4bead	20:2 5bead	20:3 5bead	20:4 22:4 5bead	22:5 22:6 5bead
PC ( <i>phosphatidylcholine</i> )	39%	48%	0%	0%	20%	0%	0%	25%	1%	0%	5%	1%
PE ( <i>phosphatidylethanolamine</i> )	20%	37%	0%	0%	20%	0%	0%	8%	0%	2%	25%	8%
SM ( <i>sphingomyelin</i> )	22%	44%	12%	20%	1%	1%	22%	0%	0%	0%	0%	0%
PI ( <i>phosphatidylinositol</i> )	3%											
PS ( <i>phosphatidylserine</i> )	7%	48%	0%	0%	10%	0%	0%	4%	0%	2%	25%	11%
PA ( <i>phosphatidylacetate</i> )	1%											
PIP ( <i>PI phosphate</i> )	1%											
Glycolip ( <i>GMs, GCER</i> )	4%											
Cer ( <i>ceramide</i> )	1%											
LPC ( <i>lyso-PC</i> )	1%											
DAG ( <i>diacylglycerol</i> )	1%											
Cholesterol/Lipid fraction	0.66											



Total of 63 different CG lipid types

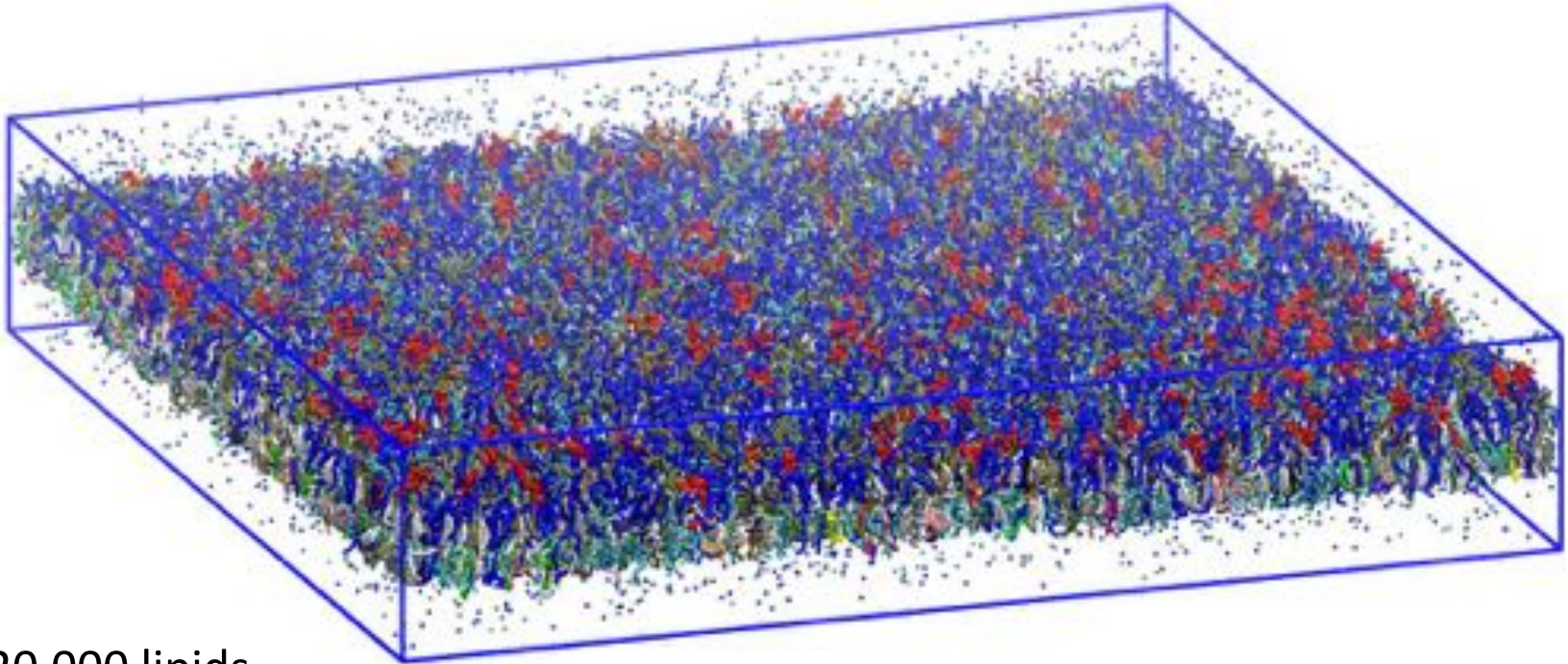
Ingólfsson, H. I., Melo, M. N., van Eerden, F. J., Arnarez, C., Lopez, C. A., Wassenaar, T. A., et al. (2014). Lipid Organization of the Plasma Membrane. *JACS*, 136, 14554–14559.

# PM – lipid composition



Lipid tail sn-1	Lipid tail sn-2	Acronym	Inner count	Inner leaflet %	Outer count	Outer leaflet %
<b>Phosphatidylcholine - PC</b>						
CCCC	CCDC	POPC	550	0.31	1205	0.69
CCDC	CCDC	DOPC	49	0.32	106	0.68
CCCC	CDDC	PIPC	810	0.31	1772	0.69
CCCC	CDDCC	PEPC	32	0.31	71	0.69
CCCC	DDDC	PAPC	129	0.31	283	0.69
DDDDC	DDDC	DAPC	16	0.31	35	0.69
CCCC	DDDDC	PUPC	32	0.31	71	0.69
<b>Total:</b>			<b>1618</b>	<b>0.31</b>	<b>3543</b>	<b>0.69</b>
<b>Phosphatidylethanolamine - PE</b>						
CCCC	CCDC	POPE	569	0.81	135	0.19
CCDC	CCDC	DOPE	190	0.81	44	0.19
CCCC	CDDC	PIPE	380	0.81	90	0.19
CCCC	CDDCC	PQPE	95	0.81	22	0.19
CCCC	DDDC	PAPE	522	0.81	124	0.19
DDDDC	DDDC	DAPE	332	0.81	78	0.19
CCCC	DDDDC	PUPE	190	0.81	44	0.19
DDDDDC	DDDDC	DUPE	95	0.81	22	0.19
<b>Total:</b>			<b>2373</b>	<b>0.81</b>	<b>559</b>	<b>0.19</b>
<b>Sphingomyelin - SM</b>						
TCC	CCCC	DPSM	279	0.31	611	0.69
TCCC	CCCCC	DBSM	61	0.31	133	0.69
TCCCC	CCCCCC	DXSM	113	0.31	247	0.69
TCC	CCDC	POSM	17	0.31	38	0.69
TCC	CCDCC	PGSM	17	0.31	38	0.69
TCC	CCDCC	PNSM	174	0.31	381	0.69
TCCC	CCDCC	BNSM	86	0.31	191	0.69
TCCCC	CCDCC	XNSM	121	0.31	267	0.69
<b>Total:</b>			<b>868</b>	<b>0.31</b>	<b>1906</b>	<b>0.69</b>
<b>Phosphatidylserine - PS</b>						
CCCC	CCDC	POPS	200	1.00	0	0.00
CCCC	CDDC	PIPS	79	1.00	0	0.00
CCCC	CDDCC	PQPS	39	1.00	0	0.00
CCCC	DDDC	PAPPS	461	1.00	0	0.00
DDDDC	DDDC	DAPPS	20	1.00	0	0.00
CCCC	DDDDC	PUPPS	180	1.00	0	0.00
DDDDDC	DDDDC	DUPPS	20	1.00	0	0.00
<b>Total:</b>			<b>999</b>	<b>1.00</b>	<b>0</b>	<b>0.00</b>
<b>Glycolip - monosialotetrahexosylganglioside - GMI</b>						
TCC	CCCC	DPG1	0	0.00	89	1.00
TCCCC	CCCCCC	DXG1	0	0.00	51	1.00
TCC	CCDCC	PNG1	0	0.00	64	1.00
TCCCC	CCDCC	XNG1	0	0.00	51	1.00
<b>Total:</b>			<b>0</b>	<b>0.00</b>	<b>255</b>	<b>1.00</b>
<b>Glycolip - monosialodihexosylganglioside - GM3</b>						
TCC	CCCC	DPG3	0	0.00	89	1.00
TCCCC	CCCCCC	DXG3	0	0.00	51	1.00
TCC	CCDCC	PNG3	0	0.00	64	1.00
TCCCC	CCDCC	XNG3	0	0.00	51	1.00
<b>Total:</b>			<b>0</b>	<b>0.00</b>	<b>255</b>	<b>1.00</b>
<b>Phosphatidylinositol - PI</b>						
CCCC	CCDC	POPI	137	1.00	0	0.00
CCCC	CDDC	PIPI	120	1.00	0	0.00
CCCC	DDDC	PAPI	120	1.00	0	0.00
CCCC	DDDDC	PUPI	51	1.00	0	0.00
<b>Total:</b>			<b>428</b>	<b>1.00</b>	<b>0</b>	<b>0.00</b>
<b>Phosphatidic acid - PA</b>						
CCCC	CCDC	POPA	46	1.00	0	0.00
CCCC	CDDC	PIPA	39	1.00	0	0.00
CCCC	DDDC	PAPA	39	1.00	0	0.00
CCCC	DDDDC	PUPA	17	1.00	0	0.00
<b>Total:</b>			<b>141</b>	<b>1.00</b>	<b>0</b>	<b>0.00</b>
<b>Phosphatidylinositol (1-3)phosphate - PIPs</b>						
CCCC	CCDC	POP1	48	1.00	0	0.00
CCCC	CCDC	POP2	48	1.00	0	0.00
CCCC	CCDC	POP3	48	1.00	0	0.00
<b>Total:</b>			<b>144</b>	<b>1.00</b>	<b>0</b>	<b>0.00</b>
<b>Ceramide - CER</b>						
TCC	CCCC	DPCE	15	0.33	31	0.67
TCCCC	CCCCCC	DXCE	9	0.35	17	0.65
TCC	CCDCC	PNCE	10	0.31	22	0.69
TCCCC	CCDCC	XNCE	9	0.35	17	0.65
<b>Total:</b>			<b>44</b>	<b>0.34</b>	<b>86</b>	<b>0.66</b>
<b>Lysophosphatidylcholine - LPC</b>						
CCCC		PFC	0	0.00	64	1.00
CCDC		OPC	0	0.00	20	1.00
CDDC		IPC	0	0.00	18	1.00
DDDDC		APC	0	0.00	18	1.00
DDDDDC		UPC	0	0.00	7	1.00
<b>Total:</b>			<b>0</b>	<b>0.00</b>	<b>127</b>	<b>1.00</b>
<b>Diacylglycerol - DAG</b>						
CCCC	CCDC	PODG	17	0.40	25	0.60
CCCC	CDDC	PIDG	15	0.39	23	0.61
CCCC	DDDC	PADG	15	0.39	23	0.61
CCCC	DDDDC	PUDG	6	0.40	9	0.60
<b>Total:</b>			<b>52</b>	<b>0.39</b>	<b>81</b>	<b>0.61</b>
<b>Cholesterol</b>						
		CHOL	2653	0.46	3107	0.54
<b>All lipids types total:</b>			<b>9323</b>	<b>0.48</b>	<b>9916</b>	<b>0.52</b>

## PM – setup with *insane*



~20,000 lipids  
~300,000 CG water  
150 mM NaCl  
+counterions

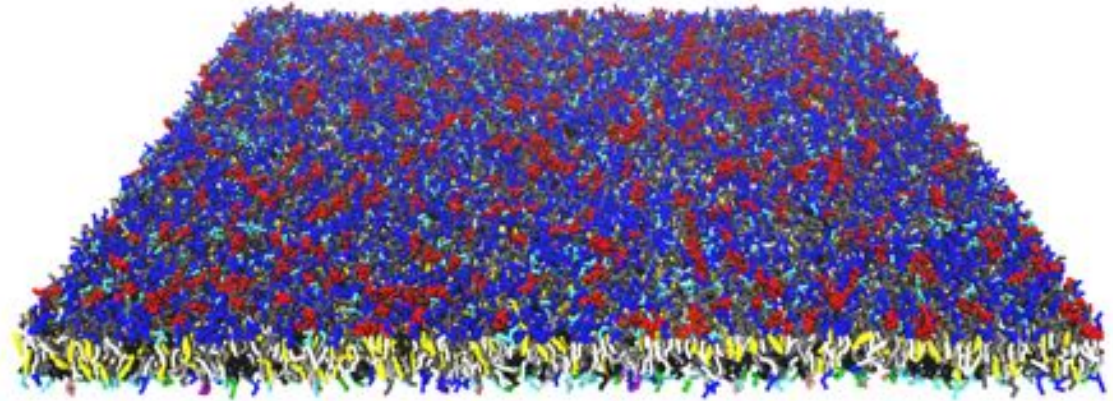
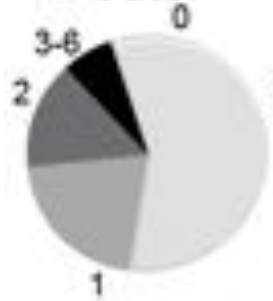
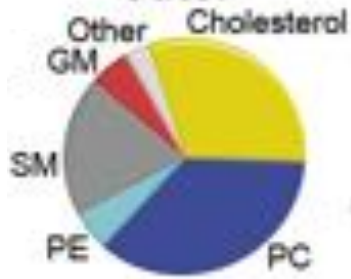
- Different area per lipid in upper/lower leaflet
- Need to measure with “all” lipids present
- Remove undulations with z-pos constraint

# PM – idealized plasma membrane

## Outer leaflet:

Headgroups

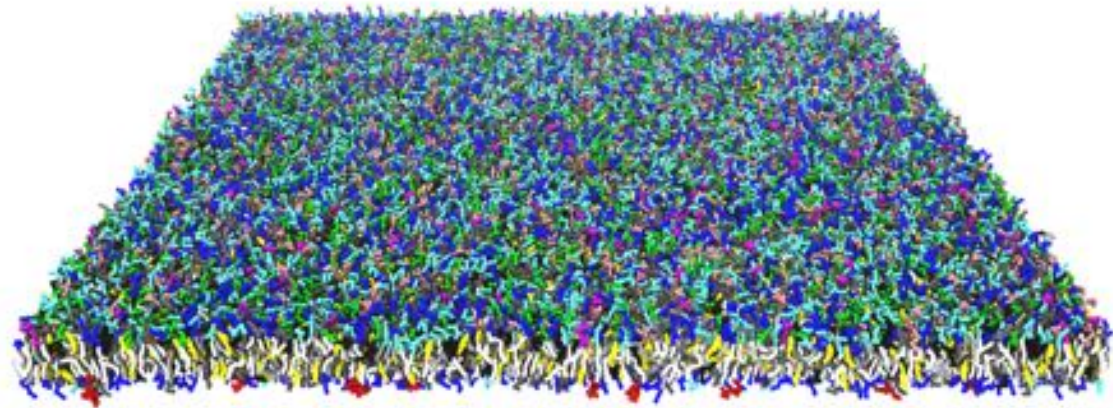
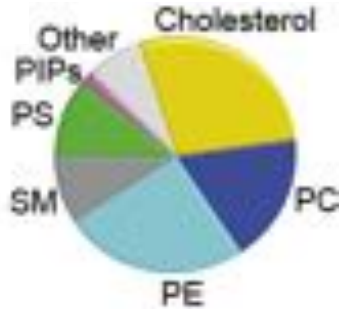
Tail unsaturation



## Inner leaflet:

Headgroups

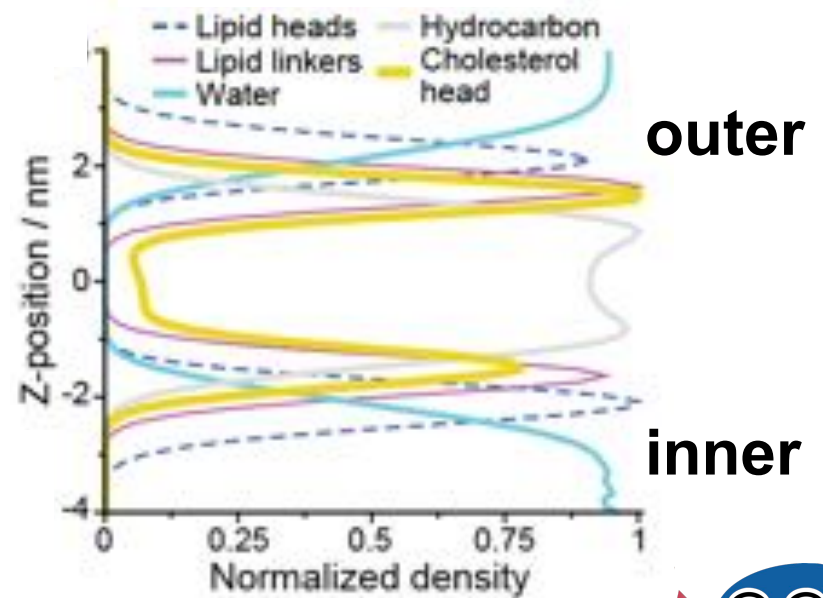
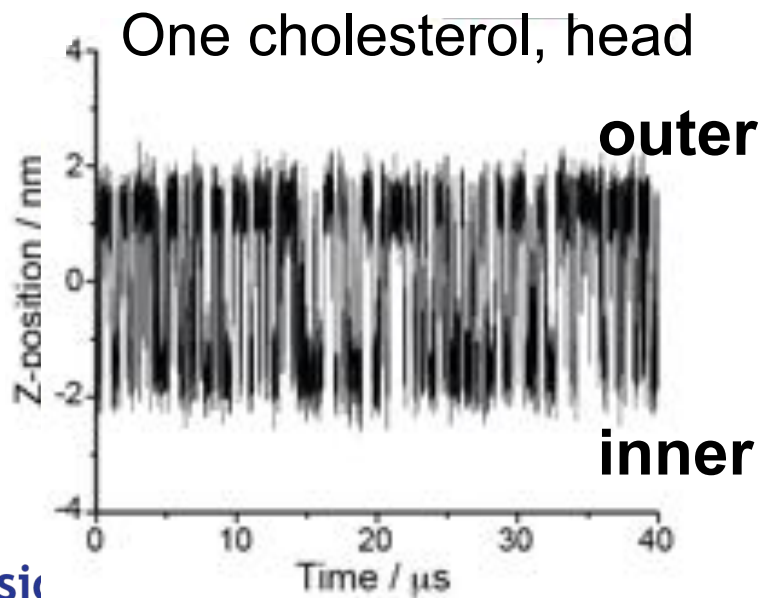
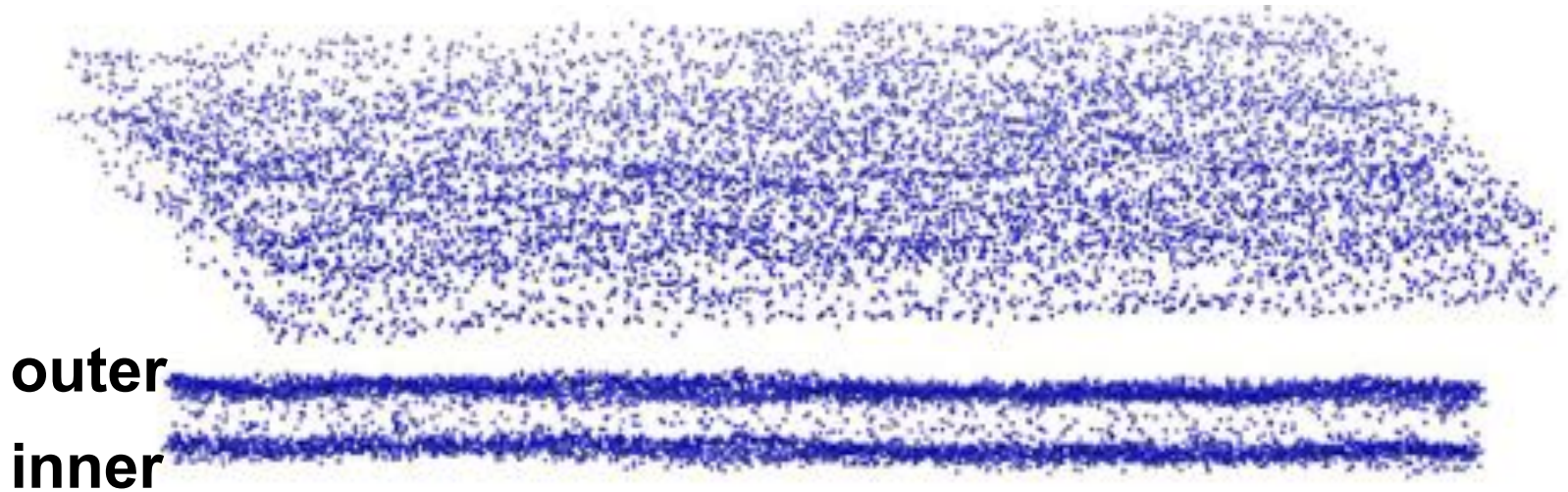
Tail unsaturation



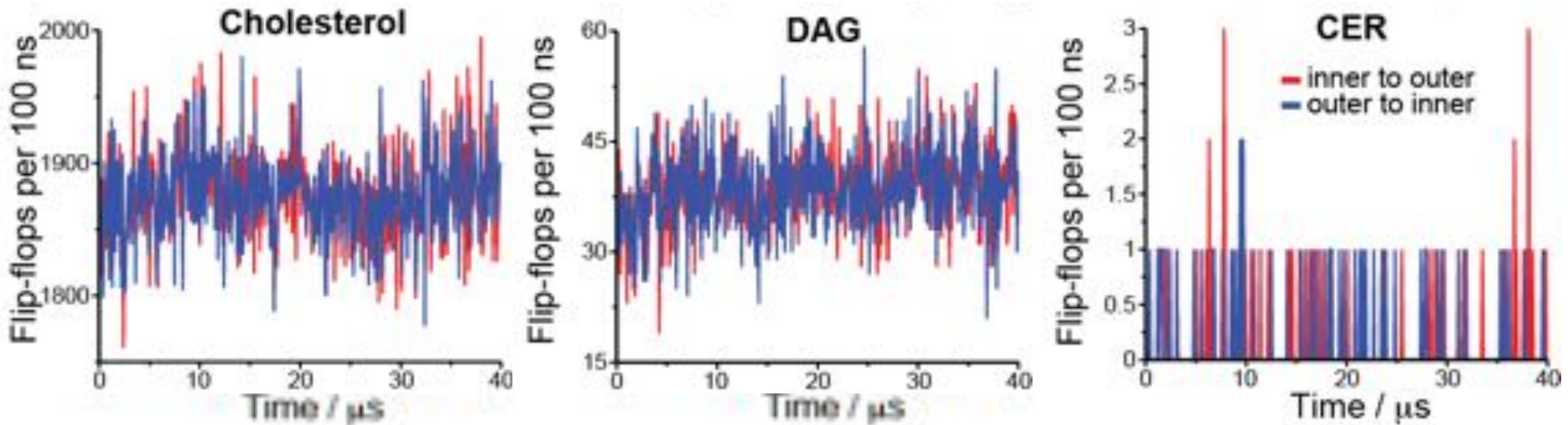
10 nm



# PM – cholesterol redistributes



# PM – flip-flops



Flip-flop rates:

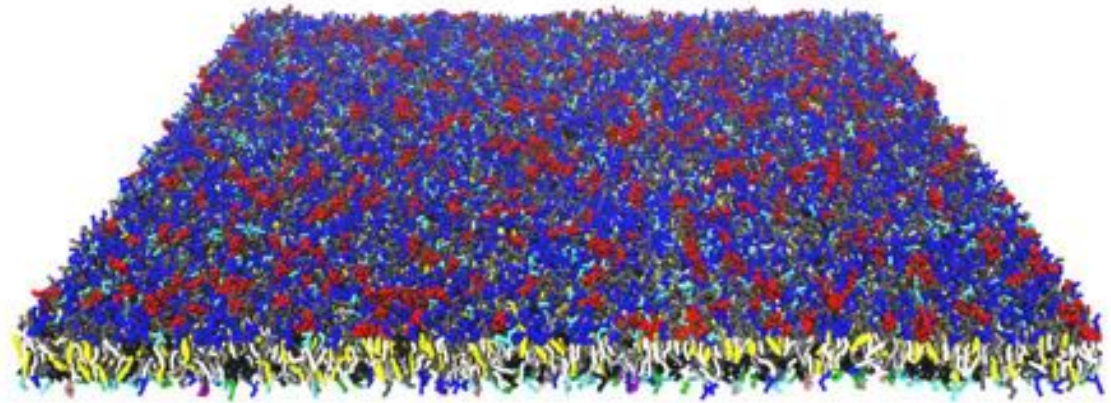
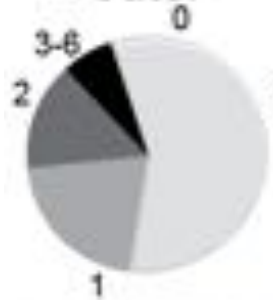
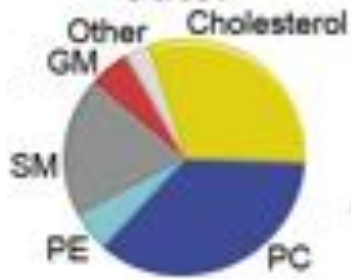
- Cholesterol  $6.53 \pm 0.01 \times 10^6 \text{ s}^{-1}$
- DAG  $5.87 \pm 0.05 \times 10^6 \text{ s}^{-1}$
- CER  $2.0 \pm 0.4 \times 10^4 \text{ s}^{-1}$

# PM – idealized plasma membrane

## Outer leaflet:

Headgroups

Tail unsaturation

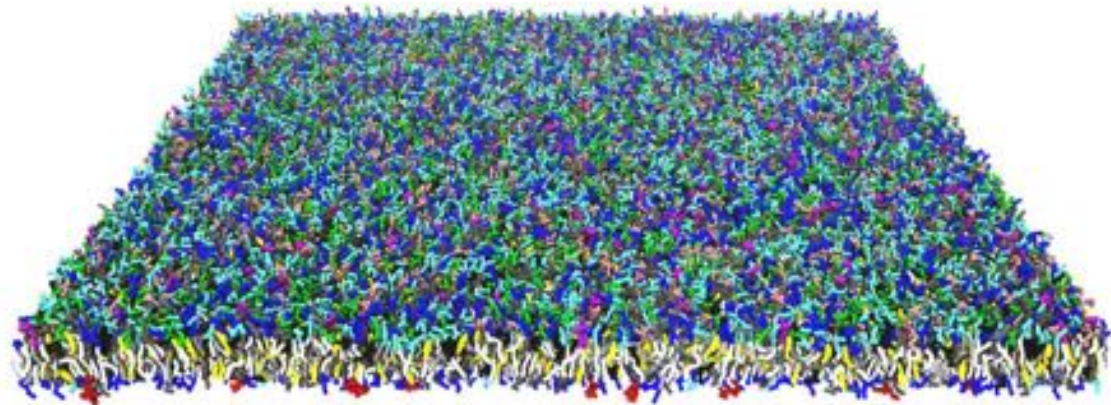
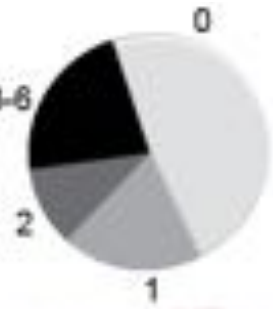
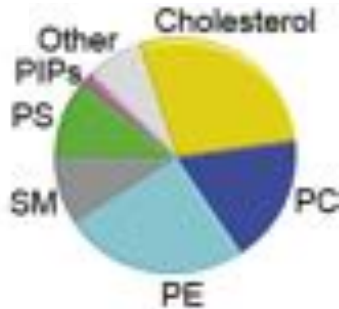


00000 ns

## Inner leaflet:

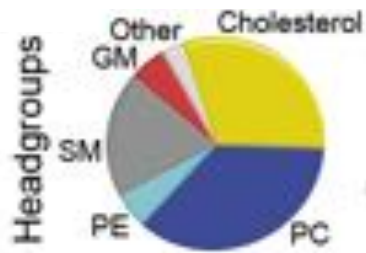
Headgroups

Tail unsaturation



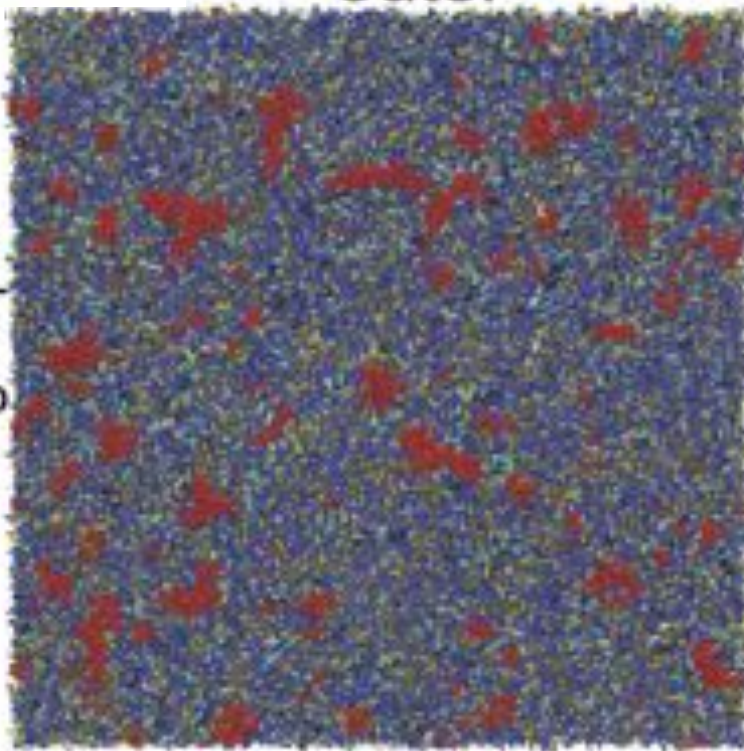
10 nm

# PM – lipid headgroups

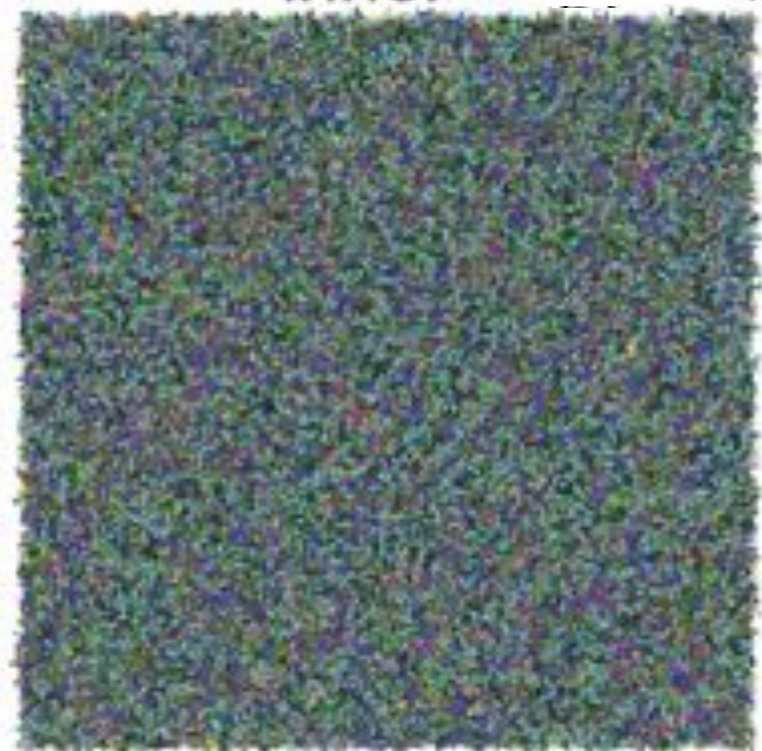
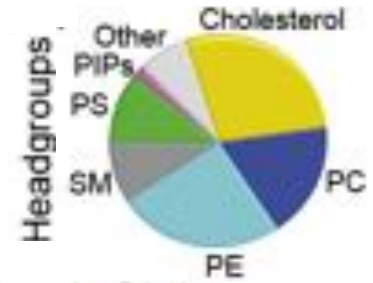


outer

Headgroups

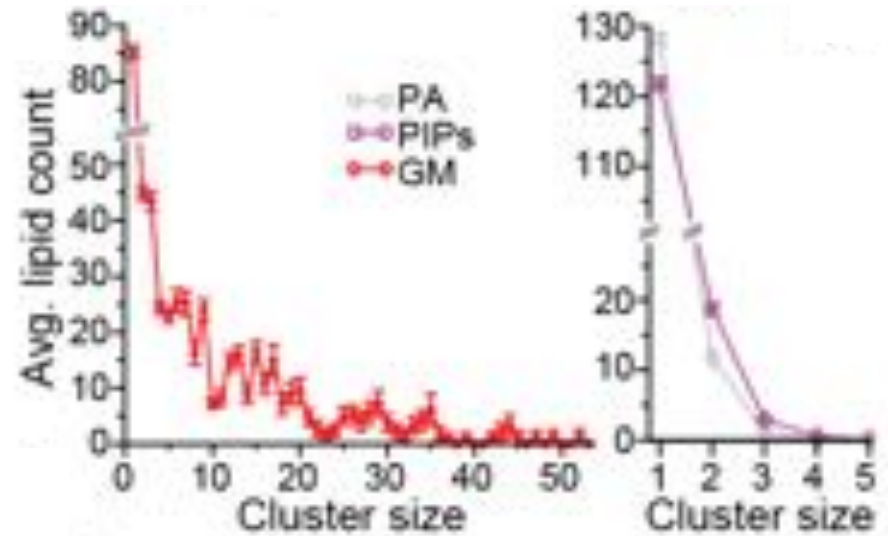
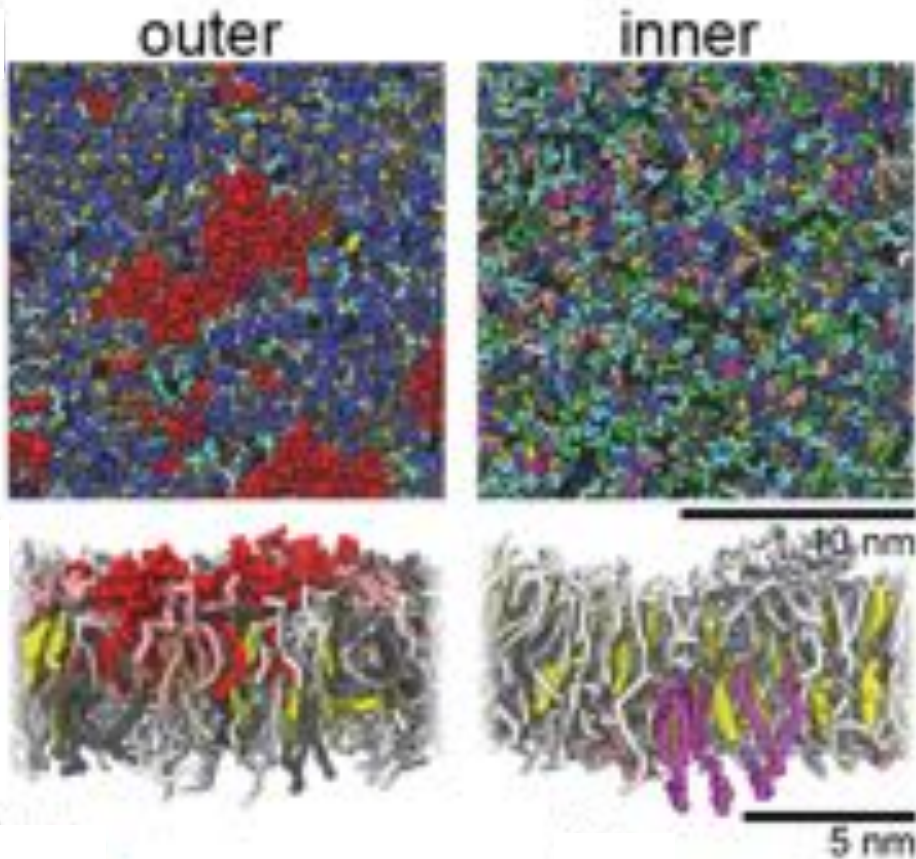


inner

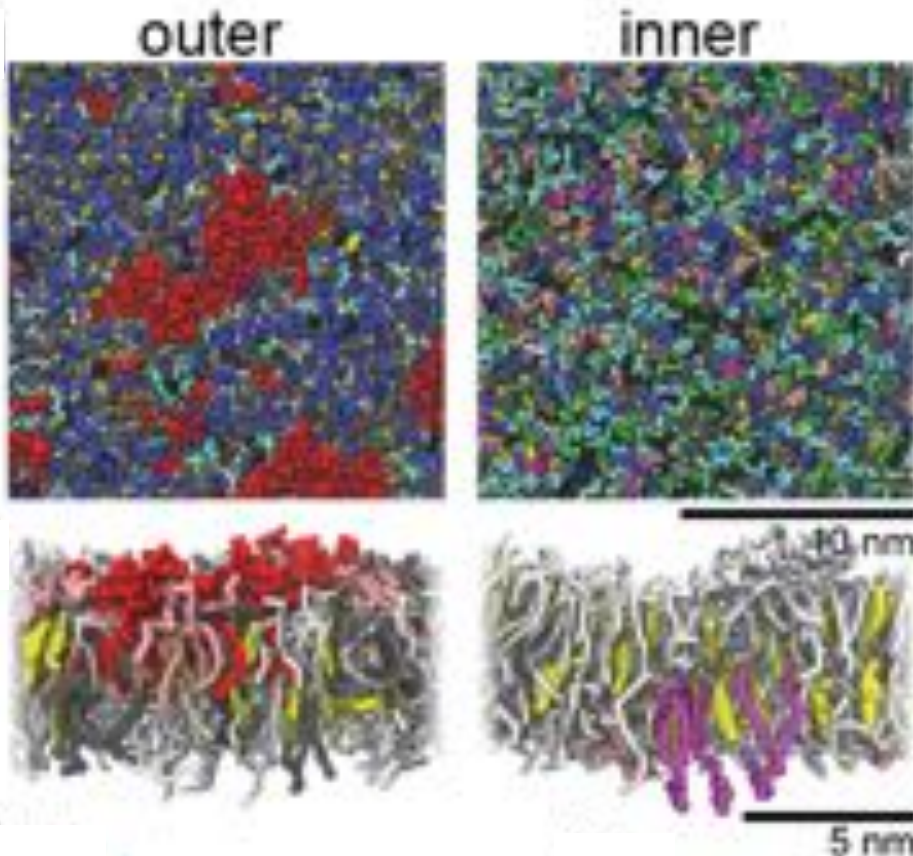


10 nm

# PM – lipid clustering



# PM – lipid clustering



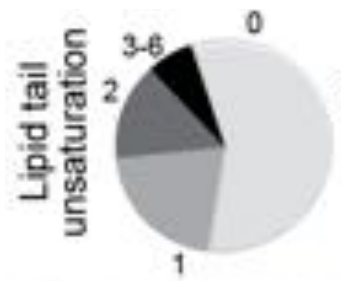
**outer**

	CHOL	PC	PE	SM	GM	
CHOL	0.93	1.04	1.02	1.09	1.05	> +25%
PC	1.00	1.03	1.01	0.96	0.81	+8 – +25%
PE	0.98	1.00	1.04	0.89	0.99	-8 – +8%
SM	1.10	0.99	0.93	1.04	0.81	-8 – -25%
GM	1.03	0.83	1.02	0.79	4.08	> -25%

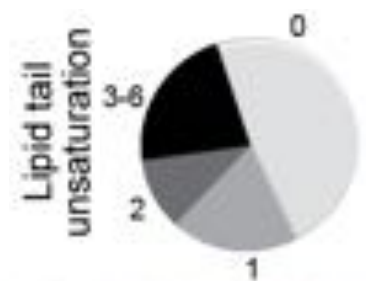
**inner**

	CHOL	PC	PE	SM	PS	PI	PIP <sub>s</sub>
CHOL	0.94	1.07	1.04	1.14	1.03	1.07	1.16
PC	1.02	0.98	0.98	0.96	1.01	0.97	0.89
PE	0.98	0.97	0.98	0.91	1.02	1.00	1.02
SM	1.15	1.01	0.95	1.08	0.97	1.00	1.06
PS	0.97	0.99	1.01	0.92	0.96	0.94	0.74
PI	1.03	0.98	1.01	0.97	0.96	0.95	0.88
PIP <sub>s</sub>	1.21	0.95	1.09	1.08	0.79	0.92	1.47

# PM – tails

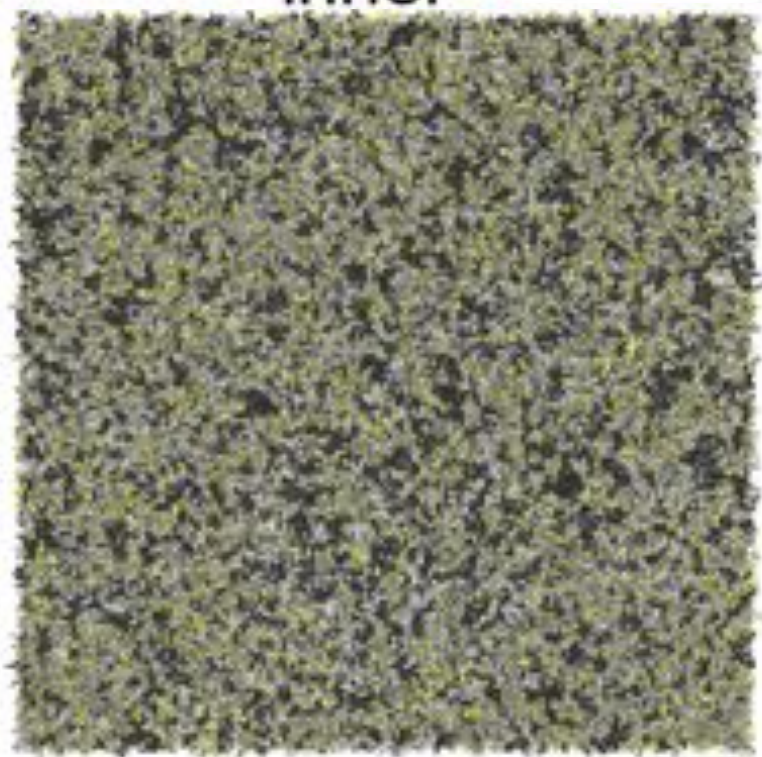
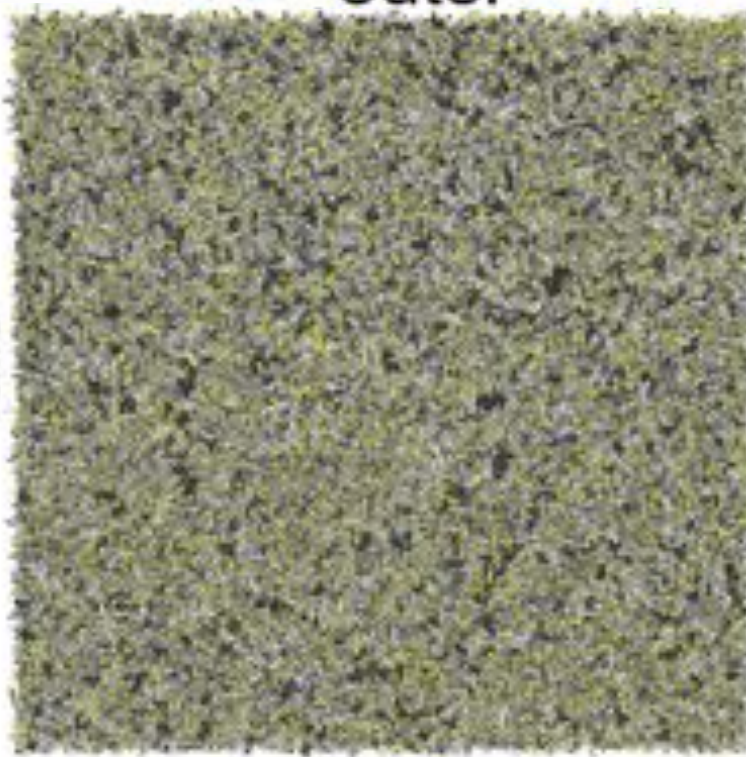


outer



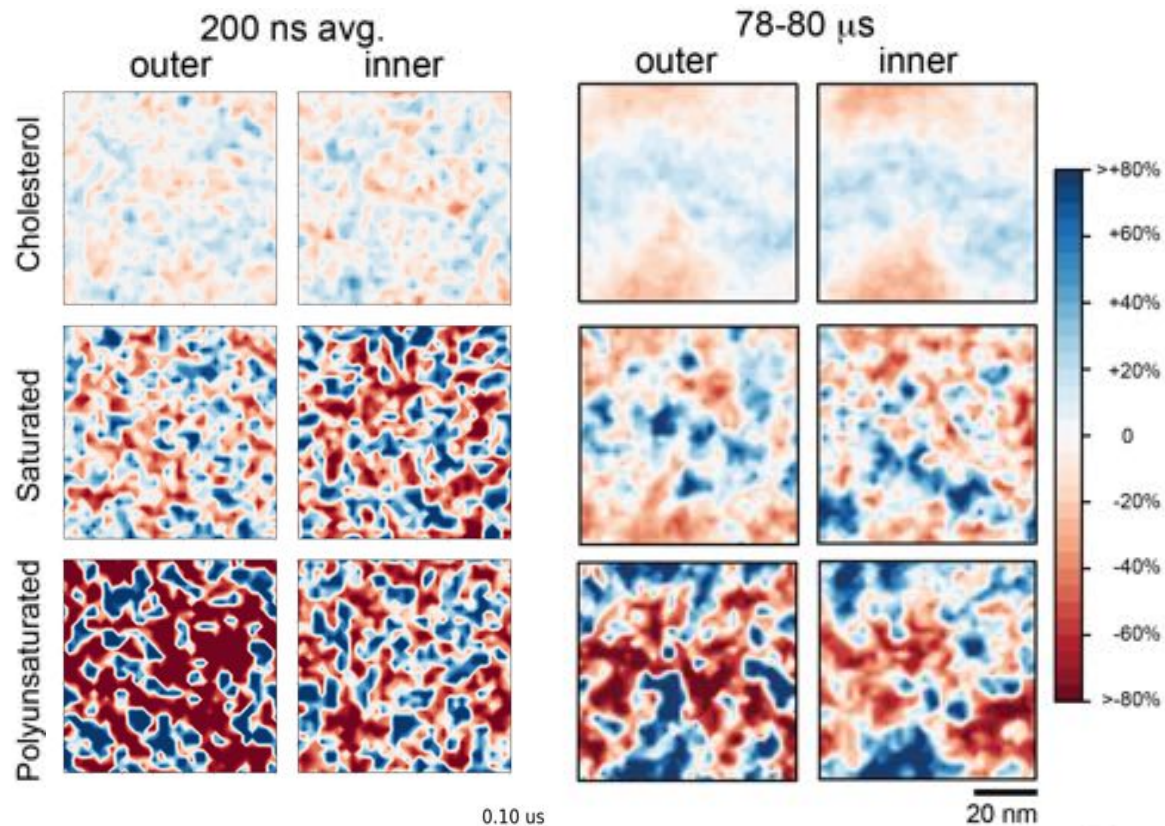
inner

Tails



10 nm

# PM – domains



**outer**

	Cholesterol	Polyunsaturated	Saturated	Other
Cholesterol	0.93	0.90	1.09	1.05
Polyunsaturated	0.77	2.41	0.74	0.95
Saturated	1.09	0.84	1.09	0.97
Other	1.02	1.05	0.94	0.98

0.10  $\mu$ s

> +25%
+8 – +25%
-8 – +8%
-8 – -25%
> -25%

**inner**

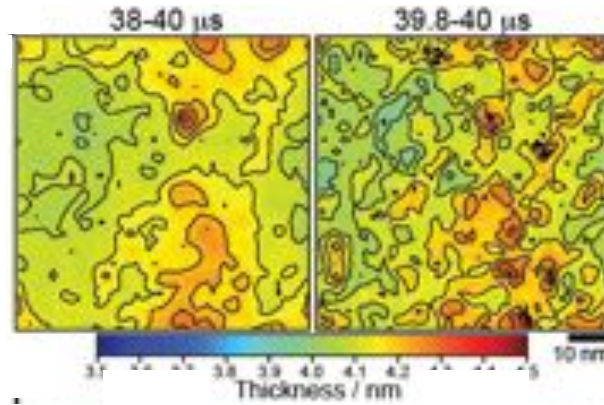
	Cholesterol	Polyunsaturated	Saturated	Other
Cholesterol	0.94	0.84	1.14	1.08
Polyunsaturated	0.67	2.19	0.64	0.86
Saturated	1.15	0.76	1.10	1.01
Other	1.04	0.98	0.97	0.98

20 nm

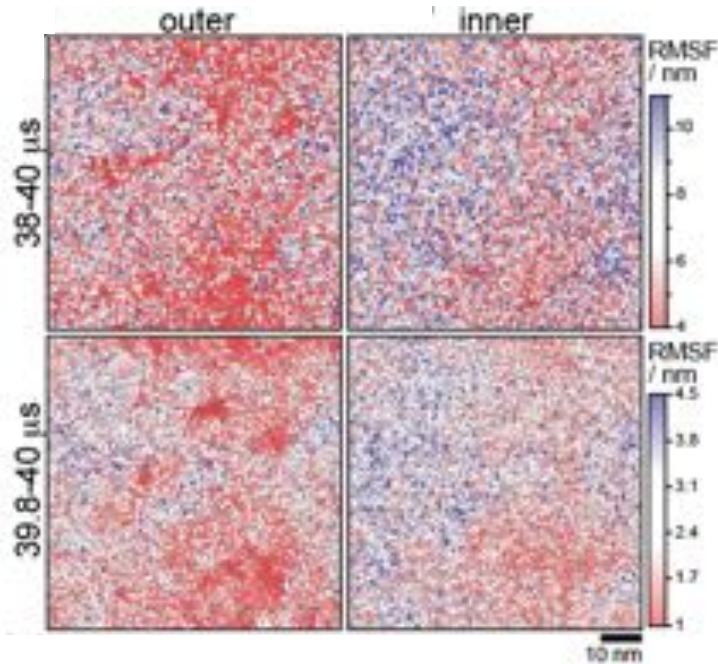


# PM – domains

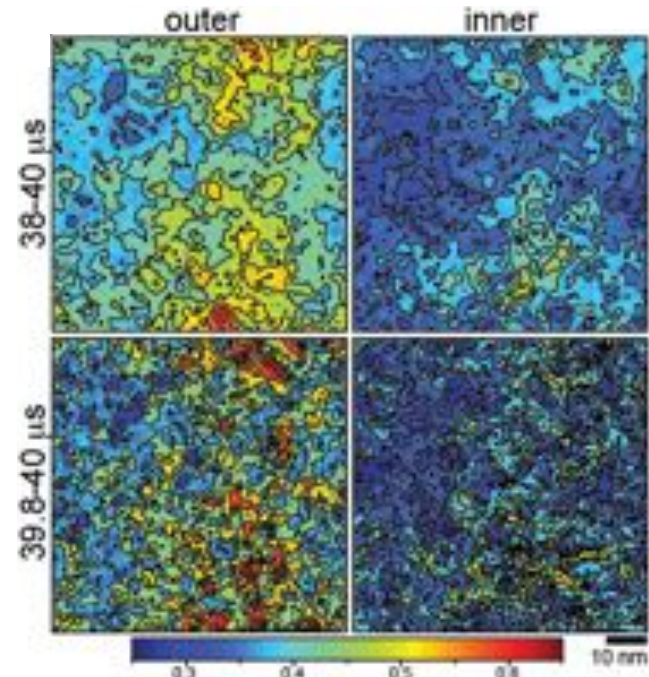
Bilayer  
Thickness



Root mean square  
fluctuations



Order parameter  
(tail 2-3)



## PM – conclusions / outlook

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**We optimized and extended the Martini CG force field lipidome and improved membrane building tools.**

**A molecular level view of the lipid organization of an idealized mammalian plasma membrane, that shows:**

- Cholesterol favors the outer leaflet
- Multiple levels of non-ideal mixing / domain formation
- GM clusters
- PIPs self associate

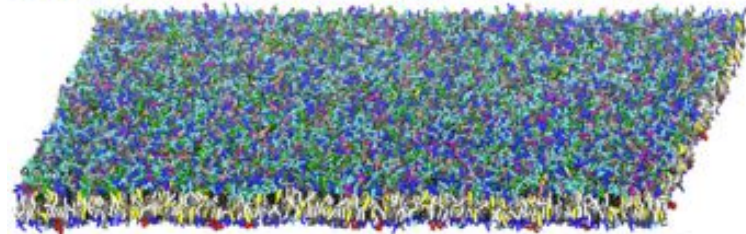
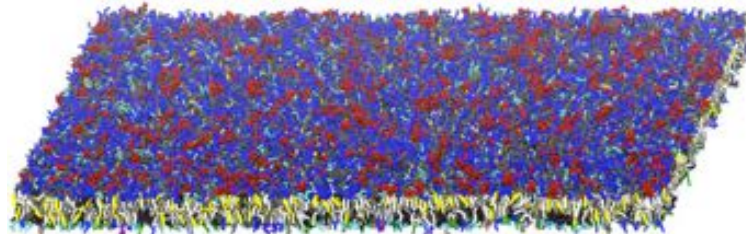
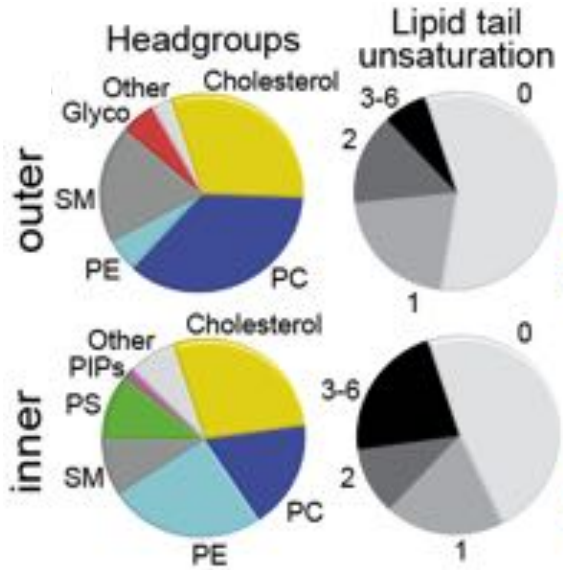
### **Next steps:**

- Membrane protein / lipids interactions
- More new lipids
- Altered PM lipid composition
- Other cell envelopes

# Plasma membranes – tissue specific

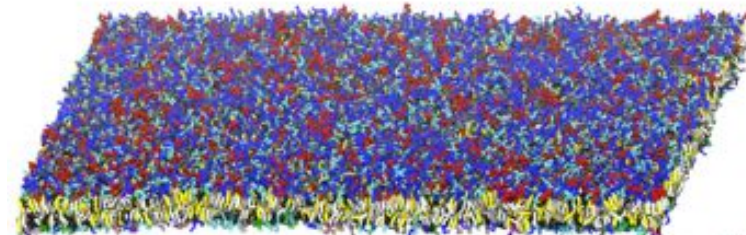
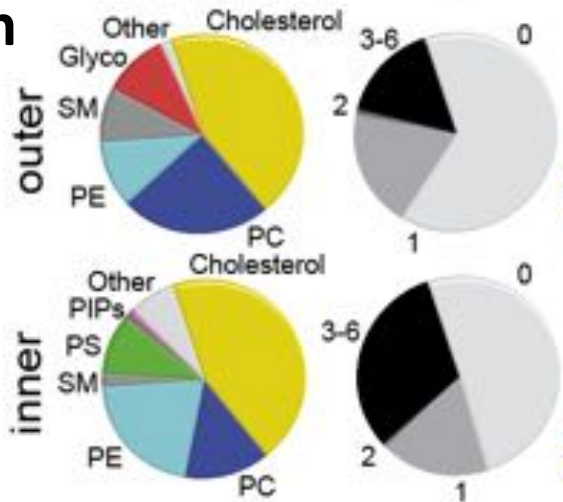
## Brain vs Avg.

Avg.



00000 ns

Brain



00000 ns

10 nm

# Brain vs Avg. – properties

Flip-flop rates ( $10^{-6} \text{ s}^{-1}$ )

	Avg.	Brain
<b>CHOL</b>	$7.29 \pm 0.02$	$4.820 \pm 0.004$
<b>DAG</b>	$7.66 \pm 0.05$	$2.80 \pm 0.07$
<b>CER</b>	$0.027 \pm 0.006$	$0.015 \pm 0.005$

Lipid lateral diffusion ( $10^{-7} \text{ cm}^2/\text{s}$ ), outer/inner leaflet

<b>Avg.</b>	$3.1 \pm 0.3$	$4.3 \pm 0.3$
<b>Brain</b>	$1.6 \pm 0.2$	$2.8 \pm 0.2$

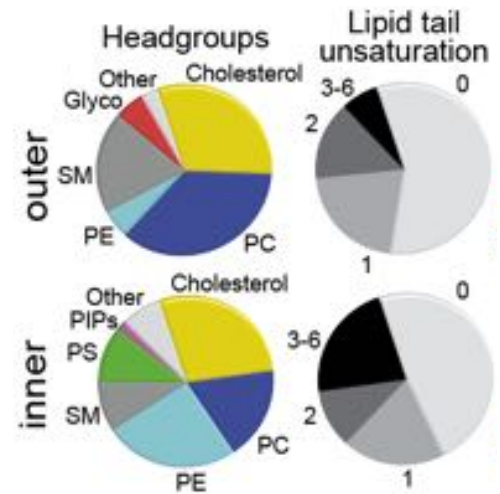
Average tail order parameter at position #3

<b>Avg.</b>	$0.425$	$0.358$
<b>Brain</b>	$0.441$	$0.306$

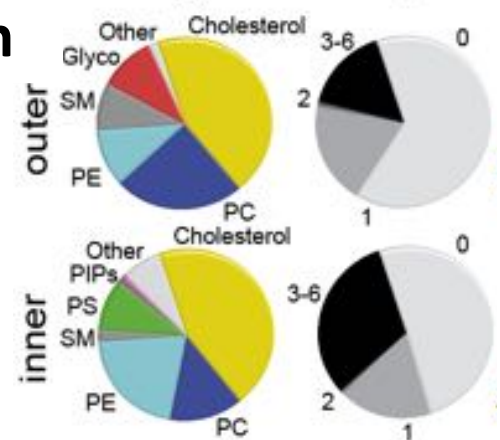
Average number of unsaturations per tail

<b>Avg.</b>	$0.77$	$1.32$
<b>Brain</b>	$0.90$	$1.63$

**Avg.**

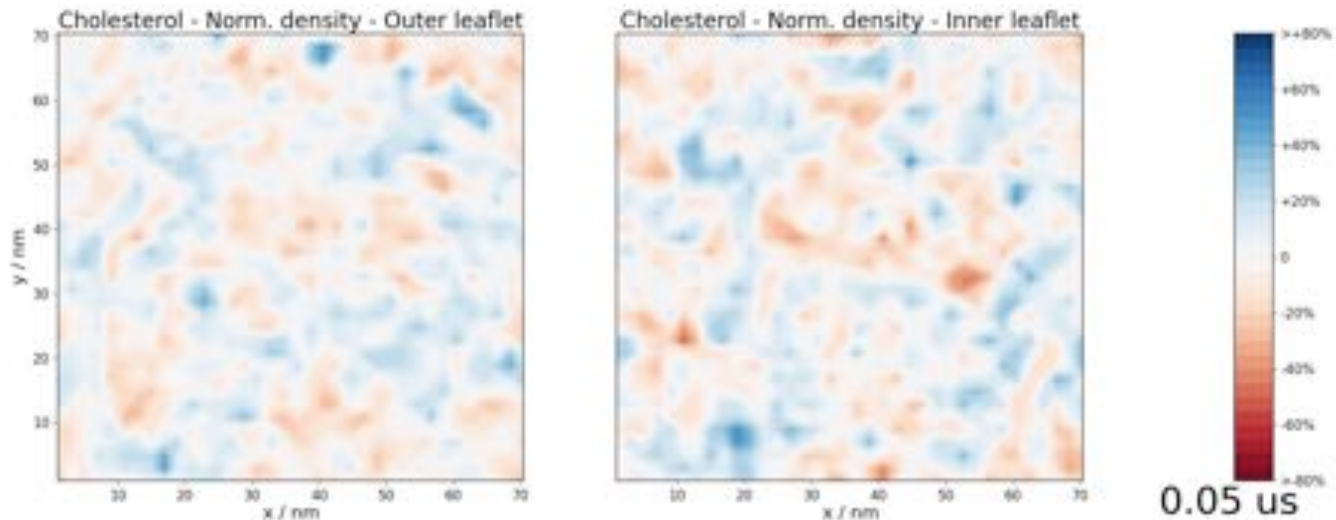


**Brain**

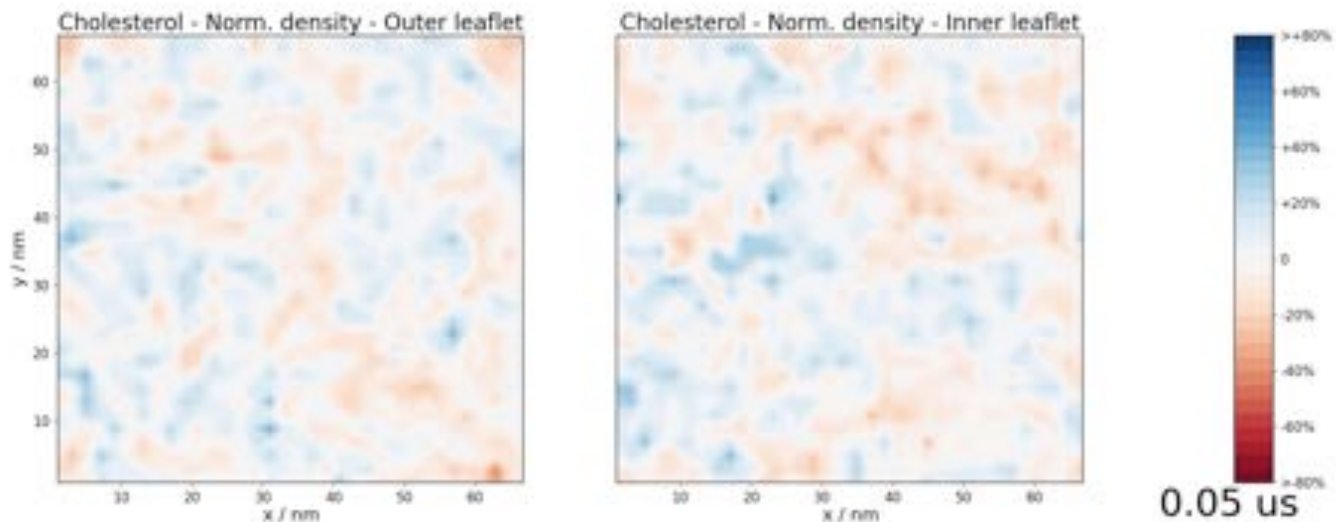


# Brain vs Avg. – cholesterol density

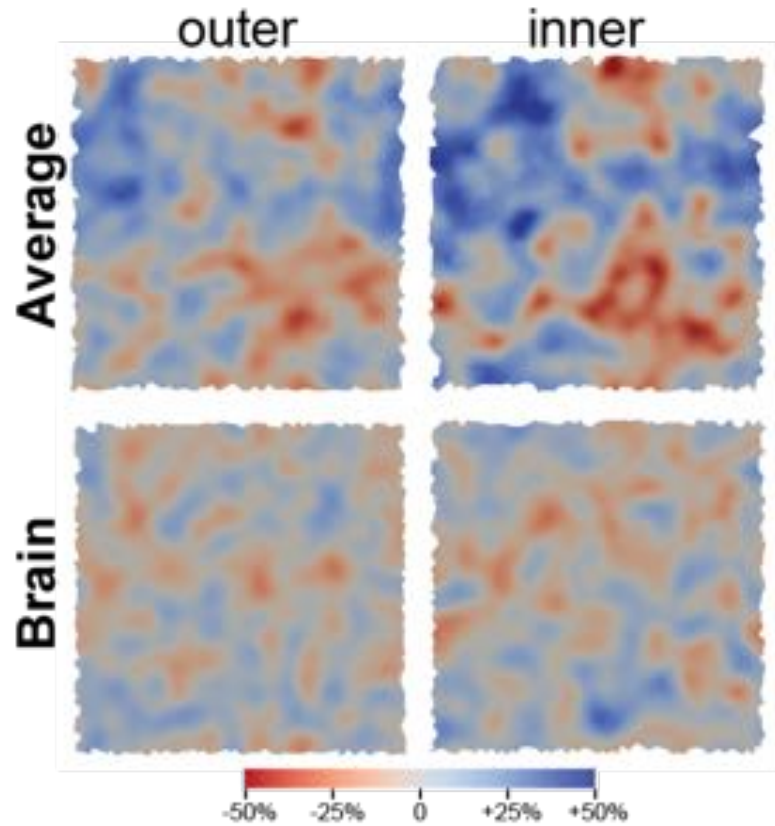
Avg.



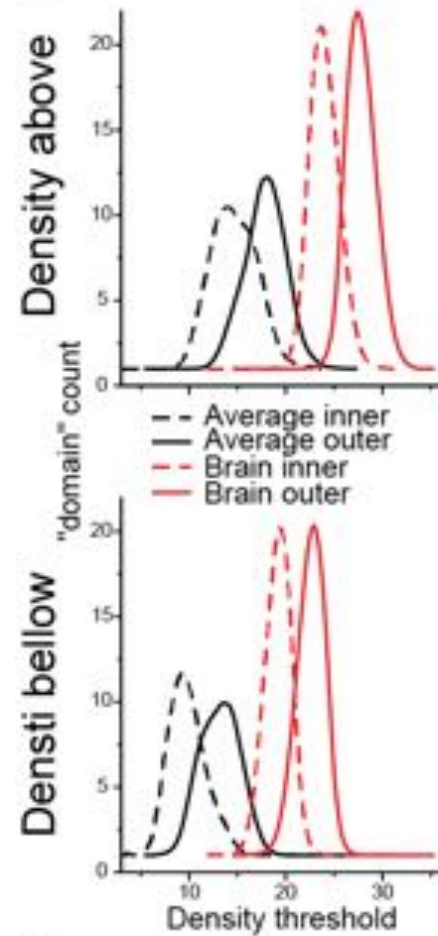
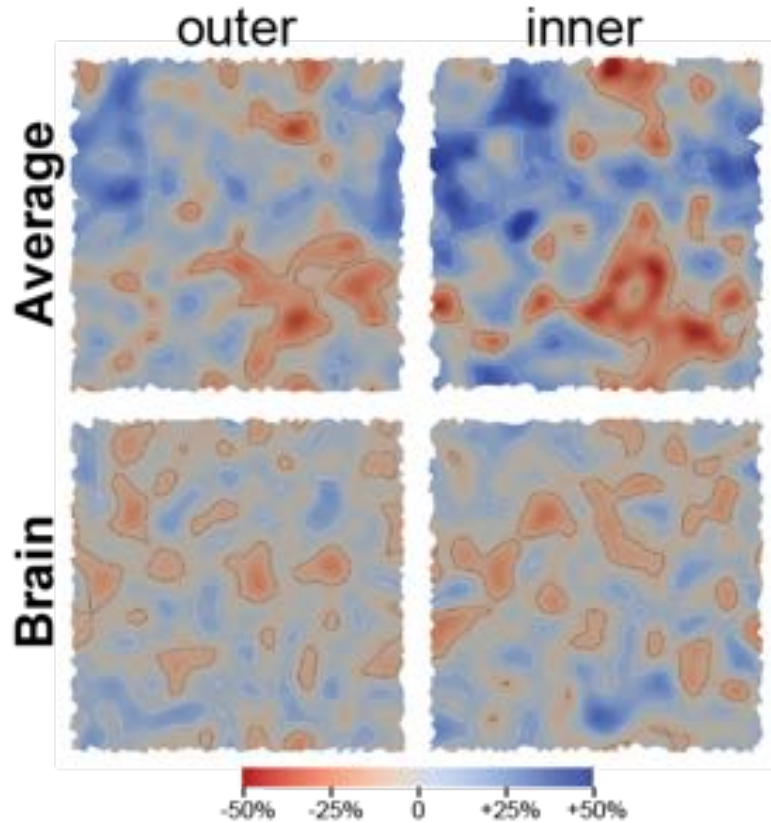
Brain



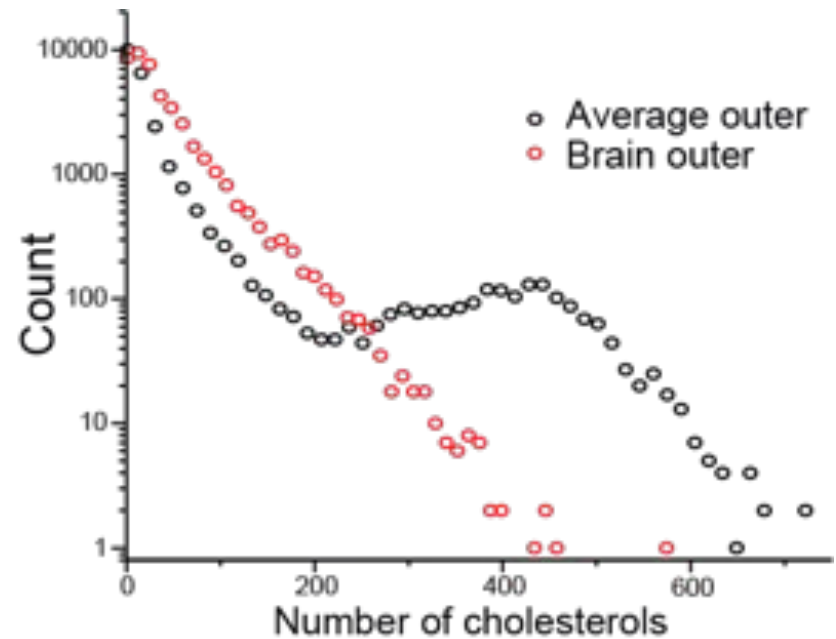
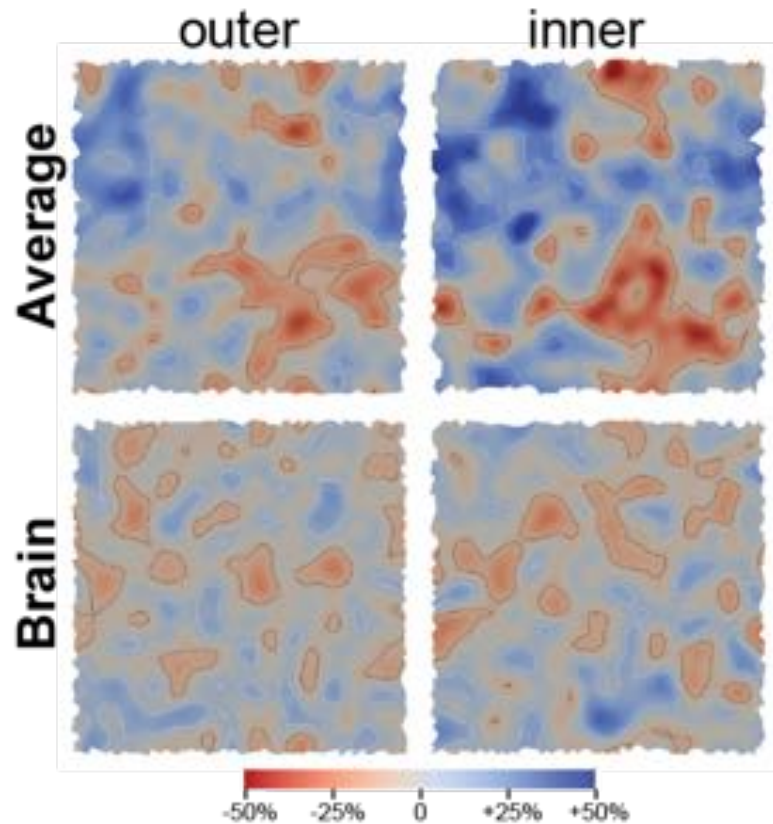
# Brain vs Avg. – domain size(s) and dynamics?



# Brain vs Avg. – domain size(s) and dynamics?

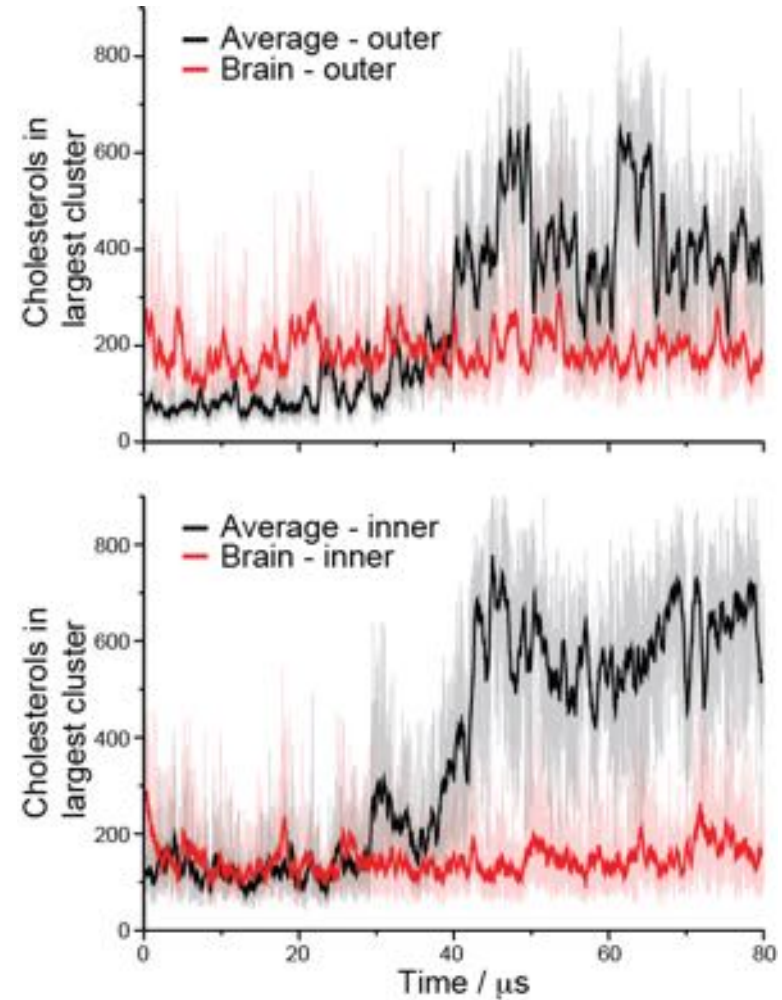
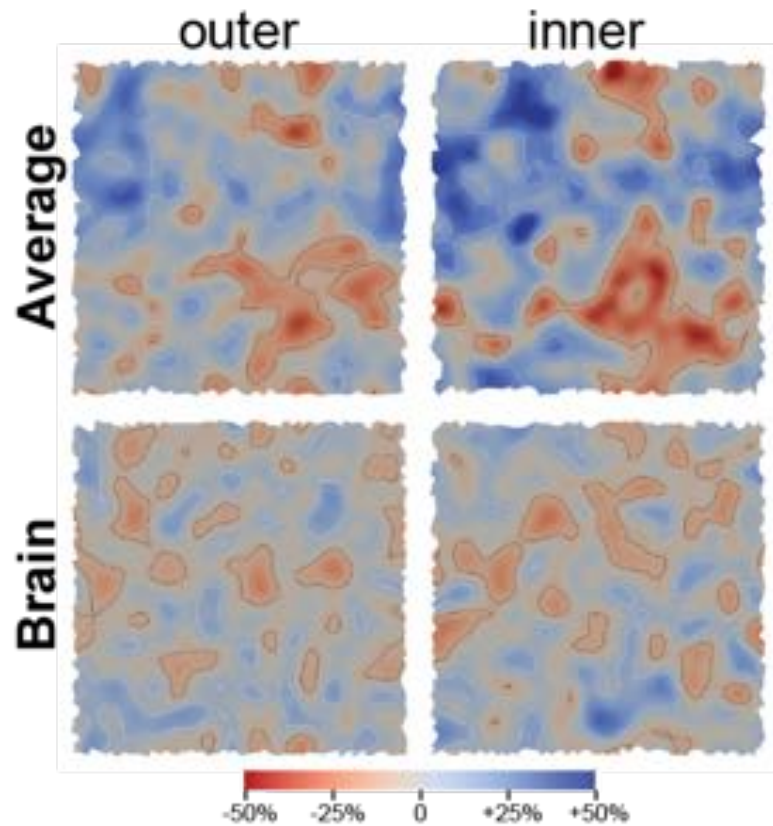


# Brain vs Avg. – domain size(s) and dynamics?

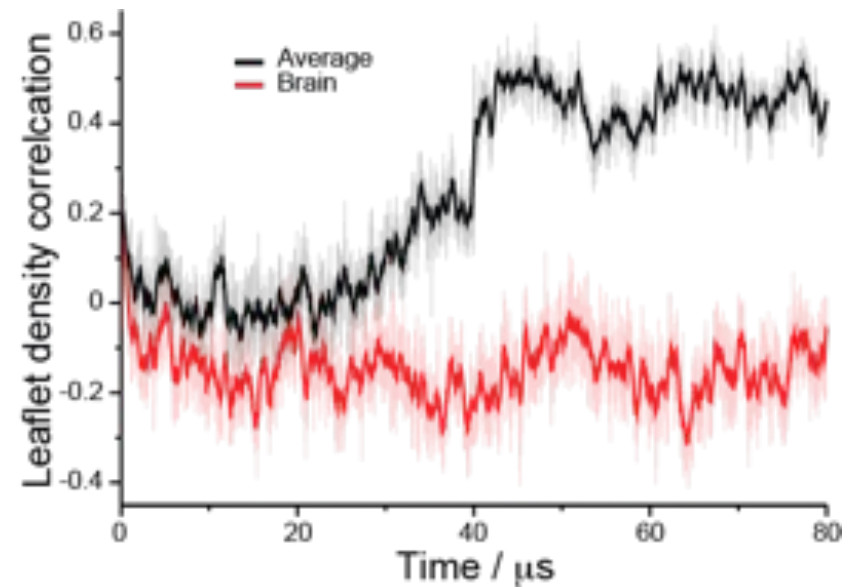
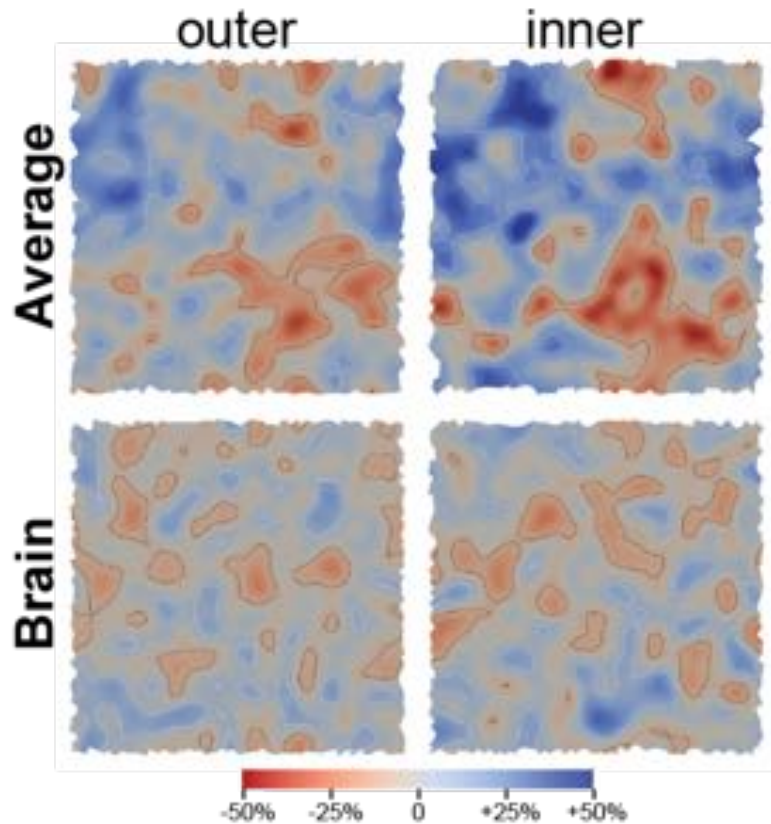




# Brain vs Avg. – domain size(s) and dynamics?

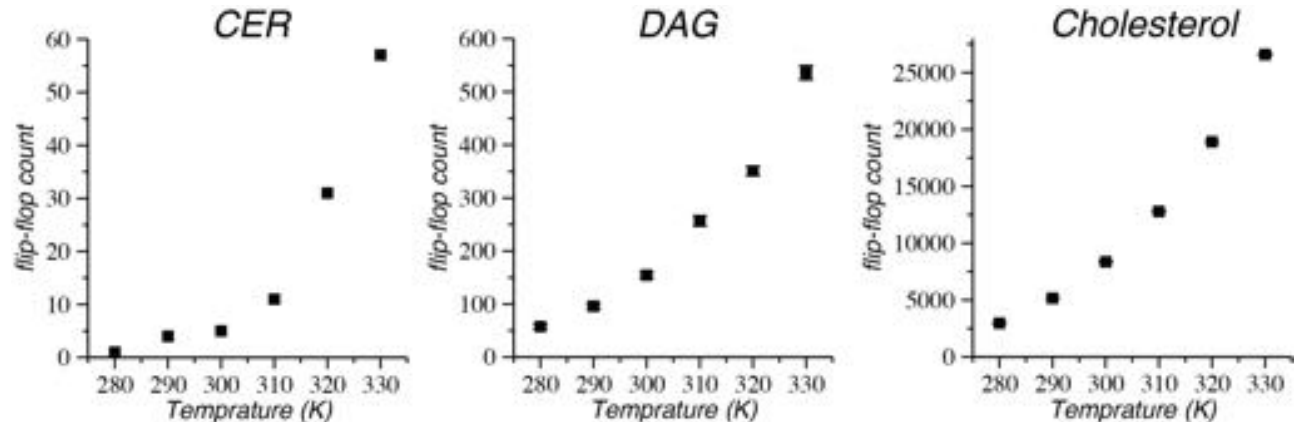


# Brain vs Avg. – domain size(s) and dynamics?



# Future – PM projects

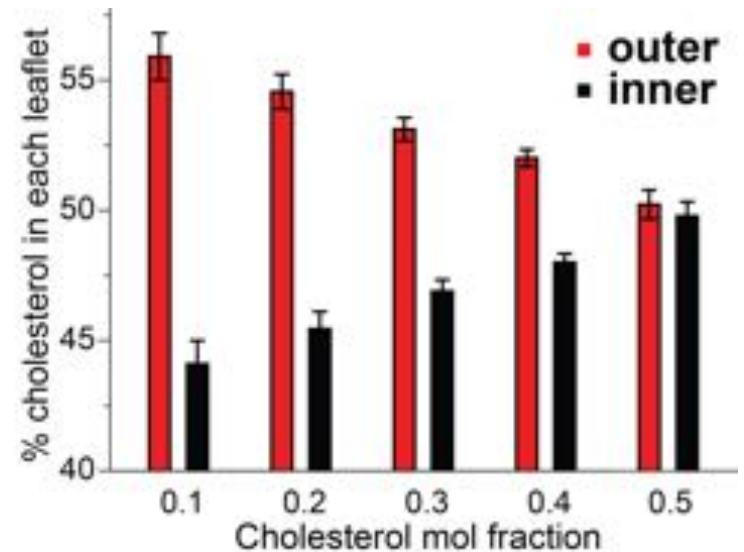
- Effect of temperature



- Cholesterol concentration

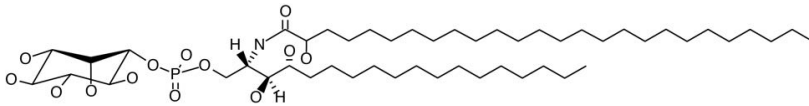
Elizabeth  
Antara  
Sebastian

- Lipid protein interactions Tieleman
- Lipid shorting and tether pulling group

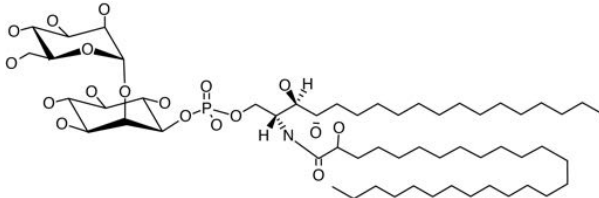


# Future – Martini lipids

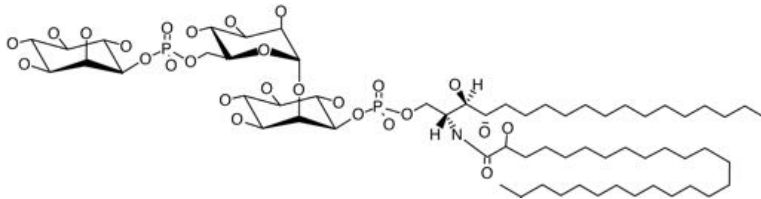
## Inositolphosphoceramide (IPC)



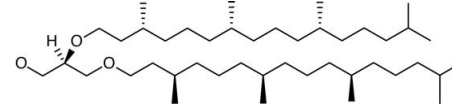
## Mannosyl-IPC (MIPC)



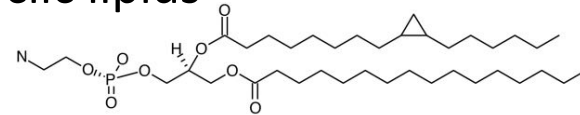
## Mannosyl-di-IPC (MIP<sub>2</sub>C)



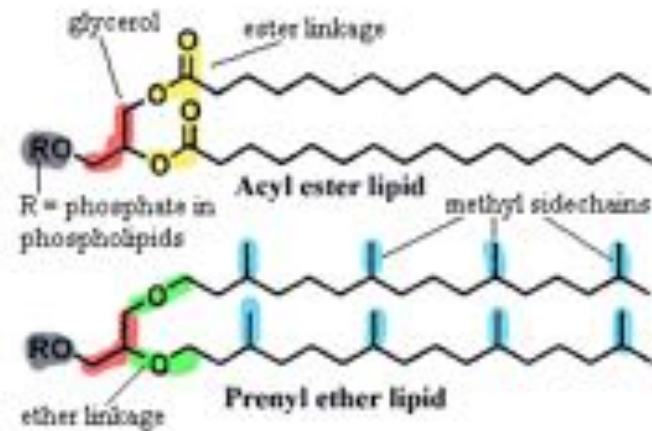
## Methyl-branched ether lipids



## Cyclic lipids



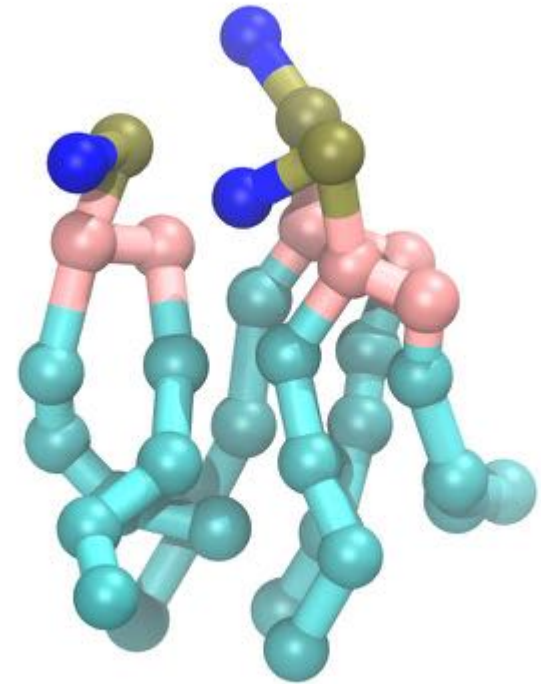
## Ester / ether lipids



[paleos.com/eukarya/eukarya\\_origins\\_1.html](http://paleos.com/eukarya/eukarya_origins_1.html)

# Future – your own new lipid

- Current naming standards
- Use what already exists
- Rationalize changes
- Be aware of over fitting
- Test, test and test
- .itp file format
- Add to Martini website



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