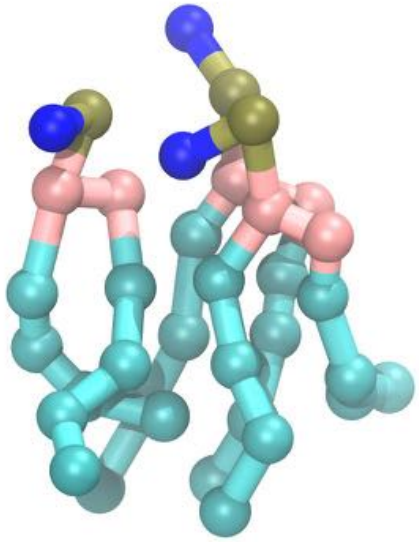
Lipid biophysics with the Martini model



2017 Martini Workshop, Groningen

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Helgi I. Ingólfsson

Physical and Life Sciences

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Lawrence Livermore National Laboratory, P.O. Box 808, Livermore, CA 94551
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BIO BBS

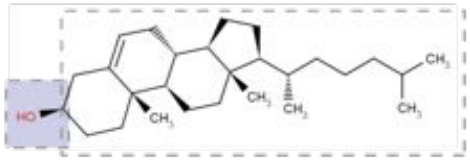
Overview

- 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 Martin lipids and projects

Lipids – definition

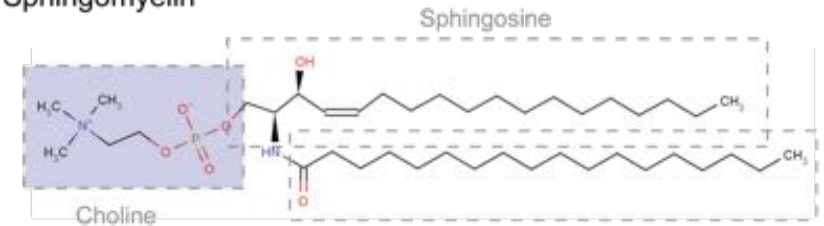
- Naturally occurring fats or fat-like compounds
- Insoluble in water
- Soluble in organic solvents
- Hydrophobic/amphipathic molecules

Cholesterol

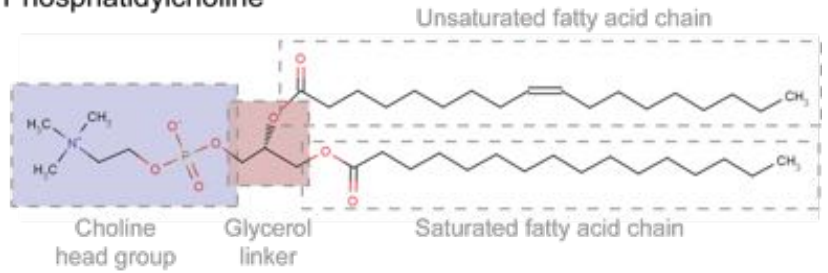


Head group Tail

Sphingomyelin



Phosphatidylcholine

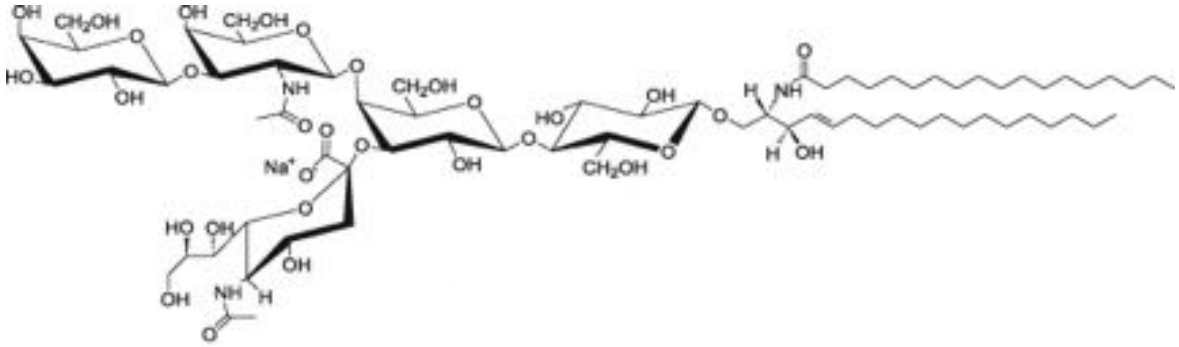


Examples of lipid head groups

Choline Ethanolamine Inositol Serine

Lipids – definition

GM1



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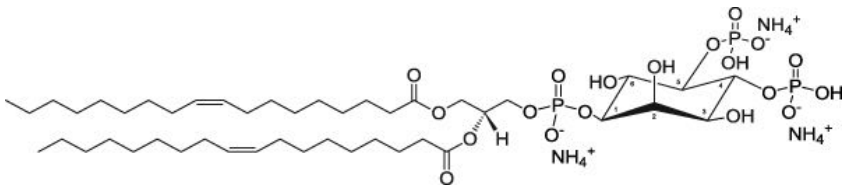
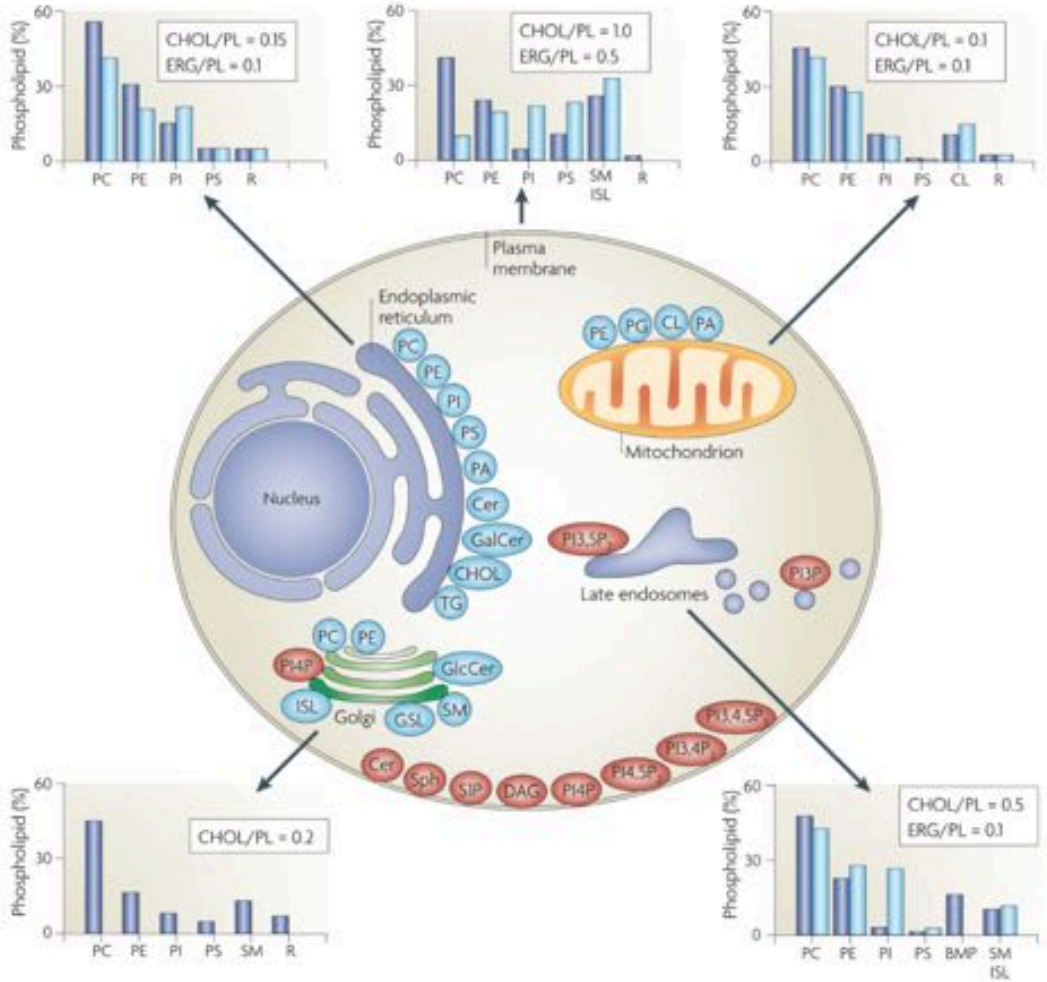
- Hydrophobic/amphipathic molecules

$PIP_2(4,5)$



Lipids – diversity

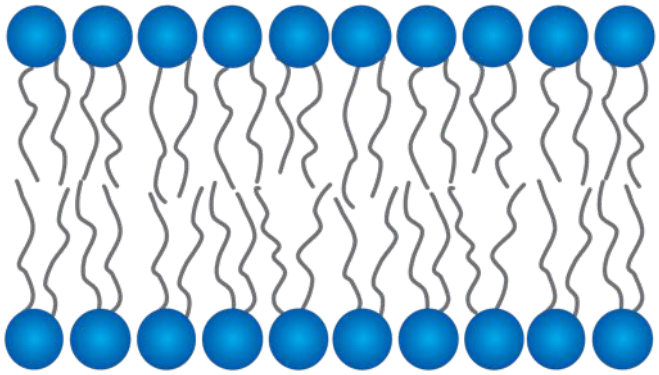


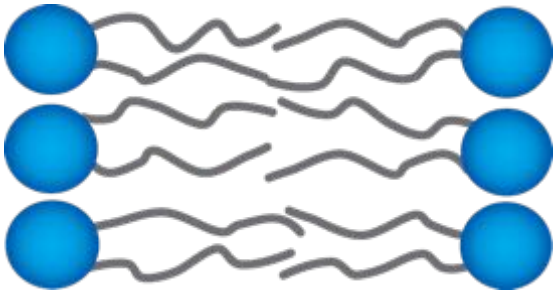
van Meer G1, Voelker DR, Feigenson GW. (2008) Membrane lipids: where they are and how they behave. Nat Rev Mol Cell Biol. 9:112-24.

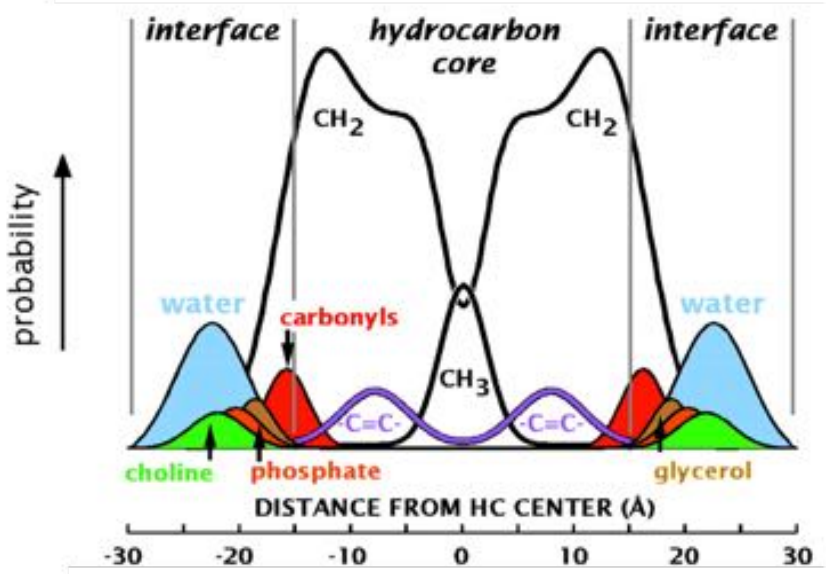
- Membranes contain 100s of different lipid types
- Cells have 1000s
- Currently www.lipidmaps.org has >40.000 unique lipid structures

Lipids – bilayers

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







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

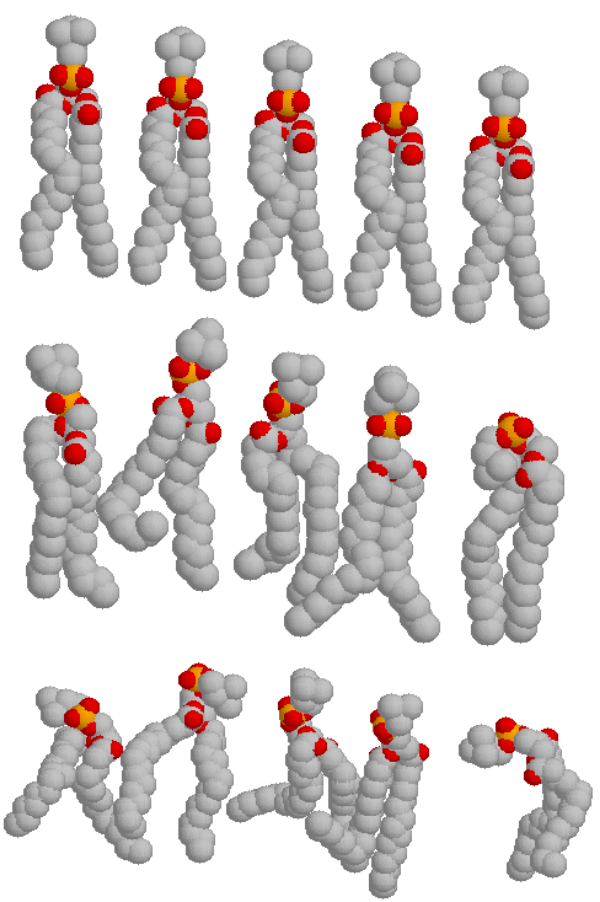
- Lipids
- Other amphiphiles
- Membrane proteins

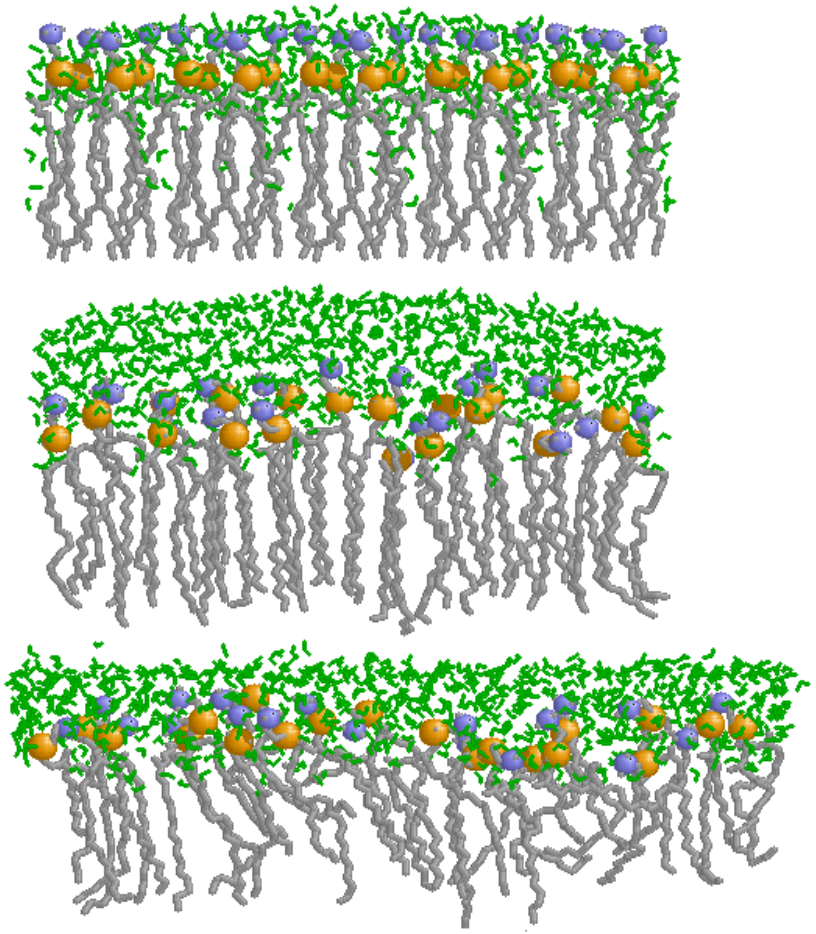
Lipids – bilayers

Crystal

Gel

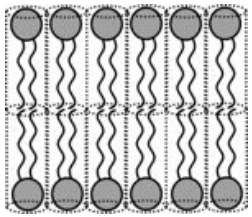
Fluid

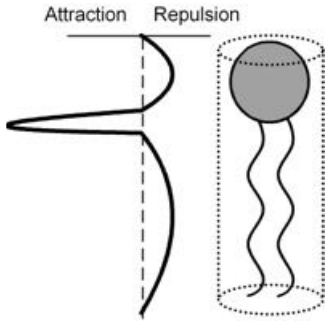




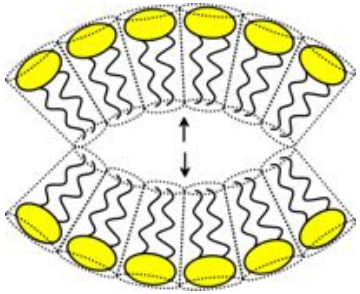
Images from Eric Martz using RasMol, structures from:
Heller et al. 1993. *J Phys Chem* 97:8343-8360

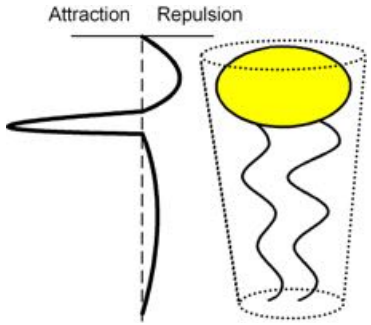
Lipids – shape



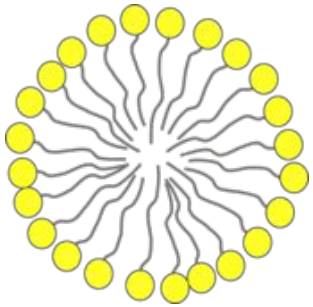


Positive intrinsic curvature

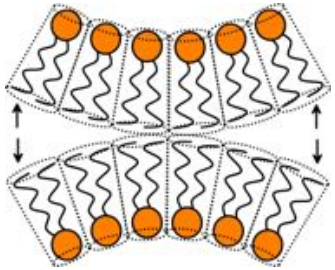


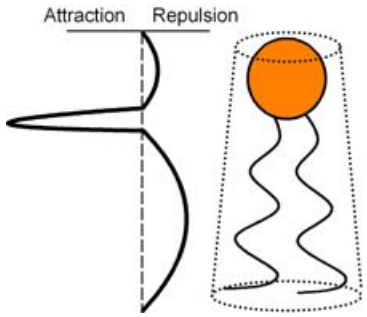


Micelle

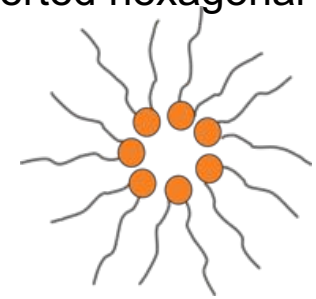


Negative intrinsic curvature

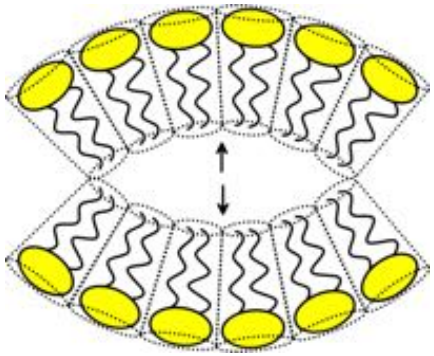


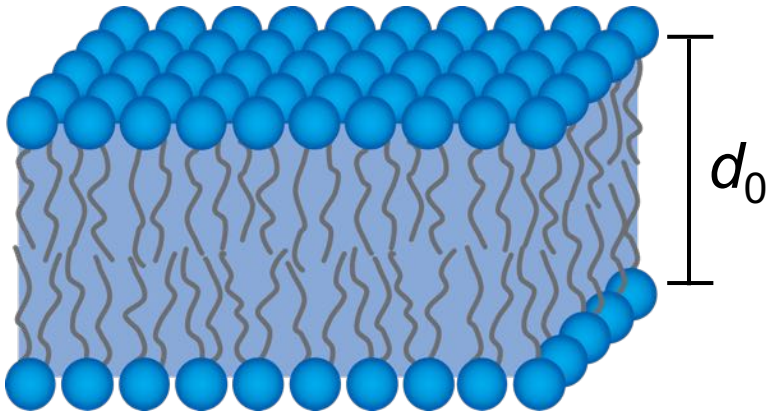


Inverted hexagonal phase



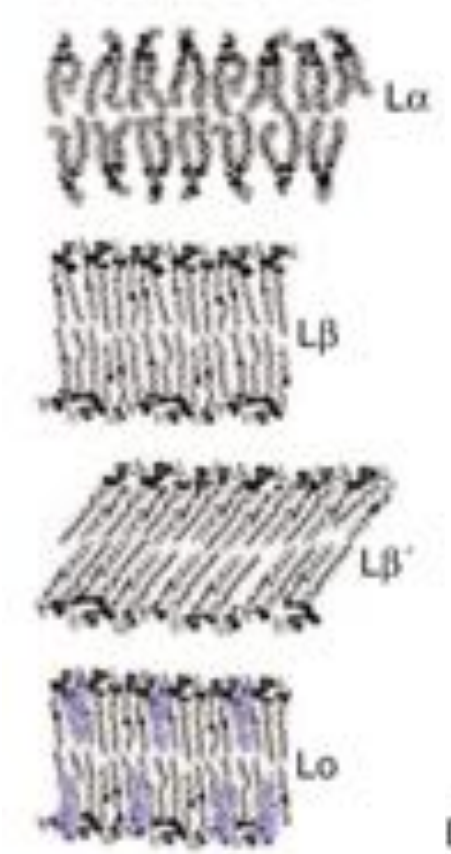
Lipids – properties

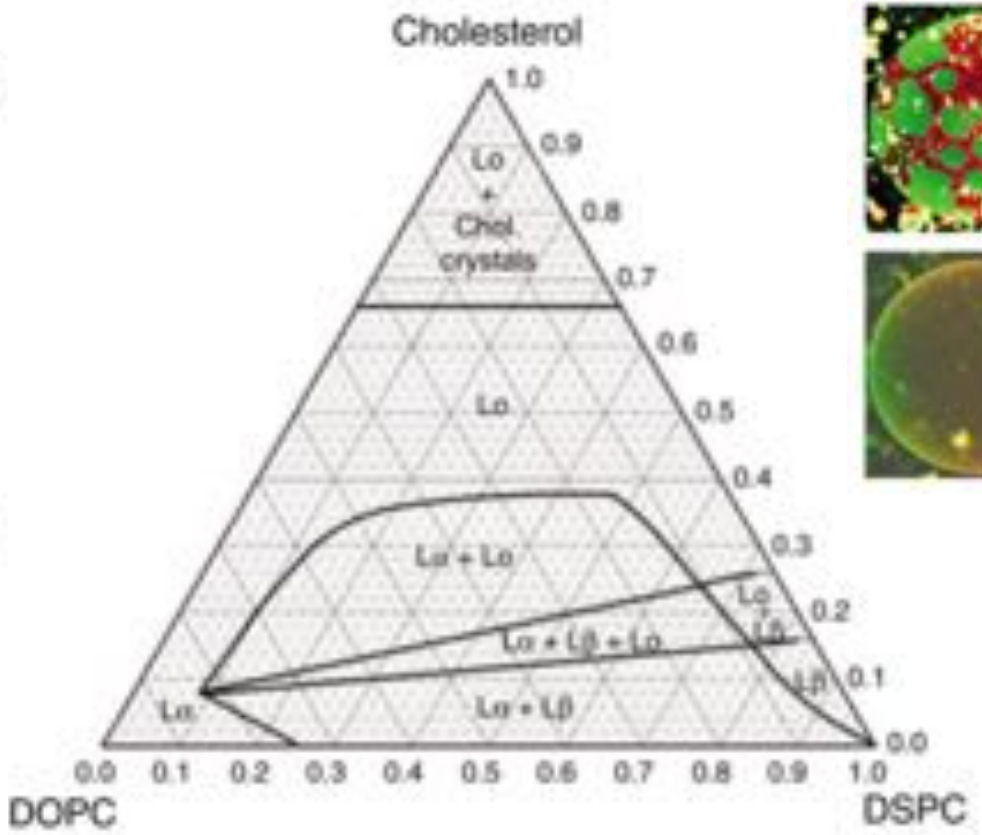


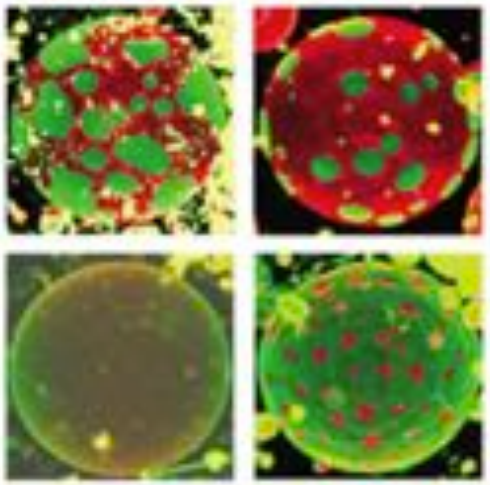


- Intrinsic lipid curvature (c_0)
- Actual curvature (c)
- Hydrophobic thickness (d_0)
- Area compression-expansion modulus (K_a)
- Splay-distortion modulus (K_c)
- Fluidity
- Diffusion
- Area per lipid
- Order parameter
- Surface tension
- Acyl chain packing
- Lateral pressure profile
- Lipid packing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

Lipids – “rafts” / domains / phases



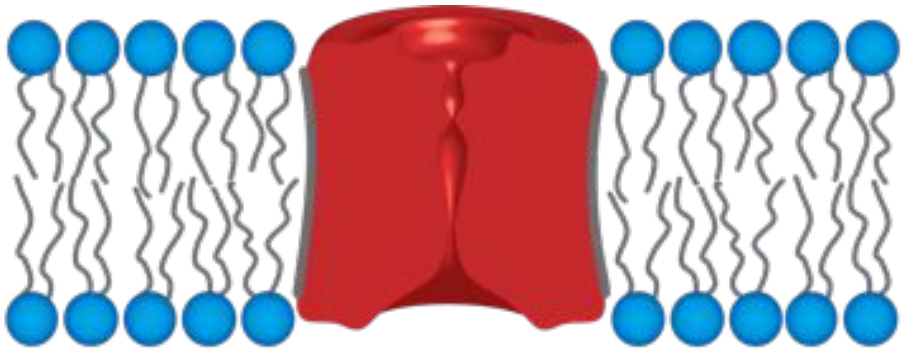


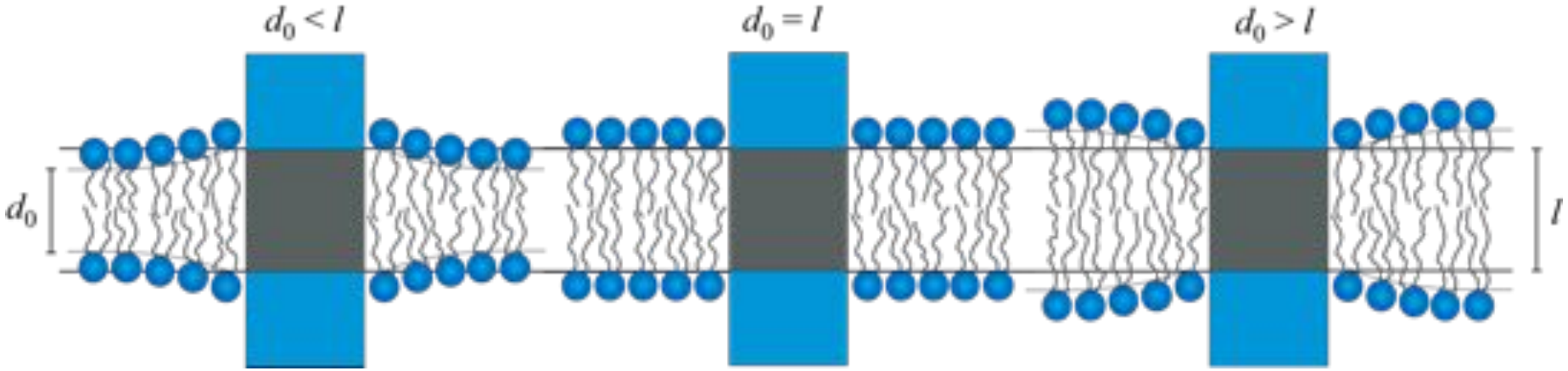


Feigenson, G.W. 2006. Phase behavior of lipid mixtures. Nat. Chem. Biol. 2: 560–563.

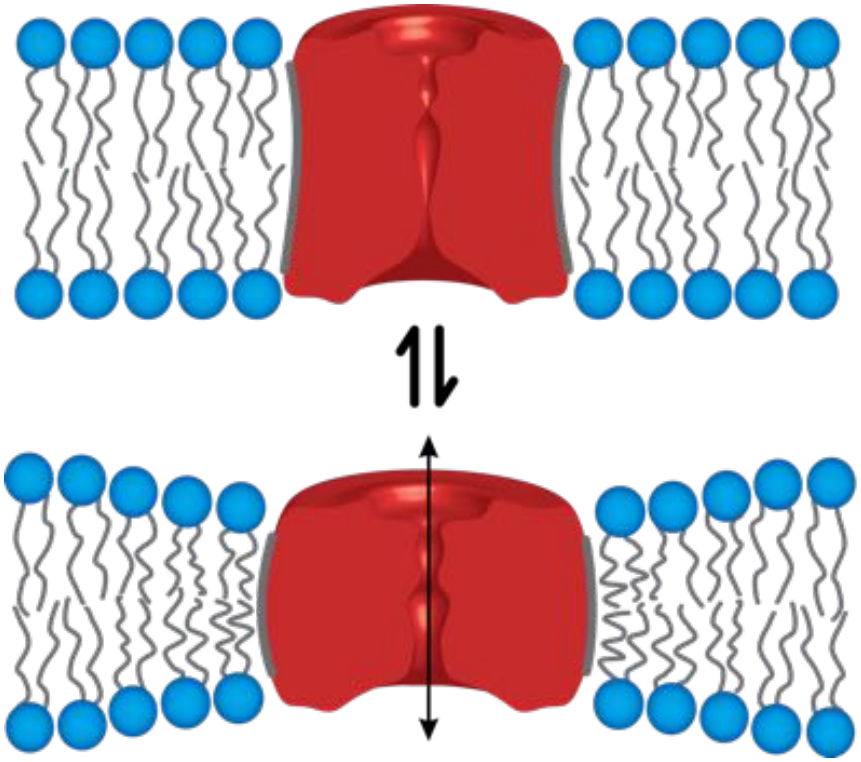
Lipids – bilayer/protein interactions

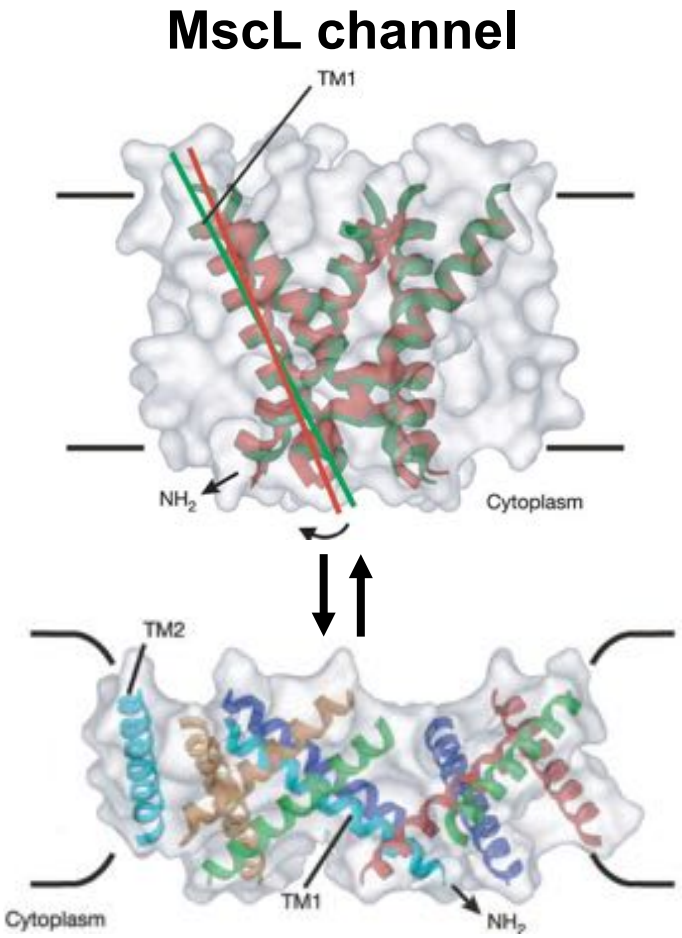
Hydrophobic matching: to minimize exposure to water, a membrane protein's hydrophobic domain is embedded in the bilayer hydrophobic core.





Lipids – bilayer/protein interactions



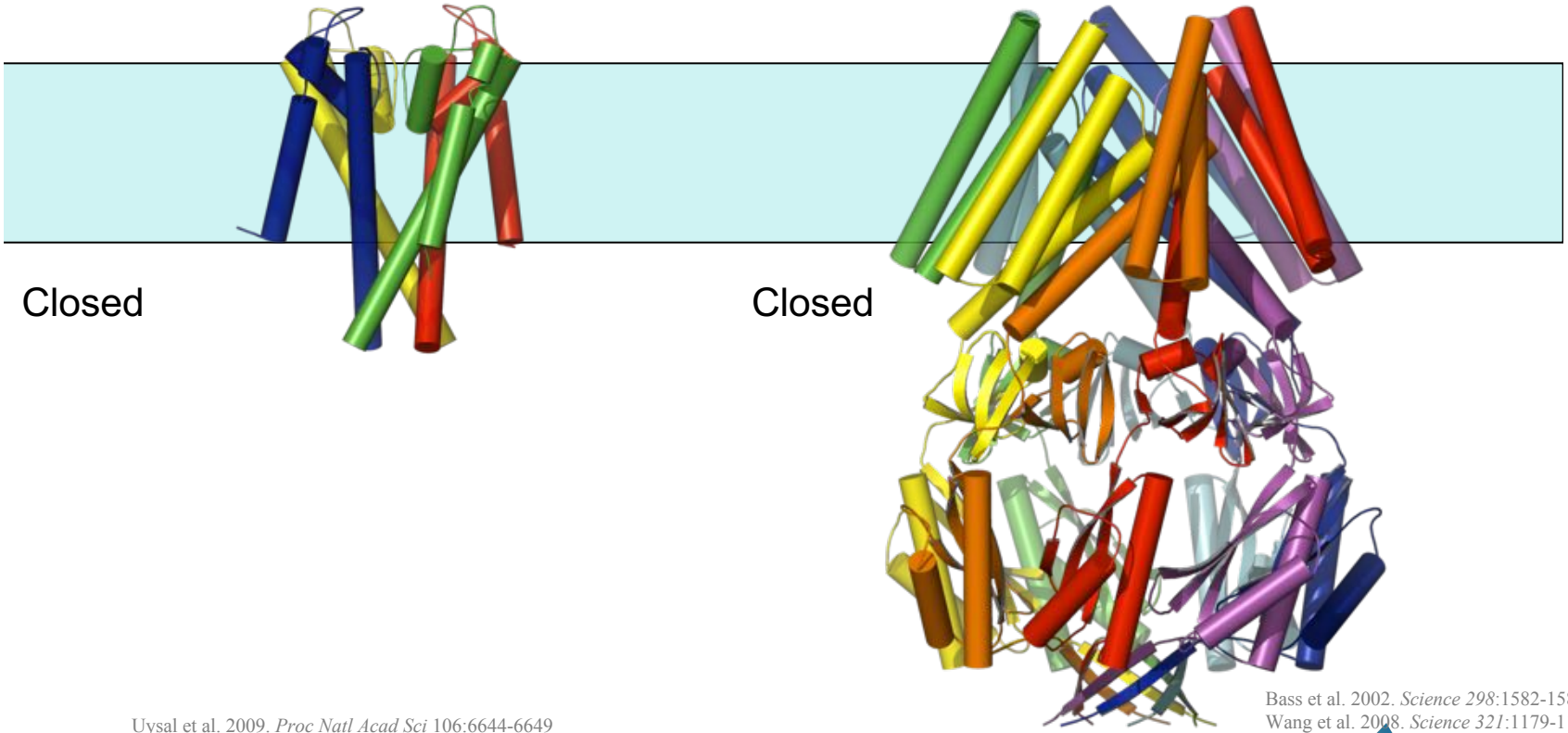


Chang et al. 1998. *Science* 282:2220-2226 and
Perozo et al. 2002. *Nature* 418:942-948

Lipids – bilayer/protein interactions

KcsA channel

MscS channel



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

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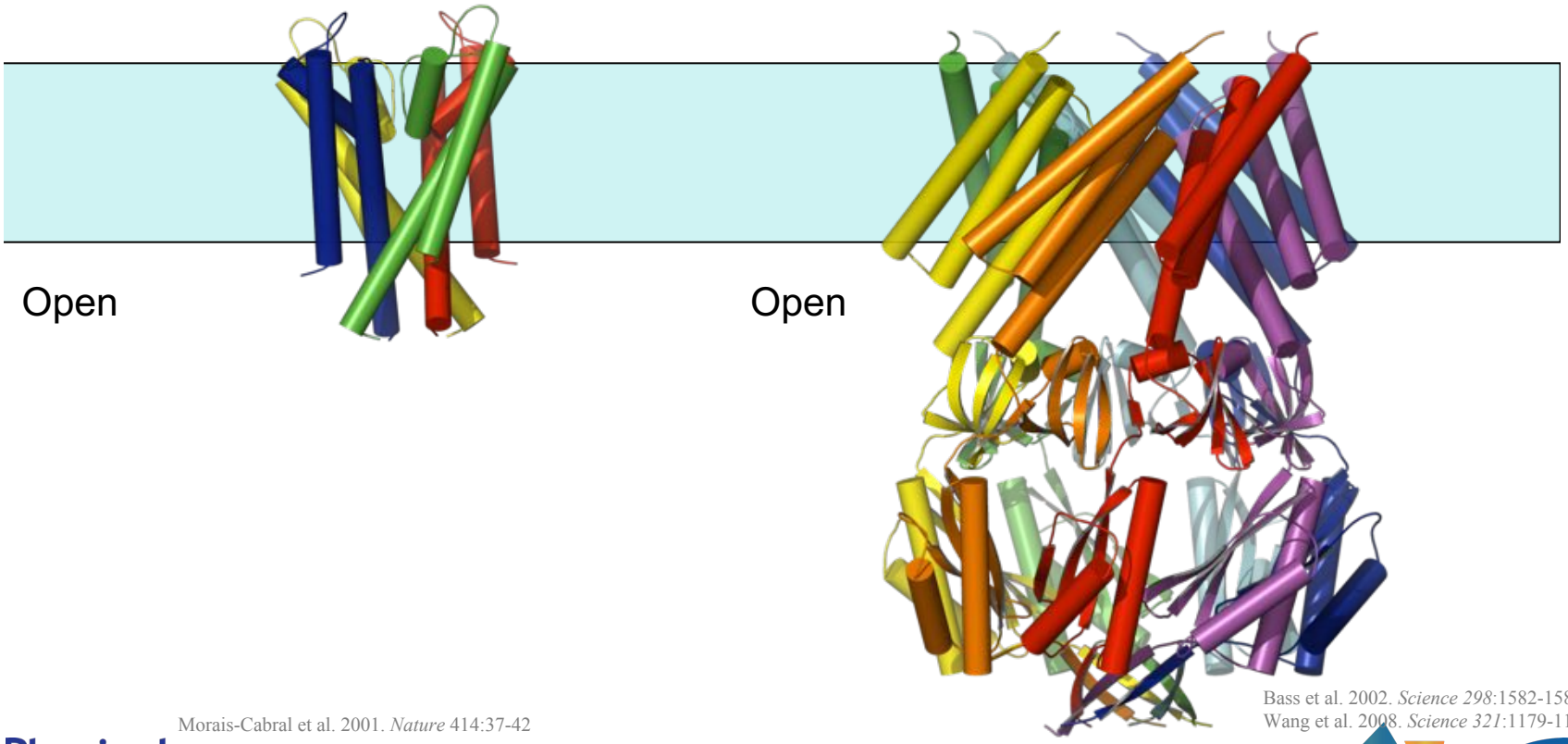
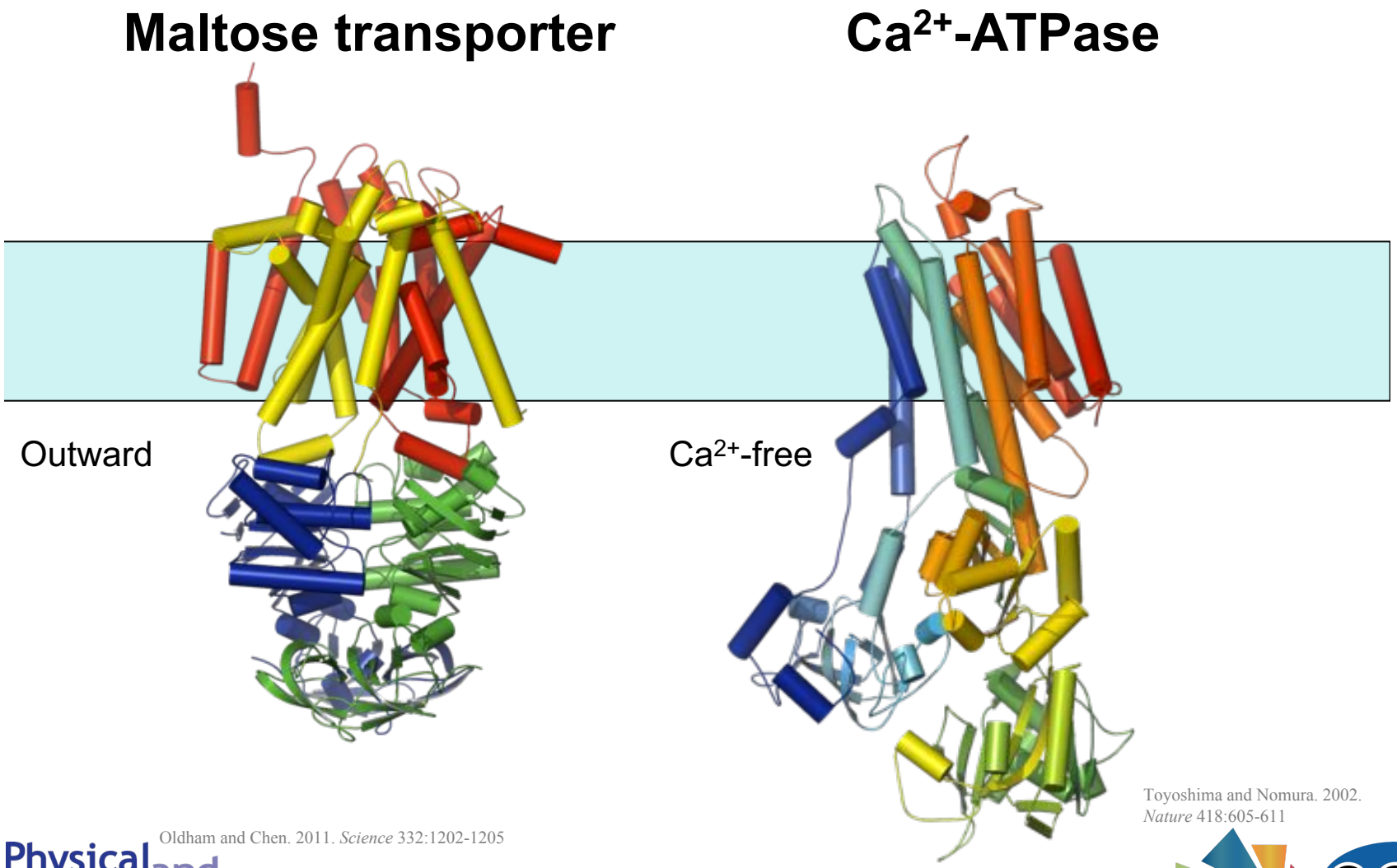


Morais-Cabral et al. 2001. *Nature* 414:37-42

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

Lipids – bilayer/protein interactions



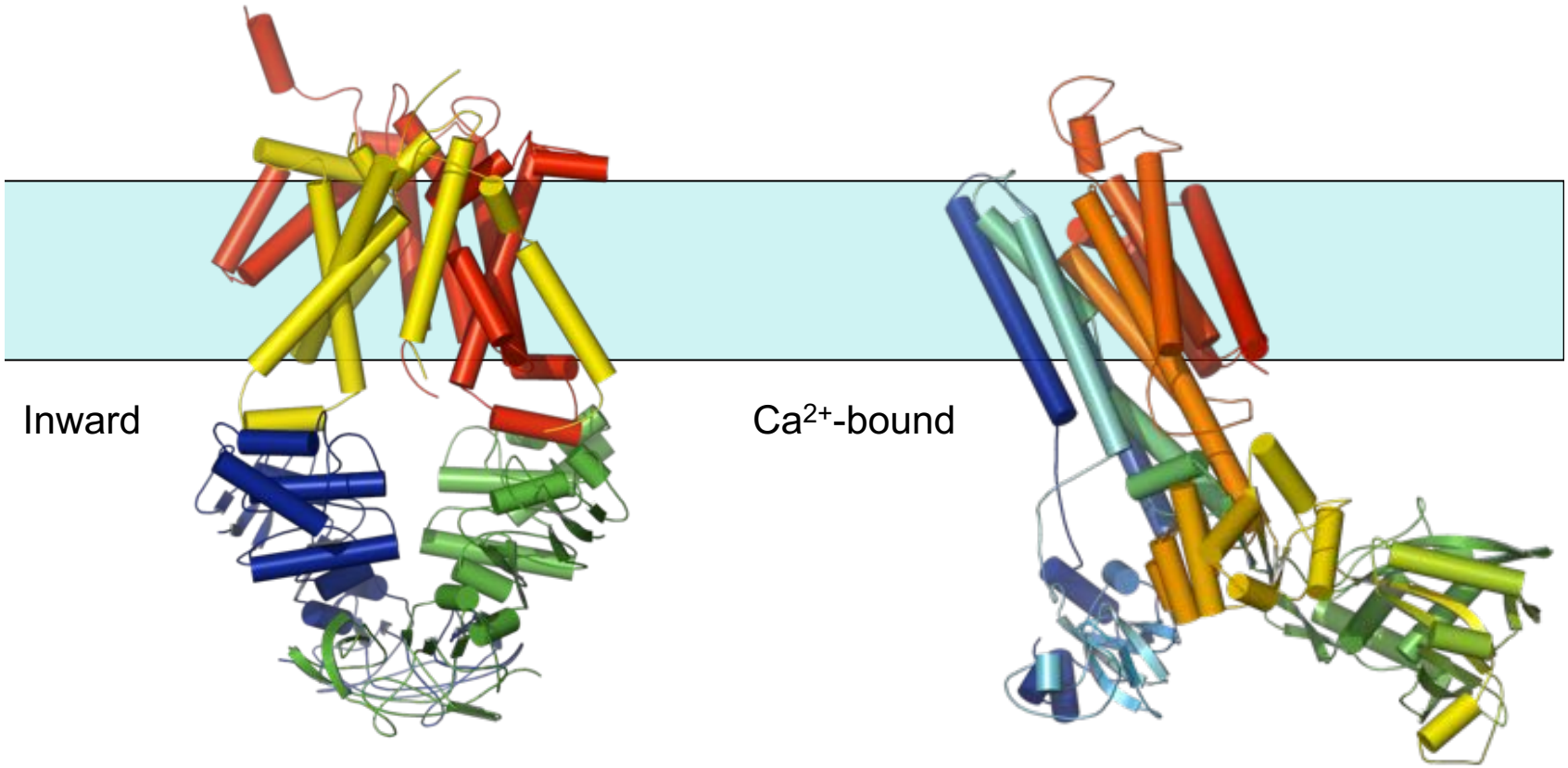
Oldham and Chen. 2011. *Science* 332:1202-1205

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

Lipids – bilayer/protein interactions

Maltose transporter

Ca^{2+}-ATPase



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

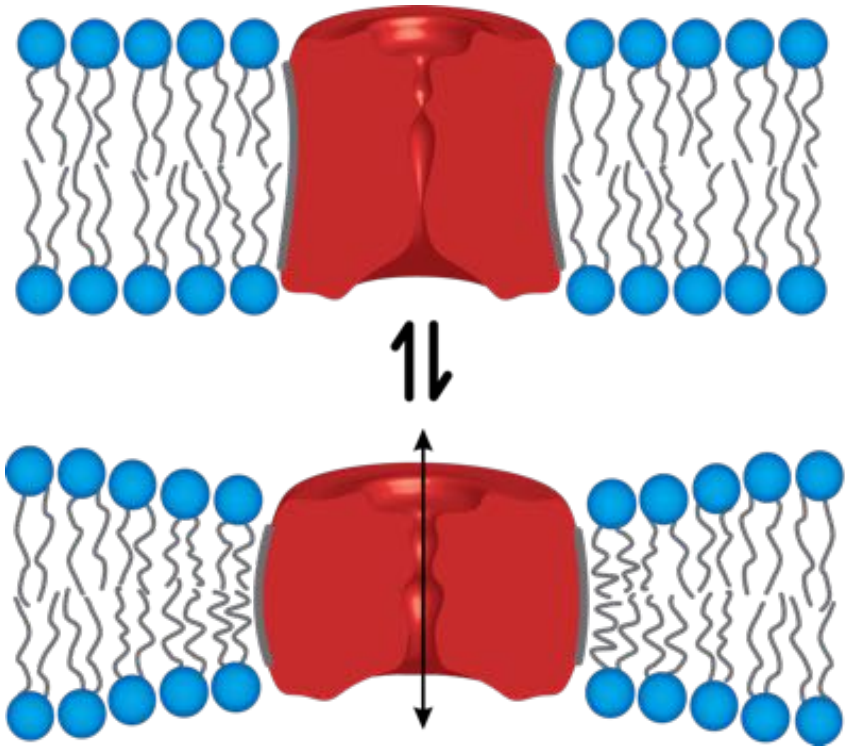
Toyoshima and Nomura. 2002. *Nature* 418:605-611

Lipids – bilayer/protein interactions

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

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

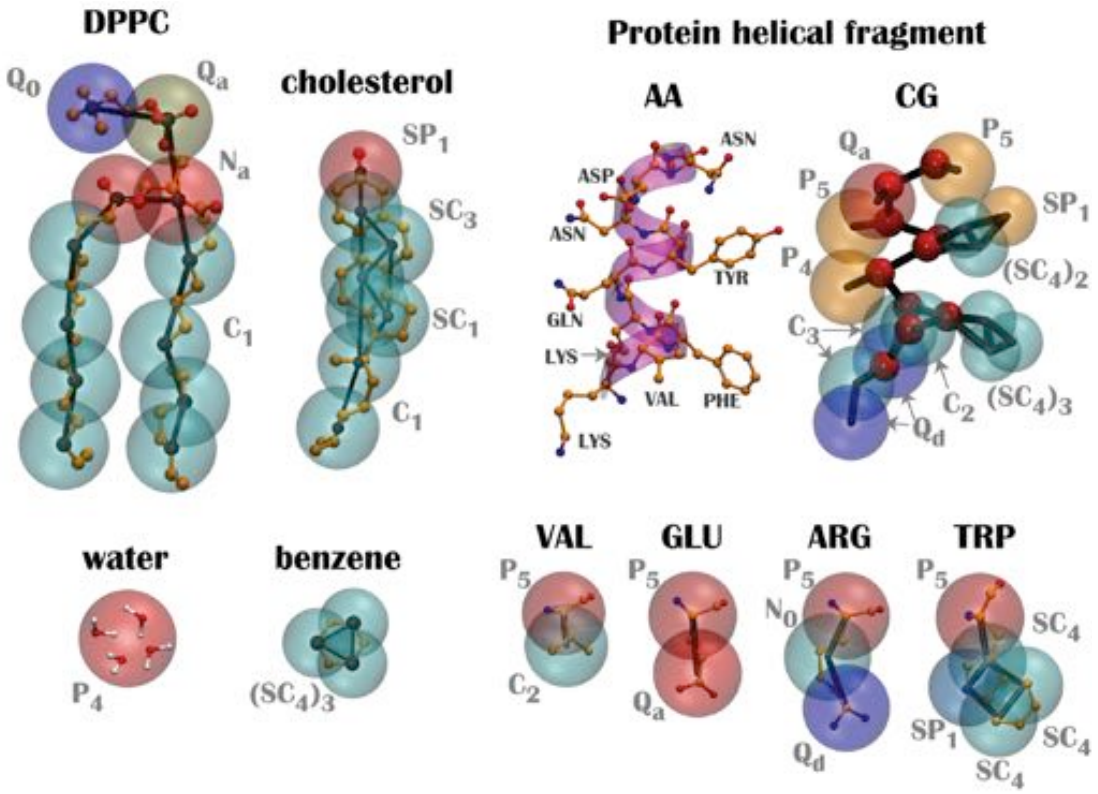
$$\Delta G_{tot}^{A\to B} = \Delta G_{prot}^{A\to B} + \Delta G_{bilayer}^{A\to B}$$



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.

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TABLE 1: Interaction Matrix[a]

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

LJ interactions depend on hydrophilicity of CG bead

nine levels with 2.0 < ε < 5.6 kJ/mol; σ = 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.

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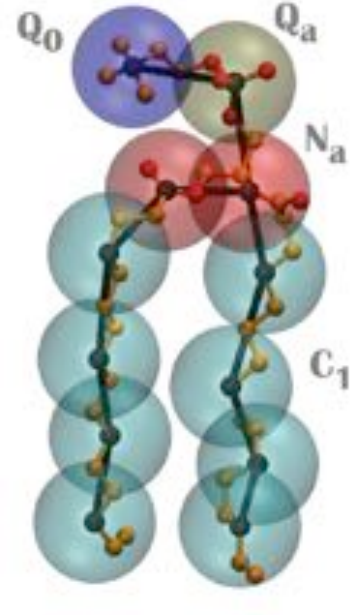
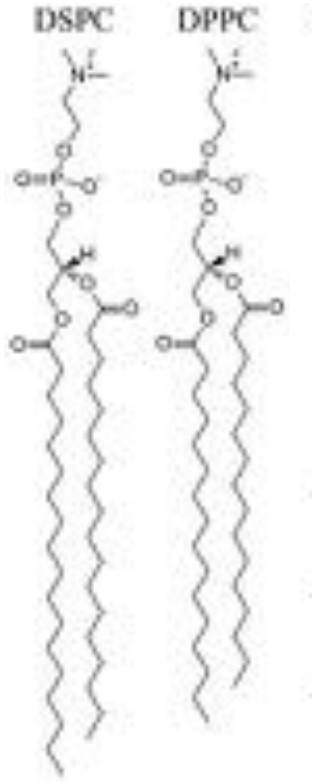
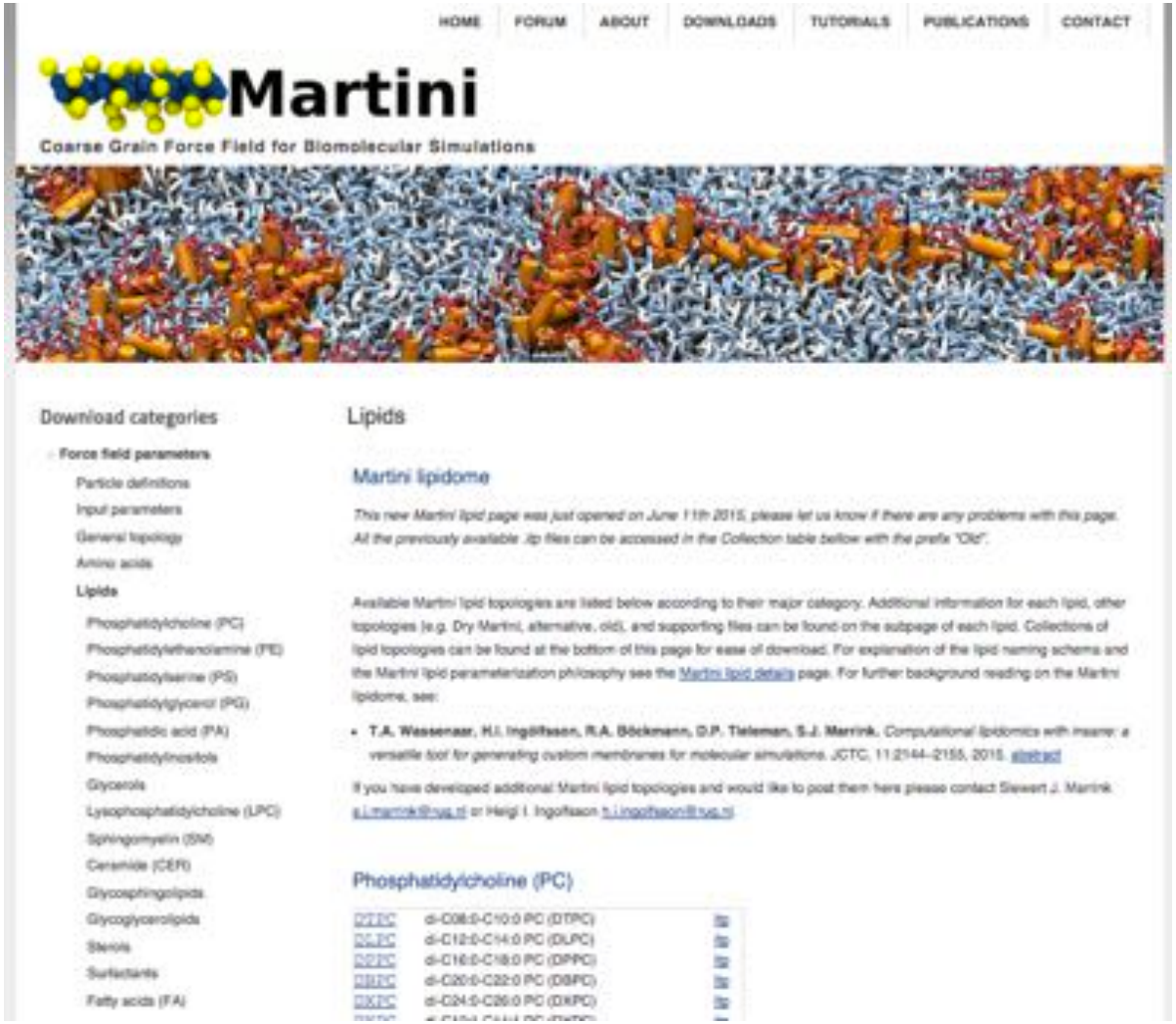




DPPC, di-C16:0 palmitic tails
DSPC, di-C18:0 stearoyl tails

Lipidome – the Martini lipids website



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

Lipidome – the Martini lipids website

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
P[a]	TCC	C(d16:1)-C(d18:1)	Sphingosine C16 palmitic acid - C18 stearoyl with a trans double bond
B[a]	TCCC	C(d20:1)-C(d22:1)	Sphingosine C20 arachidoyl - C22 behenoyl with a trans double bond
X[a]	TCCCC	C(d24:1)-C(d26:1)	Sphingosine C24 lignoceroyl - C26 hexacosanoyl with a trans double bond

[a]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**

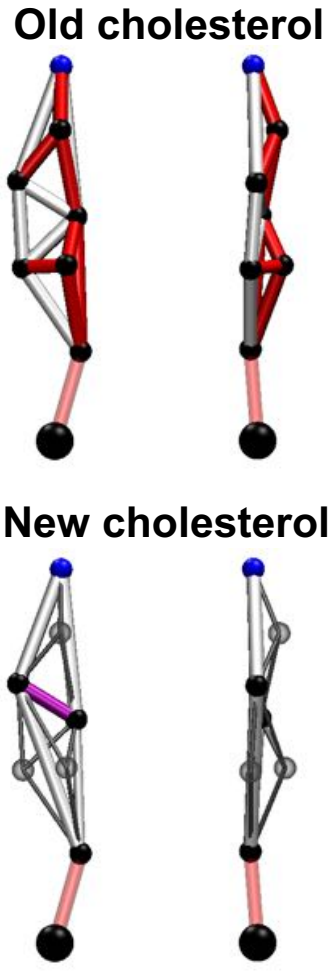
Reparameterized using virtual sites, a middle hinge and extended plane extrusions.

- **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



Manuel

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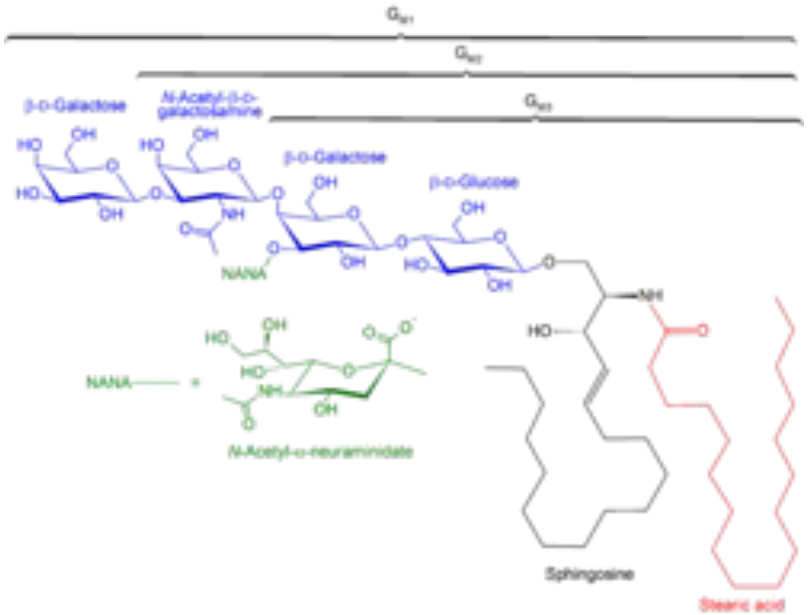

http://en.wikipedia.org/wiki/GM3

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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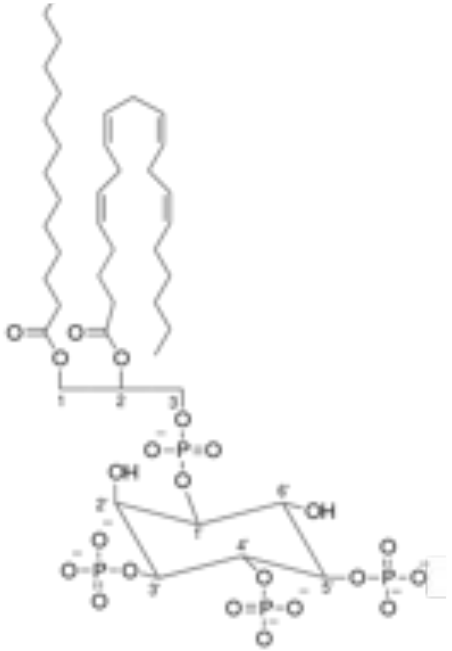

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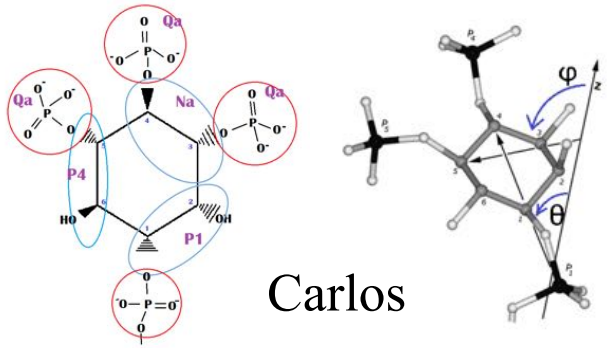

Carlos

http://en.wikipedia.org/wiki/Phosphatidylinositol_(3,4,5)-trisphosphate

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- **Lipopolysaccharides (LPS)**

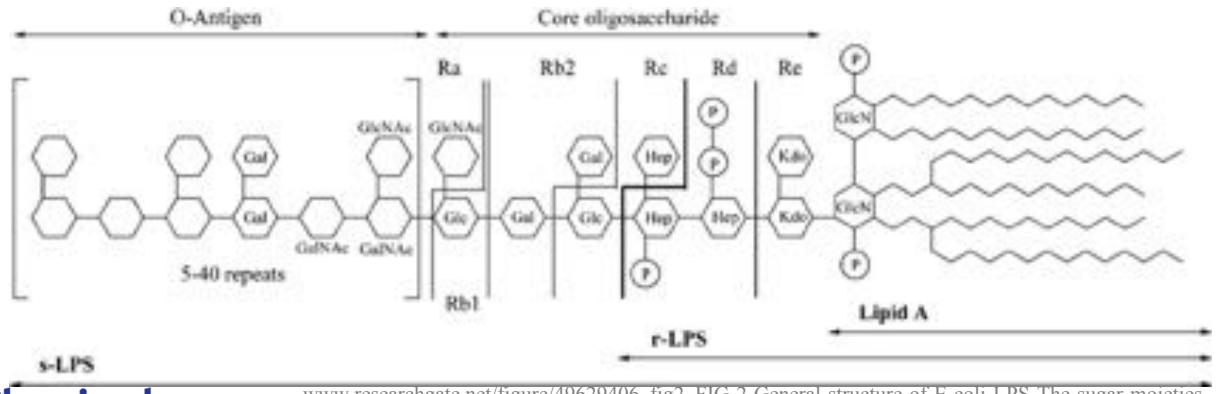
More than on set of Martini parameters

- **More sterols**

Using the same backbone as the improved cholesterol

- **Plant galactolipids**

Slightly modified parameters compared to the previous glycolipid headgroups



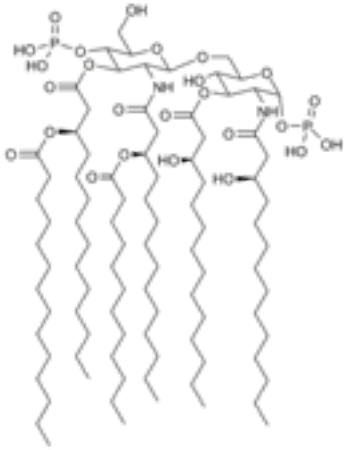
www.researchgate.net/figure/49629406_fig2_FIG-2-General-structure-of-E-coli-LPS-The-sugar-moieties-in-the-core-region-and-the

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 PAO1lipopolysaccharide, *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



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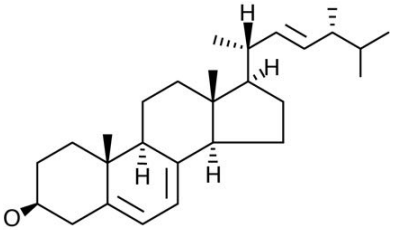
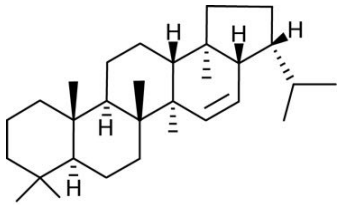
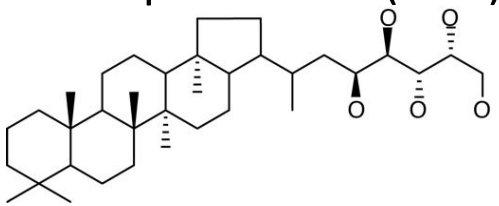


Hopanes



Bacteriohopanetetrol (BHT)



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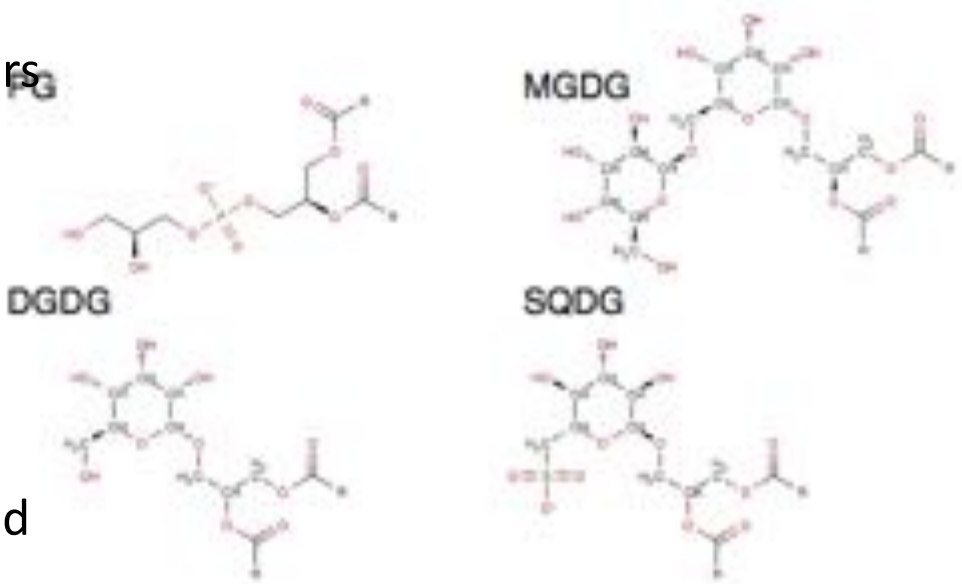

van Eerden, F.J., D.H. de Jong, A.H. de Vries, T.A. Wassenaar, and S.J. Marrink. 2015. Characterization of thylakoid lipid membranes from cyanobacteria and higher plants by molecular dynamics simulations. BBA - Biomembranes. 1848: 1319–1330.

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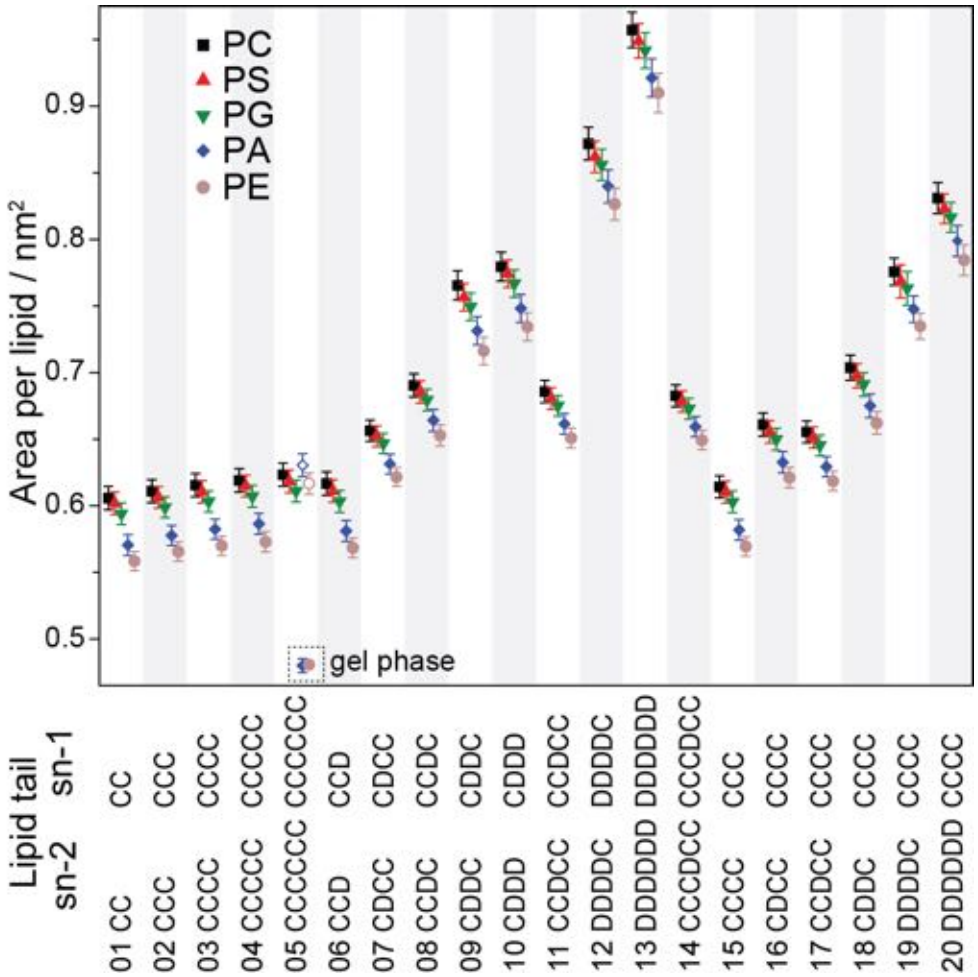

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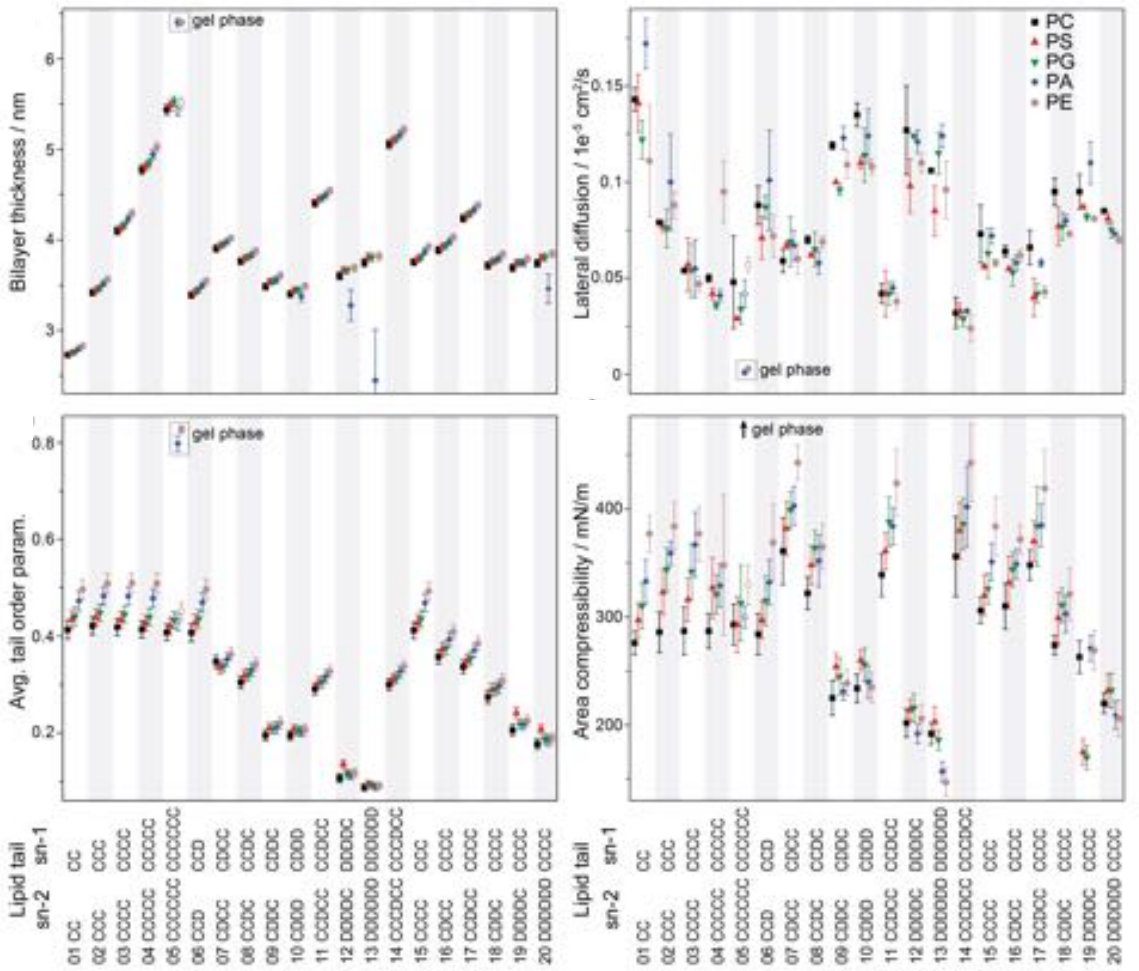

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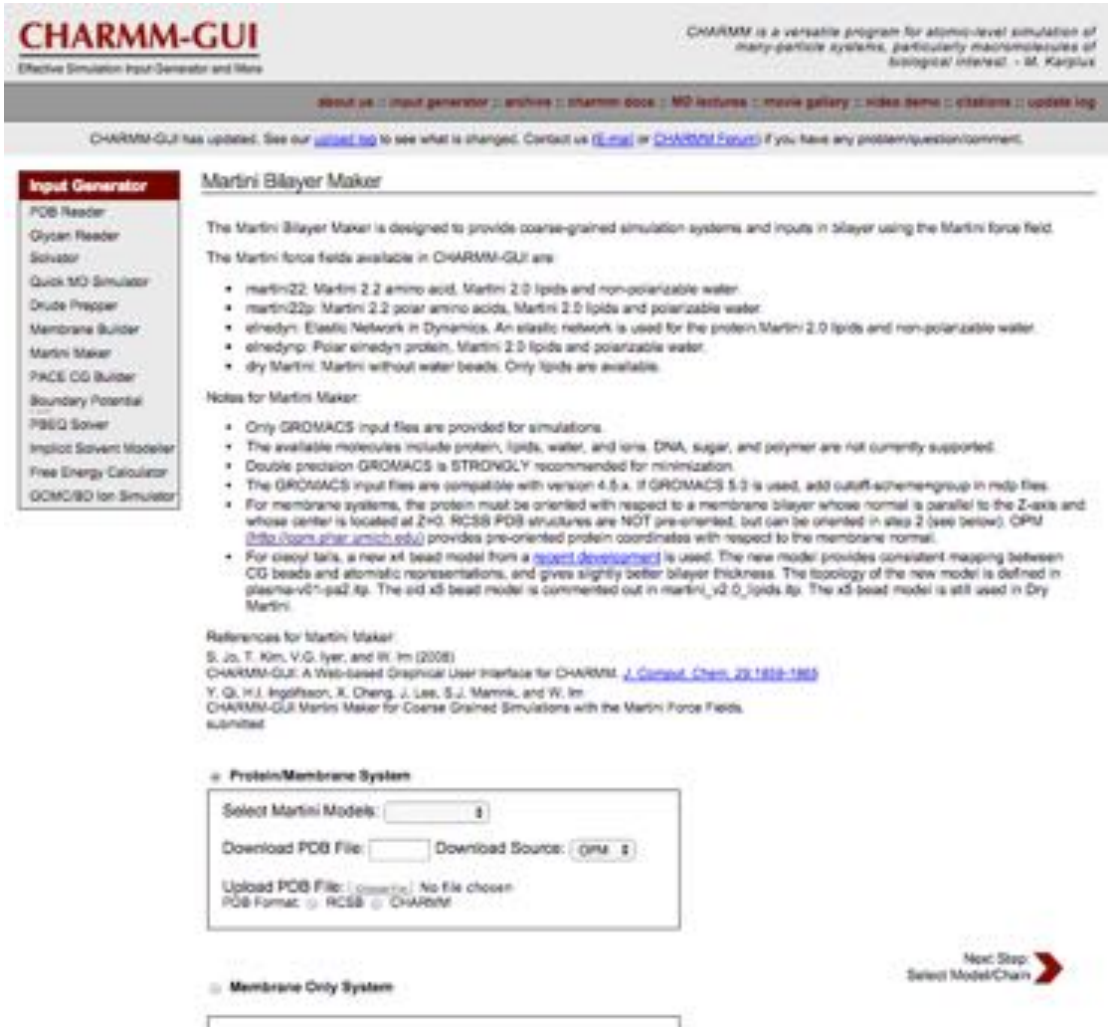
Building bilayers – CHARMM-GUI Martini Maker



Solution,
Micelle,
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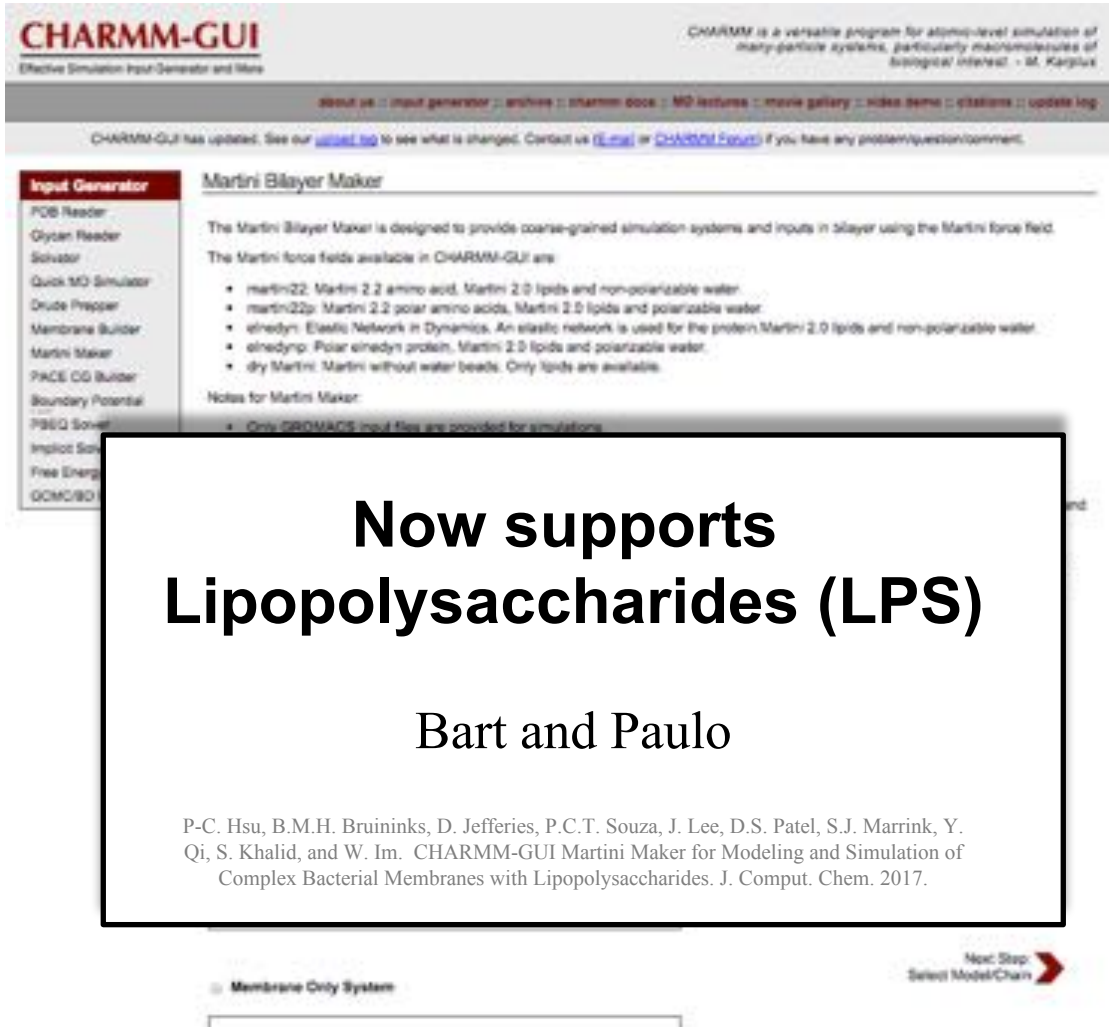

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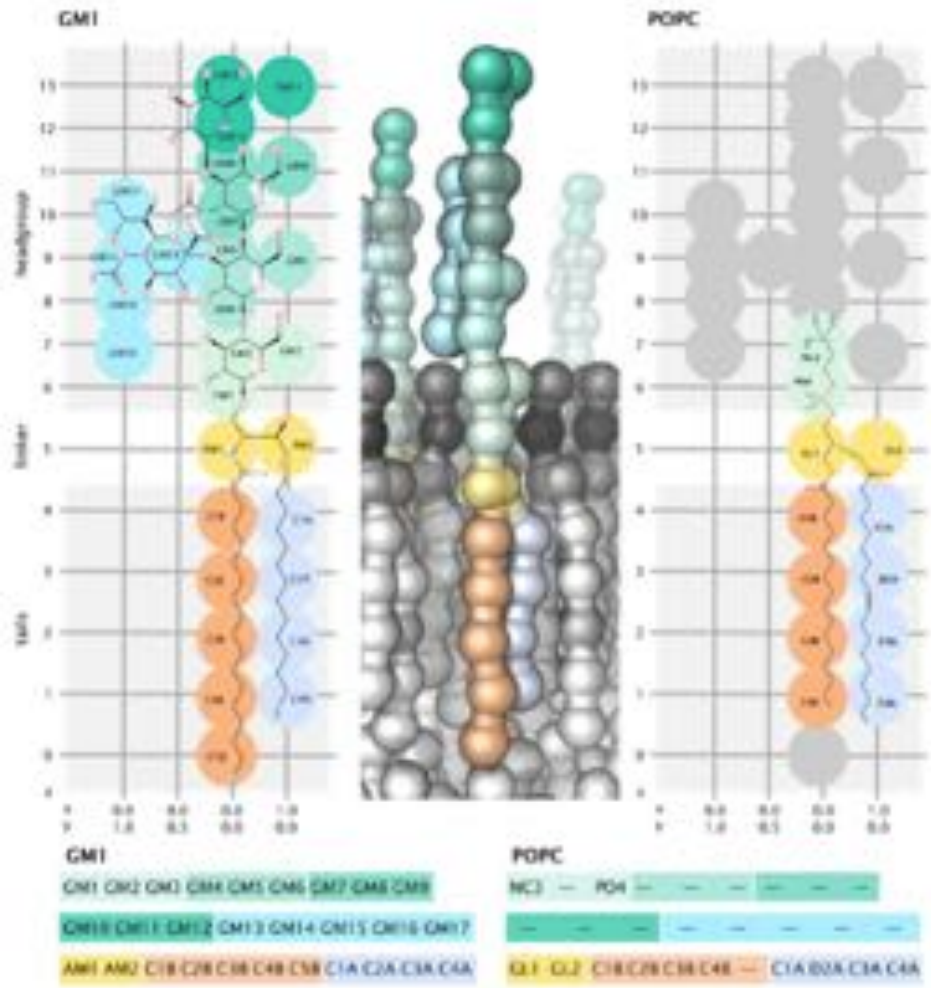
INSert membrANE

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



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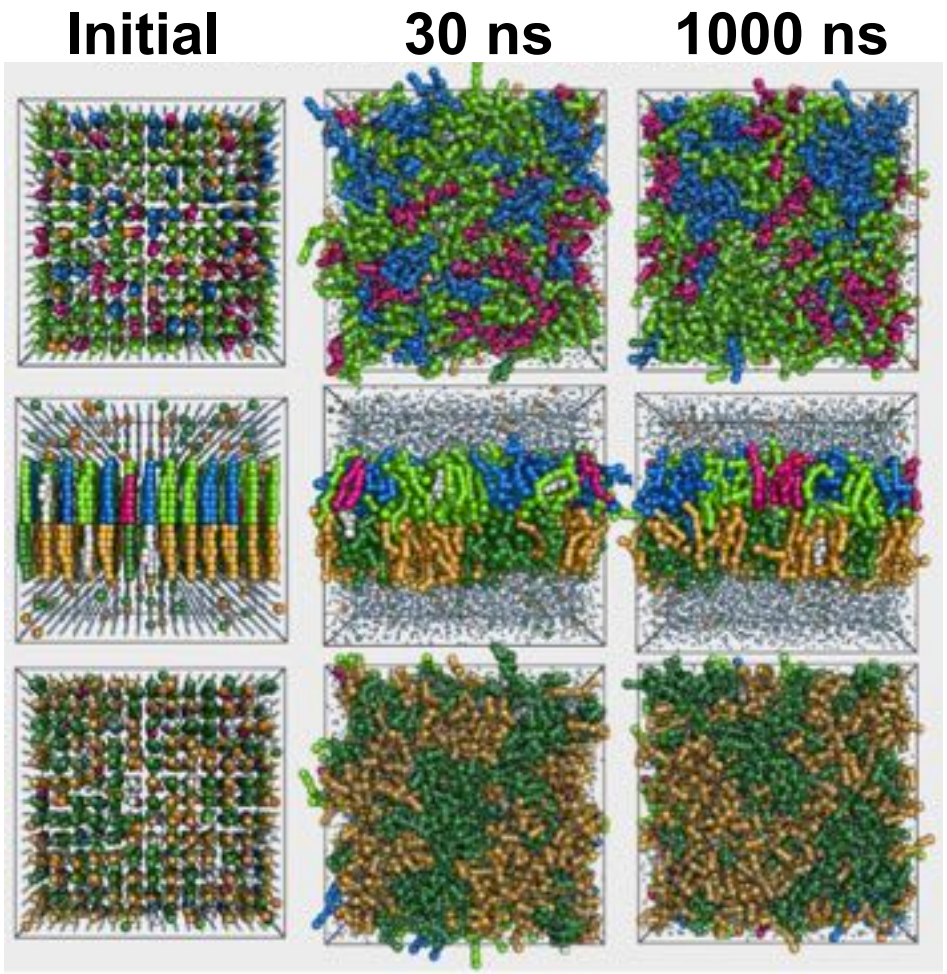
Asymmetric
DAPC:DOPC:DLPC:cholesterol
DPPC:DIPC:cholesterol

Tsjerk



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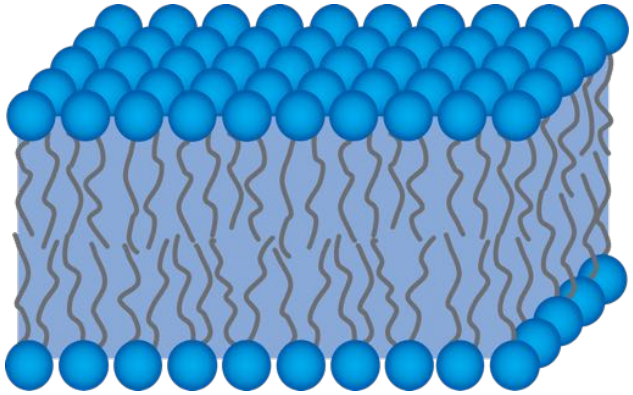

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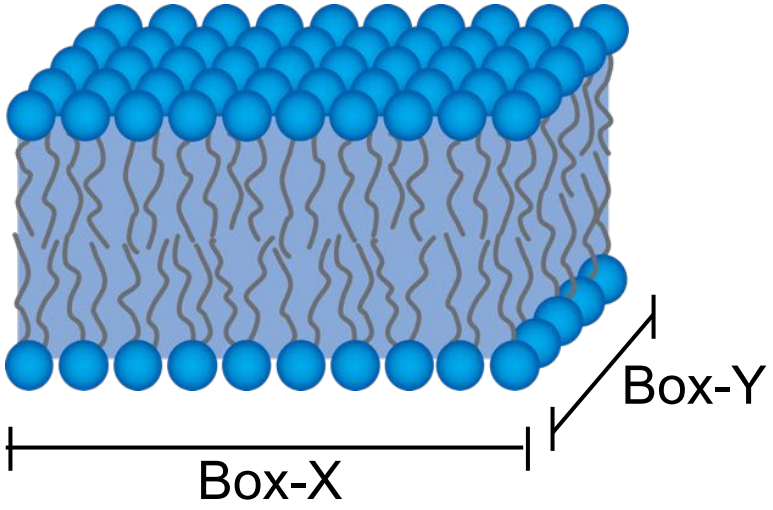

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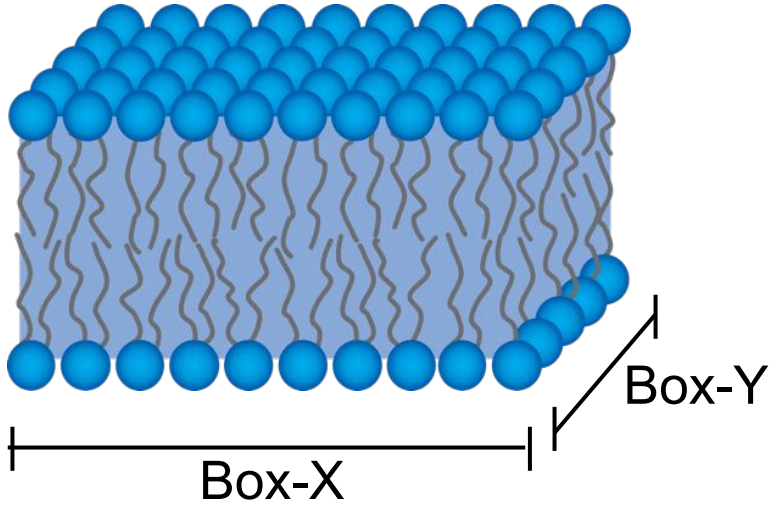

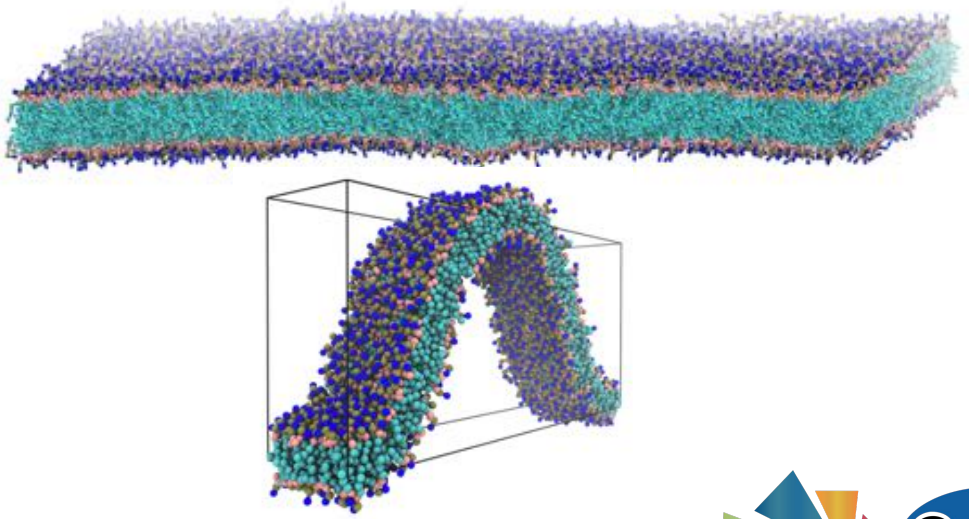

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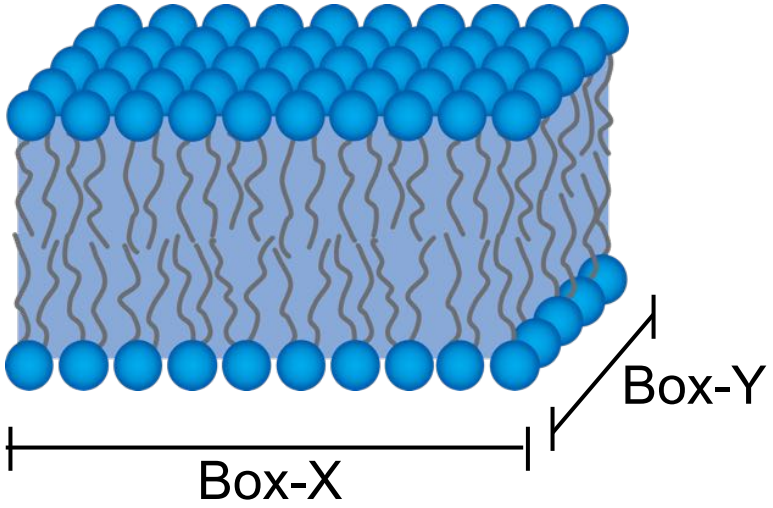

$$K_A = k_B T \frac{\langle A \rangle}{N \langle (A - A_0)^2 \rangle}$$

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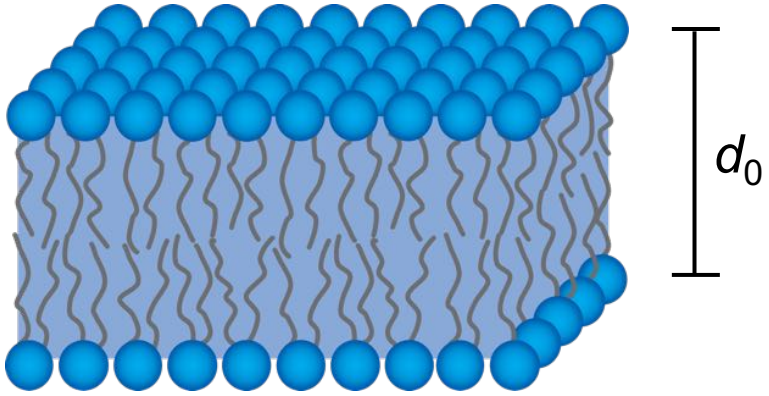

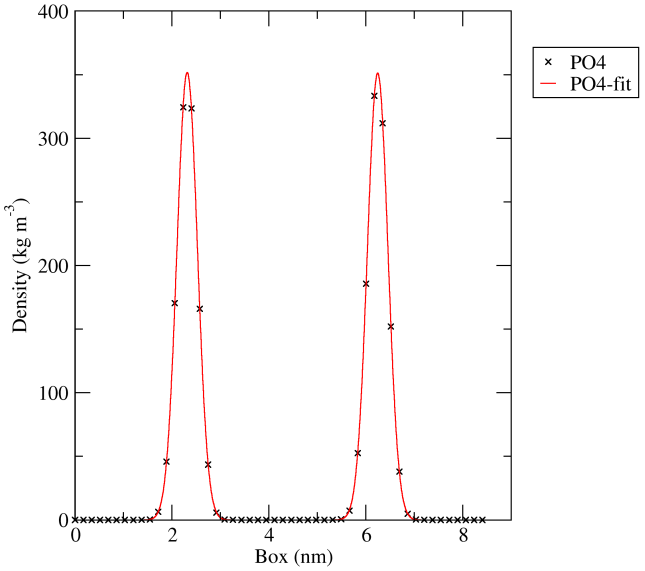

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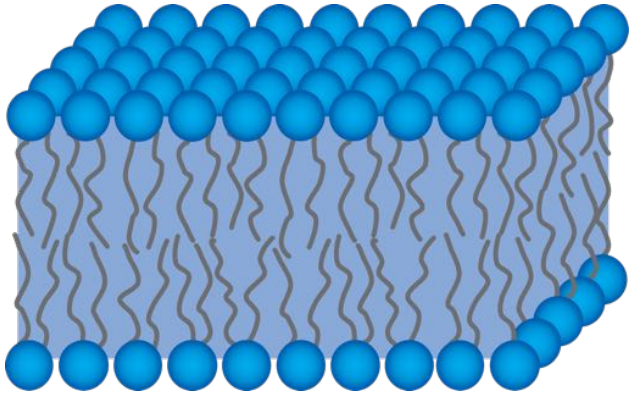

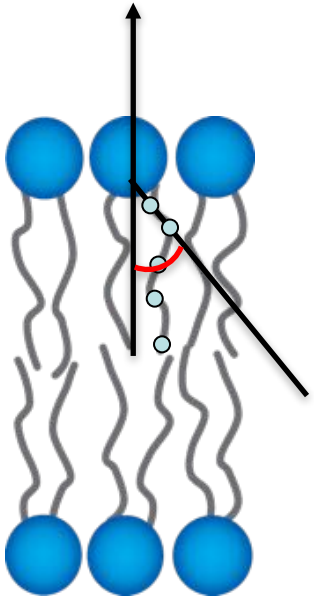

$$S_{seg} = \frac{1}{2}(3\langle\cos^2\theta\rangle - 1)$$

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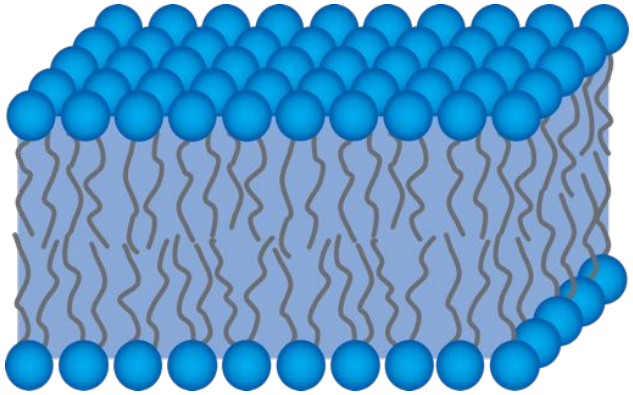

Bending modulus (K)

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

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.

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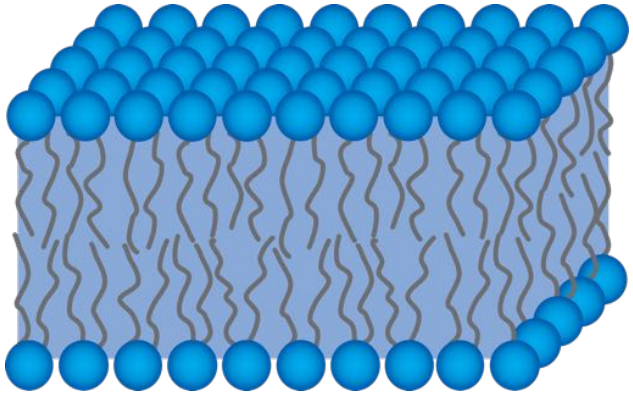

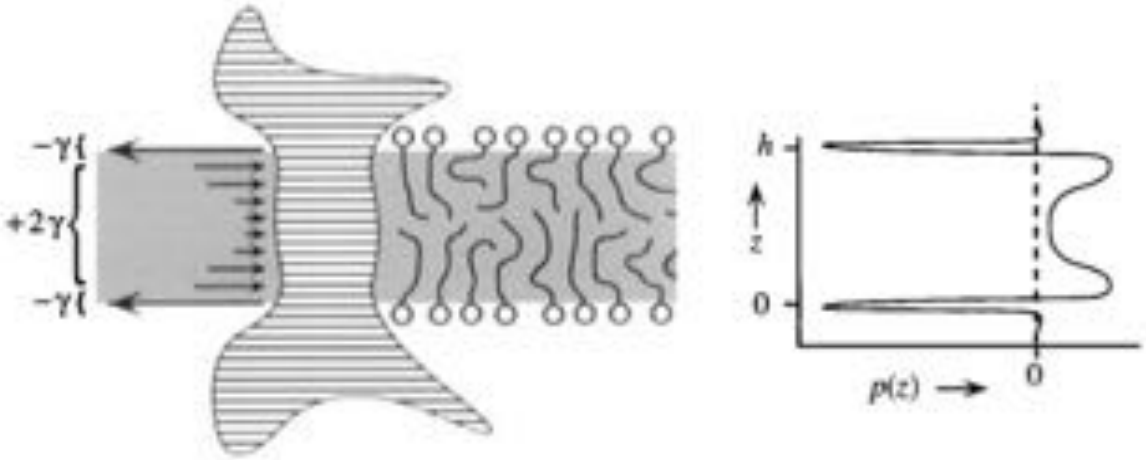

Cantor, R.S. 1997. Lateral Pressures in Cell Membranes: A Mechanism for Modulation of Protein Function. J. Phys. Chem. B. 101: 1723–1725.

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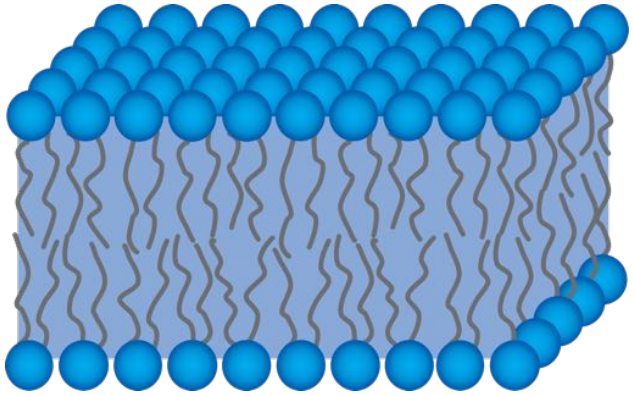

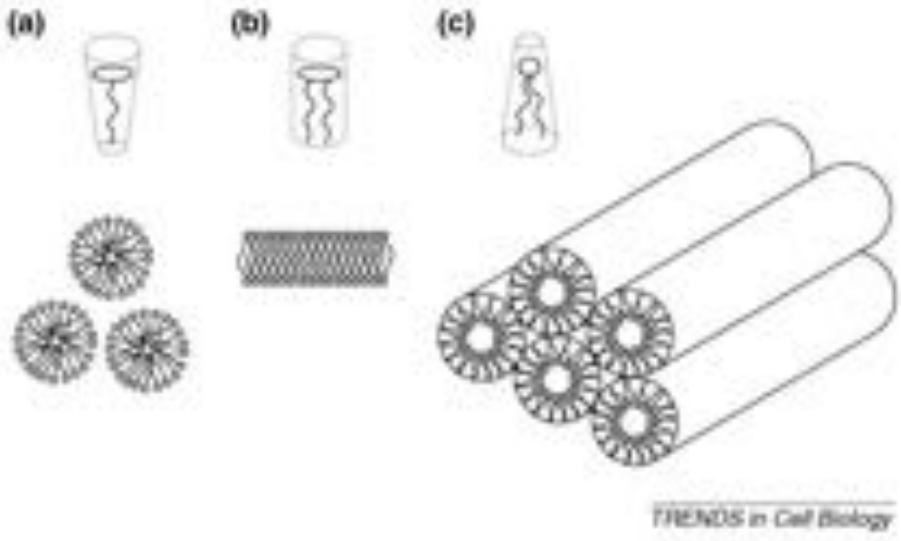

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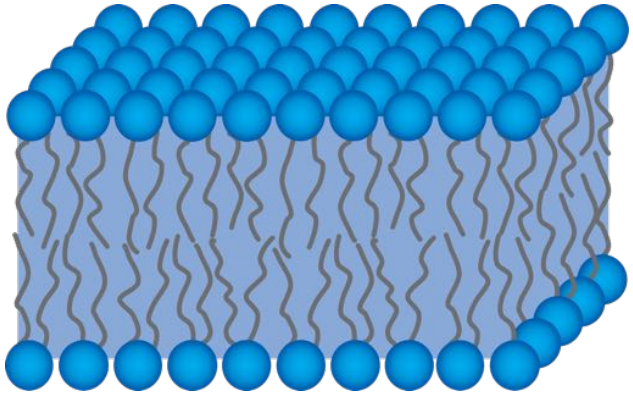
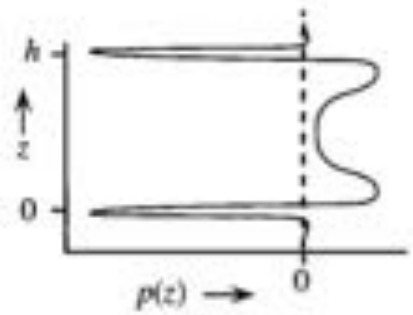




$$\frac{1}{2}\Sigma = \int_0^\infty dz\, \sigma_0(z)\,,$$

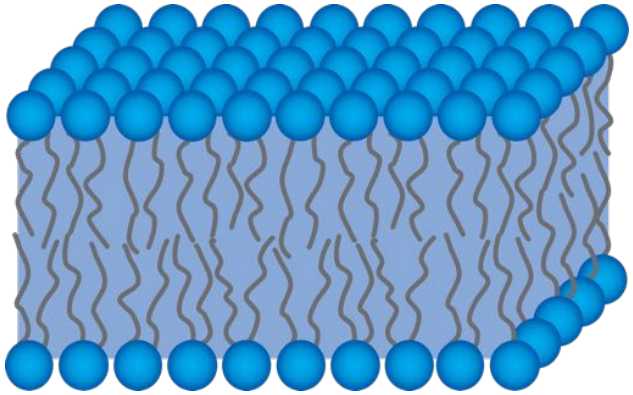
$$-\kappa_m K_{0m} = \int_0^\infty dz\, \sigma_0(z)(z - z_0)\,,$$

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

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.

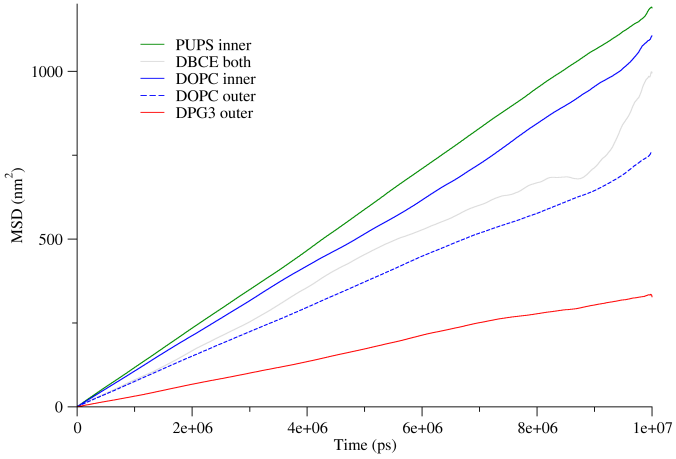
Calculating bilayer properties

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



Mean square displacement (MSD) with time

Einstein relation ($D^*t + c$) t



Calculating bilayer properties

- Intrinsic lipid curvature (c_0)
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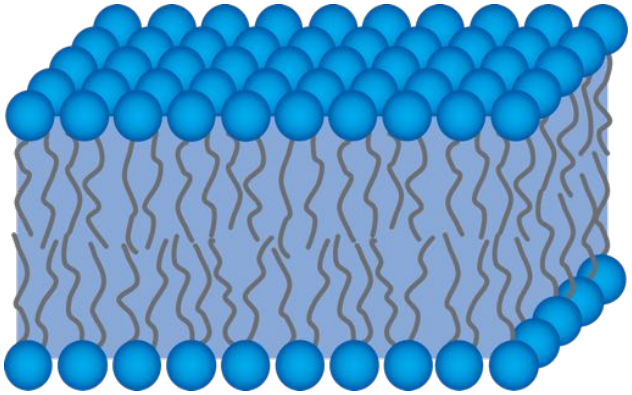
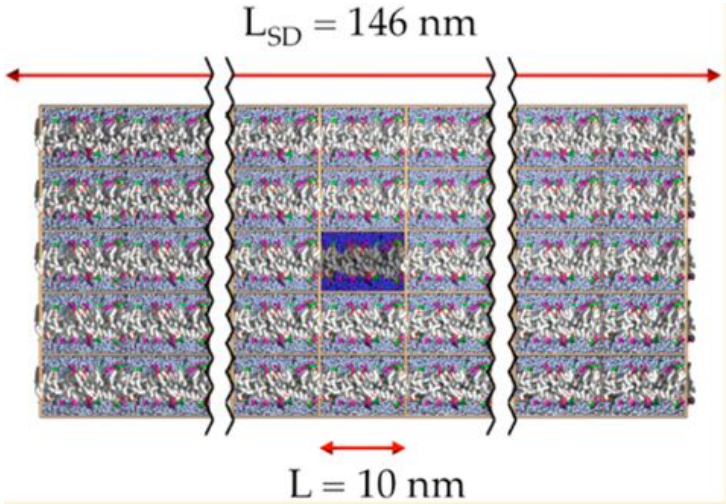
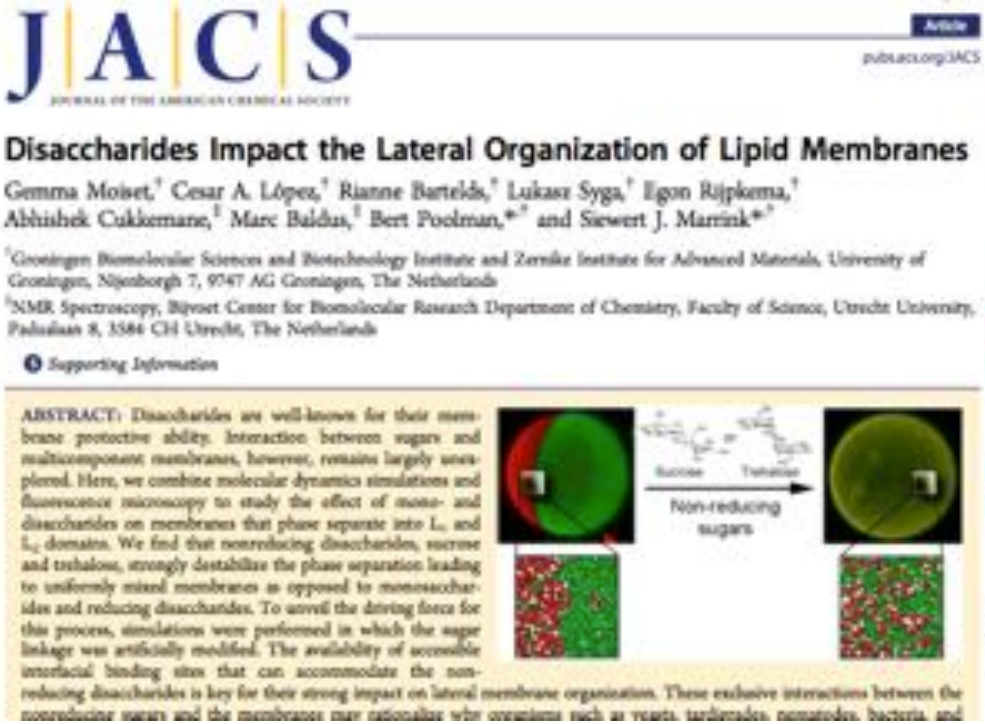


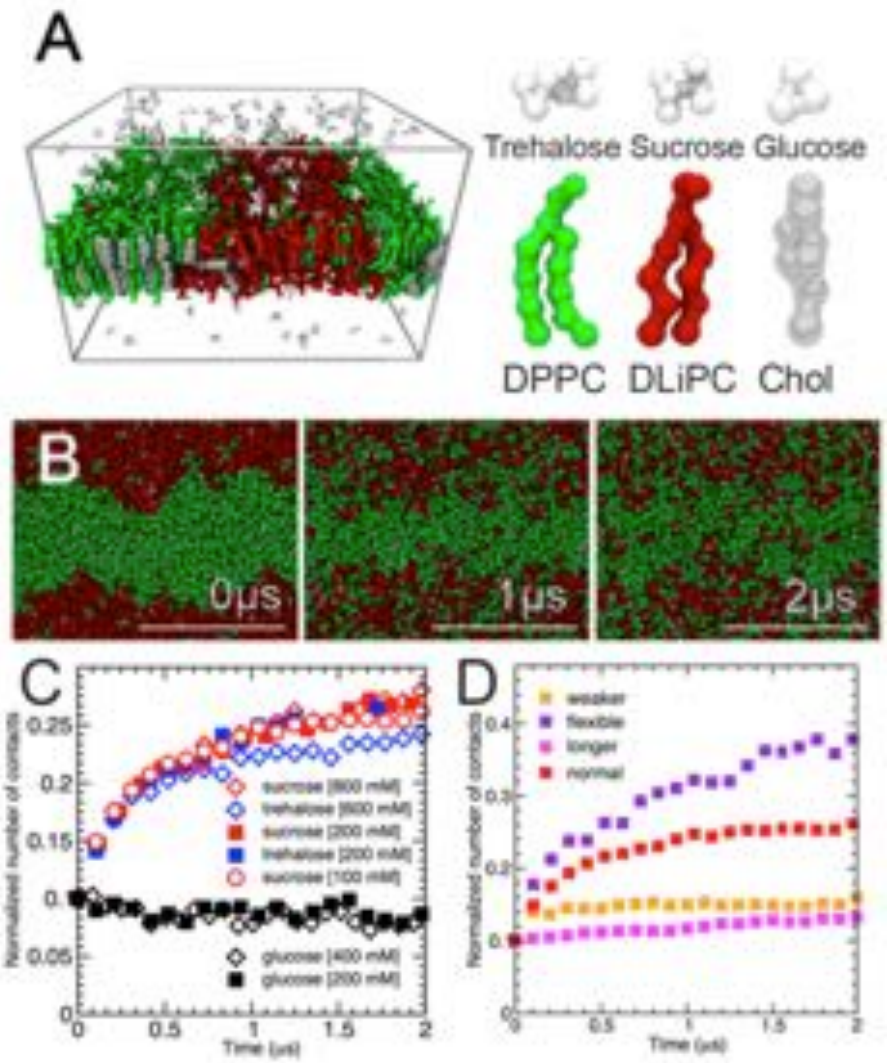


Venable, R. M., Ingólfsson, H. I., Lerner, M. G., Perrin, B. S., Camley, B. A., Marrink, S. J., et al. (2017). Lipid and Peptide Diffusion in Bilayers: The Saffman-Delbrück Model and Periodic Boundary Conditions. *The Journal of Physical Chemistry B*, *121*(15), 3443–3457.

Martini Examples

Martini Examples – lipid domains





Moiset, G., C.A. Lopez, R. Bartelds, L. Syga, E. Rijpkema, 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

OPEN ACCESS Freely available online

PLOS | COMPUTATIONAL BIOLOGY

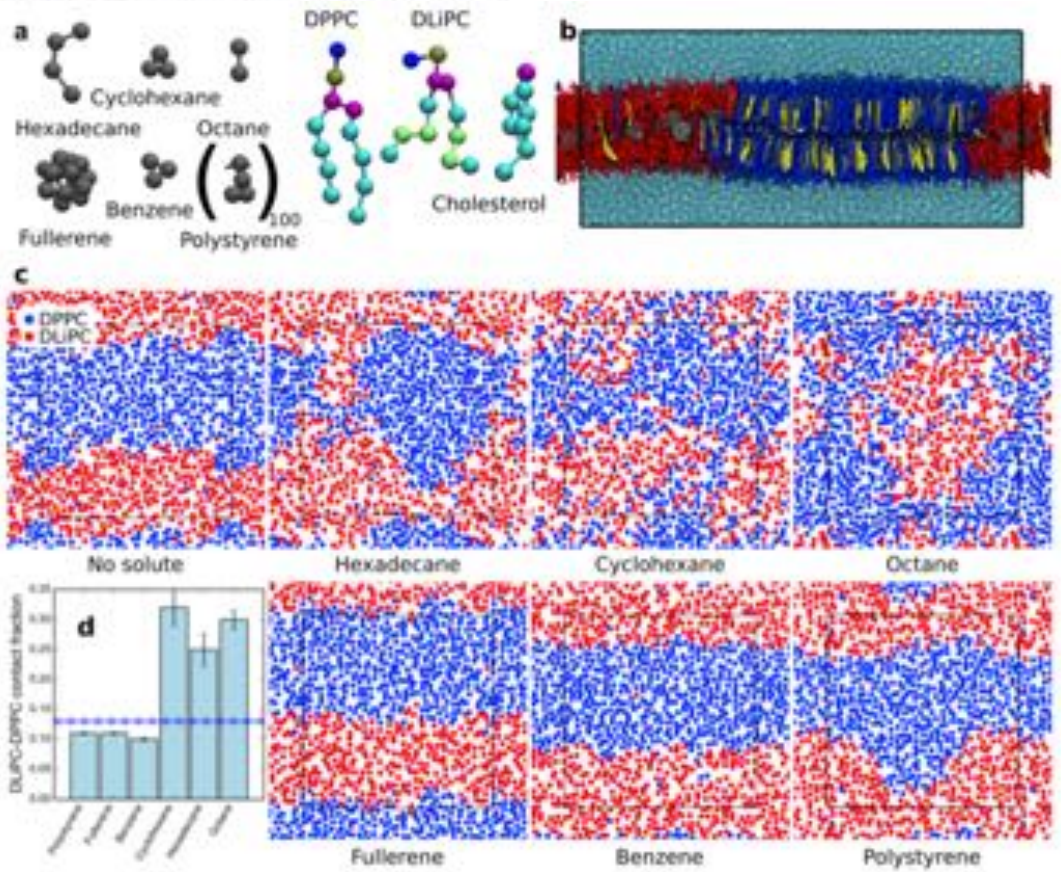
Hydrophobic Compounds Reshape Membrane Domains

Jonathan Barnoud[1,2], Giulia Rossi[3], Siewert J. Marrink[4], Luca Monticelli[1,2]*

1 IBCP, CNRS UMR 5086, Lyon, France, 2 Université Claude Bernard Lyon I, Lyon, France, 3 Dept of Pl
Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Gro

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

THE JOURNAL OF PHYSICAL CHEMISTRY B
Article
pubs.acs.org/JPCB

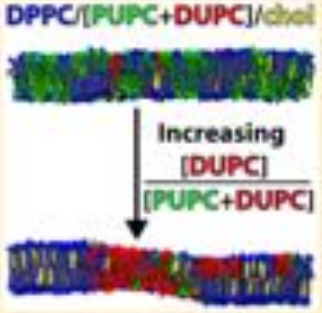
Multiscale Modeling of Four-Component Lipid Mixtures: Domain Composition, Size, Alignment, and Properties of the Phase Interface

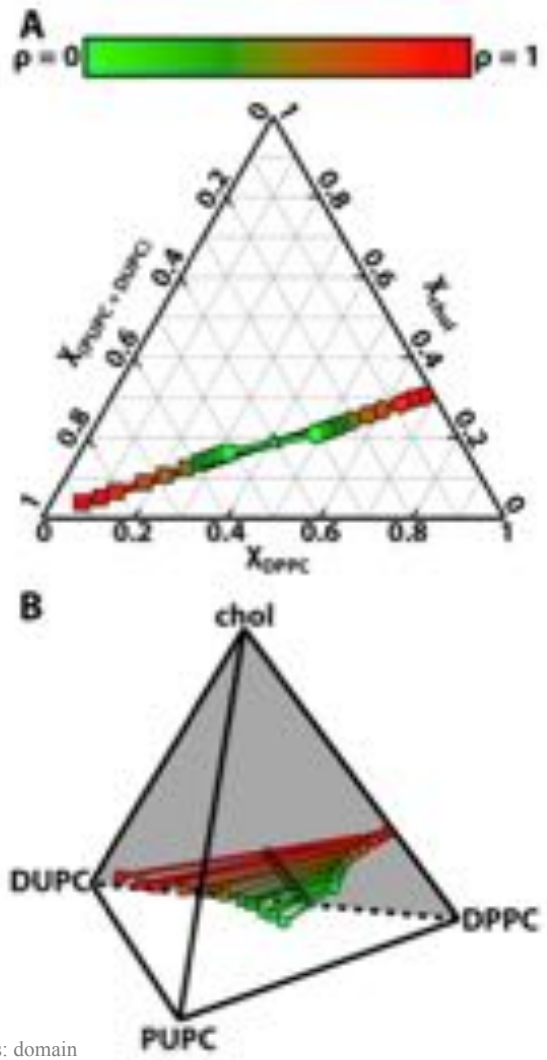
David G. Ackerman and Gerald W. Feigenson*

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

Supporting Information

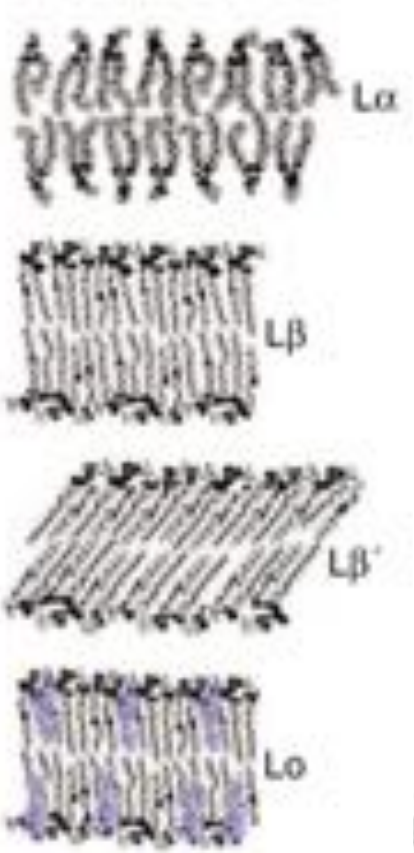
ABSTRACT: Simplified lipid mixtures are often used to model the complex behavior of the cell plasma membrane. Indeed, as few as four components—a high-melting lipid, a nanodomain-inducing low-melting lipid, a macrodomain-inducing low-melting lipid, and cholesterol (chol)—can give rise to a wide range 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.

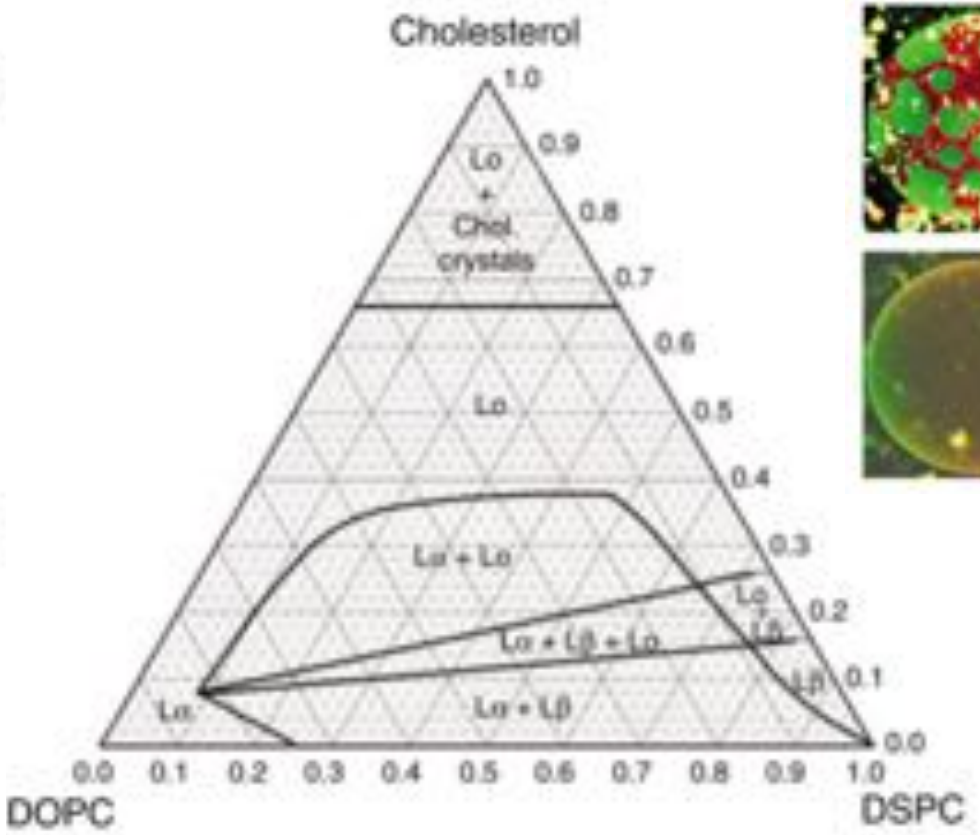


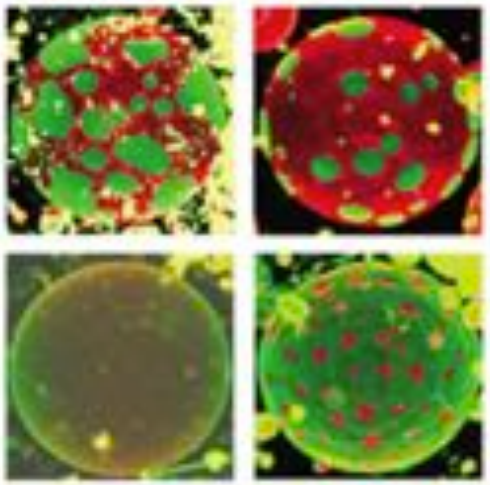


Ackerman, D.G., and G.W. Feigenson. 2015. Multiscale modeling of four-component lipid mixtures: domain composition, size, alignment, and properties of the phase interface. J. Phys. Chem. B. 119: 4240–4250.

Martini Examples – phases separation

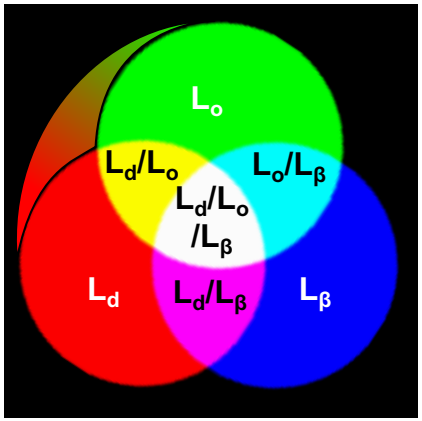


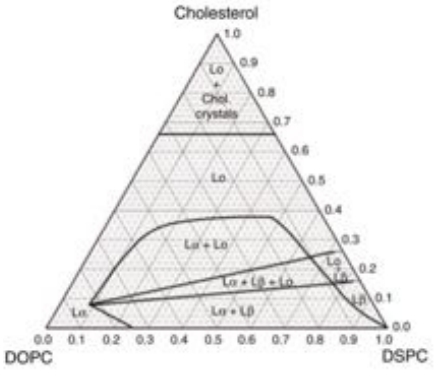




Feigenson, G.W. 2006. Phase behavior of lipid mixtures. Nat. Chem. Biol. 2: 560–563.

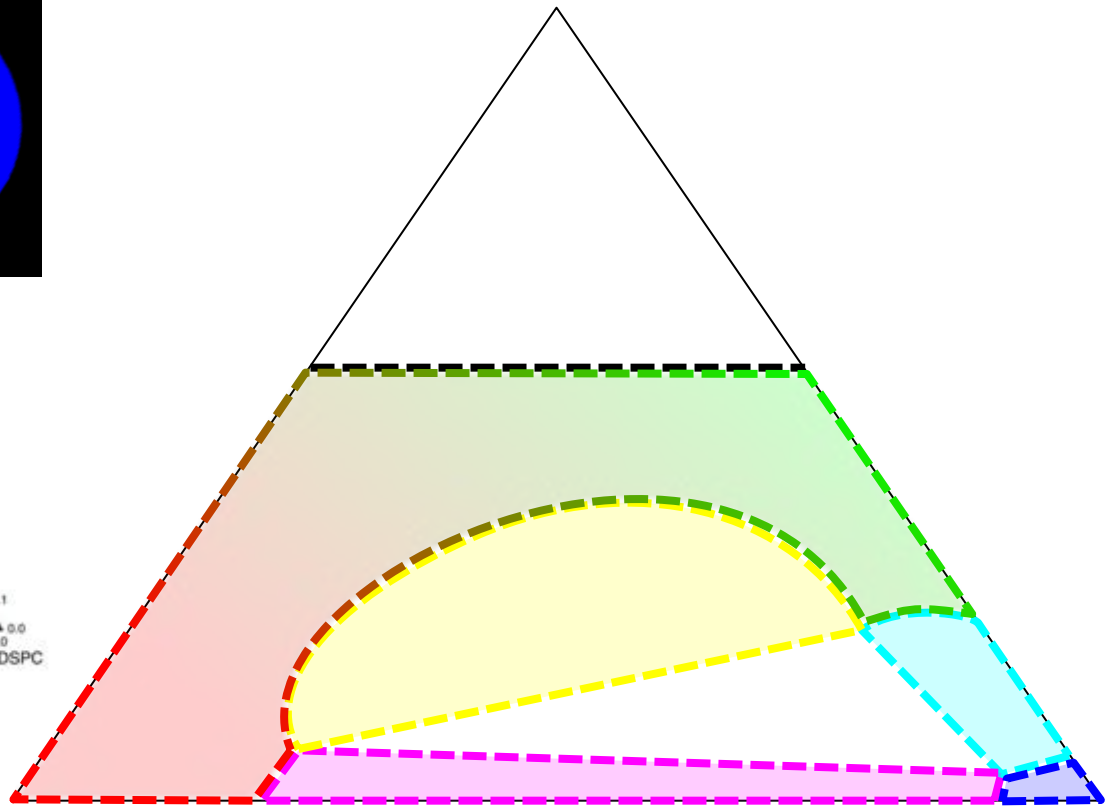
Martini Examples – phases separation





CHOL

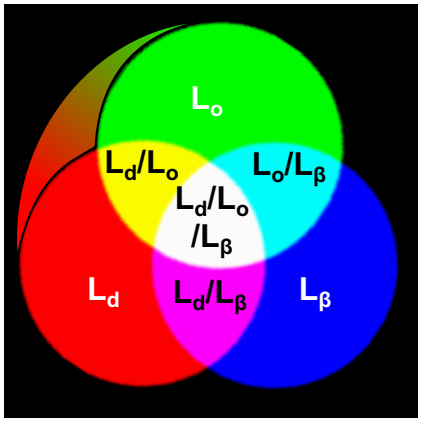
Tim Carpenter

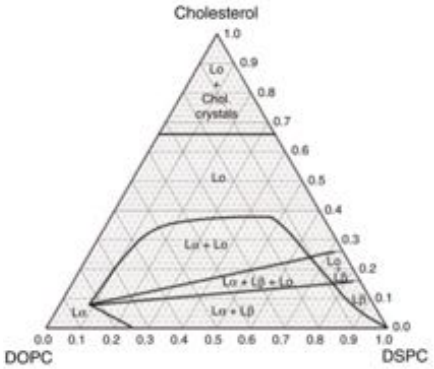


DOPC

DPPC

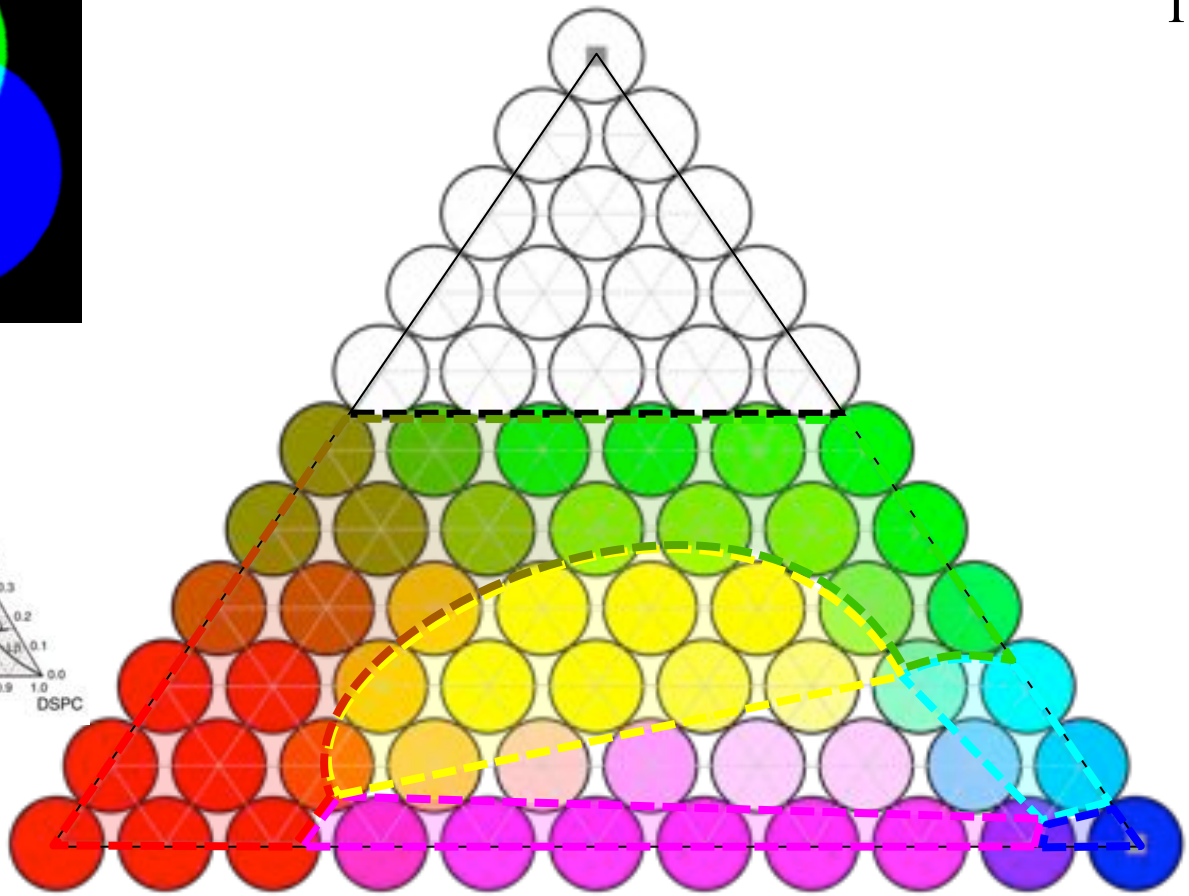
Martini Examples – phases separation





CHOL

Tim Carpenter



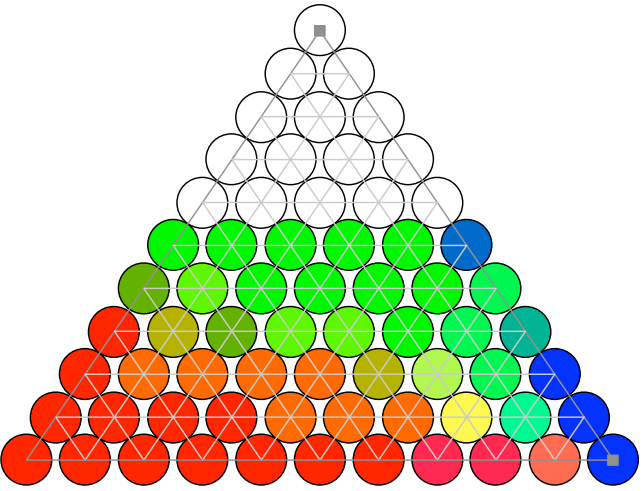
DOPC

DPPC

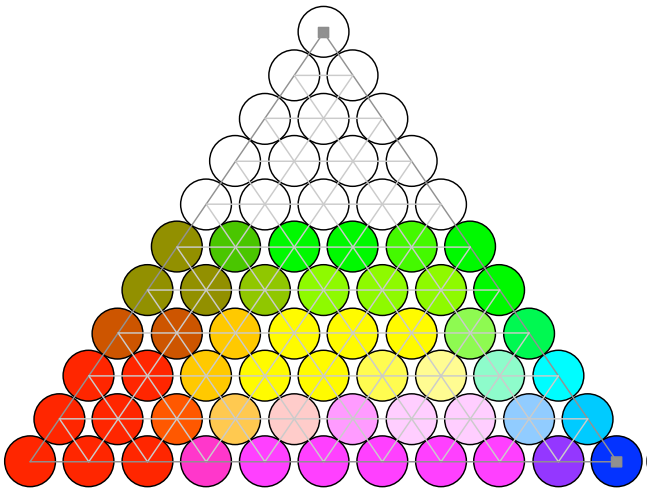
Martini Examples – phases separation

Tim Carpenter

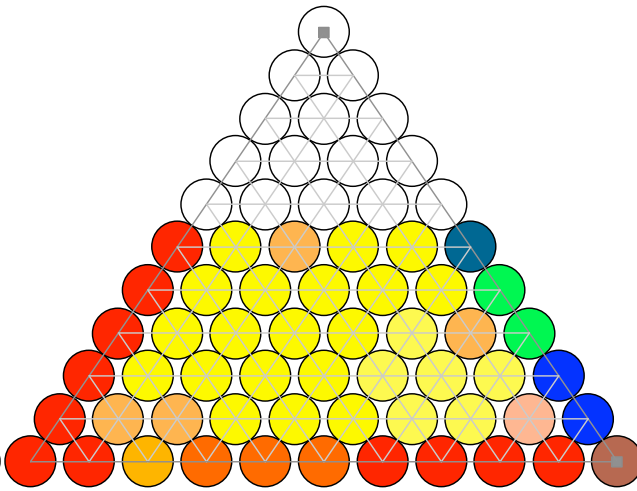
DPPC-DOPC-CHOL



Experimental average



DPPC-DIPC-CHOL



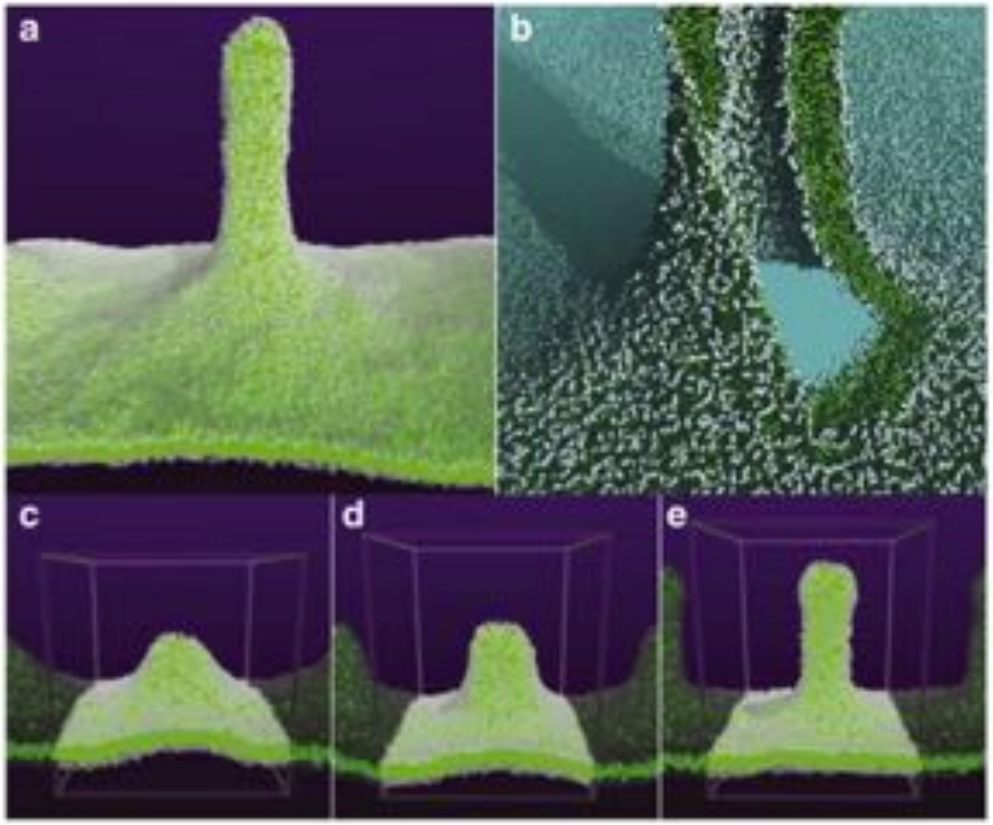
Martini Examples – tethers

1866 Biophysical Journal Volume 102 April 2012 1866–1871

Molecular Structure of Membrane Tethers

Svetlana Baoukina,[†‡] Siewert J. Marrink,[§¶] and D. Peter Tieleman[†‡*]
[†]Department of Biological Sciences and [‡]Institute for Biocomplexity and Info
[§]Groningen Biomolecular Sciences and Biotechnology Institute and [¶]Zernike
Groningen, The Netherlands

ABSTRACT Membrane tethers are nanotubes formed by a lipid bila
provide an experimental window on lipid properties. Tethers have b
theoretical models, but their molecular structure remains unknown
used molecular dynamics simulations to obtain molecular-level insig
component 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

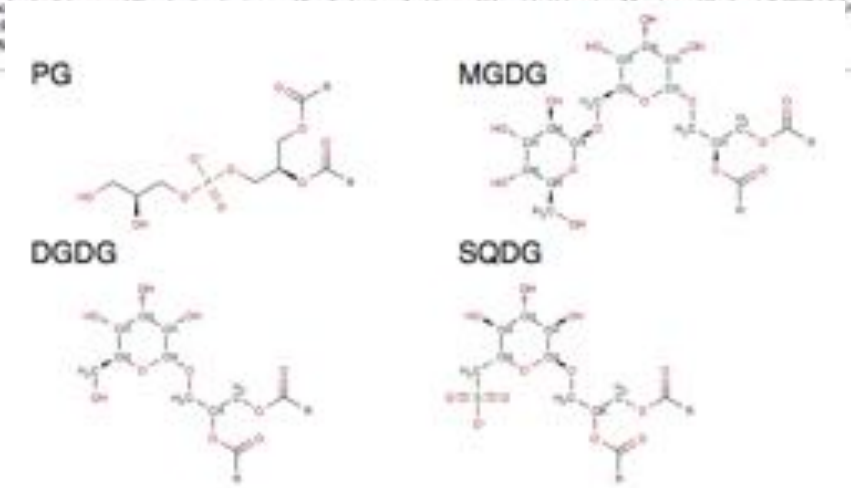
Contents lists available at ScienceDirect

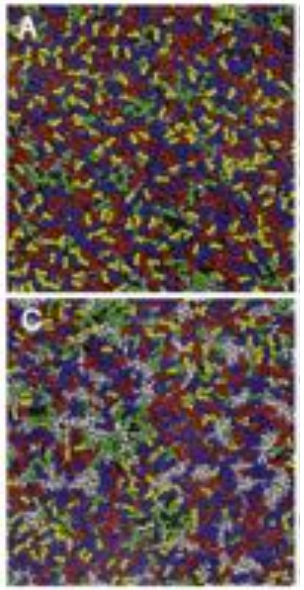
Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

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

Floris J. van Eerden [a,*], Djurre H. de Jong [b], Alex H. de Vries [a], Tsjerk A. Wassenaar [c], Siewert J. Marrink [a]





Tail ↓ Head →	Cyanobacterial membrane PG	DGDG	MGDG	SQDG	Plant membrane 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(3t)	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)	(50)
total	**6.1**	**25.6**	**43.5**	**24.8**	**12.6**	**25.1**	**40.1**	**15.2**
	(10)	**(25)**	**(40)**	**(25)**	**(15)**	**(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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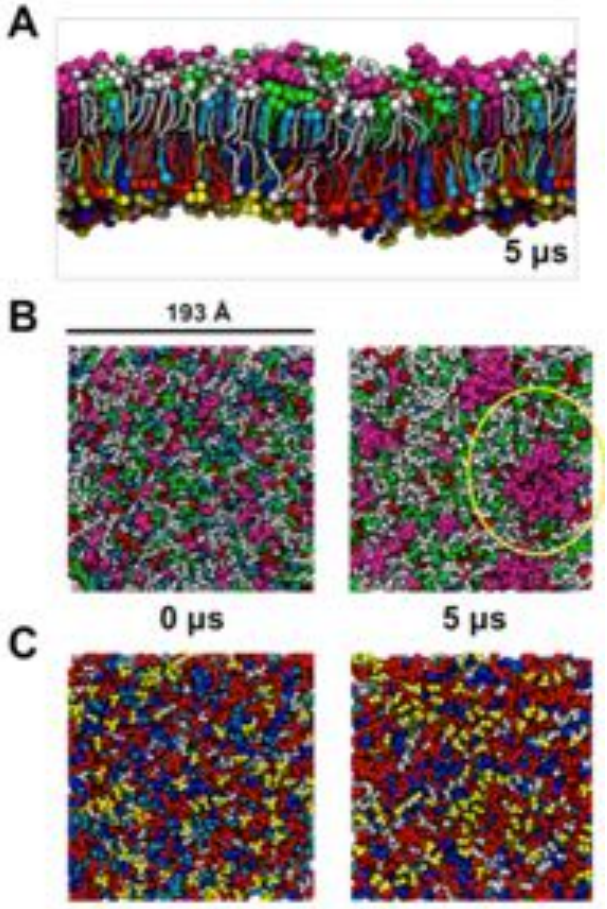
Lipid Clustering Correlates with Membrane Curvature as Revealed by Molecular Simulations of Complex Lipid Bilayers

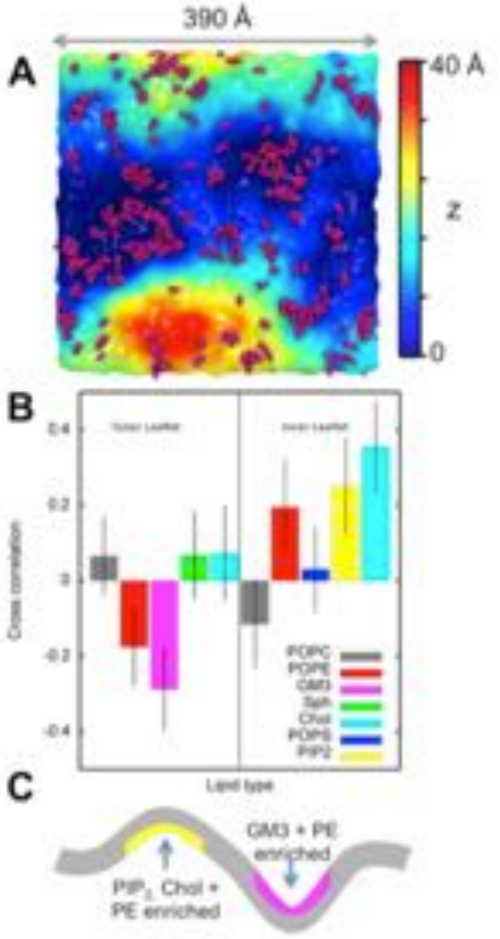
Heidi Koldsø, David Shorthouse, Jean Hélie, Mark S. P. Sansom*

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

Abstract

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





Koldsø, H., D. Shorthouse, J. Hélie, 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

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

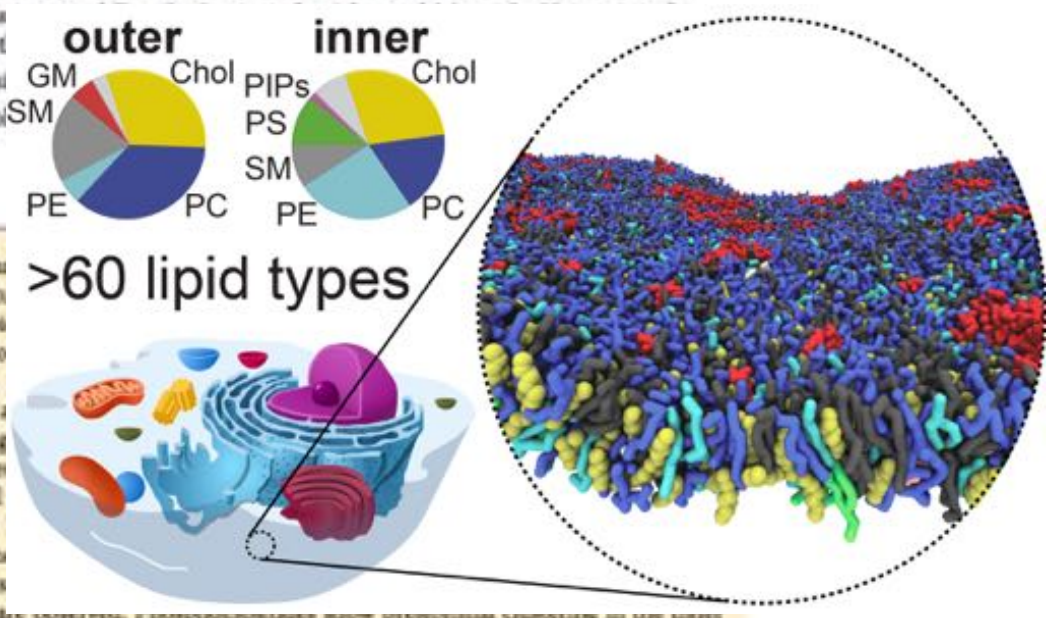
Lipid Organization of the Plasma Membrane

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

[†]Groningen Biomolecular Sciences and Biotechnology Ins
Groningen, Nijenborgh 7, 9747 AG Groningen, The Net
[‡]Computational Biology, Department of Biology, Univers
[§]Centre for Molecular Simulation and Department of Bio
Alberta T2N 1N4, Canada

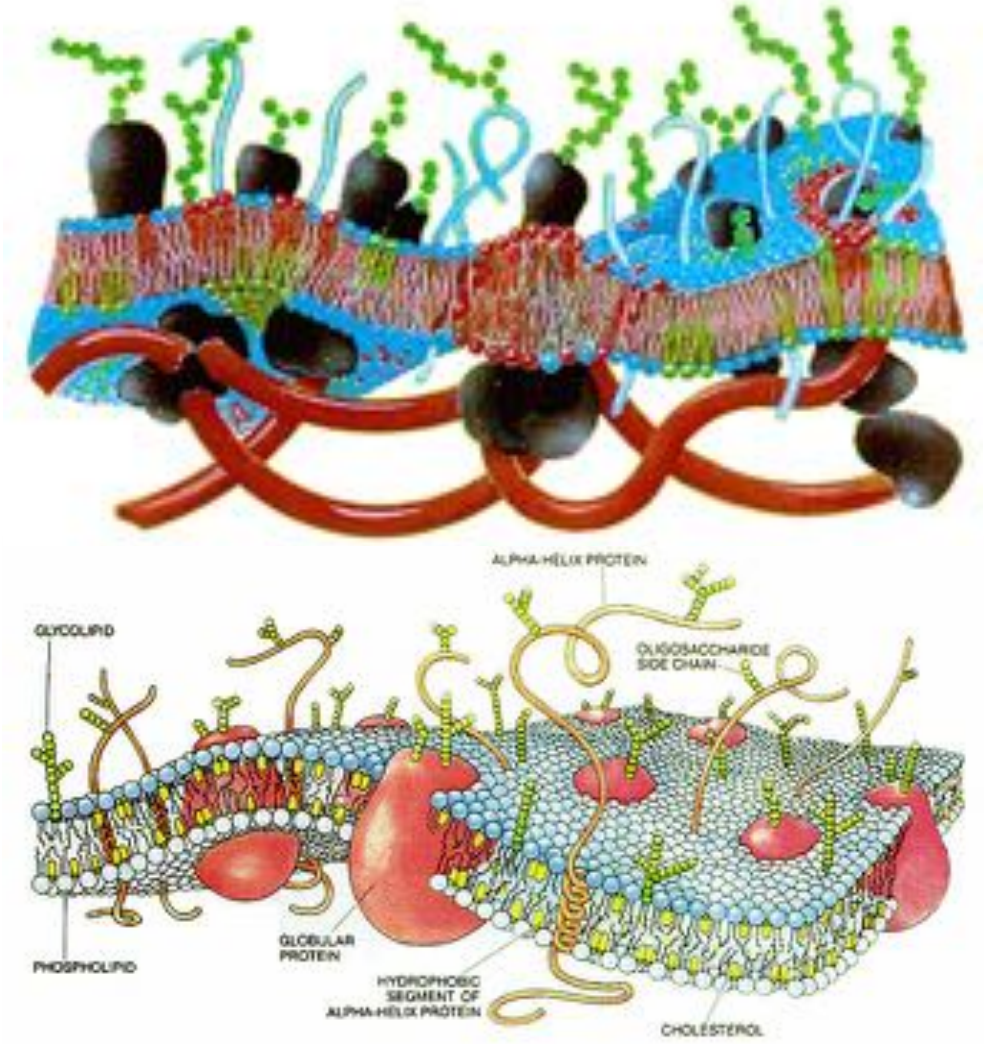
Supporting Information

ABSTRACT: The detailed organization of cellula
remains rather elusive. Based on large-scale molec
simulations, we provide a high-resolution view of the lipi
of a plasma membrane at an unprecedented level of co
plasma membrane model consists of 63 different
combining 14 types of headgroups and 11 types of tails
distributed across the two leaflets, closely mimicking
mammalian plasma membrane. We observe an e
cholesterol in the outer leaflet and a general non-ideal
of the different lipid species. Transient domains with
character form and disappear on the microsecond tim
domains are coupled across the two membrane leaflets
leaflet, distinct nanodomains consisting of gangliosides
leaflet. Our data provide a key view on the lateral organization of lipids in one of life's fundamental structures, the cell membrane.



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



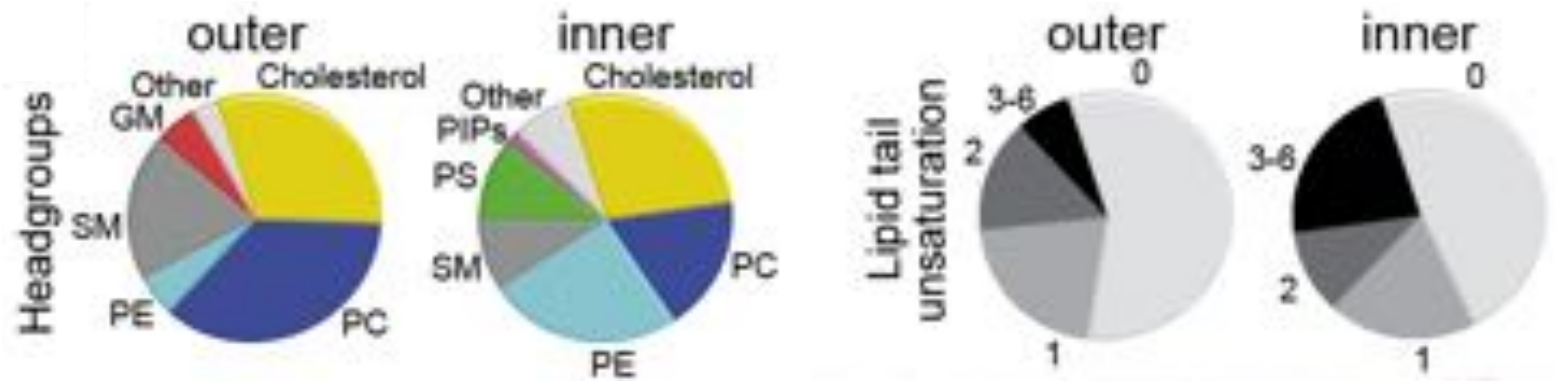
Mouritsen OG, Ansersen OS (1998) Biologiske Skrifter, Danish Royal Science Society 49:7–12.

http://en.wikibooks.org/wiki/Biochemistry/Membranes_and_Lipids

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

PM – Idealized mammalian plasma membrane

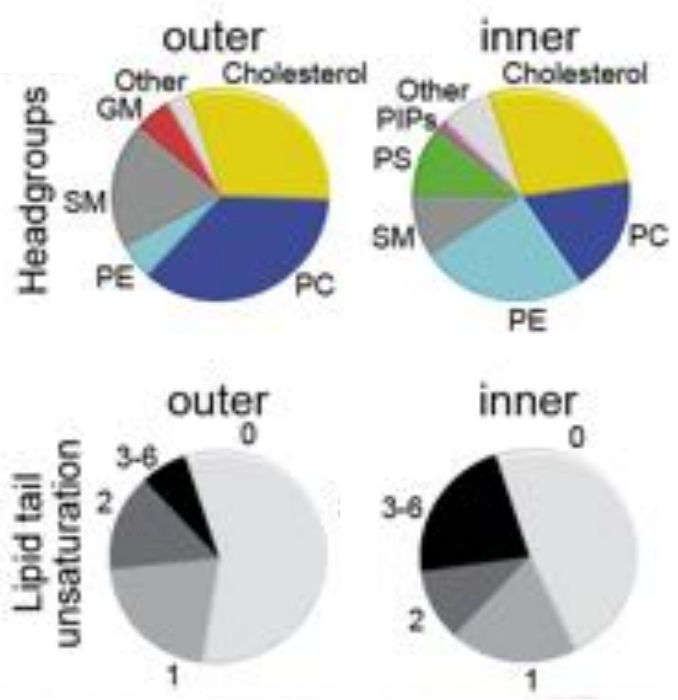
Lipids	mol %	16:0-18:0 4bead	20:0-22:0 5bead	24:0-26:0 6bead	16:1-18:1 4bead	20:1-22:1 5bead	24:1,2-26:1 6bead	18:2 4bead	20:2 5bead	20:3 5bead	20:4 22:4 5bead	22:5 22:6 5bead
PC (*phosphatidylcholine*)	39%	48%	0%	0%	20%	0%	0%	25%	1%	0%	5%	1%
PE (*phosphatidylethanolamine*)	20%	37%	0%	0%	20%	0%	0%	8%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



Total of 63 different CG lipid types

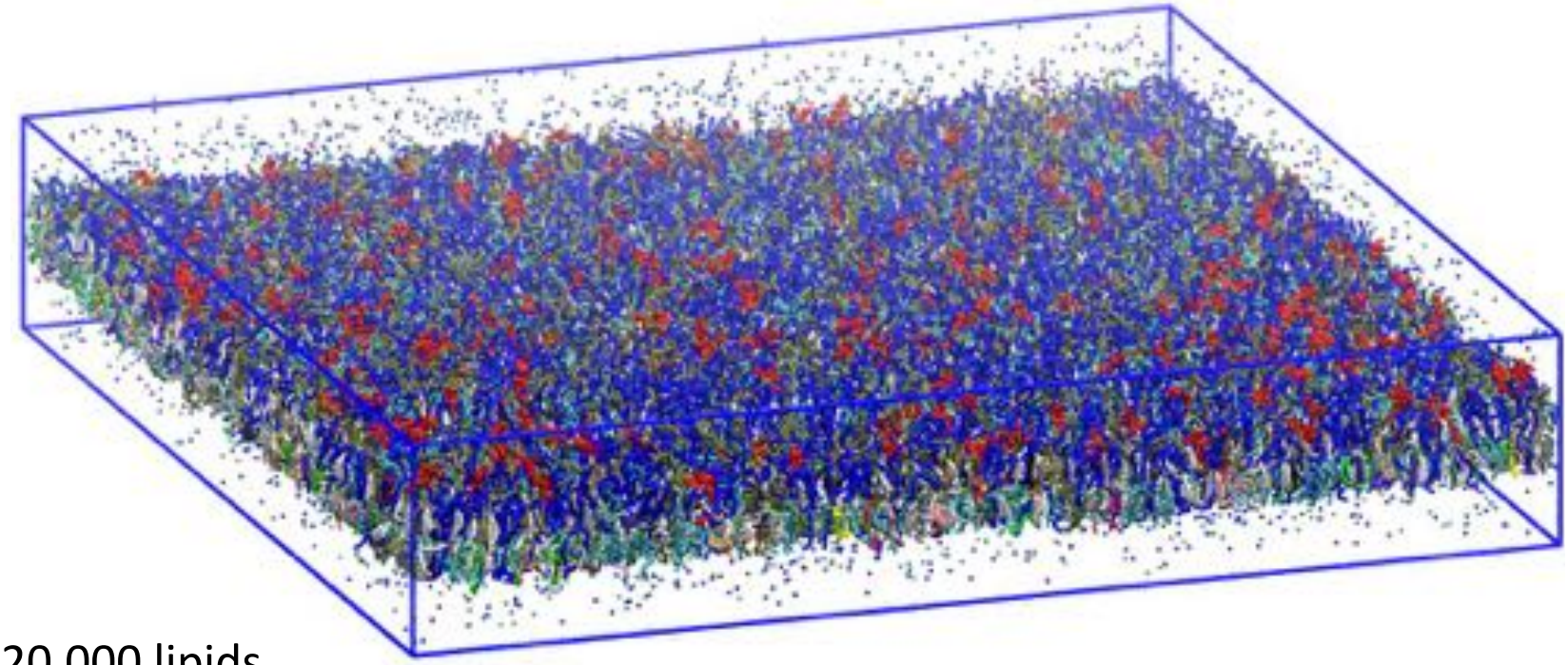
Ingólfsson, H. I., Melo, M. N., van Eerden, F. J., Arnarez, C., Lopez, C. A., Wassenaar, T. A., et al. (2014). Lipid Organization of the Plasma Membrane. *JACS*, *136*, 14554–14559.

PM – lipid composition



Lipid tail sn-1	Lipid tail sn-2	Acronym	Inner count	Inner leaflet %	Outer count	Outer leaflet %
Phosphatidylcholine - PC						
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	DDDDC	PAPC	129	0.31	283	0.69
DDDDC	DDDDC	DAPC	16	0.31	35	0.69
CCCC	DDDDDC	PUPC	32	0.31	71	0.69
		Total:	**1618**	**0.31**	**3543**	**0.69**
Phosphatidylethanolamine - PE						
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	CDDDC	PQPE	95	0.81	22	0.19
CCCC	DDDDC	PAPE	522	0.81	124	0.19
DDDDC	DDDDC	DAPE	332	0.81	78	0.19
CCCC	DDDDDC	PUPE	190	0.81	44	0.19
DDDDDC	DDDDDC	DUPE	95	0.81	22	0.19
		Total:	**2373**	**0.81**	**559**	**0.19**
Sphingomyelin - SM						
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	CCCDCC	PNSM	174	0.31	381	0.69
TCCC	CCCDCC	BNSM	86	0.31	191	0.69
TCCCC	CCCDCC	XNSM	121	0.31	267	0.69
		Total:	**868**	**0.31**	**1906**	**0.69**
Phosphatidylserine - PS						
CCCC	CCDC	POPS	200	1.00	0	0.00
CCCC	CDDC	PIPS	79	1.00	0	0.00
CCCC	CDDDC	PQPS	39	1.00	0	0.00
CCCC	DDDDC	PAPS	461	1.00	0	0.00
DDDDC	DDDDC	DAPS	20	1.00	0	0.00
CCCC	DDDDDC	PUPS	180	1.00	0	0.00
DDDDDC	DDDDDC	DUPS	20	1.00	0	0.00
		Total:	**999**	**1.00**	**0**	**0.00**
Glycolip - monosialotetrahexosylganglioside - GM1						
TCC	CCCC	DPG1	0	0.00	89	1.00
TCCCC	CCCCCC	DXG1	0	0.00	51	1.00
TCC	CCCDCC	PNG1	0	0.00	64	1.00
TCCCC	CCCDCC	XNG1	0	0.00	51	1.00
		Total:	**0**	**0.00**	**255**	**1.00**
Glycolip - monosialodihexosylganglioside - GM3						
TCC	CCCC	DPG3	0	0.00	89	1.00
TCCCC	CCCCCC	DXG3	0	0.00	51	1.00
TCC	CCCDCC	PNG3	0	0.00	64	1.00
TCCCC	CCCDCC	XNG3	0	0.00	51	1.00
		Total:	**0**	**0.00**	**255**	**1.00**
Phosphatidylinositol - PI						
CCCC	CCDC	POPI	137	1.00	0	0.00
CCCC	CDDC	PIPI	120	1.00	0	0.00
CCCC	DDDDC	PAPI	120	1.00	0	0.00
CCCC	DDDDDC	PUPI	51	1.00	0	0.00
		Total:	**428**	**1.00**	**0**	**0.00**
Phosphatidic acid - PA						
CCCC	CCDC	POPA	46	1.00	0	0.00
CCCC	CDDC	PIPA	39	1.00	0	0.00
CCCC	DDDDC	PAPA	39	1.00	0	0.00
CCCC	DDDDDC	PUPA	17	1.00	0	0.00
		Total:	**141**	**1.00**	**0**	**0.00**
Phosphatidylinositol (1-3)phosphate - PIPs						
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
		Total:	**144**	**1.00**	**0**	**0.00**
Ceramide - CER						
TCC	CCCC	DPCE	15	0.33	31	0.67
TCCCC	CCCCCC	DXCE	9	0.35	17	0.65
TCC	CCCDCC	PNCE	10	0.31	22	0.69
TCCCC	CCCDCC	XNCE	9	0.35	17	0.65
		Total:	**44**	**0.34**	**86**	**0.66**
Lysophosphatidylcholine - LPC						
CCCC		PPC	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
		Total:	**0**	**0.00**	**127**	**1.00**
Diacylglycerol - DAG						
CCCC	CCDC	PODG	17	0.40	25	0.60
CCCC	CDDC	PIDG	15	0.39	23	0.61
CCCC	DDDDC	PADG	15	0.39	23	0.61
CCCC	DDDDDC	PUDG	6	0.40	9	0.60
		Total:	**52**	**0.39**	**81**	**0.61**
Cholesterol						
		CHOL	**2653**	**0.46**	**3107**	**0.54**
All lipids types total:			**9323**	**0.48**	**9916**	**0.52**

PM – setup with *insane*



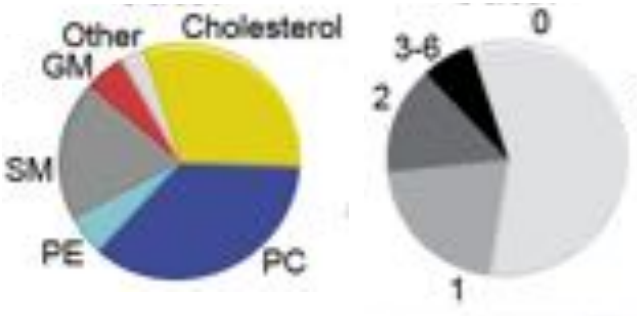
~20,000 lipids
~300,000 CG water
150 mM NaCl
+counterions

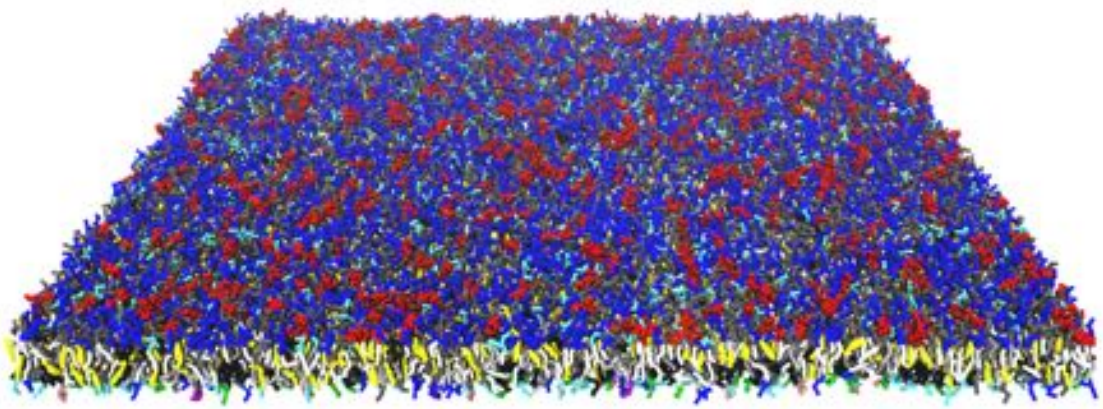
- Different area per lipid in upper/lower leaflet
- Need to measure with “all” lipids present
- Remove undulations with z-pos constraint

PM – idealized plasma membrane

Outer leaflet:

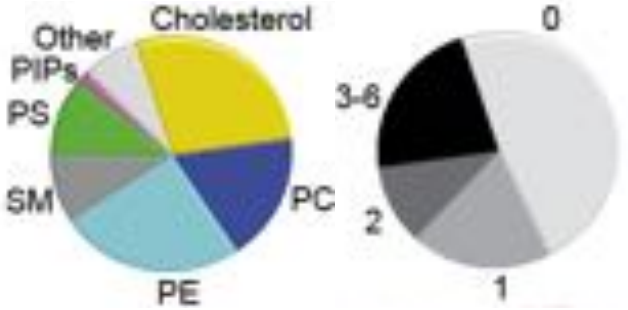
Headgroups **Tail unsaturation**

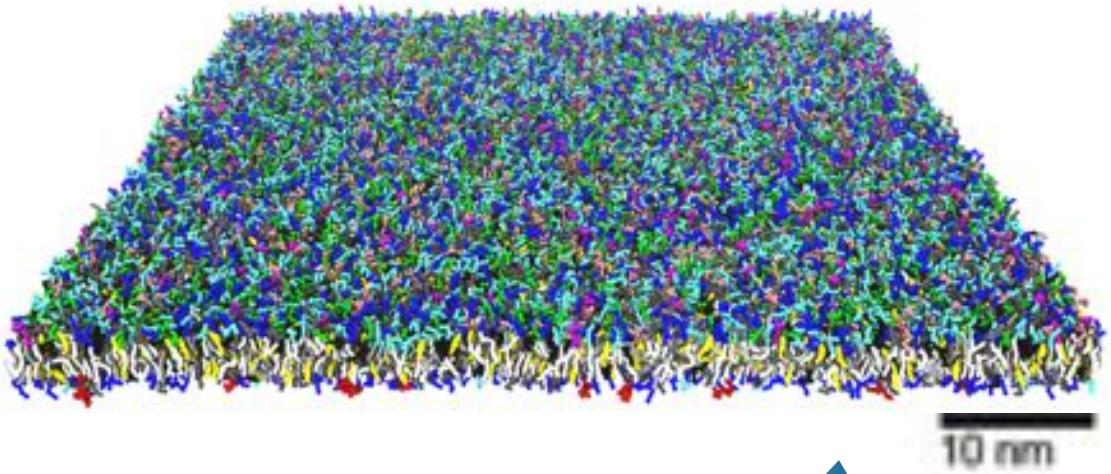




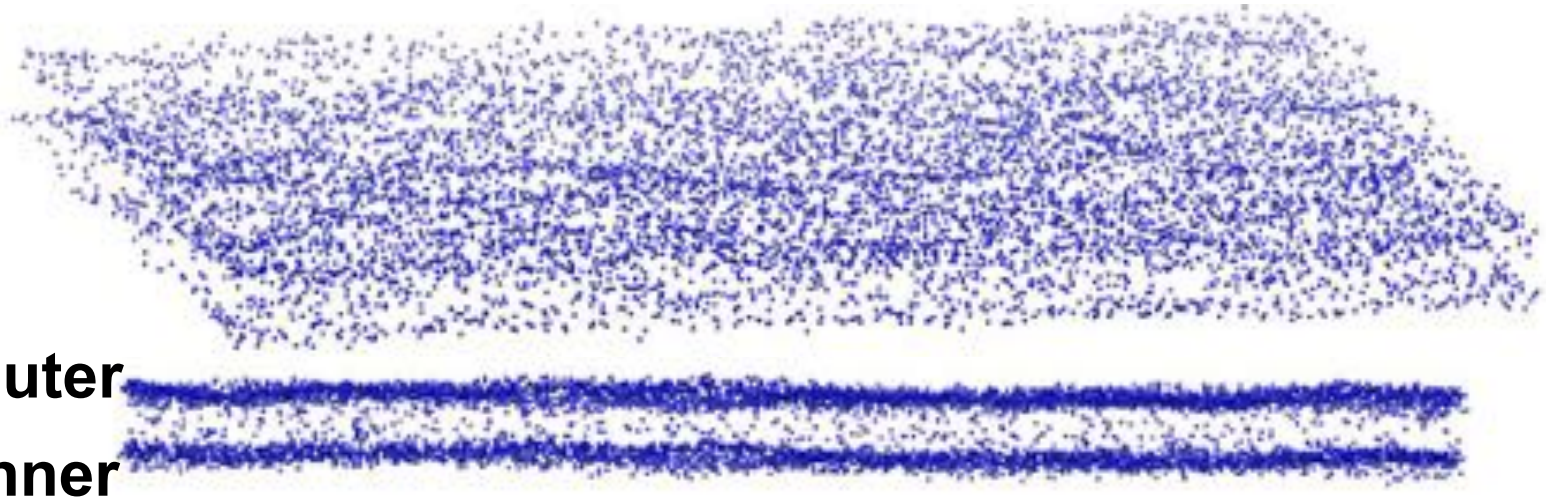
Inner leaflet:

Headgroups **Tail unsaturation**

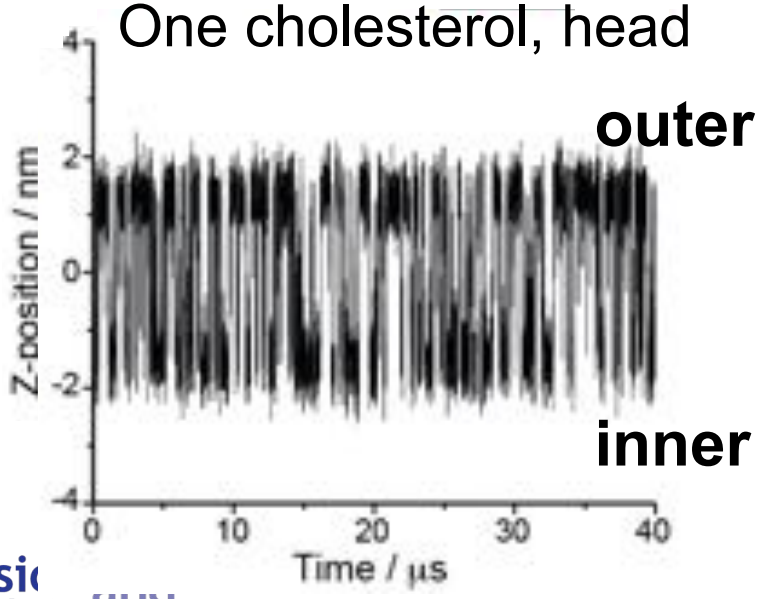


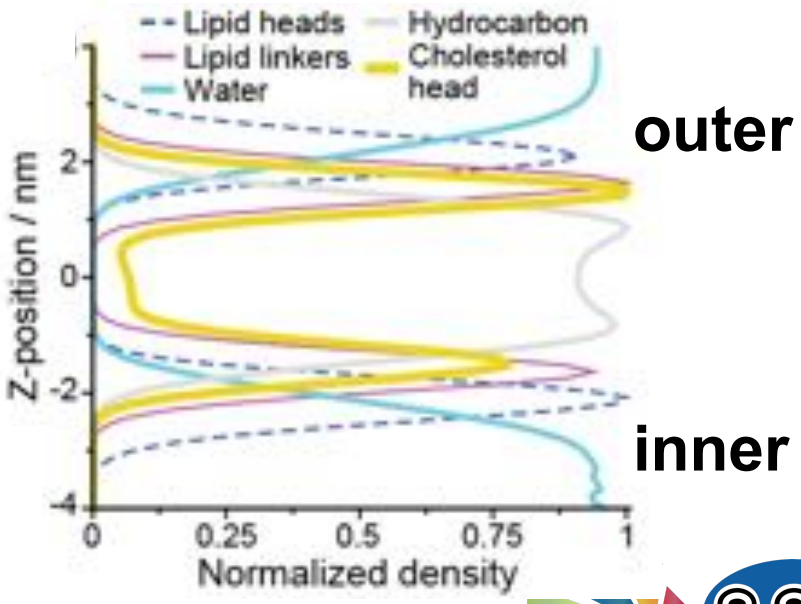


PM – cholesterol redistributes

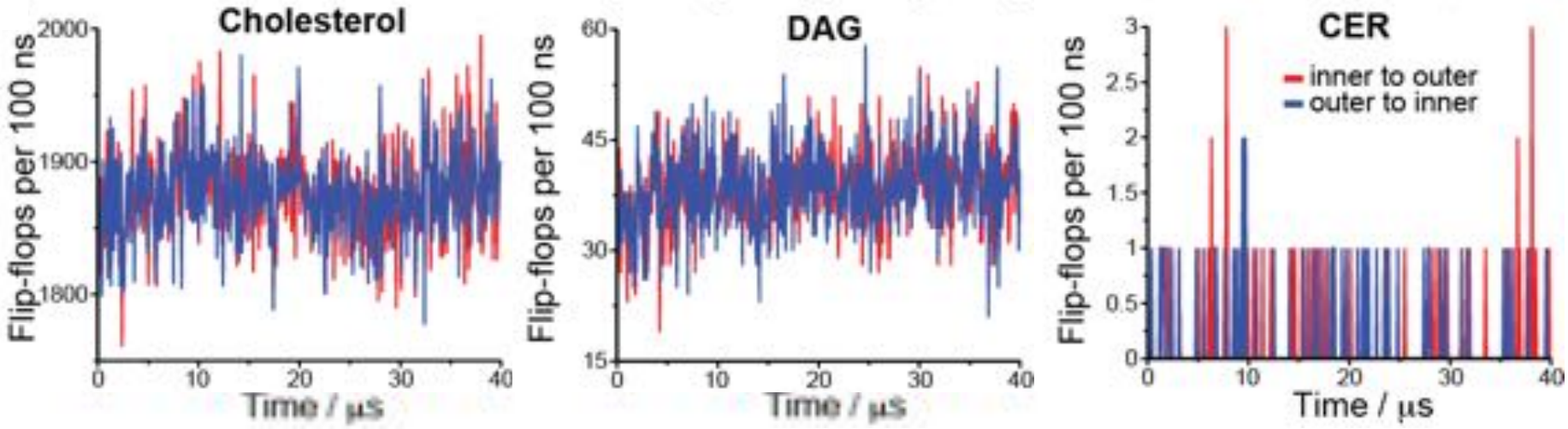


One cholesterol, head





PM – flip-flops



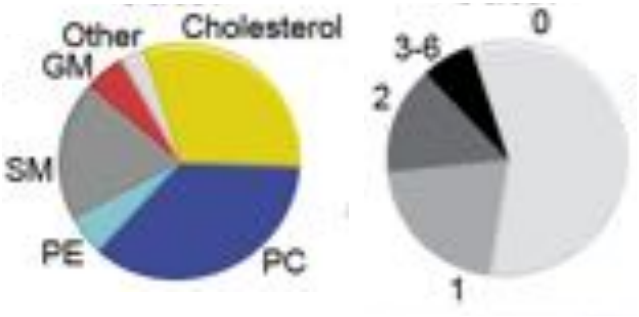
Flip-flop rates:

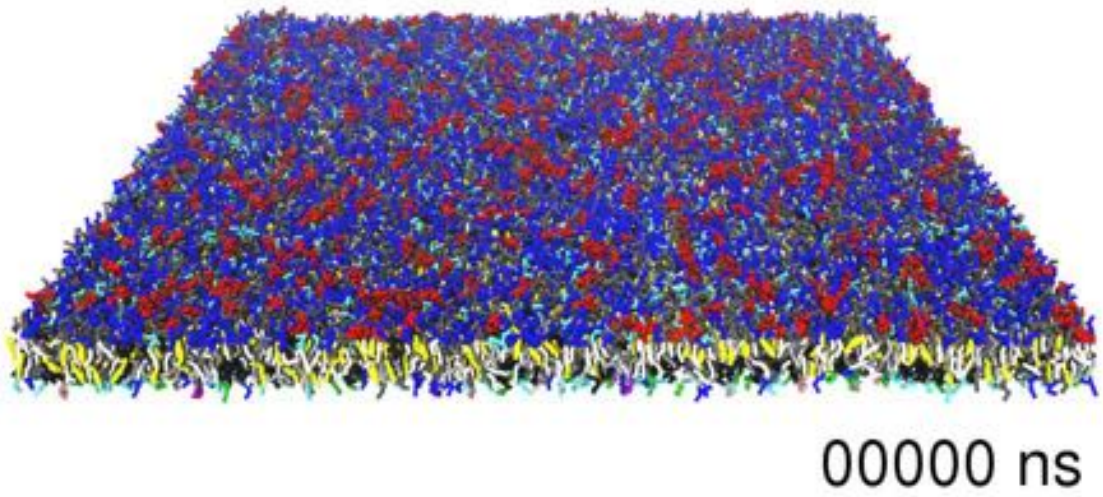
- Cholesterol $6.53 \pm 0.01 \times 10^{6}\ s^{-1}$
- DAG $5.87 \pm 0.05 \times 10^{6}\ s^{-1}$
- CER $2.0 \pm 0.4 \times 10^{4}\ s^{-1}$

PM – idealized plasma membrane

Outer leaflet:

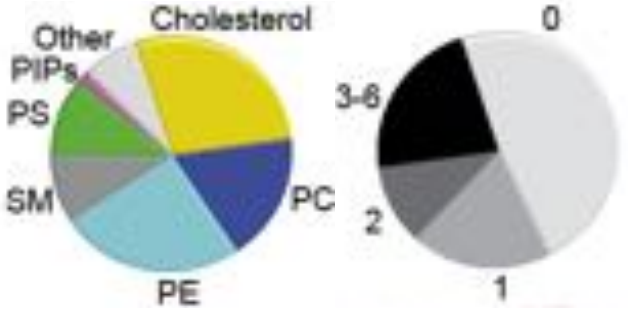
Headgroups **Tail unsaturation**

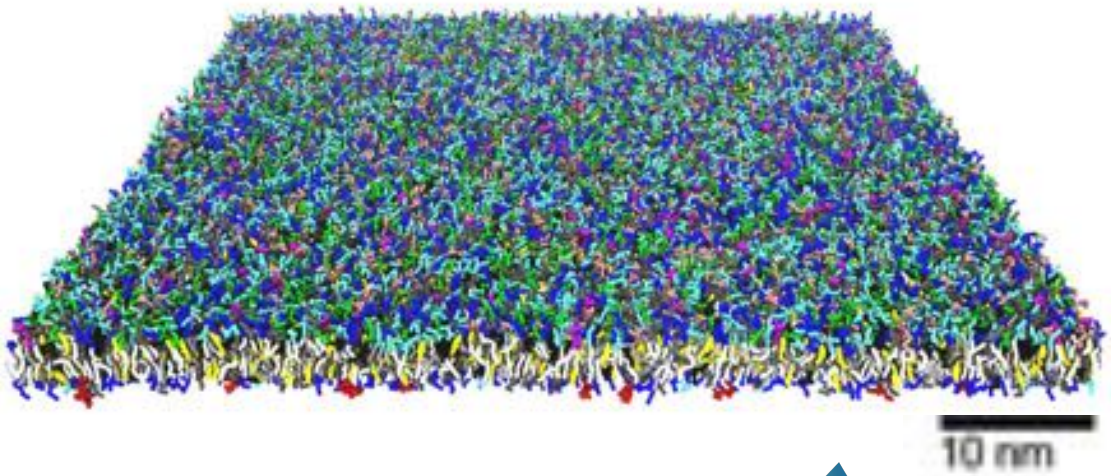




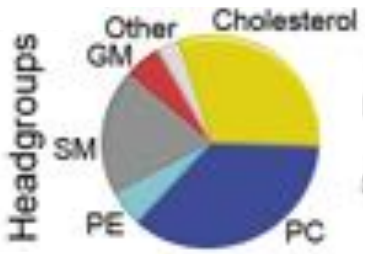
Inner leaflet:

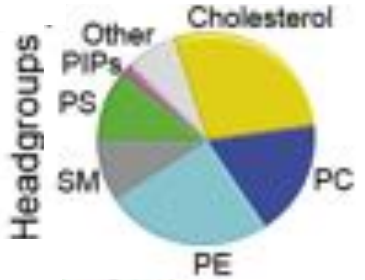
Headgroups **Tail unsaturation**

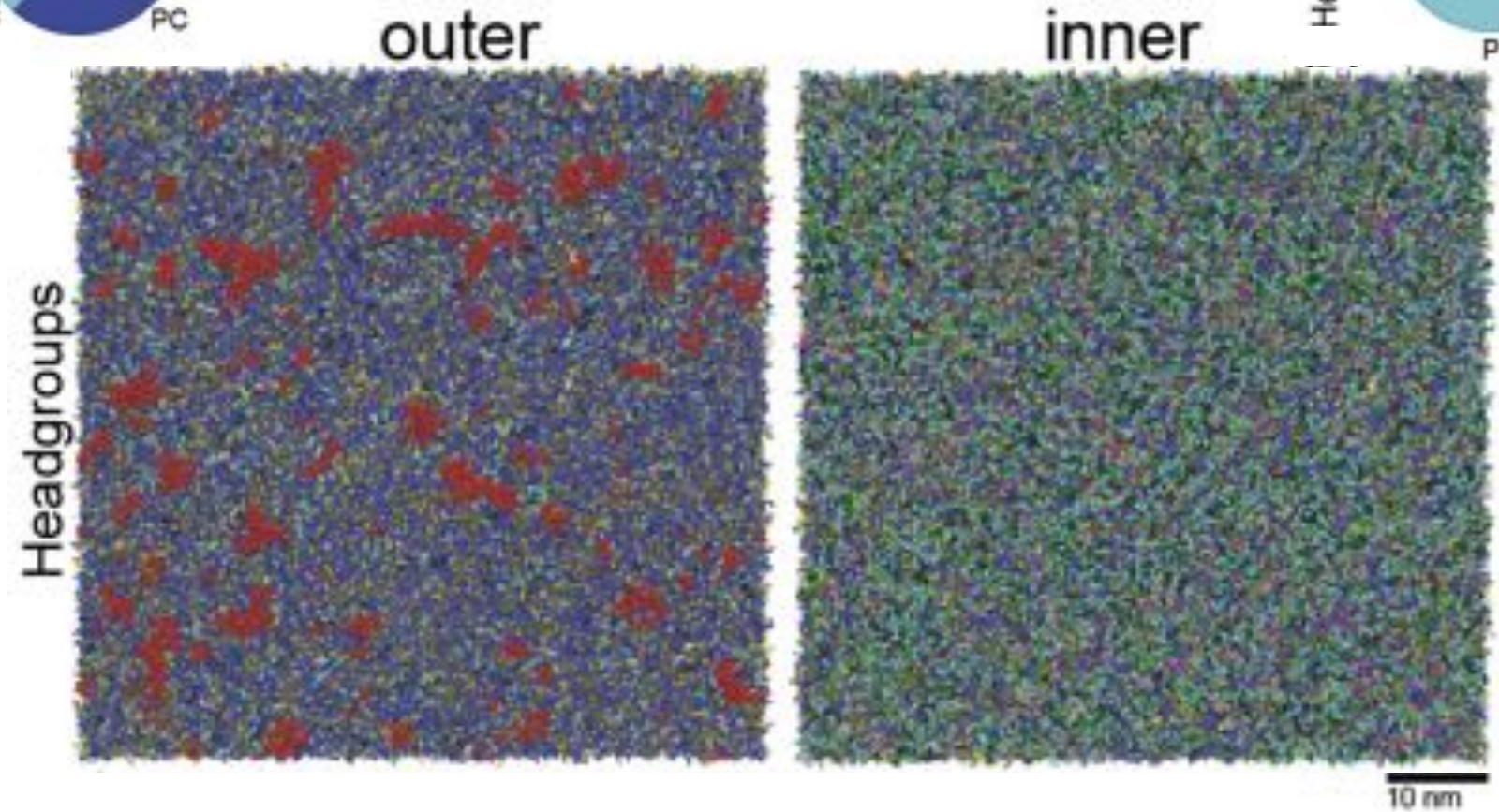




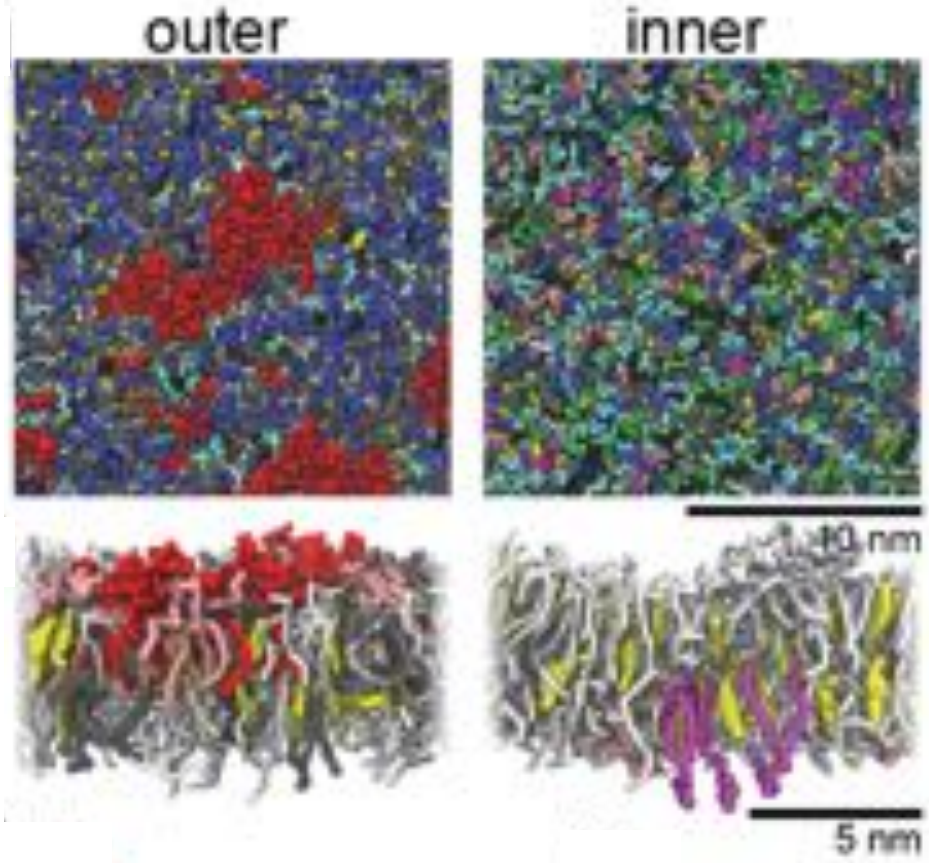
PM – lipid headgroups

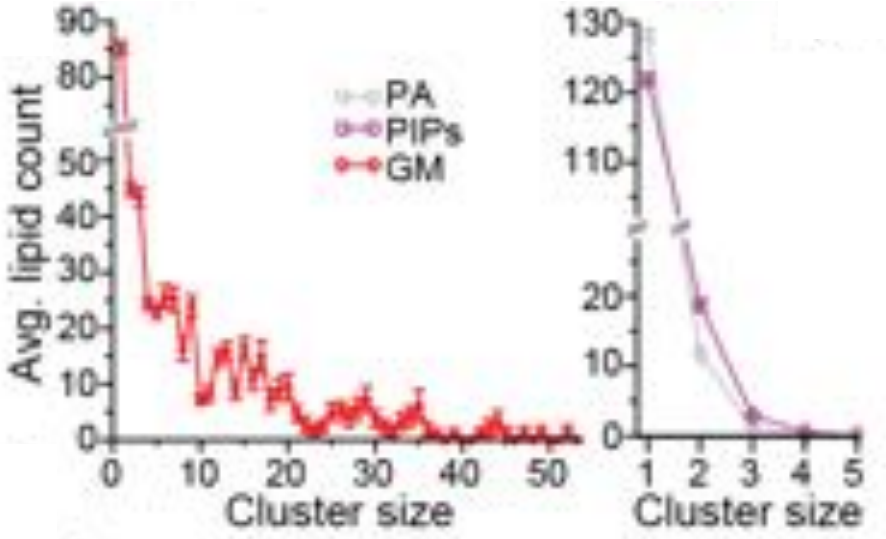




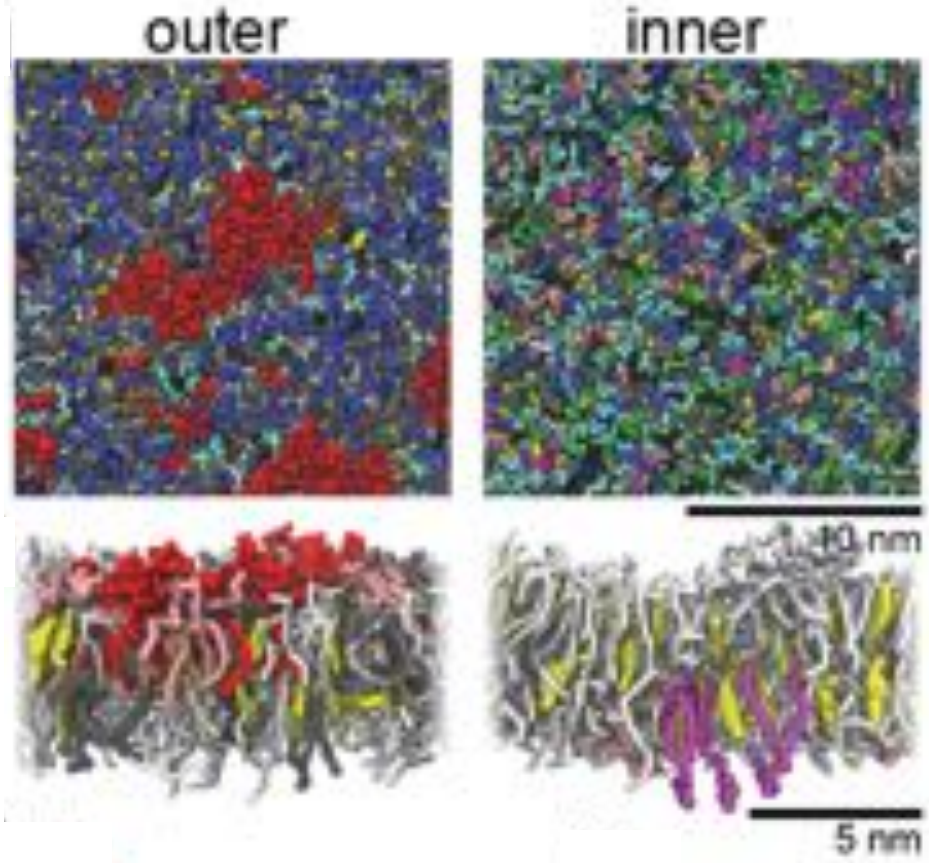


PM – lipid clustering





PM – lipid clustering



outer

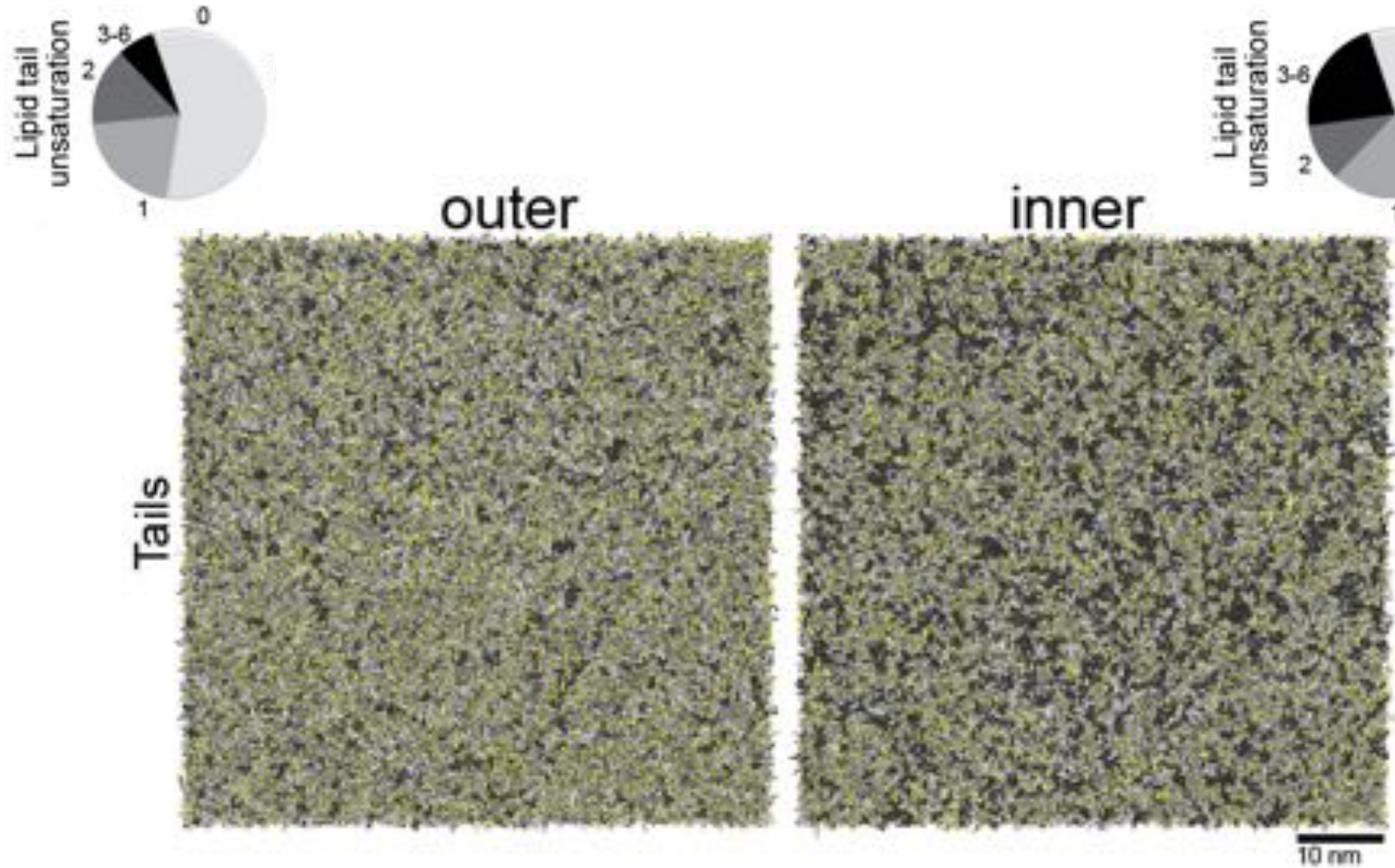
	CHOL	PC	PE	SM	GM
CHOL	0.93	1.04	1.02	1.09	1.05
PC	1.00	1.03	1.01	0.96	0.61
PE	0.98	1.00	1.04	0.89	0.99
SM	1.10	0.99	0.93	1.04	0.81
GM	1.03	0.63	1.02	0.79	4.08

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

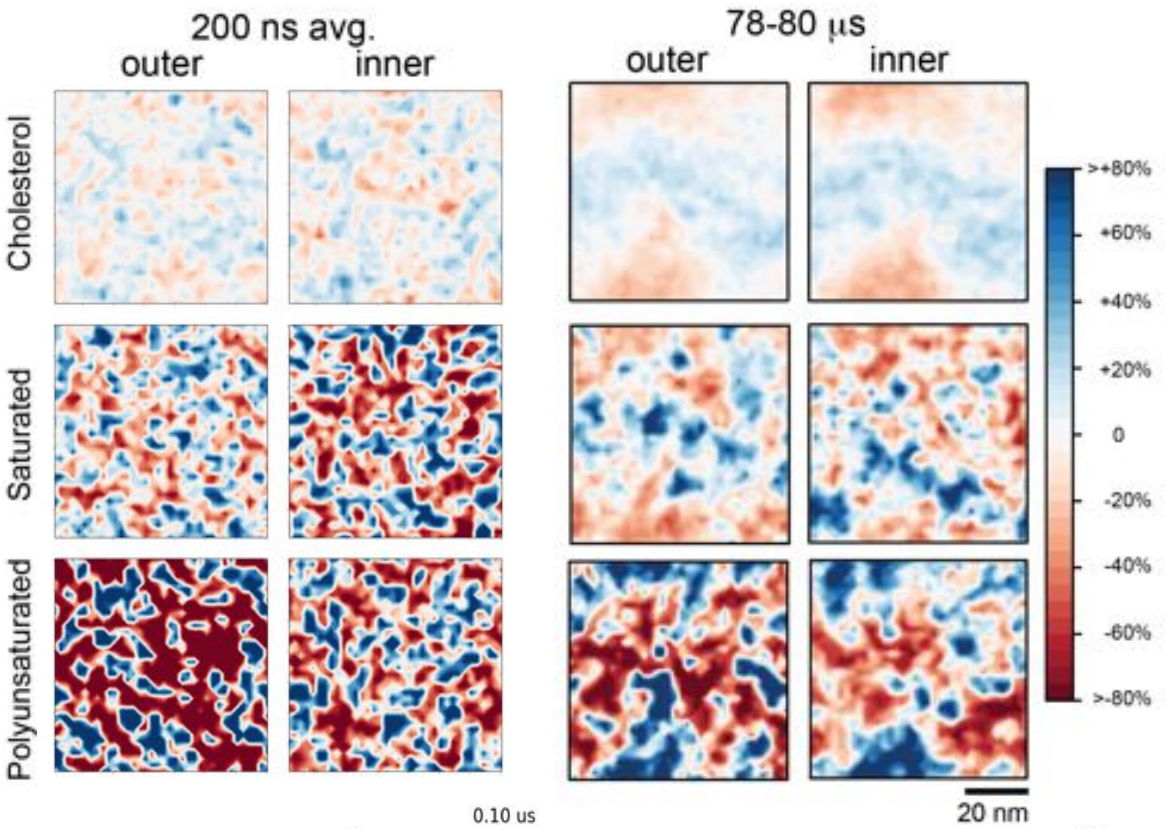
inner

	CHOL	PC	PE	SM	PS	PI	PIPs
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
PIPs	1.21	0.95	1.09	1.08	0.79	0.92	1.47

PM – tails


Lipid tail unsaturation
0
3-6
2
1
outer
inner
Lipid tail unsaturation
0
3-6
2
1
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

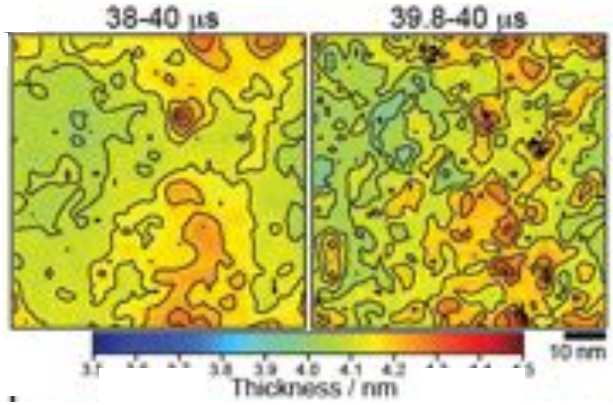
> +25%
+8 – +25%
-8 – +8%
-8 – -25%
> -25%

inner

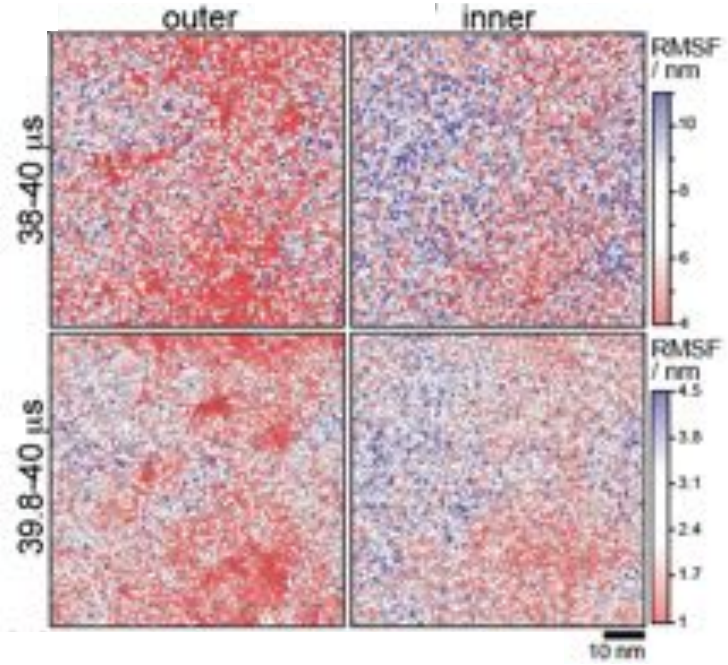
	Cholesterol	Polyunsaturated	Saturated	Other
Cholesterol	0.94	0.84	1.14	1.08
Polyunsaturated	0.67	2.19	0.64	0.86
Saturated	1.15	0.76	1.10	1.01
Other	1.04	0.98	0.97	0.98

PM – domains

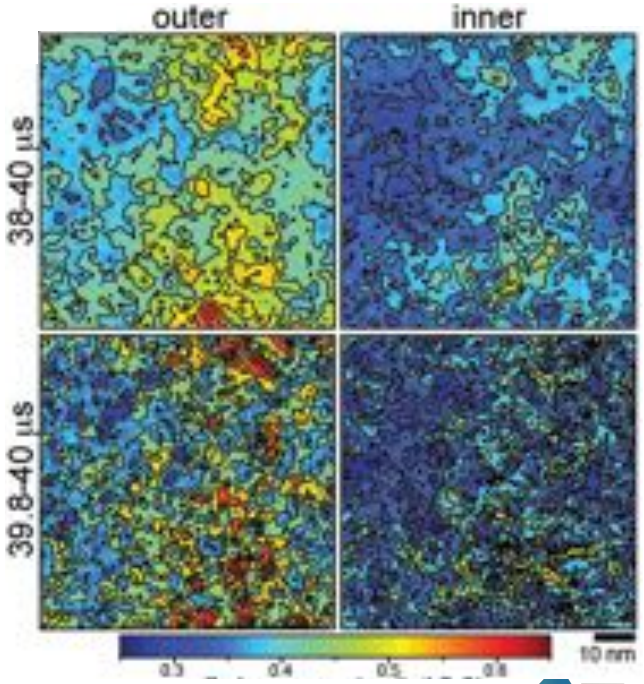
Bilayer Thickness



Root mean square fluctuations



Order parameter (tail 2-3)



PM – conclusions / outlook

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:

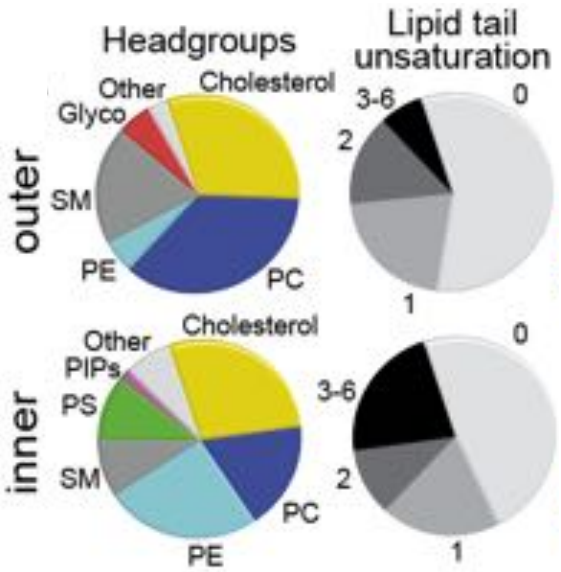
- Cholesterol favors the outer leaflet
- Multiple levels of non-ideal mixing / domain formation
- GM clusters
- PIPs self associate

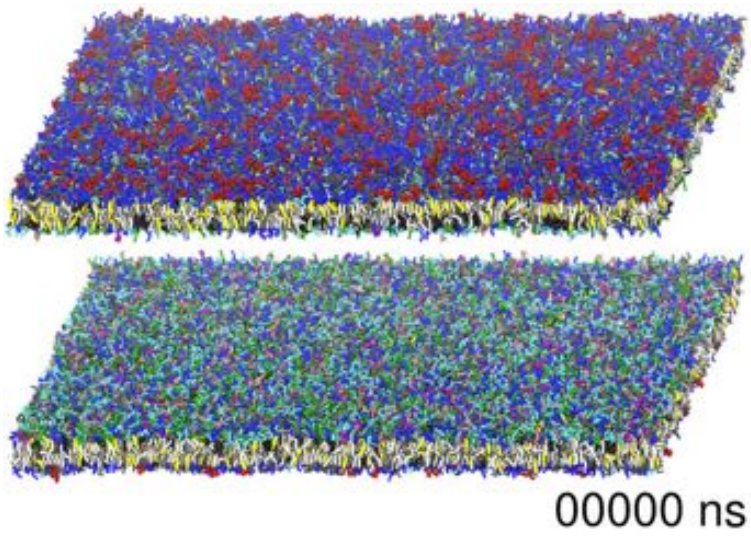
Next steps:

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

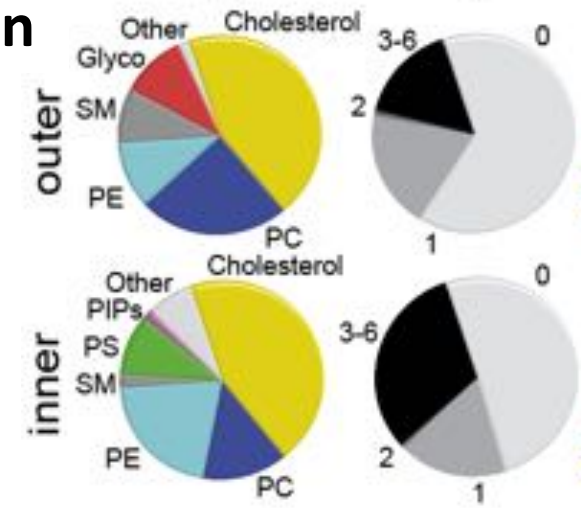
Plasma membranes – tissue specific
Brain vs Avg.

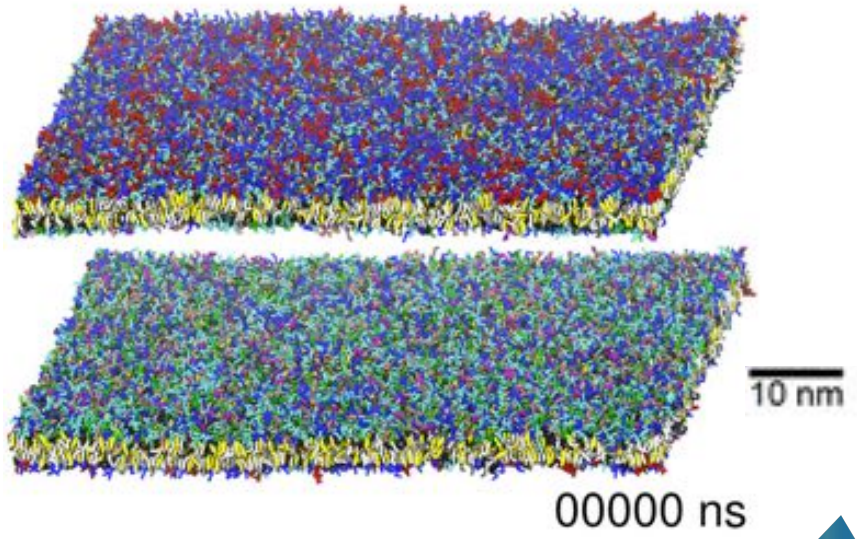
Avg.





Brain





Brain vs Avg. – properties

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

	Avg.	Brain
CHOL	7.29 ±0.02	/ 4.820±0.004
DAG	7.66 ±0.05	/ 2.80 ±0.07
CER	0.027±0.006	/ 0.015±0.005

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

Avg.	3.1±0.3 / 4.3±0.3
Brain	1.6±0.2 / 2.8±0.2

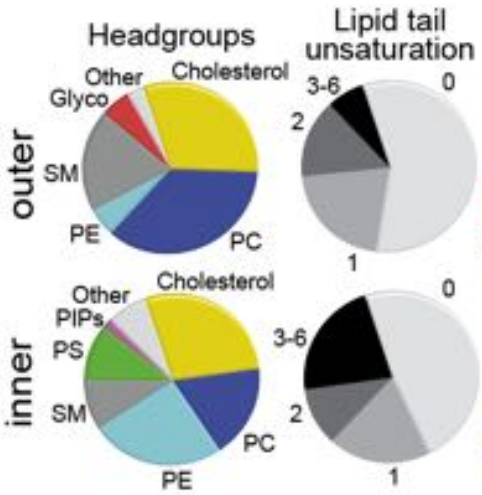
Average tail order parameter at position #3

Avg.	0.425 / 0.358
Brain	0.441 / 0.306

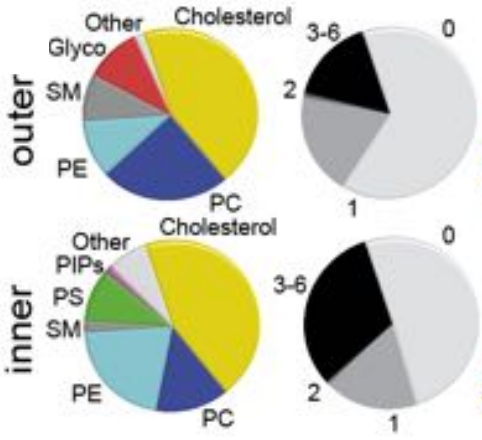
Average number of unsaturation's per tail

Avg.	0.77 / 1.32
Brain	0.90 / 1.63

Avg.

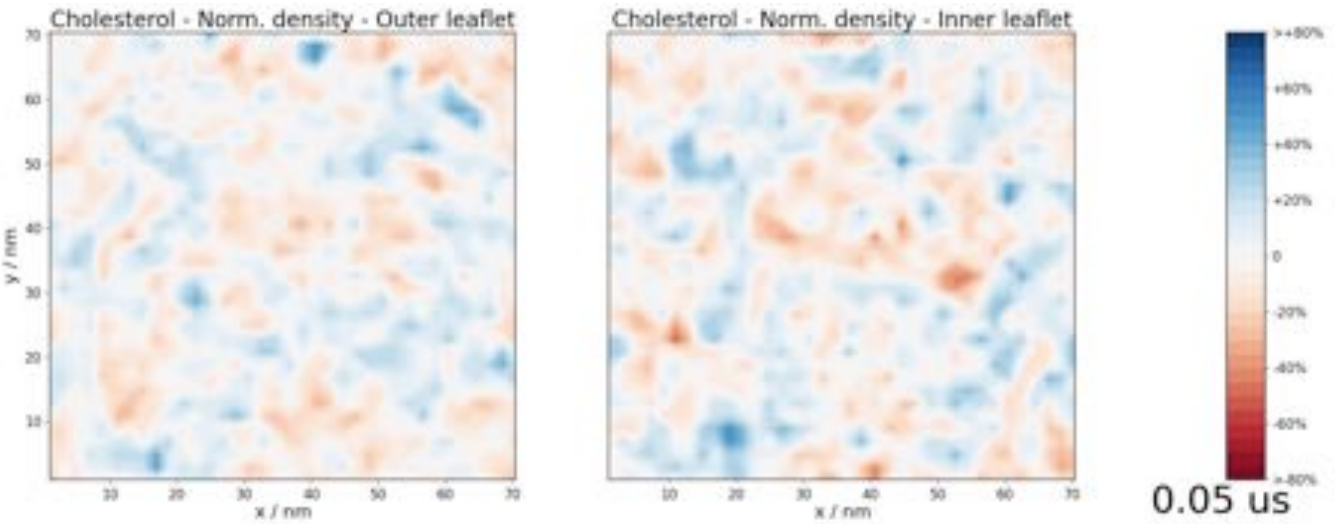


Brain

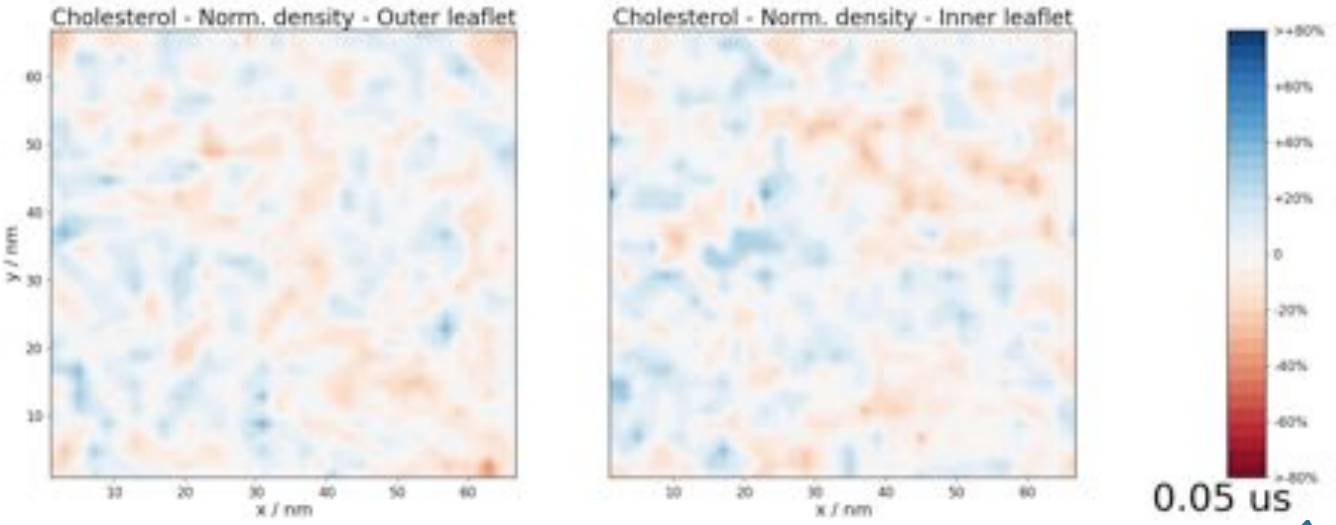


Brain vs Avg. – cholesterol density

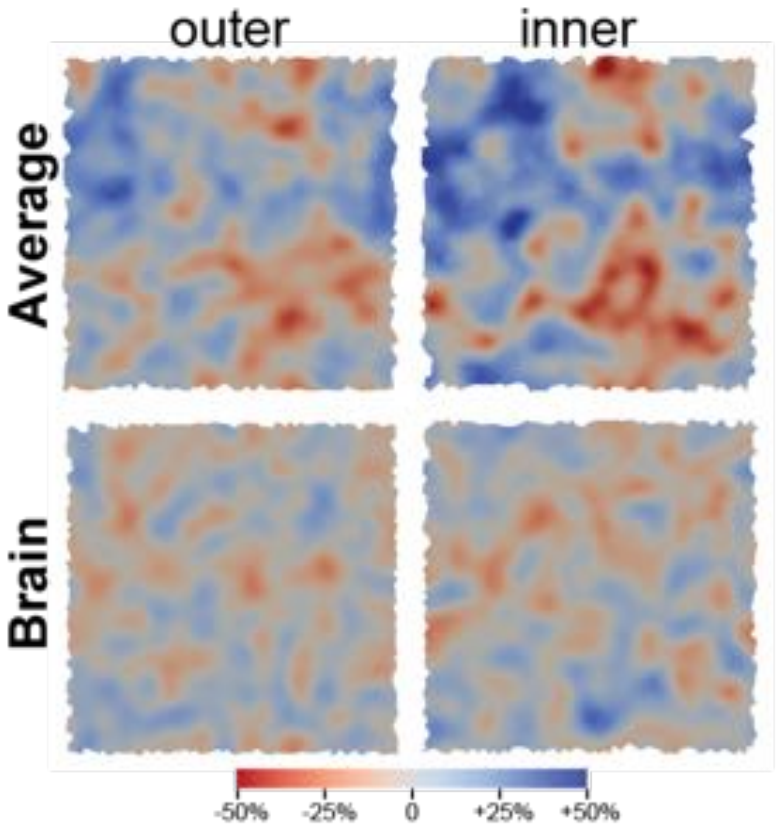
Avg.



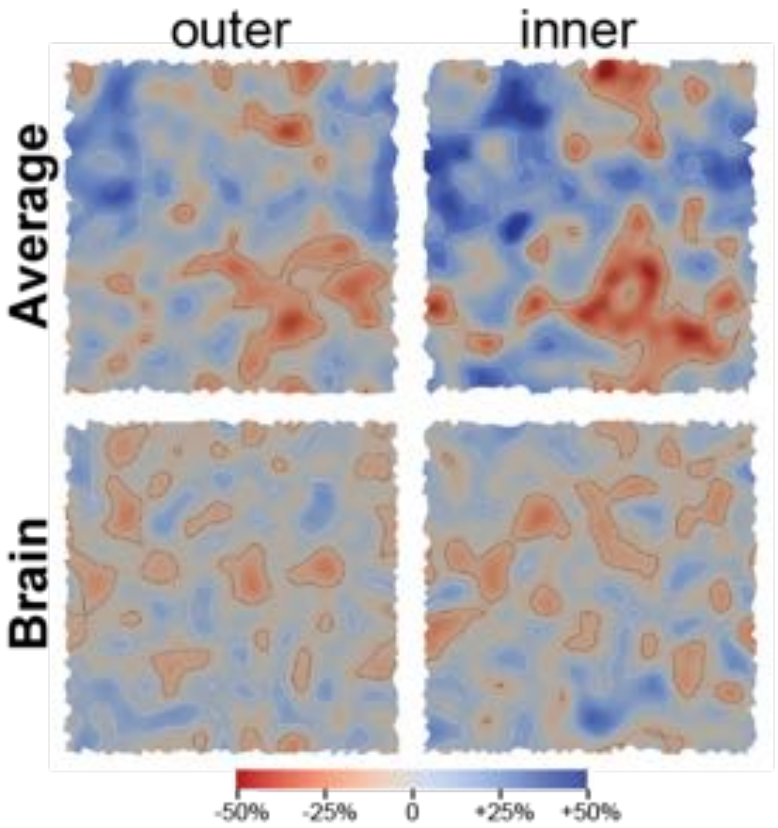
Brain

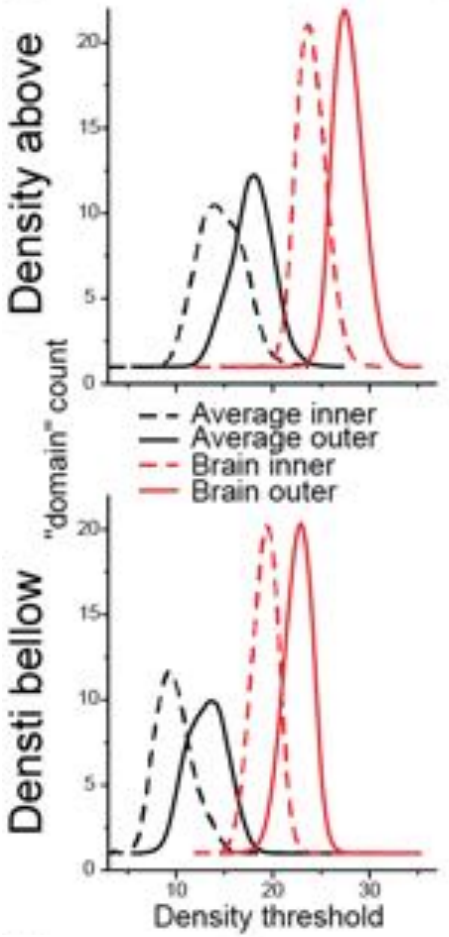


Brain vs Avg. – domain size(s) and dynamics?

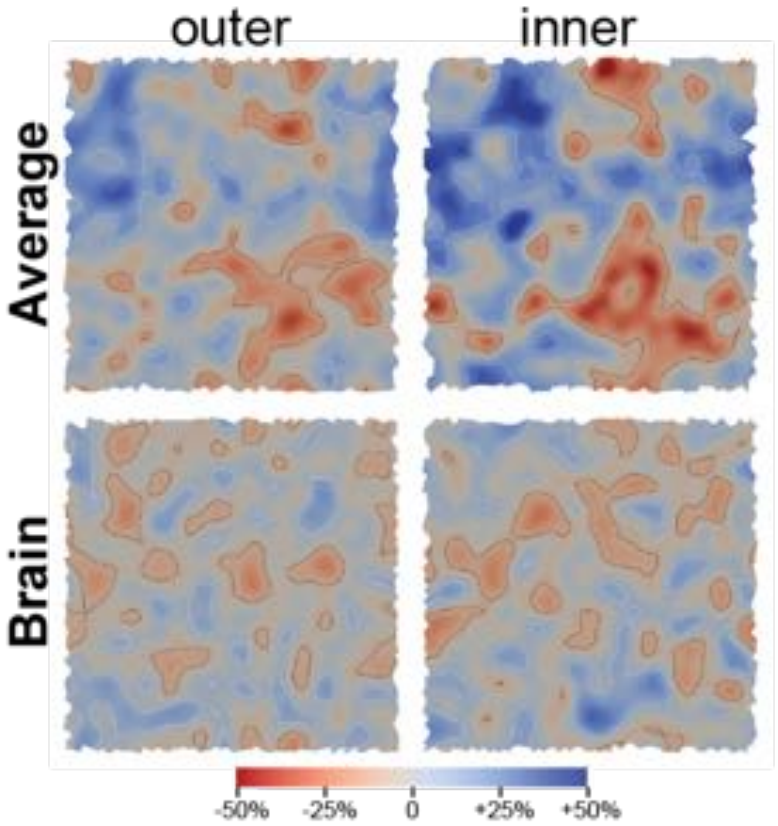


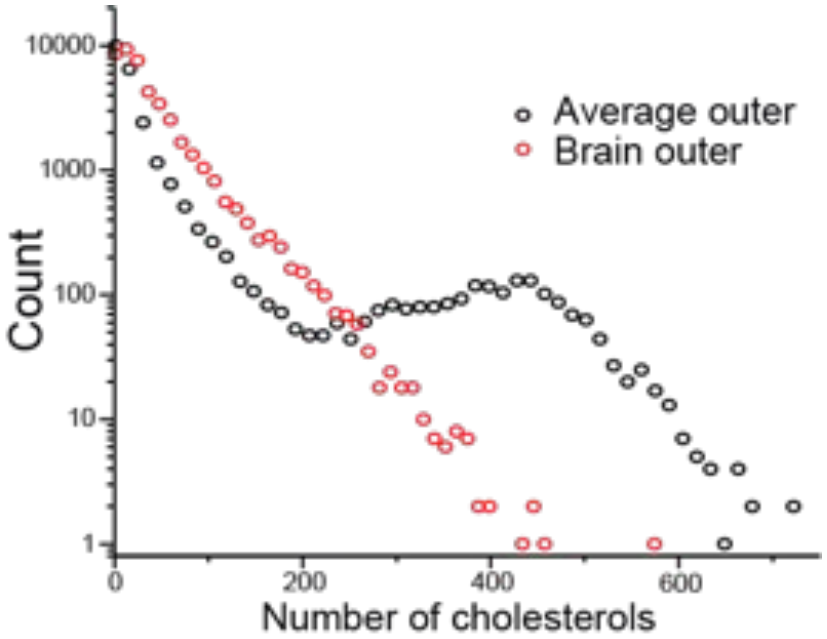
Brain vs Avg. – domain size(s) and dynamics?



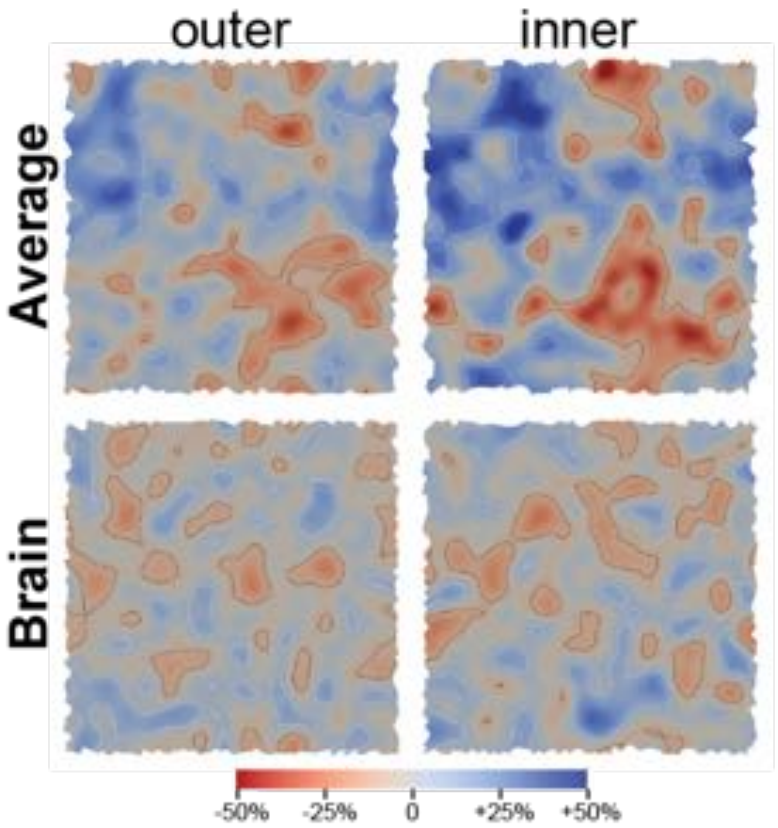


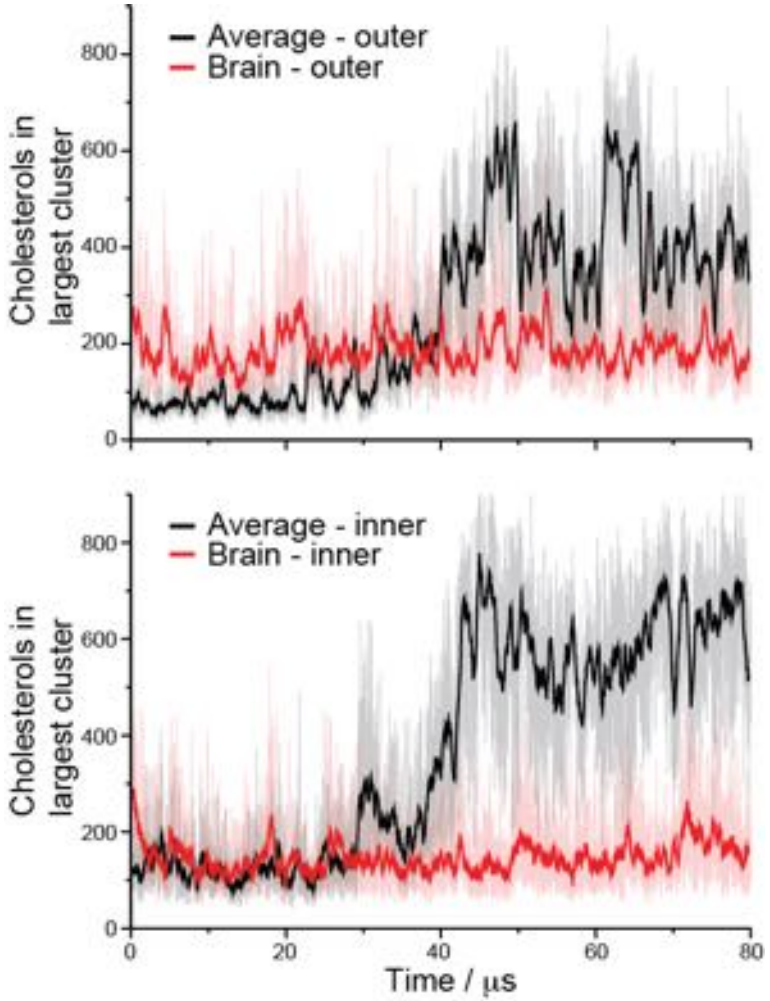
Brain vs Avg. – domain size(s) and dynamics?



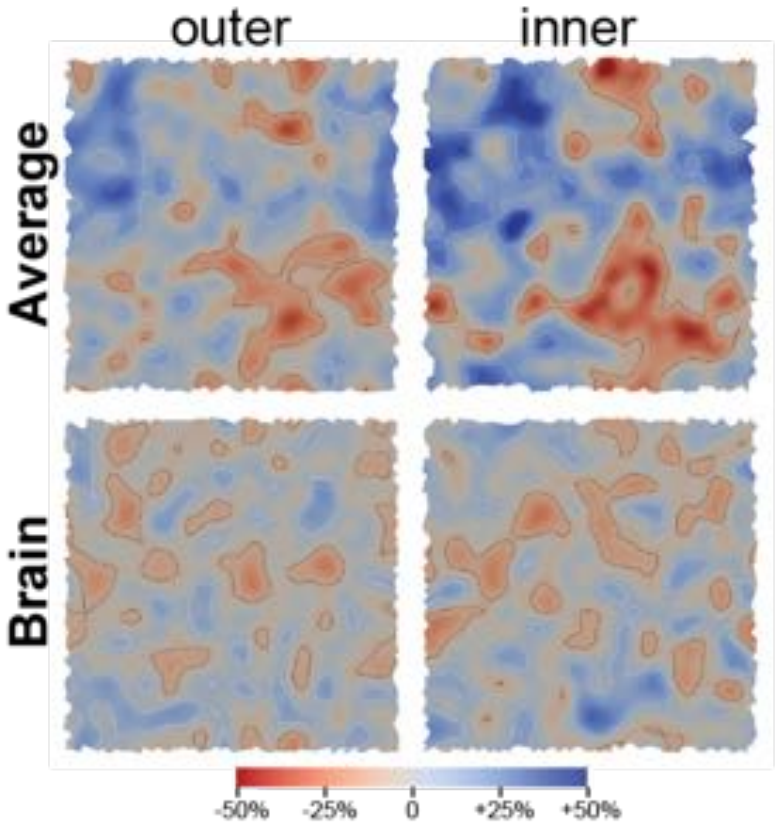


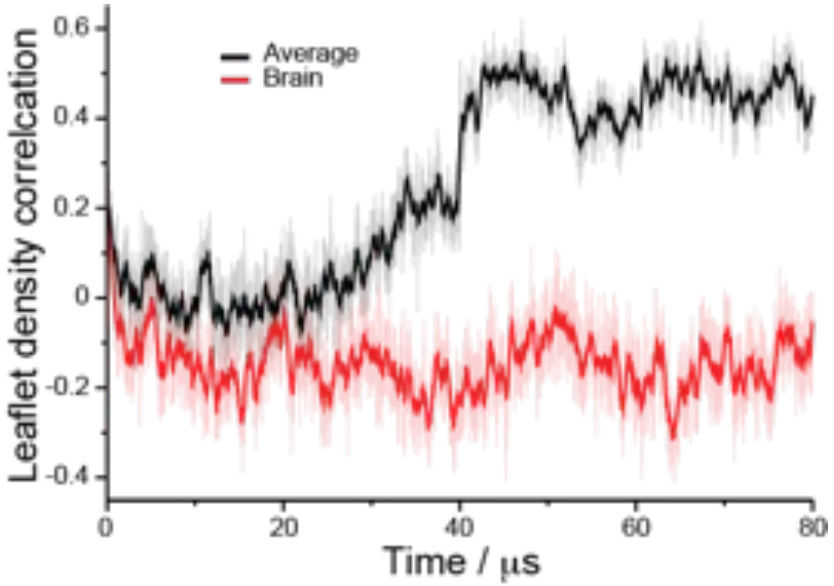
Brain vs Avg. – domain size(s) and dynamics?





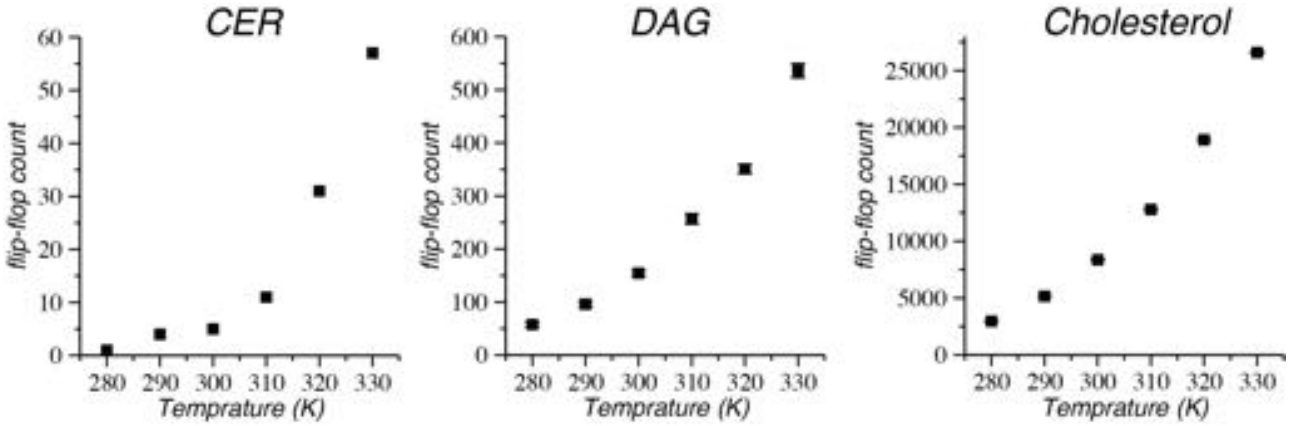
Brain vs Avg. – domain size(s) and dynamics?





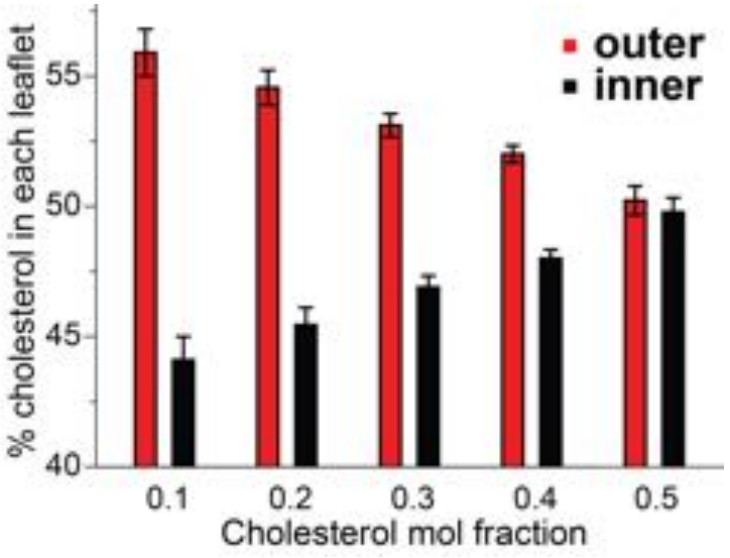
Future – PM projects

- **Effect of temperature**



- **Cholesterol concentration**

Elizabeth
Antara
Sebastian

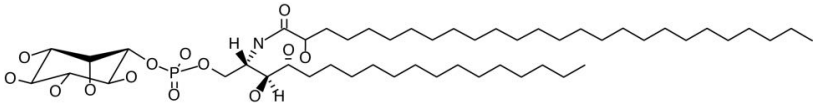


- **Lipid protein interactions**
- **Lipid shorting and tether pulling**

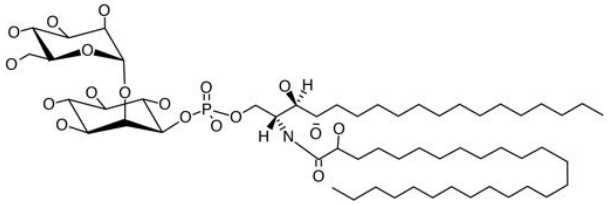
Tieleman group

Future – Martini lipids

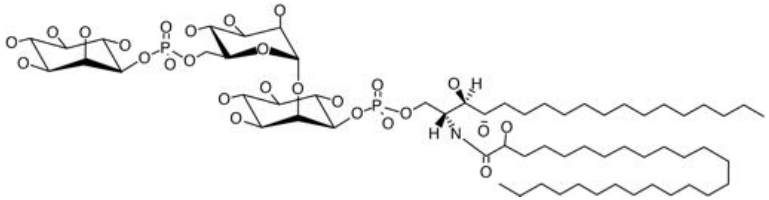
Inositolphosphoceramide (IPC)



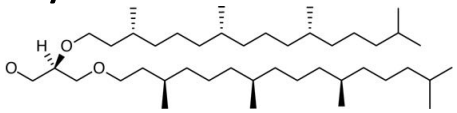
Mannosyl-IPC (MIPC)



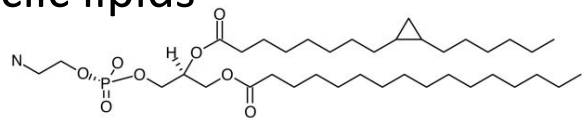
Mannosyl-di-IPC (MIP_2C)



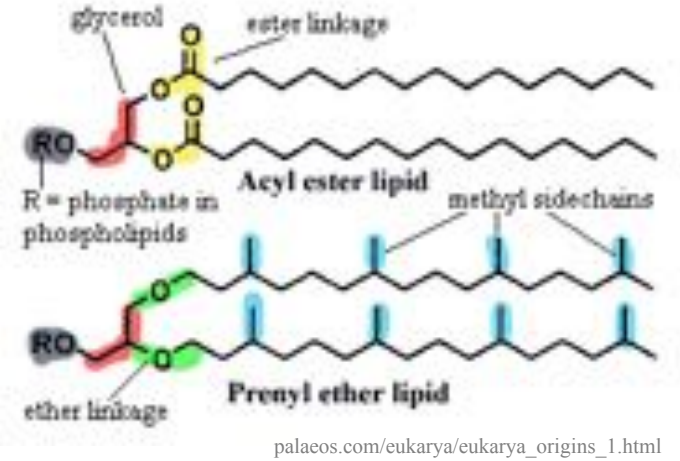
Methyl-branched ether lipids



Cyclic lipids



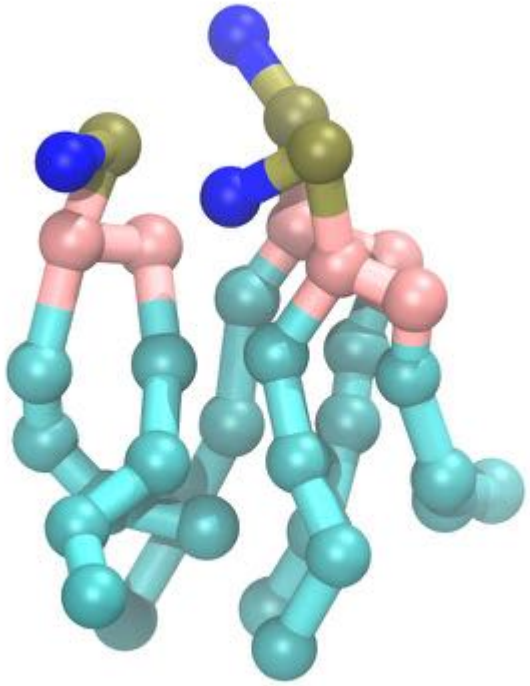
Ester / ether lipids



palaeos.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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