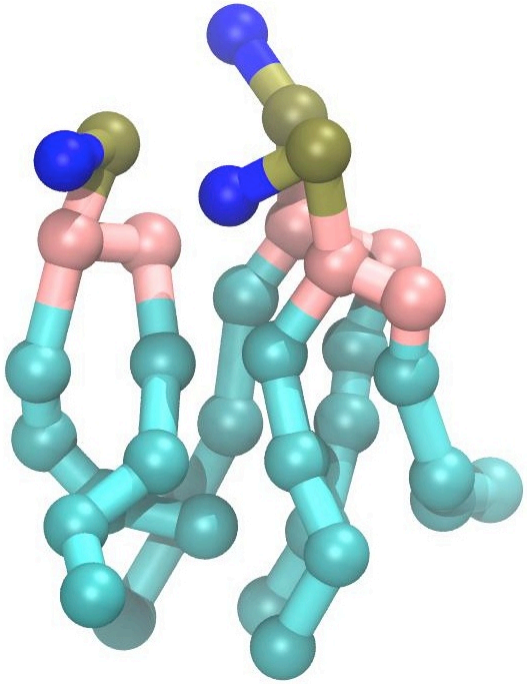
Lipid biophysics with the Martini model

Helgi I. Ingólfsson



Martini Workshop

August 25th, 2015, Groningen

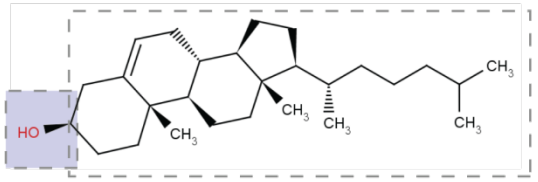
Overview

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

Lipids – definition

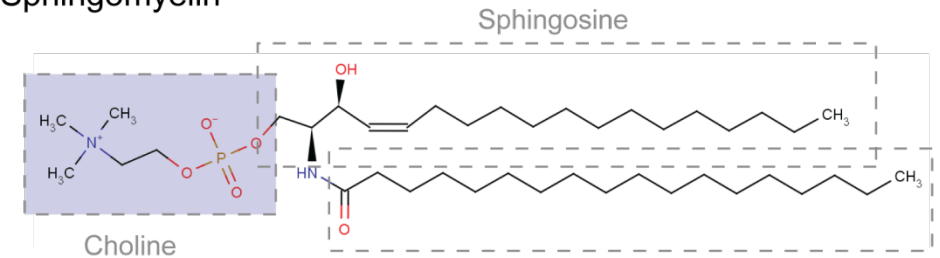
- Naturally occurring fats or fat-like compounds
- Insoluble in water
- Soluble in organic solvents
- Hydrophobic/ amphipathic molecules

Cholesterol



Head group Tail

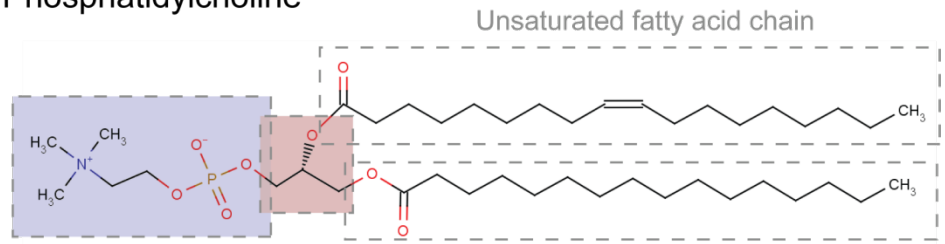
Sphingomyelin



Choline head group

Saturated fatty acid chain

Phosphatidylcholine

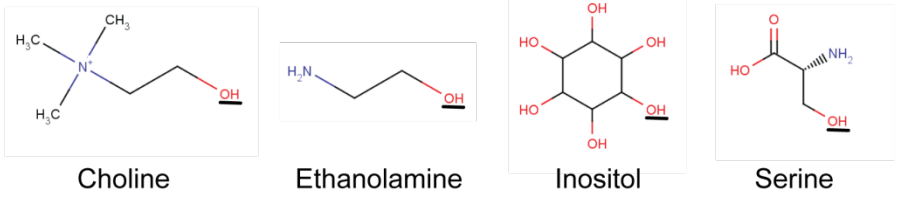


Choline head group

Glycerol linker

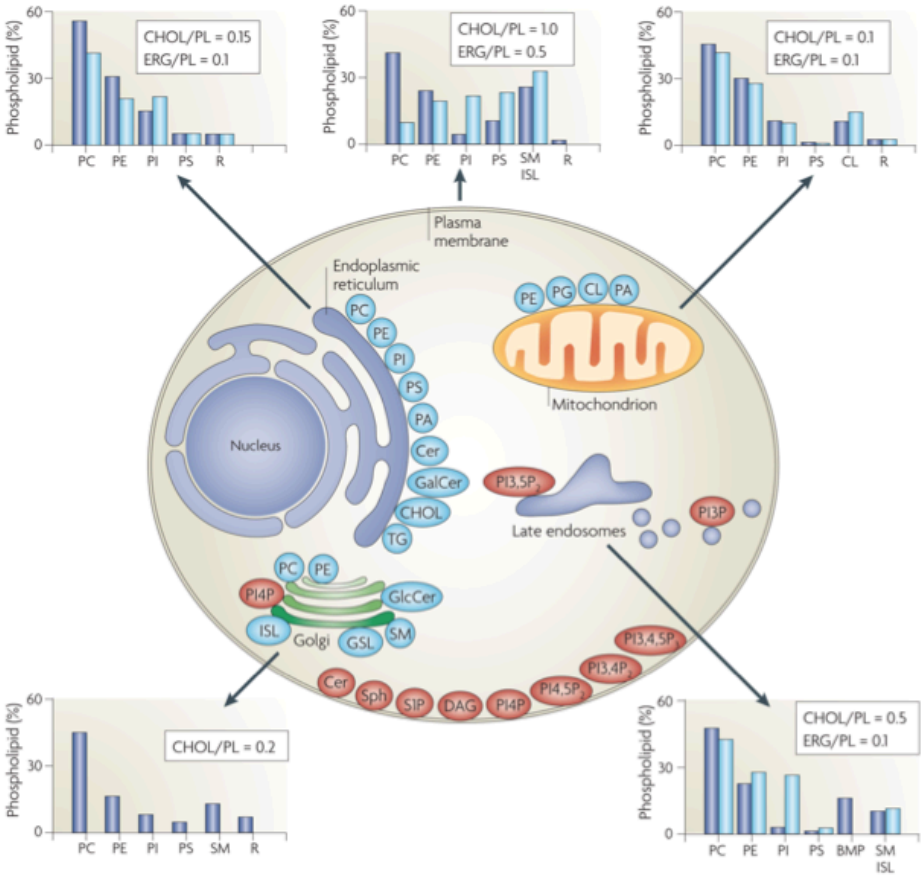
Saturated fatty acid chain

Examples of lipid head groups



Choline Ethanolamine Inositol Serine

Lipids – diversity

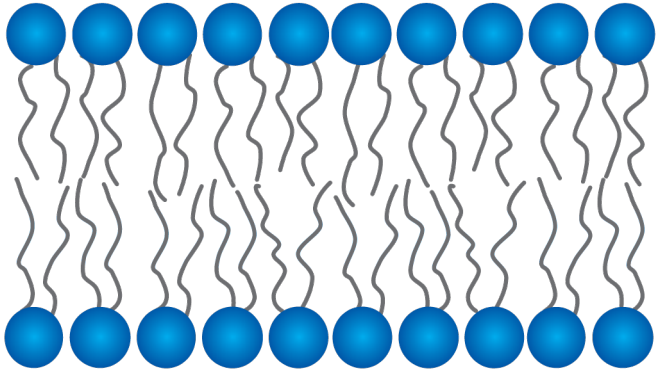


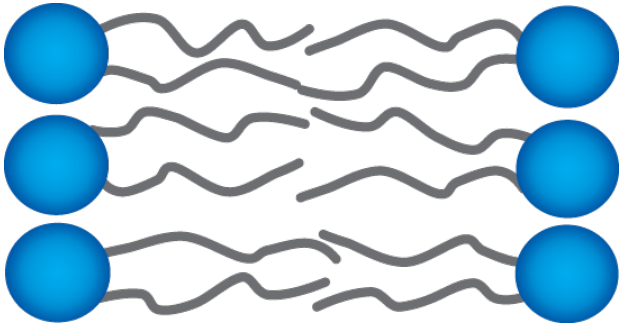
- Membranes contain 100s of different lipid types
- Cells have 1000s
- Currently www.lipidmaps.org has >40.000 unique lipid structures

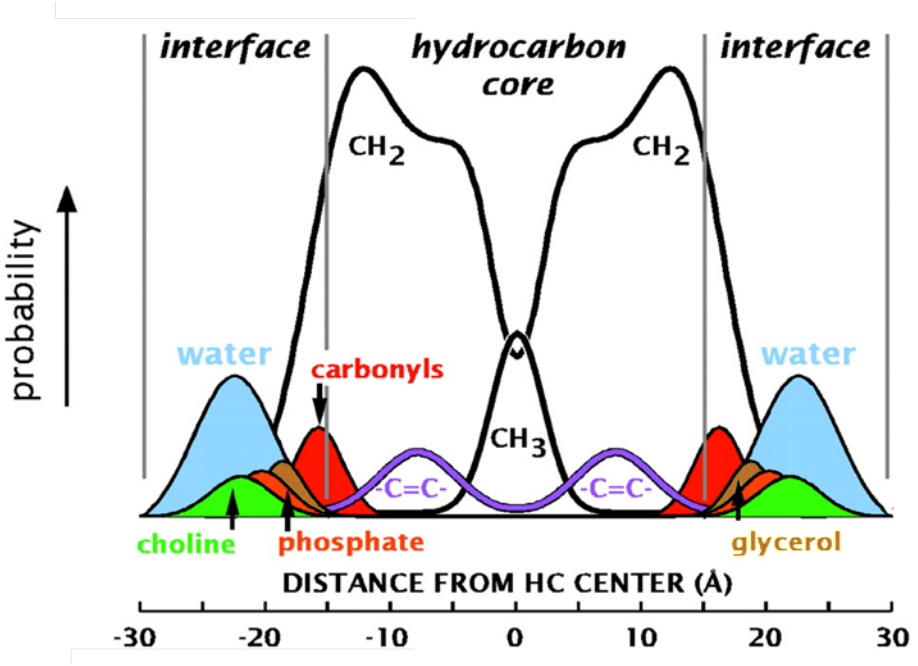
van Meer, G., D.R. Voelker, and G.W. Feigenson. 2008. Membrane lipids: where they are and how they behave. Nat. Rev. Mol. Cell Biol. 9: 112–124.

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

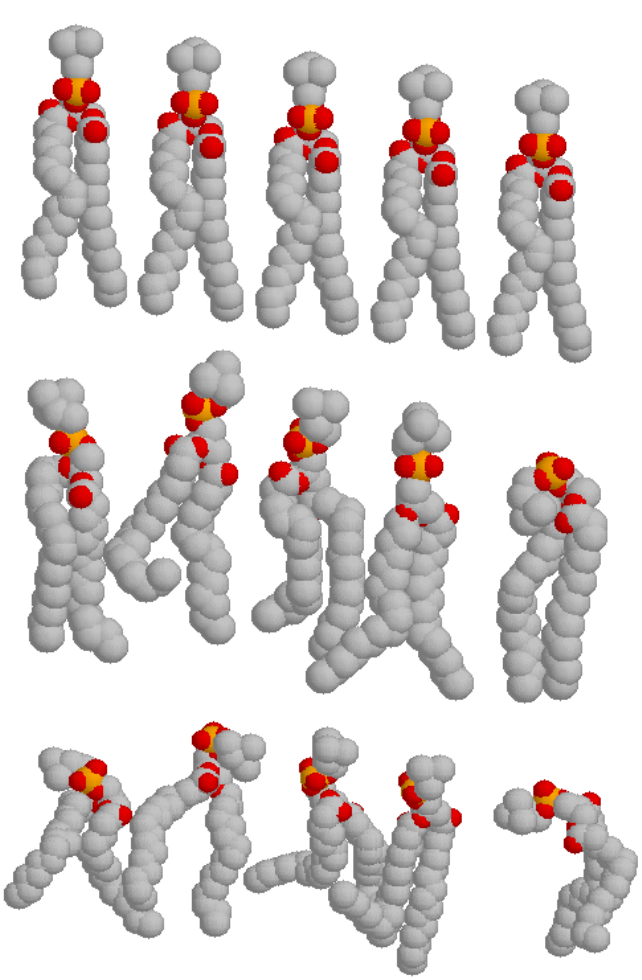
White et al. 2001. *J Biol Chem* 276:32395-32398

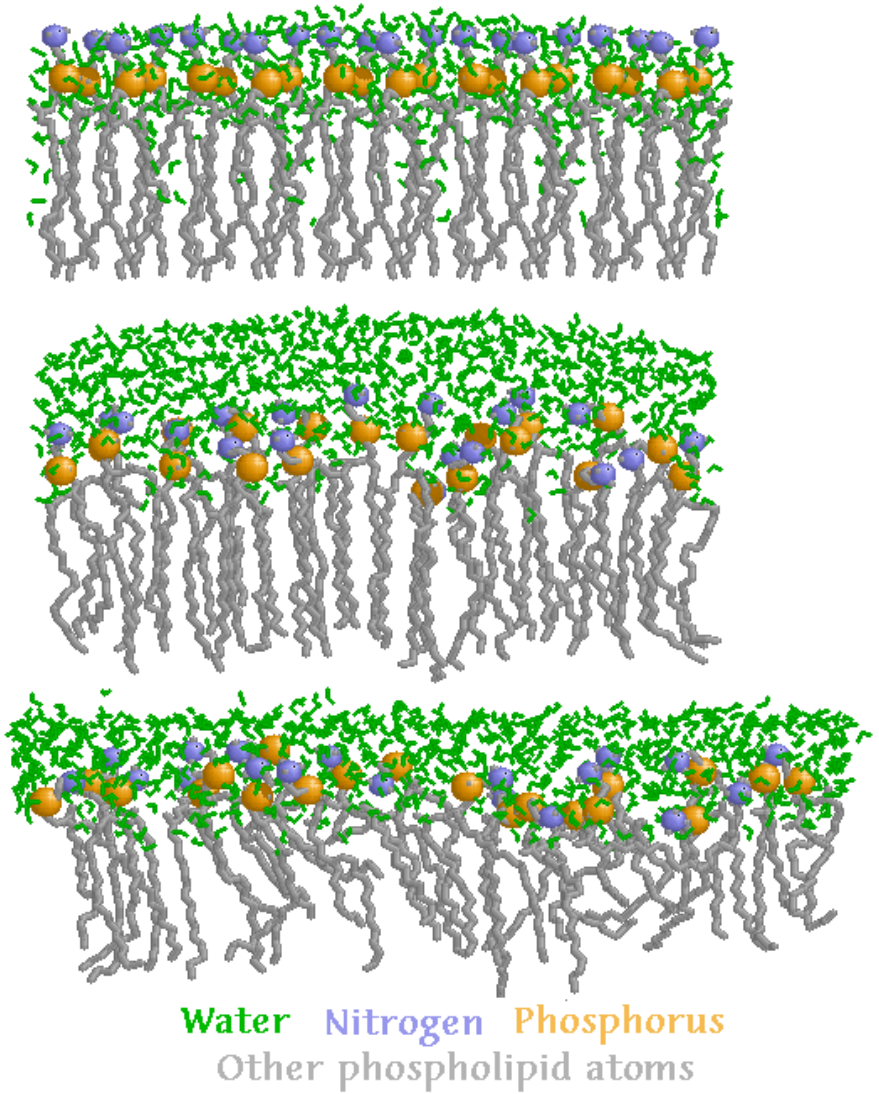
Lipids – bilayers

Crystal

Gel

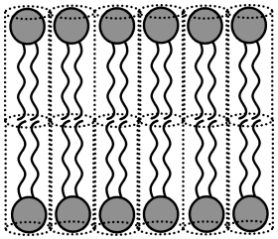
Fluid

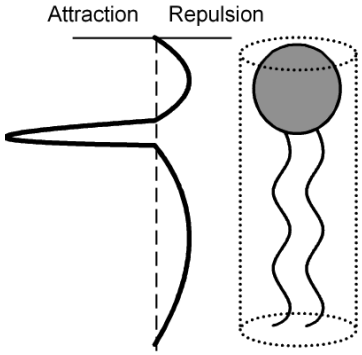




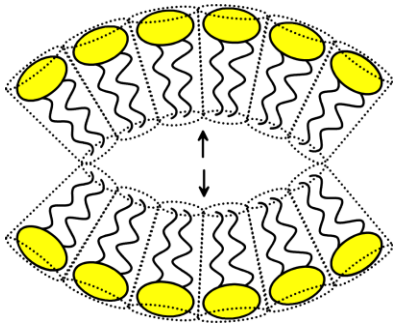
Images from Eric Martz using RasMol, structures from: Heller et al. 1993. *J Phys Chem* 97:8343-8360

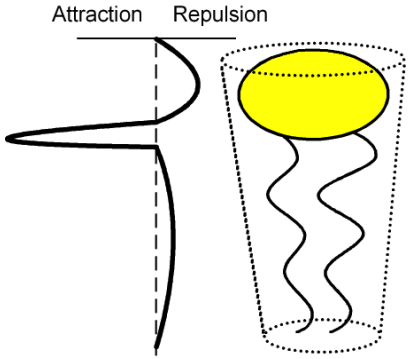
Lipids – shape



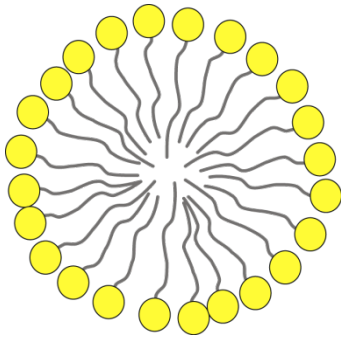


Positive intrinsic curvature

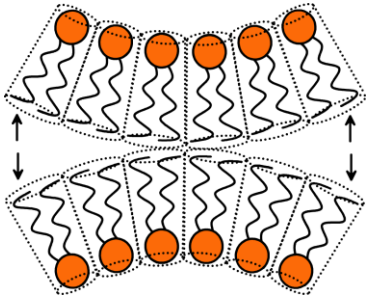


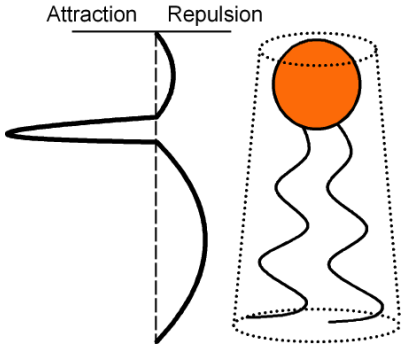


Micelle

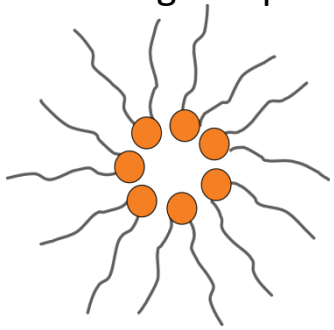


Negative intrinsic curvature

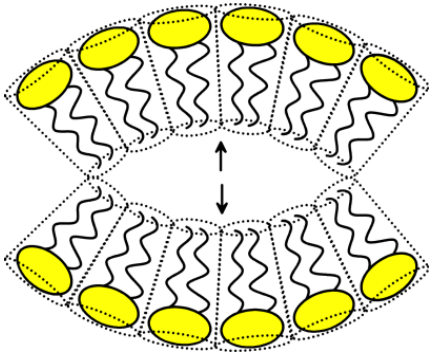


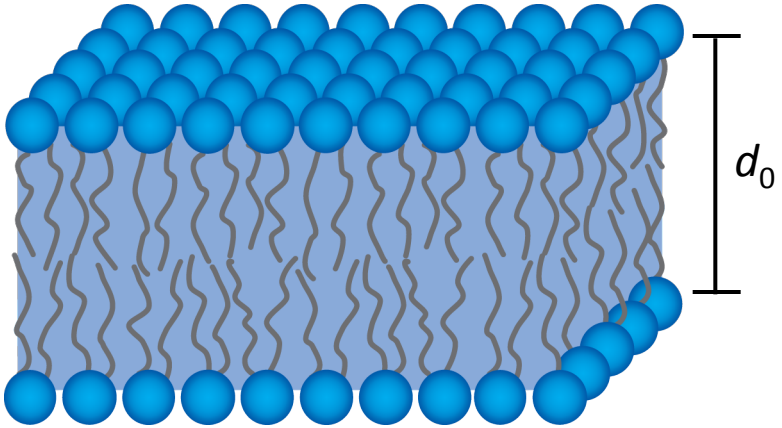


Inverted hexagonal phase



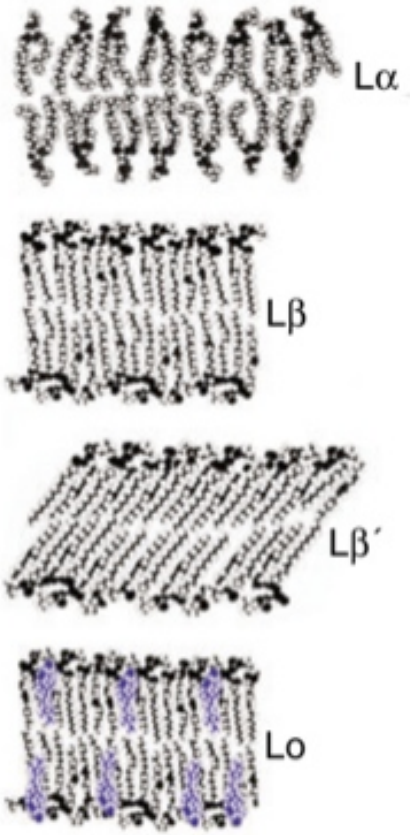
Lipids – properties

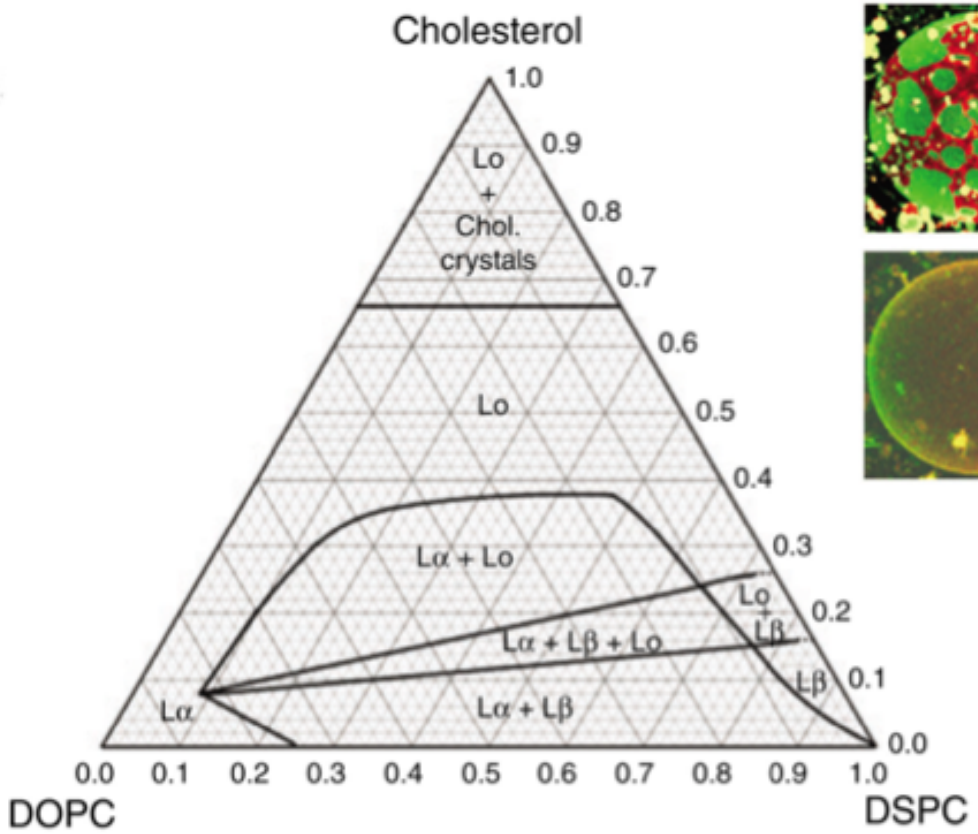


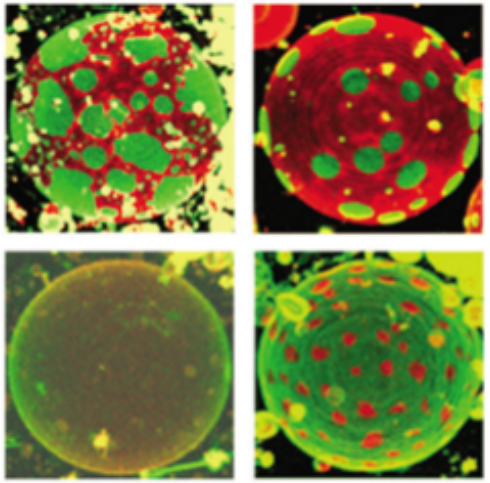


- Intrinsic lipid curvature (c_0)
- Actual curvature (c)
- Hydrophobic thickness (d_0)
- Area compression-expansion modulus (K_a)
- Splay-distortion modulus (K_c)
- Fluidity
- Diffusion
- Area per lipid
- Order parameter
- Surface tension
- Acyl chain packing
- Lateral pressure profile
- Lipid packing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

Lipids – “rafts” / domains / phases



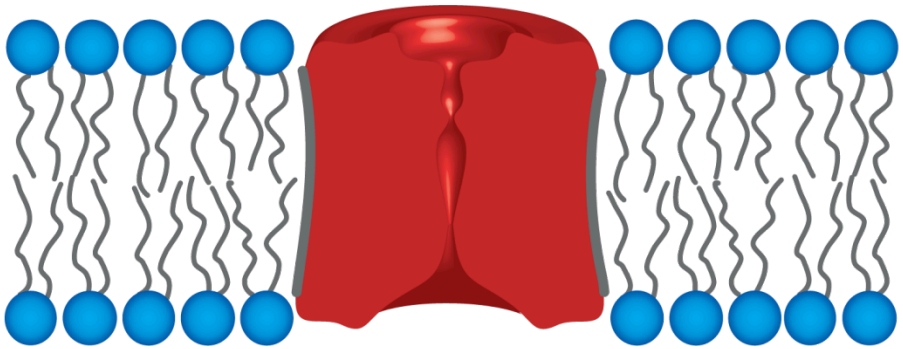


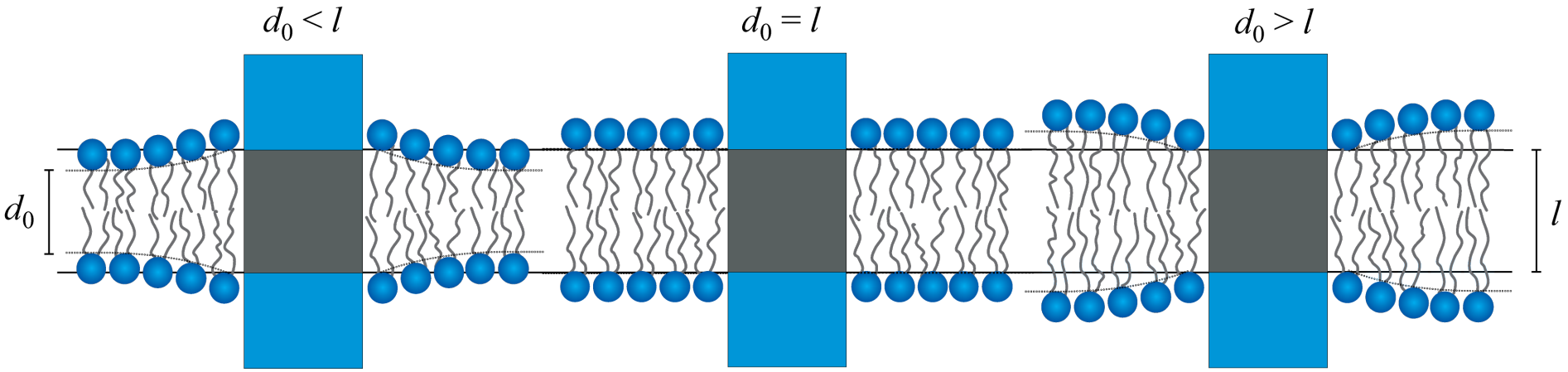


Feigenson, G.W. 2006. Phase behavior of lipid mixtures. Nat. Chem. Biol. 2: 560–563.

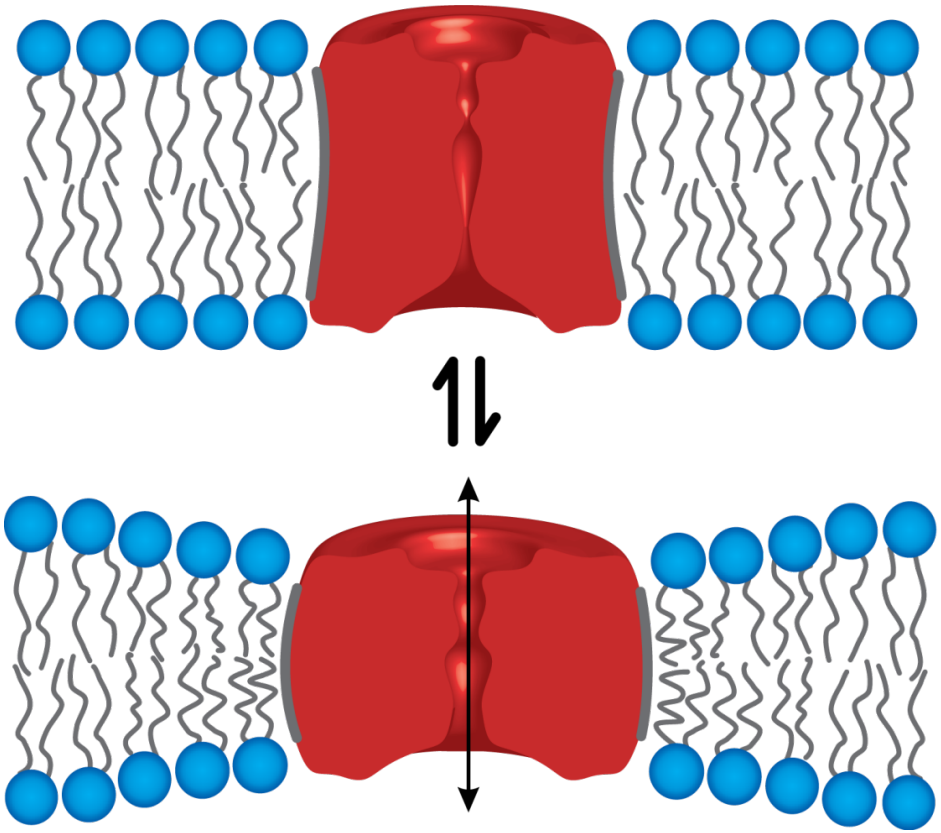
Lipids – bilayer/protein interactions

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

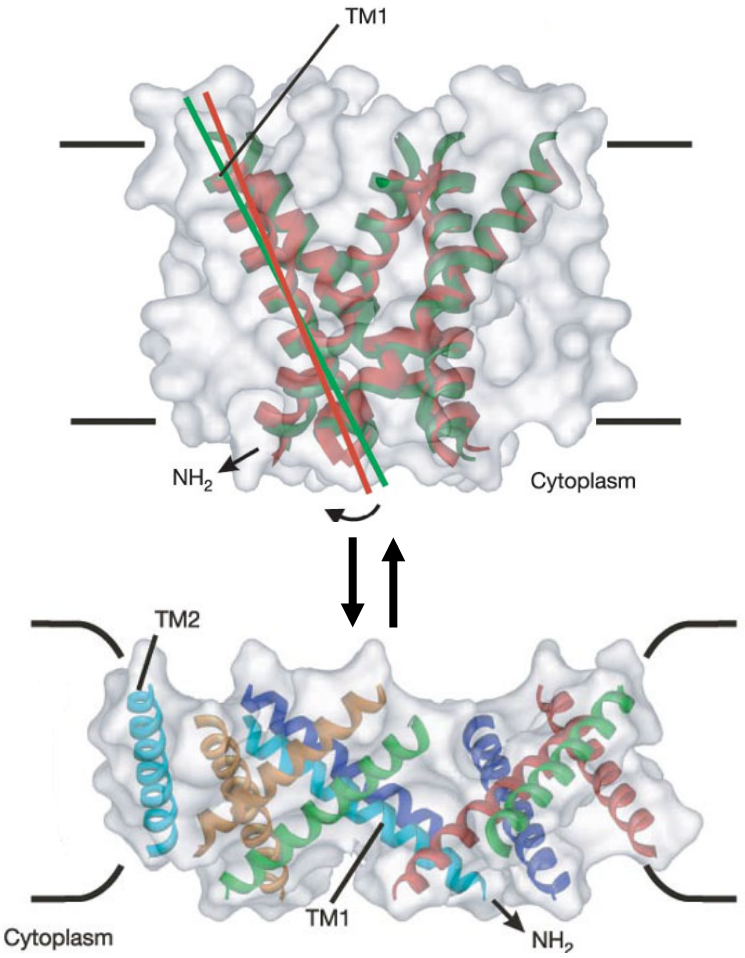




Lipids – bilayer/protein interactions



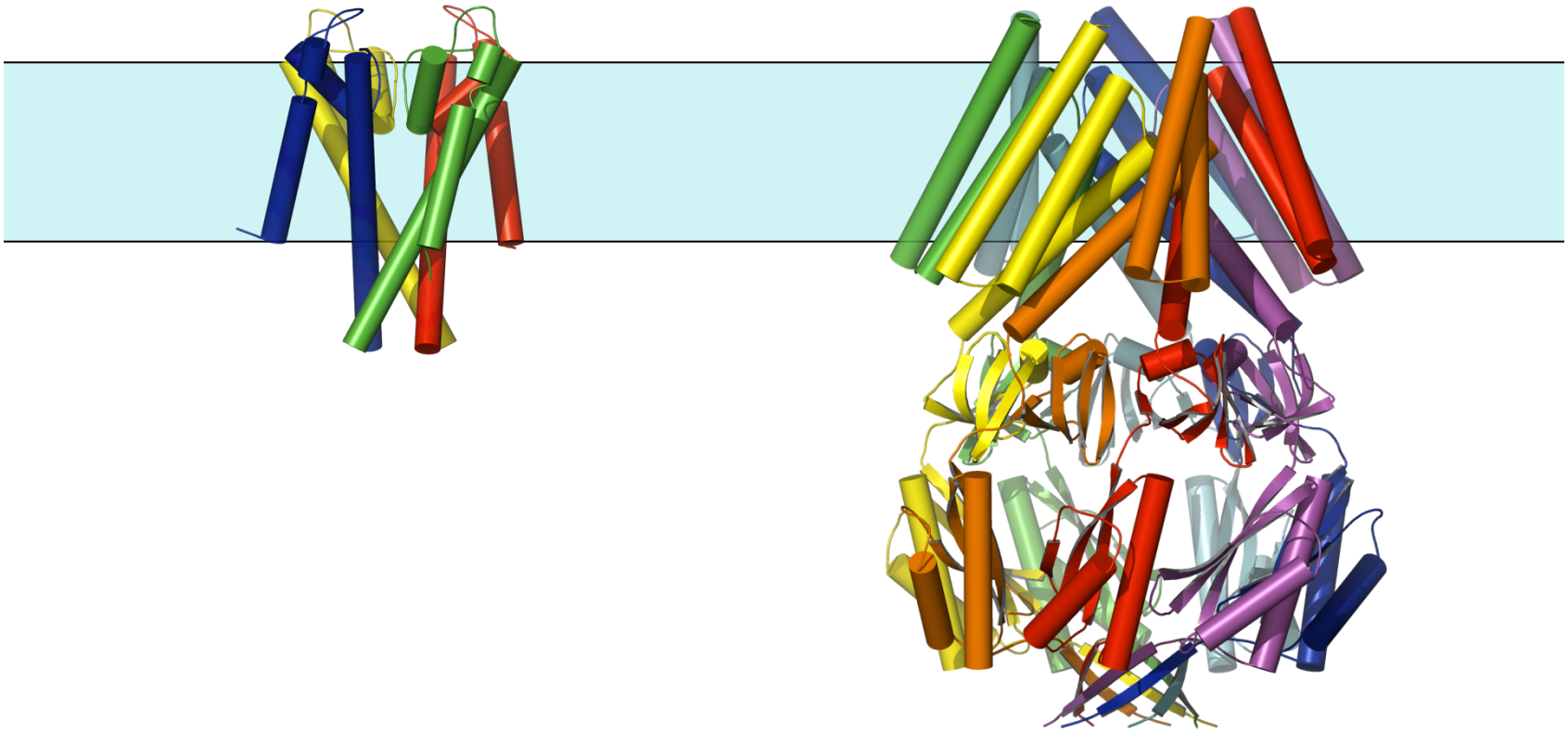
MscL channel



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

Lipids – bilayer/protein interactions

KcsA channel



Closed

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

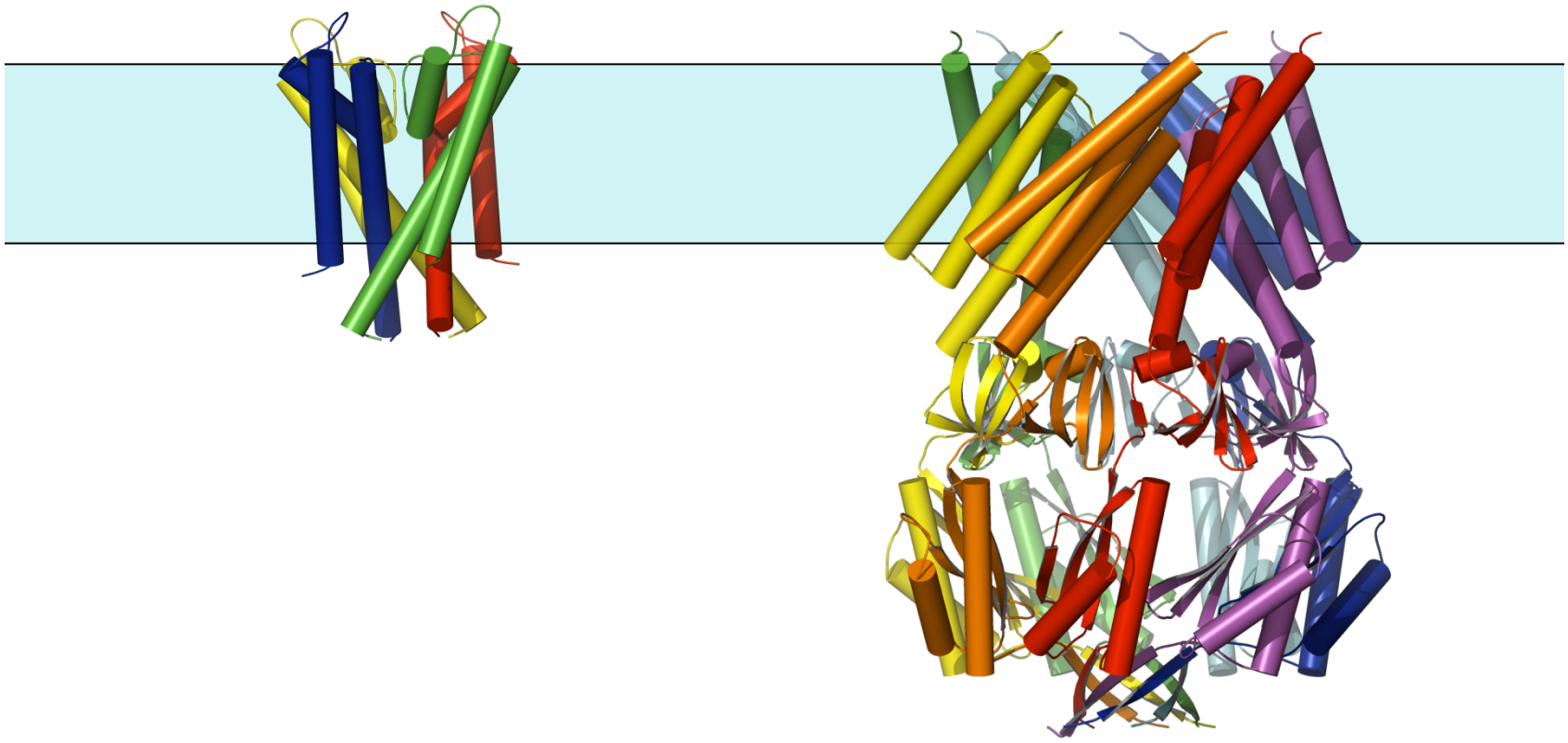
MscS channel

Closed

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

Lipids – bilayer/protein interactions

KcsA channel



Open

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

MscS channel

Open

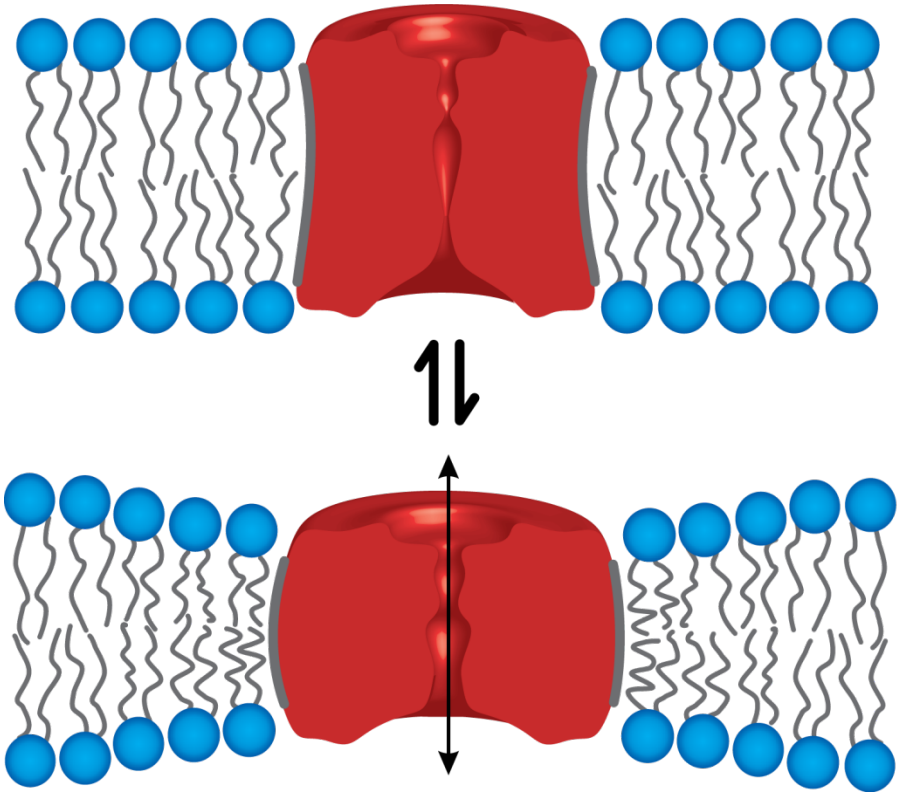
Bass et al. 2002. *Science 298*:1582-1587 and
Wang et al. 2008. *Science 321*:1179-1183

Lipids – bilayer/protein interactions

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

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

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



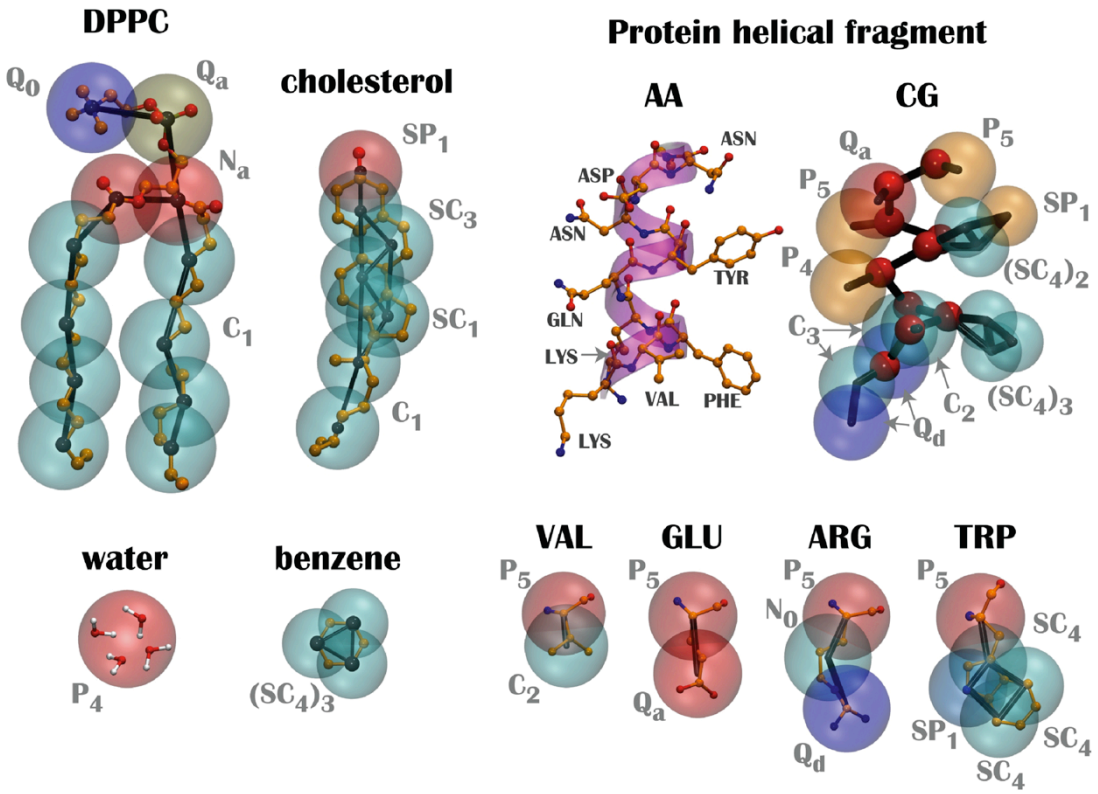
Inactive (Closed) **A**

Active (Open) **B**

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



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.

Lipidome – new lipids website

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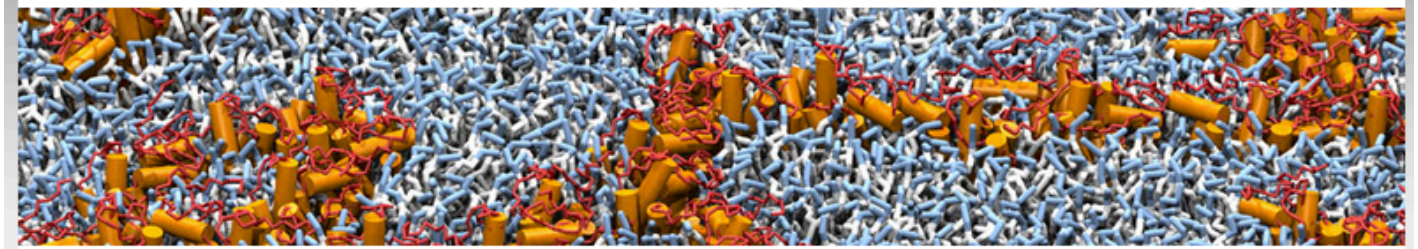
Martini

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)
    - Phosphatidylinositols
    - Glycerols
    - Lysophosphatidylcholine (LPC)
    - Sphingomyelin (SM)
    - Ceramide (CER)
    - 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 .itp files can be accessed in the Collection table bellow 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 schema 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. Tieleman, S.J. Marrink.** *Computational lipidomics with insane: 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@rug.nl or Helgi I. Ingolfsson h.i.ingolfsson@rug.nl.

Phosphatidylcholine (PC)

DTPC	di-C08:0-C10:0 PC (DTPC)	itp
DLPC	di-C12:0-C14:0 PC (DLPC)	itp
DPPC	di-C16:0-C18:0 PC (DPPC)	itp
DBPC	di-C20:0-C22:0 PC (DBPC)	itp
DXPC	di-C24:0-C26:0 PC (DXPC)	itp

Lipidome – new lipids website

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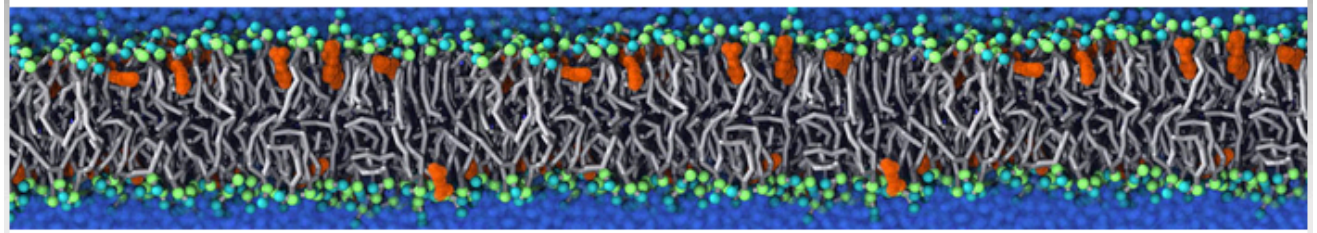
Martini

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
  - DNA
- Example applications
- Tools

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Martini topology

Lipids -> PC -> DOPC

Description:

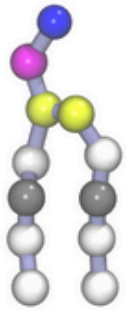
A general model phosphatidylcholine (PC) lipid corresponding to atomistic e.g. C16:1(9c), C18:1(9c) dioleoyl (DOPC) tails.

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/jp036508g
- S.J. Marrink, H.J. Risselada, S. Yefimov, D.P. Tieleman, A.H. de Vries. The MARTINI force field: coarse grained model forbiomolecular simulations. JPC-B, 111:7812-7824, 2007. doi:10.1021/jp071097f
- T.A. Wassenaar, H.I. Ingolfsson, R.A. Bockmann, D.P. Tieleman, S.J. Marrink. Computational lipidomics with insane: a versatiletool for generating custom membranes for molecular simulations. JCTC, 150410125128004, 2015. doi:10.1021/acs.jctc.5b00209



Topology files:

martini_v2.0_DOPC_02.itp	current
martini_v2.0_DOPC_01.itp	old x5 bead oleoyl tail model

Mapping files:

Coordinate files:

DOPC-em.gro	Single lipid coordinate file

Lipidome – 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 – new/improved lipids

- **Improved Cholesterol**

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

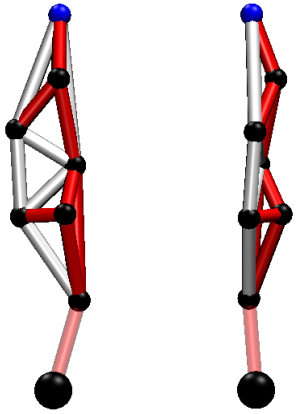
- **Gangliosides**

GM1 was stabilized using virtual sites and altered headgroup linking. GM3 created from GM1.

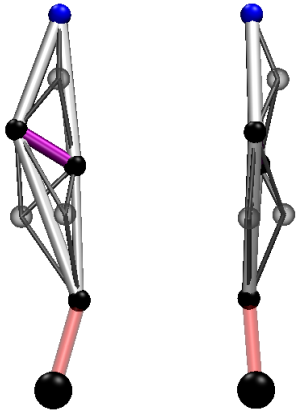
- **Phosphatidylinositol**

Stability of PI and PIP2 was improved and PIP1 and PIP3 created.

Old cholesterol



New cholesterol



Lipidome – new/improved lipids

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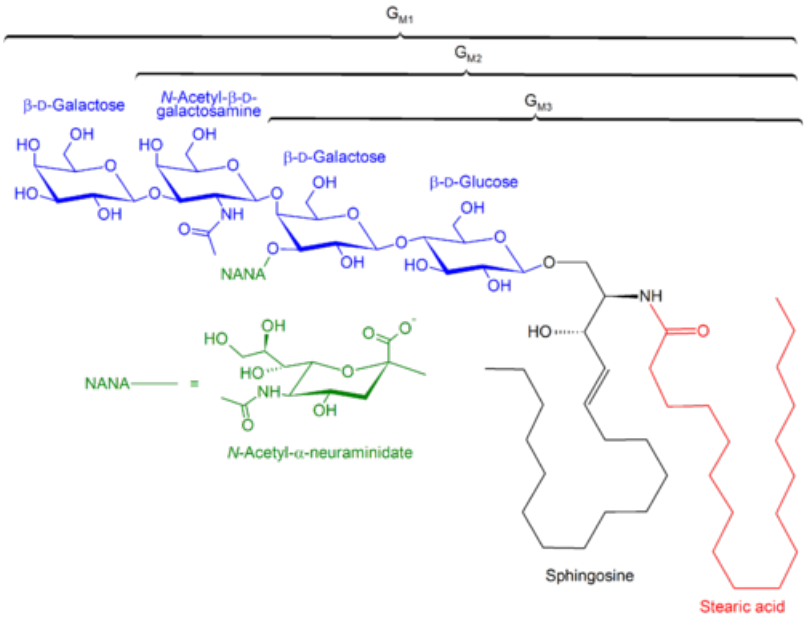

http://en.wikipedia.org/wiki/GM3

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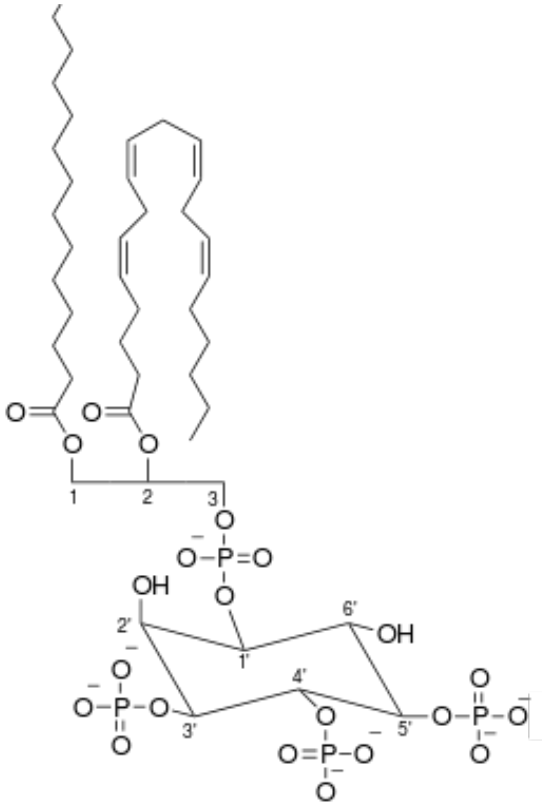

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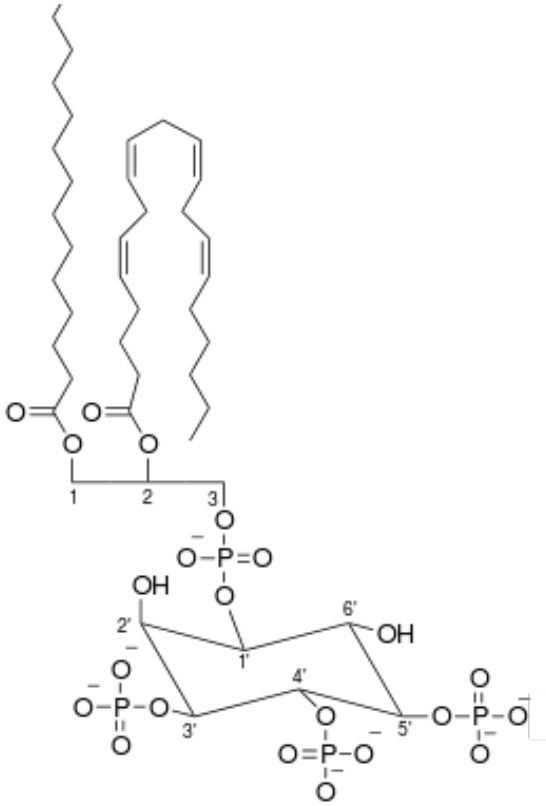

Lipid charge ???

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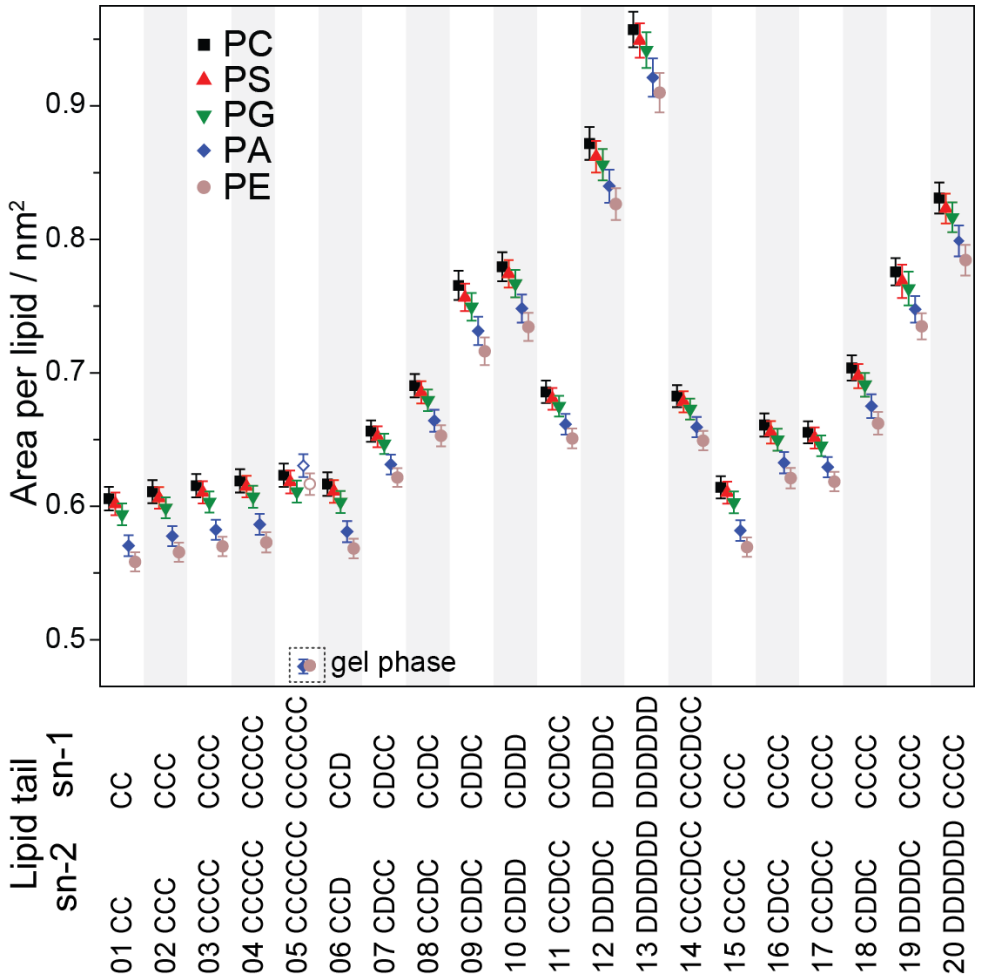
Lipidome – Martini lipidomics

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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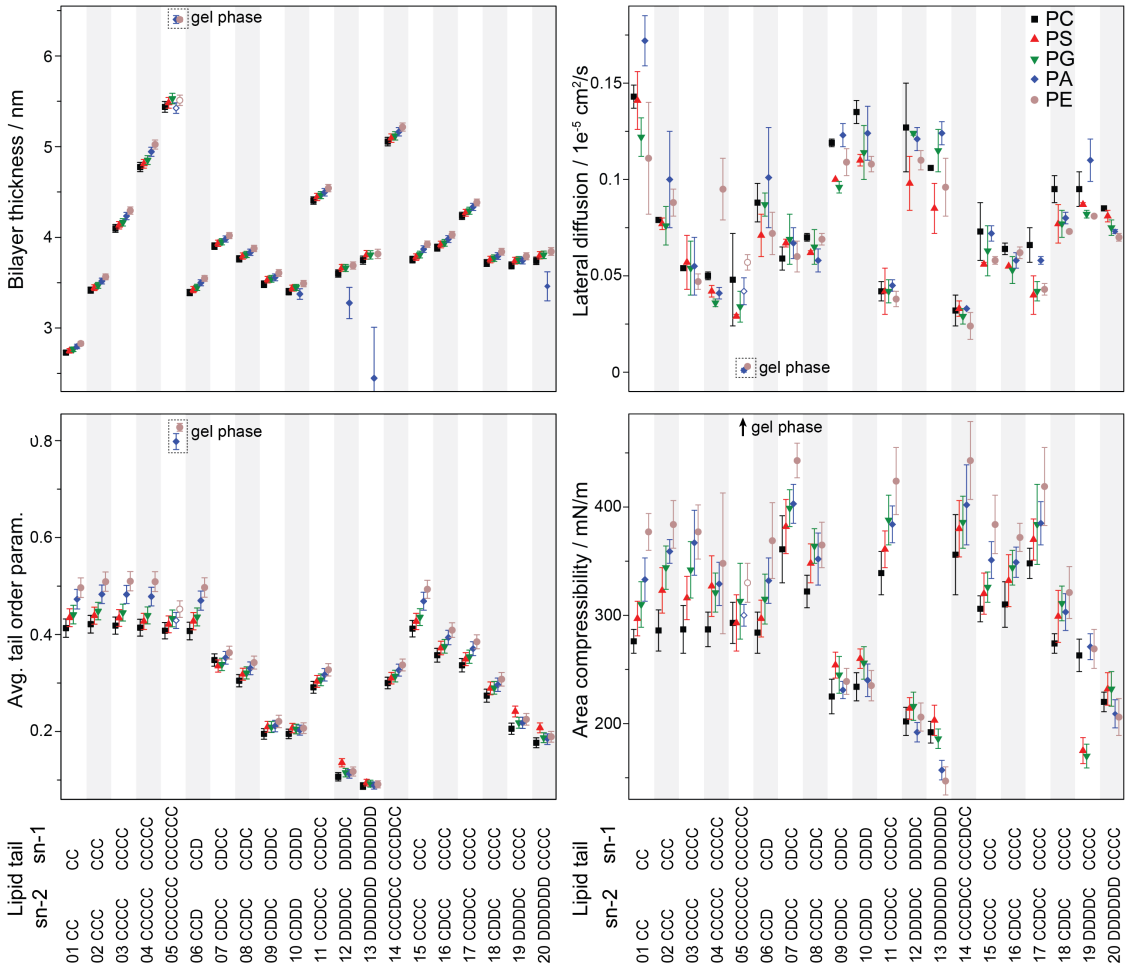

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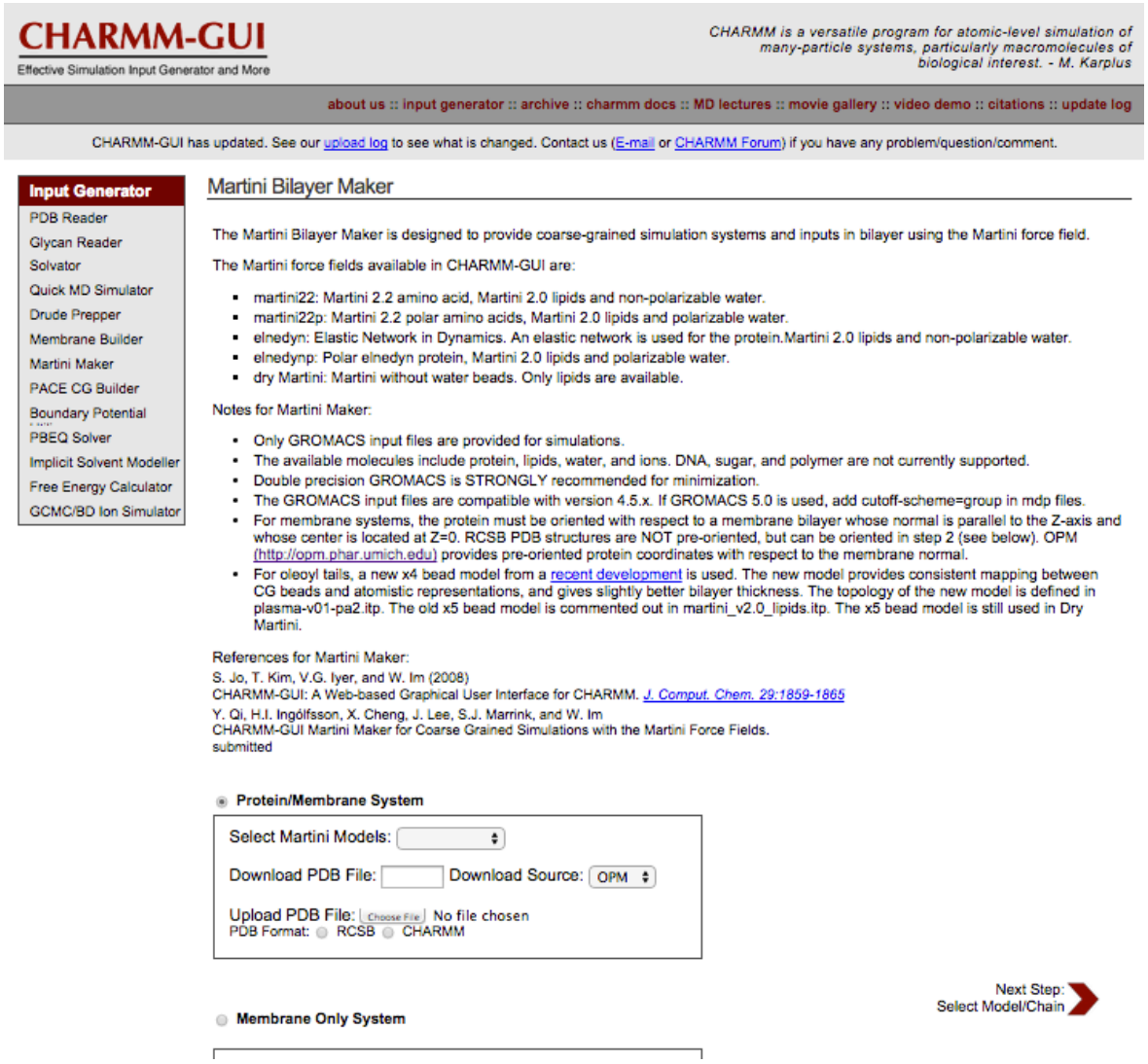
Building bilayers – CHARMM-GUI *Martini Maker*

Solution, Micelle, Vesicle, and Bilayer Builders for Martini



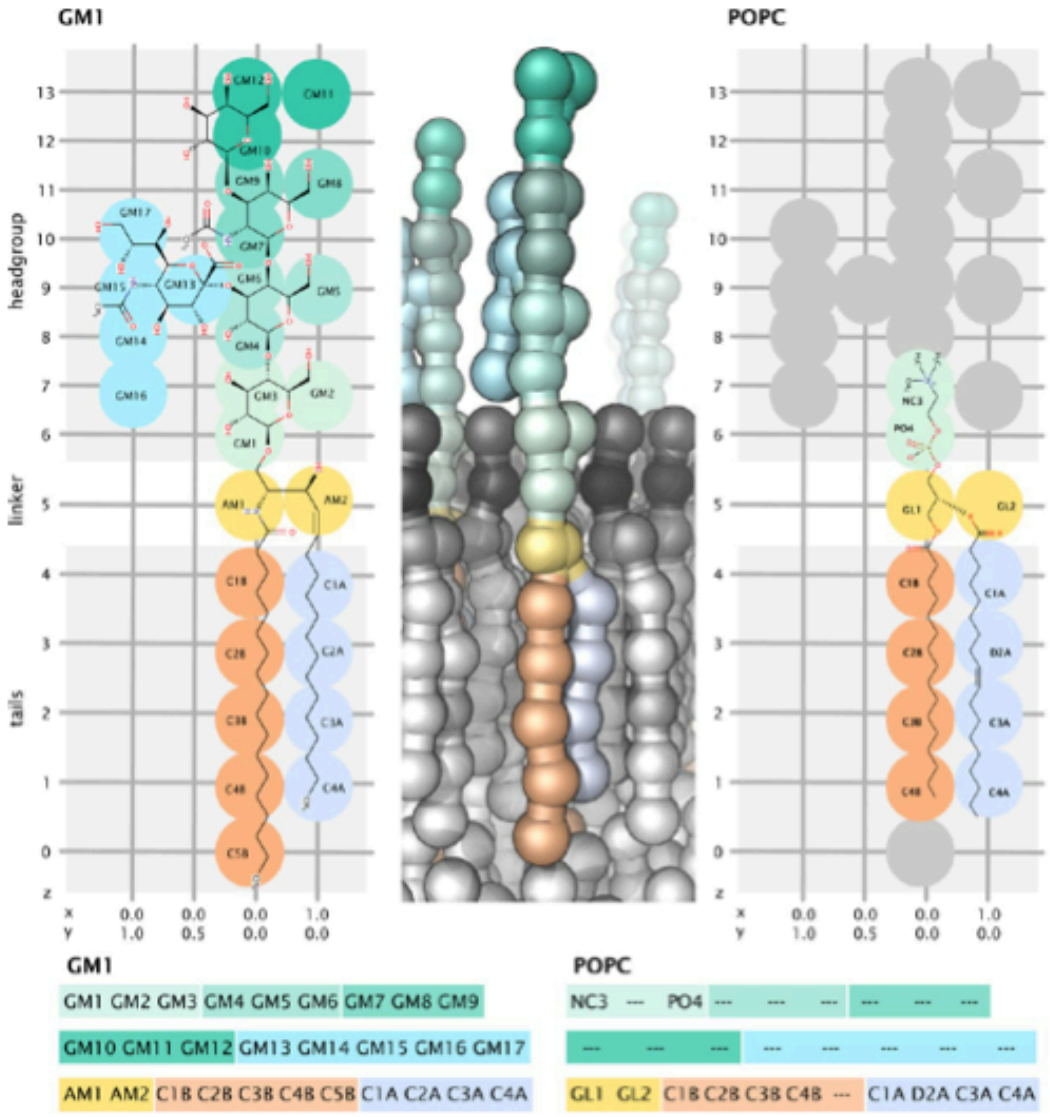
Yifei Qi,
Xi Cheng,
Jumin Lee, and
Wonpil Im

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**,

Building bilayers – *insane*

INSert membrANE

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



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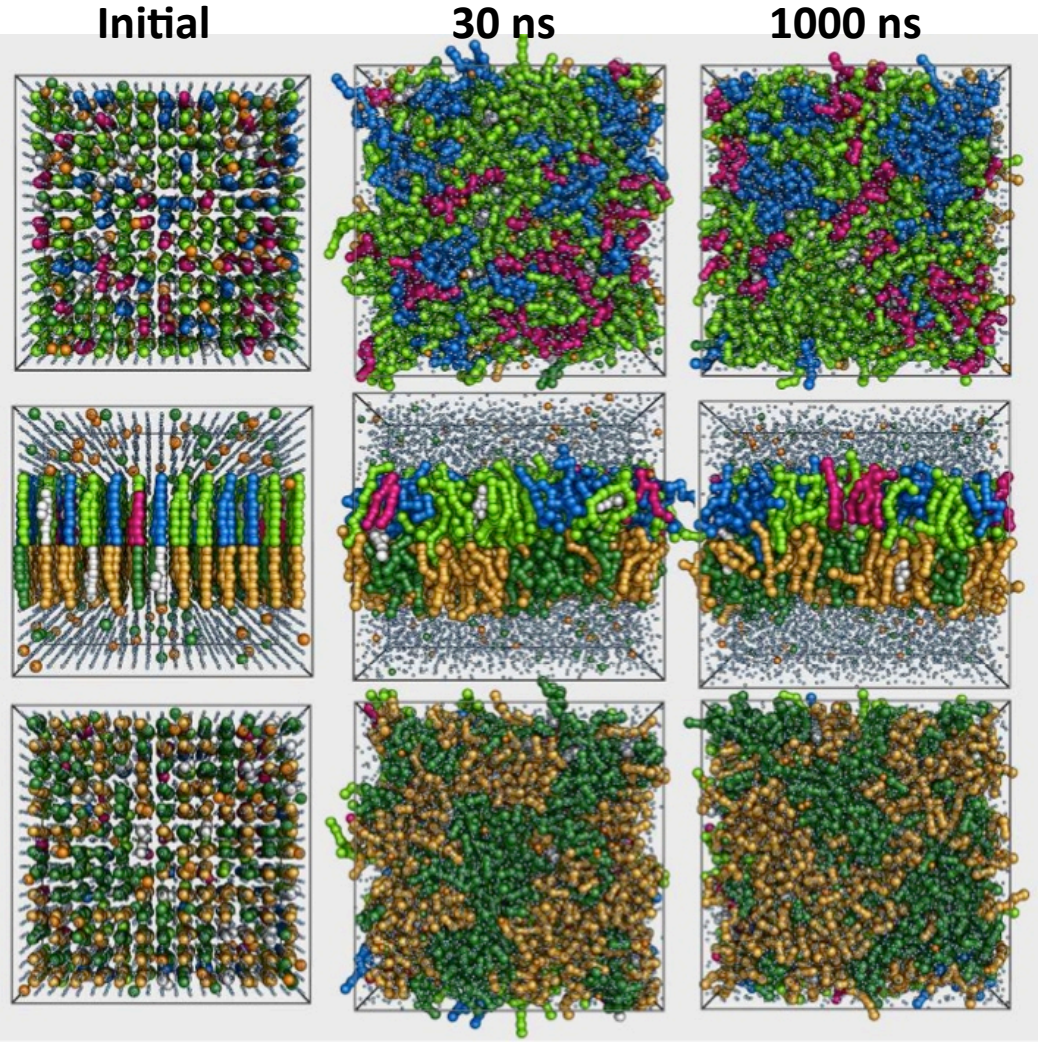
Asymmetric DAPC:DOPC:DLPC:cholesterol vs. DPPC:DIPC:cholesterol bilayer



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Calculating bilayer properties

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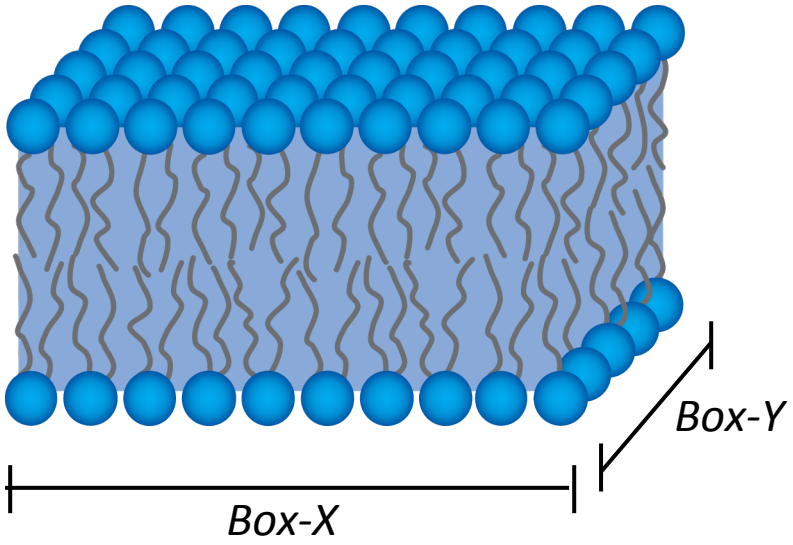

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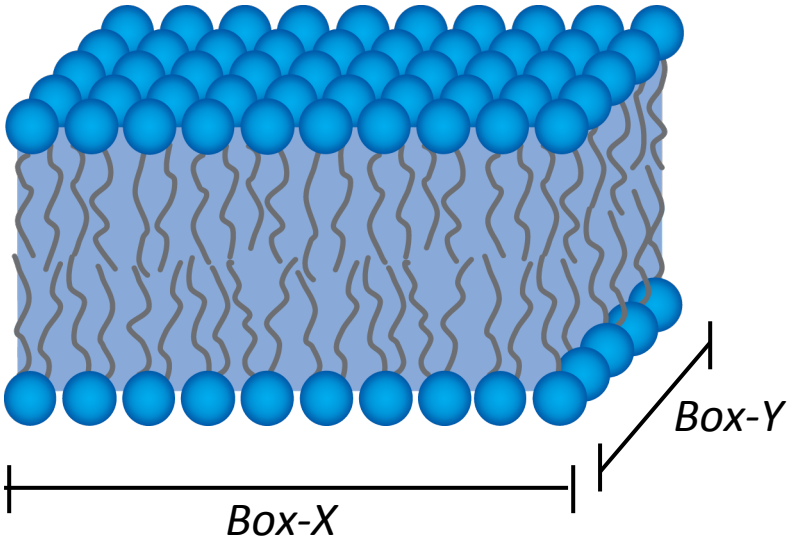

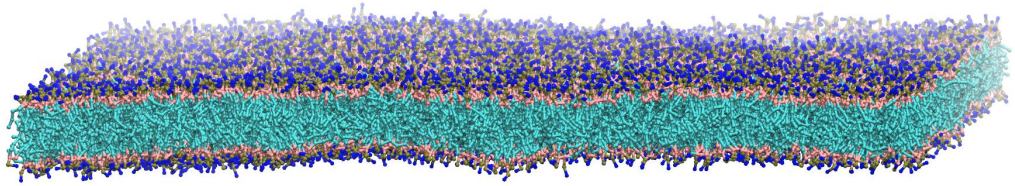

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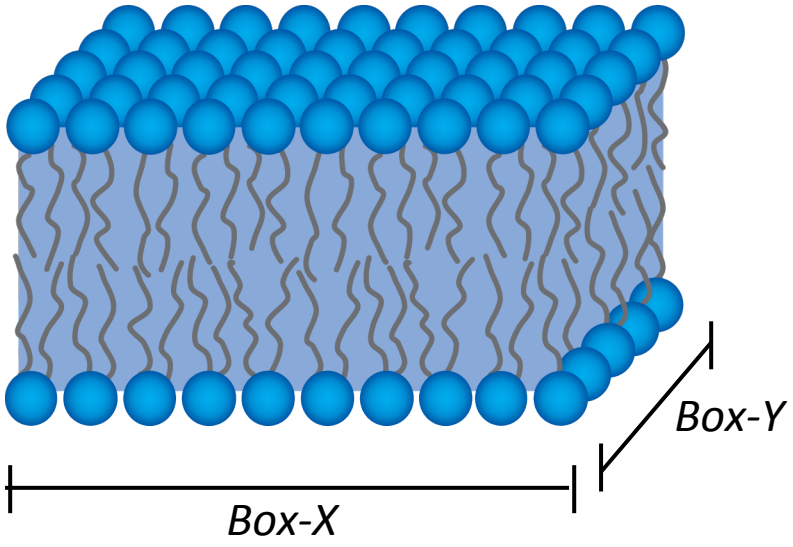

$$K_A = k_B T \frac{\langle A \rangle}{N \langle (A - A_0)^2 \rangle}$$

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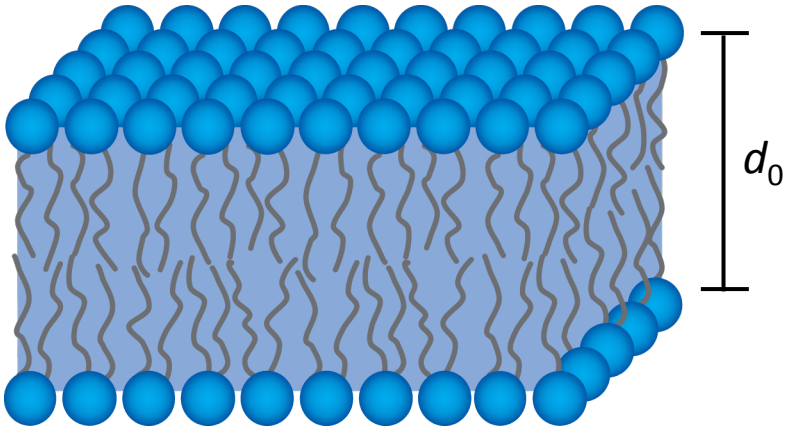

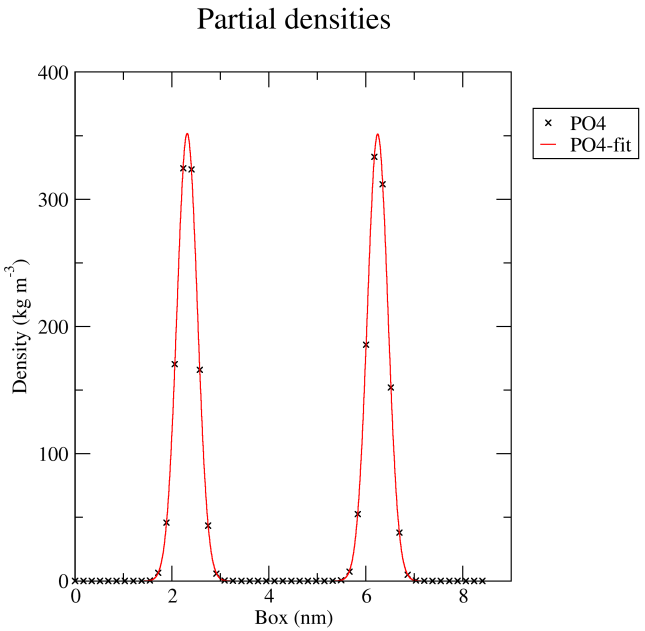

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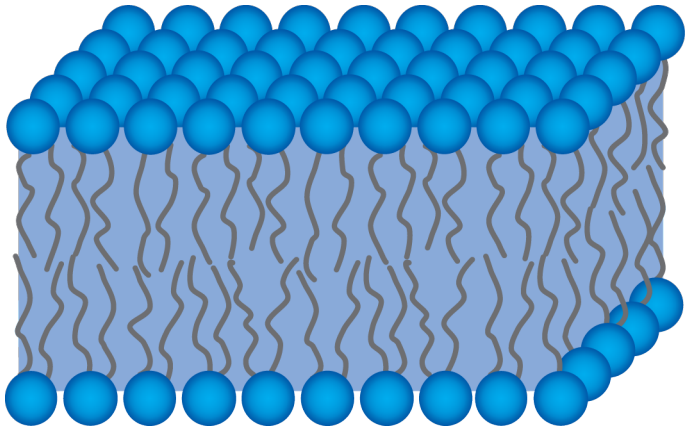

$$S_{seg} = \frac{1}{2}(3\langle \cos^2 \theta \rangle - 1)$$

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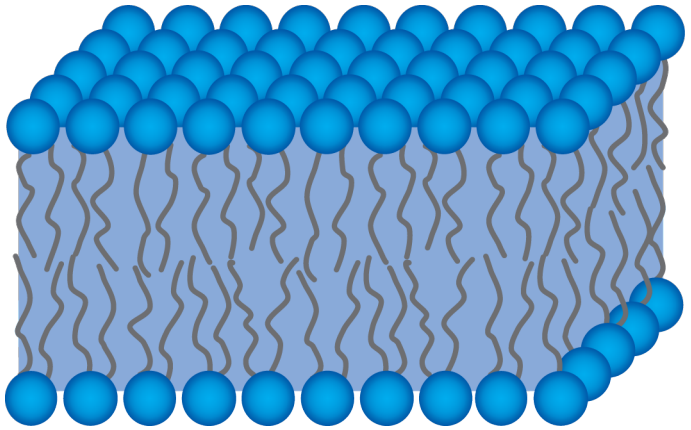

Bending modulus (K)

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

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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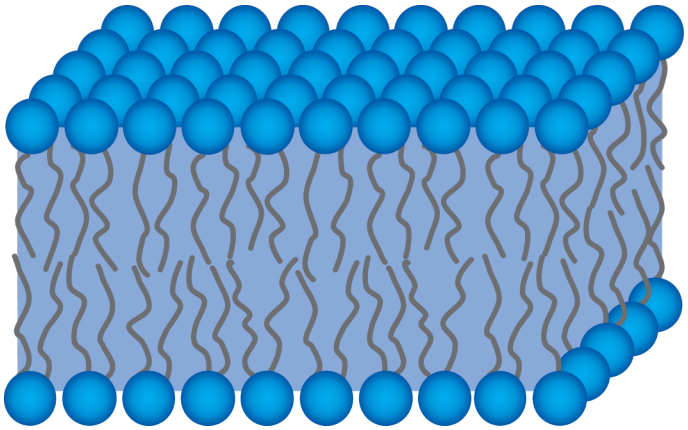

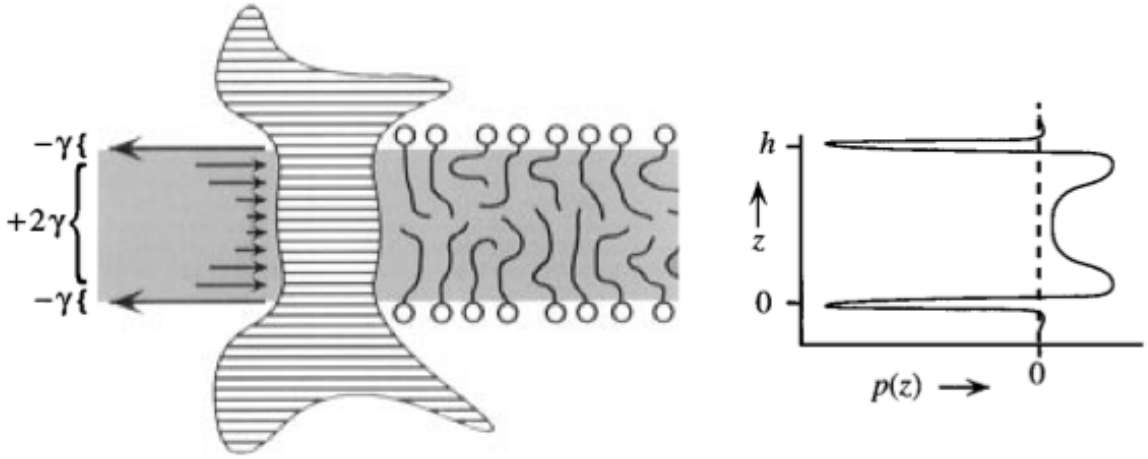

Cantor, R.S. 1997. Lateral Pressures in Cell Membranes: A Mechanism for Modulation of Protein Function. J. Phys. Chem. B. 101: 1723–1725.

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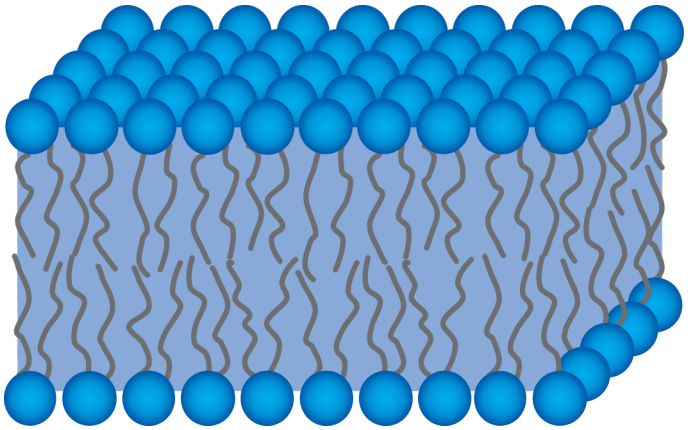

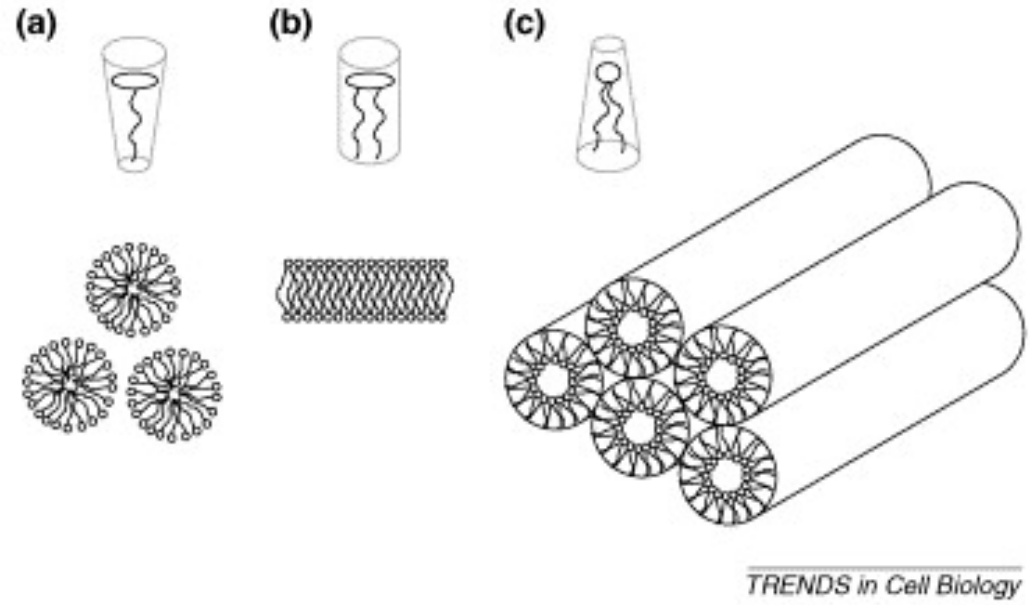

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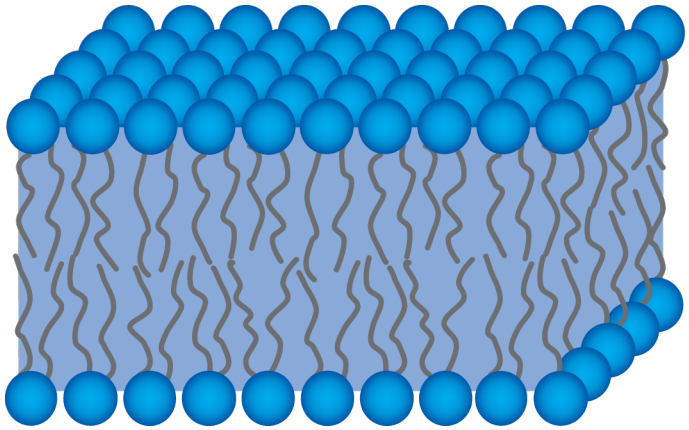

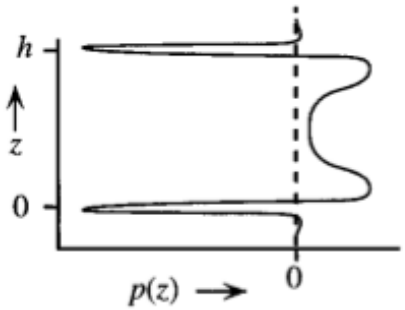

$$\tfrac{1}{2}\Sigma = \int_0^\infty dz\, \sigma_0(z)\,,$$

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

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

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.

Martini Examples – lipid domains

J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
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Disaccharides Impact the Lateral Organization of Lipid Membranes

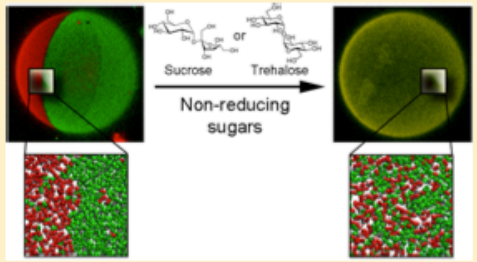
Gemma Moiset,[†] Cesar A. López,[†] Rianne Bartelds,[†] Lukasz Syga,[†] Egon Rijpkema,[†] Abhishek Cukkemane,[‡] Marc Baldus,[‡] Bert Poolman,*[,†] and Siewert J. Marrink*[,†]

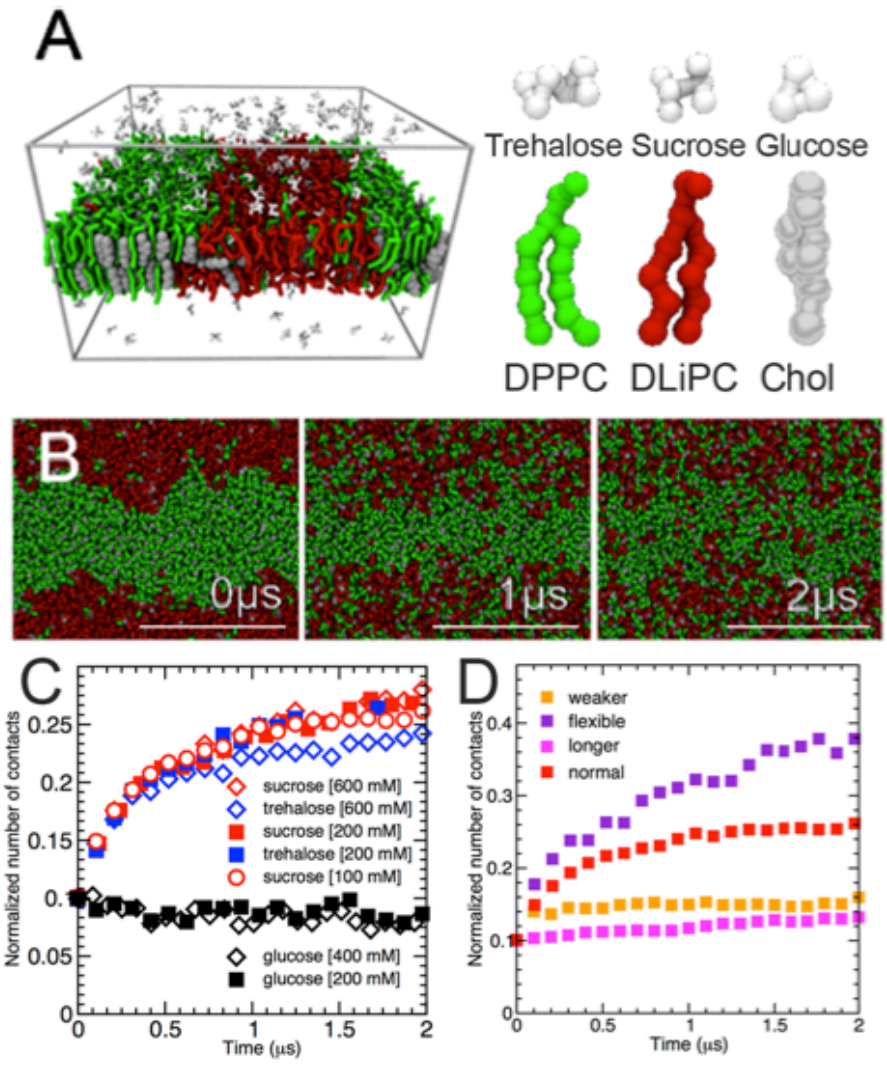
[†]Groningen Biomolecular Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands

[‡]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_o and L_d 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 nonreducing 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. 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

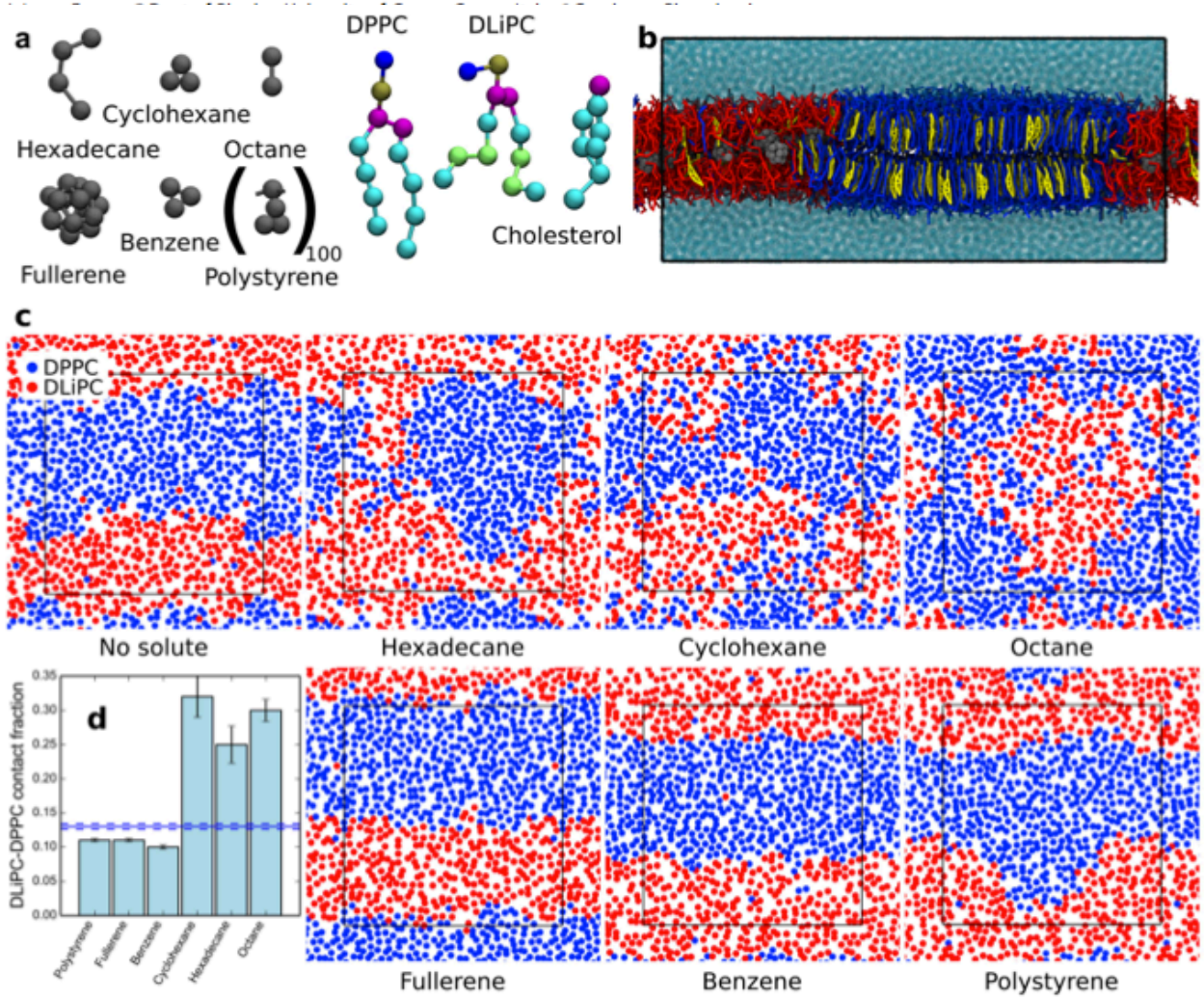
Hydrophobic Compounds Reshape Membrane Domains

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 Lyo
Sciences and Biotechnology Institute and Zernike Institute for Advanc

Abstract

Cell membranes have a complex lateral organizati
which play an essential role in cellular processes suc
membrane domains (e.g., by drugs or lipophilic co



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

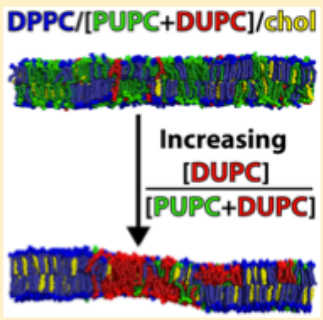
Multiscale Modeling of Four-Component Lipid Mixtures: Domain Composition, Size, Alignment, and Properties of the Phase Interface

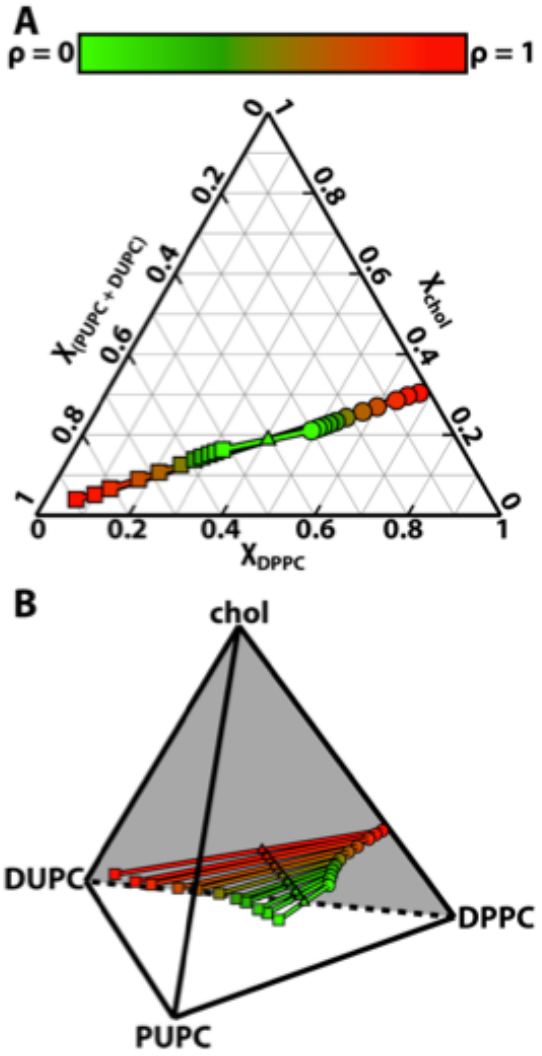
David G. Ackerman and Gerald W. Feigenson*

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 nandomain-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.

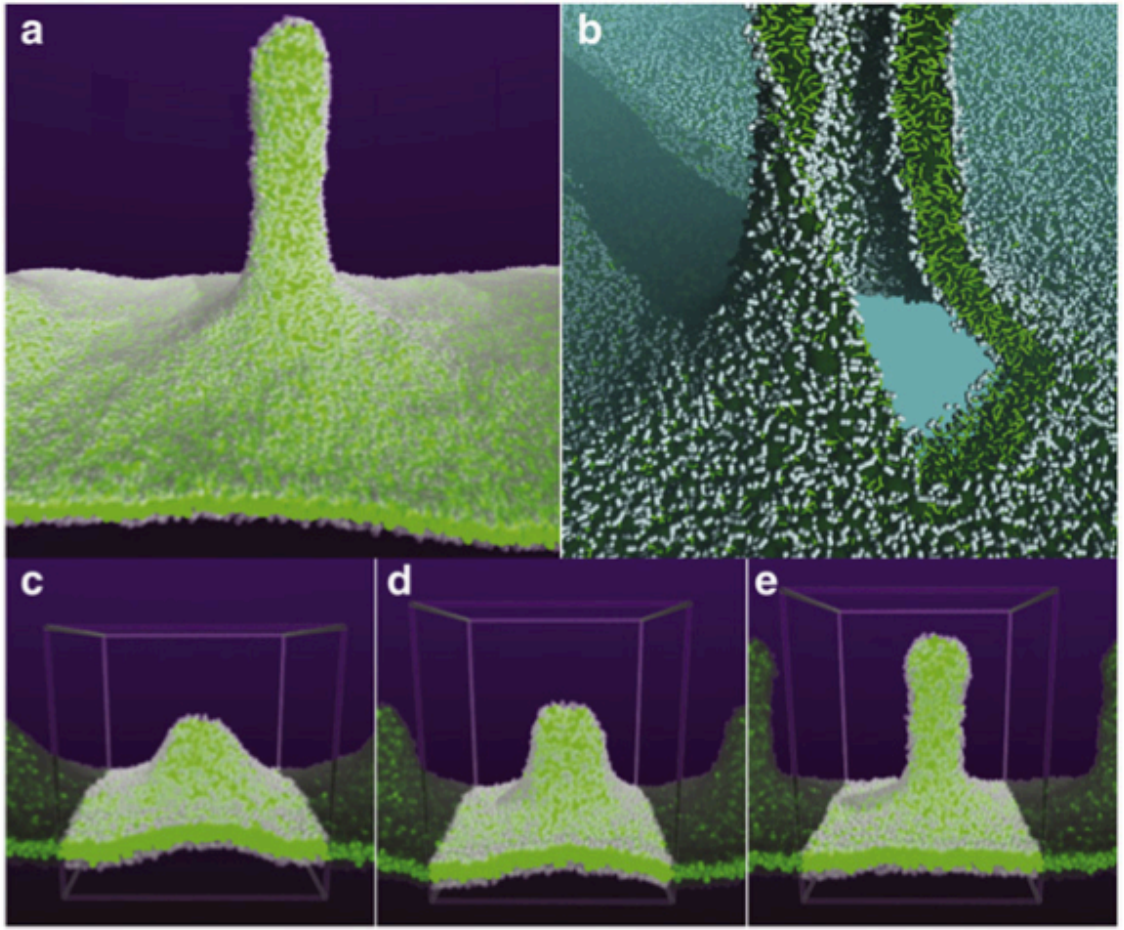
Martini Examples – tethers

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 Informatics, University of Calgary, Calgary, Alberta, Canada; and [§]Groningen Biomolecular Sciences and Biotechnology Institute and [¶]Zernike Institute for Advanced Materials, University of Groningen, Groningen, The Netherlands

ABSTRACT Membrane tethers are nanotubes formed by a
provide an experimental window on lipid properties. Tether
theoretical models, but their molecular structure remains
used molecular dynamics simulations to obtain molecular-l
component lipid bilayers by application of an external force



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

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

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

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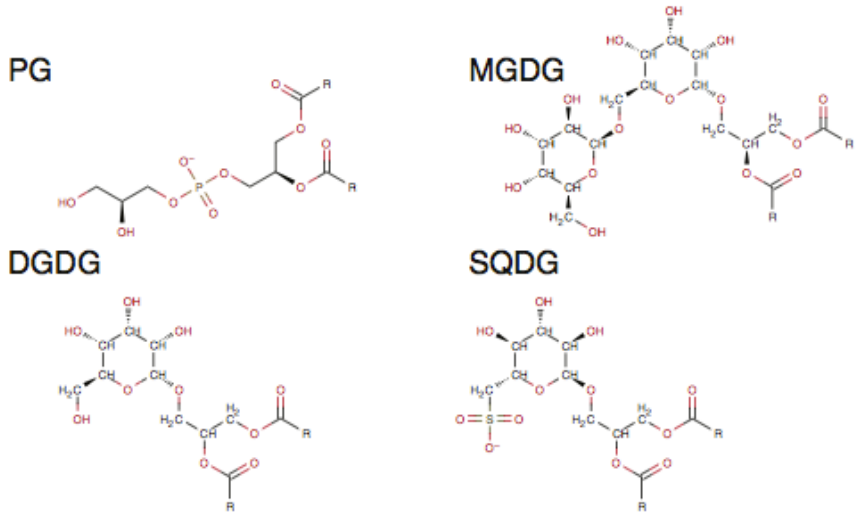
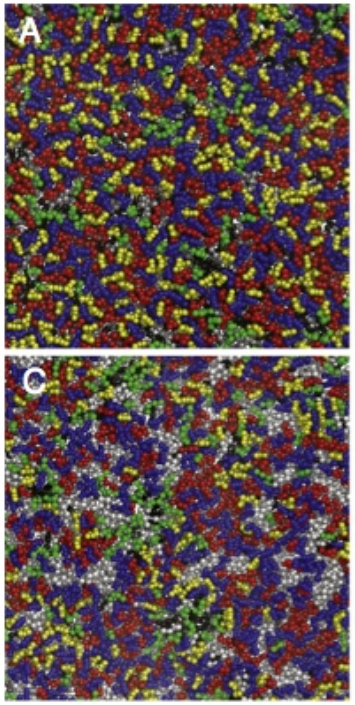




Tail ↓ Head →	*Cyanobacterial membrane* PG	DGDG	MGDG	SQDG	*Plant membrane* PG	DGDG	MGDG	SQDG
16:0	47.9	43.6	45.1	62.0	15.6	6.7	3.1	49.2
18:0	8.9	2.5	3.9	8.0	0.4	0.6	0.6	2.3
saturated	(50)	(50)	(50)	(80)	(16)	(8)	(6)	(50)
16:1(7)	nd	nd	nd	nd	nd	0.2	0.3	1.4
16:1(9)	10.7	15.1	15.5	3.9	nd	nd	nd	nd
18:1(9)	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

OPEN ACCESS Freely available online

PLOS | COMPUTATIONAL BIOLOGY

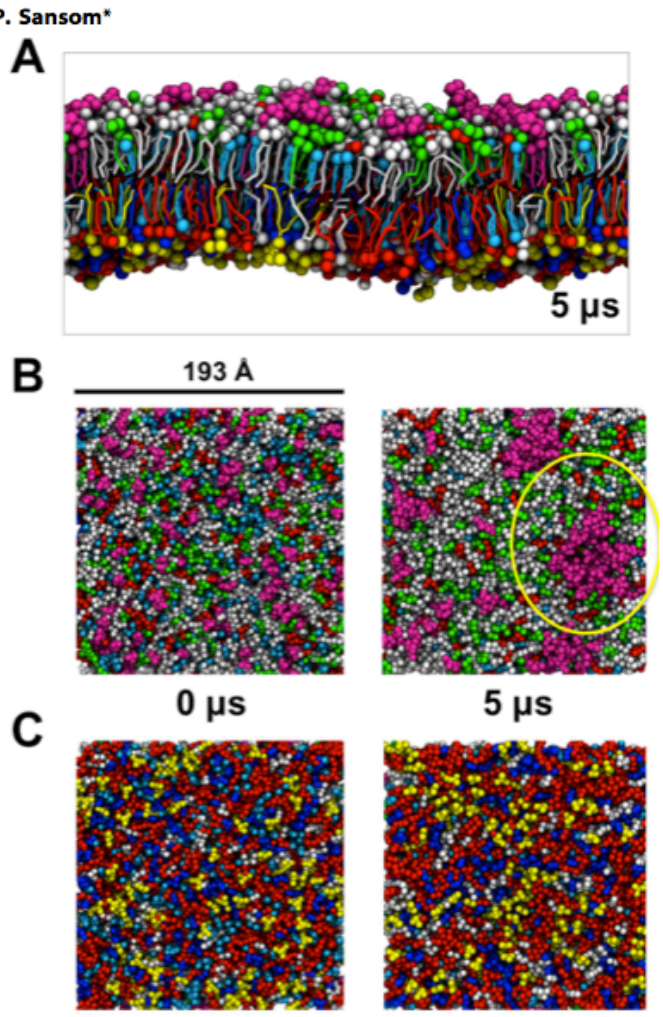
Lipid Clustering Correlates with Membrane Curvature as Revealed by Molecular Simulations of Complex Lipid Bilayers

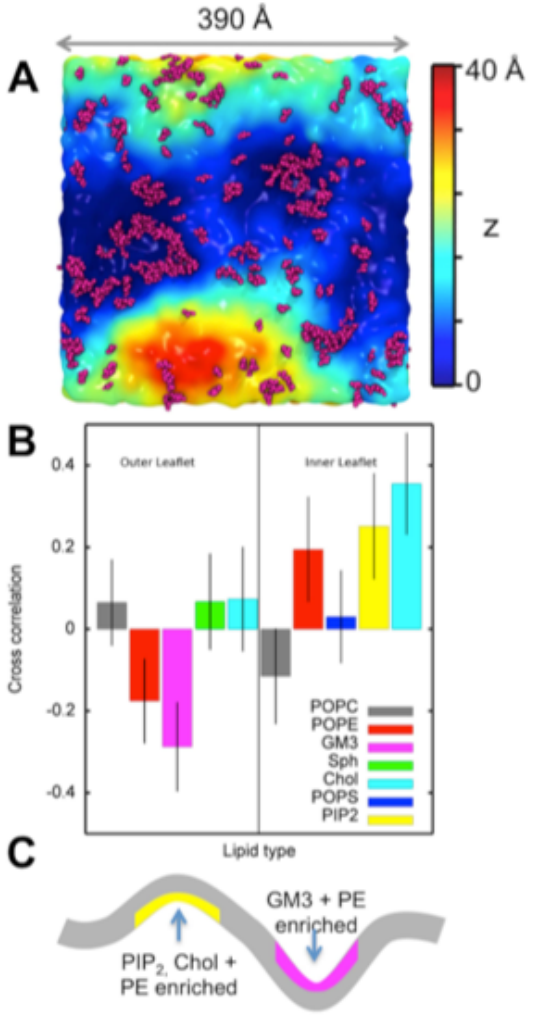
Heidi Koldsø, David Shorthouse, Jean Hélie, Mark S. P. Sansom*

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

Abstract

Cell membranes are complex multicomponent systems, which composition. To date, most molecular simulations have focussed





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 Compu Biol. 10: e1003911.

PM – plasma membranes

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*[,†]

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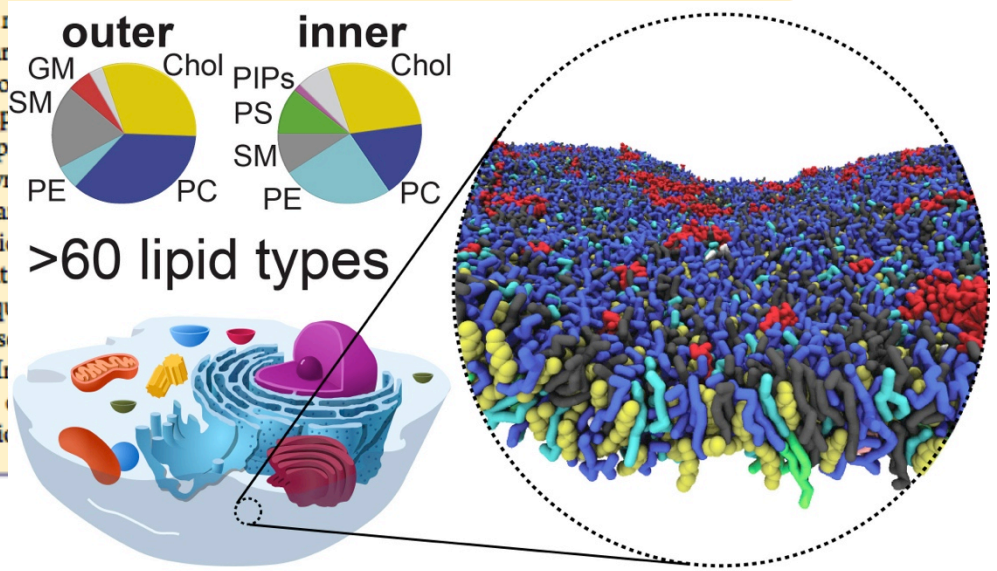
[‡]Computational Biology, Department of Biology, University of Erlangen-Nürnberg, Staudtstr. 5, 91052 Erlangen, Germany

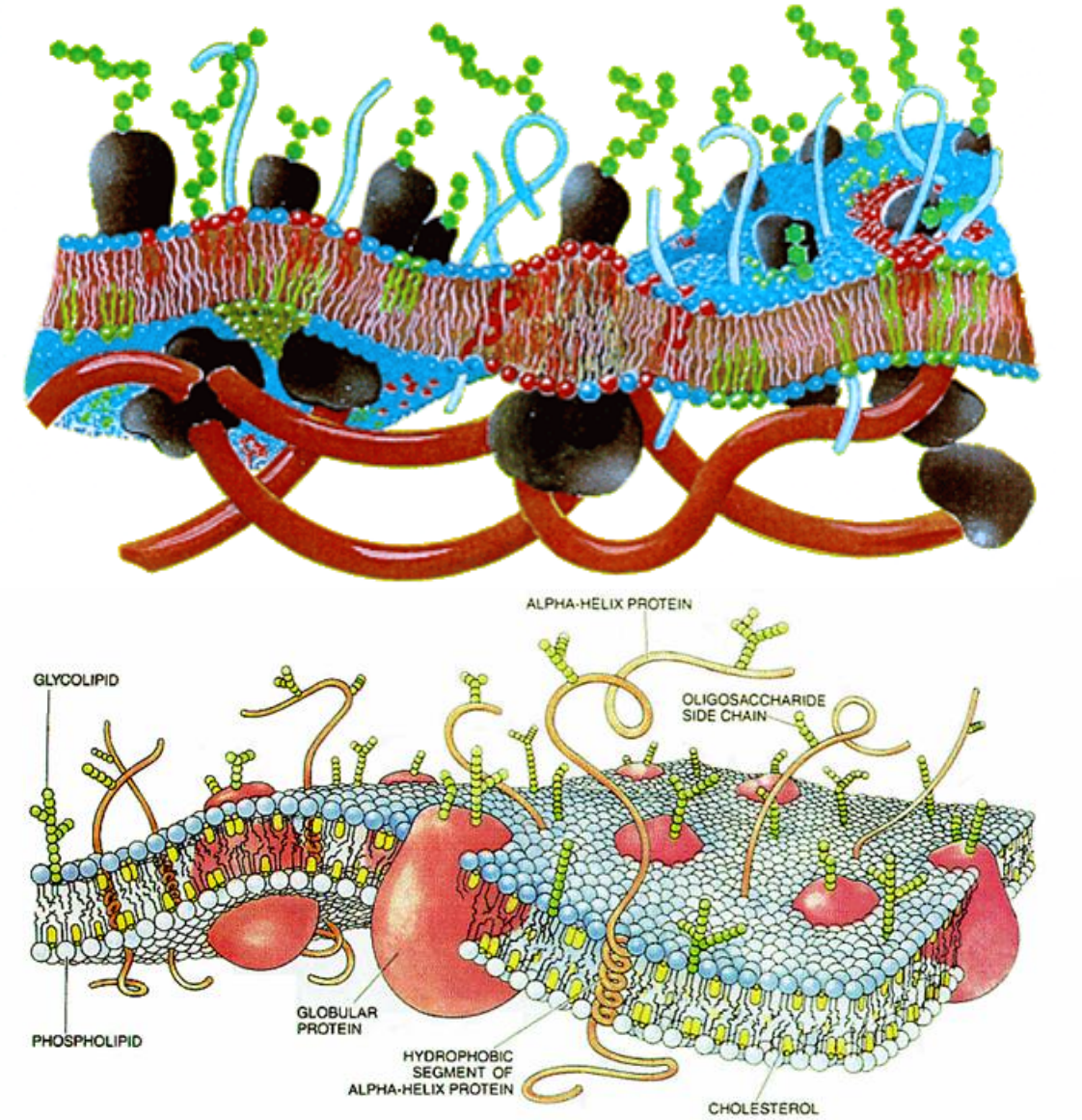
[§]Centre for Molecular Simulation and Department of Biological Sciences, University of Calgary, 2500 University Dr. NW, Calgary, Alberta T2N 1N4, Canada

Supporting Information

ABSTRACT: The detailed organization of cellular r
remains rather elusive. Based on large-scale molecular
simulations, we provide a high-resolution view of the lipid o
of a plasma membrane at an unprecedented level of comp
plasma membrane model consists of 63 different lip
combining 14 types of headgroups and 11 types of tails asy
distributed across the two leaflets, closely mimicking a
mammalian plasma membrane. We observe an enri
cholesterol in the outer leaflet and a general non-ideal lat
of the different lipid species. Transient domains with liq
character form and disappear on the microsecond time s
domains are coupled across the two membrane leaflets. I
leaflet, distinct nanodomains consisting of gangliosides are
leaflet. Our data provide a key view on the lateral organizati



PM – cell envelopes / plasma membranes

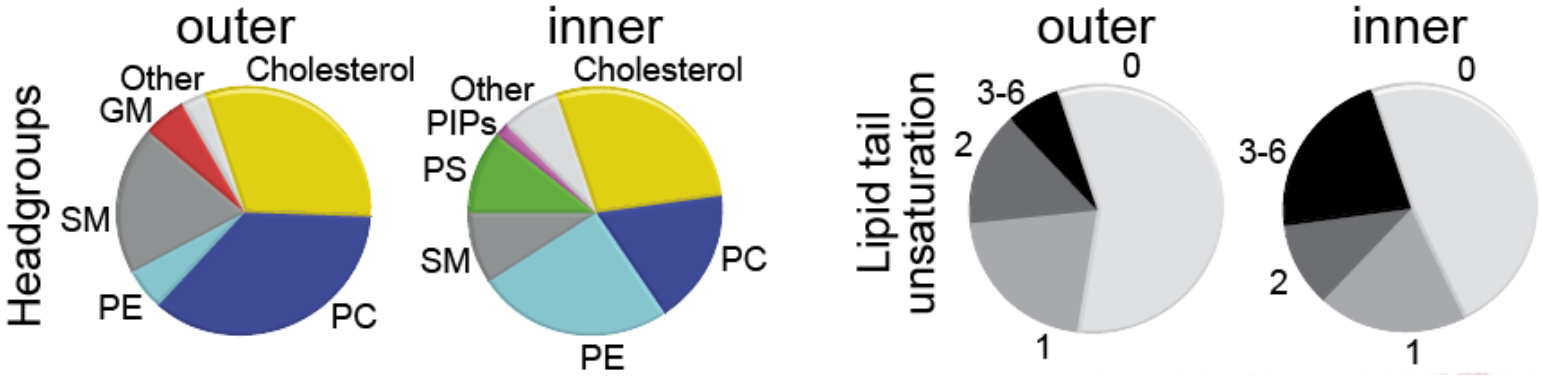


- Hundreds of different lipid species
- Asymmetric leaflet distribution
- Lateral inhomogeneity

Mouritsen OG, Ansersen OS (1998) Do we need a new biomembrane model? In: In search of a new biomembrane model, Mouritsen O G and Andersen O S ed, Biologiske Skrifter, Danish Royal Science Society 49:7–12.

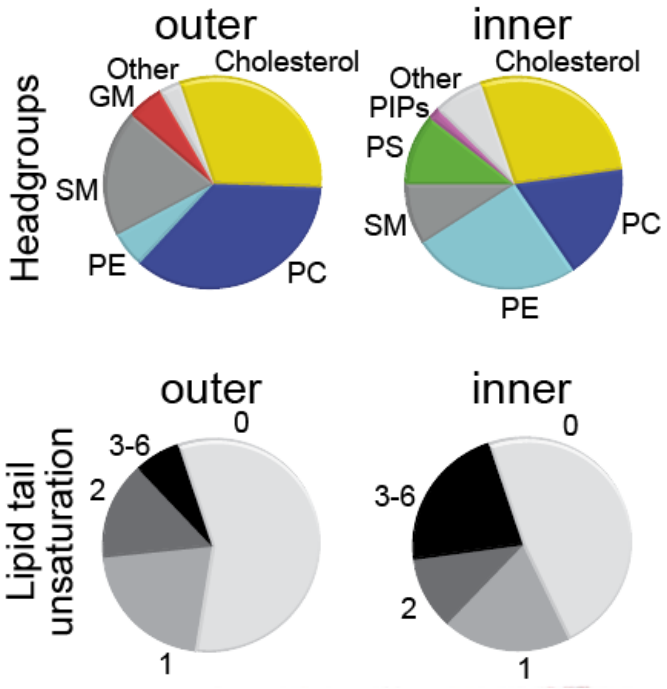
http://en.wikibooks.org/wiki/Biochemistry/Membranes_and_Lipids

PM – Idealized mammalian PM



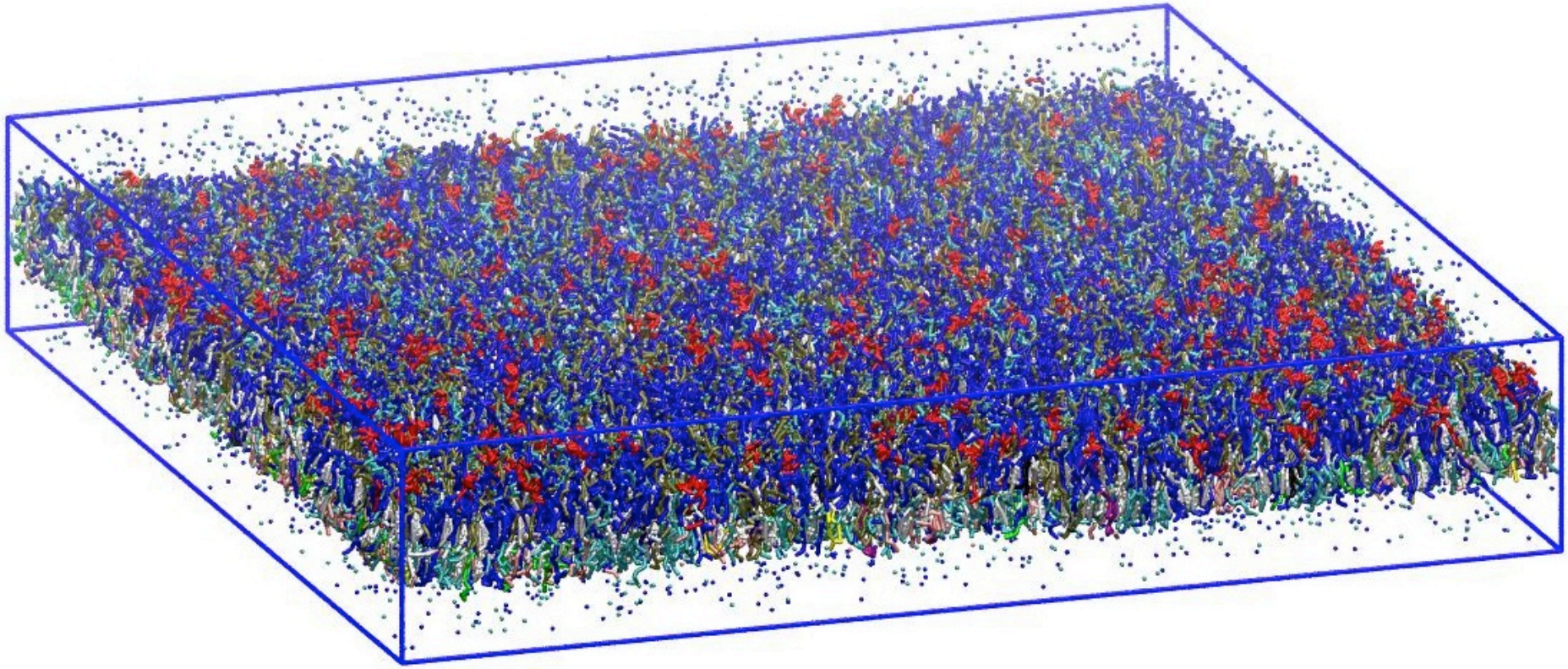
Lipids	mol %	#	16:0-18:0 4bead	20:0-22:0 5bead	24:0-26:0 6bead	16:1-18:1 4bead	20:1-22:1 5bead	24:1,2-26:1 6bead	18:2 4bead	20:2 5bead	20:3 5bead	20:4 22:4 5bead	22:5 22:6 5bead
PC (*phosphatidylcholine*)	39%	4680	48%	0%	0%	20%	0%	0%	25%	1%	0%	5%	1%
PE (*phosphatidylethanolamine*)	20%	2400	37%	0%	0%	20%	0%	0%	8%	0%	2%	25%	8%
SM (*sphingomyelin*)	22%	2640	44%	12%	20%	1%	1%	22%	0%	0%	0%	0%	0%
PI (*phosphatidylinositol*)	3%	360											
PS (*phosphatidylserine*)	7%	840	48%	0%	0%	10%	0%	0%	4%	0%	2%	25%	11%
PA (*phosphatidylacetate*)	1%	120											
PIP (*PI phosphate*)	1%	120											
Glycolip *(GMs, GCER)*	4%	480											
Cer *(ceramide)*	1%	120											
LPC (*lyso-PC*)	1%	120											
DAG (*diacylglycerol*)	1%	120											
Cholesterol/Lipid fraction	0.66	8000											

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*

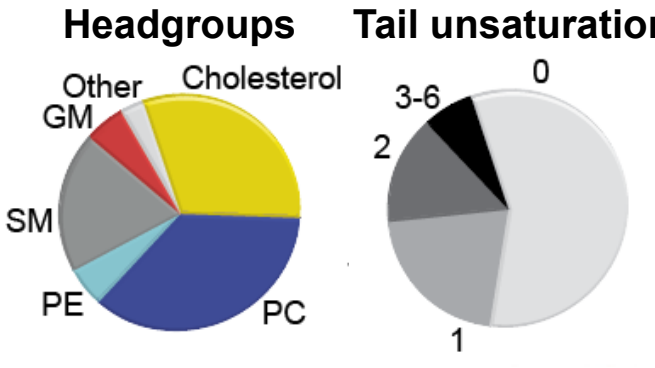


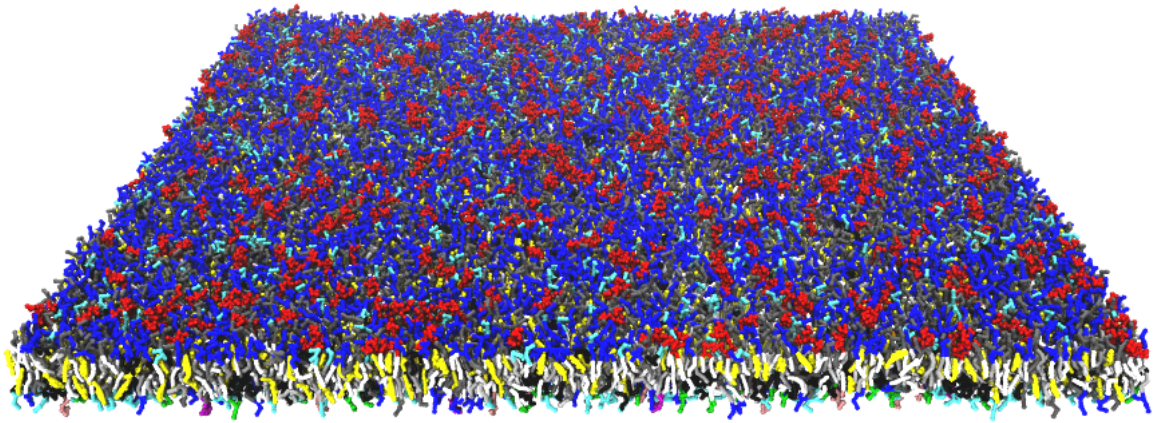
~20,000 lipids,
~300,000 CG water
~6,000 Na^+
~3,200 Cl^-

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

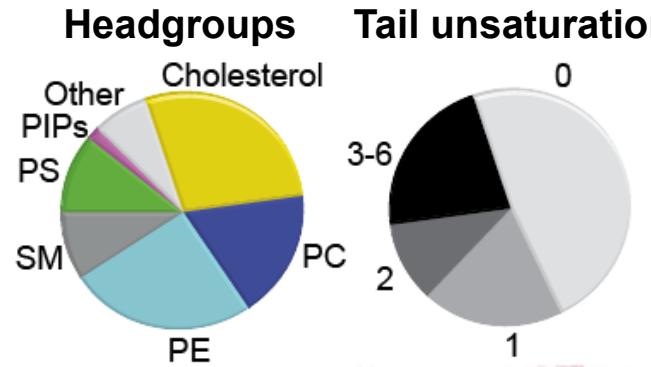
PM – idealized plasma membrane

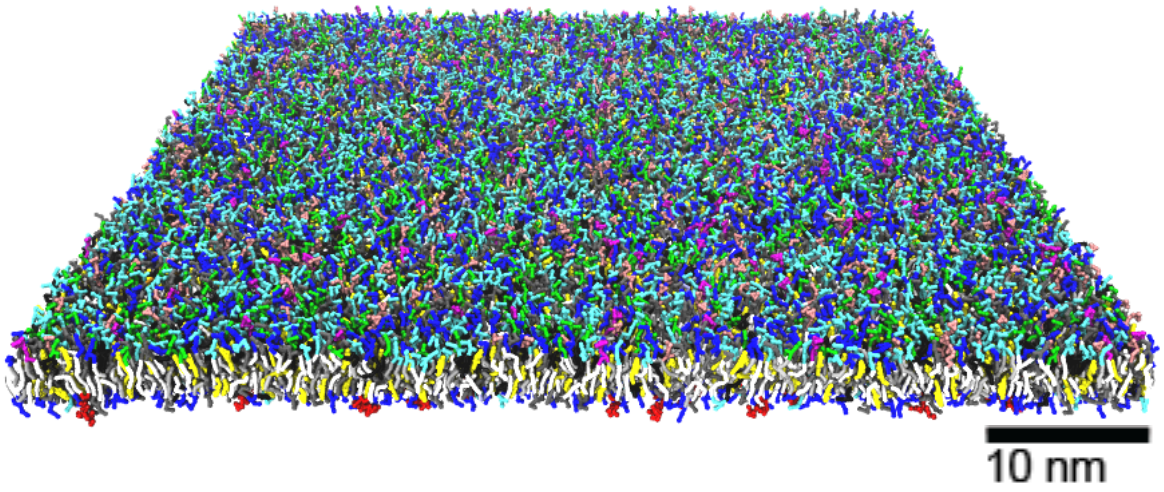
Outer leaflet:



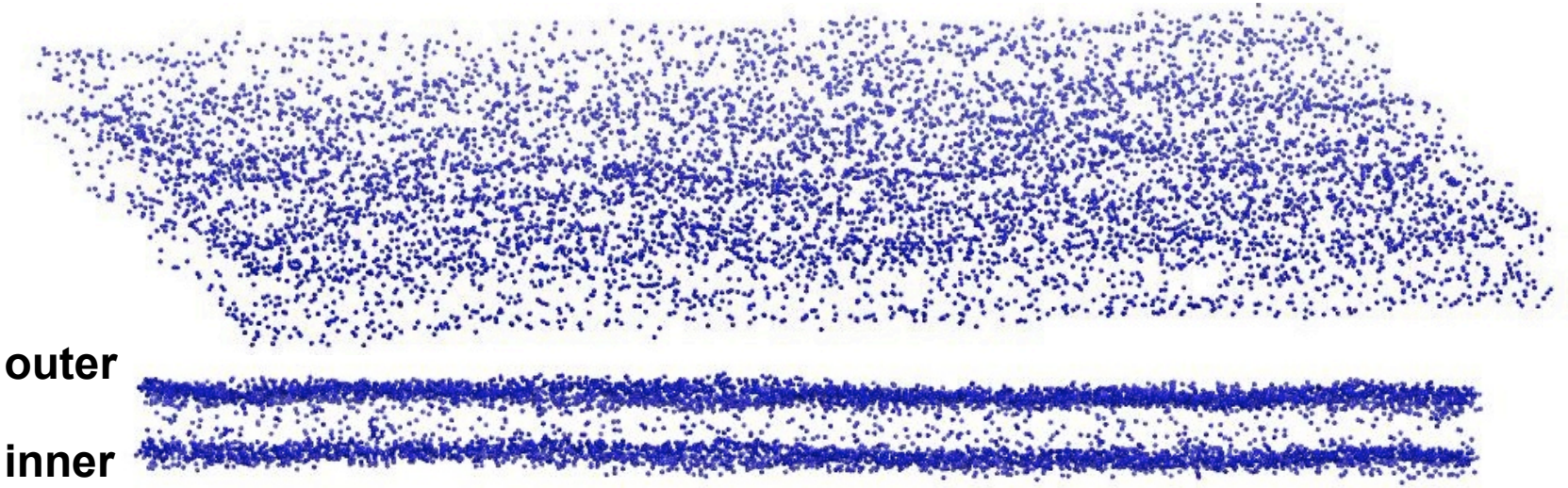


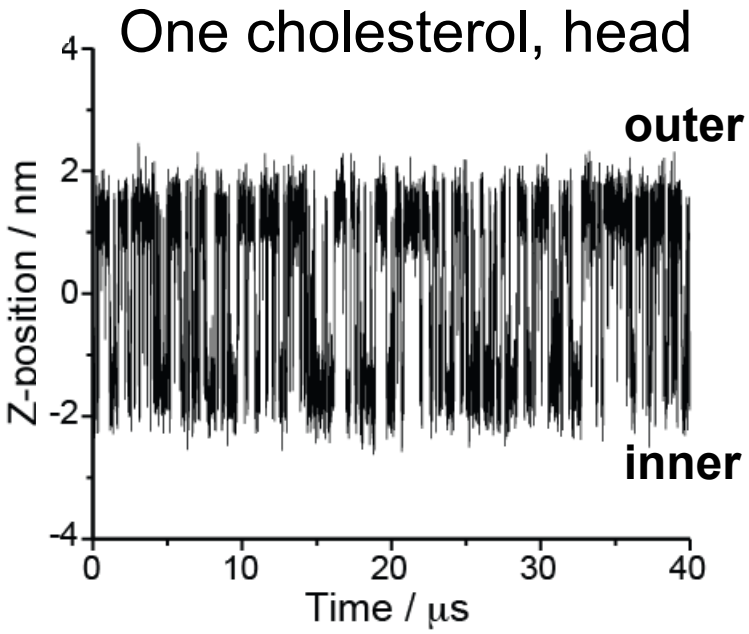
Inner leaflet:

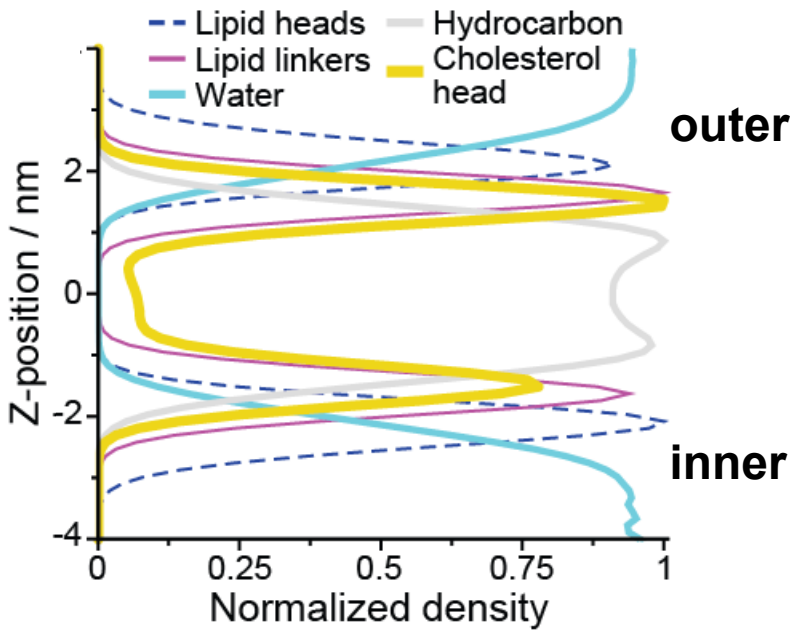




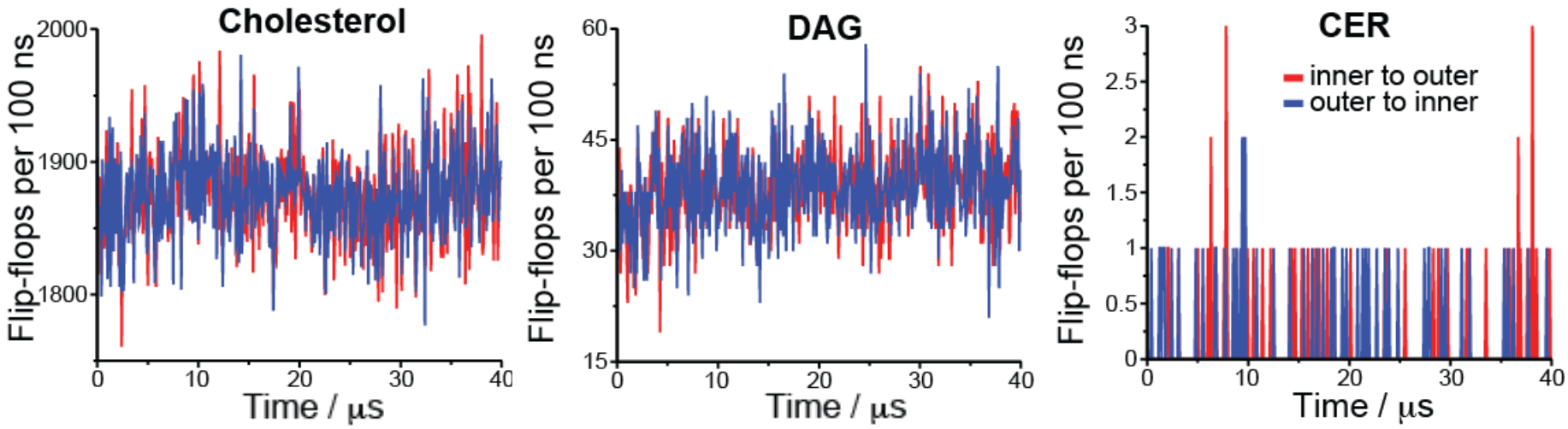
PM – cholesterol redistributes







PM – flip-flops

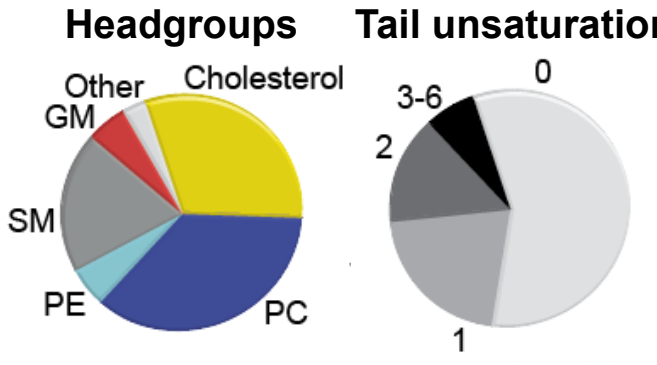


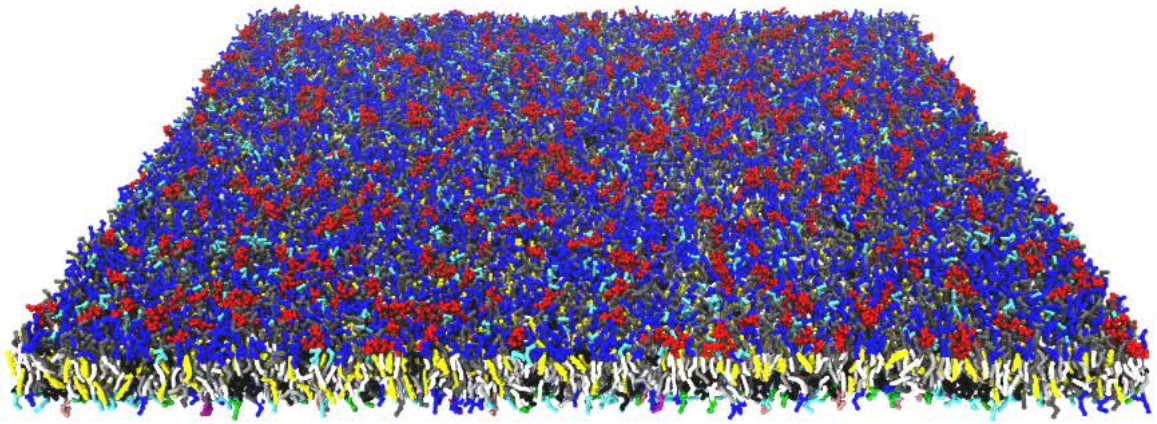
Flip-flop rates:

- 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

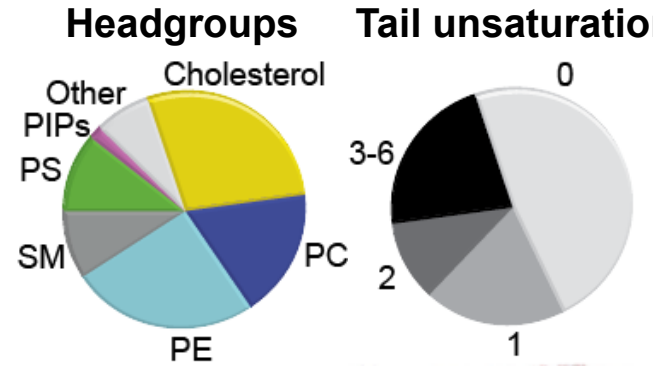
Outer leaflet:

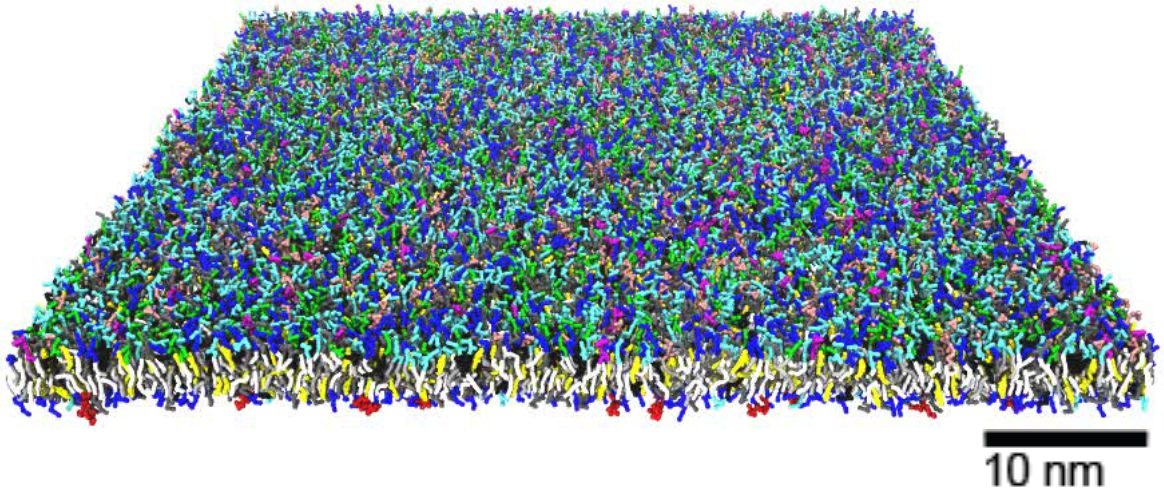




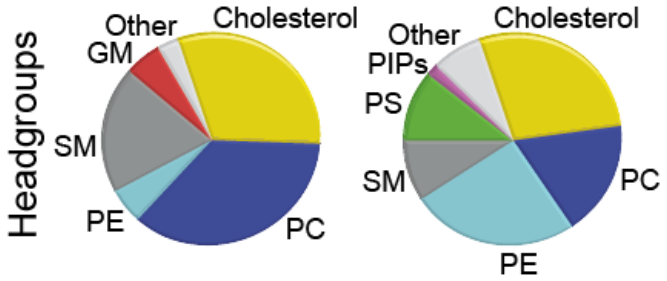
00000 ns

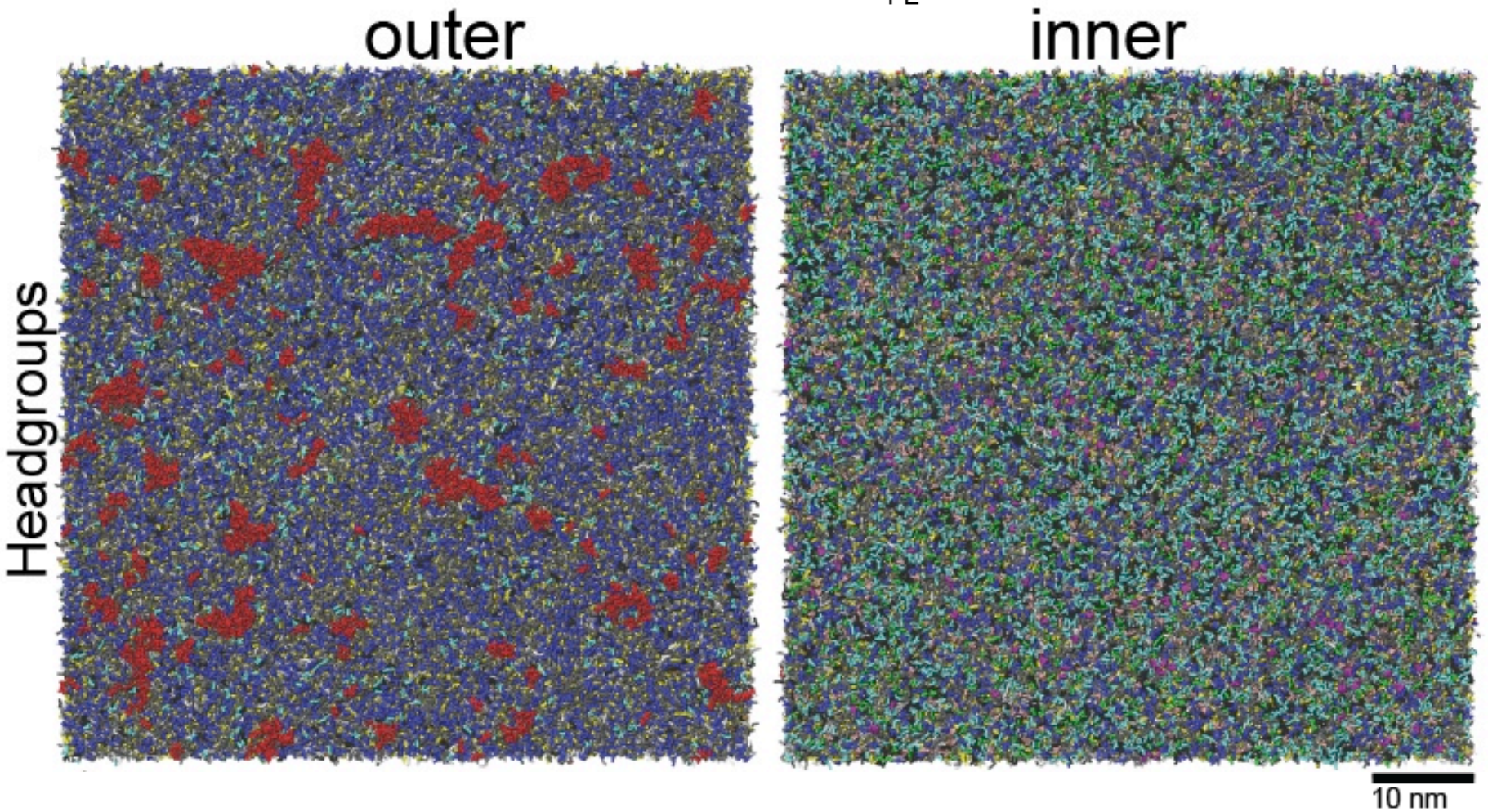
Inner leaflet:



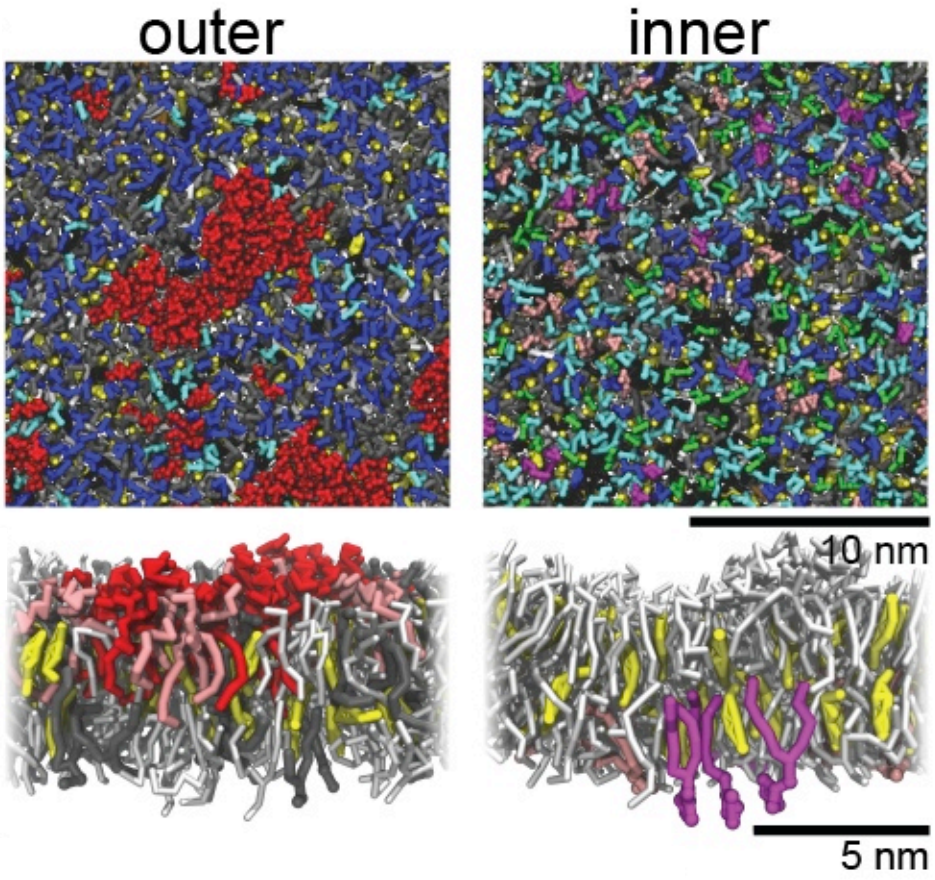


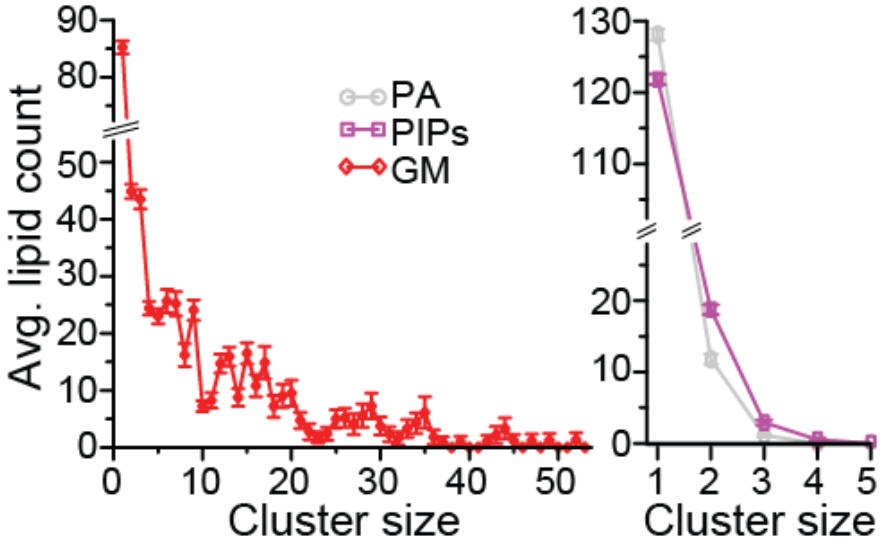
PM – lipid headgroups



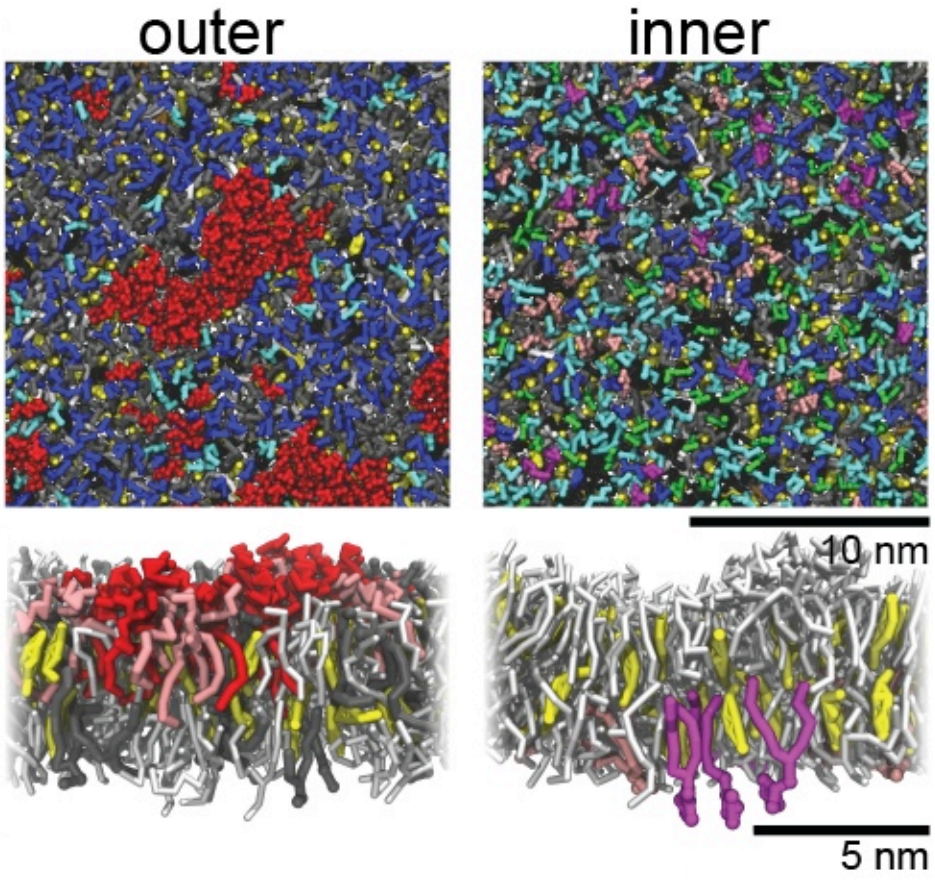


PM – lipid clustering





PM – lipid clustering



outer

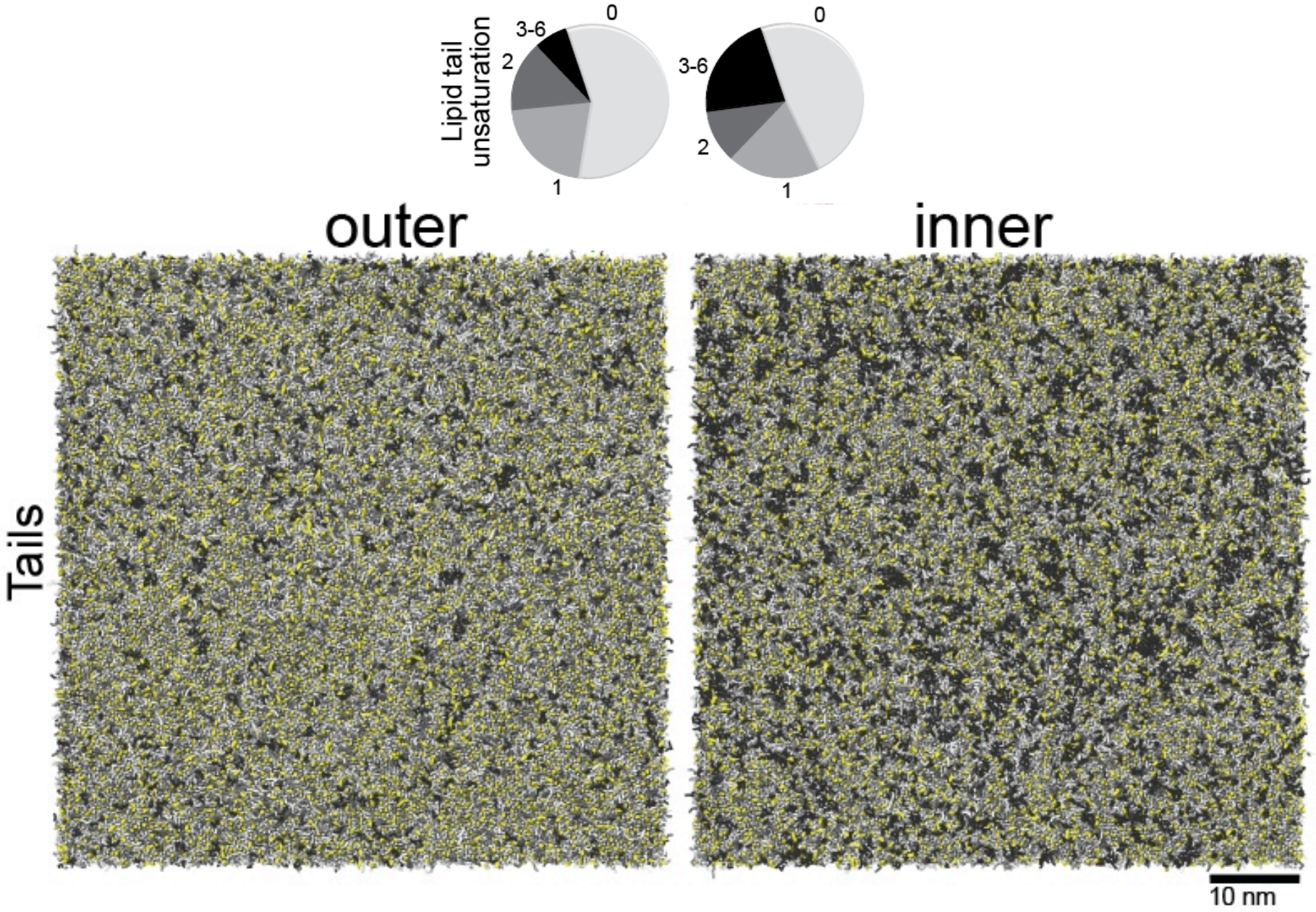
	CHOL	PC	PE	SM	GM
CHOL	0.93	1.04	1.02	1.09	1.05
PC	1.00	1.03	1.01	0.96	0.61
PE	0.98	1.00	1.04	0.89	0.99
SM	1.10	0.99	0.93	1.04	0.81
GM	1.03	0.63	1.02	0.79	4.08

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

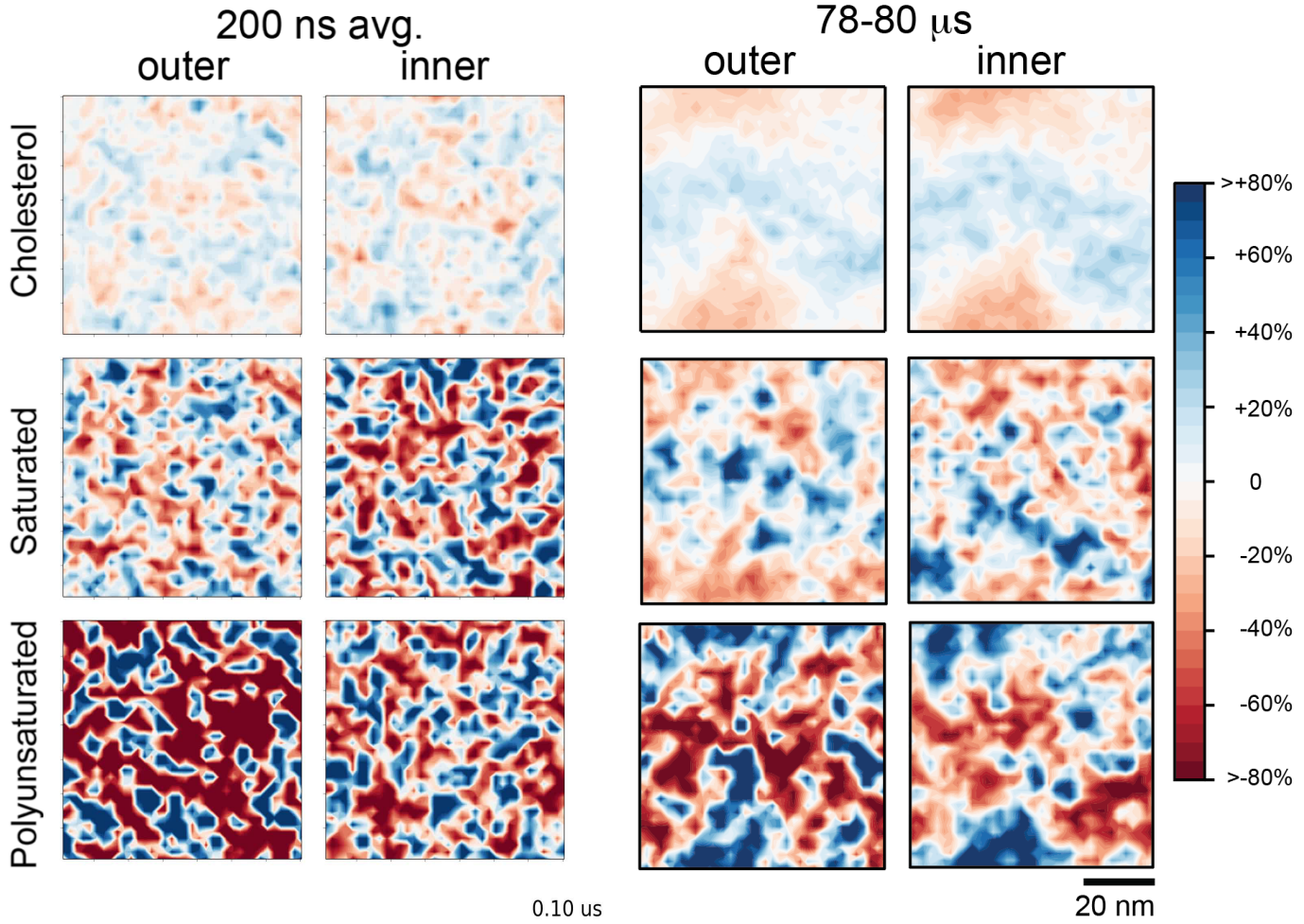
inner

	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
0
3-6
2
1
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

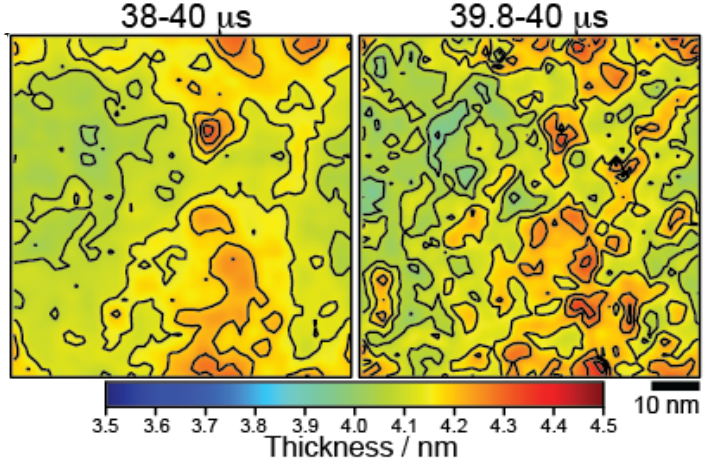
> +25%
+8 – +25%
-8 – +8%
-8 – -25%
> -25%

inner

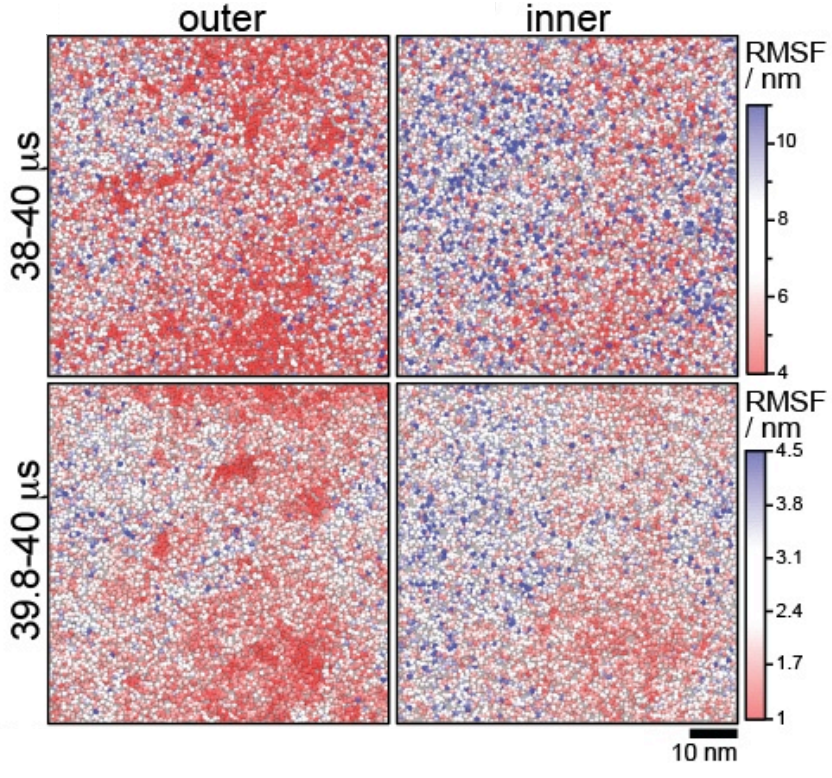
	Cholesterol	Polyunsaturated	Saturated	Other
Cholesterol	0.94	0.84	1.14	1.08
Polyunsaturated	0.67	2.19	0.64	0.86
Saturated	1.15	0.76	1.10	1.01
Other	1.04	0.98	0.97	0.98

PM – domains

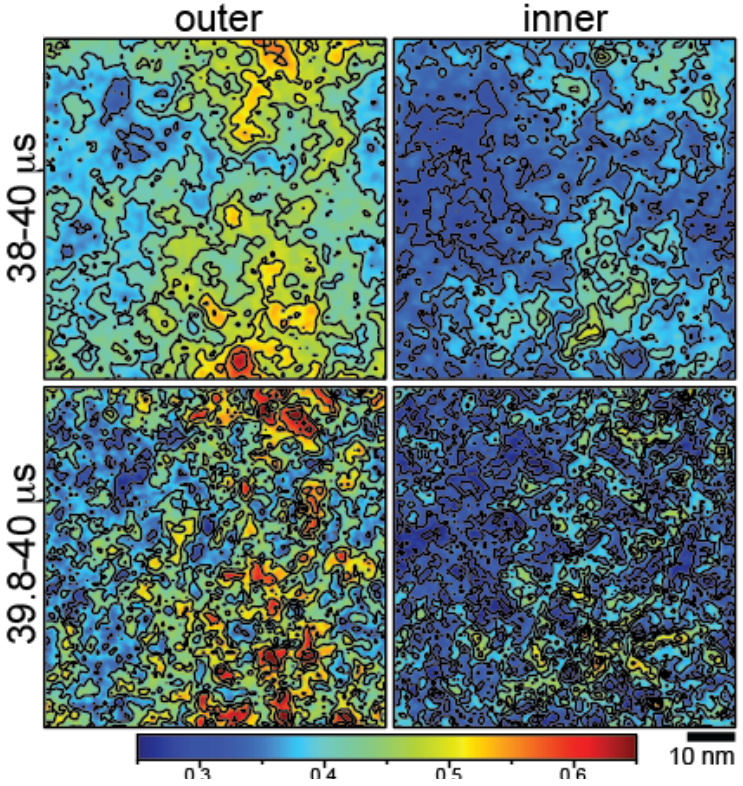
Bilayer Thickness



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:

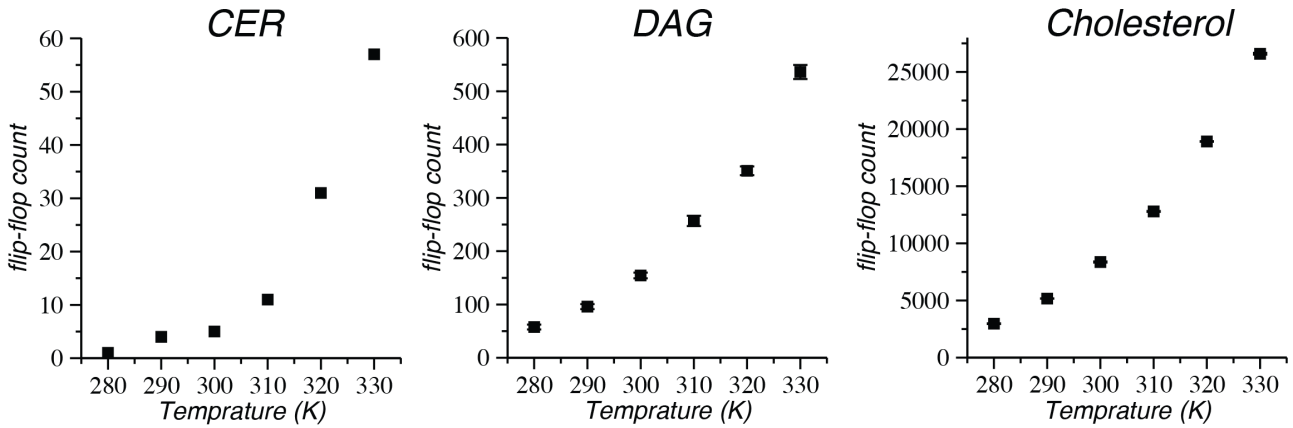
- Cholesterol favors the outer leaflet
- Multiple levels of non-ideal mixing / domain formation
- GM clusters
- PIPs self associate

Next steps:

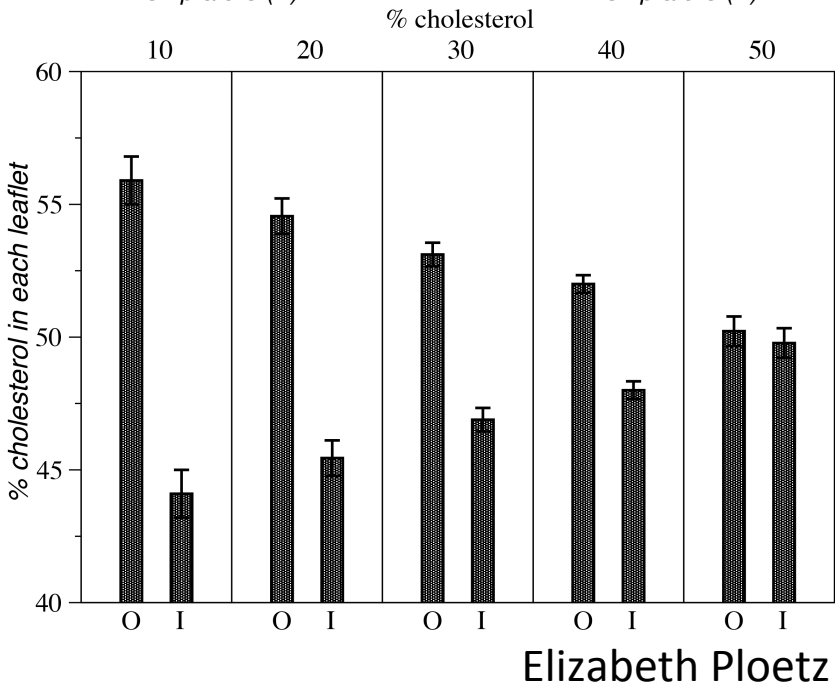
- Membrane protein / lipids interactions
- More new lipids
- Altered PM lipid composition
- Other cell envelopes

Future – PM projects

- **Effect of temperature**



- **Cholesterol concentration**

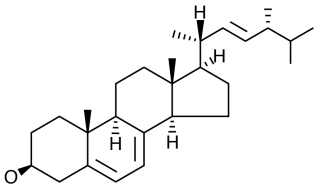


Elizabeth Ploetz

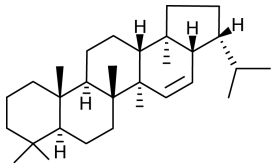
- **Lipid protein interactions**
- **Lipid shorting and tether pulling**

Future – Martini lipids

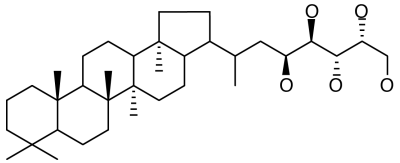
Ergosterol



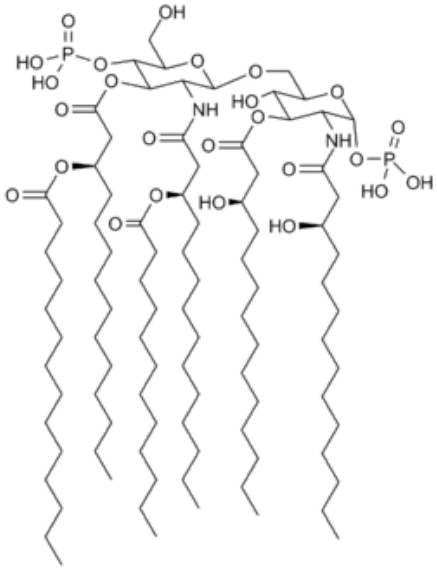
Hopanes



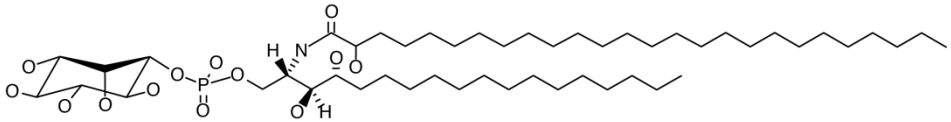
Bacteriohopanetetrol (BHT)



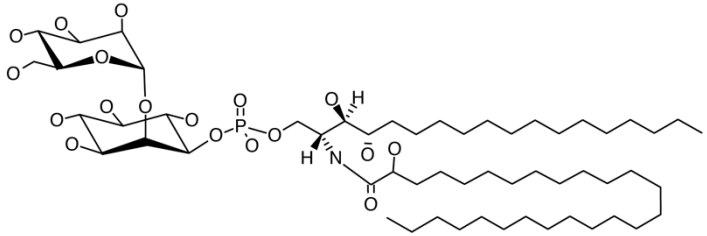
Lipid A



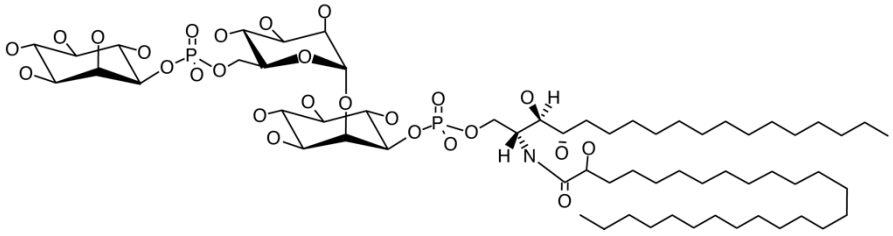
Inositolphosphoceramide (IPC)



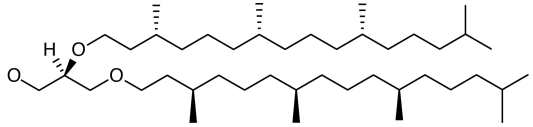
Mannosyl-IPC (MIPC)



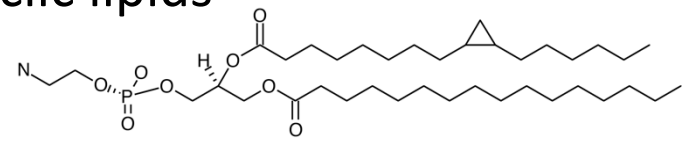
Mannosyl-di-IPC (MIP_2C)



Methyl-branched ether lipids

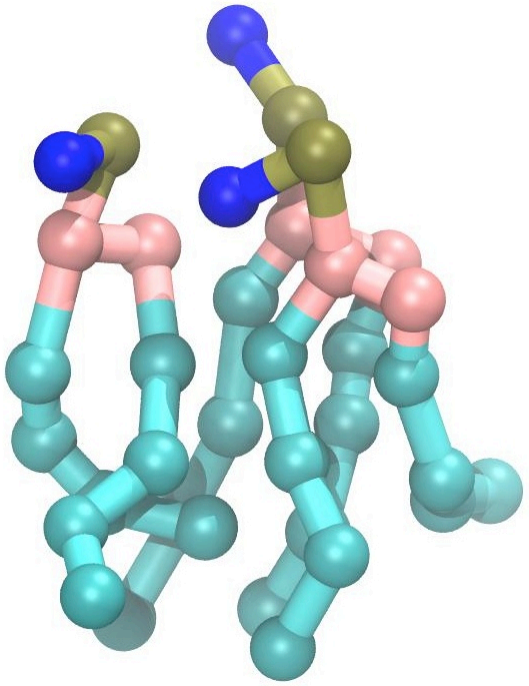


Cyclic lipids



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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Ingólfsson, H. I.; Melo, M. N.; van Eerden, F. J.; Arnarez, C.; Lopez, C. A.; Wassenaar, T. A.; Periole, X.; de Vries, A. H.; Tieleman, D. P.; Marrink, S. J. Lipid Organization of the Plasma Membrane. *JACS.* **2014**, *136*, 14554–14559.

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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