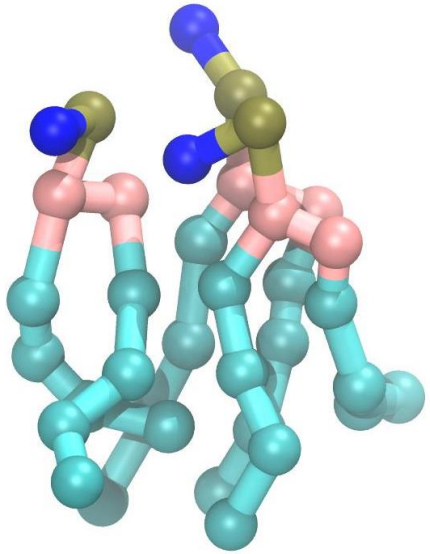
Lipid biophysics with the Martini model



2025 Martini Workshop

August 11th, 2025

Helgi I. Ingólfsson
Lawrence Livermore National Laboratory

Prepared by LLNL under Contract DE-AC52-07NA27344.

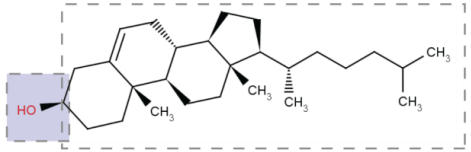
Overview

- Lipids – the what and the why
- Why use Martini to simulate lipids
- Lipids in Martini 2 and 3
  - The Martini lipidome
  - Naming standard
  - Overall properties
- Examples of Martini lipid projects

Lipids – definition

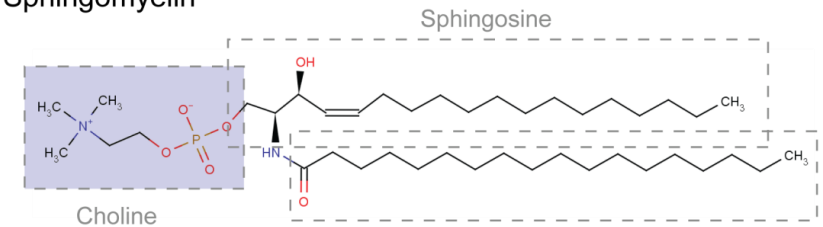
- Naturally occurring fats or fat-like compounds
- Insoluble in water
- Soluble in organic solvents
- Hydrophobic/amphipathic molecules

Cholesterol

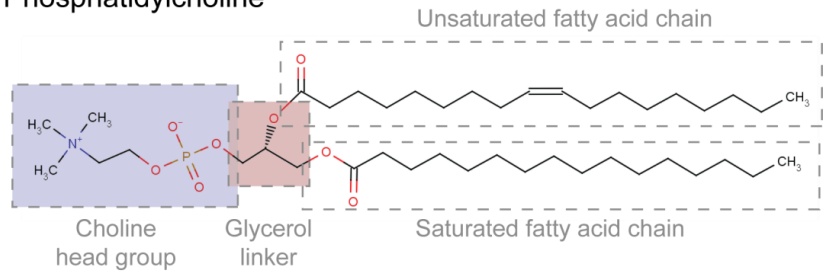


Head group Tail

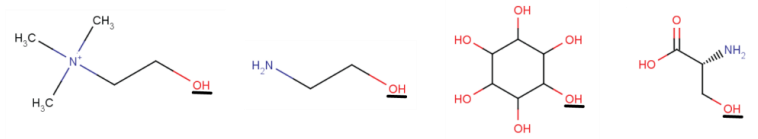
Sphingomyelin



Phosphatidylcholine

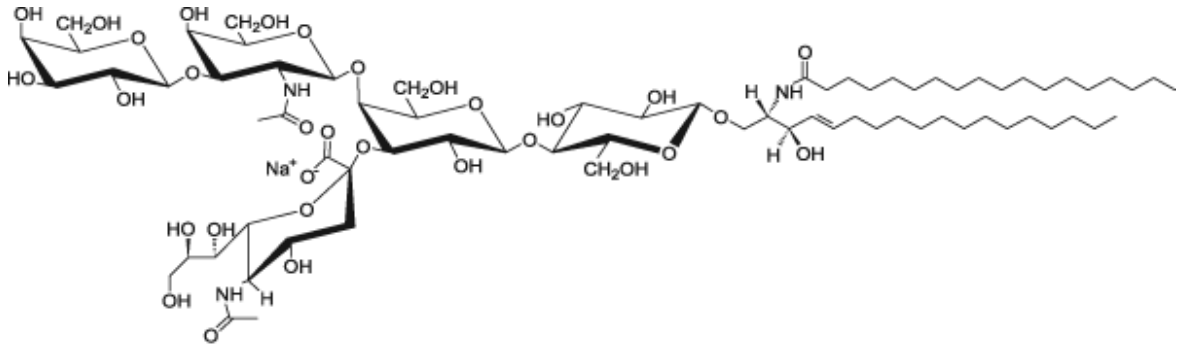


Examples of lipid head groups



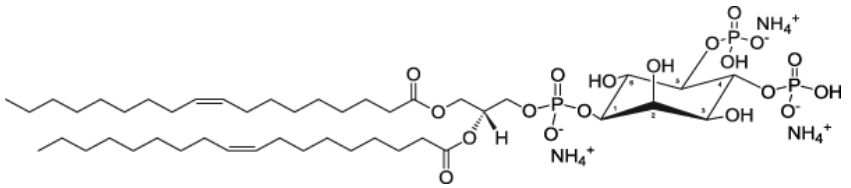
Lipids – definition

GM1

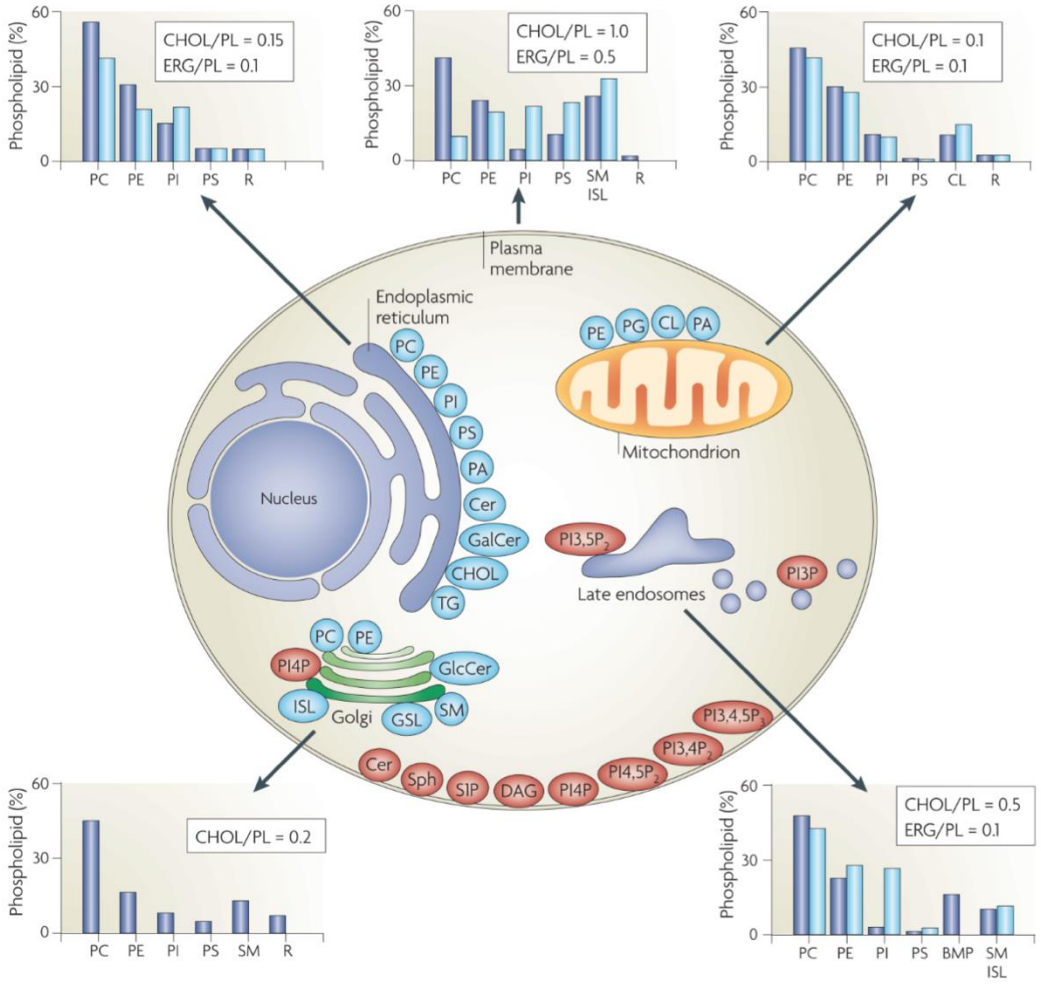


- Naturally occurring fats or fat-like compounds
- Insoluble in water
- Soluble in organic solvents
- Hydrophobic/amphipathic molecules

$PIP_2(4,5)$



Lipids – diversity

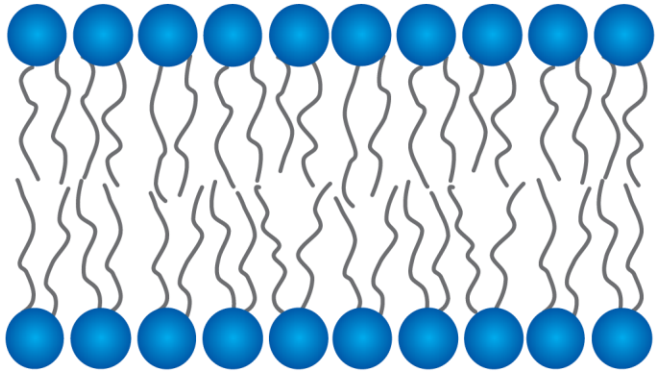


- Membranes contain 100s of different lipid types
- Cells have 1000s
- Currently www.lipidmaps.org has >50.000 unique lipid structures

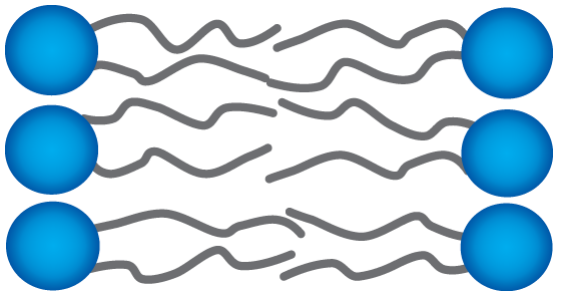
van Meer G1, Voelker DR, Feigenson GW. (2008) Membrane lipids: where they are and how they behave. Nat Rev Mol Cell Biol. 9:112-24.

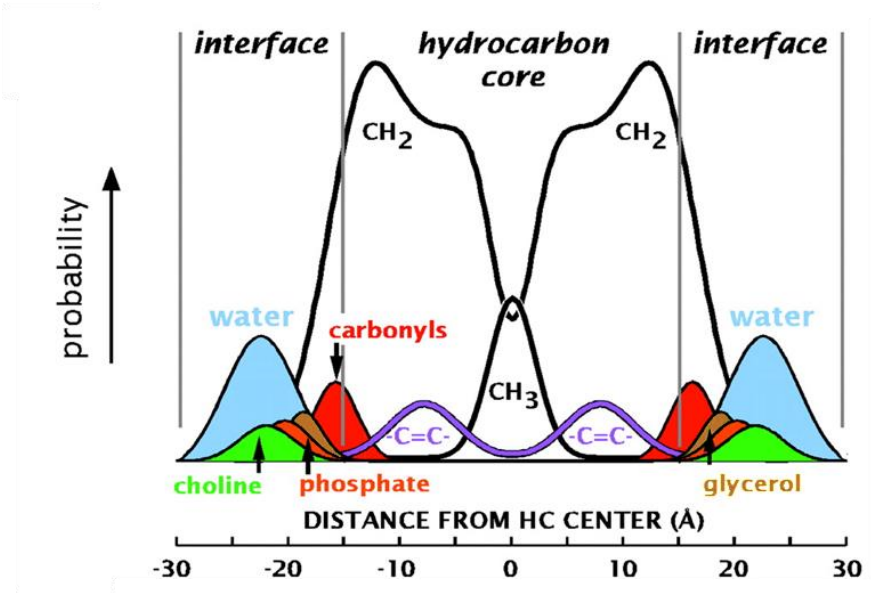
Lipids – bilayers

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



- Lipids
- Other amphiphiles
- Membrane proteins





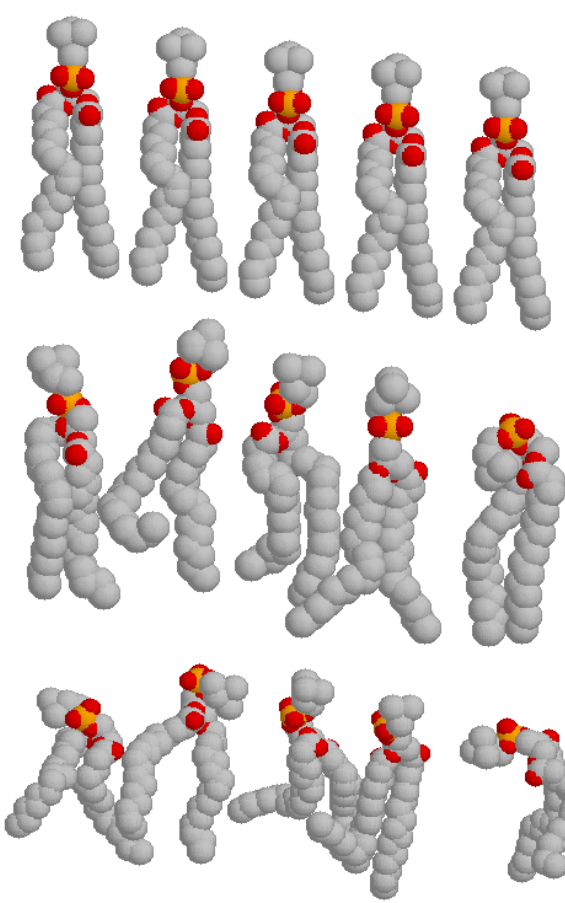
White, S. H., Ladokhin, A. S., Jayasinghe, S., & Hristova, K. (2001). How membranes shape protein structure. Journal of Biological Chemistry, 276(35), 32395–32398

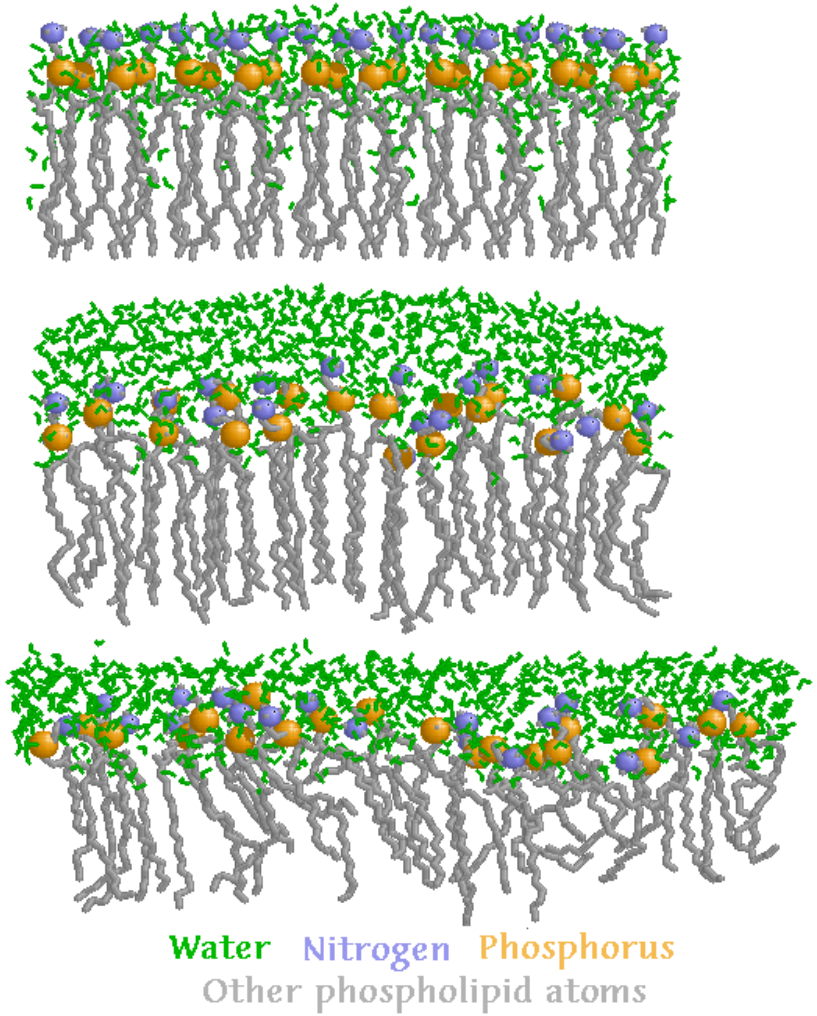
Lipids – bilayers

Crystal

Gel

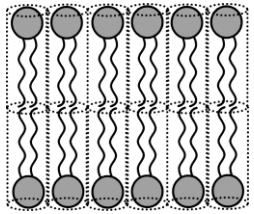
Fluid

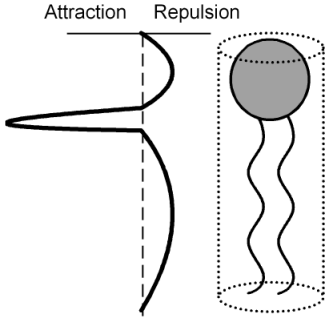




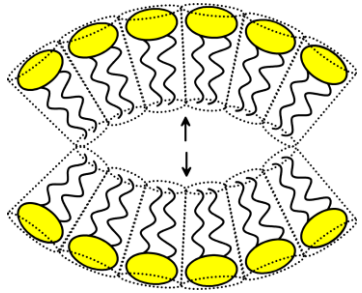
Images from Eric Martz using RasMol, structures from:
Heller et al. 1993. *J Phys Chem* 97:8343-8360

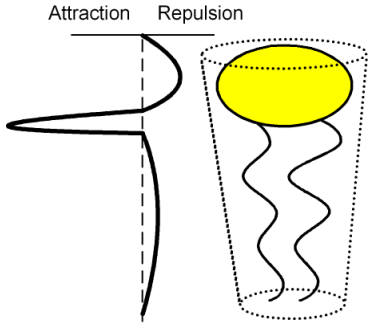
Lipids – shape



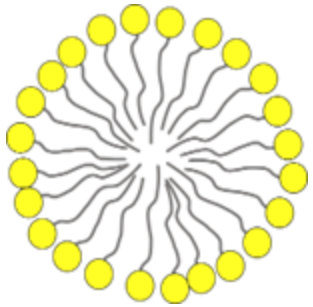


Positive intrinsic curvature

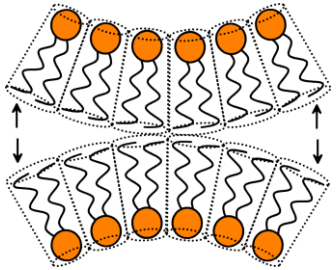


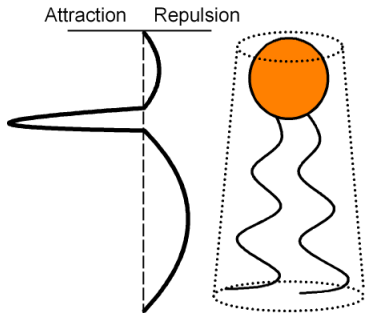


Micelle

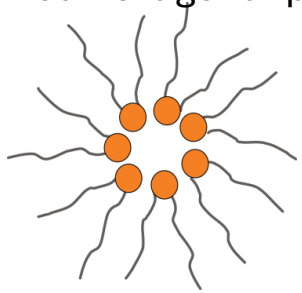


Negative intrinsic curvature

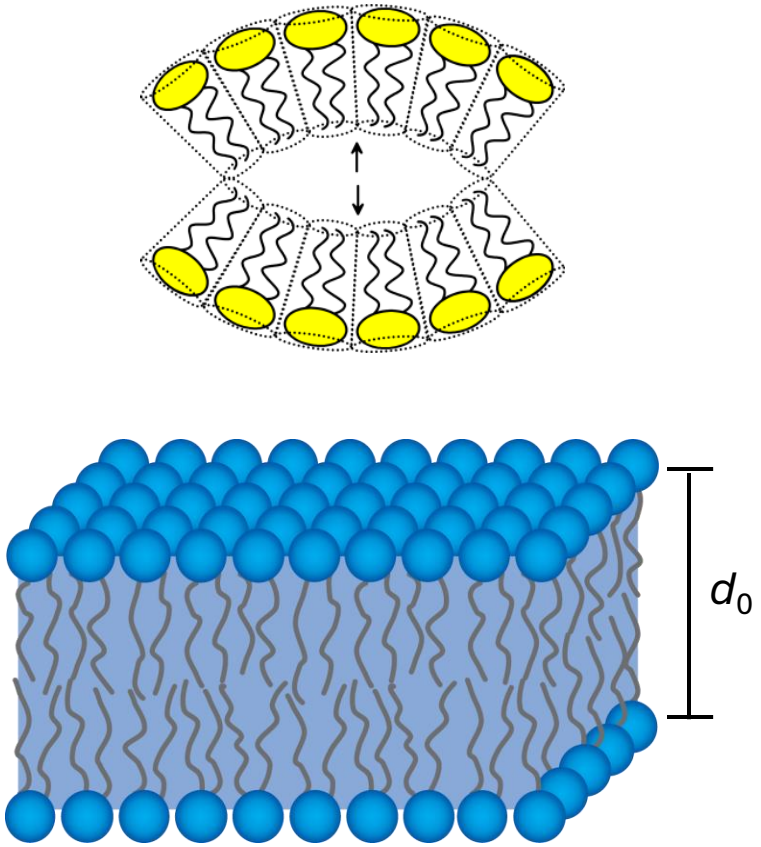




Inverted hexagonal phase

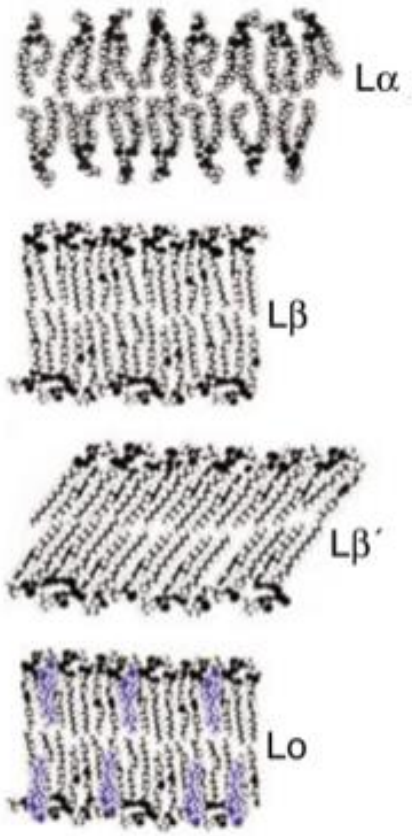


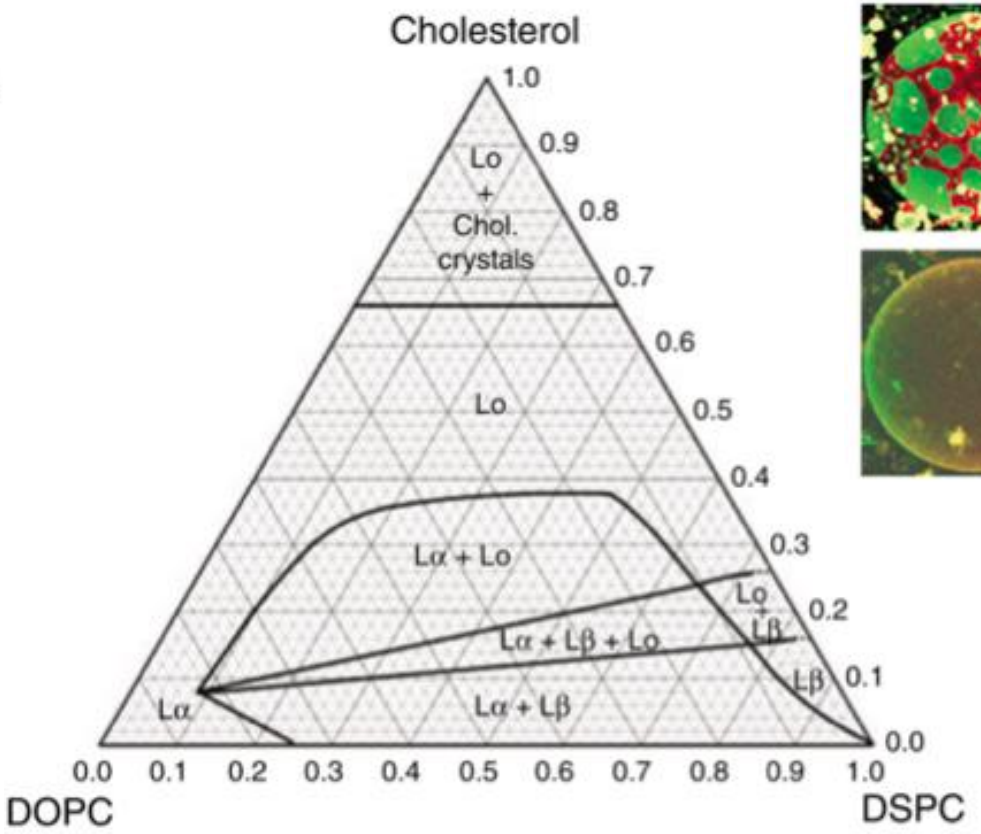
Lipids – properties

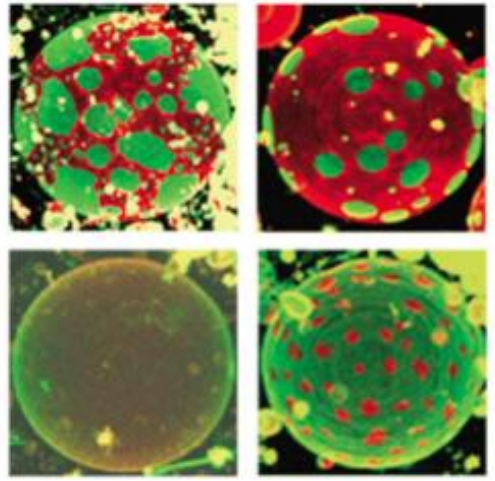


- Intrinsic lipid curvature (c_0)
- Actual curvature (c)
- Hydrophobic thickness (d_0)
- Area compression-expansion modulus (K_a)
- Splay-distortion modulus (K_c)
- Fluidity
- Diffusion
- Area per lipid
- Order parameter
- Surface tension
- Acyl chain packing
- Lateral pressure profile
- Lipid packing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

Lipids – “rafts” / domains / phases



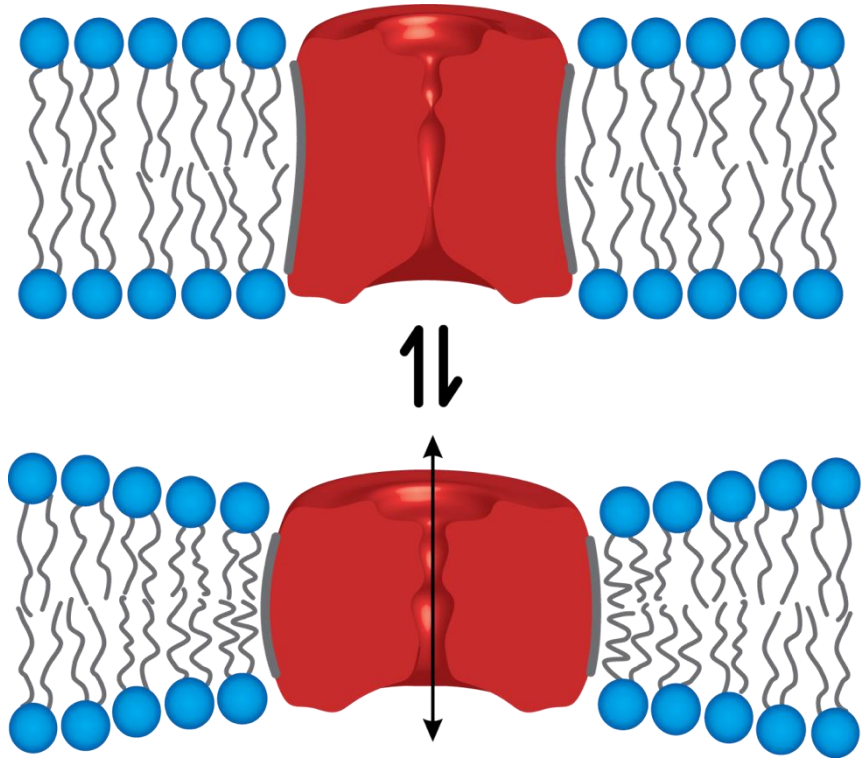




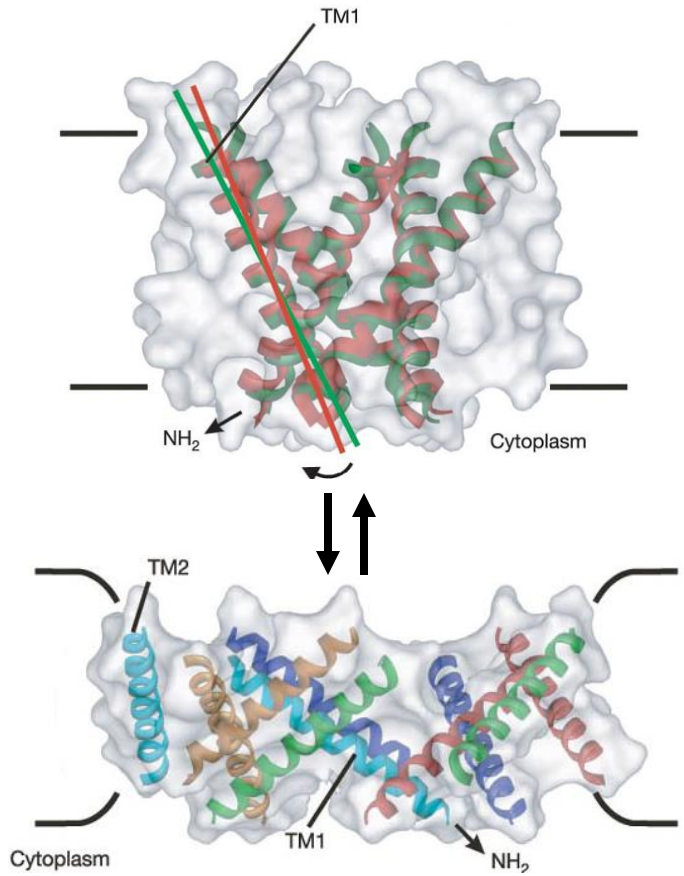
Feigenson, G.W. 2006. Phase behavior of lipid mixtures. Nat. Chem. Biol. 2: 560–563.

Lipids – bilayer/protein interactions

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

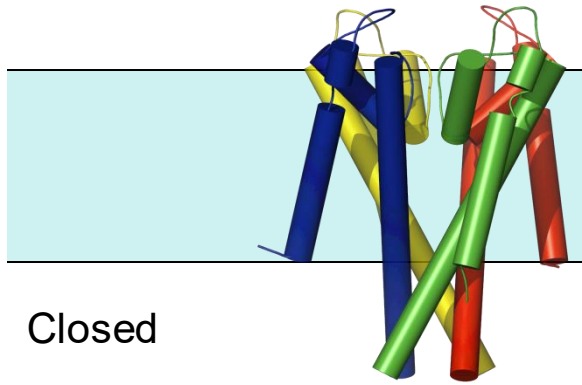


MscL channel



Lipids – bilayer/protein interactions

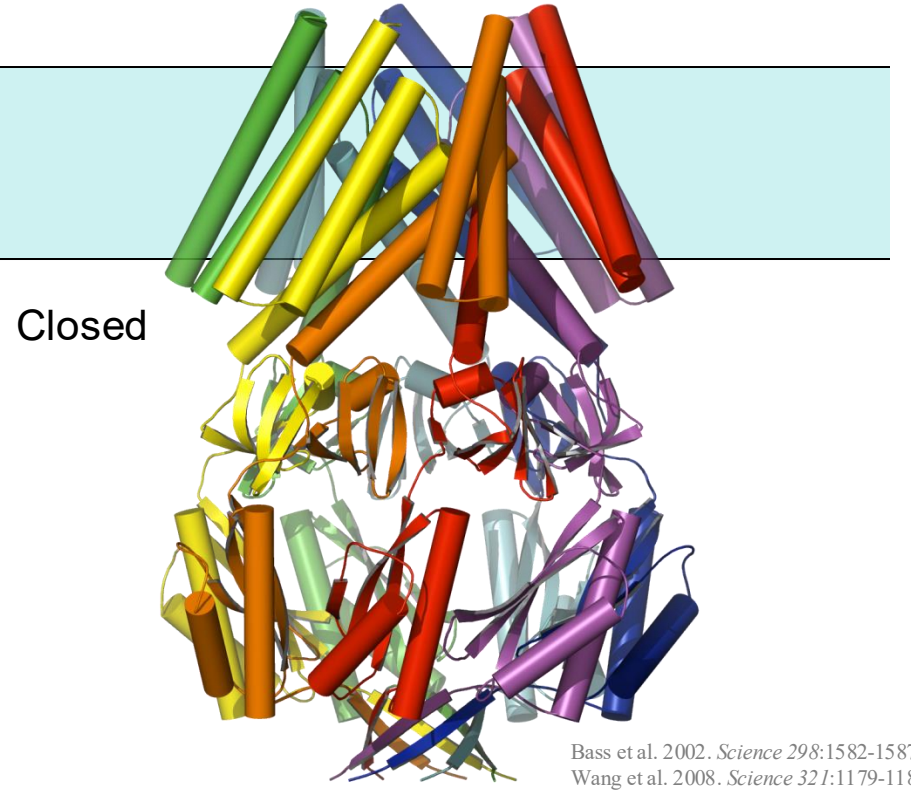
KcsA channel



Closed

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

MscS channel

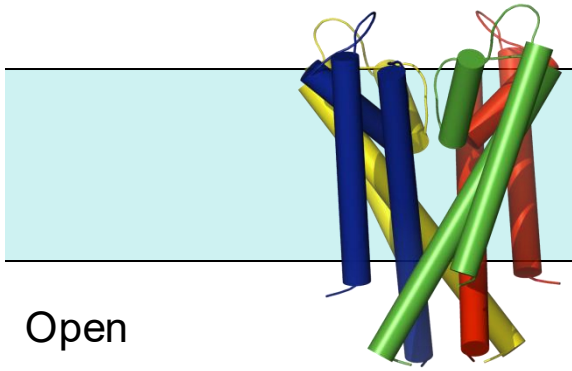


Closed

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

Lipids – bilayer/protein interactions

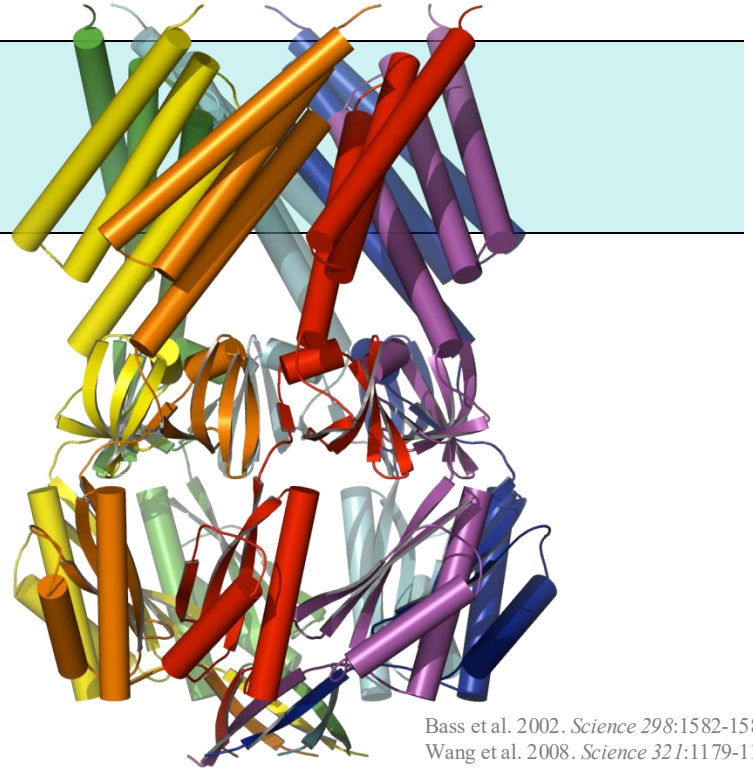
KcsA channel



Open

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

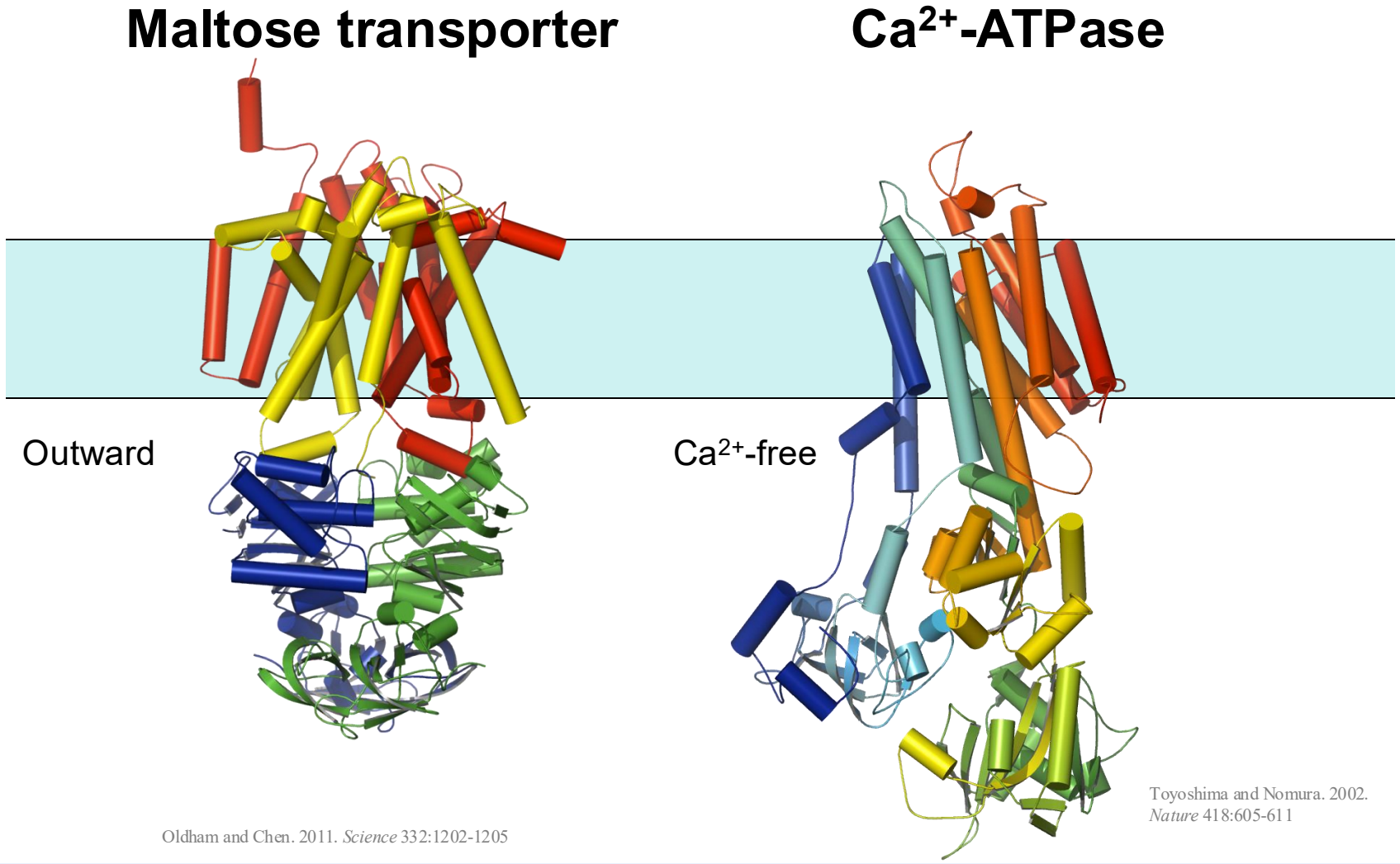
MscS channel



Open

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

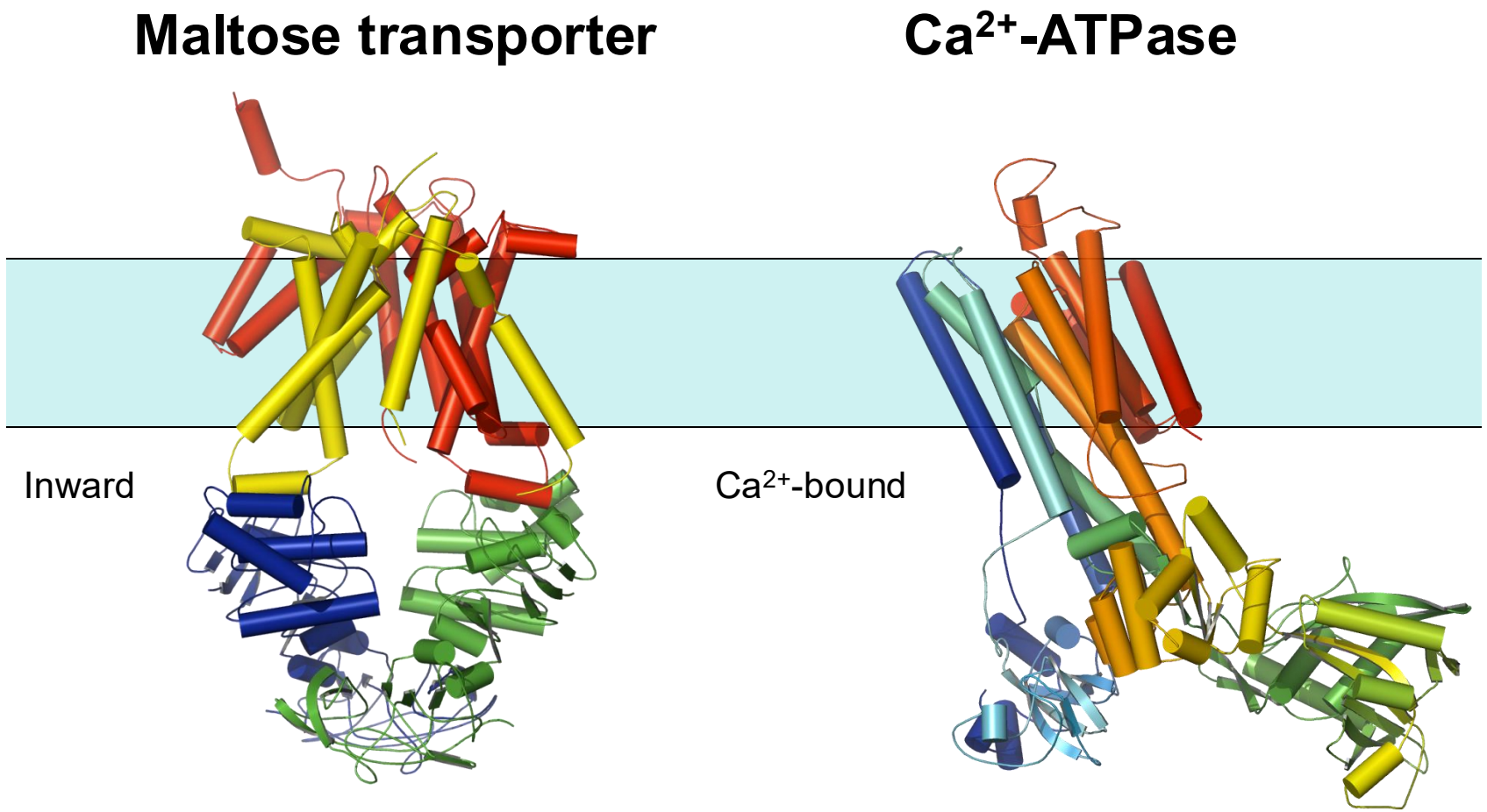
Lipids – bilayer/protein interactions



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

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

Lipids – bilayer/protein interactions

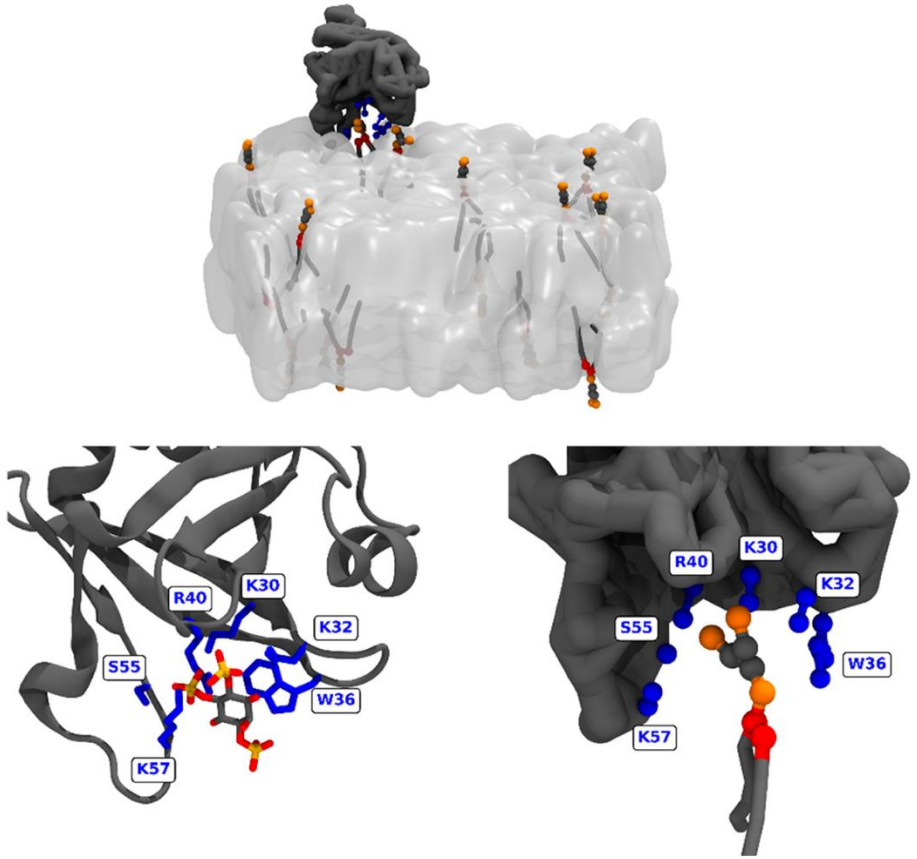


Chen, Oldham, Davidson, and Chen. 2013. *Nature* 499:364-368

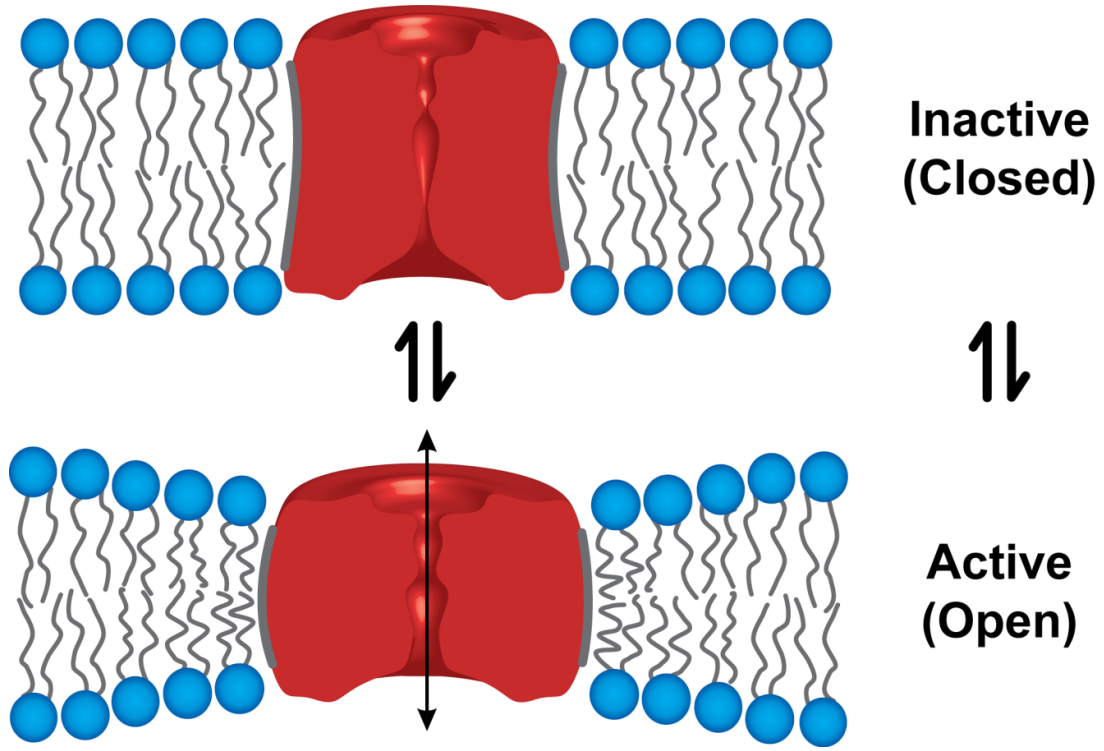
Toyoshima and Nomura. 2002. *Nature* 418:605-611

Lipids – bilayer/protein interactions

Specific lipid-protein interactions
e.g. PI(4,5)P2 and binding to PLCδ1



General membrane properties
e.g. Protein conformational changes involving the protein hydrophobic area are energetically coupled to the lipid bilayer.

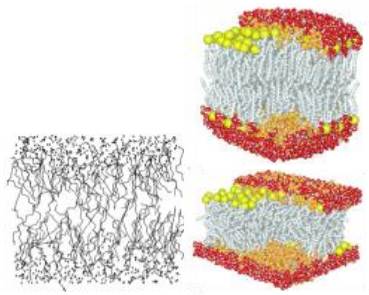


Luís Borges-Araujo et al. (2022). Improved Parameterization of Phosphatidylinositide Lipid Headgroups for the Martini 3 Coarse-Grain Force Field. *J. Chem. Theory Comput.* 2022, 18, 357−373

Lipid membrane molecule dynamics simulation have been progressing rabbity

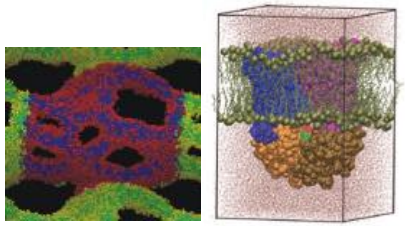
76 decanol
52 decanoate
30 ps

200 POPC
~ 55 ps



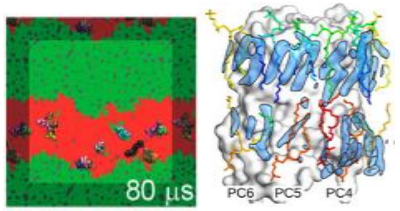
2304 DOPC
3.6 ns

288 POPE
1 BtuCD
15 ns



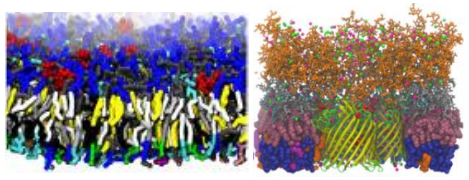
828 diC16:0PC
540 diC18:2PC
576 Chol
12 WALP23
80 μs

1 AQP0
278 DMPC
100 ns



63 lipid species
~ 20000 lipids
40 μs

1 OMPF
3 phospholipid species
25 LipA
24 Lps0
24 Lps5
300 ns

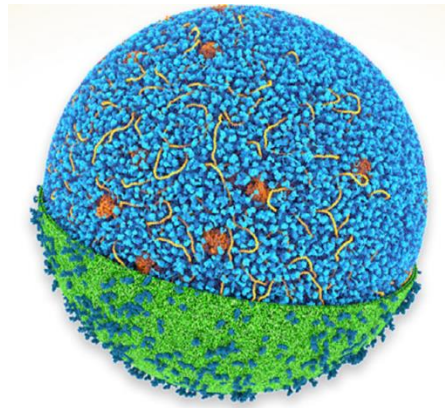


1986-1994 *Pioneering*

1994-2004 *Basic*

2004-2014 *Increasing complexity*

2014-2024 *Realistic*



Siewert J. Marrinka, Valentina Corradib, Paulo C.T. Souzaa, Helgi I. Ingólfssonc, D. Peter Tielemanb, Mark S.P. Sansomd. Computational Modeling of Realistic Cell Membranes. *Chem Rev.* 2019, 119, 9, 6184–6226.

Stevens JA, Grünewald F, van Tilburg PAM, König M, Gilbert BR, Brier TA, Thornburg ZR, Luthey-Schulten Z and Marrink SJ (2023), Molecular dynamics simulation of an entire cell.
Front. Chem. 11:1106495.

Why simulate lipids with Martini?

Most interesting lipid stuff happens beyond the μs timescale

A lot of such interesting lipid stuff happens at large size scales

↓

Computationally expensive to simulate with atomistic resolution

With Martini: Fewer degrees of freedom

+

Larger timesteps
(afforded by softer potential landscapes)

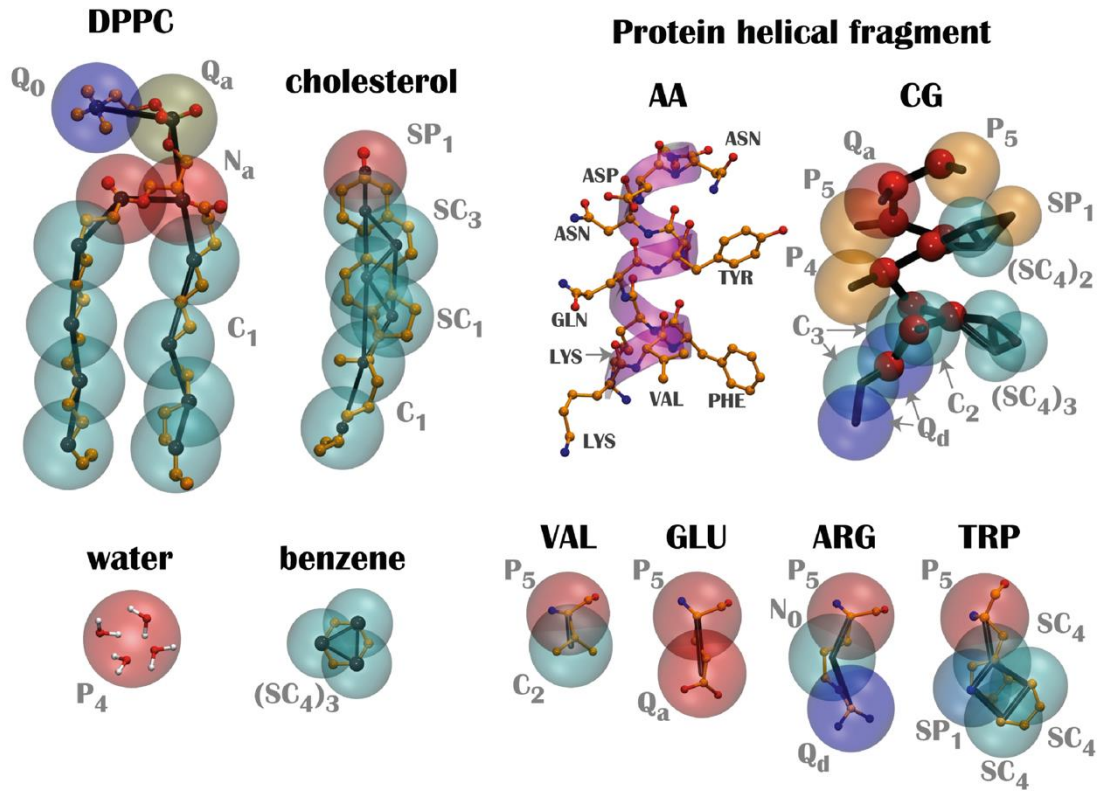
↓

Between 100x and 1000x speedup over atomistic simulations

Martini 2 coarse-grained (CG) simulations for lipids

The Martini 2 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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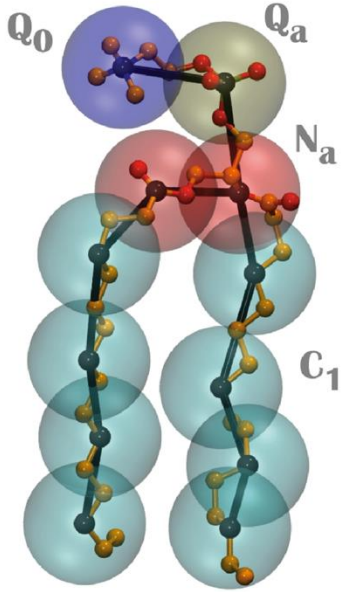
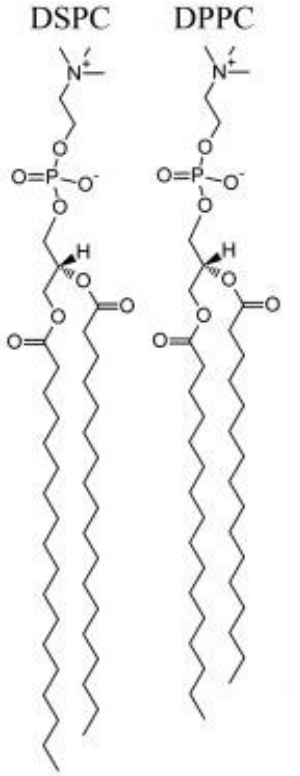
- A 2-3 orders of magnitude speedup compared to atomistic simulations
- A large number of parameterized lipids
- Easy backmapping to AA



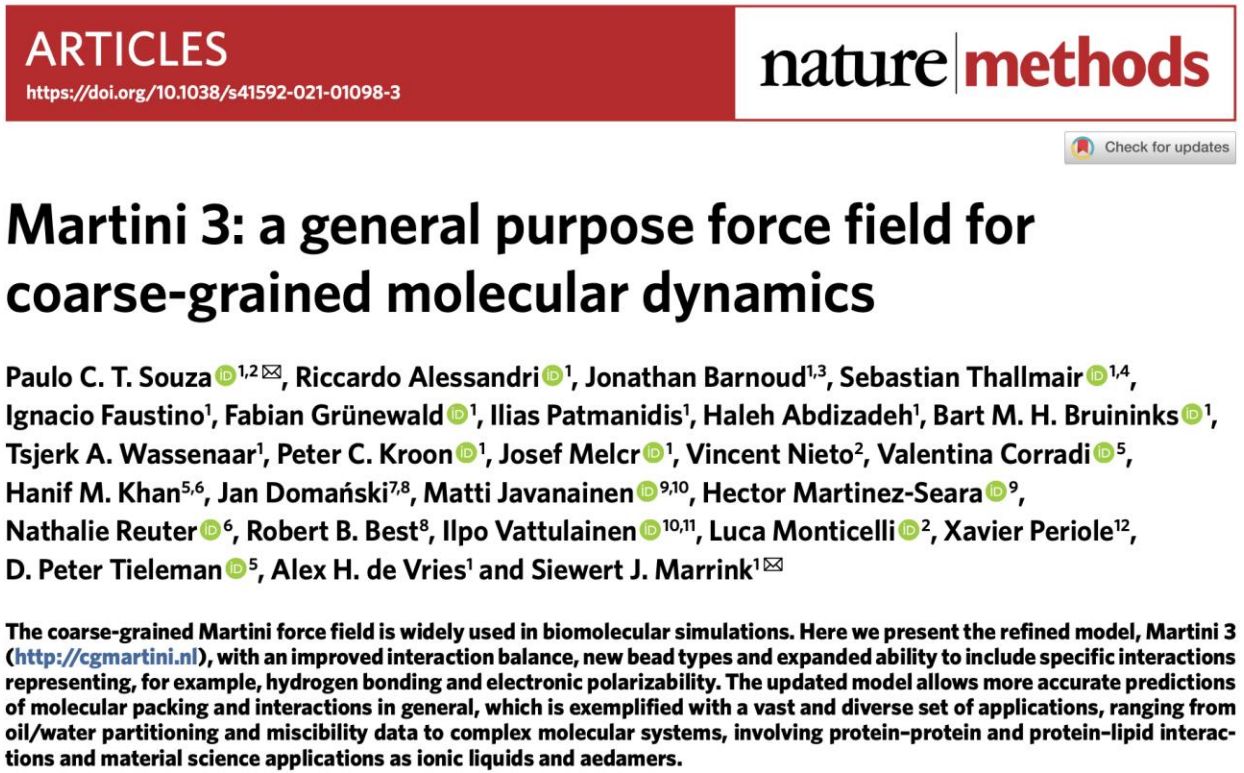


DPPC, di-C16:0 palmitic tails
DSPC, di-C18:0 stearoyl tails

Martini 3 coarse-grained (CG) simulations for lipids

The Martini 3 CG force field

- Improved interaction balance
- More granularity in bead types
- Different granularity in bead size
- And still fast



ARTICLES
https://doi.org/10.1038/s41592-021-01098-3
nature methods
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Martini 3: a general purpose force field for coarse-grained molecular dynamics

Paulo C. T. Souza[1,2]✉, Riccardo Alessandri[1], Jonathan Barnoud[1,3], Sebastian Thallmair[1,4], Ignacio Faustino[1], Fabian Grünewald[1], Ilias Patmanidis[1], Haleh Abdizadeh[1], Bart M. H. Bruininks[1], Tsjerk A. Wassenaar[1], Peter C. Kroon[1], Josef Melcr[1], Vincent Nieto[2], Valentina Corradi[5], Hanif M. Khan[5,6], Jan Domański[7,8], Matti Javanainen[9,10], Hector Martinez-Seara[9], Nathalie Reuter[6], Robert B. Best[8], Ilpo Vattulainen[10,11], Luca Monticelli[2], Xavier Periole[12], D. Peter Tieleman[5], Alex H. de Vries[1] and Siewert J. Marrink[1]✉

The coarse-grained Martini force field is widely used in biomolecular simulations. Here we present the refined model, Martini 3 (http://cgmartini.nl), with an improved interaction balance, new bead types and expanded ability to include specific interactions representing, for example, hydrogen bonding and electronic polarizability. The updated model allows more accurate predictions of molecular packing and interactions in general, which is exemplified with a vast and diverse set of applications, ranging from oil/water partitioning and miscibility data to complex molecular systems, involving protein–protein and protein–lipid interactions and material science applications as ionic liquids and aedamers.

Martini 3 coarse-grained (CG) simulations for lipids

The Martini 3 lipidome

- Tail mapping down to two carbons
- Better bulk bilayer properties
- Improved phase behavior
- Weaker protein-lipid interactions
- Pore formation still needs improvement

ACS central science

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Article

The Martini 3 Lipidome: Expanded and Refined Parameters Improve Lipid Phase Behavior

Kasper B. Pedersen, Helgi I. Ingólfsson,[▽] Daniel P. Ramirez-Echemendia,[▽] Luís Borges-Araújo,[▽] Mikkel D. Andreasen, Charly Empereur-mot, Josef Melcr, Tugba N. Ozturk, W. F. Drew Bennett, Lisbeth R. Kjølbye, Christopher Brasnett, Valentina Corradi, Hanif M. Khan, Elio A. Cino, Jackson Crowley, Hyuntae Kim, Balázs Fábián, Ana C. Borges-Araújo, Giovanni M. Pavan, Guillaume Launay, Fabio Lolicato, Tsjerk A. Wassenaar, Manuel N. Melo, Sebastian Thallmair, Timothy S. Carpenter, Luca Monticelli, D. Peter Tieleman, Birgit Schiøtt, Paulo C. T. Souza,* and Siewert J. Marrink*

Cite This: https://doi.org/10.1021/acscentsci.5c00755

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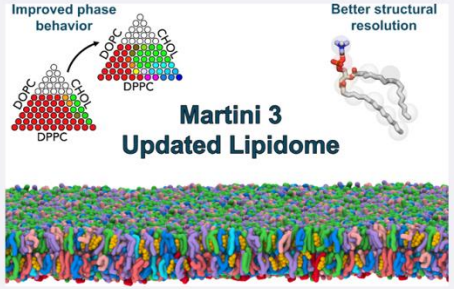
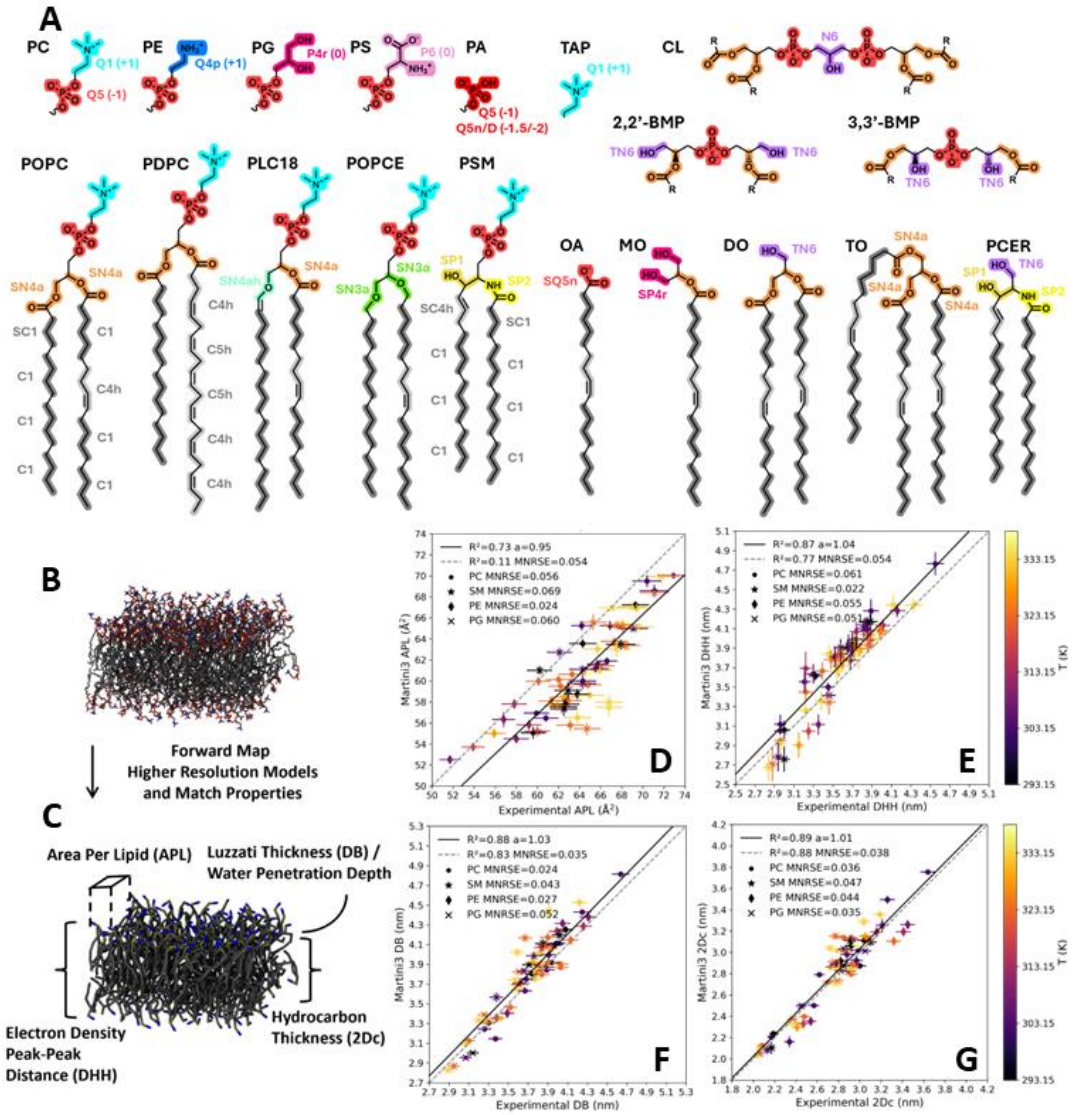
ABSTRACT: Lipid membranes are central to cellular life. Complementing experiments, computational modeling has been essential in unraveling complex lipid-biomolecule interactions, crucial in both academia and industry. The Martini model, a coarse-grained force field for efficient molecular dynamics simulations, is widely used to study membrane phenomena but has faced limitations, particularly in capturing realistic lipid phase behavior. Here, we present refined Martini 3 lipid models with a mapping scheme that distinguishes lipid tails that differ by just two carbon atoms, enhancing the structural resolution and thermodynamic accuracy of model membrane systems including ternary mixtures. The expanded Martini lipid library includes thousands of models, enabling simulations of complex and biologically relevant systems. These advancements establish Martini as a robust platform for lipid-based simulations across diverse fields.



Martini 3 coarse-grained (CG) simulations for lipids

The Martini 3 lipidome

- Tail mapping down to two carbons
- Better bulk bilayer properties
- Improved phase behavior
- Weaker protein-lipid interactions
- Pore formation still needs improvement



K. Pedersen et al. The Martini 3 Lipidome: Expanded and Refined Parameters Improve Lipid Phase Behavior. ACS Cent. Sci. 2025

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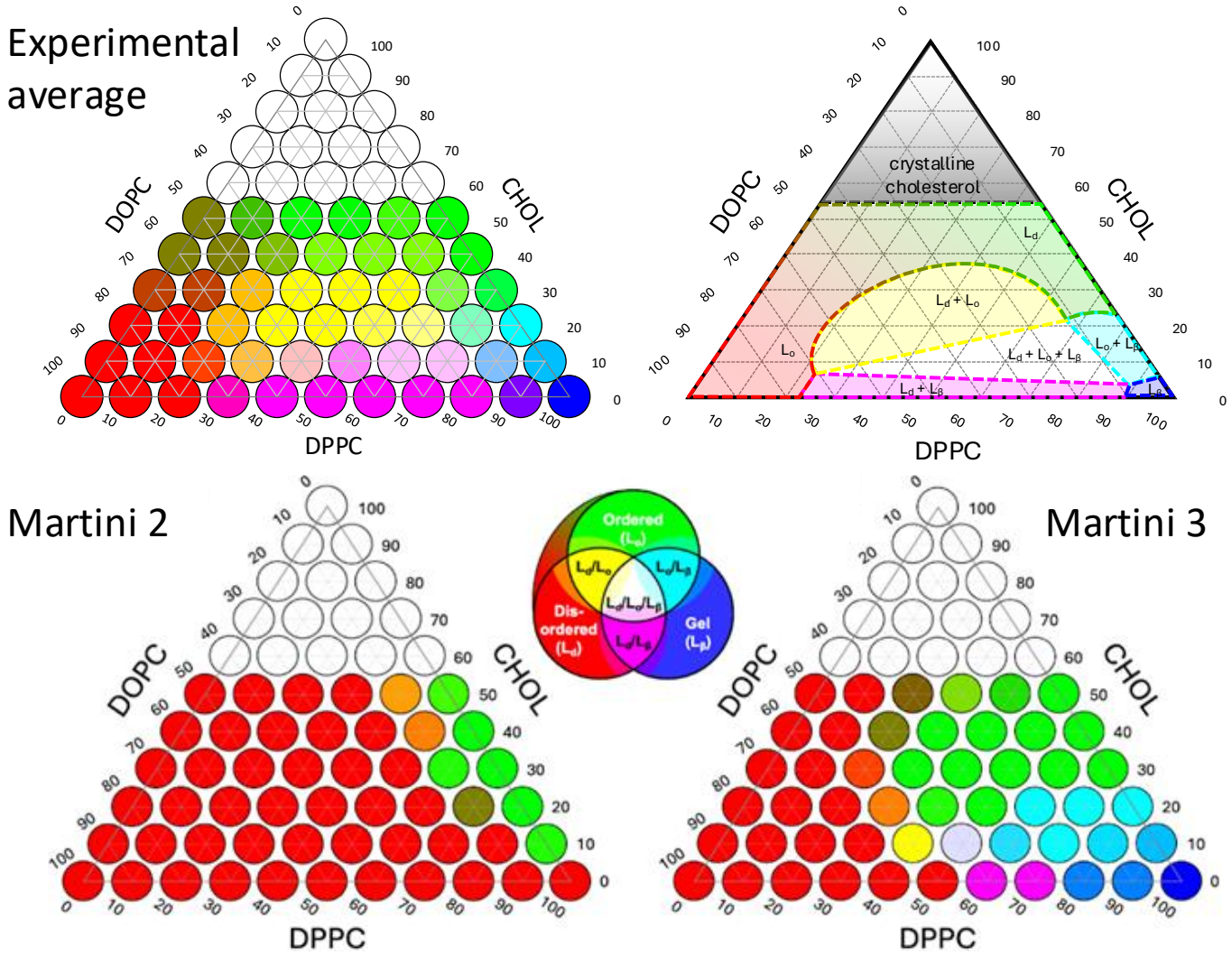

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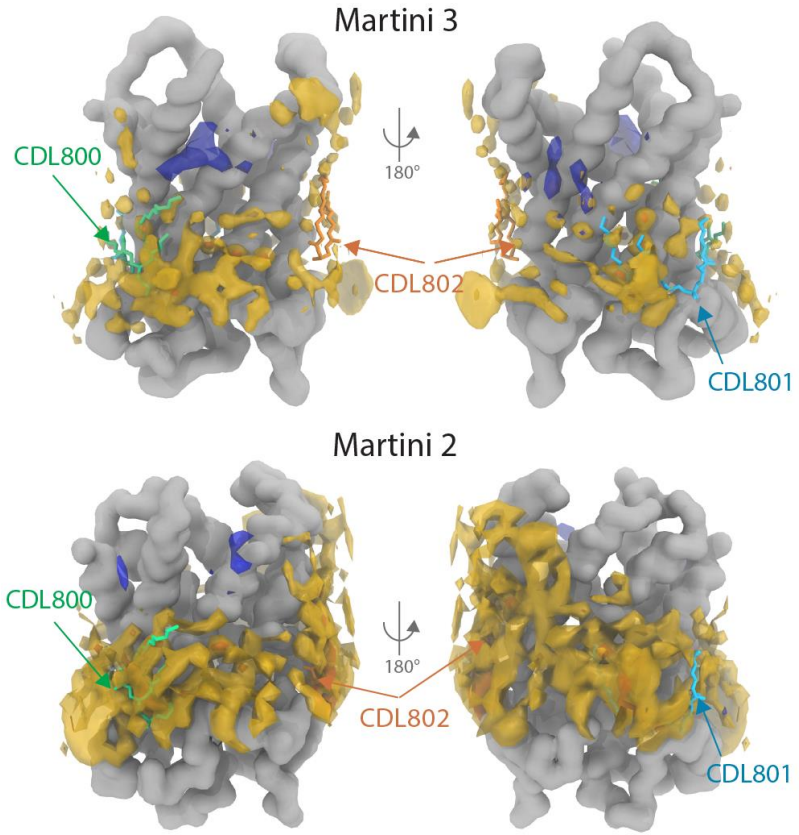

POCL and POPC arrangement around the ADP/ATP carrier

K. Pedersen et al. The Martini 3 Lipidome: Expanded and Refined Parameters Improve Lipid Phase Behavior. ACS Cent. Sci. 2025

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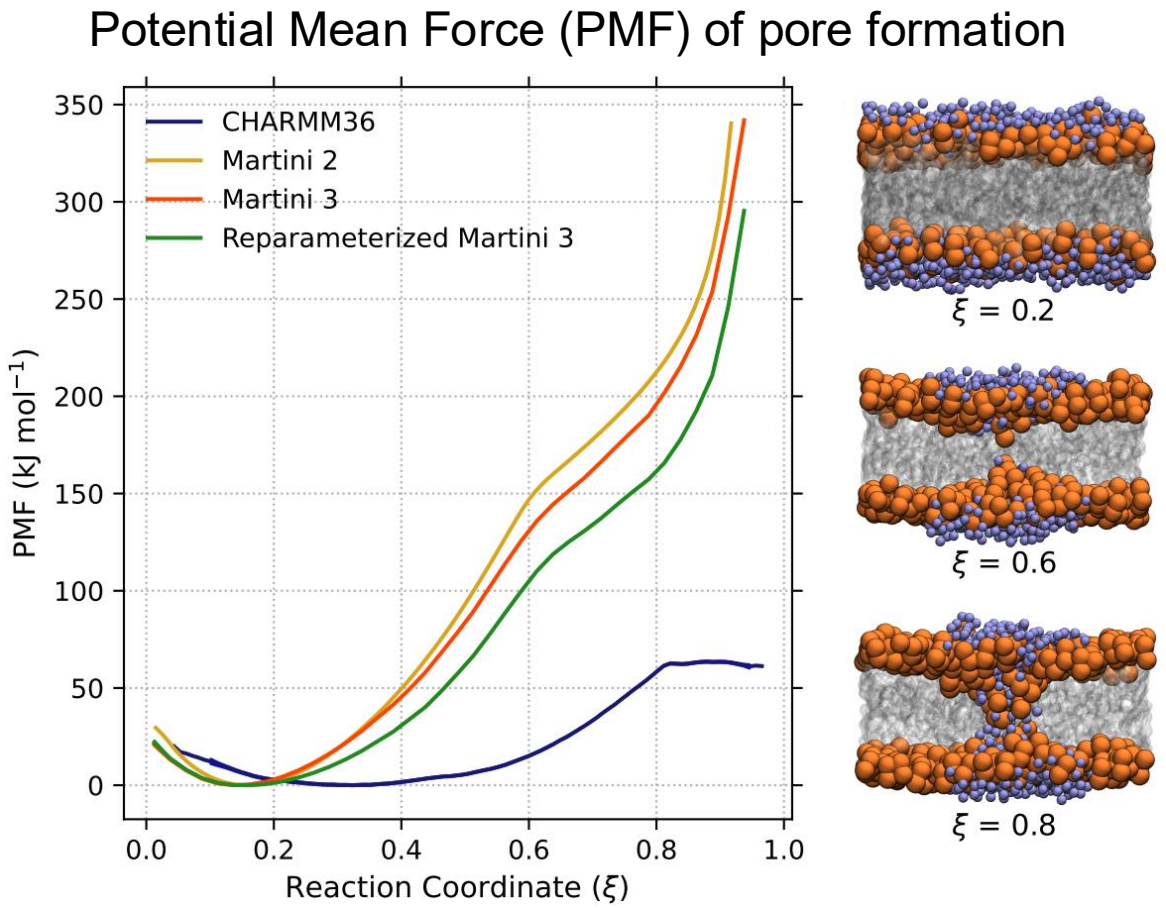

K. Pedersen et al. The Martini 3 Lipidome: Expanded and Refined Parameters Improve Lipid Phase Behavior. ACS Cent. Sci. 2025

Lipidome – Martini 3 lipidomics

The Martini 3 lipidome

- Lipid building blocks
- Lipid topology generator supporting all major headgroup and tail groups
- Setup with *insane* (next talk)
- Some changes in tail nomenclature
- https://github.com/Martini-Force-Field-Initiative/M3-Lipid-Parameters

One letter name	Bead assignment[b]	Corresponding atomistic tails	Examples of corresponding fatty acid names[c]
T	cC	C8:0	C08:0 octanoyl
J	CC	C10:0	C10:0 decanoyl
U	cCC	C12:0	C12:0 lauroyl
M	CCC	C14:0	C14:0 myristoyl
P	cCCC	C16:0	C16:0 palmitoyl
S	CCCC	C18:0	C18:0 stearoyl
K	cCCCC	C20:0	C20:0 arachidoyl
B	CCCCC	C22:0	C22:0 behenoyl
X	cCCCCC	C24:0	C24:0 lignoceroyl
C	CCCCCC	C26:0	C26:0 hexacosanoyl
R	CDC	C14:1	C14:1(9c) myristoleoyl
Y	cCDC	C16:1	C16:1(9c) palmitoleoyl
O	CDCC	C18:1	C18:1(9c) oleoyl
G	cCDCC	C20:1	C20:1(11c) eicosenoyl (11-eicosenoic acid) or gondoic acid
E	CCDCC	C22:1	C22:1(11c) or C22:1(13c) erucoyl
N	cCCDCC	C24:1	C24:1(15c) nervonic acid
V	CCDC	C18:1	C18:1(11c) cis-vaccenic acid
L	CDDC	C18:2	C18:2(9c,12c) linoleoyl
F	CDDD	C18:3	C18:3(9c,12c,15c) alpha-linolenic acid
I	cCDDC	C20:2	C20:2(11c,14c) eicosadienoyl
Q	cDDDC	C20:3	C20:3(8c,11c,14c) eicosatrienoyl or dihomo-gamma-linolenic acid
A	cFFDC	C20:4	C20:4(5c,8c,11c,14c) arachidonoyl
D[a]	DFFDD	C22:6	C22:6(4c,7c,10c,13c,16c,19c) docosahexaenoic acid

K. Pedersen et al. The Martini 3 Lipidome: Expanded and Refined Parameters Improve Lipid Phase Behavior. ACS Cent. Sci. 2025

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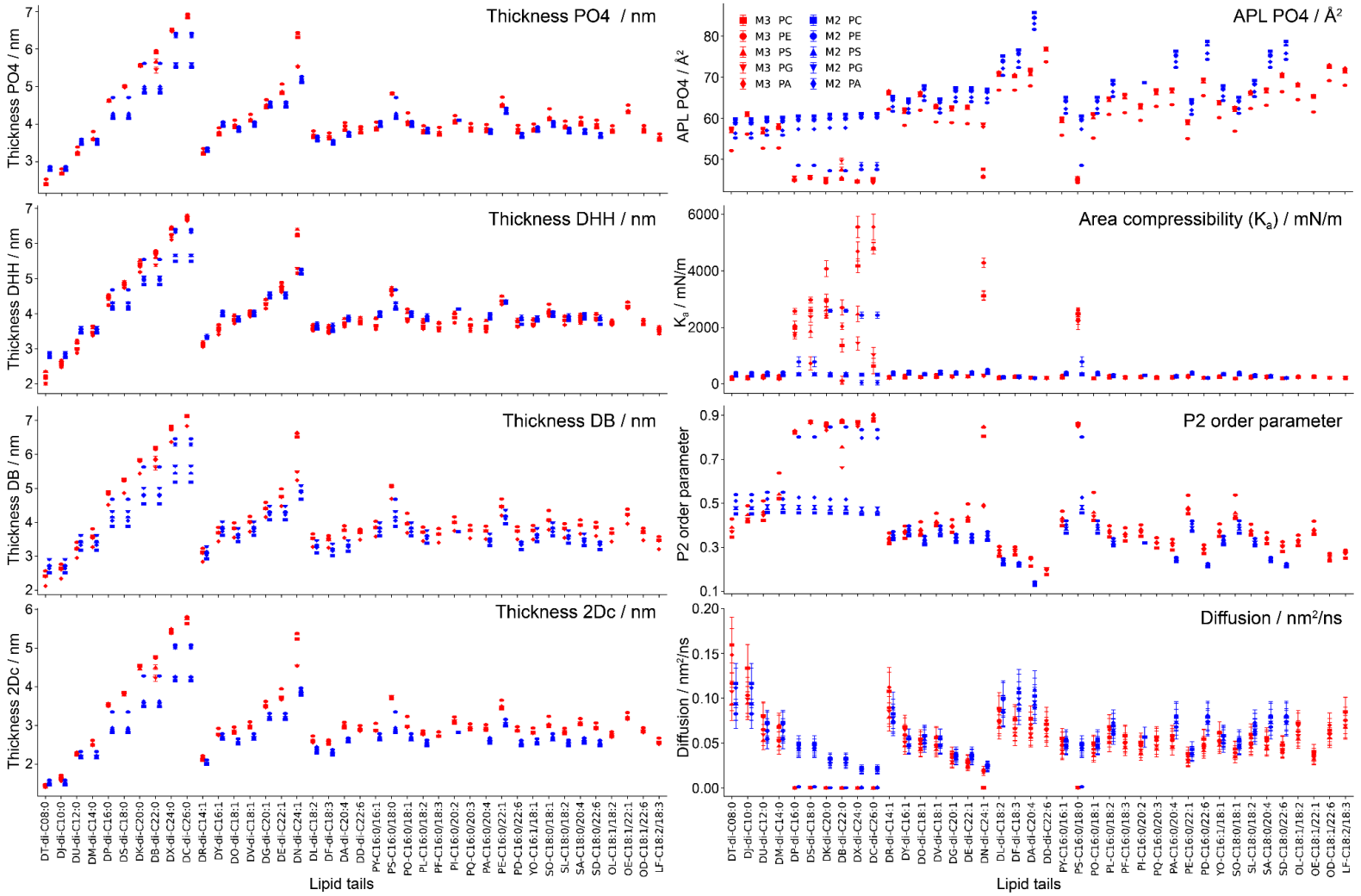


K. Pedersen et al. The Martini 3 Lipidome: Expanded and Refined Parameters Improve Lipid Phase Behavior. ACS Cent. Sci. 2025

Lipidome – Martini 3 lipidomics

- **Cholesterol**

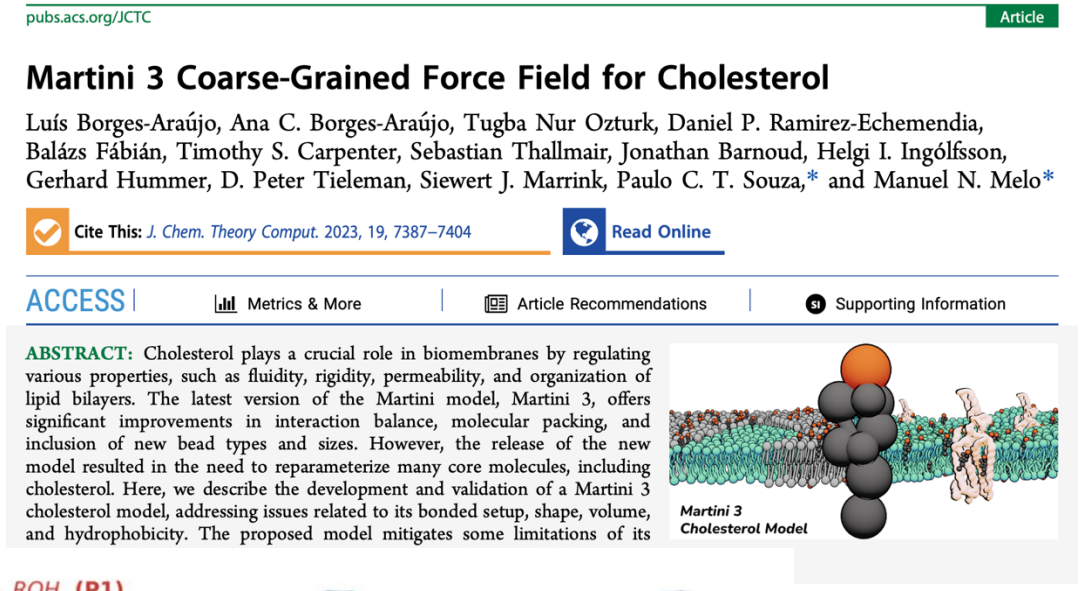
Updated bonded setup, shape, volume, and hydrophobicity

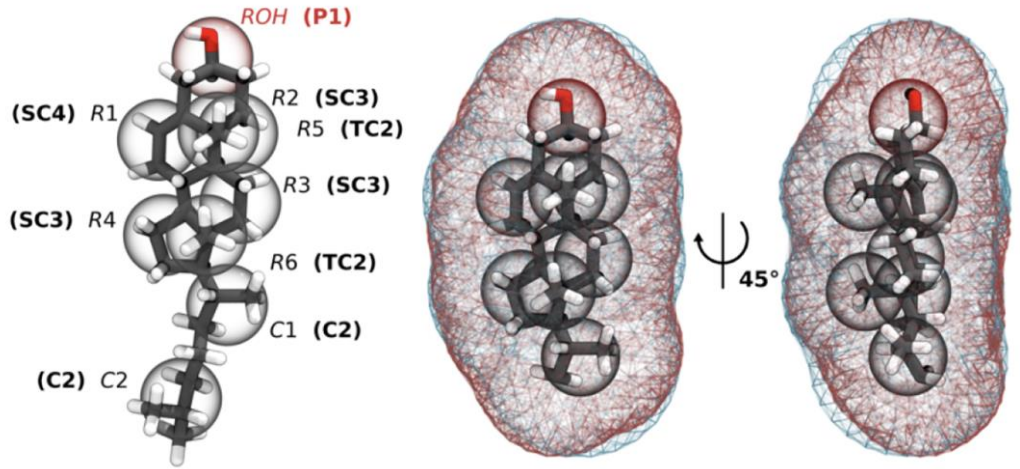
- **Phosphatidylinositol**

Improved conformational dynamics and stability for all PIPs

- **Glycolipids**

Some lipopolysaccharide (LPS) and a protocol for parameterizing disaccharides





Luís Borges-Araújo et al. (2023). Martini 3 Coarse-Grained Force Field for Cholesterol . *J. Chem. Theory Comput. 2023, 19, 7387−7404*

Lipidome – Martini 3 lipidomics

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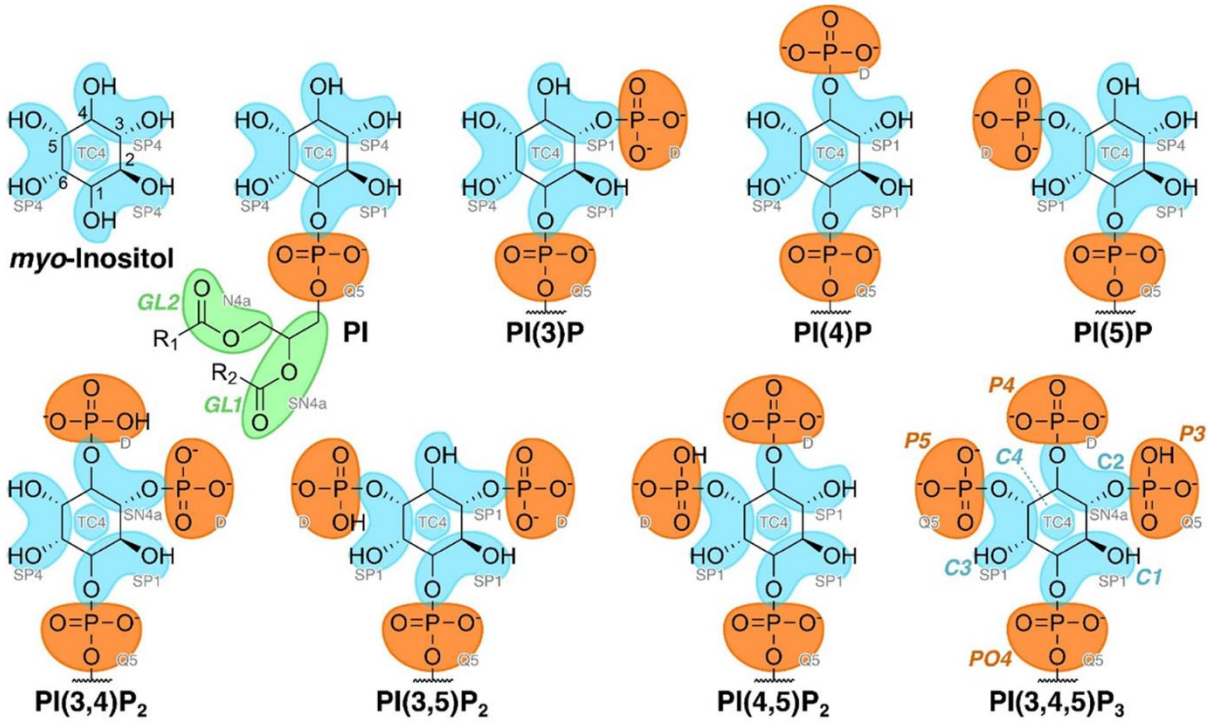

Luís Borges-Araújo et al. (2022). Improved Parameterization of Phosphatidylinositide Lipid Headgroups for the Martini 3 Coarse-Grain Force Field. *J. Chem. Theory Comput.* 2022, 18, 357−373

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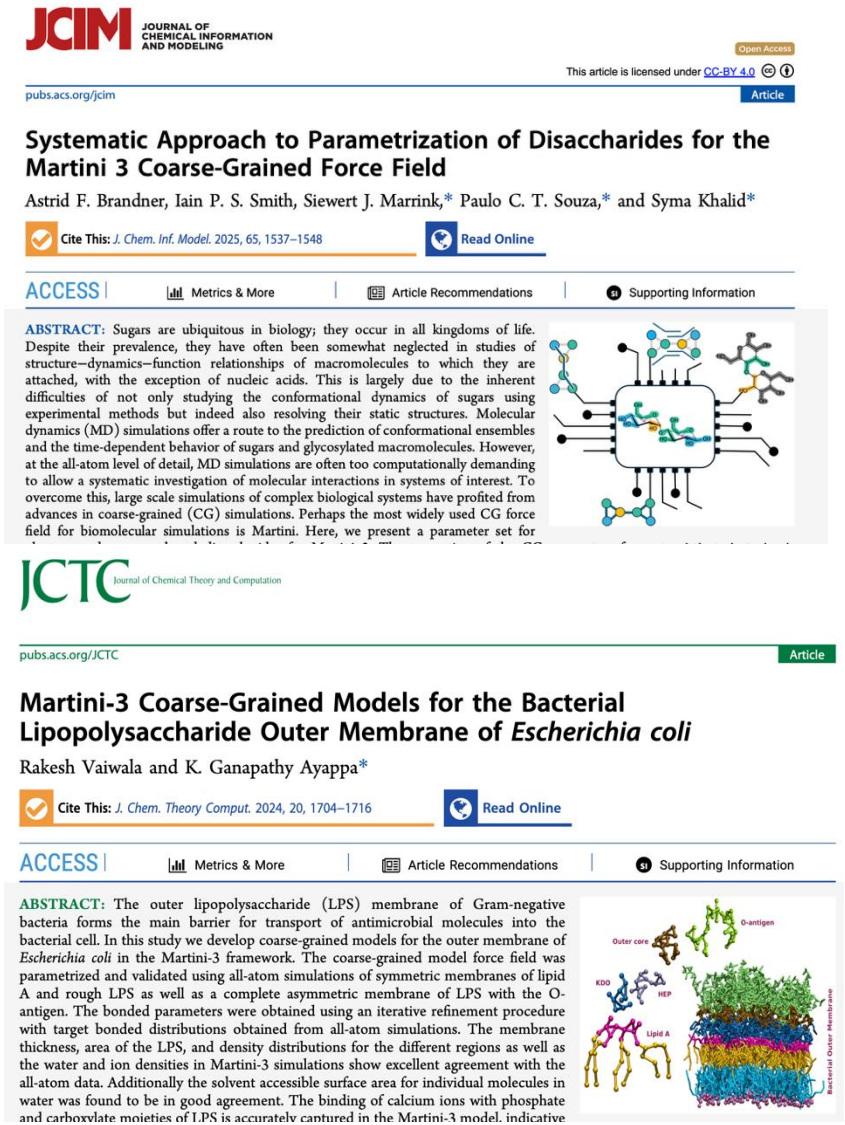

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

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Systematic Approach to Parametrization of Disaccharides for the Martini 3 Coarse-Grained Force Field

Astrid F. Brandner, Iain P. S. Smith, Siewert J. Marrink,* Paulo C. T. Souza,* and Syma Khalid*

Cite This: *J. Chem. Inf. Model.* 2025, 65, 1537−1548 Read Online

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ABSTRACT: Sugars are ubiquitous in biology; they occur in all kingdoms of life. Despite their prevalence, they have often been somewhat neglected in studies of structure−dynamics−function relationships of macromolecules to which they are attached, with the exception of nucleic acids. This is largely due to the inherent difficulties of not only studying the conformational dynamics of sugars using experimental methods but indeed also resolving their static structures. Molecular dynamics (MD) simulations offer a route to the prediction of conformational ensembles and the time-dependent behavior of sugars and glycosylated macromolecules. However, at the all-atom level of detail, MD simulations are often too computationally demanding to allow a systematic investigation of molecular interactions in systems of interest. To overcome this, large scale simulations of complex biological systems have profited from advances in coarse-grained (CG) simulations. Perhaps the most widely used CG force field for biomolecular simulations is Martini. Here, we present a parameter set for

JCTC Journal of Chemical Theory and Computation

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Martini-3 Coarse-Grained Models for the Bacterial Lipopolysaccharide Outer Membrane of *Escherichia coli*

Rakesh Vaiwala and K. Ganapathy Ayappa*

Cite This: *J. Chem. Theory Comput.* 2024, 20, 1704−1716 Read Online

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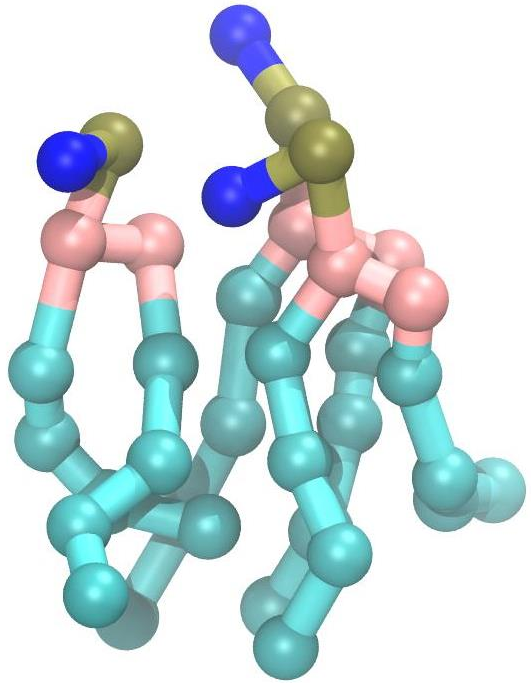
ABSTRACT: The outer lipopolysaccharide (LPS) membrane of Gram-negative bacteria forms the main barrier for transport of antimicrobial molecules into the bacterial cell. In this study we develop coarse-grained models for the outer membrane of *Escherichia coli* in the Martini-3 framework. The coarse-grained model force field was parametrized and validated using all-atom simulations of symmetric membranes of lipid A and rough LPS as well as a complete asymmetric membrane of LPS with the O-antigen. The bonded parameters were obtained using an iterative refinement procedure with target bonded distributions obtained from all-atom simulations. The membrane thickness, area of the LPS, and density distributions for the different regions as well as the water and ion densities in Martini-3 simulations show excellent agreement with the all-atom data. Additionally the solvent accessible surface area for individual molecules in water was found to be in good agreement. The binding of calcium ions with phosphate and carboxylate moieties of LPS is accurately captured in the Martini-3 model, indicative

Make your own lipid Martini force field

- Bartender, SwarmCG, etc
- Use what already exists
- Rationalize changes
- Current naming standards
- Be aware of over fitting
- Test, test and test
- .itp file format
- Make accessible to others, git, MAD, Martini website



Martini Examples – lipid domains

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Disaccharides Impact the Lateral Organization of Lipid Membranes

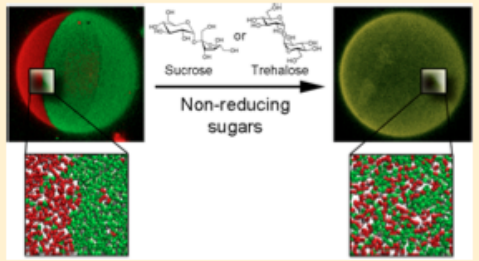
Gemma Moiset,[†] Cesar A. López,[†] Rianne Bartelds,[†] Lukasz Syga,[†] Egon Rijpkema,[†] Abhishek Cukkemane,[‡] Marc Baldus,[‡] Bert Poolman,*[,†] and Siewert J. Marrink*[,†]

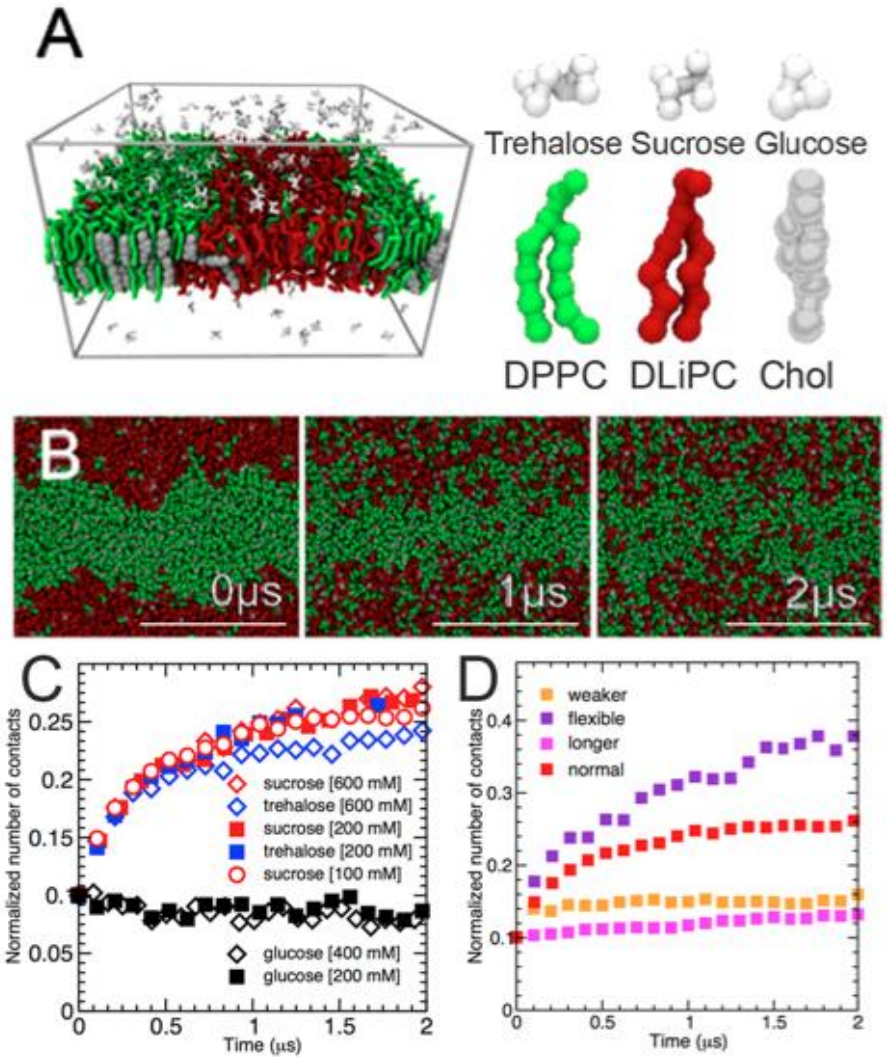
[†]Groningen Biomolecular Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands

[‡]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 – complex membranes

Biochimica et Biophysica Acta 1848 (2015) 1319–1330

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

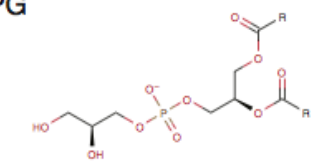
journal homepage: www.elsevier.com/locate/bbamem

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

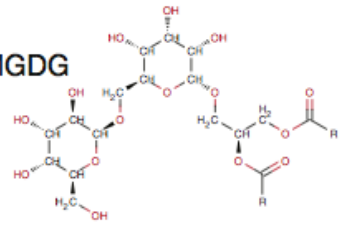
Floris J. van Eerden [a,*], Djurre H. de Jong [b], Alex H. de Vries [a], Tsjerk A. Wassenaar [c], Siewert J. Marrink [a]

[a] Groningen Biomo
[b] Institut für Physik
[c] Computational Bi
roningen, The Netherlands

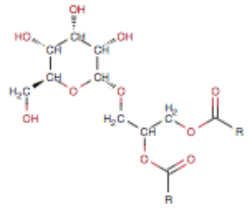
PG



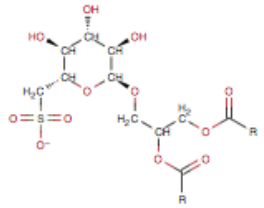
MGDG

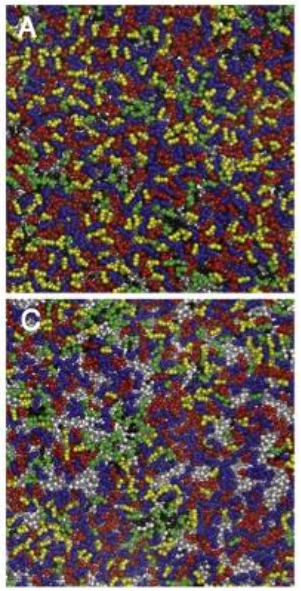


DGDG



SQDG





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 membranes

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PLOS | COMPUTATIONAL BIOLOGY

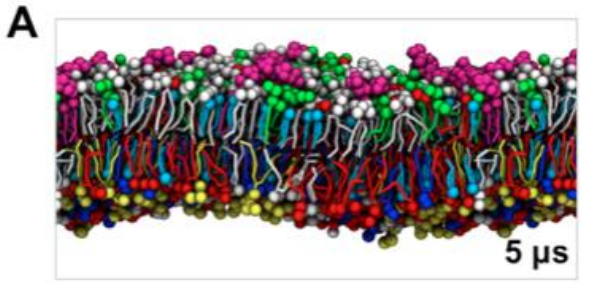
Lipid Clustering Correlates with Membrane Curvature as Revealed by Molecular Simulations of Complex Lipid Bilayers

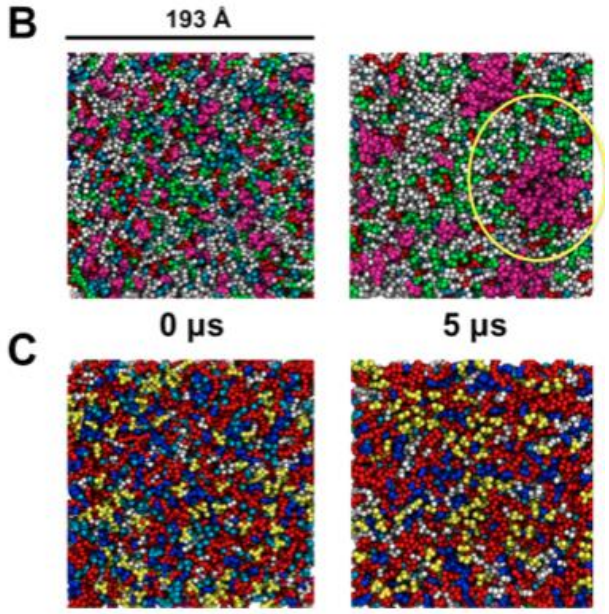
Heidi Koldsø, David Shorthouse, Jean Hélie, Mark S. P. Sansom*

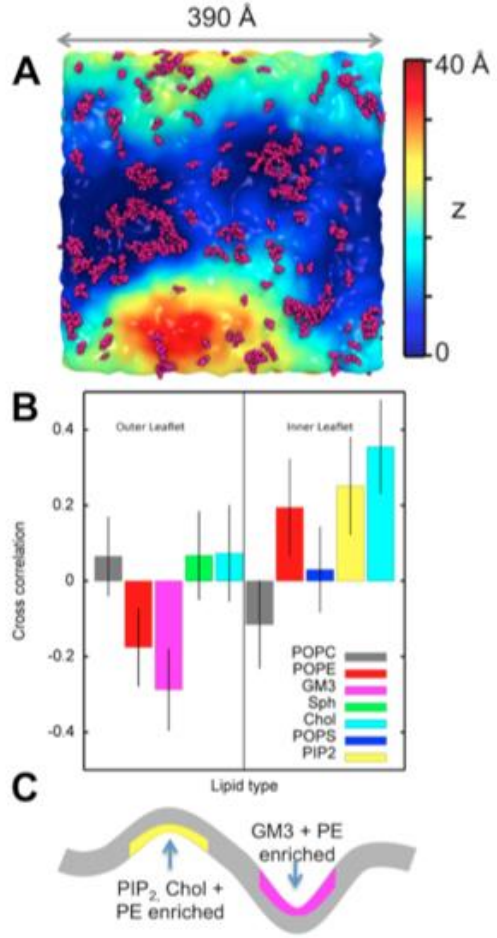
Department of Biochemistry, University of Oxford, Oxford, United Kingdom

Abstract

Cell membranes are complex multicomponent systems, which are highly heterc
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.

Martini Examples – complex membranes

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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
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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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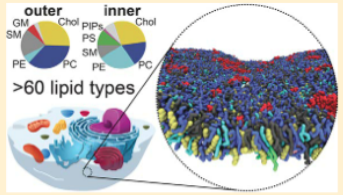
[‡]Computational Biology, Department of Biology, University of Erlangen-Nürnberg, Staudtstr. 5, 91052 Erlangen, Germany

[§]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 membranes remains rather elusive. Based on large-scale molecular dynamics simulations, we provide a high-resolution view of the lipid organization of a plasma membrane at an unprecedented level of complexity. Our plasma membrane model consists of 63 different lipid species, combining 14 types of headgroups and 11 types of tails asymmetrically distributed across the two leaflets, closely mimicking an idealized mammalian plasma membrane. We observe an enrichment of cholesterol in the outer leaflet and a general non-ideal lateral mixing of the different lipid species. Transient domains with liquid-ordered character form and disappear on the microsecond time scale. These domains are coupled across the two membrane leaflets. In the outer leaflet, distinct nanodomains consisting of gangliosides are observed. Phosphoinositides show preferential clustering in the inner leaflet. Our data provide a key view on the lateral organization of lipids in one of life's fundamental structures, the cell membrane.



Biophysical Journal
Article
Biophysical Society

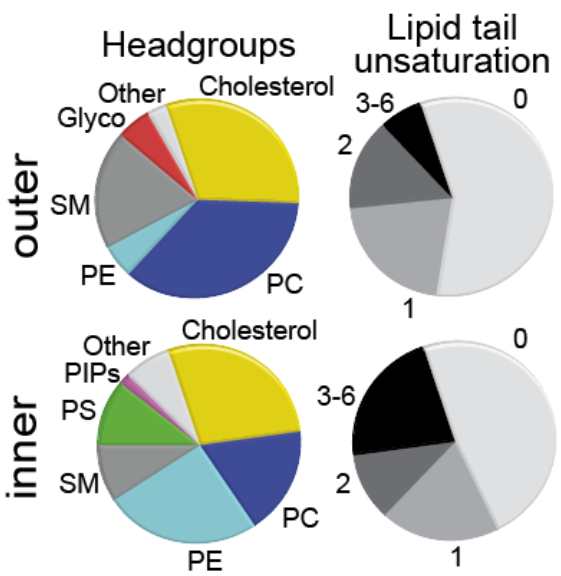
Computational Lipidomics of the Neuronal Plasma Membrane

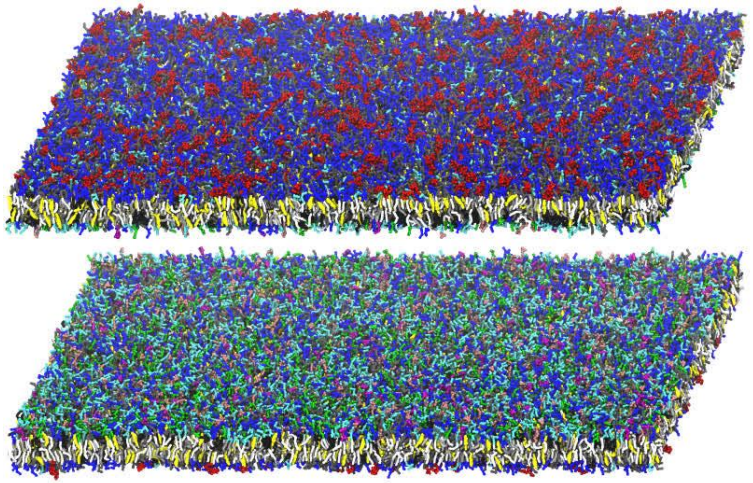
Helgi I. Ingólfsson,[1] Timothy S. Carpenter,[1] Harsh Bhatia,[2] Peer-Timo Bremer,[2] Siewert J. Marrink,[3] and Felice C. Lightstone[1,*]

[1]Biosciences and Biotechnology Division, Physical and Life Sciences Directorate; [2]Center for Applied Scientific Computing (CASC), Computational Directorate, Lawrence Livermore National Laboratory, Livermore, California; and [3]Groningen Biomolecular Science and Biotechnology Institute and the Zernike Institute for Advanced Materials, University of Groningen, Groningen, the Netherlands

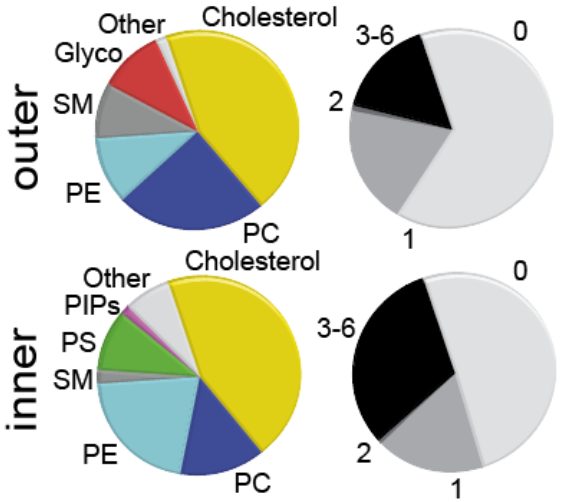
ABSTRACT Membrane lipid composition varies greatly within submembrane compartments, different organelle membranes, and also between cells of different cell stage, cell and tissue types, and organisms. Environmental factors (such as diet) also influence membrane composition. The membrane lipid composition is tightly regulated by the cell, maintaining a homeostasis that, if disrupted, can impair cell function and lead to disease. This is especially pronounced in the brain, where defects in lipid

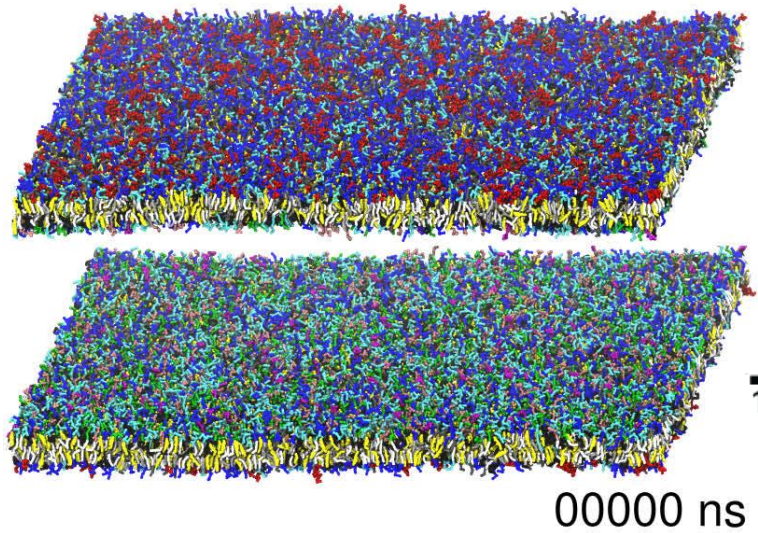
Avg.





Brain





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.

Ingólfsson, H. I., et al. (2017). Computational Lipidomics of the Neuronal Plasma Membrane. *Biophysical Journal* 113, 2271–2280.

Martini Examples – lipids fingerprints

ACS central science

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Research Article

Cite This: ACS Cent. Sci. XXXX, XXX, XXX−XXX

Lipid–Protein Interactions Are Unique Fingerprints for Membrane Proteins

Valentina Corradi,[†] Eduardo Mendez-Villuendas,[†] Helgi I. Ingólfsson,[‡] Ruo-Xu Gu,[†] Iwona Siuda,[†] Manuel N. Melo,[‡] Anastassiia Moussatova,[†] Lucien J. DeGagné,[†] Besian I. Sejdiu,[†] Gurpreet Singh,[†] Tsjerk A. Wassenaar,[‡] Karelia Delgado Magnero,[†] Siewert J. Marrink,[‡] and D. Peter Tieleman*,[†]

y of Calgary, 2500 University Drive NW, Calgary,

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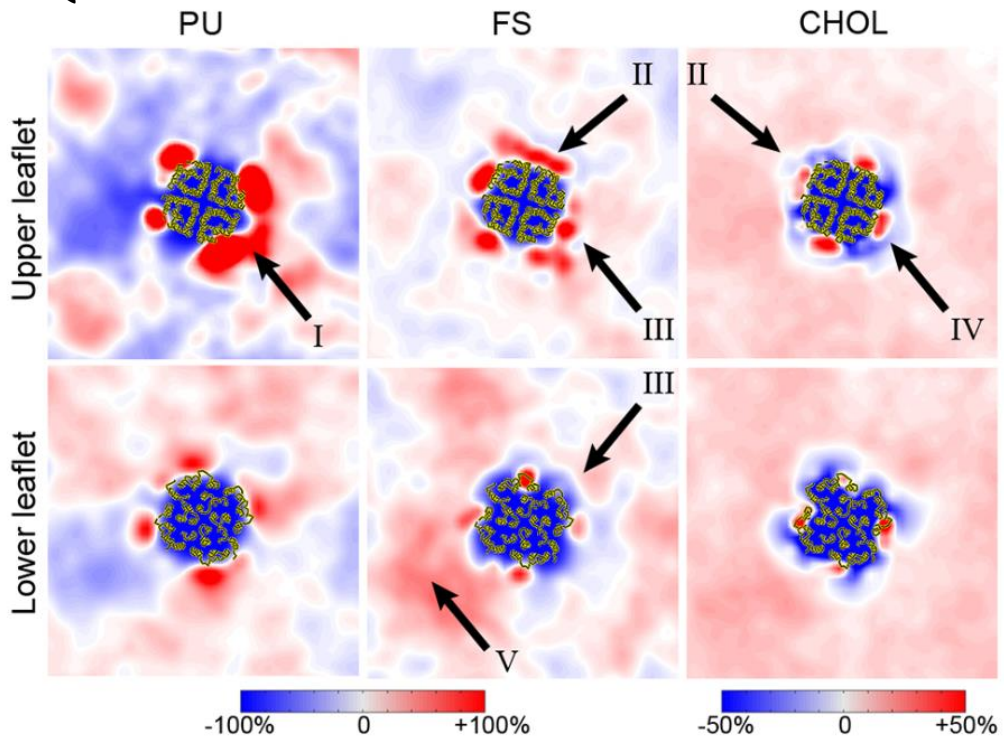
ds in an asymmetric membranes remains of lipids and proteins mics simulations to ovide a realistic lipid more than 60 lipid mulations detail how ichment or depletion Our results provide a tentially far-reaching branes.

AQP1

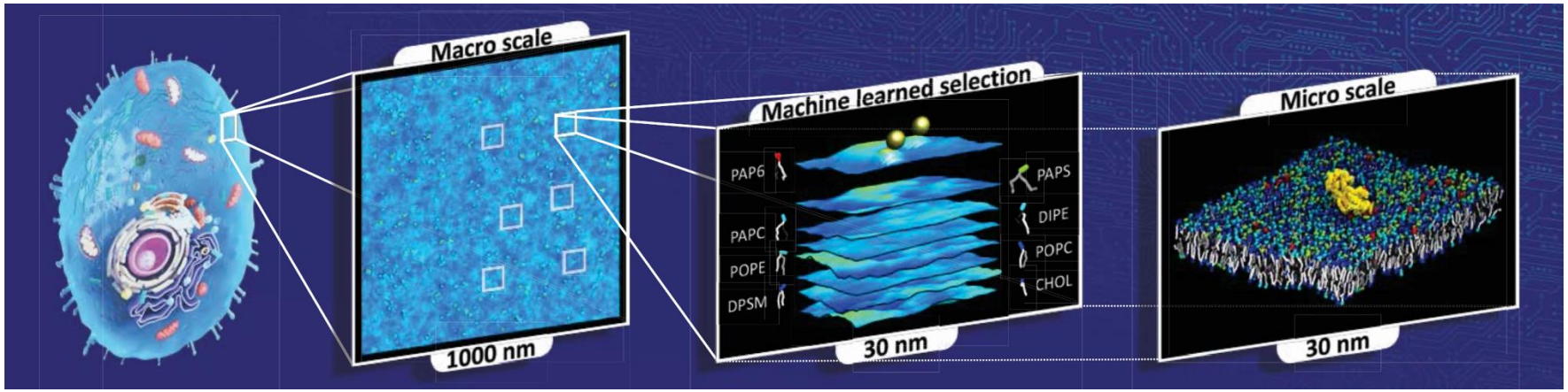


	AQP1	COX1	DAT	EGFR	GluA2	GLUT1	Kv1.2	Na,K-ATPase	δ-OPR	P-gp
PC	0.40	0.77	0.46	0.22	0.57	0.30	0.39	0.39	0.23	0.41
PE	1.00	0.62	1.34	0.83	1.38	1.26	1.17	1.00	0.96	1.65
PS	1.05	-	1.13	0.64	1.23	1.24	1.20	0.70	1.02	1.41
PA	1.80	-	1.78	1.42	1.00	0.83	0.52	0.73	1.90	2.17
DAG	2.95	9.59	7.02	4.68	10.62	3.25	2.52	7.68	4.57	3.25
LPC	0.14	1.41	0.30	0.03	0.09	0.28	0.12	0.43	0.57	0.30
SM	0.24	0.43	0.17	0.29	0.27	0.21	0.15	0.13	0.22	0.18
CER	0.50	3.46	0.25	2.77	0.28	0.37	0.54	0.21	0.25	0.26
PI	1.96	-	2.83	2.69	1.61	1.71	3.21	2.38	1.23	2.43
PIPs	9.05	-	6.66	17.05	1.09	10.28	4.16	9.18	8.72	5.36
GM	5.76	8.94	6.37	4.98	3.81	5.97	5.56	6.47	6.82	4.06
CHOL	1.18	1.04	0.81	1.22	1.04	1.10	1.21	1.13	1.29	1.00
FS	1.26	1.70	1.26	1.11	0.68	1.05	0.90	1.40	0.99	0.87
PU	1.76	1.33	4.16	0.89	4.57	3.89	2.96	2.99	2.10	4.79
Others	0.82	0.84	0.87	0.87	0.83	0.77	0.79	0.75	0.79	0.80

Corradi et al. (2018). Lipid–Protein Interactions Are Unique Fingerprints for Membrane Proteins. *ACS Cent. Sci.*, doi: 10.1021/acscentsci.8b00143.

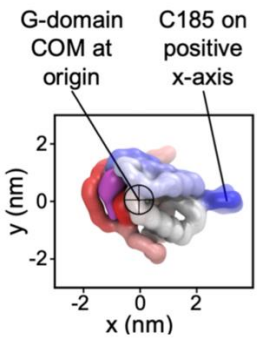
Martini Examples – lipids fingerprints

MuMMI multiscale simulations to highlight RAS plasma membrane dynamics

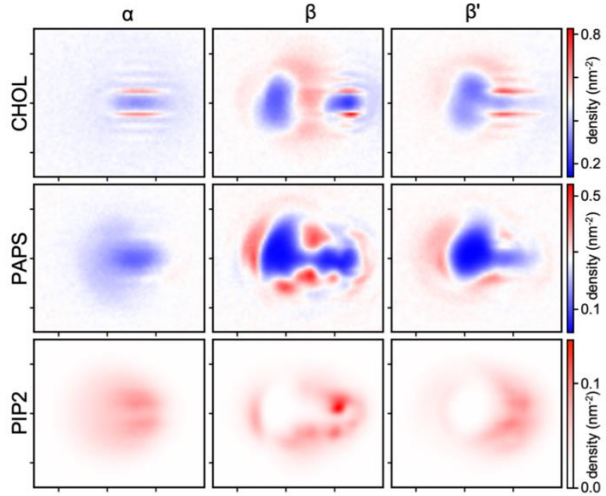


- A very-large and well sampled simulation ensemble (120K simulations with different PM compositions)
- Revealed strong RAS-lipid coupling
- Lipid composition dictating RAS aggregation and membrane configuration

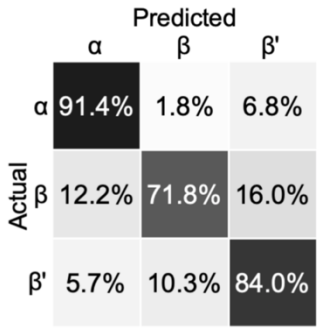
RAS



Averaged lipid densities for different RAS states



ML RAS state prediction from lipid snapshots



Ingólfsson, Neale, Carpenter, et al. 2022. Machine learning-driven multiscale modeling reveals lipid-dependent dynamics of RAS signaling proteins. *PNAS*

Di Natale et al. 2019. A massively parallel infrastructure for adaptive multiscale simulations: modeling RAS initiation pathway for cancer. In *SC19*.

Martini Examples – membrane deformation/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 Mem
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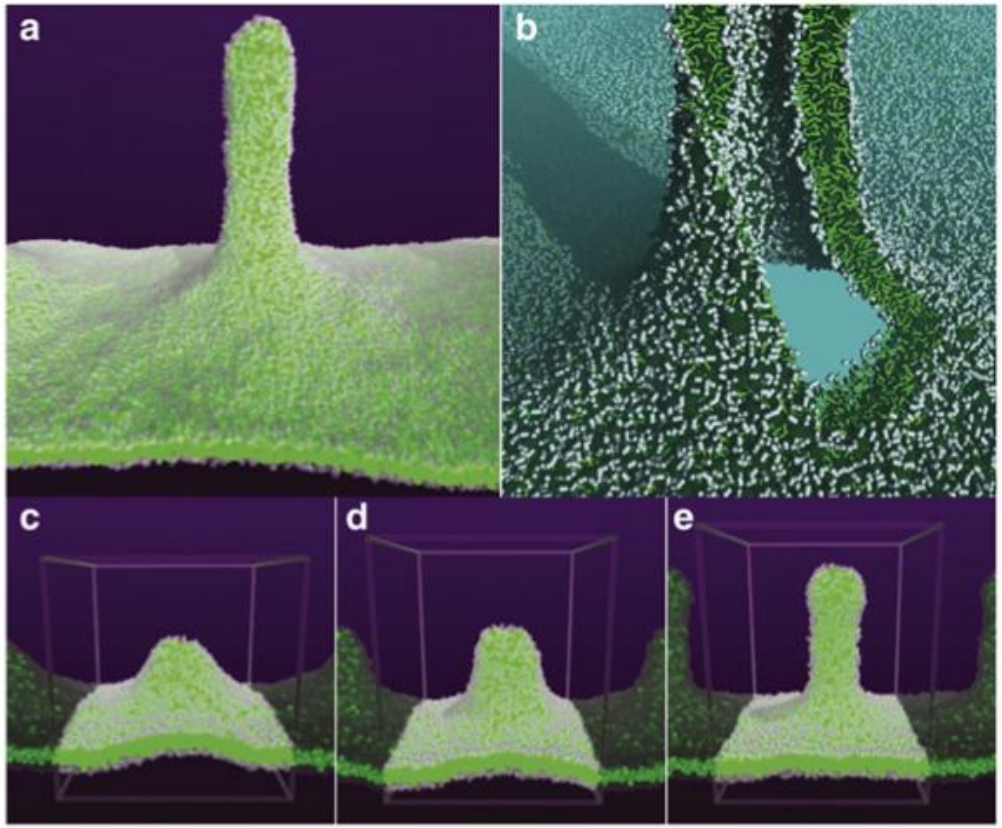

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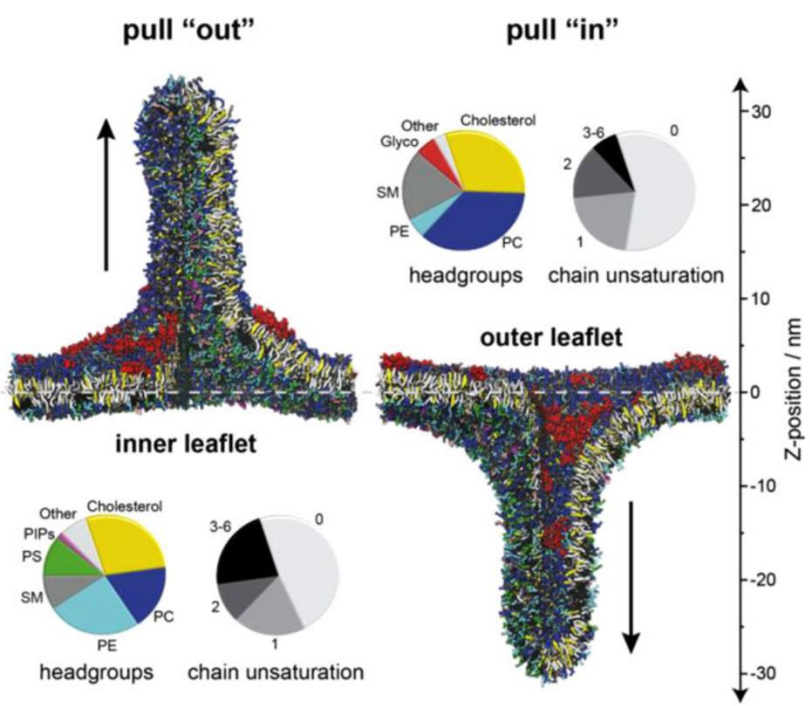
Curvature-Induced Sorting of Lipids in Plasma Membrane Tethers

*Svetlana Baoukina, Helgi I. Ingólfsson, Siewert J. Marrink, and D. Peter Tieleman**

Membrane curvature controls the spatial organization and activity of cells. Lipid sorting in cell… shape to regions of… curvature-induced… dynamics. A model…

spontaneous curvatures of lipids alone are insufficient; high curvatures of intracellu- …ermediates …ant leaflet …by special However, generated



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

Baoukina, S., H.I. Ingolfsson, S.J. Marrink, and D.P. Tieleman. 2018. Curvature-Induced Sorting of Lipids in Plasma Membrane Tethers. *Adv. Theory Simul.* 2018, 1800034

Martini Examples – small molecules change membrane bulk properties

ACS chemical biology

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Open Access on 06/05/2015

Phytochemicals Perturb Membranes and Promiscuously Alter Protein Function

Helgi I. Ingólfsson,*[,†,‡] Pratima Thakur,[§] Karl F. Herold,[∥] E. Ashley Hobart,[⊥] Nicole B. Ramsey,[⊥] Xavier Periole,[‡] Djurre H. de Jong,[†,‡] Martijn Zwama,[‡] Duygu Yilmaz,[‡] Katherine Hall,[#] Thorsten Maretzky,[#] Hugh C. Hemmings, Jr.,[∥] Carl Blobel,[#] Siewert J. Marrink,[†,‡] Armağan Koçer,[‡] Jon T. Sack,*[,§] and Olaf S. Andersen*[,⊥]

[†]Zernike Institute for Advanced Materials, [‡]Groningen Biomolecular Science and Biotechnology Institute, University of Groningen, Groningen, The Netherlands

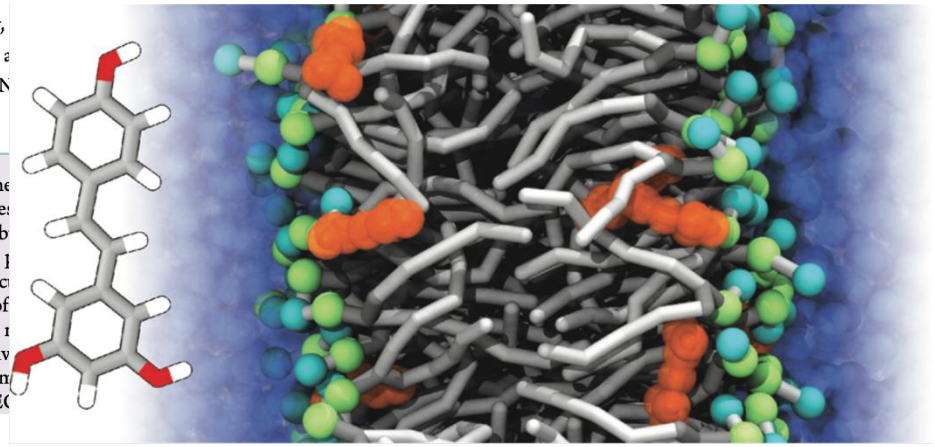
[§]Dept. Physiology and Membrane Biology,

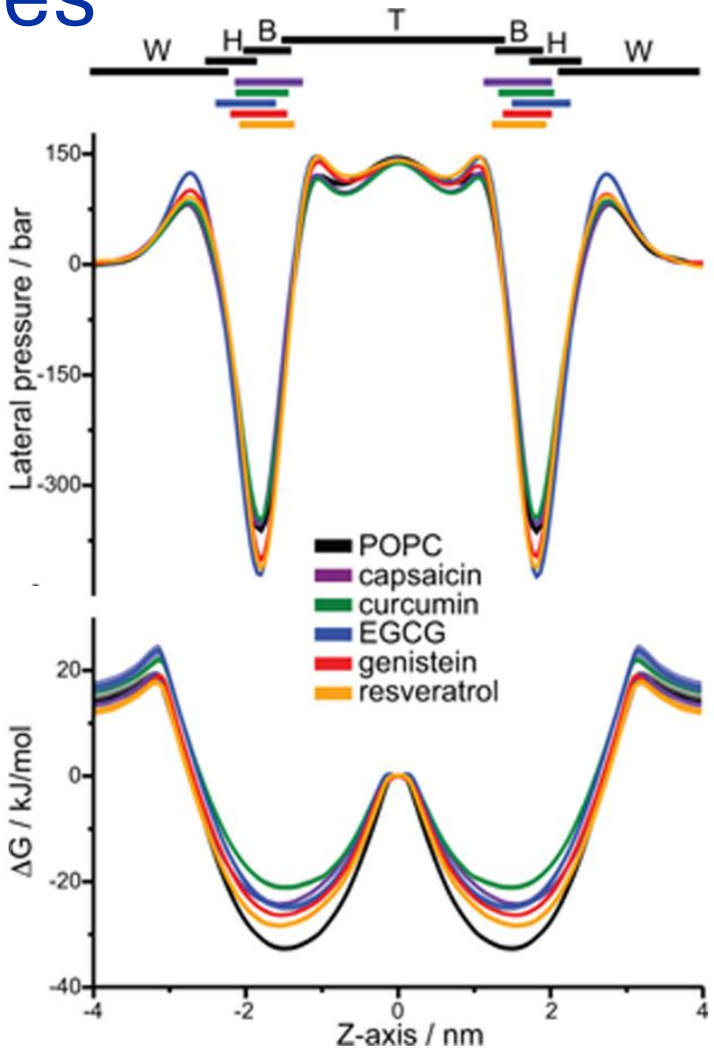
[∥]Dept. Anesthesiology, [⊥]Dept. Physiology a

[#]Hospital for Special Surgery, New York, N

Supporting Information

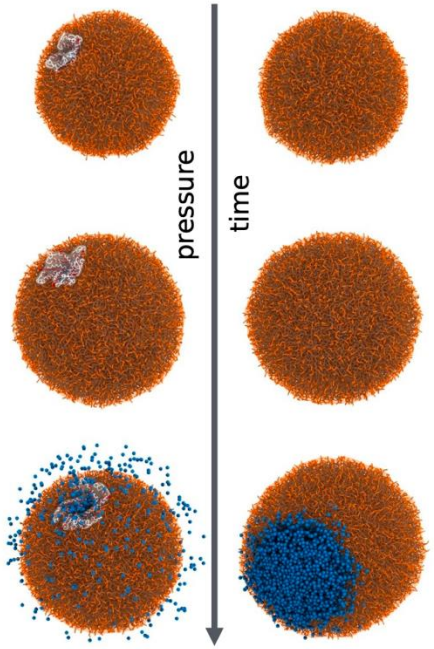
ABSTRACT: A wide variety of phytoche
perceived health benefits. Many of thes
found to alter numerous cell functions, b
their biological activity tend to be p
phytochemicals are particularly promisc
protein function, suggesting that some of
common, membrane bilayer-mediated r
bilayer perturbation may underlie this div
five bioactive phenols reported to have n
chili peppers, curcumin from turmeric, EG

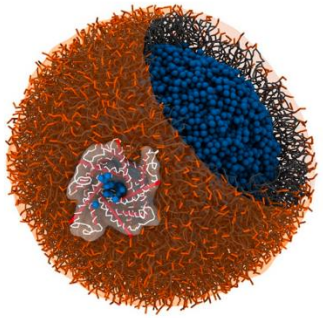




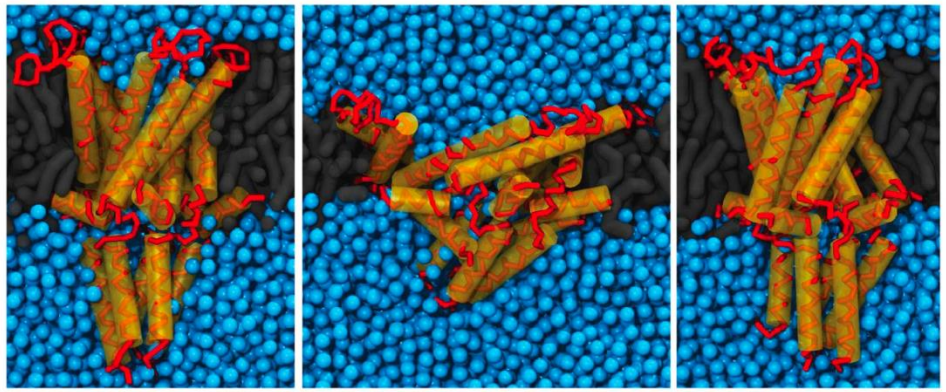
H.I. Ingolfsson, et al. 2015. Phytochemicals Perturb Membranes and Promiscuously Alter Protein Function. *ACS Chem. Biol.* 2014, 9, 1788−1798

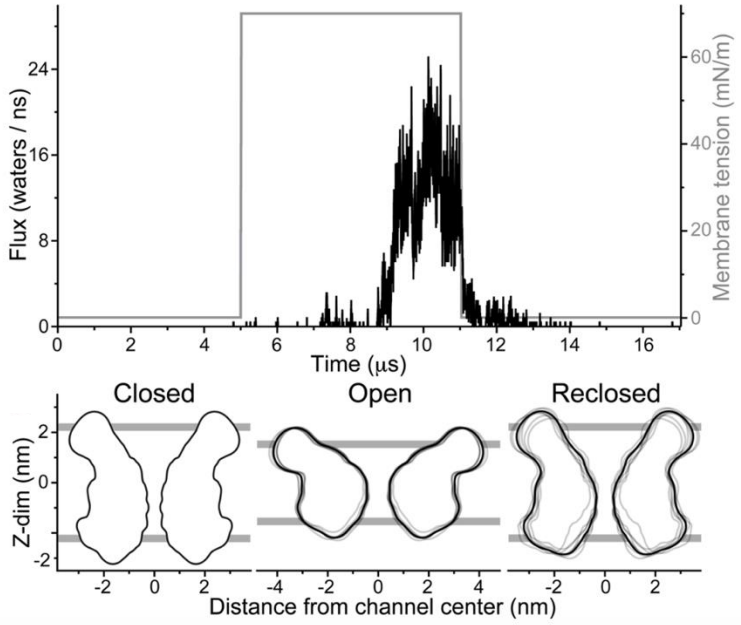
Martini Examples – proteins sensing change in membrane properties

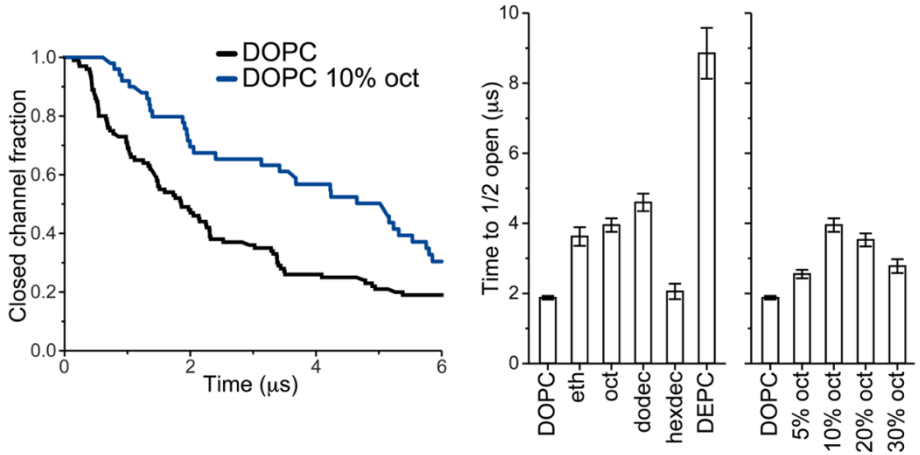




Gating of MscL embedded in a vesicle/bilayer under high tension



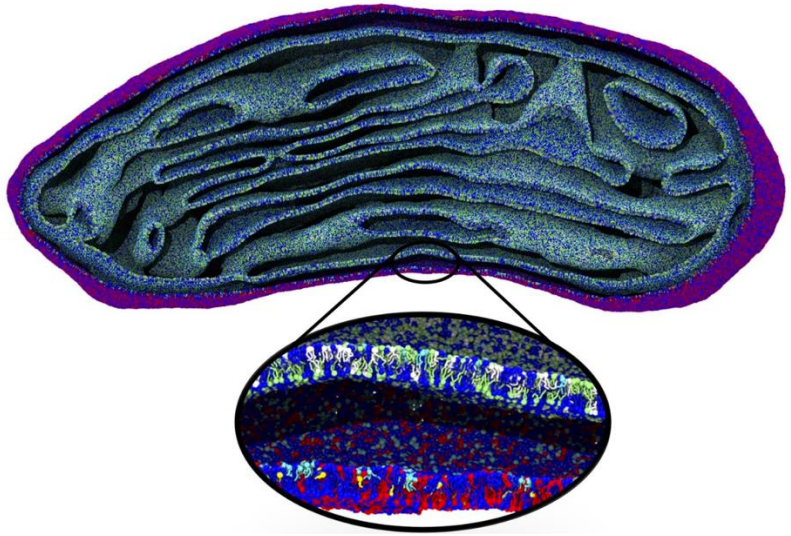




Louhivuori, Proc. Nat. Ac. Sci., 2010 Melo, JACS, 2017

Melo et al. 2017. High-Throughput Simulations Reveal Membrane-Mediated Effects of Alcohols on MscI Gating. *J. Am. Chem. Soc.*, 139, 2664−2671

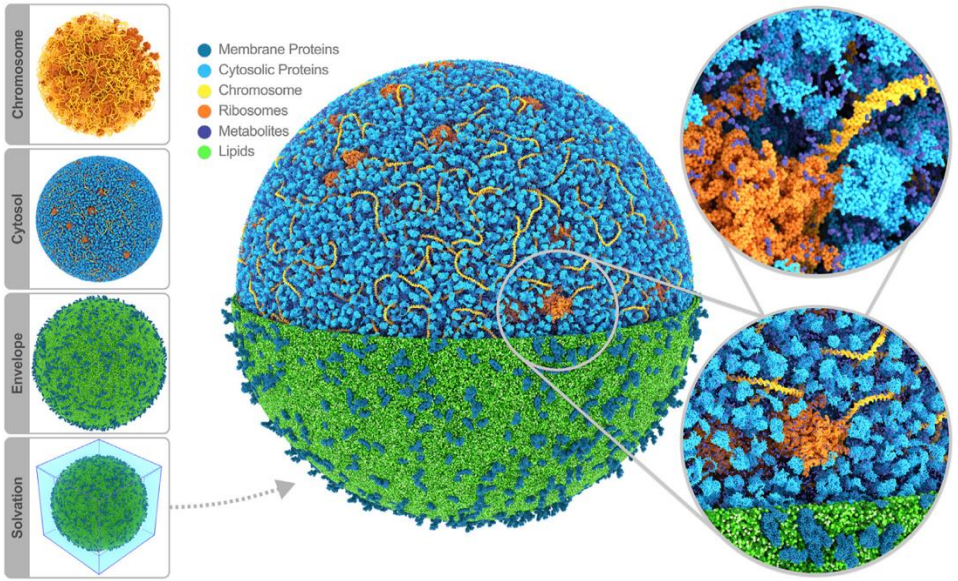
Martini Examples – even bigger and more complex



https://doi.org/10.1038/s41467-020-16094-y OPEN

Backmapping triangulated surfaces to coarse-grained membrane models

Weria Pezeshkian[1✉], Melanie König[1], Tsjerk A. Wassenaar[1] & Siewert J. Marrink[1✉]



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PUBLISHED 18 January 2023
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*CORRESPONDENCE

Molecular dynamics simulation of an entire cell

Jan A. Stevens[1], Fabian Grünewald[1], P. A. Marco van Tilburg[1], Melanie König[1], Benjamin R. Gilbert[2], Troy A. Brier[2], Zane R. Thornburg[2], Zaida Luthey-Schulten[2] and Siewert J. Marrink[1]*

[1]Molecular Dynamics Group, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Groningen, Netherlands, [2]Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Champaign, IL, United States

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