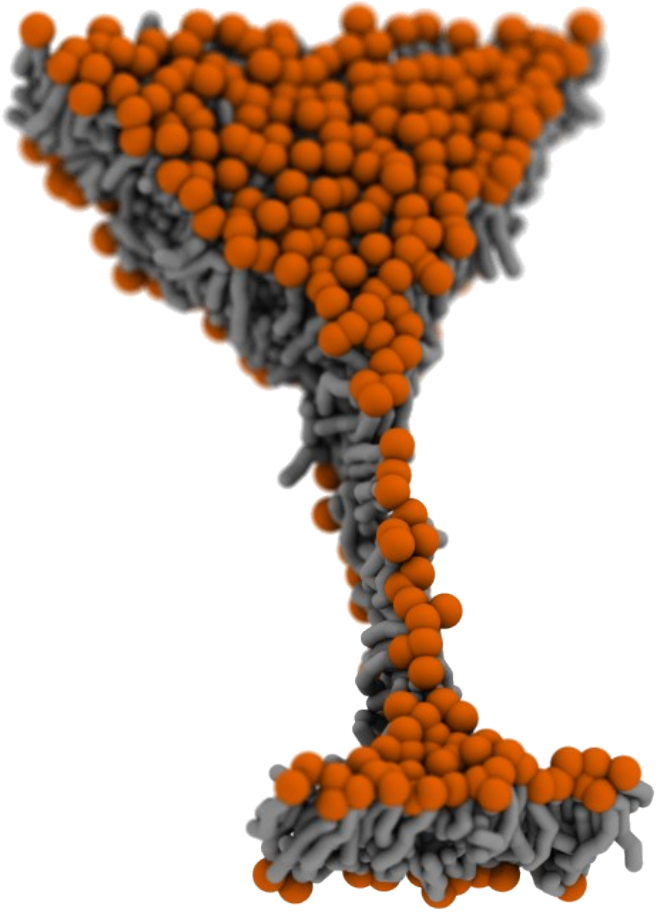
The Martini Lipids

Martini 3 Online Workshop, September 2021

Manuel N. Melo

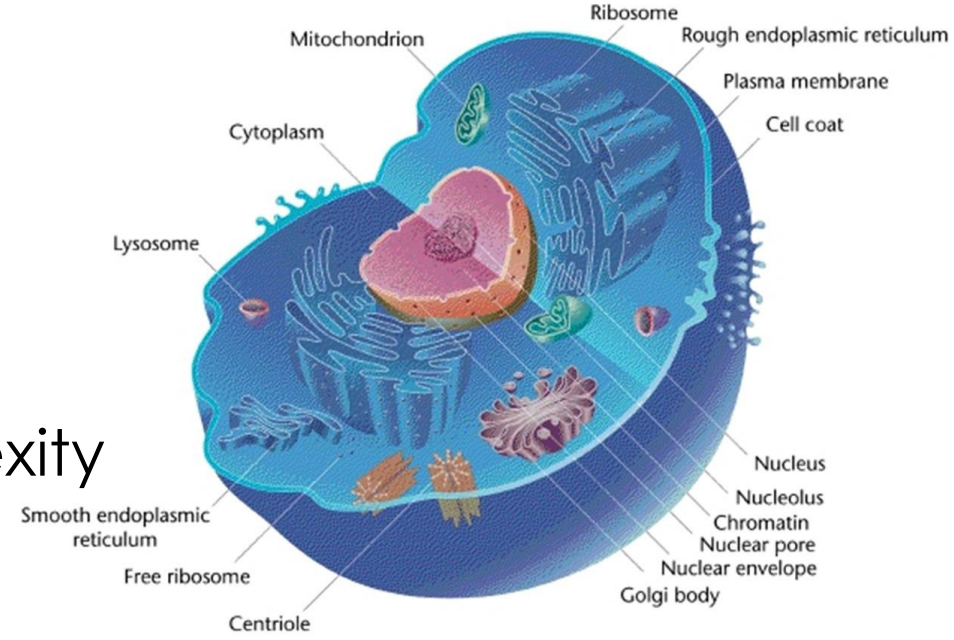


Multiscale Modeling Lab
Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa

Why simulate lipids?

Lipids form membranes

Compartmentalization by membranes is a cornerstone of life and of biological complexity

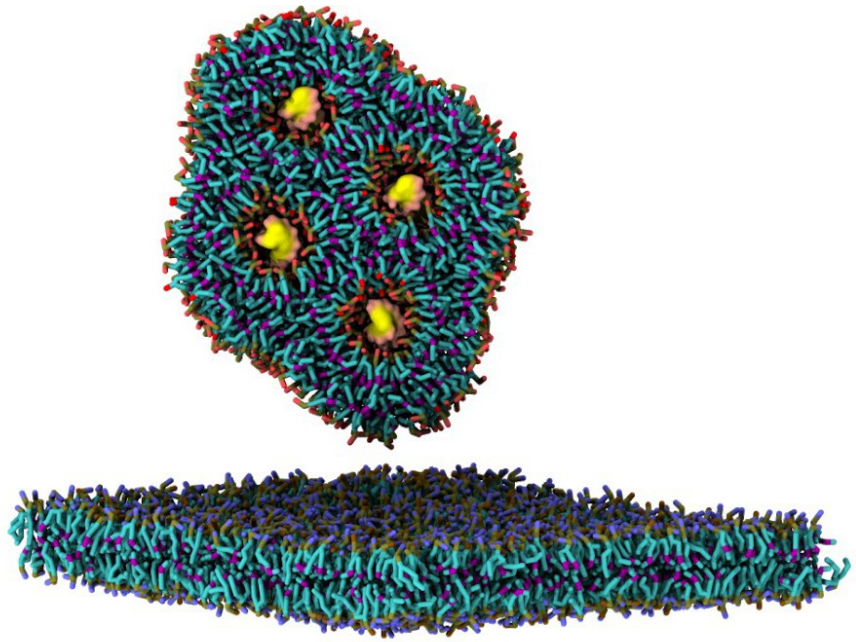


Lipids have important non-structural roles

as metabolites and/or signaling molecules

Lipids are also a biotechnological tool

case in point, mRNA vaccine lipoplexes



Bart MH Bruininks, Paulo CT Souza, Helgi Ingolfsson, Siewert J Marrink
eLife 2020;9:e52012 doi: 10.7554/eLife.52012

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

Membrane biophysics – How lipids interact

Lipids are amphipathic

The hydrophobic effect drives aggregation

Lipid characteristics (tail number, length, and saturation; headgroup size) dictate the lipid phases accessible to aggregates

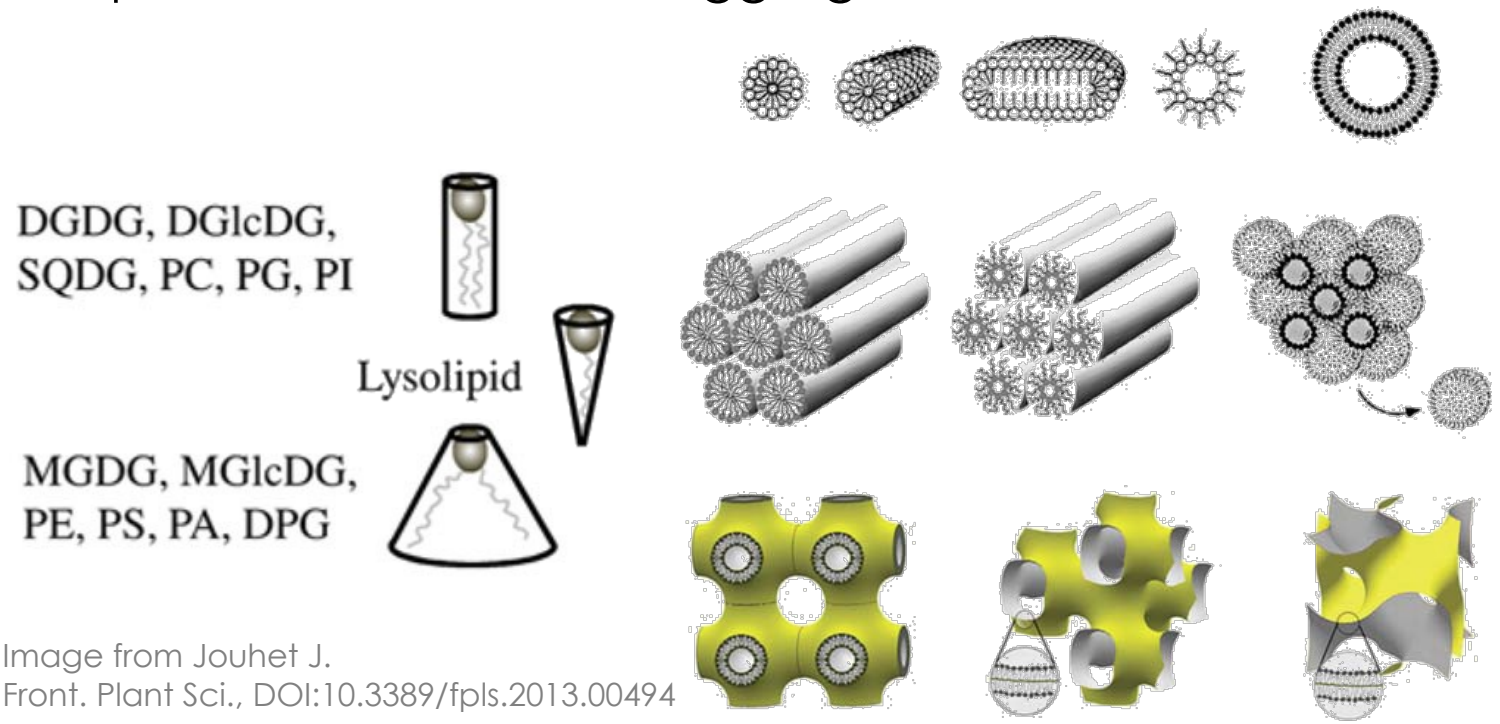
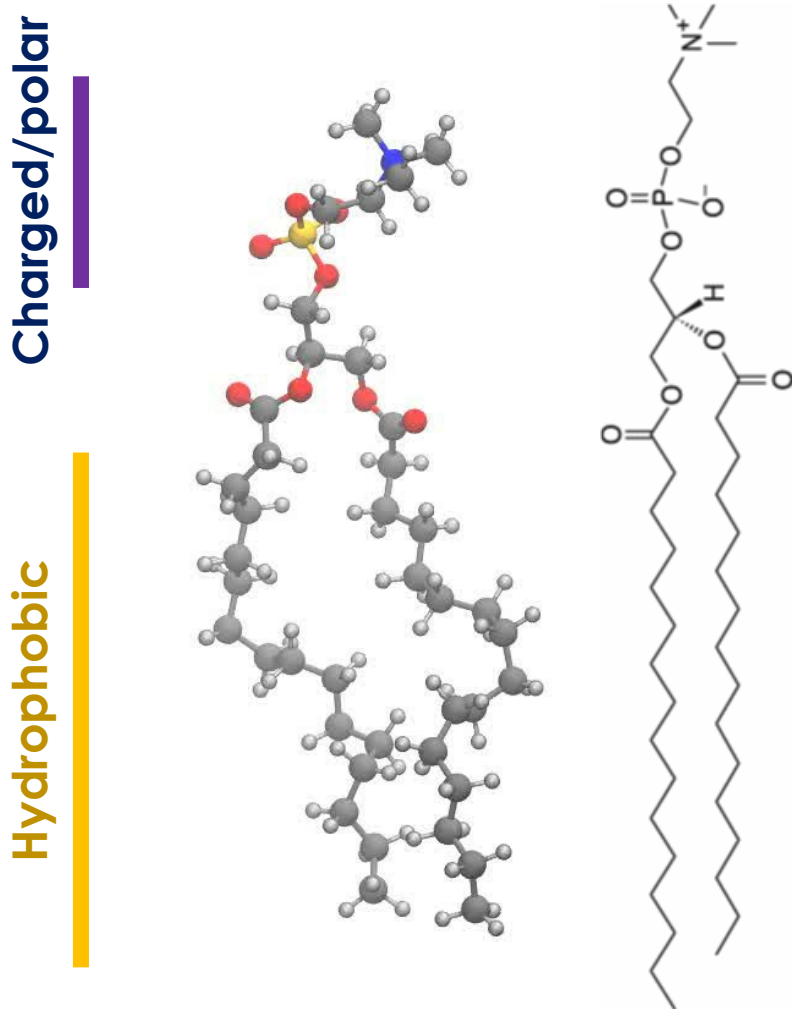


Image from Jouhet J.
Front. Plant Sci., DOI:10.3389/fpls.2013.00494

Image from Koynova R, Tenchov B.
OA Biochemistry 2013;1(1):9



Dipalmitoyl phosphocholine
di-16:0 tails
(DPPC)

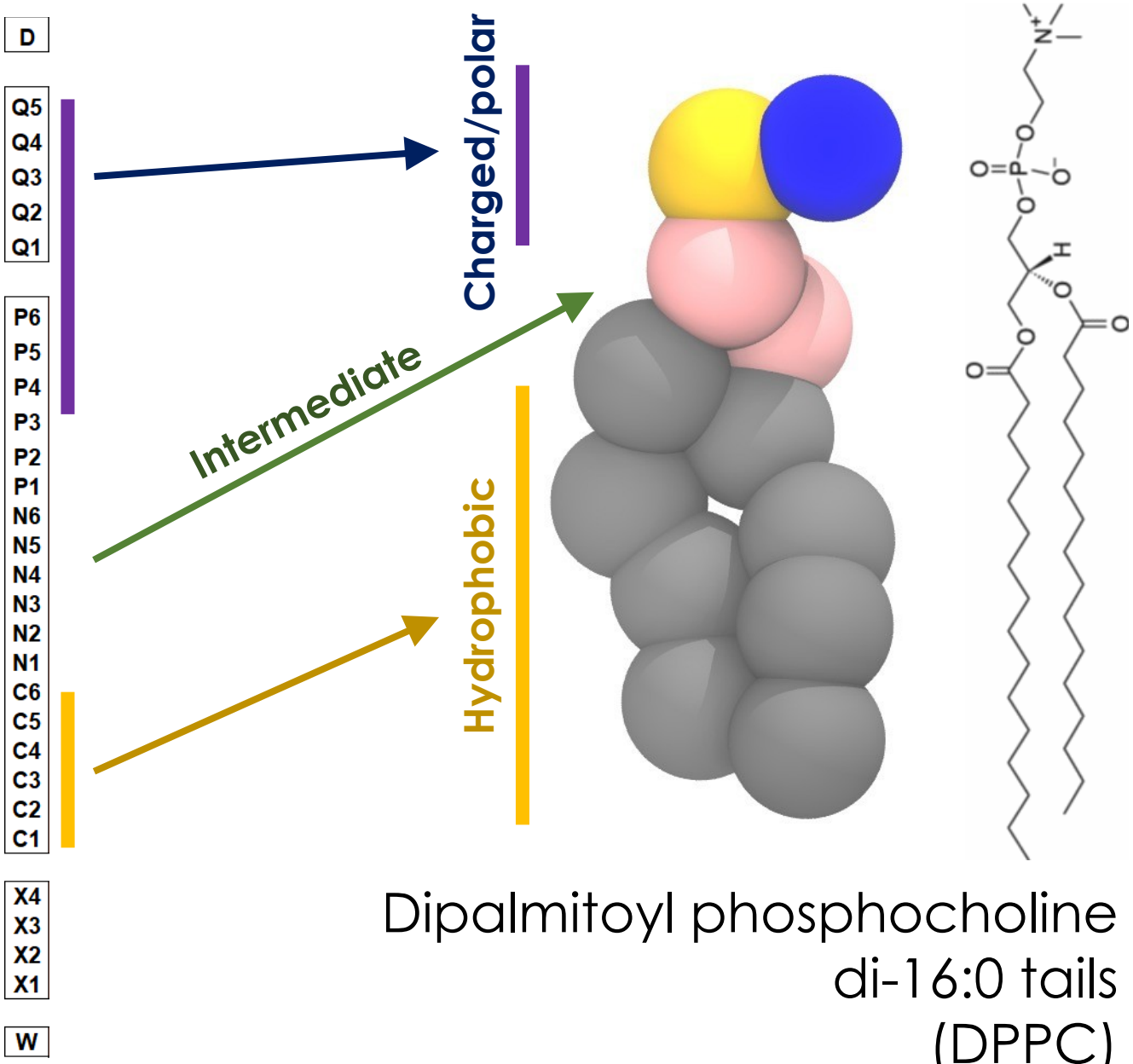
How Martini lipids interact

Polarity-based building block approach

Martini particle types follow scales of polarity character.

Polar/charged particles interact stronger with one another and water. Hydrophobic particles interact stronger with one another. Cross-polarity interactions are weaker.

Caveat: the entropic component of the hydrophobic effect is recovered mostly by enthalpic terms.



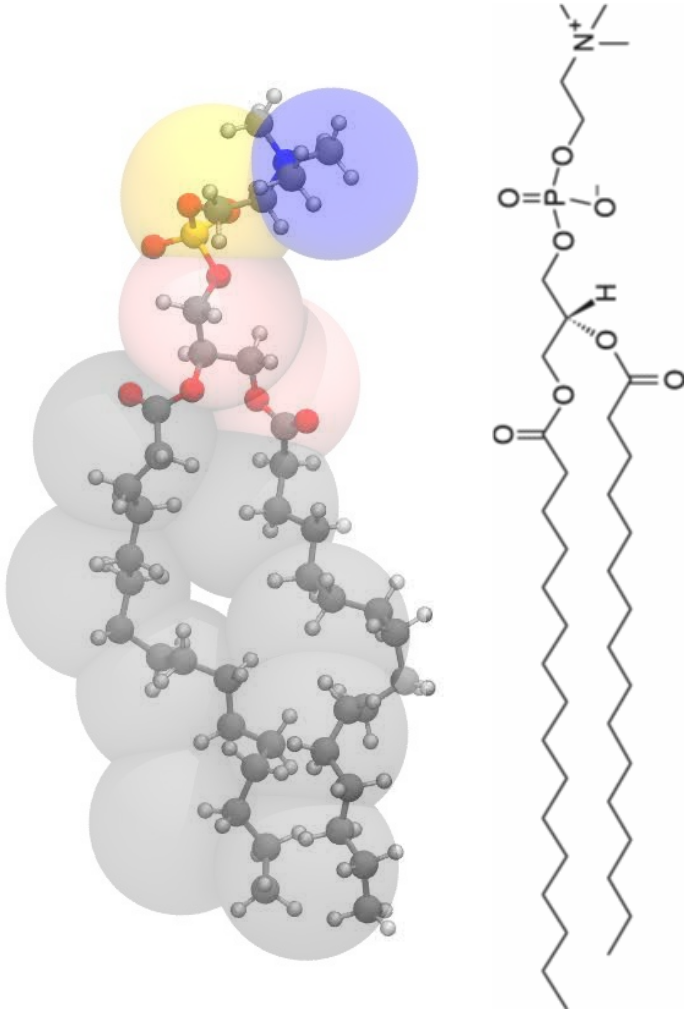
Dipalmitoyl phosphocholine
di-16:0 tails
(DPPC)

How Martini lipids interact

4-to-1 tail mapping + fragment-based building block approach

Same mapping and bonded/nonbonded parameters as free alkanes

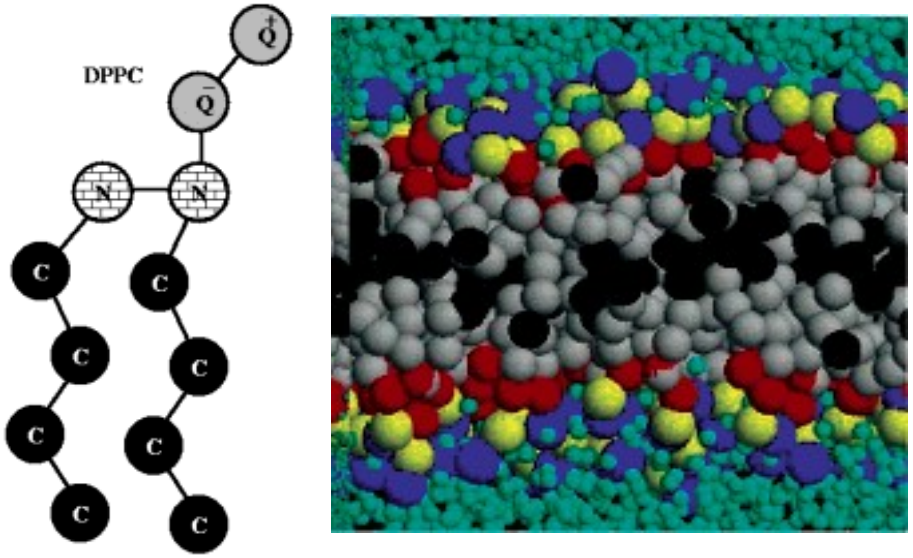
Caveat: Coarseness in the described chemical space: di-16:0 PC (DPPC) is the same model as di-18:0 PC (DSPC).



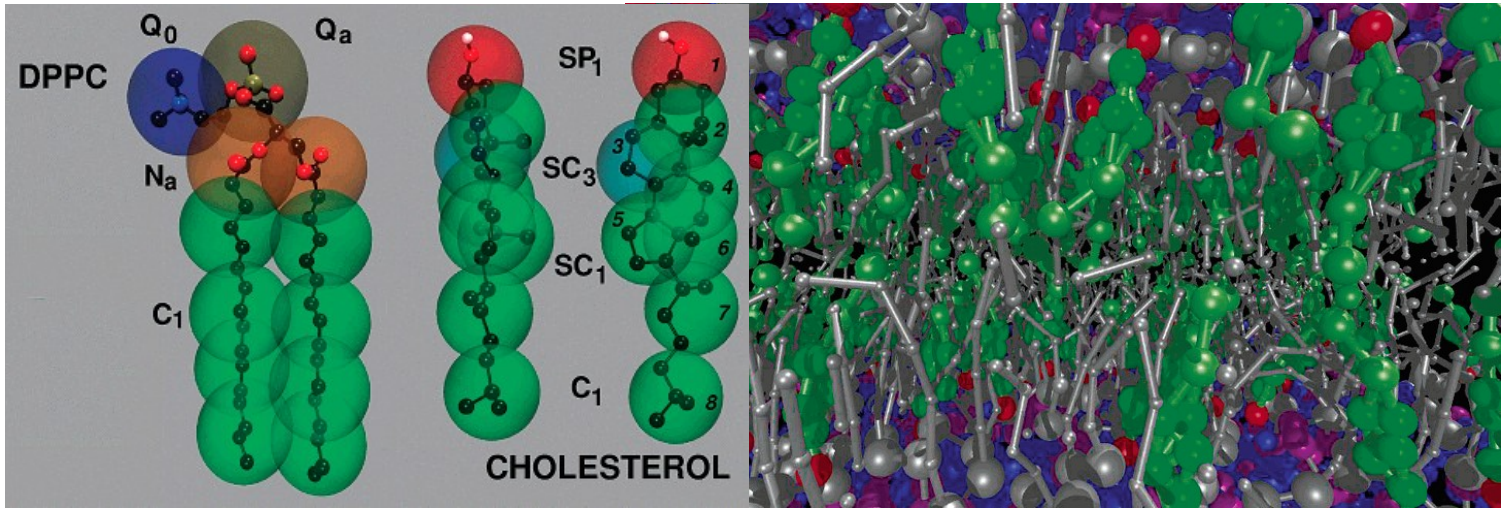
Dipalmitoyl phosphocholine
di-16:0 tails
(DPPC)

Historical overview

Martini 1: 10 particle types
(5 cross interaction potentials)



Martini 2: 18 particle types
(10 cross interaction potentials)
Cholesterol!

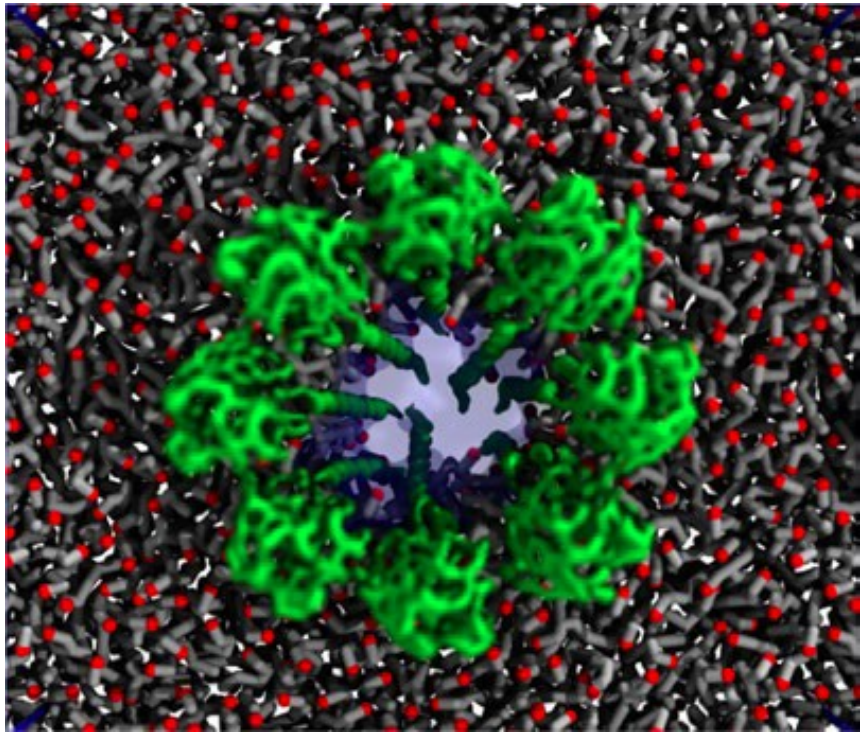


Marrink, S.J., de Vries, A.H. and Mark, A.,
J. Phys. Chem. B 2004, 108, 750-760

Marrink, S.J. et al., J. Phys. Chem. B 2007, 111, 7812-7824

Historical overview

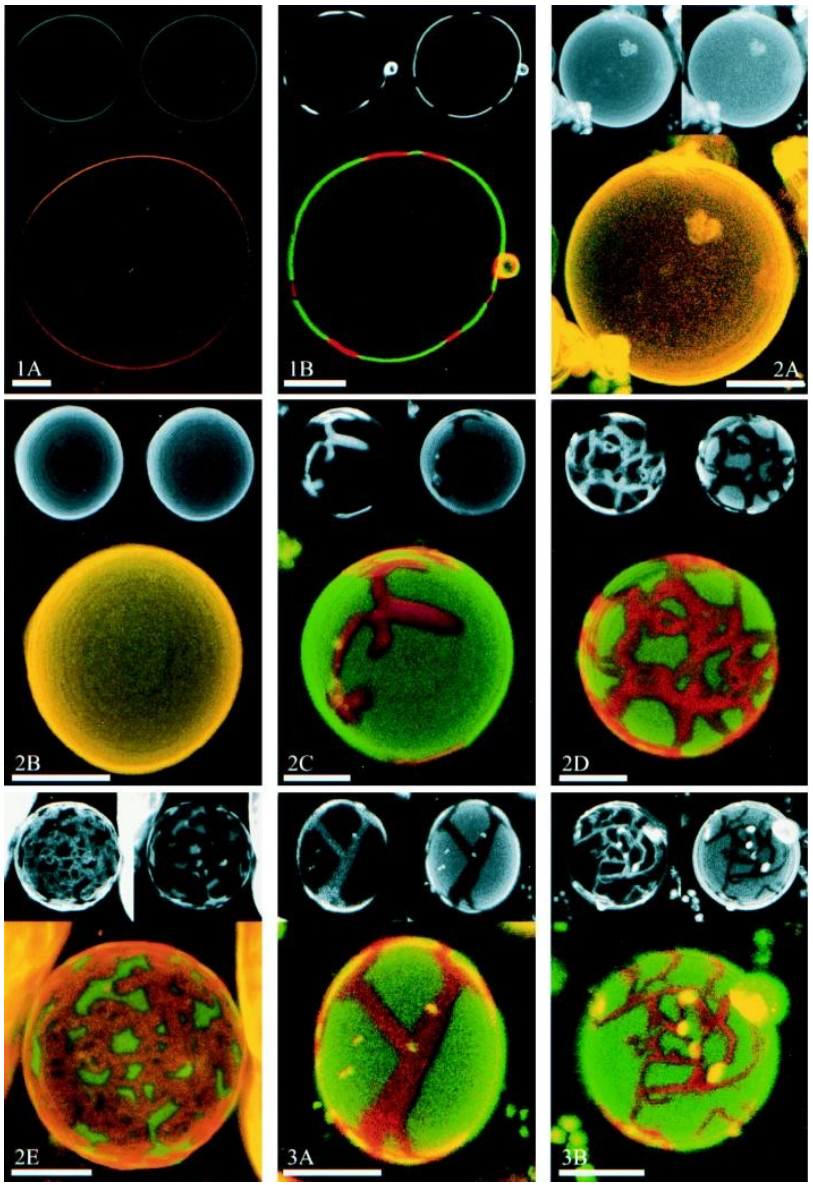
Martini 3: 29 particle types
(77 cross interaction potentials)



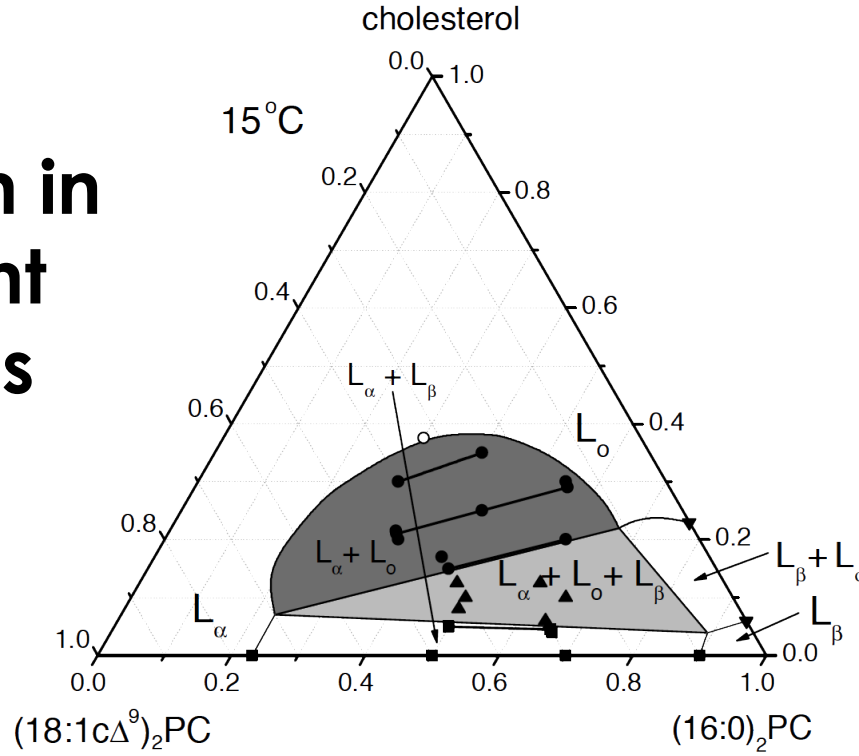
Souza, P.C.T. et al.,
J. Phys. Chem. B 2004, 108, 750-760

Some success stories

Phase separation in multicomponent bilayer mixtures

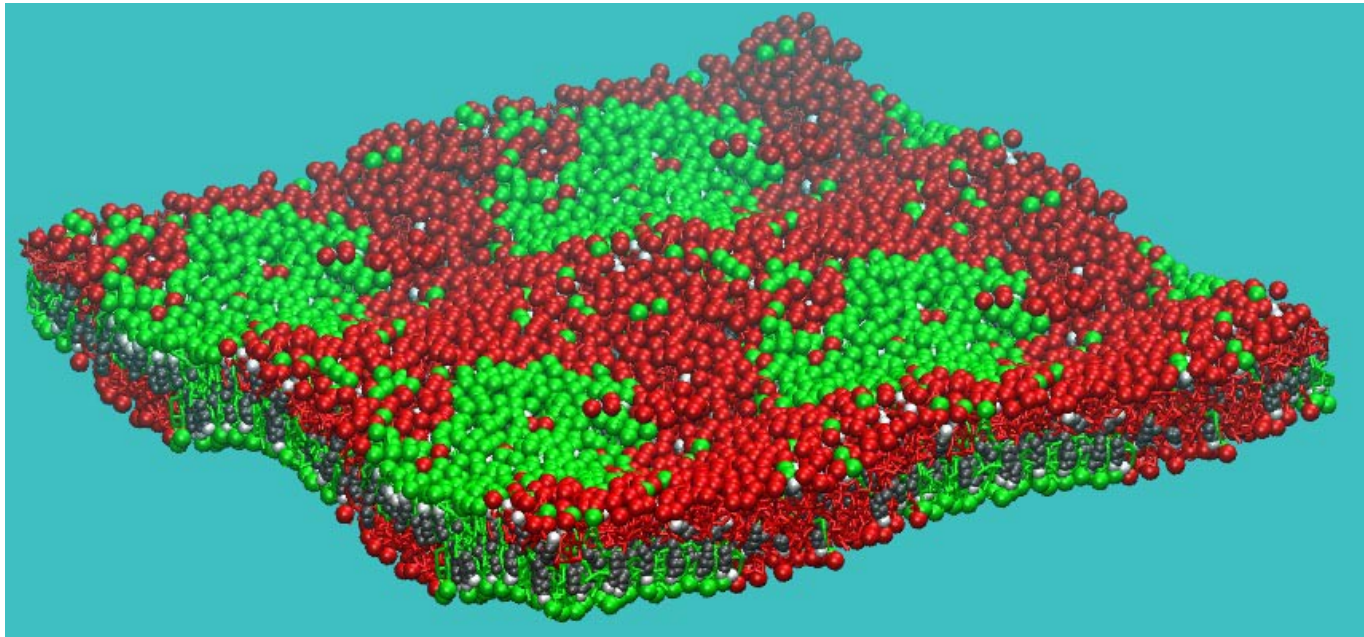


Korlach et al. (1999)
PNAS. 96(15) : 8461–8466.



Uppamoochikkal, P., Tristram-Nagle, S., and Nagle, J. F., Langmuir, 26, 17363, 2010.

Risselada, H.J., Marrink, S.J.
PNAS, 2008, 105(45), 17367–17372



Interactions with phase-separated membranes

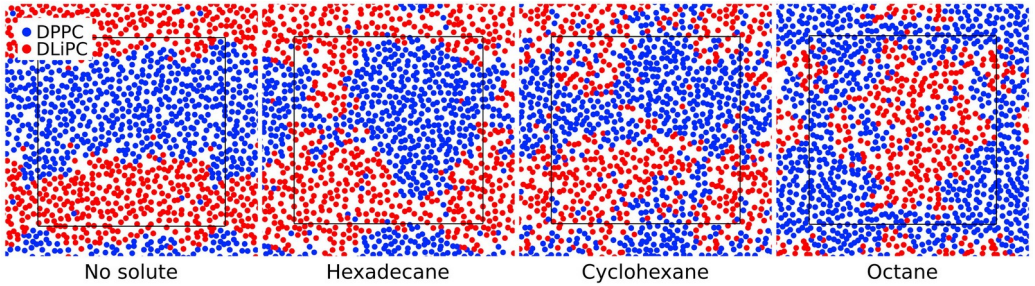
OPEN ACCESS Freely available online

PLOS | COMPUTATIONAL BIOLOGY

Hydrophobic Compounds Reshape Membrane Domains

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

1 IBCP, CNRS UMR 5086, Lyon, France, **2** Université Claude Bernard Lyon I, Lyon, France, **3** Dept of Physics, University of Genoa, Genoa, Italy, **4** Groningen Biomolecular Sciences and Biotechnology Institute and Zernike Institute for Advanced Materials, University of Groningen, Groningen, The Netherlands



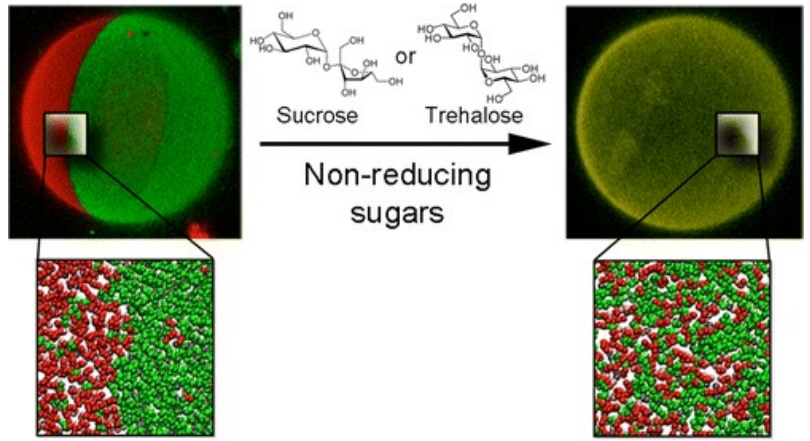
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

Disaccharides Impact the Lateral Organization of Lipid Membranes

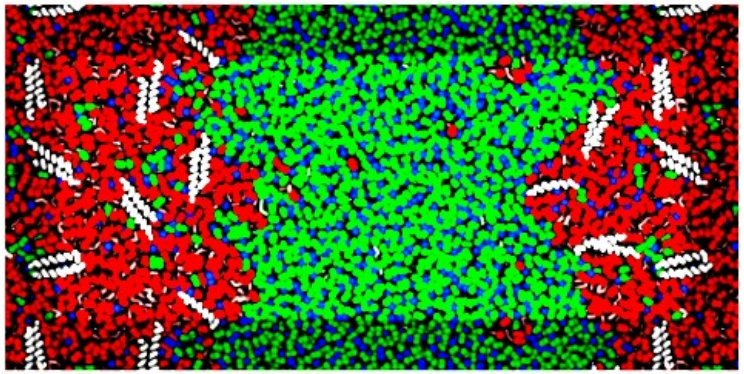
Gemma Moiset,[†] Cesar A. López,[†] Rianne Bartelds,[†] Lukasz Syga,[†] Egon Rijpkema,[†] Abhishek Cukkemane,[‡] Marc Baldus,[‡] Bert Poolman,*[,†] and Siewert J. Marrink*[,†]



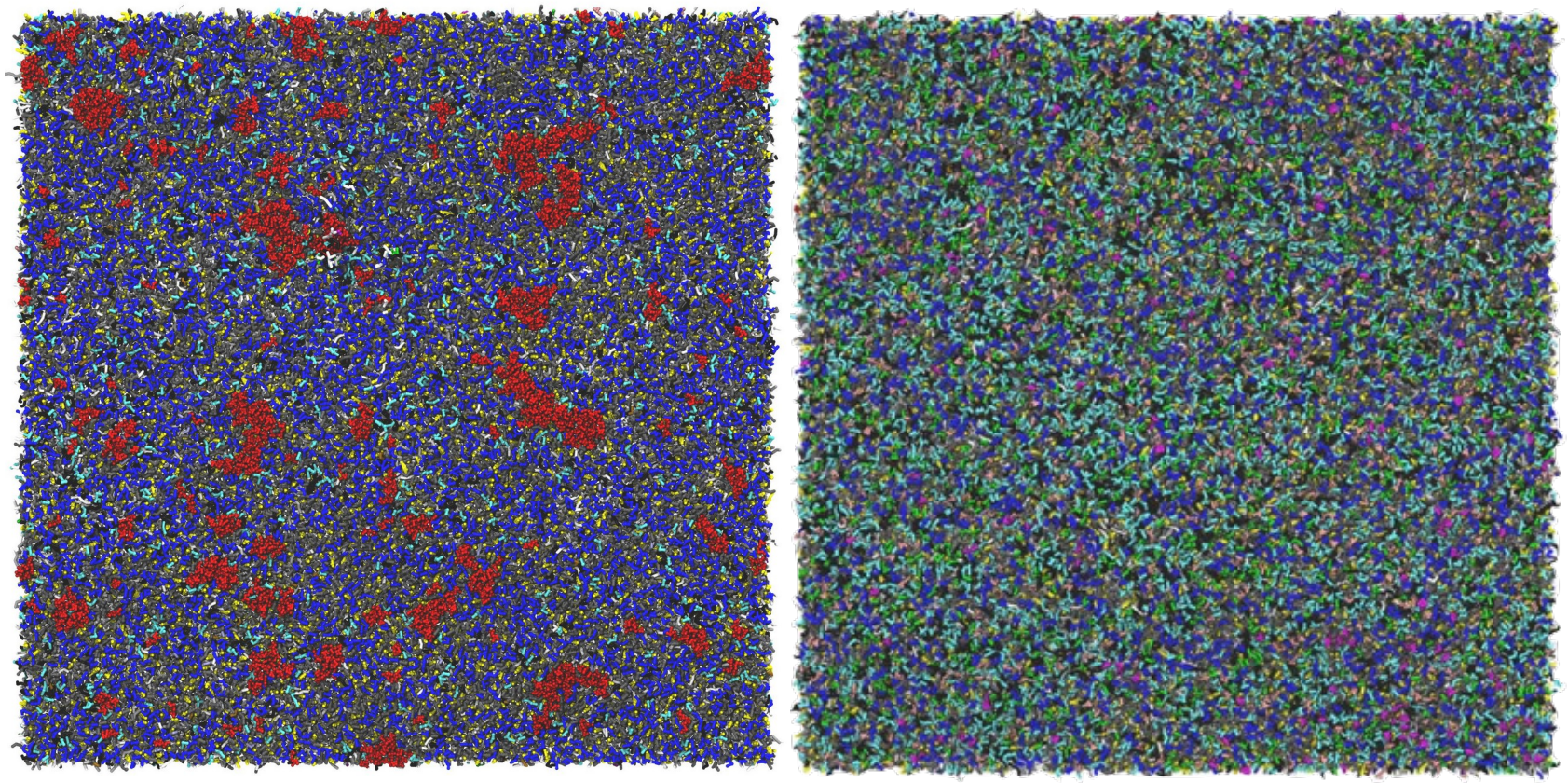
frontiers
in Cell and Developmental Biology

Localization Preference of Antimicrobial Peptides on Liquid-Disordered Membrane Domains

*Juanjuan Su[1], Siewert J. Marrink[1] and Manuel N. Melo[2]**



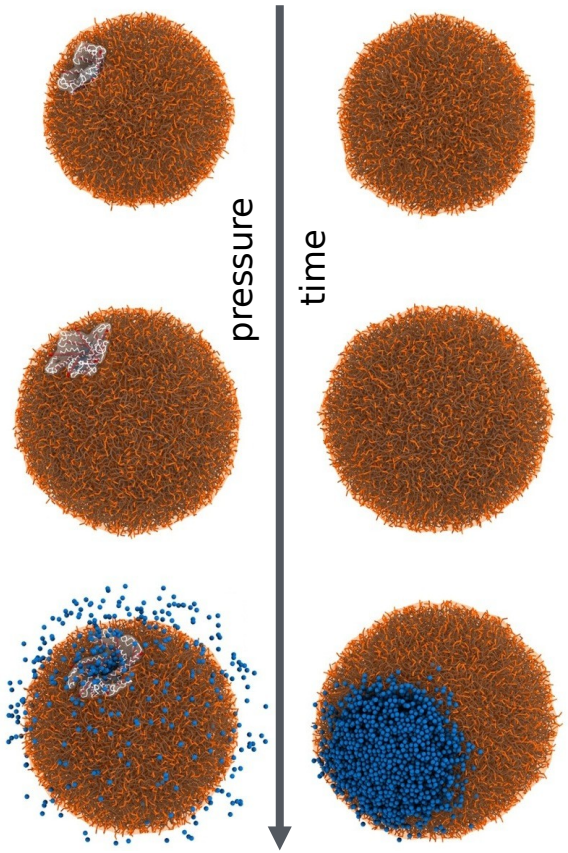
Membranes of pioneering size and complexity

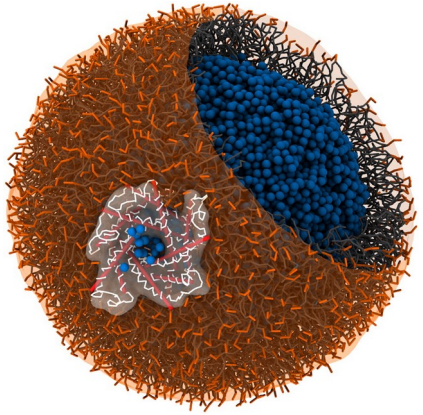


~80×80 nm, several million particles
>60 lipid species built and refined using only Martini building blocks
>80 μs

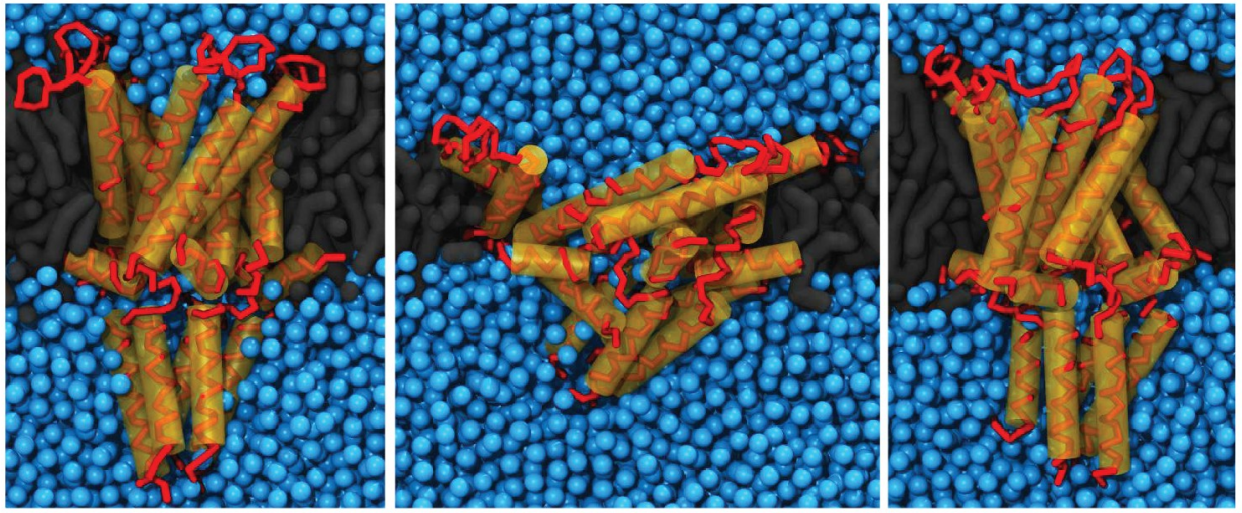
H.I. Ingólfsson et al., J. Am. Chem. Soc. 2014, 136, 41, 14554–14559

Functional embedding of proteins





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



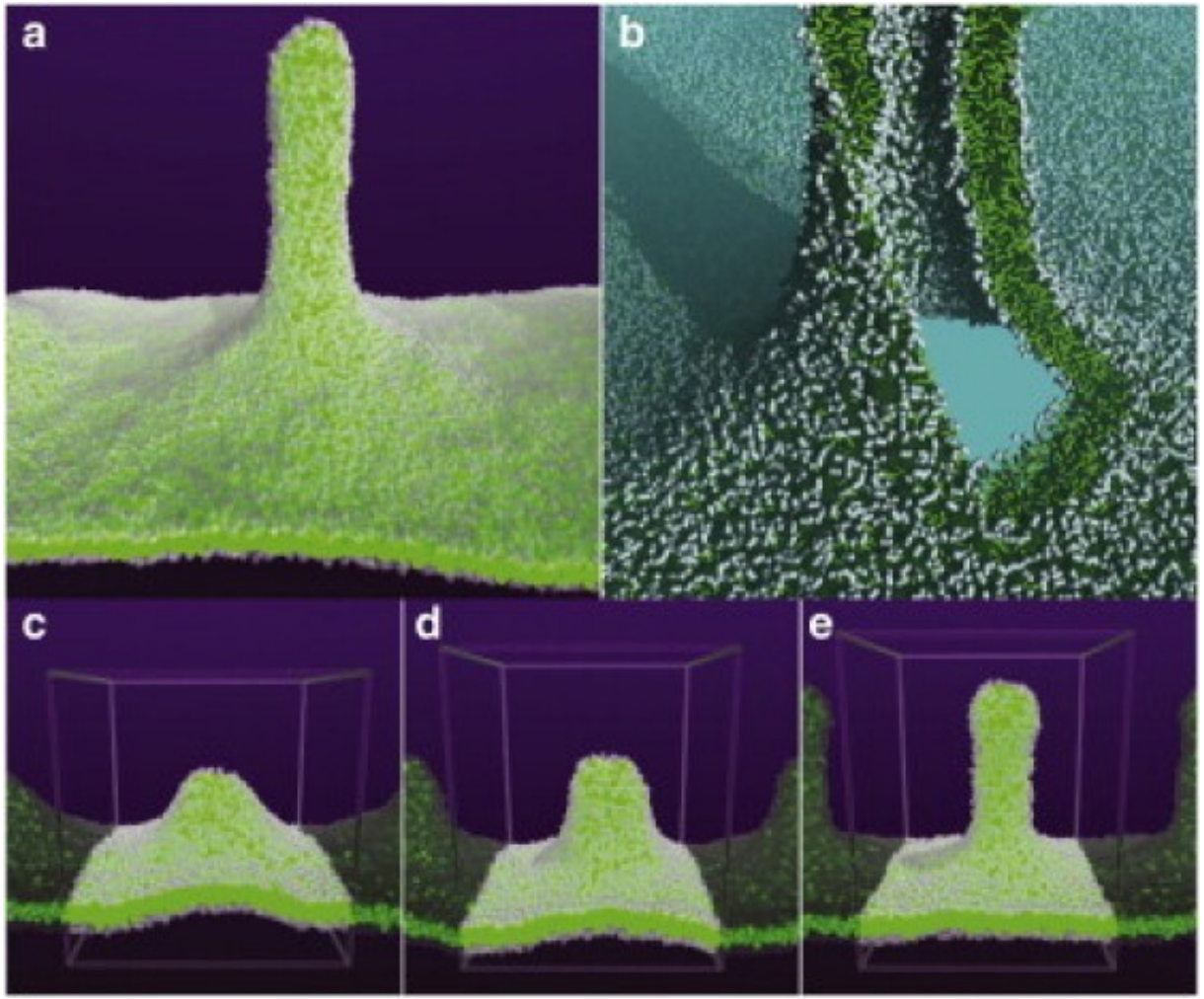
Louhivuori, *Proc. Nat. Ac. Sci.*, 2010
Melo, *JACS*, 2017

Membrane deformation

Biophys J. 2012 Apr 18; 102(8): 1866–1871.
doi: 10.1016/j.bpj.2012.03.048

Molecular Structure of Membrane Tethers

Svetlana Baoukina,[†‡] Siewert J. Marrink,[§¶] and D. Peter Tieleman[†‡*]

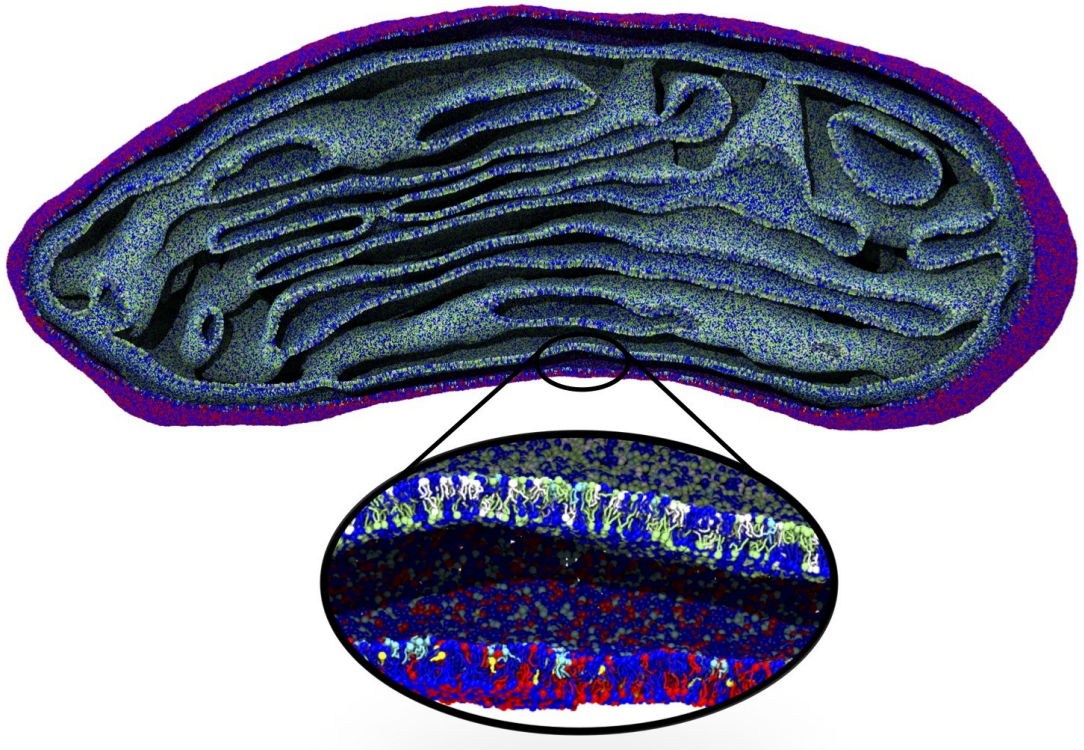


Multiscale into the micron scale

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✉]

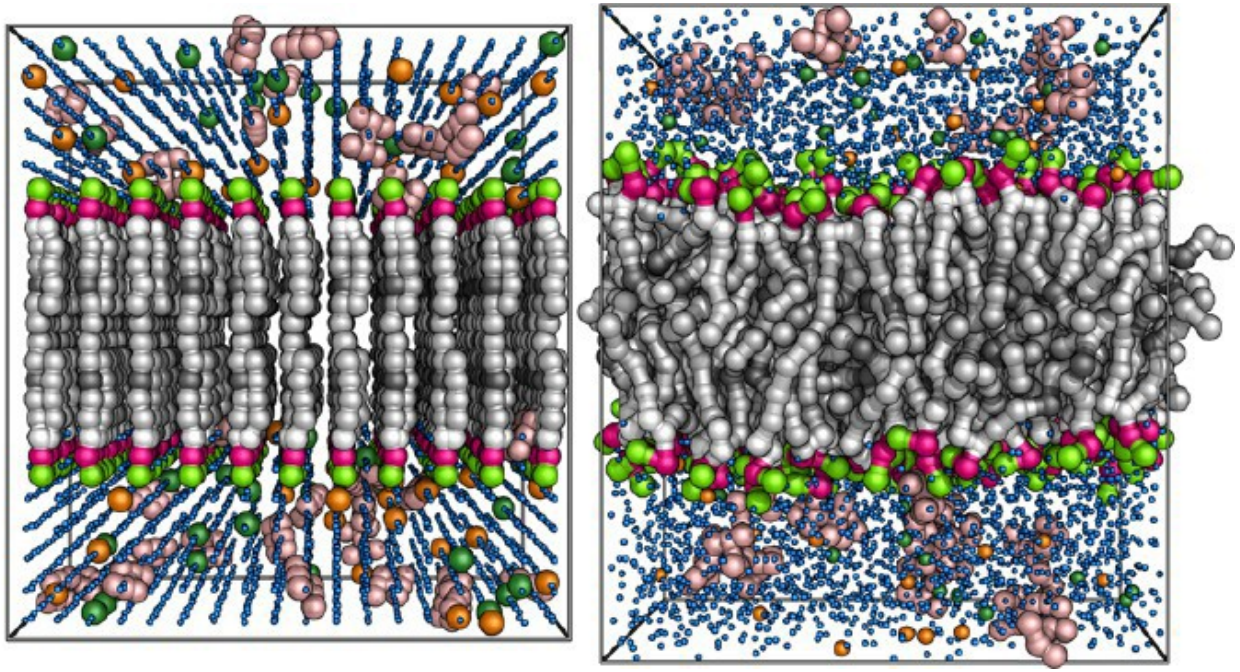


Robustness for use with template-based bilayer construction methods

JCTC Journal of Chemical Theory and Computation Article
pubs.acs.org/JCTC

Computational Lipidomics with *insane*: A Versatile Tool for Generating Custom Membranes for Molecular Simulations

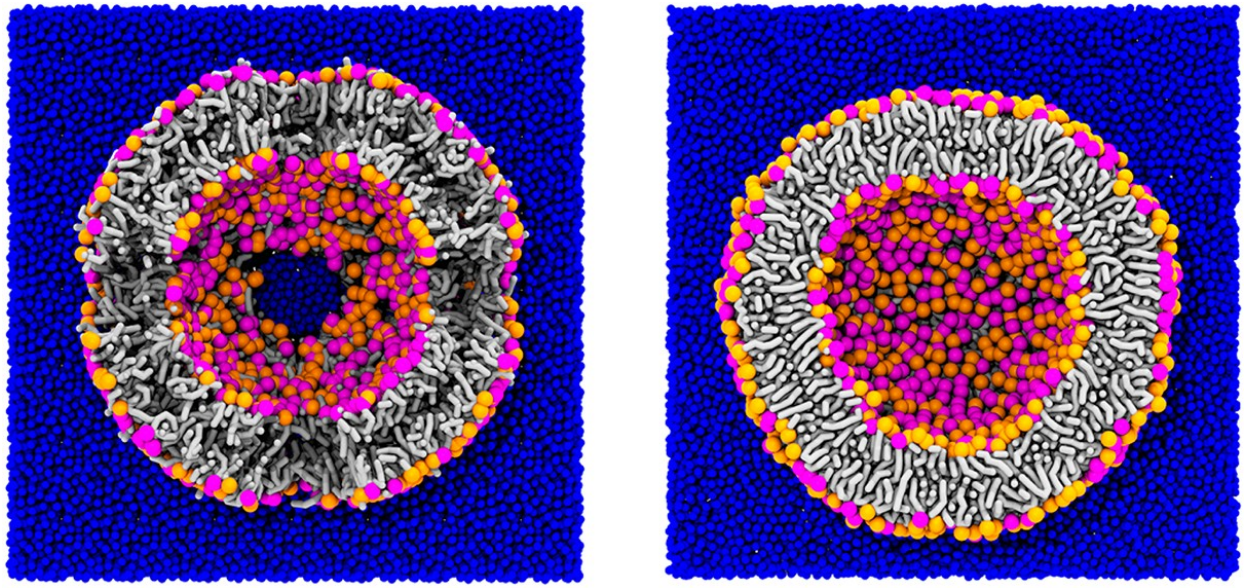
Tsjerk A. Wassenaar,*[,†,‡,∥] Helgi I. Ingólfsson,[†,∥] Rainer A. Böckmann,[‡] D. Peter Tieleman,[§] and Siewert J. Marrink[†]



JCTC Journal of Chemical Theory and Computation Article
pubs.acs.org/JCTC

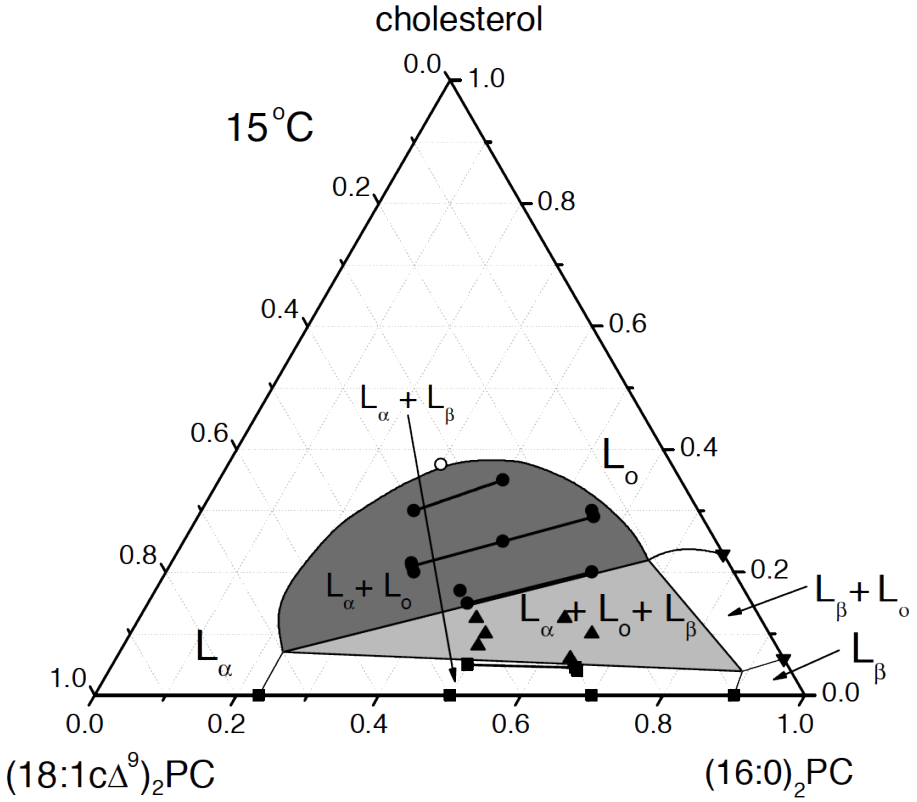
CHARMM-GUI Martini Maker for Coarse-Grained Simulations with the Martini Force Field

Yifei Qi,[†] Helgi I. Ingólfsson,[‡] Xi Cheng,[†] Jumin Lee,[†] Siewert J. Marrink,[‡] and Wonpil Im*[,†]

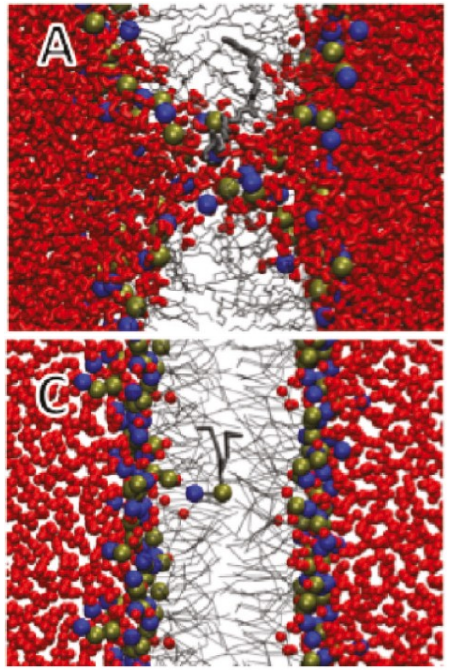


Some yet-to-be successful stories

Accurate description of all aspects of phase separation



More realistic pore formation



Bennett, D. and Tieleman, D.P
J. Chem. Theory Comput. 2011, 7, 2981–2988

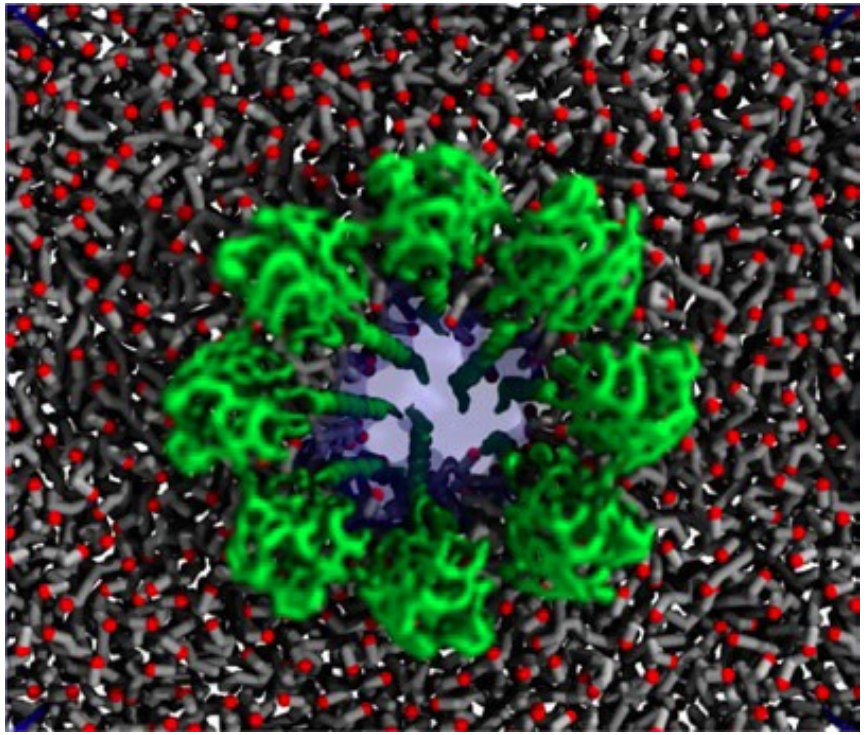
What about Martini 3 specific models?

Martini 3 was not lipid-centered

It solves problems mostly related with the need for greater chemical discrimination and multiple mapping sizes

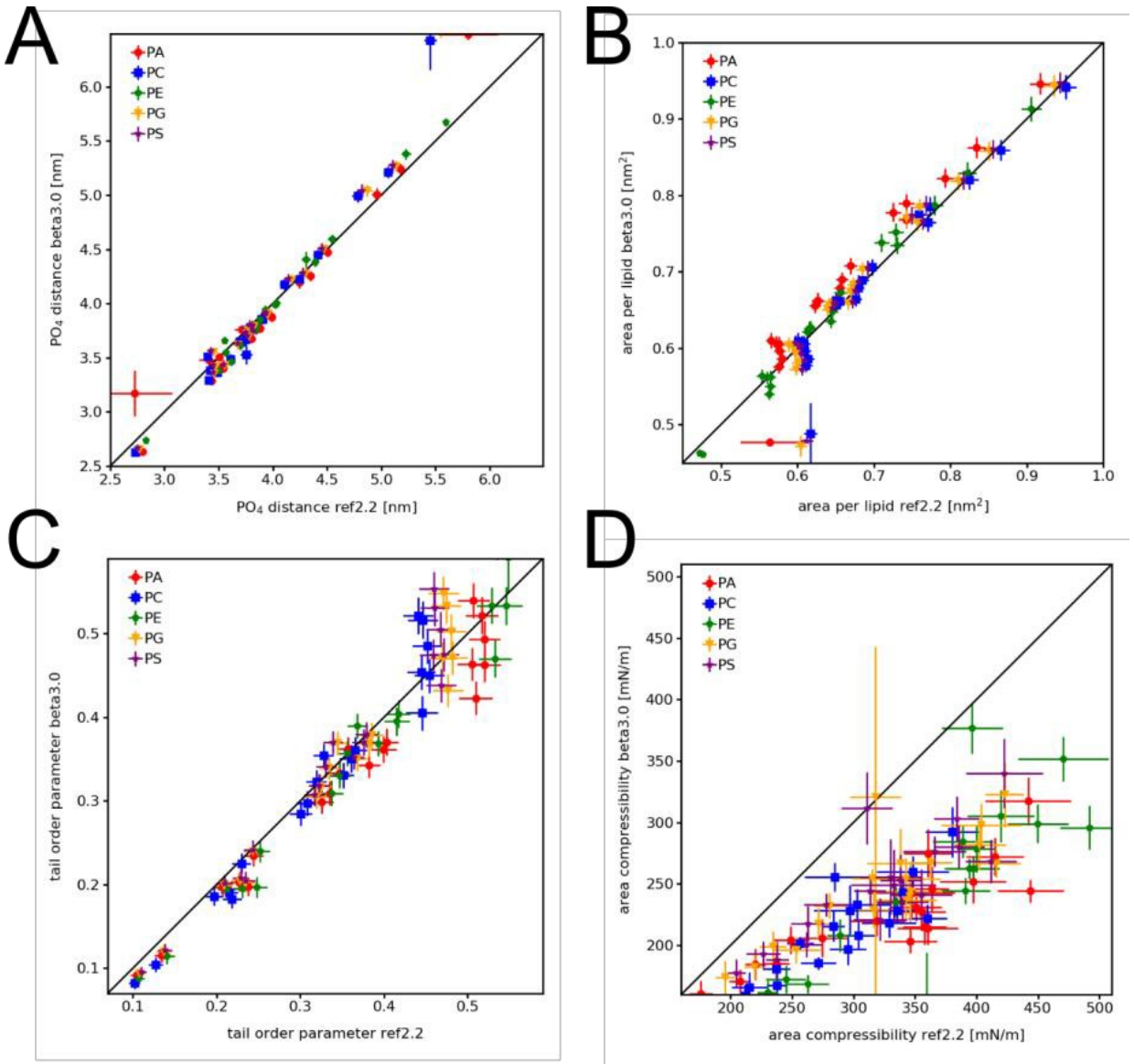
Many lipids already work without such improvements (but some don't! see next slides)

Martini 3: 29 particle types
(77 cross interaction potentials)



Souza, P.C.T. et al.,
J. Phys. Chem. B 2004, 108, 750-760

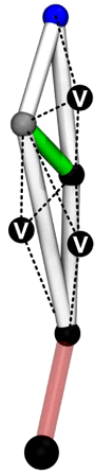
Martini 3 retains or improves Martini 2 lipid behavior



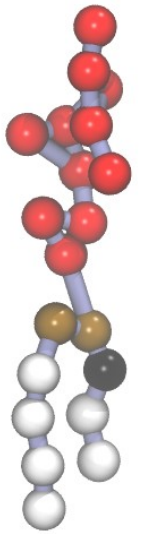
Initial Martini 3 strategy: direct translation of lipid bead types from Martini 2

Only applicable to lipids that don't require finer mappings than 4-to-1

Notable currently absent models:

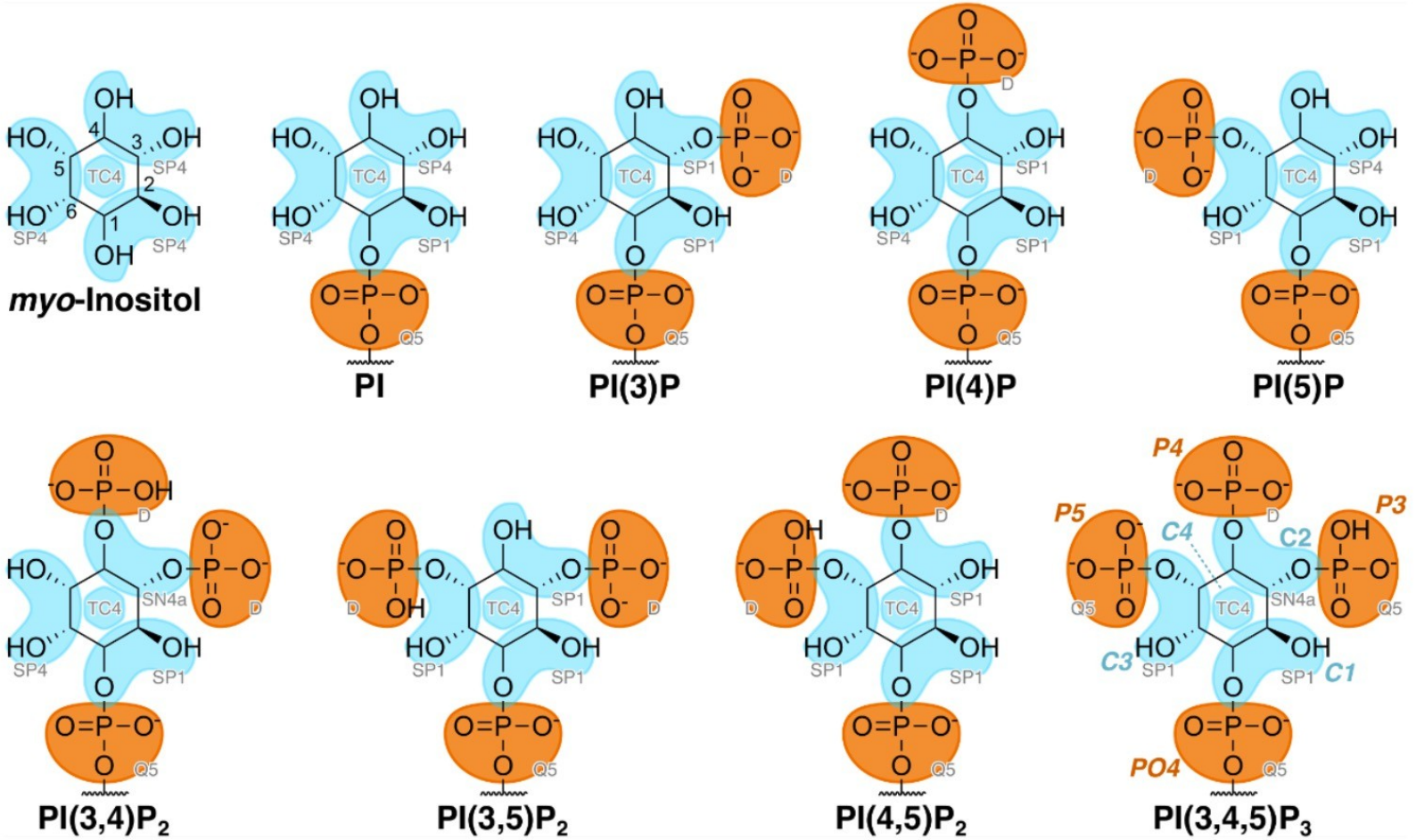


Cholesterol
(was too hydrophobic)



Glycolipids and sphingolipids
(were potentially too sticky)

Ongoing effort to update models for Martini 3 compatibility

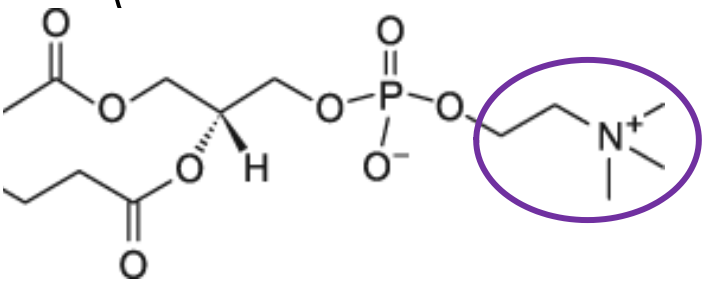


L. Borges-Araújo, P.C.T. Souza, F. Fernandes and M.N. Melo, doi:10.26434/chemrxiv.14759991

Other upcoming Martini 3 lipid developments

More bonded parameters in the headgroups
Martini lipid headgroup bonded interactions have always been underparameterized – work is being done to test the refinement of this aspect

Finer mappings
Headgroup mappings are not exactly compatible with Martini 3 guidelines (choline has a 6-to-1 mapping). New alternatives are being tested.



Alkane parameterization revisited
Alkane parameters, which are used in lipid tails essentially unchanged, may be refined for Martini 3, which could improve overall lipid behavior.

Happy Lipid Modeling!