Coarse-Grained Simulations of the Self-Assembly of Skin-Relevant Lipid Structures

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Overview

Stratum corneum:

- Outermost layer of skin; controls barrier properties
- Composed of flattened dead skin cells held together with lipid lamellar structures
- Known lipid composition including ceramides, cholesterol, and free fatty acids
- Molecular structural details are unknown

Molecular modeling:

- Precise control over lipid concentration, easily visualized
- Atomistic models: useful, but slow kinetics can yield results influenced by the initial configuration - fixed with self-assembly
- Self-assembly: formation of physically-relevant lamellar structures for use in future simulations and structure analysis
- Inefficiently-large computation times preclude modeling of self-assembly using atomistic models
- Coarse-grained (CG) models, used here, capture molecular behavior with fewer interaction sites

Project goals:

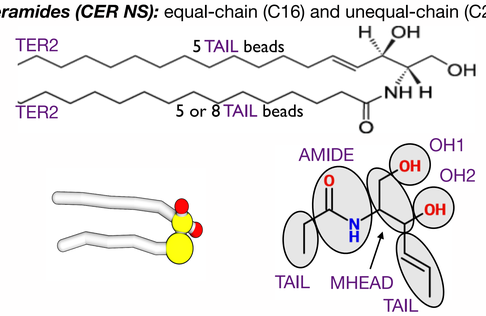
- Validate CG force fields currently being developed in the group
- Improve force fields and interaction potentials if needed
- Examine structural properties of validated CG models to gain insight into the role of each lipid in stratum corneum organization
- Applications: skin barrier repair, transdermal drug delivery

Coarse-Grained Models

CG models treat groups of atoms as single interaction sites, known as CG beads. Groups of atoms are "mapped" to CG beads. The mappings used in these simulations are as follows[2]:

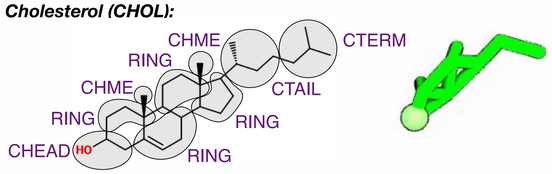
Water: 4:1; each blue bead of water represents 4 water molecules[2]

Ceramides (CER NS): equal-chain (C16) and unequal-chain (C24)



- 3:1 tails; each tail bead represents 3 carbon atoms
- 4-bead headgroup, including individual OH group beads
- C16 and C24 models identical except C24 has extra 3 tail beads in fatty acid tail

Cholesterol (CHOL):



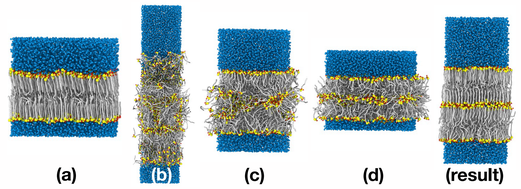
- OH group mapped to head bead; rings mapped to 5-bead mesh
- Ring and tail beads different from tail beads used for ceramides

diagrams courtesy of Tim Moore

Self-Assembly Process

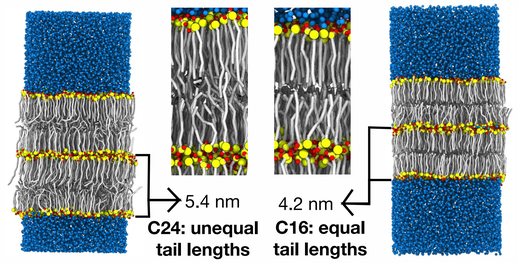
Self-assembly is useful in that the resulting lamellar structures are representative of those found in the body, making them more useful in analysis than arbitrarily chosen structures. The self-assembly simulations shown here follow the following process:

a) Begin with an already-formed lamellar structure
b) Increase simulation temperature to destroy structural order
c) Return to skin temperature and allow lamellae to reform
d) Promote faster lamellae formation by compressing and expanding the system



Pure Ceramide Simulations

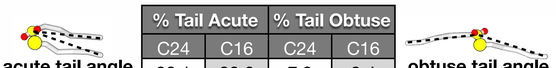
Stacked bilayer self-assembly was simulated for systems of both pure C16 and pure C24.



Due to the mixture of tail lengths in C24 molecules, the C24 bilayers are less ordered (visible above, and by the somewhat greater tilt angles of the C24 bilayers).

	S2		Tilt Angle	
	C24	C16	C24	C16
Top Outer	0.855	0.979	14.0°	6.54°
Top Inner	0.976	0.977	6.65°	5.92°
Bottom Inner	0.975	0.842	7.85°	16.8°
Bottom Outer	0.985	0.983	5.39°	5.41°

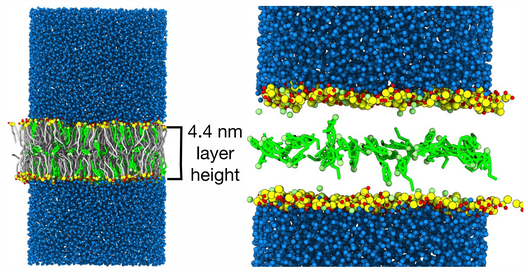
Nematic parameter (S2) is a measure of orientational ordering: 1 signifies ordering in the same direction and 0 represents random ordering. Tilt angle is the angle of the tails relative to the bilayer normal; closer to 0° indicates more ordering in a layer. Tail angle of lipids in inner layers also characterizes a system.



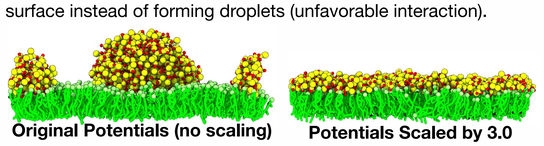
% Tail Acute		% Tail Obtuse	
C24	C16	C24	C16
92.1	90.6	7.9	9.4

Ceramide-Cholesterol Simulations

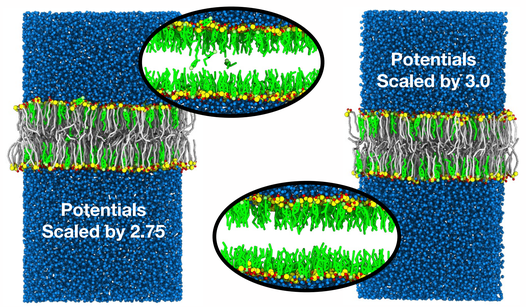
Self-assembly of a single bilayer composed of 2:1 C24:CHOL was simulated. While a bilayer formed, 25% of the CHOL molecules migrated between the lipid layers. This is not representative of biological cholesterol bilayers.



Surface wetting simulations were used to tune CER-CHOL headgroup interactions. Potentials were multiplied by a scaling factor until CER NS headgroups spread across a CHOL headgroup surface instead of forming droplets (unfavorable interaction).



Simulation of the bilayer using scaled potentials resulted in a more accurate bilayer with far fewer CHOL molecules between layers.



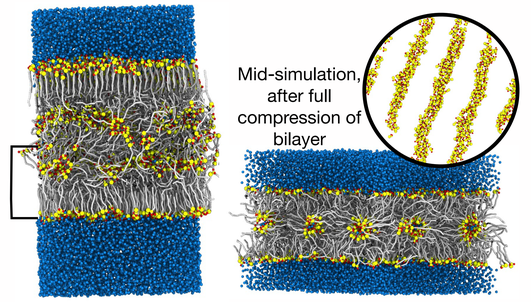
	S2			Tilt Angle		
	x1.0	x2.75	x3.0	x1.0	x2.75	x3.0
Top Outer	0.738	0.847	0.827	22.3°	16.1°	17.3°
Bottom Outer	0.822	0.817	0.846	17.5°	18.1°	16.1°

Adding CHOL to C24 is shown to decrease bilayer ordering (lower nematic parameter and greater tilt angle). However, using scaled potentials increased bilayer stability over the original model. The correct scaling factor will be chosen by comparing other bilayer parameters, such as area per lipid, to atomistic simulations.

Mixed Lipid Simulations

1:1 C24:C16 Mixture

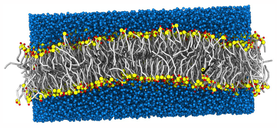
Attempts to simulate self-assembly of a C24:C16 stacked system were unsuccessful. The ceramides formed cylindrical structures instead of the expected flat layers after heating.



4.5 nm layer height

	S2	Tilt Angle
Top Outer	0.988	4.75°
Top Inner	0.285	44.0°
Bottom Inner	0.326	42.0°
Bottom Outer	0.981	5.94°

Altering the self-assembly process did not allow bilayer formation, including compressing the bilayer further in attempt to deform the cylinders and greatly increasing simulation time to allow deformities to work out naturally. However, simulations with lower heating temperatures that prohibit full disordering of the original bilayer appear promising, albeit not yet truly self-assembled.



Partial disorder after heating to 405°C
(previous simulations at 605°C)

The cylindrical structures suggest that these bilayers may not form naturally, or potentials between CER NS headgroups, or between CER NS headgroups and tails, may not be correct.

Conclusions

- Stacked pure ceramide simulations provided expected results
- C24 simulations slightly less ordered than C16 simulations
- Original C24:CHOL simulations and potentials were inaccurate
- Scaling headgroup potentials improved CER:CHOL interactions
- CER:CHOL bilayers less ordered than pure CER
- Mixed C24:C16 simulations insufficient
- Ongoing research:
  - Matching scaled potential CER:CHOL simulations to atomistic simulations in order to determine accurate scaling
  - Determining if C24:C16 bilayers are naturally disordered or if scaling factors are insufficient
  - Simulating bilayer systems with free fatty acids

References

1) Moore, T.C., Iacovella, C.R., Hartkamp, R., McCabe, C., *Journal of Physical Chemistry B*, in revision.
2) Moore, T.C.; Iacovella, C.R.; McCabe, C., *Foundations of Molecular Modeling and Simulation Molecular Modeling and Simulation* 2016, 37–52.

Acknowledgements

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