Self-Assembly of Stratum Corneum Lipid Bilayers Via Coarse-Grained Simulations

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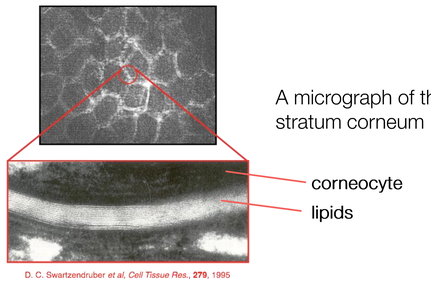
Overview

- Skin barrier function localized to stratum corneum (SC)
- Cholesterol, free fatty acids, and ceramides make up lipid matrix
- Connection between lipid composition, structure, and barrier function remains unclear



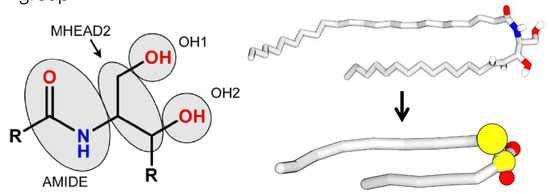
A micrograph of the stratum corneum

D. C. Swartzendruber *et al*, *Cell Tissue Res.*, **279**, 1995

- Accurate models of skin enable efficient toxicology assessments, further transdermal drug delivery development, and help design effective treatments for skin diseases

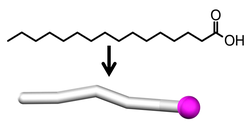
Coarse-grained (CG) Models

- CG models are computationally cheaper than atomistic models and allow for self-assembly to be simulated
- Self-assembly is used to study lipid assemblies without relying on the assumed initial configuration
- Interaction parameters derived from previous work in the group[1, 2]

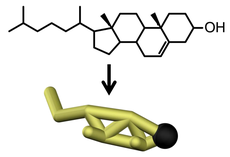


The CG mapping for a ceramide molecule

- A 3:1 mapping was used for carbon tails
- Ceramide (eCER2): 4-bead headgroup with OH group beads and equal carbon tail lengths
- Free Fatty Acid (FFA16): Single bead headgroup with 16 carbon tail length
- Cholesterol (CHOL): OH group mapped to headgroup with 5-bead mesh rings
- Water: Each blue bead of water represents 4 water molecules

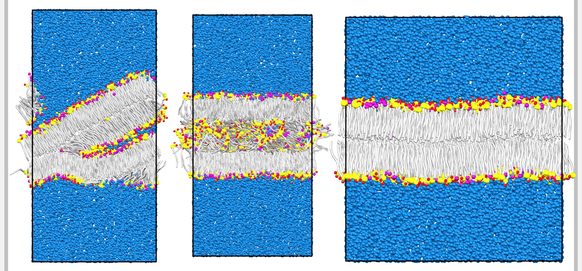


The CG mapping for a free fatty acid molecule



The CG mapping for a cholesterol molecule

Self-Assembly Process



Start from gas and compress to target density → Massage the system to work out defects → Simulate longer to collect data

Results of CG Simulations

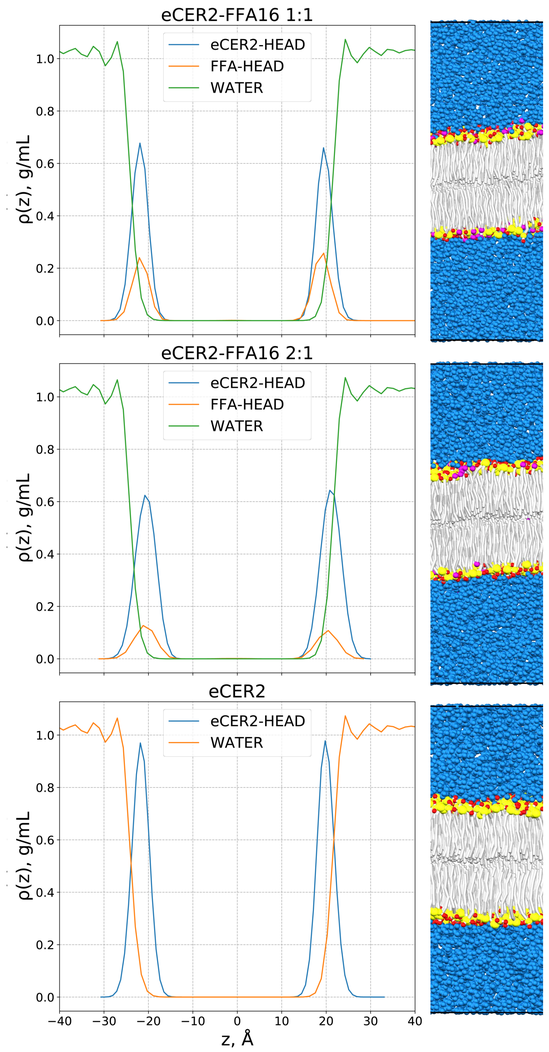
Simulation	APL (Å²)
eCER2:FFA16:CHOL (2:1:1)	35.90 ± 0.013
eCER2:FFA16:CHOL (2:2:1)	32.63 ± 0.013
eCER2:FFA16 (1:1)	31.27 ± 0.007
eCER2:FFA16 (2:1)	34.34 ± 0.007
Pure eCER2	41.73 ± 0.008

As the percent of eCER2 increases, the area per lipid (APL) increases. Due to different morphologies and packing densities, these systems may have different properties such as permeability.

Simulation	Tilt Angle
eCER2:FFA16:CHOL (2:1:1)	8.48° ± 5.00
eCER2:FFA16:CHOL (2:2:1)	9.83° ± 9.79
eCER2:FFA16 (1:1)	5.90° ± 4.07
eCER2:FFA16 (2:1)	5.25° ± 2.99
Pure eCER2	5.40° ± 3.47

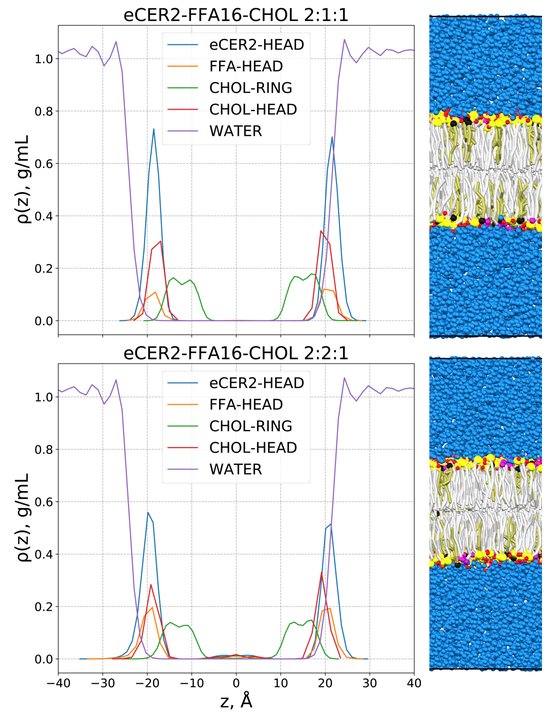
The addition of CHOL causes more tilt as the bulky ring structure affects the balance between the head and tail packing. This bulky ring spacing may be the cause of unstable bilayers in binary mixtures involving CHOL.

Mass Density Profiles



Mass density profiles compare the distance from the center of the bilayer to the headgroup density. Near the lipid-water interface, the profiles contain a peak which represents the heavy atoms in the headgroups. Headgroup spacing does not change as a function of composition.

Ternary Systems



All three headgroups sit in the same location in the bilayer.

Conclusion

- Systems containing FFA tend to have smaller APLs due to the single alkyl chain whereas eCER2 and CHOL have similar APLs due to similar cross-sectional areas
- Lamellar organization is mostly independent of lipid composition for the systems studied
- Systems with high concentrations of CHOL have difficulty forming lamellar structures like the other mixtures

Future Work

- Investigate the stability of bilayer systems with high concentrations of CHOL
- Examine mixtures over a wide composition range to uncover composition-structure relationships

References

1. Moore, T. C., Iacovella, C. R., Hartkamp, R., Bunge, A. L. & McCabe, C. A Coarse-Grained Model of Stratum Corneum Lipids: Free Fatty Acids and Ceramide NS. *J. Phys. Chem. B* **120**, 9944–9958 (2016).
2. Moore, T. C., Iacovella, C. R. & McCabe, C. in *Foundations of Molecular Modeling and Simulation: Select Papers from FOMMS 2015* (eds. Snurr, R. Q., Adjiman, C. S. & Kofke, D. A.) 37–52 (Springer Singapore, 2016).

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