Molecular dynamic simulations of interactions of bile salts and their acids with a DMPC lipid bilayer

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**Purpose of Project**

**Goal:** Obtain better understanding of the physiological function of bile salts and their acids on the atomic scale.

Investigate:
- Bile molecules’ trajectories during simulations
  - Descent into lipid bilayer
  - Orientation during interactions
- Intermolecular interactions
  - Hydrogen bonding
Bile Molecules (BM)

- BM are bio-surfactants which facilitate fat digestion, transportation, & cell membrane absorption of lipids, nutrients, and other molecules in the small intestine.

Modified from http://cdn.aboutgastro.com
Molecular Dynamics (MD) Methodology

Molecular System
- Total atoms: **24,943**
- Background salt concentration: **0.15 M**

Running Simulations
- Energy Minimization
- **2.5 ns** Equilibration
- Full simulation
  - Run time: **144 hours**
  - Output: **110 ns**

Simulations were performed Groningen Machine for Chemical Simulations\(^4\) (GROMACS) 4.6.1, visualized using Visual Molecular Dynamics \(^5\) (VMD) 1.9.1, & run on the LONI supercomputers.
Results  MD Simulation

1 snapshot = 4ns
**Results**

**Trajectory of BM**

**Greatest depth** into bilayer:

1.23 nm **DCA** > 1.15 nm **DCD** > 1.07 nm **UDA** > 1.01 nm **UDD** > 0.19 nm **CHA** > 0.11 nm **CDD** > 0.07 nm **CDA** > 0.02 nm **CHD**
Axis 1:
- Initially, the hydrophilic face will point toward bilayer center
- Then will flip as BM descends to hydrophobic region

Axis 3:
- DCD & UDD continuously pointed tail away from bilayer center
- DCA & UDA prefer to lay parallel to the plane of the bilayer
Results

Intermolecular Interactions

Average hydrogen bonds in hydrophilic regions:
1.75 bonds CHD > 1.43 bonds CHA > 1.03 bonds CDD > 0.76 bonds CDA

Average hydrogen bonds in hydrophobic region:
1.90 bonds DCA > 1.64 bonds DCD > 1.62 bonds UDD > 1.35 bonds UDA
Conclusions

- DCA appears to most successfully absorbing into the bilayer
- Primary BM remain near or above the bilayer surface
- Secondary BM settle into the hydrophobic region
- Protonation of COO\(^{-}\) facilitates greater descent
- Reduced number of OH groups allows absorption into bilayer
- Stereochemistry differences between CDD-CDA and UDD-UDA pairs indicates OH orientation affects absorption greatly
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Future Work

- Investigations of a forced BM bilayer flip
- BM micelle interactions with bilayer
- Effects of BM on membrane permeability and flexibility

Understanding interfacial interactions can yield development of new drugs for improving:
- lipid digestion
- absorption of fat-soluble nutrients and vitamins
- possible reduction of saturated trans-fats and exogenous cholesterol intake
References and Acknowledgments

1 Maldonado-Valderrama et al., Ad. in Colloid & Interface Science, 165, 36-46 (2011).
3 Hofmann & Hagey, Cellular & Molecular Life Sciences, 65, 2461-2483

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