Coarse-Grained Molecular Dynamics Simulations of Passive Partitioning of Ionic Surfactants into Cell Membranes

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Objectives

- The Environment and Health – Risk Assessment & Management (ERASM) is a joint research platform of the European Detergents and Surfactants Industries. The ERASM 'Membrane Water Partitioning of Surfactants' project aims to evaluate the alignment between 3 experimental and 3 computational methods to measure the phospholipid membrane-water partition ratio (K_{mw}) for 12 surfactant structures, covering 4 surfactant types. This poster focuses on computational methods.
- Previously our group developed an automatic coarse-graining script to allow rapid setup of membrane-water partitioning simulations using molecular dynamics [1].
- We aim to derive best practice for use of the Martini coarse-grained force field for simulation of charged surfactants, and ultimately to benchmark it and other computational methods.

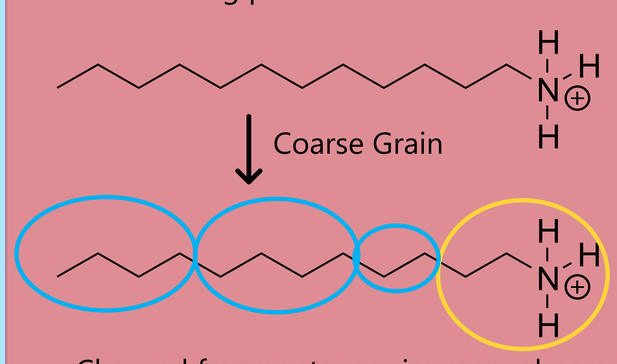
Background

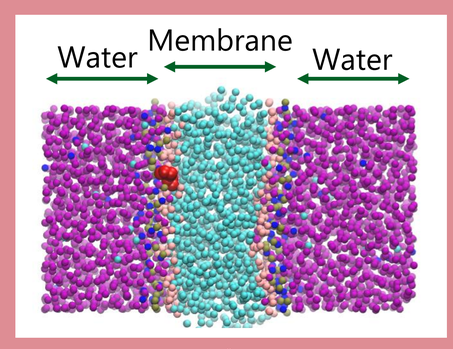
- Membrane-water partitioning K_{mw}(or D_{mw}) is a key metric for baseline toxicity (narcosis) and bioaccumulation.
- Octanol-Water Partitioning, K_{ow}, has well-publicised [2] deficiencies for charged surfactants; log K_{mw} is a more representative alternative.
- Surfactants are an experimentally challenging species to study i.e. difficulties studying mixtures, issues with compound solubility or adhesion to glassware; simulation can overcome these problems.
- Goal: High-throughput models for K_{mw} simulation of surfactants.
- Membrane simulations can then be performed and are related to experiment via calculation of the Gibbs energy, ΔG:

$$K_{\mathrm{MW}} = \frac{[\mathrm{Solute}]_{\mathrm{Membrane}}}{[\mathrm{Solute}]_{\mathrm{Water}}} = e^{-\Delta \mathrm{G}/\mathrm{RT}}$$

Computational Methods: Molecular Dynamics Simulation

- cg_param is a python script to convert a SMILES code into a coarse-grained structure, ready for simulation in a coarse-grained membrane.
- The script uses two main parts:
  - ❑ A graph-based spectral mapping algorithm to break large molecules up into roughly four-atom beads while preserving symmetry.
  - ❑ ALOGPS [3] a web-based neural network to generate log K_{ow} values for the fragments, allowing parameterisation into the Martini force field [4].





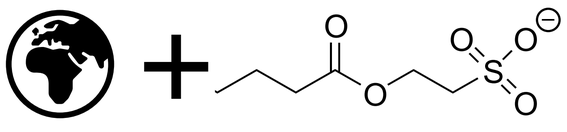
- Charged fragments require manual parameterisation, due to the unreliability of K_{ow}.
- Validated for neutral [1] and ionized [5] small molecules.

Computational Methods: COSMOmic

- Widely used proprietary software to calculate partition coefficients [6].
- Combines quantum chemical calculations of atomic orbitals with a continuum solvation model, thus avoid simulating many water molecules.
- Simulations of charged species use the membrane potential developed by Bitterman et al [7].
- Issues in simulation of cationics were uncovered: data below uses literature values (Timmer et al. values [8]).

COSMOmic

Electronic Structure Calculation



Environmental Impact?

→ Experimental K_{mw}

-Reliable.
-Slow.
-Experimental determination of Kmw for Surfactants is challenging due to solubility and sorption etc.
-For the underpinning experimental work see poster 3.01P-Th136 (Droge et al.)

+ Computational K_{mw}

-Validated for limited chemical space.
-Complements experimental data.
- Cationic QSAR values from Timmer et al. (2017) [8].

3 Methods →

QSPR

- Quantitative Structure-Property Relationship.
- Sum atomic contributions.
- Site of future work.

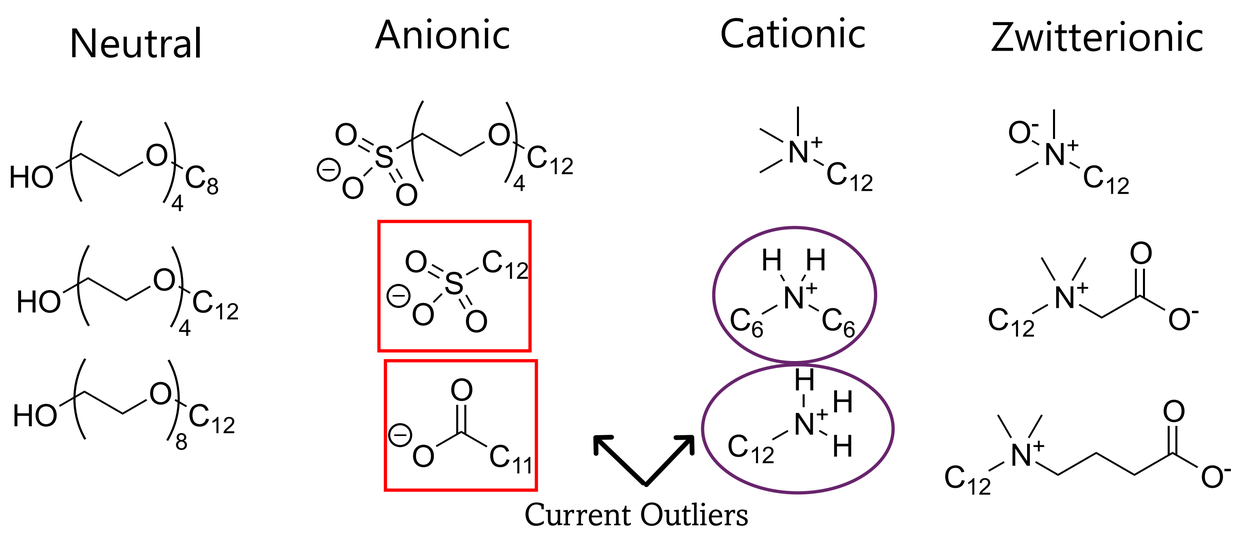
Molecular Dynamics

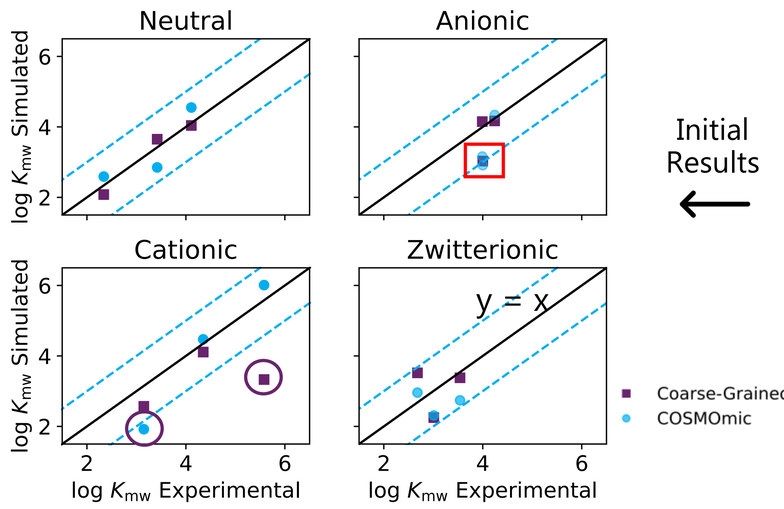
- Classical simulation using the Martini force field.
- Simulate movement of molecule through cell membrane, as an ongoing trajectory.
- Coarse-Grained to allow rapid simulation.

COSMOmic

- Electronic Structure Method.
- Calculate atomic orbital contributions.

ERASM Project Surfactants





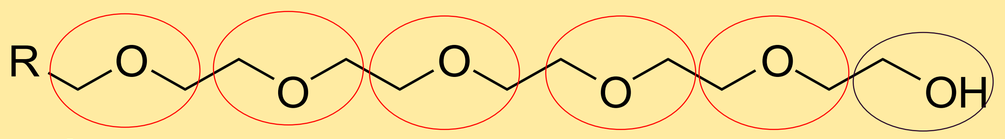
Initial Results ←

Results

- As part of ERASM, 12 representative surfactants were picked and subjected to computational and experimental study with the goal of establishing best practice when applying K_{mw} for surfactants.
- Results comparing simulated and experimental ERASM K_{mw} values are in the graph above right.
- Good performances for 10/12 molecules with both methods: Prediction for all surfactants within 1 log unit achieved with values from both methods.
- Note cationic COSMOmic values are sourced from Timmer et al. (2017) due to issues with recent simulations; cationics are especially sensitive to membrane potential values [8].
- Standard deviation of replica coarse-grained simulations: ~0.15.
- Molecular Dynamics Outliers: C12CO2 and C12NH3 – variably ionizable species.
- COSMOmic Outliers: C12SO3 and Dihexylamine.

Molecular Dynamics Development

- Custom parameterization for ether functional group were required.
- Ethers are a known issue in simulation [9]: individual ethers are sparingly hydrophilic and well-captured, but several ethers combine to form hydrophilic section of the molecule.
- Default coarse-grained models fail to capture this effect, but custom parameterisation targeting polyethers allows capture of this effect for the ERASM K_{mw} values.



Future work:

- ❑ Improve coarse-grained and COSMOmic parameterisations to improve results, and compare with alternative computational methods, e.g. pp-LFER [10].
- ❑ Full compilation and evaluation of K_{mw} results with experimental values.

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