Prediction of rhamnolipid partitioning into lipid bilayers and aggregation behaviour using coarse-grained molecular dynamics with the Martini 3 force field

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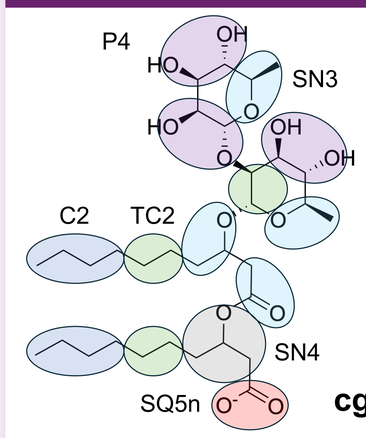
1. Background

- ***Rhamnolipids (RLs)*** are biodegradable and low-hazard ***biosurfactants*** sourced from bacteria. They are widely used as food/cosmetic additives and as oil capture agents. We aim to efficiently and accurately predict the ***membrane-water partition coefficient*** (**log K_{MW}**), which positively correlates to uptake in biological systems.
- RLs are ***coarse-grained (CG)*** automatically by cg_param[1] and manually for the ***Martini 3*** force field ***(M3)***. ***CG umbrella sampling*** simulations are conducted to capture ***free energy profiles*** of ***RLs*** partitioning between water and a lipid bilayer.
- Osmotic pressure is predicted to validate the parameters of rhamnose groups. Aggregation of ***RLs*** in different solutions is simulated to test ***RL CG*** models and understand the properties of RLs to capture oil molecules. The all-atom ***CHARMM36*** force field (***C36***) is used to obtain bonded parameters for manual models and to validate self-assembly and the salt effect on the aggregation process.

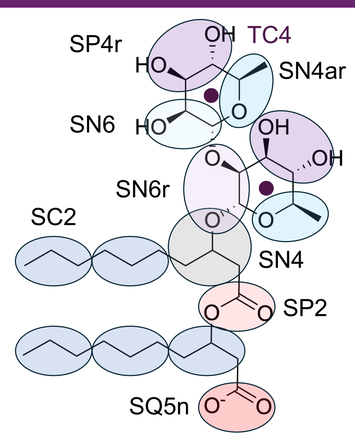
2. Parametrisation of rhamnolipids



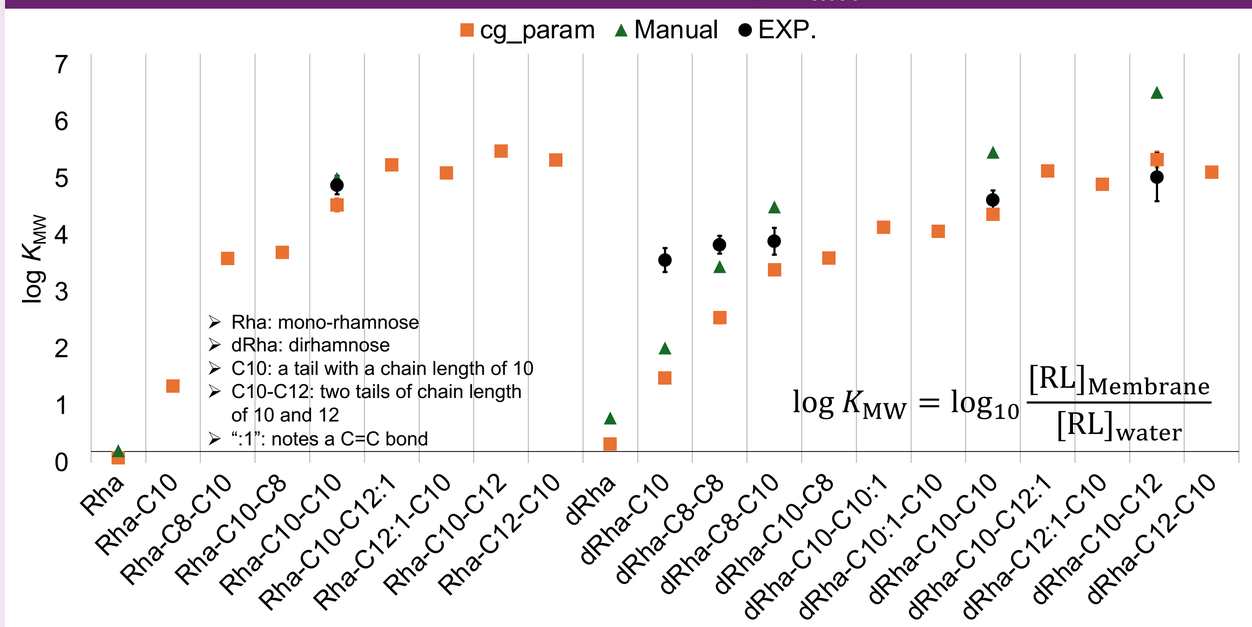
- Maximise **diol/diether**[2]
- Uniform mapping of **lipid tails**
- Adding **virtual sites**[2]
- Avoid splitting **ester**
- Bonded parameters are from atomistic simulations

Increasing resolution

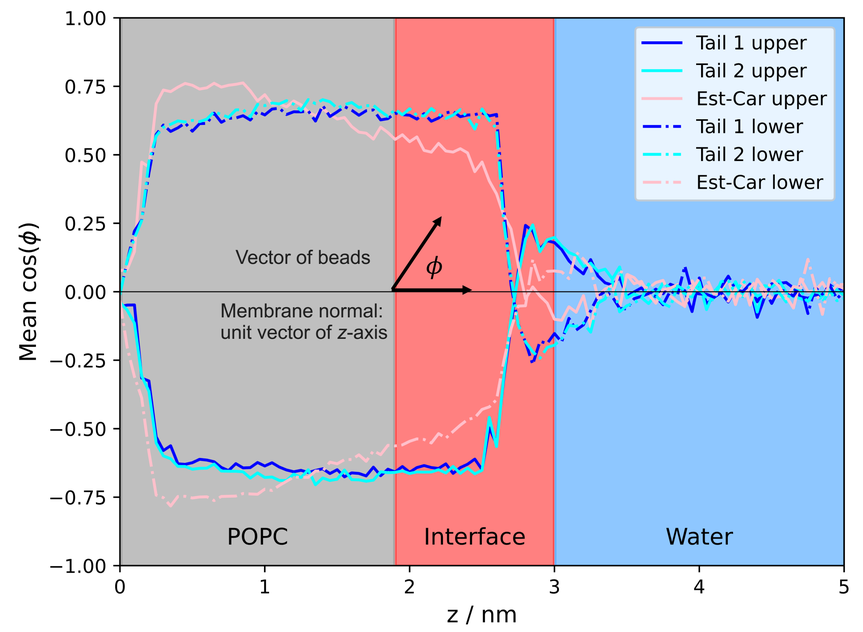
cg_param model[1] → **Manual model**

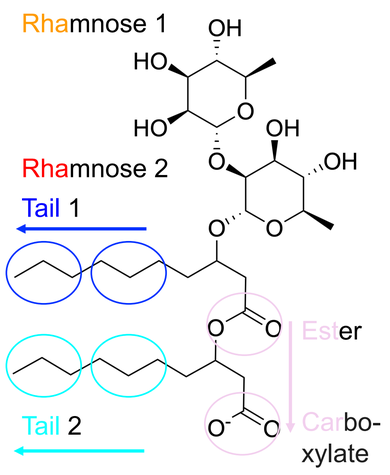


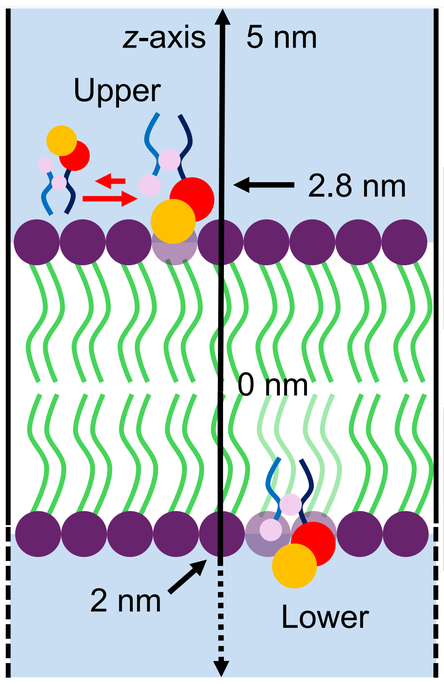
3. Prediction of log K_{MW}

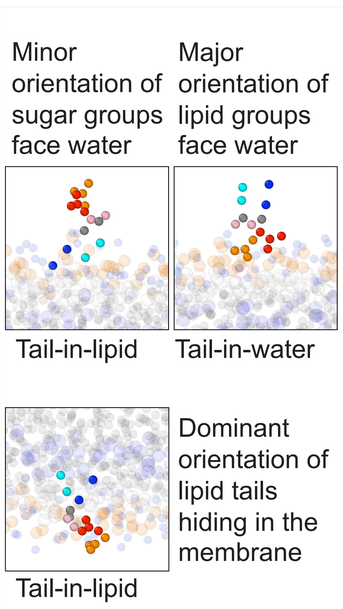


4. Interactions of dRha-C10-C10 along the *z*-axis



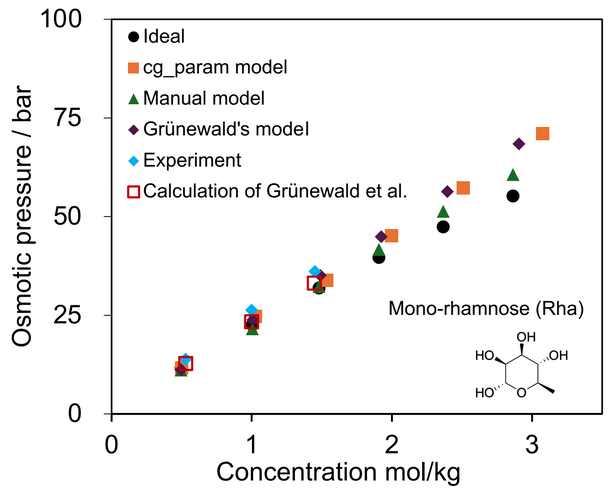


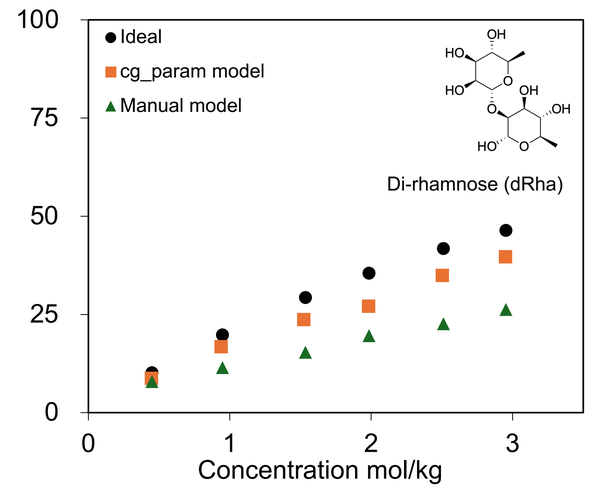




- Mean $\cos(\phi)$ measures the average angle between the vector of beads to the membrane normal.
- Lipid tails on ***RLs*** favour the membrane centre from 0 to 2.8 nm at the interface.
- Tail-in-water orientation becomes a major orientation due to the competition of hydrophobic and electrostatic interactions.
- Re-orientation is observed as ***RLs*** reaching the interface from bulk water until ***RLs*** enter the membrane.

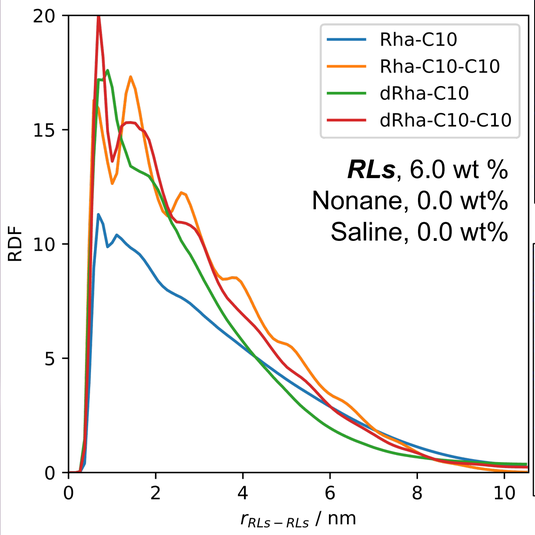
5. Prediction of osmotic pressure

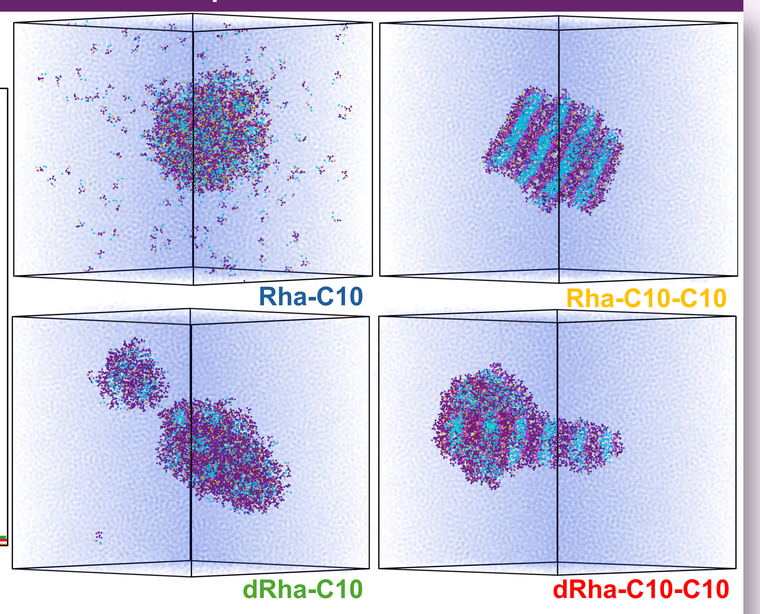




6. Aggregation of rhamnolipids in solutions

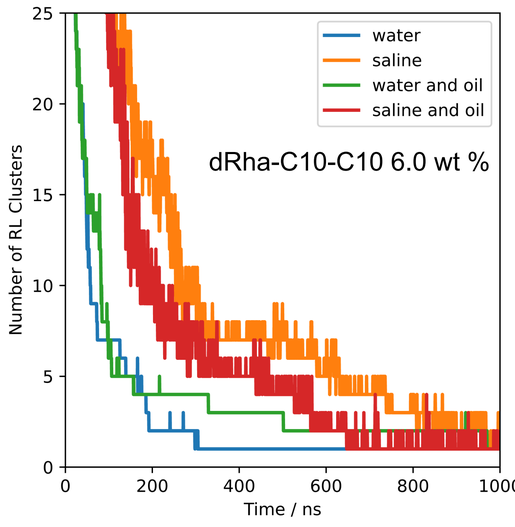
Morphology of RLs aggregates

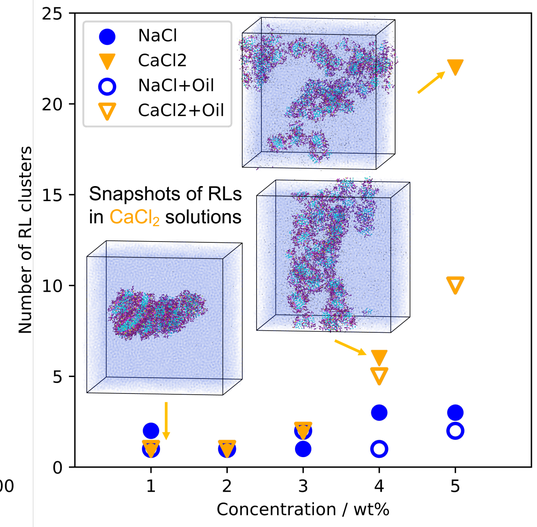




- Single-tail congeners form small micelles while double-tail congeners form layered aggregates.
- Strong affinity between rhamnoses is persistent in manual models.

Salt effects in *M3* simulations





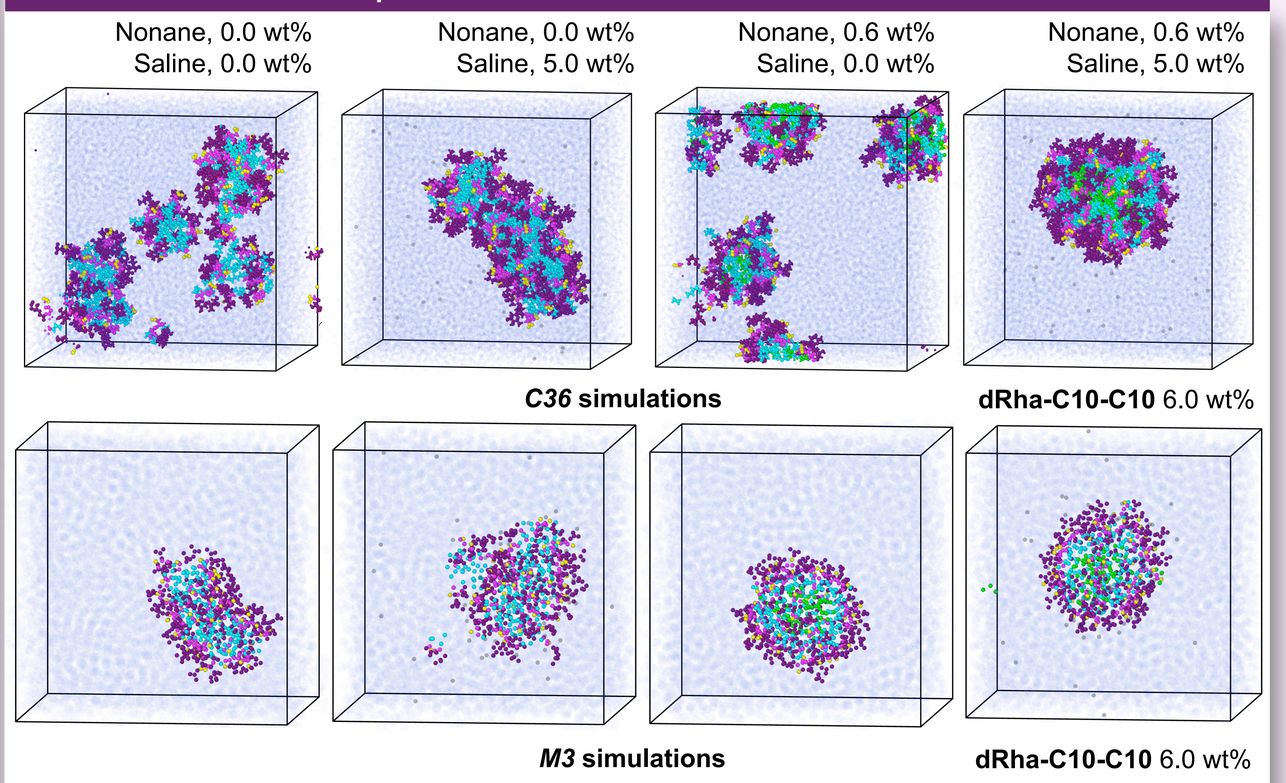
dRha-C10-C10 6.0 wt %

Colour scheme for functional groups for ***M3*** and ***C36*** snapshots:

- Rhamnoses
- Ester and adjacent groups
- Lipid tails
- Carboxylate groups
- Nonane oils
- Calcium ions
- Water beads, sodium and chlorine ions

- Kinetics of ***M3 RLs*** and ***RLs***+oil self-assembling is unexpectedly slower with excess Na^+, Ca^{2+}, and Cl^- ions
- A high concentration of the $CaCl_2$ solution further limits the formation of large micelles within the same amount of time

7. Comparison of *M3* and *C36* simulations



- The number of molecules in atomistic boxes is 10% of the equivalent beads in the original ***CG*** boxes.
- ***C36 RLs*** without salt are kinetically trapped in smaller micelles, while ***RLs*** with salt aggregate into one large micelle in less than 100 ns.
- In a smaller system, ***M3 RLs*** form single spherical micelles; layered aggregates are not present for insufficient solutes.
- Tails of ***M3 RLs*** in stable micelles can expose to water, which agrees with ***C36***.
- ***C36*** micelles in saline may further evolve as their volume is not minimised.

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GROMACS reminds you:
"Shaken, not Stirred". (J. Bond)

Reference

1. Environ. Sci. Process. Impacts 2023, **25** (6), 1082–1093
2. J. Chem. Theory Comput., 2022, **18**, 7555–7569
3. ACS Omega, 2022, **7**, 6223–6237

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