Safety & Environmental Assurance Centre

Development of coarse-grained simulation methods to study membrane partitioning

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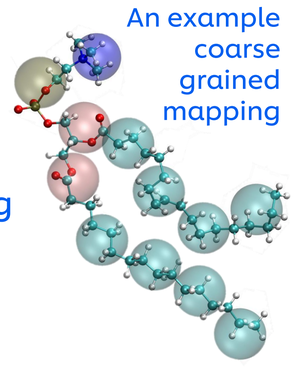
Introduction

$$\log K_{MW} = \log_{10}\left(\frac{[\text{solute}]_{membrane}}{[\text{solute}]_{water}}\right)$$

- In risk assessment, log K_{OW} can be used to predict chemical absorption, distribution and accumulation through environmental systems.
- Use of log K_{OW} may not be relevant for polar, charged, or amphiphilic compounds, can use log K_{MW} instead [1]
- We have developed a molecular simulation-based method for calculating log K_{MW}, using coarse-grained simulations
- Here we present initial results of predictions of log K_{MW} generated using our coarse-grained approach

Method

- Molecular dynamics (MD) is a molecular simulation method in which dynamics of the system are calculated using Newton's Laws
- MD gives a complete view of the movement of atoms in the system, but is very slow for large systems
- Coarse graining is a method which involves the grouping of multiple atoms into a single 'site', and simulating the movement of each 'site' rather than individual atoms [2]
- This decreases the number of degrees of freedom, reducing the computational expense of a calculation

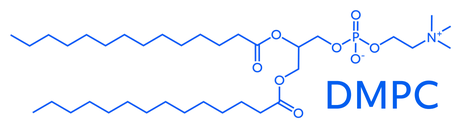


An example coarse grained mapping

Calculating log K_{MW}

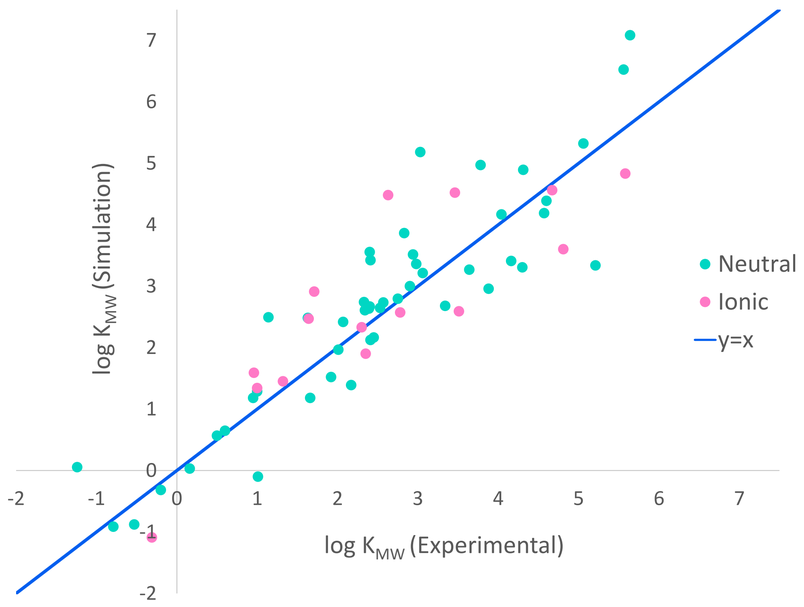
Simulation → Probability profile for molecule across the membrane → log K_{MW}

- Results were compared to experimental data for a diverse set of small organic molecules
- Additionally, log K_{MW} was calculated for partitioning into both pure DMPC and membranes made of DMPC + 30% cholesterol



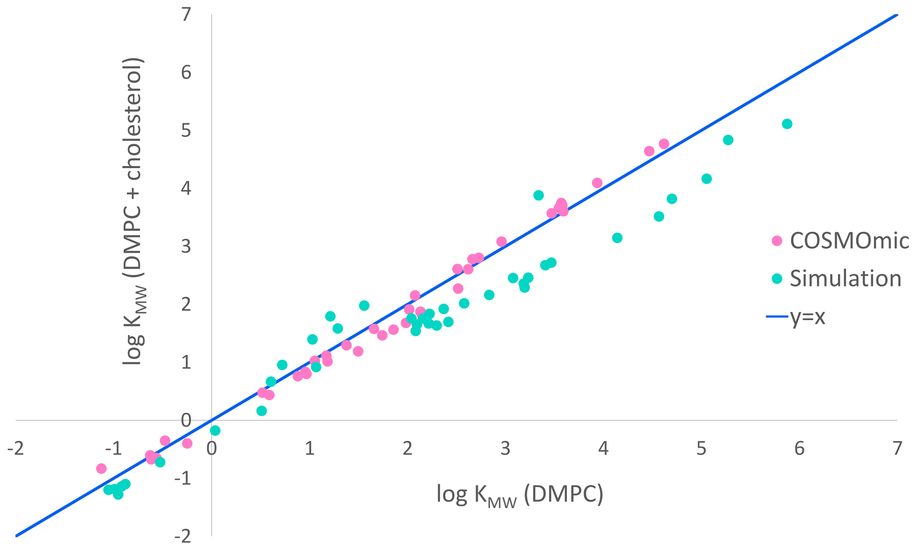
DMPC

Results for pure phospholipid membranes



- Good accuracy for the majority of small neutral and ionic molecules in DMPC.
- For ionisable molecules, parametrisation in the neutral form appears to give better results

Results for multicomponent membranes



- Investigated the effect of adding cholesterol on log K_{MW} from simulation and COSMOmic [3]
- Systematic reduction in log K_{MW} with cholesterol, especially for hydrophobic molecules.
- Simulations agree with evidence from atomistic simulation. [4]
- This difference is not seen from COSMOmic

Conclusions

- Coarse-grained simulation can be used to quickly obtain log K_{MW} values for molecules, including those which are large or ionic, with the same accuracy as all-atom simulations.
- Additionally, coarse-grained simulation shows a change in log K_{MW} with the addition of cholesterol to the membrane
- This suggests that coarse-grained simulation can capture energetic or steric effects missed by other computational methods in the prediction of partitioning

References

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