Case Study Template 3

Please complete 3 short case studies (max. 2 pages each). These case studies can be updates of the ones that have already been submitted (if so please note this in the case study title) or new case studies that have been developed in the current reporting period.

1. Title of Case Study: Development of hybrid coarse-grain/atomistic simulation models and their application to membrane-bound proteins

2. Grant Reference Number: EP/L000253/1

3. One sentence summary:

Hybrid simulation methods have been developed to explore biological membranes and the behaviour of drugs and proteins therein.

4. One paragraph summary:

The membrane environment is really important. It acts as a barrier to maintain the integrity of cells, and many important biological processes take place in the membrane, including the requirement of drugs to pass through to reach their binding sites. Computer modelling of membrane systems is therefore crucial to obtaining a full understanding. However, simulating all the atoms, while generally accurate, is expensive to perform owing to the large number of interaction sites. A common method to improve computational efficiency is to reduce the number of interaction sites by subsuming groups of atoms into larger beads. However, this simplification leads to a loss of accuracy. A solution to this problem is to keep part of the system at the atomistic level, and to use a hybrid coarse-grain/atomistic approach. In this project we have developed and tested just such an approach, using it to explore proteins in biological membranes, and how readily small molecules permeate, a critical component of the drug delivery process.

5. Key outputs in bullet points:

- Trained staff
- Methodology has been implemented and is now available in one of the major simulation programs, LAMMPS. This means that it is available for anyone to use.
- The ability to simulate proteins and drugs in the membrane environment.

6. Main body text

The membrane environment is crucial for the efficient functioning of living systems. It acts as a semi-permeable barrier maintaining the integrity of cells, and many important biological process arise from the proteins bound within the membrane. Computer simulations of membrane systems allow us to understand their structure and function – the membrane environment affects the bound proteins, while drugs must pass through membranes to reach their active site. However, in conventional molecular dynamics simulations all the atoms are represented, making these calculations very time consuming. A solution to this problem is to simplify the representation of the system by merging groups of atoms into larger beads. Such a coarse-grain approach, while faster, is less accurate. To maintain the overall accuracy of our calculations, while

improving efficiency, we have therefore developed a hybrid model in which the membrane molecules and surrounding solvent are represented at a coarse-grain level, while bound proteins and drugs are modelled at the atomistic level – we use the higher resolution model for the more important parts of the system.

To develop and test such a model, we calculated how the amino-acid side chains pass through the membrane, and how a range of peptides tilt and fold in the membrane (figures 1 and 2). Our model was able to reproduce the results seen using more complex atomistic models.

Figure 1. Schematic showing our hybrid simulation model. Note: to publish this you will need copyright approval from the ACS to use this image.

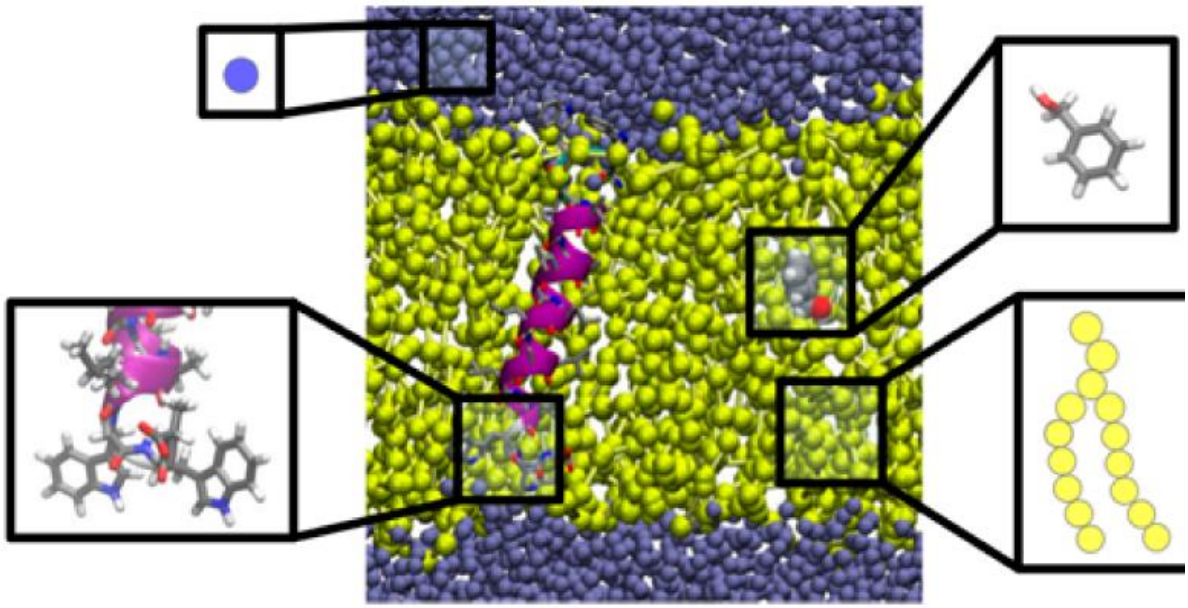
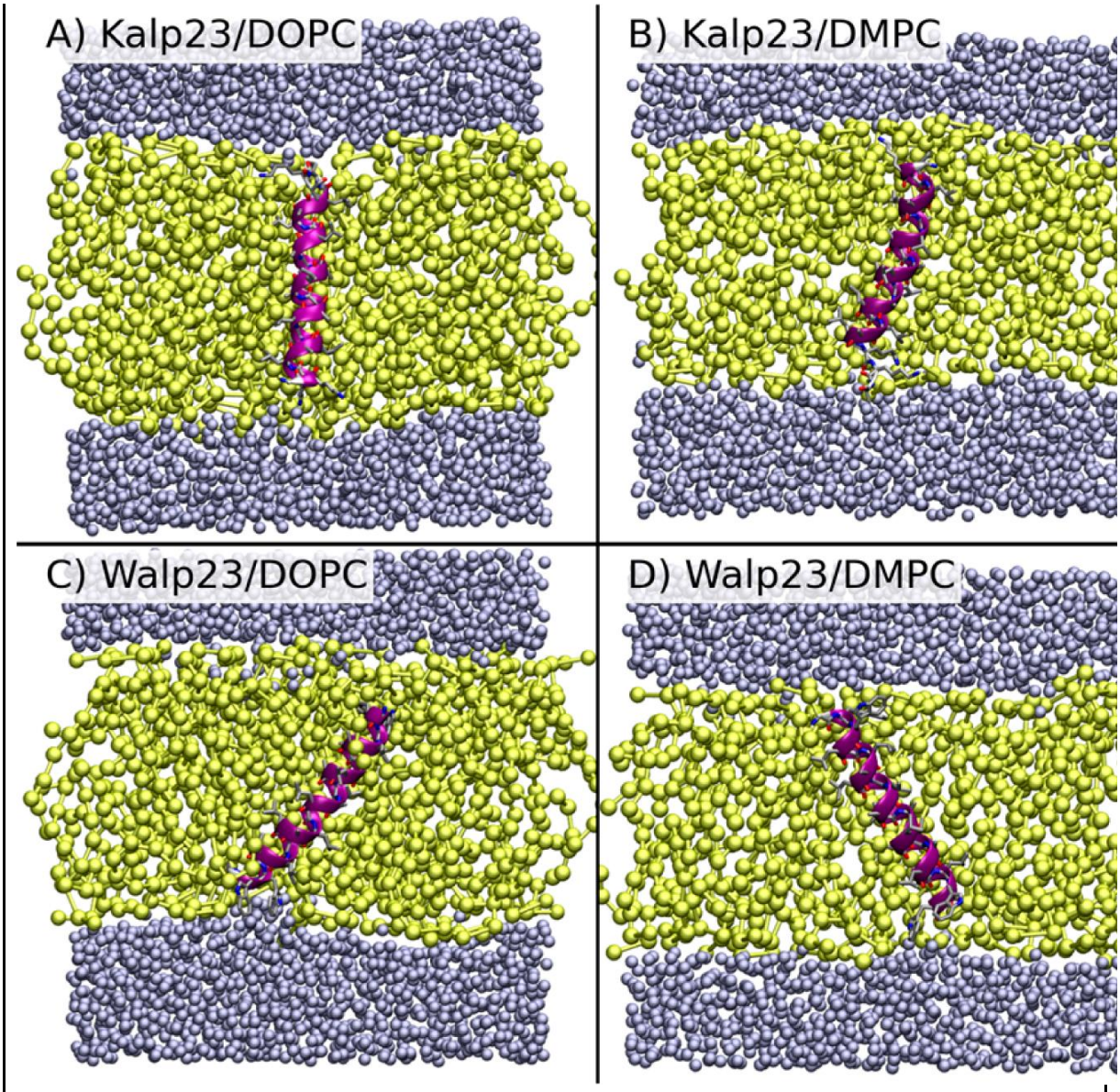


Figure 2. Snapshots from hybrid simulations of Kalp23 and Walp23 peptides in either a DOPC or DMPC membrane. Water beads are shown in blue, lipids in yellow, and the AA helix in purple cartoon representation. Copyright approval will again be required.



We have subsequently tested the model in a blind trial to predict the distribution coefficient of small molecules between water and cyclohexane. The distribution coefficient reflects how readily the small molecule separates into the aqueous and non-aqueous phases. In our approach the water and cyclohexane solvents are modelled at a coarse-grain level, and the small molecules at the atomistic level. In the blind trial, we were able to predict the distribution coefficients with accuracy comparable to that of more detailed atomistic models (figure 3).

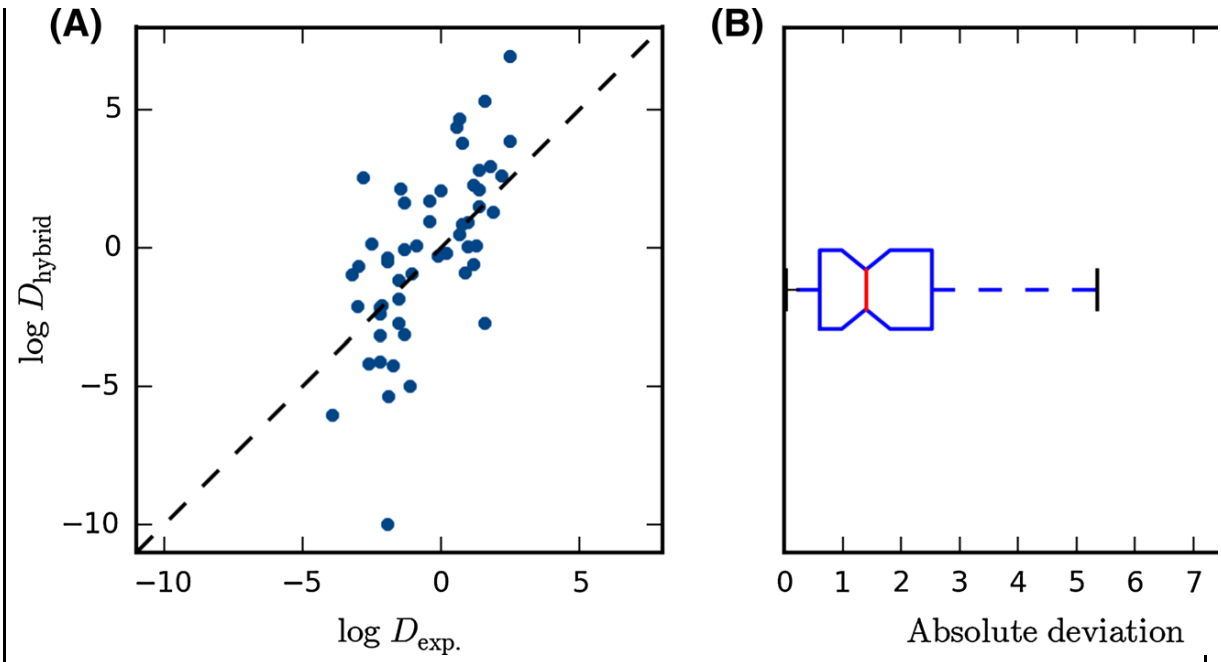


Figure 3. Experimental versus predicted log D and b boxplot of absolute deviations compared to experiments. Copyright approval again required.

(1-2 pages maximum, including figures/pictures, tables, quotes, infographics)

7. Names of key academics and any collaborators:

Jonathan Essex (University of Southampton); Samuel Genheden (University of Southampton, University of Gothenburg)

8. Sources of significant sponsorship (if applicable):

Wenner-Gren foundation

(Amount, sponsoring organisation, date)

9. Who should we contact for more information?

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10. Please indicate if you would like this case study to be included on the Consortium's ARCHER web-page.

Provided you get the appropriate permissions to publish the figures, yes.