Permeability of Small and Medium Sized Photoactive Molecules through Lipid Bilayers and Vesicles

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1 Introduction

Photodynamic therapy (PDT) is a method used to treat cancer and viral diseases. It is a three-step process where a drug is first administrated which, due to its photoactive properties, is excited when combined with light and this results in different reactive oxygen species (ROS). The generated ROS then kill the cancerous lesion.

There are several possibilities for delivering this photosensitizer, one way is to directly add it to the blood stream and let it diffuse through the cell membrane. Another possibility is to add precursors of heme such as 5-aminolevulinic acid (5-ALA) that can, in excess, lead to a *in situ* production of protoporphyrin IX (PpIX). For the former case hypericin, see Figure 1, can be used. The mechanism of the delivery of this molecules is not yet fully understood but several pathways have been proposed.[1–9] One interesting way of transporting hypericin into the cell is via drug-carrier, e.g. a liposome.[10] Encapsulation of the photosensitizers prohibits aggregation which is very beneficial since the aggregated state reduces the photodynamic properties of hypericin.

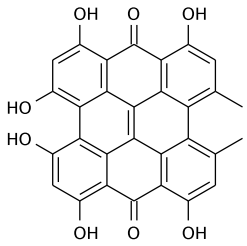

Figure 1. Chemical structure of hypericin.

1.1 Purpose of the Visit

As was mentioned in the previous section, the permeability of different molecules intended for PDT through cell membranes is very essential. However, the partition coefficient for a drug between a membrane and the aqueous phase is difficult to measure. This makes these transport phenomena perfect for computer studies. By performing molecular dynamics (MD) simulations it is possible to obtained a very detailed picture of how of the mentioned molecules partition between the different phase and also the free energy energy of transfer can be determined by computing the potential of mean force (PMF).

During the scientific visit to National University of Ireland and prof. Leif A. Eriksson's group we focused mainly on how hypericin can enter a liposome and how the photosensitizers behave while they are encapsulated in the liposome. Further ideas are discussed in the last section.

2 Methods and Models

Liposomes have been studied by computer simulations in many different ways, such as the membrane fusion,[11–13] formation from lipid bilayers[14,15] and the

encapsulation of anesthetics.[16] In order to cover cover relevant time and length scale the popular MARTINI coarse grained force field[17] was used. Hypericin was coarse grained by assigning MARTINI building blocks to the functional groups of the molecules, see Figure 2. The hypericin model was condensed down to 11 coarse grain (CG) particles. Similar procedures have been used with success previously.[16] Once the coarse graining of hypericin was finished the quality of the simplified model was checked by performing simulations with hypericin together with a DPPC lipid bilayer and comparing the results to published work on a more detailed level.[18]

Two model liposomes were then used, one with only DPPC lipids and one with only DOPC lipids. The liposomes were built up from 2528 lipids and solvated with 165120 MARTINI water particles. This gave a system size corresponding more than 2 million atoms, making it unfeasible to use an atomistic description of the particles on the time scales of interest.

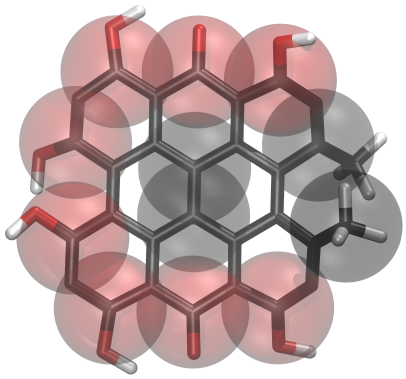

Figure 2. Coarse grained model of hypericin superimposed on the atomistic description of the same molecule. The color of the beads represents the 'polarity' of the beads, red: polar, dark: unpolar.

3 Preliminary Results

The density distribution of a lipid bilayer simulation with hypericin after a 400 ns simulation is shown in Figure 3. As can be seen, the hypericin molecules prefers the most dense regions of the lipid bilayer, i.e. he head group region. Due to the amphiphilic nature of hypericin the molecule stay in contact with water, mostly via the hydroxyl rich side of the molecule.

Due to the fact that the two hypericin molecules are absorbed at the same side of the bilayer the density distribution is not symmetric. The agreement with a previous atomistic simulation[18] is good which means that CG model of hypericin works well together with the lipids, however, further testing is needed to make sure that the model is accurate enough (see the following paragraph).[1]

[1]The position of the hypericin molecules relative the DPPC lipids is the important thing to compare, not absolute density numbers.

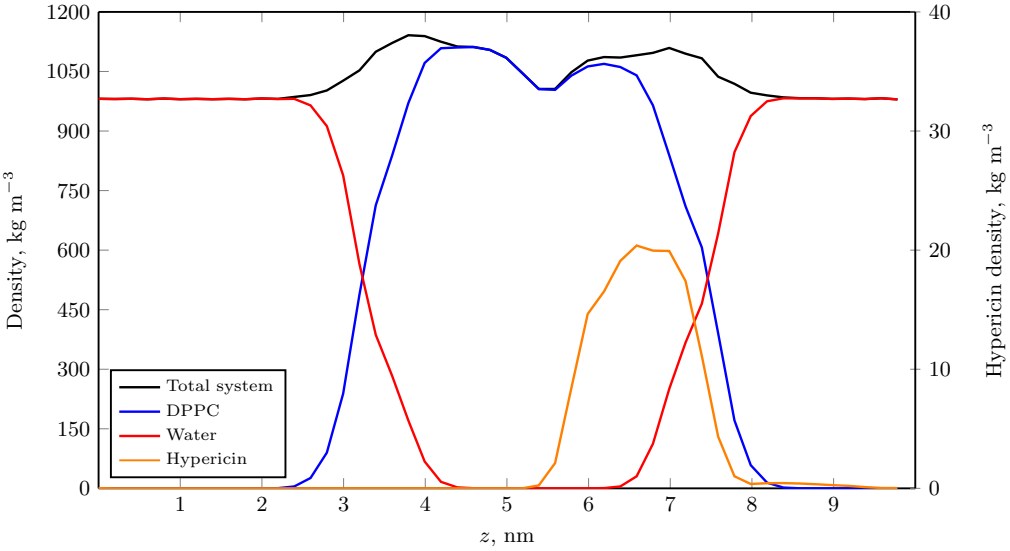

Figure 3. Density distribution in the simulation box. The z-axis is defined as the bilayer normal.

4 Concluding Remarks and Future Plans

Results presented show that the obtained CG model of hypericin might work well together with the MARTINI FF lipids and water. In order to make sure that the model is satisfactory when investigating the dynamics other studies have to be performed before the studies of how hypericin behaves in a liposome can be done. Thermodynamic data like partitioning or free energies are properties that are important and should be computed and compared to available experimental data. It is also important to verify crucial findings with the CG model by performing all-atomistic simulations. This also gives an understanding of the system on a multi-scale level and these kinds of verifications will be performed in the future.

For the future we are interested in saturating lipid vesicles with hypericin and investigate how the molecules behave in such potential drug-carriers. It is also of interest to simulate the actual drug-release when the carrier delivers the photoactive compounds to the cell membrane. In order to perform simulations on such a large scale the MARTINI FF has to be used again and therefore it is crucial that the CG model of hypericin is as accurate as possible.

Acknowledgements

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