Molecular dynamics simulation of lipid membranes with AMBER and application to the study of radioimaging pharmaceuticals

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Positron emission tomography (PET) scanning is a molecular imaging technique allowing the detection and analysis of biological processes, including metabolism and disease. PET scanning is regularly implemented in the imaging and study of diseases such as cancer, Alzheimer's and Parkinson's disease and is also becoming increasingly popular to aid the drug discovery process.

To perform a PET scan, the patient is administered a small molecule radiotracer, which emits a trace amount of radiation and binds to the site of interest, allowing an image to be constructed. In order to image new targets, novel radiotracers must be designed. However a limitation in the design of new radiotracers is non-specific binding, whereby the tracer binds to off-target species, such as cell membranes, creating an uninformative image with poor contrast. An *in silico* indicator, able to predict the level of non-specific binding a new radiotracer may undergo *in vivo* prior to synthesis and testing, would be extremely beneficial to the PET community.

In this work we investigate non-specific binding using molecular dynamics (MD) to study the interaction of PET radiotracers with lipid bilayers, a simple model for the cell membrane, using the AMBER MD package. To accurately model lipid bilayers, suitable parameters were first constructed.[1] These parameters are currently being combined with the AMBER Lipid11 modular lipid force field [2] to create an updated, unified AMBER lipid force field. The potential of mean force (PMF) method has been inserted into AMBER, in order to calculate the free energy of transfer of radiotracers through a lipid membrane. The PMF method is currently being applied to a dataset of well characterised PET radiotracers to investigate the relationship between membrane permeability and non-specific binding.

[1] C. J. Dickson, L. Rosso, R. M. Betz, R. C. Walker and I. R. Gould, *Soft Matter*, **2012**, *8*, 9617-9627.

[2] Å. A. Skjevik, B. D. Madej, R. C. Walker and K. Teigen, *The Journal of Physical Chemistry B*, **2012**, *116*, 11124-11136.