Parameterization of a Coarse-Grained Model for Ceramides

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The *stratum corneum* is the main barrier to prevent drugs from penetrating the skin. It's the outermost layer of the epidermis consisting of corneocytes embedded in a lipid membrane region which contains ceramides, cholesterol and free fatty acids [1]. The lipid region which is the only continuous structure in the *stratum corneum* plays an important role in the barrier function. We use molecular dynamics simulations to investigate this barrier function on an atomic scale. Due to the large amount of degrees of freedom in the membrane, coarse-grained models were used to enlarge the time scale and the accessible system size in the simulation.

Our work is based on the forcefield called MARTINI developed by Marrink and co-workers [2, 3]. This coarse-grained model is simple and has only a small number of coarse-grained atom types and can reproduce a lot of properties of amino acids, lipids, polymers, etc. For example the model can correctly reproduce the lipid bilayer self-assembly process.

However, the forcefield parameters of the ceramides which are the most abundant lipid class in the *stratum corneum* [1] is not available in MARTINI. So parameterizing the ceramides becomes one of the most important tasks for the *stratum corneum* simulations. In general there are two ways to parameterize a coarse-grained forcefield. First, we can compare the results with more accurate simulations such as all-atom simulations. Second, comparing the results with available experimental results is more preferred. The suggested ceramide parameters were derived from all atom simulations using GAFF [4] and complement preexisting MARTINI lipid parameters. The preliminary results show that with our parameters, the main phase-transition temperature of ceramide (~90.0 ℃ [5]) and the area per lipid (55.1 $\pm$ 0.7 Å^2 [5]) can be reproduced.

[1] P.W. Wertz, B. van den Bergh, *Chem. Phys. Lipids*, **1998**, *91*, 85-96.
[2] L. Monticelli, S. Kandasamy, X. Periole, R. Larson, D.P. Tieleman, S.J. Marrink, *J. Chem. Th. Comp.*, **2008**, *4*, 819-834.
[3] S.J. Marrink, A.H. de Vries, A.E. Mark, *J. Phys. Chem. B*, **2004**, *108*, 750-760.
[4] J. Wang, R.M. Wolf, J.W. Caldwell, P.A. Kollman, D.A. Case, *J. Comput. Chem.*, **2004**, *25*, 1157-1174.
[5] S.A. Pandit, H.L. Scott, *J. Chem. Phys.*, **2006**, *124*, 014708-014714.