Molecular dynamics simulations of glycolipids using high performance computing

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Carbohydrates are the most naturally abundant biomolecule. Polysaccharides are involved in a range of functions, from energy storage to structural integrity. In addition to constituting a key component of DNA and RNA, carbohydrates form conjugates with proteins and lipids. With a hydrophilic carbohydrate headgroup and a hydrophobic lipid tail, glycolipids are amphilic molecules, able to dissolve hydrophobic moieties and self-assemble in different ways to form bilayers, vesicles and micelles. These assemblies have nanotechnological potential, with liquid crystal behaviour, in addition to uses as non-ionic detergents, drug delivery agents and as a model to probe aspects of the glycocalyx. The relationship between structural and physical properties of glycolipid assemblies is not fully understood. Coarse-grained models have been employed to simulate these systems, but have struggled to describe the subtlety of their physicochemical behaviour.

Therefore, the research groups of Richard Bryce at the University of Manchester and Rauzah Hashim at the University of Malaya, Malaysia, are employing detailed molecular dynamics (MD) simulations in an effort to understand the structure-property relationships of glycolipids in lamellar phases. Carbohydrates themselves exhibit considerable conformational complexity: even the simple monosaccharide glucose has 729 possible conformers, assuming three rotamers per single rotatable bond. Thus, to equilibrate the multiple flexible carbohydrate headgroups requires long time scale simulations. The computational expense is also increased by the need for a realistic description of (1) the long-tail electrostatics interactions engendered by the polar headgroups and (2) interaction with aqueous solvent. For this, the micelle is simulated in a bath of explicit solvent molecules, using truncated octahedral periodic boundary conditions and the particle-mesh Ewald method (Figure 1).

High performance computing is well-suited to the molecular dynamics technique, where the large number of pairwise nonbonded interaction energies and forces can be distributed over many processors. We use a message-passing version of AMBER where bonded and nonbonded energies and forces, pairlist creation and integration steps are parallelized. Thus, simulation times can be reduced from weeks to days, permitting improved statistics using different initial conditions. Results from the simulations are providing insights into the molecular-level behaviour of glycolipid micelles. For example, an MD snapshot of a micelle of 1-*O*-*n*-octyl β-D-glucopyranoside is shown in Figure 2. The snapshot is taken from a 5 ns simulation at a temperature of 300 K and a high solute concentration of

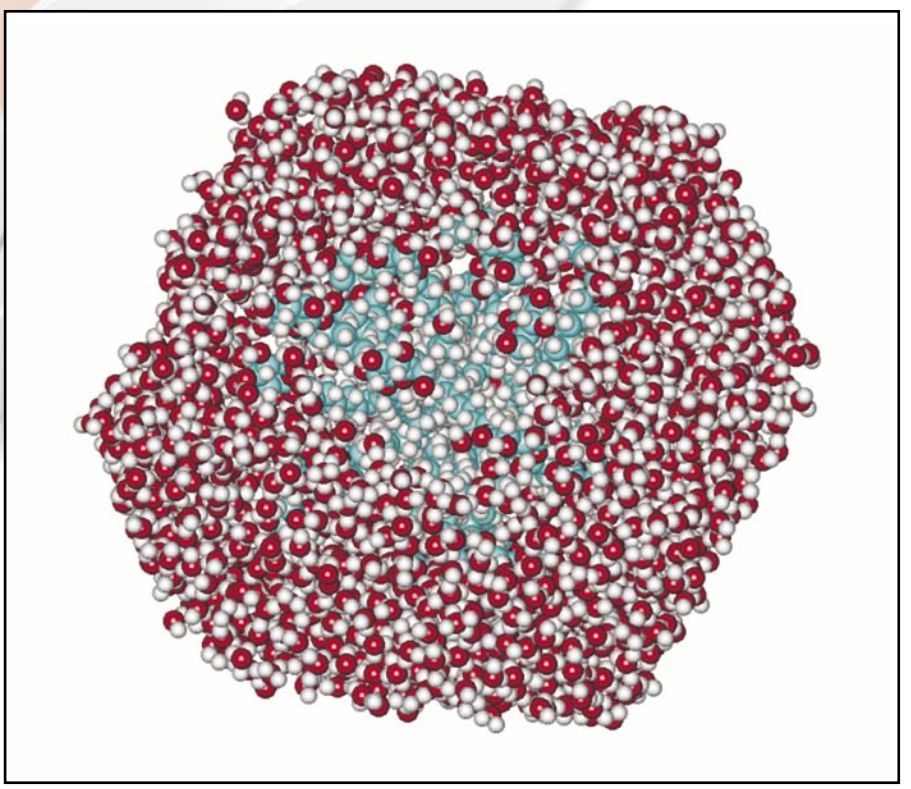

Figure 1 Micelle in a truncated octahedral periodic box of water

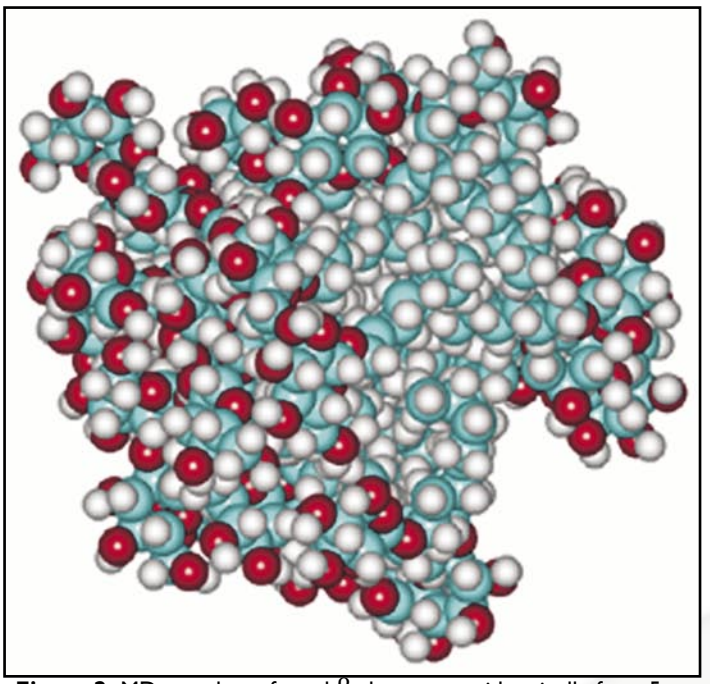

Figure 2 MD snapshot of octyl β-glucopyranoside micelle from 5 ns simulation. Oxygen (red), carbon (cyan) and hydrogen (white) atoms are shown.

0.6 M (well above the critical micelle concentration), performed using the program AMBER 7 on the SGI Altix Newton. The density profile (Figure 3) indicates the broad distribution of the headgroups over 7 to 23 Å from the centre of mass of the micelle. Also apparent is the penetration of the aqueous solvent within the micelle into the headgroup region. This arises in part from the exposure of hydrophobic surface area (Figure 2) to surrounding water. The average headgroup radius is ~14 Å (Figure 3), which is in reasonable agreement with a hydrodynamic radius of 15±1 Å (an upper limit for actual micelle radius), determined from chromatographic experiments for an aggregation number of 27 [1]. Thus, molecular dynamics simulations on supercomputers are enabling access to detailed studies of glycolipid structure and dynamics, deepening our understanding of these therapeutically and commercially important materials.

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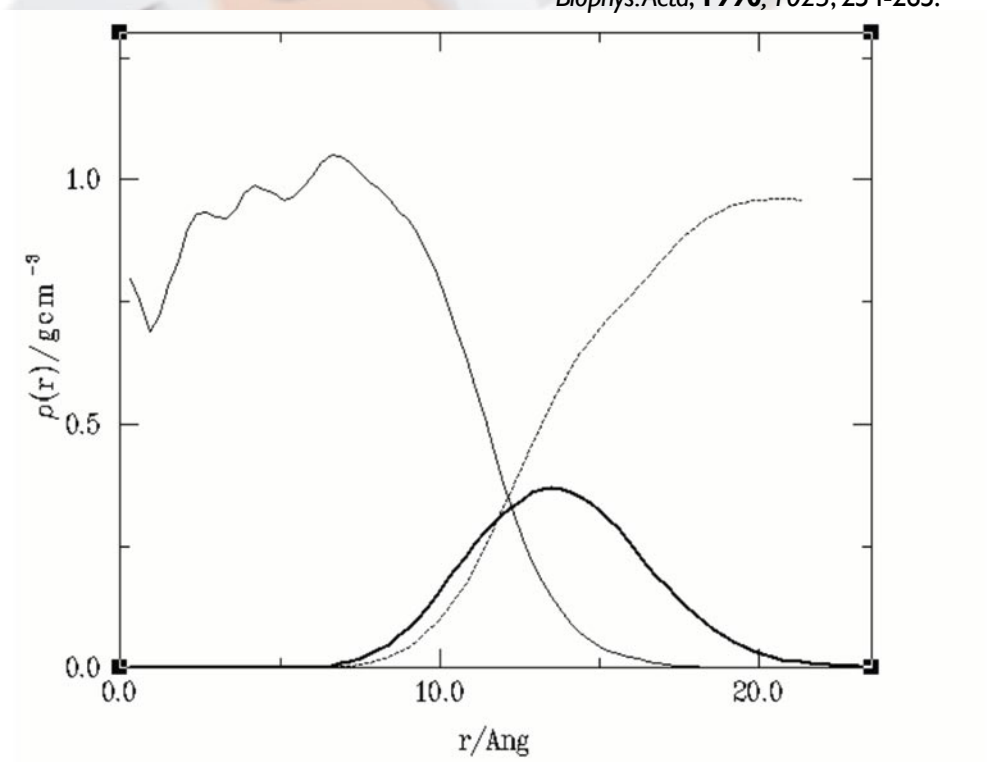

Figure 3 Local density profile of micelle/solvent system: glucose headgroup (bold solid line), lipid tail (solid line) and water (dashed line).