

# **A computational study of room-temperature ionic liquids interacting with phospholipid bilayers**

**Richard Bingham and Pietro Ballone**

*School of Mathematics and Physics, Queen's University Belfast, Belfast BT7 1NN, UK*

Phospholipid bilayers (Fig. 1), stabilised by their interaction with an aqueous medium, represent the major structural component of bio-membranes surrounding cells and sub-cellular organelles. The role of this molecularly thin, flexible and yet resilient envelope goes beyond containment and protection, since it also regulates the flow of nutrients and waste compounds in and out of cells, and contributes to the exchange of chemical and sometimes electrical signals among cells. Last but not least, bio-membranes provide the physical support for a variety of energy conversion processes powering life on Earth.

The structural and functional integrity of this essential cellular component is imperative, and hence a primary factor determining the biological effect of any new chemical species synthesised, is precisely its interaction with bio-membranes.

In this respect, a case in point is provided by the so-called room-temperature ionic liquids (RTILs)<sup>1</sup>, a vast class of organic ionic materials, currently investigated because of their high potential for applications. Widespread usage of these compounds in industrial processes would certainly result in their intentional or unintentional release into the environment.

Even though RTILs are heralded as the spearhead of a new and greener chemistry, it is nevertheless necessary to assess the biological effect of each of them. Concerns about their toxicity have been highlighted by experimental studies<sup>2,3</sup> that revealed strong association of RTILs with bio-membranes, leading at high concentration to the disruption of the phospholipid bilayer, especially in the case of RTILs with long hydrocarbon side chains. It should be noted that the RTIL concentrations considered in these measurements are orders of magnitude higher than those expected to arise in biological tissue from environmental pollution. Still, the experimental observations do point to aspects that need a closer scrutiny, especially taking into account that the complexity of living organisms, together with the intricate interdependence of biochemical pathways, almost guarantee that unexpected effects are the most likely result of introducing new chemicals into our environment. Alternatively,

strong and specific interaction with membranes of ionic and, in some cases, amphiphilic compounds such as RTILs might have fundamental implications for pharmacology applications or biomedical technologies concerning, in particular, novel strategies to deliver drugs to cells across their protective membrane.

The state of the art in molecular modelling and high performance computing is such that computer simulation can play a relevant role in assessing the interaction of RTILs with lipid bilayers, and might provide a working tool for a first preliminary screening of RTILs on the basis of their expected interaction with bio-membranes. Additionally, simulation can advance our understanding of the microscopic mechanisms underlying positive or negative effects of RTILs on the stability of bio-membranes.

In our study, we investigated the evolution of a POPC bilayer interacting with a few prototypical RTIL's (Fig. 2), whose chemical structure is illustrated in Fig. The simulation sample consisted of 340 Palmitoyloleoylphosphatidylcholine (POPC) phospholipids, surrounded by  $\sim 18,000$  water molecules, enclosed in an orthorhombic cell, periodically repeated in space. The time evolution of the system is simulated by molecular dynamics, based on an empirical interatomic force field. Constant pressure and constant temperature conditions are enforced using standard simulation algorithms. The system size corresponds to  $\sim 70,000$  atoms, and each system has been simulated for 100ns, at a rate of 6ns per day on 128 CPU's.

At ambient conditions, simulation reproduces the stability and chemical-physics properties of real POPC bilayers in pure water. The addition of RTIL molecules at 0.5 M concentration, initially located at random position within the water layer, changes somewhat this reassuring picture. Three different RTIL compounds have been considered at this stage, i.e., [bmim][Cl], [bmim][PF<sub>6</sub>], and [bmim][Tf<sub>2</sub>N], providing a sequence of imidazolium-based ionic liquids of decreasing water solubility.

Snapshots of the POPC bilayer in [bmim][Cl] (Fig. 3), and in [bmim][PF<sub>6</sub>] water solution (Fig. 4) already provide a visual confirmation that RTIL molecules are preferentially adsorbed onto and into the phospholipid bilayer, somewhat increasing its volume, affecting its planarity, and enhancing the amplitude of thermal fluctuations at the water-lipid interface. Quantitative determination of the ion density distribution, and detailed analysis of configurations shows that the close interaction of RTILs and phospholipids is due to the alkane portion of the [bmim]<sup>+</sup> cation, whose hydrophobicity and high affinity for the hydrocarbon tails of POPC drives their penetration into the bilayer. Anions' penetration depends on

their size and polarisability. Small anions such as Cl tend to remain in solution, where their charge is effectively screened by the high dielectric constant of water. This effect is less important for larger anions, which are increasing adsorbed at the lipid surface. Complex, highly polarisable species such as  $[\text{Tf}_2\text{N}]^-$ , tend to follow the cations into the lipid bilayer.

Comparison of the computational results display important similarities with the experimental data. More importantly, the atomistic detail provided by simulations allows us to understand the origin of the observed trends, and to identify the important factors affecting the interaction of RTILs with phospholipid bilayers.

The investigation describe in the present document is part of a broader computational study of phospholipid interactions with ionic species and electric fields, motivated by applications in sensing technology<sup>4</sup>. A pictorial view of our studies in this direction is given in Fig. 5, showing a snapshot from a simulation of an electrochemical cell consisting of a POPC layer adsorbed on a metal electrode, surrounded by an electrolyte solution screening the electric fields applied through the electrode.

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<sup>1</sup> T. Welton, *Chem. Rev.*, 1999, **99**, 2071.

<sup>2</sup> K. O. Evans, *Colloids Surf. A* **274**, 11 (2006).

<sup>3</sup> K. O. Evans, *J. Phys. Chem. B* **112**, 8558 (2008).

<sup>4</sup> A. Nelson, *J. Electroanal. Chem.* **601**, 83 (2007).

## FIGURES

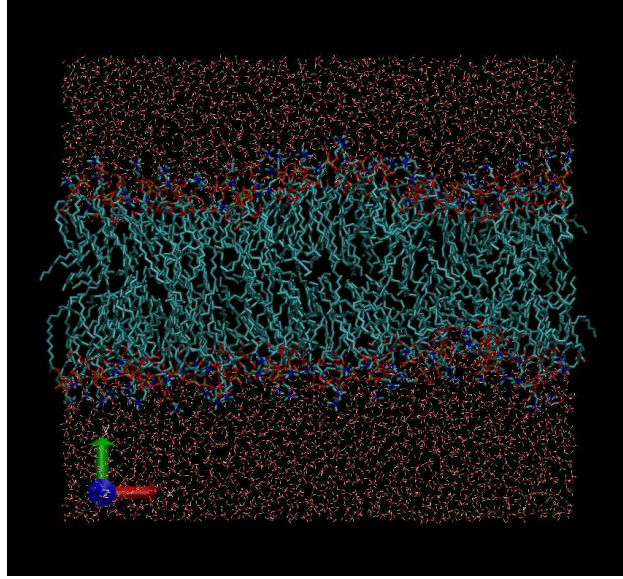


FIG. 1: The structure of a Phospholipid bilayer.

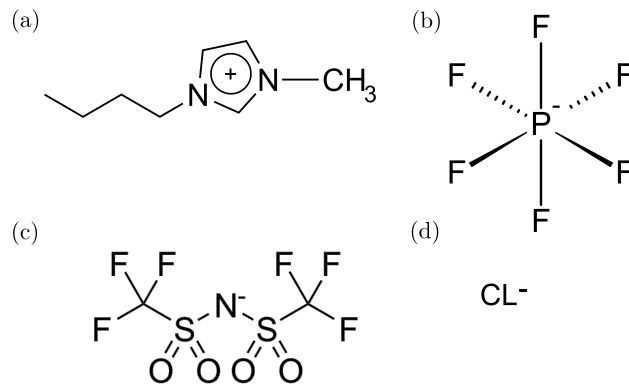


FIG. 2: The RTIL cation (a) and anions (b),(c) and (d) considered in our investigation.  
 (a) Butylmethylimidazolium (bmim), (b) Hexafluorophosphate ( $\text{PF}_6$ ), (c)  
 bis(trifluoromethylsulfonyl)imide  $\text{Tf}_2\text{N}$  and (d) a chloride ion.

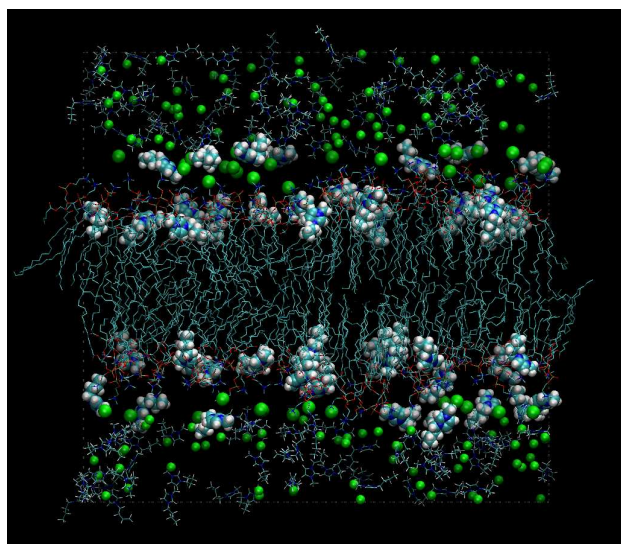


FIG. 3: A POPC bilayer in a solution of [bmim][Cl].

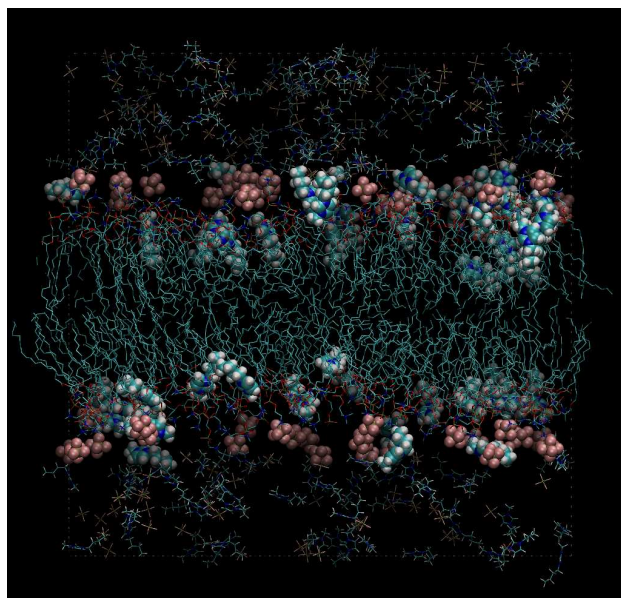


FIG. 4: A POPC bilayer in a solution of [bmim][PF<sub>6</sub>].

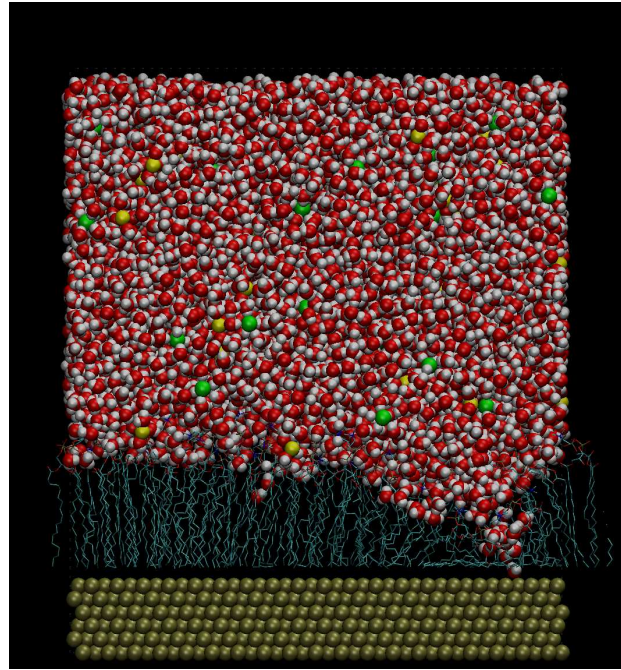


FIG. 5: A POPC monolayer adsorbed on a metal electrode, showing disruption to the monolayer surface under the action of an applied electric field.