Biochimica et Biophysica Acta 1841 (2014) 1130–1145

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

The challenges of understanding glycolipid functions: An open outlook based on molecular simulations☆

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ARTICLE INFO

Article history:
Received 18 October 2013
Received in revised form 29 December 2013
Accepted 30 December 2013
Available online 7 January 2014

Keywords:
Molecular dynamics simulation
Computer simulation
Carbohydrate
Lipid
Glyco
Glycosphingolipid

ABSTRACT

Glycolipids are the most complex lipid type in cell membranes, characterized by a great diversity of different structures and functions. The underlying atomistic/molecular interactions and mechanisms associated with these functions are not well understood. Here we discuss how atomistic and molecular simulations can be used to shed light on the role of glycolipids in membrane structure and dynamics, receptor function, and other phenomena related to emergence of diseases such as Parkinson's. The cases we discuss highlight the challenge to understand how glycolipids function in cell membranes, and the significant added value that one would gain by bridging molecular simulations with experiments. This article is part of a Special Issue entitled Tools to study lipid functions.

1. Introduction

During the last decade, molecular simulations of biological systems have matured to a level where they can provide a great deal of added value to complement experiments. In part, this progress stems from the development of ever more accurate simulation models and novel simulation approaches. At the same time, as the computational resources and the performance of simulation software packages have advanced significantly, the scales in time and space that one can simulate have increased quite dramatically. Together, these improvements have rendered ever more detailed considerations of complex biomolecular processes possible.

What is more, the nature of biomolecular simulations has gone through a major change. Still quite recently molecular simulations focused on repeating what had been observed in experiments, and the primary objective was to explain the observed phenomena. Things are quite different today, since in addition to shedding light on the experimentally observed processes, molecular simulations are nowadays used more and more often as a tool to make predictions of, e.g., novel dynamic phenomena and structures of drugs binding to their target molecules [1,2]. Also, important to stress is the added value given by molecular simulations to unravel how the use of experimentally used probes affects the behavior of the studied systems. Simulations can be done with and without those probes, thus revealing the true behavior of the systems as well as the influence of probes. By bridging these simulations to experiments one can better understand what really happens and why, and one can design new probes with less severe side effects [3–6]. Overall, the predictions produced by simulation models are to be tested by experiments, and this paves the way for a highly optimized and beneficial research strategy to aim for better science at a higher pace and with more reasonable costs.

Those who like exceptionally challenging but rewarding research topics may like to consider glycolipids as one of the next themes of research. In Greek, "glyco" refers to sugar, and "lipos" to fat, thus together they make up a quite sweet combination. In cellular membranes glycolipids have a variety of functions in terms of recognition and signaling, among other roles, and they have also been shown to modulate the function of membrane proteins acting as receptors [7–9]. The current paradigm for membrane structure and function known as the lipid raft model [10] is also related to glycolipids: lipid rafts are considered to be functional nanoscale membrane units, and it is intriguing to realize that in many cases these functional units have been found to contain glycolipids. The biological functions associated with glycolipids highlight the importance to understand their roles in cells, yet this is not a simple feat. It is quite justified to say that glycolipids, and glycomolecules in general are the most tricky (or at least among the most intricate) molecules found in cells. This view stems from the fact that in glycomolecules every structural detail may be decisive for their function.

In this review, we discuss how molecular models for biological systems can be developed, how these models can be validated, and how the simulations of these models can be put into practice. We concentrate here on glycolipids and their function in cellular membranes,

☆ This article is part of a Special Issue entitled Tools to study lipid functions.

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http://dx.doi.org/10.1016/j.bbalip.2013.12.016

and we also discuss their potential role in biological processes associated with diseases. Given the exceptional bearing of glycolipids in cell biology, we hope that the readers will find the topic as exciting as we do and will join the effort to unlock the detailed mechanisms by which glycolipids influence cellular function.

2. How simulations can complement experiments

Biological membranes are highly complex and composed of thousands of different lipids and proteins, and many of them are glycosylated, implying that carbohydrates are an integral component of membranes, too. As individual molecular processes often take place on a molecular level, the spatial resolution needed to clarify what really happens in biological membranes, and why, is of the order of the size of an atom. Despite major progress in the development of experimental techniques, their resolution is still too limited for considerations of numerous biological phenomena. The profound benefit of molecular dynamics (MD) simulations lies in their ability to provide detailed insight into biomolecular processes on an atomistic and/or molecular level, thereby generating considerable added value to complement experimental research. Extensive and detailed descriptions of computer simulation techniques are available elsewhere [11,12]. In this review, we focus on classical molecular dynamics simulations of lipid-based systems, with emphasis on glycolipids.

2.1. Force field is the heart of a simulation model

In MD simulations, the system to be simulated is considered an ensemble of interacting particles, such as atoms, which are assumed to obey the laws of classical mechanics. Therefore, the time evolution of the system is obtained by numerically integrating the Newton's equations of motion for the particles comprising the system. The heart of the simulation is the force field, which describes interactions in the molecular system in terms of a potential energy function shown in Fig. 1. There are two types of interactions: bonded (including bonds between two particles, angles between three particles connected to one another, and dihedral (torsional) terms for a set of four particles) and non-bonded (electrostatic and Lennard–Jones (van der Waals)) interactions. These interactions, together with their parameter values, constitute the force field. In bio-molecular simulations the most frequently used force fields are AMBER, CHARMM, OPLS, and GROMOS [13]. Typically they differ in how many terms they have in the potential energy function, and how their parameter values have been derived.

Before one starts to develop a force field for any molecular system, one has to define the descriptions for the target molecules. In this respect, there are often three commonly used possibilities. First, in an all-atom description every individual atom of the system is described explicitly. Second, in united-atom models apolar hydrogen atoms are not described as such but they are included in the parameters of the carbon atom to which they are attached, thereby forming a united-atom model (e.g., CH_2 is described as one unit instead of three atoms). Third, in so-called coarse-grained (CG) models a group or a cluster of atoms is lumped together and described as a single particle. For all of these three model types one can develop a force field, but only in the all-atom case the force field is truly based on energetic interactions only. In united-atom and coarse-grained models some of the entropic degrees of freedom have been averaged over, thus the force field in these models is effectively a free energy based description (including an entropic component) instead of a purely energetic one. This should be taken into account when atomistic models are being simplified, since validation of all-atom and other model descriptions is rigorously speaking not the same thing. Finally, a lot of work has been done recently to bridge different model descriptions to each other, such as all-atom models with coarse-grained ones. The objective of this approach is the same as in the use of coarse-grained models overall, that is, to speed up simulations while preserving the most important features of the system for a given process of interest.

Most of the force fields used in (all-atom and united-atom) biomolecular simulations were initially developed for proteins and/or nucleic acids. Meanwhile, for a long period of time, parameterization of lipids was not paid as much attention. The first lipid models that were able to reproduce lipid bilayer properties adequately were the united-atom models developed for phosphatidylcholine (PC) bilayers [14–19]. Of these force fields, the ones described in refs [16,18] were most advanced due to the development of specific parameters for, e.g., torsion angles in the lipids' head groups. More recently united-atom models have been developed further, and some of them have performed quite well, too, forming a sort of minimal standard against which other force fields have been compared. The most recent united-atom force field suggested to the field includes a large number of lipid classes (PC, phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylglycerol (PG), etc.) and is an extension to the TraPPE (Transferable Potentials for Phase Equilibria) force field [20]. Overall, it gives very good agreement with experimental data.

Although this may sound somewhat surprising, the all-atom force fields for lipids have matured only rather recently. For instance, in the CHARMM force field the previous models for saturated PCs did not reproduce phase behavior, and consequently fluid lipid bilayers had to be simulated under constant surface tension to avoid ending up in the gel phase [21]. Re-parameterization of the force field for the PC head group has provided a set of parameters that reproduces the correct phase, and the area per PC for several lipid types [22,23]. More extensive

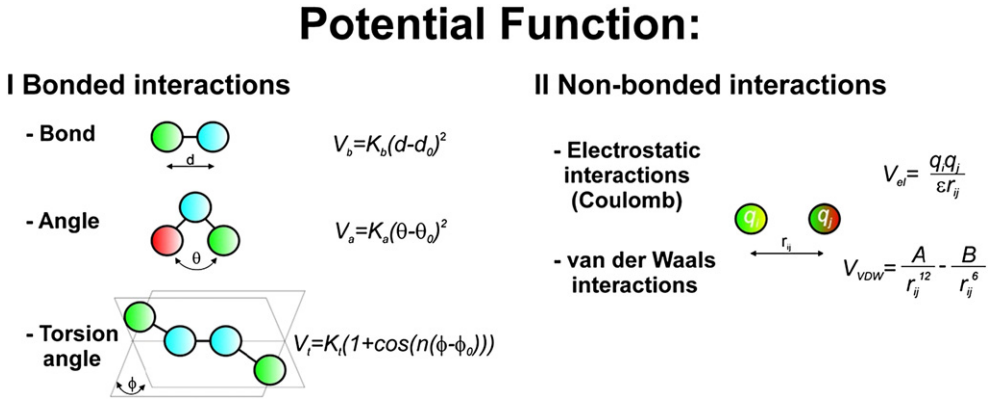

Fig. 1. Force field in terms of its distinct potential function (interaction) terms. The potential function terms (bond, angle, torsion angle, Coulomb, and van der Waals) often used in classical molecular dynamics simulations. In the figure, 'd' represents the bond length; 'd_0' is the equilibrium bond length; 'θ' is the valence angle with its equilibrium value 'θ_0'; 'ϕ' is the torsion angle; 'ϕ_0' stands for 0 or 180°, and 'n' represents the phase. 'K_b', 'K_a', and 'K_t' are the force constants. 'q_i' and 'q_j' denote partial charges on atoms that are not covalently bonded, and 'ε' is the dielectric constant. 'r_{ij}' represents the distance between a pair of interacting atoms, and A and B are two constants that depend on the chemical nature of interacting atoms.