

MemBuilder: a web-based graphical interface to build heterogeneously mixed membrane bilayers for the GROMACS biomolecular simulation program

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ABSTRACT

Motivation: Molecular dynamics (MD) simulations have had a profound impact on studies of membrane proteins during past two decades, but the accuracy of MD simulations of membranes is limited by the quality of membrane models and the applied force fields. Membrane models used in MD simulations mostly contain one kind of lipid molecule. This is far from reality, for biological membranes always contain more than one kind of lipid molecule. Moreover, the lipid composition and their distribution are functionally important. As a result, there is a necessity to prepare more realistic lipid membranes containing different types of lipids at physiological concentrations.

Results: To automate and simplify the building process of heterogeneous lipid bilayers as well as providing molecular topologies for included lipids based on both united and all-atom force fields, we provided MemBuilder as a web-based graphical user interface.

Availability and implementation: MemBuilder is a free web server available from www.membuilder.org.

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1 INTRODUCTION

The plasma membrane forms a boundary between the cytoplasm and the extracellular environment and as such plays fundamental roles in the chemistry of living organisms. Membranes also partition eukaryotic cytoplasm into intracellular compartments. They are home to membrane proteins, accounting for ~25–30% of the genome, that carry out a variety of functions ranging from membrane trafficking and signal transduction to transportation of organic and inorganic compounds (Bond and Sansom, 2006). Therefore, there is an urgent need to understand membrane-associated proteins better and to know how they interact with membrane components. The spatial inhomogeneity of lipid

molecules, in particular, that of sphingomyelin and cholesterol, across the secretory membrane system affects localization of membrane proteins (Sprong *et al.*, 2001) and permeability (Wennberg *et al.*, 2012). A fluid membrane structure is needed to model how membranes affect protein structure (White *et al.*, 2001). It has proved difficult to determine high-resolution 3D structure of membrane proteins to map protein–membrane interactions in atomic detail (White, 2004). Structural and energetic information on these interactions would provide important clues about membrane protein function and assembly.

Molecular dynamics (MD) simulations have provided significant new insight into fundamental interactions within membrane systems (Kandt *et al.*, 2007). One major concern in setting up a membrane protein simulation is the construction of realistic lipid bilayers (Kandt *et al.*, 2007; Tieleman *et al.*, 1997). It is well known that lipid molecules are distributed asymmetrically between the leaflets of biomembranes, which have functional importance (Rahmanpour *et al.*, 2012; Rothman and Lenard, 1977; Spector and Yorek, 1985). Accordingly, MD simulation of membrane models should aim to model membranes with physiologically relevant lipid compositions. Heterogeneous membrane models with specified lipid composition should be used for obtaining additional details on the properties of membrane proteins, even though it is realized that the equilibration of complex membranes will take a long time. To this end, Jo *et al.* (2009) published the CHARMM-GUI Membrane Builder for mixed bilayers. Following this approach, here we provide MemBuilder, a web server with a simple interface, to automate the building of heterogeneous membranes for the biomolecular simulation program GROMACS (Fig. 1). Because there is a large user base for the GROMACS package (Pronk *et al.*, 2013), there will be a significant demand for this kind of service. Using MemBuilder, one can select a set of lipid molecules with specified quantities to build heterogeneous lipid bilayers based on both all atom and united atom force fields with explicit support for bilayers with asymmetric lipid composition. MemBuilder provides GROMACS topology input files and energy-minimized coordinates.

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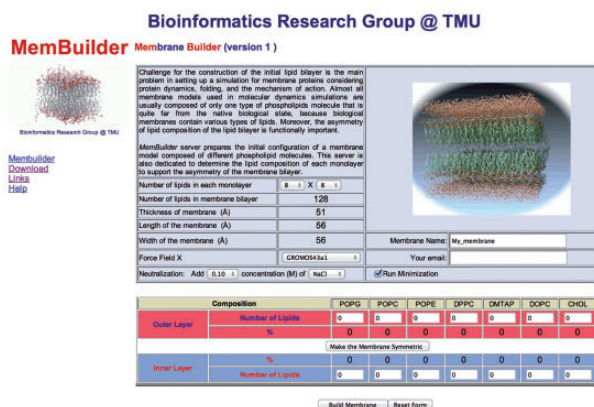


Fig. 1. MemBuilder user interface

Table 1. List of all included lipid molecules

Lipid full name	Name
Cholesterol	CHL
1,2-dilauroyl-sn-glycero-3-phosphocholine	DLC
1,2-dilauroyl-sn-glycero-3-phosphoethanolamine	DLE
1,2-dimyristoyl-sn-glycero-3-phosphocholine	DMP
1,2-dioleoyl-sn-glycero-3-phosphocholine	DOC
1,2-dioleoyl-sn-glycero-3-phosphoethanolamine	DOE
1,2-di-octadecenoyl-sn-glycero-3-phospho-(1-rac-glycerol)	DOG
1,2-di-octadecenoyl-sn-glycero-3-phospho-L-serine	DOS
1,2-dipalmitoyl-sn-glycero-3-phosphocholine	DPP
1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine	DPE
Lipid A (<i>Escherichia coli</i>)	LAE
Lipid A (<i>Pseudomonas aeruginosa</i>)	LAP
1,2-dipalmitoyl-sn-glycero-3-phosphoinositol-4,5-bisphosphate	DPI
1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine	POC
1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine	POE
1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine	POG
18:0 <i>N</i> -stearoyl- <i>D</i> -erythro-sphingosylphosphorylcholine	SGM
1-stearoyl-2-oleoyl-sn-glycero-3-phosphocholine	SOP

2 METHODS

MemBuilder supports 18 different lipid molecules (Table 1). Users can specify type and quantity of lipid molecules for each membrane layer on their request. Lipid molecules' structure and force field parameters are obtained from the Lipidbook database (Domanski *et al.*, 2010), Tieleman laboratory (<http://www.ualgarny.ca/tieleman/>) and SoftSimu group (<http://www.softsimu.net/>). MemBuilder supports four different force fields optimized for molecular simulation of lipids including GROMOS96 43a1 (van Gunsteren *et al.*, 1996), GROMOS96 43a1-S3 (Chiu *et al.*, 2009; Pandit *et al.*, 2008), GROMOS96 53a6 (Oostenbrink *et al.*, 2004) and Slipid/amber (Jambeck and Lyubartsev, 2012a, b, c). MemBuilder contains GROMACS parameter files (.itp) for the entire included lipid molecules. Parameter files of the both GROMOS96 43a1-S3 and Slipid/amber force fields are linked to the original.

MemBuilder builds a grid rectangular box for each membrane layer. The number of cells is equal to the number (64–400) of lipid molecules selected for each layer. The lipid molecules are distributed randomly over the grid cells but with fixed conformation. The process uses a different

random seed number each time and thus will generate different lipid bilayer conformations for each trial. Simple Point Charge (SPC) water molecules solvate the bilayer on both sides. To neutralize the charge of the system and to generate the appropriate ionic strength, monovalent ions (Na^+ , K^+ , Cl^-) and divalent ions (Ca^{+2} , Mg^{+2}) can be added to the solvent. Water molecules will be randomly replaced by ions. Finally, MemBuilder performs an energy minimization to relax local stress in the lipid bilayer.

3 DISCUSSION

MemBuilder assists GROMACS users in building membrane bilayers. It provides topology files of 18 lipid molecules in GROMACS format. Currently the GROMOS96 (43a1, 43a1-S3 and 53a6) and AMBER (Slipid/Amber) force fields are supported. To demonstrate the correctness of the output, six simulations with generated bilayers are reported in the supporting information. All simulations are stable and equilibrate within 10 ns. Further lipids, force fields and geometries such as micelles, nanodisks and liposomes will be supported in future versions to help users to investigate membranes through molecular dynamics simulations.

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