Molecular dynamics simulations of membrane electroporation C3

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Duration of the experiments: 90 min
Max. number of participants: 18
Location: Computer room (CIT)
Level: Basic

PREREQUISITES

No specific knowledge is required for this laboratory practice.

THEORETICAL BACKGROUND

The application of high electric fields to cells or tissues permeabilizes the cell membrane and is thought to produce aqueous-filled pores in the lipid bilayer. Electroporation is witnessed when the lipid membrane is subject to transmembrane voltages (TMV) of the order of few hundred millivolts, which results from the application of electrical pulses on a microsecond to millisecond time scale

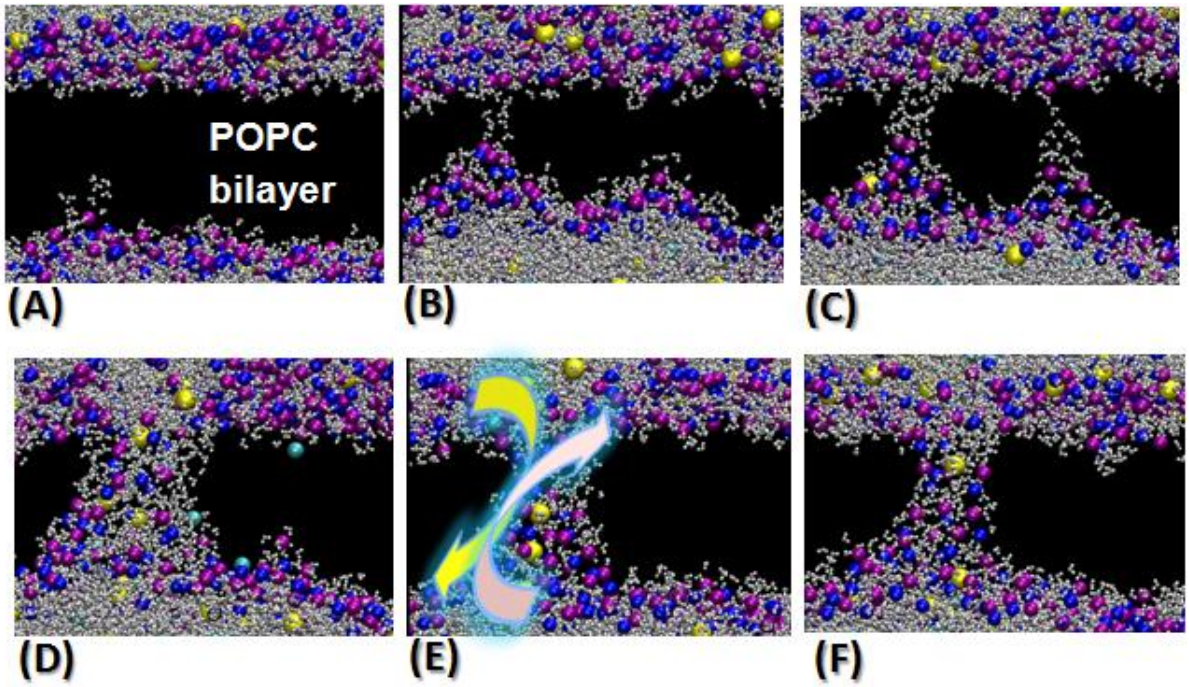

Figure 1: Configurations from the MD simulation for a large POPC subject to a transverse electric field (A) Bilayer at equilibrium. (B-C) Formation of water wires at the initial stage of the electroporation process (D-F) Formation at a later stage of large water pores that conduct ions across the membrane and that are stabilized by lipid head-group (yellow cyan). (Delemotte and Tarek. *J. Membr. Biol.* 2012).

which are sufficient to produce a transient trans-membrane potential and an electrical field across the membrane of the order of ~ 10^8 V/m. This process is believed to involve (1) charging of the membrane due to ion flow, (2) rearrangement of the molecular structure of the membrane, (3) formation of pores, which perforate the membrane and are filled by water molecules (so-called aqueous, or hydrophilic, pores), (4) an increase in ionic and molecular transport through these pores, and, under appropriate conditions, membrane integrity recovery when the external field stress is removed.

Molecular Dynamics (**MD**) simulations belong to a set of computational methods in which the dynamical behaviour of an ensemble of atoms or molecules, interacting via approximations of physical pair potentials, is determined from the resolution of the equation of motions. MD simulations enable ones to investigate the molecular processes affecting the atomic level organization of membranes when these are submitted to voltage gradient of magnitude similar to those applied during electropulsation. The aim of this practical exercise is to characterize from MD simulations trajectories the electrostatic properties of membranes subject to a transmembrane potential (0 to 2 V).

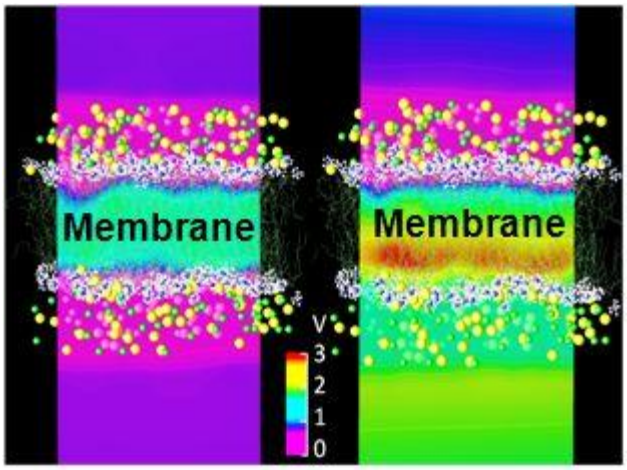

Figure 2: Electrostatic potential maps generated from the MD simulations of a POPC lipid bilayer (acyl chains, green; head groups, white) surrounded by electrolyte baths at 1 M NaCl (Na+ yellow, Cl- green, water not shown) terminated by an air/water interface. Left: net charge imbalance Q = 0 e (TMV=0 mV). Right: Q = 6 e (TMV=2 V).

The aim of this laboratory practice is to get familiar with the tools for molecular dynamics, possibilities to set on models and graphical presentation of atomistic models.

EXPERIMENT

Due to the limited time and large resources needed to generate MD trajectories of membranes, the latter will be provided to the students. The simulations concern pure planar phospholipid bilayers (membrane constituents) and water described at the atomic level. A set of long trajectories spanning few nanoseconds generated with or without a transmembrane voltage induced by unbalanced ionic concentrations in the extracellular and intracellular will be provided. The students will (1) determine the distribution of potential and electric field in model membrane bilayers (2) measure the membrane capacitance, (3) visualize at the molecular level the formation of membrane pores under the influence of a transmembrane voltage, and measure the intrinsic conductance of such pores.

FURTHER READING:

Tarek M. Membrane electroporation: A molecular dynamics study *Biophys. J.* 88:4045-4053, 2005.
Dehez F., Tarek M., Chipot C. Energetics of ion transport in a peptide nanotube *J. Phys. Chem. B* 111:10633-10635, 2007.
Andrey A.G., Jamshed A., Vattulainen I. Defect-mediated trafficking across cell membranes: insights from in silico modeling, *Chem. Rev.* 110:6077-6103, 2010.
Delemotte L., Tarek, M. Molecular dynamics simulations of membrane electroporation. *J. Membr. Biol.* 245/9:531-543, 2012.
Polak A., Tarek M., Tomšič M., Valant J., Poklar Ulrih N., Jamnik A., Kramar P., Miklavčič D. Electroporation of archaeal lipid membranes using MD simulations. *Bioelectrochemistry* 100:18-26, 2014.

NOTES & RESULTS

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