URSI AP-RASC, Sydney, Australia, 17-22 August 2025

Effects of Intense Electric Fields on TRPV4 Ion Channels: investigating the role of water with a molecular dynamic approach

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Electroporation is a well-established technique that induces transient pores in the cell membrane by applying intense electric fields (E-fields). This technique has demonstrated significant potential in various fields, including biomedicine, biotechnology, and food processing [1]. A well-known aspect of electroporation is the role of interfacial water in pore formation [2], but the plasma membrane is not solely composed of lipids and water but also includes various membrane proteins, which play essential structural and functional roles [3]. In [4] it was demonstrated that the activation of a membrane protein by nanosecond pulsed electric fields (nsPEF) facilitates pore formation during electroporation, indicating that proteins play an active role in this process beyond merely being affected by changes in lipid organization. This finding highlights the importance of considering membrane proteins in electroporation studies. Among the key membrane components potentially involved in electroporation, this study focuses on TRPV4, involved in critical biological functions [5] and possible target for therapeutic application. This study employs molecular dynamics (MD) simulations to investigate the effects of intense E-fields on the TRPV4 ion channel, particularly the role of water molecules. MD simulations were performed using a homology model of human TRPV4 embedded in a POPC lipid bilayer with a surrounding ionic solution, as shown in Fig. 1(a). The procedure to perform and analyze MD simulation is reported in Fig. 1(b). By distinguishing interfacial water at the membrane surface from channel-confined water inside TRPV4, the authors analyzed the dipole alignment under varying E-field intensities (5×10^7–8×10^7 V/m), implementing ad hoc codes and by using MATLAB and GRO2MAT. Preliminary results indicate that interfacial water remains stable due to strong interactions with lipid head groups, whereas channel-confined water exhibits increased dipole alignment under stronger E-fields. This suggests a direct E-field influence on water molecules within TRPV4, potentially facilitating membrane permeabilization. These findings propose that TRPV4 could serve as an additional pathway for membrane permeabilization, emphasizing the need for further research into protein-associated electroporation mechanisms.

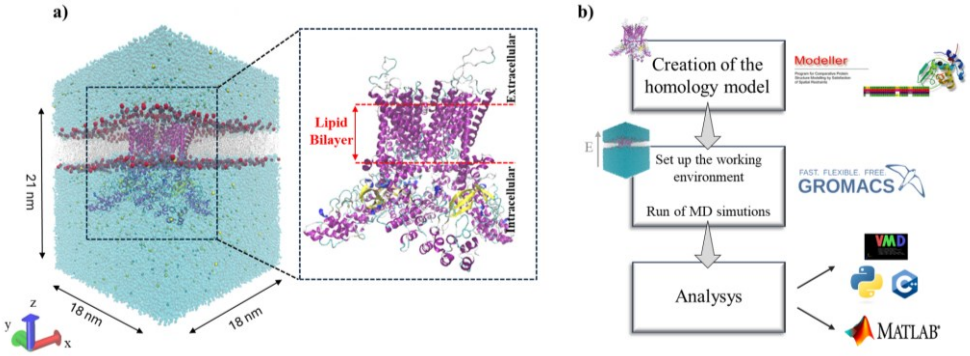

Figure 1 (a) hTRPV4 embedded in the hydrated membrane. The lipid bilayer is highlighted in red, showing its extracellular and intracellular orientation. (b) Workflow for setting up molecular dynamics (MD) simulations and data analysis.

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