Terahertz perturbation of the nanoscale biomembrane landscape

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Abstract— **Interfacial water is the primary transducer of stress induced in biological membranes by electromagnetic fields. Experimental observations of neurostimulation with picosecond-duration electric pulses and picosecond-resolution molecular simulations of lipid bilayers in moderate to intense electric fields help to define the physical boundaries of potentially significant terahertz radiation-induced modifications and modulations of water-lipid and water-protein configurations in cell membrane structures and functions.**

I. INTRODUCTION

NONTHERMAL stimulation and perturbation with picosecond electric pulses and terahertz electromagnetic radiation may lead to new, minimally invasive diagnostic and therapeutic procedures and to methods for remote monitoring and analysis of biological systems – plants, animals, and humans. To optimize utilization of these tools we need an understanding of the underlying biophysical mechanisms. Sub-nanosecond (≤ 500 ps) electric pulses induce action potentials in neurons and cause calcium transients in neuroblastoma-glioma hybrid cells, and in complementary molecular dynamics simulations of phospholipid bilayers in intense electric fields membrane permeabilization occurs in less than 1 ns (Fig. 1). Water dipoles in the interior of these model membranes align in the direction of the field, responding at terahertz frequencies to field reversals. Sub-nanosecond lipid electropore formation is similar to that observed on longer time scales – energy-minimizing intrusions of interfacial water into the membrane interior and subsequent reorganization of the bilayer into hydrophilic, conductive structures. This suggests that membrane permeabilization may be the mechanism for the activation of neural cells by picosecond electric pulses.

II. RESULTS

Picosecond membrane reorganization in molecular simulations. How can this be? Since there is no hydrogen-bonded network in the intruding water fingers, the effective relaxation time is much less than it is in bulk water. The isolated water molecules that stack up in the membrane interior during pore initiation have escaped their interfacial associations. A field-stabilized water column penetrating the membrane remains a lower energy configuration for interfacial water than the planar lipid-water junction of an unperturbed bilayer regardless of the 180-degree flips of the individual molecules making up the structures.

One might expect that each picosecond reversal of the electric field direction would "undo" whatever dipole rearrangements had occurred in the preceding cycle, with no net effect, and that since the textbook water dipole relaxation time is on the order of 8 ps [1], water molecule orientation should not be affected by symmetrical electric field reversals occurring at 1 ps intervals. Molecular simulation results are contrary to these expectations. ***Stabilization of intruding water in the applied electric field*** [2] is not reversed when the field direction changes. Transbilayer water bridges grow, rather than shrink, cycle after cycle, and the phospholipid head groups follow.

Terahertz spectral signature of electroporated cells. Electroporation (electropermeabilization) increases the electrical conductivity of biological cell membranes and lowers transport barriers for normally impermeant materials. The interior of the electroporated membrane contains water, unlike the interior of an intact membrane, which should create a signature for detection of the electropermeabilized state. In a previous report, we described the use of terahertz time-domain spectroscopy to detect electroporation in human cells subjected to permeabilizing pulsed electric fields with a commercial terahertz, time-domain spectrometer [3]. We observed a higher absorption of terahertz radiation by pulse-exposed cells than in controls, consistent with the intrusion of water into the membrane into the cell through the permeabilizing structures presumed to be associated with electroporation.

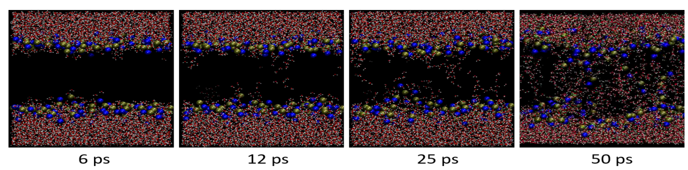

Fig. 1. Permeabilization of POPC bilayer in 500 GHz alternating electric field. Water, then phospholipid head groups bridge the membrane interior in a very high porating electric field with polarity reversals every picosecond. Multiple water bridges appear, followed by head groups, in a few tens of picoseconds.

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