International Autumn School

Biophysics & Bioelectrochemistry for Medicine: Basic Concepts, New Techniques, and Application Perspectives

Vulcan, October 1–6, 2010

NANOELECTROPORATION OF EXTERNAL AND INTERNAL MEMBRANES — THE DIELECTRIC LANDSCAPE OF THE LIPID BILAYER INTERFACE

P. Thomas Vernier[1,2]

[1] *MOSIS, Information Sciences Institute, Viterbi School of Engineering (VSOE), University of Southern California (USC), Marina del Rey, USA,* [2] *Ming Hsieh Department of Electrical Engineering, VSOE, USC, Los Angeles, USA.*

vernier@usc.edu

Experimental and molecular dynamics (MD) modeling studies show that inhomogeneities — including sites of oxidative damage and cholesterol inclusion — in phospholipid bilayers affect the frequency of water intrusion into the bilayer interior and the subsequent formation of conductive pores [1–7]. Ultra-short (ns), high-field (MV/m) electric pulses facilitate the formation of these pores in cell suspensions and tissues in both plasma and intracellular membranes [8–14]. We couple these observations to new MD investigations of the kinetics and energetics of membrane interfacial water configurations in electric fields. Entropic and enthalpic terms associated with clustered water dipole alignments are subject to modification by an applied external electric field and by the atomic-scale details of the local (dynamic) dielectric landscape. The thermodynamic balance determines the probability of the formation of the electropore-initiating structure, a membrane-spanning water bridge. For pure, homogeneous lipid bilayers, the number of significant determinants in the process is small, and a fundamental analysis is achievable. Heterogeneous and asymmetric bilayers and those that include cholesterol and other non-phospholipid components, and especially cell membranes containing proteins and attachments to intracellular and extracellular structures, present significant computational challenges. These may be addressed by access to increasingly powerful computing systems and by new algorithms and analytical procedures. Improved understanding of the biomolecular details of membrane permeabilization will contribute to optimization of electroporation and electrotransfection protocols on the bench and in clinical applications involving electrochemotherapy or electrotransfection.

Keywords: electropermeabilization peroxidation cholesterol electroporation molecular dynamics

References:

1. Bennett, W. F., J. L. MacCallum, and D. P. Tieleman. 2009. Thermodynamic analysis of the effect of cholesterol on dipalmitoylphosphatidylcholine lipid membranes. *J. Am. Chem. Soc.* 131:1972-1978.
2. Fernandez, M. L., G. Marshall, F. Sagues, and R. Reigada. Structural and kinetic molecular dynamics study of electroporation in cholesterol-containing bilayers. 2010. *J Phys Chem B.*, in press.
3. Heiner, A. L., E. Gibbons, J. L. Fairbourn, L. J. Gonzalez, C. O. McLemore, T. J. Brueseke, A. M. Judd, and J. D. Bell. 2008. Effects of cholesterol on physical properties of human erythrocyte membranes: impact on susceptibility to hydrolysis by secretory phospholipase A_2. *Biophys. J.* 94:3084-3093.
4. Kakorin, S., U. Brinkmann, and E. Neumann. 2005. Cholesterol reduces membrane electroporation and electric deformation of small bilayer vesicles. *Biophys. Chem.* 117:155-171.
5. Kucerka, N., J. D. Perlmutter, J. Pan, S. Tristram-Nagle, J. Katsaras, and J. N. Sachs. 2008. The effect of cholesterol on short- and long-chain monounsaturated lipid bilayers as determined by molecular dynamics simulations and X-ray scattering. *Biophys. J.* 95:2792-2805.
6. Vernier, P. T., Z. A. Levine, Y. H. Wu, V. Joubert, M. J. Ziegler, L. M. Mir, and D. P. Tieleman. 2009. Electroporating fields target oxidatively damaged areas in the cell membrane. *PLoS ONE* 4:e7966.
7. Wong-Ekkabut, J., Z. Xu, W. Triampo, I. M. Tang, D. P. Tieleman, and L. Monticelli. 2007. Effect of lipid peroxidation on the properties of lipid bilayers: a molecular dynamics study. *Biophys. J.* 93:4225-4236.
8. Ibey, B. L., S. Xiao, K. H. Schoenbach, M. R. Murphy, and A. G. Pakhomov. 2009. Plasma membrane permeabilization by 60- and 600-ns electric pulses is determined by the absorbed dose. *Bioelectromagnetics* 30:92-99.
9. Napotnik, T. B., M. Rebersek, T. Kotnik, E. Lebrasseur, G. Cabodevila, and D. Miklavcic. 2010. Electropermeabilization of endocytotic vesicles in B16 F1 mouse melanoma cells. *Med Biol Eng Comput* 48:407-413.
10. Pakhomov, A. G., R. Shevin, J. A. White, J. F. Kolb, O. N. Pakhomova, R. P. Joshi, and K. H. Schoenbach. 2007. Membrane permeabilization and cell damage by ultrashort electric field shocks. *Arch. Biochem. Biophys.* 465:109-118.
11. Rebersek, M., M. Kranjc, D. Pavliha, T. Batista-Napotnik, D. Vrtacnik, S. Amon, and D. Miklavcic. 2009. Blumlein configuration for high-repetition-rate pulse generation of variable duration and polarity using synchronized switch control. *IEEE Trans. Biomed. Eng.* 56:2642-2648.
12. Schoenbach, K. H., S. J. Beebe, and E. S. Buescher. 2001. Intracellular effect of ultrashort electrical pulses. *Bioelectromagnetics* 22:440-448.
13. Tekle, E., H. Oubrahim, S. M. Dzekunov, J. F. Kolb, K. H. Schoenbach, and P. B. Chock. 2005. Selective field effects on intracellular vacuoles and vesicle membranes with nanosecond electric pulses. *Biophys. J.* 89:274-284.
14. Vernier, P. T., Y. Sun, and M. A. Gundersen. 2006. Nanoelectropulse-driven membrane perturbation and small molecule permeabilization. *BMC Cell Biol.* 7:37.