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Mechanistic models describing electroporation at the cell level need to be improved

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Electroporation, electropermeabilization, and pulsed-electric-field (PEF) treatment are all terms naming the treatment of cells with short (ns–ms) electric pulses, which induce reversible or irreversible increase in cell membrane permeability. This increase in permeability enables transmembrane translocation of molecules, which otherwise cannot readily cross the cell membrane, such as nucleic acids and certain chemotherapeutic drugs. While electroporation is already used in many medical treatments and technological procedures [1], the molecular mechanisms of increased membrane permeability remain to be fully elucidated [2]. By understanding these molecular mechanisms, we can begin to link the molecular alterations of the cell membrane with the biological response of the cells to pulsed electric fields and design protocols that will enable us to reach the desired treatment outcome. Approaching electroporation from a theoretical perspective is one of the essential means to this end. Currently, the most widely used models, that describe electroporation at the whole-cell level, consider that pores can form only in the lipid domains of the plasma membrane and that all pores exhibit a similar kinetic behavior [3, 4]. However, accumulating evidence from experiments and simulations on model systems speaks against these assumptions, pointing towards oxidative lipid damage and membrane protein denaturation as additional mechanisms of increased membrane permeability [5–6]. In this work we critically examine how well the existing mechanistic models of electroporation can predict intracellular uptake of small molecules in different quantitative experimental measurements. We demonstrate that none of the tested models agrees well with all key experimental observations. We further show that, to validate an electroporation model properly, the model predictions should be compared against quantitative experimental measurements of molecular uptake of different molecules measured for a wide range of pulse durations and amplitudes, whereby the measurements should include the kinetics of molecular uptake and the asymmetry of molecular uptake with respect to the anodic and cathodic side of the cell. We suggest further directions on developing mechanistic cell-level electroporation models utilizing molecular modeling and experiments on model systems.

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