Modeling of Electroporation for Ventricular Tachycardia at the Cellular Scale

Master Internship and PhD subject

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Context - The project is part of an ANR[1] project coordinated by Annabelle Collin for Inria Monc's team[2] in collaboration with IHU Liryc[3]. One task of the project is dedicated to the building of experimental data which to used in the mathematical part presented below. If the internship goes well, there is a possibility of PhD funding.

Subject - This project aims at modeling cardiac electroporation at the cellular scale. One of the main characteristics of a biological cell membrane is that it is a semi-permeable layer, that is, it can allow only certain molecules to pass through it. For example, a cell can regulate the concentration of certain ions inside it by letting in more or less ions from its environment through its membrane. The membrane of a cell is mostly made up of a lipid-bilayer, as a result when it is under the influence of an electric field it behaves like a dielectric. In contrast, the inside of the cell behaves mostly like an electrolyte. When an electric field is applied to a cell, there is an accumulation of charge at the membrane and so a transmembrane voltage appears. When this voltage goes above a certain threshold the permeability of the cell membrane dramatically increases and so molecules that before could not enter the cell now are able to. This phenomenon is called **electroporation**, see Figure 1.

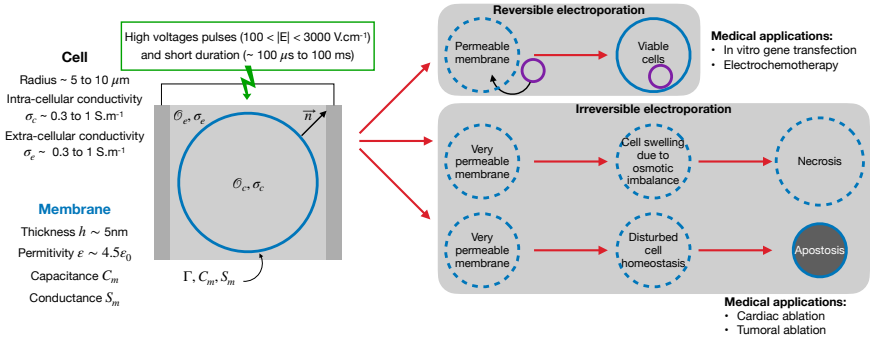

Figure 1. Electroporation.

A number of models have been proposed to understand and describe this phenomenon [1]. Among them, one of the most used in the literature was proposed by W. Krassowska and C. Neu [2] in which the state of the cell membrane through a pore density function N, meaning that $N(t,x)$ is the number of pores per unit of membrane area at a point x on the membrane and at a time t. Even though this model does fit experimental data, there are many limitations as the dependence of non-physical constants, the inability to determine membrane rupture or to model interaction between pores or to determine pore-size evolution and to consider different pore shapes other than ideal round ones. Furthermore, this model makes strong assumptions that cannot be verified as no pore has ever been directly seen or measured and lead to not expecting behaviors. Based on our expertise, we prefer to **model the state of the membrane by a function $\phi: \Gamma \longrightarrow \mathbb{R}$ measuring the amount of lipid in the membrane** at any position x at time t. The evolution is then given by the L^2 derivative of the following energy functional

$$F[\phi] = \frac{D}{2}\int_\Gamma |\nabla \phi|^2 + \int_\Gamma W(\phi) - \frac{1}{2}\int_\Gamma C_m(\phi)\left([U]_{|\Gamma}\right)^2,$$

where the 1st term corresponds to the membrane diffusion, the 2nd to the potential energy of the membrane (W is a double-well potential) and the 3rd to the influence of the transmembrane voltage U.

[1] https://anr.fr/en/
[2] https://team.inria.fr/monc/
[3] https://www.ihu-liryc.fr/

The equation on ϕ is coupled to **the microscopic bidomain model**

$$\Delta U = 0,\ \Omega_{c,e},\ \text{Poisson equation,}$$

$$\sigma_{c,e}\,\nabla U_{|\Gamma^-}\,.\,n = \sigma_{c,e}\,\nabla U_{|\Gamma^+}\,.\,n,\ \text{conservation of charge across the membrane,}$$

$$\sigma_{c,e}\,\nabla U_{|\Gamma^-}\,.\,n = C_m(\phi)\partial_t[U]_\Gamma + S_m(\phi)[U]_\Gamma + I_{ep}(t,[U]_\Gamma),\ \text{modeling of current through } \Gamma,$$

with appropriate initial and boundary conditions. In the above equation, Ω_c and Ω_e denote respectively the cytoplasm and the extracellular medium whose conductivities are σ_c and σ_e. The cell membrane is referred to as Γ. C_m and S_m are the membrane capacitance and conductance. Several models of the electroporation current I_{ep} have been derived since several years. However, the changes in the ionic and ATP concentrations, and in the cellular volume have not been addressed. **This requires to complexify dramatically the above PDE to include other aspects of the electroporation phenomenon and to adapt it to cardiac cells.** In particular, the increasing of cell membrane permeability when short high voltage pulses are applied, presumably leads to death of cardiac cells via Ca^{2+} uptake. To quantify what happens for cardiac cells under PFA – apoptosis or necrosis – we will complexify the model to describe the in vitro process of the internalization of extracellular species. This new model will be included in addition to the creation of conducting defects, the ions and molecules effluxes and influxes, as well as cell swelling.

More precisely, since electroneutrality may be broken transiently in the vicinity of the membrane due to ion exchanges, electroosmosis model should be preferred. Denoting by $\boldsymbol{v}$ the velocity of the incompressible fluid of viscosity η, by P the pression inside the fluid, by n_k the ion concentration of the species k with valency z_k and diffusion coefficient D_k , the coupled system should read

$$-\eta\Delta\boldsymbol{v} + \nabla P = q\ \textstyle\sum_k z_k n_k\,\nabla U,\ \Omega_{c,e},\ \text{with } \nabla\,.\,\boldsymbol{v} = 0,\ \text{Stokes equation,}$$

$$\partial_t\, n_k - \nabla.(D_k\, n_k) + \nabla.(\boldsymbol{v}\, n_k) = q\, z_k/(k_b T)\,\nabla.(D_k\,\nabla U),\ \Omega_{c,e},\ \text{Charge conservation}$$

$$-\nabla.(\varepsilon_m\,\nabla U) = q\ \textstyle\sum_k z_k n_k,\ \text{Gauss Law,}$$

where ε_m is the electric permittivity of the medium, q the Coulomb's charge, k_b the Boltzmann constant and T the temperature. The transmission across the cell membrane has not yet been derived for this complete model, especially in the context of electroporation but our objective is to couple it with the equation of the state of the membrane ϕ and to define a realistic electroporation current I_{ep}. The aim is to take into account the currents due to passive ion channels, the Na/K-ATPase and the calcium pumps, and the Na/H channels which are essential in the cell equilibrium. One can refer to the electrophysiological laws as in [3,4,5]. In addition, specific nonlinearities in the **jump conditions** have to be imposed to account for the different degrees of membrane permeabilization. We expect to derive such jump conditions thanks to the knowledge of electroporation acquired by classical electroporation modeling [6,7] and with a rigorous asymptotic analysis in the same vein as [8]. Our approach will then generalize the standard electro quasistatic models [7] by describing the ions and molecules fluxes and integrating the morphological characteristics of cardiac cells through adapted geometries.

Bibliography

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