Numerical studies of electroporation: from microscopic models to clinical applications

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Research framework

General Team presentation

The aim of the project is to develop **modelling tools** for problems arising from **fluid mechanics** and **electromagnetism** in order to **explain, control, simulate and predict** some phenomena coming from physics, chemistry, biology or engineering.
The complexity can be in the model itself, in the coupled phenomena, in the geometry or in non-standard applications. The challenges consists in developing stable models and adapted numerical methods that enable us to recover the main physical features and that can be used in **realistic situations**.
With these modeling tools we develop **numerical codes** that can be used for **practical and industrial applications**.
Our approach is the following: we first determine some reliable models and then we perform a mathematical analysis (including stability). We develop the numerical methods that are adapted to the specific situations and we implement them on some applications

Cancer modelling coupled with Electrochemotherapy

We aim at proposing a comprehensive study of **the tumor growth modeling**, including microscopic (cell level) and macroscopic (tissues and organ level) elements and to apply these modeling tools to therapeutic innovation in oncology. The long-term goal is to improve electrochemothera-peutic protocols for clinical trial.
This crucial aim requires as a first step the mathematical analysis and control of complex models of tumor growth. The main points that we want to address are the following:
1) This problem is clearly a multiscale problem and each level has to be tackled separately before beeing integrated into a complete model.
2) In order to be useful for therapeutic innovation, one needs some data that can be obtained either from *in vitro* or *in vivo* experiments or from medical imaging.
3) Finally, some low order (simple) models are needed for the clinical trials.
The key point of this project is to establish some **links between the micro and the macroscopic levels**. More precisely we aim at building a macroscopic model that can be parameterized using *in vitro* and *in vivo* experimental data and medical imaging.
Parameter estimation is a critical issue in mathematical biology. Usually, researchers in the biomathematical communities, develop mechanistic complex models without paying much attention to parameter estimation. We want to validate our mathematical models using biological and clinical data.

Principles of the electropermeabilization modeling

Based on the experimental data of the vectorology team, we *first* aim at providing ***microscopic models*** that describes precisely the phenomenon for *in vitro* experimental conditions.

The *second task* consists in modeling the phenomenon at the ***macroscopic scale***, using once again the experimental data of the vectorology team of the CNRS at the IGR. Since biological tissues are very complex materials, we chose to model the electroporation separately and simultaneously at the microscopic and at the macroscopic scales, instead of providing the macroscopic models by an homogenization of the microscopic models. However we eventually will try to ***link*** both scales once the models of each level will be developed using ***homogenization process***.

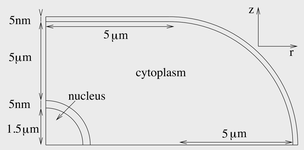
Principles of the tumor growth modeling

The model proposed here is tuned for each patient thanks to two medical images from *the Institut Bergonié* following the evolution of a nodule. From this analysis, it is possible to obtain an estimate of the evolution of a targeted nodule using only non-invasive techniques.

Our model describes, not only the volume of the tumour, but also its localization and shape. It takes into account nutrient concentration, cell-cycle regulation and evolution of populations of cells, as well as mechanical effects. Our prediction relies on parameters estimation using temporal series of MRI or scans. The approach uses optimization techniques and Proper Orthogonal Decomposition (POD) to estimate the parameters of the chosen mathematical model (adapted to the type of cancer studied) that best fit with the real evolution of the tumour shown on the images.

Electroporation modelling at the cell scale

Electric fields in egg-shaped cells with nucleus.



region	σ(S/m)	ε_r
nucleus cytoplasm	0.3	80
nucleus membrane	10^{-9}	5
cell cytoplasm	0.3	80
cell membrane	10^{-9}	5
exterior bath	1.2	80

Figure 1: 1/4 of the geometry of the cell considered in this work (z-axis is an axis of revolution) and its electrical parameters.

The thin membranes are replaced by appropriate equations

$$\Delta V = 0, \quad \text{in } \Omega_e \cup \Omega_c \cup \mathcal{O}_n, \quad V|_{\partial\Omega_D} = V_{imp}, \quad \partial_{\mathbf{n}} V|_{\partial\Omega_N} = 0.$$

with the transmission conditions across the membranes:

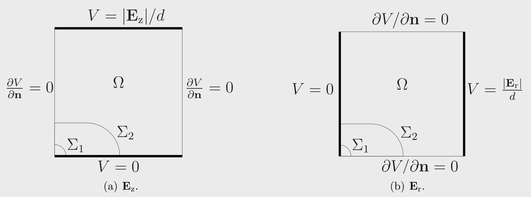
$$\text{on } \Gamma_c \begin{cases} \varepsilon_0 \partial_t \left[\varepsilon_r \partial_n V\right]_{\Gamma_c} + \left[\sigma \partial_n V\right]_{\Gamma_c} = 0, \\ C_m \partial_t \left[V\right]_{\Gamma_c} + S_m \left[V\right]_{\Gamma_c} = \left(\varepsilon_0 \varepsilon_c \partial_t \partial_n V|_{\Gamma_c^-} + \sigma_c \partial_n V|_{\Gamma_c^-}\right), \end{cases}$$

$$\text{on } \Gamma_n \begin{cases} \varepsilon_0 \partial_t \left[\varepsilon_r \partial_n V\right]_{\Gamma_n} + \left[\sigma \partial_n V\right]_{\Gamma_n} = 0, \\ C_m \partial_t \left[V\right]_{\Gamma_n} + S_m \left[V\right]_{\Gamma_n} = \left(\varepsilon_0 \varepsilon_n \partial_t \partial_n V|_{\Gamma_n^-} + \sigma_n \partial_n V|_{\Gamma_n^-}\right). \end{cases}$$

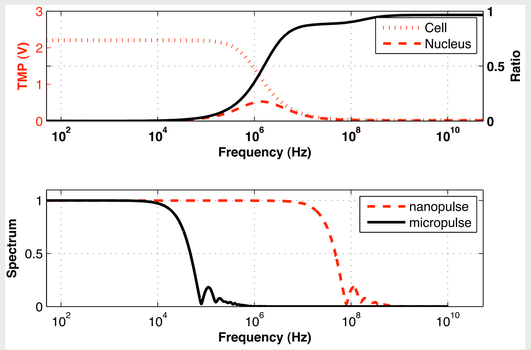
Hence discontinuous finite elements are needed. The rigidity matrix writes:

$$M_{kl} = \int_\Omega \left(\frac{\varepsilon_0 \varepsilon_c}{\Delta t} + \sigma_c\right) \nabla\psi^k . \nabla\psi^l \, \mathrm{d}x + \int_{\Gamma_c \cup \Gamma_n} \left(\frac{C_m}{\Delta t} + S_m\right) [\psi^k][\psi^l] \mathrm{d}\sigma.$$

Axi-symmetric configuration:



(a) $\mathbf{E}_z$. (b) $\mathbf{E}_r$.



Electropermeabilization modelling

The membrane permeabilization is a **time-dependent** and **non-linear** phenomenon.
Any membrane widening for numerical simulations is not relevant.

The modelling consisting in a description of the membrane conductivity.
We consider electropermeabilization as a **membrane wetting**, without any pore creation

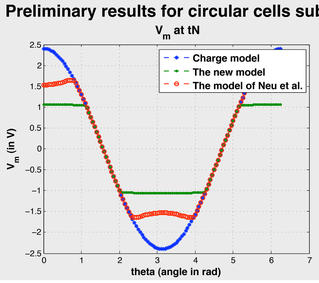
$$S_m(t,s) = S_{Lip} + x(t,s) S_{ep}$$

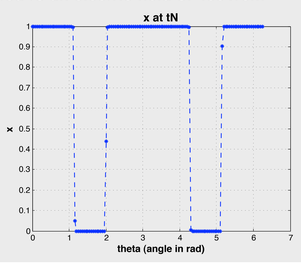
S_{Lip} and S_{ep} denote respectively the lipid and the pore conductivity.

x represents the (time-dependent) local electropermeabilized membrane area that satisfies:

$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t}(t,s) = \dfrac{1}{\tau_{ep}} \max\Big(\beta(s) - x(t,s); \dfrac{\tau_{ep}}{\tau_{reseal}} \left(\beta(s) - x(t,s)\right)\Big), \\ x\left(t=0,s\right) = x_0, \end{cases}$$

Preliminary results for circular cells submitted to an electric field of 400V/cm





System identification in tumor growth modeling

Macroscopic description of cellular densities

We use a macroscopic model describing cellular densities. The cellular division is controlled by the oxygen concentration denoted by C.

The cellular densities evolve through :

$$\begin{aligned} \partial_t P + \nabla \cdot (P\mathbf{v}) &= \gamma P - (1-\gamma) P + \gamma Q, \\ \partial_t Q + \nabla \cdot (Q\mathbf{v}) &= (1-\gamma) P - \gamma Q - \gamma_2 Q, \\ \partial_t N + \nabla \cdot (N\mathbf{v}) &= \gamma_2 Q, \\ \partial_t S + \nabla \cdot (S\mathbf{v}) &= 0. \end{aligned}$$

where

$$\gamma(C) = \frac{1 + \tanh(C - \tau_h)}{2}.$$

The velocity **v** is related to the movement created by the growth of volume due to the cellular division.
We make the assumption that cells are incompressible which gives

$$\nabla \cdot \mathbf{v} = \gamma P.$$

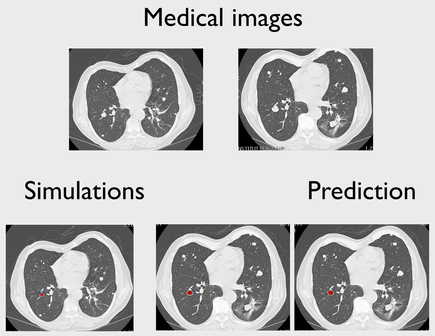
Description of the movement
In order to close the system and compute the velocity, we have to make an additional assumption: the movement is considered as fluid or visco-elastic. For the simulations presented here, we have used a Darcy-type law:

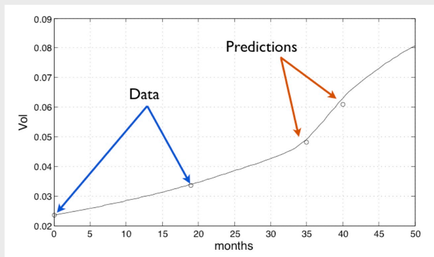
$$\mathbf{v} = -k \nabla \Pi,$$

where the potential ∏ can be computed thanks to the expression of the divergence of the velocity.

Recovery of the parameters

We recover the parameters of the mathematical model adapted for a particular patient. We use an algorithm based on Proper Orthogonal Decomposition (POD). From the two initial images, we obtain the parameters that fit the best the two images. The parametrized model can then be used for prognosis.

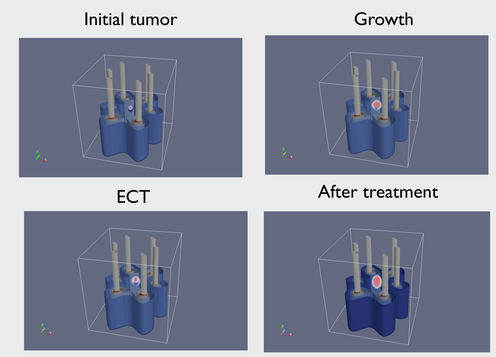




Towards electrochemotherapy modeling

We have also coupled a generic non-linear model of tissue electroporation with our tumor growth model, in order to model the treatment effect on the tumor growth.

Clinical data are needed to parameterize and validate the models.



References

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