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Research article

Spatial mechanistic modeling for prediction of 3D multicellular spheroids behavior upon exposure to high intensity pulsed electric fields

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Abstract: The objective of this work was to investigate the growth specificities of cancer cells spheroids subjected to pulsed electric field. Multicellular HCT-116-GFP spheroids were exposed to different electric field intensities and the volume of multicellular spheroids was monitored by fluorescence and bright field microscopy. Thanks to an advanced mathematical model, based on differential equations and well-adapted estimation strategies, our modeling enables us to characterize the multicellular spheroids growth after permeabilizing pulsed electric field. In particular, we identify the percentage of cells which are destroyed and the percentage of cells which exhibit an altered growth pattern for different magnitudes of the electric field. We also quantify the growth resumption upon reversible and partially irreversible electroporation. Our preliminary results provide a first quantification of the impact of electroporation on multicellular spheroids growth, and suggest a booming growth of partially irreversible electric pulses, leading to an accelerated regrowth.

Keywords: PDE modeling; parameters estimation; electroporation; spheroids

A. Validation of the SAEM algorithm using few measurements

To check whether the SAEM algorithm works correctly with a low number of multicellular spheroids and a low number of measurements, Figure 1 shows the error $\|V_0 - V_0^{obj}, k - k^{obj}, b - b^{obj}\|_2$ using various cohorts with y individuals, drawn at random from the control group and x consecutive times. The values $\{V_0, k, b\}^{obj}$ correspond to the values estimated with the maximum number of measurements and multicellular spheroids (top, right of Figure 1).

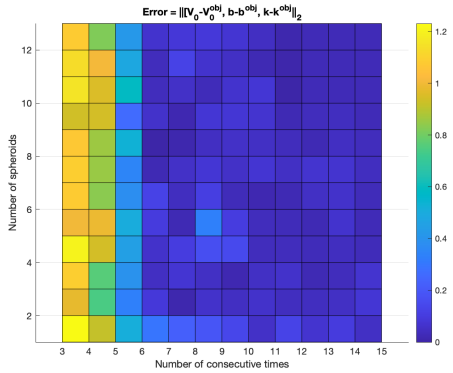

Figure 1. Errors $\|V_0 - V_0^{obj}, k - k^{obj}, b - b^{obj}\|_2$ according to the number of consecutive measurements (x-axis) and to the number of multicellular spheroids (y-axis).

Radial equation of multicellular spheroids evolution in case of free growth

When considering free growth, we have $F(t,x) = 0, \forall t, \forall x$ leading to study the following system

$$\begin{aligned} \partial_t P + \nabla \cdot (\vec{v}P) &= \tau_G(P+Q) - \tau_{PtoQ}P, \\ \partial_t Q + \nabla \cdot (\vec{v}Q) &= \tau_{PtoQ}P, \\ \nabla \cdot \vec{v} &= \tau_G(P+Q), \\ \tau_G(t) &= ae^{-bt},, \end{aligned} \tag{A.1}$$

coupled with the dynamics of τ_{PtoQ}.

The first equation of System A.1 can be rewritten as

$$\partial_t P + \vec{v} \cdot \nabla P = \tau_G(P+Q)(1-P) - \tau_{PtoQ}P. \tag{A.2}$$

Simplified equation for the density of proliferating cells - We will search the simplified equation followed by P

$$\begin{aligned} \partial_t P(t,x) &= \frac{d}{dt}\tilde{P}(t, r(t,x)) \\ &= \partial_t \tilde{P}(t, r(t,x)) - r(t,x)\frac{R'(t)}{R(t)}\partial_r \tilde{P}(t, r(t,x)) \end{aligned}$$

Concerning the gradient term ∇P, we have

$$\nabla P(t,x) = \nabla \tilde{P}(t, r(t,x)) = \nabla r(t,x)\partial_r \tilde{P}(t, r(t,x)).$$

As $\nabla r(t,x) = \frac{1}{R(t)}\frac{x}{\|x\|}$, we obtain

$$\nabla P(t,x) = \frac{1}{R(t)}\frac{x}{\|x\|}\partial_r \tilde{P}(t, r(t,x))$$

and using the fact that the velocity is radial and Equation A.2, we obtain

$$\partial_t \tilde{P}(t, r(t,x)) + \frac{\tilde{v} - rR'(t)}{R(t)}\partial_r \tilde{P}(t, r(t,x)) = \tau_G(\tilde{P}+\tilde{Q})(1-\tilde{P}) - \tilde{\tau}_{PtoQ}\tilde{P}. \tag{A.3}$$

Using Eq. 3.7, this equation can be rewritten

$$\partial_t \tilde{P}(t, r(t,x)) + \left(\frac{\tilde{v}}{R(t)} - \frac{r}{3}\tau_G(t)\right)\partial_r \tilde{P}(t, r(t,x)) = \tau_G(\tilde{P}+\tilde{Q})(1-\tilde{P}) - \tilde{\tau}_{PtoQ}\tilde{P}.$$

Equation for the radial velocity - The equation $\nabla \cdot \vec{v} = \tau_G(P+Q)$ becomes in radial coordinates

$$\frac{1}{R(t)}\frac{1}{r^2}\partial_r(r^2\tilde{v}(t,r)) = \tau_G(\tilde{P}+\tilde{Q}).$$

By integration of the previous equation between 0 and r (the invariance by rotation implies that $\tilde{v}(t,0) = 0$), we obtain

$$\frac{\tilde{v}(t,r)}{R(t)} = \frac{1}{r^2}\int_0^r \tilde{r}^2\tau_G(\tilde{P}+\tilde{Q})d\tilde{r}.$$

and this gives as $\tilde{P}+\tilde{Q}=1$ inside the tumor

$$\frac{\tilde{v}(t,r)}{R(t)} = \frac{r}{3}\tau_G(t).$$

This implies that $\tilde{P}$ follows for each $r \in [0, R(t)]$, the following EDO

$$\tilde{P}' = \tau_G(1-\tilde{P}) - \tilde{\tau}_{PtoQ}\tilde{P}.$$