Deciphering tumor response to propranolol in angiosarcomas by mathematical modeling and data assimilation

Annabelle COLLIN, Laboratoire de Mathématiques Jean Leray - Nantes
Tiphaine DELAUNAY, Institut de Mathématiques de Bordeaux - Talence

Christèle ETCHEGARAY, Inria Bordeaux - Talence
François MOISAN, BRIC - Talence **Faiza LAANANI**, BRIC - Talence

Angiosarcoma is a rare and aggressive cancer of vascular origin that still needs more effective treatment. Recently, propranolol, a beta blocker, was observed to have an encouraging effect [4]. This project aims to better understand the action of propranolol on angiosarcoma using the close combination of mathematical modeling with *in vitro* biological experiments on 3D tumor spheroids.

Spheroids are 3D cell cultures that are used as tumor model. In these experiments, growing spheroids are observed from above. It is observed that over time, the areas increase and pixel intensities decrease, suggesting spheroids flattening. The biological observations motivate the need to take into account not only the volumetric evolution but also the shape and heterogeneity of tumors. We build a PDE-based model on healthy and tumor cell densities [1]. The reaction-advection dynamics writes

$$\begin{cases} \partial_t P + \nabla \cdot (vP) = f(t,P,Q), & \text{in } \mathcal{D}, \text{ (proliferative cells)}, \\ \partial_t Q + \nabla \cdot (vQ) = g(t,P,Q), & \text{in } \mathcal{D}, \text{ (quiescent cells)}, \\ \partial_t S + \nabla \cdot (vS) = 0, & \text{in } \mathcal{D} \text{ (healthy cells)}, \end{cases} \tag{1}$$

where f, g model proliferation, interactions between different cell states, or response to treatment and $\mathcal{D}$ is the domain containing the spheroid. A saturation hyppothesis leads to $\nabla \cdot v = f(t,P,Q) + g(t,P,Q)$ so that cells advection velocity follows from cell proliferation. The system is closed using a Darcy law $v = -K\nabla\Pi$ where Π is the pression and K the constraint tensor.

Under the assumption that spheroids remain spherical, the model can be rewritten in radial coordinates [3]. In our case, this assumption can no longer be made. Consequently, we consider an axial symmetry along the z-direction together with an ellipsoidal shape hypothesis. This allows to take into account both the nontrivial spheroid shape and the spheroid heterogeneity. Finally, calibration to the experimental data requires a robust estimation method. We propose studying the use of a Luenberger observer to correct the state, coupled with a Kalman filter for the parameters [2].

[1] A. Collin, H. Bruhier, J. Kolosnjaj, M. Golzio, M.-P. Rols, C. Poignard. *Spatial mechanistic modeling for prediction of 3d multicellular spheroids behavior upon exposure to high intensity pulsed electric fields.* AIMS bioengineering, **9(2)**, 102–122, 2022.

[2] A. Collin, T. Kritter, C. Poignard, O. Saut. *Joint state-parameter estimation for tumor growth model.* SIAM Journal on Applied Mathematics, **81(2)**, 355–377, 2021.

[3] T. Michel, J. Fehrenbach, V. Lobjois, J. Laurent, A. Gomes, T. Colin, C. Poignard. *Mathematical modeling of the proliferation gradient in multicellular tumor spheroids.* Journal of theoretical biology, **458**, 133–147, 2018.

[4] V. Sans, E. D. de la Roque, J. Berge, N. Grenier, F. Boralevi, J. Mazereeuw-Hautier, D. Lipsker, E. Dupuis, K. Ezzedine, P. Vergnes, et al. *Propranolol for severe infantile hemangiomas : follow-up report.* Pediatrics, **124(3)**, e423–e431, 2009.

Contact : `tiphaine.delaunay@inria.fr`