Mathematical advances in modelling cancer treatment

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Despite the tremendous progress made to improve treatments, cancer remains one of the leading causes of death worldwide. Furthermore, due to the aging of the population in developped contries, even non-deadly cancer types pose a dangerous threat to public medical structures and society at large. The design, analysis and optimisation of cancer treatments are expensive and time-consuming tasks, which can be eased thanks to the use of more theoretical tools.
Ranging from the analysis and simulation of ODEs and PDEs to optimisation, machine learning and computational statistics, mathematical oncology is nowadays one of the corner stones of interdisciplinary research to improve cancer treatments. We propose in this minisymposium to showcase some recent progress in this this very rich field.

We will give the floor to 4 researchers :

- **Annabelle Ballesta** (Inserm U900, Cancer Systems Pharmacology ATIP-Avenir team, Institut Curie, MINES ParisTech, CBIO, PSL Research University, Saint-Cloud, France) : *"Systems pharmacology and machine learning for optimizing treatments of brain tumors"*
- **Tiphaine Delaunay** (Université Bordeaux, CNRS, Inria, Bordeaux INP, IMB, UMR 5251) : *"Deciphering tumor response to propranolol in angiosarcomas by mathematical modeling and data assimilation"*
- **Emma Leschiera** (De Vinci Higher Education, De Vinci Research Center, Paris, France) : *"Modelling the impact of electroporation on spheroid growth and the release of damage-associated molecular pattern molecules"*
- **Federica Padovano** (Sorbonne Université, CNRS, Université de Paris, Laboratoire Jacques-Louis Lions UMR 7598, Paris, France) : *"The development of drug resistance in metastatic tumours under chemotherapy : An evolutionary perspective"*

Abstracts of the individual talks are available in the following pages.

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Systems pharmacology and machine learning for optimizing treatments of brain tumors

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Glioblastoma (GBM), the most frequent and aggressive brain tumor in adults, is associated with a dismal prognostic despite intensive treatment involving surgery, radiotherapy and temozolomide (TMZ)-based chemotherapy. The initial or acquired resistance of GBM to TMZ appeals for precision medicine approaches for the design of novel efficient combination pharmacotherapies. To that end, a comprehensive approach combining quantitative systems pharmacology (QSP) and machine learning was undertaken to design TMZ-based drug combinations circumventing the initial resistance to the alkylating agent. A QSP model representing TMZ cellular pharmacokinetics-pharmacodynamics and dysregulated pathways in GBM based on ordinary differential equations was developed and validated using multi-type time- and dose-resolved datasets. In silico drug screening based on numerical optimization and subsequent experimental validation identified a strategy to re-sensitize TMZ-resistant cells consisting in combining TMZ with inhibitors of the base excision repair and of homologous recombination. Using machine learning, model parameters driving response to such optimal multi-agent therapy were derived to assist decision making in patients. Thus, we successfully demonstrated the relevance of combined QSP and machine learning to design efficient drug combinations re-sensitizing glioblastoma cells initially resistant to TMZ. The developed framework may further serve to identify personalized therapies and administration schedules by extending it to account for additional patient-specific altered pathways and whole-body features.

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

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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.

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Modelling the impact of electroporation on spheroid growth and the release of damage-associated molecular pattern molecules

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Abstract

Electroporation is a technique in which electric pulses are applied to cells in order to increase the permeability of cell membrane. In reversible electroporation (RE), the pulse duration is sufficiently short to ensure that the cell membrane reseals within several minutes. In irreversible electroporation (IRE), however, the pulses are too long, too numerous or their amplitude too high so that the cell membrane is irreversibly destroyed, and the cells are killed. While the cells are destroyed, the integrity of tissue remains preserved, making IRE very appealing for ablation of tumour. Recent studies have shown that IRE used for cancer treatment also induces immunogenic cell death (ICD), a form of cell death resulting in a regulated activation of the immune response. In particular, damaged or dying tumour cells release damage-associated molecular pattern molecules (DAMPs) which may ultimately trigger an immunological response. In this talk, we present a hybrid model to investigate the ICD and regrowth of tumour spheroids exposed to IRE. In this model, a stochastic individual-based model tracking the dynamics of single tumour cells is coupled with a partial differential equation describing IRE dynamics. Here, the death of tumour cells and the release of DAMPs correlates with the intensity of the IRE electric pulses. The model is confronted to biological measures of DAMPS release and volume evolution of tumour spheroids submitted to electric pulses with different intensities. The results of computational simulations obtained from the proposed model shed light on the way in which the intensity of the IRE electric pulses may affect the regrowth of tumour spheroids, as well as their release of DAMPs.

The development of drug resistance in metastatic tumours under chemotherapy: An evolutionary perspective

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Abstract

We present a mathematical model of the evolutionary dynamics of a metastatic tumour under chemotherapy, comprising non-local partial differential equations for the phenotype-structured cell populations in the primary tumour and its metastasis. These equations are coupled with a physiologically-based pharmacokinetic model of drug administration and distribution, implementing a realistic delivery schedule. The model is carefully calibrated from the literature, focusing on BRAF-mutated melanoma treated with Dabrafenib as a case study. By means of long-time asymptotic and global sensitivity analyses, as well as numerical simulations, we explore the impact of cell migration from the primary to the metastatic site, physiological aspects of the tumour tissues and drug dose on the development of chemoresistance and treatment efficacy. Our findings provide a possible explanation for empirical evidence indicating that chemotherapy may foster metastatic spread and that metastases may be less impacted by the chemotherapeutic agent.

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