– MSIAM MSc thesis project proposal –
Parameter estimation in a stochastic model for immunotherapy of cancer

1 MSc thesis advisors

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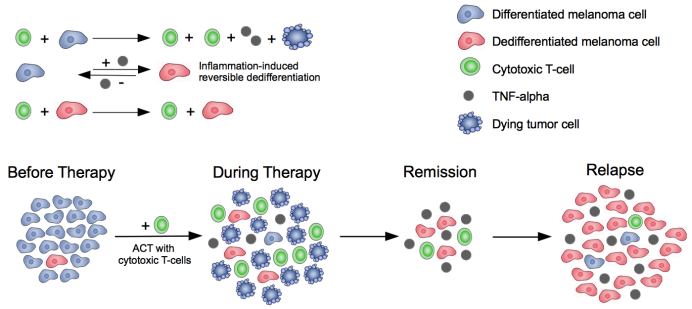
2 Description of the project

Melanomas are tumors associated with skin cancer. The so-called immunotherapeutic approach against them involves the use of T cells that are capable of killing a specific type of melanomas, the blue ones on the picture. It is known that during such a treatment, a significant problem occurs: the injection of T cells produces an inflammation and cancer cells react by loosing some markers (blue cells switch to red). The T cells are not capable of killing the red cells, and a relapse is observed : the tumor grows again. The switch thus allows tumors to be resistant to the therapy.



The article [1] propose a stochastic model to describe mathematically these observations: the time at which each individual event (reproduction, death, switch) happens is modeled with an exponential distribution. An interesting phenomenon of stochastic bifurcation is pointed out: a relapse with a large amount of "blue melanoma" occurs when the T cells die out. Moreover, in the limit of large populations, the model converges to the following quadratic dynamical system containing a few parameters (reproduction, death and switch rates):

$$\begin{cases} \dot{x} = x(b_x - d_x - c_{xx}x - c_{xy}y) - swx + s_{yx}y - s_{xy}x - tzx \\ \dot{y} = y(b_y - d_y - c_{yy}y - c_{yx}x) + swx + s_{xy}x - s_{yx}y \\ \dot{z} = b_z xz - d_z z \\ \dot{w} = b_w xz - d_w w \end{cases}$$

It is argued in [1] that there exist biologically reasonable parameters for which the two kinds of relapses appear with high probability, but no statistical estimation of the parameters is performed.

The goal of this project is to obtain such a statistical parametric estimation with biological data provided by the authors of [2]. The data of several subexperiments are available. A first step will consist in estimating parameters of each experiment separately, using a maximum likelihood. Then models with random parameters (mixed effects models) will be applied to analyze simultaneously all the data. This work will help to develop the precise understanding of tumors resistance to immunotherapeutic approaches and, through its quantitative results, will have useful consequences on futur tumor treatment protocols. There is a possibility to pursue with a PhD.

Competence required: probability, stochastic processes, maximum likelihood estimation.

References

[1] M. Baar, L. Coquille, H. Mayer, M. Hölzel, M. Rogava, T. Tüting, and A. Bovier, *A stochastic individual-based model for immunotherapy of cancer*, (2015), arXiv:1505.00452 [q-bio.PE].

[2] J. Landsberg, J. Kohlmeyer, M. Renn, T. Bald, M. Rogava, M. Cron, M. Fatho, V. Lennerz, T. Wolfel, M. Holzel, and T. Tuting, *Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation*, Nature, 490 (2012), pp. 412–416.