Institut Camille Jordan (Maths department),
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Simon Girel

Education and current position

From 09/2018 **ATER (*Temporary Research and Teaching Assistant)***, *Université Claude Bernard Lyon 1*, France.
Mathematics for 1^{st} year students; Numerical analysis; Preparation for engineering school oral entrance exams.

2015-2018 **PhD degree in Applied Mathematics**, *University of Lyon*, France.
Supervised by Fabien Crauste, PhD, and defended on Nov. 13th, 2018.
Title: *Modeling the CD8 T-cell Immune Response: Mathematical Analysis and Multiscale Models.*

2015 **Master's degree in *Mathematics for Biology and Medicine: Theory and Applications* (2^{nd} year)**, Université Claude Bernard Lyon 1.
France

03-08/2015 **Master's research internship**, *Inria team Dracula, Lyon*, France.
Supervised by Fabien Crauste, PhD, and Olivier Gandrillon, PhD.
Subjet: Contribution to the study of a multiscale model of the CD8 T-cell immune response.

2014 **Master's degree in Applied Mathematics and Statistics (1^{st} year)**, *Université Claude Bernard Lyon 1*, France.

2013 **Bachelor degree in Mathematics**, *Université Claude Bernard Lyon 1*, France.

Research interests

Multiscale modeling; Agent-based modeling; Ordinary differential equations; Impulsive differential equations; CD8 T-cells; Immune response; Theoritical Immunology.

Conferences

2018 - **ICSB 2018 (International Conference on Systems Biology)**, *Lyon*, France.
Poster: Regulation of cellular heterogeneity by uneven molecular partitioning during the CD8 T-cell immune response.

- **Lab Annual Meeting (*Modélisation Mathématique et Calcul Scientifique* team, Institut Camille Jordan)**, *Lyon*, France.
Talk: Modélisation de la réponse immunitaire T-CD8 : conséquences d'un partage inégal du contenu moléculaire à la division.
- **CEMRACS 2018 Summer school**, *Marseille*, France.
- **{MB}^{2} 2018 (Mathematical Biology Modelling days of Besançon)**, *Besançon*, France.
Talk: Regulation of cellular heterogeneity by uneven molecular partitioning during the CD8 T-cell immune response.

2017 - **Forum des Jeunes Mathématicien-ne-s (Young Mathematicians' Forum)**, *Nancy*, France.
Talk: Modélisation mathématique de la réponse immunitaire T-CD8.

- **MOBI 2017 (Modeling and computational approaches to Biology and Medicine)**, *Roma*, Italy.
Talk: Multiscale Modeling of the CD8 T-Cell Immune Response.
- **Congrès SMAI 2017**, *Ronce-les-Bains*, France.
Talk: Modélisation mathématique de la réponse immunitaire T-CD8.

2016 - **LyonSysBio 2016**, *Lyon*, France.
Poster: Multiscale Hybrid Model of the CD8 T-cell Immune Response.

- **HSB 2016 (Hybrid Systems Biology)**, *Grenoble*, France.
  Poster: Multiscale Hybrid Model of the CD8 T-cell Immune Response.

2015 - **{MB}^{2} 2015 (Mathematical Biology Modelling days of Besançon)**, *Métabief*, France.
Talk: Modèle multi-échelles de la réponse immunitaire T-CD8.

Teaching and supervision

2018 - **Numerical analysis (with python)**, *Université Lyon 1*, undergraduate, 10h.

- ***Colles* (oral exams) in mathematics**, *Université Lyon 1*, Preparatory classes for engineering schools, 22h.
- **Mathematics**, *Université Lyon 1*, undergraduate, 64h.

2016-2017 - **Mathematics**, *Institut National des Sciences Appliquées (INSA, engineering school), Lyon, France*, undergraduate, 80h.

2015-2016 - **Mathematics**, *Institut National des Sciences Appliquées (INSA, engineering school), Lyon, France*, undergraduate, 59h.

2017 - **Co-supervisor of Gaëlle Brunet's internship (1^{st} year of master's degree)**.
Title: Multiscale modeling of the T-CD8 immune response

2016 - **Co-supervisor of Nicolas Corthon's internship (2^{nd} year of master's degree)**.
Title: Combination of continuous and agent based models for describing the immune response of CD8 T-cells.

Collective responsibilities

From 2016 **Member of the laboratory council and scientific committee**, *Institut Camille Jordan (ICJ)*.

Publications

S. Girel, C. Arpin, J. Marvel, O. Gandrillon and F. Crauste, *Model-based assessment of the role of uneven partitioning of molecular content on heterogeneity and regulation of differentiation in CD8 T-cell immune responses*, *Frontiers in Immunology*, 10: 230 (2019), doi: 10.3389/fimmu.2019.00230.

S. Girel and F. Crauste, *Existence and stability of periodic solutions of an impulsive differential equation and application to CD8 T-cell differentiation*, *Journal of Mathematical Biology*, 76: 1765 (2018), doi: 10.1007/s00285-018-1220-3.

Popularisation

2016 **Co-organiser of BioSyl (m)eating day**, *ENS de Lyon*, France.

2016 **Supervision of a working group at Mathinfoly (an international summer school of initiation to research in mathematics and informatics dedicated to high school students)**, *ENS de Lyon, France.*

01/2016 **Presentation of mathematical experiments with MathαLyon (a team of mathematician aiming at promoting mathematics high schools)**, *Lacassagne high school, Lyon.*

Miscellaneous

Living languages **French** (mother tongue), **English** (B2 Level, Toeic score: 865/990), **Spanish** (Basics, 5 years in high school).

Softwares Matlab, Scilab, R, Excel, CompuCell3D.

Computer languages C++ (basics), Python (basics).

PhD Thesis summary

Infection of an organism by intracellular pathogen triggers the activation of the CD8 T-cells and the initiation of the immune response. The result is a complex program of proliferation and differentiation of the CD8 T-cells, controlled by the evolution of their molecular content. After a first *expansion* phase, during which the cell population size increases by factor 10^3 to 10^5, most of those cells die during the so called *contraction* phase. The surviving cells, called memory cells, can provide a more efficient response in the event of re-infection with the same pathogen. The generation of memory cells is the basic principle of vaccination.

My thesis project was part of a series of works, carried out at the Camille Jordan Institute (Laboratory of mathematics, Lyon, France) and within the Inria *Dracula* team, aiming at proposing a mathematical model of the CD8 T-cell immune reponse. This work has been conducted in close collaboration with a team of immunologists of the International Center for Infectiology Research (*CIRI*, Inserm, Lyon, France). A specific feature of this work is to adopt a multiscale approach, coupling the modeling of a population of CD8 T-cells with that of the expression of different key intracellular proteins by the CD8 T-cells. My thesis manuscript (in french) can be found here. I focused on two projects summarised hereafter:

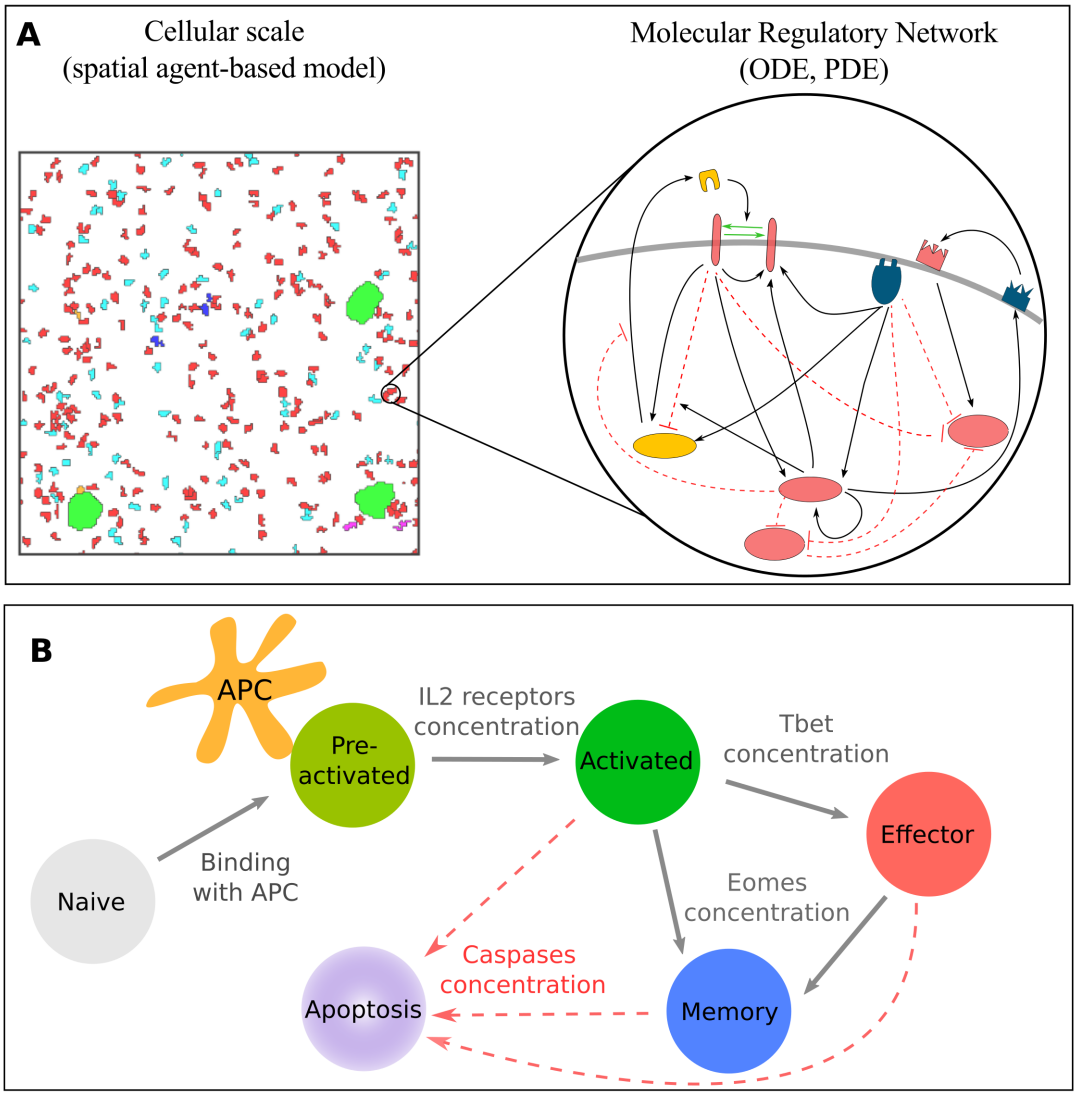
- The development of a multiscale model of the CD8 T-cell immune response, initiated by former members of the *Dracula* team. This work has been accepted for publication in the journal *Frontiers in Immunology* (clickable link).
- The analysis of an impulsive differential equation, derived from the agent-based model and describing the effects of the uneven and stochastic partitioning of intracellular content between two daughter cells upon cell division. This study was published in March 2018 in the *Journal of Mathematical Biology* (clickable link).

Multiscale modeling of the CD8 T-cell immune response

The construction of this model was initiated by S. Prokopiou (Prokopiou *et al.*, *Computation*, 2014) and X. Gao (Gao *et al.*, *BMC Syst Biol*, 2016), then continued during my thesis. This model describes the dynamics of a discrete CD8 T-cell population during an immune response, coupled with a description of the activity of a molecular regulatory network, embedded in each CD8 T cell and influenced by cell-cell interactions and by cell's environment. Each cell is represented by a set of pixels and can move on a two-dimensional grid (Cellular Potts Model). Each cell interacts with other cells, divides, differentiates (naive cells activation, differentiation into activated cells, then into effector cell and finally into memory cells), or dies depending on the state of its molecular network. Molecular regulation is described by a system of six ordinary differential equations and one partial differential equation. This system determines the state of a single cell at any given time.

My main contribution to this model was to add an additional state of differentiation (the memory state) and to model a full CD8 T-cell immune response (up to day 29 after infection, while the previous versions of the model stand for the two first days of the response, that is the beginning of the expansion phase). This has required enriching the molecular regulatory network and the associated system of differential equations, to analyse the properties of this system and to redefine some assumptions from the previous model.

The biological consistence of the mathematical model developed has regularly been discussed with immunologists from J. Marvel's team (*CIRI*) in Lyon. The model parameters were adjusted to *in vivo* data provided by J. Marvel's team for the cell scale, and by the Immgen project database for the molecular scale. The agent-based approach being particularly convenient for describing heterogeneous populations, we used our model to study the origin and the role of phenotypic and molecular heterogeneity within a cell population — a question currently being discussed within the immunology community.



Graphical abstract of the multiscale model. A) at the cellular level, an agent-based model describes a population of CD8 T-cells and antigen-presenting cells (APC). At the molecular level, the activity of a molecular regulatory network is modelled by a system of ordinary differential equations (ODE) describing the concentrations of six proteins in each lymphocyte. A partial differential equation models the secretion of the prorein IL2 by the CD8 T-cells and its spatial diffusion. B) The molecular content of each CD8 T-cell determines its properties. For example: lymphocyte differentiation and apoptosis are governed by a system of thresholds on the concentrations of various proteins (namely, IL2 receptors, Tbet, Eomes and Caspases)

Study of an impulsive differential equation

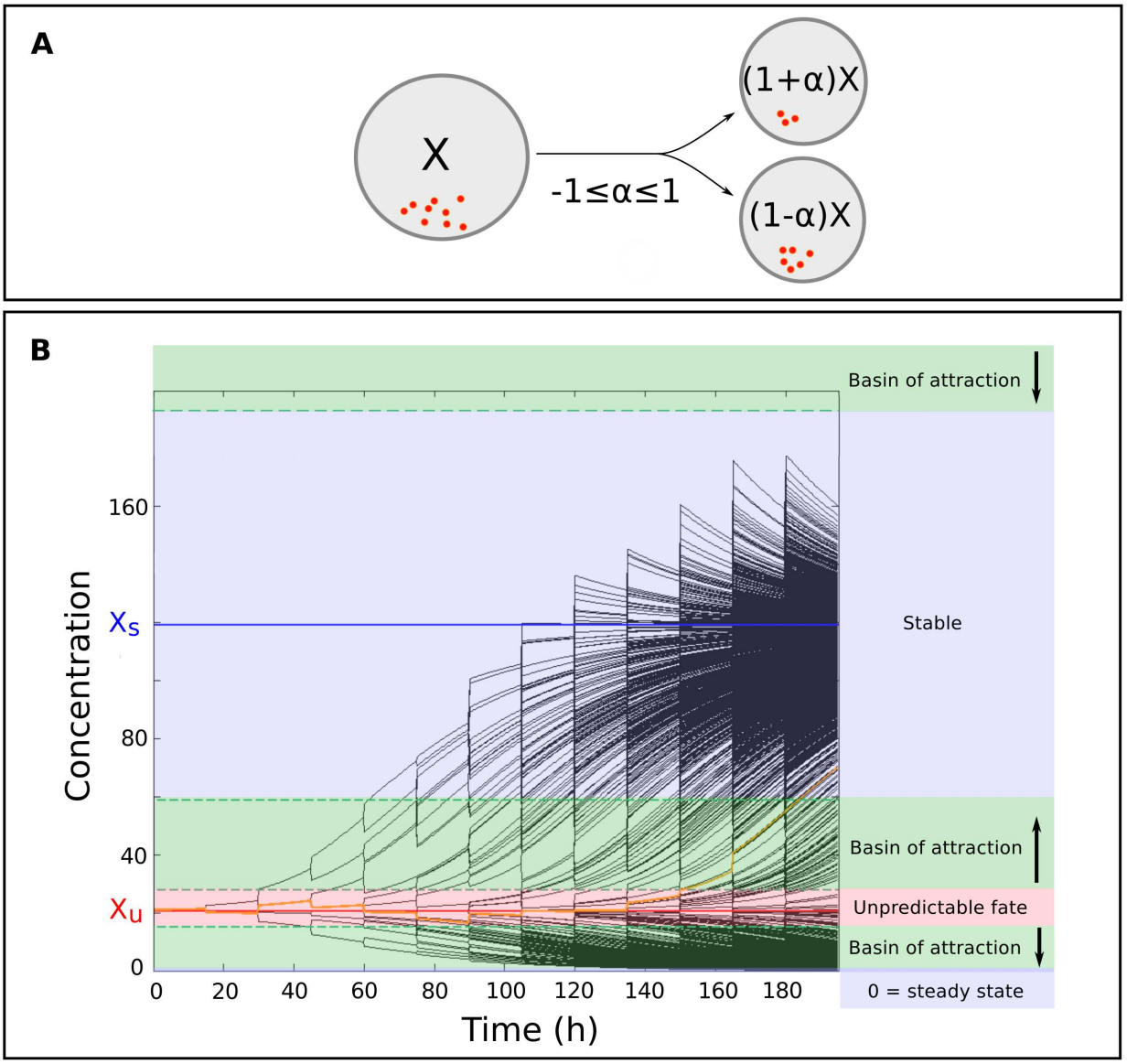
In the above-mentioned multiscale model, it is assumed that when a cell divides, the proteins it contained are not evenly distributed between the two daughter cells from the division. For each protein, there is therefore a discontinuity between the concentration observed in the mother cell and the concentrations observed in the two daughter cells. This suggest than the uneven molecular partitioning at division could be part of the emergence of heterogeneity among the CD8 T-cell population during the immune response.

This biological question motivated our modelling work. Mathematically, this phenomenon can be described by means of an impulsive differential equation, i. e. a differential equation subject to instantaneous perturbations. The protein Tbet is known to be associated with the effector phenotype, while repressing the memory phenotype. The following impulsive equation, derived from the multiscale model, models the concentration of proteins Tbet in a CD8 T-cell cell dividing at fixed times. The differential equation being associated with protein synthesis, degradation and dilution while the impulses are associated with the uneven partitioning of proteins.

$$\begin{cases} \dfrac{\mathbf{d}X(t)}{\mathbf{d}t} = \eta \dfrac{X(t)^n}{\theta^n + X(t)^n} - \delta X(t),\ t \in \mathbb{R}^+ \backslash \{\tau_k, k \in \mathbb{N}^*\}, \\ X(\tau_k^+) = (1+\alpha_k) X(\tau_k^-), \qquad k \in \mathbb{N}^*, \\ X(0) = X_0, \end{cases} \tag{1}$$

where $0 < \tau_1 < \tau_2 < \tau_3 < \dots$ are fixed values such that $\lim_{k\to\infty} \tau_k = +\infty$ and $(\alpha_k)_{k\geq 1}$ is a sequence of real numbers such that, for all $k \geq 1, \alpha_k$ is randomly chosen on an interval $[-A, A] \subset (-1, 1)$.

We have studied how the degree of unevenness (*i.e.* the parameter A) affects the cell differentiation process and its reversibility. Our study also suggests that the lengthening of the cell cycle along the immune response precipitates cell differentiation. The results from this study can be used to configure the multiscale model, by restricting the parameter values to the values that allow the model to develop the expected behaviour. In this article, results on the existence and stability of periodic solutions are demonstrated for a more general class of impulsive equations. These results mainly rest upon the study of the flow of an autonomous ordinary differential equation, and in particular on its convexity.



Graphical abstract of the impulsive equation study. A) Uneven partitioning of molecular content leads to different Tbet concentrations (number of proteins/cell size) among daughter cells. B) Tbet concentrations in a cell lineage, with uneven molecular partitioning and fixed cell cycle time. In the absence of impulses ($A = 0$), equation (1) exhibits bistable behaviour with 3 steady states (0, X_u and X_s). One of our findings is that if the degree of unevenness A in sufficiently small, there exist two asymptotic stable intervals of concentrations (associated with the effector and memory phenotypes) while intermediate concentrations correspond to CD8 T-cells with unpredictable fates, that can still generate both effector and memory cells.