Multi-scale modeling of the CD8 immune response

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Abstract. During the primary CD8 T-Cell immune response to an intracellular pathogen, CD8 T-Cells undergo exponential proliferation and continuous differentiation, acquiring cytotoxic capabilities to address the infection and memorize the corresponding antigen. After cleaning the organism, the only CD8 T-Cells left are antigen-specific memory cells whose role is to respond stronger and faster in case they are presented this very same antigen again. That is how vaccines work : a small quantity of a weakened pathogen is introduced in the organism to trigger the primary response, generating corresponding memory cells in the process, giving the organism a way to defend himself in case it encounters the same pathogen again.
To investigate this process, we propose a non linear, multi-scale mathematical model of the CD8 T-Cells immune response due to vaccination using a maturity structured partial differential equation. At the intracellular scale, the level of expression of key proteins is modeled by a delay differential equation system, which gives the speeds of maturation for each cell. The population of cells is modeled by a maturity structured equation whose speeds are given by the intracellular model.
We focus here on building the model, as well as its asymptotic study. Finally, we display numerical simulations showing the model can reproduce the biological dynamics of the cell population for both the primary response and the secondary responses.

Keywords: Cell population dynamics, Immune response, Multi-scale modeling, Structured partial differential equations
PACS: 02.30.Ks, 02.30.Jr, 02.30.Oz

MODELING THE CD8 IMMUNE RESPONSE

Upon infection by a pathogen, the human body initiates the immune response in which different types of body cells take a part. We focus here on the role of CD8 T-lymphocytes which play a key role in the recognition, removal and the memorizing of intracellular pathogens. Initially in a quiescent (naive) state in lymphoid organs, their activation occurs through presentation of an antigen by means of contact with an Antigen Presenting Cell (APC). The APC present a corresponding antigen to CD8 T-cells, triggering this way the processes of clonal expansion and cellular differentiation that constitutes the immune response [1].

The immune response starts with a strong proliferation phase, where the naive cells, after their activation, proliferate and become effector cells presenting cytotoxic capabilities (they can attack other cells) [1]. Then comes the contraction phase, where only 5-10% of the cells survive and become memory cells [2]. These cells are quiescent long-lasting cells that can trigger a much stronger and faster secondary immune response in case they encounter the same pathogen again.

Mathematical modeling in immunology has become an useful tool in the past decade to try and bridge the gaps in immunological knowledge. Usual designs include modeling the population kinetics using ordinary or partial differential equations [3, 4] or more sophisticated cellular interactions using agent based models [5].

In our previous work [6], we developed a hybrid, agent-based/continuous model describing both the intracellular scale and the population scale with interactions between the two scales. This kind of design allowed us to reproduce cellular heterogeneity by including stochasticity in the model. We propose here a fully continuous, deterministic, multi-scale model, similar in design to the ones described in [7].

Intracellular model

CD8 T-cells can be sorted in subpopulations that behave differently at the population scale. Our goal is to characterize which subpopulation a cell belongs to depending on its intracellular content. The different cell subpopulations considered are displayed on figure 1 .

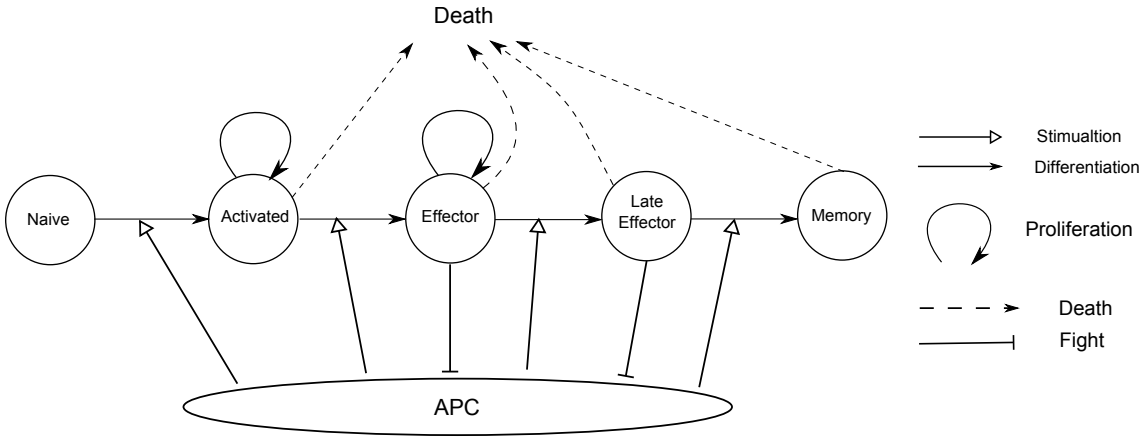

Figure 1. The different states of CD8 T-cells differentiation. *We consider five subpopulations (we add late effector cells to the four already described) with a linear differentiation scheme due to stimulation by APC. Effector and activated cells proliferate, while naive, activated and memory cells have high survival rates.*

To describe the intracellular state of one cell, we use a simplified version of intracellular model developed in [6] using only two key proteins: Ki-67 (proliferation marker) and Bcl-2 (survival marker). The intracellular model is given on figure (2).

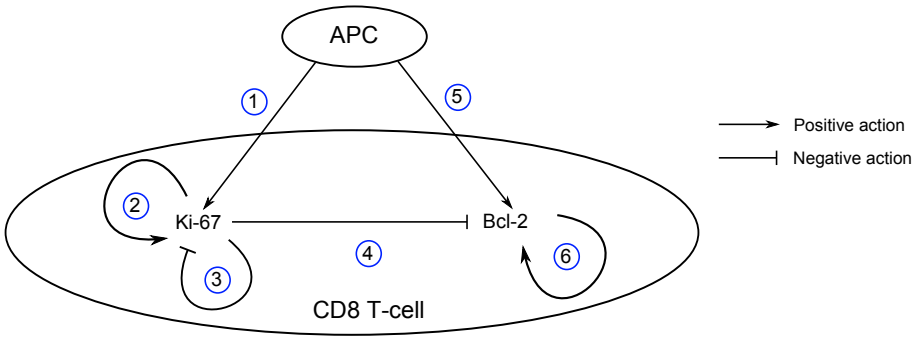

Figure 2. Reduced interaction network between Ki67, Bcl2 and APC (P(t)). *Upon stimulation by an APC, Ki67 and Bcl2 synthesis starts (arrows 1 and 5). It sustains itself with a fast positive feedback (arrow 2), and a slower negative feedback (arrow 3), which kicks in late and represents exhaustion of proliferating cells. Bcl2 sustains itself independently of other stimulus (arrow 6) and it's expression is reduced by Ki67 expression.*

The associated ordinary differential equation system is :

$$\begin{cases} \dfrac{d\mu_1}{dt}(t) = v_1(\mu_1(t),P(t)) = \underbrace{\dfrac{\gamma_{P1}P(t)}{\theta_{P1}+P(t)}\mu_1(t)}_{1} + \underbrace{\dfrac{\gamma_{r1}\mu_1(t)}{\theta_{r1}+\mu_1(t)}\mu_1(t)}_{2} - k_1\mu_1(t) - \underbrace{\dfrac{\gamma_{l1}\mu_1^2(t-\tau)}{\theta_{l1}^2+\mu_1^2(t-\tau)}\mu_1(t)}_{3}, \\ \dfrac{d\mu_2}{dt}(t) = v_2(\mu_1(t),\mu_2(t),P(t)) = \underbrace{\dfrac{\gamma_{P2}P(t)}{\theta_{P2}+P(t)}\mu_2(t)}_{5} + \underbrace{r_2(K_2-\mu_2(t))\mu_2(t)}_{6} - \underbrace{k_{KB}\mu_1(t)\mu_2(t)}_{4} - k_2\mu_2(t), \end{cases} \tag{1}$$

where $P(t)$ accounts for the APC count at time t and $\mu_1(0),\mu_2(0) > 0$. The numbers under each term corresponds to the numbers on each interaction displayed on figure (2).

Population model

These two markers allow us to distinguish four subpopulations of CD8 T-cells depending on their intracellular content (see figure 3). The cell population is modeled by its density $\rho(t,\mu_1,\mu_2)$, who moves at the speeds v_1 and v_2 in the (μ_1,μ_2) plane, and follows the following structured equation :

$$\begin{cases} \dfrac{\partial \rho}{\partial t} + \dfrac{\partial}{\partial \mu_1}(v_1\rho) + \dfrac{\partial}{\partial \mu_2}(v_2\rho) = F(\mu_1,\mu_2,E(t),P(t))\rho + f_{source}(P(t),N(t),\mu_1,\mu_2), t>0,\ \mu_1,\mu_2>0, \\ \rho(t,0,\mu_2) = \rho(t,\mu_1,0) = 0, \quad t \geq 0, \mu_1,\mu_2 \geq 0, \\ \rho(0,.,.) = \rho_0(.,.) \in L^1(\mathbb{R}^2_+), \end{cases} \tag{2}$$

where F accounts for the phenomenons occurring at the population scale (death and division), and f is a source of activated cells coming directly from stimulation of naive cells ($N(t)$). The equations ruling $N(t)$ and $P(t)$ are :

$$\frac{dN}{dt}(t) = \underbrace{\frac{-\gamma_N P(t)}{\theta_N + P(t)} N(t)}_{\text{stimulation by APC}}, \quad N(0)>0, \quad \frac{dP}{dt}(t) = \underbrace{-k_P P(t)}_{\text{natural degradation}} \underbrace{-\frac{\gamma_E E(t)}{\theta_E + E(t)} P(t)}_{\text{death by effector and late effector contact}}, \quad P(0)>0. \tag{3}$$

This model is designed to describe both the primary and secondary responses and its expected behavior is displayed on figure 3.

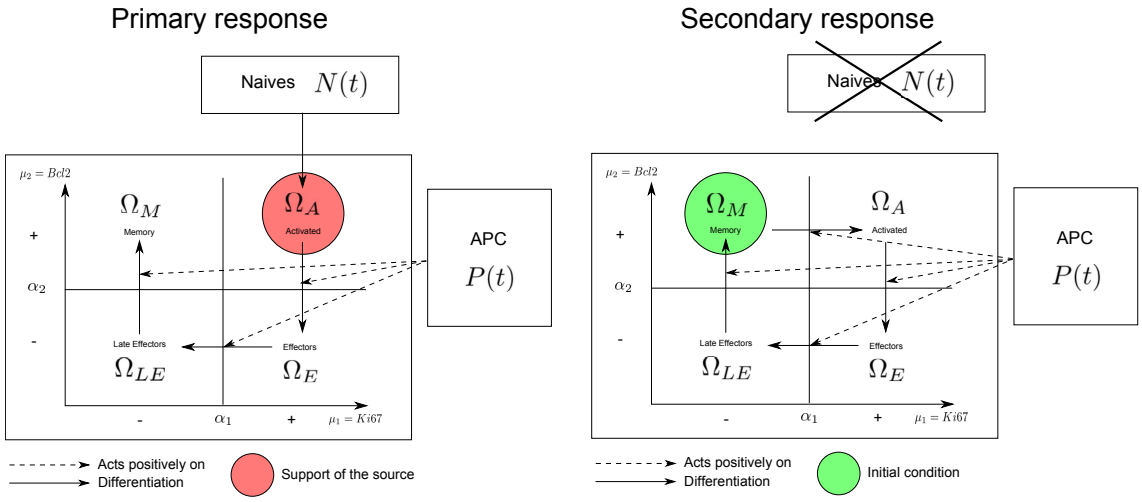

Figure 3. Expected behavior of our model. *Before the primary response, the main domain is empty ($\rho_0 = 0$) and all the CD8 T cells are naive, in a separate compartment. The the APC stimulate the naive cells which start to differentiate into activated cells (f_{source}). The support of the source is located in Ω_A. Then the cells from the source start to move in the (μ_1,μ_2) maturity plane according to system* (1)*. For the secondary response, it is the opposite. There are no naive cells left and therefore $f_{source} = 0$, but the initial condition is not null. The reappearance of APC restarts the quiescent memory cells who move once again following* (1)*.*

RESULTS AND SIMULATIONS

The intracellular delay equation system (2) presents up to one strictly positive, and locally stable for $\tau = 0$, steady state. It can model the quiescent memory population, and in this case, the density ρ tends towards a Dirac mass located in that very same steady state (see figure 4.c). This steady state becomes unstable as τ increases (Hopf bifurcation), and (1) has a limit cycle at, and past, the point of bifurcation. We use it to model an heterogeneous memory population: the density's support is located on a closed curve inside the memory compartment and we obtain memory cells with different maturities (see figure 4.i). In both cases, the model also behaves correctly, in terms of dynamics, regarding the secondary response: memory cells move back to the activated compartment, then follow the differentiation scheme 1 as expected on figure 3 (see figure 4).

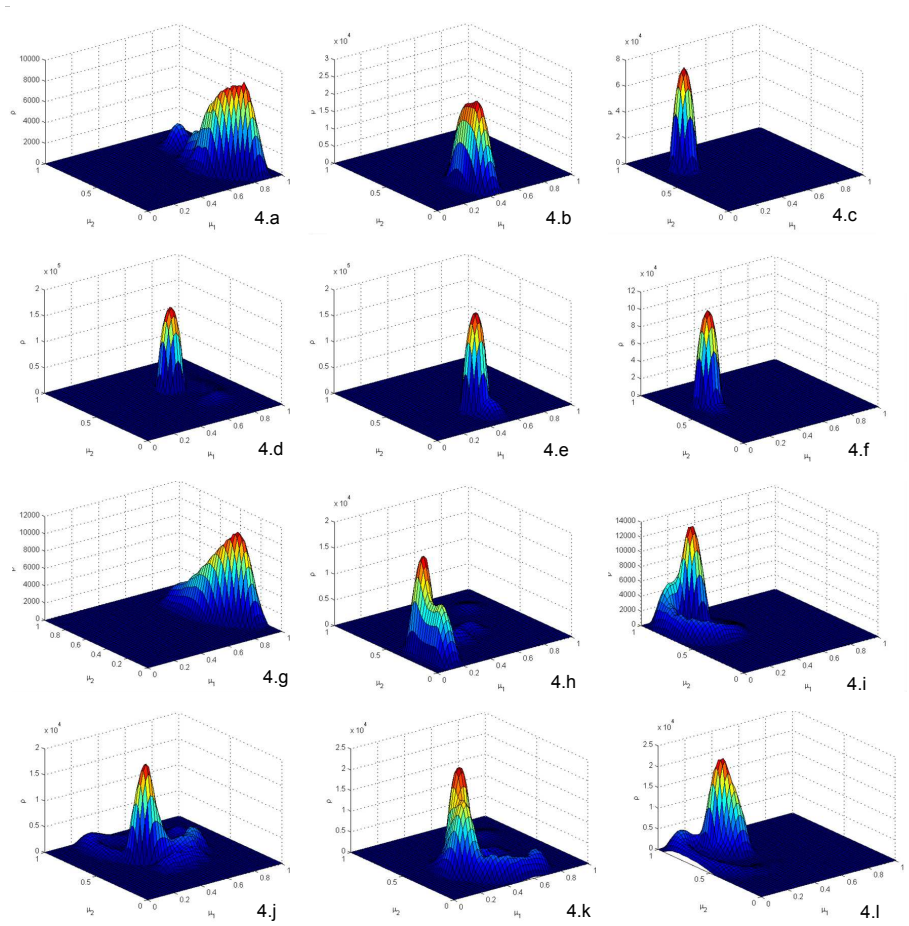

Figure 4. Simulations of the model. *Numerical simulations were made using a deterministic particle method (see [8]). Subfigures 4.a to 4.f show the behavior of the model when there exist a stable steady state in the memory compartment, while subfigures 4.g to 4.l correspond to the case where the bifurcation occurred (existence of a limit cycle). In each case, the primary response is showed on the first three figures, then the other three show a secondary response obtained after re-injecting another dose of pathogen.*

REFERENCES

1. A. K. Abbas, A. H. H. Lichtman, S. Pillai, Basic Immunology: Functions and Disorders of the Immune System 4th edition, *Saunders*, 2012.
2. K. Murali-Krishna , J. D. Altman, M. Suresh, D. J. Sourdive, A. J. Zajac, J. D. Miller, J. Slansky, R. Ahmed, Counting antigen-specific CD8 T cells: a reevaluation of bystander activation during viral infection, *Immunity*, **8(2)**, 1998, pp. 177-187.
3. E. Terry, J. Marvel, C. Arpin, O. Gandrillon, F. Crauste, Mathematical model of the primary CD8 T cell immune response : stability analysisof a non linear age-structured system, *J. Math. Biol.*, **65**, 2012, pp. 263-291.
4. F. Crauste, E. Terry, I. Le Mercier, J. Mafille, S. Djebali, T. Andrieu, B. Mercier, G. Kaneko, C. Arpin, J. Marvel, O. Gandrillon, Predicting pathogen-specific CD8 T cell immune responses from a modeling approach, *J. Theor. Biol.*, **374**, 2015, pp. 66-82.
5. M. Bernaschi, F. Castiglione, Design and implementation of an Immune System Simulator, *Comp in Biol and Med*, **31(5)**, 2001, pp. 303-331.
6. S.A. Prokopiou, L. Barbarroux, S. Bernard, J. Mafille, Y. Leverrier, C. Arpin, J. Marvel, O. Gandrillon, F. Crauste, Multiscale Modeling of the Early CD8 T-Cell Immune Response in Lymph Nodes: An Integrative Study, *Computation*, **2**, 2014, pp. 159-181.
7. A. Friedman, C. Kao, C. Shih, Asymptotic limit in a cell differentiation model with consideration of transcription, *J. Differential equations*, **252**, 2012, pp. 5679-5711.
8. P.A. Raviart, An analysis of particle methods, *Springer Berlin Heidelberg*, 1985, pp. 243-324.