Regulation of cellular heterogeneity by uneven molecular partitioning during the CD8 T-cell immune response

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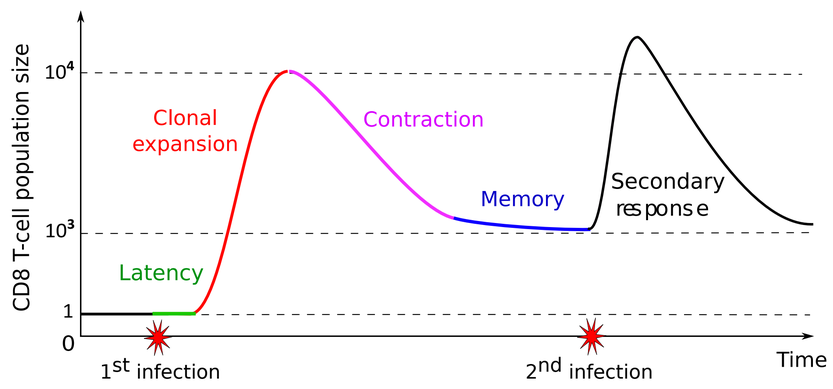
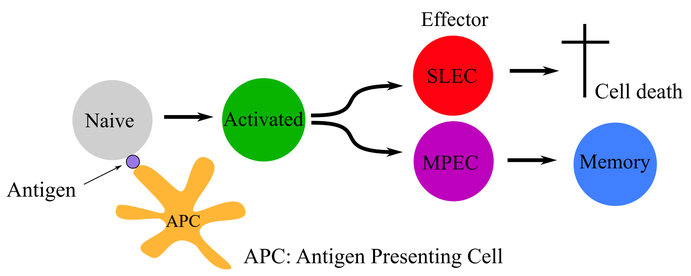
Introduction

We designed a hybrid multiscale model of the CD8 T-cell immune response in which cells are modeled as agents on a 2D grid and can interact together. In the meantime, a system of differential equations, embedded in each cell, continuously describes the production and degradation of key proteins, defining the molecular profile and then the phenotype of the cell. We extended previous models [1,2] to allow cells to differentiate into memory cells in order to model a complete response. With the help of an impulsive differential equation (IDE), we studied the putative effect of uneven partitioning of molecular content at cell division upon cellular heterogeneity.



The different phases of an "autonomous" CD8 T-cell immune response.



SLEC : *Short Lived Effector Cell* ($CD127^{low}KLRG1^{high}$) : **Tbet high**

MPEC : *Memory Precursor Effector Cell* ($CD127^{hi}KLRG1^{low}$) : **Tbet low**

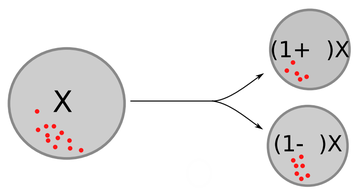
Tbet

Branched CD8 T-cell differentiation scheme

Study of an IDE [5]

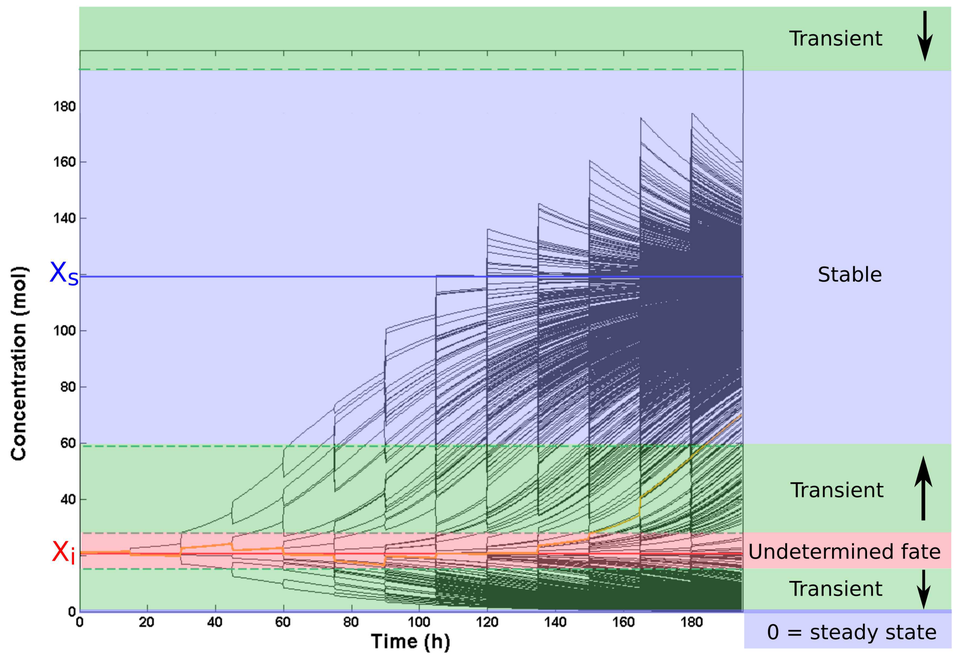
Tbet concentration in a CD8 T-cell with cell cycle length $\omega \geqslant 0$

$$\begin{cases} \dfrac{\mathrm{d}X}{\mathrm{d}t} = \eta \dfrac{X^n}{\theta^n + X^n} - \delta X, & t \in \mathbb{R}^+ \backslash \{k\omega,\ k \in \mathbb{N}^*\} \\ X(k\omega) = \alpha_k X(k\omega^-), & \alpha_k \in [\alpha_{min}, 2-\alpha_{min}],\ k \in \mathbb{N}^* \\ X(0) = X_0 \in \mathbb{R}^+ \quad . \end{cases}$$



Assume $n \geq 2$ and $\eta(n-1)^{\frac{n-1}{n}} > n\eta\delta$ (bistability of the non-impulsive equation).

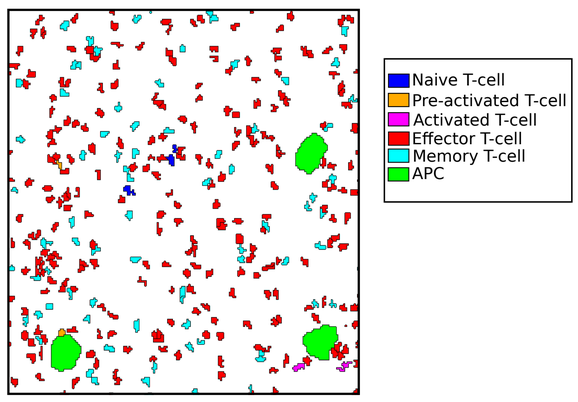
There exists $\alpha^* \in (0,1)$ such that if $\alpha_k \in [\alpha_{min}, 2-\alpha_{min}] \subset (\alpha^*, e^{\delta\omega})$ for all $k \geq 1$, then:



Multiscale modeling of the CD8 immune response [4]

Cellular scale

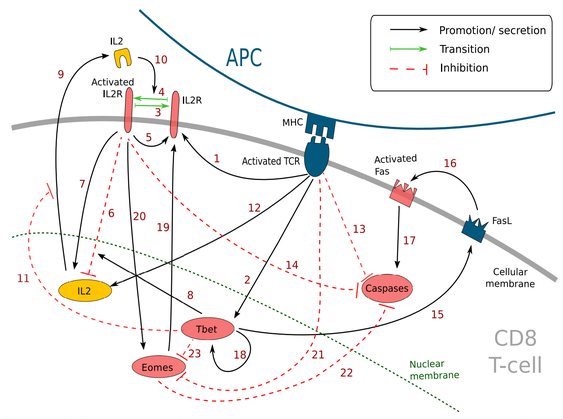
A dicrete population of CD8 T-cells and APC is modeled with an agent-based model. Cells can move, interact, divide and die.



Cell population with heterogeneous phenotypes (Screenshot from software CompuCell3D [5]).

Molecular scale

Molecular concentrations in each CD8 T-cell as well as IL2 spatial diffusion are modeled by a system of differential equations.



Simplified molecular signalling pathway of a CD8 T-cell activated by antigen presenting cell.

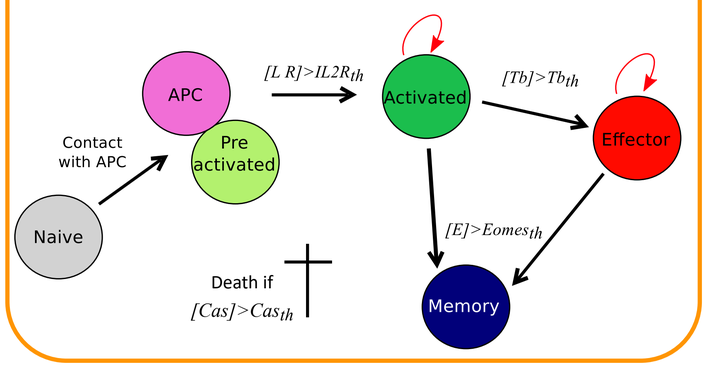
$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t}[R] = \lambda_{R1} f_{APC} + (\mu^-_{IL2} + \lambda_{R2})[LR] + \lambda_{E1}[E] - \left(\mu^+_{IL2}[IL2^{cm}] + k_R\right)[R], \\ \frac{\mathrm{d}}{\mathrm{d}t}[LR] = \mu^+_{IL2}[IL2^{cm}][R] - \mu^-_{IL2}[LR] - k_e[LR], \\ \frac{\mathrm{d}}{\mathrm{d}t}[Tb] = \lambda_{T1} f_{APC} + \lambda_{T2} \frac{[Tb]^n}{\lambda^n_{T3} + [Tb]^n} - k_T[Tb], \\ \frac{\mathrm{d}}{\mathrm{d}t}[Fs^*] = H\mu^+_F[Tb^{cm}]\left(\frac{\lambda_F}{k_F} - [Fs^*]\right) - \mu^-_F[Fs^*] - k_F[Fs^*], \\ \frac{\mathrm{d}}{\mathrm{d}t}[Cas] = G\lambda_{c1} \frac{1}{1+\lambda_{c2}[LR]} \cdot \frac{1}{1+\lambda_{c3} f_{APC}} \cdot \frac{1}{1+\lambda_{E2}[E]} + \lambda_{c4}[Fs^*] - k_c[Cas], \\ \frac{\mathrm{d}}{\mathrm{d}t}[E] = \frac{1}{1+\lambda_{E5} f_{APC}} \cdot \left(\frac{\lambda_{E3}[LR]}{\lambda_{E6} + [LR]} + \frac{G\lambda_{E4}}{1+\lambda_{E7}[Tb]}\right) - k_E[E]. \end{cases}$$

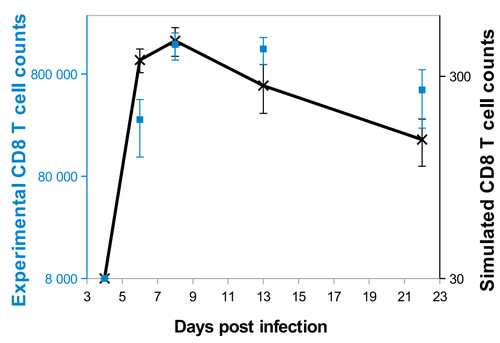
Intracellular concentrations

$$\frac{\partial[IL2]}{\partial t} = D\nabla^2[IL2] + \left(\lambda_{R3}\frac{[LR]}{\lambda_{R4}+[LR]} + \lambda_1 f_{APC}\right)\frac{1}{1+\lambda_{T4}[Tb]} - \delta[IL2].$$

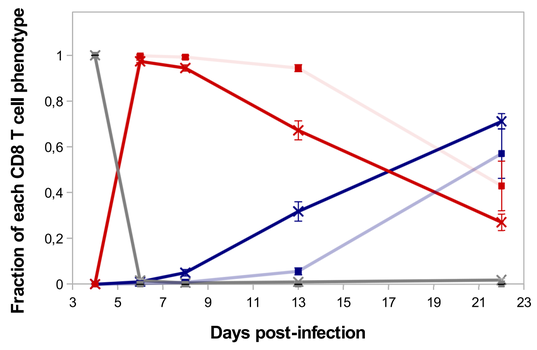
IL2 secretion and diffusion

Differentiation scheme based on thresholds

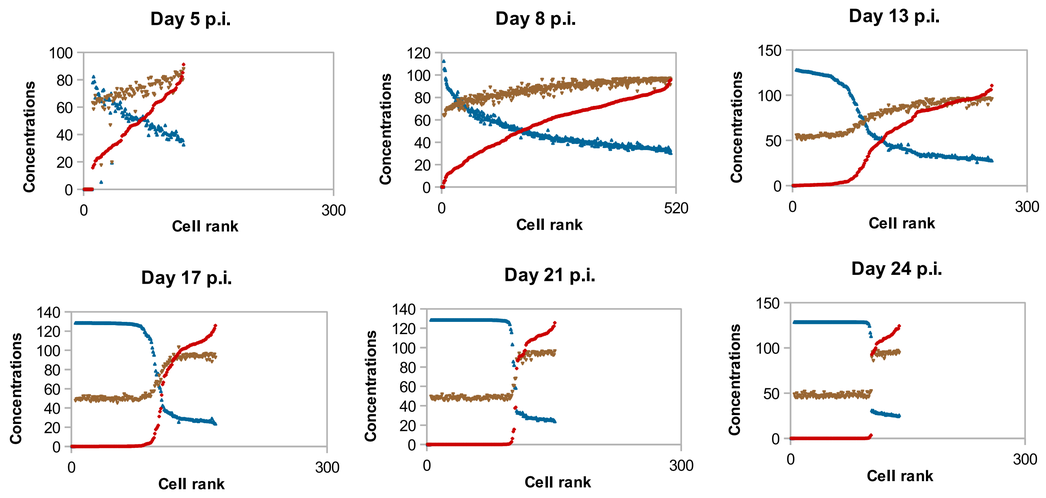




CD8 T-cell population size **in silico** and **in vivo**



Fraction of each phenotype among the CD8 T-cell population.
(naive+pre-activated; activated+effector; memory.)
Full lines : in silico; transparent lines with squares: in vivo



Concentration of Tbet (red), Eomes (blue) and Caspases (brown) at different time points in all T-cells, arranged in ascending Tbet concentration order.

References

- Multiscale model: **[1]** Prokopiou *et al.* (2014), *Computation*; **[2]** Gao *et al.* (2016), *BMC Systems Biology*; **[3]** Girel *et al.* (2018), *submitted in Frontiers in Immunology.*
- Compucell3D software: **[4]** Swat *et al.* (2012), *Methods in Cell Biology.*
- Impulsive equation study: **[5]** Girel and Crauste (2018), *Journal of Mathematical Biology.*