Multiscale Hybrid Model of the CD8 T-cell Immune Response

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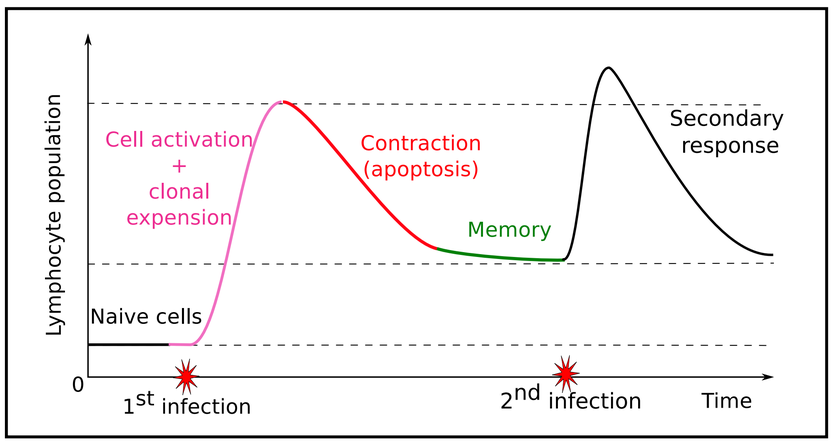
Introduction

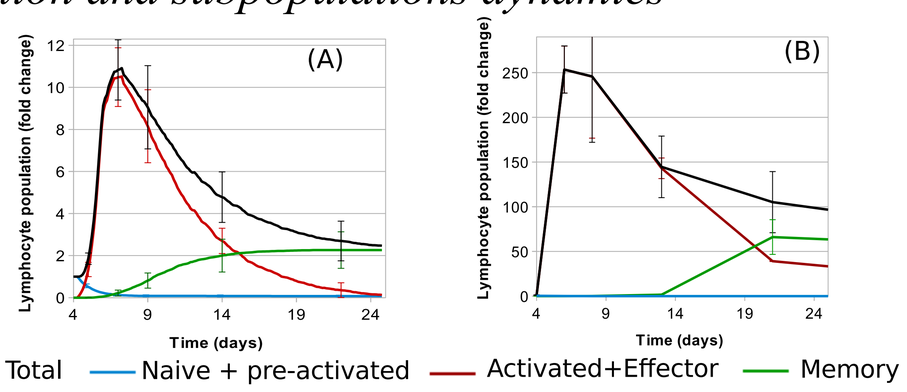
We propose a hybrid multiscale model of the CD8 T-cell immune response, in which cells are modeled as agents on a 2D grid and can interact together via contact or cytokines. In the meantime, a system of differential equations, embedded in each cell, continuously describes the production and degradation of key proteins, defining the molecular profile and then the phenotype of the cell. Finally, IL2 diffusion is modeled through a PDE. We complexified previous models [1,2] to allow cells to differentiate into memory cells, then we aim at modeling the dynamics of a discrete CD8 T-cell population in a murine lymph node, from the activation of naive cells to the development of a memory population.



The different phases of the CD8 T-cell immune response.

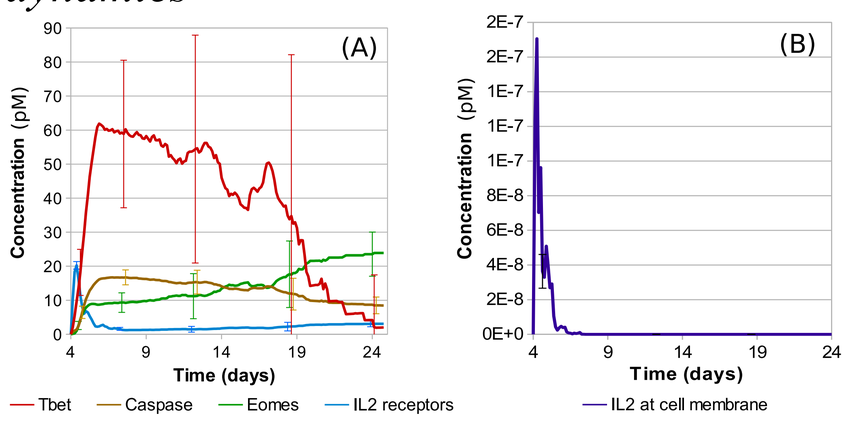
Model results

Population and subpopulations dynamics



T-cell total population and sub-populations dynamics, mean value and standard error bars. (A) In silico (n=20). (B) in vivo (n=4).

Proteins dynamics

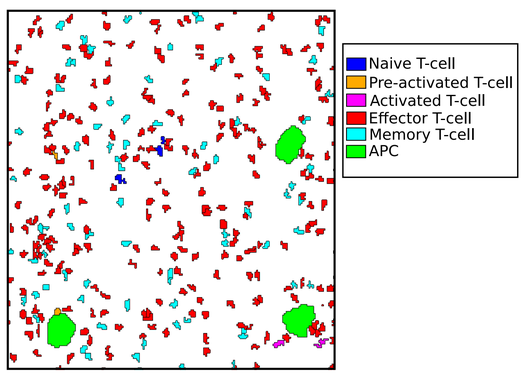


In silico mean concentration of some intracellular (A) and extracellular (B) key proteins in the cell population with standard error bars showing the variability in the population (from 1 simulation)

The model

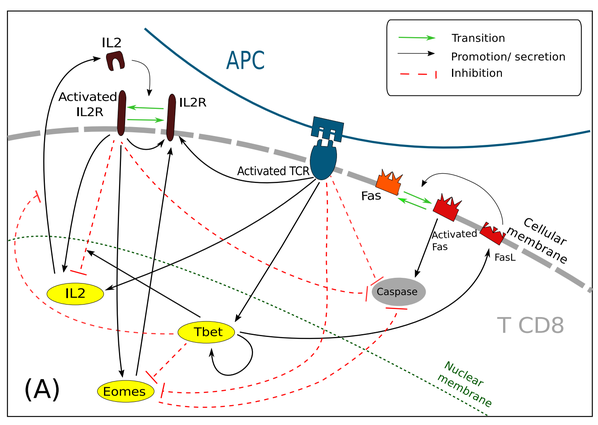
Cellular scale (Cellular Potts Model)

A cell = a set of pixels:
-Moves according to energy minimisation,
-Interacts with antigen presenting cells (APC) and lymphocytes,
-Differentiates/die according to molecular profile,
-Divides at the end of cell cycle,
-Secretes cytokines (IL2),



Heterogeneous cell population (Screenshots from software CompuCell3D [3]).

Molecular scale

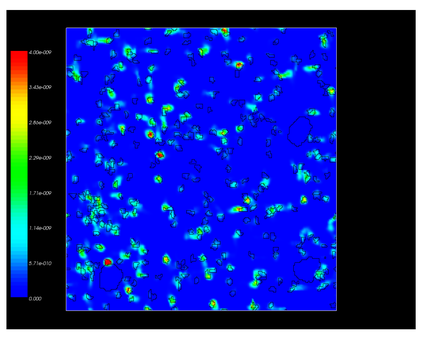


Intracellular

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

IL2 secretion and diffusion

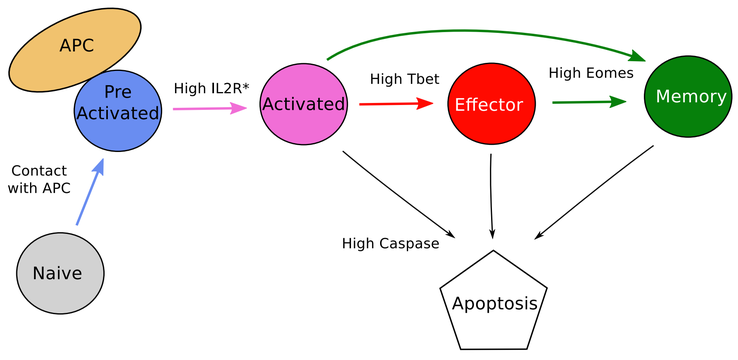
(B) $$\frac{\partial[IL2]}{\partial t} = D\nabla^2[IL2] + \left(\lambda_{R3}\frac{[L \bullet R]}{\lambda_{R4} + [L \bullet R]} + \lambda_1 f(APC)\right)\frac{1}{1+\lambda_{T4}[Tb]} - \delta[IL2].$$



(C)

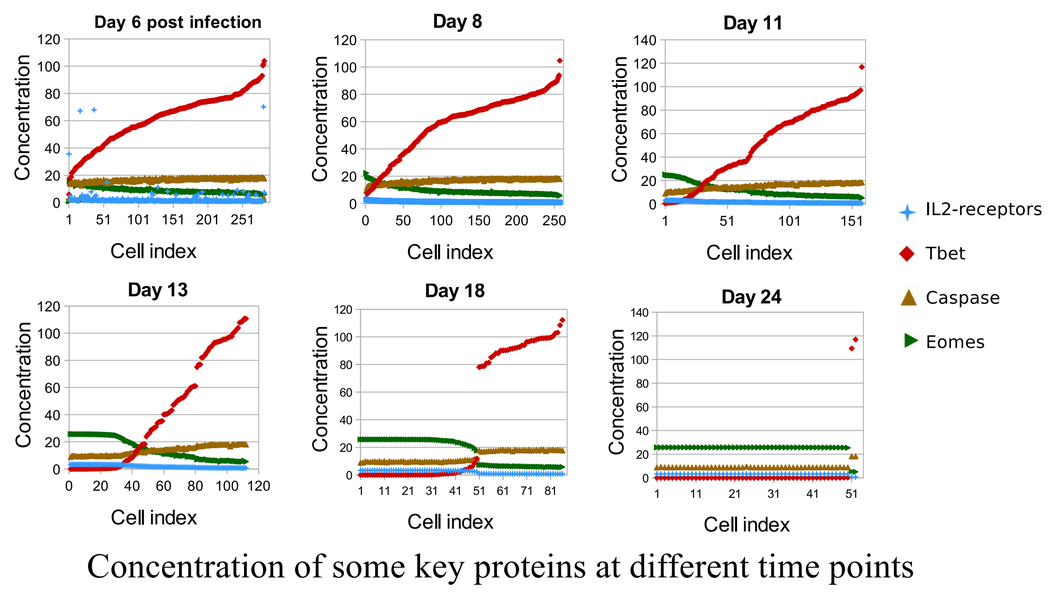
(A) Simplified molecular signalling pathway of a CD8 T-cell activated by antigen presenting cell. (B) Associated system of differential equations. (C) IL2 diffusion (CompuCell3D [3]).

Differentiation scheme



Generating a heterogeneous population from a single cell

Unequal repartition of protein Tbet at cell division and emergence of two pools of effector cells.



Concentration of some key proteins at different time points in all T-cells, arranged in ascending Tbet concentration order.

Conclusion

This model qualitatively reproduces the population dynamics along with differentiation from naive to memory phenotypes. Once the cells are activated, further stimulations by APCs are not necessary to produce a complete response with development of a memory population.

The model can be used to test different hypothesis about the consequences of early molecular events on the development of a memory population.

Perspectives

Simulate a response to a second infection to evaluate the quality of the memory population.

Build a hybrid discrete-continuous version of the population model, with the possibility to switch between discrete and continuous descriptions to make it faster.

Provide a formal analysis of the effects of protein distribution at division on cell fate.

References

[1] Prokopiou *et al.* 2014. Multiscale modeling of the early CD8 T-Cell immune response in lymph nodes: An integrative study. *Computation*, 2(4):159-181.

[2] Gao *et al.* 2016. Il-2 sensitivity and exogenous Il-2 concentration gradient tune the productive contact duration of CD8+ T cell-APC: a multiscale modeling study. *BMC Systems Biology*, 10(1).

[3] Swat *et al.* 2012. Multi-scale modeling of tissues using CompuCell3D. *Methods in Cell Biology*, 325-366