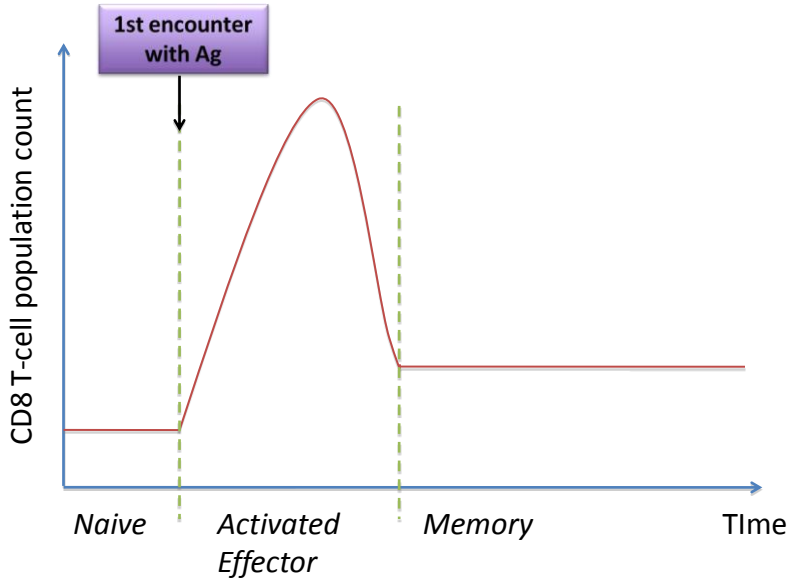
MULTI-SCALE MODELLING OF THE PRIMARY CD8 T-CELL RESPONSE

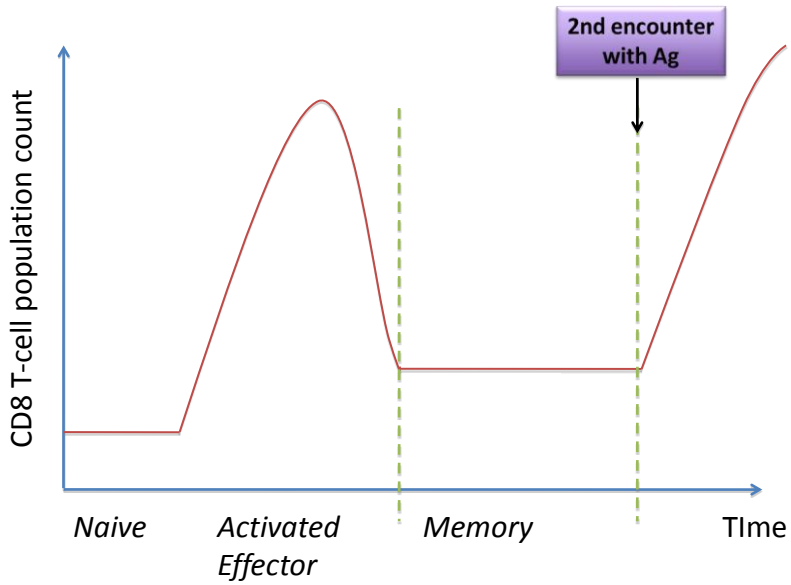
Olivier Gandrillon, June 2010

Warning: in order to make this presentation public, all sensitive non-published material has been blurred…

The primary CD8 T cell response



The secondary CD8 T cell response



Objective:

To develop an accurate multi-scale mathematical model of the primary CD8 T cell response to an antigen encounter, including feedback loops to explain the whole dynamics of the populations, notably the time of the switch between the expansion and contraction phases.

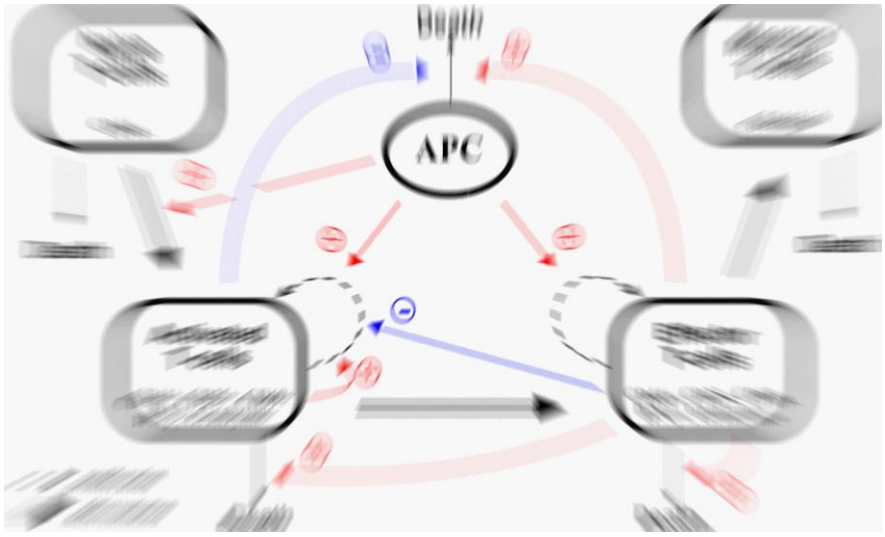
(The term multi-scale indicates that different levels will be discussed and incorporated to the model, from the protein network (restrained to key proteins) that regulates cell decision, to the cell population level.)

Interest:

Fundamental research:
1. Test the extent of our understanding of the biological process.
2. In the end one should be able to predict the effect of a molecular mutation on the global system behavior.

Applied research:
3. Bring novel insights on the development of improved vaccines by better deciphering the dynamics of response
4. Speed up the development of vaccines.

After long hours of discussion between immunologists and mathematicians, a first draft emerged:



For *bona fide* immunologists this is an outrageous oversimplication (no CD4!)

But for mathematicians, this is already a very complex model

$$dN/dt = \pi - \delta_N N - \alpha_{NA}(APC)N,$$

$$dA/dt = \alpha_{NA}(APC)N + \sigma_A(APC, A, E)A - \delta_A(APC, E)A - \alpha_{AE}A,$$

$$dE/dt = \alpha_{AE}A + \sigma_E(APC, A, E)E - \delta_E(APC, E)E - \alpha_{EM}E,$$

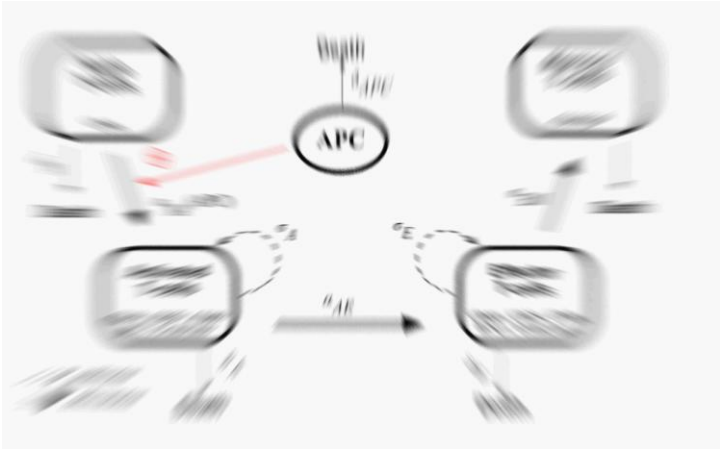
$$dM/dt = \alpha_{EM}E - \delta_m M,$$

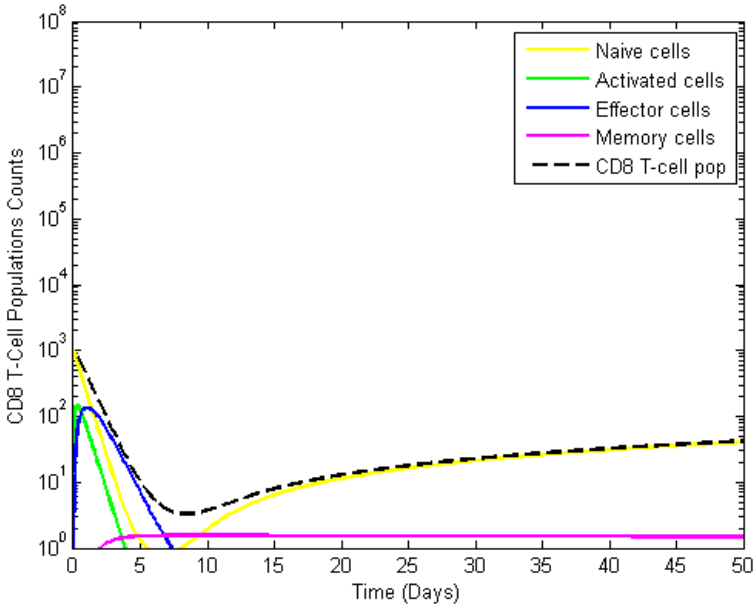
$$dAPC/dt = -\delta_D(A,E)APC$$

$N(0) = \pi/\delta_N$, $A(0)=E(0)=M(0)=0$, APC given

Production / Apoptosis / Differentiation / Self-renewal

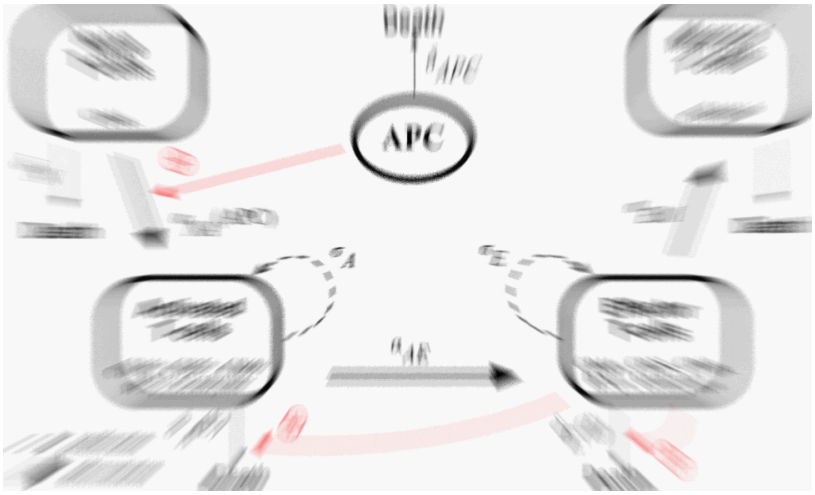
But is such a complex model really needed? Let's try a very simplified one.

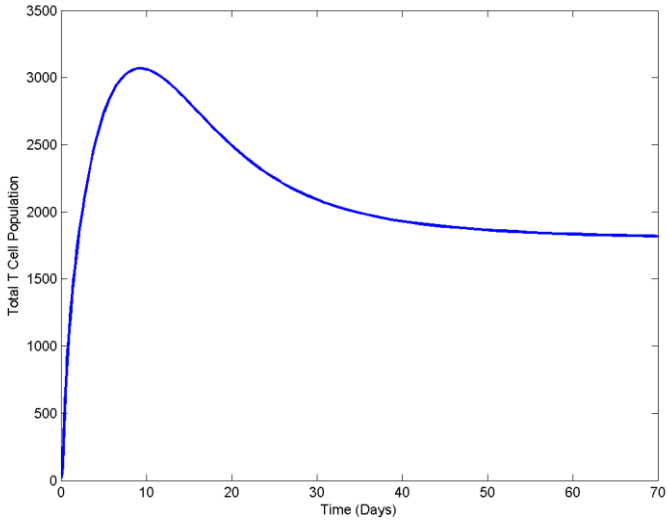




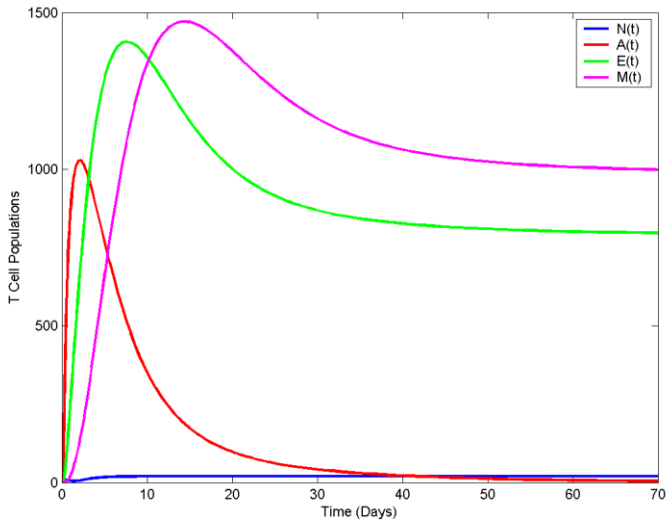
Oooops…

OK, if really needed, then let's complexify things a little bit!



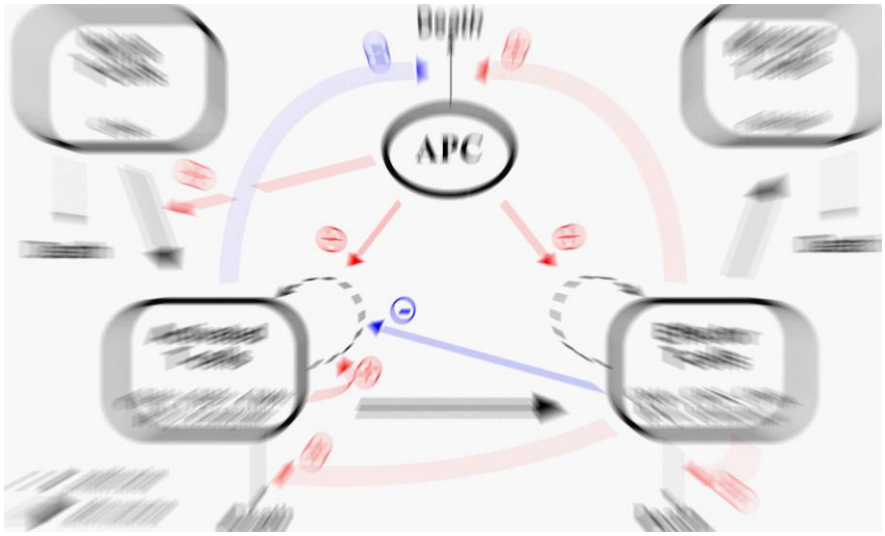


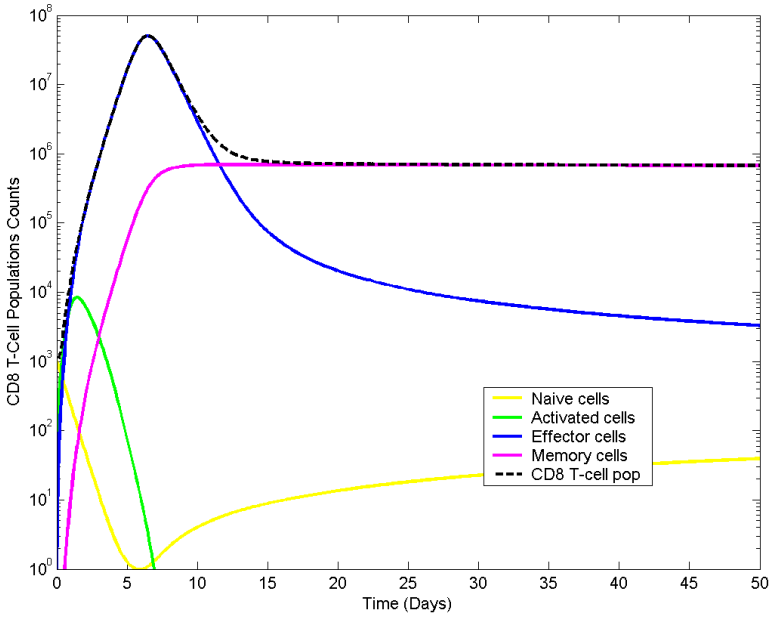
At the global scale, it is *much* better. The amplitude of the expansion phase can be easily controlled.



But, persistence of effector cells...

So, in the end, let's try the COMPLETE model!


APC

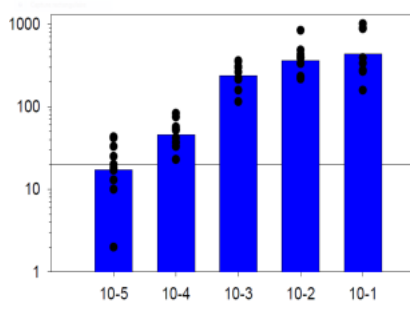

CD8 T-Cell Populations Counts
Time (Days)
Naive cells
Activated cells
Effector cells
Memory cells
CD8 T-cell pop

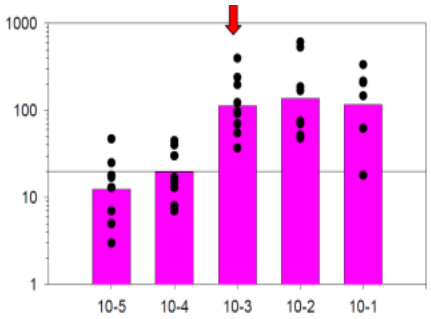
Perfect!
At that stage, what SHOULD be done:
Test some model prediction, for example regarding the dynamics of activated cells. This should help in determining the proper values of some parameters.

This is ongoing, but yet preliminary…

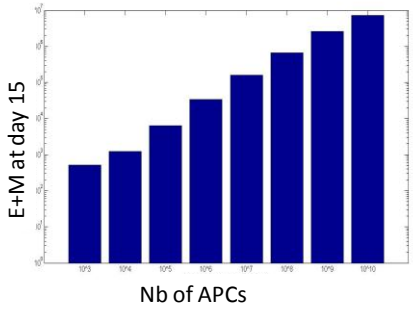
Instead, we USED our model to see what can be learned from the dynamics

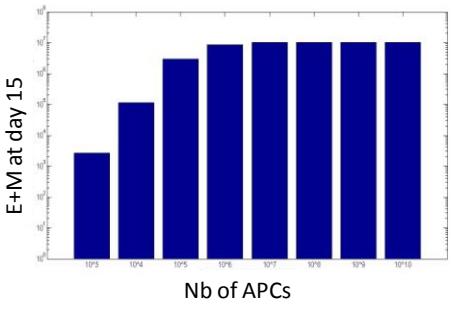
Two different antigens, same backbone, same doses, different type of responses…. Why?





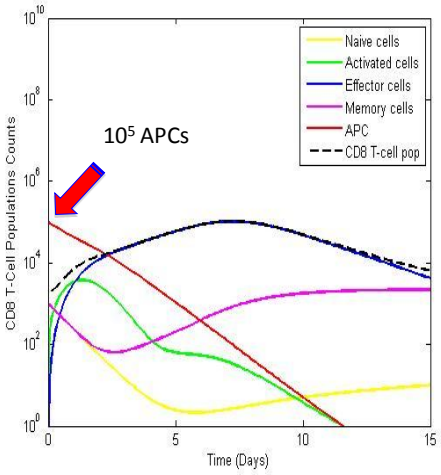
One can reproduce such a differential response using the model:

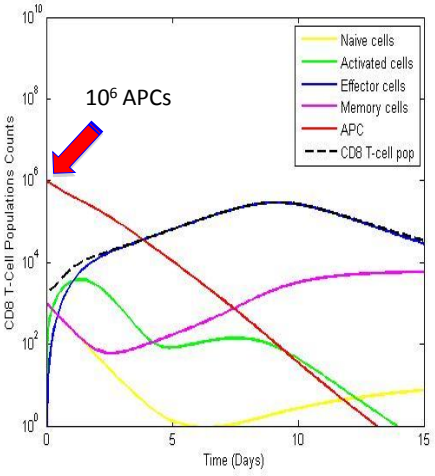




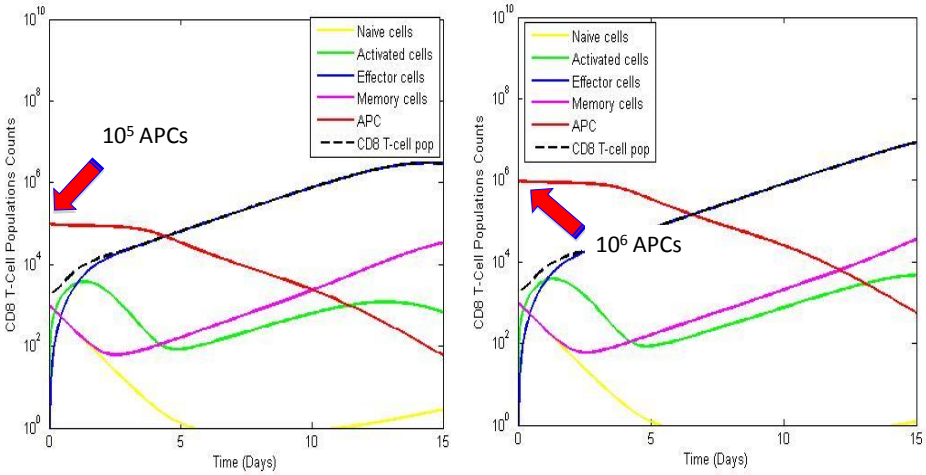
By modifying the half-life of the APCs

Dose escalade with short lived APCs

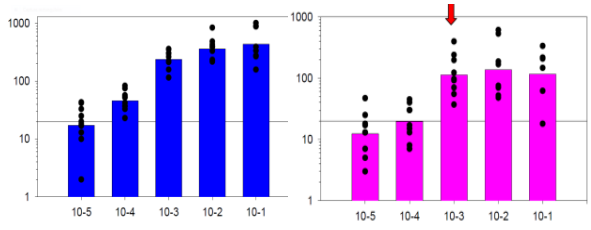




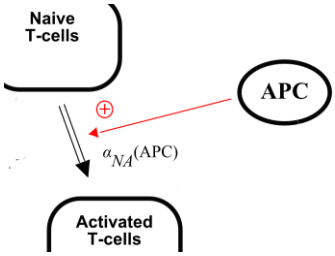
Dose escalade with long lived APCs



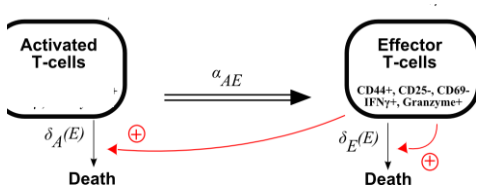
What the model says: no need for qualitative differences. Only quantitative differences can explain two different behaviour.
Our hypothesis: differences in the half-life of both antigens is responsible for the observed differences



Could be tested: measure the persistence of APC in both cases; or adapt the assessment time to the antigen.



The next step: let the value of the “macro”parameters emerge from the dynamics of the underlying molecular networks



To do:

1. Confront with real life data

2. Complexify the model (CD4, adjuvants, …)

Opened questions:

1. what is the best formalism for integrating all those scales?

2. What about stochasticity inherent to molecular reactions? Should that be integrated and if yes, how?

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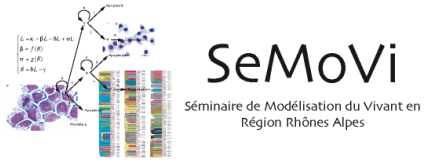

SeMoVi

Séminaire de Modélisation du Vivant en Région Rhônes Alpes

Stanislas Leibler

Fluctuations, information, and survival: some lessons from bacteria

Mercredi 27 Juin 2007 14h00 - 17h00.
Amphithéatre du CNRS
Délégation Régionale, Campus de la DOUA

Carole Knibbe (LIRIS): Evolvability, robustness and genome structure: where is the link?

Matthieu Piel (Institut Curie): From microfluidics to yeast mating: new modelling and experimental developments to understand gradient sensation in the context of a cell-cell communication process

Plus d'info sur:
http://www.cgmc.univ-lyon1.fr/Semovi/index.php

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