Université Paris Cité

LABORATOIRE MAP5

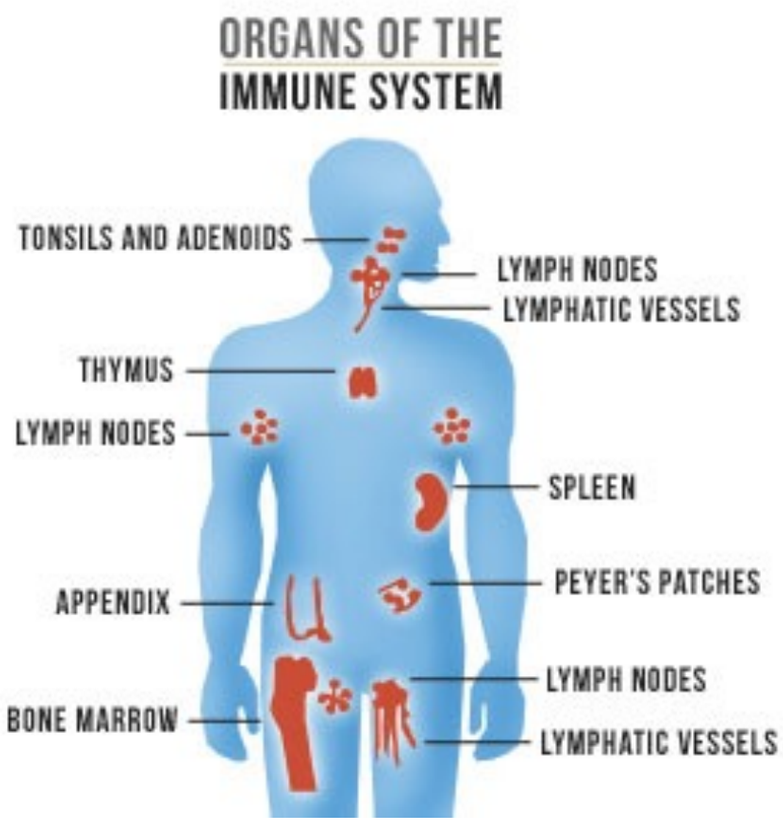
Mathematical and Computational Immunology

Differentiation, Heterogeneity, and Multiscale Descriptions of the CD8 T Cell Immune Response

Fabien CRAUSTE

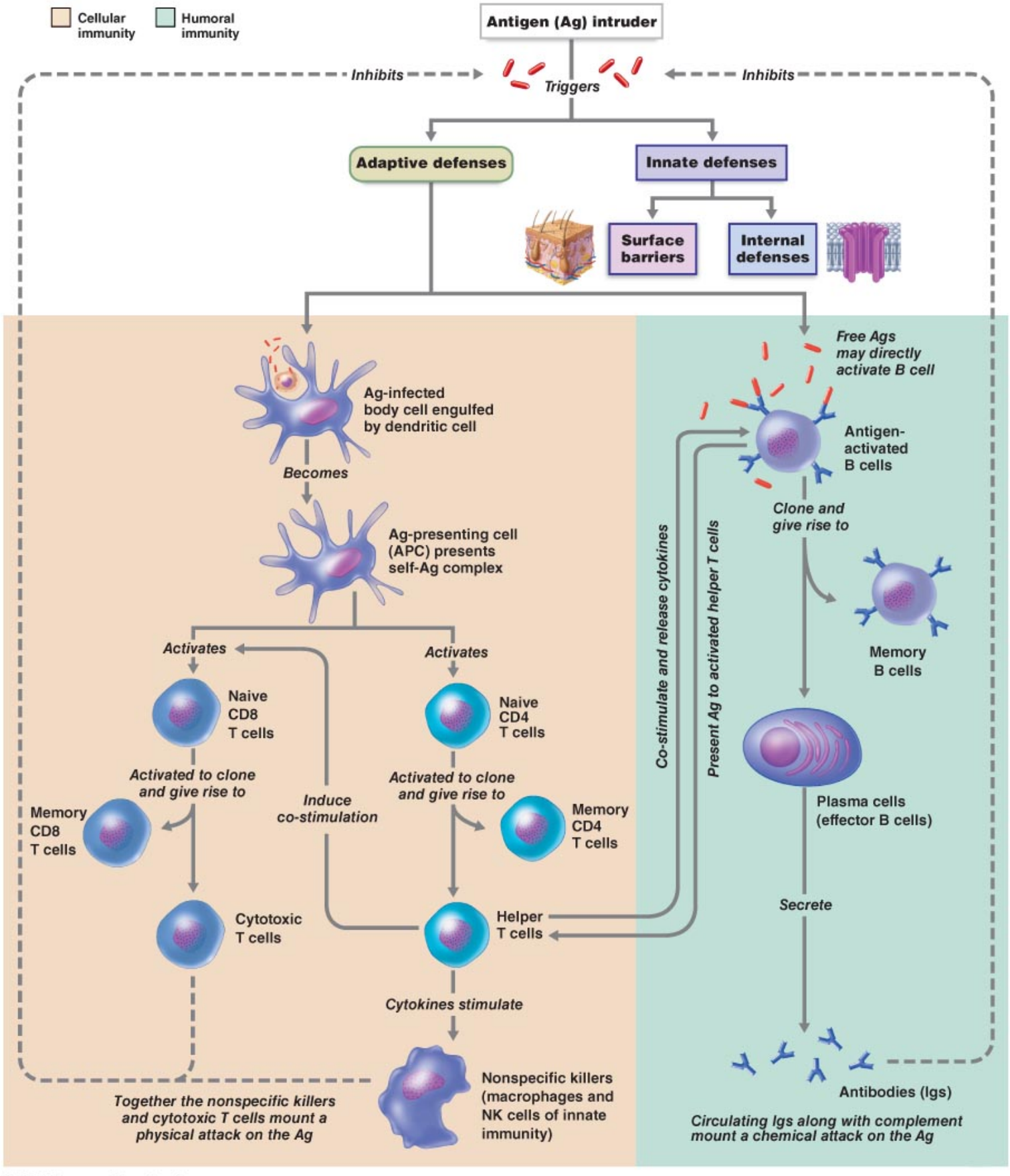
[*Chaire MMB - IPP - Apr 25th, 2022*]

What is an immune response?



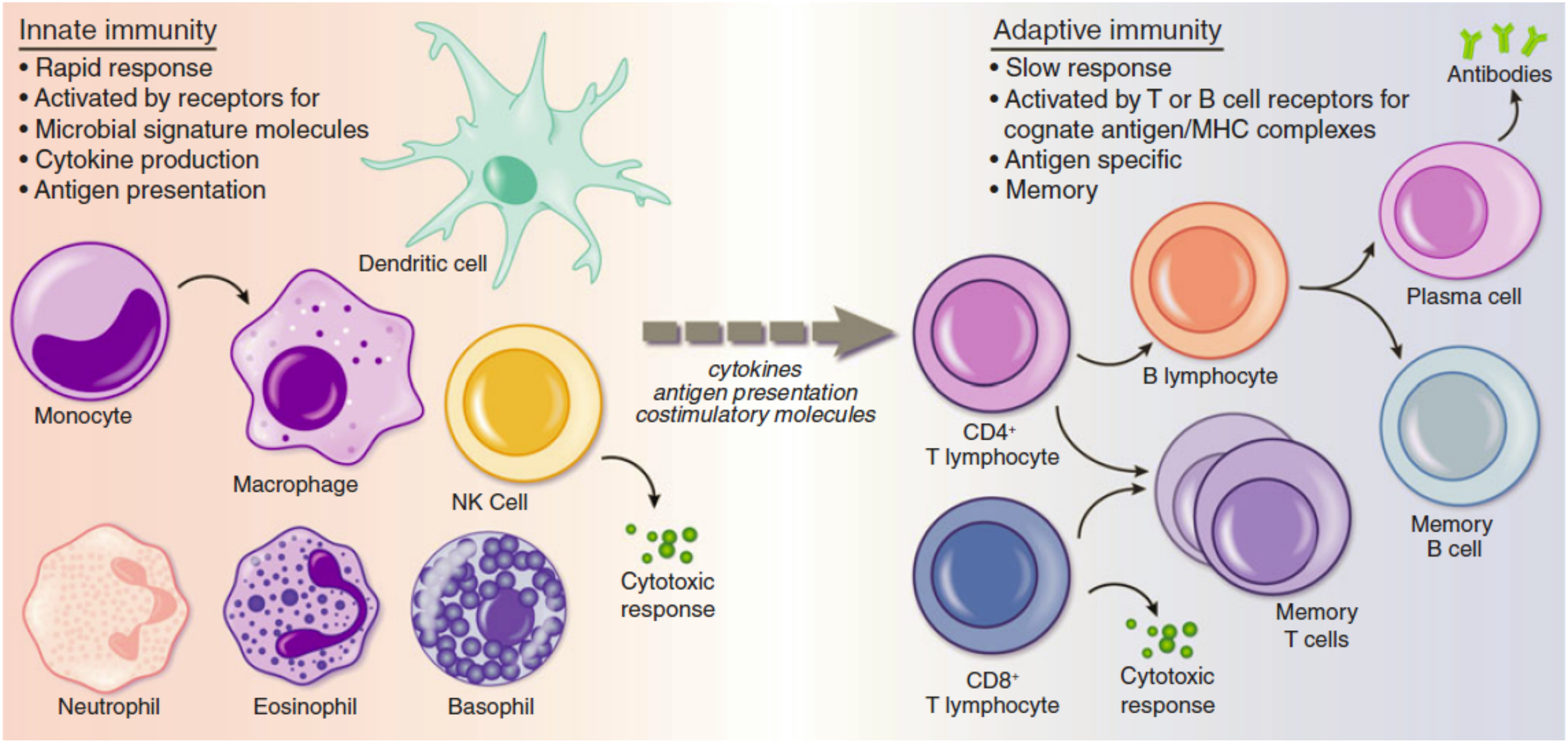
courtesy of aids.gov

It is a set of biological processes performed in order to protect an organism against diseases, by *identifying*, *kiling*, and *eliminating* pathogens.



Acquired/Specific Responses

Variety of cell types and differentiation stages

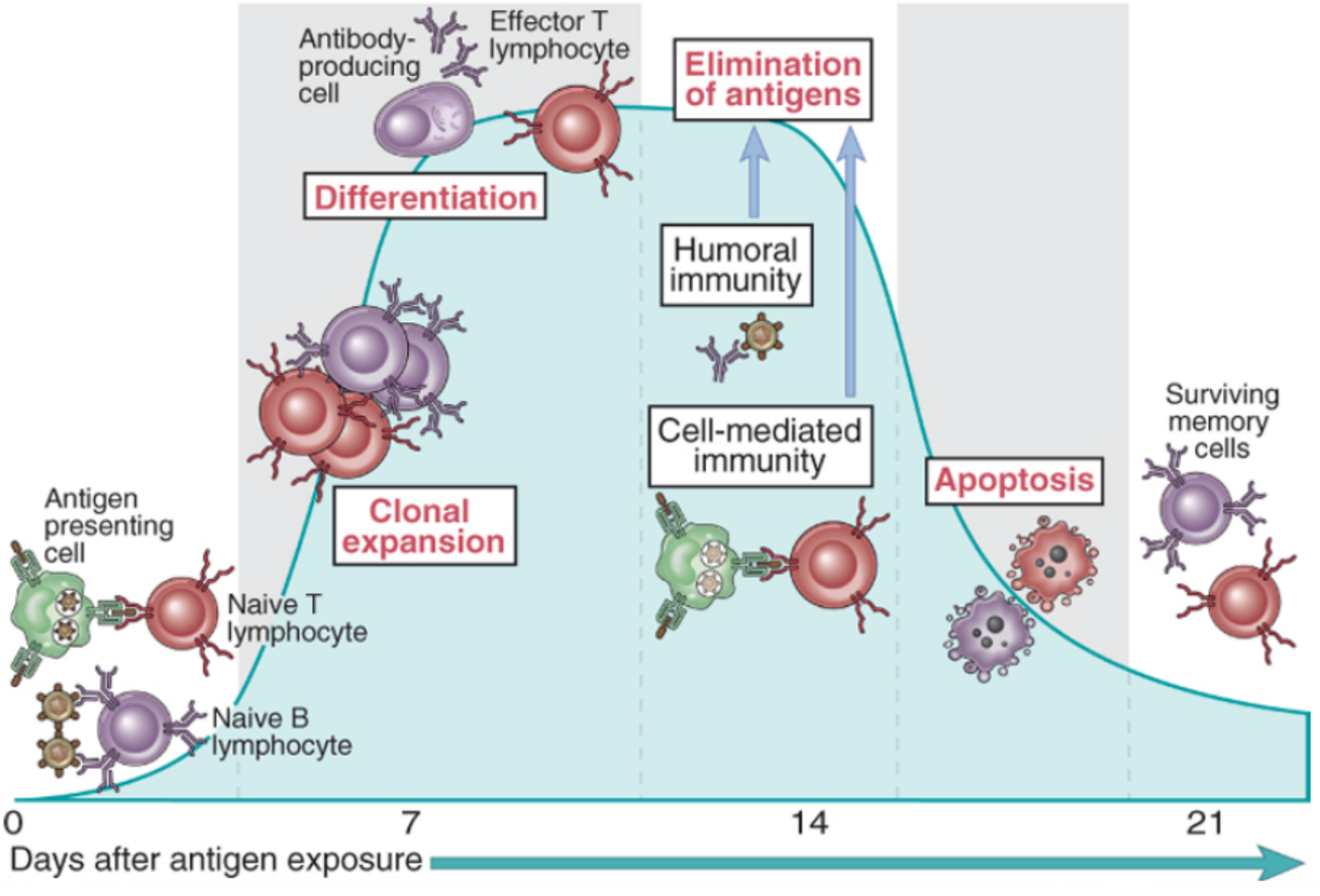


Beutler & Goodnow (2011)

Acquired/Specific Responses

Huge cellular expansion ($x10^3$)

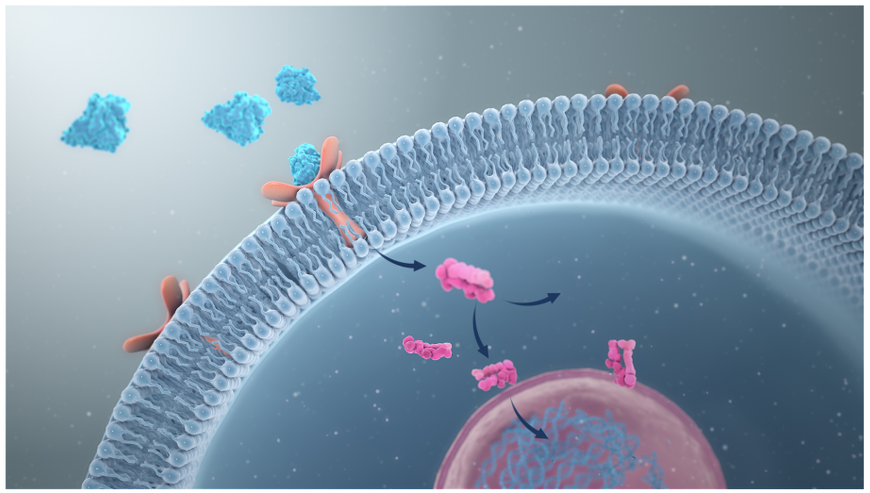
Huge cellular contraction



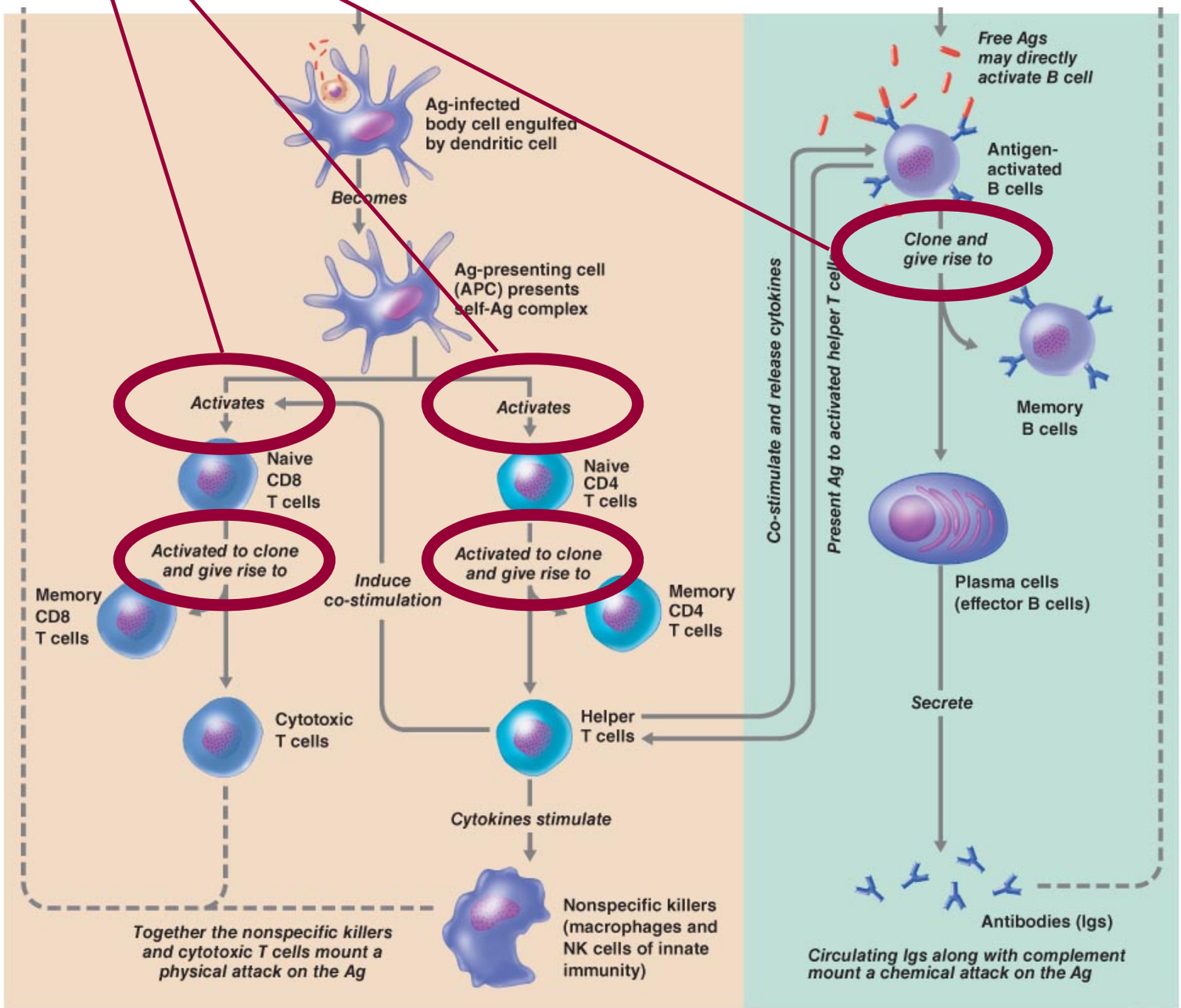
Abbas et al (2010) Cellular and Molecular Immunology, 6th Edition, Elsevier

Acquired/Specific Responses

This means: **integration of molecular signals**
(cell cell interactions, gene regulatory network…)



By www.scientificanimations.com - http://www.scientificanimations.com/wiki-images/, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=77499254

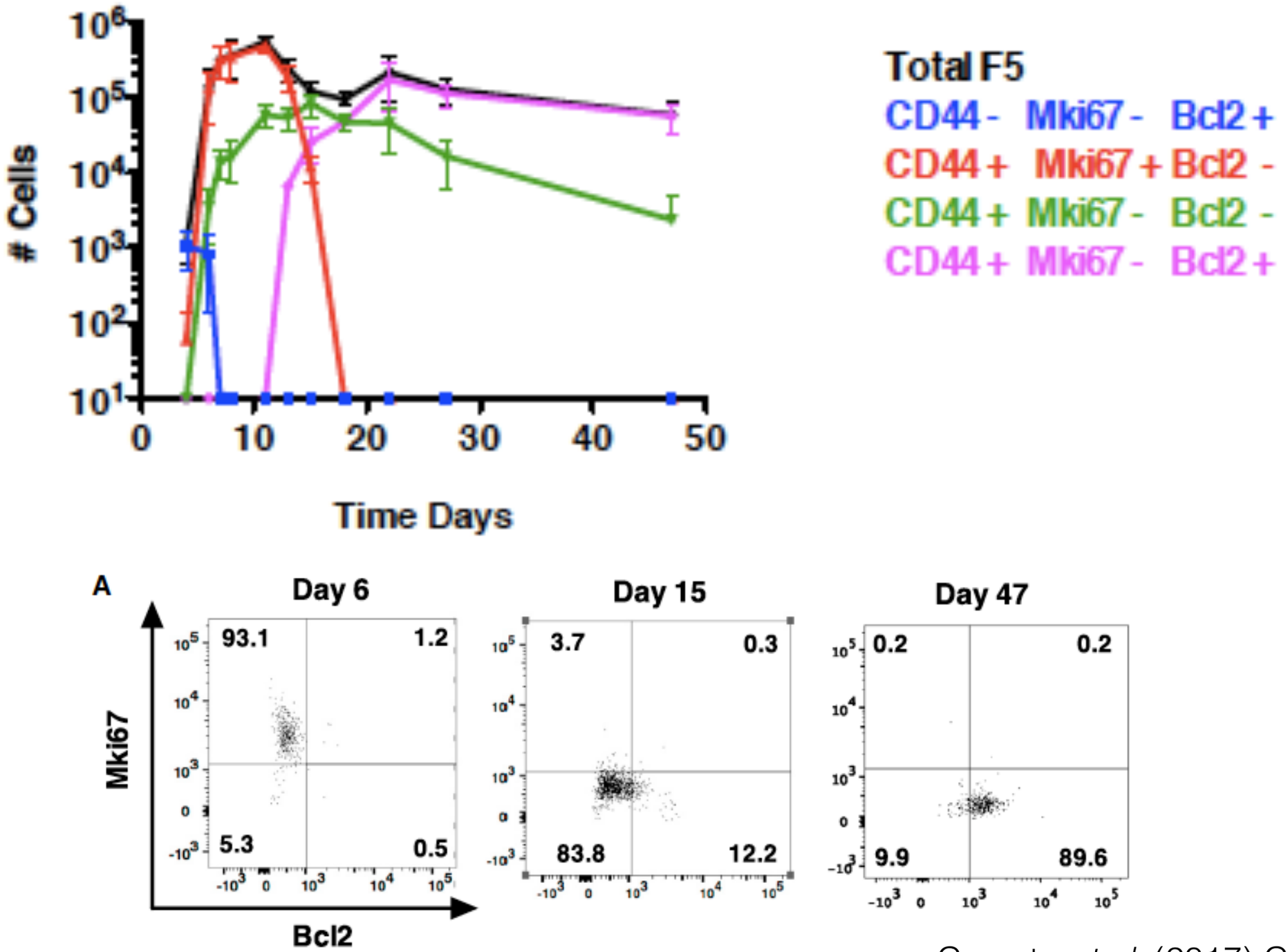


1/

CD8 T Cell Differentiation & Models

1/ CD8 T cell differentiation

Experimental data

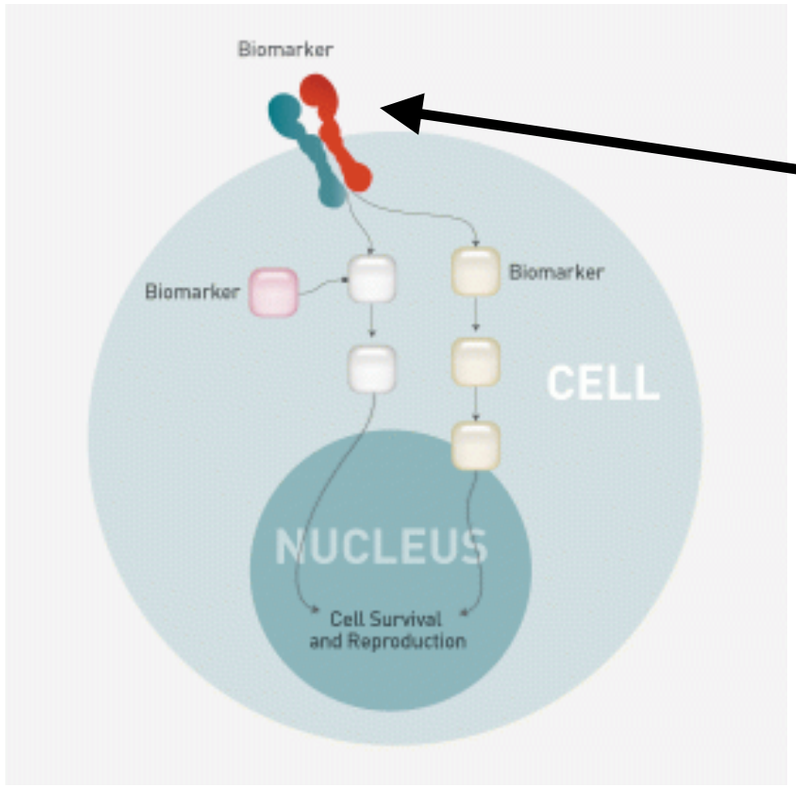


Crauste *et al.* (2017) Cell Systems

[digression…]

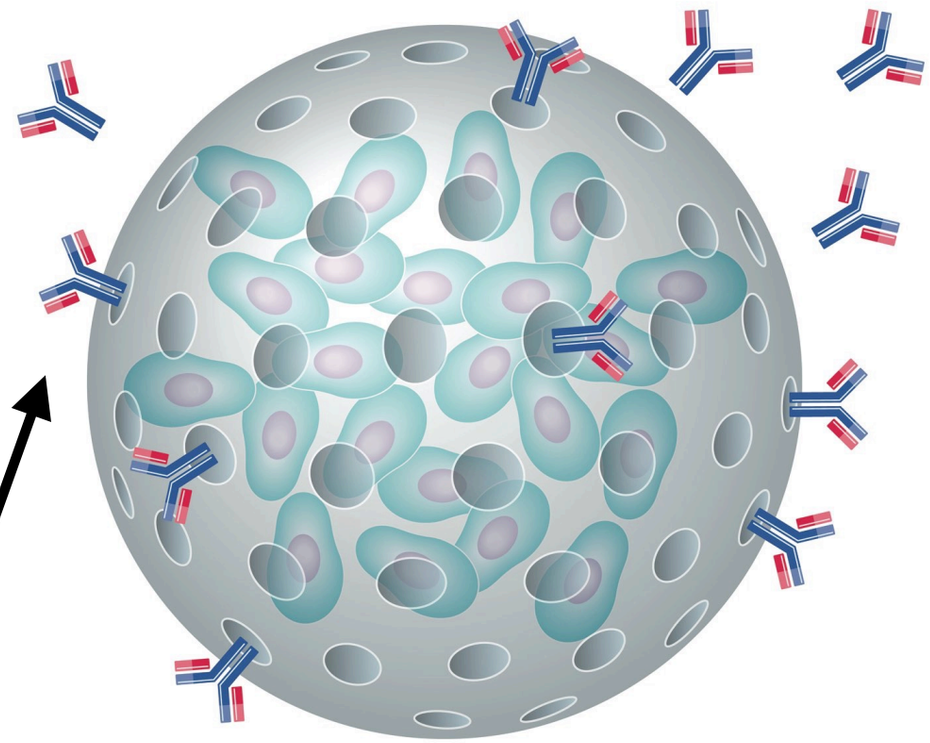
What is a ‘biomarker’?

It is a protein, or a combination of proteins, expressed at the surface of a cell (called ‘membrane proteins’) that can be identified by dedicated antibodies and contribute to defining a cell state, function, or identity



biomarker

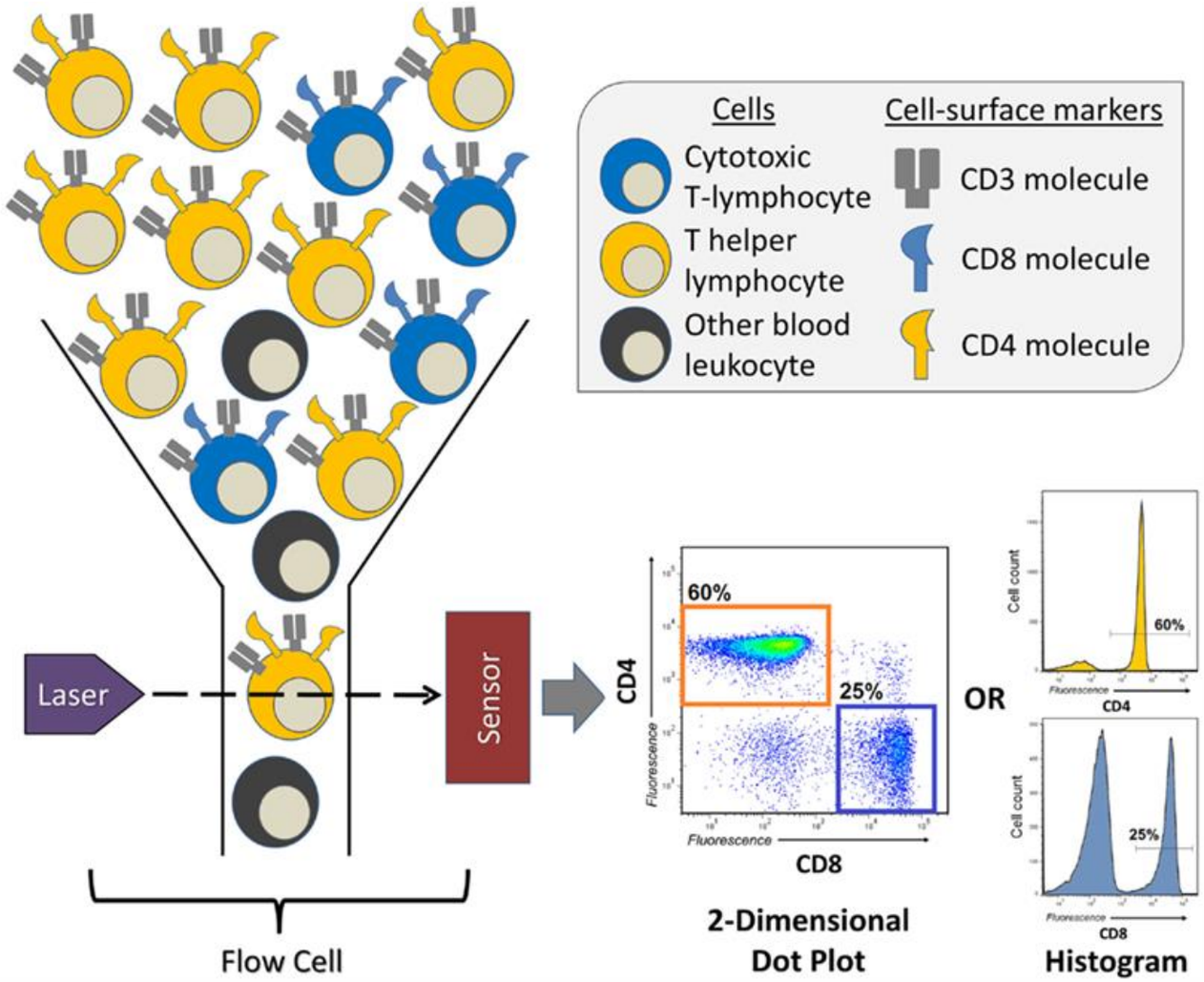
Antibody



[digression…]

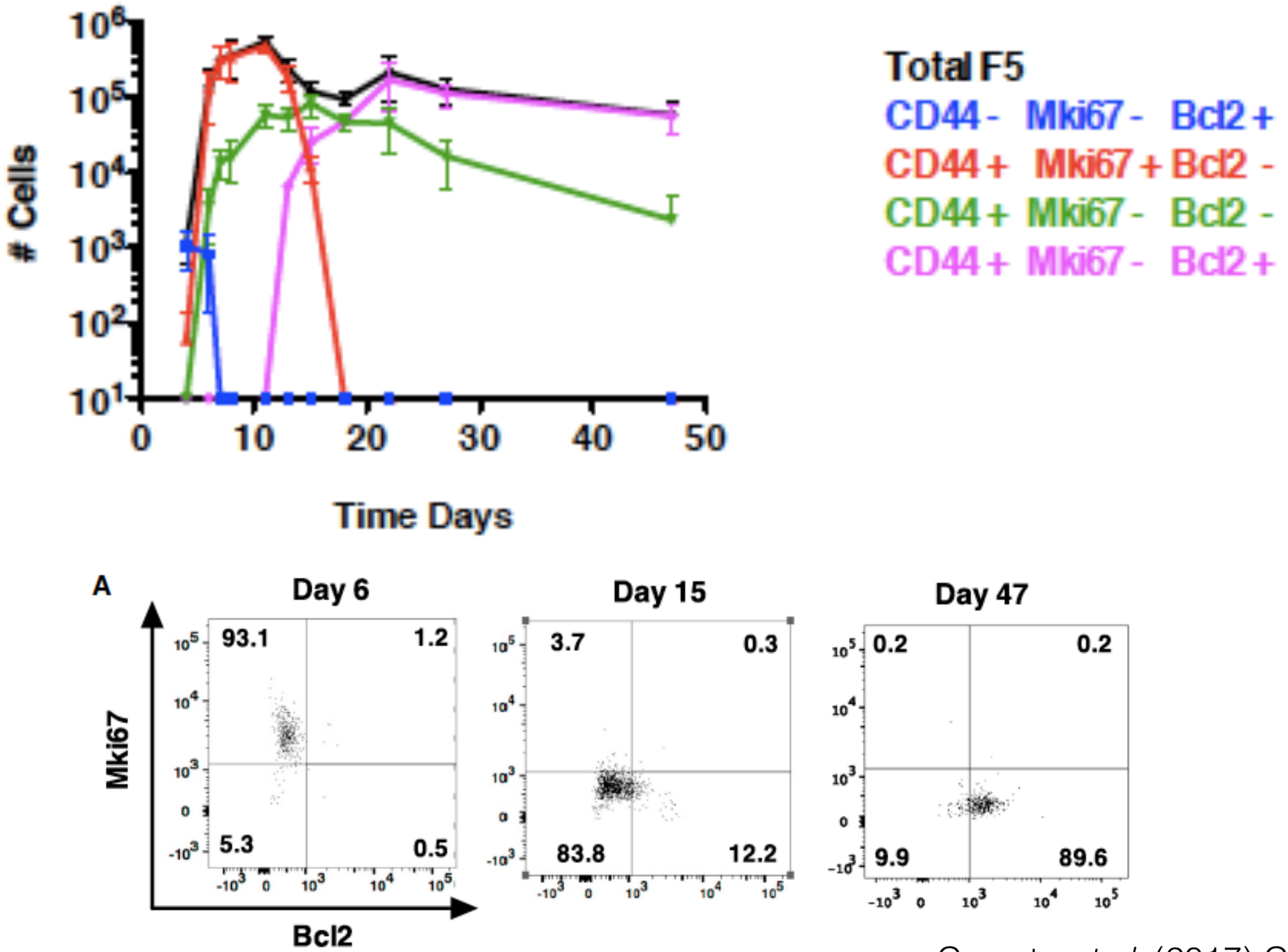
What is ‘flow cytometry’?

It is a technique that measures the expression of fluorescent biomarkers on the surface of single cells, and results in distributions of fluorescent levels of expression



1/ CD8 T cell differentiation

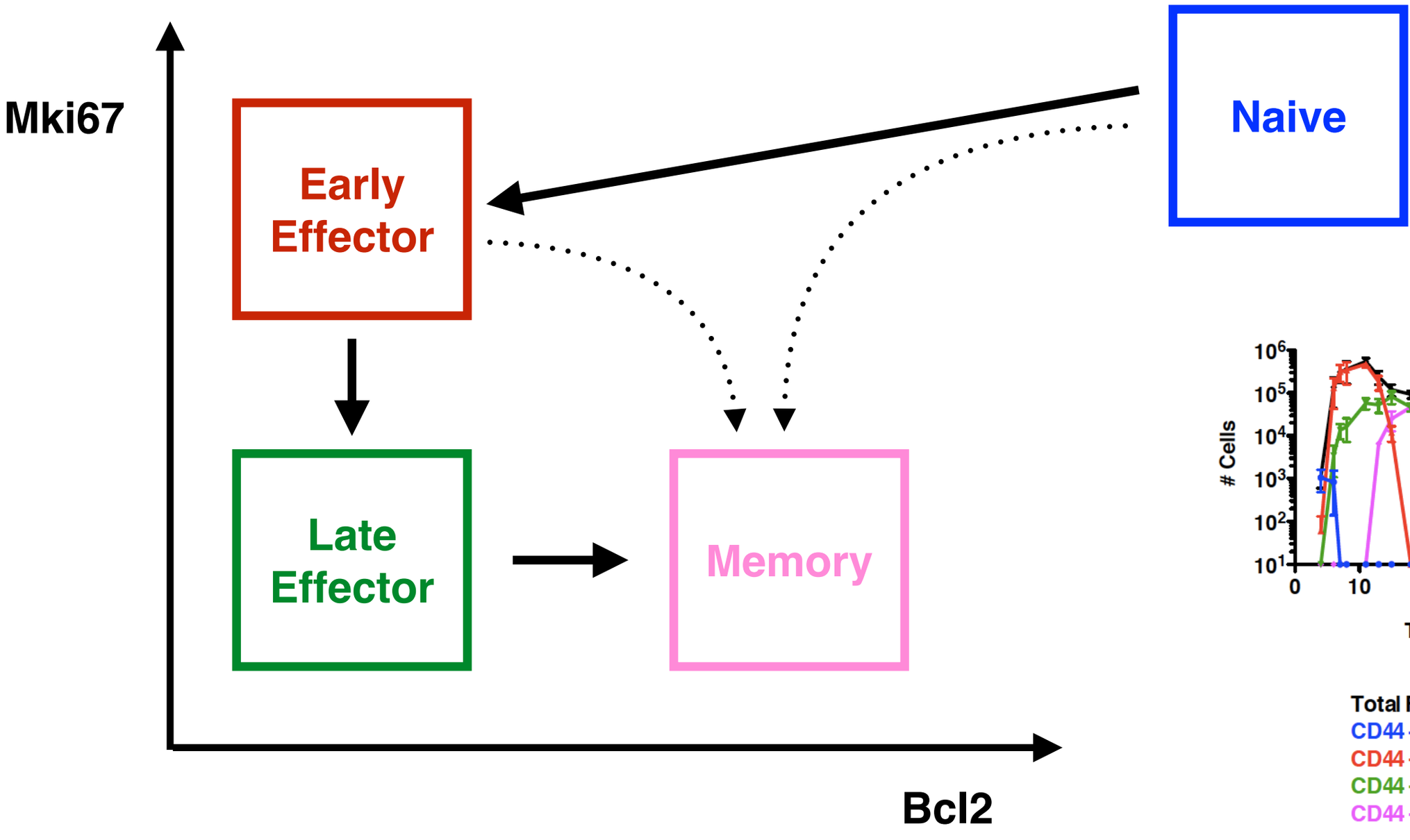
Experimental data

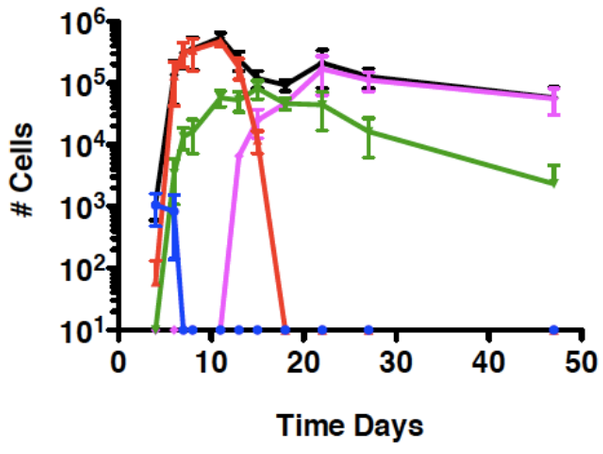


Crauste *et al.* (2017) Cell Systems

1/ CD8 T cell differentiation - Mathematical modeling

Selection of a mathematical model

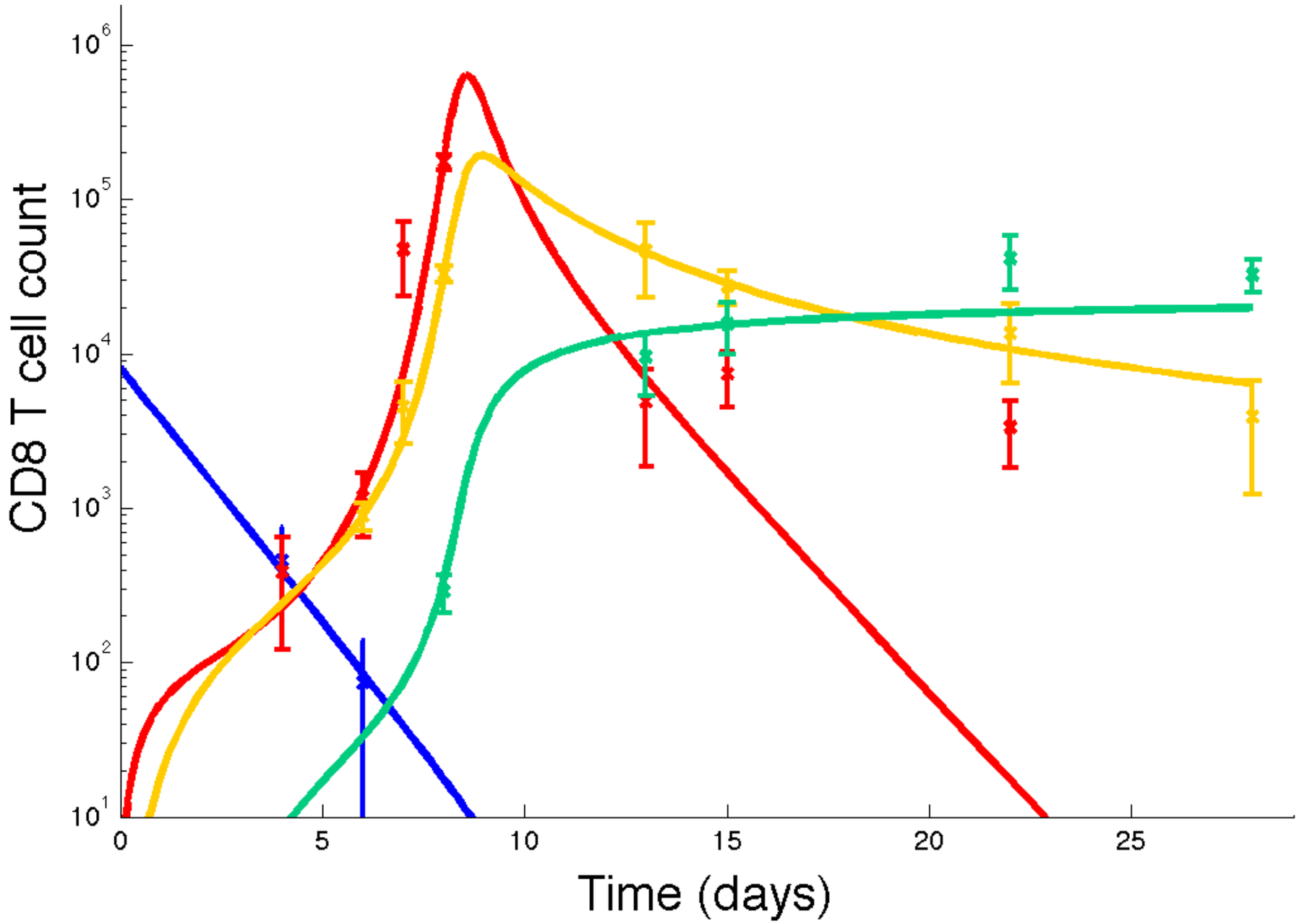




Crauste *et al.* (2017) Cell Systems

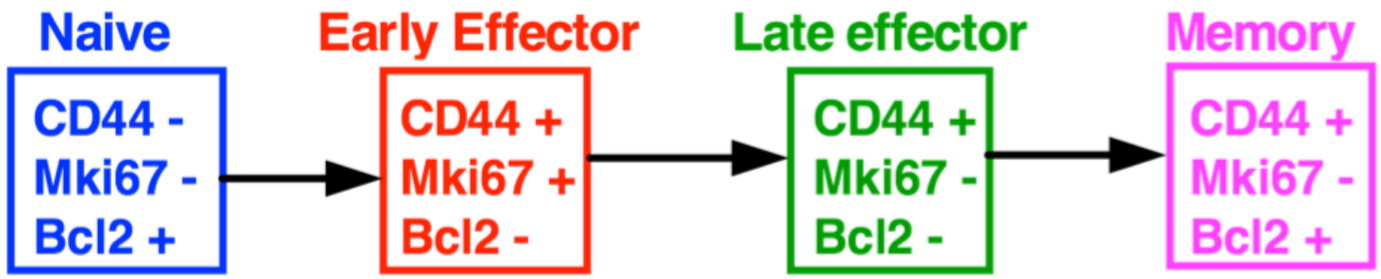
1/ CD8 T cell differentiation - Mathematical modeling

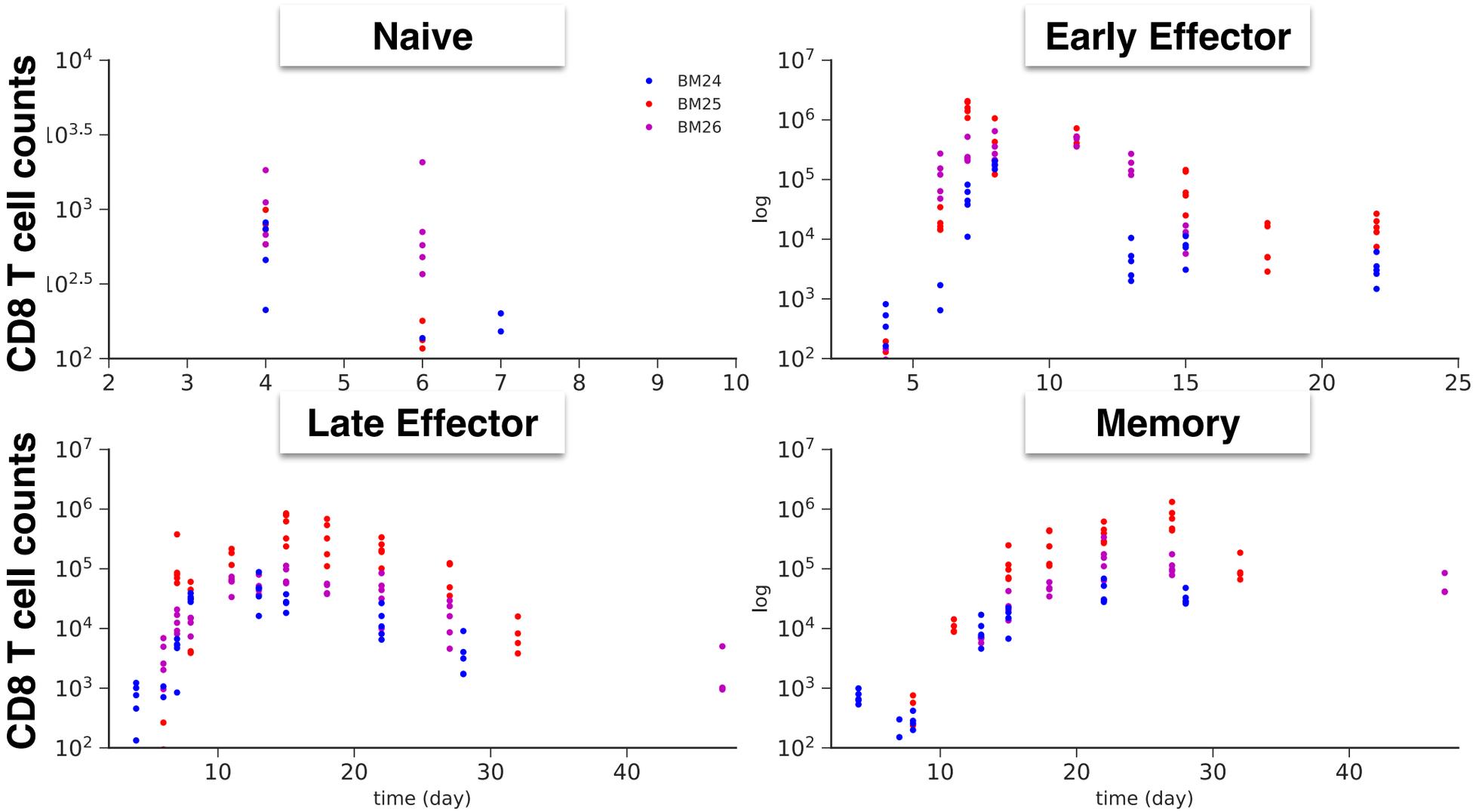
The selected model allows to describe the dynamics of an "average" individual…



Crauste *et al.* (2017) Cell Systems

1/ CD8 T cell differentiation… and variability

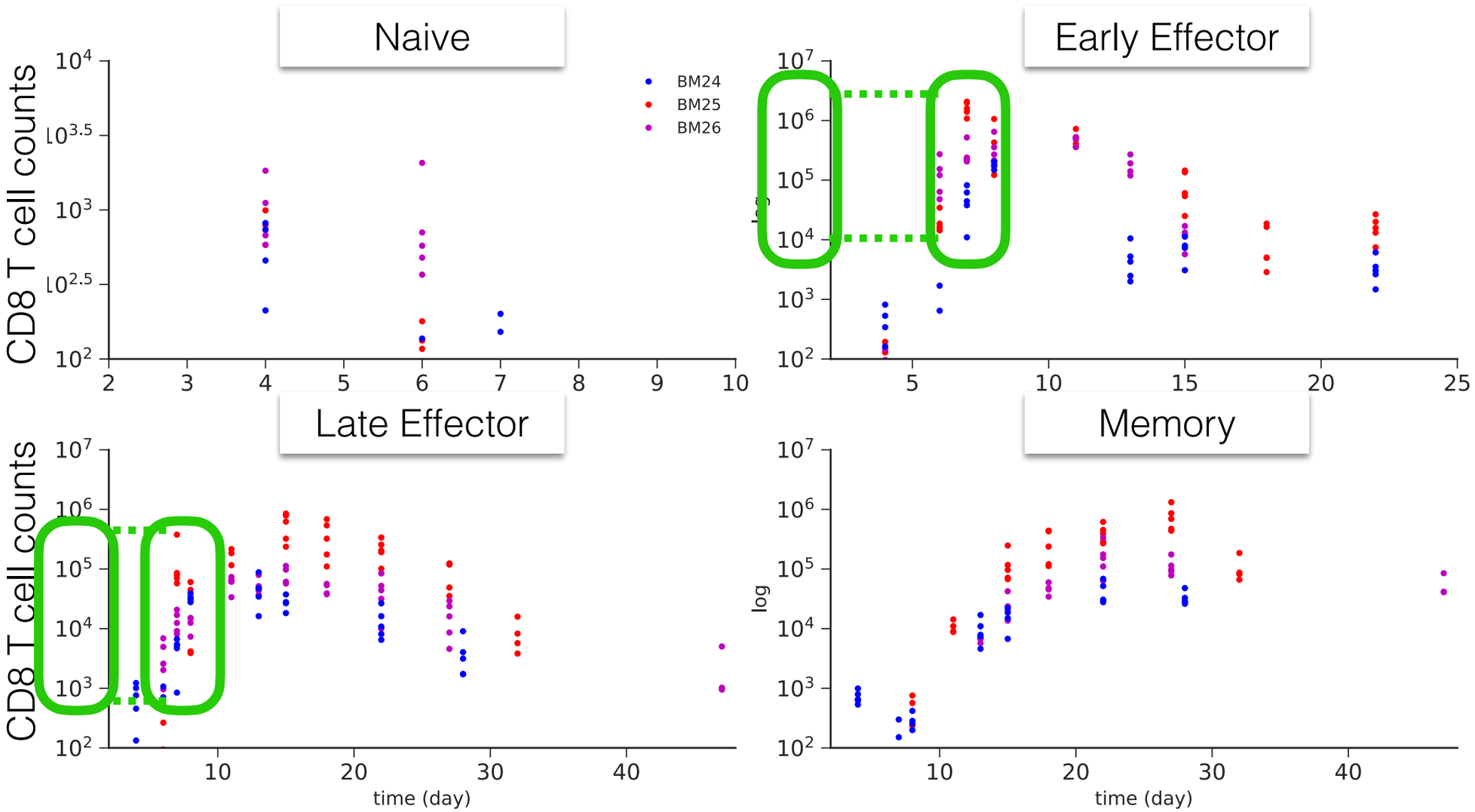




Audebert *et al.* (2021) In Silico Biology

1/ CD8 T cell differentiation… and variability

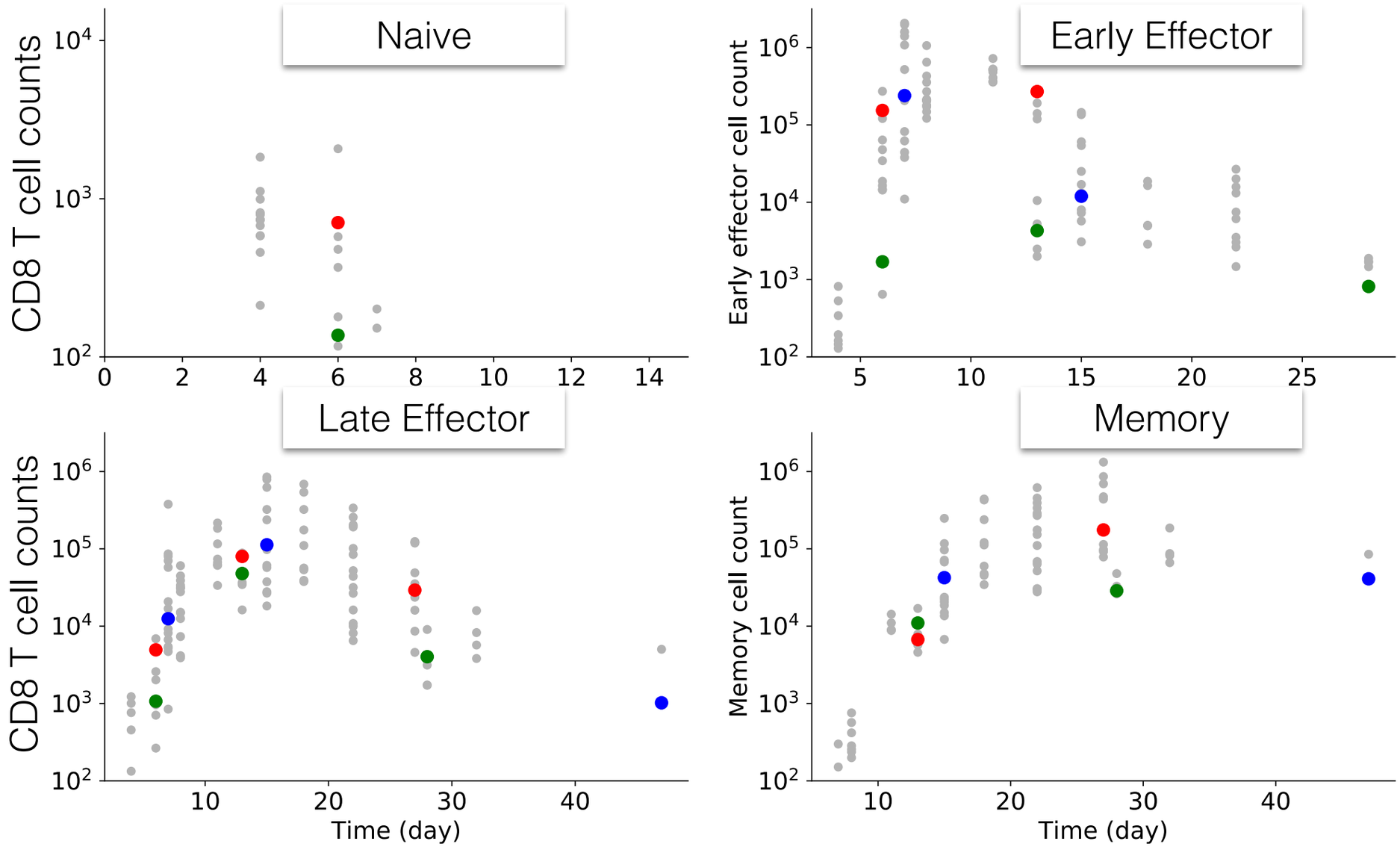
Large variations in the amount of cells between individuals



Audebert *et al.* (2021) In Silico Biology

1/ CD8 T cell differentiation… and variability

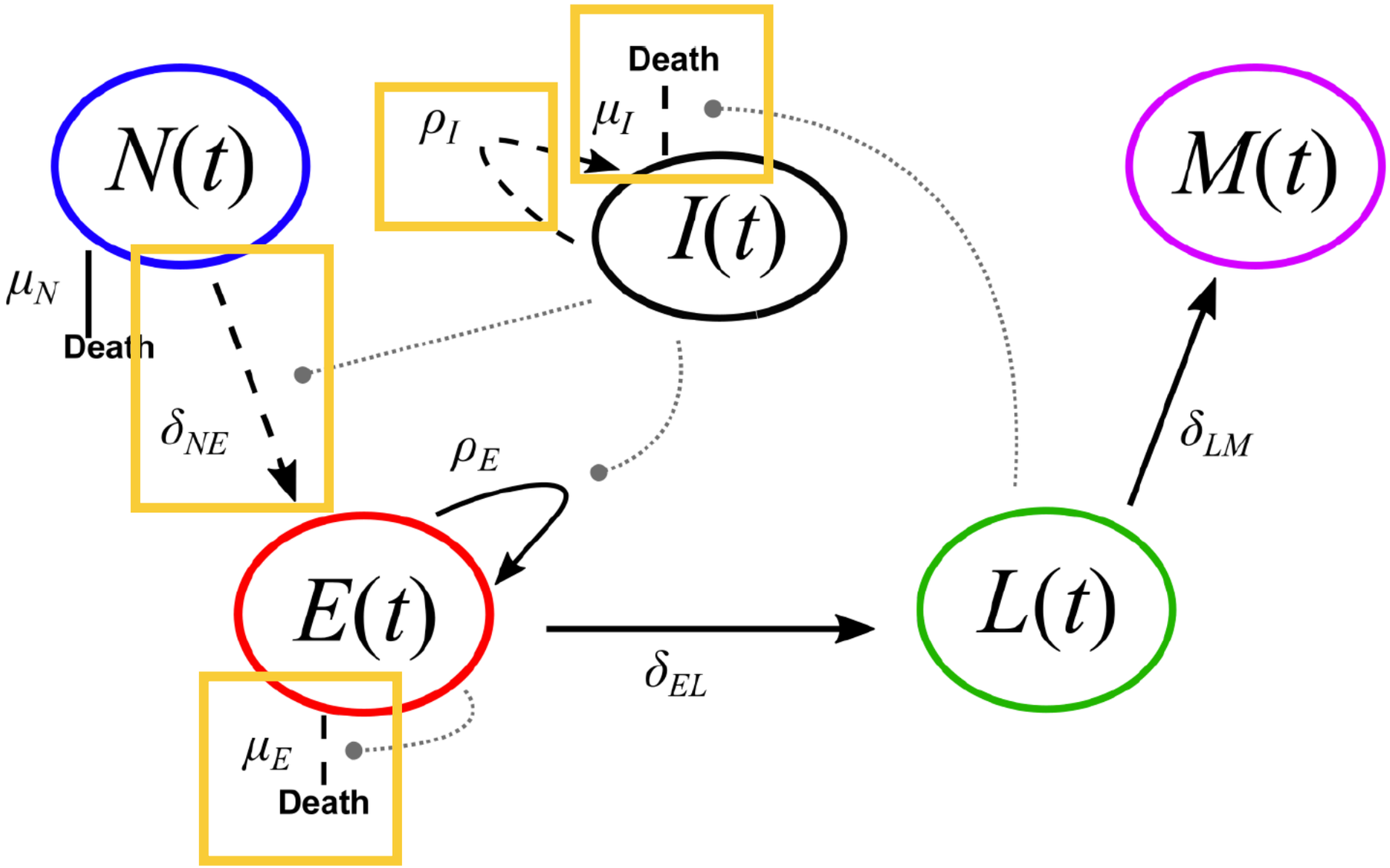
Only few measurements per individual



Audebert *et al.* (2021) In Silico Biology

1/ CD8 T cell differentiation… and variability

Identification of the sources of heterogeneity using nonlinear mixed-effect modeling



Parameters *varying* within the population: δ_{NE}, μ_E, μ_I, ρ_I

Audebert *et al.* (2021) In Silico Biology

1/ CD8 T cell differentiation & models

Summary:

- CD8 T cell differentiation is mostly a linear differentiation process

- Nonlinear models qualitatively & quantitatively account for cell population dynamics

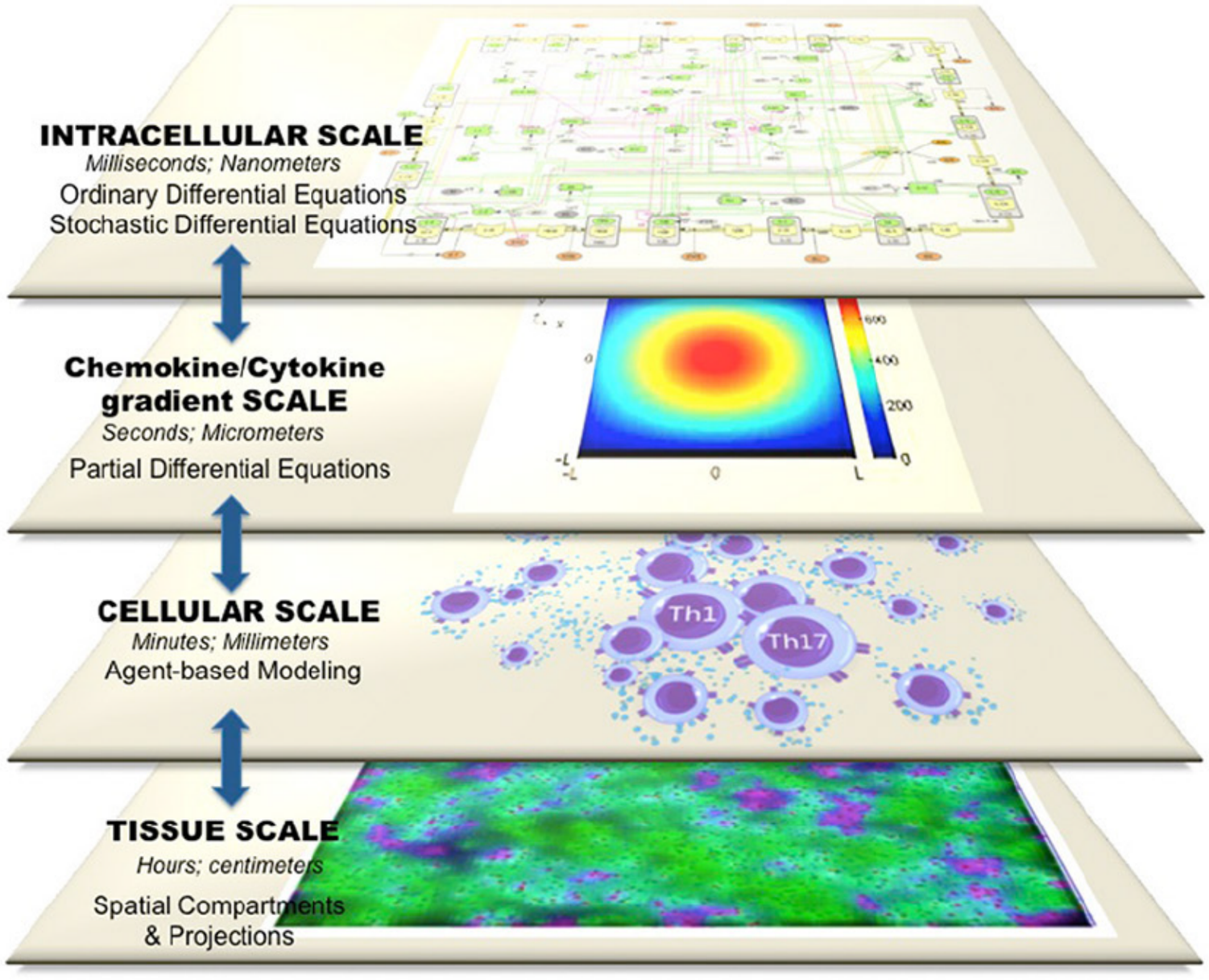
- Various sources of stochasticity (activation, cell death, immunization process) induce inter-individual variability

- All processes are driven by molecular dynamics, which are inherently stochastic

2/

Multiscale models of the CD8 T cell response

2/ Multiscale models of the CD8 T cell response

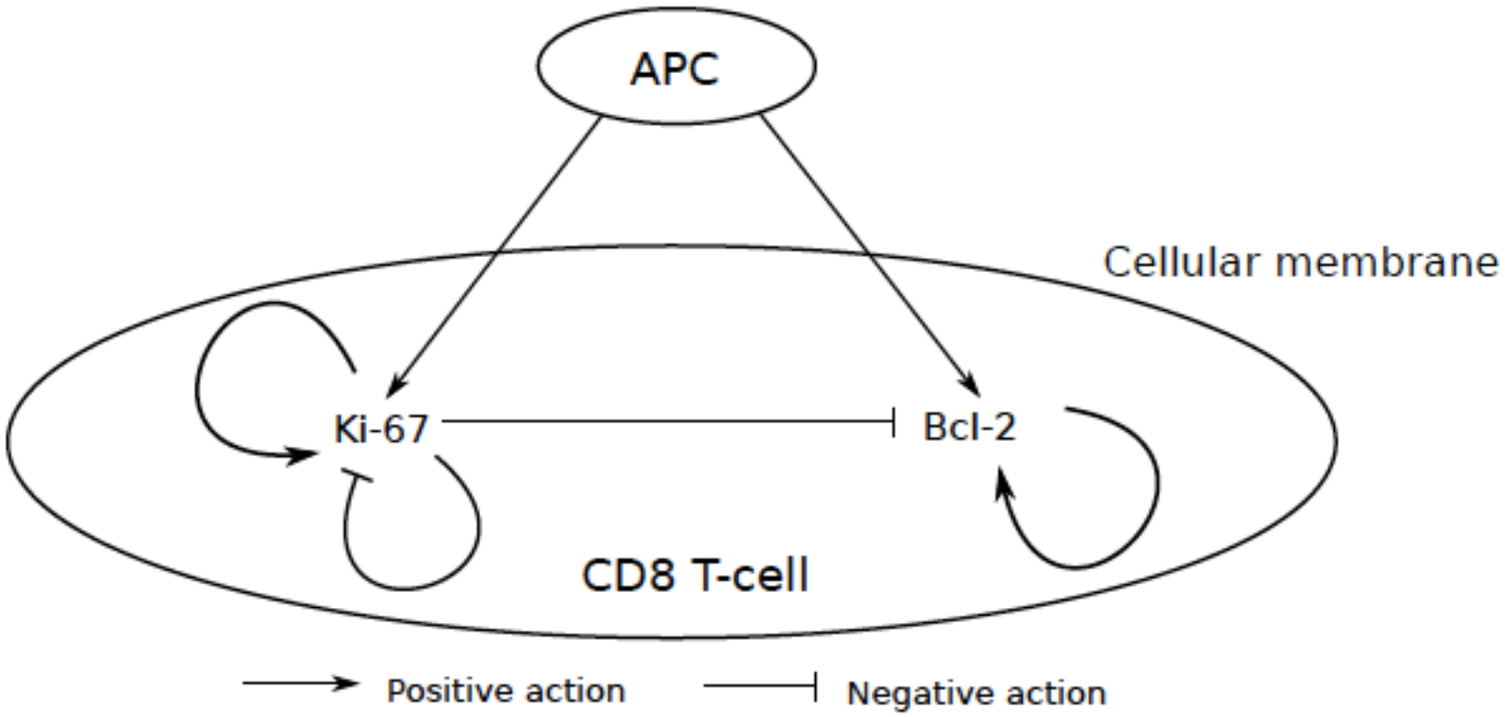


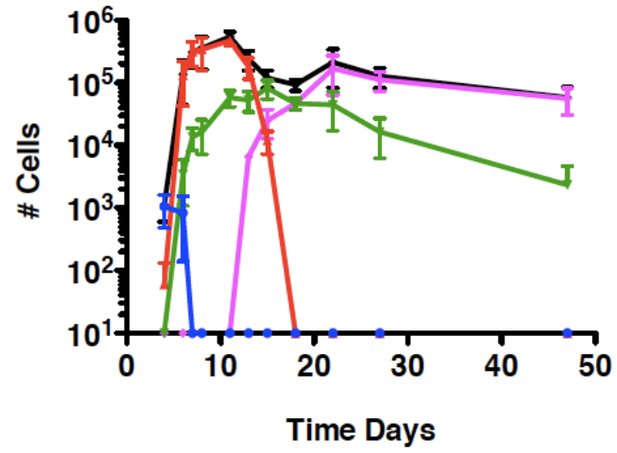
Carbo *et al* (2014) Frontiers in Cell and Developmental Biology

2.1/

Multiscale models of the CD8 T cell response
A mathematical approach

2.1/ Multiscale models: Intracellular molecular scale





$$\begin{cases} \dfrac{d\mu_1}{dt}(t) = \left(\dfrac{\gamma_{P1} P(t)}{\theta_{P1} + P(t)} + \dfrac{\gamma_{r1} \mu_1(t)}{\theta_{r1} + \mu_1(t)} - k_1 - \dfrac{\gamma_{l1} \mu_1^2(t-\tau)}{\theta_{l1}^2 + \mu_1^2(t-\tau)} \right) \mu_1(t), \\ \dfrac{d\mu_2}{dt}(t) = \left(\dfrac{\gamma_{P2} P(t)}{\theta_{P2} + P(t)} + r_2(K_2 - \mu_2(t)) - k_{12}\mu_1(t) - k_2 \right) \mu_2(t), \end{cases}$$

Barbarroux *et al* (2018) DCDS-B

2.1/ Multiscale models: Cell population scale

Density of CD8 T cells: $$\rho(t,\mu_1,\mu_2)=\sum_{k=1}^{q}\sum_{i,j=1}^{n}\omega^{i,j,k}(t)\delta_{X^{i,j,k}(t)}(\mu_1,\mu_2),\ t,\mu_1,\mu_2>0,$$

$$\begin{cases}\dfrac{d}{dt}\omega^{i,j,k}(t)=F(\mu_1,\mu_2,P(t),E(t))\omega^{i,j,k}(t), & t>t_k,\\ \omega^{i,j,k}(t)=0, & t\in[0,t_k),\\ \omega^{i,j,k}(t_k)=\alpha^{i,j}\dfrac{\gamma_N P(t_k)}{\theta_N+P(t_k)}N(t_k)\Delta t,\end{cases}$$

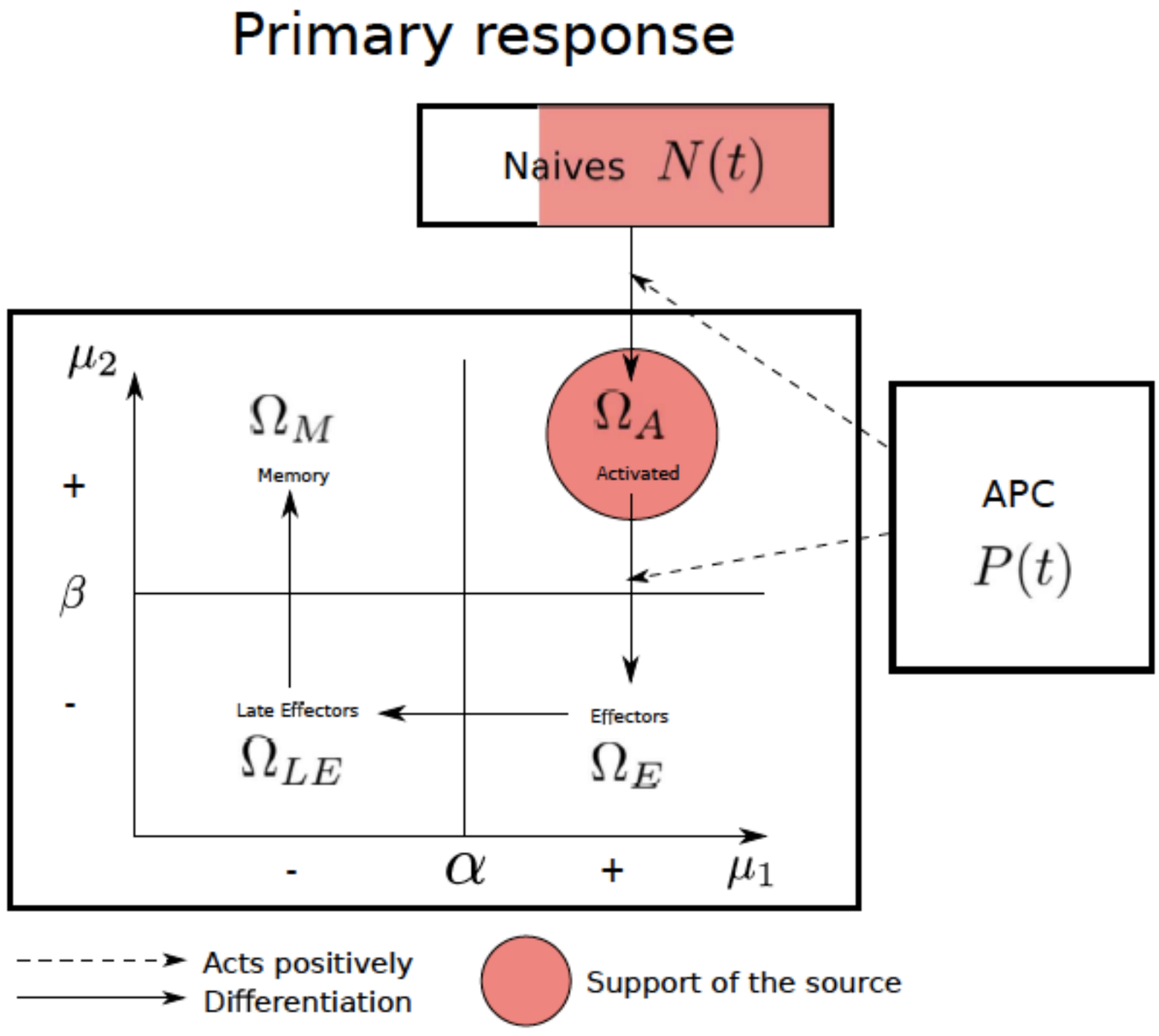
$$X^{i,j,k}(t)=\left(\mu_1^{i,j,k}(t),\mu_2^{i,j,k}(t)\right)$$

$$\begin{cases}\dfrac{d\mu_1^{i,j,k}}{dt}(t)=v_1(P(t),\mu_1^{i,j,k}(t),\mu_1^{i,j,k}(t-\tau)), & t>t_k,\\ \dfrac{d\mu_2^{i,j,k}}{dt}(t)=v_2(P(t),\mu_1^{i,j,k}(t),\mu_2^{i,j,k}(t)), & t>t_k,\\ \mu_1^{i,j,k}(t)=x_0^{i,j}, & t\in[-\tau,t_k],\\ \mu_2^{i,j,k}(t)=y_0^{i,j}, & t\in[0,t_k].\end{cases}$$

$$\begin{cases}\dfrac{dN}{dt}(t)=-\dfrac{\gamma_N P(t)}{\theta_N+P(t)}N(t),\\ \dfrac{dP}{dt}(t)=-k_P P(t)-\dfrac{\gamma_E E(t)}{\theta_E+E(t)}P(t),\end{cases}$$

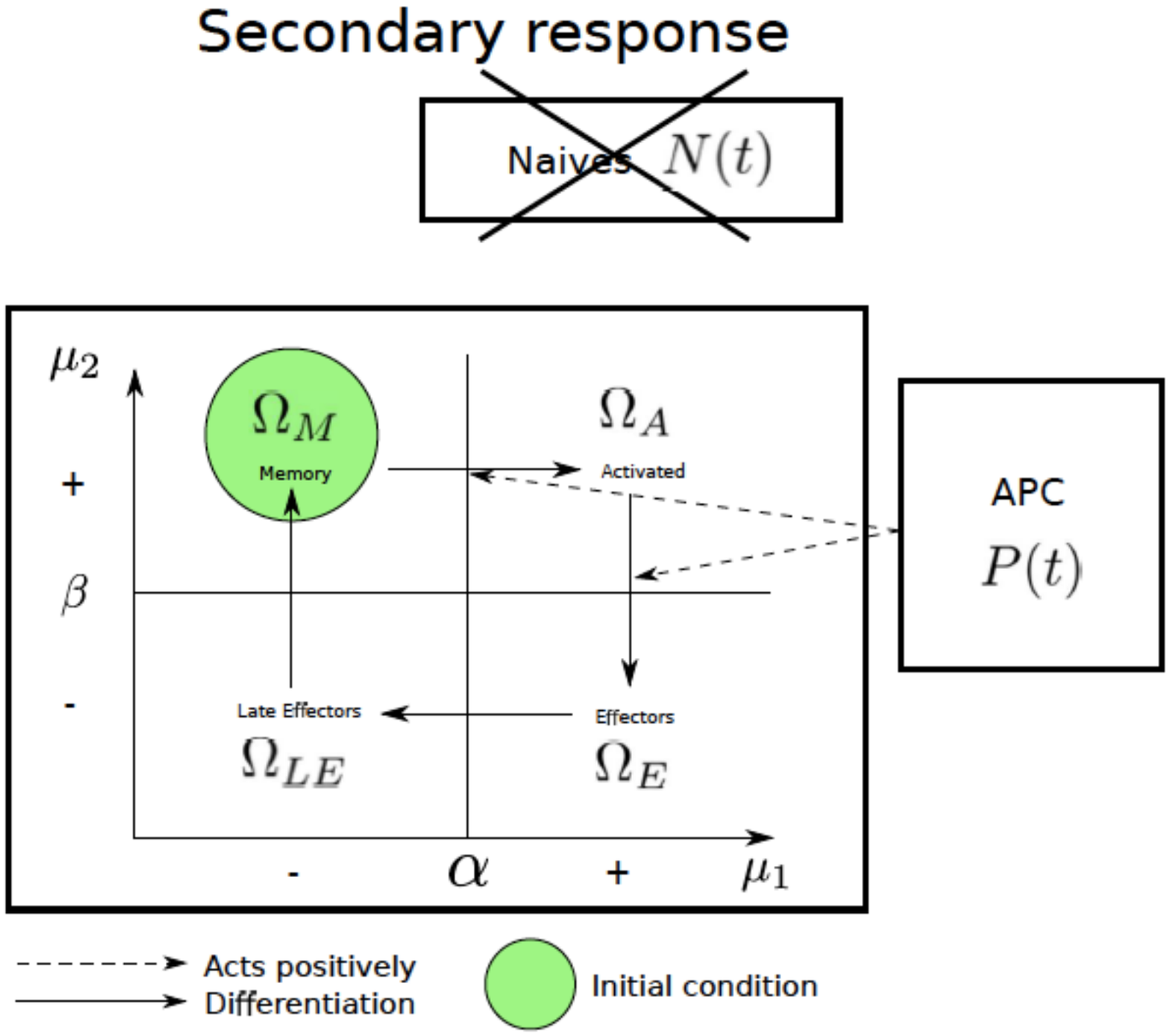
Barbarroux *et al* (2018) DCDS-B

2.1/ Multiscale models: Cell population scale



Barbarroux *et al* (2018) DCDS-B

2.1/ Multiscale models: Cell population scale



Barbarroux *et al* (2018) DCDS-B

2.1/ Multiscale models: Results - Stability

- **Existence and uniqueness of solutions**

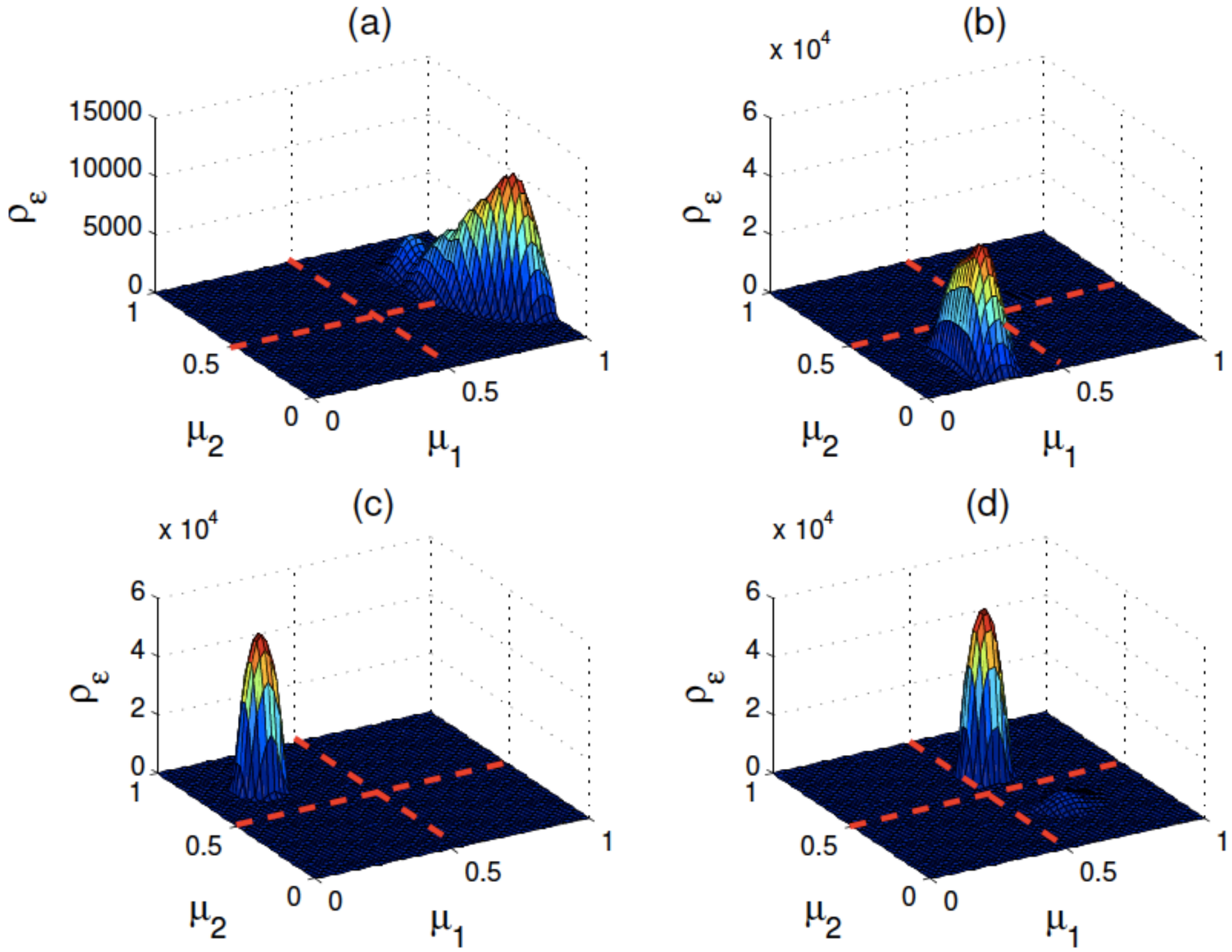
- **Existence of steady states (up to 3)**

- **Asymptotic stability:**
  Cell population density converges towards Dirac masses located at the steady states of the intracellular model [*Friedman et al (2009, 2012)*]

- **When the system has 3 steady states**:
  2 unstable steady states and **a stable/unstable steady state**, with existence of a **local Hopf bifurcation** (delay dependent)

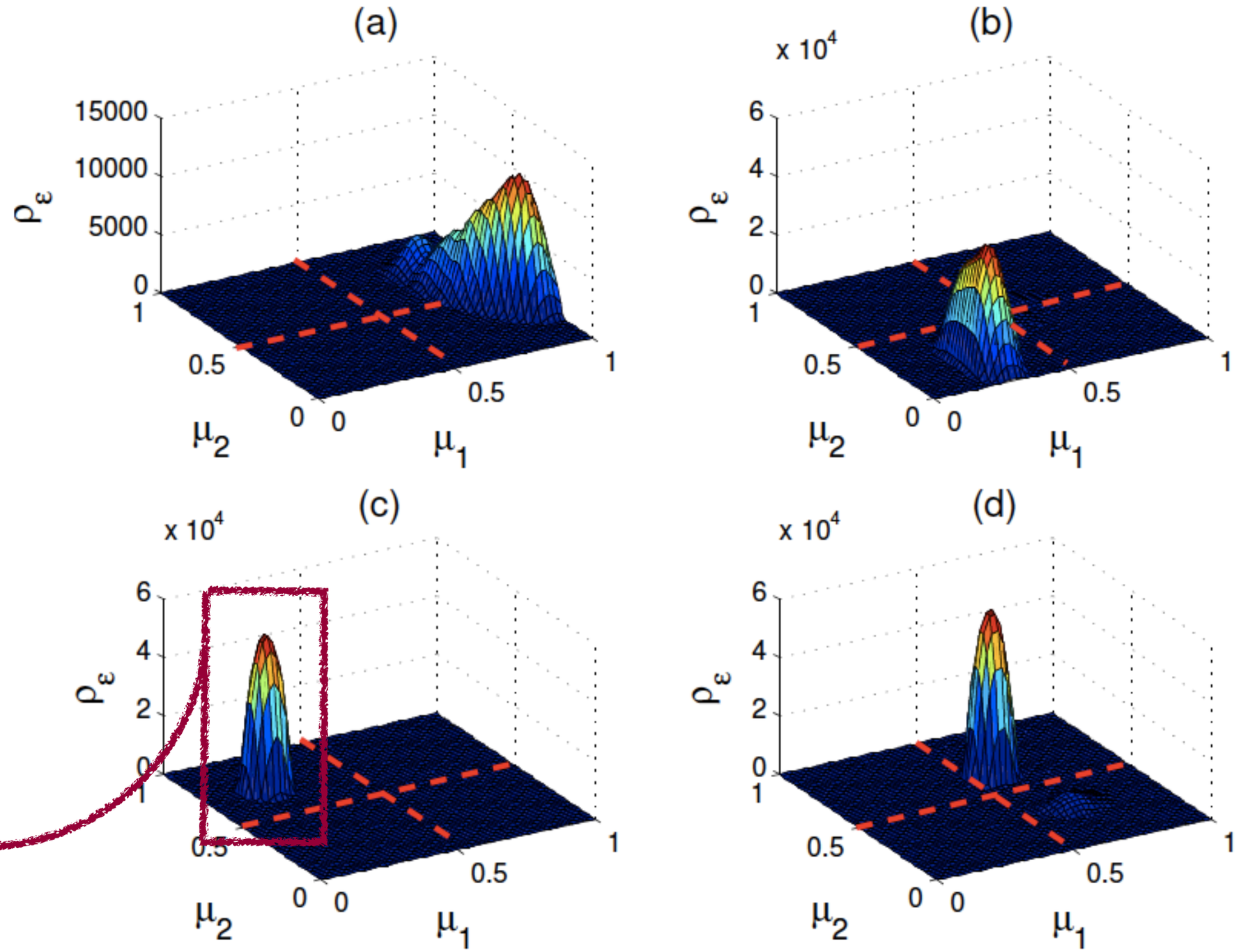
Barbarroux *et al* (2018) DCDS-B

2.1/ Multiscale models: Results - Simulations



Barbarroux *et al* (2018) DCDS-B

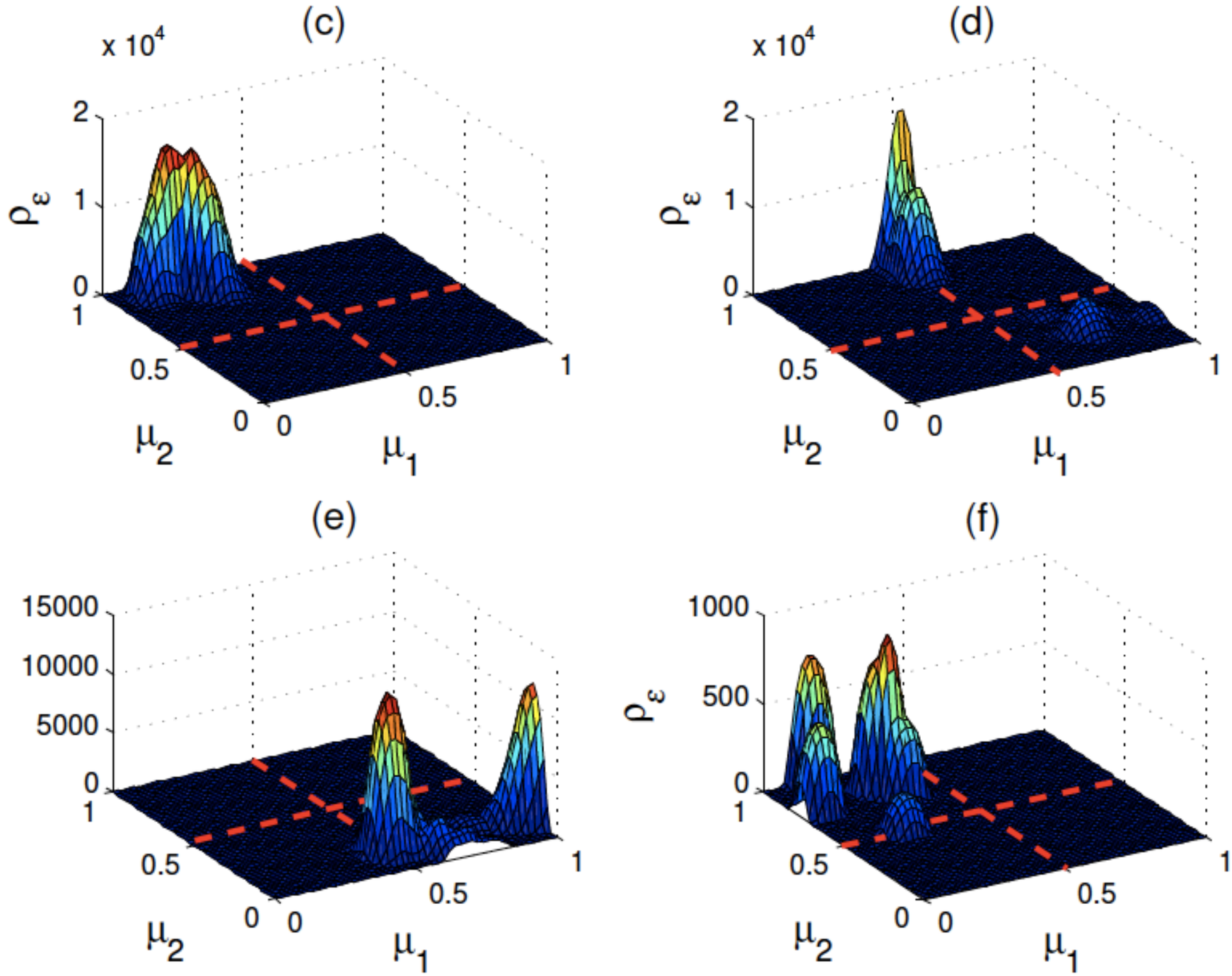
2.1/ Multiscale models: Results - Simulations



loss of hetero-geneity

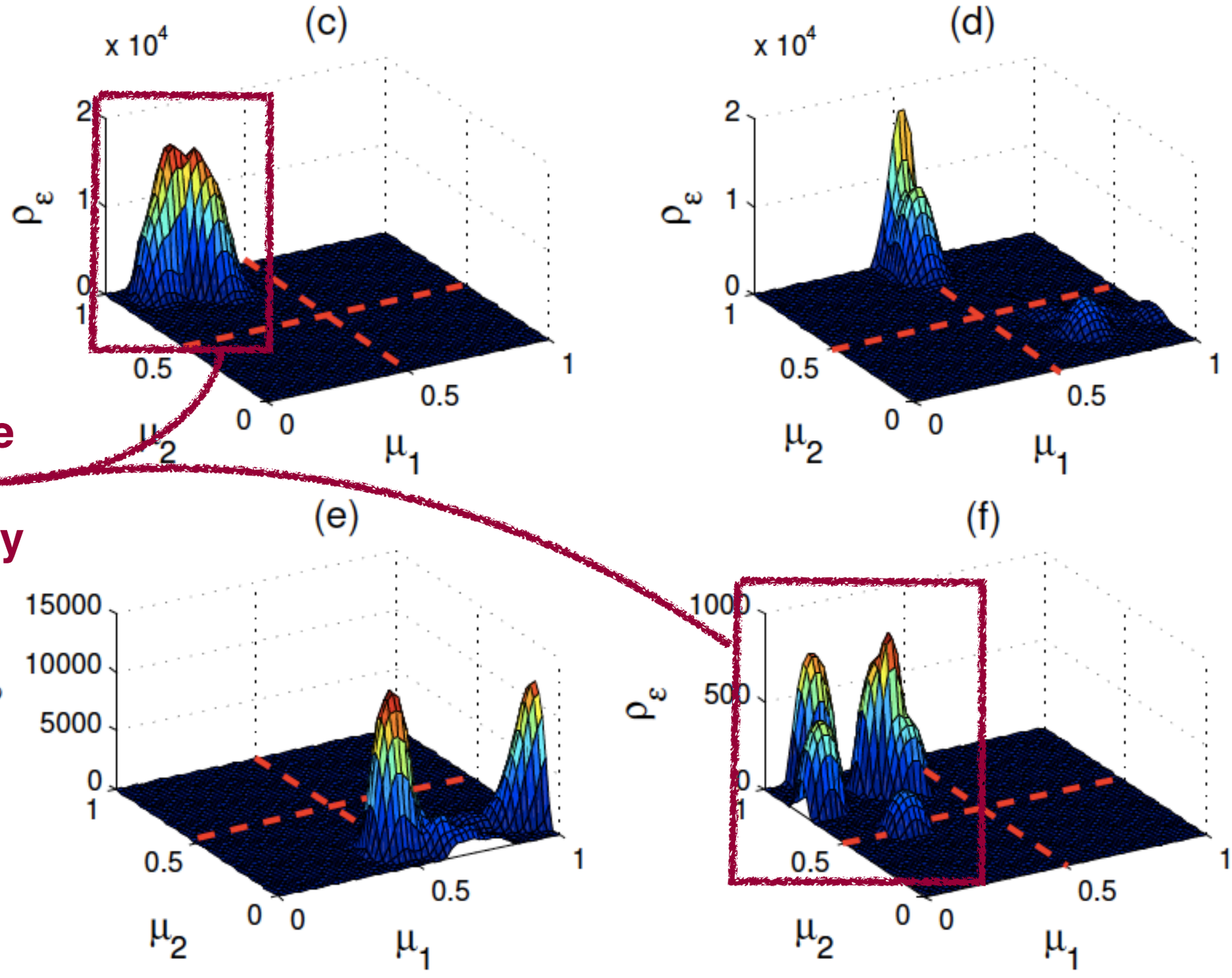
Barbarroux *et al* (2018) DCDS-B

2.1/ Multiscale models: Results - Simulations



Barbarroux *et al* (2018) DCDS-B

2.1/ Multiscale models: Results - Simulations



maintenance of heterogeneity

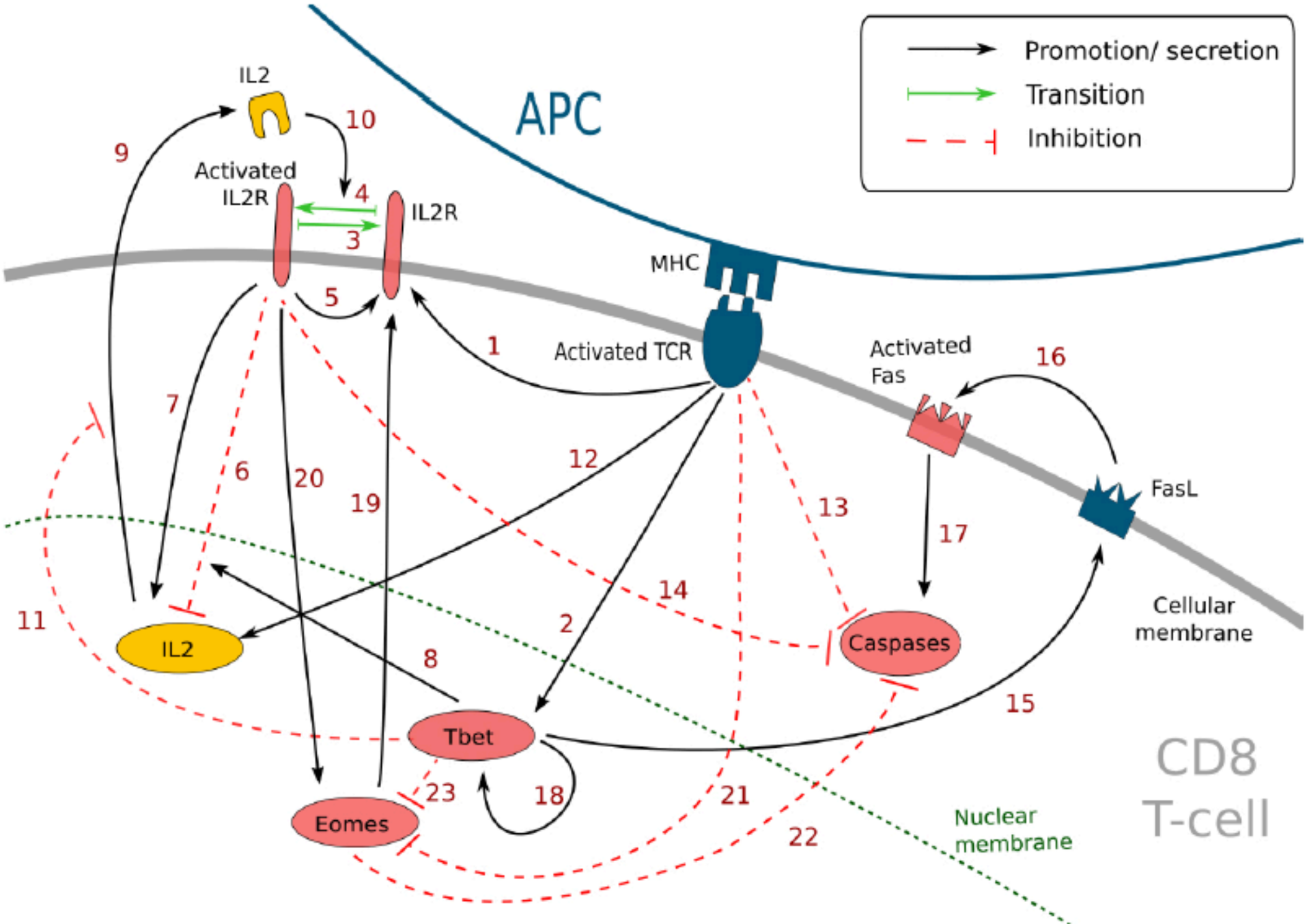
Barbarroux *et al* (2018) DCDS-B

2.2/

Multiscale models of the CD8 T cell response
A computational approach

2.2/ Multiscale models: Intracellular scale

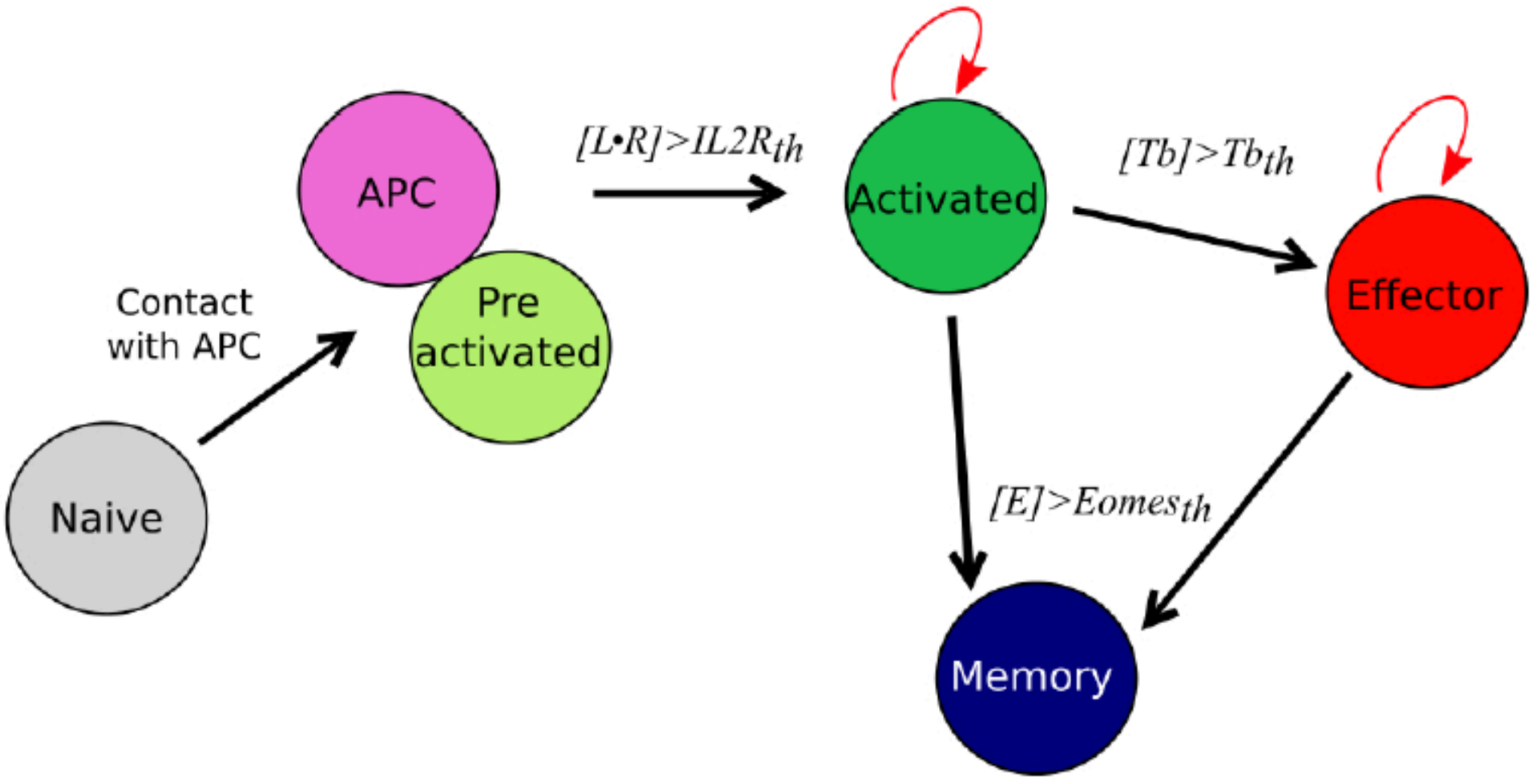
Simplified molecular signaling pathway (for each single CD8 T cell)



Prokopiou *et al* (2014)

2.2/ Multiscale models: Cellular scale

Schematic diagram of the linear differentiation pathway

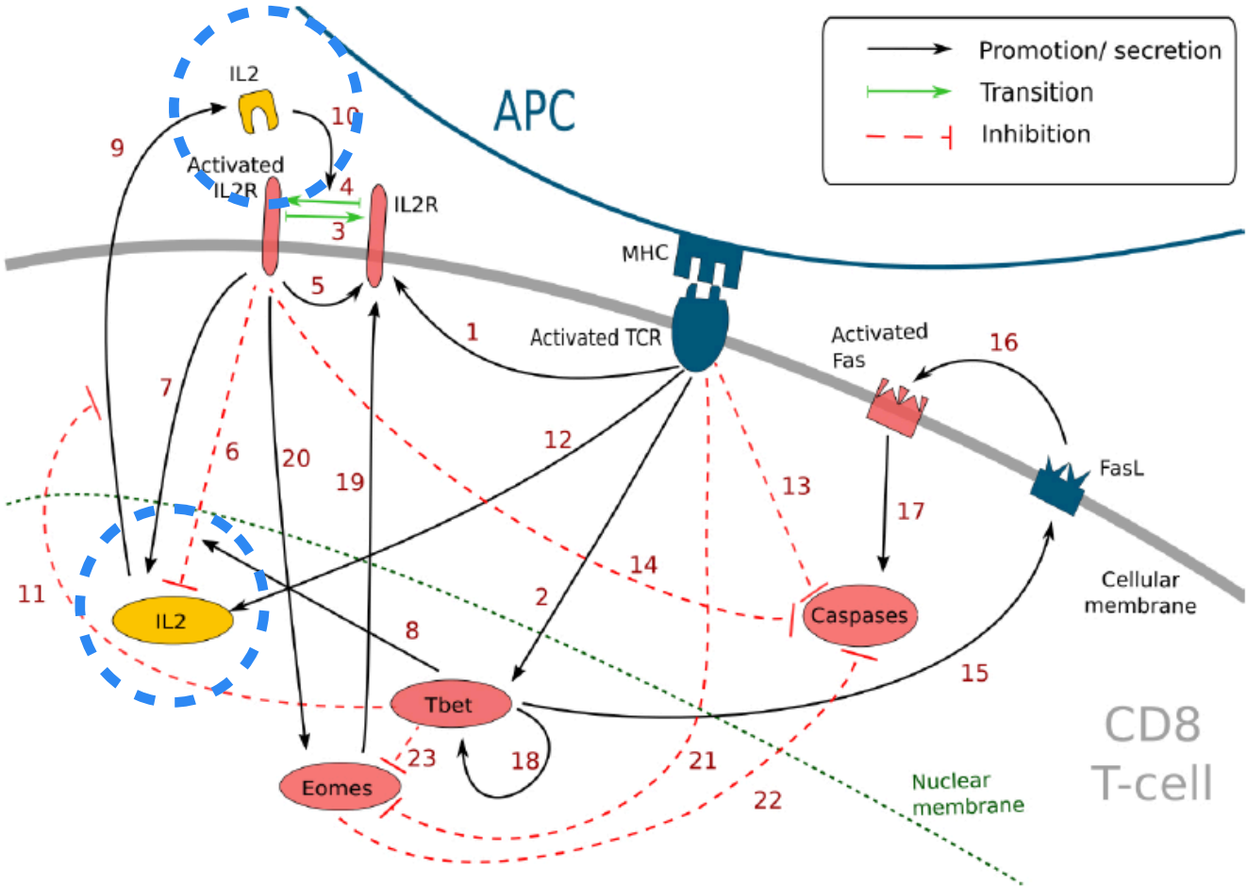


Prokopiou *et al* (2014), Girel *et al.* (2019)

2.2/ Multiscale models: Extracellular environment

IL2 secretion and diffusion to neighbour cells

CD8 T cells release IL2 when in contact with an APC

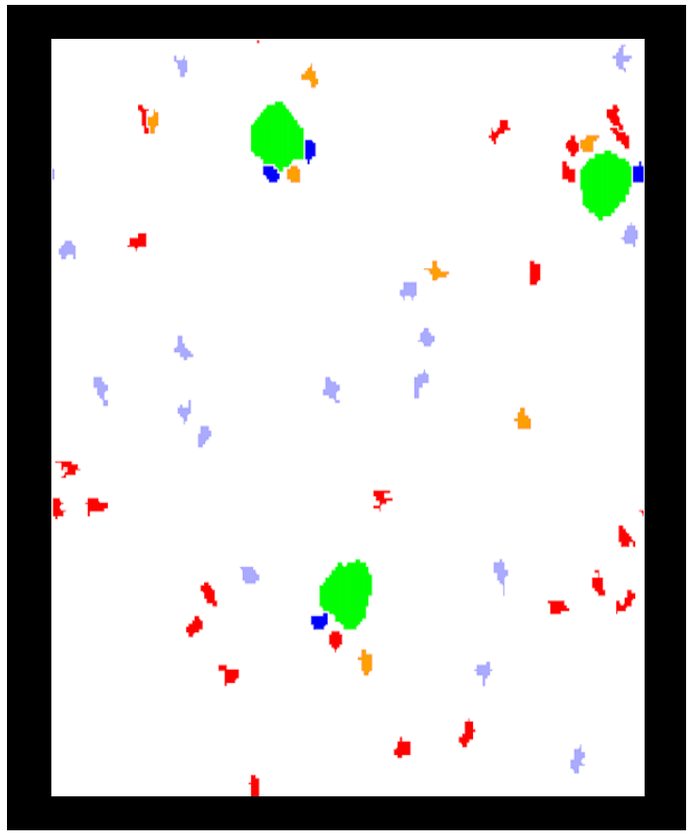


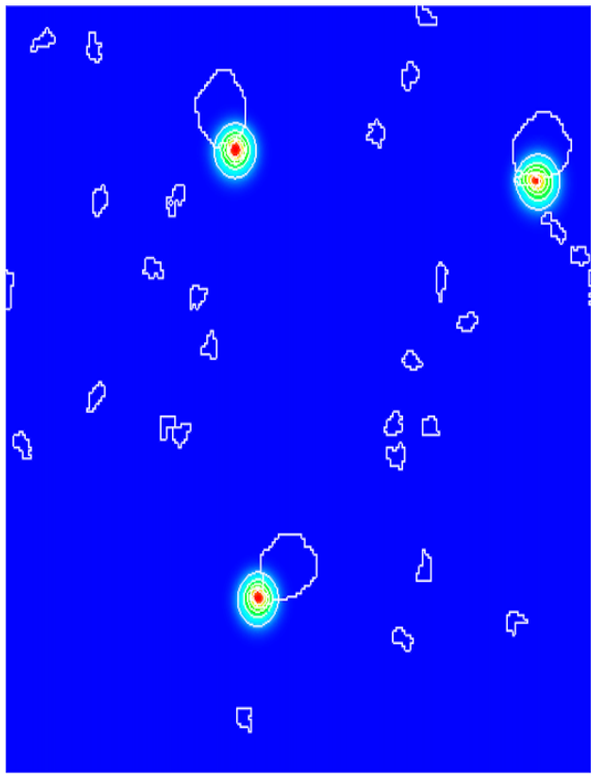
IL2 is *externalized* and *diffuses* in the cell neighborhood:

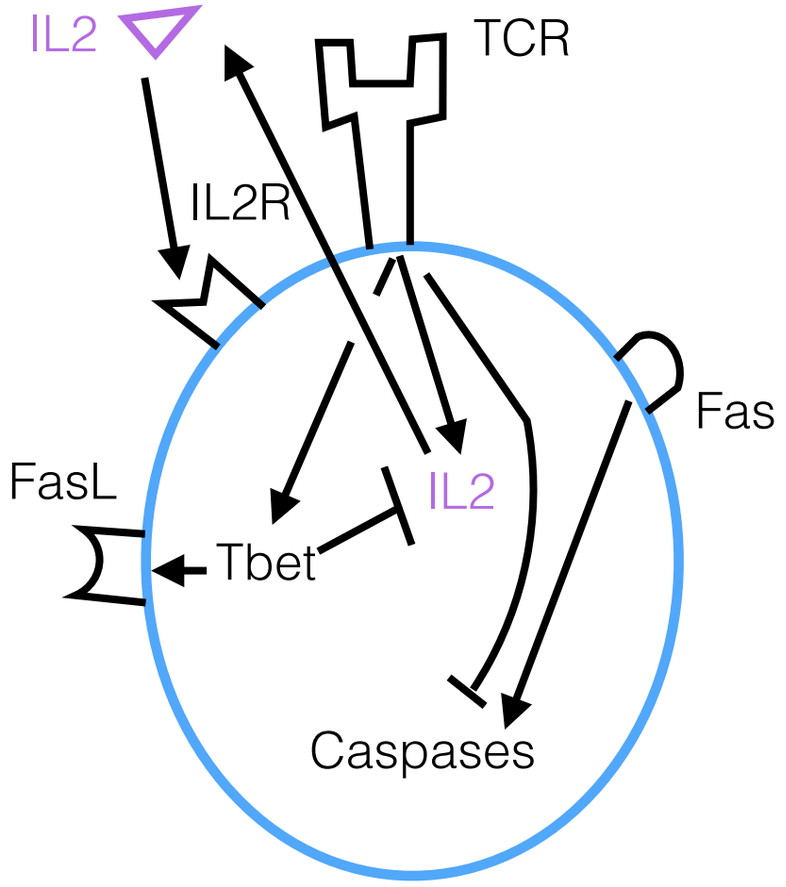
$$\frac{\partial [IL2]}{\partial t} = D\nabla^2[IL2] + \left(\lambda_{R3}\frac{[L \bullet R]}{\lambda_{R4} + [L \bullet R]} + \lambda_1 f_{APC}\right)\frac{1}{1 + \lambda_{T4}[Tb]} - \delta[IL2]$$

Prokopiou *et al* (2014)

2.2/ Multiscale models: Agent-based approach



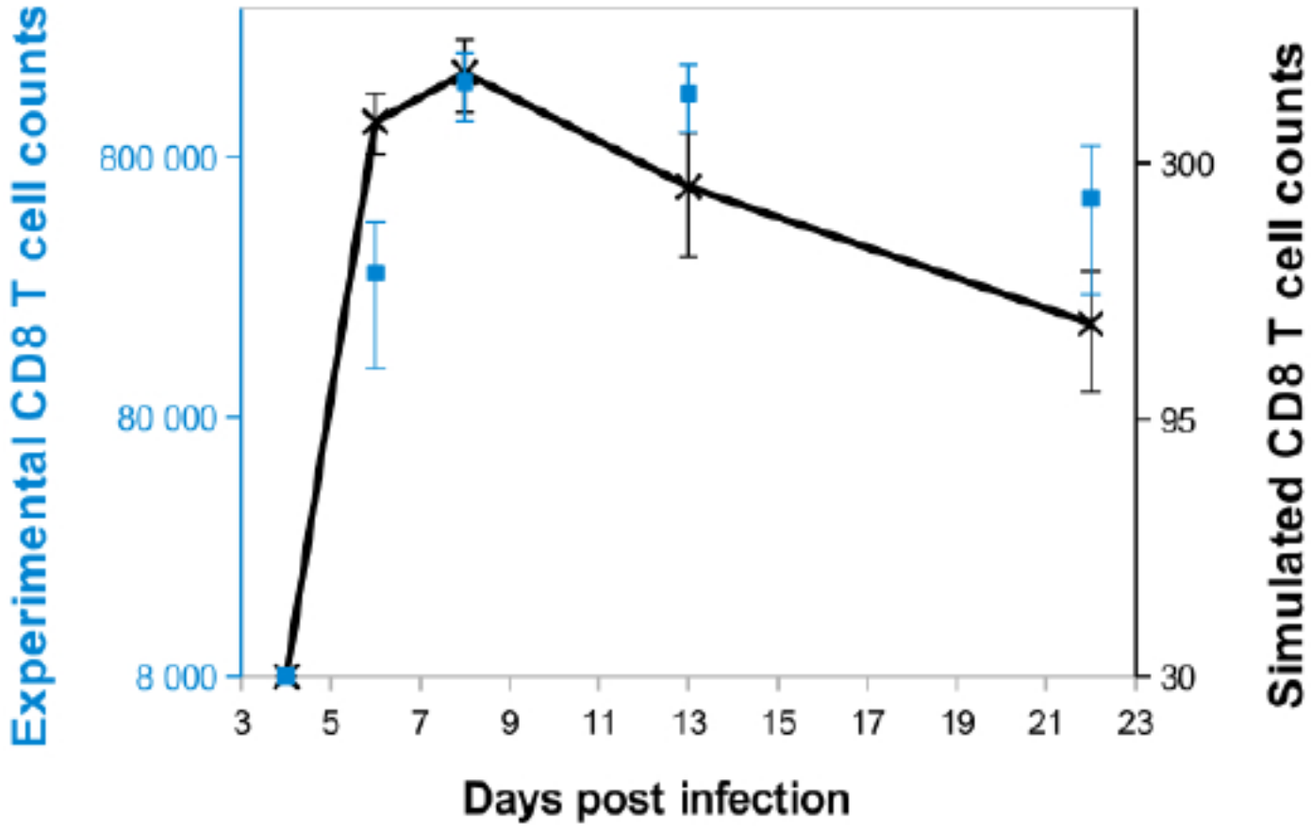




Cell Population **Extracellular** **Single Cell**

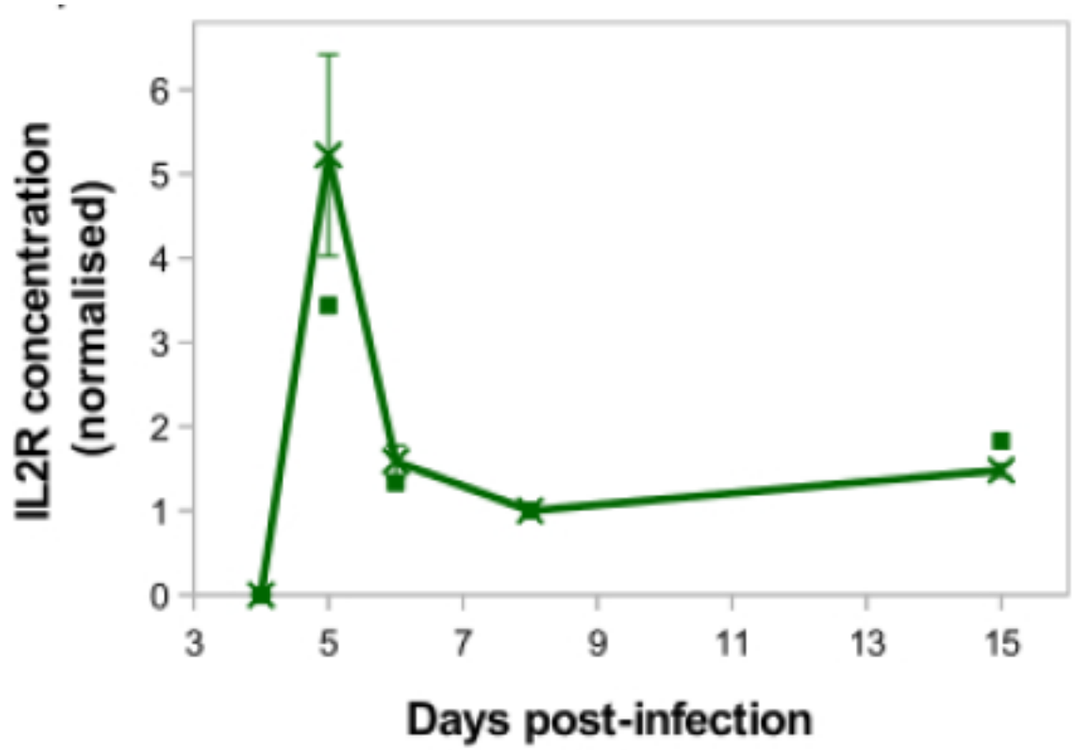
Prokopiou *et al.* (2014), Gao *et al.* (2016), Girel *et al.* (2019)

2.2/ Multiscale models: Agent-based approach



Qualitative fit of cellular dynamics

Fit of molecular dynamics



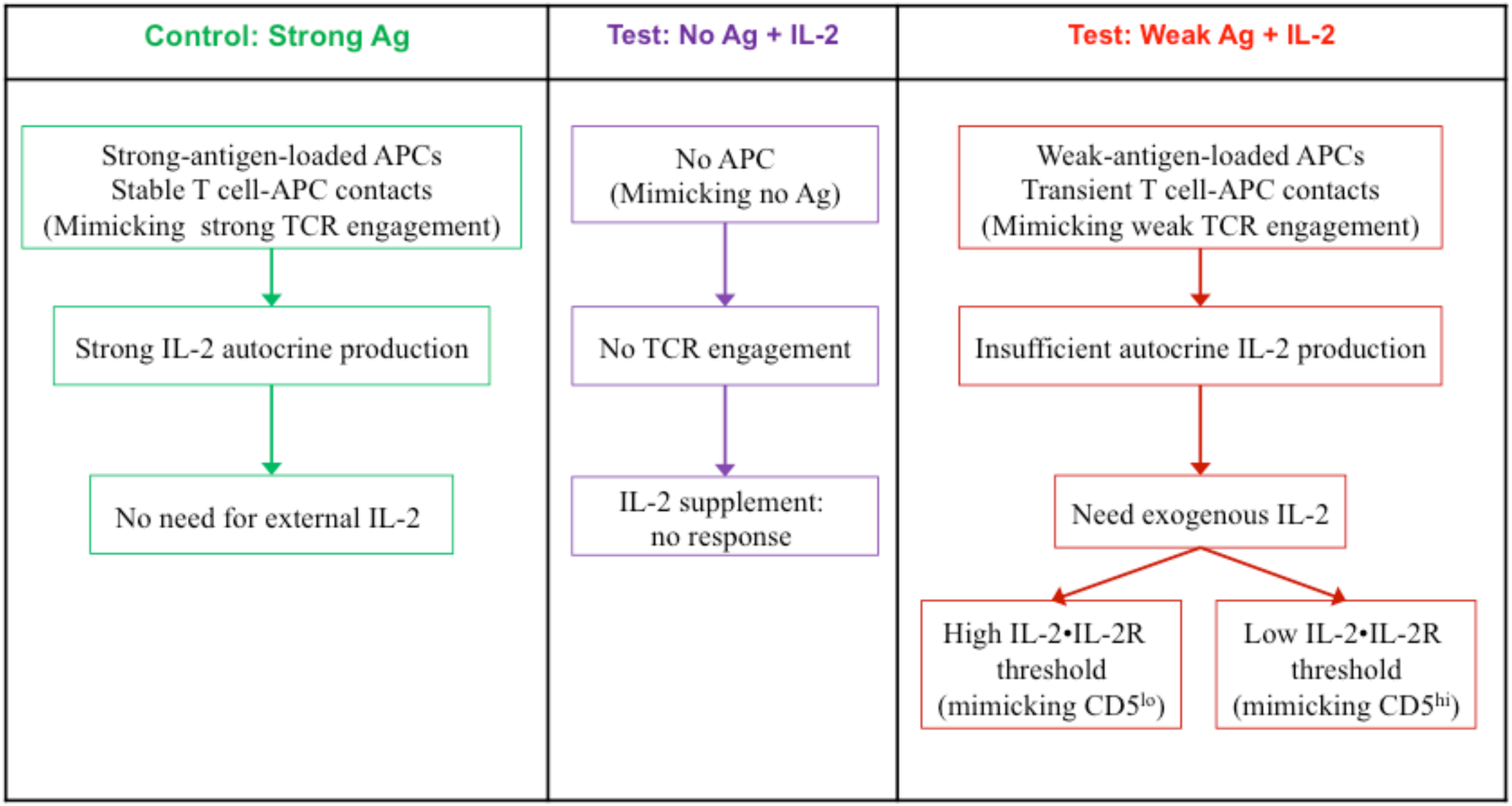
Girel *et al.* (2019)

2.2/ Multiscale models: Agent-based approach

How can early molecular events influence the overall dynamics of the CD8 T cell immune response?

2.2/ Multiscale models: in-silico testing

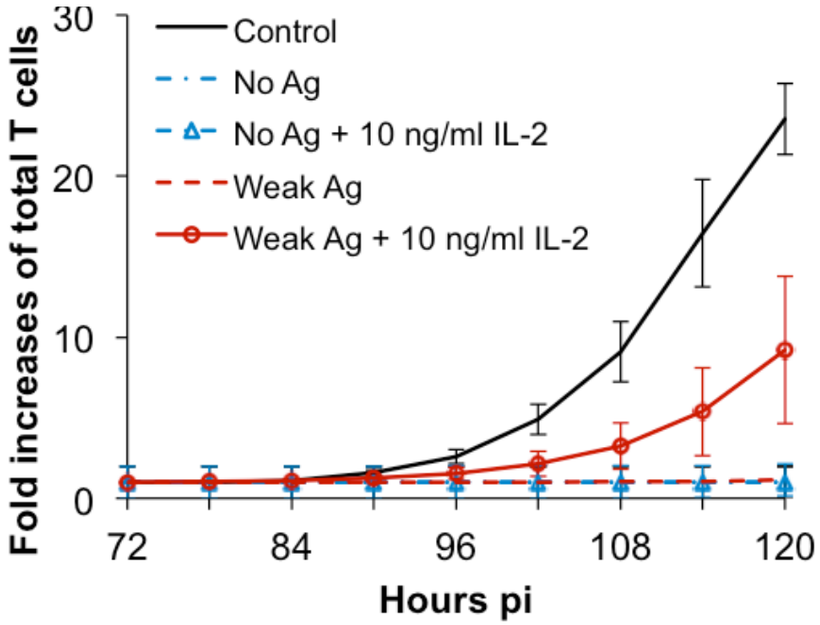
3 different conditions tested with the model



Gao *et al.* (2016)

2.2/ Multiscale models: in-silico testing - Results

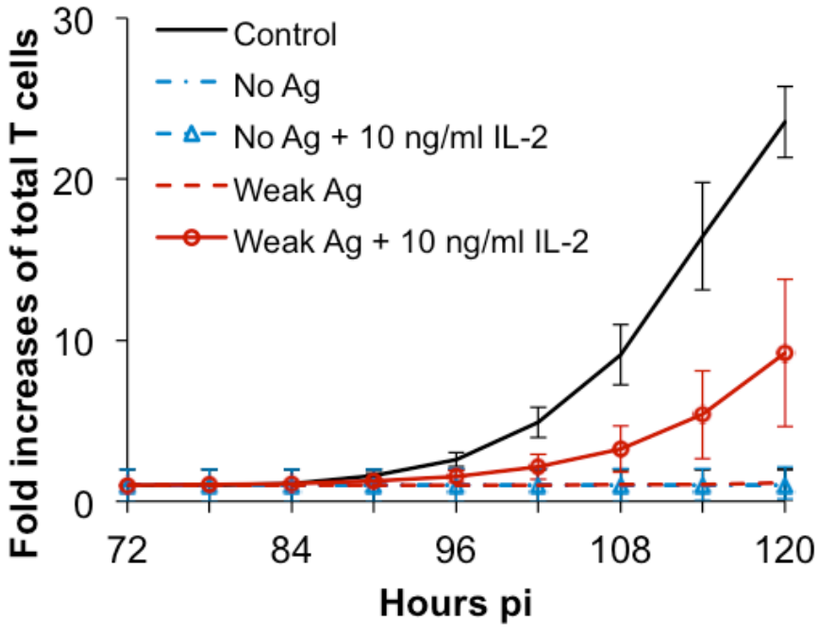
[simulation results]

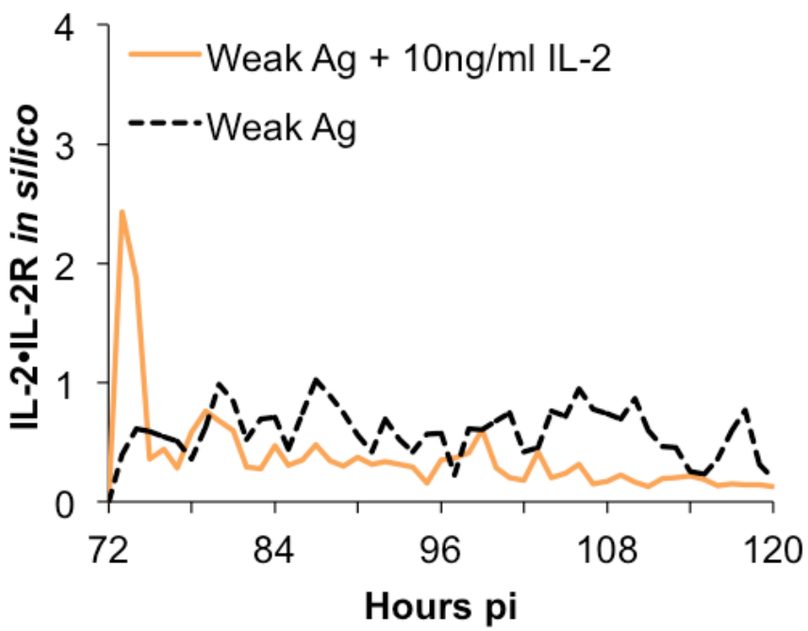


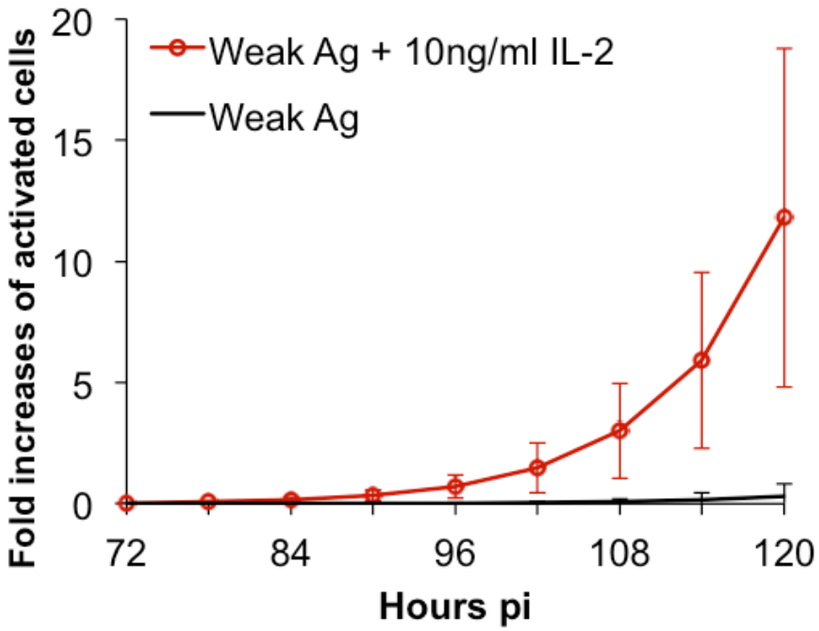
Gao *et al.* (2016)

2.2/ Multiscale models: in-silico testing - Results

[simulation results]



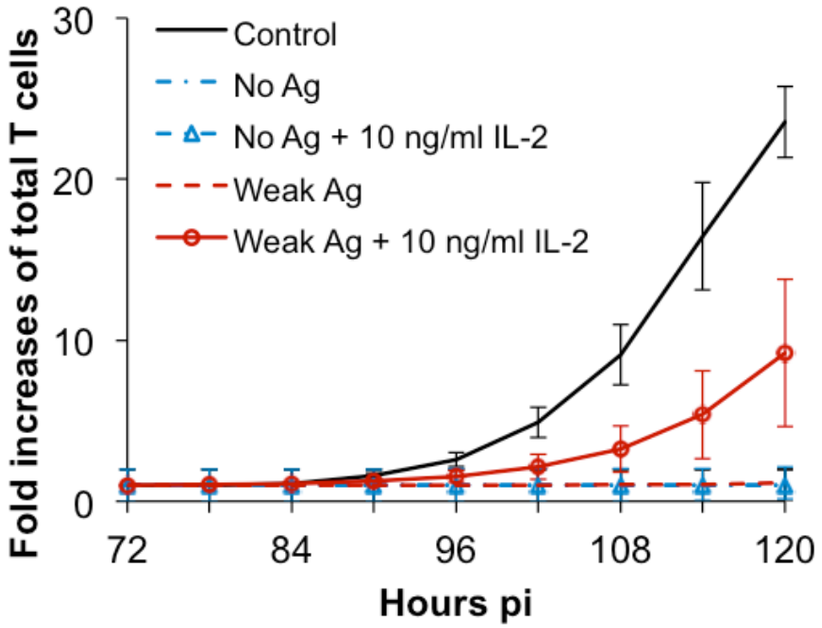


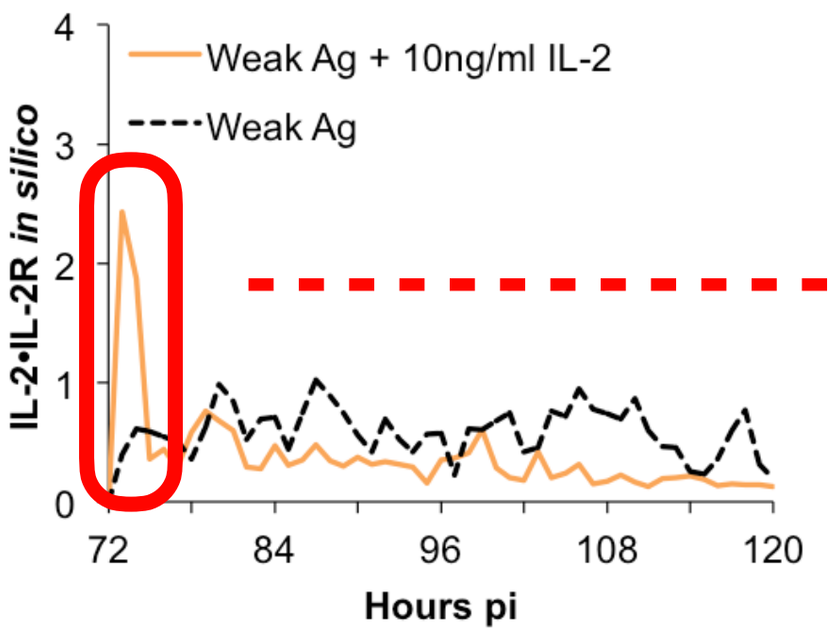


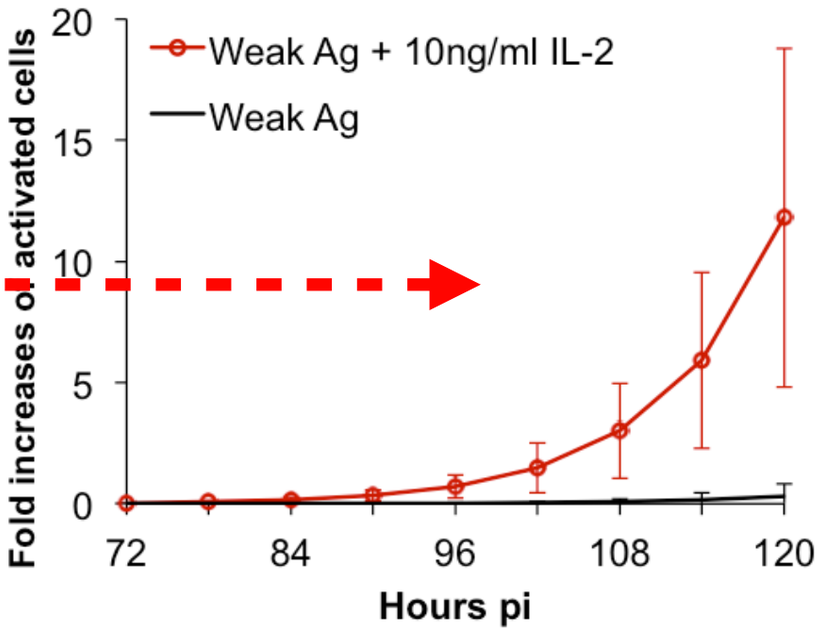
Gao *et al.* (2016)

2.2/ Multiscale models: in-silico testing - Results

[simulation results]







Gao *et al.* (2016)

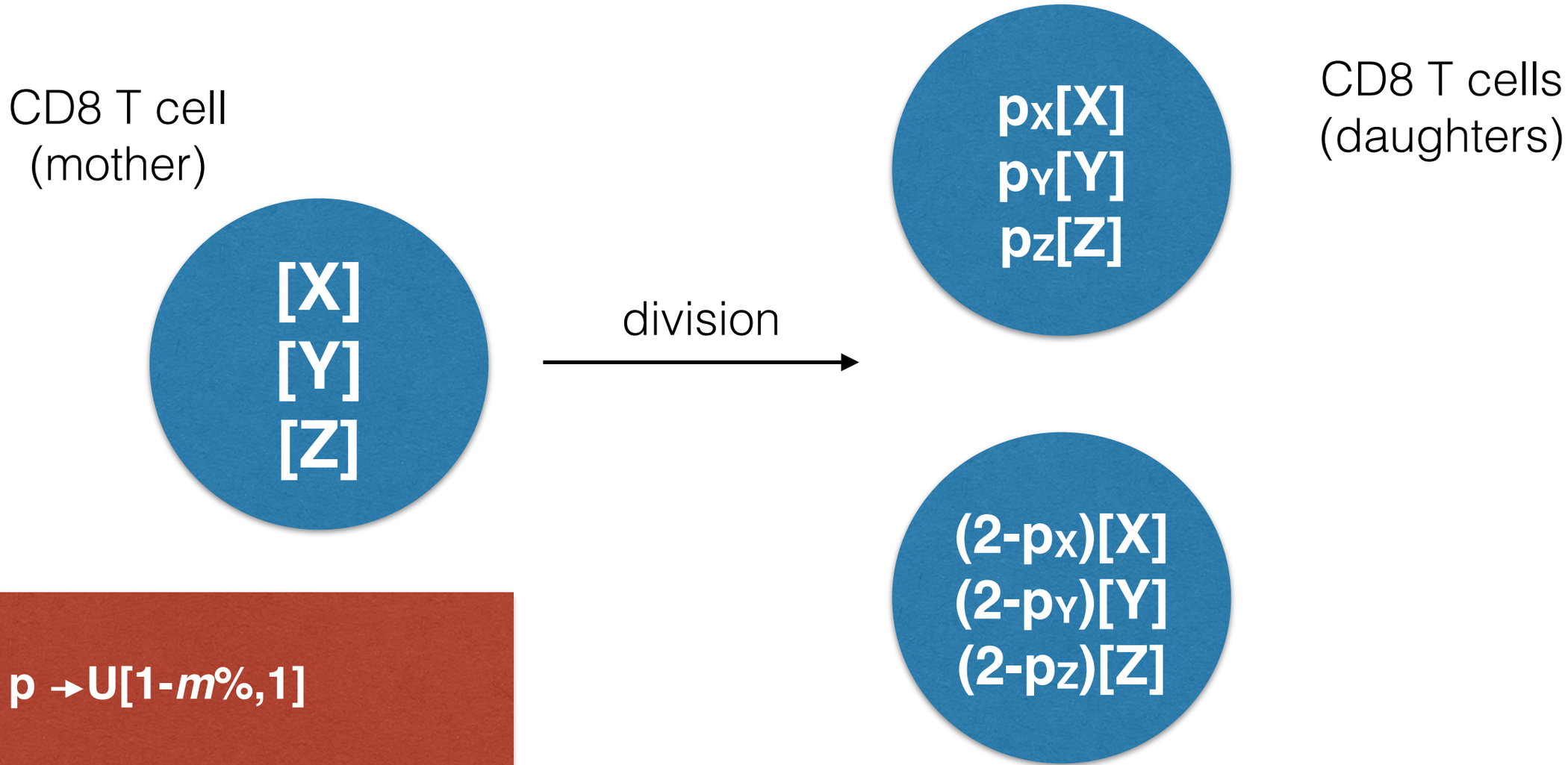
2.2/ Multiscale models: Agent-based approach

Uneven partitioning of molecular contents sustains heterogeneity and regulates CD8 T cell differentiation

(Girel and Crauste, 2018 ; Girel et al, 2019)

2.2/ Multiscale models: Agent-based approach

Uneven partioning of intracellular content at division

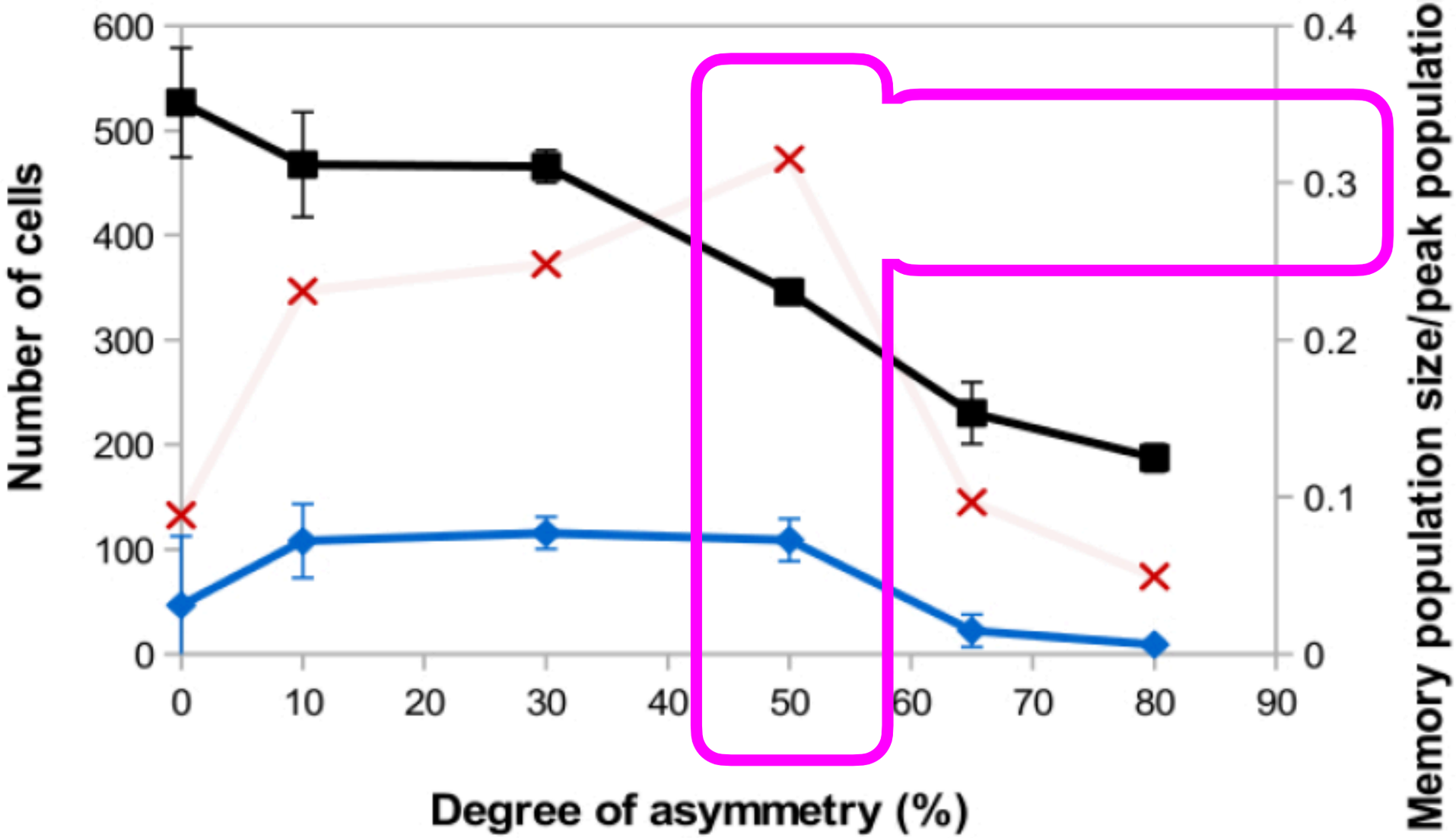


p → U[1-*m*%,1]

m* is the *degree of unequal partitioning

Girel *et al.* (2019)

2.2/ Multiscale models: Agent-based approach



5% to 10% of cells at the peak of the response become memory cells?

Girel *et al.* (2019)

Conclusions

Conclusions

1. **Biologically relevant description** of the immune response dynamics with emphasize on **improving vaccine design needs new mathematical and computational approaches**

2. Models that reproduce **key immunological features** of the CD8 T cell response in mice **-> suitable for testing hypotheses**

3. Models account for **inter-individual variability** and allow the investigation of the **consequences of early events** (activation of *IL2* pathway) on the dynamics of CD8 T cells and consequences of molecular heterogeneity

4. **Several PhD theses and postdocs:** E. Terry, S. Prokopiou, X. Gao, L. Barbarroux, S. Girel (MCF UCA), C. Audebert (MCF SU), and a **collaborative effort through interdisciplinary research** (immunologists/mathematicians/ modelers)

Math/Modeling

Chloé Audebert (Sorbonne Université, Paris)
Loic Barbarroux
Samuel Bernard (ICJ, Lyon)
Olivier Gandrillon (ENS de Lyon, Lyon)
Xuefeng Gao (Shenzen University, Chine)
Simon Girel (Université de Côte d'Azur, Nice)
Philippe Michel (Ecole Centrale de Lyon, Lyon)
Sotiris Prokopiou
Emmanuelle Terry

Inserm

Christophe Arpin
Lilia Boucinha
Sophia Djebali
Daphné Laubreton
Julien Mafille
Jacqueline Marvel
Yann Leverrier

AGENCE NATIONALE DE LA RECHERCHE
ANR

La Région
Auvergne-Rhône-Alpes

0111010
MILYON
UNIVERSITE DE LYON

Institut des Systèmes Complexes
Complex Systems Institute
Rhône Alpes
IXXI

Bonus

GDR Mathématiques, Santé, Sciences de la Vie - MathSAV

https://mathsav.math.cnrs.fr/

Liste de diffusion : math-bio-sante@listes.math.cnrs.fr

67 unités/équipes, dont 43 rattachées à l'INSMI
~ 700 collègues

Objectifs :

- Gérer la liste de diffusion
- Organiser un événement scientifique pérenne (en 2022, journées du GDR à Besançon)

Co-financement d'événements scientifiques, respectant la parité des oratrices et orateurs et des comités scientifiques, et soutenant la participation des jeunes collègues