Multiscale Models of Cancer Immunotherapy: *In Silico* Approaches

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Mathematical and Computer Modeling to Study Tumors Heterogeneity in its ecosystem
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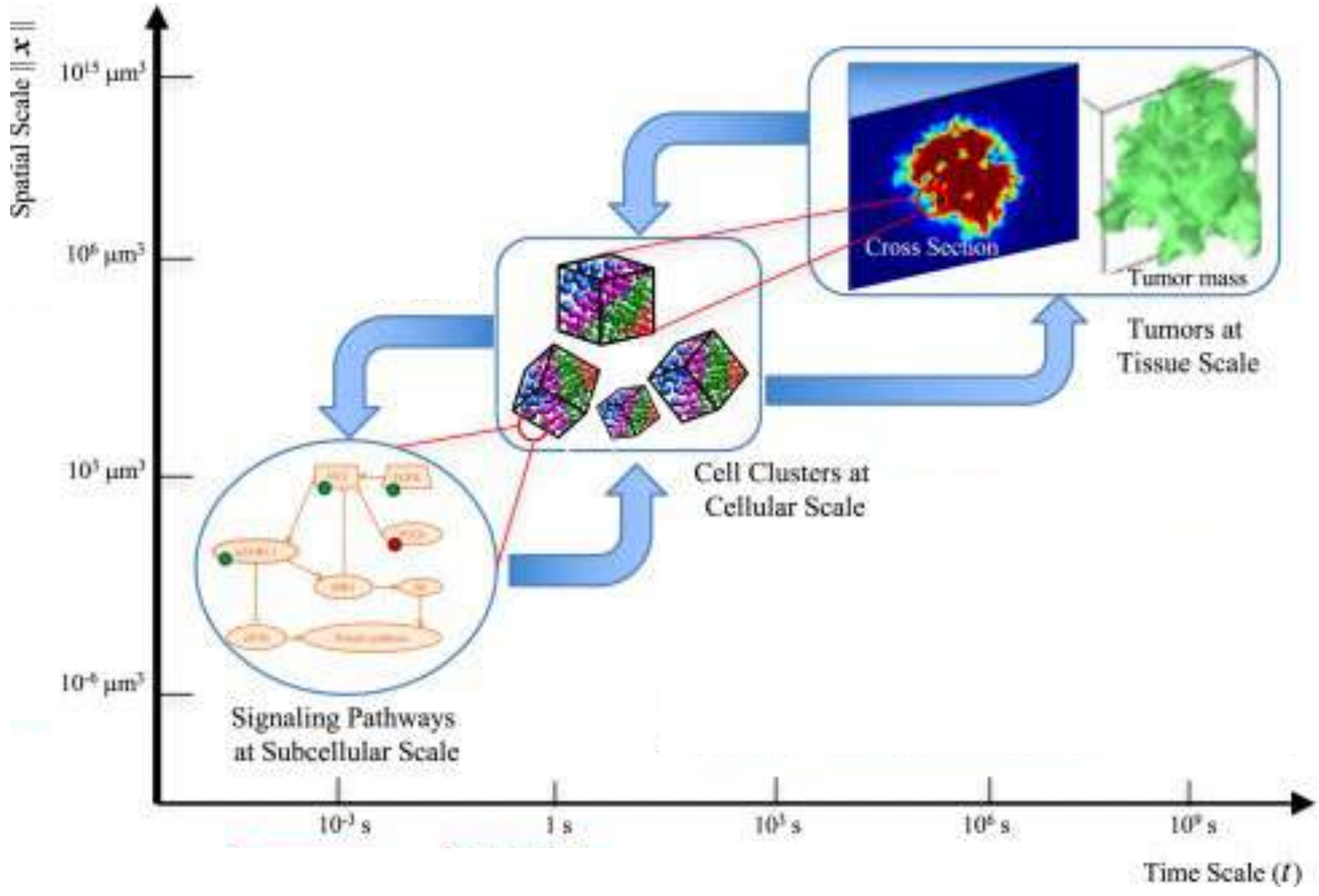
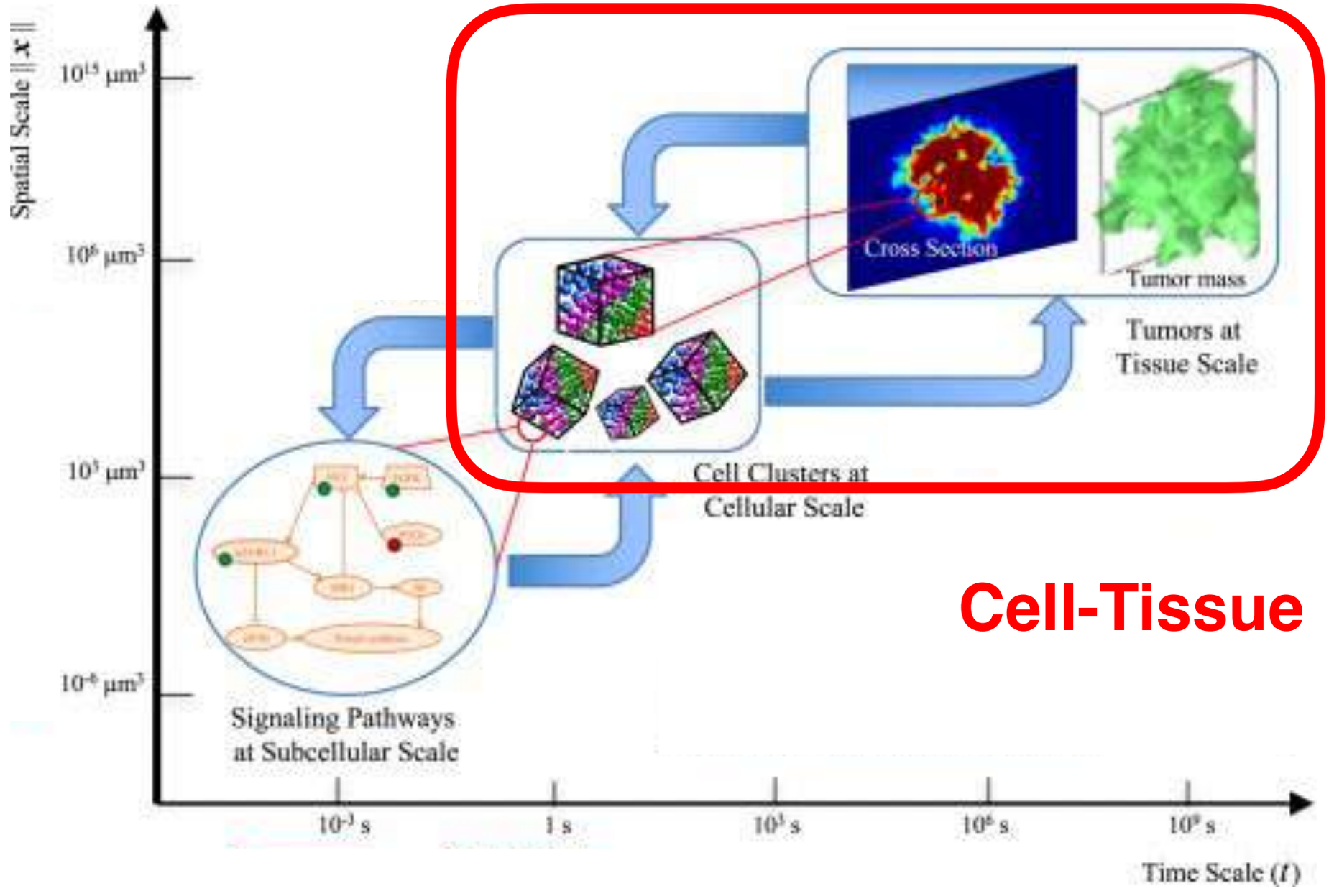
Multiscale Models

Multiscale usually means several time and/or spatial levels described in the same model



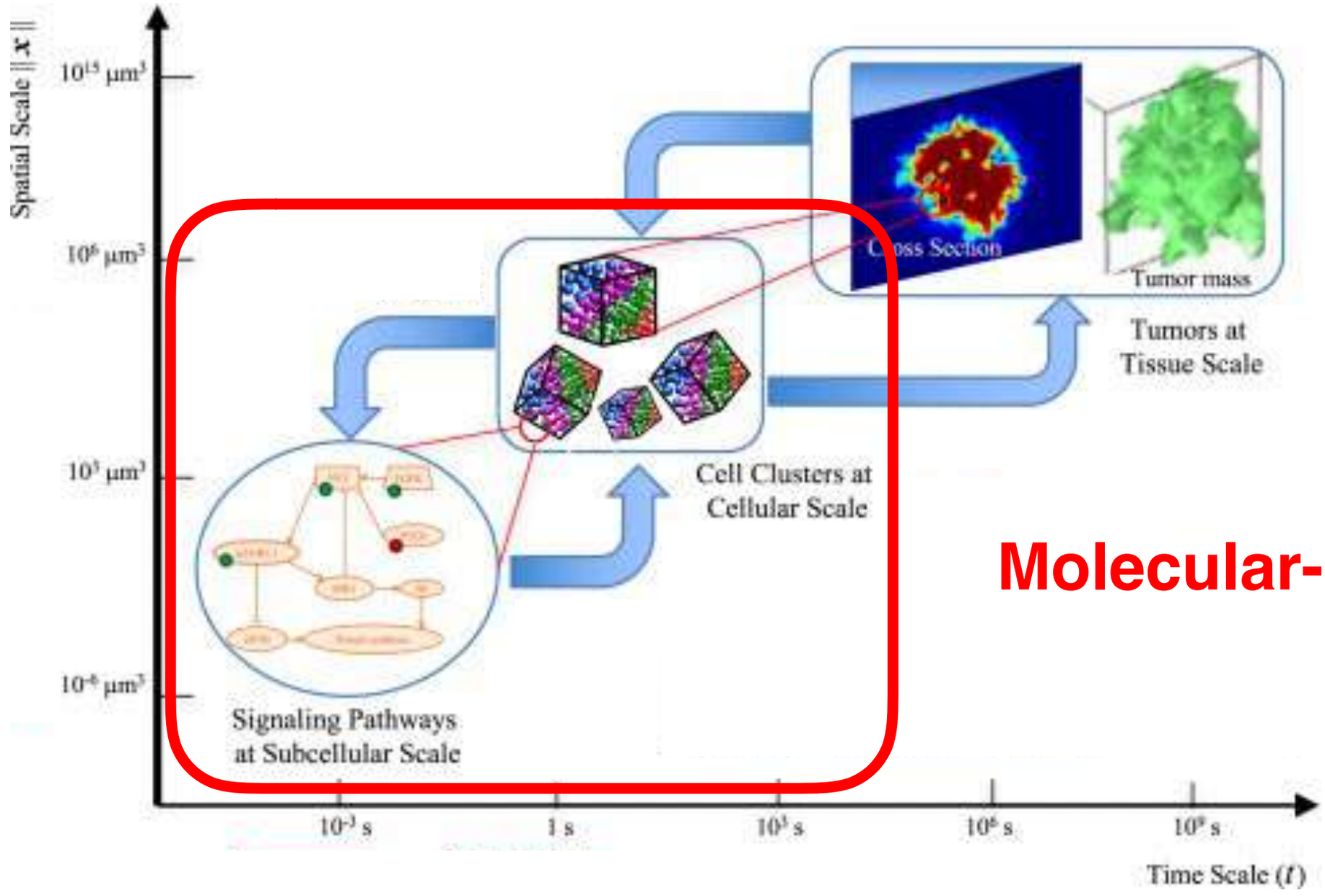
From Rhaman et al. (2017)

Often only 2 scales are described: Cell and tissue dynamics…



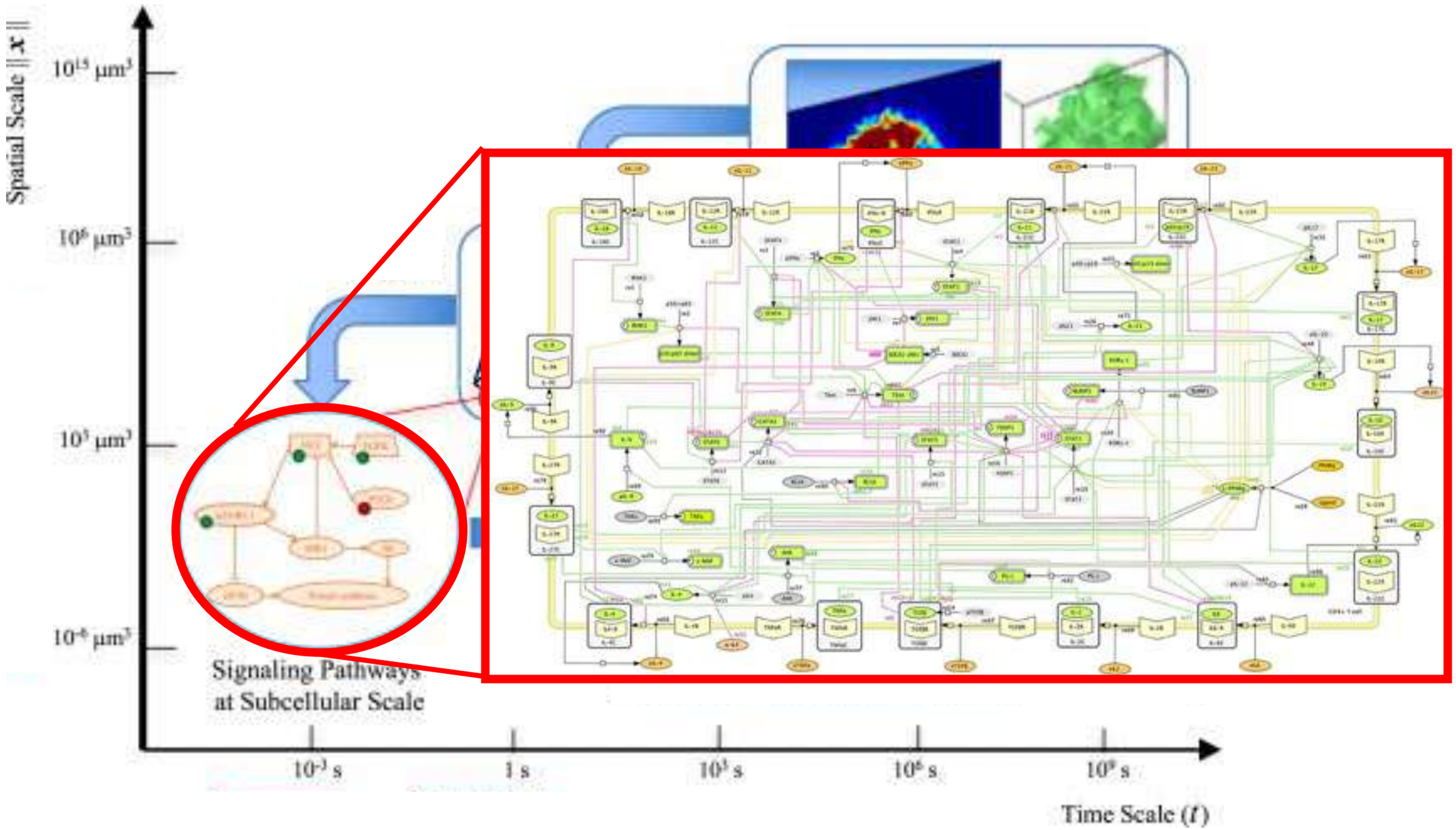
From Rhaman et al. (2017)

…Or
molecular and cellular dynamics



From Rhaman et al. (2017)

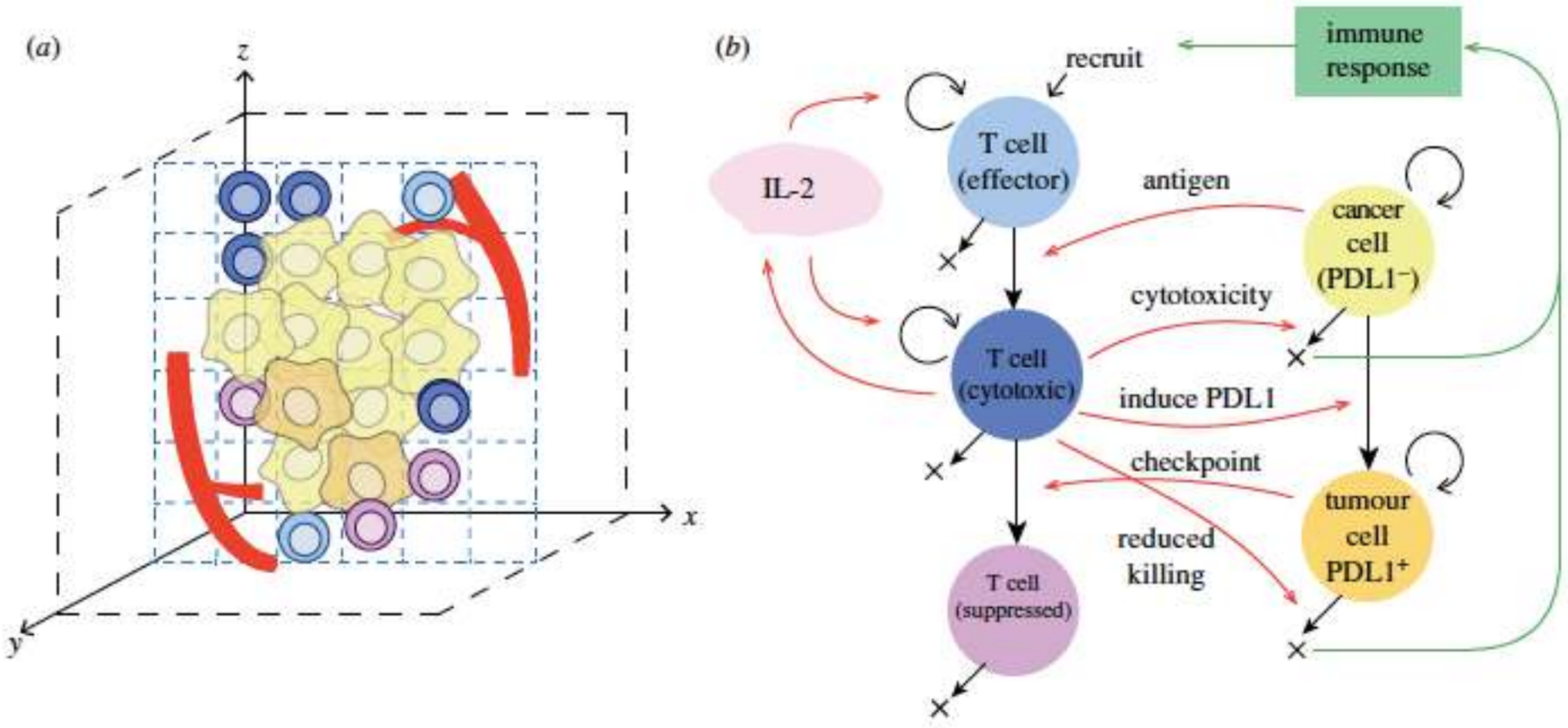
At each scale, dynamics are most of the time quite complex



From Rhaman et al. (2017)

Multiscale Models of Cancer Immunotherapy

A computational multiscale agent-based model for simulating spatio-temporal tumour immune response to PD1 and PDL1 inhibition (Gong et al., 2017)



→ Parameter values (probabilities) are modified during the simulation to account for treatment

→ Cell-Tissue interactions, without molecular description

Gong et al. (2017)

In silico tumor control induced via alternating immunostimulating and immunosuppressive phases (Reppas *et al.*, 2015)

Mathematical Model

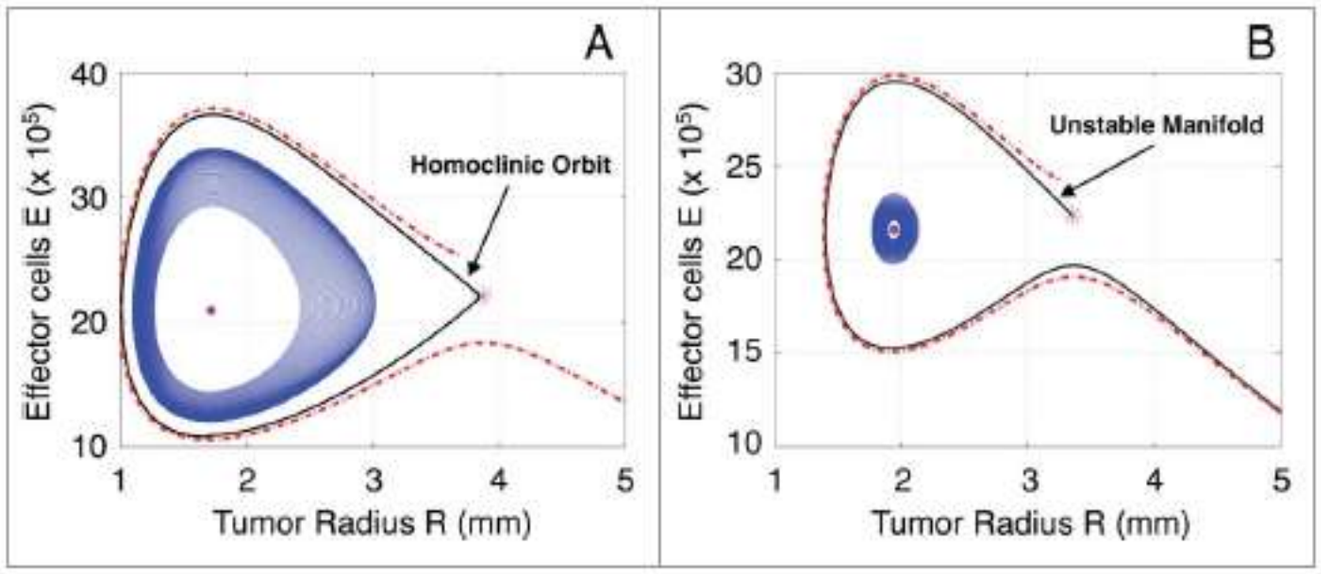
$$\frac{dR}{dt} = \frac{1}{3}(\lambda_M B - \lambda_A)R + \lambda_M(1-B)L_D\left(\frac{1}{tanh(R/L_D)} - \frac{L_D}{R}\right) - cER\,f(R,B),$$

Radial Tumor Growth

$$\frac{dE}{dt} = r\frac{R^3}{K+R^3}E - d_1ER^3\,f(R,B) - d_0E + \sigma,$$

Effector cell concentration

Dynamical System



→ Theoretical study based on bifurcation analysis suggests therapy

→ Cell-Tissue interactions, without molecular description

Reppas et al. (2015)

Cancer Immunotherapy is basically about acting on *molecular signaling pathways* (PD1/PDL1, CTLA4, IL2…) to alter T cell-Tumor interactions

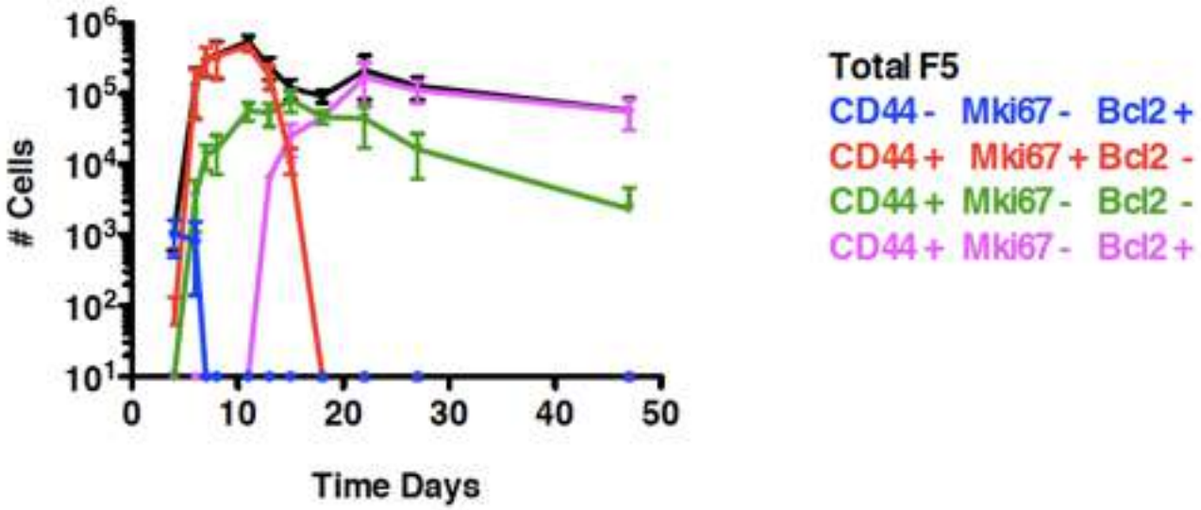
Hence, it would be necessary to include *molecular dynamics* in cell-tissue-based multiscale models of cancer immunotherapies

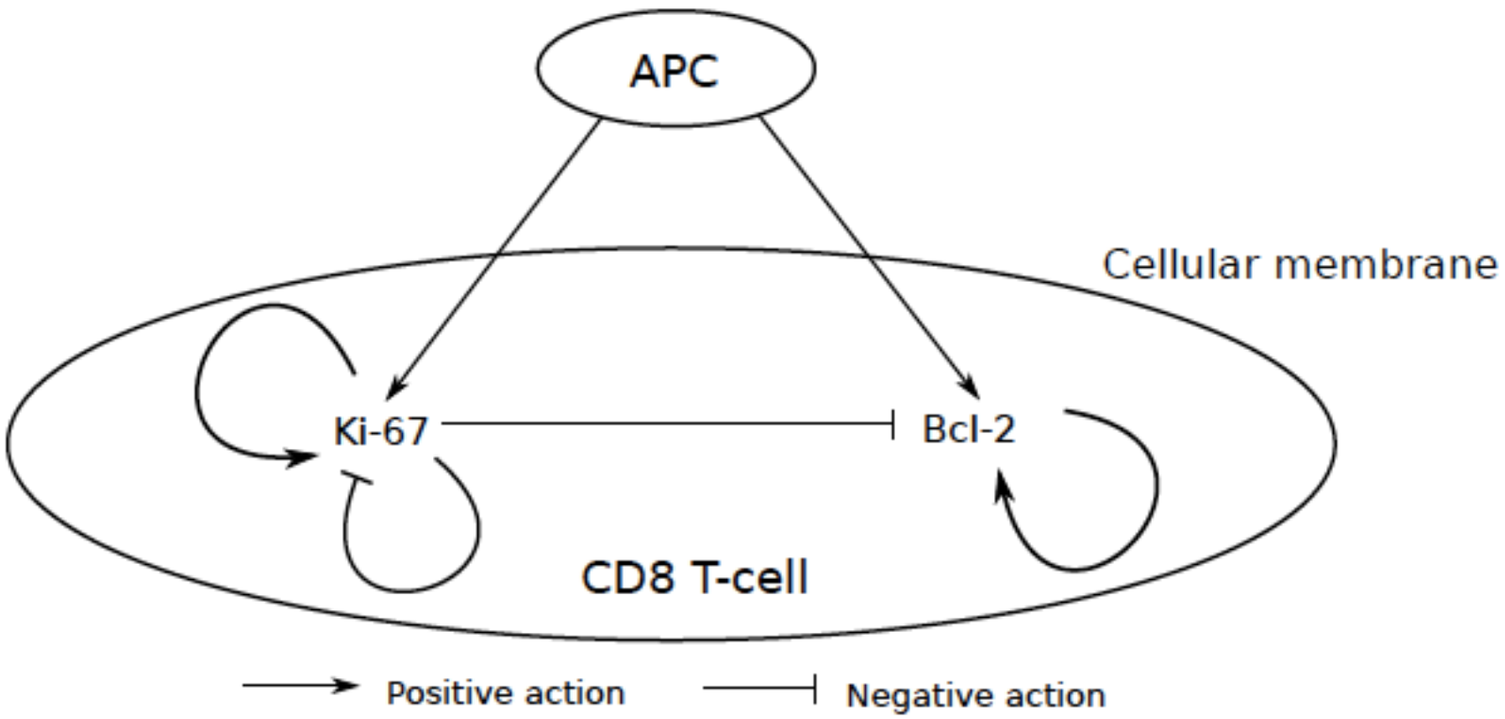
Multiscale models of the CD8 T cell immune response [computational and mathematical approaches]

A mathematical multiscale model of the CD8 T cell immune response

(Barbarroux et al, 2018)

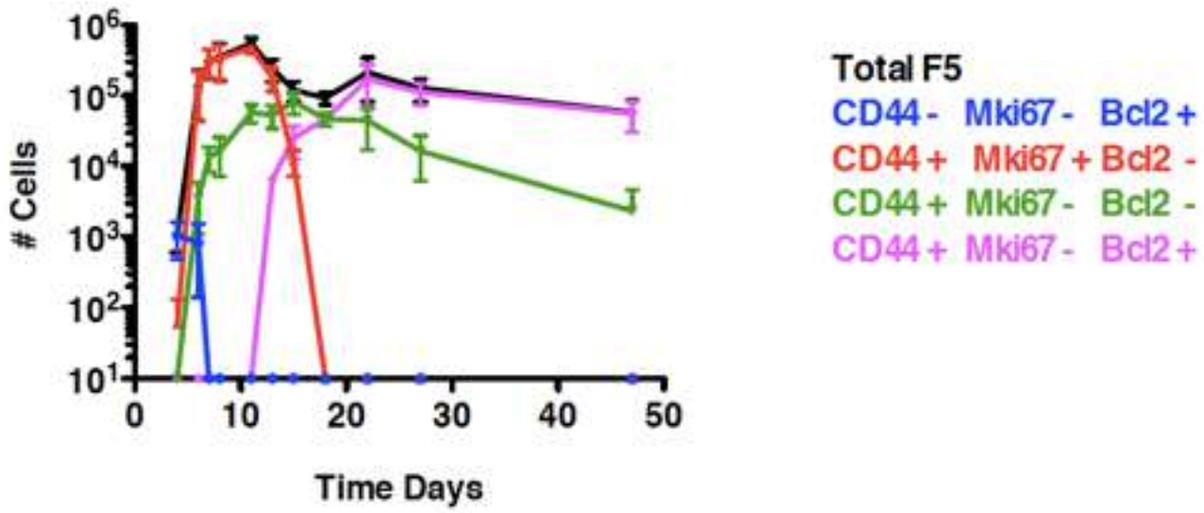
Multiscale Model: Intracellular molecular scale





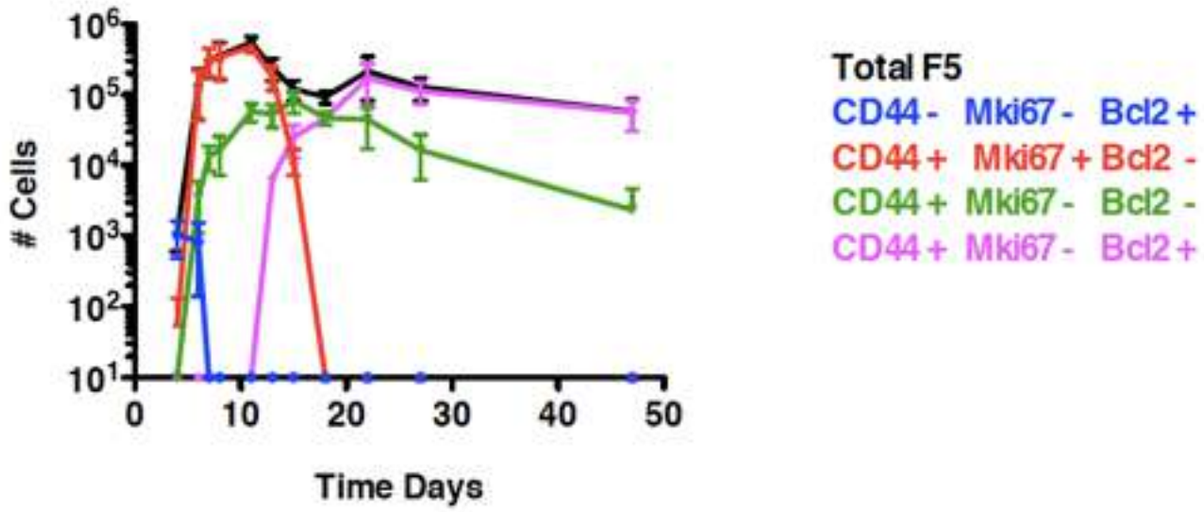
$$\begin{cases} \dfrac{d\mu_1}{dt}(t) = \left(\dfrac{\gamma_{P1} P(t)}{\theta_{P1} + P(t)} + \dfrac{\gamma_{r1} \mu_1(t)}{\theta_{r1} + \mu_1(t)} - k_1 - \dfrac{\gamma_{l1} \mu_1^2(t-\tau)}{\theta_{l1}^2 + \mu_1^2(t-\tau)} \right) \mu_1(t), \\ \dfrac{d\mu_2}{dt}(t) = \left(\dfrac{\gamma_{P2} P(t)}{\theta_{P2}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

Multiscale Model: Cell population scale



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

Multiscale Model: Cell population scale



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

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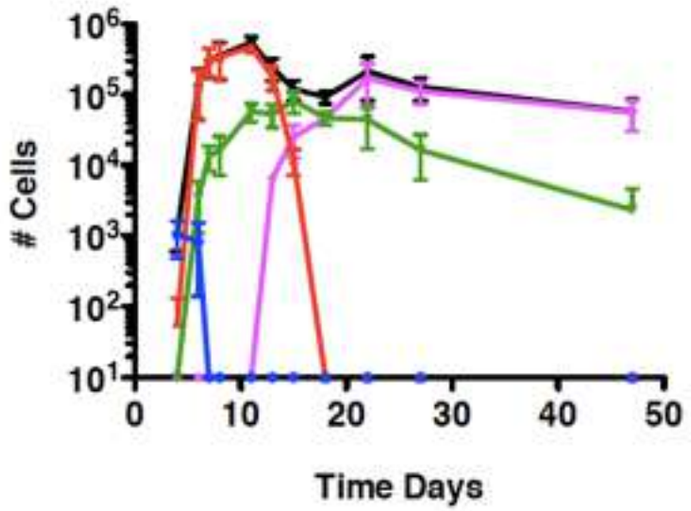

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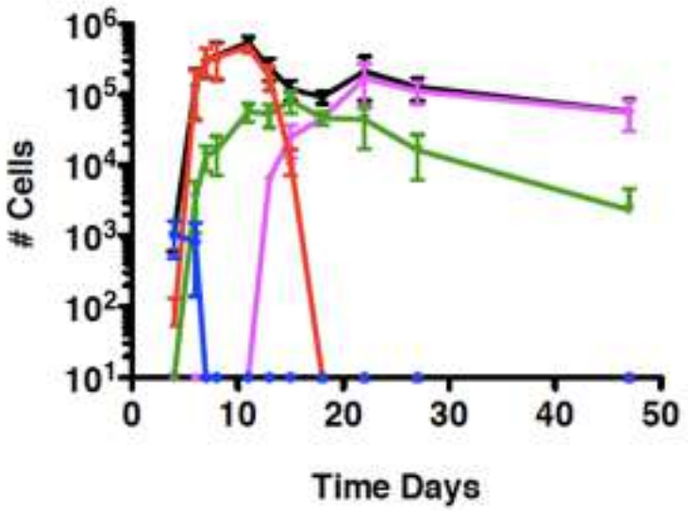
$$X^{i,j,k}(t)=\left(\mu_1^{i,j,k}(t),\mu_2^{i,j,k}(t)\right)$$

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

Multiscale Model: Cell population scale



Density of CD8 T cells:

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

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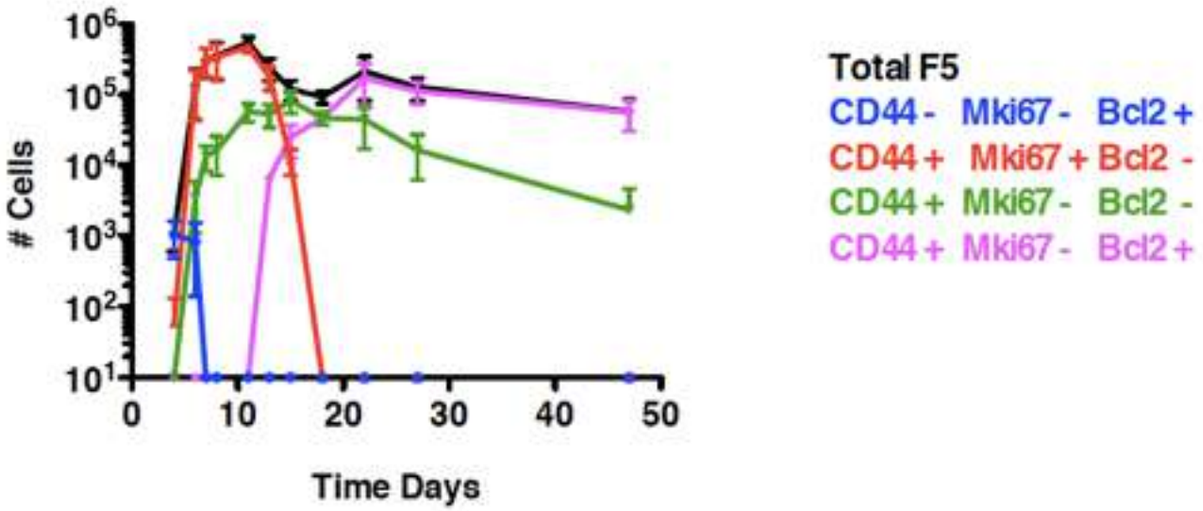
Multiscale Model: Cell population scale



Density of CD8 T cells:

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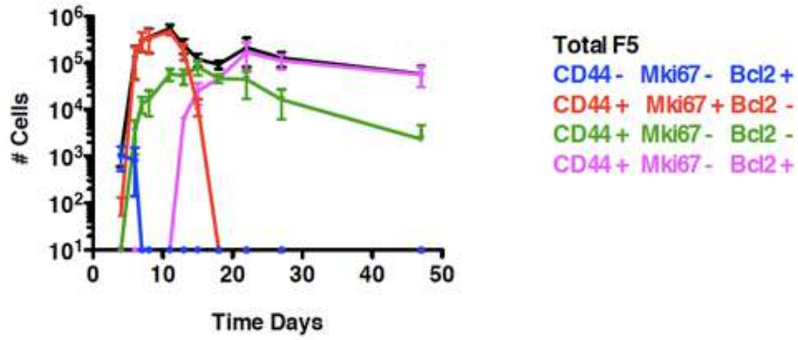
$$X^{i,j,k}(t)=\left(\mu_1^{i,j,k}(t),\mu_2^{i,j,k}(t)\right)$$

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

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

Multiscale Model: Stability



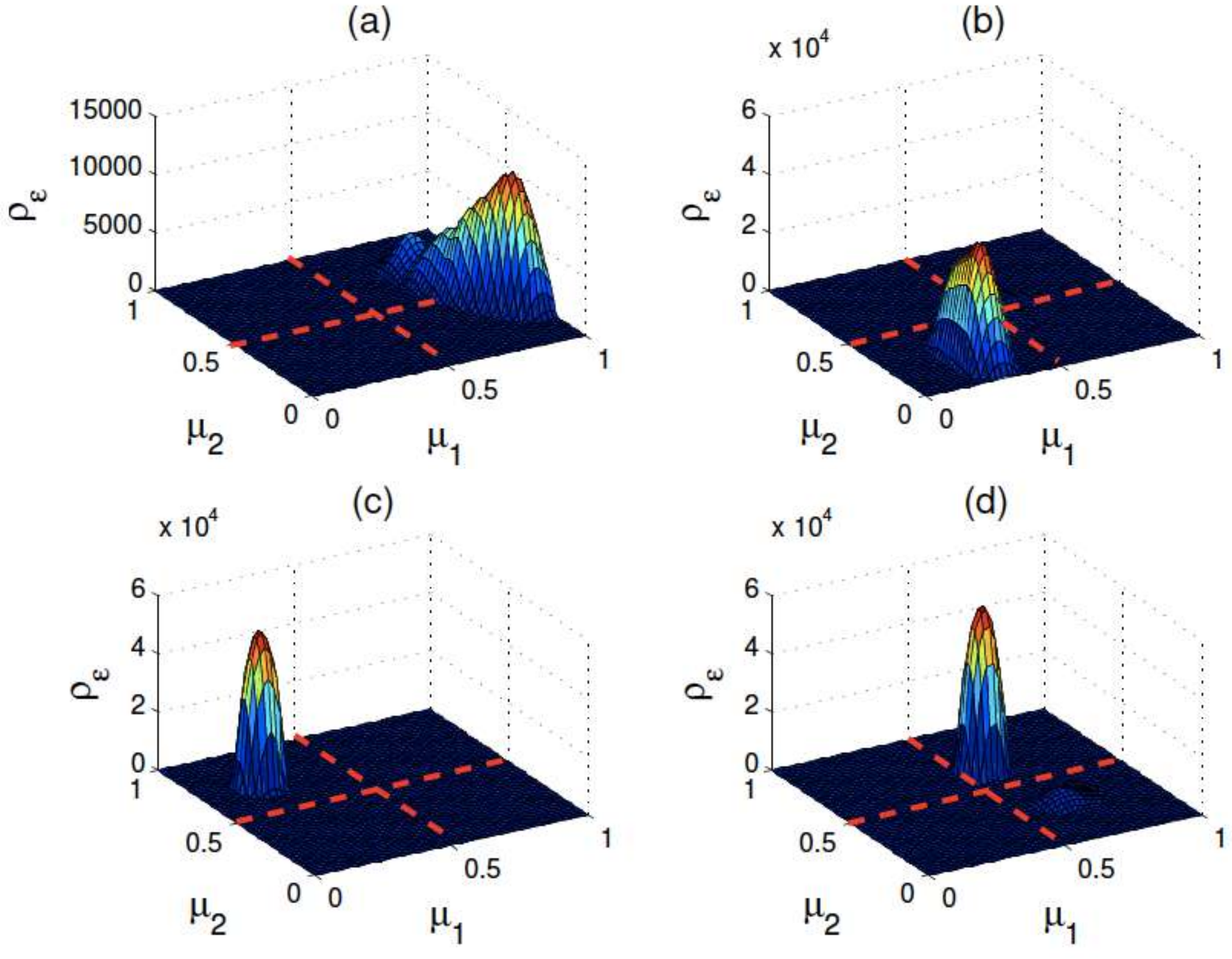
- **Existence and uniqueness of solutions**

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

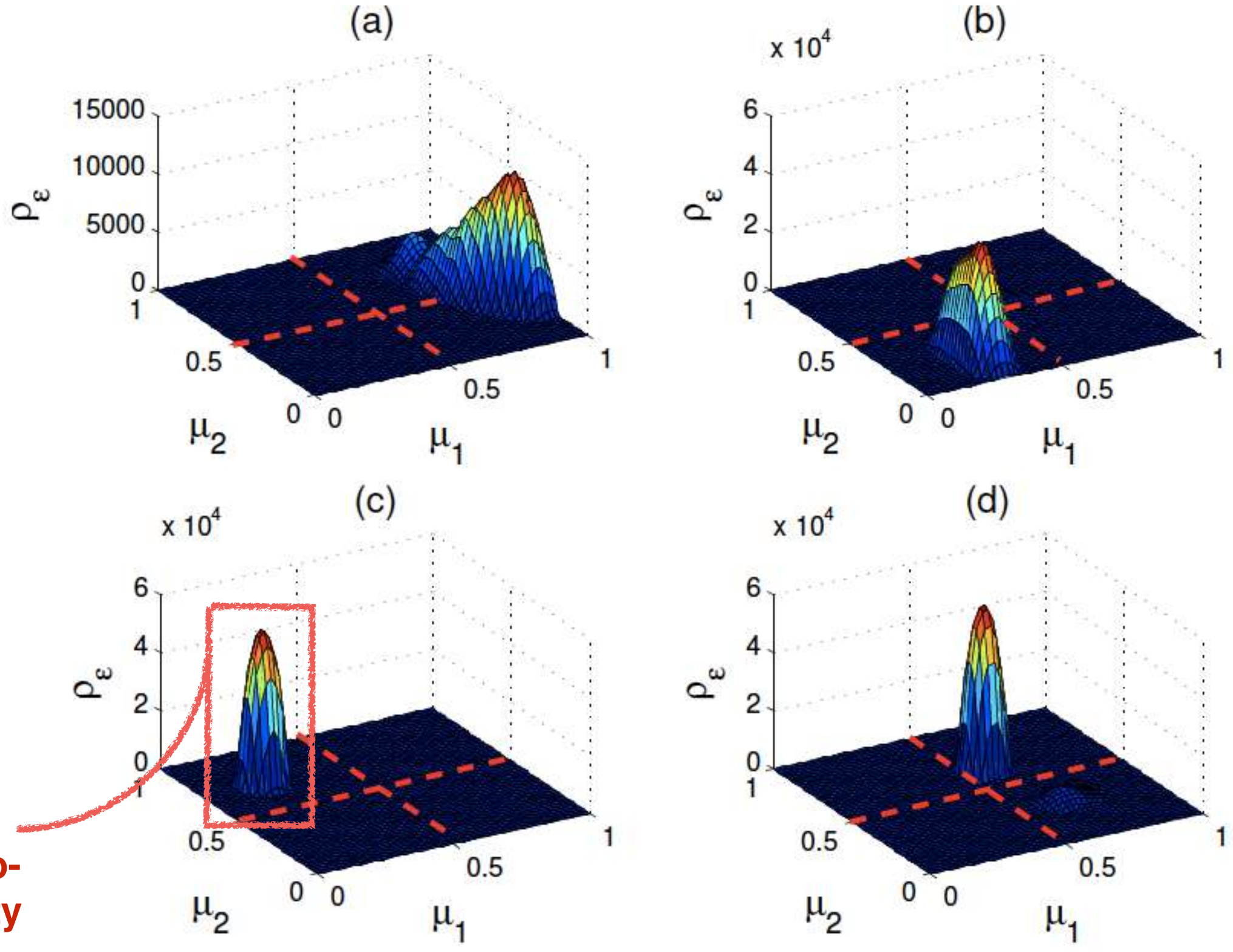
- **Asymptotic stability:**
  Cell population density converges towards Dirac masses located at the steady states of the intracellular model
  [*Friedman et al (2009, 2012)*]

- **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)

Multiscale Model: Results

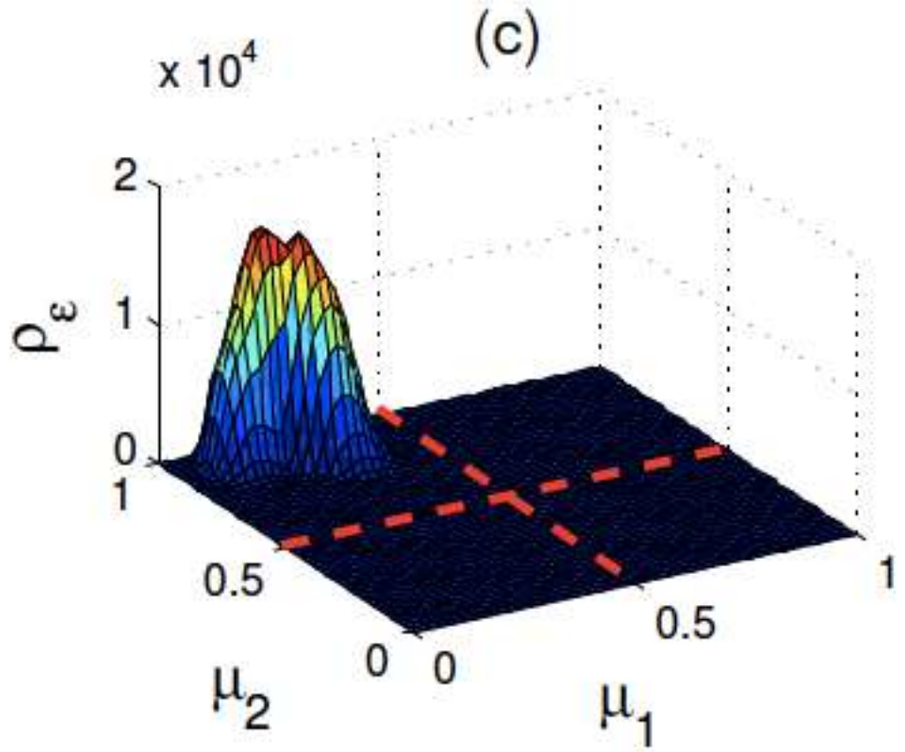


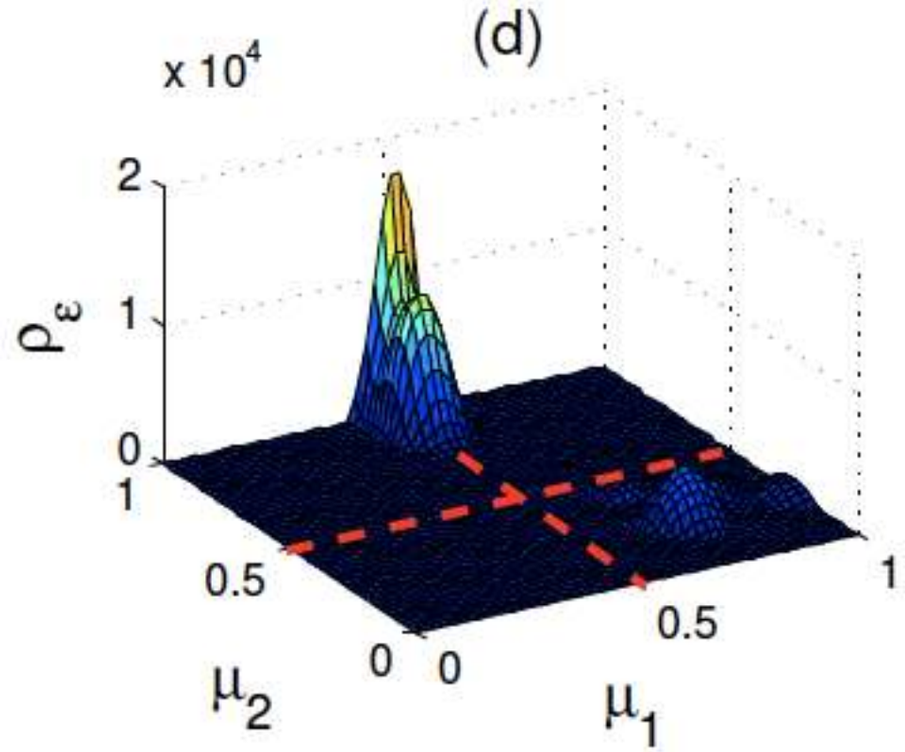
Multiscale Model: Results

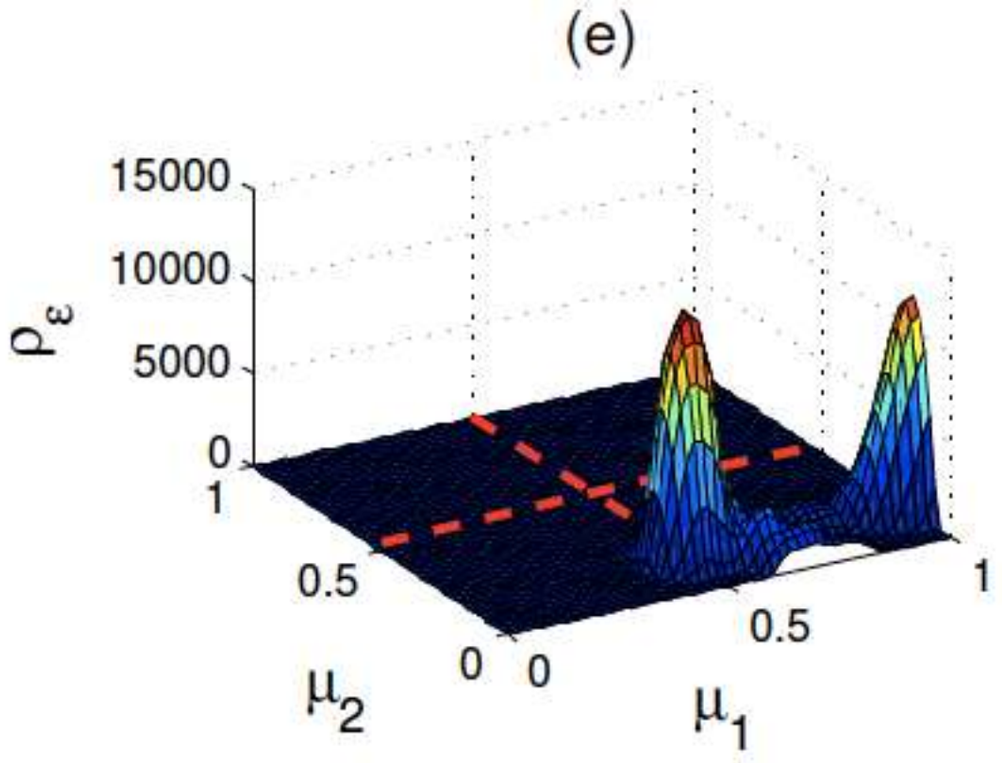


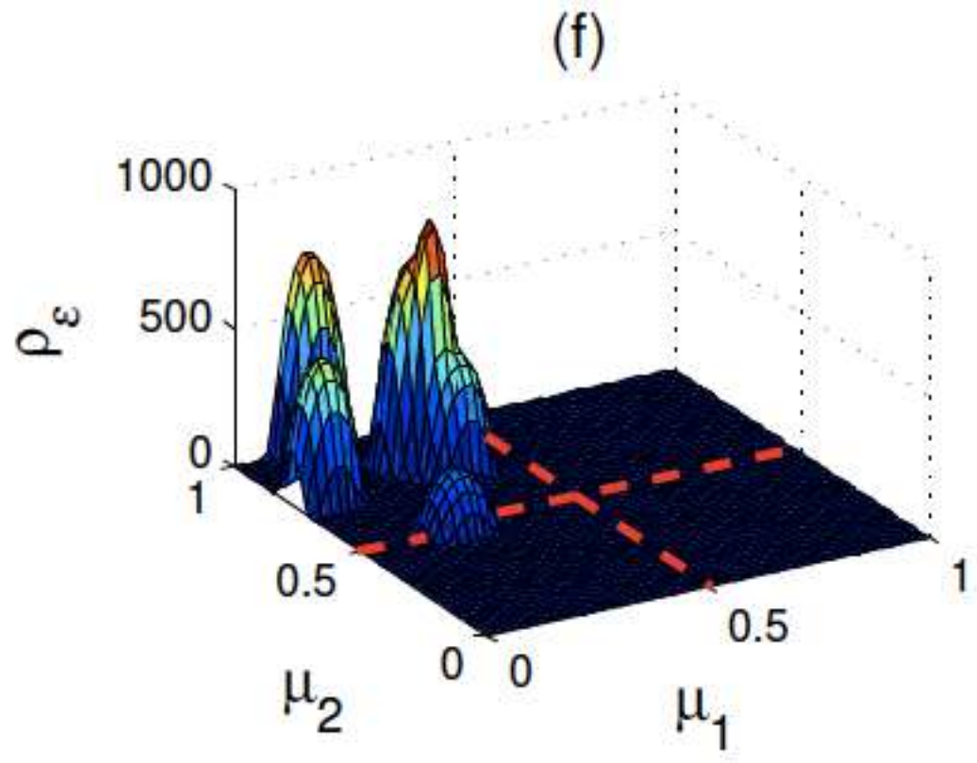
loss of hetero-geneity

Multiscale Model: Results









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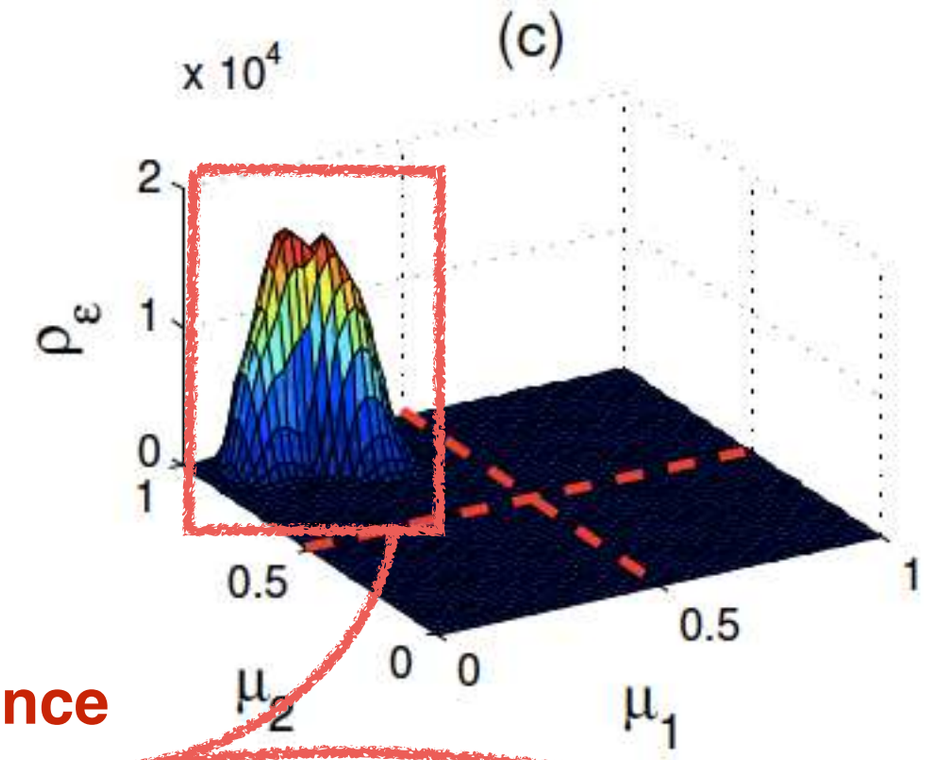
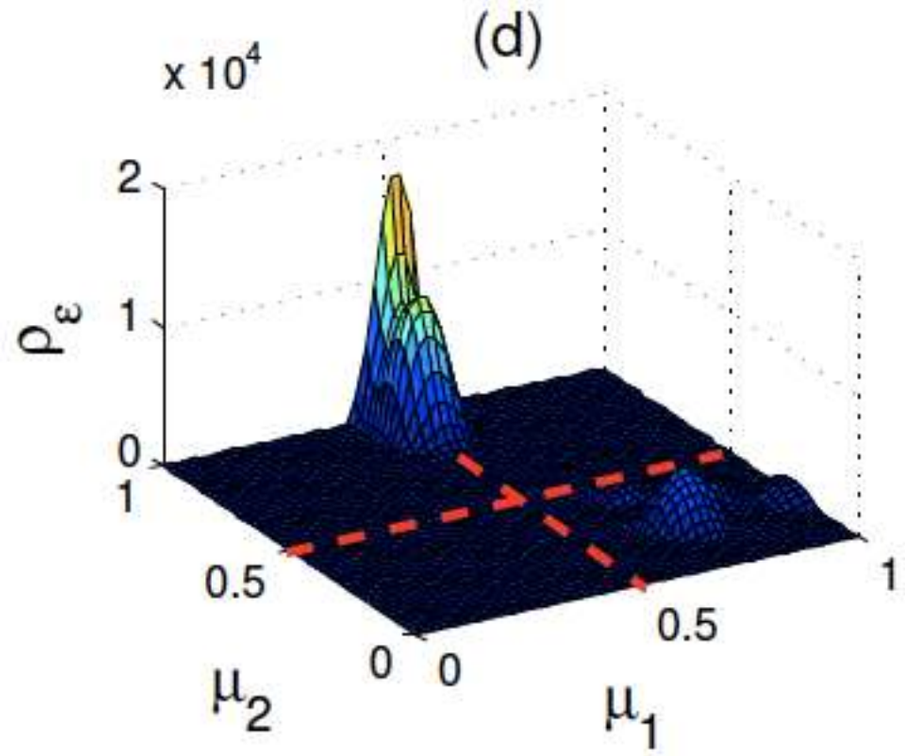
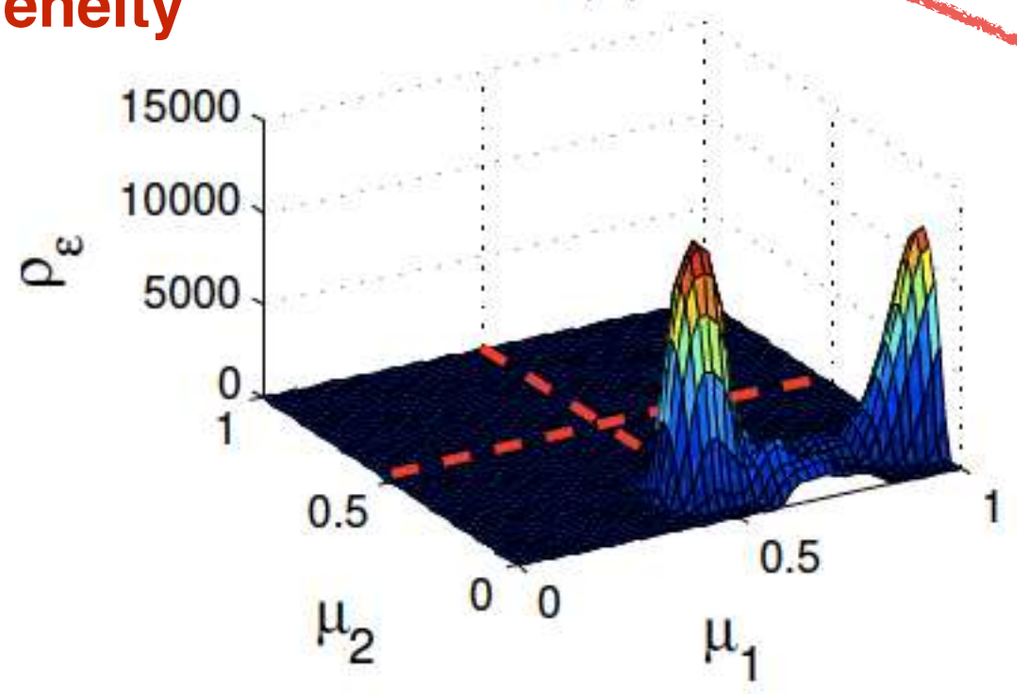
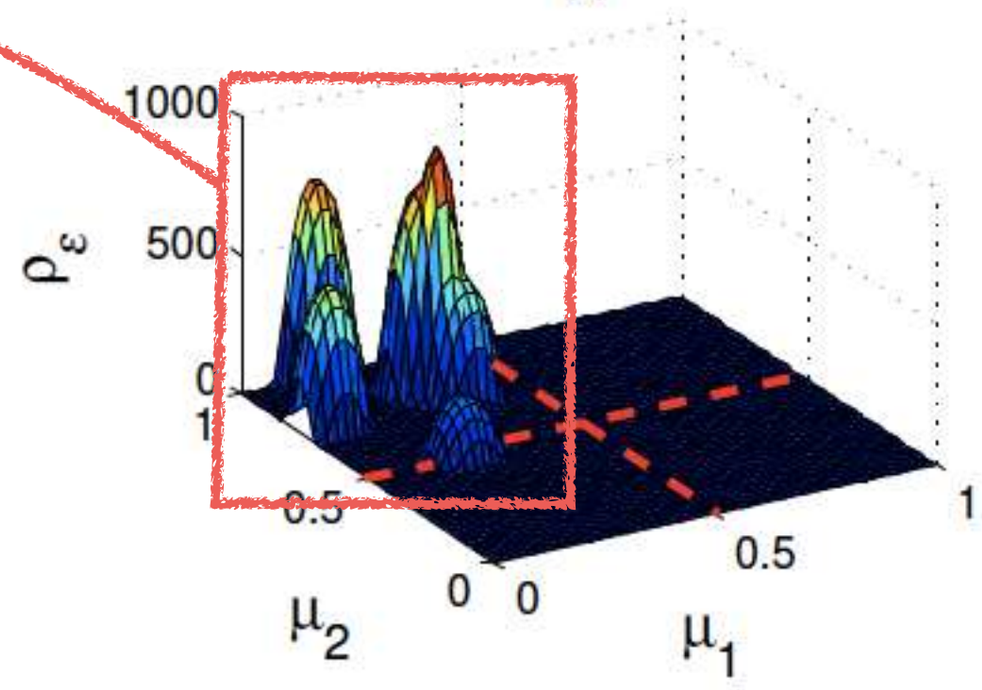




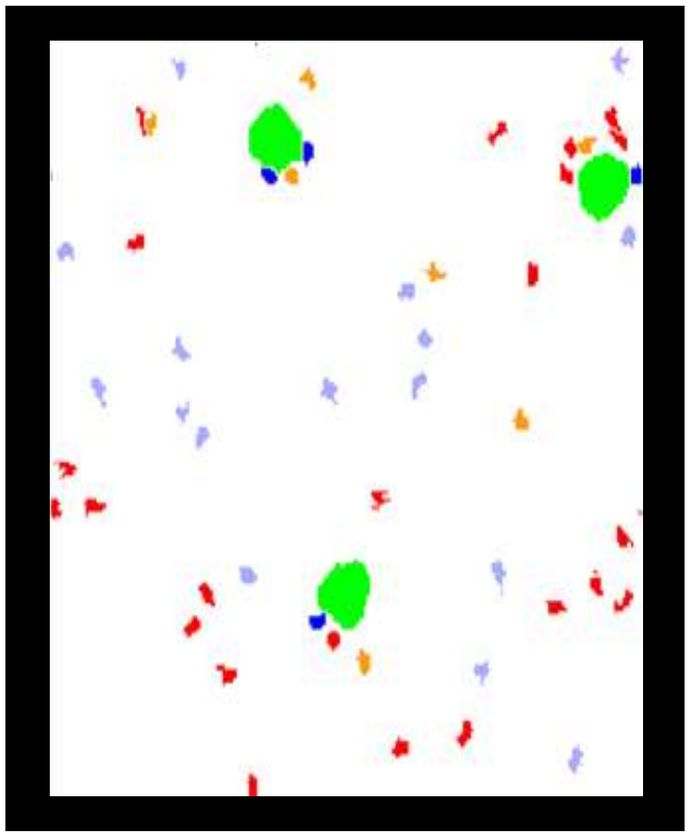
maintenance of heterogeneity

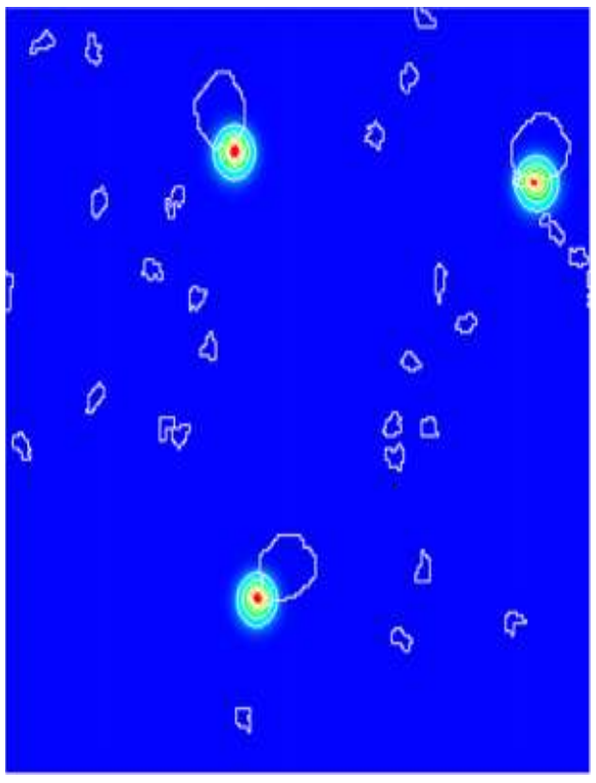


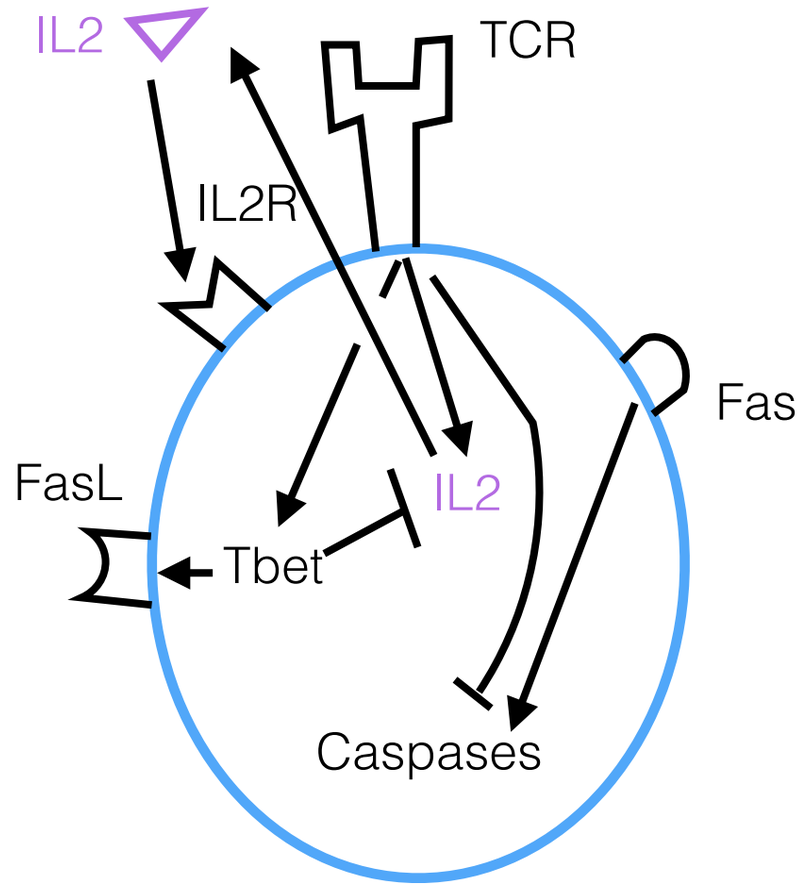


A computational hybrid multiscale model of the CD8 T cell immune response

(Prokopiou et al, 2014 ; Girel's PhD thesis)

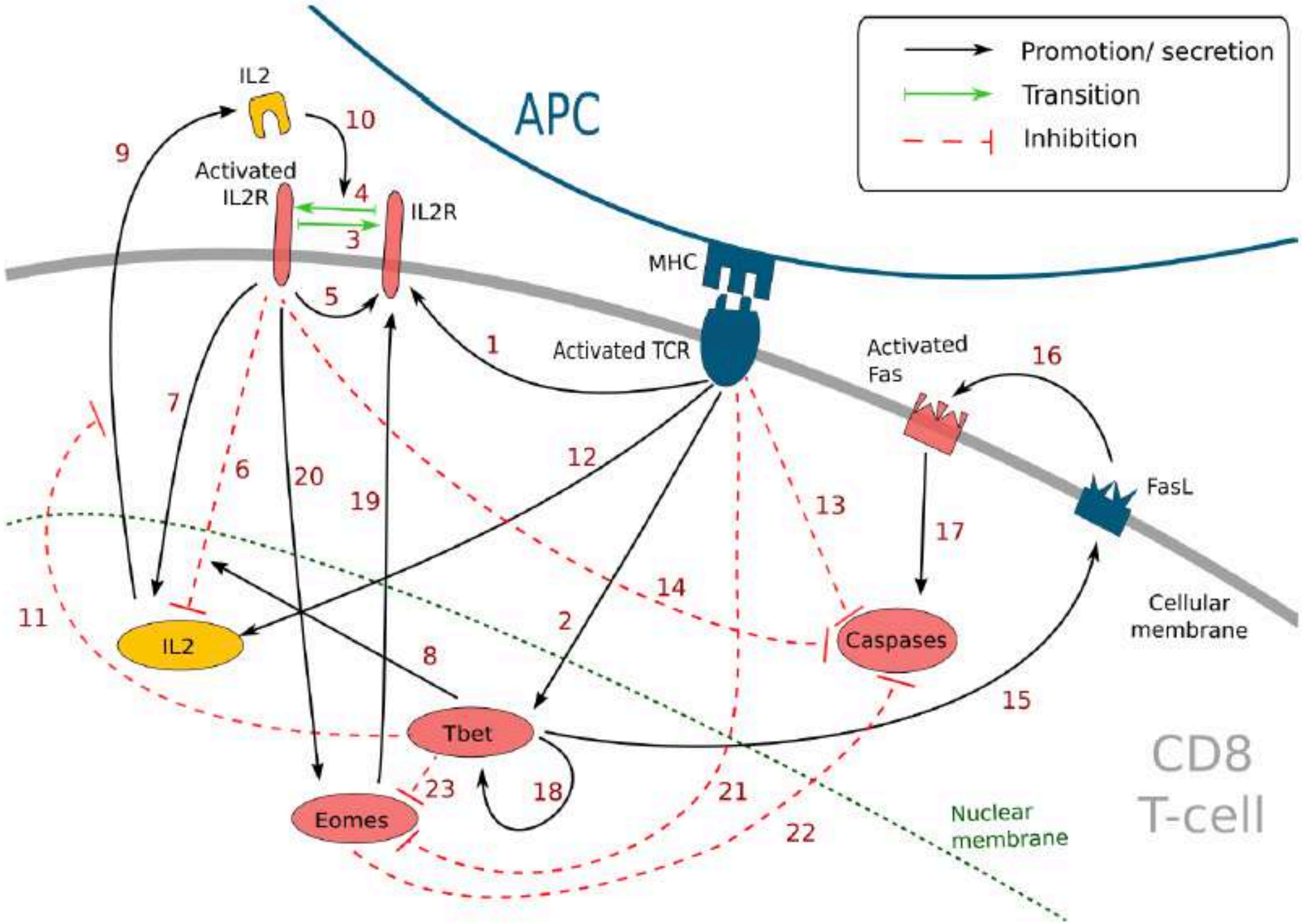






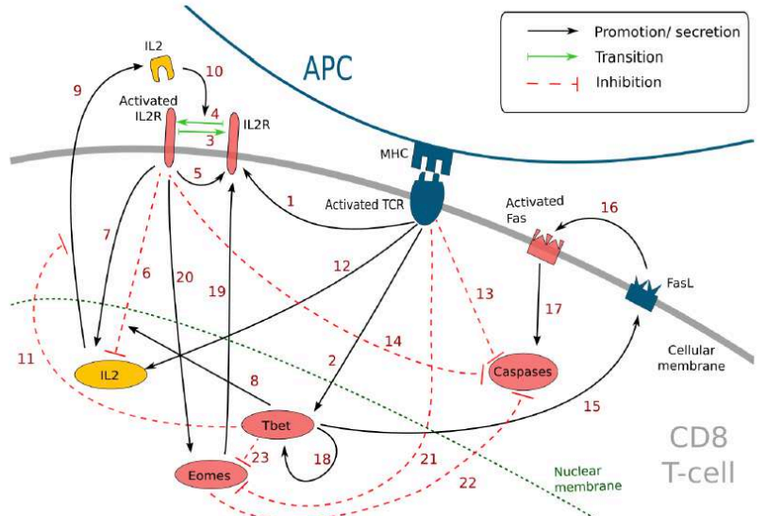
CD8 T cell

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



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

Deterministic nonlinear ordinary differential equations coupled to other cells through membrane dynamics



IL2 receptors

$$\frac{\mathbf{d}}{\mathbf{d}t}[R] = \lambda_{R1} f_{APC} + (\mu^{-}_{IL2} + \lambda_{R2})[L \bullet R] + \lambda_{E1}[E] - \left(\mu^{+}_{IL2}[IL2^{cm}] + k_R\right)[R],$$

IL2-IL2R complex

$$\frac{\mathbf{d}}{\mathbf{d}t}[L \bullet R] = \mu^{+}_{IL2}[IL2^{cm}][R] - \mu^{-}_{IL2}[L \bullet R] - k_e[L \bullet R],$$

Tbet

$$\frac{\mathbf{d}}{\mathbf{d}t}[Tb] = \lambda_{T1} f_{APC} + \lambda_{T2}\frac{[Tb]^n}{\lambda^n_{T3} + [Tb]^n} - k_T[Tb],$$

Activated Fas

$$\frac{\mathbf{d}}{\mathbf{d}t}[Fs^*] = H\mu^{+}_{F}[Tb^{cm}]\left(\frac{\lambda_F}{k_F} - [Fs^*]\right) - \mu^{-}_{F}[Fs^*] - k_F[Fs^*],$$

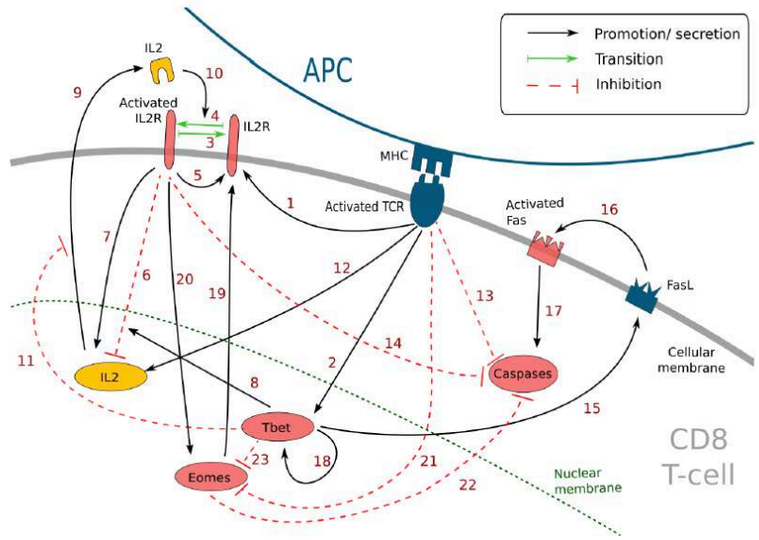
Caspases

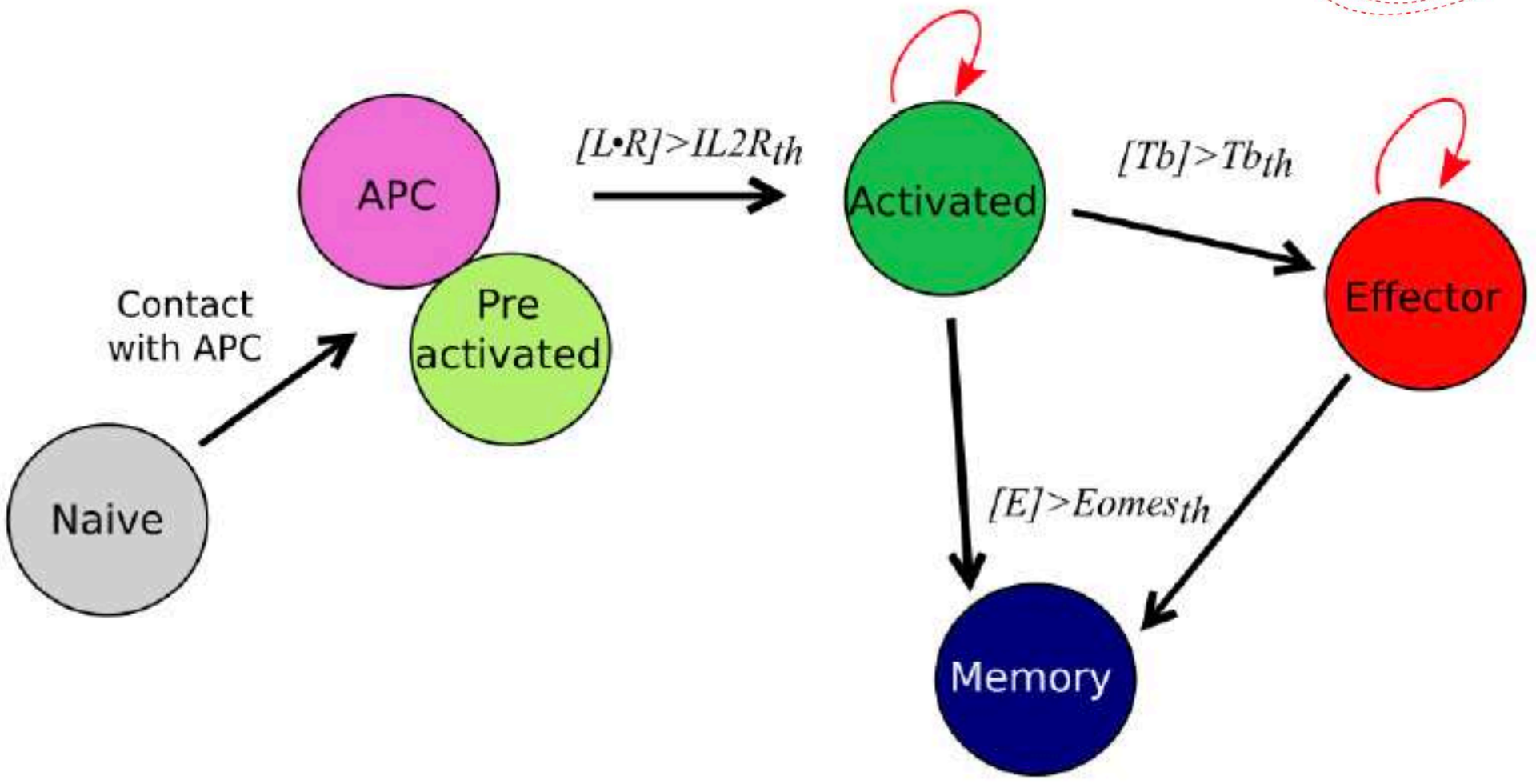
$$\frac{\mathbf{d}}{\mathbf{d}t}[Cas] = G\lambda_{c1}\frac{1}{1+\lambda_{c2}[L \bullet R]} \cdot \frac{1}{1+\lambda_{c3} f_{APC}} \cdot \frac{1}{1+\lambda_{E2}[E]} + \lambda_{c4}[Fs^*] - k_c[Cas],$$

Eomes

$$\frac{\mathbf{d}}{\mathbf{d}t}[E] = \frac{1}{1+\lambda_{E5} f_{APC}} \cdot \left(\frac{\lambda_{E3}[L \bullet R]}{\lambda_{E6} + [L \bullet R]} + \frac{G\lambda_{E4}}{1+\lambda_{E7}[Tb]}\right) - k_E[E].$$

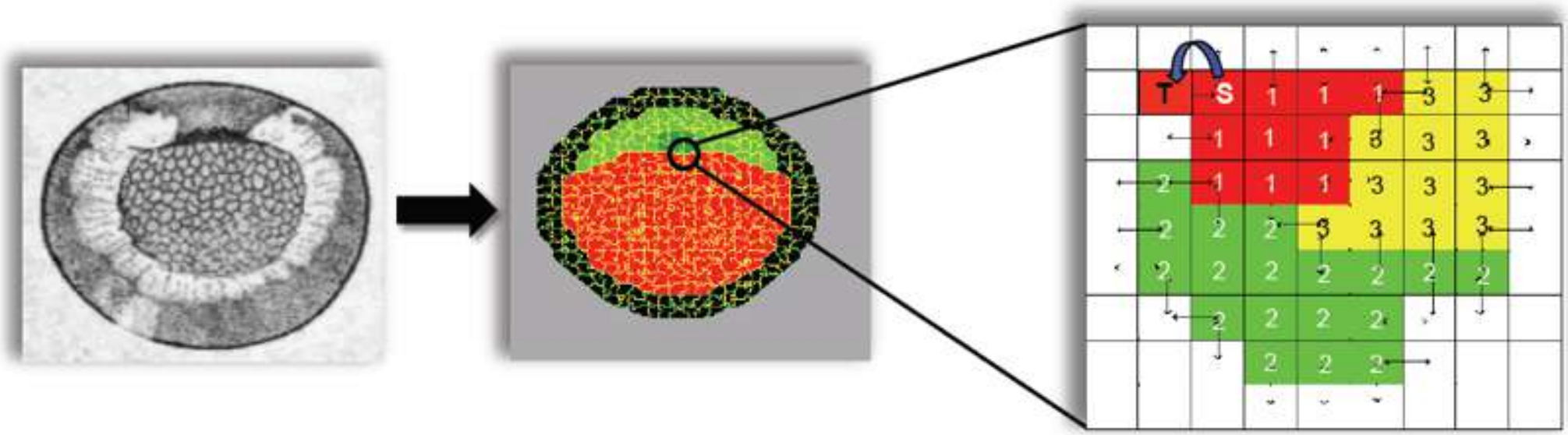
Simplified molecular signaling pathway (for each single CD8 T cell)





Schematic diagram of the linear differentiation pathway

Cellular Potts Model (CompuCell3D)

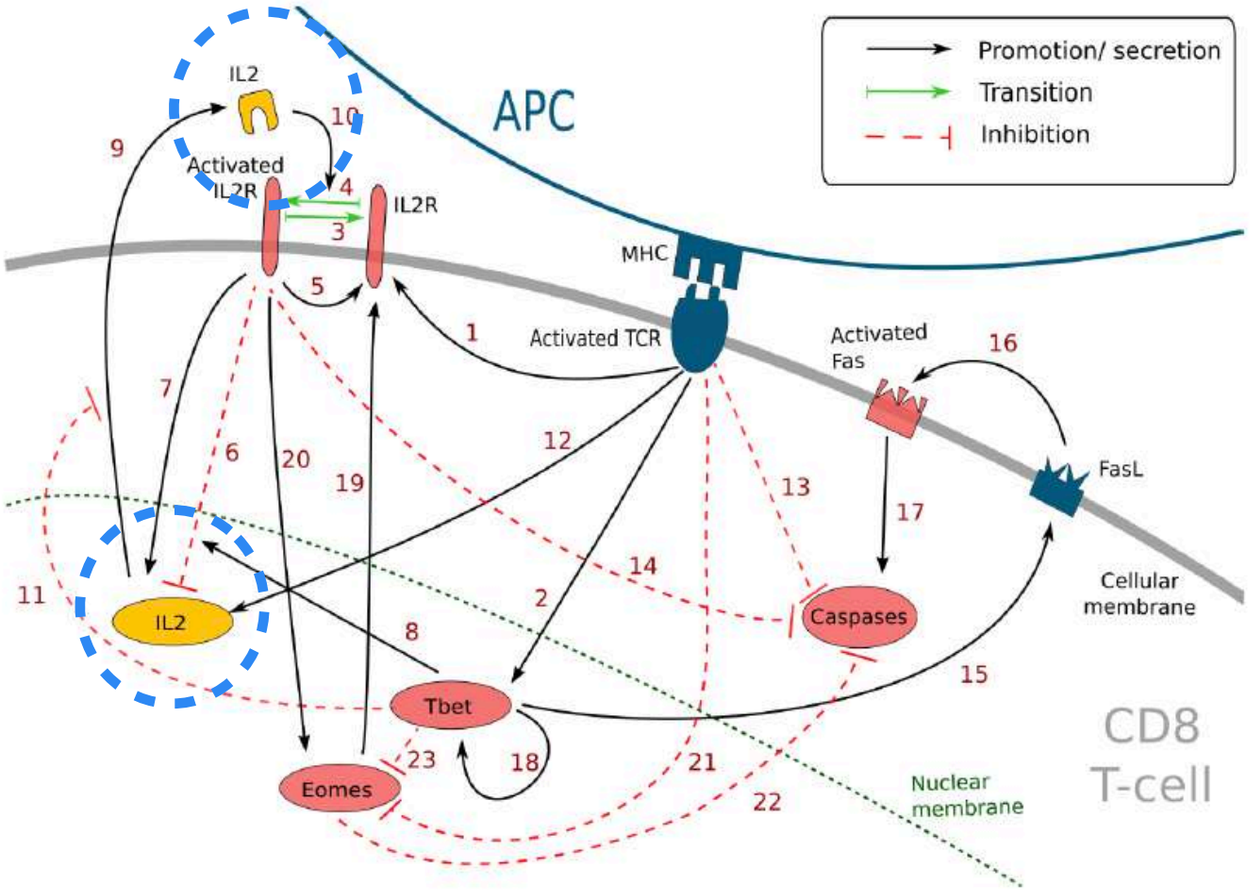


Effective energy

$$\Omega = \underbrace{\lambda_{pm} \sum_{\sigma \neq \sigma_e} (p_\sigma - P_{\tau(\sigma)})^2}_{\text{perimeter}} + \underbrace{\lambda_{area} \sum_{\sigma \neq \sigma_e} (a_\sigma - A_{\tau(\sigma)})^2}_{\text{area}}$$

$$+ \underbrace{\sum_{\text{neighbours } (\vec{x},\vec{x^*})} J_{\tau(\sigma(\vec{x})),\tau(\sigma(\vec{x^*}))} (1 - \delta_{\sigma(\vec{x}),\sigma(\vec{x^*})})}_{\text{contact}},$$

CD8 T cells release IL2 when in contact with an APC



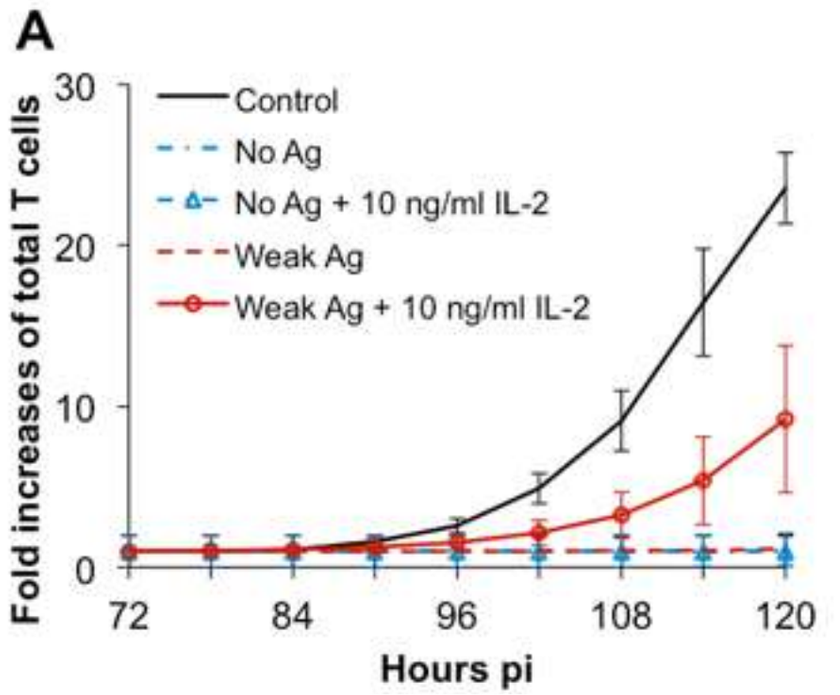
IL2 is *externalized* and *diffuses* in the cell neighborhood:

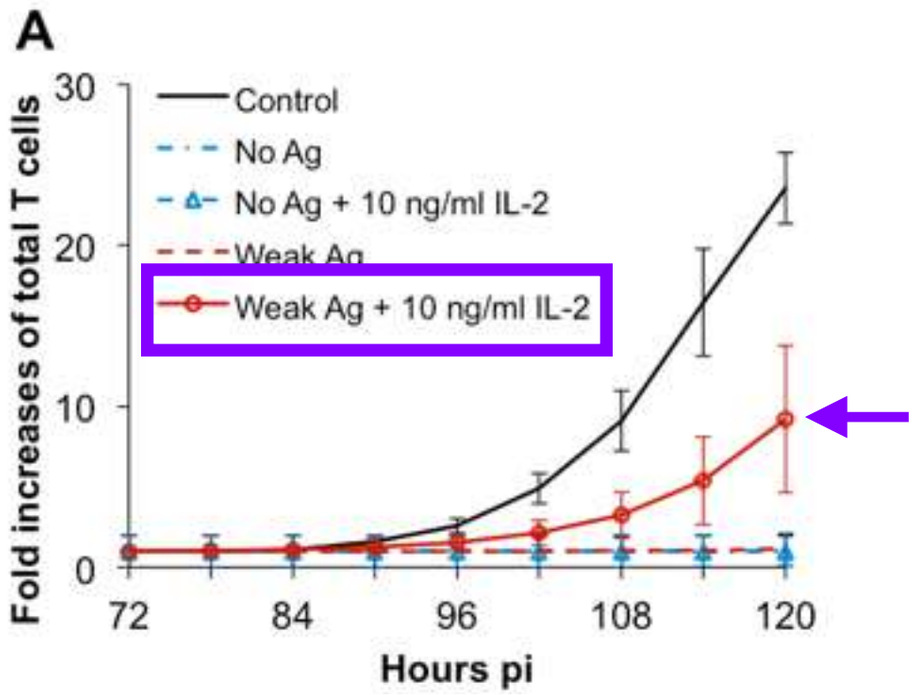
$$\frac{\partial[IL2]}{\partial t} = D\nabla^2[IL2] + \left(\lambda_{R3}\frac{[L \bullet R]}{\lambda_{R4} + [L \bullet R]} + \lambda_1 f_{APC}\right)\frac{1}{1 + \lambda_{T4}[Tb]} - \delta[IL2]$$

Extracellular environment: IL2 secretion and diffusion

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

(Gao et al, 2016)


A
Control
No Ag
No Ag + 10 ng/ml IL-2
Weak Ag
Weak Ag + 10 ng/ml IL-2
Fold increases of total T cells
30
20
10
0
72
84
96
108
120
Hours pi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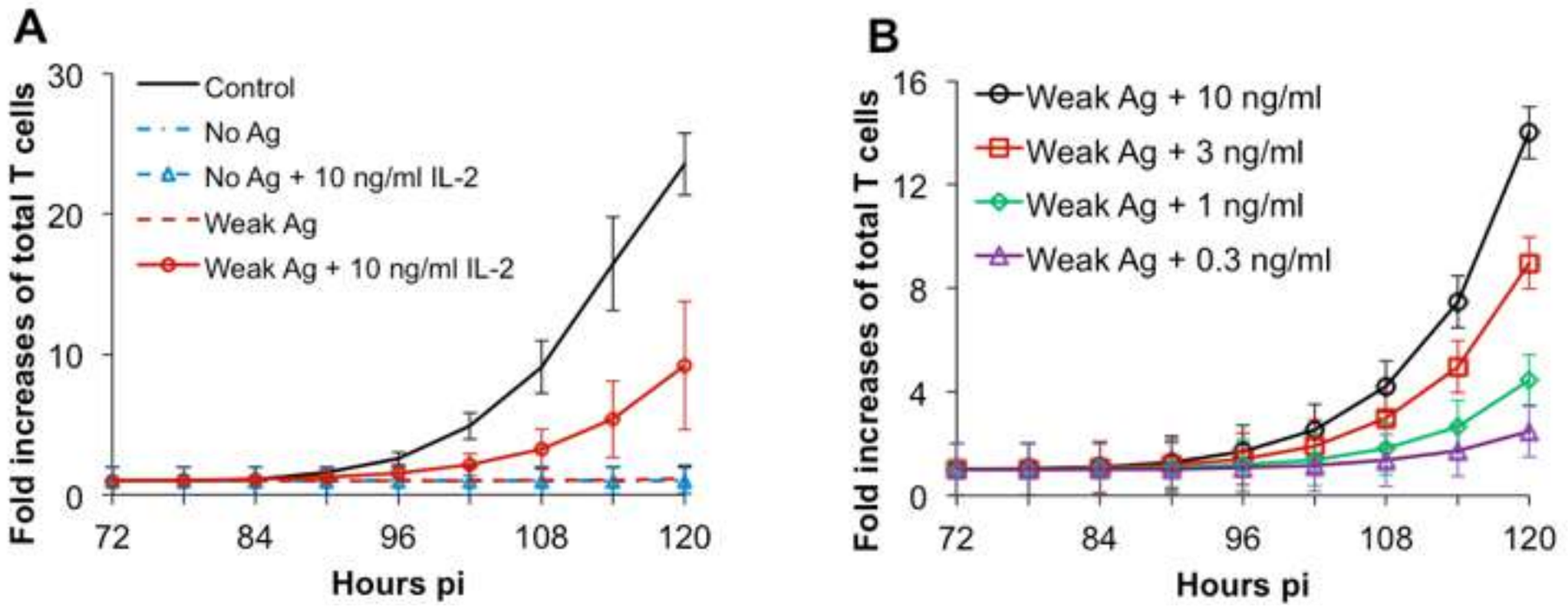
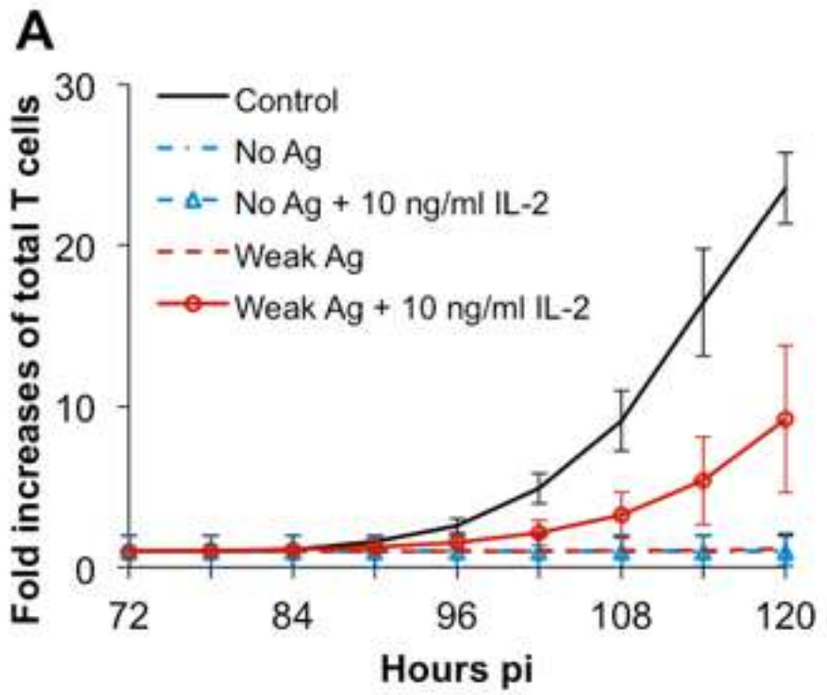
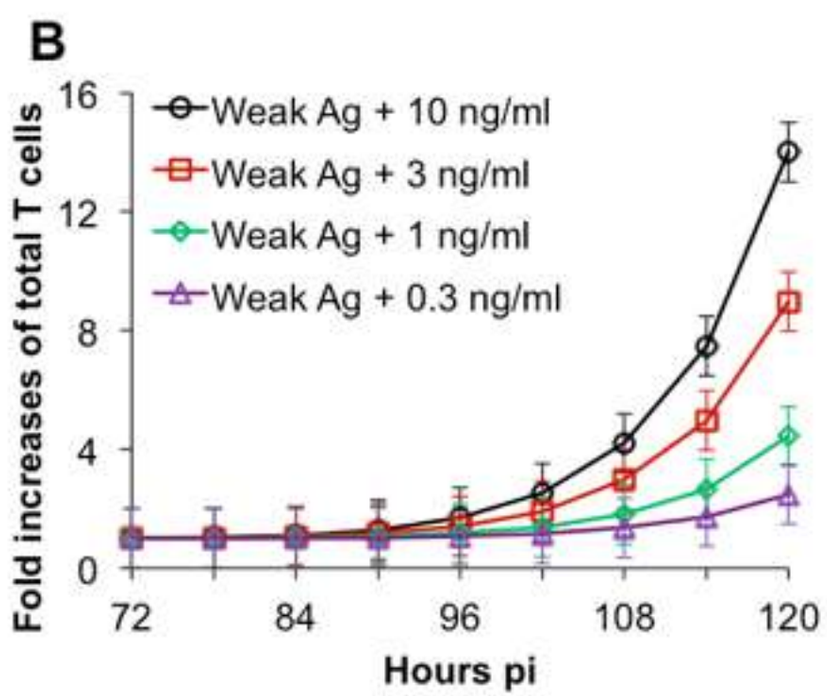
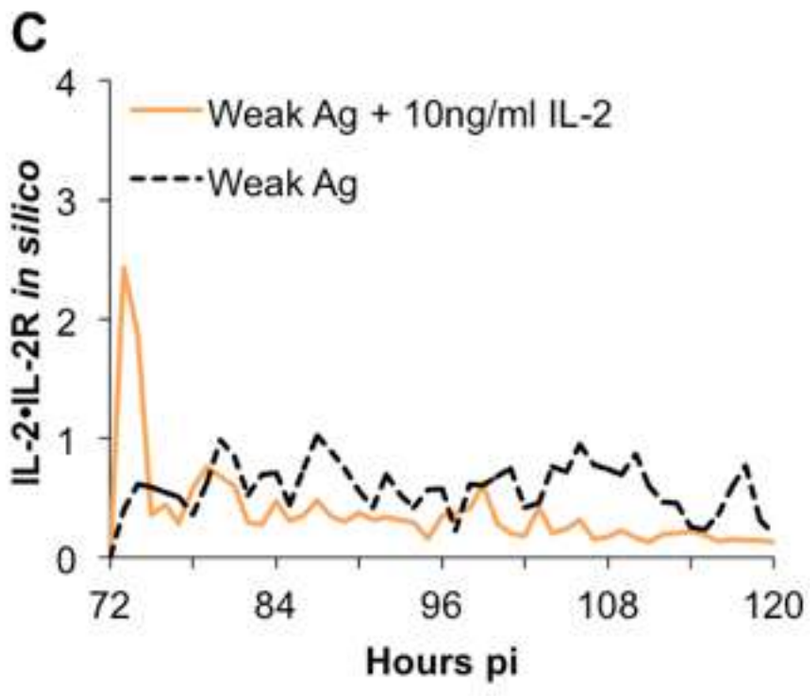
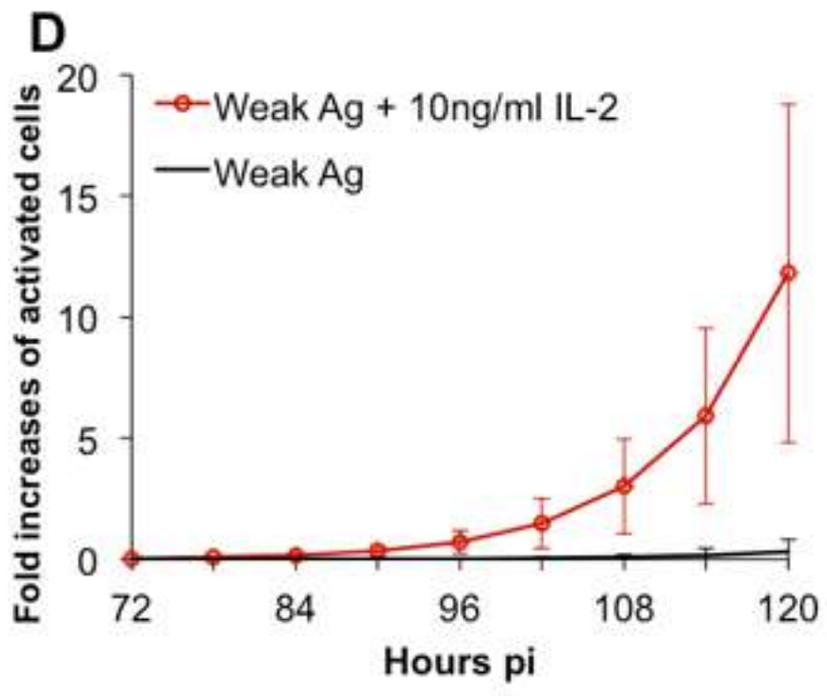
120
Hours pi

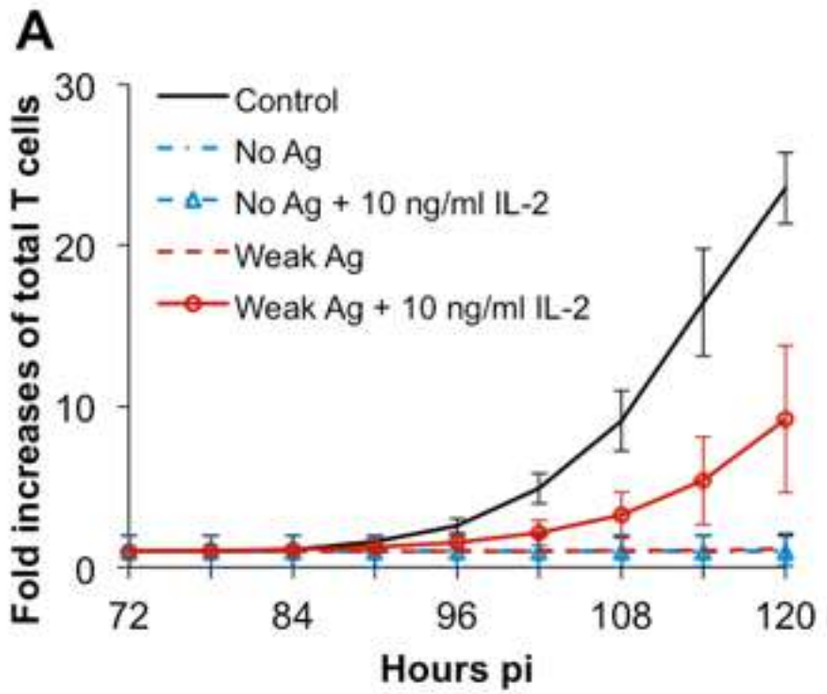

A
Fold increases of total T cells
30
20
10
0
Control
No Ag
No Ag + 10 ng/ml IL-2
Weak Ag
Weak Ag + 10 ng/ml IL-2
72
84
96
108
120
Hours pi
B
Fold increases of total T cells
16
12
8
4
0
Weak Ag + 10 ng/ml
Weak Ag + 3 ng/ml
Weak Ag + 1 ng/ml
Weak Ag + 0.3 ng/ml
72
84
96
108
120
Hours pi

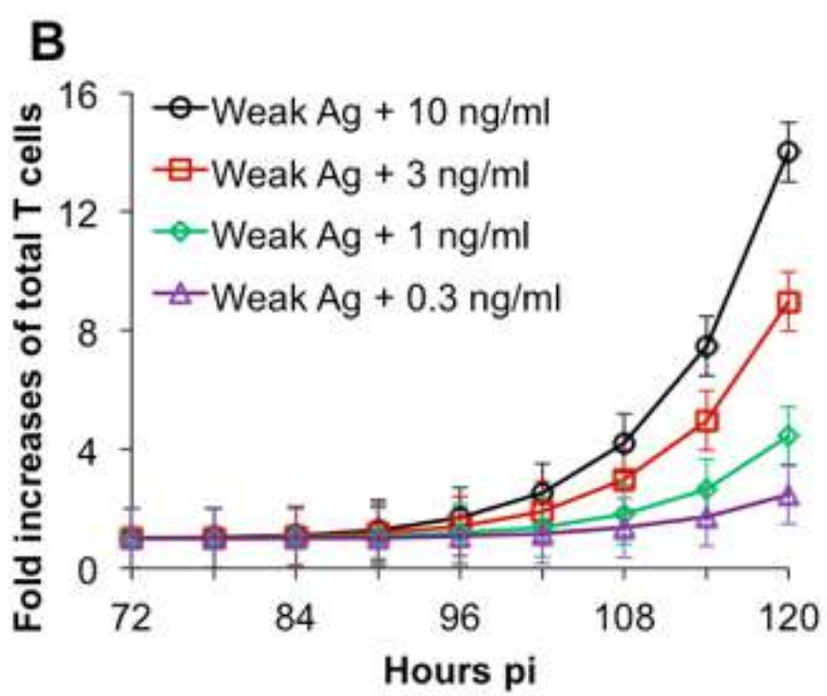

A
Control
No Ag
No Ag + 10 ng/ml IL-2
Weak Ag
Weak Ag + 10 ng/ml IL-2
Fold increases of total T cells
0
10
20
30
72
84
96
108
120
Hours pi

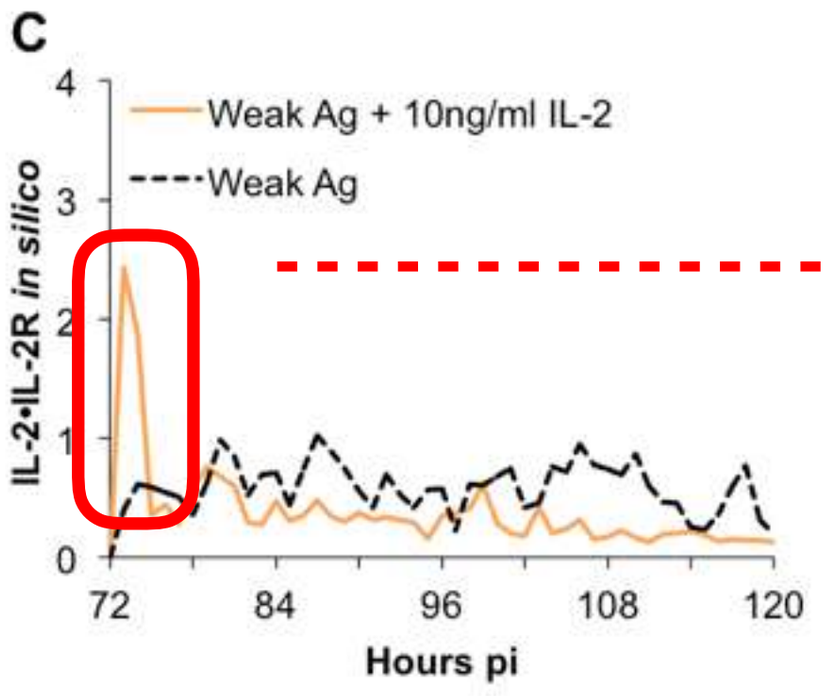

B
Weak Ag + 10 ng/ml
Weak Ag + 3 ng/ml
Weak Ag + 1 ng/ml
Weak Ag + 0.3 ng/ml
Fold increases of total T cells
0
4
8
12
16
72
84
96
108
120
Hours pi

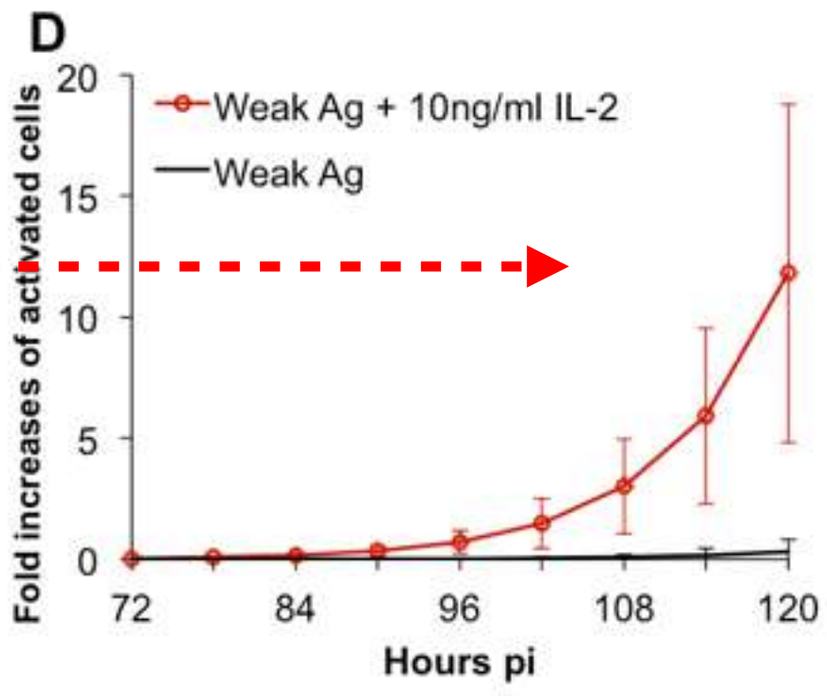

C
Weak Ag + 10ng/ml IL-2
Weak Ag
IL-2•IL-2R in silico
0
1
2
3
4
72
84
96
108
120
Hours pi


D
Weak Ag + 10ng/ml IL-2
Weak Ag
Fold increases of activated cells
0
5
10
15
20
72
84
96
108
120
Hours pi


A
Control
No Ag
No Ag + 10 ng/ml IL-2
Weak Ag
Weak Ag + 10 ng/ml IL-2
Fold increases of total T cells
Hours pi

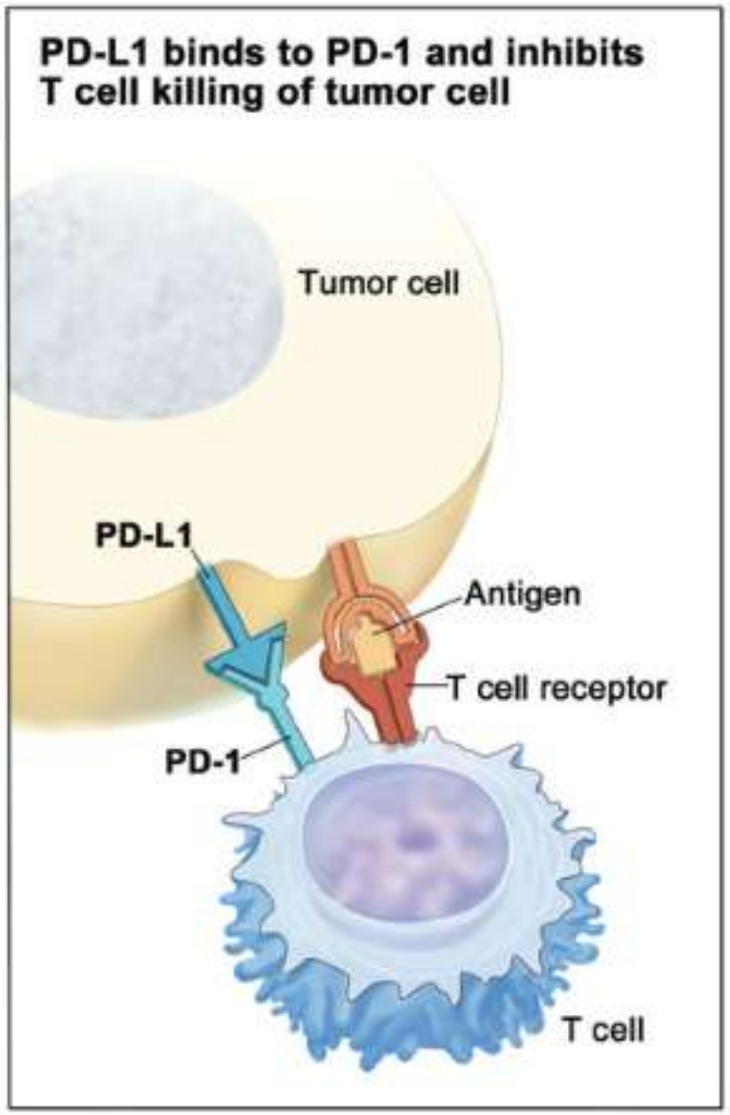

B
Weak Ag + 10 ng/ml
Weak Ag + 3 ng/ml
Weak Ag + 1 ng/ml
Weak Ag + 0.3 ng/ml
Fold increases of total T cells
Hours pi

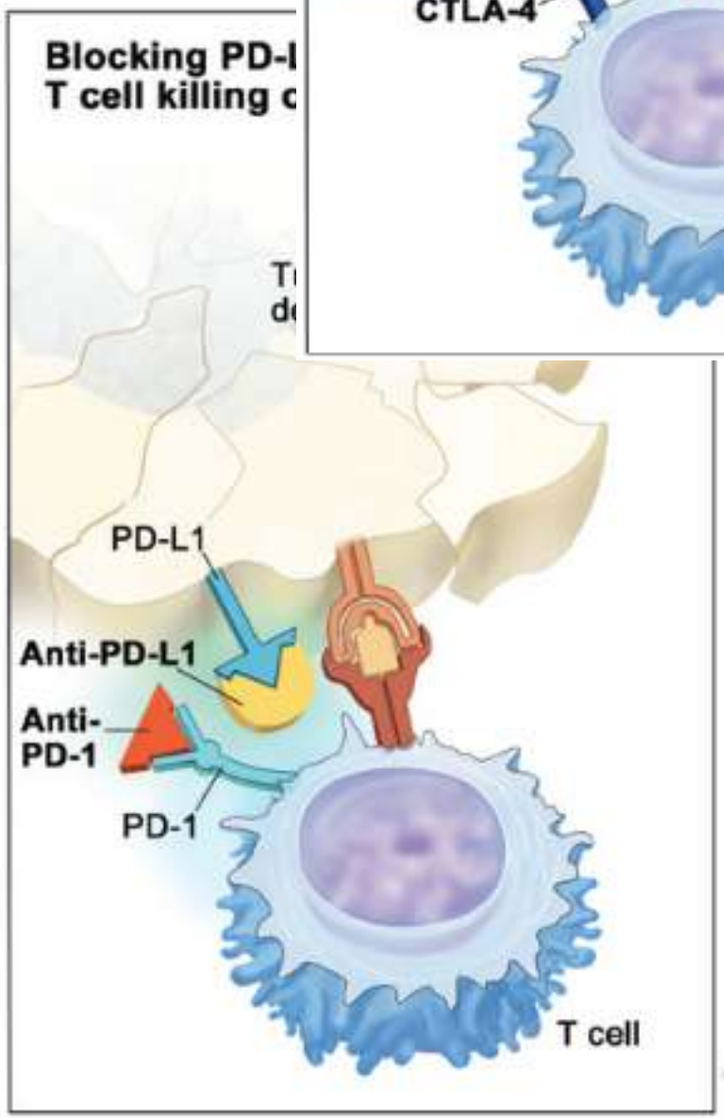

C
Weak Ag + 10ng/ml IL-2
Weak Ag
IL-2•IL-2R in silico
Hours pi

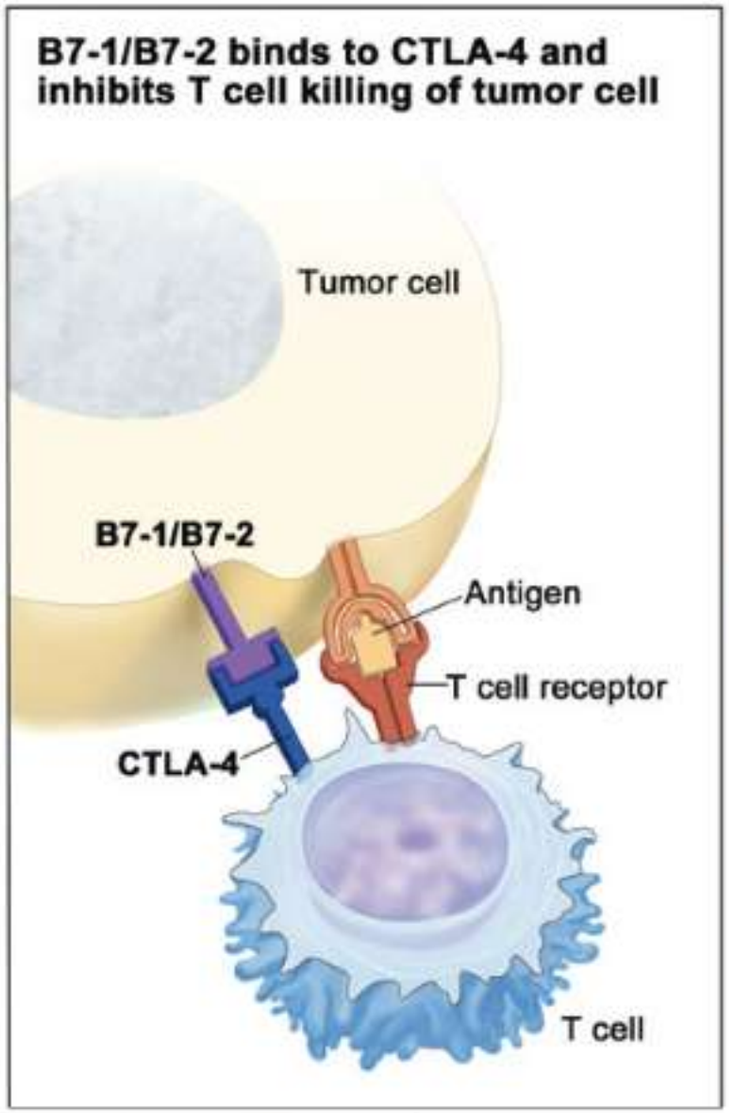

D
Weak Ag + 10ng/ml IL-2
Weak Ag
Fold increases of activated cells
Hours pi

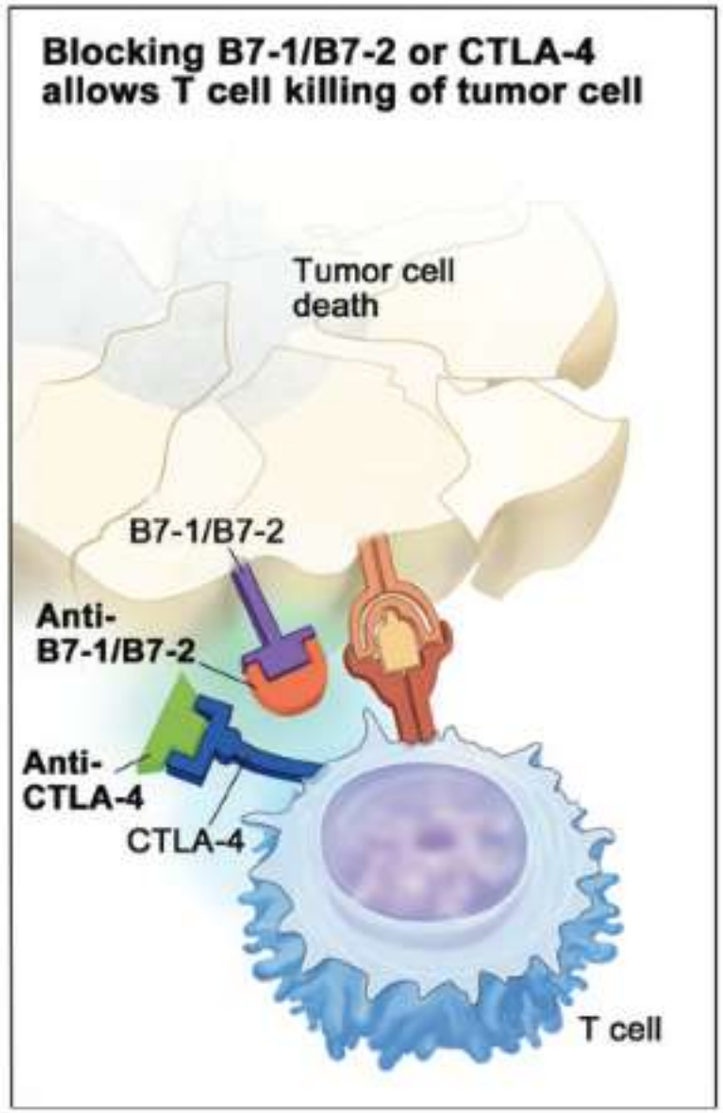
Towards multiscale models of cancer immunotherapies including molecular signaling pathways?

Immune Checkpoint Inhibitors





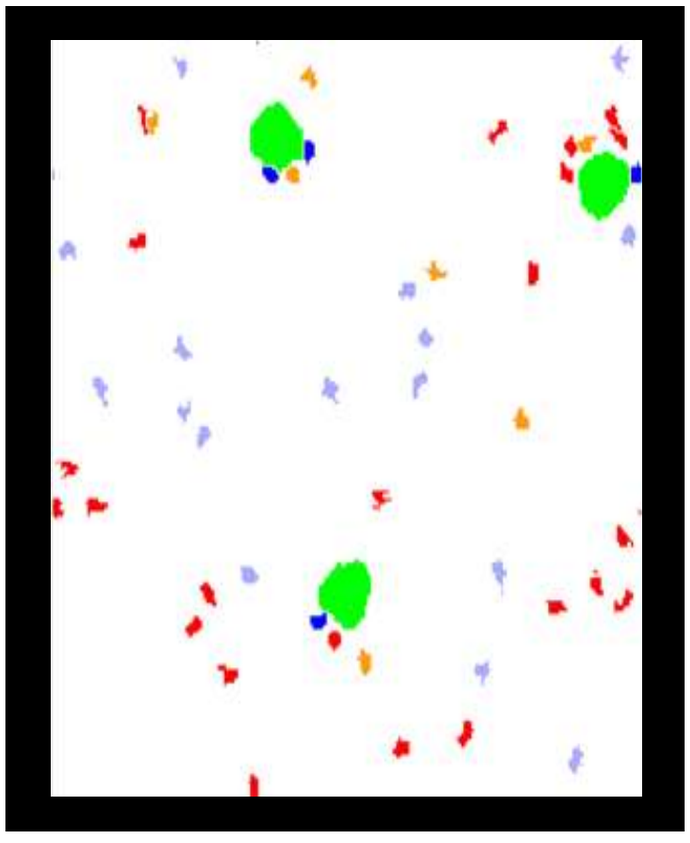




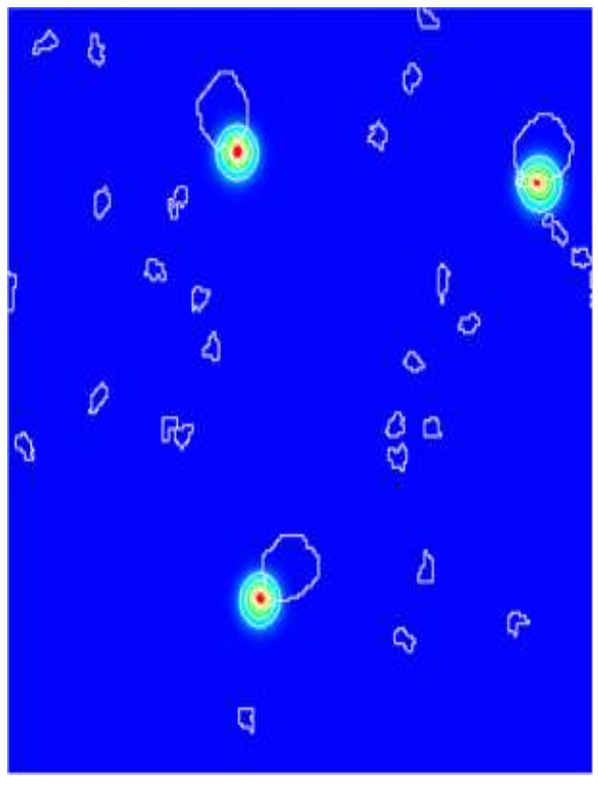
NationalCancer Institute

Multiscale Models of Immune Checkpoint Inhibitors?

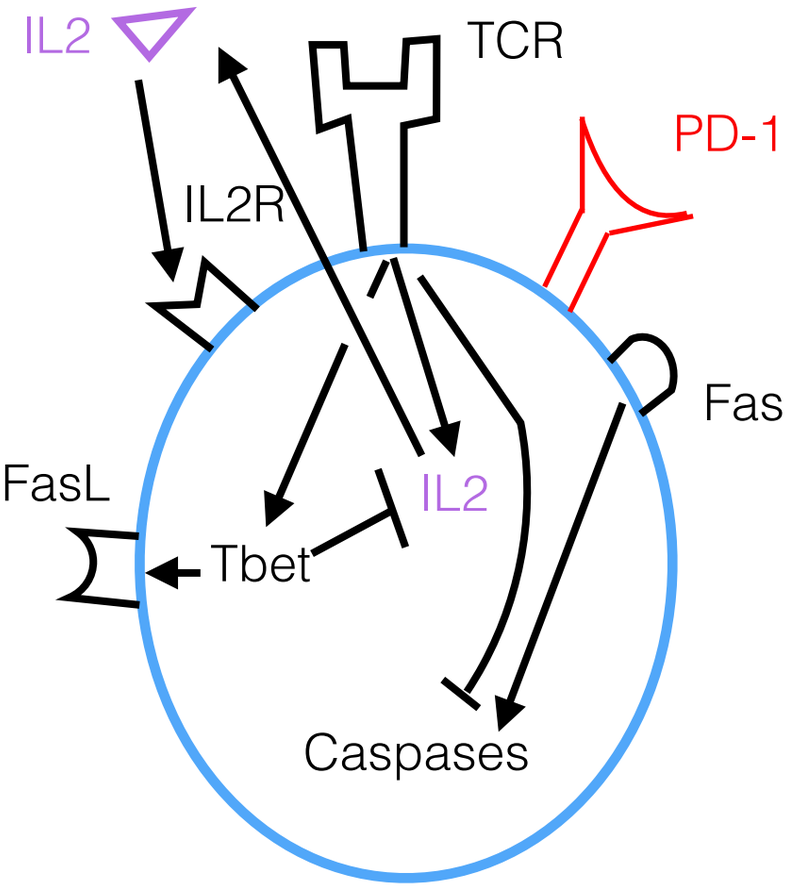
Add Tumor ? Treatment ? Signaling pathways ?



Cell Population



Extracellular



Single Cell

Thanks for your attention

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Mélanie Wencker

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PrediVac Project
Innovative modeling tools
for the prediction of CD8 T cell
based vaccine efficacy