Competition between cancer and immune system cells: A thermostatted kinetic theory approach

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Outline

Biological context: Competition between immune system and cancer

The model

- interactions
- thermostat of cell activity
- kinetic equations
- adaptation of a kinetic Monte Carlo algorithm introduced for dilute gases

Results

- reproduction of the 3 E's (elimination, equilibrium, escape) of immunotherapy
- spatio-temporal evolution of a tumor (pseudo-oscillations, waves, …)

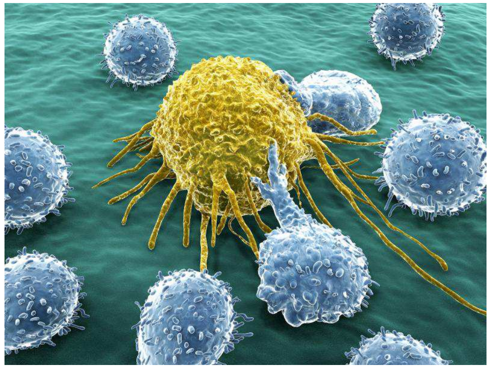
Conclusions and perspectives

Competition between immune system and cancer

Different types of immune system cells

Dendritic cells
- ingest cancer cells
- isolate antigens
- present antigens to T cells
- trigger activation and proliferation of T cells including killer T cells

Cancer cells
- proliferate
- develop the ability to blend into the surrounding tissue
- may mislead the immune system cells which limit their own production (regulatory T cells)



Competition between immune system and cancer

Model?

A single type of immune system cells I, cancer cells C, normal cells N

- Proliferation (division) $\quad \mathrm{I} \rightarrow \mathrm{I} + \mathrm{I} \qquad \mathrm{C} \rightarrow \mathrm{C} + \mathrm{C}$

- Cell death $\quad \mathrm{I} \rightarrow \phi \qquad \mathrm{C} \rightarrow \phi$

- Interactions (if I=killer T cell) $\quad \mathrm{I} + \mathrm{C} \rightarrow \mathrm{I}$

- Mutations $\quad \mathrm{N} \rightarrow \mathrm{C}$

- Activation (learning)? $\quad$ Cells possess an activity u

The model (interactions)

Only 3 processes including interaction, activation, proliferation (or death)

Learning = increase of activity by ε

if $u > u'$

$$\mathrm{I}(u) + \mathrm{C}(u') \longrightarrow \mathrm{I}(u+\varepsilon) + \mathrm{I}(u')$$

$$\mathrm{C}(u) + \mathrm{I}(u') \longrightarrow \mathrm{C}(u+\varepsilon) + \mathrm{C}(u')$$

$$\begin{cases} \mathrm{C}(u) + \mathrm{N}(u') \longrightarrow \mathrm{C}(u+\varepsilon) + \mathrm{C}(u') \\ \text{Reservoir} \longrightarrow \mathrm{N}(u'') \end{cases}$$

Bianca, Lemarchand, J. Chem.Phys. **145**, 154108 (2016)

The model (interactions)

proliferation = autocatalytic processes

Rate constants proportional to the relative activity of the interacting couple

if $u > u'$

$$\mathrm{I}(u) + \mathrm{C}(u') \xrightarrow{k_{ic}(u'-u)} \mathrm{I}(u+\varepsilon) + \mathrm{I}(u')$$

$$\mathrm{C}(u) + \mathrm{I}(u') \xrightarrow{k_{ci}(u'-u)} \mathrm{C}(u+\varepsilon) + \mathrm{C}(u')$$

$$\begin{cases} \mathrm{C}(u) + \mathrm{N}(u') \xrightarrow{k_{nc}(u'-u)} \mathrm{C}(u+\varepsilon) + \mathrm{C}(u') \\ \text{Reservoir} \longrightarrow \mathrm{N}(u'') \end{cases}$$

The model (thermostat of cell activity)

Regulation of cell activity using a “thermostat” mimicking loss of information due to:
- cell death
- Action of regulatory T cells

Mechanics

$$m\frac{\mathrm{d}v}{\mathrm{d}t} = E - \alpha v$$

By analogy

$$\frac{\mathrm{d}u}{\mathrm{d}t} = E - \alpha u$$

$$\left\langle u^2 \right\rangle \approx \mathrm{Const} \Rightarrow \alpha = \frac{\langle u \rangle E}{\left\langle u^2 \right\rangle}$$

Kinetic theory approach

Distribution function $f_j(t, x, v, u)$ for each type of cell $j = i, c, n$

Interactions

$$(\partial_t + \boldsymbol{v} \cdot \nabla_{\boldsymbol{x}}) f_j(t, \boldsymbol{x}, \boldsymbol{v}, u) + \partial_u \left((E - \alpha u) f_j \right) = I_j + V_j$$

Advection

'Thermostat'
controls activity fluctuations

Velocity randomization

Example $j{=}i$

$$I_i = \int_{\mathbb{R}^+} k_{ic}(u - \epsilon - u')H(u - \epsilon - u')f_c(t, u')f_i(t, u - \epsilon)\mathrm{d}u'$$
$$+ \int_{\mathbb{R}^+} k_{ic}(u' - u)H(u' - u)f_c(t, u)f_i(t, u')\mathrm{d}u'$$
$$- \int_{\mathbb{R}^+} k_{ci}(u' - u)H(u' - u)f_c(t, u')f_i(t, u)\mathrm{d}u'.$$

$I + C \rightarrow 2I$

$C + I \rightarrow 2C$

Wennberg, Wondmagegne, J Stat Phys **124**, 859 (2006)
Masurel, Bianca, Lemarchand, AIP Conference Proc. **2132**, 190005 (2019)

Adaptation of the Direct Simulation Monte Carlo method

During Δt

- Interactions in each spatial box $\Rightarrow$ updating of natures *j* and activities *u*
- Updating of positions *x*
- Randomization of velocities *v*
- Thermalization $\Rightarrow$ updating of activities *u*

Simulation algorithm

- Cancer cell
- Immune system cell
- Normal cell

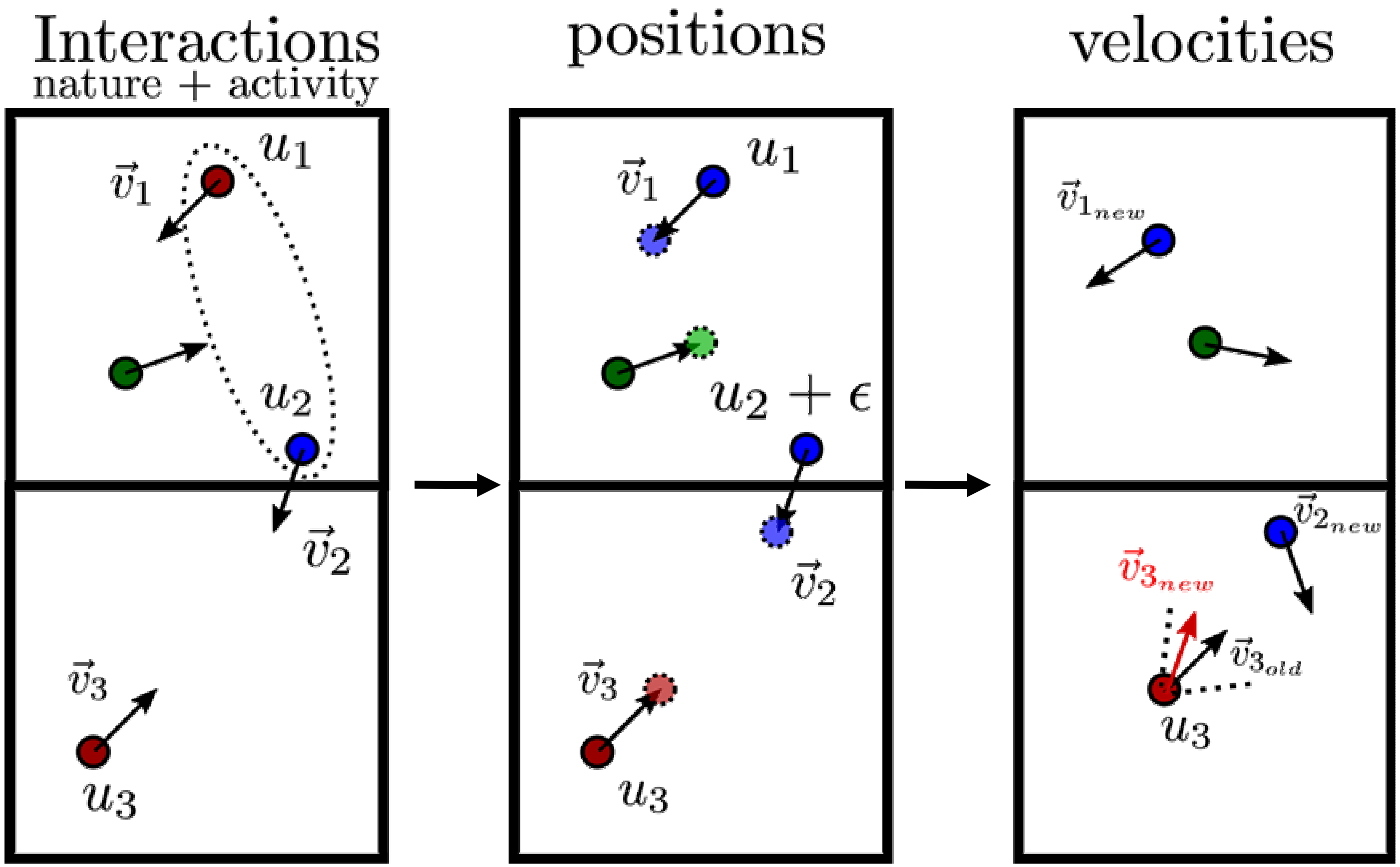
Conditions for interaction

Cells in the same box

$$\widehat{(\vec{v}_1, \vec{v}_2)} < \frac{\pi}{3}$$

example :

$$u_1 < u_2$$
$$C + I \rightarrow 2I$$



Activity thermalization: $\Delta u_i = (E - \alpha u_i)\Delta t$

Results

- 2D simulations

- Rate constants

  Boosted immune system $k_{ic} = 10k_{ci}$

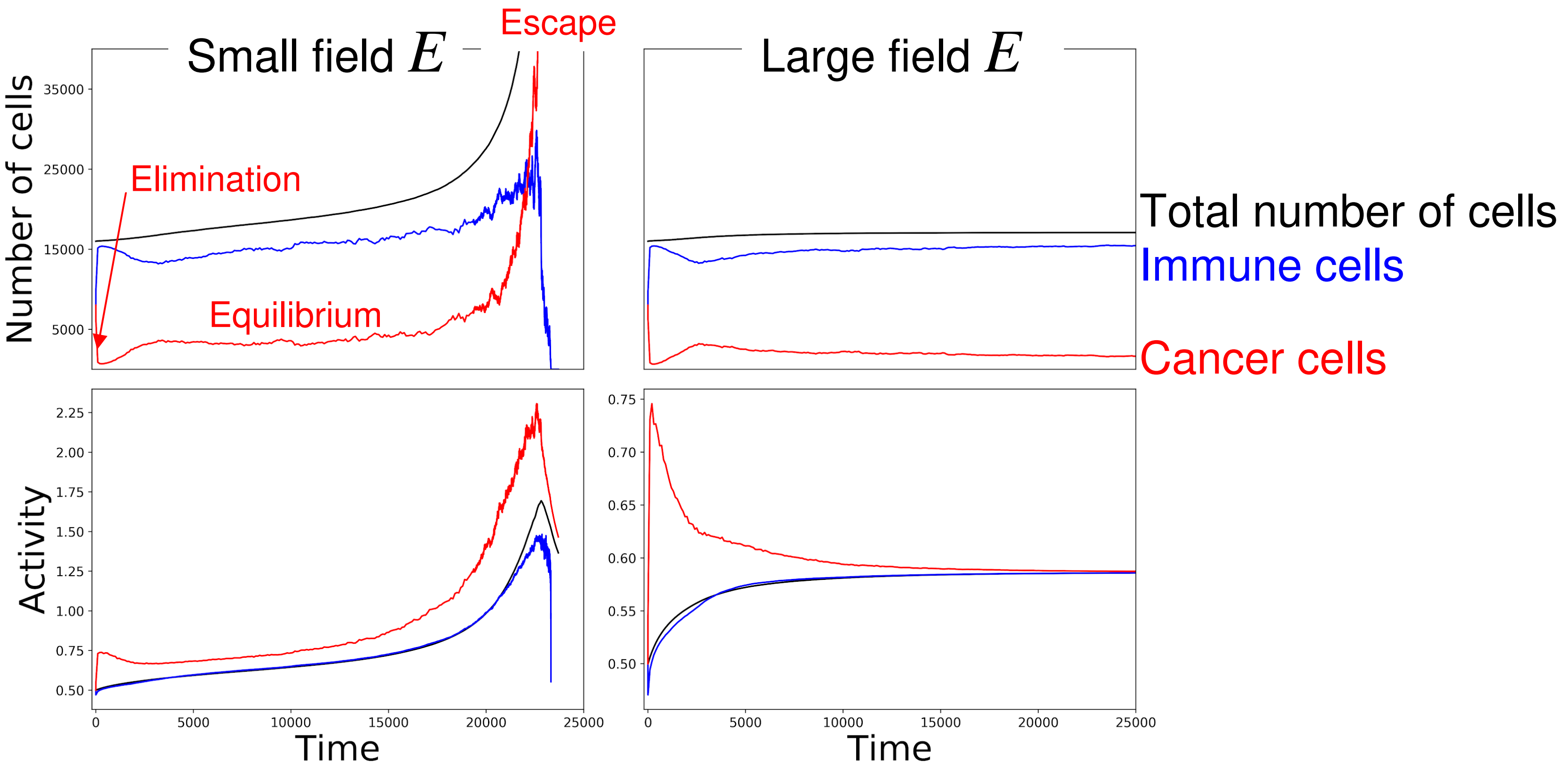
  Slow mutation rate of normal cells $k_{nc} << k_{ci}$

- Speed $|v| << \dfrac{\Delta x}{\Delta t}$

- Intermediate value of the field associated with the thermostat

Video for homogeneous initial conditions $N_c^0 = N_i^0 = 20$

Role of the thermostat

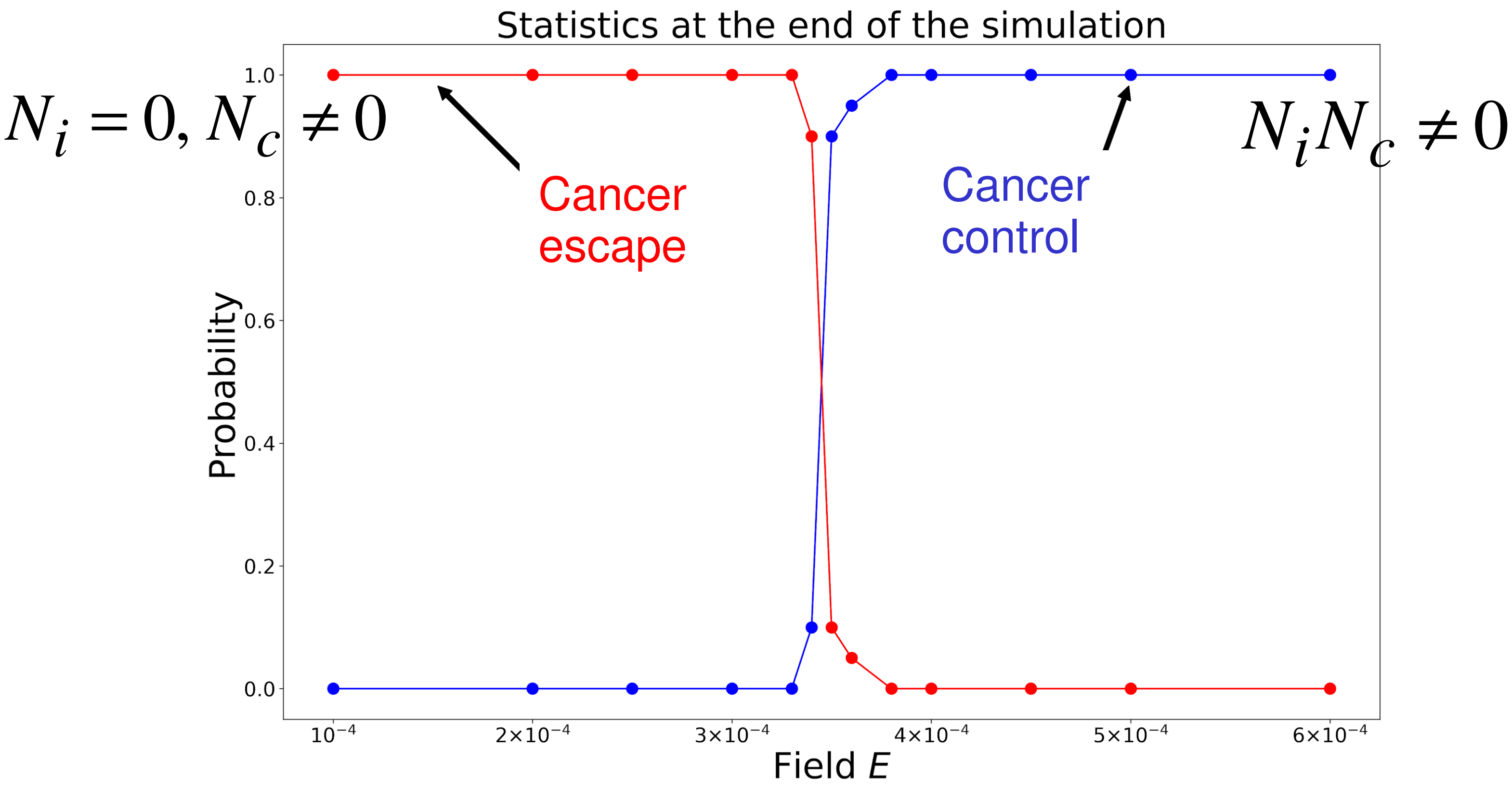


The three E's of immunotherapy

Cancer control

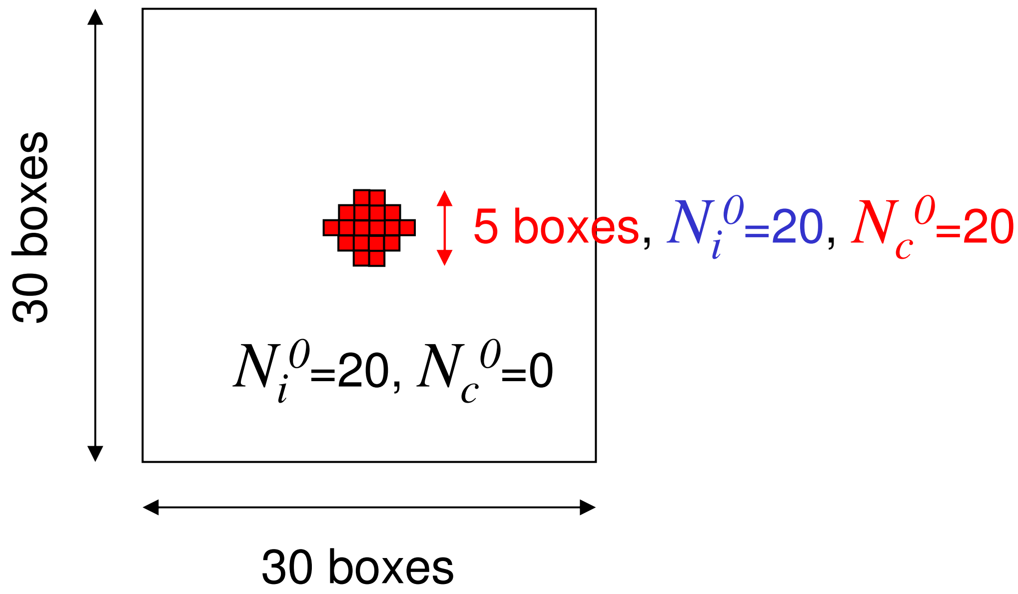
Dunn *et al,* Nat Immunol **3**, 991 (2002)
Masurel, Bianca, Lemarchand, Physica A **506**, 462 (2018)

Role of the thermostat



Transition between two behaviors for E_c

Inhomogeneous initial conditions



$$C + I \xrightarrow{\alpha k_{ic}} 2I$$

$$C + I \xrightarrow{\alpha k_{ci}} 2C$$

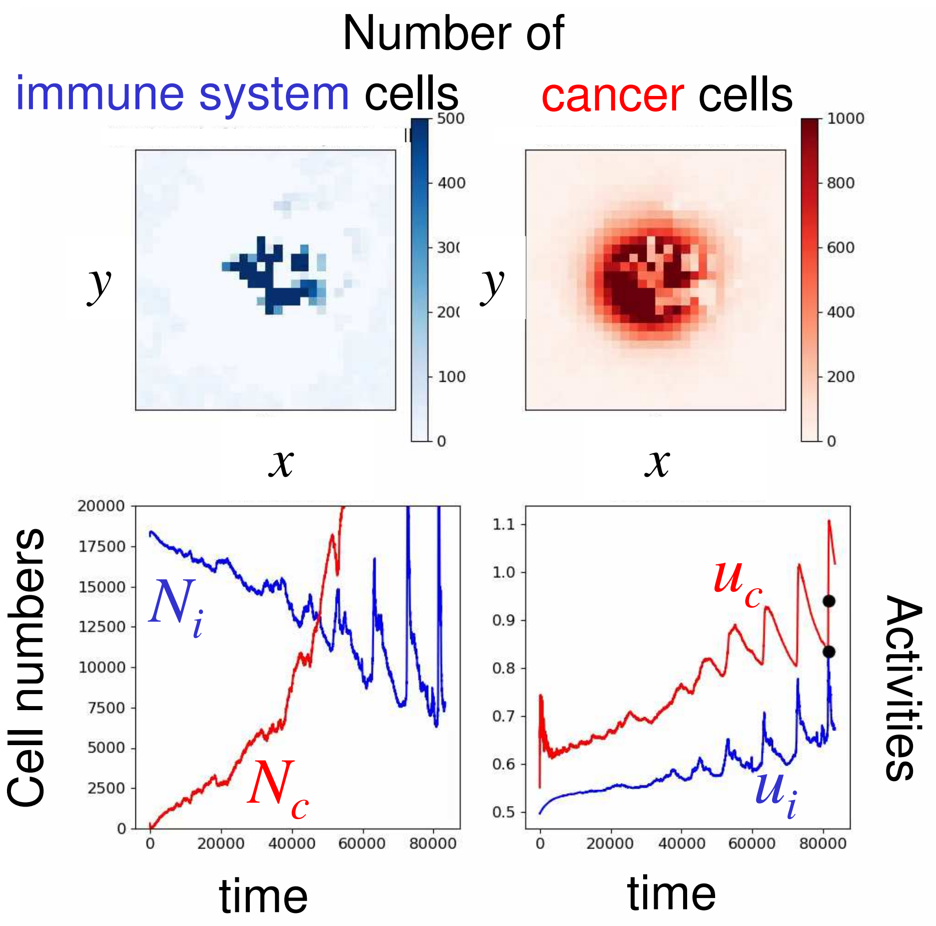
$$k_{ic} = 10 k_{ci}$$

$$E < E_c$$

(tumor escape expected)

video

Inhomogeneous initial conditions

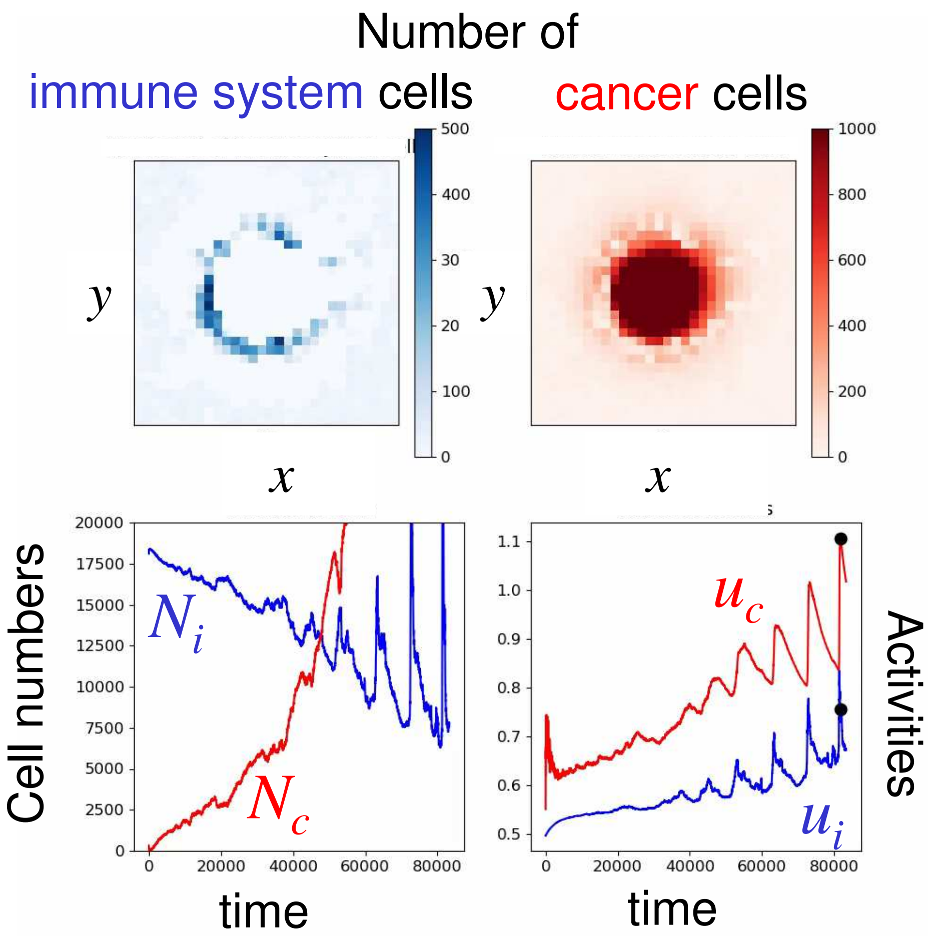


Local increase of the number N_i of immune system cells

Pseudo-oscillations of total cell numbers and mean activities

Maximum of the mean activity u_i of immune system cells

Inhomogeneous initial conditions



Restoration of initial cylindrical symmetry

Maximum of the mean activity u_c of cancer cells

Pseudo-oscillations of total cell numbers and mean activities

$$\begin{array}{ccc} \mathrm{C} + \mathrm{I} & \xrightarrow{k_{ci}(u_c\text{-}u_i)} & \mathrm{C} + \mathrm{C} \\ u_c > u_i & & u_c+\varepsilon \quad u_i \end{array}$$

$N_c \nearrow$

$u_c \searrow$ if $u_i+\varepsilon - u_c<0$

$$\begin{array}{ccc} \mathrm{C} + \mathrm{I} & \xrightarrow{k_{ic}(u_i\text{-}u_c)} & \mathrm{I} + \mathrm{I} \\ u_c < u_i & & u_c \quad u_i+\varepsilon \end{array}$$

$N_c \searrow$

$u_c \nearrow$ Depletion of low-activity cancer cells

$$\mathrm{C} + \mathrm{N} \longrightarrow 2\mathrm{C}$$

Source of C

Conclusion

- Crucial role played by the thermostat (control of activity fluctuations)
  Transition between two behaviors
  Non intuitive cancer proliferation for inefficient thermalization ($k_{ic} = 10k_{ci}$)

  Cancer control for efficient thermalization

- The model reproduces the observed three E's (Elimination, Equilibrium, Escape of cancer) of immunotherapy
  Dunn *et al,* Nat Immunol **3**, 991 (2002)

- Complex spatiotemporal behaviors for inhomogeneous initial conditions (derivation of macroscopic equations for mean cell numbers and activities in progress)

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Bianca, Lemarchand, J. Chem.Phys.**145**, 154108 (2016)
Masurel, Bianca, Lemarchand, Physica A **506**, 462 (2018)
Masurel, Bianca, Lemarchand, AIP Conference Proc. **2132**, 190005 (2019)