Kinetic and hydrodynamic descriptions of tumor-immune system competition

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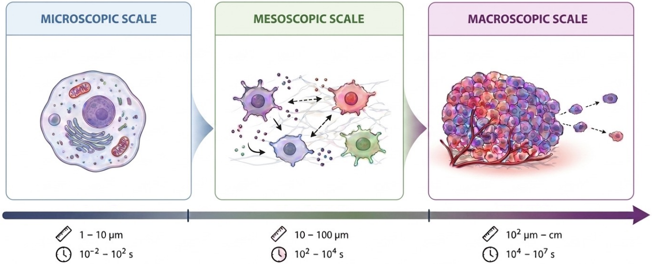
Context and Motivation

Tumor-Immune System Interactions

Tumor progression involves a large variety of **complex** and **multi-scale** mechanisms:

- **Microscopic scale:** alterations at the cellular and intracellular level driving population heterogeneity;
- **Mesoscopic scale:** intercellular encounters and cross-talk with the local microenvironment, including cell velocity changes (*turning*) and state transitions.
- **Macroscopic scale:** tissue-level spatio-temporal evolution, characterized by large-scale displacement (diffusion/taxis) and proliferative/destructive phenomena.



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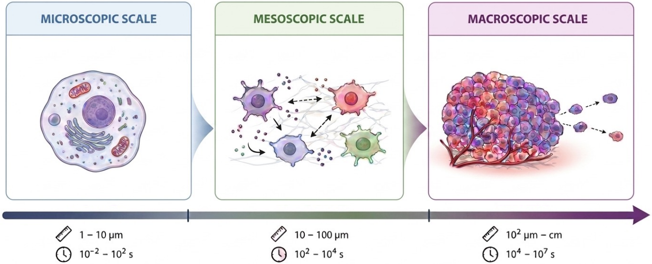

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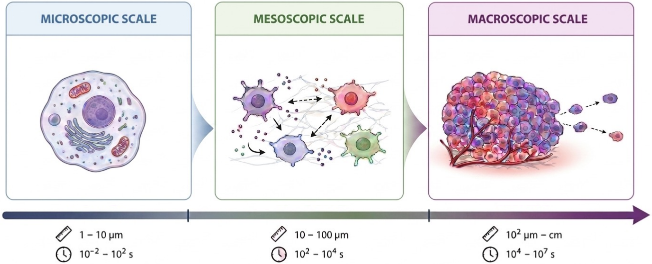

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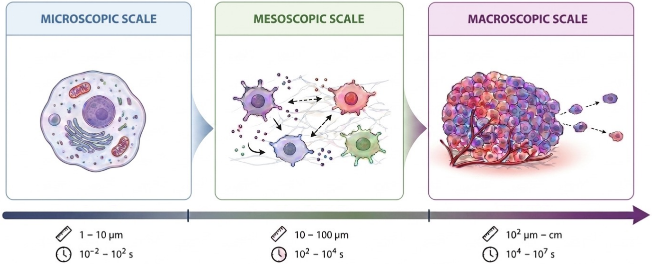

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Key Focus

Describing the cross-talk between **tumor cells** and the **immune system** (active and passive) using kinetic transport equations and proper asymptotic procedures.

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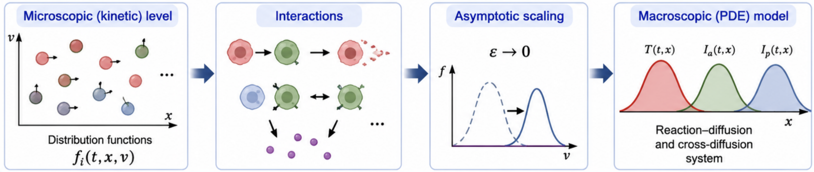
Why Kinetic Modeling?

- **Microscopic Detail:** Integrates sub-cellular variables like cell activity, state, and efficacy.
- **Early-Stage Suitability:** Ideal for modeling the initial phases of tumor development.
- **Multiscale Bridging:** Captures individual cell behaviors and links them to population-level dynamics.



Mathematical framework

Preliminaries

Each cell population is described through a distribution function $f_i(t, \mathbf{x}, \mathbf{v}, u)$ which depend on time $t > 0$, position $\mathbf{x} \in \Omega \subseteq \mathbb{R}^d$, microscopic velocity $\mathbf{v} \in \mathbf{V}$, and activity $u \in \mathbf{U}$.

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The pair $\{\mathbf{x},\mathbf{v}\}\in\Omega\times\mathbf{V}$ represents the microscopic mechanical state, while $u\in\mathbf{U}$ represents the microscopic biological state.

Setting $\mathbf{U}=[-1,1]$, u represents the capability of a cell to compete with others: $u\geq 0$ characterizes active cells, while $u<0$ the passive cells.

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Basic assumptions:

- without loss of generality, we set $|\mathbf{V}| = 1$;
- only binary interactions are effective;
- encounters can be of conservative type (only state can change) or of nonconservative type (destruction or proliferation of cells).

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The goal is to derive the macroscopic evolutionary for the population densities

$$n_i(t, \mathbf{x}) = \int_{\mathbf{V}} \int_{\mathbf{U}} f_i(t, \mathbf{x}, \mathbf{v}, u) du d\mathbf{v}.$$

Kinetic transport equations

Each population evolves accordingly to the following kinetic transport equation

$$\frac{\partial}{\partial t} f_i + \mathbf{v} \cdot \nabla_{\mathbf{x}} f_i = \mathscr{L}[f_i] + \sum_{j=1}^{N} Q_{ij} + \sum_{\substack{j,k=1 \\ j \neq i}}^{N} J_{jk}^{i} + K[f_i]\,.$$

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Here:

- the *turning operator* $\mathscr{L}[f_i]$ models the changes in cell velocity as

$$\mathscr{L}[f_i](t,\mathbf{x}\mathbf{v},u) := \int_{\mathbf{V}} \lambda(\mathbf{x},\mathbf{v}') T(\mathbf{x},\mathbf{v}|\mathbf{v}') f_i(t,\mathbf{x},\mathbf{v}',u) d\mathbf{v}' - \int_{\mathbf{V}} \lambda(\mathbf{x},\mathbf{v}) T(\mathbf{x},\mathbf{v}''|\mathbf{v}) f_i(t,\mathbf{x},\mathbf{v},u) d\mathbf{v}''$$

  with transition probability $T(\mathbf{x},\mathbf{v}|\mathbf{v}')$ and turning frequency $\lambda(\mathbf{x},\mathbf{v})$. We assume $\lambda(\mathbf{x},\mathbf{v}) = \lambda(\mathbf{x})$ and

$$\underbrace{T(\mathbf{x},\mathbf{v}|\mathbf{v}') = T(\mathbf{x},\mathbf{v})}_{\text{memoryless turning}}, \qquad \underbrace{T(\mathbf{x},\mathbf{v}) = T(\mathbf{x},-\mathbf{v})}_{\text{symmetric distribution}}$$

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$$Q_{ij}(t,\mathbf{x},\mathbf{v},u) = \iint\limits_{\mathbf{V}} \iint\limits_{\mathbf{U}} \mu_{ij}(\mathbf{v}_*,\mathbf{v}',u_*,u')\varepsilon_{ij}(,\mathbf{v}_*,\mathbf{v}',u_*,u';\mathbf{v},u) f_i(t,\mathbf{x},\mathbf{v}_*,u_*) f_j(t,\mathbf{x},\mathbf{v}',u')du_*\,du'\,d\mathbf{v}_*\,d\mathbf{v}'$$

$$- f_i(t,\mathbf{x},\mathbf{v},u) \int\limits_{\mathbf{V}} \int\limits_{\mathbf{U}} d_{ij}(\mathbf{v},\mathbf{v}',u,u') f_j(t,\mathbf{x},\mathbf{v}',u')du'\,d\mathbf{v}\,.$$

In particular, $d_{ij}(\mathbf{v}_*,\mathbf{v}',u_*,u')$ is the collision frequency for destructive encounters between $(i,\mathbf{v}_*,u_*)$ and $(j,\mathbf{v}',u')$, $\mu_{ij}(\mathbf{v}_*,\mathbf{v}',u_*,u')$ the one for proliferative encounters, while $\varepsilon_{ij}(\mathbf{v}_*,\mathbf{v}',u_*,u';\mathbf{v},u)$ is the expected density of new i-th cells in state $(\mathbf{v},u)$.

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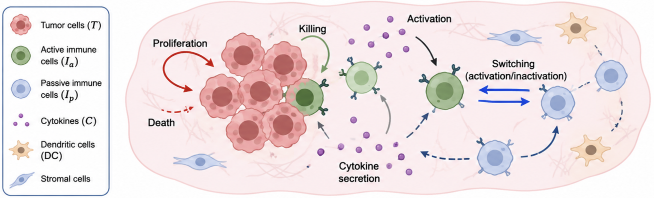
Here:

- the operator $K[f_i]$ collects all contributions to the i-th population (if any) that arise from factors other than cellular interactions.

Derivation of the macroscopic systems

Model set up

We consider three different cell populations, namely **tumor cells** ($i = 1$), **active immune cells** ($i = 2$), and **passive immune cells** ($i = 3$), together with two static (homogeneous and non-evolving) components: the host environment ($i = 4$) and cytokines ($i = 5$), which enhance immune system activity.



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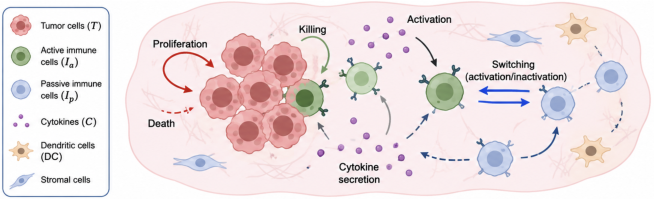

We consider two modelling scenarios:

Conservative case (CC)

- No immune cell proliferation or death
- Immune cells only switch their state.

Proliferative case (PC)

- Immune cell proliferation and apoptosis are included.
- A self-regulatory mechanisms prevent excessive inflammation.

Conservative scenario

Main assumption: the total number of immune cells is preserved,

$$I(t) = \sum_{i=2}^{3} \int_{\Omega} n_i(t, \mathbf{x})\, d\mathbf{x} = I_0.$$

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Tumor cells

- Killed by active immune cells.
- Proliferate through interactions with passive immune cells or host environment.
- Non-conservative dynamics.

Immune cells

- Active $\leftrightarrows$ Passive
- State changes only through interactions.

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Tumor cells

- Killed by active immune cells.
- Proliferate through interactions with passive immune cells or host environment.
- Non-conservative dynamics.

Immune cells

- Active ⇆ Passive
- State changes only through interactions.

Conservative scenario

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- Active $\leftrightarrows$ Passive
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Main assumption: immune cells proliferate and undergo a self-regulatory mechanism described by:

$$K[f_2] = -\kappa_2(f_2(t,\mathbf{x},\mathbf{v},u) - f_2^*(t,\mathbf{x},\mathbf{v},u)).$$

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From kinetic to macroscopic models

Goal 1: using hydrodynamics limiting procedure to derive macroscopic systems featuring different type of diffusive behaviors

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$$f_i^{\varepsilon}(t,\mathbf{x},\mathbf{v},u) = g_i^{\varepsilon}(t,\mathbf{x},\mathbf{v},u) + \varepsilon^k\, h_i^{\varepsilon}(t,\mathbf{x},\mathbf{v},u) + O(\varepsilon^k)$$

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Key assumption: separation of time scales

- fast: velocity changes (run-and-tumble)
- slow: binary interactions and background coupling

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Case	Regime	Macroscopic outcome
(CC)-(PC)	All operators have the same order	Linear diffusion
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From kinetic to macroscopic model: linear diffusion

Let start from the rescaled kinetic equations

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and the expansions

$$f_i^\varepsilon = g_i^\varepsilon + \varepsilon h_i^\varepsilon + O(\varepsilon^2),$$

with

$$\int_{\mathscr{V}} h_i^\varepsilon \, d\mathbf{v} = 0 \Longrightarrow \text{mass concentrates in the leading order}$$

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Leading order:

$$\mathscr{L}[g_i^\varepsilon] = 0 \qquad \Longrightarrow \qquad g_i^\varepsilon = T(\mathbf{x},\mathbf{v})\, p_i^\varepsilon(t,\mathbf{x},u) \quad \text{with} \;\; p_i^\varepsilon := \int_{\mathbf{V}} f_i^\varepsilon(\mathbf{v})d\mathbf{v}.$$

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At the next order, integrating over $\mathbf{V}\times\mathbf{U}$ and using the symmetry condition on $T(\mathbf{x},\mathbf{v})$, for $\varepsilon \to 0$ we get

$$\partial_t n_i = \nabla_{\mathbf{x}}\nabla_{\mathbf{x}} : (\mathbb{D}_i n_i) + R_i[n_1,n_2,n_3] \quad \text{with} \quad \mathbb{D}_i(\mathbf{x}) := \frac{1}{\lambda(\mathbf{x})}\int_{\mathbf{V}} T(\mathbf{x},\mathbf{v})\mathbf{v}\otimes\mathbf{v} d\mathbf{v}$$

It representes linear (myopic) diffusion with reaction, where motion depends on the local reorientation frequency $\lambda(\mathbf{x})$ and transition probability $T(\mathbf{x},\mathbf{v})$.

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From kinetic to macroscopic model: cross-diffusion

Let consider the following time scales

$$\frac{1}{\varepsilon^2}\mathscr{L}_i \ll \varepsilon(Q_{21}, Q_{35}, J_{12}^3, J_{35}^2) \ll \varepsilon^2(Q_{12}, Q_{13}, Q_{14})$$

and the expansion

$$f_i^\varepsilon = g_i^\varepsilon + \varepsilon^2 h_i^\varepsilon + O(\varepsilon^3)\,.$$

For the tumor population $n_1(t, \mathbf{x})$ we recover the same macroscopic equation.

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For $i = 2, 3$, integrating first over $\mathbf{V}$, at leading order we obtain that

$$\int_{\mathbf{V}} \mathbf{Q_i}[T\mathbf{p}^\varepsilon] + \mathbf{J_i}[T\mathbf{p}^\varepsilon] d\mathbf{v} = 0 \Longrightarrow n_2^\varepsilon = \frac{\bar{d}_{35} n_5}{\bar{d}_{35} n_5 + \bar{d}_{21} n_1^\varepsilon} N^\varepsilon \text{ and } n_3^\varepsilon = \frac{\bar{d}_{21} n_1^\varepsilon}{\bar{d}_{35} n_5 + \bar{d}_{21} n_1^\varepsilon} N^\varepsilon.$$

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At the next order, similar to the linear case, for $\varepsilon \to 0$ we get

$$\partial_t n_i = \nabla\nabla : (\mathbb{D}_i(\mathbf{x}) n_i)$$

which, in terms of the total immune system $N(t, \mathbf{x}) = n_2(t, \mathbf{x}) + n_3(t, \mathbf{x})$ yields to the effective cross-diffusion equation

$$\partial_t N = \nabla\nabla : (\mathbb{D}_{\text{eff}}[n_1] N) \quad \text{with} \quad \mathbb{D}_{\text{eff}}[n_1] = \frac{\mathbb{D}_2(\mathbf{x})\, \bar{d}_{35}\, n_5 + \mathbb{D}_3(\mathbf{x})\, \bar{d}_{21}\, n_1}{\bar{d}_{35}\, n_5 + \bar{d}_{21}\, n_1}$$

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From kinetic to macroscopic model: self-diffusion

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and the same expansion

$$f_i^\varepsilon = g_i^\varepsilon + \varepsilon^2 h_i^\varepsilon + O(\varepsilon^3).$$

For the tumor and active immune populations ($i = 1,2$), we recover the same macroscopic equations as in the linear diffusion case.

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but now, writing the equation for the total immune population $N(t,\mathbf{x}) = n_2(t,\mathbf{x}) + n_3(t,\mathbf{x})$ yields

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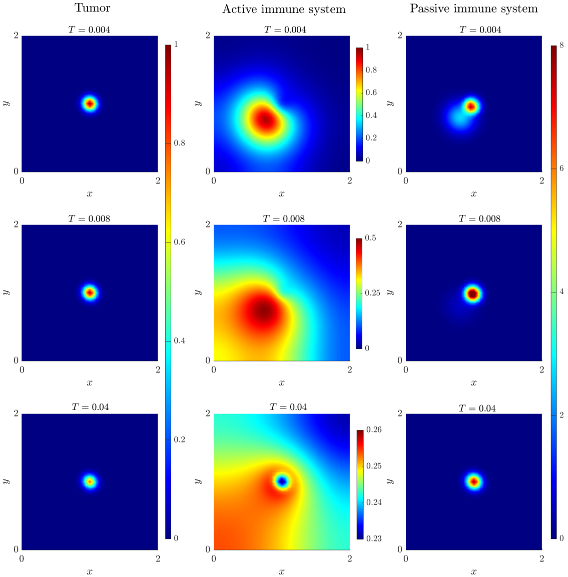
From kinetic to macroscopic model: summary

Different assumptions on the **relative time scales** of the kinetic interactions lead to different macroscopic diffusion mechanisms.

Scaling assumption	**Macroscopic limit**
All interaction operators evolve on the same time scale	**Linear diffusion** $\partial_t n_i = \nabla_{\mathbf{x}}\nabla_{\mathbf{x}} : (\mathbb{D}_i(\mathbf{x}) n_i) + R_i[n_1, n_2, n_3] \quad i = 1, 2, 3$
Fast immune switching, slow tumor dynamics (CC)	**Cross-diffusion** $\partial_t n_1 = \nabla_{\mathbf{x}}\nabla_{\mathbf{x}} : (\mathbb{D}_1(\mathbf{x}) n_1) + R_1[n_1, N],$ $\partial_t N = \nabla\nabla : (\mathbb{D}_{\text{eff}}[n_1]\, N).$
Fast passive immune dynamics (PC)	**Self-diffusion** $\partial_t n_1 = \nabla_{\mathbf{x}}\nabla_{\mathbf{x}} : (\mathbb{D}_1(\mathbf{x}) n_1) + R_1[n_1, N]$ $\partial_t N = \nabla\nabla : (\mathbb{D}_{\text{eff}}[N]\, N) + R_N[n_1, N]$

Numerical comparison

First settings. Conservative case: linear vs cross-diffusion



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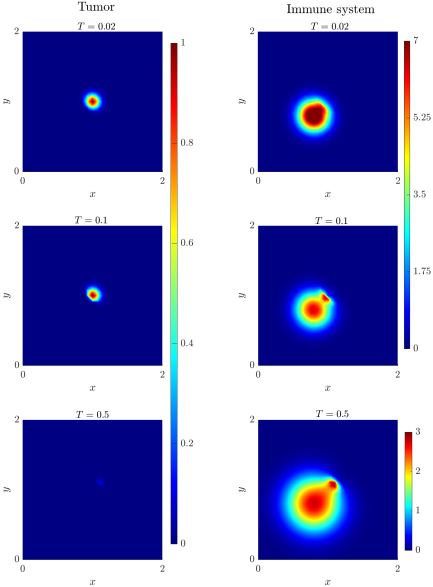
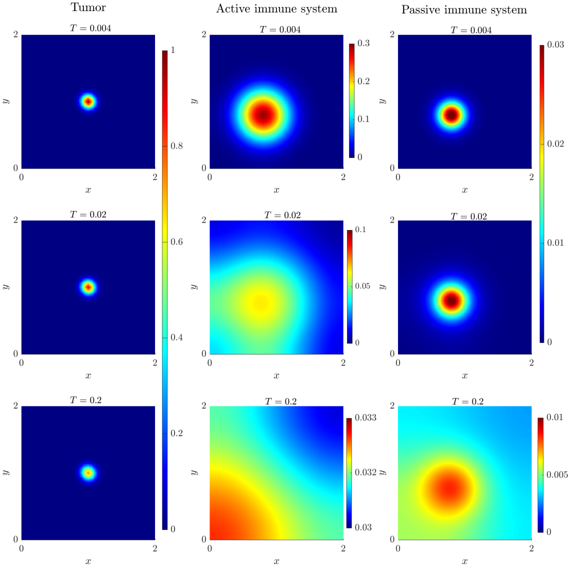


Numerical comparison

Second settings. Proliferative case: linear vs self-diffusion



Numerical comparison

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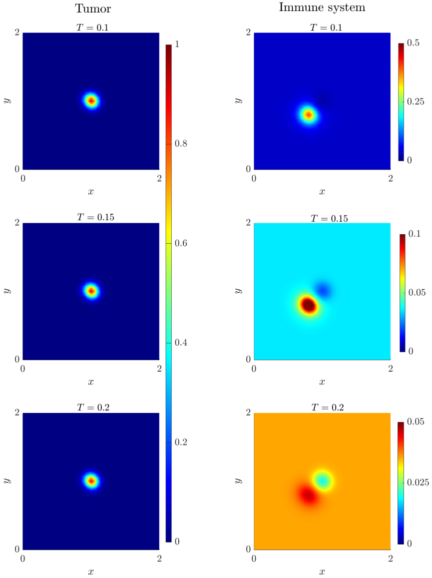

Homogenous Stability Analysis

Qualitative analysis of the spatially homogeneous settings

Goal 2: comparing the macroscopic homogenous settings to investigate which properties are invariant of the relative time scales and only determined by the kinetic collision structure.

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First settings. Conservative case: linear vs cross-diffusion

$$\textbf{Linear:}\begin{cases}\dot{Y}_1(t) = -A\,Y_1(t)\,Y_2(t) + B\,Y_1(t)\big[I - Y_2(t)\big] + Y_1(t),\\[2ex] \dot{Y}_2(t) = -A\,Y_1(t)\,Y_2(t) + C\big[I - Y_2(t)\big].\end{cases}$$

$$\textbf{Cross:}\quad \dot{Y}_1(t) = \frac{A\,I\,Y_1(t)}{C + A\,Y_1(t)}\big(B\,Y_1(t) - C\big) + Y_1(t),$$

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Despite the different diffusion scalings, the homogeneous reductions provide the same identical asymptotical distributions:

$$\underbrace{E_1 = (0, I)}_{\text{tumor eradication}}, \qquad \underbrace{E_2 = \left(\frac{C}{A}\,\frac{AI-1}{1+BI}, \frac{1+BI}{A+B}\right)}_{\text{co-existence}}$$

as well as the same transcritical bifurcation condition $AI \geq 1$.

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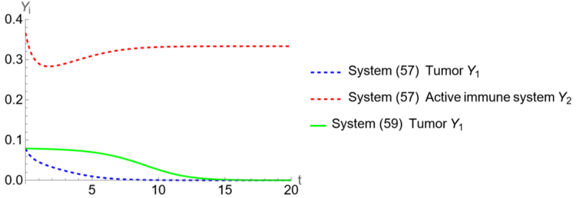

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$$\textbf{Self:} \begin{cases} \dot{Y}_1(t) = \dfrac{Y_1(t)\, Y_N(t)}{1 + P\, Y_N(t)} \Big[B\, P\, Y_N(t) - A \Big] + Y_1(t)\,, \\[2ex] \dot{Y}_N(t) = \dfrac{Y_N(t)}{1 + P\, Y_N(t)} \Big[-A\, Y_1(t) + D\, P\, Y_N(t) - G \Big] + H\,, \end{cases}$$

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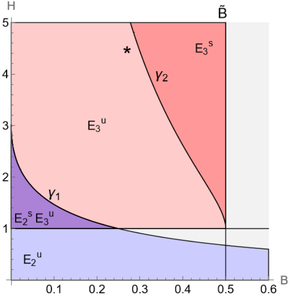

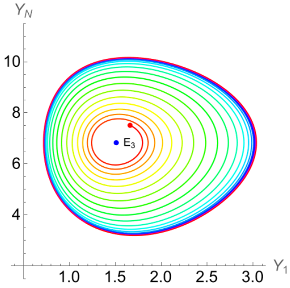

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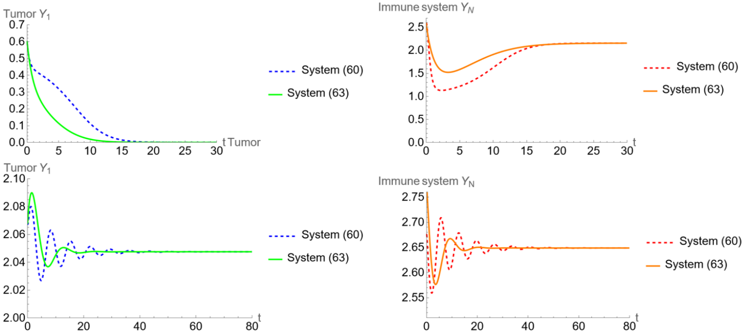

Conclusion and Perspective

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Main outcomes

- We propose a unified kinetic framework for modeling spatio-temporal tumor–immune interactions.
- Different hydrodynamic regimes yield macroscopic models featuring linear, cross-, and self-diffusion in the immune cell population.
- Equilibria and bifurcations are determined by the underlying collision structure, while the hydrodynamic scaling mainly affects transient and spatial dynamics.

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- Different hydrodynamic regimes yield macroscopic models featuring linear, cross-, and self-diffusion in the immune cell population.
- Equilibria and bifurcations are determined by the underlying collision structure, while the hydrodynamic scaling mainly affects transient and spatial dynamics.

On-going work and perspective

- Introduction of time-delay in the tumor-immune interaction term.
- Rigorous derivation of the macroscopic model.

Thank you for your attention

Main references

- M. Conte and R. Travaglini. A kinetic derivation of spatial distributed models for tumor-immune system interactions. *Chaos Solit. Fractals*. **200(2)** (2025): 116969.
- M. Conte, M. Groppi, and G. Spiga. Qualitative analysis of kinetic-based models for tumor-immune system interaction. *Discrete Contin. Dyn. Syst. Ser. B* **23(6)** (2018): 2393–2414.

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