Modeling tumor-immune dynamics with stochastic delay differential equations

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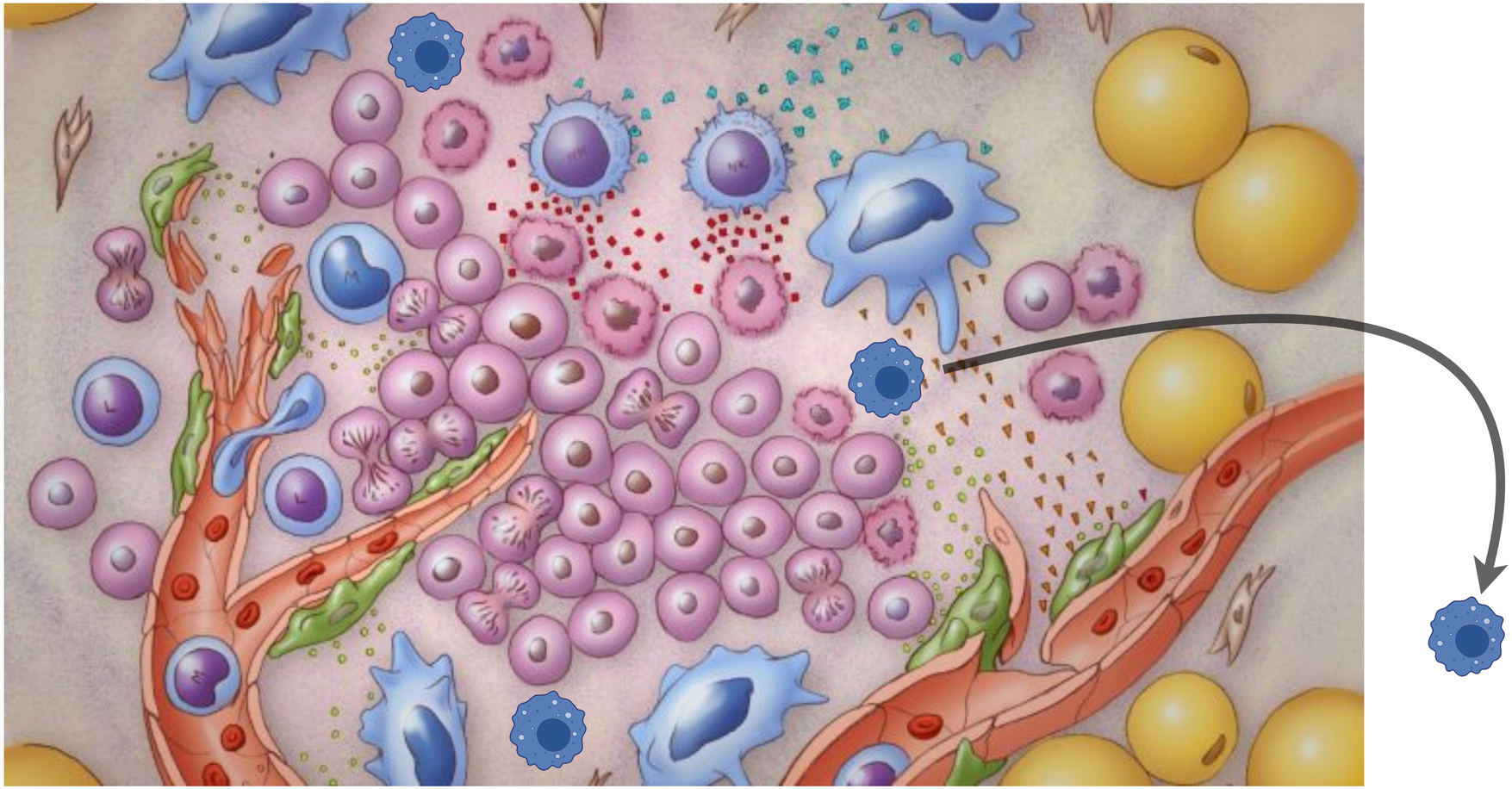
Overview

- Metastatic breast cancer is a leading cause of death worldwide
- Immunotherapies in combination with epigenetic modulators show great promise but…
- their effects shaping tumor-immune interactions are poorly understood
- We develop models of stochastic tumor-immune dynamics informed by scRNA-seq metastasis data
- Modeling & inference predict a key role for MDSC activation and offer new avenues for precision therapy

No cell is an island

The metastatic tumor microenvironment (TME)



Credit: MD Anderson Cancer Center

- Tumors do not metastasize or grow without co-opting systems (angiogenesis, immune response) for their own good
- The set of cell types and interactions that define the TME is large, complex, and dynamic

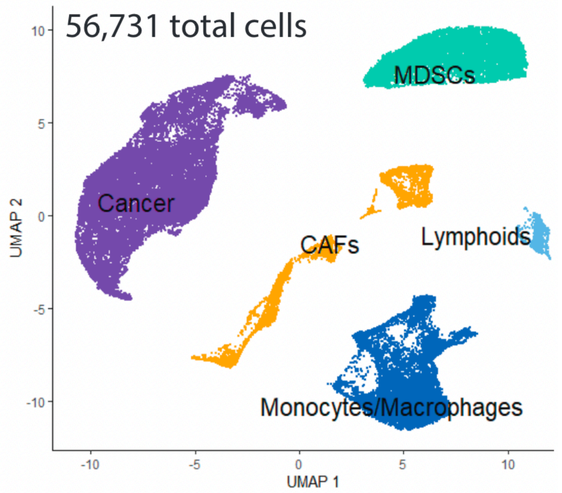
Myeloid-derived suppressor cells (MDSCs)

Review > Trends Pharmacol Sci. 2019 Jan;40(1):4-7. doi: 10.1016/j.tips.2018.10.008.
Epub 2018 Dec 6.

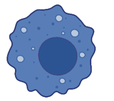
MDSC; the Most Important Cell You Have Never Heard Of

R J Tesi [1]

Clustering scRNA-seq of primary breast tumor (NT2.5 mouse)



- Pathologically activated monocytes/neutrophils with potent immunosuppressive activity
- MDSCs have been implicated in the regulation of immune responses in many biological contexts: cancer, inflammation, wound healing, autoimmune disorders, …
- Two subtypes of MDSC are typically defined: monocytic (M-MDSC) and granulocytic (G-MDSC), also known as poly-mononuclear (NB labels somewhat controversial - I don't want to get into a neutrophil fight)



MDSC

Bergenfelz & Leandersson (2020) *Front Oncol*; Veglia et al. (2021) *Nat Rev Immun*

Why MDSCs in breast cancer?

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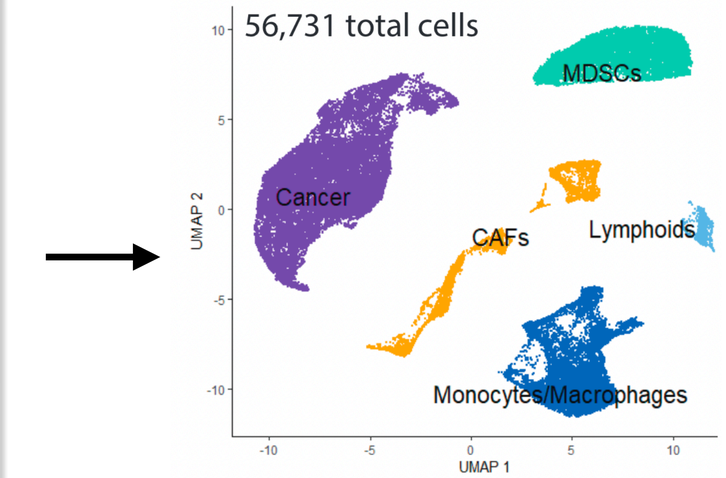
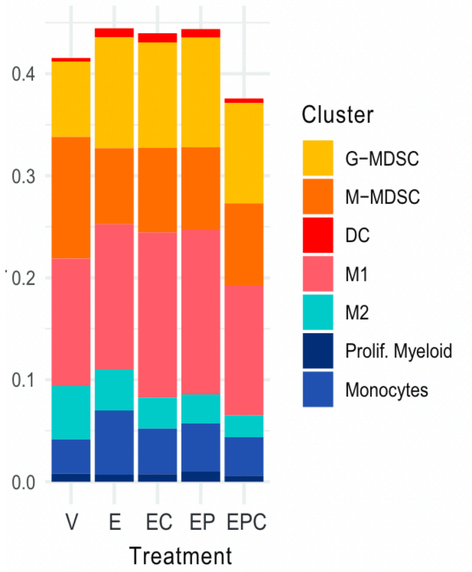
RESEARCH ARTICLES | MAY 03 2022

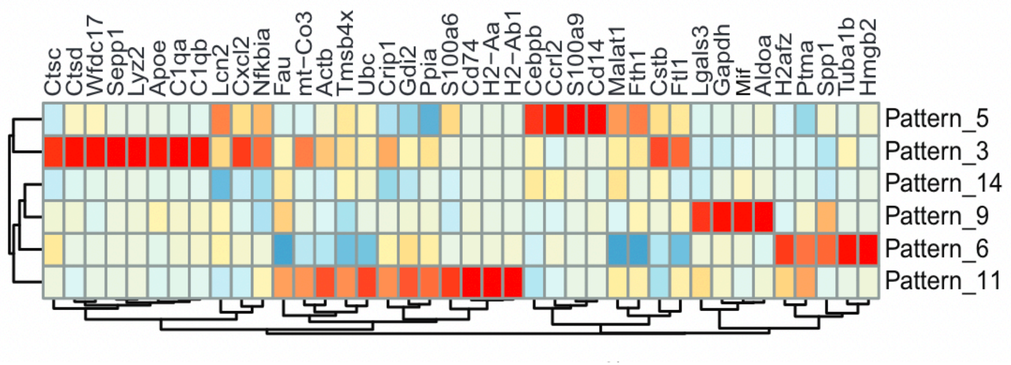
Entinostat Decreases Immune Suppression to Promote Antitumor Responses in a HER2⁺ Breast Tumor Microenvironment

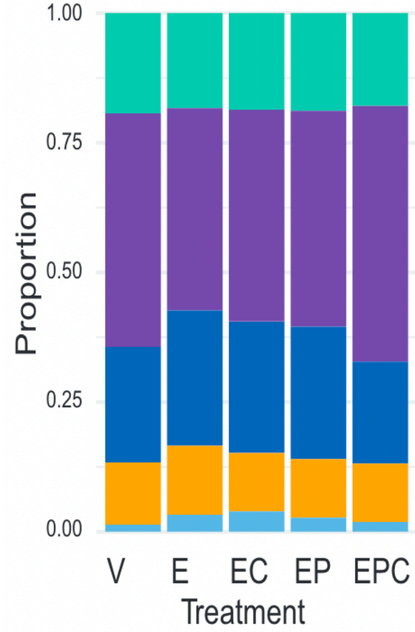
Dimitrios N. Sidiropoulos; Christine I. Rafie ; Julie K. Jang; Sofi Castanon; Aaron G. Baugh ; Edgar Gonzalez ; Brian J. Christmas; Valerie H. Narumi; Emily F. Davis-Marcisak ; Gaurav Sharma; Emma Bigelow; Ajay Vaghasia; Anuj Gupta; Alyza Skaist; Michael Considine; Sarah J. Wheelan ; Sathish Kumar Ganesan ; Min Yu; Srinivasan Yegnasubramanian; Vered Stearns ; Roisin M. Connolly ; Daria A. Gaykalova; Luciane T. Kagohara ; Elizabeth M. Jaffee ; Elana J. Fertig ; Evanthia T. Roussos Torres

+ Author & Article Information
Cancer Immunol Res (2022) 10 (5): 656–669.









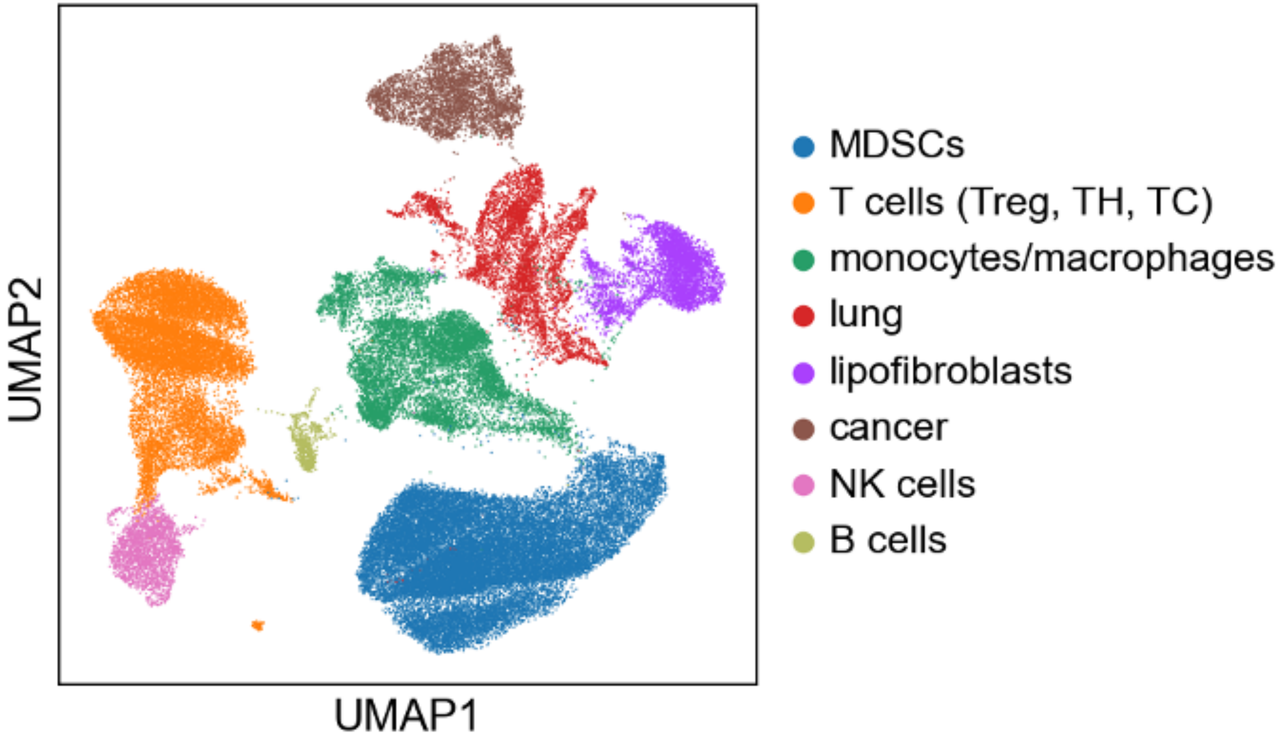
V: Vehicle
E: Entinostat
P: anti-PD-1
C: anti-CTLA-4

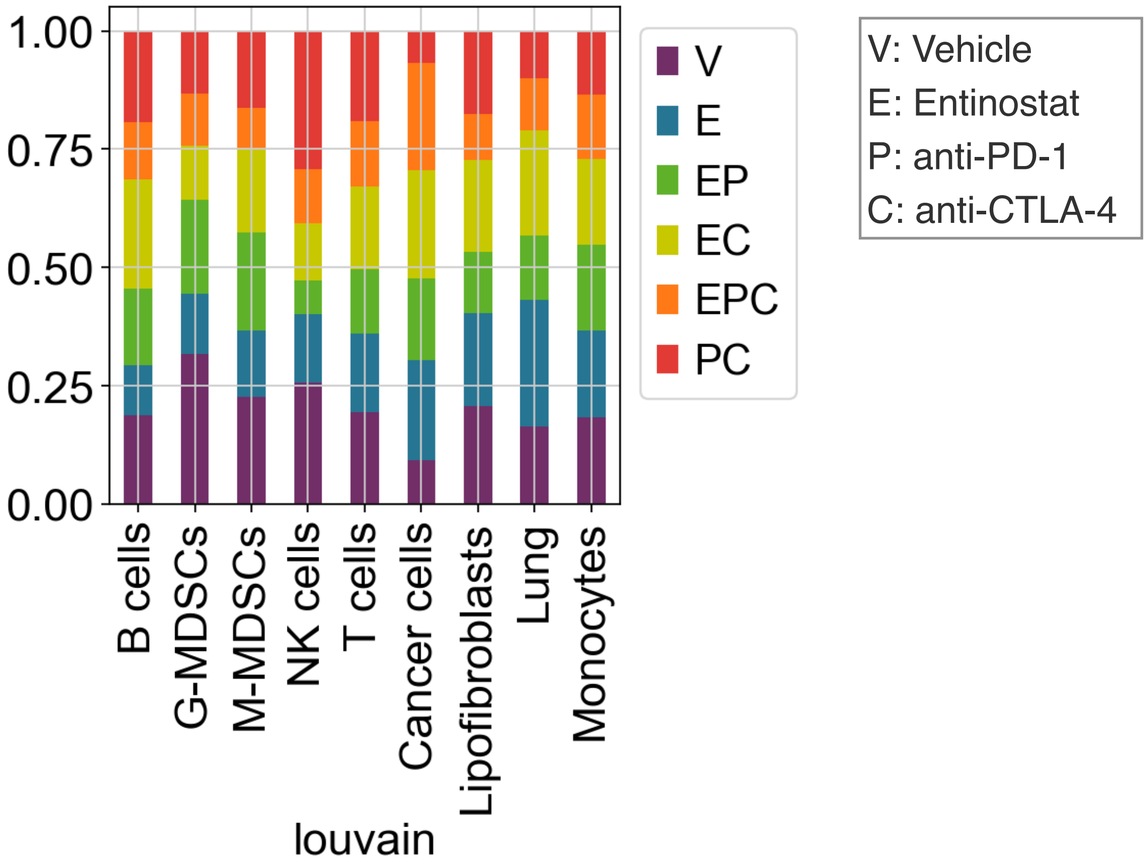
Sirodopolous et al. (2022) *Cancer Immunol Res*

What is the role of MDSC suppression in metastasis (specifically breast-to-lung metastasis)?

The TME in breast-to-lung metastasis

Clustering scRNA-seq NT2.5LM mouse metastasis model (BALB/c)





V: Vehicle
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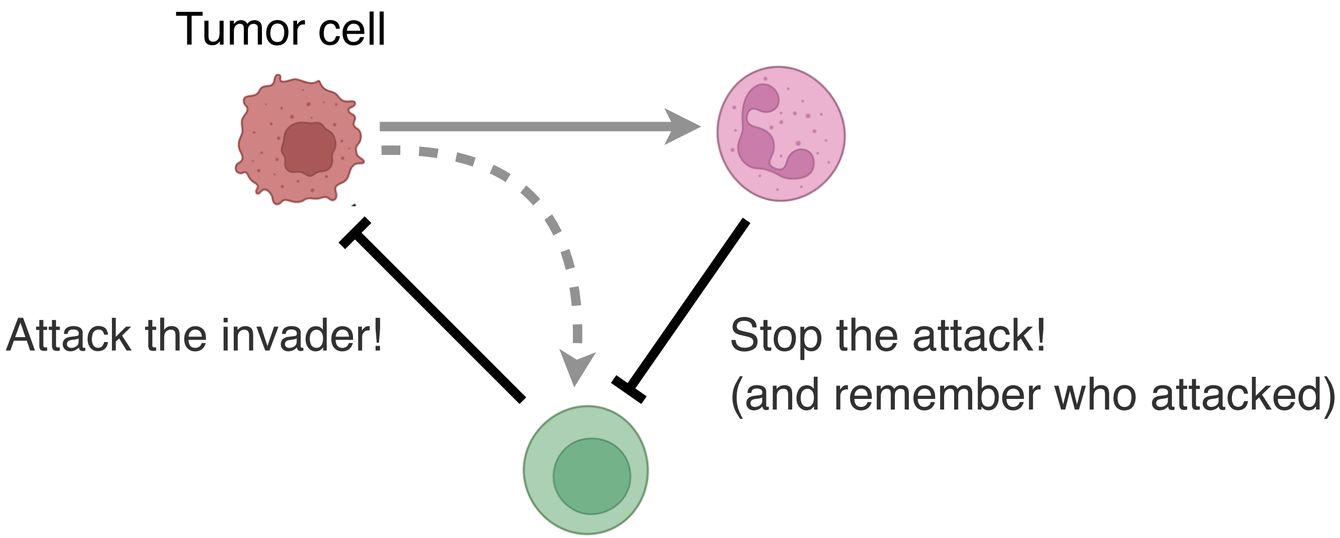
Evanthia Roussos Torres lab, unpublished

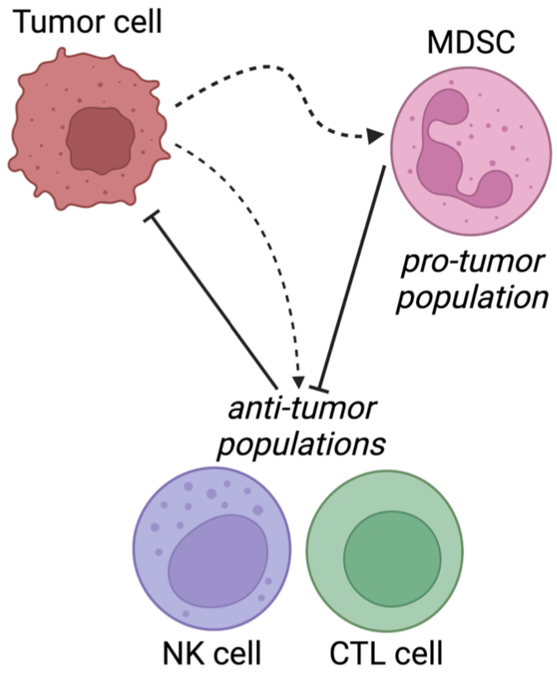
What minimal model captures the dynamics between tumor cells and MDSCs at the site of metastasis?

(What does the immune system do?)

Modeling tumor-immune dynamics

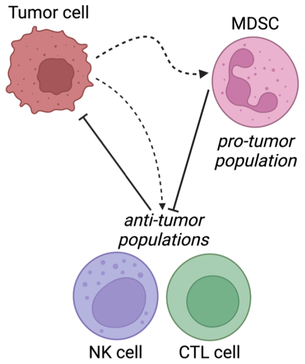


Modeling tumor-MDSC dynamics



Modeling tumor-MDSC dynamics

Model description:



$$
\begin{aligned}
\frac{dx_{\mathrm{T}}(t)}{dt} &= \boxed{\text{growth of tumor cells}} - \boxed{\text{tumor cells inhibited by NK cells}} \\
&- \boxed{\text{tumor cells inhibited by CTL cells}} - \boxed{\text{death of tumor cells}}, \qquad (1) \\
\frac{dx_{\mathrm{MDSC}}(t)}{dt} &= \boxed{\text{circulating level of MDSCs}} + \boxed{\text{recruitment of MDSCs in presence of tumor}} \\
&- \boxed{\text{death of MDSCs}}, \qquad (2) \\
\frac{dx_{\mathrm{NK}}(t)}{dt} &= \boxed{\text{circulating level of NK cells}} + \boxed{\text{recruitment of NK cells in presence of tumor}} \\
&- \boxed{\text{NK cells inhibited by MDSCs}} - \boxed{\text{death of NK cells}}, \qquad (3) \\
\frac{dx_{\mathrm{CTL}}(t)}{dt} &= \boxed{\text{CTL cells stimulated by NK-tumor interaction}} + \boxed{\text{recruitment of CTL cells in presence of tumor}} \\
&- \boxed{\text{CTL cells inhibited by MDSCs}} - \boxed{\text{death of CTL cells}}, \qquad (4)
\end{aligned}
$$

SDDE model:

$$
\begin{aligned}
\frac{dx_{\mathrm{T}}(t)}{dt} &= \alpha_7 x_{\mathrm{T}}(t) \log\left(\frac{\alpha_8}{x_{\mathrm{T}}(t)}\right) - \alpha_9 x_{\mathrm{T}}(t) x_{\mathrm{NK}}(t) - \alpha_{10} x_{\mathrm{T}}(t) x_{\mathrm{CTL}}(t) - \alpha_{11} x_{\mathrm{T}}(t) + \xi_{\mathrm{T}}(t), \\
\frac{dx_{\mathrm{MDSC}}(t)}{dt} &= \alpha_1 + \alpha_2 \frac{x_{\mathrm{T}}(t-\tau_1)}{\gamma_1 + x_{\mathrm{T}}(t-\tau_1)^n} - \alpha_3 x_{\mathrm{MDSC}}(t) + \xi_{\mathrm{MDSC}}(t), \\
\frac{dx_{\mathrm{NK}}(t)}{dt} &= \alpha_{12} + \alpha_{13} \frac{x_{\mathrm{T}}(t)^2}{\gamma_2 + x_{\mathrm{T}}(t)^2} - \alpha_{14} x_{\mathrm{MDSC}}(t) x_{\mathrm{NK}}(t) - \alpha_{16} x_{\mathrm{NK}}(t) + \xi_{\mathrm{NK}}(t), \\
\frac{dx_{\mathrm{CTL}}(t)}{dt} &= \alpha_{17} x_{\mathrm{T}}(t) x_{\mathrm{NK}}(t) + \alpha_{18} \frac{x_{\mathrm{T}}(t)^2}{\gamma_3 + x_{\mathrm{T}}(t)^2} - \alpha_{19} x_{\mathrm{MDSC}}(t) x_{\mathrm{CTL}}(t) - \alpha_{21} x_{\mathrm{CTL}}(t) + \xi_{\mathrm{CTL}}(t).
\end{aligned}
$$

Tumor-MDSC model parameters

Notation	Description	Value	Units	Reference	Range
τ_1	delay parameter for MDSCs	varies	days	-	-
$x_{\mathrm{T}}(t), t \leq 0$	initial condition for tumor cells	1 or 2	-	-	-
$x_{\mathrm{MDSC}}(0)$	initial condition for MDSCs	α_1/α_3	-	-	-
$x_{\mathrm{NK}}(0)$	initial condition for NK cells	$\frac{\alpha_3\alpha_{12}}{\alpha_1\alpha_{14}+\alpha_3\alpha_{16}}$	-	-	-
$x_{\mathrm{CTL}}(0)$	initial condition for CTL cells	0	-	-	-
n	delay exponent	1	-	set	-
α_1	MDSCs circulating rate	10^2, varies	days^{-1}	estimated [6]	$[0, 10^3]$
α_2	MDSCs expansion coefficient	10^8	days^{-1}	[1, 10, 1, 55]	$[10^7, 10^9]$
α_3	MDSCs death rate	0.2	days^{-1}	[48, 59]	$[0, 1]$
α_7	tumor growth rate	10^{-1}	days^{-1}	[34, 17, 49]	$[10^{-2}, 5 \times 10^{-1}]$
α_8	tumor maximum size	10^7	-	estimated	$[10^6, 10^8]$
α_9	tumor cells inhibition rate by NK cells	3.5×10^{-6}	days^{-1}	[34, 17, 49]	$[10^{-7}, 10^{-6}]$
α_{10}	tumor cells inhibition rate by CTL cells	1.1×10^{-7}	days^{-1}	[34]	$[10^{-7}, 10^{-6}]$
α_{11}	tumor cell death rate	0, varies	days^{-1}	[55]	$[0, 0.01]$
α_{12}	NK cells circulating rate	1.4×10^4	days^{-1}	[34]	$[10^3, 10^5]$
α_{13}	NK cells expansion coefficient	2.5×10^{-2}	days^{-1}	[34, 17, 49]	$[10^{-2}, 10^{-1}]$
α_{14}	NK cells inhibition rate by MDSCs	4×10^{-5}, varies	days^{-1}	[55]	$[10^{-5}, 10^{-4}]$
α_{16}	NK cells death rate	4.12×10^{-2}	days^{-1}	[34]	$[10^{-2}, 10^{-1}]$
α_{17}	CTL stimulation by tumor-NK cell interaction	1.1×10^{-7}	days^{-1}	[5, 38]	$[10^{-7}, 10^{-6}]$
α_{18}	CTL expansion coefficient	10^{-1}	days^{-1}	[29]	$[5 \times 10^{-2}, 5 \times 10^{-1}]$
α_{19}	CTL inhibition rate by MDSCs	10^{-4}, varies	days^{-1}	[55]	$[5 \times 10^{-5}, 5 \times 10^{-4}]$
α_{21}	CTL death rate	2×10^{-2}	days^{-1}	[5, 49]	$[10^{-2}, 10^{-1}]$
γ_1	steepness of MDSC production	10^{10}	-	[1, 55]	$[10^9, 10^{11}]$
γ_2	steepness of NK production	2.02×10^7	-	[34, 49]	$[10^6, 10^8]$
γ_3	steepness of CTL production	2.02×10^7	-	[34, 17, 49]	$[10^6, 10^8]$

Modeling tumor-MDSC dynamics

Tumor-free steady state or tumor at its carrying capacity

$$\begin{aligned}
\hat{x}_{\mathrm{T}} &= 0, \\
\hat{x}_{\mathrm{MDSC}} &= \frac{\alpha_1}{\alpha_3}, \\
\hat{x}_{\mathrm{NK}} &= \frac{\alpha_3\alpha_{12}}{\alpha_1\alpha_{14}+\alpha_3\alpha_{16}}, \\
\hat{x}_{\mathrm{CTL}} &= 0,
\end{aligned}$$

$$\hat{x}_{\mathrm{MDSC}} = \frac{\alpha_1(\hat{x}_{\mathrm{T}}+\gamma_1)+\alpha_2\hat{x}_{\mathrm{T}}}{\alpha_3(\hat{x}_{\mathrm{T}}+\gamma_1)}, \tag{22}$$

$$\hat{x}_{\mathrm{NK}} = \frac{\alpha_3(\hat{x}_{\mathrm{T}}+\gamma_1)\left(\alpha_{12}\left(\hat{x}_{\mathrm{T}}^2+\gamma_2\right)+\alpha_{13}\hat{x}_{\mathrm{T}}^2\right)}{\left(\hat{x}_{\mathrm{T}}^2+\gamma_2\right)\left(\alpha_1\alpha_{14}(\hat{x}_{\mathrm{T}}+\gamma_1)+\alpha_2\alpha_{14}\hat{x}_{\mathrm{T}}+\alpha_3\alpha_{16}(\hat{x}_{\mathrm{T}}+\gamma_1)\right)}, \tag{23}$$

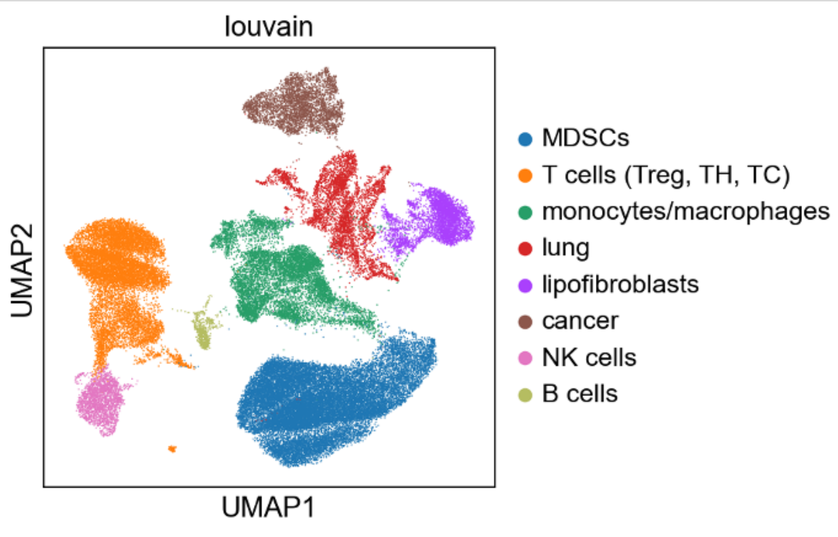
$$\hat{x}_{\mathrm{CTL}} = \frac{\alpha_3\hat{x}_{\mathrm{T}}(\gamma_1+\hat{x}_{\mathrm{T}})g_1}{\left(\gamma_2+\hat{x}_{\mathrm{T}}^2\right)\left(\gamma_3+\hat{x}_{\mathrm{T}}^2\right)g_2}, \tag{24}$$

where

$$\begin{aligned}
g_1 &= \left(\hat{x}_{\mathrm{T}}\left(\alpha_1\alpha_{14}\alpha_{18}(\gamma_1+\hat{x}_{\mathrm{T}})\left(\gamma_2+\hat{x}_{\mathrm{T}}^2\right)+\alpha_3\alpha_{13}\alpha_{17}\hat{x}_{\mathrm{T}}(\gamma_1+\hat{x}_{\mathrm{T}})\left(\gamma_3+\hat{x}_{\mathrm{T}}^2\right)+\alpha_2\alpha_{14}\alpha_{18}\hat{x}_{\mathrm{T}}\left(\gamma_2+\hat{x}_{\mathrm{T}}^2\right)\right.\right. \\
&+ \left.\left.\alpha_3\alpha_{16}\alpha_{18}(\gamma_1+\hat{x}_{\mathrm{T}})\left(\gamma_2+\hat{x}_{\mathrm{T}}^2\right)\right)+\alpha_3\alpha_{12}\alpha_{17}(\gamma_1+\hat{x}_{\mathrm{T}})\left(\gamma_2+\hat{x}_{\mathrm{T}}^2\right)\left(\gamma_3+\hat{x}_{\mathrm{T}}^2\right)\right), \\
g_2 &= (\alpha_1\alpha_{14}(\gamma_1+\hat{x}_{\mathrm{T}})+\alpha_2\alpha_{14}\hat{x}_{\mathrm{T}}+\alpha_3\alpha_{16}(\gamma_1+\hat{x}_{\mathrm{T}}))(\alpha_1\alpha_{19}(\gamma_1+\hat{x}_{\mathrm{T}})+\alpha_2\alpha_{19}\hat{x}_{\mathrm{T}}+\alpha_3\alpha_{21}(\gamma_1+\hat{x}_{\mathrm{T}})).
\end{aligned}$$

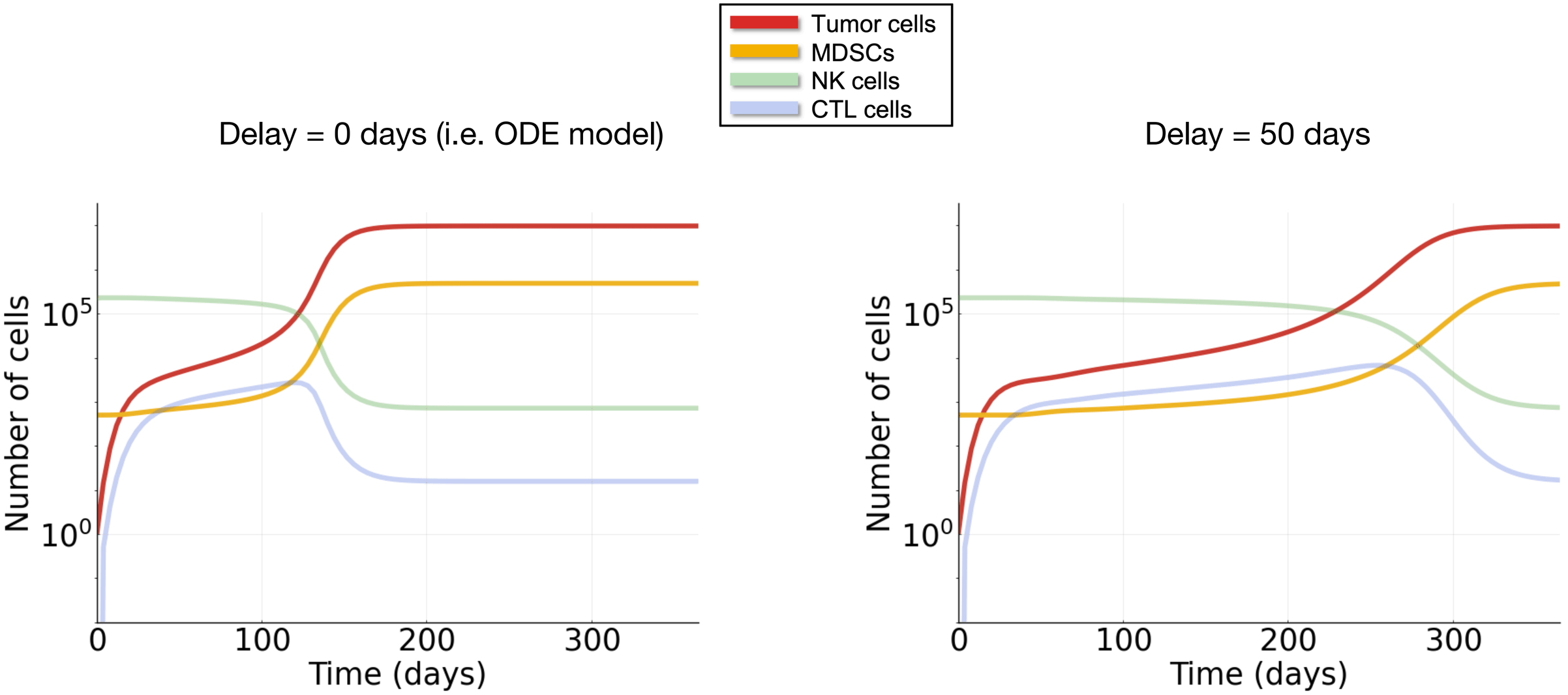
"R_0" of a new metastasis

$$\mathcal{G} = \alpha_7\log(\alpha_8) - \frac{\alpha_3\alpha_9\alpha_{12}}{\alpha_1\alpha_{14}+\alpha_3\alpha_{16}} - \alpha_{11}.$$

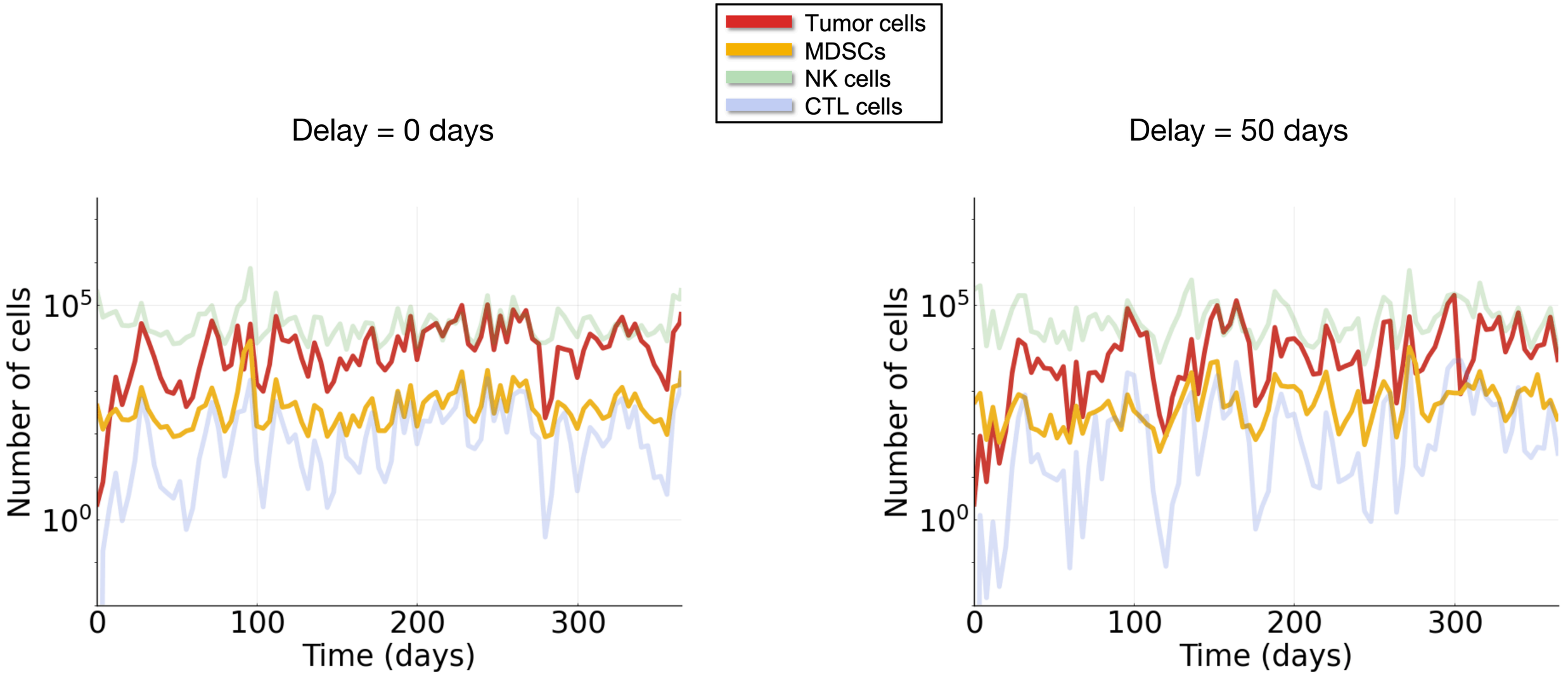


=> initial conditions for mets in the presence of various combination therapies

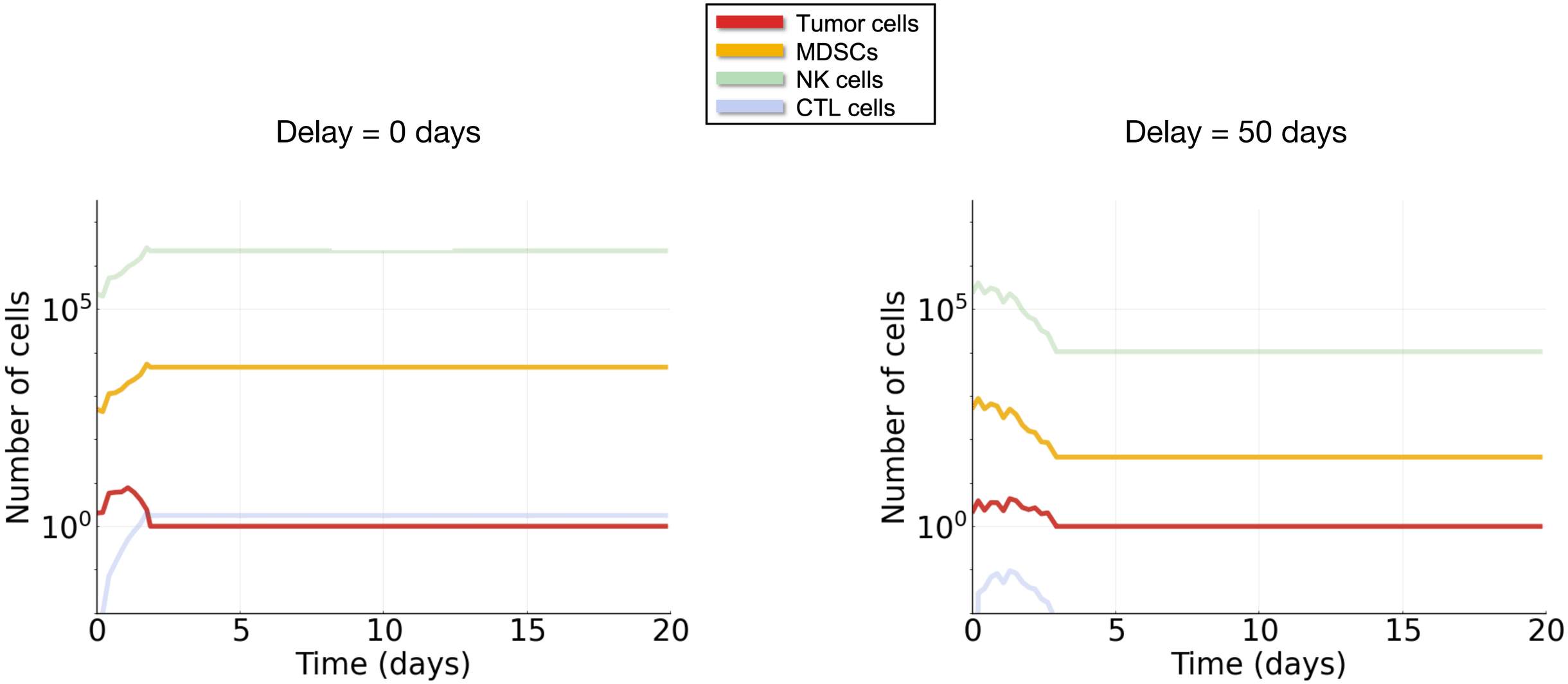
Deterministic delay tumor-MDSC dynamics



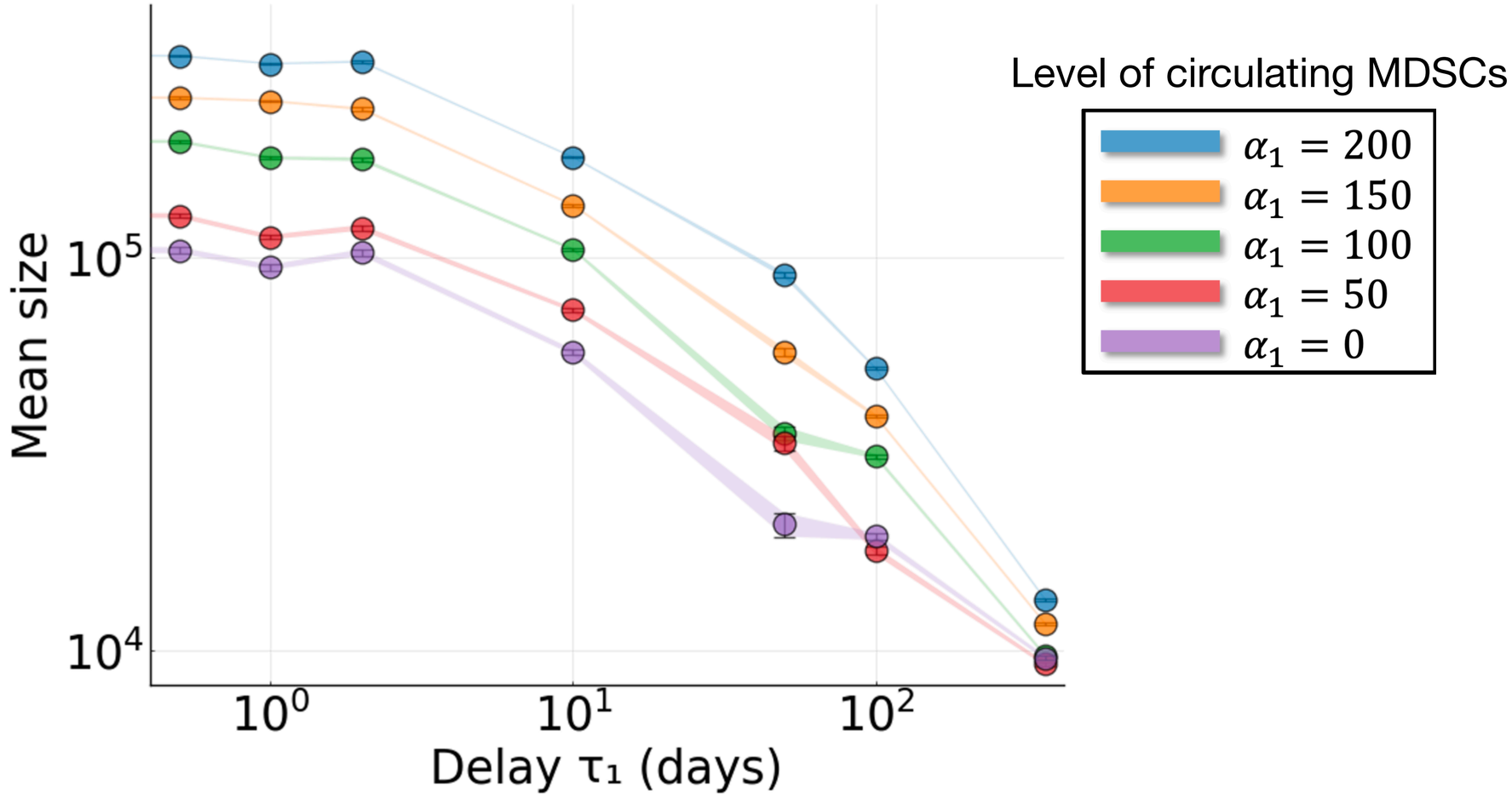
Stochastic delay tumor-MDSC dynamics



In the presence of noise not all tumors persist

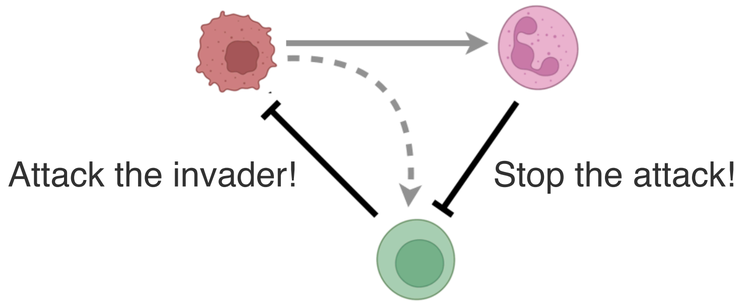


MDSC delay controls the growth dynamics & probability of establishing a new metastasis



Where are we going next?

- Validate key mechanisms of MDSC action ex vivo: T/NK cell proliferation assays in the presence of MDSCs
- Determine drug-combination specific effects on tumor-MDSC dynamics (fit using single-cell data from mouse model)
- Fit patient-specific tumor-MDSC dynamics using response data from NCI-9844
- Use patient-specific tumor response models to:
    1. discover new biomarkers
    2. characterize the TMEs
    3. propose best course of treatment



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