Mathematical modeling of immune response in breast cancer: the effect of tBregs and rituximab

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Bregs and Breast Cancer

- One of the least studied cells.
- Mathematical models in the bibliography:
  1. The property of B cells to produce antigens.
  2. The relationship between mature B cells and progenitor B cells in B-cell acute lymphoblastic leukemia.
- In recent publications Olkhanud, et al. (2009) and (2011) discovered a new subcategory of Bregs, called tumor-evoked regulatory B cells (**tBregs**).
- "new hallmark of breast cancer".

Rituximab

- Monoclonal antibody that targets the CD20 protein.
- Results in the death of B cells.
- Administered as a therapy for blood cancers, rheumatoid arthritis etc.
- Possible cure for breast cancer**?**

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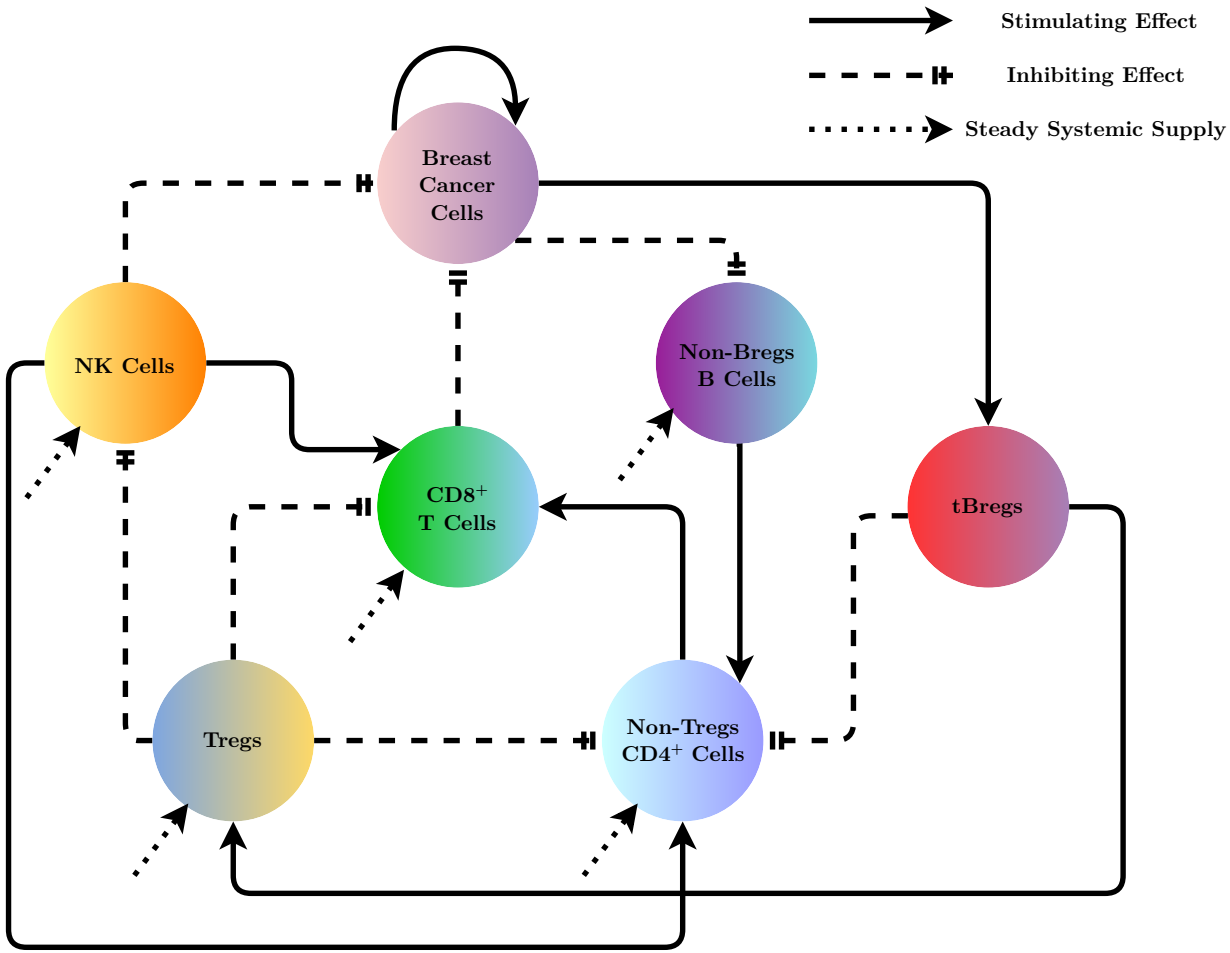
Cell Interactions



Bitsouni, V., & Tsilidis, V. (2022). Mathematical modeling of tumor-immune system interactions: the effect of rituximab on breast cancer immune response. *Journal of Theoritical Biologry, , 539, 111001. DOI: 10.1016/J.JTBI.2021.111001*

The Model

$$\frac{\mathrm{d}T}{\mathrm{d}t} = aT(1-bT) - ce^{-\lambda_R R}\frac{N^\delta}{s_N T^\delta + N^\delta}T - d\frac{C^l}{s_C T^l + C^l}T\,,$$
$$\frac{\mathrm{d}N}{\mathrm{d}t} = \sigma_N - \theta_N N - pTN - \gamma_N R^{\delta_N} N + \kappa HN\,,$$
$$\frac{\mathrm{d}C}{\mathrm{d}t} = \sigma_C - \theta_C C - qTC - \gamma_C RC + rNT + \frac{j_C T}{k_C + T}C + \frac{\eta_1 H}{\eta_2 + H}C\,,$$
$$\frac{\mathrm{d}H}{\mathrm{d}t} = \sigma_H - \theta_H H + \frac{j_H T}{k_H + T}BH - c_1 HB_T\,,$$
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \sigma_R - \theta_R R + c_1 HB_T\,,$$
$$\frac{\mathrm{d}B}{\mathrm{d}t} = \sigma_B - \theta_B B - c_2 TB - \gamma_B X^2 B\,,$$
$$\frac{\mathrm{d}B_T}{\mathrm{d}t} = -\theta_{B_T} B_T + c_2 TB\,,$$
$$\frac{\mathrm{d}X}{\mathrm{d}t} = -\theta_X X + v(t)\,.$$

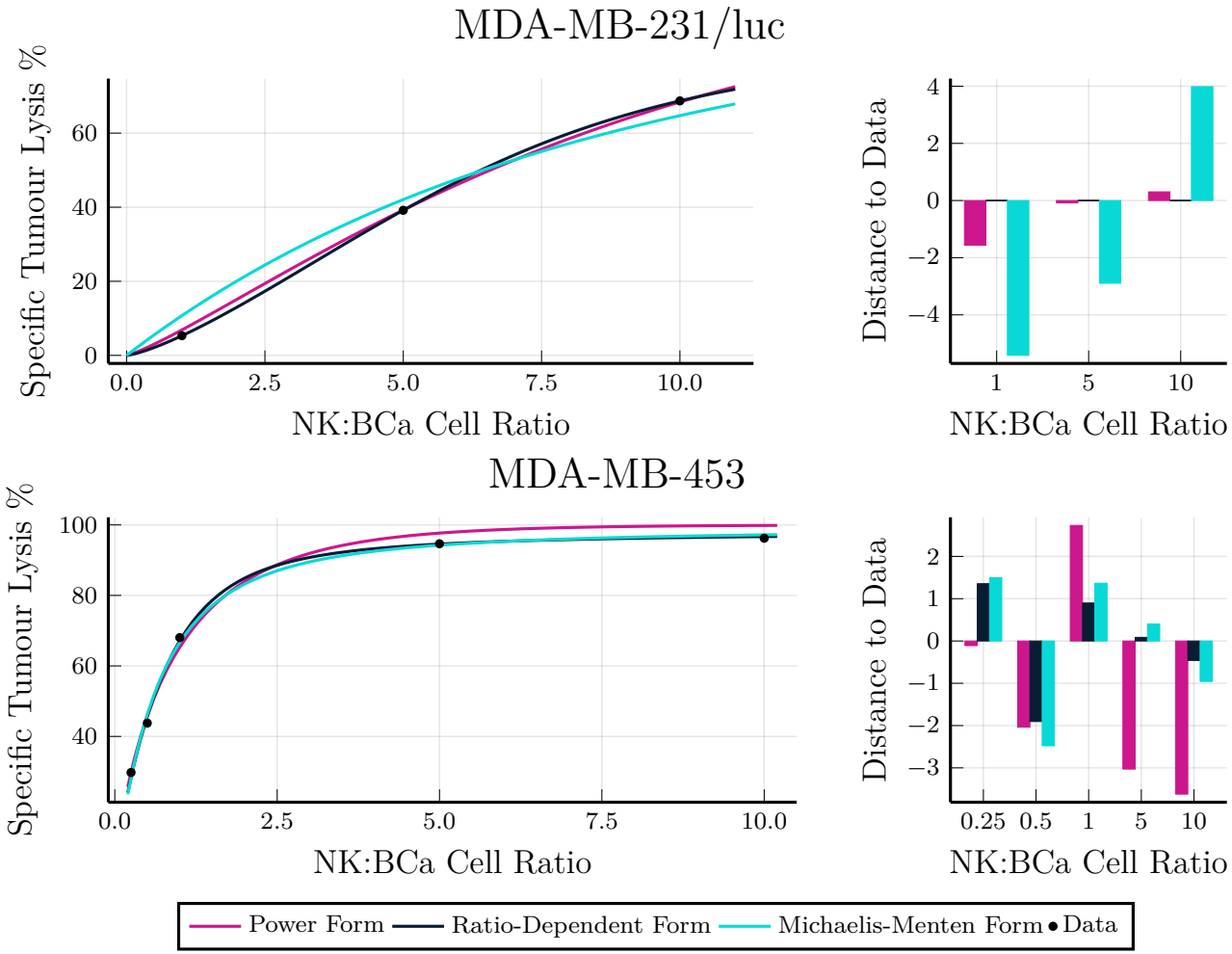
$(T, N, C, H, R, B, B_T, X) = (T_0, N_0, C_0, H_0, R_0, B_0, B_{T_0}, X_0) \in \mathbb{R}^8_{\geq 0}$, for $t = 0$.

Data Fitting: Lysis of Cancer Cells by NK Cells

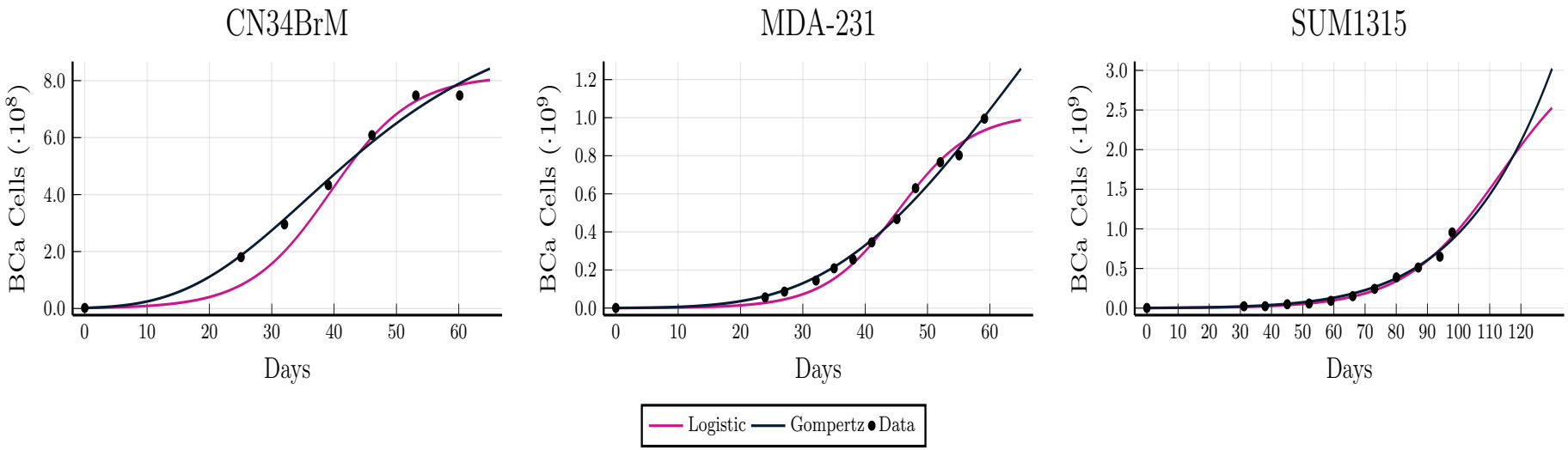
$$\frac{\mathrm{d}T}{\mathrm{d}t} = -f(N,T)\,T(t)\,,$$
$$T(0) = T_E\,,$$

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -\theta_{N_E} N(t)\,,$$
$$N(0) = ratio \cdot T_E\,,$$

$$f(N,T) = cN^{\delta} = c\frac{N^{\delta}}{s_N T^{\delta} + N^{\delta}} = c\frac{N}{\delta + N}\,.$$



Data Fitting: Cancer Growth



Cell Line	Logistic Model		Gompertzian Model	
	Growth Rate	Carrying Cap.	Growth Rate	Carrying Cap.
CN34BrM	0.16511	$7.58 \cdot 10^8$	0.0513	$1.05 \cdot 10^9$
MDA-231	0.16835	$1.03 \cdot 10^9$	0.0328	$3.6 \cdot 10^9$
SUM1315	0.06554	$3.39 \cdot 10^9$	0.007	$4.92 \cdot 10^{11}$

Homeostasis States

- Healthy state:

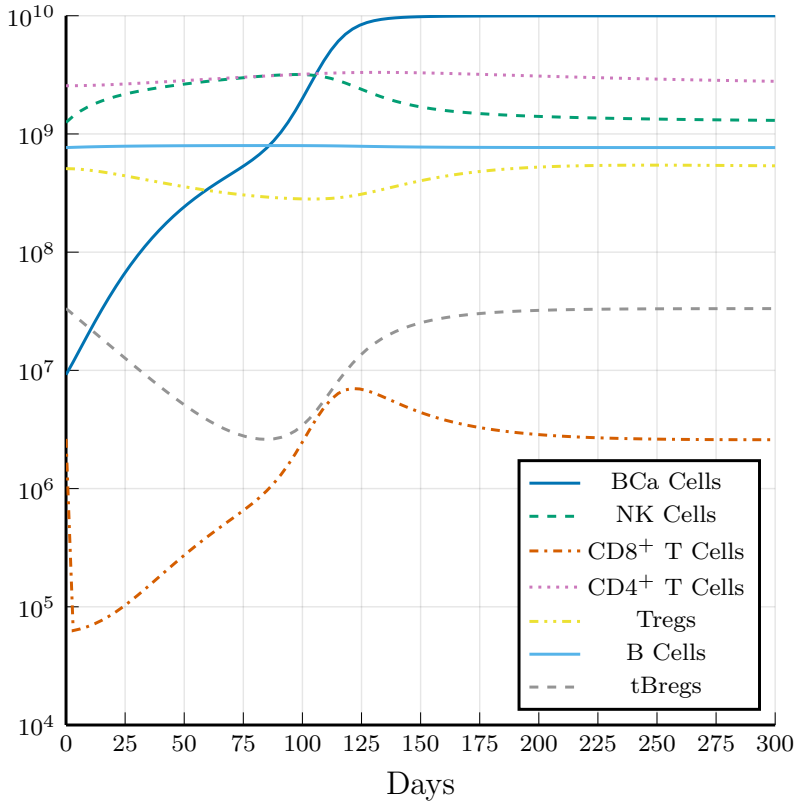
$$E_0 = \left(0, 3.38 \cdot 10^9, 1.263 \cdot 10^5, 2.76 \cdot 10^9, 2.4 \cdot 10^8, 8 \cdot 10^8, 0\right) \cdot \text{cell}\,.$$

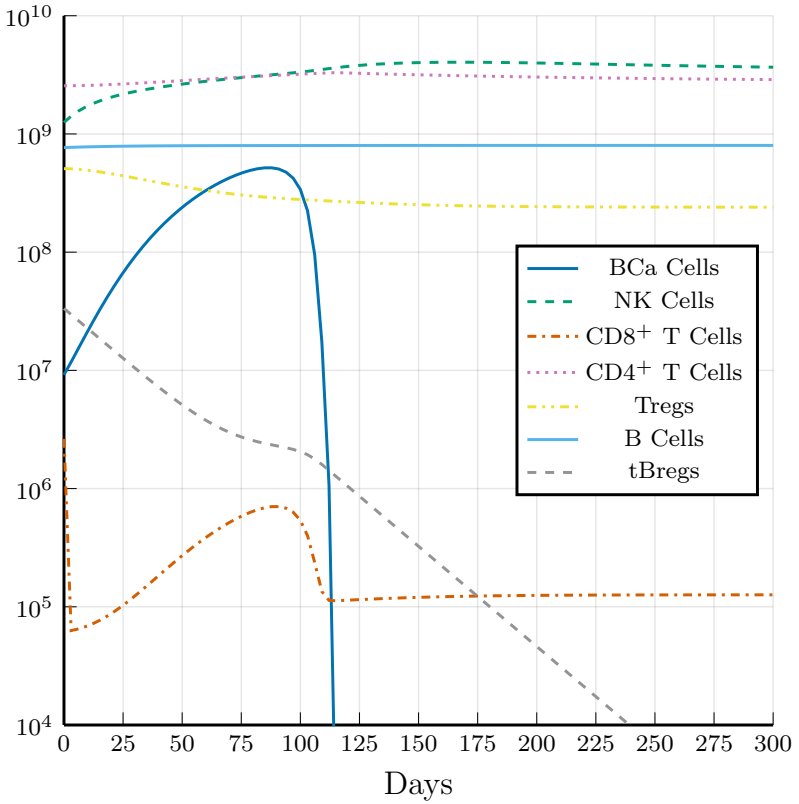
- Tumour state:

$$E_1 = \left(10^{10}, 1.25 \cdot 10^9, 2.634 \cdot 10^6, 2.55621 \cdot 10^9, 5.0879 \cdot 10^8, 7.67 \cdot 10^8, 3.34 \cdot 10^7\right) \cdot \text{cell}\,.$$

Stability of Tumour Equilibrium

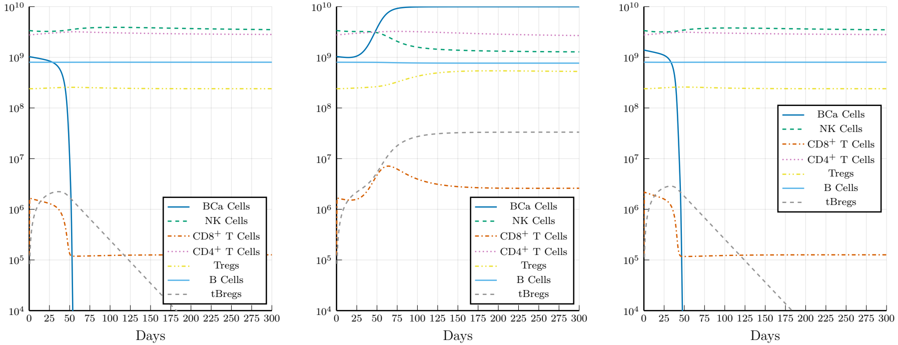
Left: $T(0) = 9.18 \cdot 10^6$ cells. **Right**: $T(0) = 9.17 \cdot 10^6$ cells. Rest of cells at E_1.





Stability of Healthy Equilibrium

Left: $T(0) = 1.03 \cdot 10^9, \delta = 1$, **Center**: $T(0) = 1.04 \cdot 10^9, \delta = 1$.
Right: $T(0) = 1.39 \cdot 10^9, \delta = 1.3$.
Rest of cells at E_0.

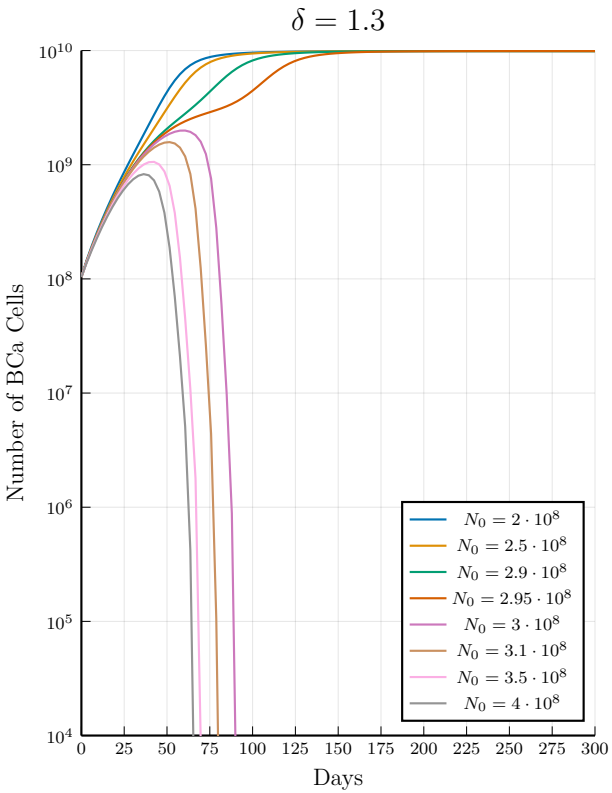


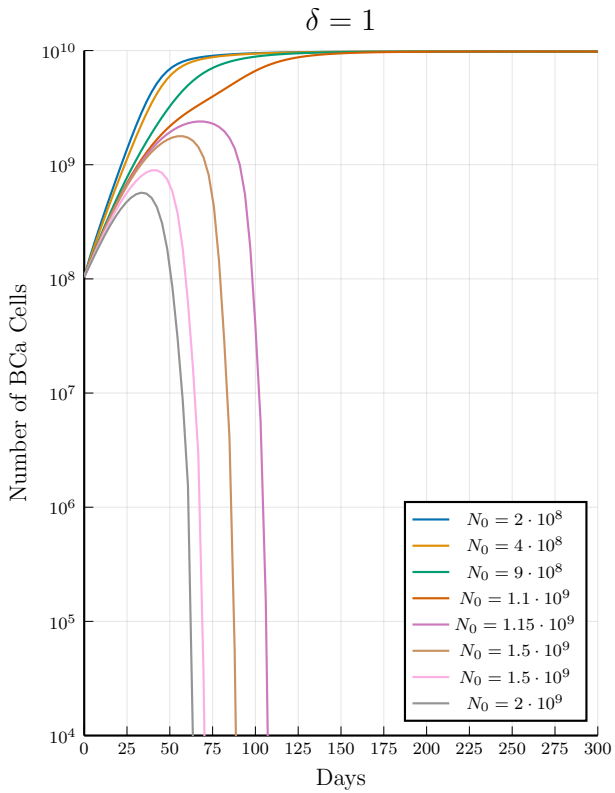
Importance of δ

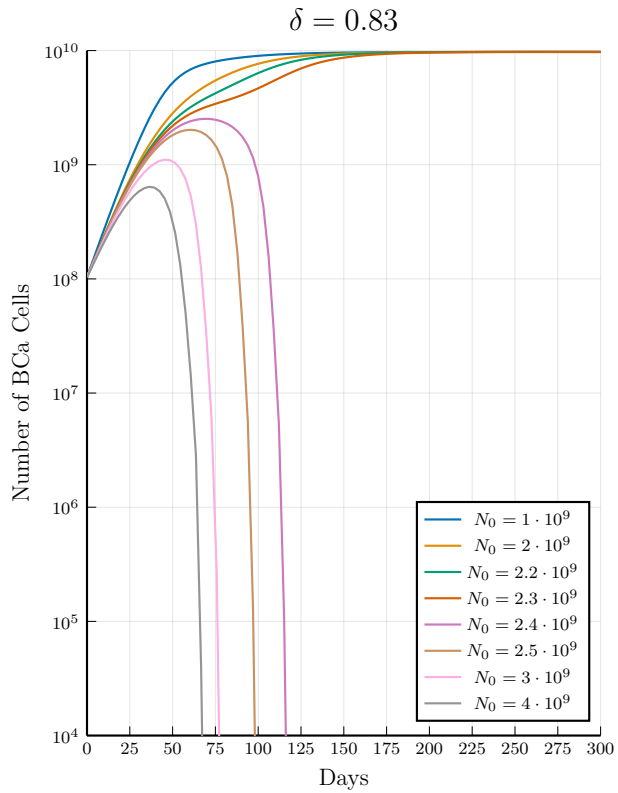
$N(0)/T(0) < 1$:

Value of δ	0.0002	0.002	0.02	0.2	1	2
BCa cells after 300 days	$8.182 \cdot 10^9$	$8.190 \cdot 10^9$	$8.259 \cdot 10^9$	$8.810 \cdot 10^9$	$9.777 \cdot 10^9$	$9.970 \cdot 10^9$

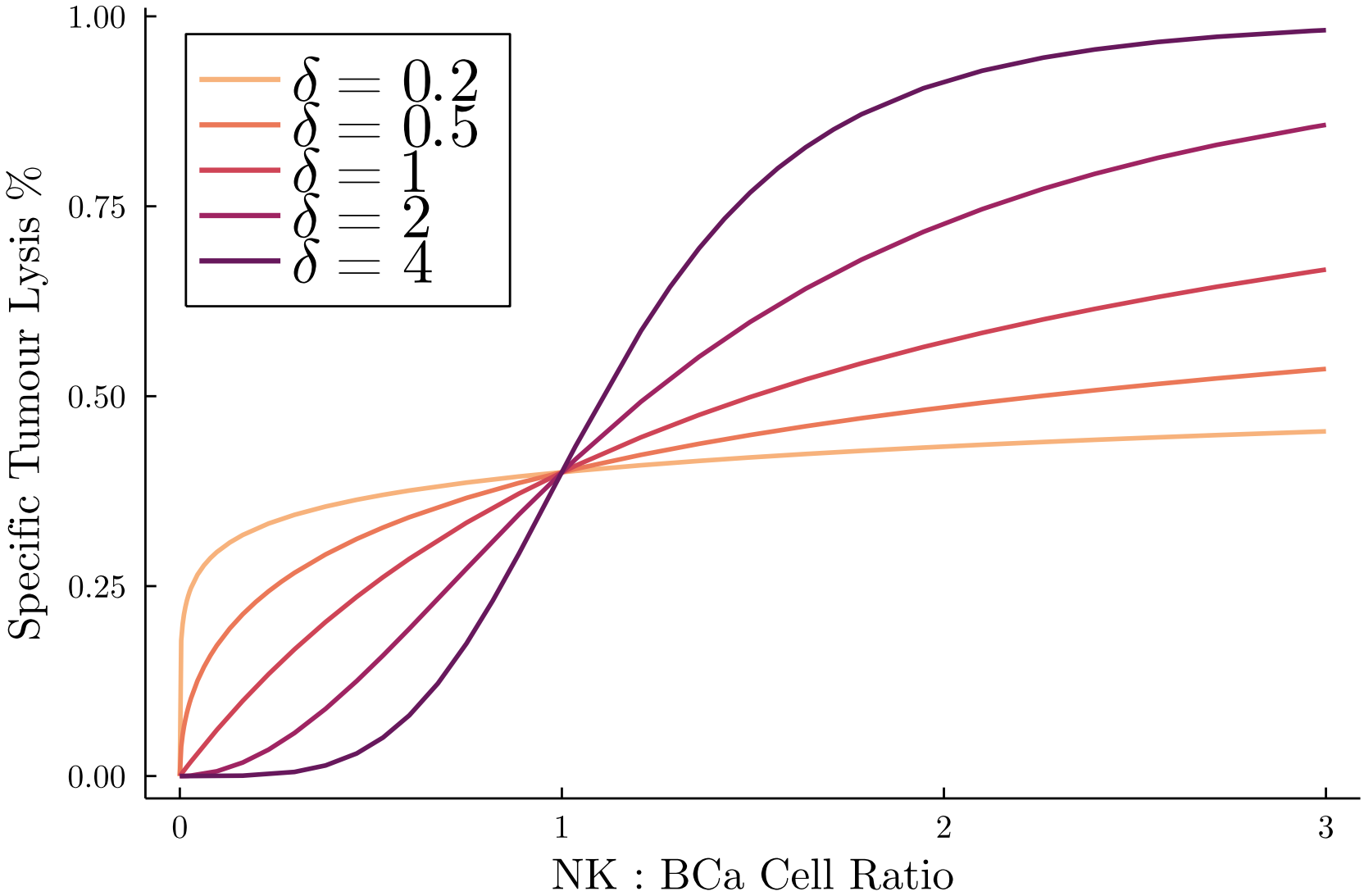
$N(0)/T(0) > 1$:





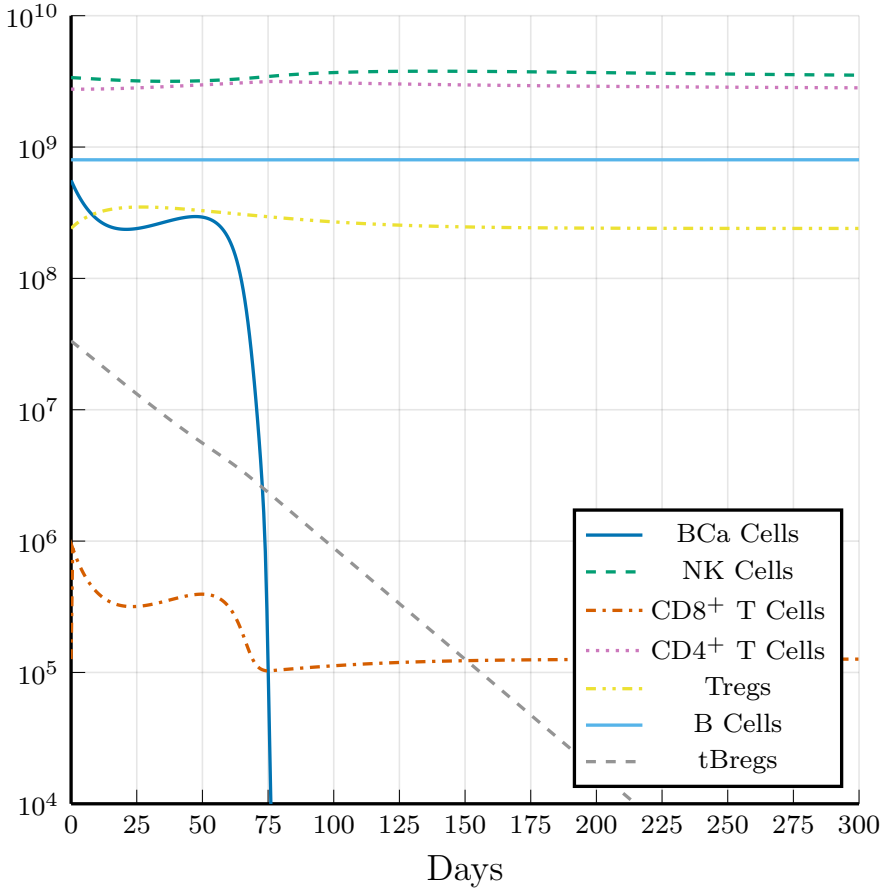


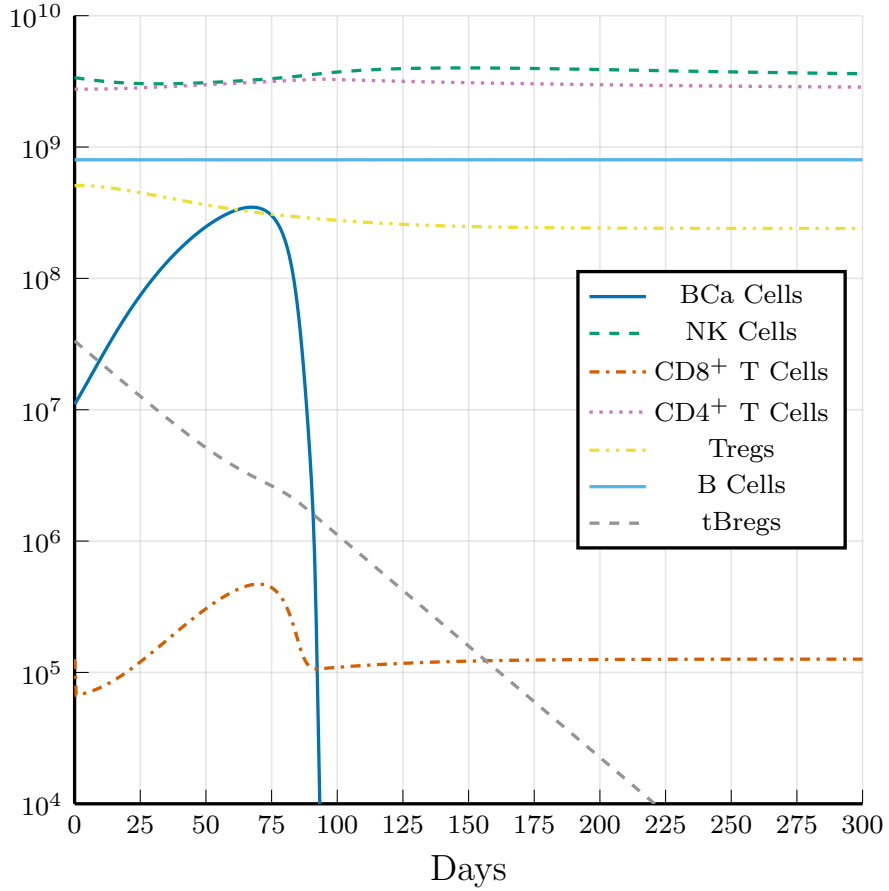
Functional Response



Regulatory Cells

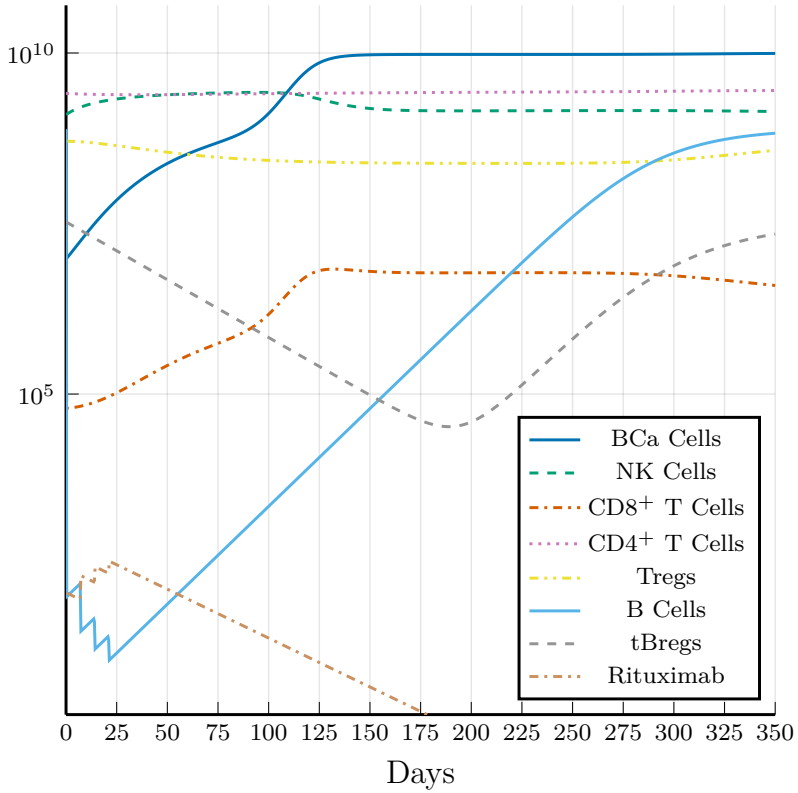
Left: $T(0) = 5.58 \cdot 10^8$ cells and tBregs at E_1.
Right: $T(0) = 1.10 \cdot 10^7$ cells and tBregs, Tregs at E_1.
Rest of the cells at E_0.

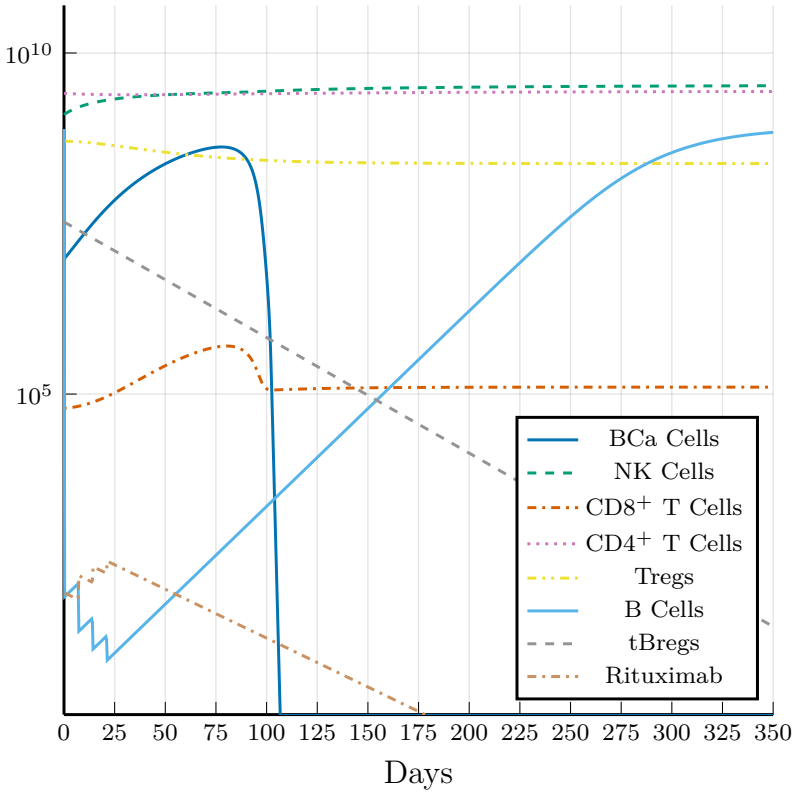




Rituximab: Standard Dosage

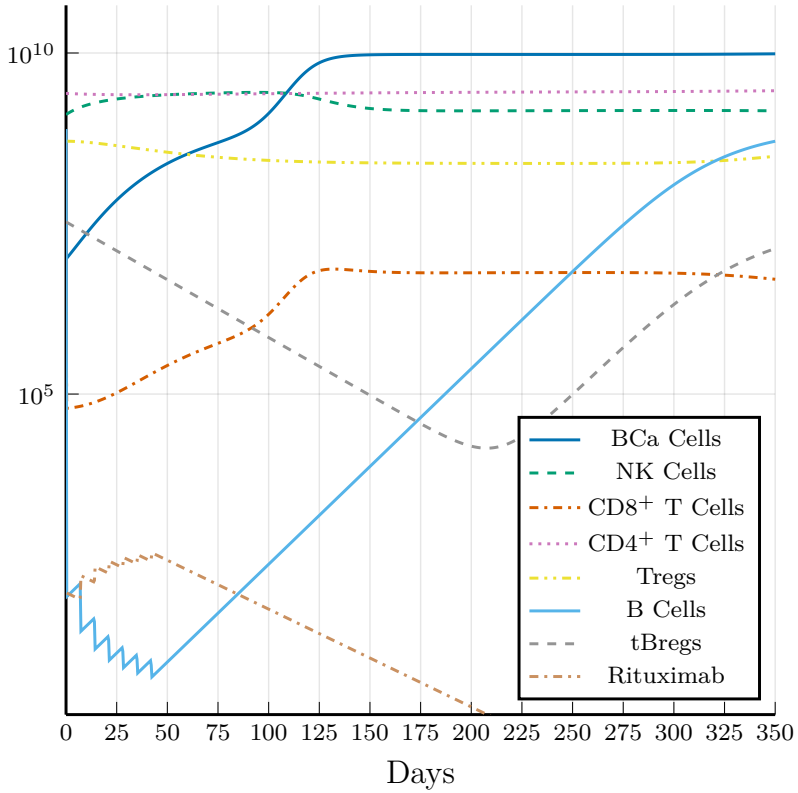
Left: $T(0) = 9.55 \cdot 10^6$ cells. **Right**: $T(0) = 9.54 \cdot 10^6$ cells. Rest of the cells at E_1. Weekly dosing of 375 mg/m^2 rituximab for 4 weeks.

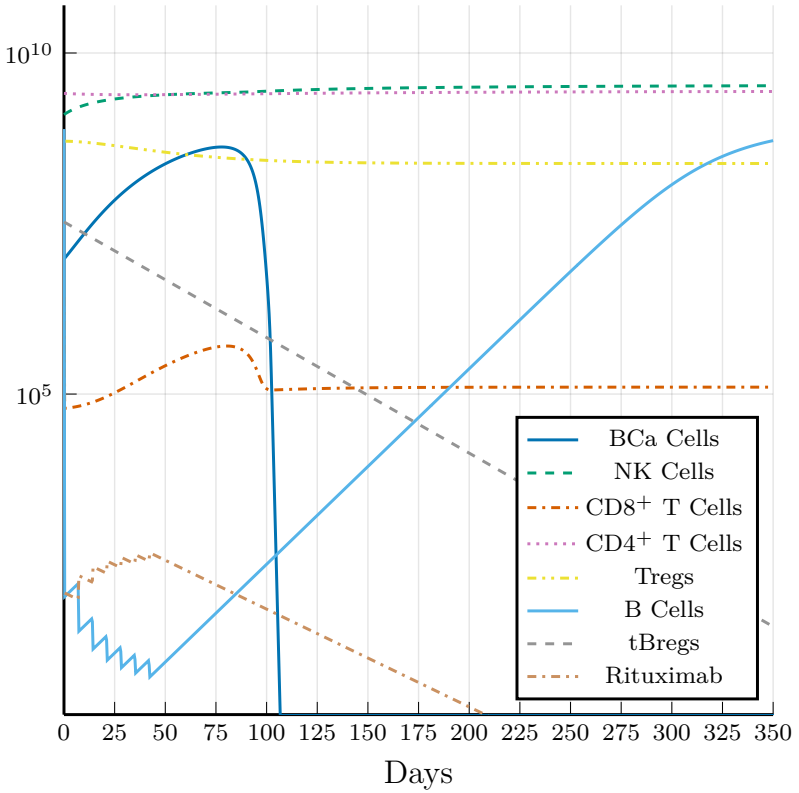




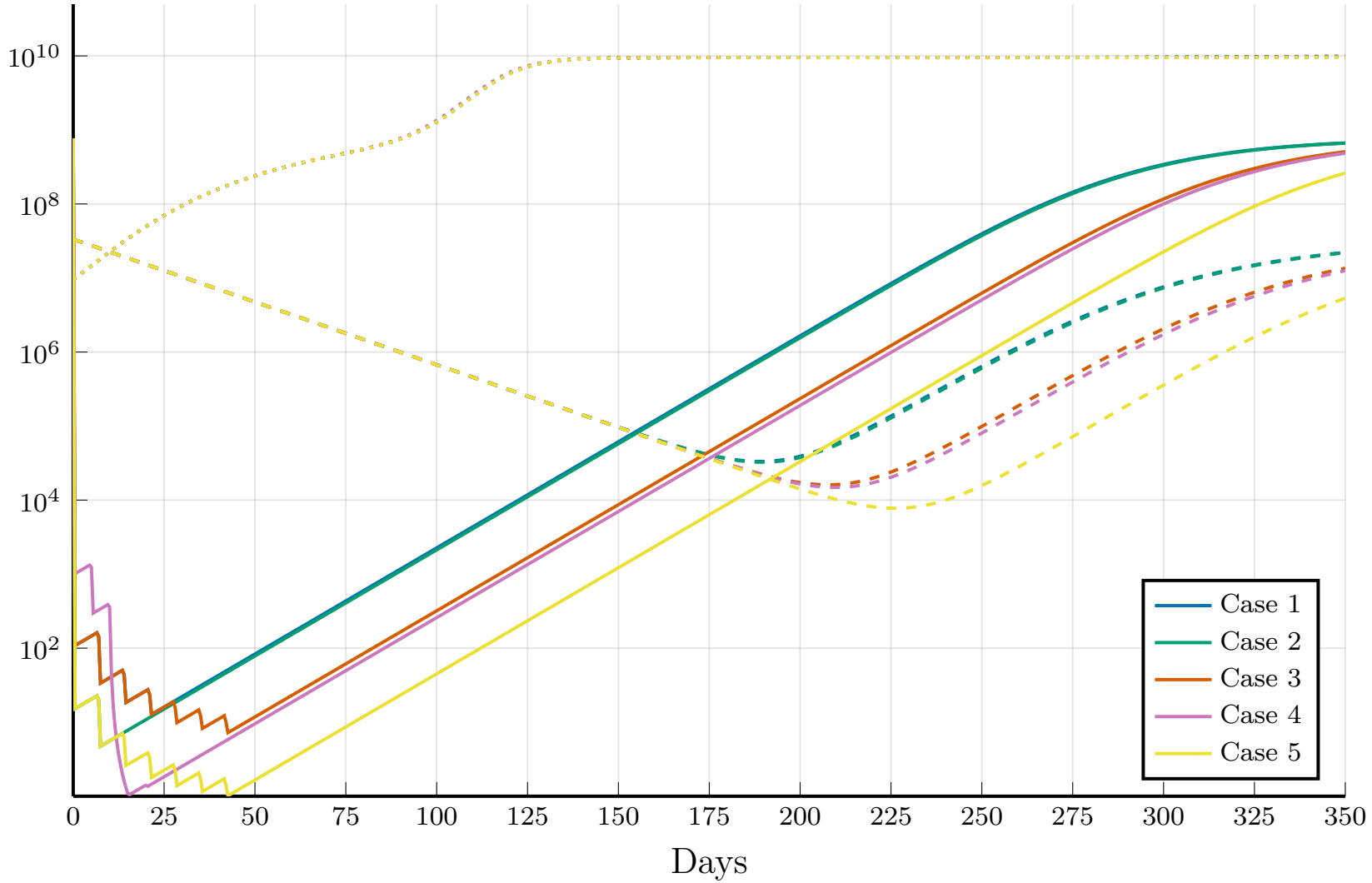
Rituximab: 8 Doses

Left: $T(0) = 9.55 \cdot 10^6$ cells. **Right**: $T(0) = 9.54 \cdot 10^6$ cells. Rest of the cells at E_1. Weekly dosing of 375 mg/m^2 rituximab for 8 weeks.

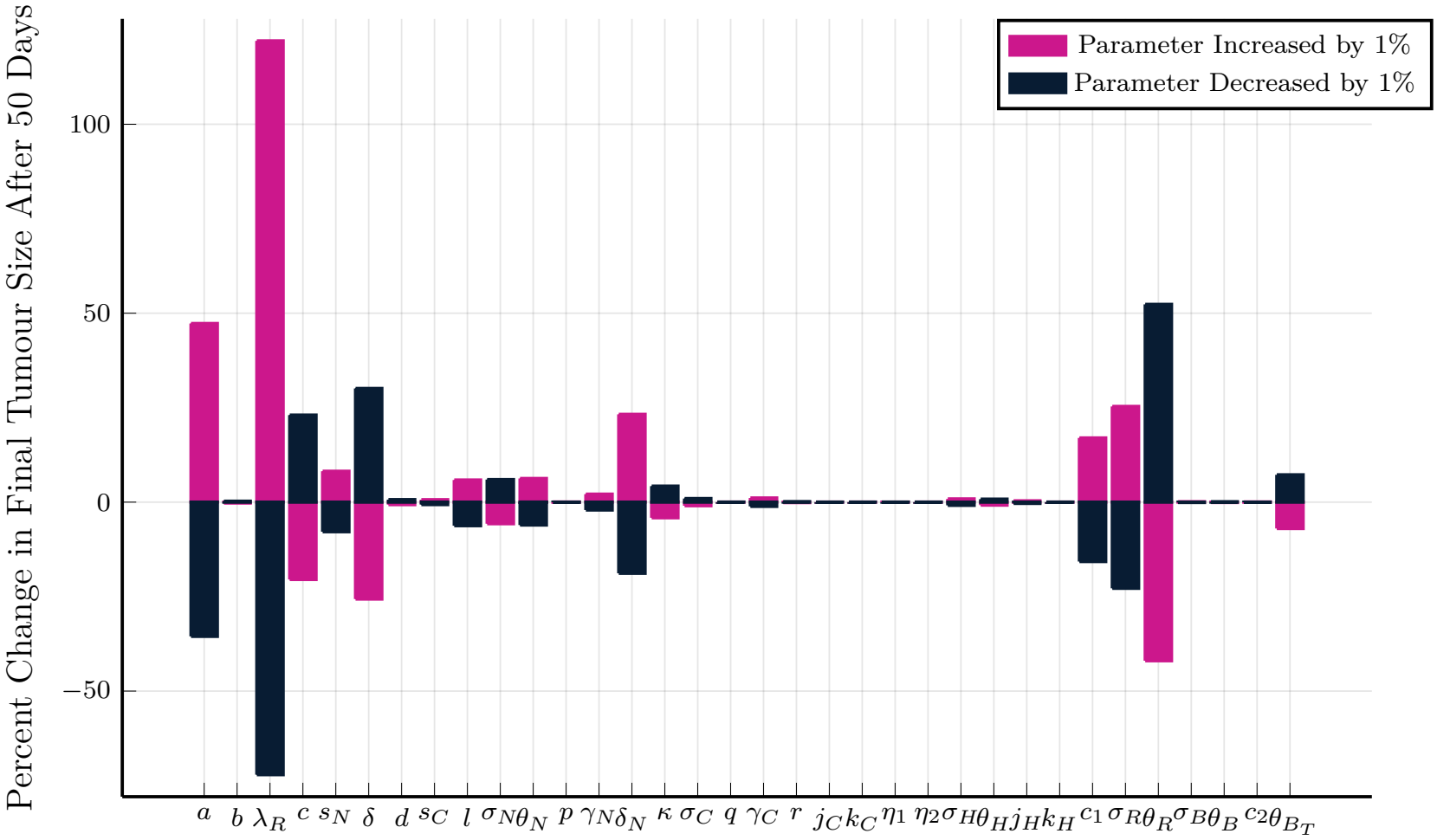




Experimenting with Different Rituximab Dosing Schedules



Parameter Sensitivity



Takeaways

- NK cells kill breast cancer cells in a ratio-dependant way.
- Tregs and tBregs make it harder for the organism to kill beast cancer cells.
- Rituximab's aid in curing breast cancer is small.

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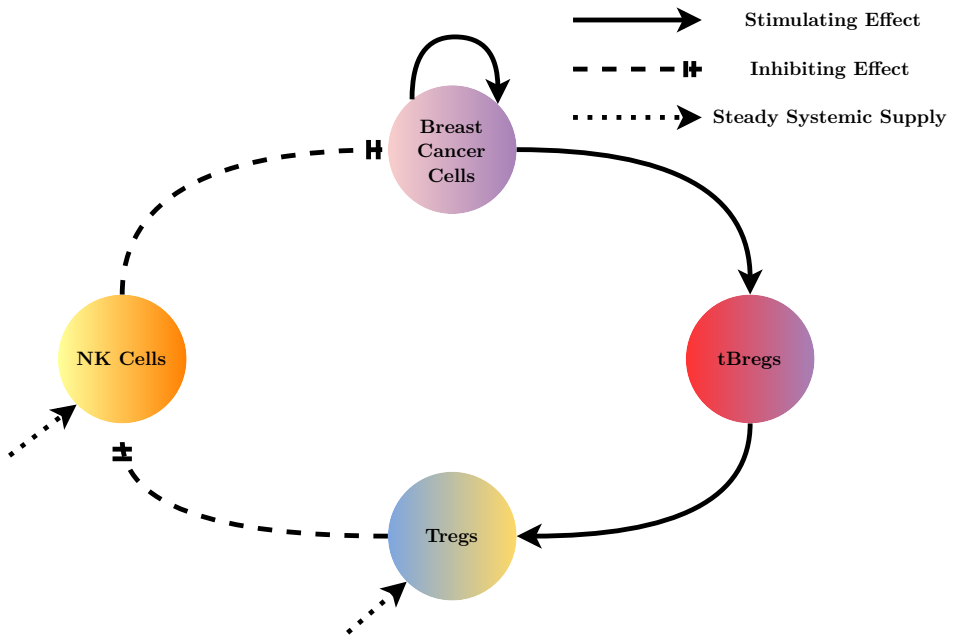
The Model

Let T, N, R and B be the breast cancer cells, NK cells, Tregs and tBregs, respectively.

$$\frac{\mathrm{d}T}{\mathrm{d}t}(t) = aT(1-bT) - cNT\,,$$
$$\frac{\mathrm{d}N}{\mathrm{d}t}(t) = \sigma - \theta_N N - \gamma RN\,,$$
$$\frac{\mathrm{d}R}{\mathrm{d}t}(t) = \kappa - \theta_R R + m_B BR\,,$$
$$\frac{\mathrm{d}B}{\mathrm{d}t}(t) = -\theta_B B + m_T TB\,,$$
$$(T(0), N(0), R(0), B(0)) = (T_0, N_0, R_0, B_0) \in \mathbb{R}^4_{\geq 0}.$$

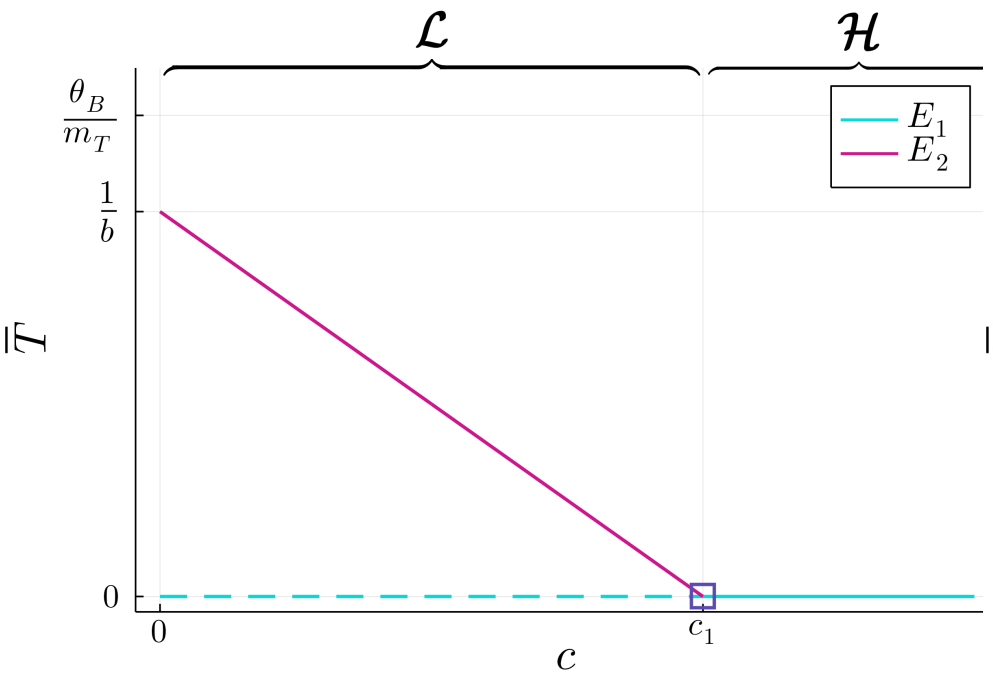


Bitsouni, V., Gialelis, N. & Tsilidis, V. (2022) A mathematical study of the role of tBregs in breast cancer. *Bull. Math. Biol., 84, 112, DOI: 10.1007/s11538-022-01054-y*

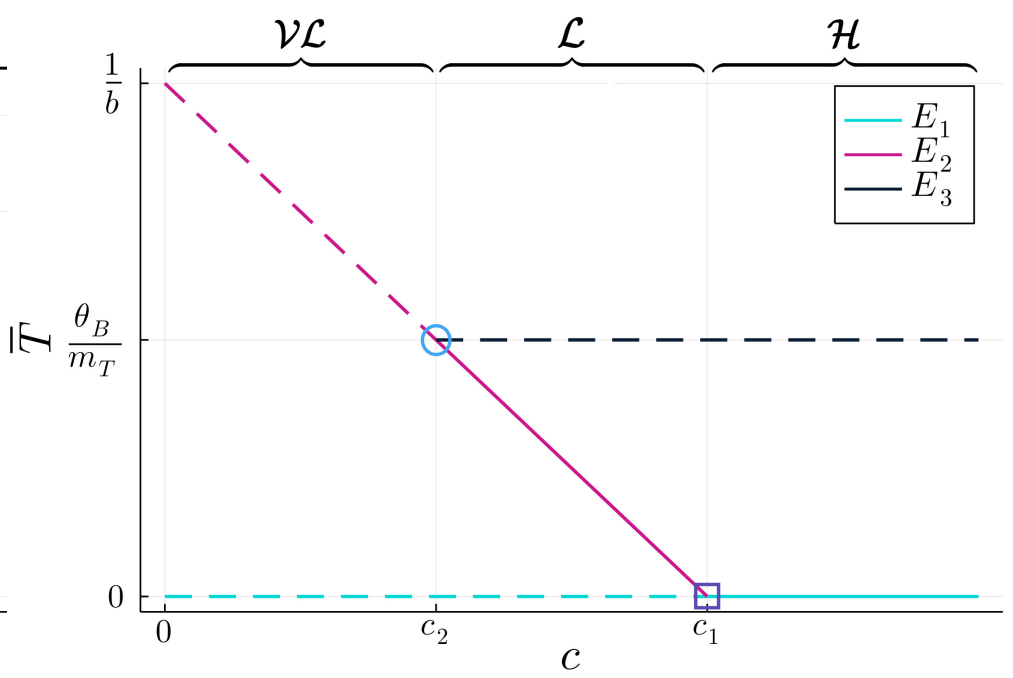
Preliminary Results

- Uniqueness and non-negativity
- Boundedness of T (The set $[0, 1/b]$ is positively invariant for T)
- Globality of the solution for $T_0 \leq 1/b$

Bifurcation Diagram

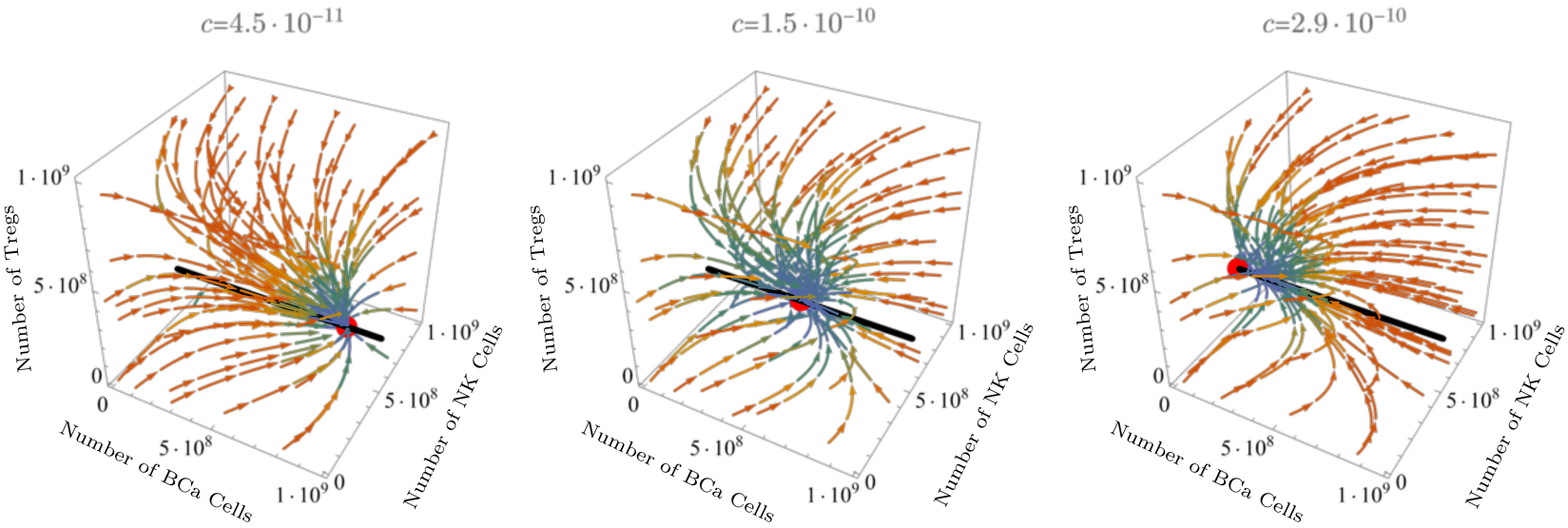


$$\frac{\theta_B}{m_T} \geq \frac{1}{b}$$



$$\frac{\theta_B}{m_T} < \frac{1}{b}$$

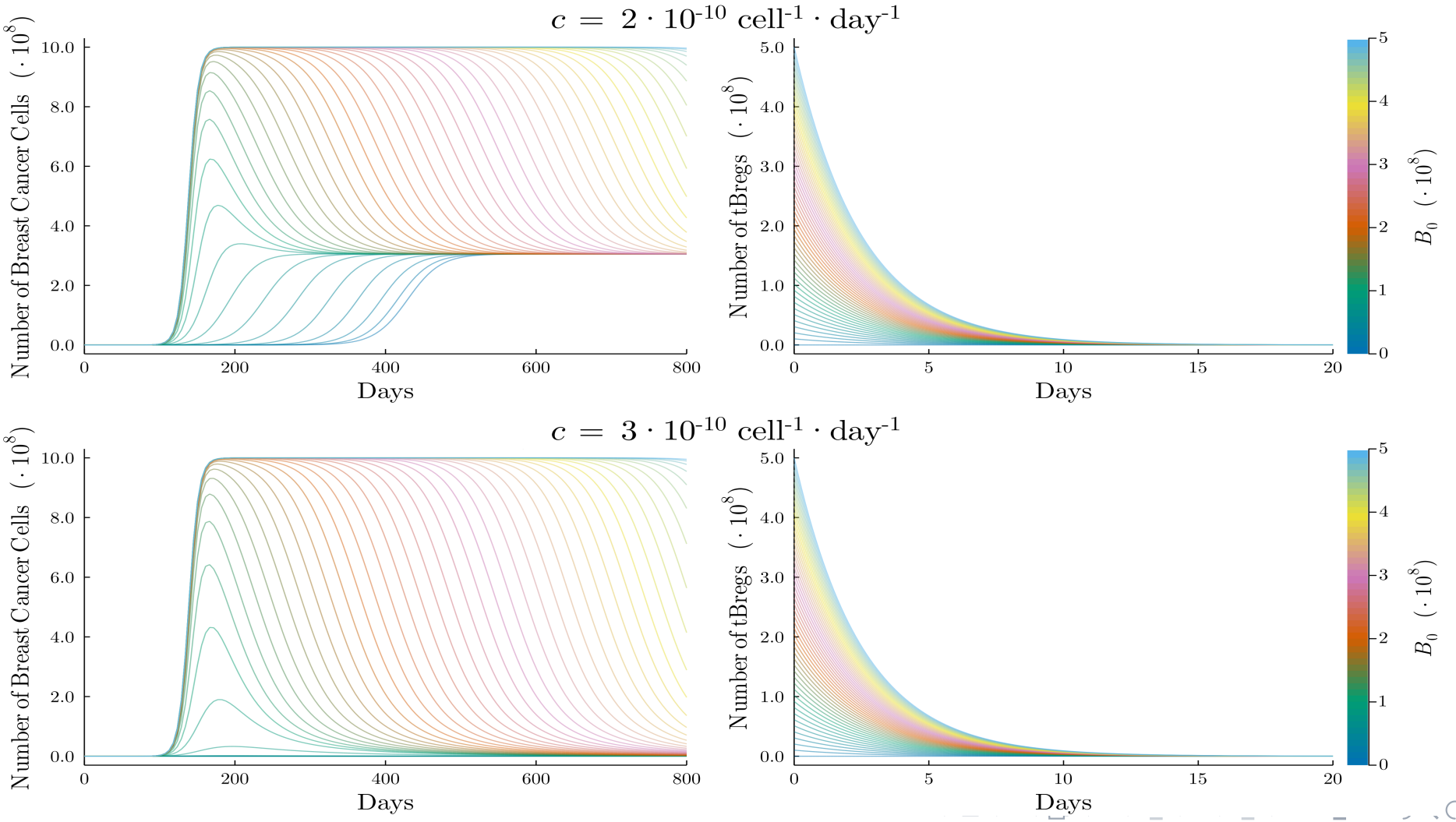
The Scenario of Absent tBregs ($B_0 = 0$)



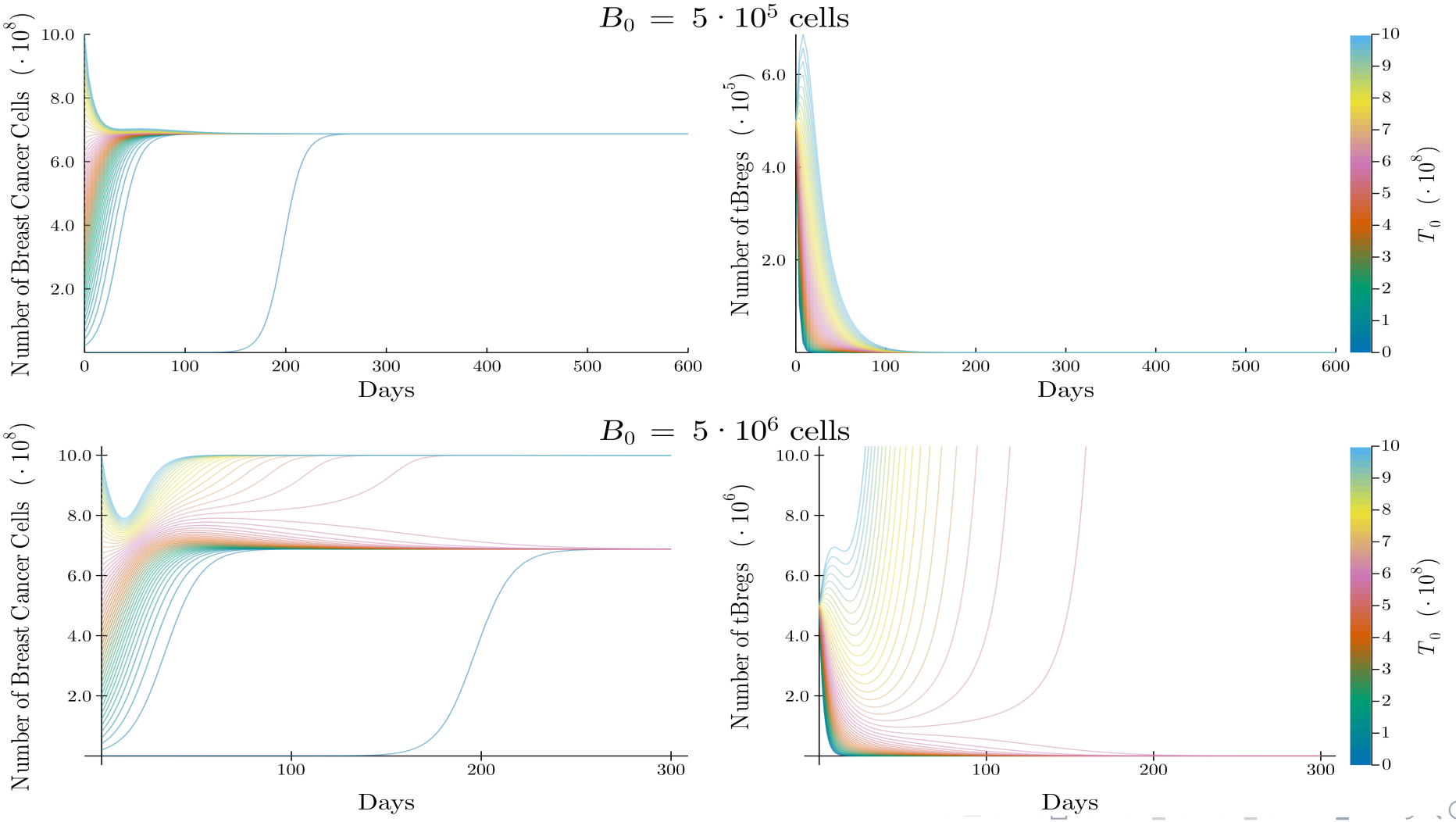
Conclusion 1_a:

In the absence of tBregs, the breast tumour will reach its carrying capacity due to NK cell insufficiency, i.e. $T \nearrow \frac{1}{b}$ when $c \searrow 0$.

The Scenario of Present tBregs ($B_0 \neq 0$) and Bounded-From-Above Tumour Carrying Capacity ($\frac{\theta_b}{m_T} \geq \frac{1}{b}$)



The Scenario of Present tBregs ($B_0 \neq 0$) and Bounded-From-Bellow Tumour Carrying Capacity ($\frac{\theta_b}{m_T} < \frac{1}{b}$)



The Scenario of Present tBregs ($B_0 \neq 0$) and Bounded-From-Bellow Tumour Carrying Capacity ($\frac{\theta_b}{m_T} < \frac{1}{b}$)

Conclusion 2:

In the presence of tBregs, if tumour carrying capacity is bounded from above, then the breast tumour will initially reach its carrying capacity due to the effect of tBregs, i.e. initially $T \nearrow \frac{1}{b}$ when $B_0 \nearrow$.

Takeaways

- In the absence of tBregs, breast cancer reaches its carrying capacity, only if $c \to 0$.
- A sufficient large amount of tBregs, causes breast cancer to reach its carrying capacity, regardless of the value of c.

Thank you for your attention!