

A Validated Mathematical Model of Cell-Mediated Immune Response to Cell Growth

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Mathematical Models | 2023

Vocabulary

01

NK Cells (natural killer cells)

large granular lymphocytes that do not express markers of either T- or B-cell lineage

02

CD8+ T cells (CD3+CD8+ T cells)

a critical subpopulation of T cells which can be cytotoxic to tumor cells

03

Ligand

A substance that binds to a receptor and alters a cellular response

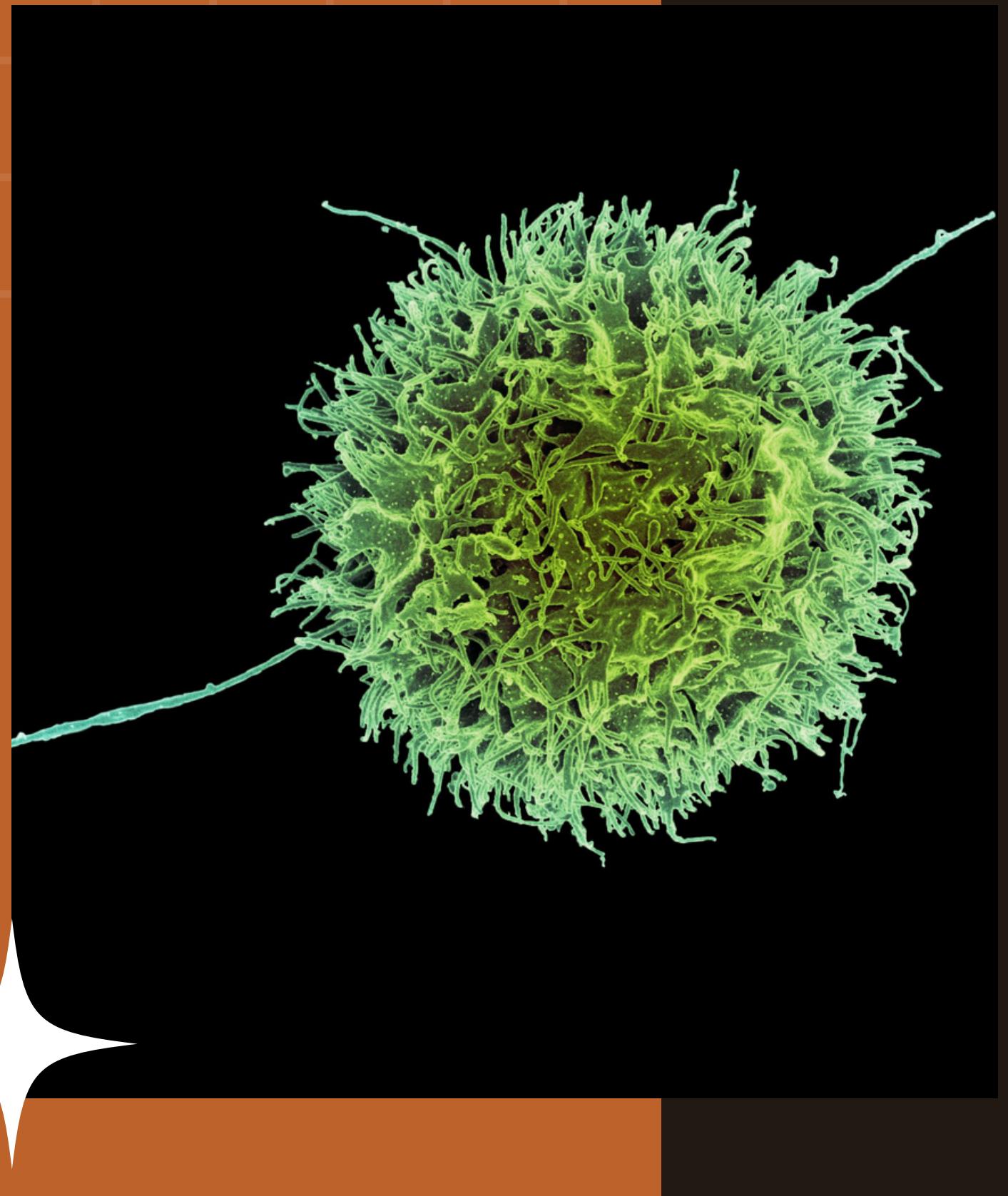
04

Lysis

The breaking down of the membrane of a cell to compromises the integrity of the cell

Introduction

Therapeutic vaccines are being developed and tested as a new approach to treatment for cancer patients. The ultimate goal is to create models that can reflect a system's response to emerging biological therapies, such as vaccine therapy. This mathematical model of tumor-immune interactions sheds light on the differing roles of the natural killer (NK) and CD8+ T cells in suppressing various tumor cell lines in mice and humans.



Biological Aspects

- ◆ The tumor cells grow logistically in the absence of an immune response
- ◆ Both NK cells and CD8+ T cells can kill tumor cells
- ◆ Tumor cells have the potential to engender cytotoxic activity in previously native and noncytotoxic cells
- ◆ As part of innate immunity, NK cells are always present and active in the system, even in the absence of tumor cells
- ◆ Tumor-specific CD8+ T cells are recruited once tumor cells are present
- ◆ Each NK cell and CD8+ cell will eventually become inactivated after some number of encounters with tumor cells

ODES

$$\frac{dT}{dt} = aT(1 - bT) - cNT - D$$

$$\frac{dN}{dt} = \sigma - fN + \frac{gT^2}{h + T^2}N - pNT$$

$$\frac{dL}{dt} = -mL + \frac{jD^2}{k + D^2}L - qLT + rNT$$

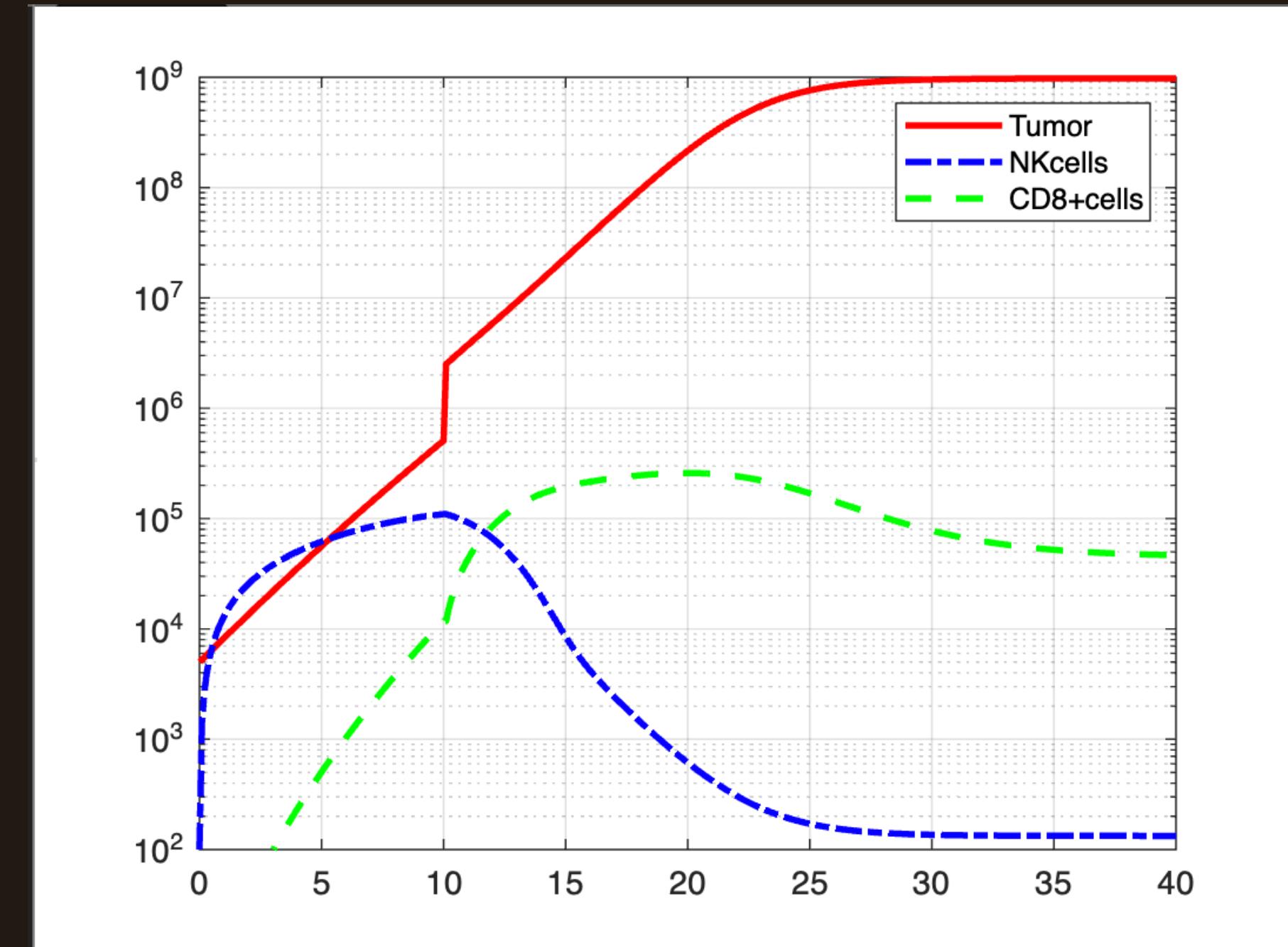
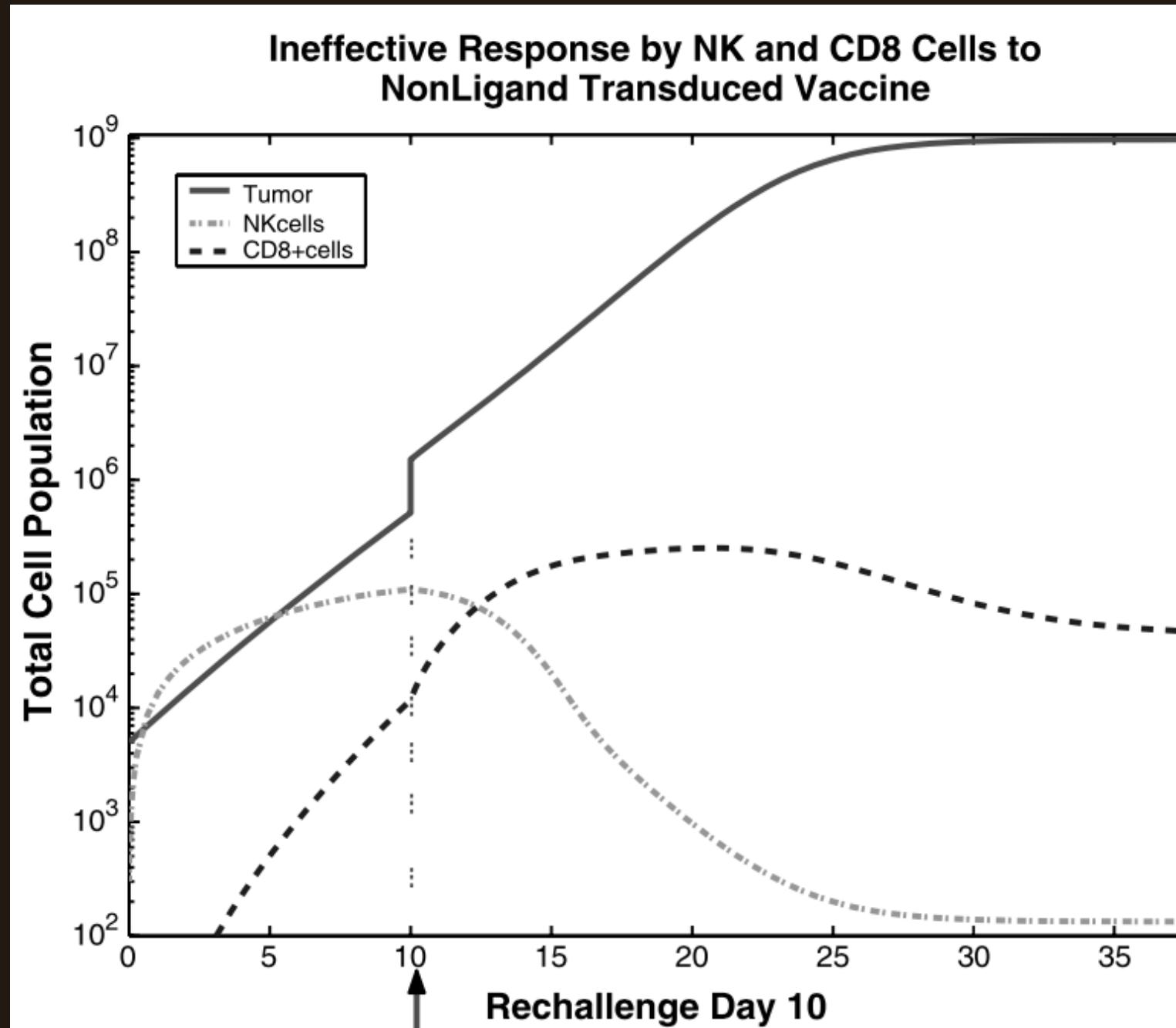
$$D = d \frac{(L/T)^\lambda}{s + (L/T)^\lambda} T$$

Parameters

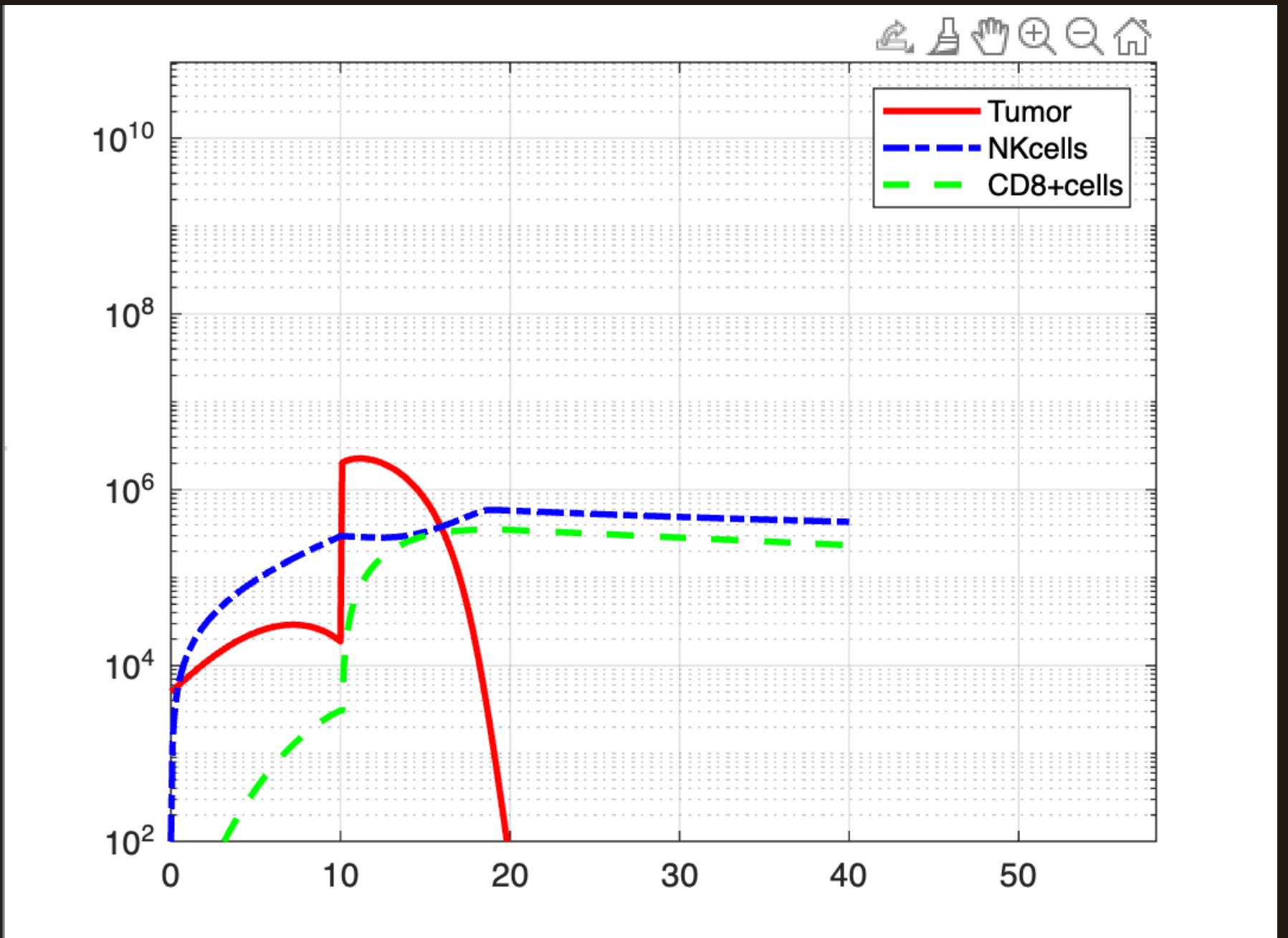
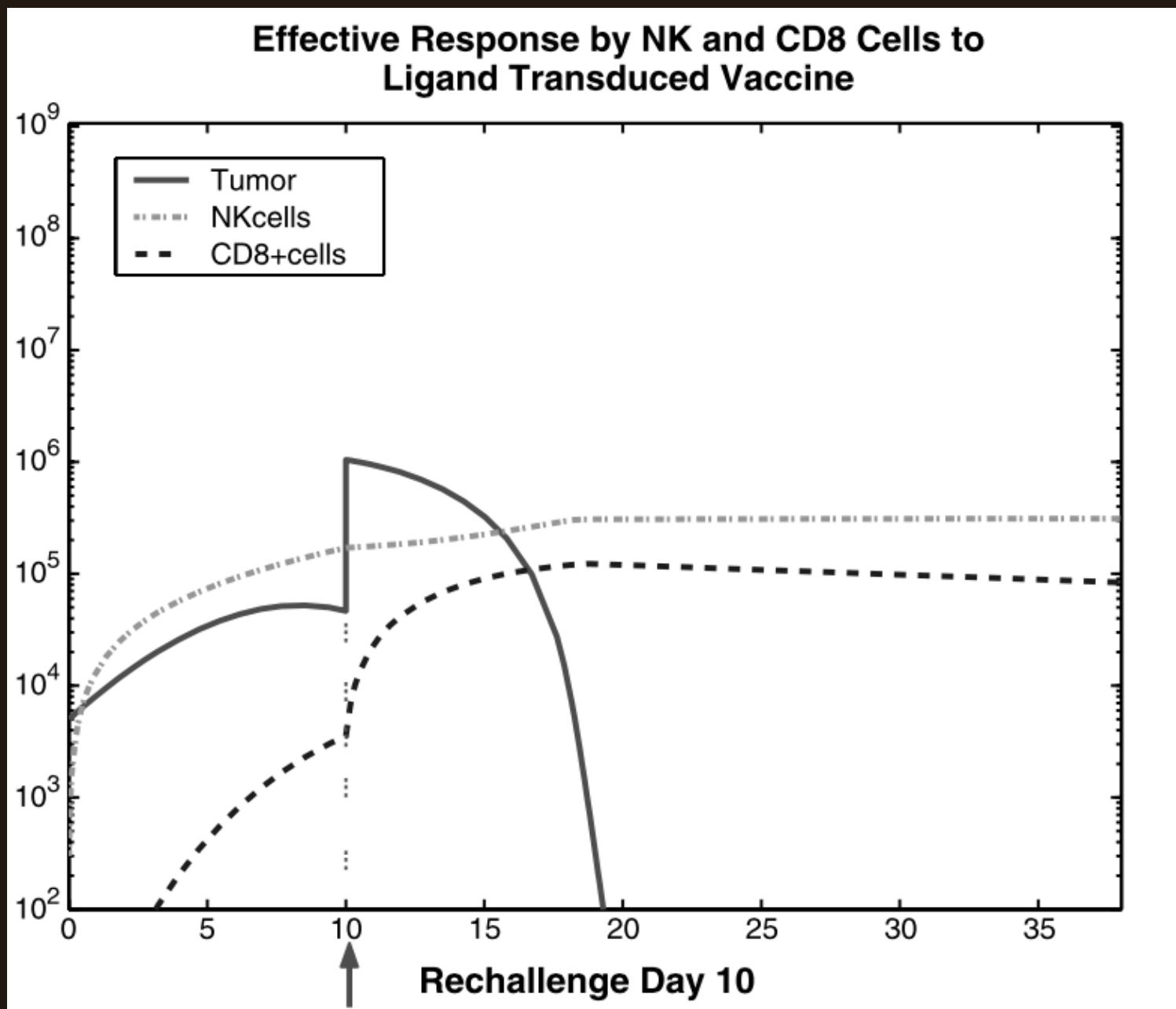
Table 1. Estimated mouse parameters

Parameters	Units	Estimated value	Description	Source
a	day^{-1}	5.14×10^{-1}	Tumor growth rate	(6)
b	cell^{-1}	1.02×10^{-9}	$1/b$ is tumor carrying capacity	(6)
$c(n)$	$\text{cell}^{-1} \text{ day}^{-1}$	3.23×10^{-7}	Fractional (non)-ligand-transduced	(6)
$c(l)$		3.50×10^{-6}	tumor cell kill by NK cells	
$d(nn)$	day^{-1}	1.43	Saturation level of fractional	(6)
$d(nl)$		3.60	tumor cell kill by CD8 ⁺ T cells.	
$d(ln)$		3.51	nn, nl, ln, ll : primed with	
$d(ll)$		7.17	(non)-ligand-transduced cells,	
			challenged with (non)-ligand-transduced cells.	
$\lambda(nn)$	None	5.80×10^{-1}	Exponent of fractional tumor	(6)
$\lambda(nl)$		4.60×10^{-1}	cell kill by CD8 ⁺ T cells. nn, nl, ln, ll:	
$\lambda(ln)$		9.00×10^{-1}	primed with (non)-ligand-transduced cells,	
$\lambda(ll)$		7.50×10^{-1}	challenged with (non)-ligand-transduced cells.	
$s(nn)$	None	2.73	Steepness coefficient of the Tumor-(CD8 ⁺ T cell)	(6)
$s(nl)$		1.61	competition term. nn, nl, ln, ll: primed with	
$s(ln)$		5.07	(non)-ligand-transduced cells, challenged	
$s(ll)$		4.00×10^{-1}	with (non)-ligand-transduced cells (smaller $s \Rightarrow$ steeper curve)	
σ	cells day^{-1}	1.30×10^4	Constant source of NK cells.	(10)
f	day^{-1}	4.12×10^{-2}	Death rate of NK cells.	(10)
$g(n)$	day^{-1}	2.5×10^{-2}	Maximum NK cell recruitment rate by	(10, 6)
$g(l)$		$4g(n) = 2 \times 10^{-1}$	(non)-ligand-transduced tumor cells.	
h	cell^2	2.02×10^7	Steepness coefficient of the NK cell recruitment curve	(10)
p	$\text{cell}^{-1} \text{ day}^{-1}$	1.0×10^{-7}	NK cell inactivation rate by tumor cells	(6)
m	day^{-1}	2.0×10^{-2}	Death rate of CD8 ⁺ T cells	(27)
$j(nn)$	day^{-1}	3.75×10^{-2}	Maximum CD8 ⁺ T-cell recruitment rate. nn, nl, ln, ll:	(10, 6)
$j(nl)$		3.75×10^{-2}	primed with (non)-ligand-transduced cells, challenged	
$j(ln)$		$3j(nn) = 1.13 \times 10^{-1}$	with (non)-ligand-transduced cells.	
$j(ll)$		$8j(nn) = 3.0 \times 10^{-1}$		
k	cell^2	2.02×10^7	Steepness coefficient of the CD8 ⁺ T-cell recruitment curve	(10, 6)
q	$\text{cell}^{-1} \text{ day}^{-1}$	3.42×10^{-10}	CD8 ⁺ T-cell inactivation rate by tumor cells	(10)
r	$\text{cell}^{-1} \text{ day}^{-1}$	1.1×10^{-7}	Rate at which tumor-specific CD8 ⁺ T cells are	(27, 29)
			stimulated to be produced as a result of	
			tumor cells killed by NK cells	

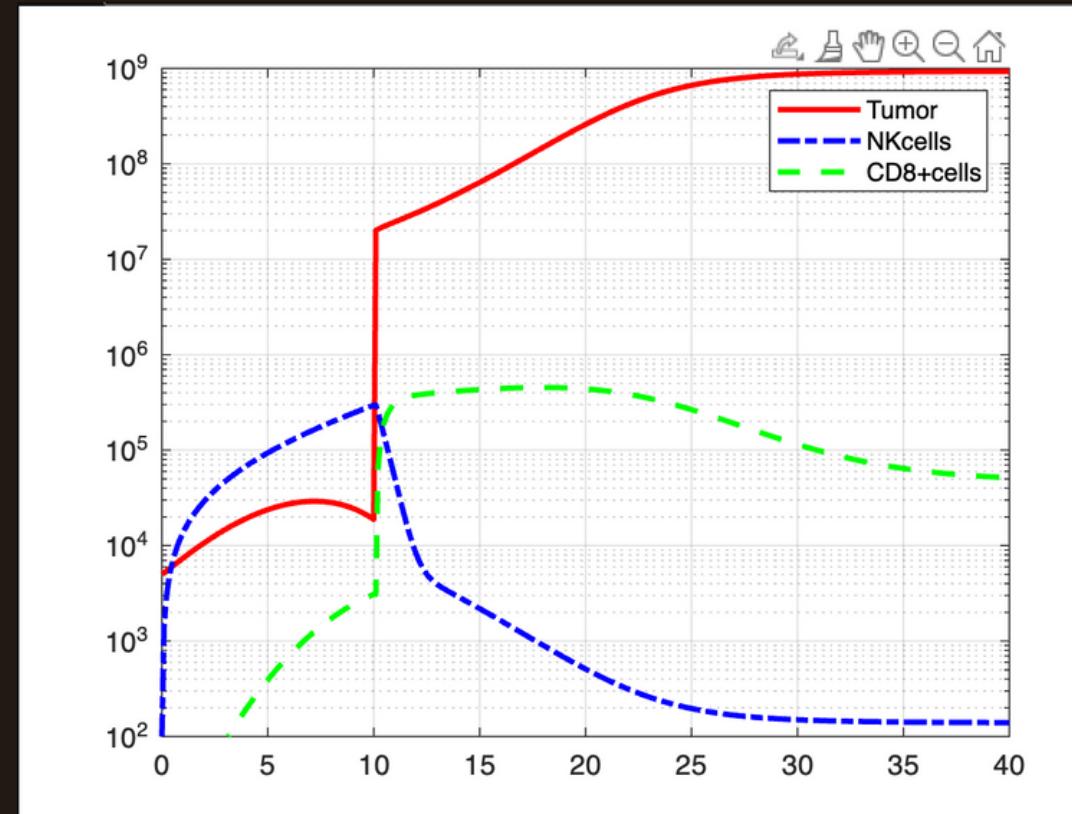
Replicated Graph (Ineffective Response)



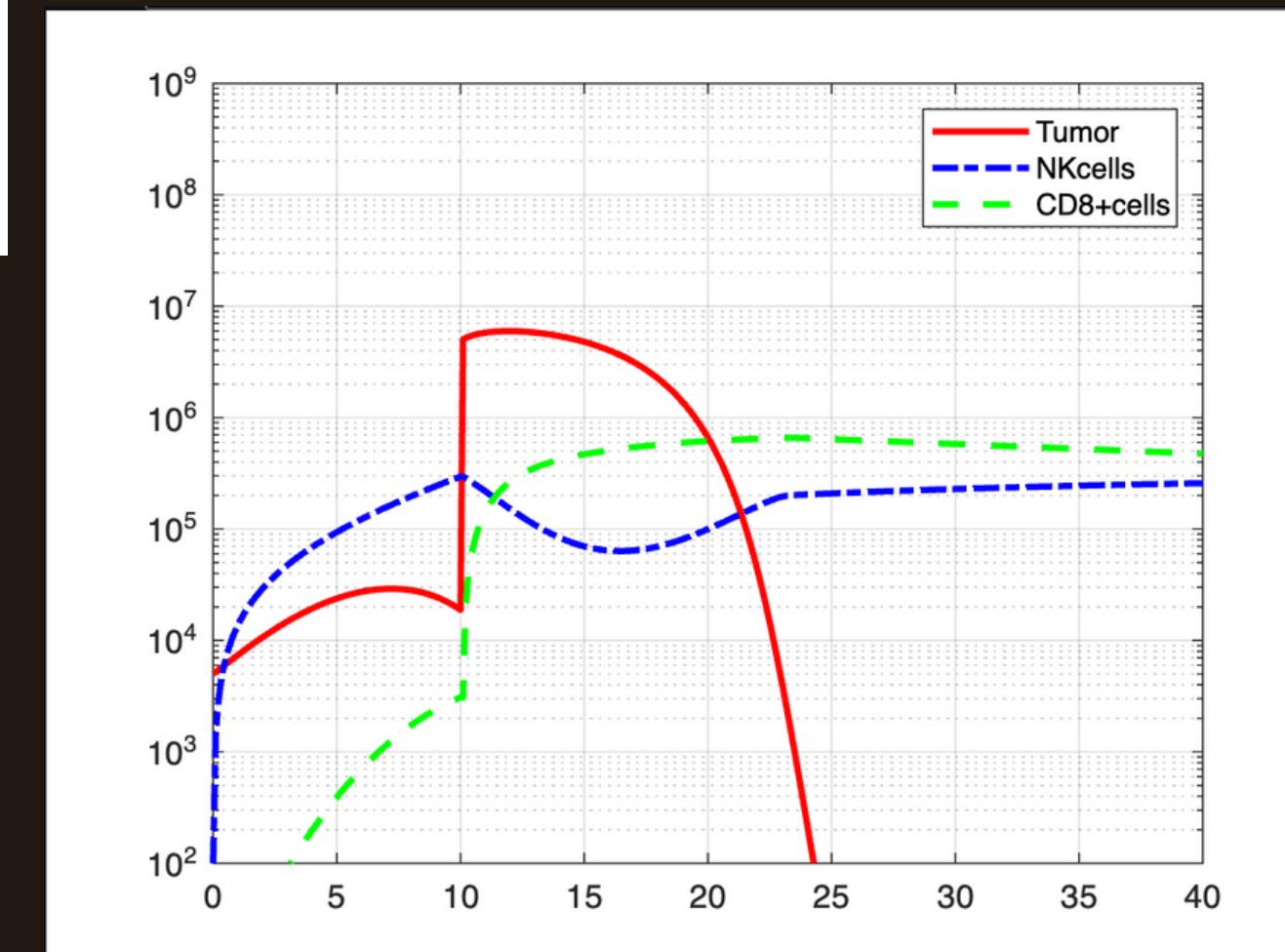
Replicated Graph (Effective Response)



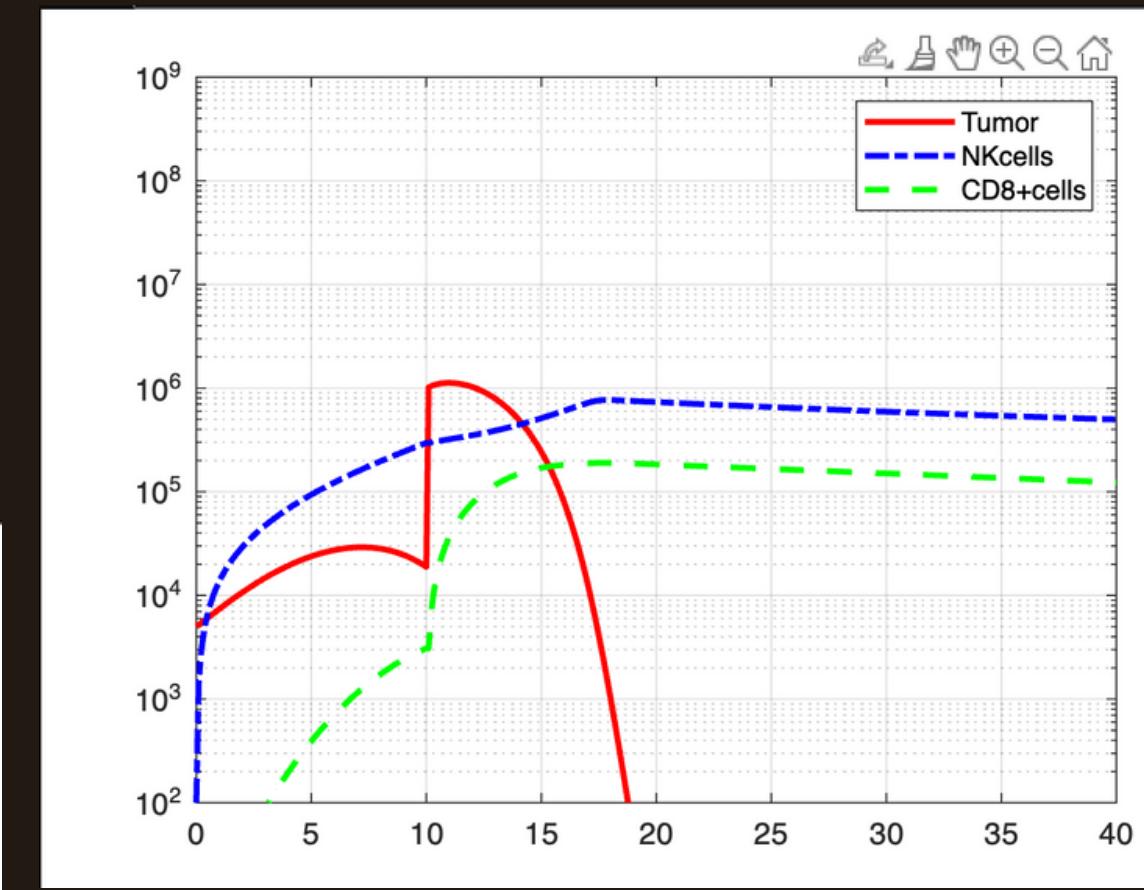
Investigation: Challenge Amounts



20 million

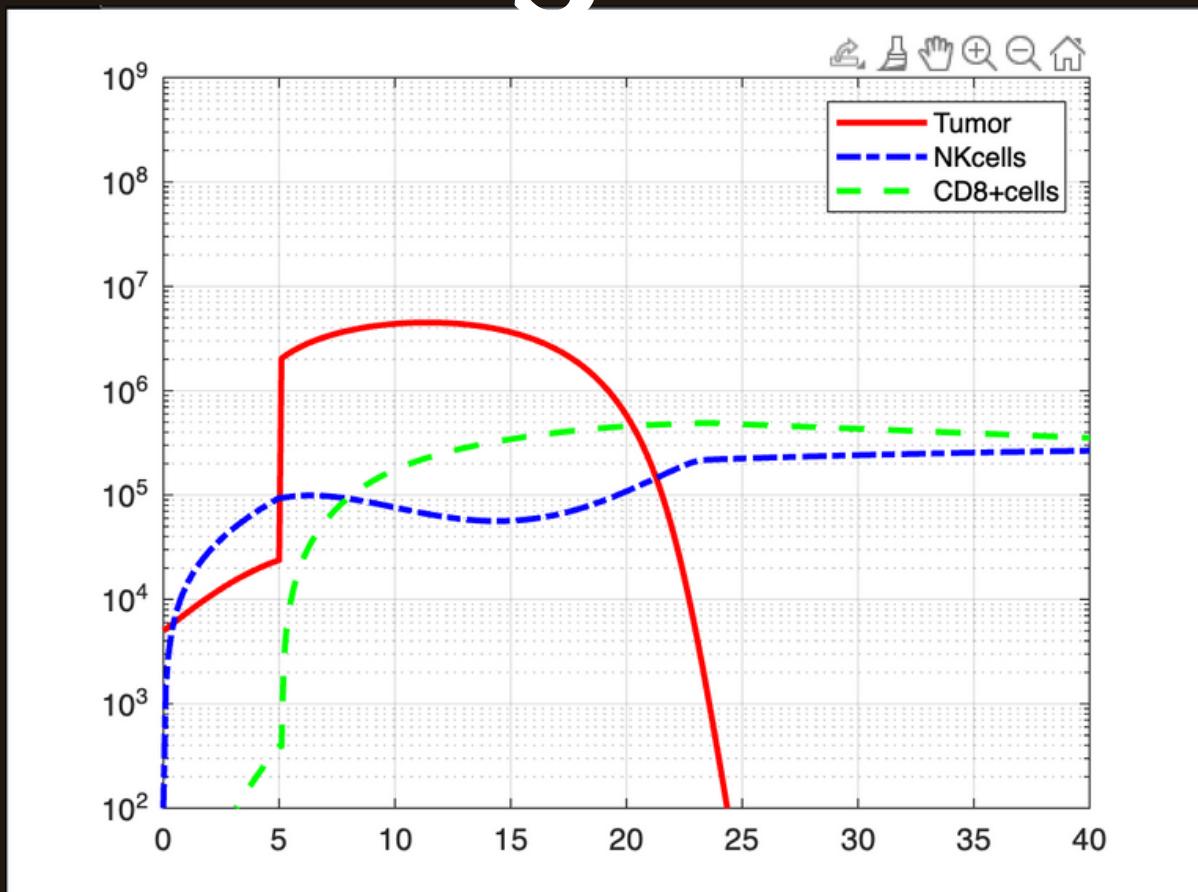


5 million

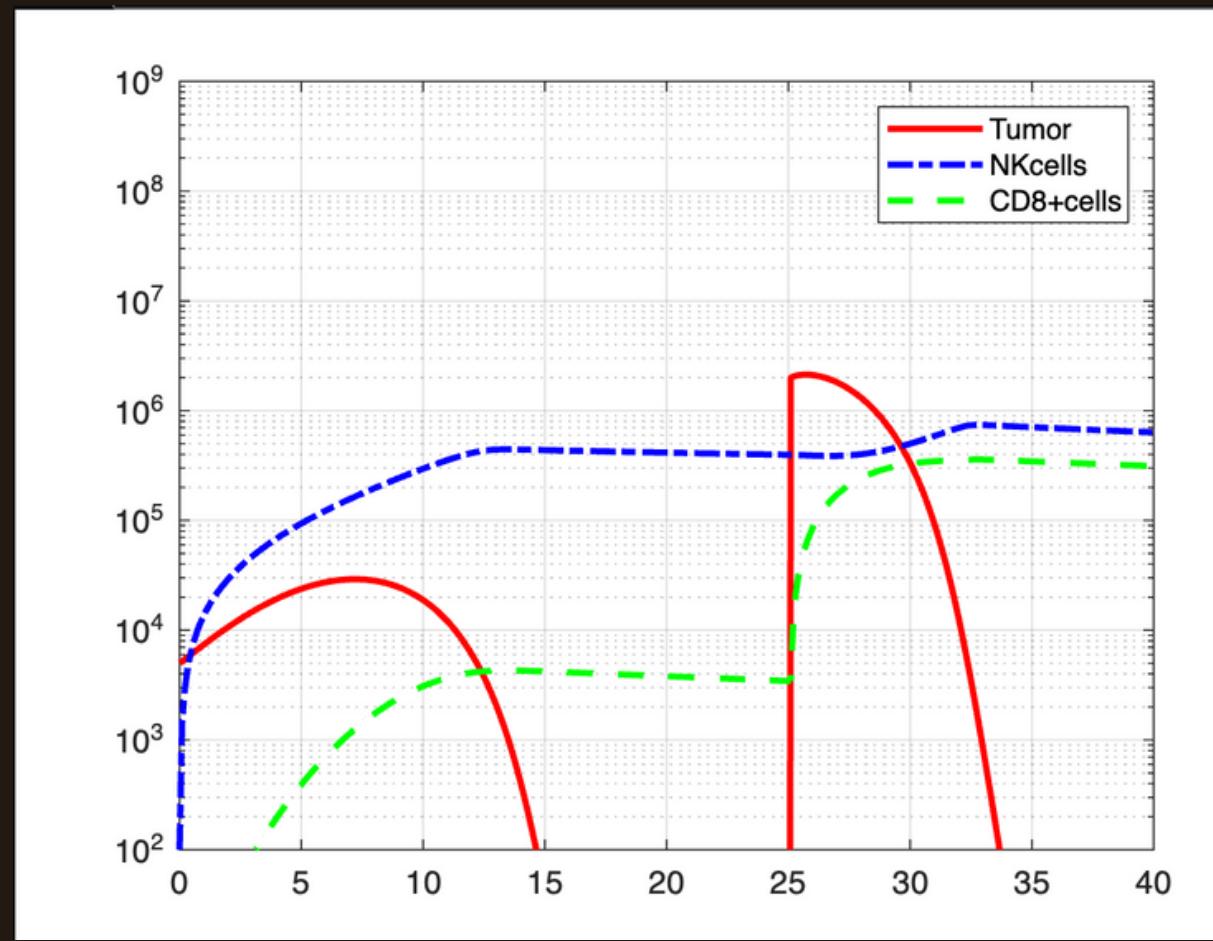


1 million

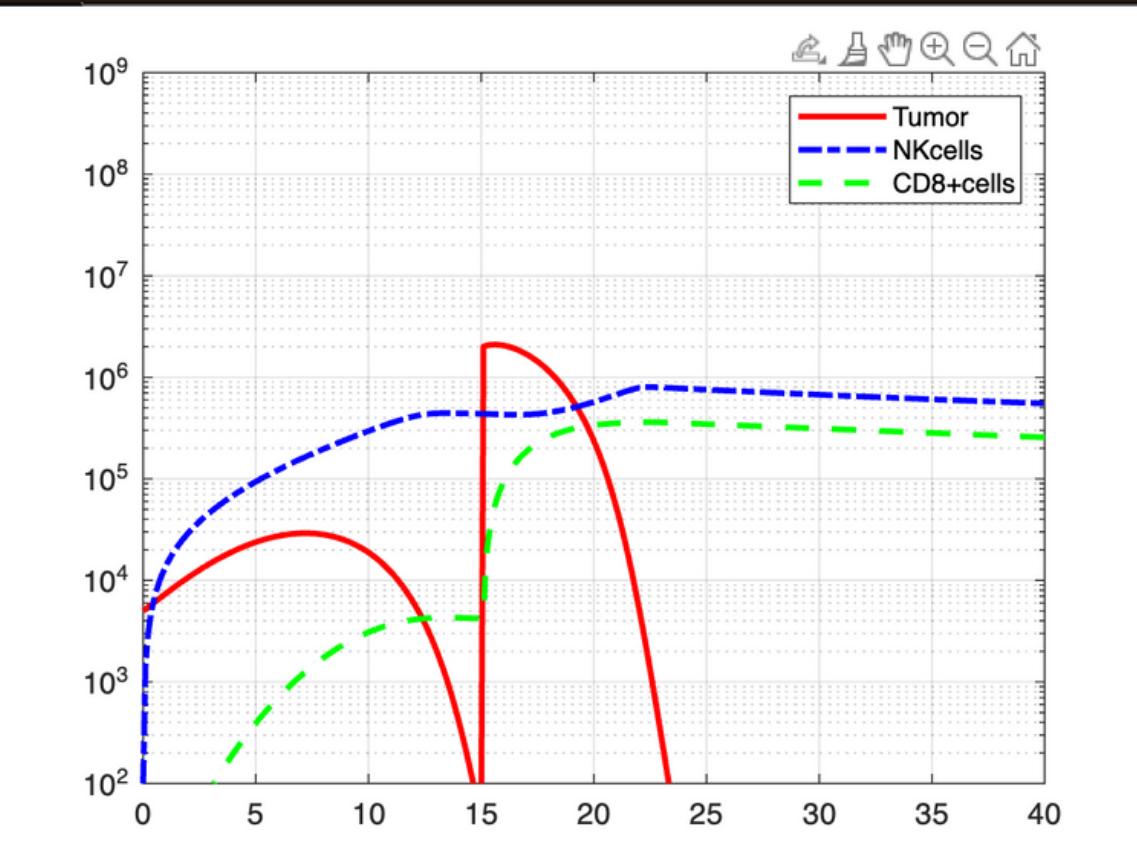
Investigation: Challenge Days



5 days

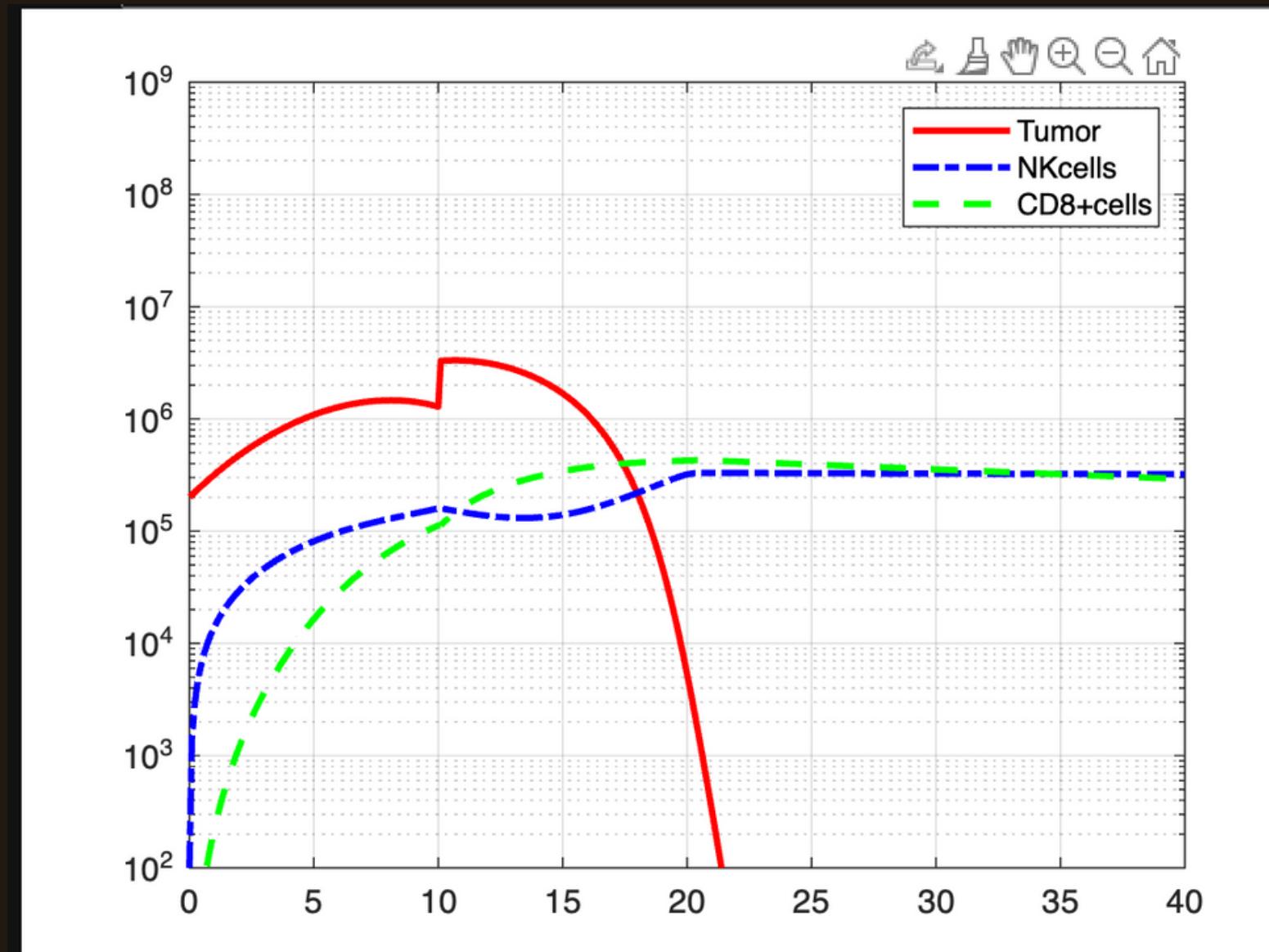


25 days

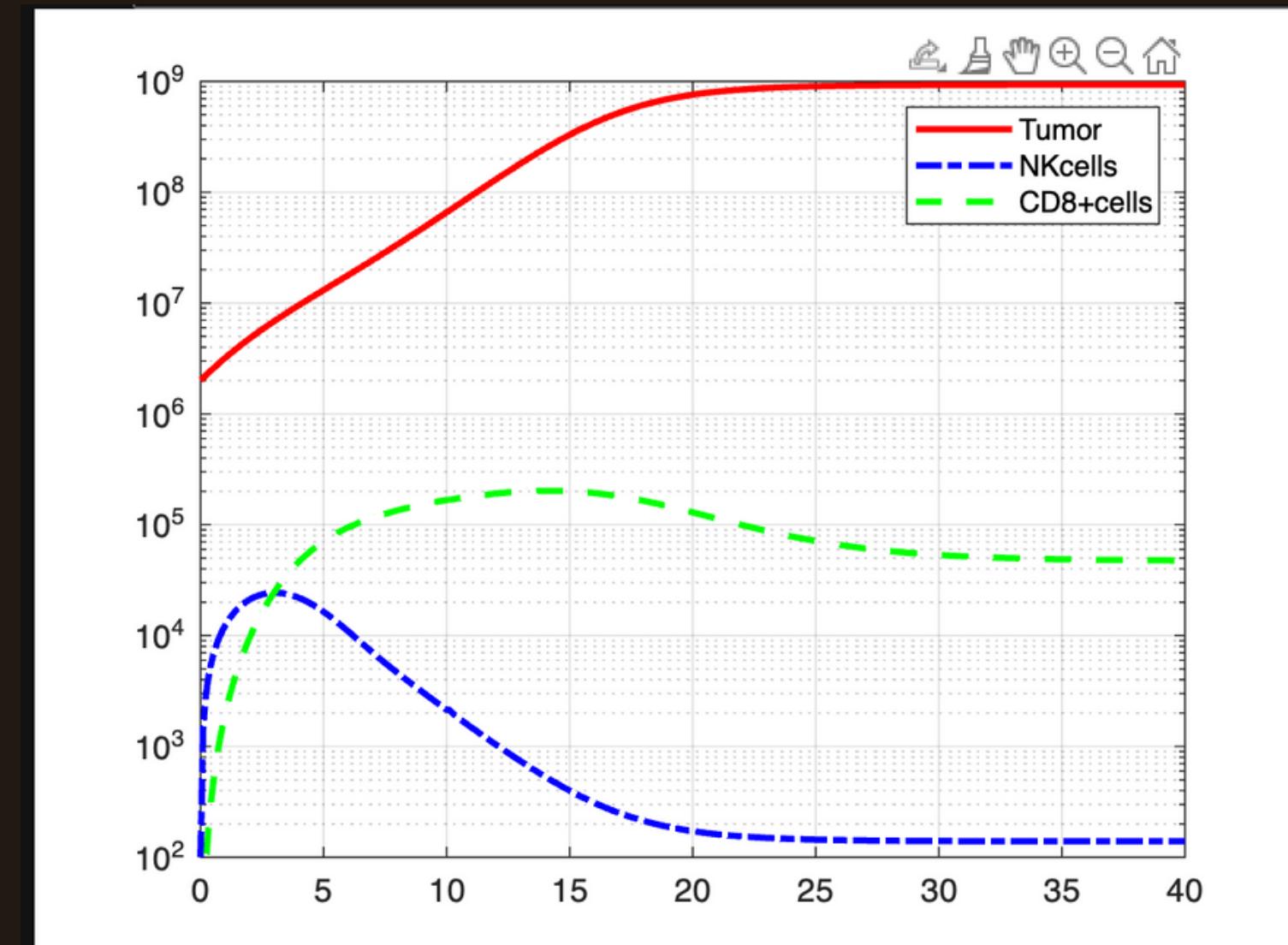


15 days

Initial Tumor Burden T0



200,000



2 million