A Mathematical Model for Immunomodulation of Tumor Growth

Kathleen Wilkie

Workshop on Mathematical Oncology IV:
Integrative Cancer Biology

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Tufts UNIVERSITY | School of Medicine

St. Elizabeth's Medical Center
A STEWARD FAMILY HOSPITAL

Cancer as a **Systemic** Disease

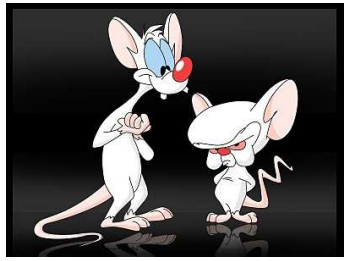
Cancer is not simply a disease of the genome or of the local microenvironment. As evidence, consider the following:

- blood flows through tumors continuously
- recruitment of stem cells to tumor sites
- circulation of cancer cells throughout body - **metastasis**
- creation of metastatic niches
- involvement of cytokines, growth factors, and chemokines
- recruitment of an **immune response**
- development of a **targeted immune response**

The Immune **Systems** Response

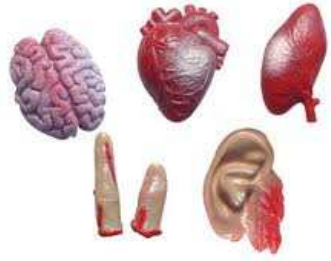
a Host-level Response:

- blood circulation of chemical factors or microvessicles for communication
- immune cell circulation and recruitment
- hematopoietic stem cell recruitment



a Tissue/Organ-Level Response:

- heterogeneous cell–cell interactions
- cell–microenvironment interactions



and a Cellular-Level Response:

- cell phenotype changes
- gene expression changes
- DNA methylation changes
- protein phosphorylation changes

sciencephotogallery.com

An old, but uncommon view:

- Willy Meyer, Ann Surg. 1931, 93(1): 35-39.
  Is Cancer a Systemic Disease?

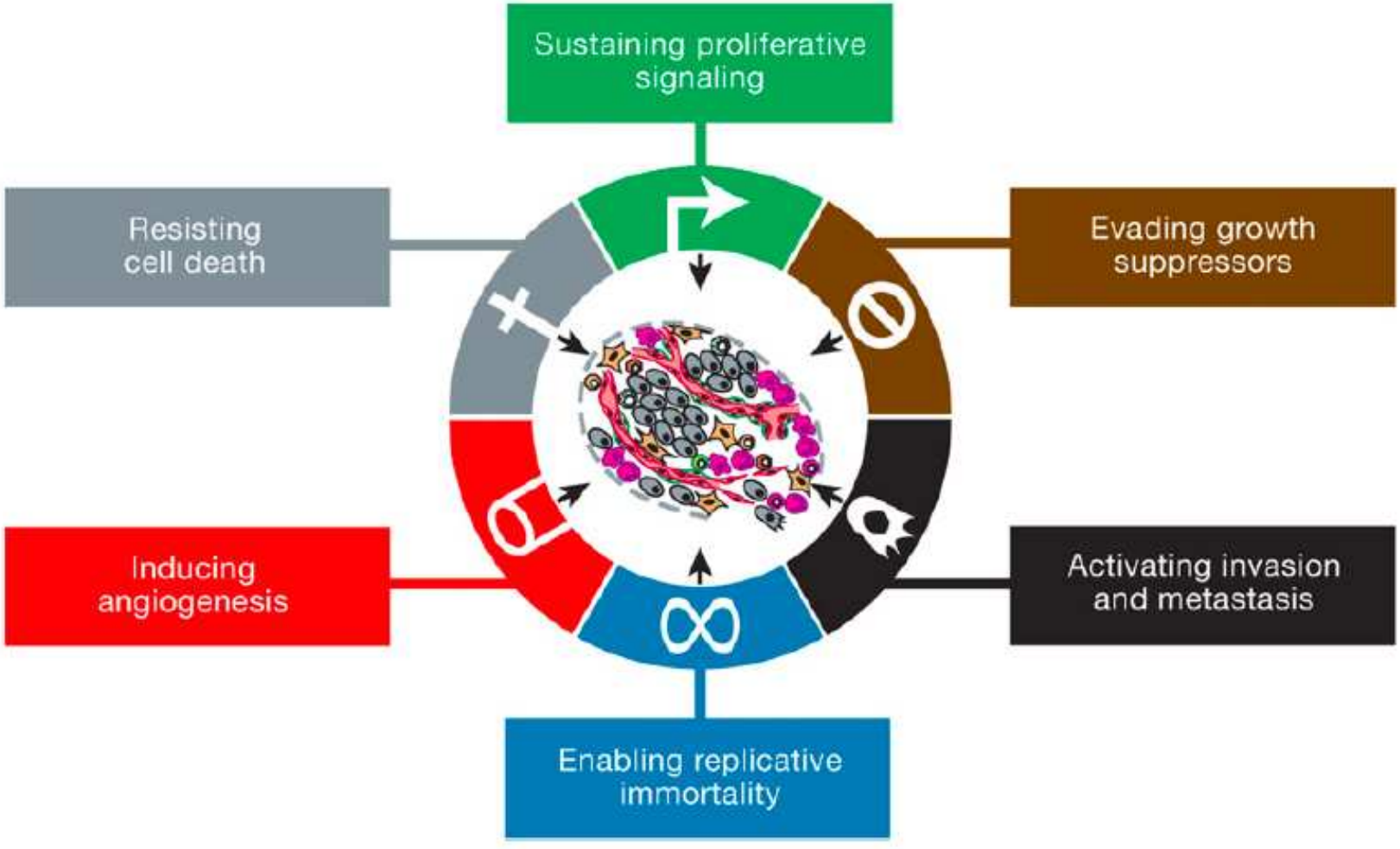
  " The conception of cancer as a systemic disease seemingly reverts to antiquated ideas which have been denouced as heresies by generations of medical men. These students sought in the cell alone the hidden secret of the cancer problem and, more or lesss, disregarded possible influences of the humors."

An old, but uncommon view:

- G Zajicek, Med Hypotheses. 1978, 4(3): 193-207.
  Cancer as a systemic disease

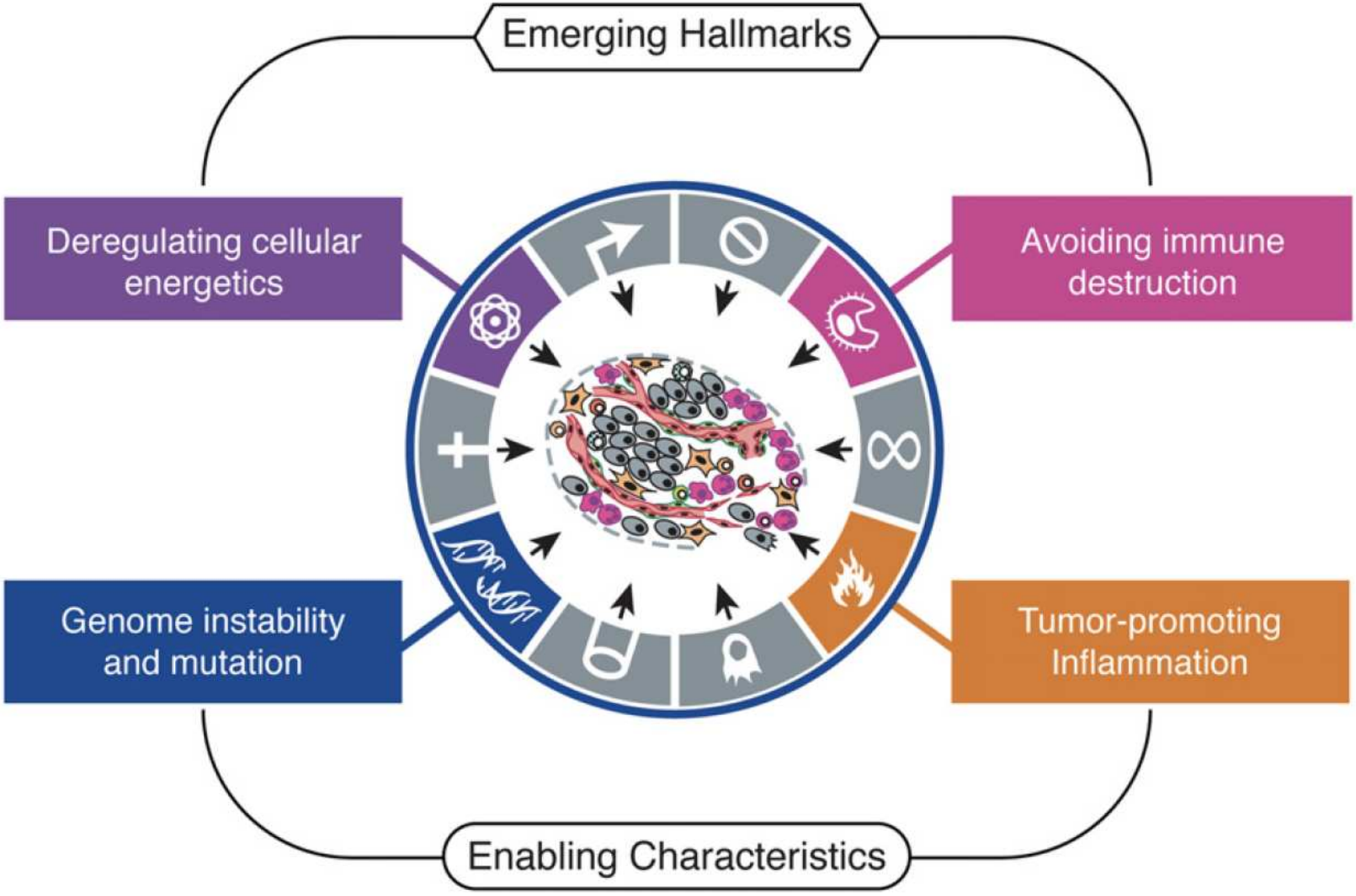
  "Theories on the nature of cancer may be classified into two categories. One regards cancer strictly as a local phenomenon while the second looks at cancer as a local manifestation of a systemic process or disease. Although the first dominates current medical thought, the theories of immunological surveillance and of protovirus-oncogene implicitly assume cancer to represent a local manifestation of a systemic process or disease. ... it is proposed to regard cancer as one systemic disease which presents itself clinically by local phenomena like carcinoma, lymphoma and sarcoma. These local manifestations may lead further to secondary systemic sequelae like metastasis. "

Hallmarks of Cancer circa 2000



[Hanahan and Weinberg, Cell, 144, 2011]

Hallmarks of Cancer circa 2011



[Hanahan and Weinberg, Cell, 144, 2011]

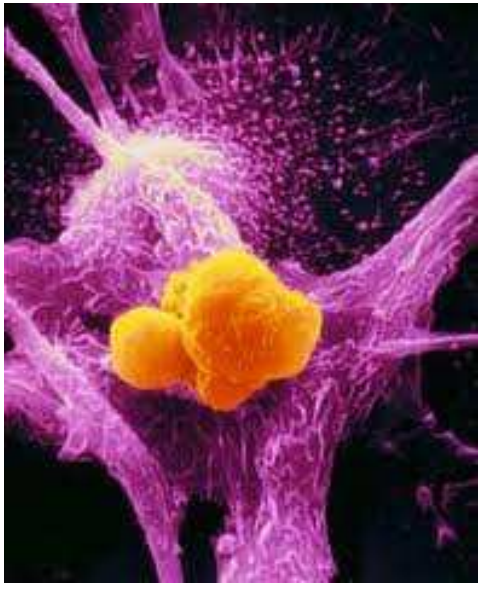
Upon immune detection of cancer . . .

innate immune cells such as:

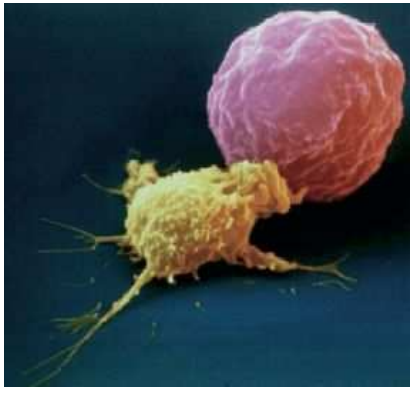
- natural killer cells
- macrophages
- neutrophils
- dendritic cells
- platelets

perform the following actions:

- recognize and respond to pathogens
- initiate inflammation
- recruit immune cells through cytokines
- activate adaptive response
- and more



macrophage (purple) eating a cancer cell (orange) `www.gcmaf.eu/info/`



natural killer cell (yellow) attacking a cancer cell (red) `www.biotechnologie.de`

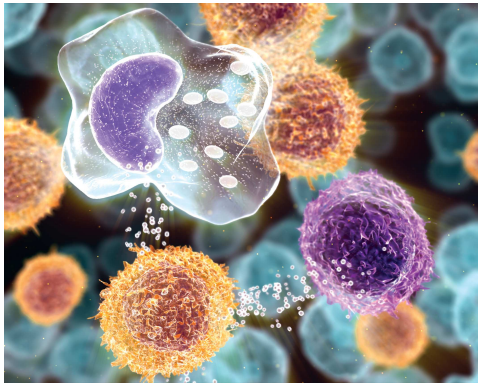
Upon immune detection of cancer . . .

adaptive immune cells such as:

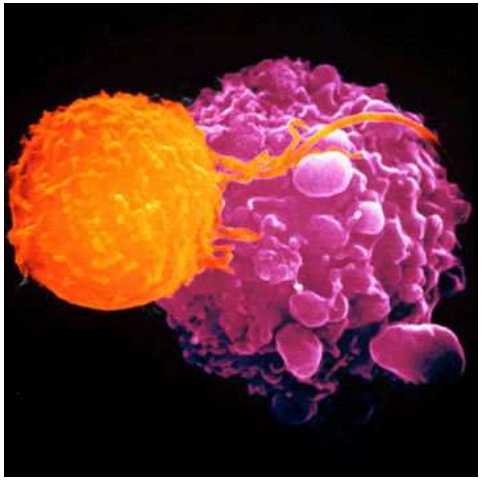
- B cells
- T cells
  - cytotoxic T cells (CD8+)
  - helper T cells (CD4+)

perform the following actions:

- recognize and remember specific pathogens
- repeated pathogen presentation strengthens efficacy
- generate tailored immune response
- develop immunological memory

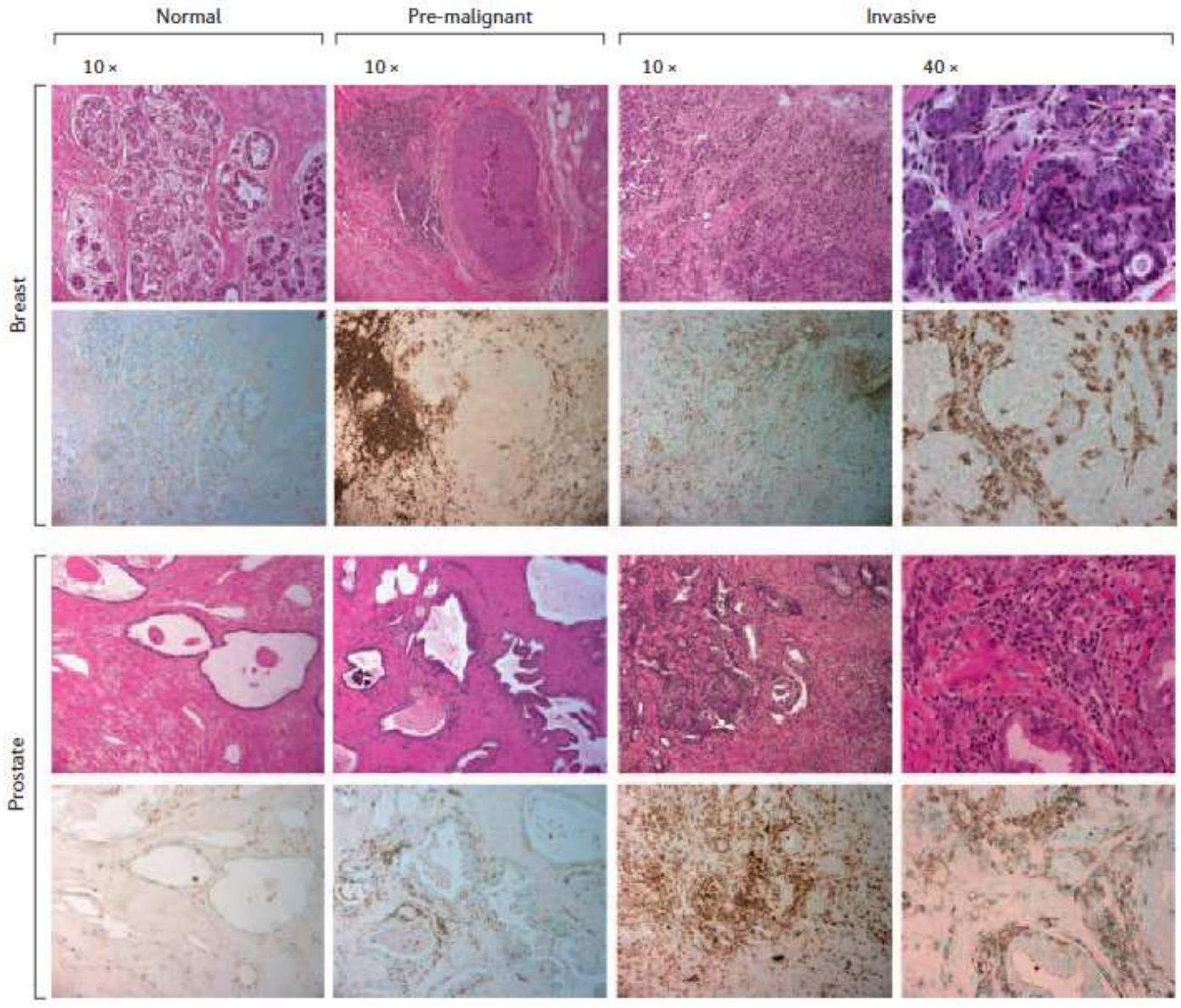


B cell producing cytokines for T cells and macrophages to amplify cycle of inflammation
F. Hoffmann-La Roche Ltd. `www.roche.com`



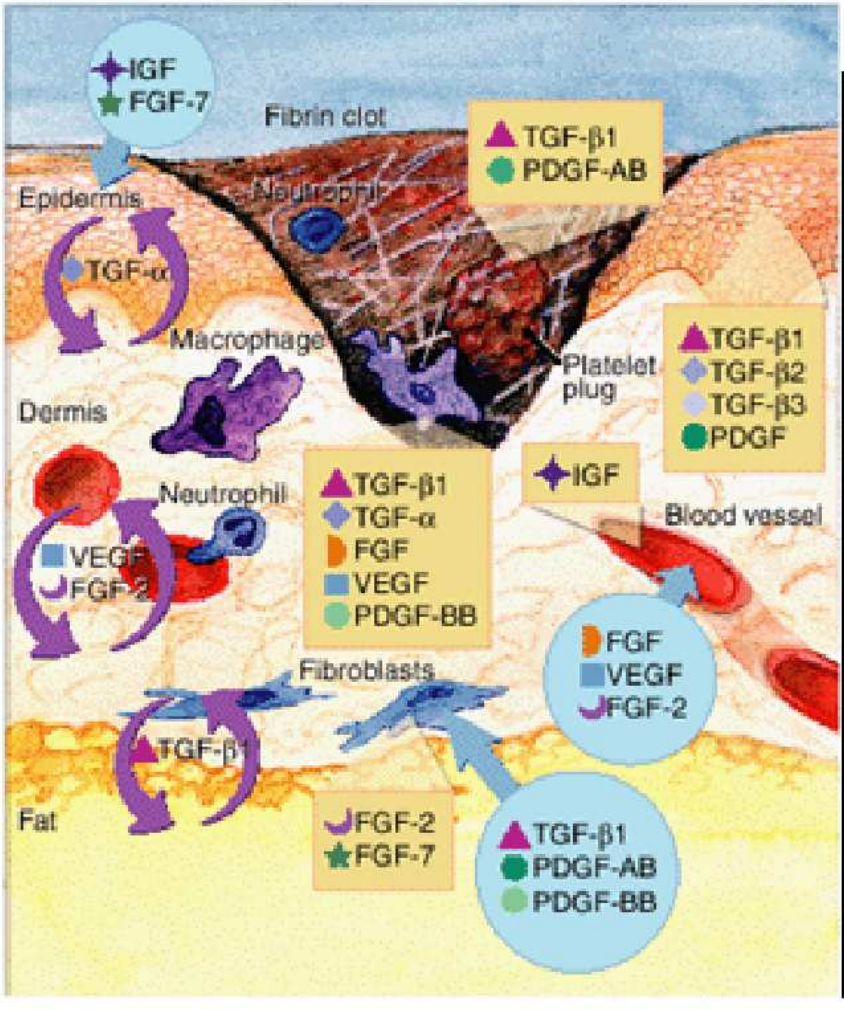
T cell (orange) killing a cancer cell (red)
University of New Mexico
`www.abstractphilly.org`

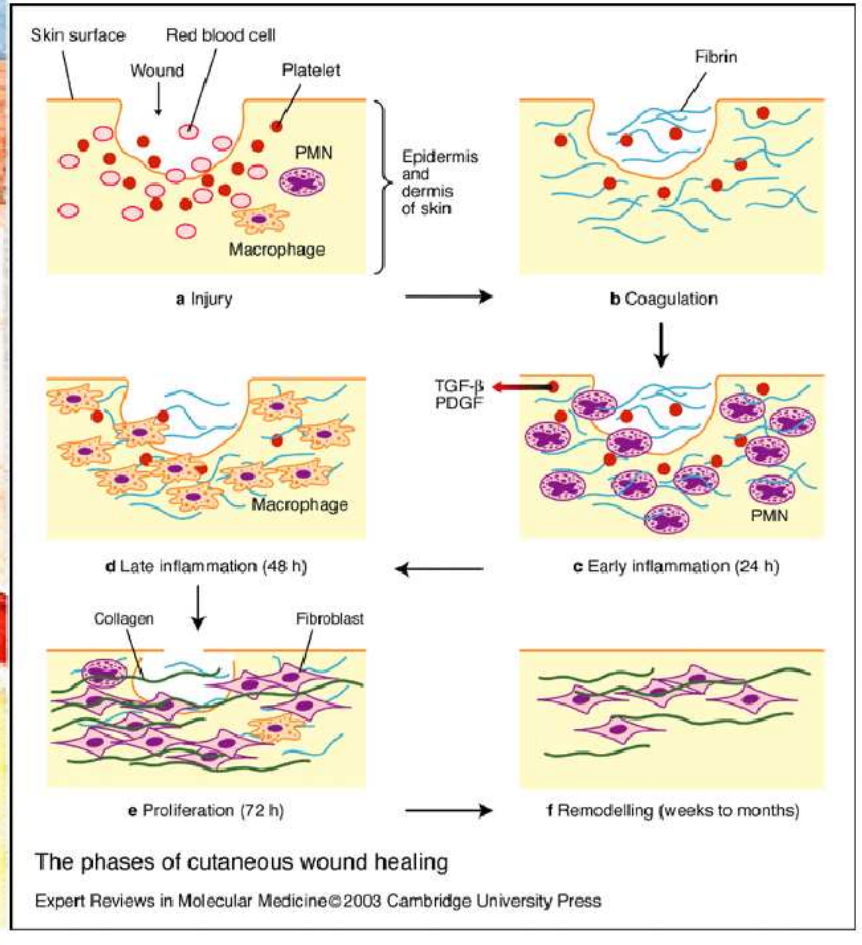
Immune cells are a part of the tumor microenvironment



[de Visser, Eichten, Coussens, Nat Rev Cancer, 2006. 6: 24-37.]

Inflammation is a natural process of Wound Healing



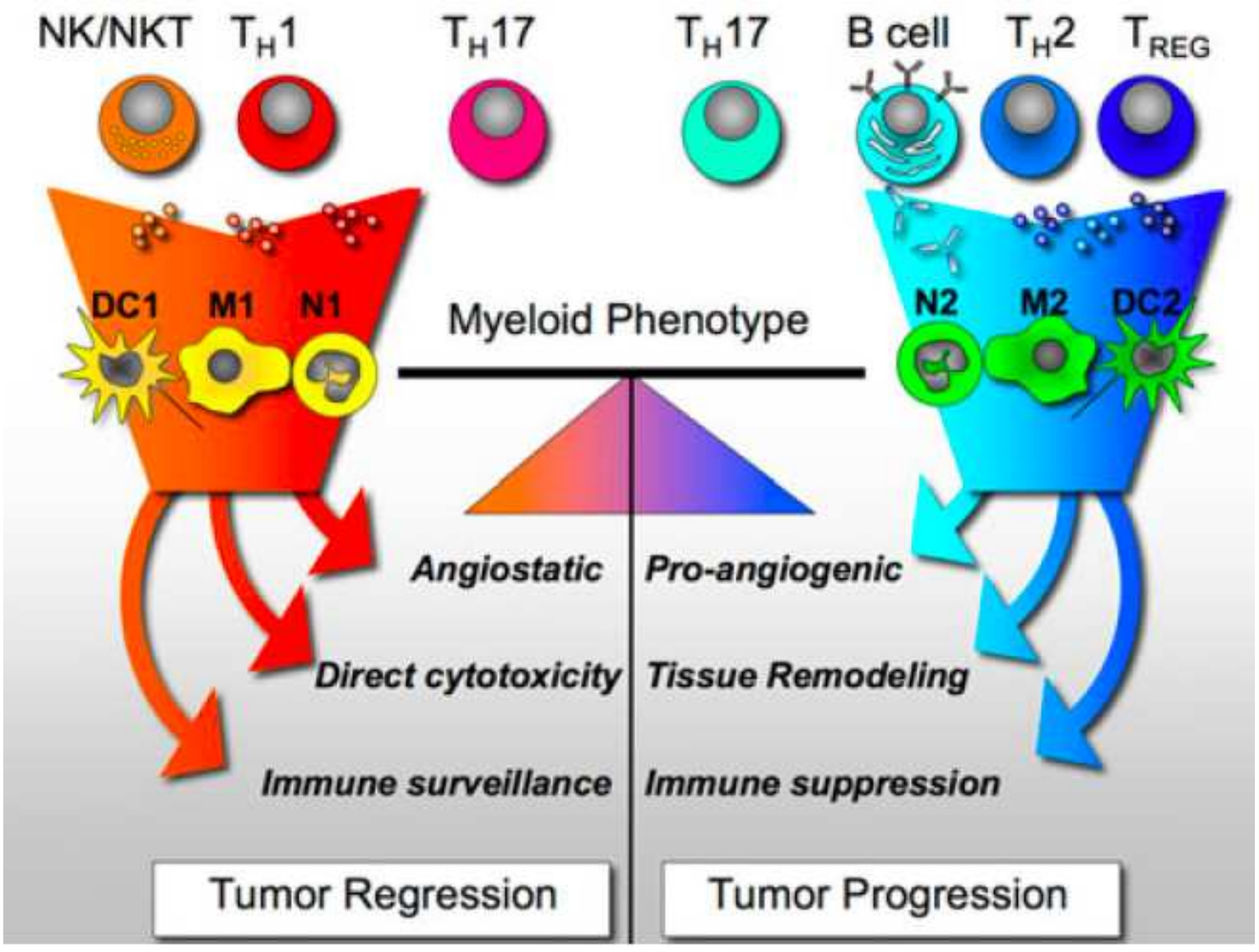


The phases of cutaneous wound healing

Cancer and Inflammation

- Chronic inflammation increases cancer risk
- inflammation impacts every single step of tumorigenesis from initiation to tumor promotion to metastatic progression
- various types of immune / inflammatory cells present within tumors
- immune cells affect cancer cells through production of cytokines, chemokines, growth factors, ROS, NOS
- within a tumor both anti-tumor and pro-tumor immune and inflammatory mechanisms coexist
- signalling pathways that mediate protumorigenic effects are often within positive-feed-forward loops (i.e. NF-κB activation in immune cells induces production of cytokines that activate NF-κB in cancer cells that produce chemokines that attract more inflammatory cells)

Pro-Tumor and Anti-Tumor Inflammation



[DeNardo, Andreu, Coussens, Cancer Metast. Rev, 2010. 29(2): 309-16.]

Pro-Tumor and Anti-Tumor Immune Cell Activities

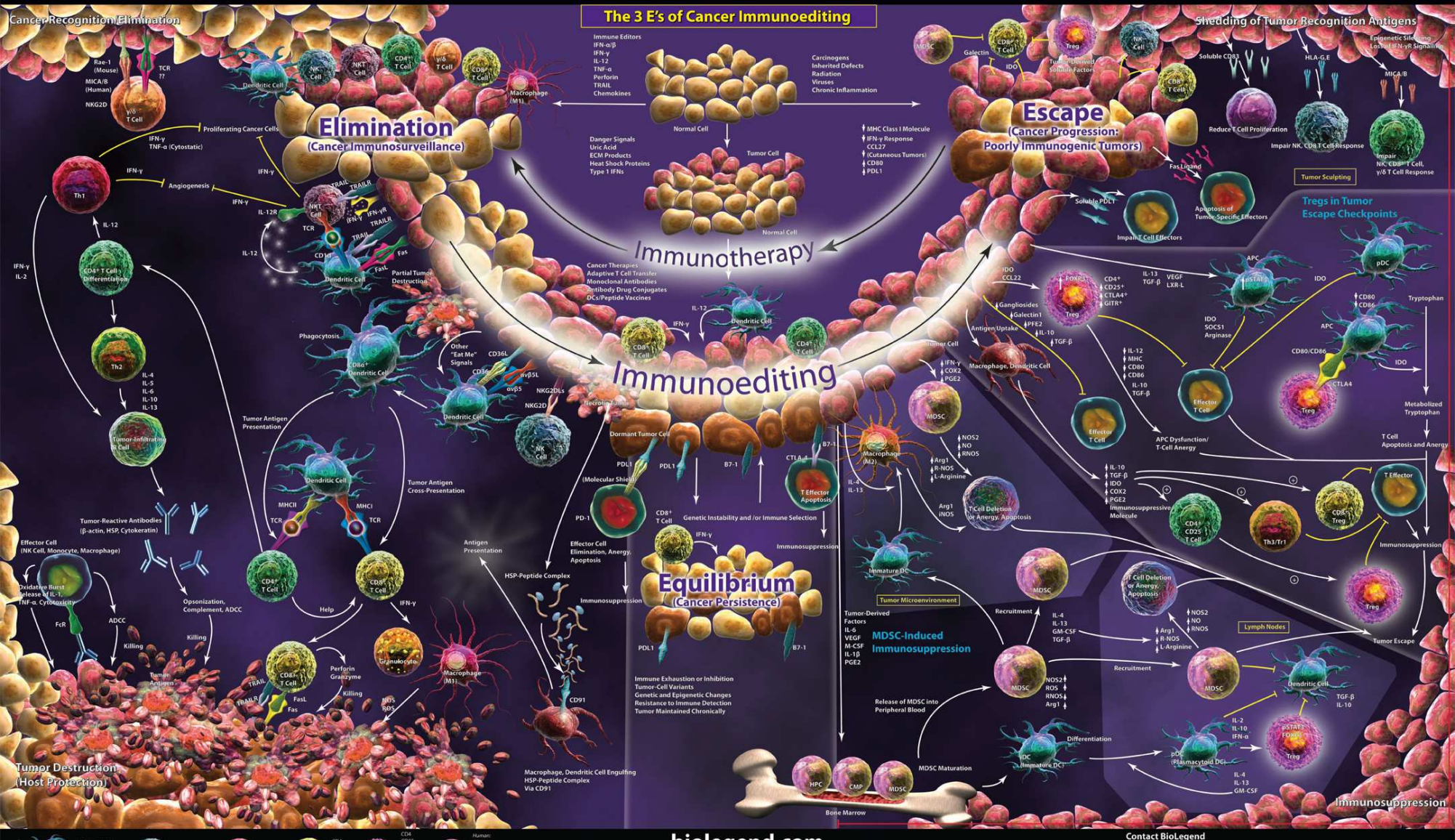
Table 1. Roles of Different Subtypes of Immune and Inflammatory Cells in Antitumor Immunity and Tumor-Promoting Inflammation

Cell Types	Antitumor	Tumor-Promoting
Macrophages, dendritic cells, myeloid-derived suppressor cells	Antigen presentation; production of cytokines (IL-12 and type I IFN)	Immunosuppression; production of cytokines, chemokines, proteases, growth factors, and angiogenic factors
Mast cells		Production of cytokines
B cells	Production of tumor-specific antibodies?	Production of cytokines and antibodies; activation of mast cells; immunosuppression
$CD8^+$ T cells	Direct lysis of cancer cells; production of cytotoxic cytokines	Production of cytokines?
$CD4^+$ Th2 cells		Education of macrophages; production of cytokines; B cell activation
$CD4^+$ Th1 cells	Help to cytotoxic T lymphocytes (CTLs) in tumor rejection; production of cytokines ($IFN\gamma$)	Production of cytokines
$CD4^+$ Th17 cells	Activation of CTLs	Production of cytokines
$CD4^+$ Treg cells	Suppression of inflammation (cytokines and other suppressive mechanisms)	Immunosuppression; production of cytokines
Natural killer cells	Direct cytotoxicity toward cancer cells; production of cytotoxic cytokines	
Natural killer T cells	Direct cytotoxicity toward cancer cells; production of cytotoxic cytokines	
Neutrophils	Direct cytotoxicity; regulation of CTL responses	Production of cytokines, proteases, and ROS

[Grivennikov, Greten, Karin, Cell. 2010. 140:883-899.]

Cancer Immunoediting

BioLegend®



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Interactive Poster: biolegend.com/cancerimmunoediting

We would like to thank Dr. Robert Schreiber of Washington University - School of Medicine for his contributions to this poster.

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04-0017-00

very complicated so must SIMPLIFY

Typical mathematical approach to immune-cancer modelling:

Predators:

Immune Cells

Prey:

Cancer Cells

The Einstein Principle

states that ...

A Scientific theory should be as simple as possible, but no simpler.

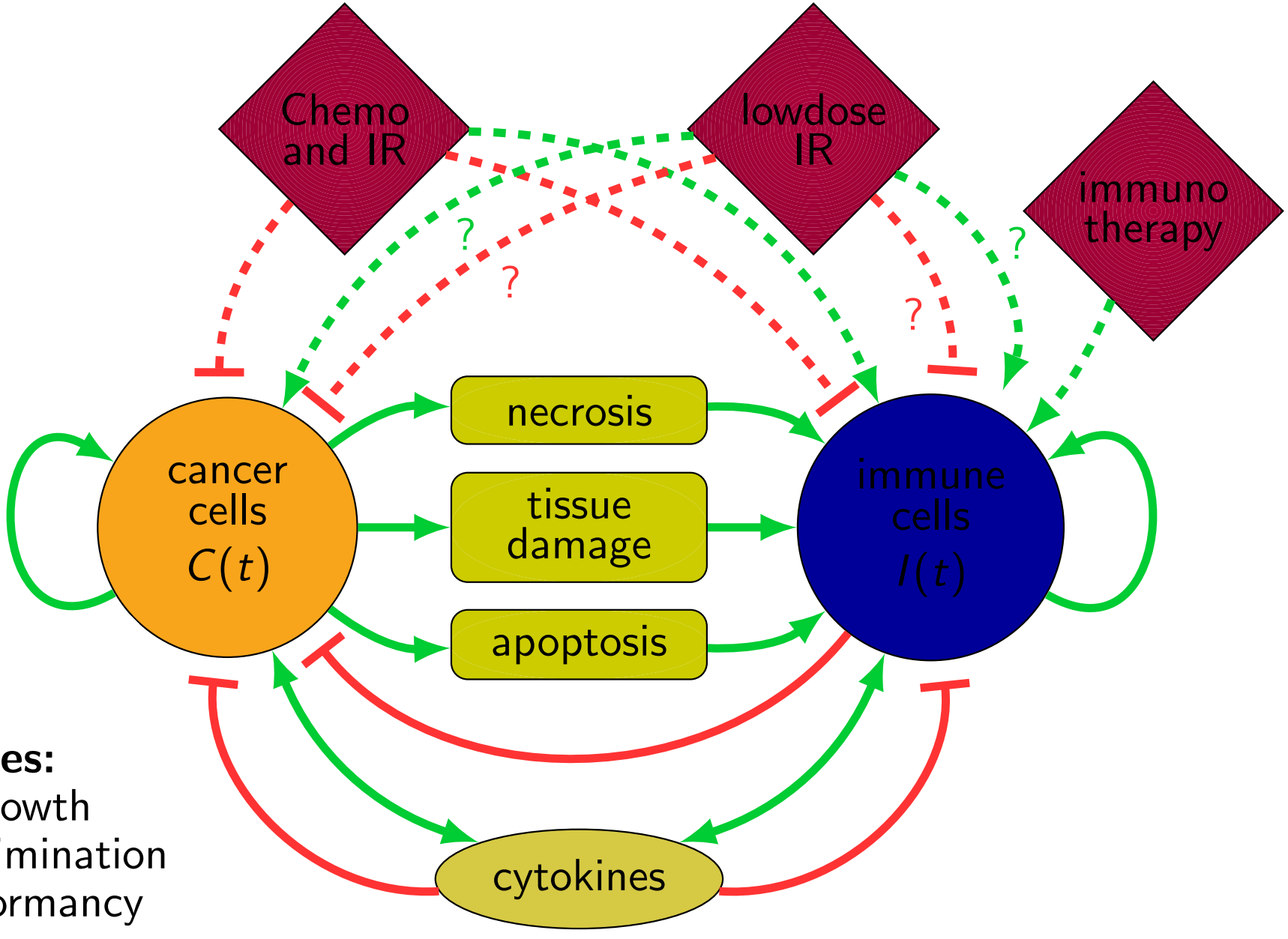
Predator-Prey models provide a simple view of tumor-immune interactions that neglect one of the emerging hallmarks of cancer - Tumor-promoting Inflammation!

A slightly less simple model

Cancer and Immune interactions are more like:

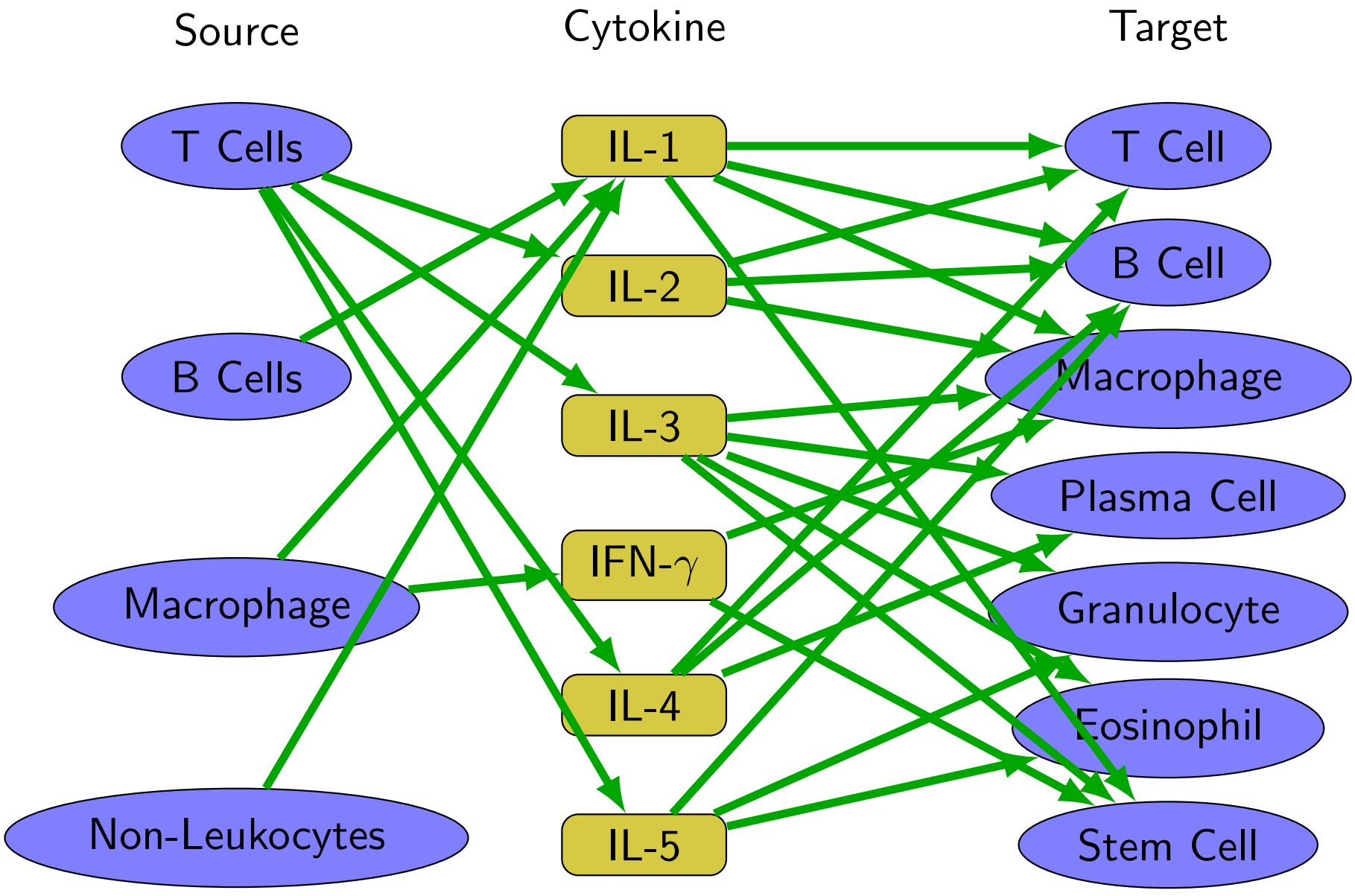
Tumor Inhibition

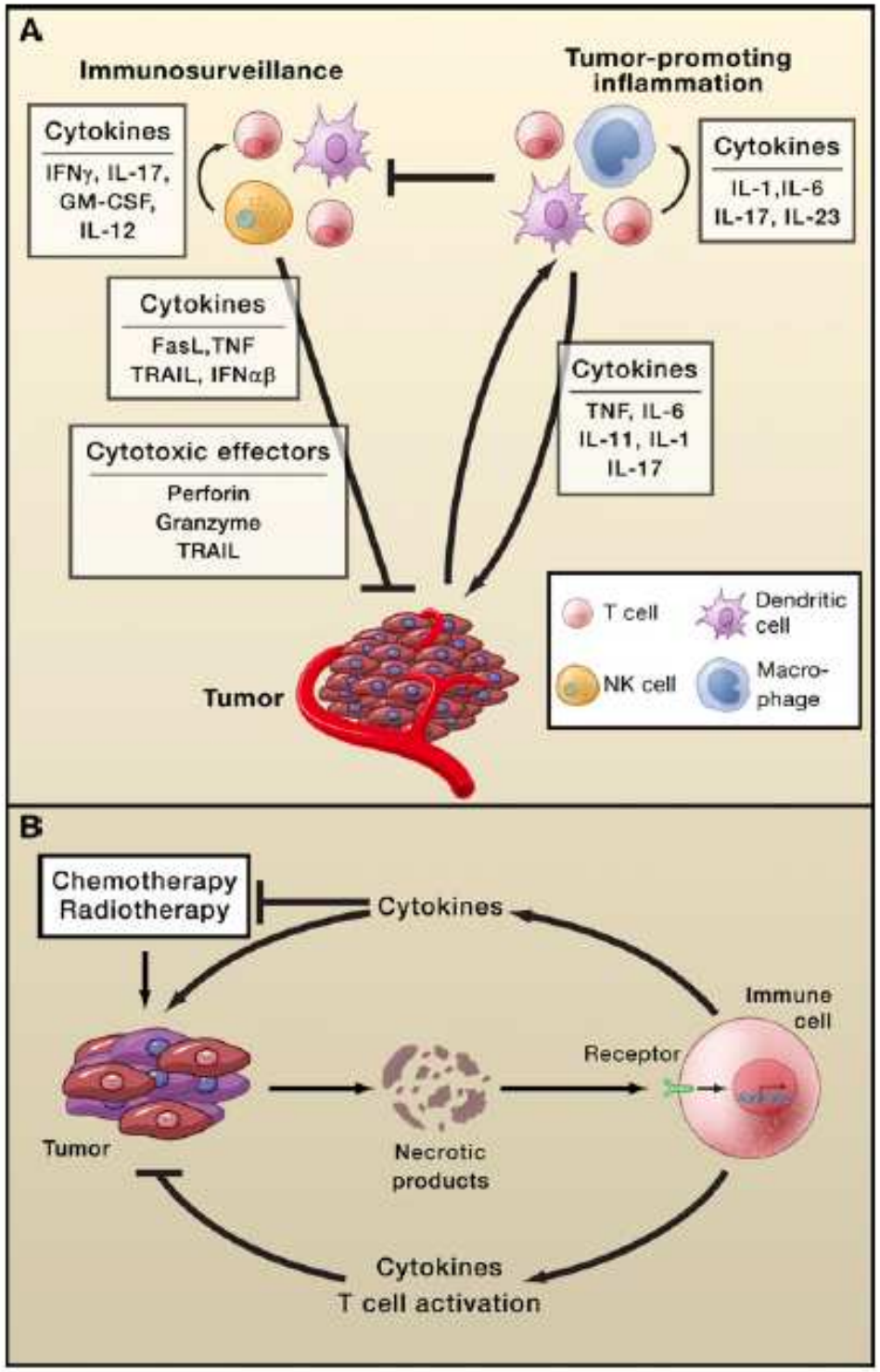
Tumor Stimulation



Outcomes:
tumor growth
tumor elimination
tumor dormancy

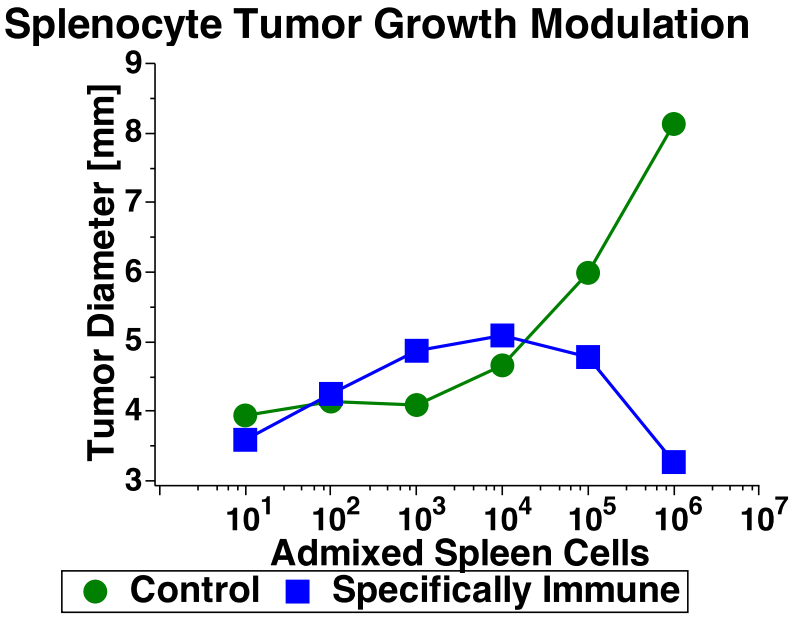
BUT this is all very complicated . . .





[Grivennikov, Greten, Karin, Cell, 2010. 140: 883-899.]

The Idea of Ratio-Dependence

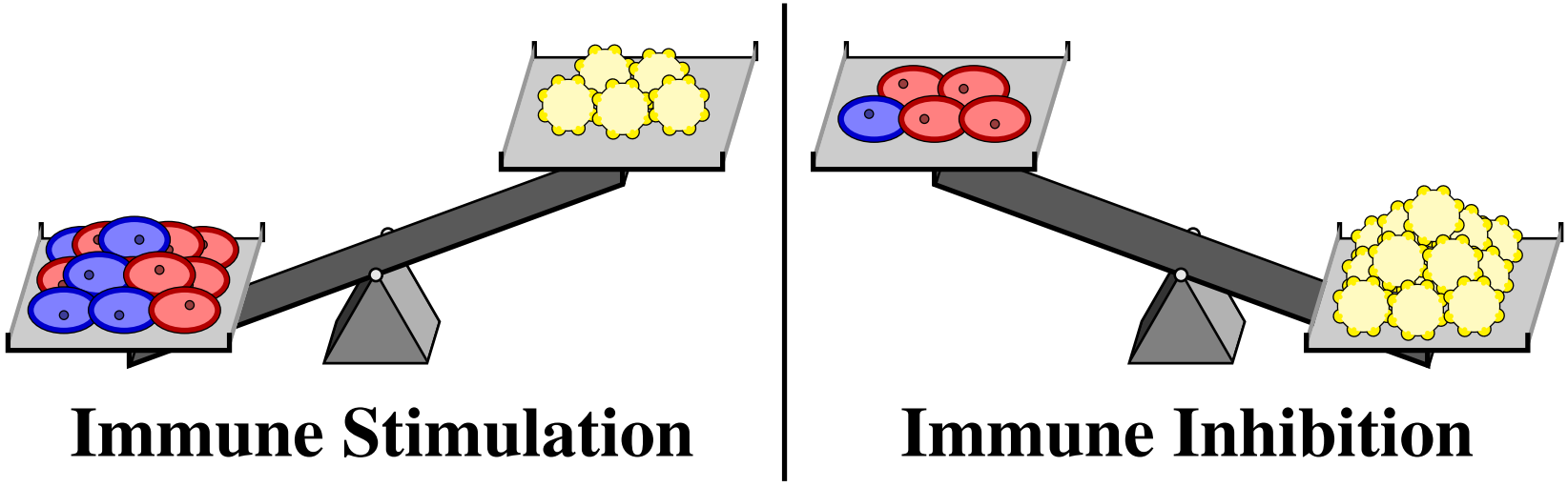


[Adapted from Prehn, 1972, Science]

Tumor Modulation

- Mix varying numbers of splenocytes with 10^4 cancer cells subcu. injected in mice
- specifically immune: tumor stimulation when cancer cells outnumber splenocytes and tumor inhibition when splenocytes outnumber cancer cells
- control: more stimulation less effective inhibition

Generalization of this Experiment

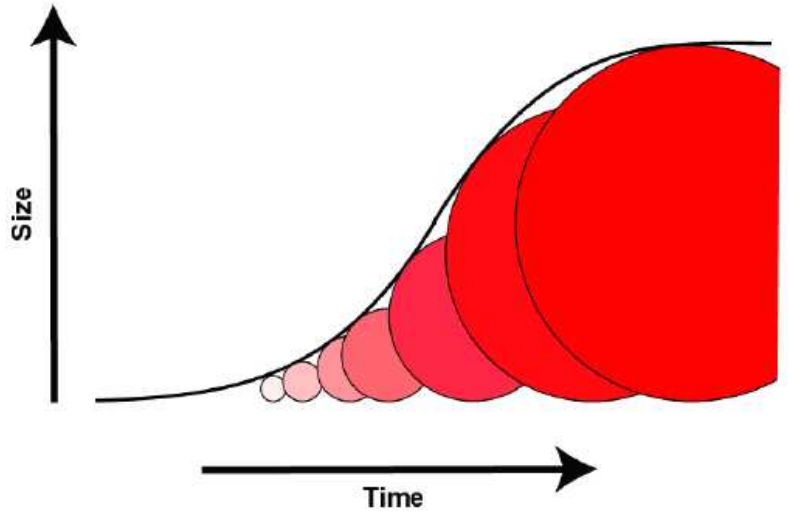


Mathematical Model

- Utilize Generalized logistic growth

Gompertz in the Limit

$$\lim_{\alpha \to 0} \frac{\mu}{\alpha} C \left(1 - \left(\frac{C}{K}\right)^{\alpha}\right) = -\mu C \log\left(\frac{C}{K}\right)$$



Mathematical Model

- Utilize Generalized logistic growth
- Cancer-Immune interactions modulate growth

Coupled System of ODEs:

Cancer $C = C(t)$ and Immune $I = I(t)$ cell populations:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{\mu}{\alpha}\left(1 + \Psi(I, C)\right) C(t) \left(1 - \left(\frac{C(t)}{K_C(t)}\right)^{\alpha}\right)$$

Predation dynamic carrying capacity

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \lambda\left(I(t) + rC(t)\right) \left(1 - \frac{I(t)}{K_I(t)}\right)$$

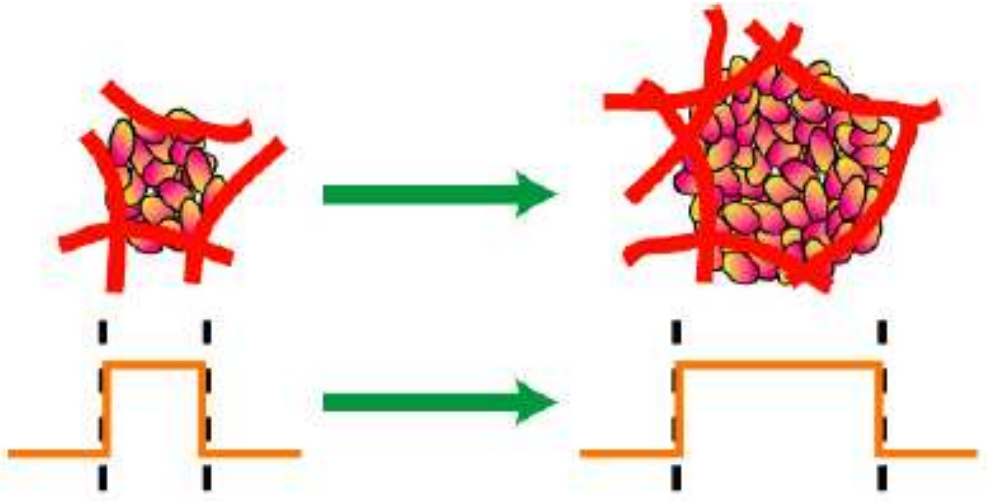
Recruitment dynamic carrying capacity

Diffusion - Consumption DE for growth factor concentration:

$$0 = D\nabla^2 n - cn + s$$

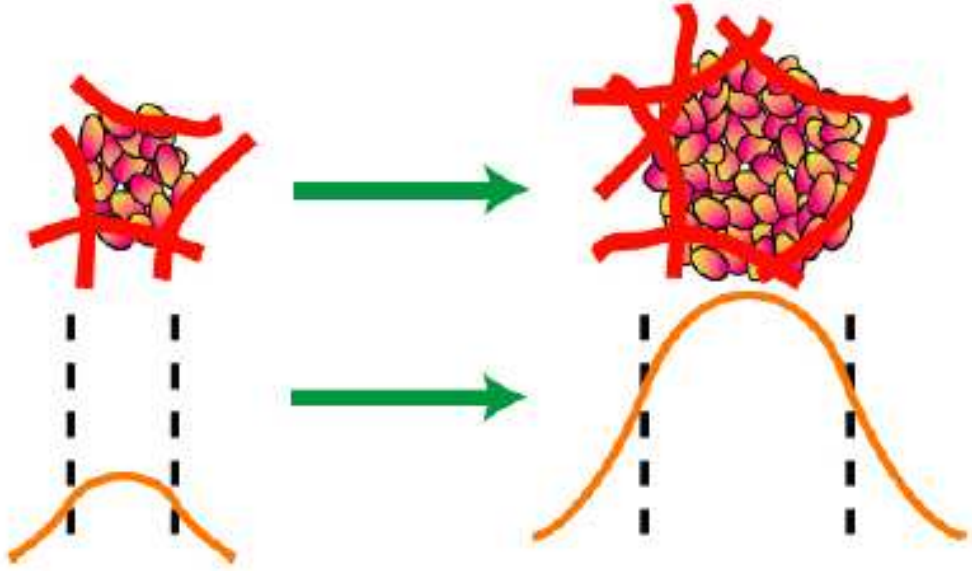
STIMULATORS

Fast Clearance
constant concentration
within tumor



INHIBITORS

Slow Clearance
r_0^2-dependent
concentration



Mathematical Model

Dynamic carrying capacities:

$$\frac{\mathrm{d}K_C}{\mathrm{d}t} = p\big(1+I(t)\big)^{a} C(t)^{1-a} - qK_C(t)\big(1+I(t)\big)^{b} C(t)^{\frac{2}{3}-b}$$

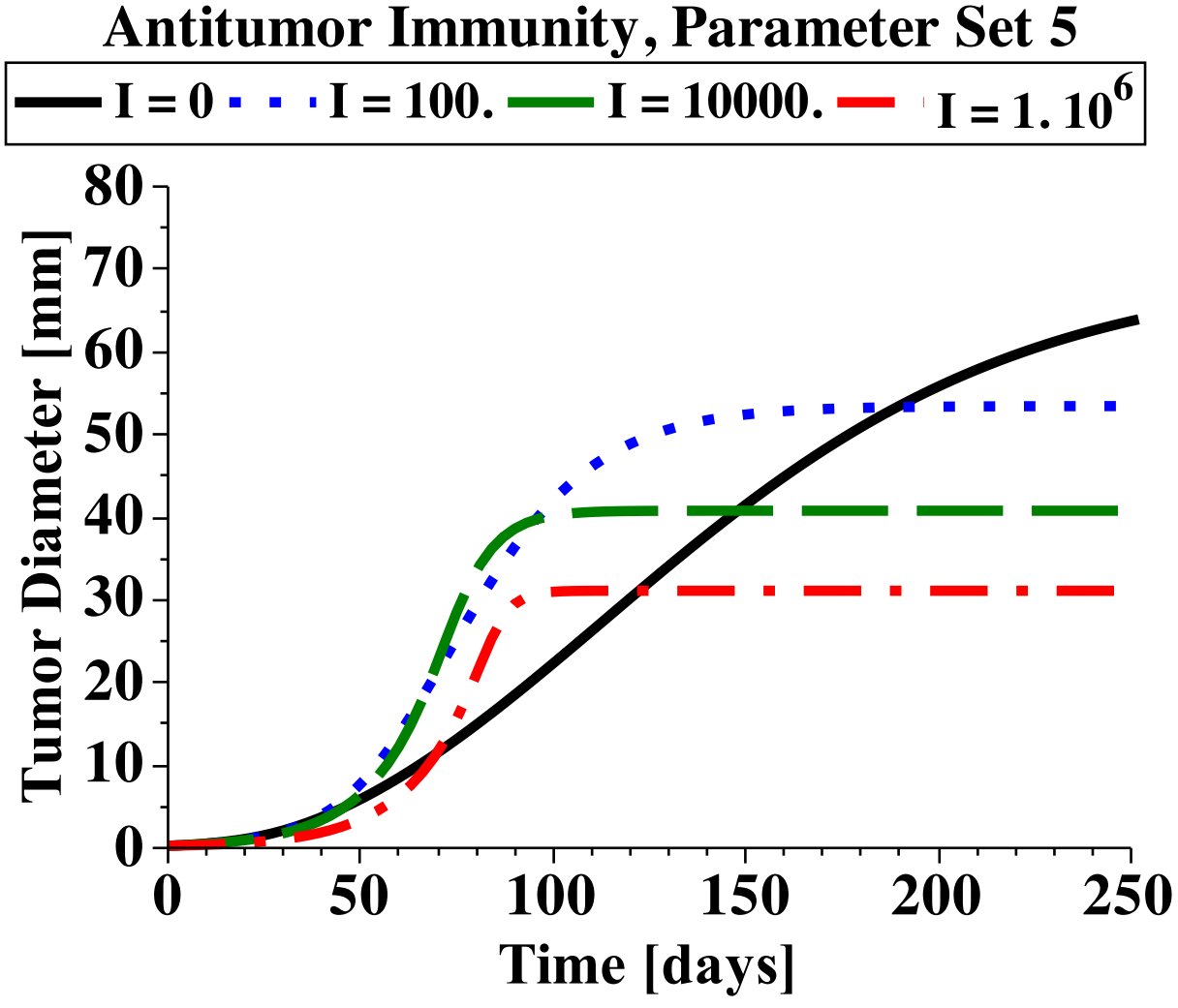
stimulation inhibition

$$\frac{\mathrm{d}K_I}{\mathrm{d}t} = xI(t)^{\frac{1}{2}} C(t)^{\frac{1}{2}} - yK_I(t)I(t)^{\frac{1}{3}} C(t)^{\frac{1}{3}} - z\big(K_I(t) - I_e\big)$$

stimulation inhibition homeostasis

Inflammation Type - Antitumor Immunity

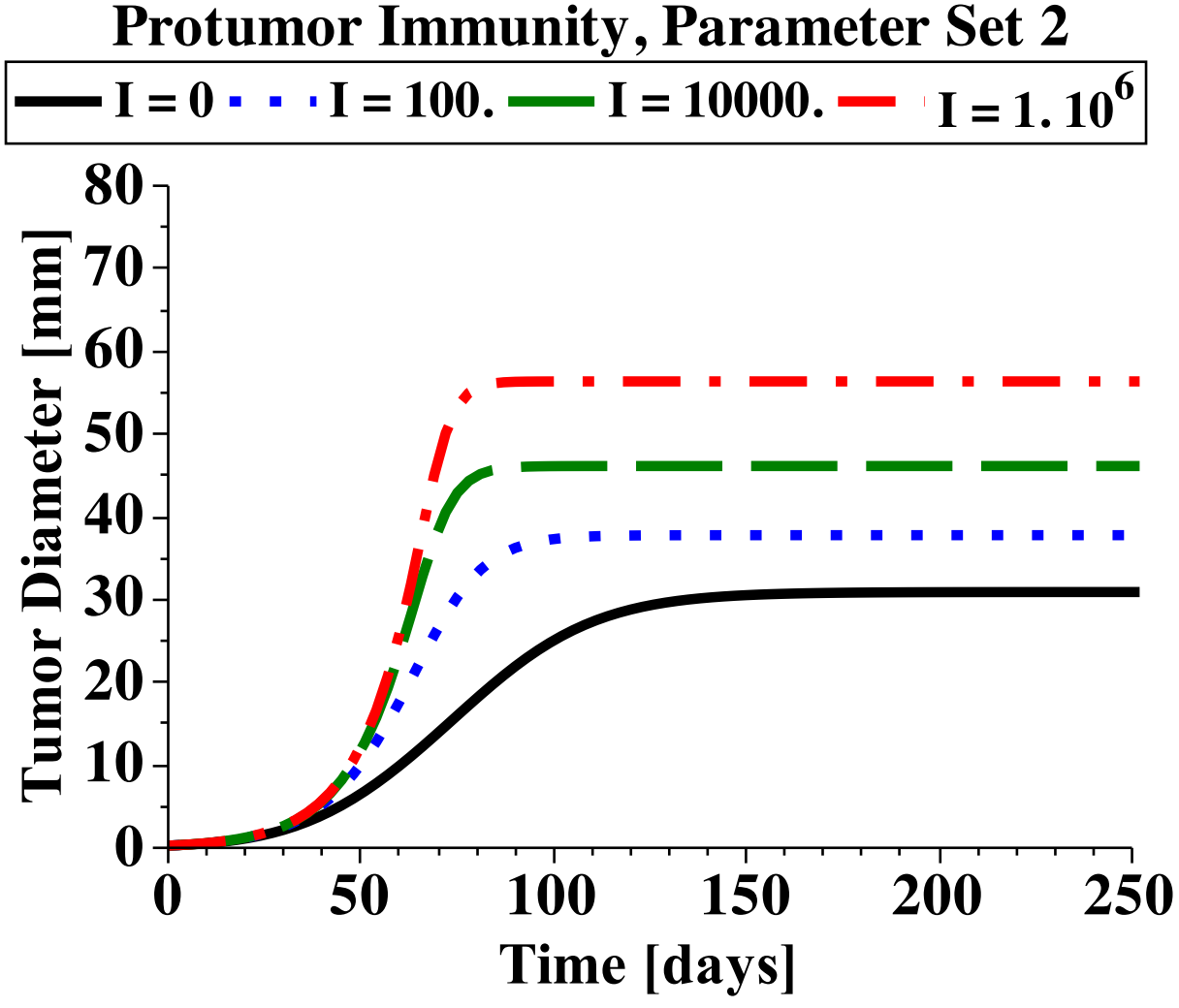
If $a < b$ then more weight is placed on the inhibiting actions of inflammation:



Here $\Psi = 0$ and $I(t) = K(t) =$ Constant.

Inflammation Type - Antitumor Immunity

If $a > b$ then more weight is placed on the stimulating actions of inflammation:



Here $\Psi = 0$ and $I(t) = K(t) =$ Constant.

Immune Predation

Immunomodulatory effects are incorporated into the model via:

1. inflammatory actions that alter the tumor microenvironment
2. immune cytotoxic actions that reduce the number of proliferating cancer cells (or the growth rate of the tumor)

Direct Cell Lysis

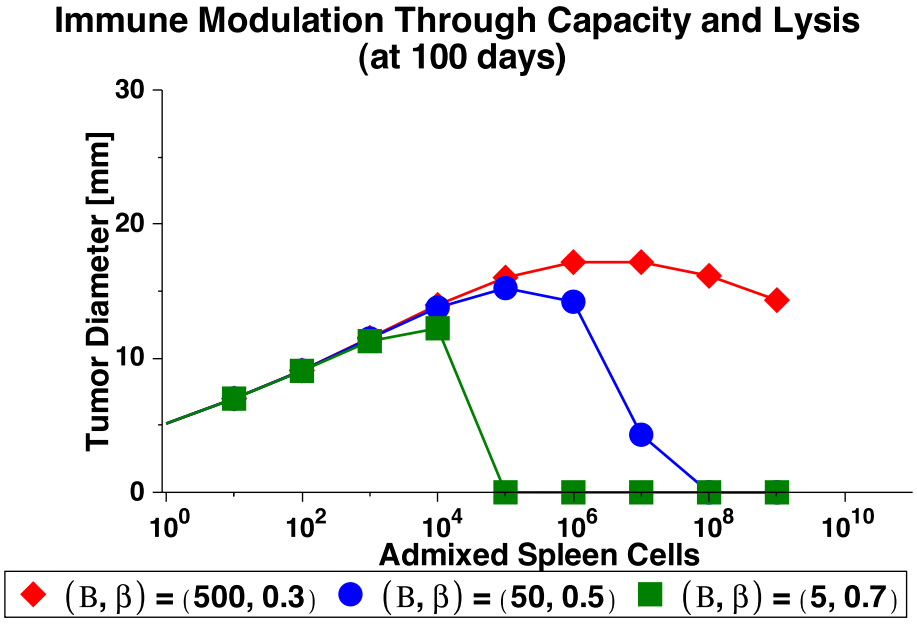
$$\Psi\big(I(t), C(t)\big) = -\theta\left(\frac{I^{\beta}}{BC^{\beta} + I^{\beta}} + 0.01\log_{10}(I+1)\right)$$

fast saturation kinetics

slow increase in saturation limit

Combined Immunomodulation Effects

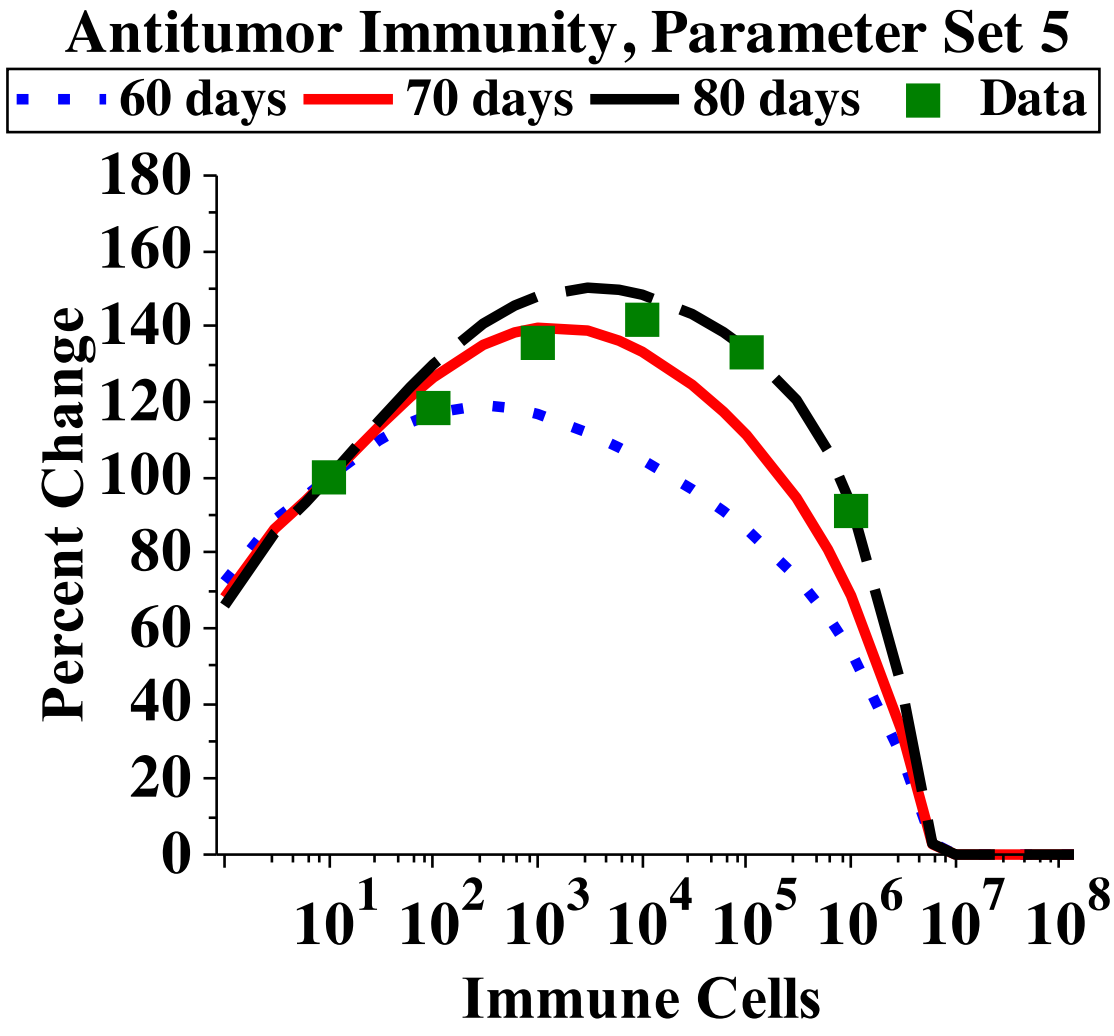
The antigenicity of the cancer cells determines the strength of the immune response via the recruitment parameter r, and the immune lysis efficacy parameter θ.
B and β control the saturation curve break-point and shape.



Varying Antigenicity

- level of antigen presentation by cancer cells determines the efficacy of immune mediated cell lysis
- three levels of antigenicity (weak, average, and strong can be modeled with three pairs of the parameters (B, β) in Ψ with $\theta = 2$.

Dose Response



Full predation but no immune growth ($I(t) = K_I(t) =$ Constant).

Parameterization, or the Quest for Validation

Tumor Growth Data

1. Tanooka et al. [1982] measured subcutaneous fibrosarcomas induced by 3-methylcholanthrene (the same cancer type/ induction method as used by Prehn [1972]) in wild-type mice.
2. These mice had competent immune systems except for a mast cell deficiency which can inhibit the host inflammatory response.
3. Cohen et al. [2010] showed that fibrosarcomas induced in this manner in wild-type mice are nonimmunogenic due to early immunoediting.
4. Furthermore, Betts et al. [2007] showed that regulatory T cells inhibit immune-mediated tumor rejection in these tumors.
5. We therefore assume that the tumor growth data (for observable tumors) represents a system wherein immune recruitment and immune predation are negligible.

Assume no Immune Response

These assumptions simplify the mathematical model to

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{\mu}{\alpha} C(t) \left(1 - \left(\frac{C(t)}{K_C(t)}\right)^{\alpha}\right) \tag{1}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = 0 \tag{2}$$

$$\frac{\mathrm{d}K_C}{\mathrm{d}t} = p\big(1 + I(t)\big)^{a} C(t)^{1-a} - qK_C(t)\big(1 + I(t)\big)^{b} C(t)^{\frac{2}{3}-b} \tag{3}$$

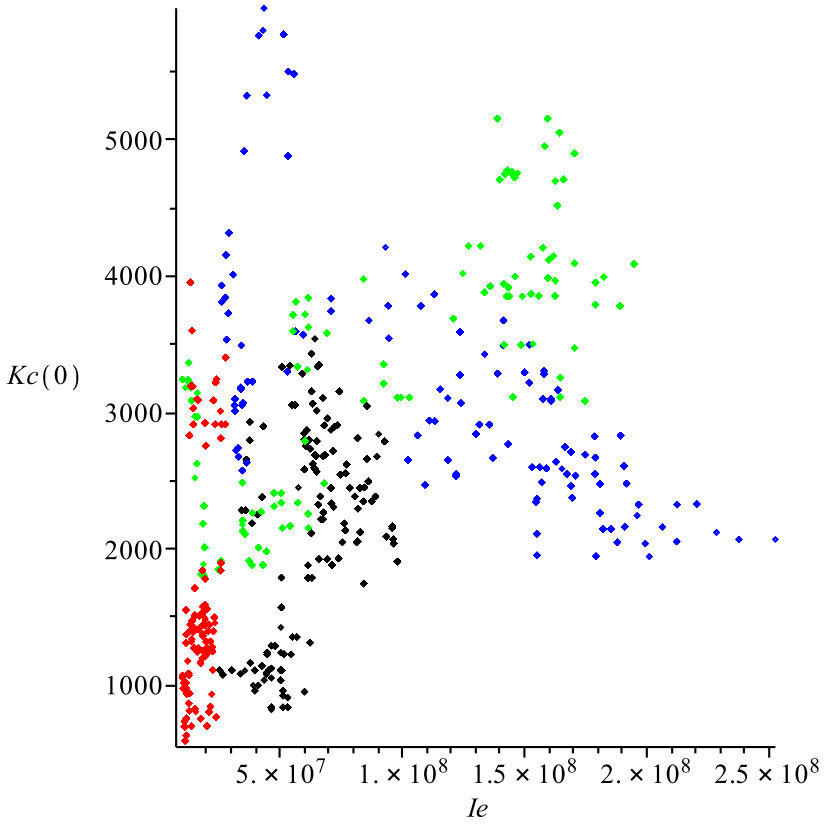
$$\frac{\mathrm{d}K_I}{\mathrm{d}t} = 0 \tag{4}$$

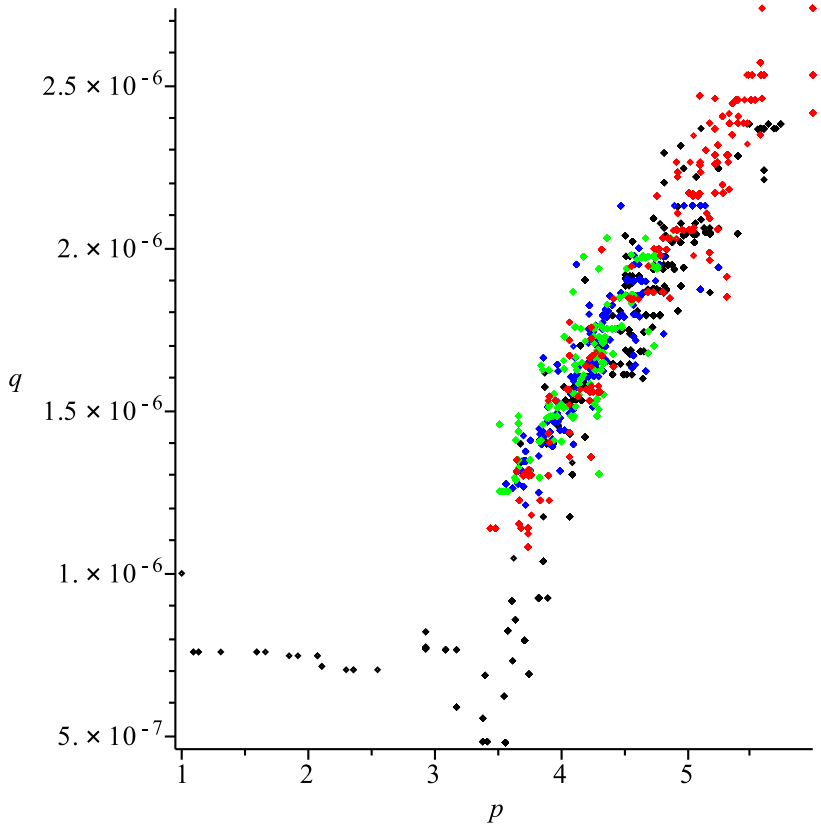
assume antitumor immunity, set $a = \frac{2}{10}$ and $b = \frac{3}{10}$ so $b > a$.

Parameters to estimate are μ, α, p, q, $K_{C,0}$, and $I_0 = K_{I0} = Ie$.
C_0 is determined by the data as the first observable measurement.

How to Estimate Parameters?

I used a Markov Chain Monte Carlo Method





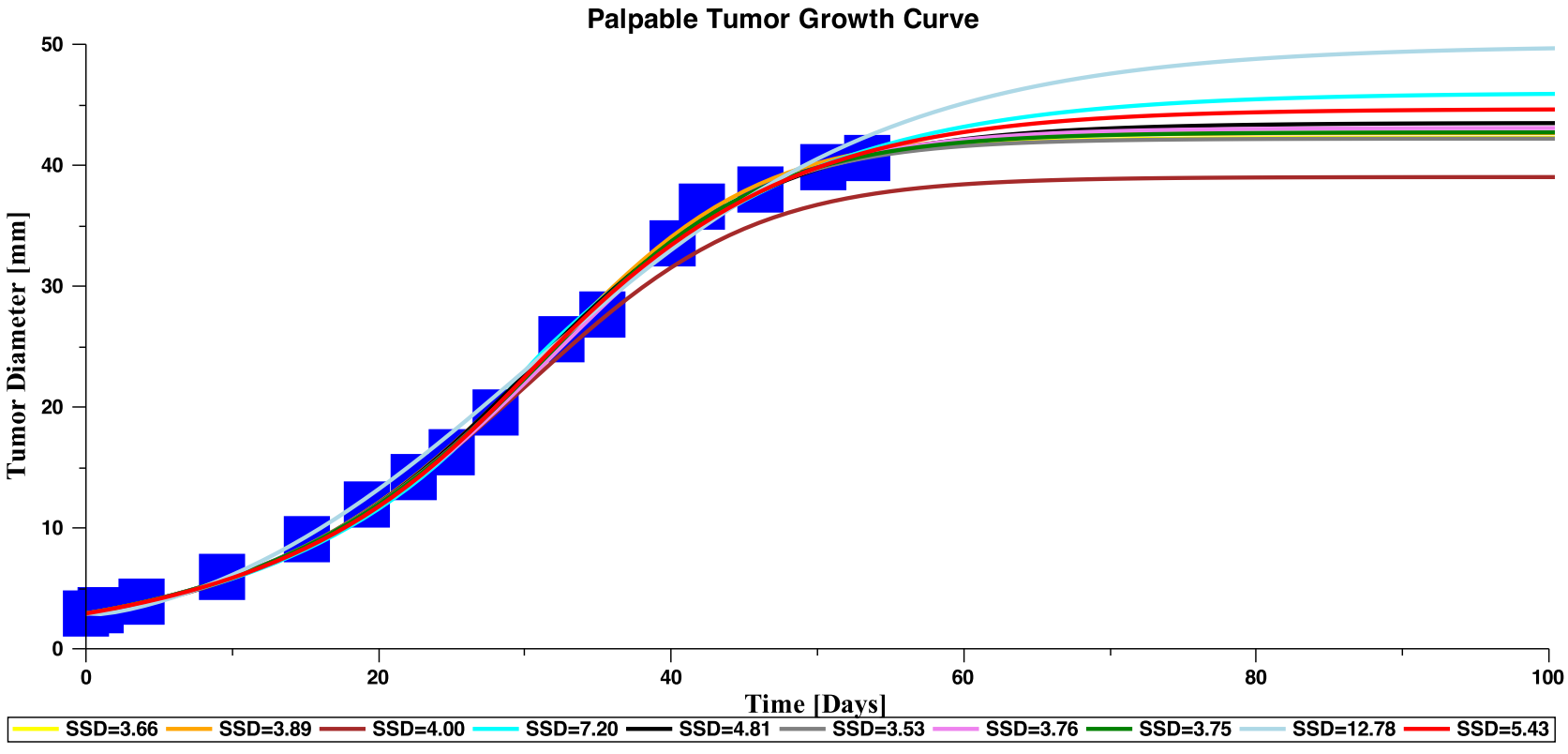
Results of MCMC estimation:

Run this method 10 times each with 20, 000 iterations.
Record the parameter set corresponding to the smallest SSD:

Antitumor Inflammation ($a < b$):

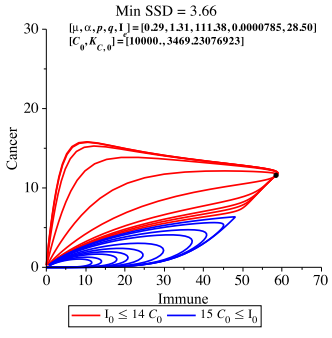
Min SSD	μ	α	p	q	K_{C0}	I_e
3.66	0.29	1.31	111.38	$7.83 \cdot 10^{-5}$	$4.51 \cdot 10^{6}$	28.50
3.89	0.34	1.46	20.07	$9.54 \cdot 10^{-6}$	$9.11 \cdot 10^{6}$	1294
4.00	0.29	1.23	18.39	$8.52 \cdot 10^{-6}$	$4.54 \cdot 10^{6}$	7612
7.20	8.81	42.63	4.61	$1.86 \cdot 10^{-6}$	$3.02 \cdot 10^{7}$	1850
4.81	0.88	4.09	5.79	$2.42 \cdot 10^{-6}$	$2.88 \cdot 10^{7}$	3363
3.53	0.43	1.94	10.81	$4.72 \cdot 10^{-6}$	$4.55 \cdot 10^{7}$	3635
3.76	0.53	2.44	7.39	$3.02 \cdot 10^{-6}$	$4.09 \cdot 10^{7}$	4964
3.75	0.59	2.73	7.53	$3.19 \cdot 10^{-6}$	$5.11 \cdot 10^{7}$	3993
12.78	0.17	$1.26 \cdot 10^{-7}$	47.49	$3.42 \cdot 10^{-5}$	17195	0.41
5.43	1.29	6.16	5.07	$2.04 \cdot 10^{-6}$	$7.43 \cdot 10^{7}$	3156

Antitumor Inflammation



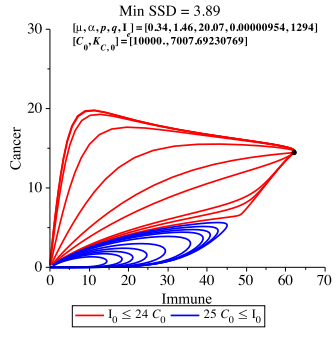
Phase Portraits for the 10 Parameter Sets

Set 1



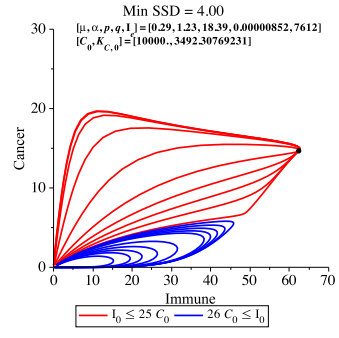
Split 14/15

Set 2



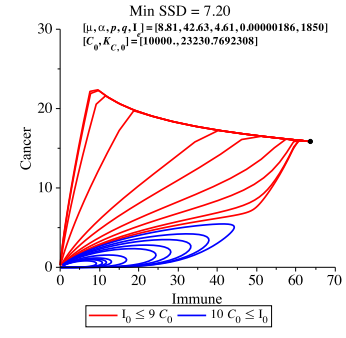
Split 24/25

Set 3



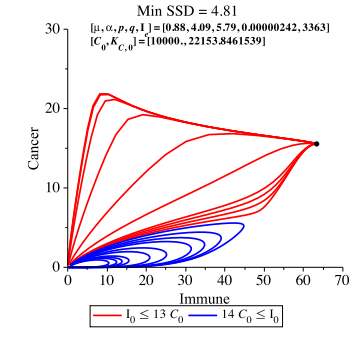
Split 25/26

Set 4



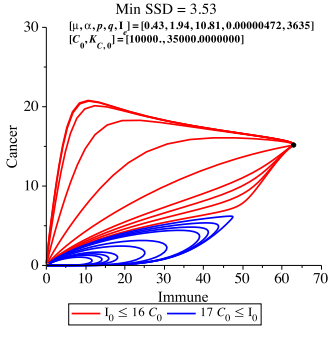
Split 9/10

Set 5



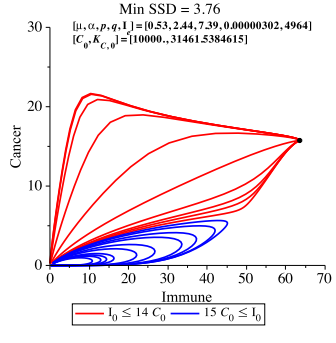
Split 13/14

Set 6



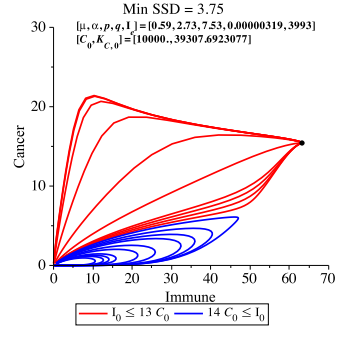
Split 16/17

Set 7



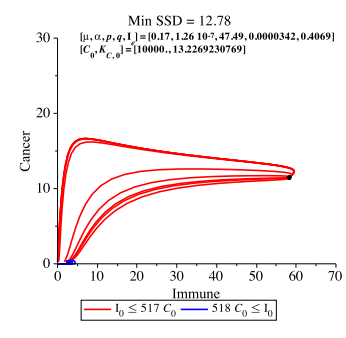
Split 14/15

Set 8



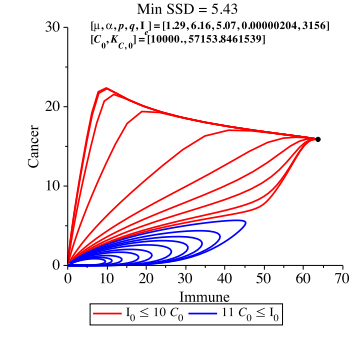
Split 13/14

Set 9



Split 517/518

Set 10

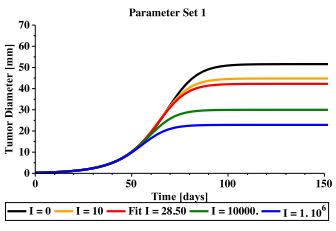


Split 10/11

Tumor Growth over Time with Various I_0

Note: no immune growth or immune predation.

Set 1



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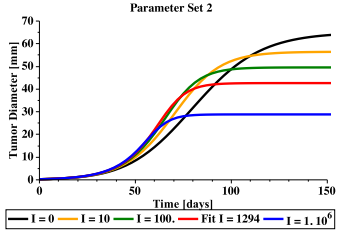

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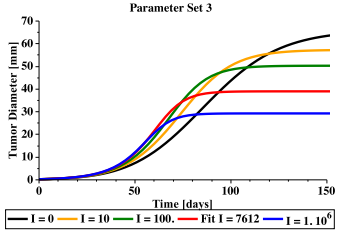

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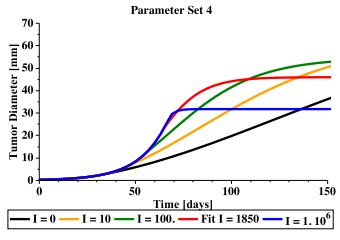

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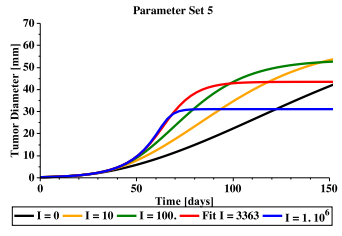

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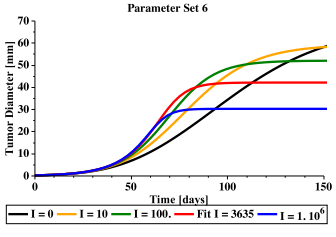
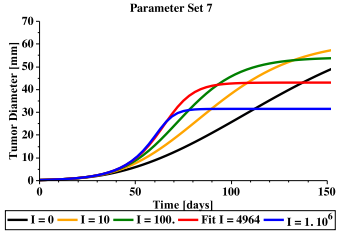


Set 7



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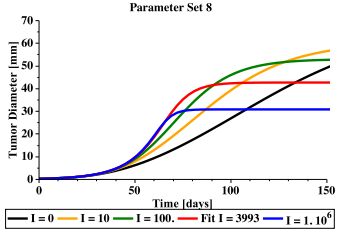

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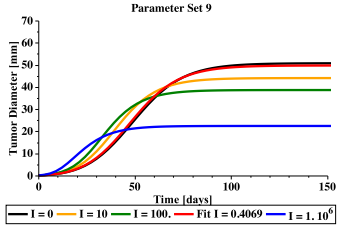
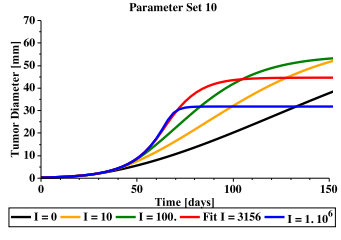


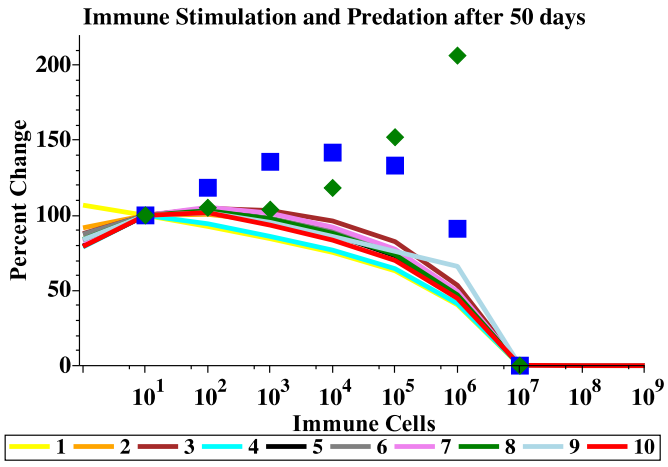
Set 10



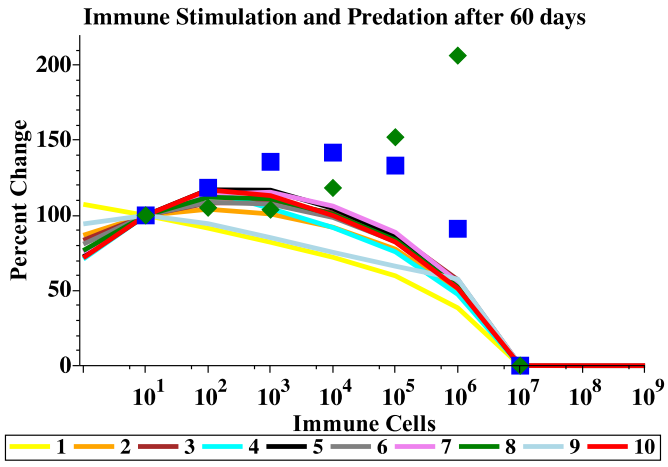
Anti-tumor inflammation causes tumors to grow faster but smaller when compared to no immune presence.

Immune Dose Response Curves

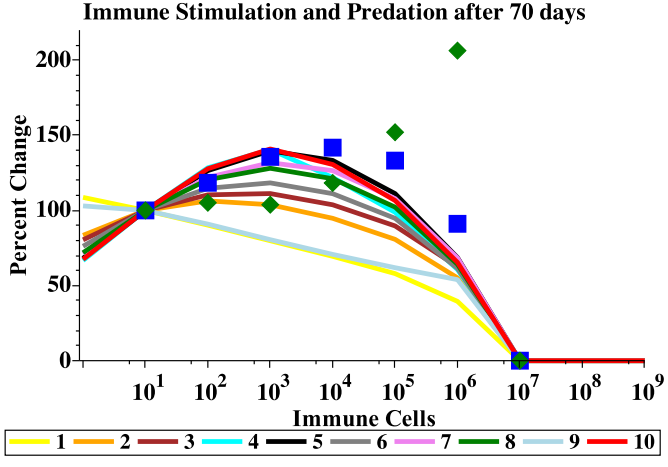
After 50 days



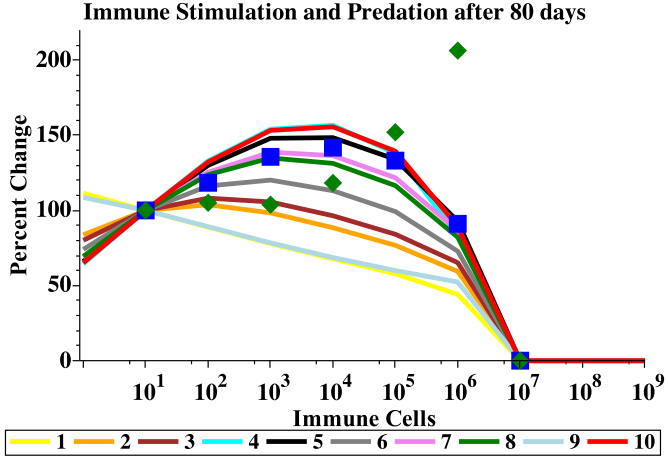
After 60 days



After 70 days



After 80 days



Pro-Tumor Inflammation

If $a > b$ in the DE for K_C then the inflammatory actions are mostly proangiogenic and thus pro-tumor.

For data fitting, we let $a = \frac{2}{10}$ and $b = \frac{1}{10}$ in

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{\mu}{\alpha} C \left(1 - \left(\frac{C}{K_C}\right)^{\alpha}\right) \tag{5}$$

$$\frac{\mathrm{d}K_C}{\mathrm{d}t} = p(1+I)^a C^{1-a} - qK_C(1+I)^b C^{\frac{2}{3}-b} \tag{6}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = 0 \qquad \text{and} \qquad \frac{\mathrm{d}K_I}{\mathrm{d}t} = 0 \tag{7}$$

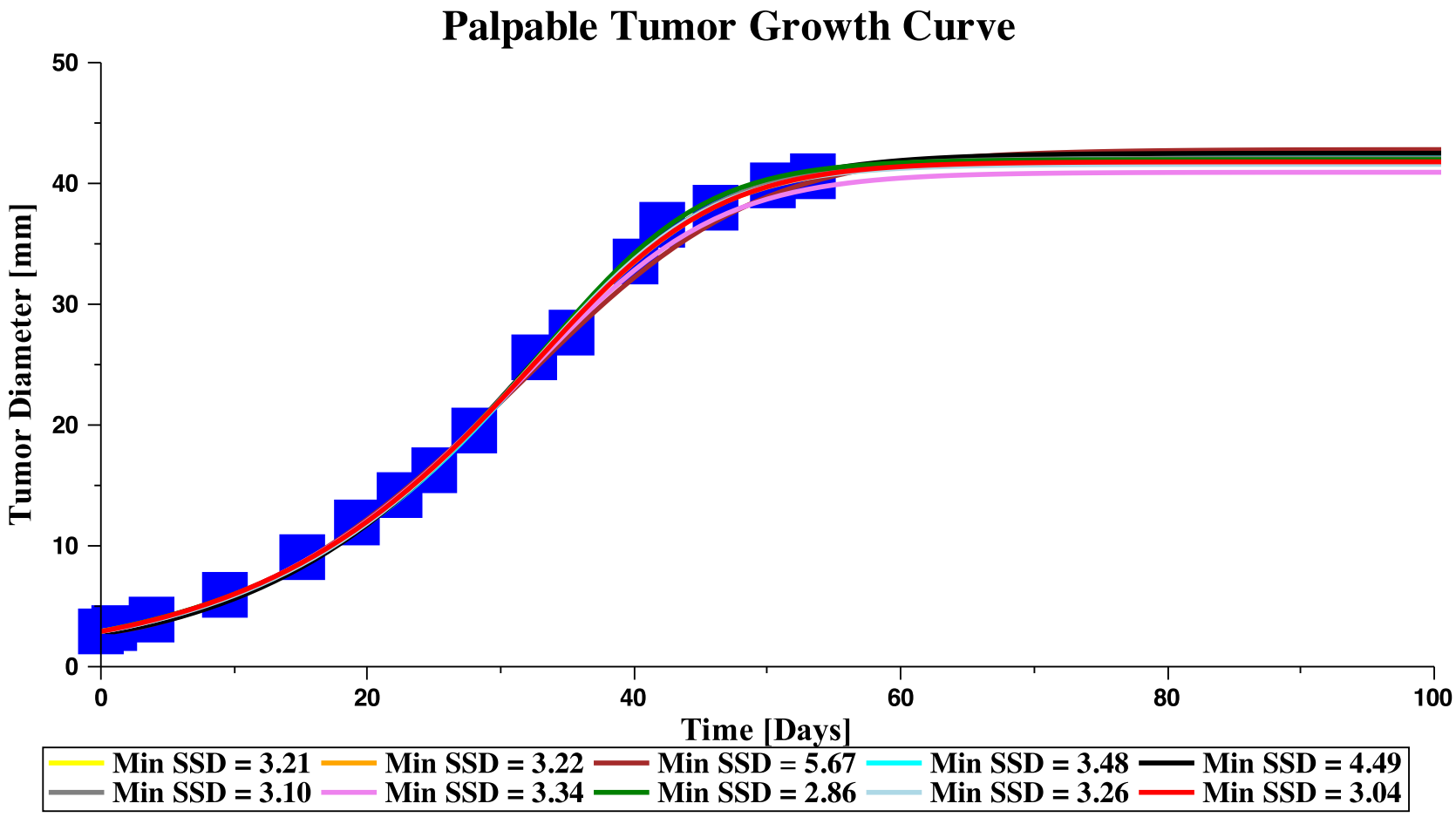
MCMC Parameter Fitting

Fitting this pro-tumor model to the growth data with the MCMC method estimates the following 10 parameter sets:

Min SSD	μ	α	p	q	K_{C0}	I_e
3.21	0.33	1.34	8.52	$1.43 \cdot 10^{-7}$	$2.81 \cdot 10^{7}$	2669
3.22	0.44	1.91	8.95	$1.38 \cdot 10^{-7}$	$3.24 \cdot 10^{7}$	985
5.67	0.23	0.43	9.24	$1.37 \cdot 10^{-7}$	$4.50 \cdot 10^{6}$	1237
3.48	0.55	2.55	9.43	$1.28 \cdot 10^{-7}$	$8.91 \cdot 10^{7}$	374
4.49	0.21	0.77	35.74	$4.17 \cdot 10^{-7}$	$3.76 \cdot 10^{5}$	93
3.10	0.34	1.39	8.70	$1.46 \cdot 10^{-7}$	$4.27 \cdot 10^{7}$	2914
3.34	0.37	1.46	9.66	$1.50 \cdot 10^{-7}$	$2.55 \cdot 10^{7}$	667
2.86	0.37	1.70	13.55	$1.91 \cdot 10^{-7}$	$2.46 \cdot 10^{8}$	466
3.26	0.29	1.22	11.72	$2.00 \cdot 10^{-7}$	$3.17 \cdot 10^{7}$	2483
3.04	0.33	1.39	11.28	$1.71 \cdot 10^{-7}$	$5.55 \cdot 10^{7}$	863

Still some variability within these parameter sets.

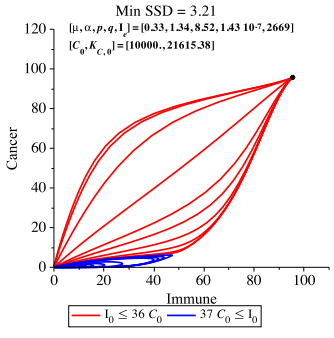
Tumor Growth with Pro-Tumor Inflammation



All parameter sets fit the data well.

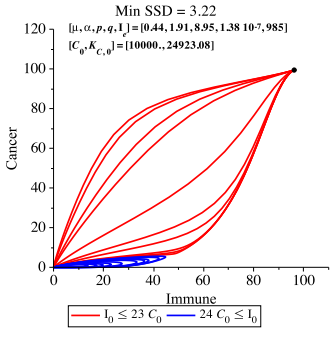
Phase Portraits for the 10 Parameter Sets

Set 1



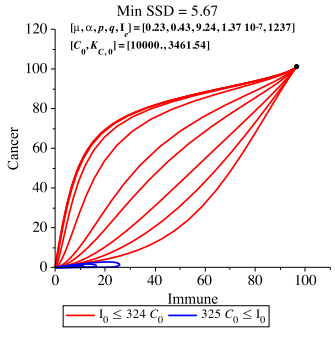
Split 36/37

Set 2



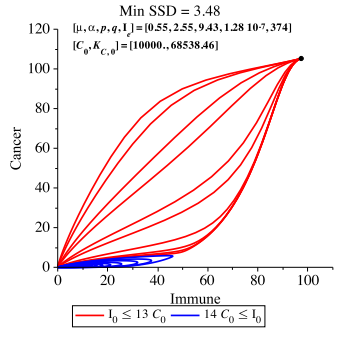
Split 23/24

Set 3



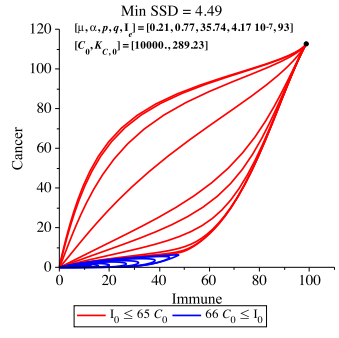
Split 324/325

Set 4



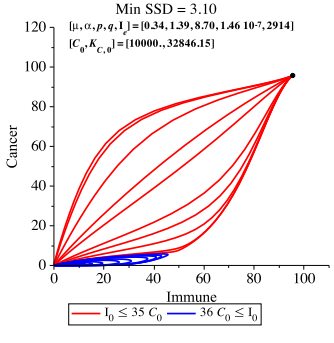
Split 13/14

Set 5



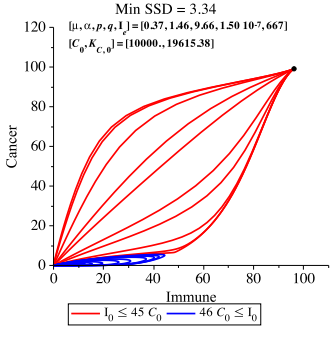
Split 65/66

Set 6



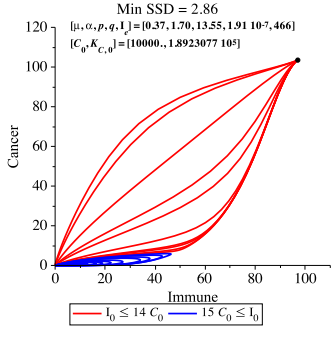
Split 35/36

Set 7



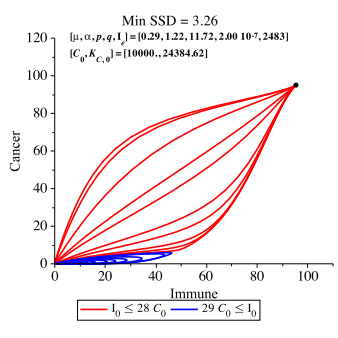
Split 45/46

Set 8



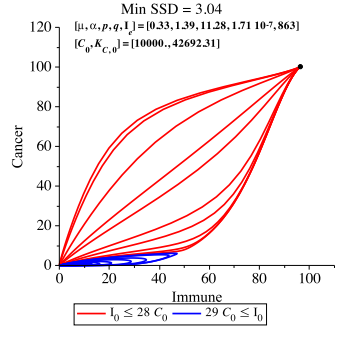
Split 14/15

Set 9



Split 28/29

Set 10

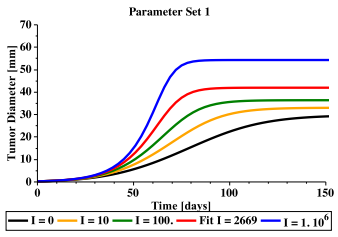


Split 28/29

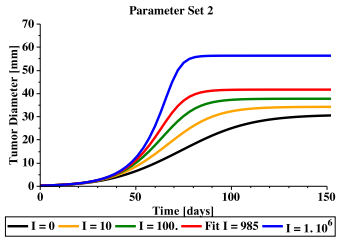
Tumor Growth over Time with Various I_0

Note: no immune growth or predation.

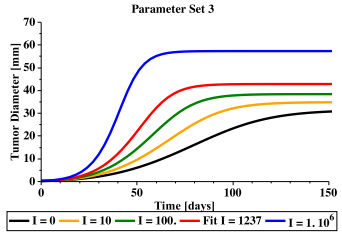
Set 1



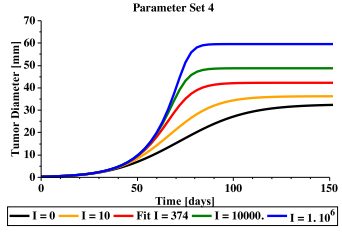
Set 2



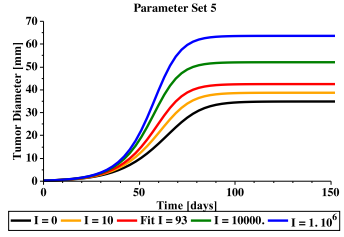
Set 3



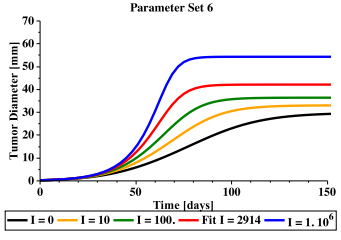
Set 4



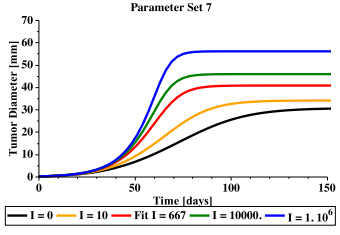
Set 5



Set 6



Set 7



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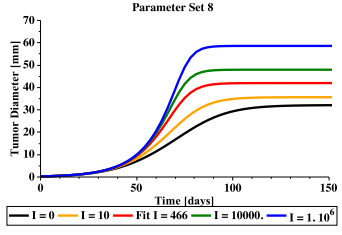
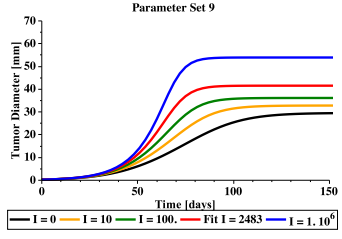
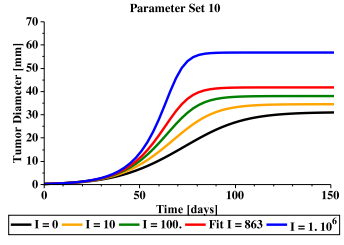


Set 9



Set 10

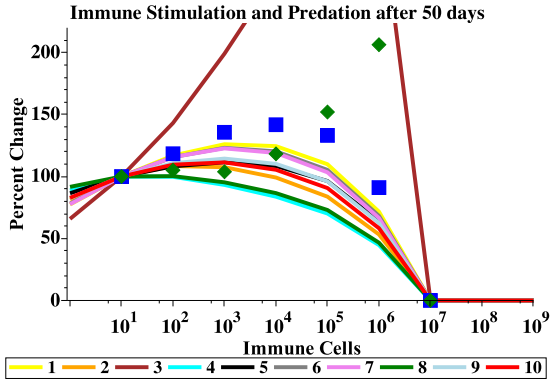


Pro-tumor inflammation causes tumors to grow faster and larger when compared to no immune presence.

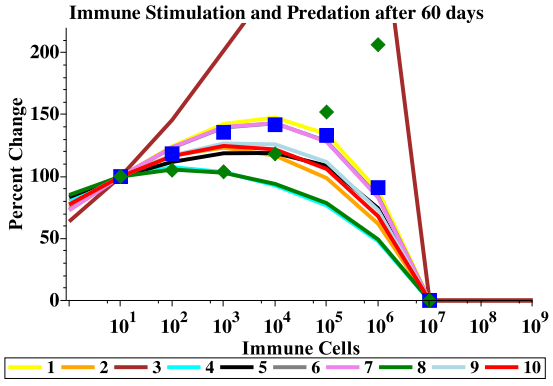
Immune Dose Response Curves

Pro-tumor inflammation and full predation:

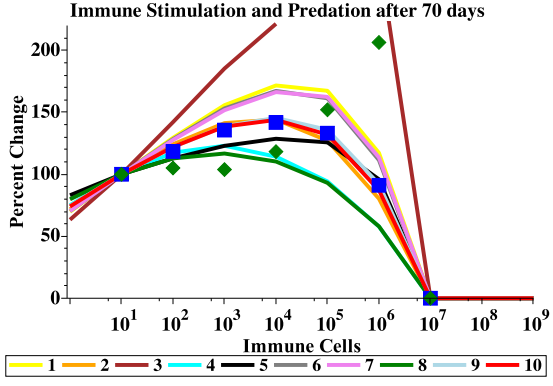
After 50 days



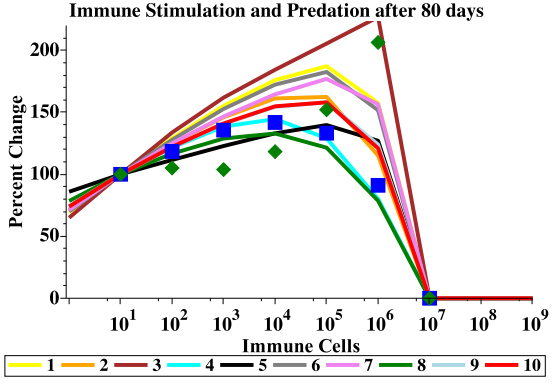
After 60 days



After 70 days

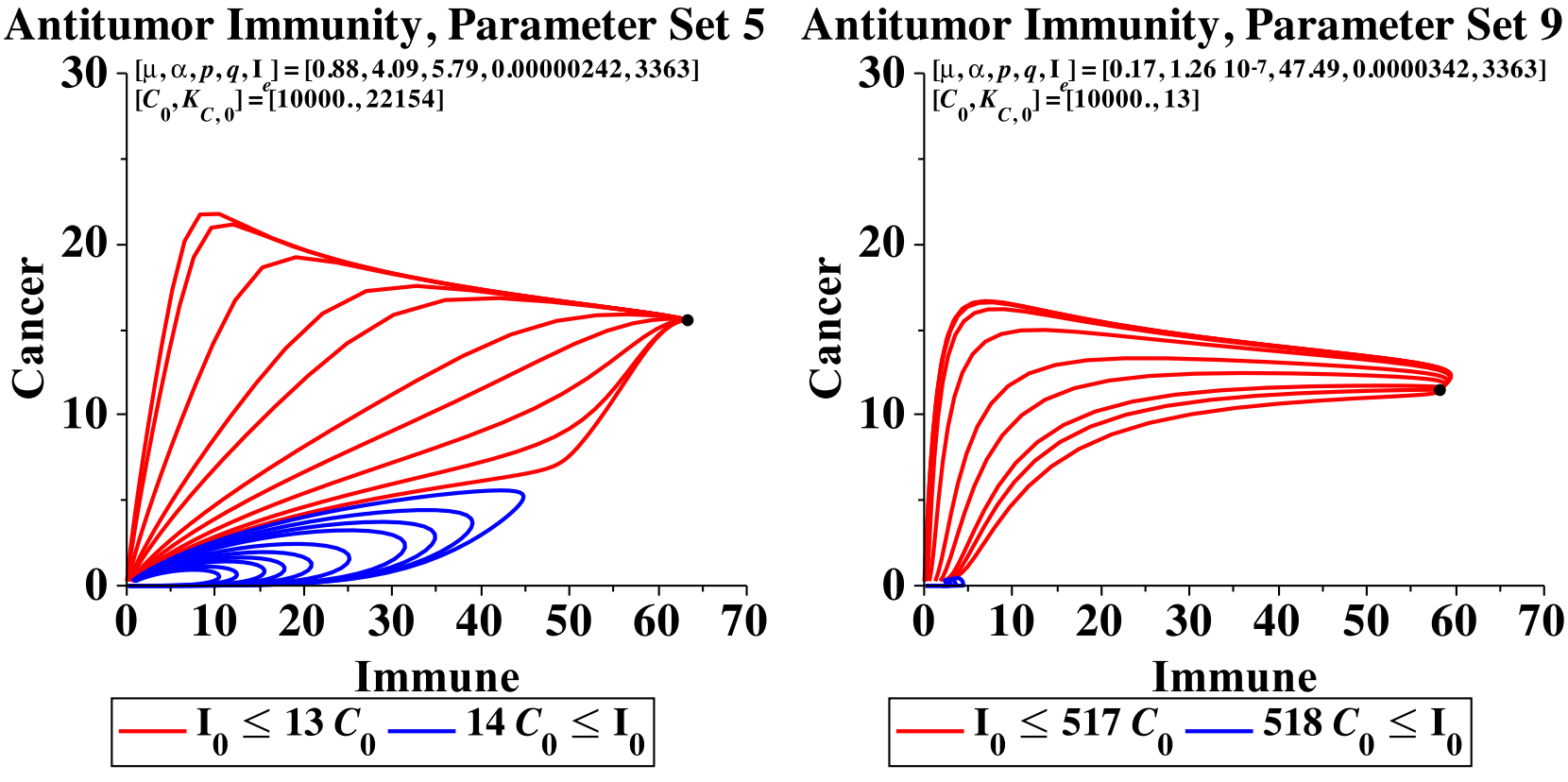


After 80 days



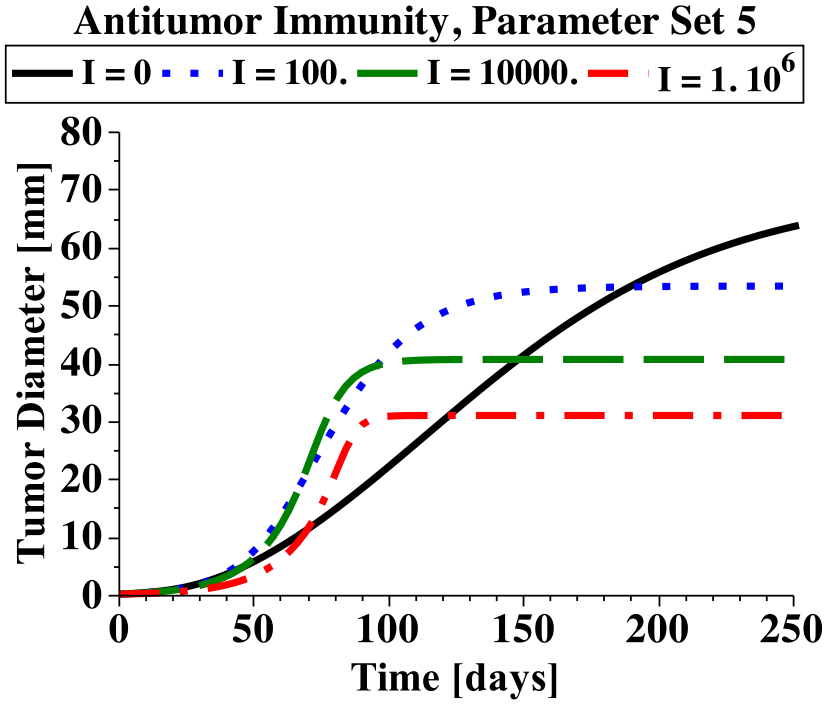
Summary so far...

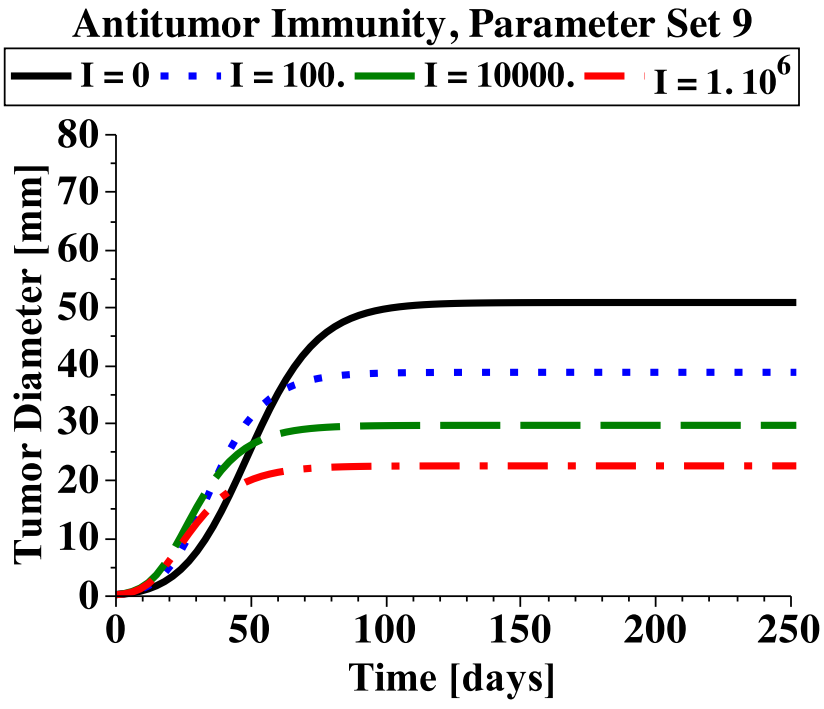
(1) Variability exists inherent in tumor growth and generalized logistic growth can capture some of this variability:



Summary so far...

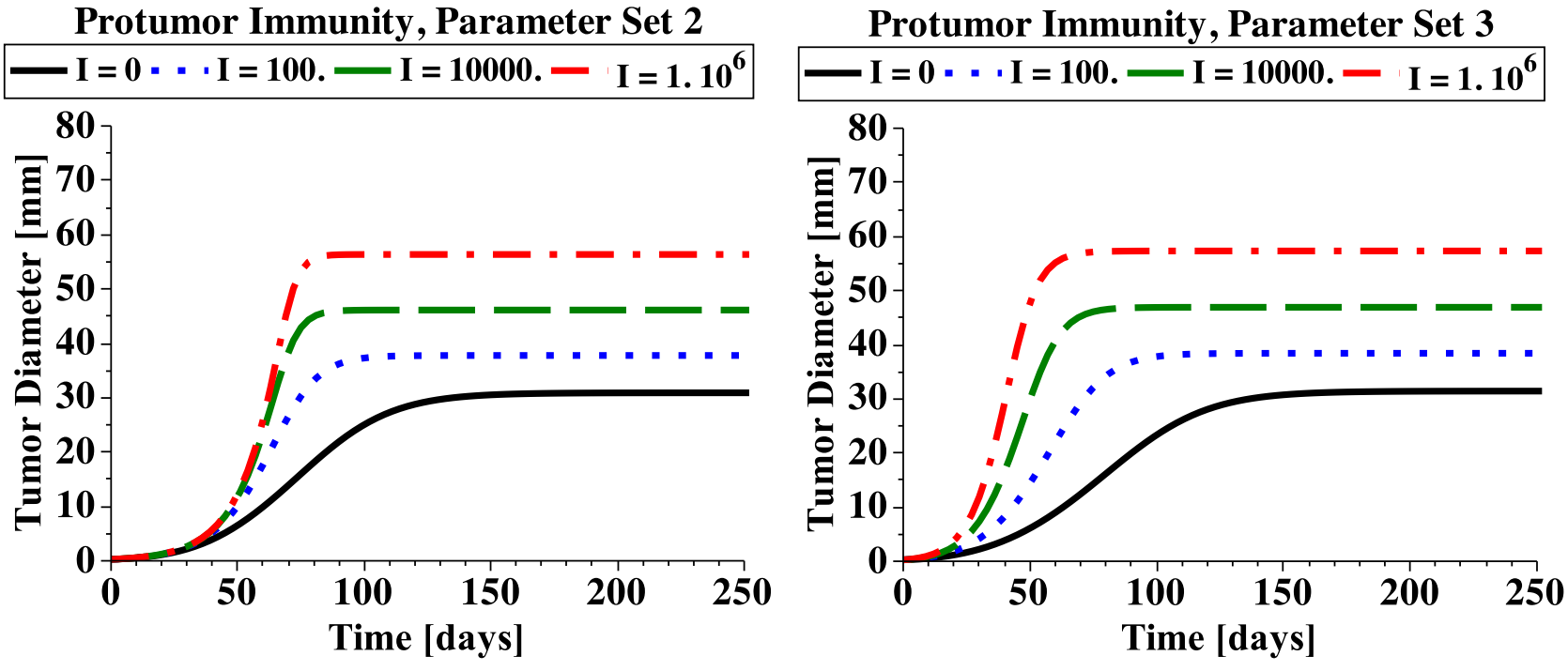
(2) Anti-tumor inflammation may initially promote tumor growth, but it may also limit the final tumor burden





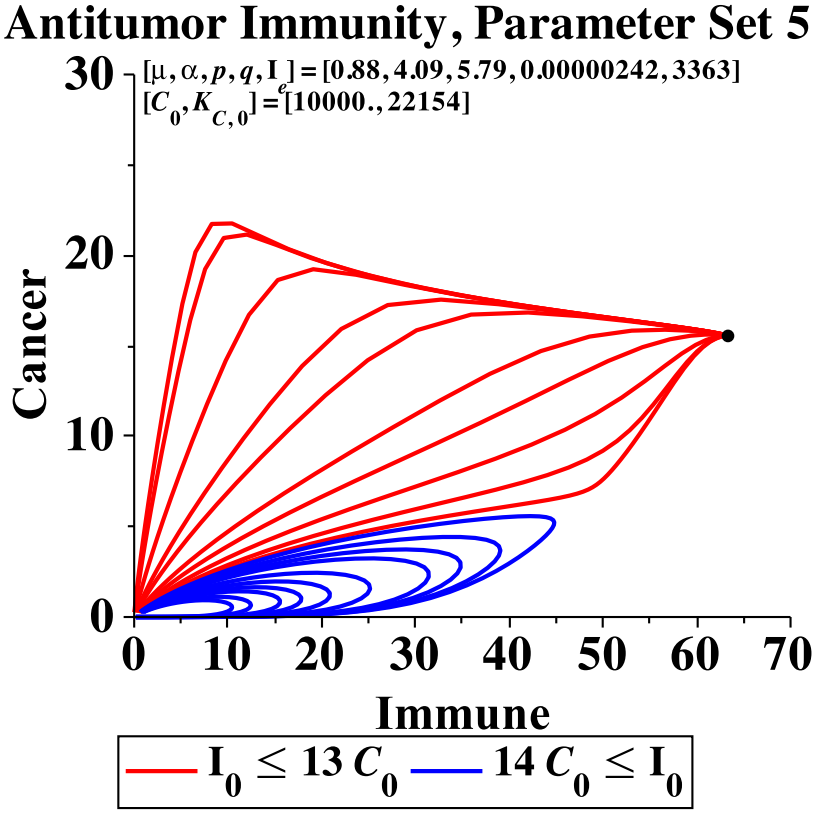
Summary so far...

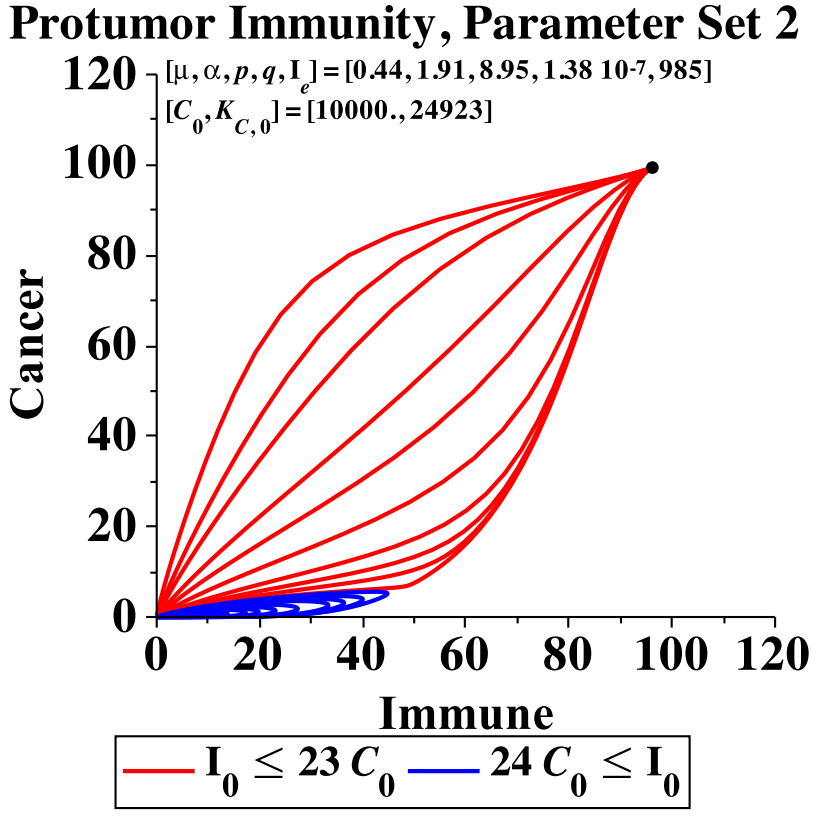
(3) Pro-tumor inflammation may initially promote tumor growth and it may also enlarge the final tumor burden



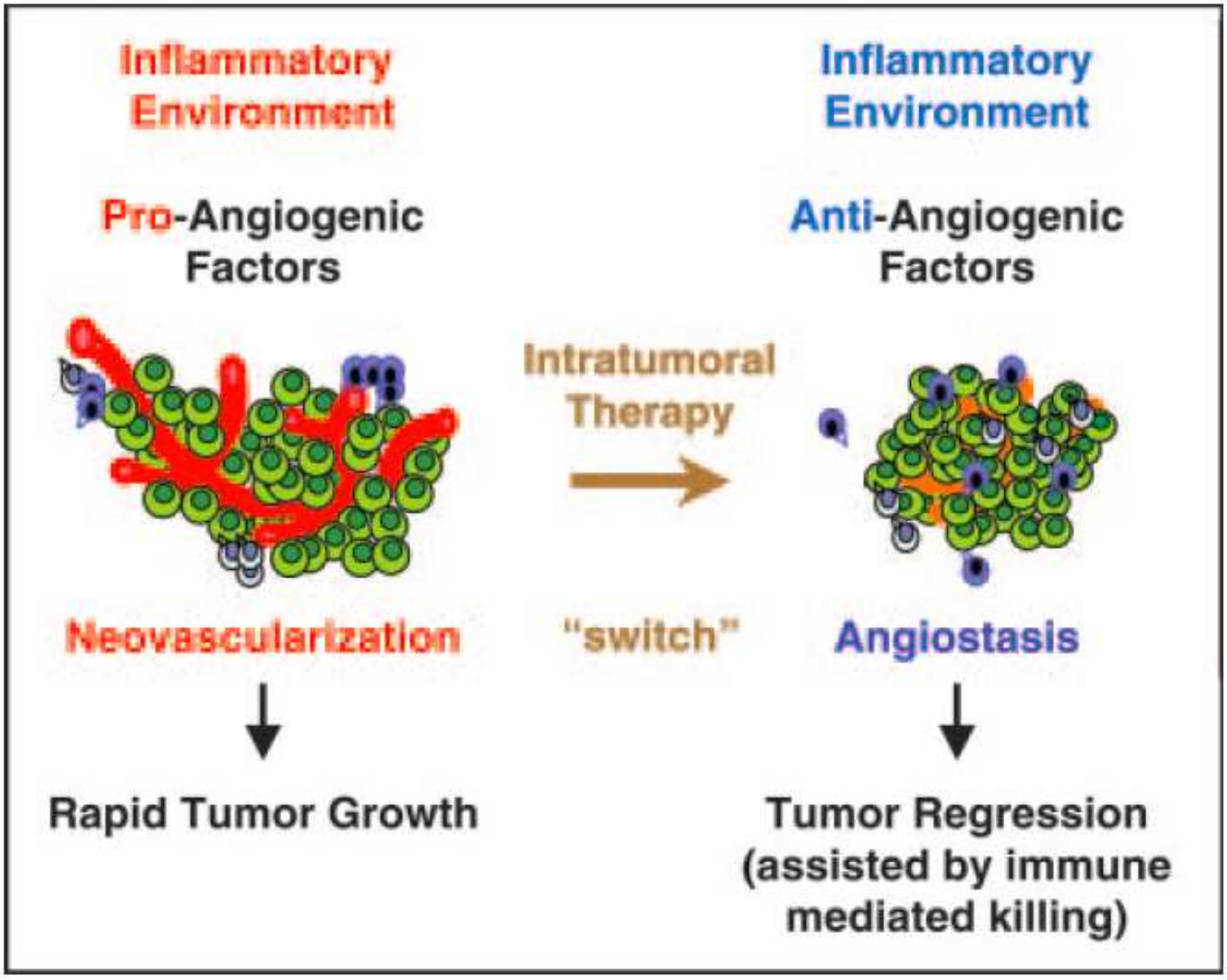
Summary so far...

(4) Anti-tumor inflammation increases the likelihood of immune-mediated tumor control



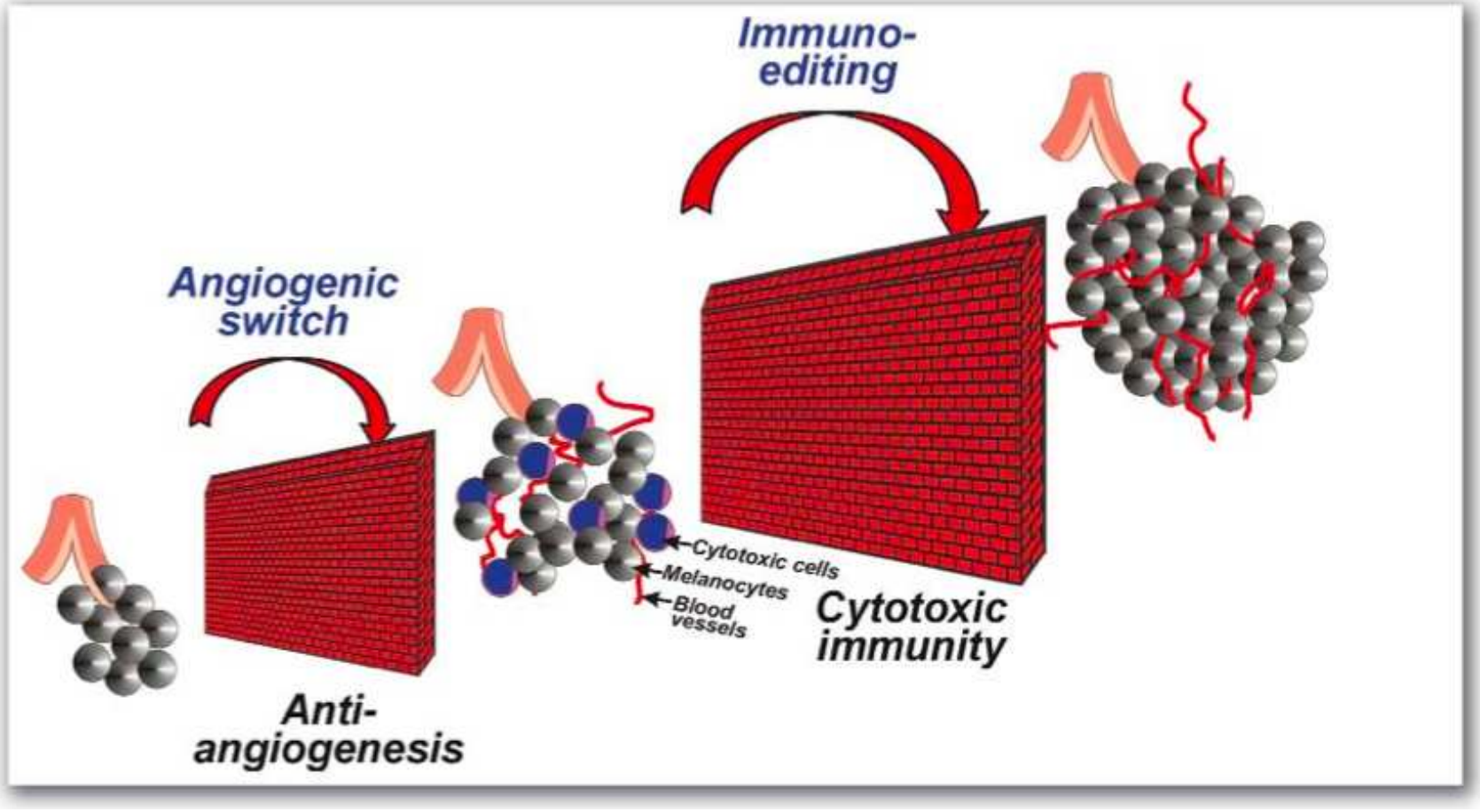


Need to switch Inflammation for tumor Control



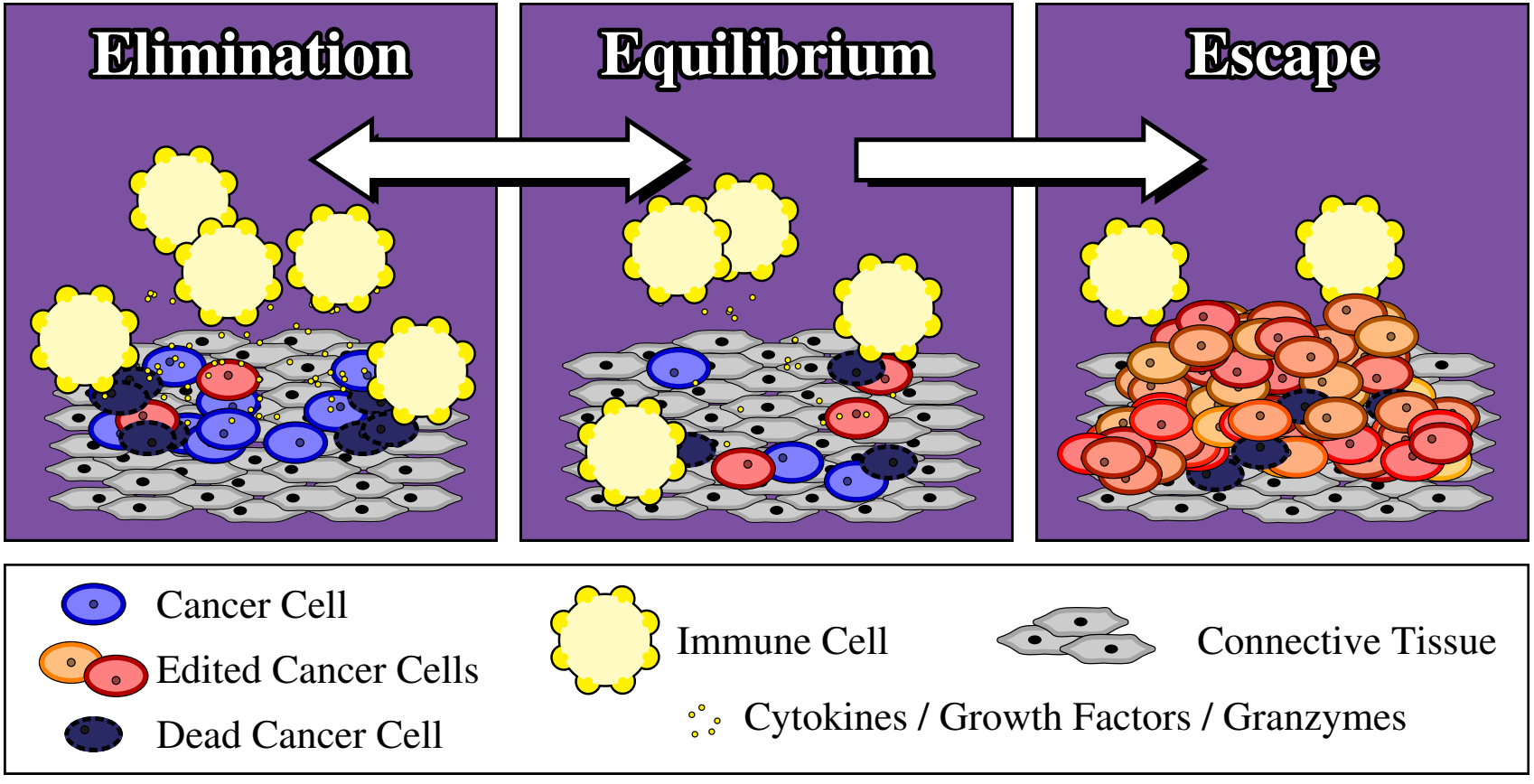
D Nelson, J Leukocyte Biol, 2006, 80: 685-670.

Two Barriers of Tumor Escape

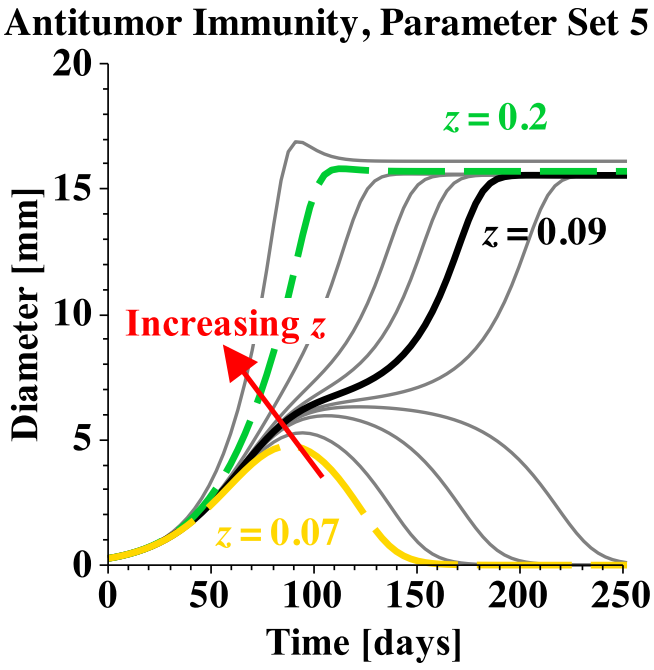


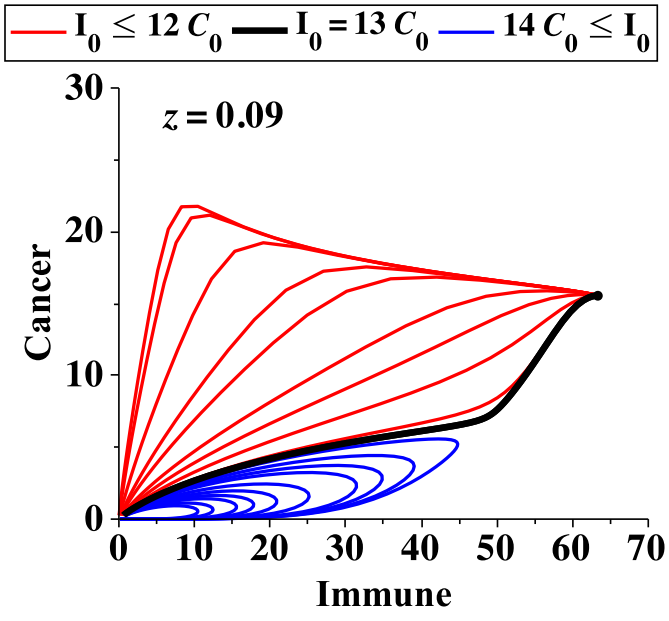
[Rankin et al. Cancer Biol. Ther. 2003. 2(6): 687-693.]

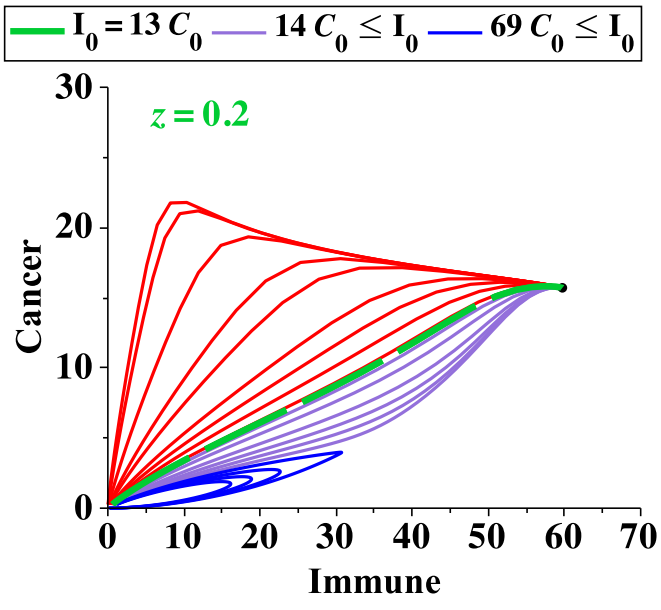
The Process of Immunoediting

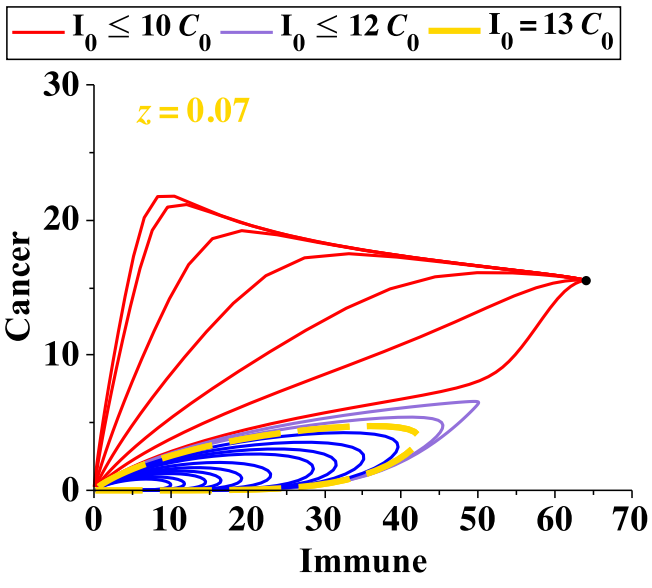


Anti-Tumor Inflammation - Homeostatic Parameter

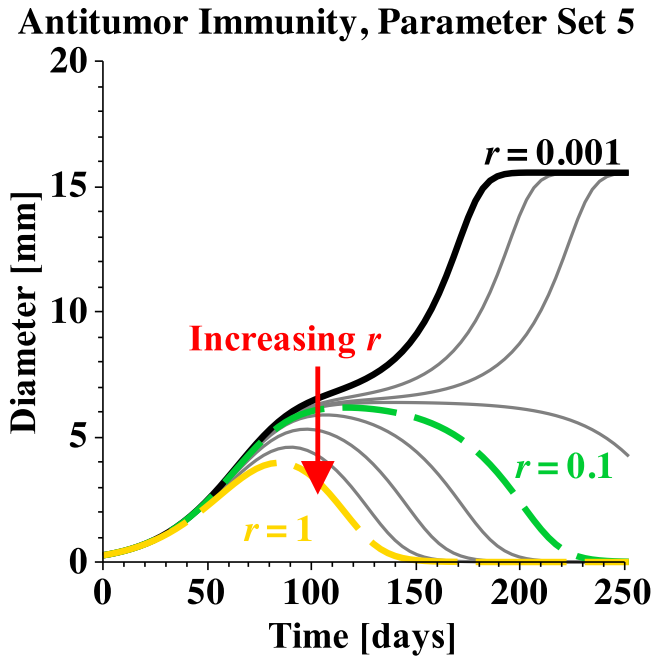


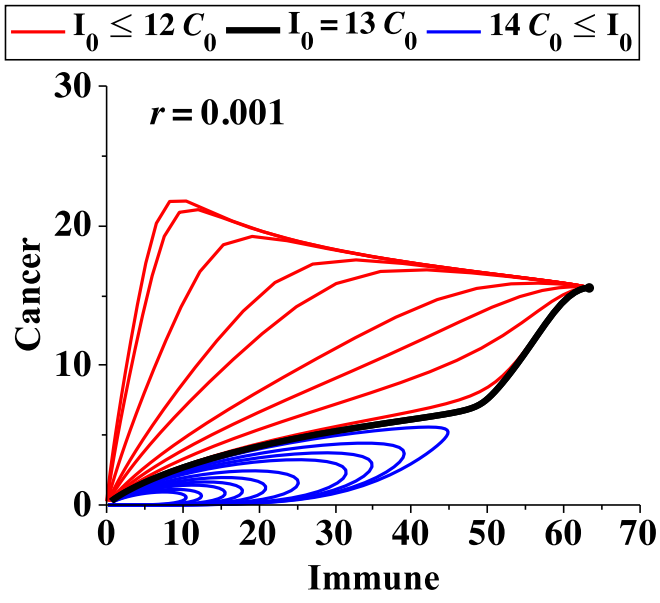


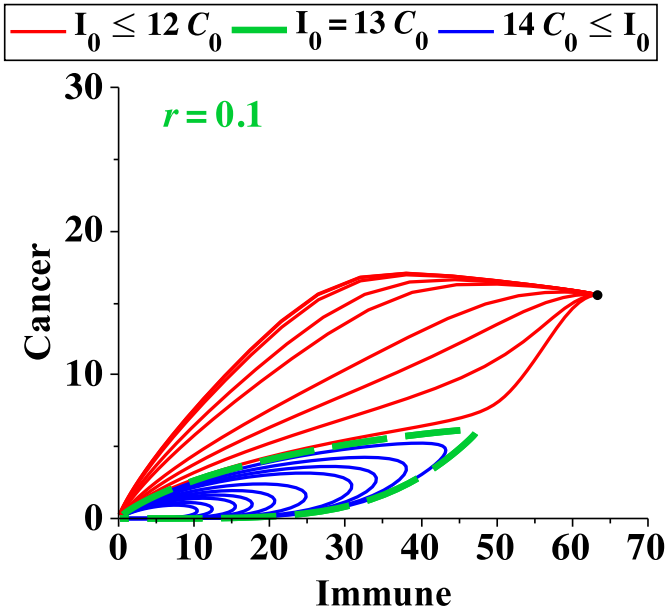


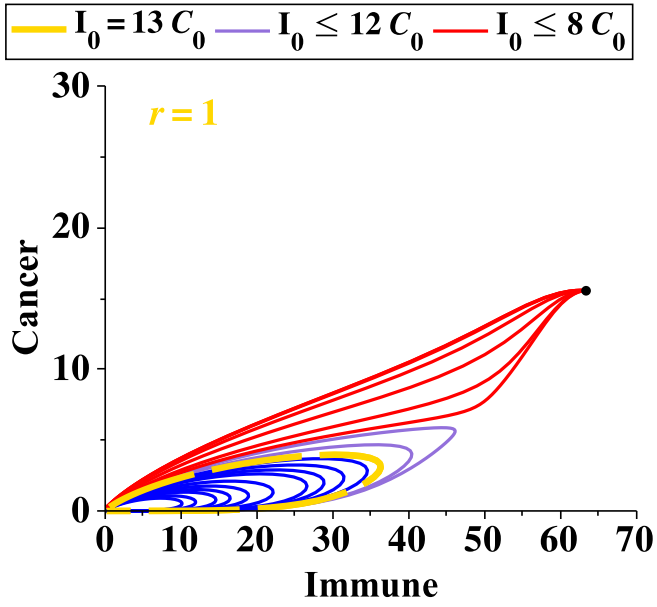


Anti-Tumor Inflammation - Recruitment Parameter









A Simplification of our Model

First we fit the basic tumor growth model using Generalized Logistic Growth with the MCMC method:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{\mu}{\alpha} C(t) \left(1 - \left(\frac{C(t)}{K_C(t)}\right)^{\alpha}\right)$$

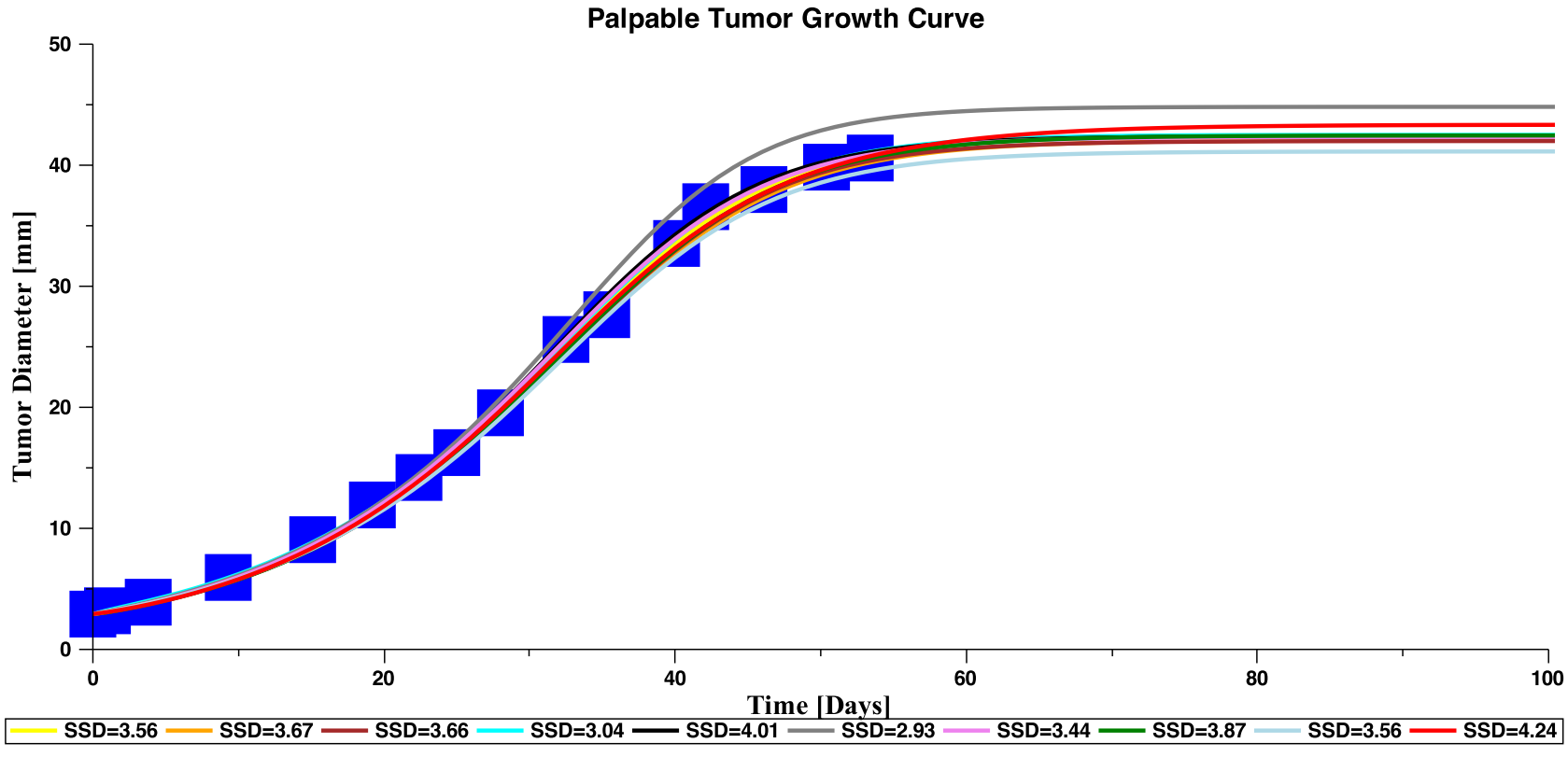
$$\frac{\mathrm{d}K_C}{\mathrm{d}t} = pC(t) - qK_C(t)C(t)^{\frac{2}{3}}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = 0 \quad \frac{\mathrm{d}K_I}{\mathrm{d}t} = 0$$

Model Still Captures Variability

Min SSD	μ	α	p	q	K_{C0}
3.56	0.22	0.99	30.13	$2.57 \cdot 10^{-6}$	$1.55 \cdot 10^{6}$
3.67	0.22	1.00	11.10	$9.66 \cdot 10^{-7}$	$1.20 \cdot 10^{7}$
3.66	0.23	1.06	16.96	$1.48 \cdot 10^{-6}$	$1.28 \cdot 10^{6}$
3.04	0.70	0.02	0.29	$2.47 \cdot 10^{-8}$	$2.16 \cdot 10^{7}$
4.01	0.24	1.03	3.90	$3.34 \cdot 10^{-7}$	$3.29 \cdot 10^{7}$
2.93	0.34	0.98	0.59	$4.52 \cdot 10^{-8}$	$4.21 \cdot 10^{7}$
3.44	0.23	1.04	27.72	$2.38 \cdot 10^{-6}$	$3.12 \cdot 10^{7}$
3.87	0.22	0.97	6.02	$5.14 \cdot 10^{-7}$	$1.41 \cdot 10^{7}$
3.56	0.23	1.03	3.54	$3.22 \cdot 10^{-7}$	$1.59 \cdot 10^{8}$
4.24	0.19	$1.44 \cdot 10^{-5}$	0.73	$5.98 \cdot 10^{-8}$	$2.90 \cdot 10^{7}$

Parameter Estimates All "Good"



Analyzing a Simplified Model

We allow immune predation and recruitment but with constant carrying capacities:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{\mu}{\alpha}(1 + \Psi(I, C))\, C \left(1 - \left(\frac{C}{K_C}\right)^{\alpha}\right)$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \lambda(I + rC)\left(1 - \frac{I}{K_I}\right)$$

$$\frac{\mathrm{d}K_C}{\mathrm{d}t} = 0 \quad \frac{\mathrm{d}K_I}{\mathrm{d}t} = 0$$

$$\Psi(I, C) = -\theta\left(\frac{I^{\beta}}{BC^{\beta} + I^{\beta}} + \frac{1}{100}\log_{10}(1 + I)\right)$$

Equilibrium Points and Stability

1. $(0, 0)$ is an unstable point
2. $(K_I, 0)$ is a stable point if $1 + \Psi(K_I, 0) < 0$ (else a saddle)
3. (K_I, K_C) is a stable point if $1 + \Psi(K_I, K_C) > 0$ (else a saddle)
4. (K_I, C^*) is a saddle point with

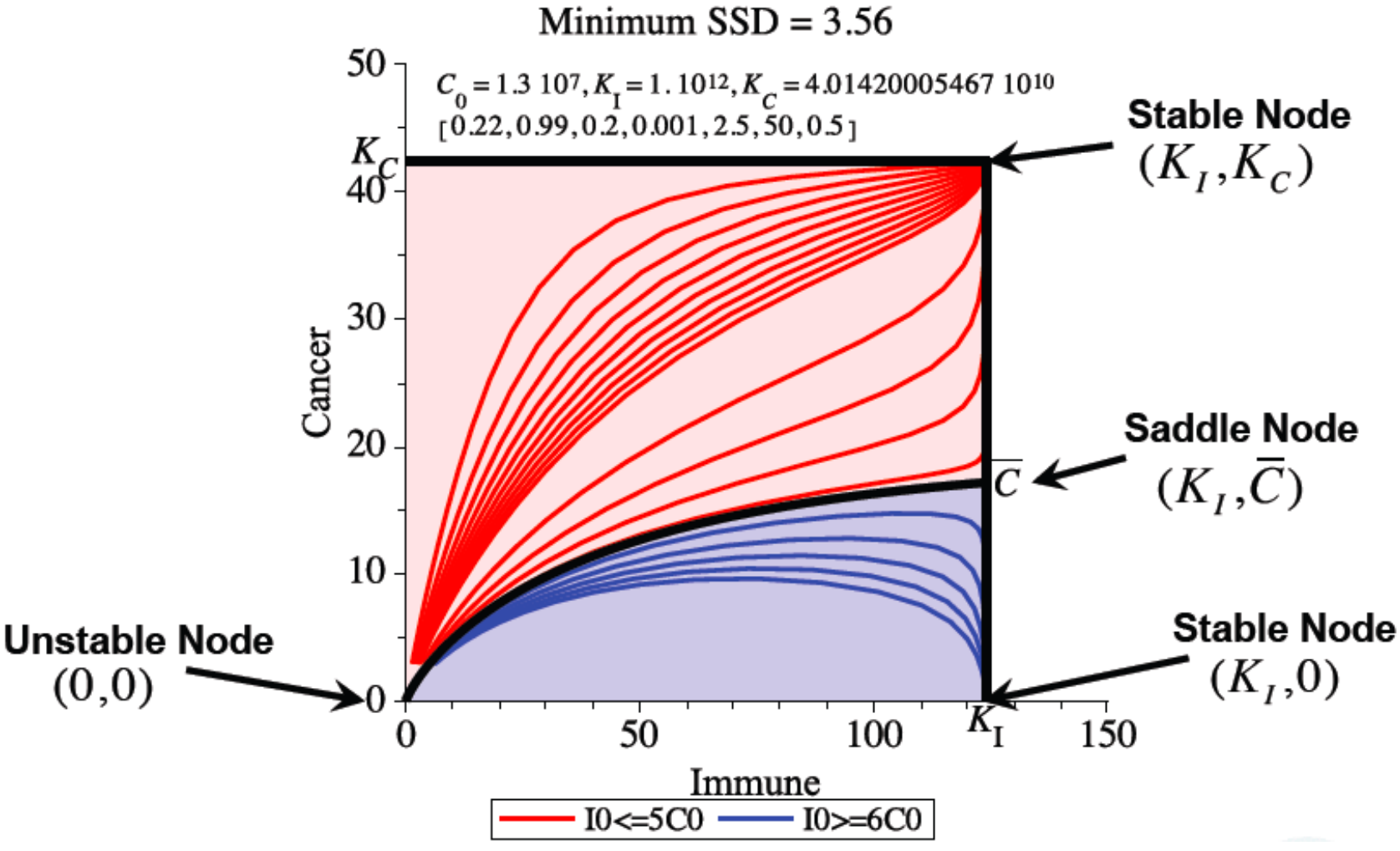
$$C^* = \left(\frac{K_I^\beta}{B} \left(\frac{\theta}{1 - \frac{\theta}{100} \log(1 + K_I)} - 1 \right) \right)^{\frac{1}{\beta}}.$$

Note that (1) and (2) require that

$$\left(1 + \frac{1}{100} \log(1 + K_I)\right)^{-1} < \theta < \left(\frac{K_I^\beta}{B K_C^\beta + K_I^\beta} + \frac{1}{100} \log(1 + K_I) \right)^{-1}$$

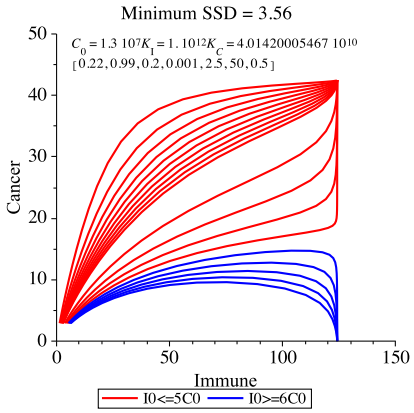
which gives a theoretical range on the predation efficacy.

Immunomodulation Phase Plane



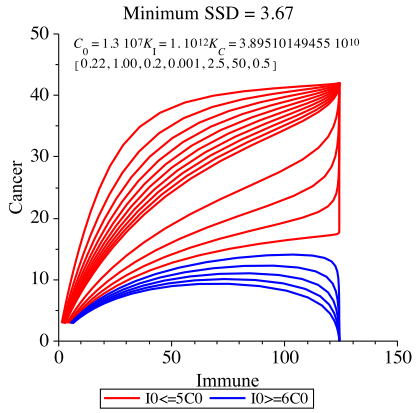
Similar Phase Portraits

Sets 1



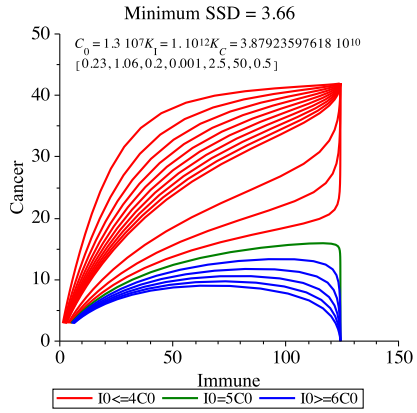
Split 5/6

2



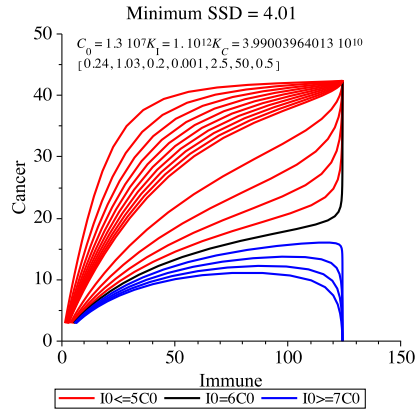
5/6

3



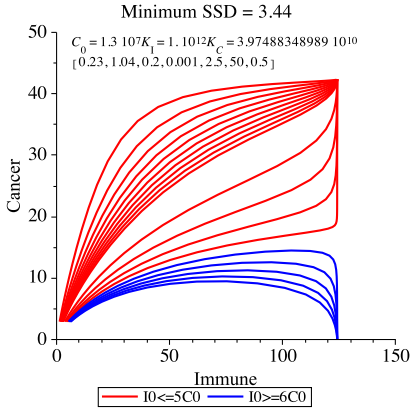
4/5

5



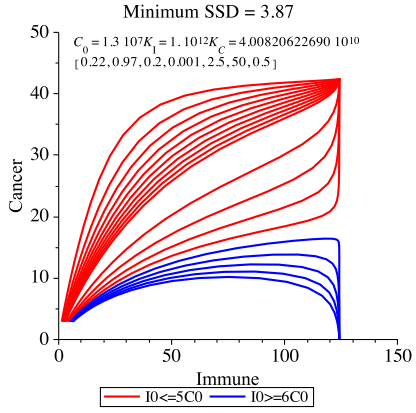
6/7

Sets 7



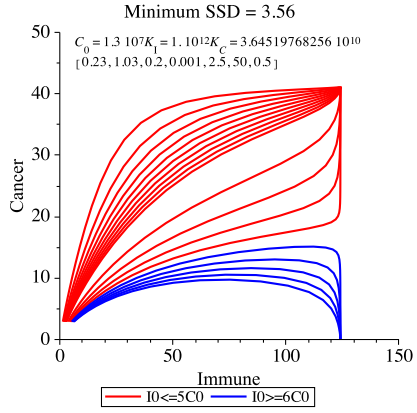
Split 5/6

8



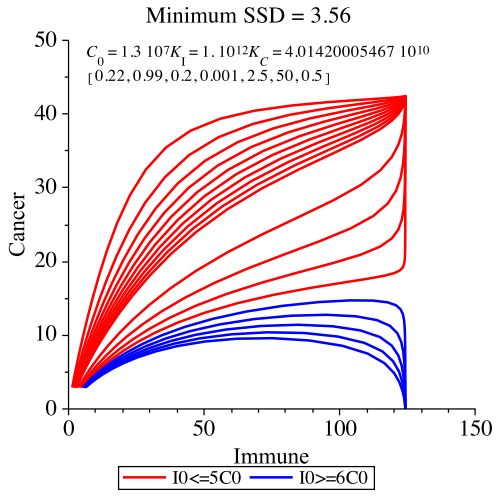
5/6

9



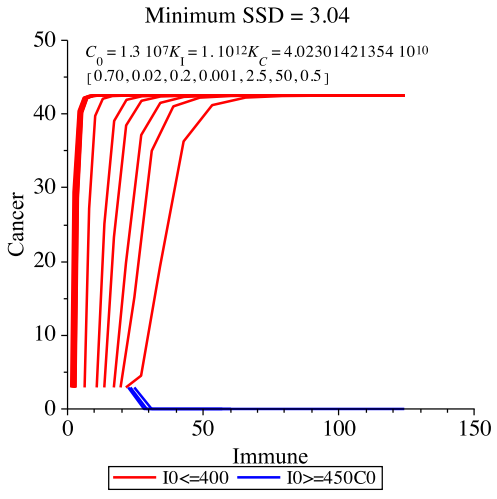
5/6

Different Phase Portraits



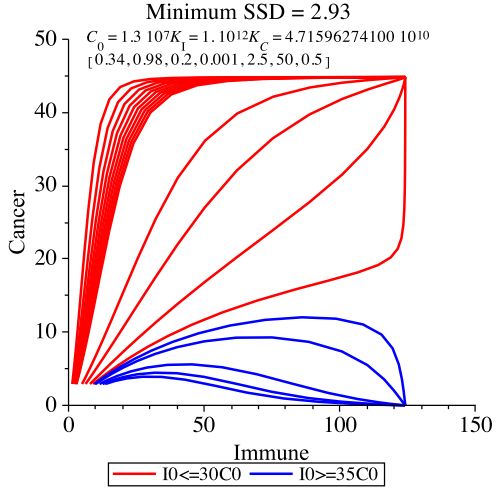
Set 1:

Split 5/6



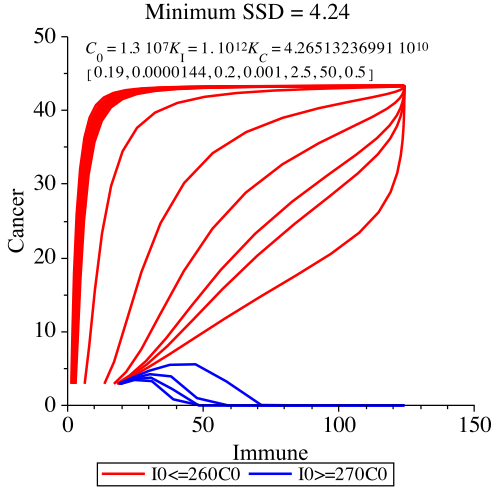
Set 4:

400/450



Set 6:

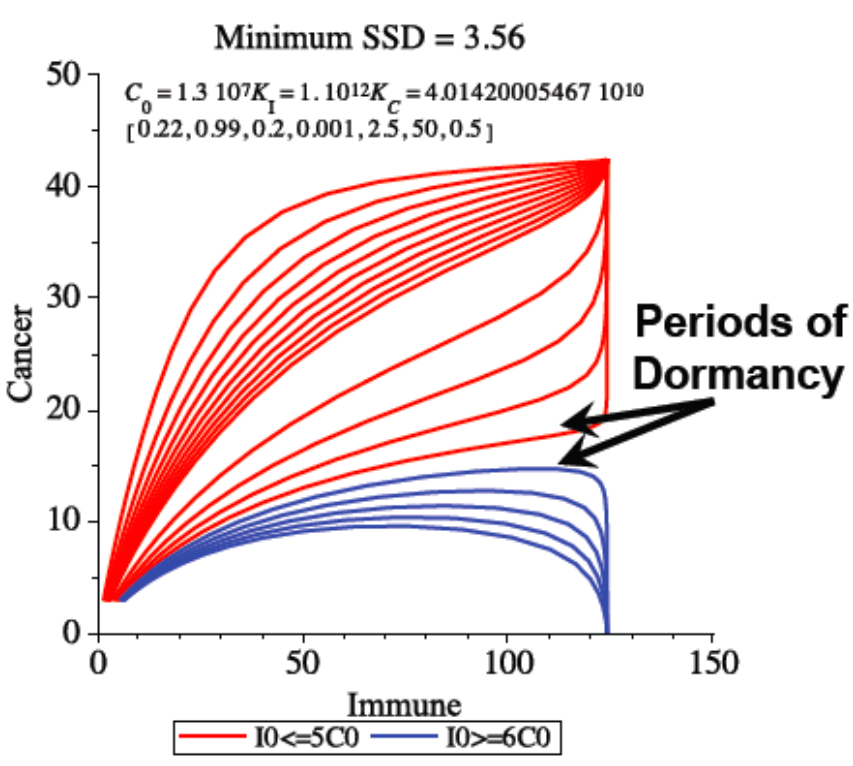
Split 30/35

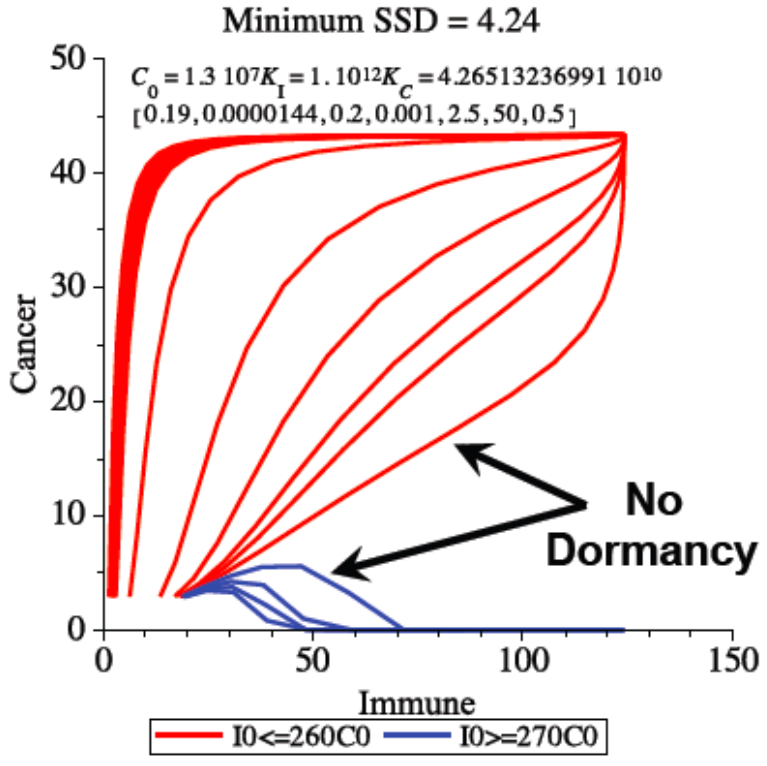


Set 10:

260/270

Dormancy is subject to Variability





Conclusions - Variability

- Variability in tumor growth is inherent and is masked by macroscopic observations
- Generalized Logistic Growth can capture some of this variability
- Physiological sources of this variability may include sensitivity of cancer cells to carrying capacity cues or to the sensitivity of the host to pro / anti-angiogenic cues
- Theoretically, this variability suggests a reason why treatments planned for "average" patients do not work for ALL patients
- Theoretically, this works suggests a limit for effectiveness of treatments even with patient-specific data due to the limitation of macroscopic observations to capture inherent variability

Conclusions - Immunomodulation

- Pro-tumor inflammation may speed the progression of tumors causing a larger tumor burden
- Anti-tumor inflammation may speed the progression of tumors causing a smaller tumor burden
- Should faster tumor progression in the short-term be acceptable if it results in smaller, more controllable masses in the long-term?
- Dormancy is significantly affected by inherent variability, how can we use therapies to maintain a dormant state? Is such a state always obtainable?

Thank You to:

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2nd Annual Workshop on Cancer Systems Biology

Tumor Metronomics:
Timing and Dose Level Dynamics

July 17-20, 2012

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Guest Speaker

Larry Norton, MD - Memorial Sloan-Kettering Cancer Center, USA

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