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Gaming the cancer-immunity cycle by synchronizing the dose schedules

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Key point: Synchronizing and optimizing the chemotherapy and immunotherapy dosing schedules with the underlying periodicity of the cancer-immunity cycle can compensate for lower total dose

PNAS RESEARCH ARTICLE | APPLIED MATHEMATICS MEDICAL SCIENCES

Gaming the cancer–immunity cycle by synchronizing the dose schedules

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Affiliations are included on p. 11.

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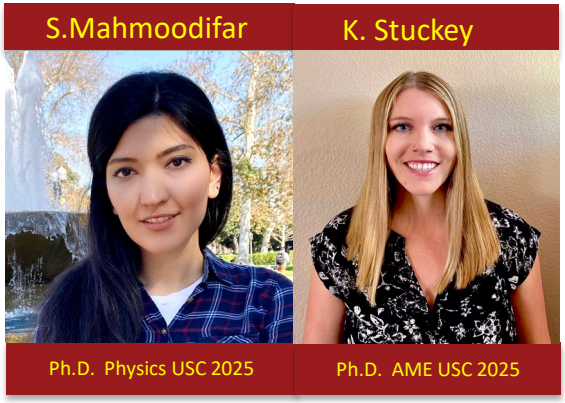
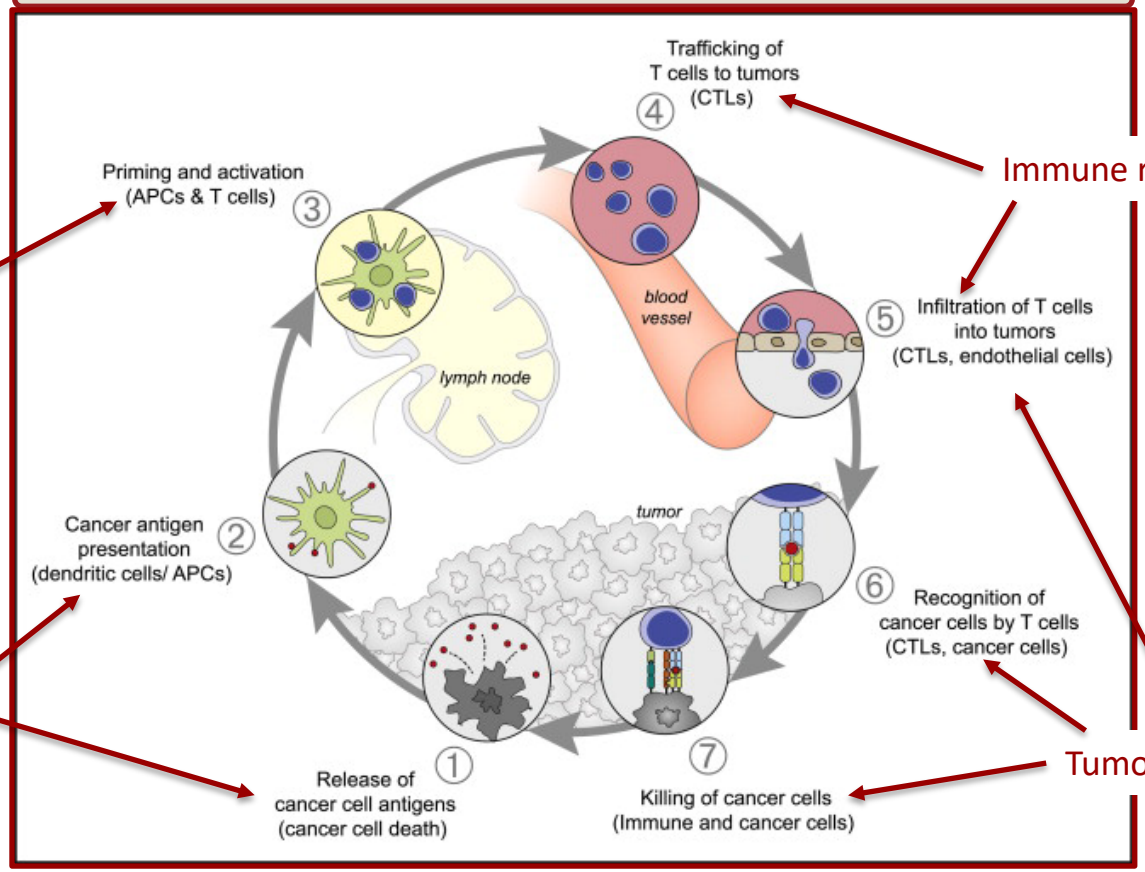


IPAM Workshop: Mathematics of Cancer
Feb 23-27, 2026

The cancer-immunity cycle



Immune response phase

Immune response phase

Tumor growth phase

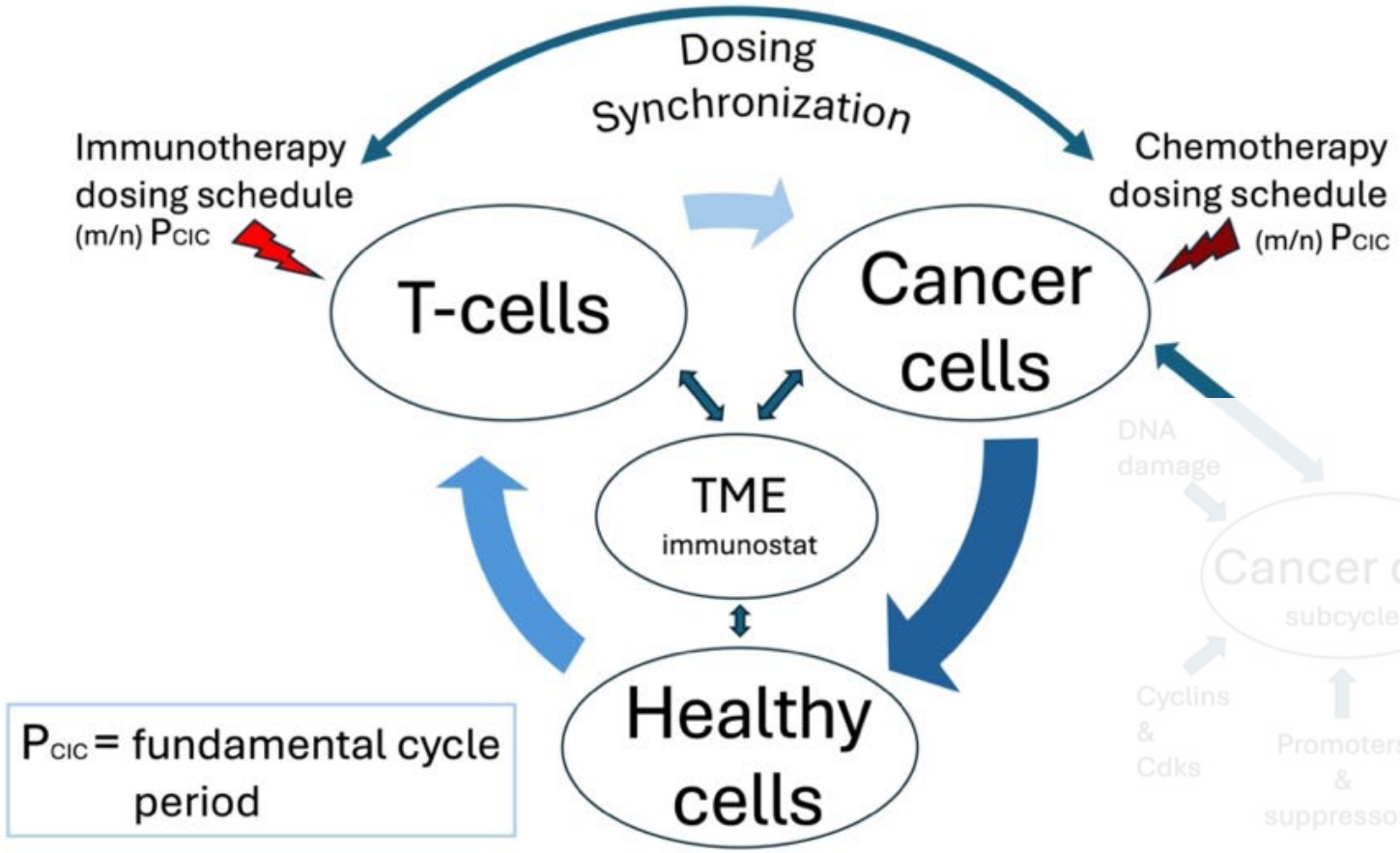
Tumor regression phase

1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activation of T-cells
4. Trafficking of T-cells to tumor
5. Infiltration of T-cells into tumor
6. Recognition of cancer cells by T-cells
7. Killing of cancer cells

Oncology meets immunology: The cancer-immunity cycle, D.S. Chen, I. Mellman, **Immunology** (2013)

The cancer-immunity cycle: Indication, genotype, immunotype I. Mellman, D.S. Chen, , T. Powles, S.J. Turley, **Immunology** (2023)

Key players in the cancer-immunity cycle



The model: Part 1
The evolutionary game & biological mechanisms

$$x_1 + x_2 = 1 \text{ (fractions)} \quad 0 \le V(t) \le K$$
$$0 \le n \le 1$$

Healthy cells

Tumor cells

T-cells

$$\dot{x}_1 = (f_1 - \langle f \rangle) x_1$$
$$\dot{x}_2 = (f_2 - \langle f \rangle) x_2$$
$$\dot{n} = \epsilon n(1 - n) h(x_2; \theta(t)) - S(V(t))$$

Replicator dynamics evolutionary game, frequency-dependent fitness, couples to T-cell eqn through fitness functions

T-cell suppression mechanism that increases with tumor burden and adjusts for how immunogenic the tumor is

immune response timescale

$$h(x_2; \theta(t)) = \theta(t) x_2 - x_1$$

$$x_2 < \frac{1}{1+\theta} \Rightarrow h < 0$$
$$x_2 > \frac{1}{1+\theta} \Rightarrow h > 0$$

Activation threshold

$$A_T = \frac{1}{1+\theta}$$

Immune system growth/decay based on sign of h

$$\dot{V} = (\delta + \alpha_G) V (1 - V/K)$$

Tumor volume growth/decay

Tumor carrying capacity

Growth/regression discrepancy parameter

T-cell suppression

$$S(V(t)) = \phi V(t) / (1 + \lambda I_t(t))$$

$$I_t(t) = 1/(\alpha + \beta \exp(-\gamma t))$$

Immunogenicity function to model immune evasion under selection pressure

$\theta(t)$: Immunotherapy control function

C(t): Chemotherapy control function

Lowers activation threshold (checkpoint blockade immunotherapy)

Imposes selection pressure on cancer cells

The model: Part 2
The payoff matrix A

$$\dot{\vec{x}}_i = \underbrace{[(A\vec{x})_i - (\vec{x}^T A\vec{x})]}_{f_i - \langle f \rangle}\vec{x}_i$$

x_1 (*healthy*)
x_2 (*tumor*)

$$A(n(t)) = [1 - g(n(t); I_t(t)]A_G + g(n(t); I_t(t))A_R$$

growth

regression

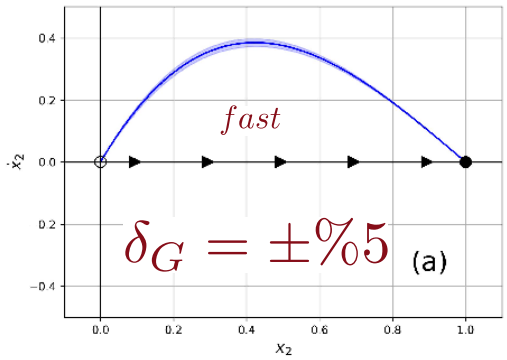
$$g(n; I_t) = \tanh(n(t)/I_t(t))$$

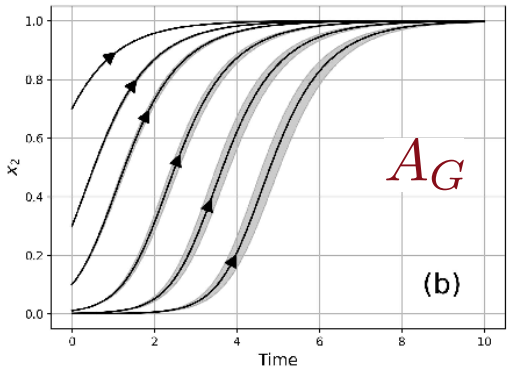
$$A_G = \begin{array}{c} \\ x_1 \\ x_2 \end{array}\begin{array}{c} \begin{array}{cc} x_1 & x_2 \end{array} \\ \begin{pmatrix} 3 & 0 \\ 5 \pm \delta_G & 1 \end{pmatrix} \end{array}$$

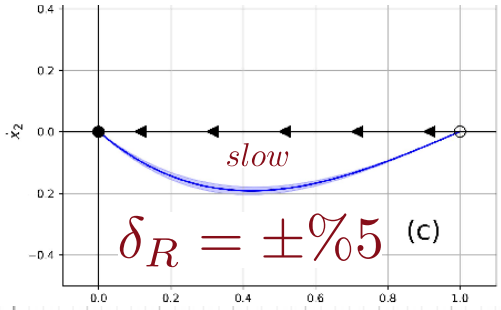
fitness advantage

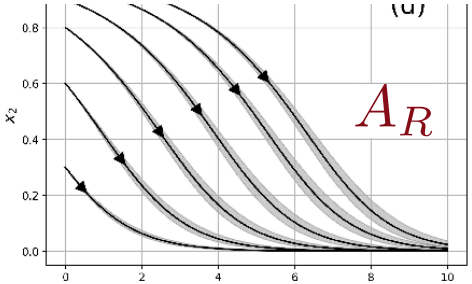
$$A_R = \begin{array}{c} \\ x_1 \\ x_2 \end{array}\begin{array}{c} \begin{array}{cc} x_1 & x_2 \end{array} \\ \begin{pmatrix} 4 & 1/2 \\ 3 \pm \delta_R & 0 \end{pmatrix} \end{array}$$

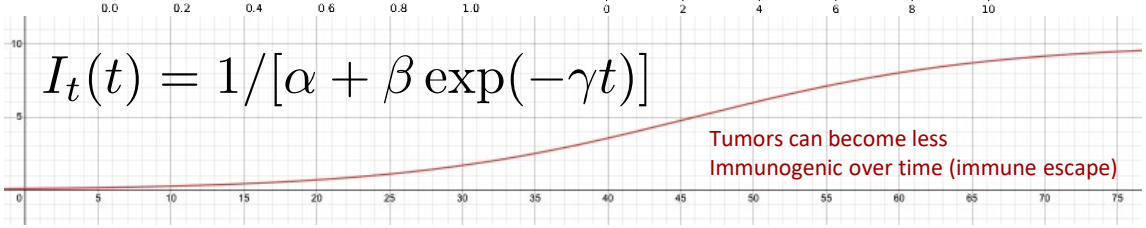
reduced fitness

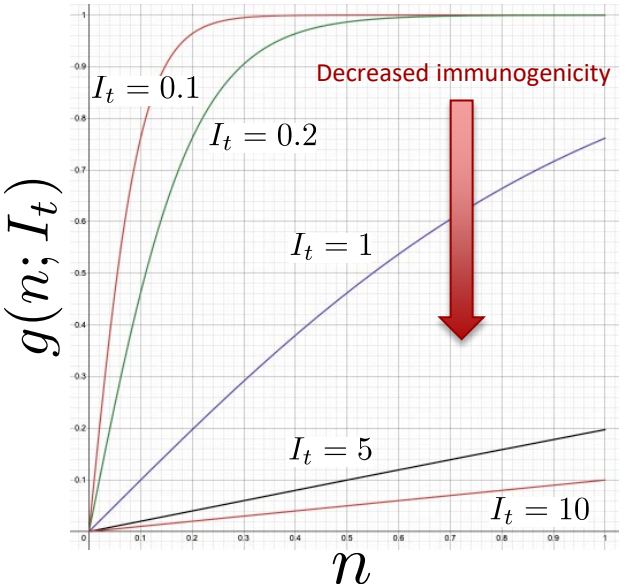




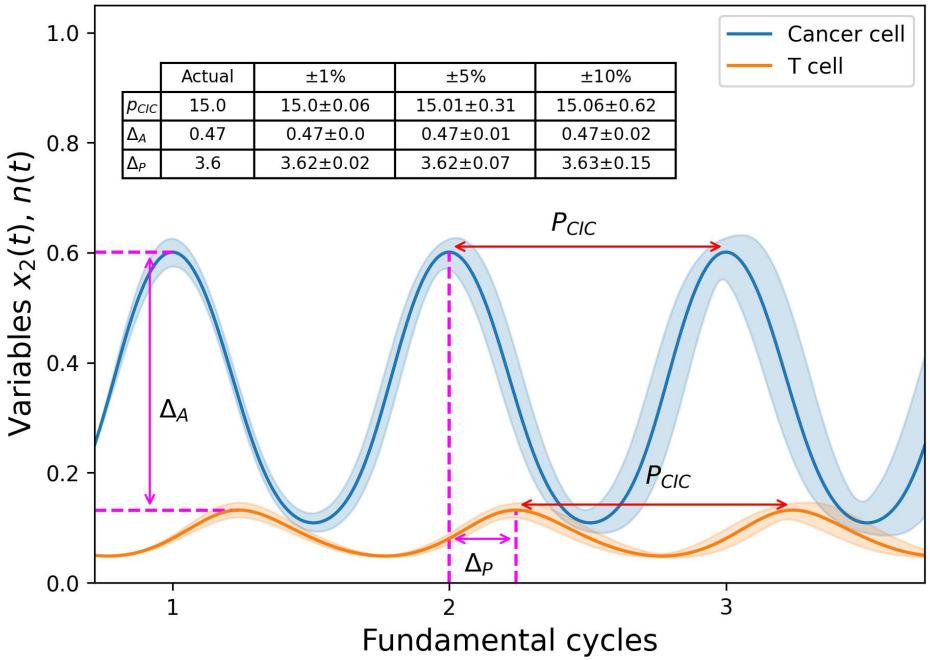


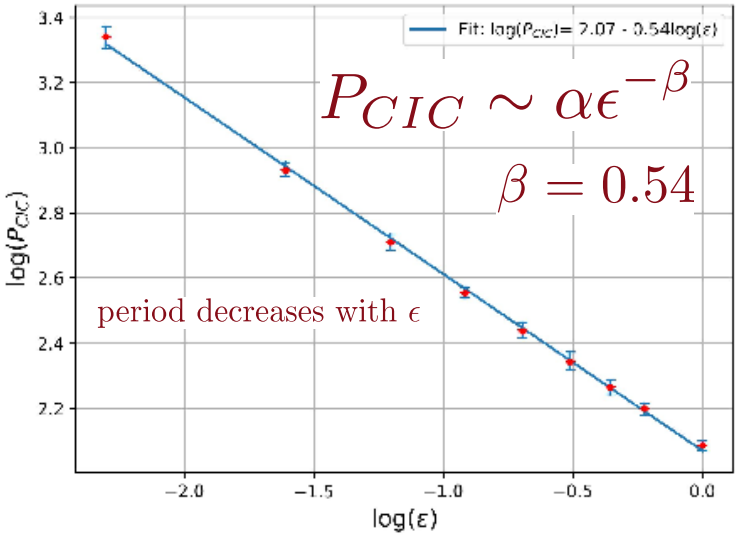


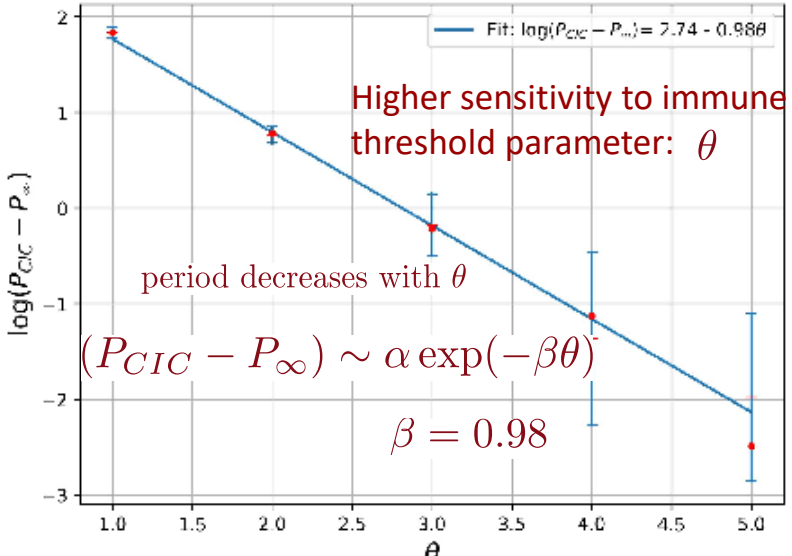




The fundamental cycle: results from the interplay of positive and negative feedback mechanisms







δ growth/regression discrepancy parameter

Volumetric growth

Kuznetsov et. al. 1994

$$V(mP) = \frac{1}{\left[\left(\frac{1}{V_0} - \frac{1}{K} \right) \exp\left(- \int_0^{mP} (\delta + \alpha_G) dt \right) + \frac{1}{K} \right]}$$

Questions we address

1. Do chemotherapy and immunotherapy schedules commute?
2. Is it better to combine chemotherapy and immunotherapy dose schedules sequentially or concomitantly?
3. When is the optimal time to start/stop immunotherapy treatment?
4. What is the benefit of using more complicated time-varying dosing schedules compared to pulse-dosing protocols?

Cocktails for cancer with a measure of immunotherapy
H. Ledford, **Nature** 532 (2016)

Dose combinations

What, why, where, and when: Bringing timing to immuno-oncology
A.M. Rothschilds, K. Dane Wittrup, Trends in **Immunology** (2018)

Dose timing

The model: Part 3
Control theory

$$\vec{x}(t) = (x_1(t), x_2(t), n(t))$$ *(system response variables)*

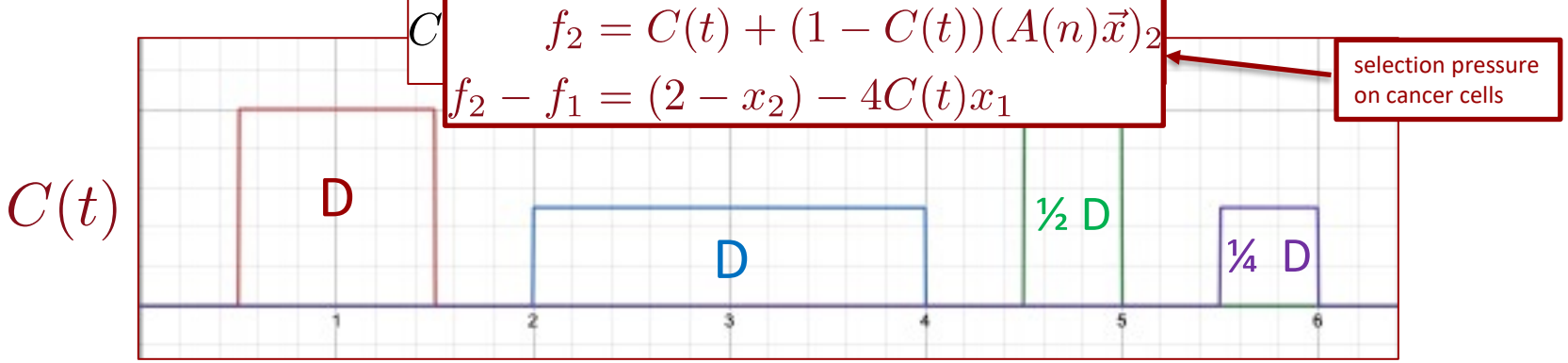
$$\vec{u}(t) = (C(t), \theta(t))$$ *(controls)*

$$0 \le C \le 1$$
$$2 \le \theta \le 5$$

$$f_1 = (A(n))\vec{x})_1$$
$$f_2 = C(t) + (1 - C(t))(A(n)\vec{x})_2$$
$$f_2 - f_1 = (2 - x_2) - 4C(t)x_1$$

selection pressure on cancer cells

Chemo pulse-dosing

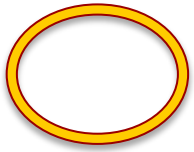


$$C(t) = (\frac{m}{n})P_{CIC}$$
$$m, n = 1, 2, 3, 4$$

b_1=0.01
b_2=0.01

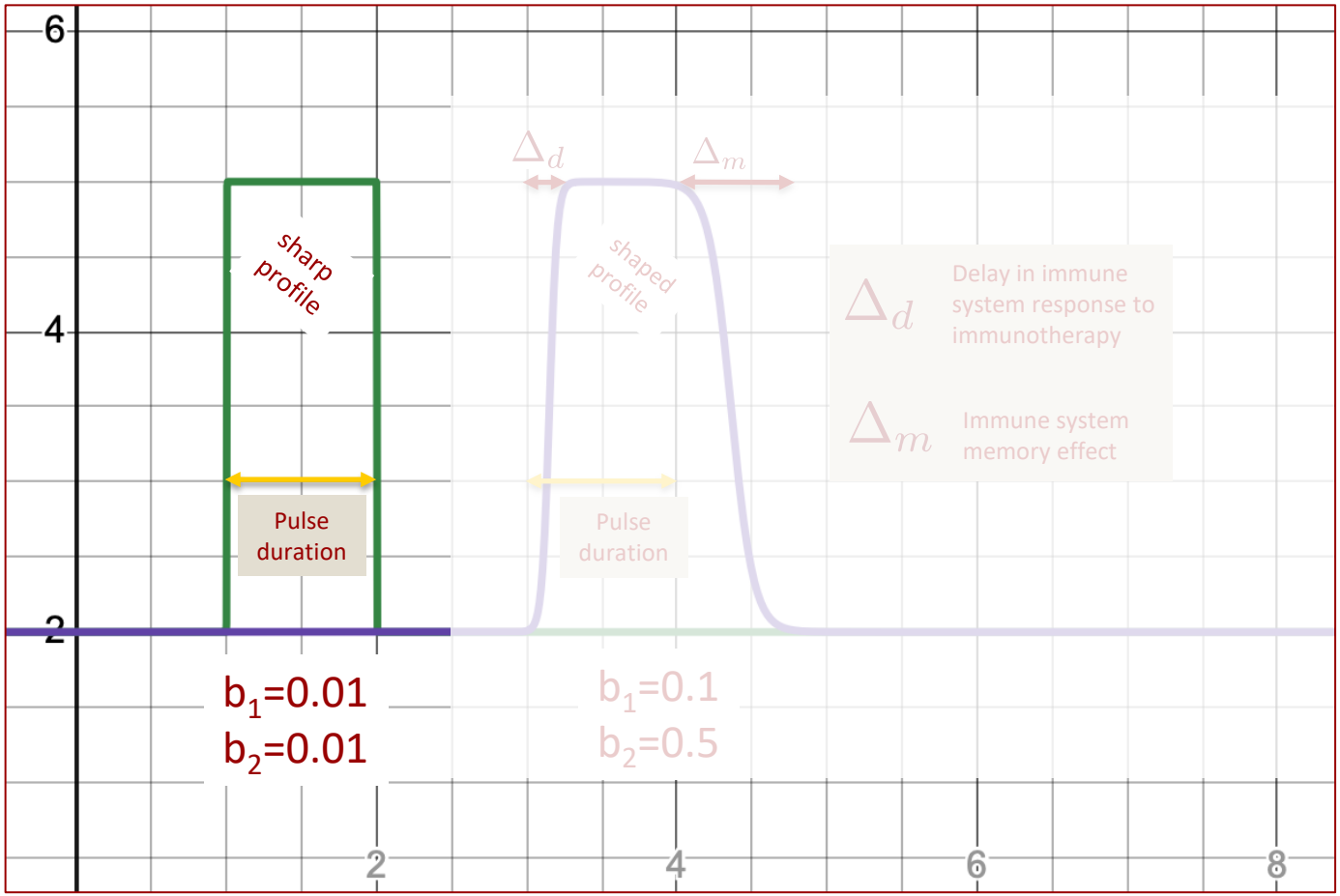
Begin chemotherapy at peak of cancer cell level when immune response begins to rise

Begin at peak
¼ pulse



Begin at trough

Immuno-pulse dosing

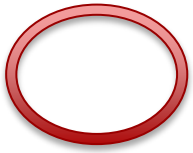


$$\theta_{eff}(t) = \frac{3}{2}[\tanh(\frac{t-a_1}{b_1}) - \tanh(\frac{t-a_2}{b_2})] + 2$$

Immuno-pulse dosing

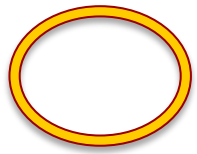
$$\theta_{eff}(t) = \frac{3}{2}[\tanh(\frac{t-a_1}{b_1}) - \tanh(\frac{t-a_2}{b_2})] + 2$$

Begin at peak
¼ pulse



Begin immunotherapy at cancer cell trough when immune system level is in decline

Begin at trough
½ pulse



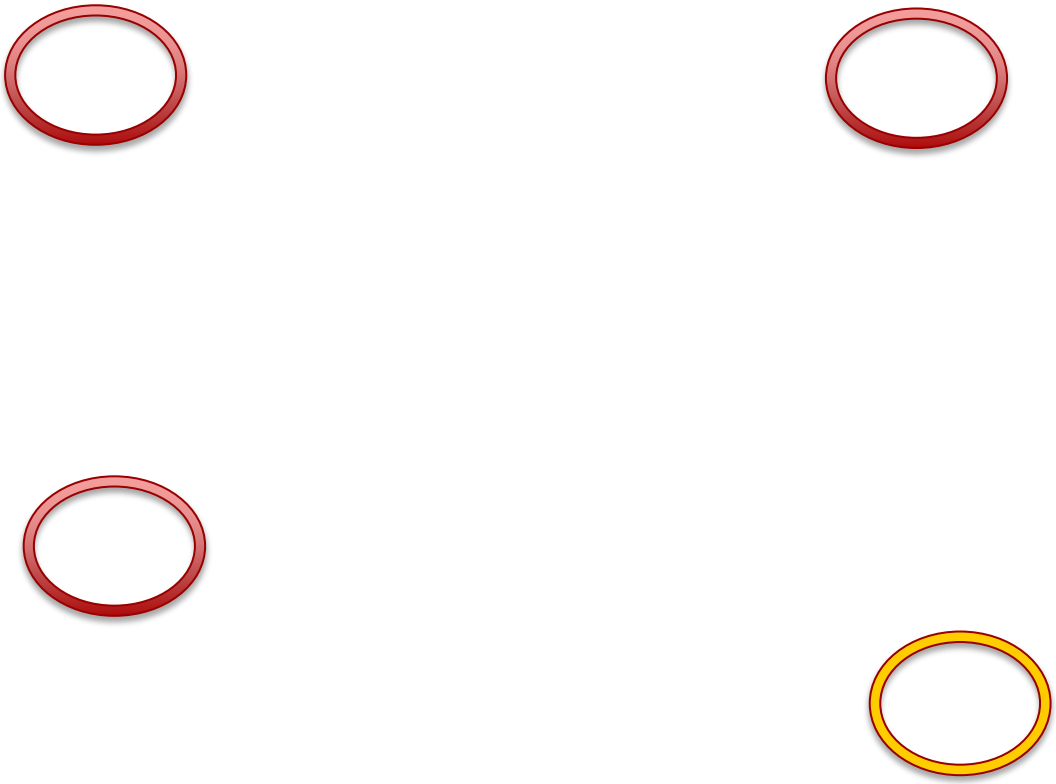
Multi-pulse sequential therapy

Sequential pulse-therapies do not commute

Why?

The system response to the first immuno-pulse is different from the first chemo-pulse

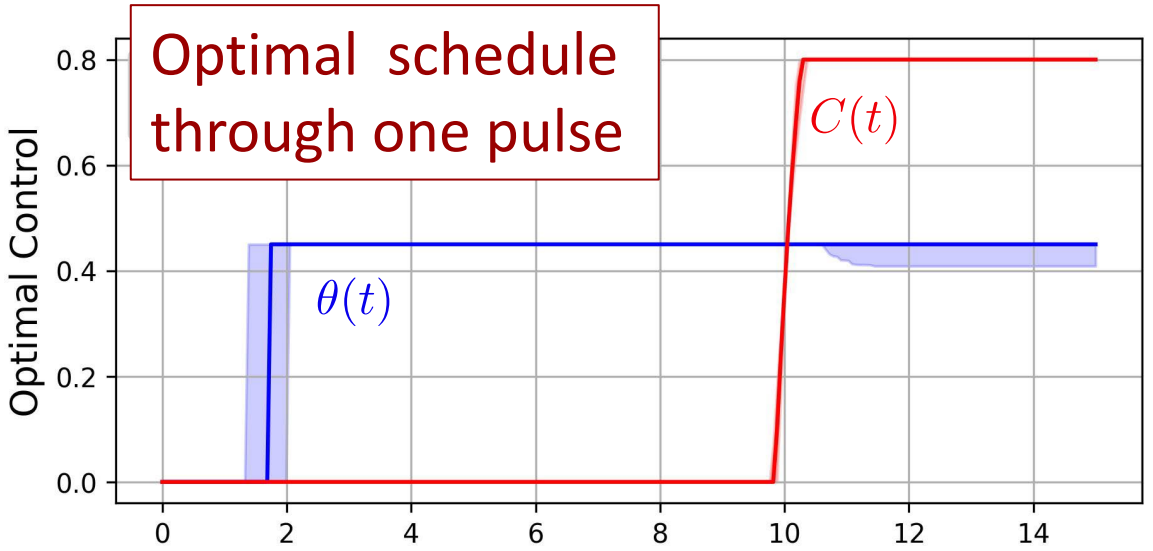
Concomitant pulse therapy

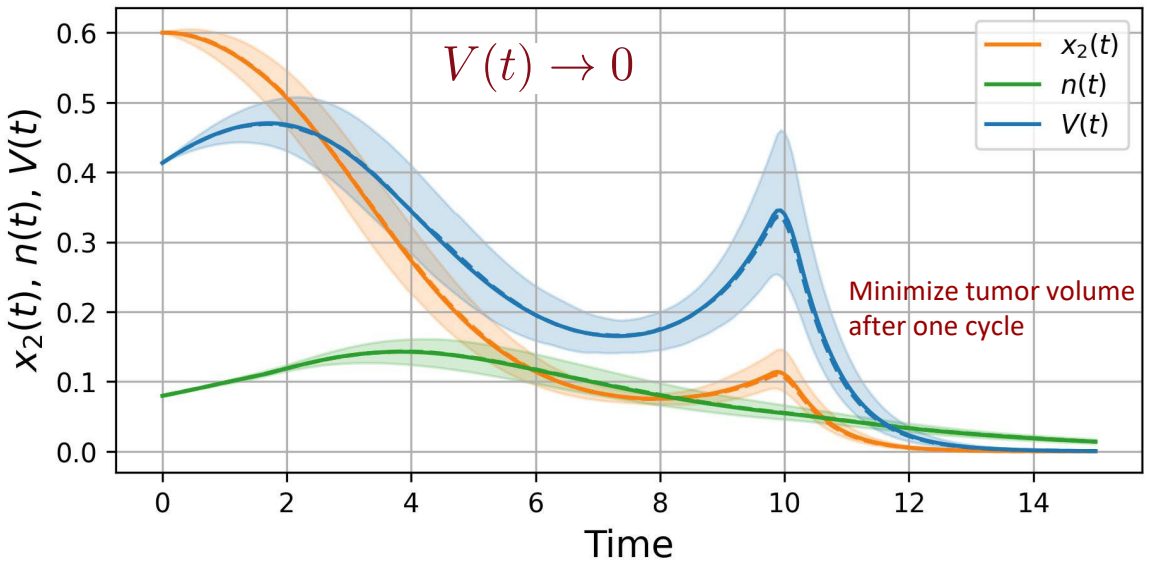


¼ pulse chemotherapy
½ pulse immunotherapy
Both start at trough

Optimized therapy

Immunotherapy should precede chemotherapy and pulse should be (roughly) twice as long



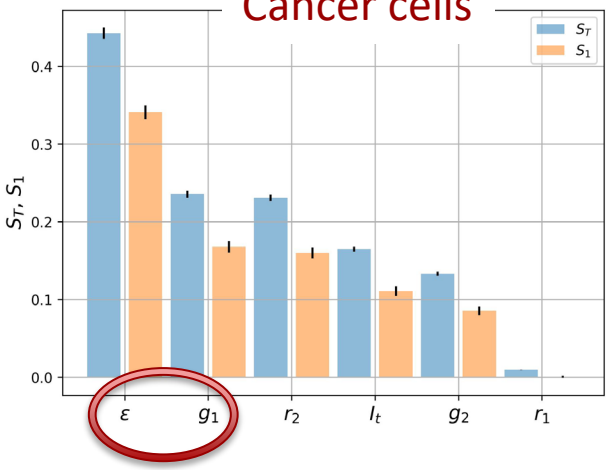


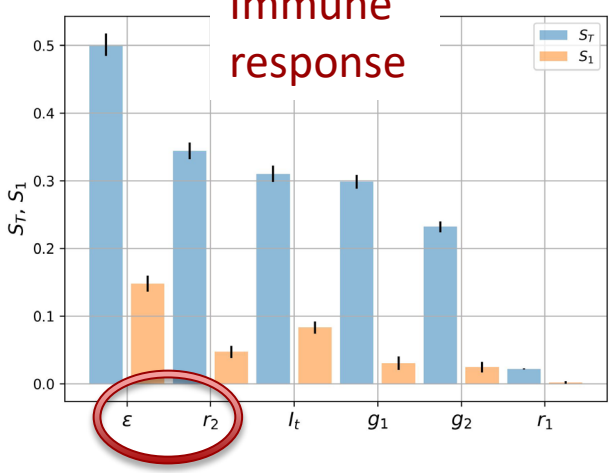
Optimizing

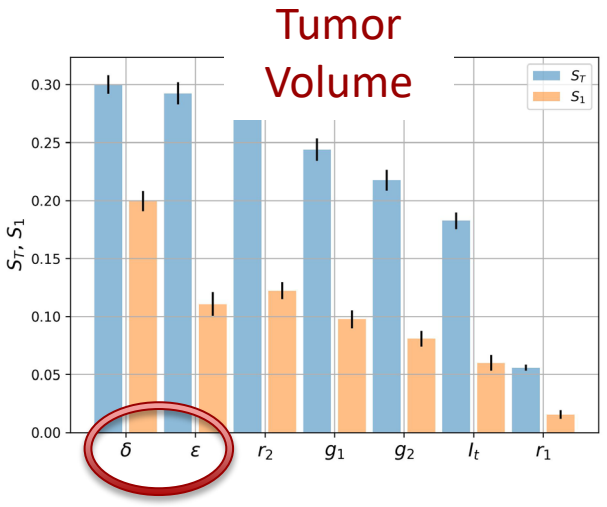
$$J = \underbrace{\int_0^t \mathcal{L}(\vec{x}(t), n(t); \vec{u}(t), V(t), t))dt}_{\text{Running cost}} + \underbrace{\varphi(\vec{x}(t), n(t); \vec{u}(t), V(t))}_{\text{End cost}}$$

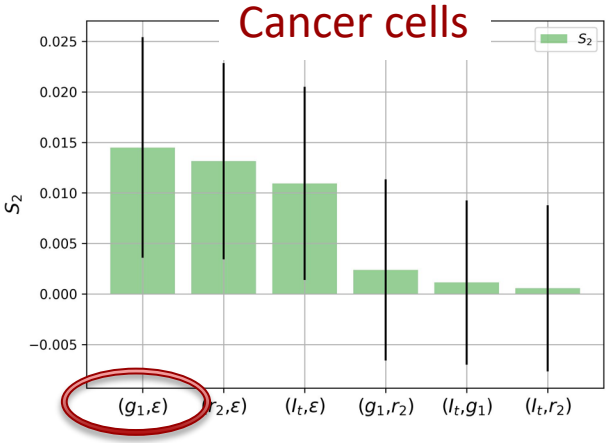
Sensitivity analysis: Sobol indices

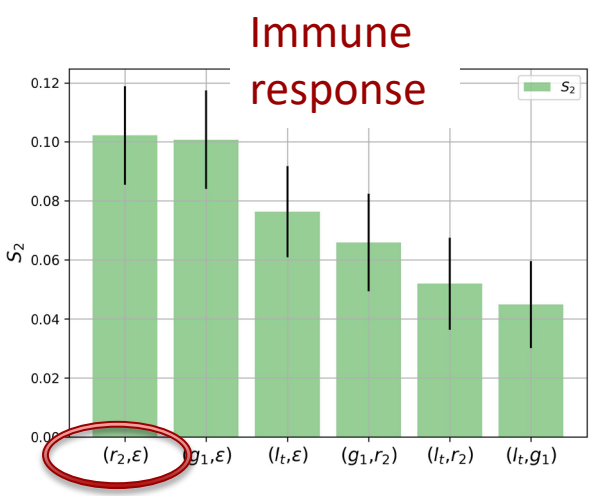
- Variance based UQ method that decomposes output variance into components based on variances of each parameter
- Parameters are sampled stochastically with uniform random distributions

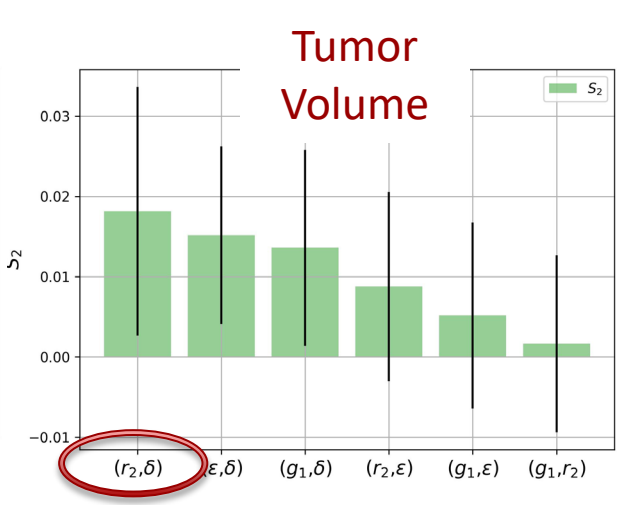




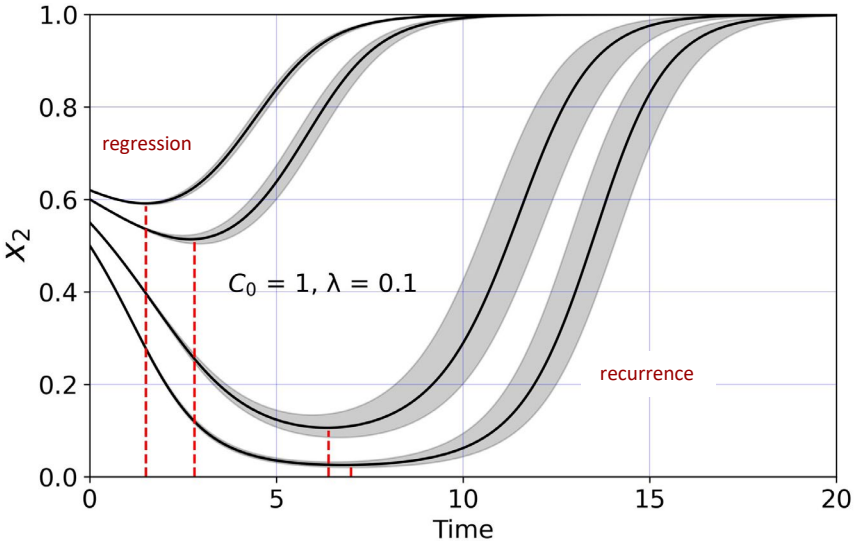






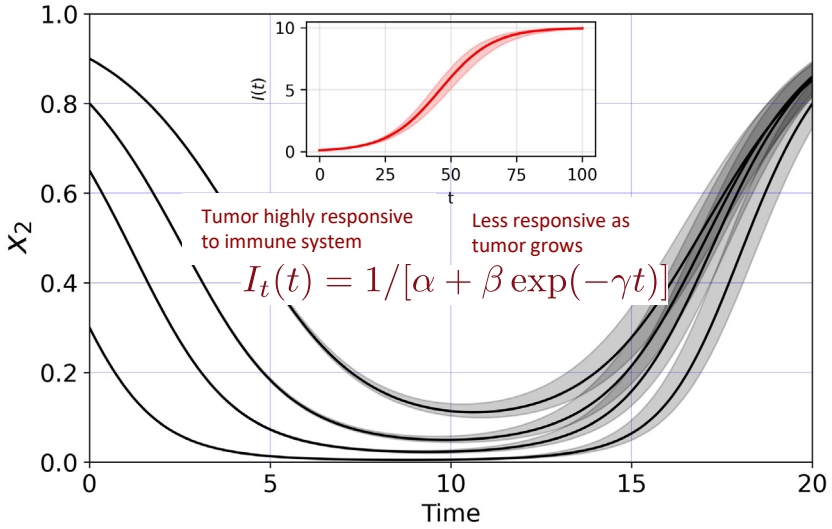


Three additional important biological mechanisms in the model



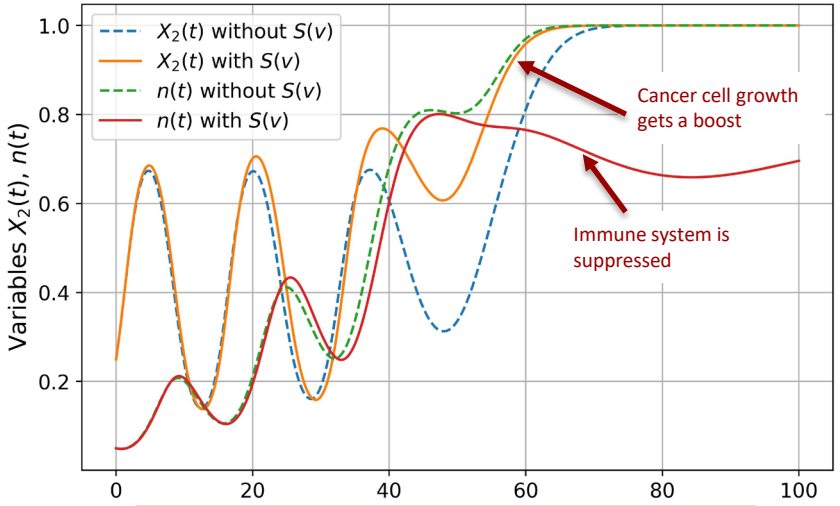
Chemo-resistance over longer timescales

$$C(t) = C_0(t)\exp(-\lambda t)$$



Tumor immunogenicity allowing for immune evasion as tumor matures

$$S(V(t); I_t(t)) = \sigma V(t)/(1 + \lambda I_t(t))$$



Immune suppression as a mechanism for immune evasion

Timing trials are beginning…

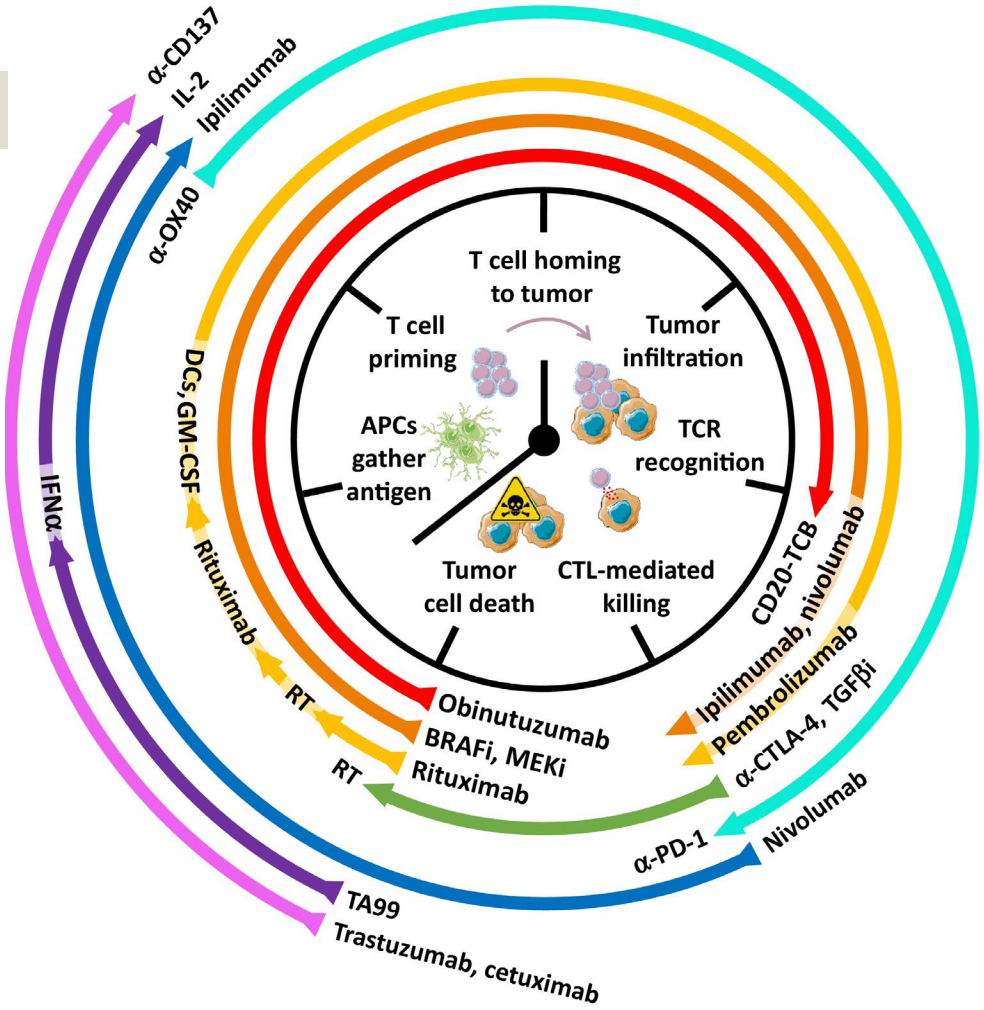
Impact of timing on treatment outcomes

What, Why, Where, and When: Bringing Timing to Immuno-Oncology
A.M. Rothschilds, K. Dane Wittrup, Trends in **Immunology** (2018)

Temporally programmed CD8+ DC activation enhances combination cancer immunotherapy
A. Tzeng,…, K. Dane Wittrup, **Cell Reports** (2016)

Order of administration of combination cytokine therapies can decouple toxicity from efficacy in syngeneic mouse tumor models
A.M. Rothschilds,…, K. Dane Wittrup, **Oncoimmunology** (2019)

SECOMBIT: The best sequential approach with combo immunotherapy and combo target therapy in patients with BRAF mutated metastatic melanoma: A phase II randomized study,
P.A. Ascierto,…, **Annals of Oncology** (2021)



Important model ingredients

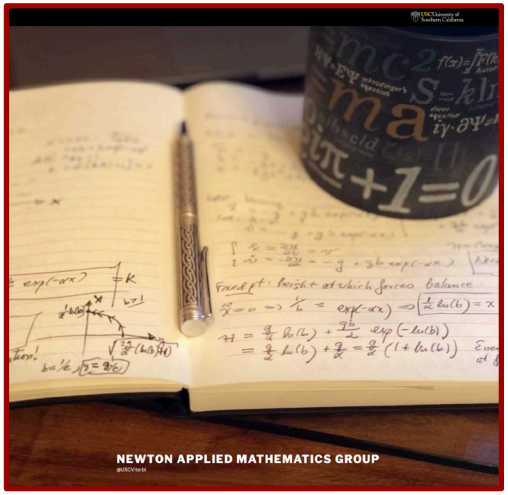
1. Cancer cells – healthy cells: replicator dynamics
2. Cyclic process
3. Stochastic parameter variation
4. Immune evasion mechanisms
5. Immune suppression mechanisms
6. Immune activation threshold
7. Immunotherapy delay response
8. Immunotherapy memory response
9. Chemo-resistance mechanisms
10. Chemotherapy and immunotherapy time-dependent control knobs
11. Single pulse and multi-pulse dosing
12. Optimized dosing

Conclusions:

Lot's more to learn from this model!

thank you

(newton.usc.edu)



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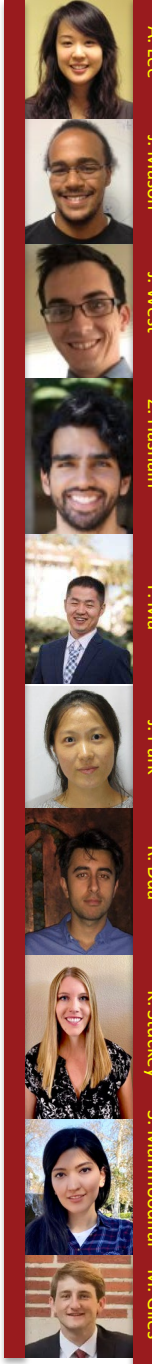
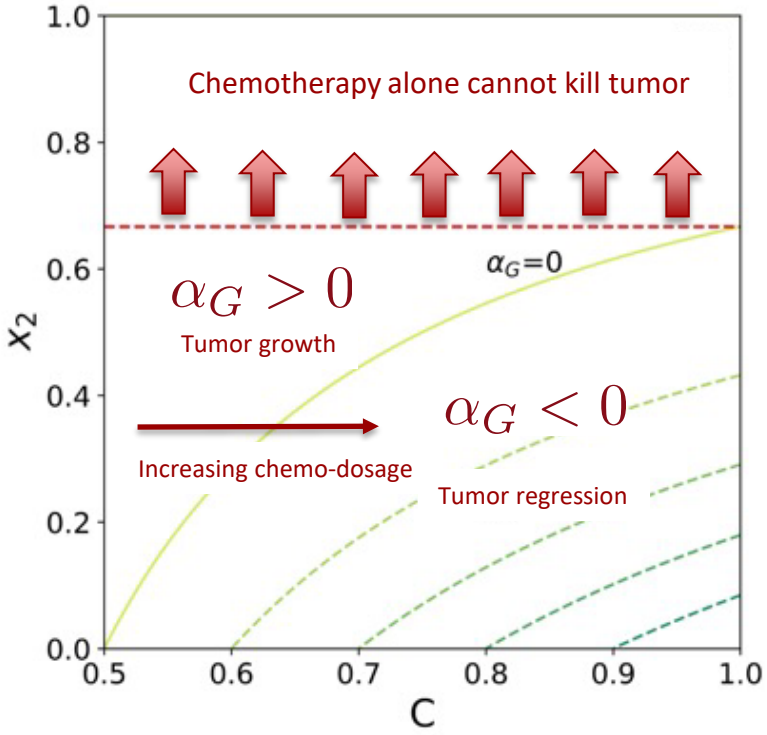
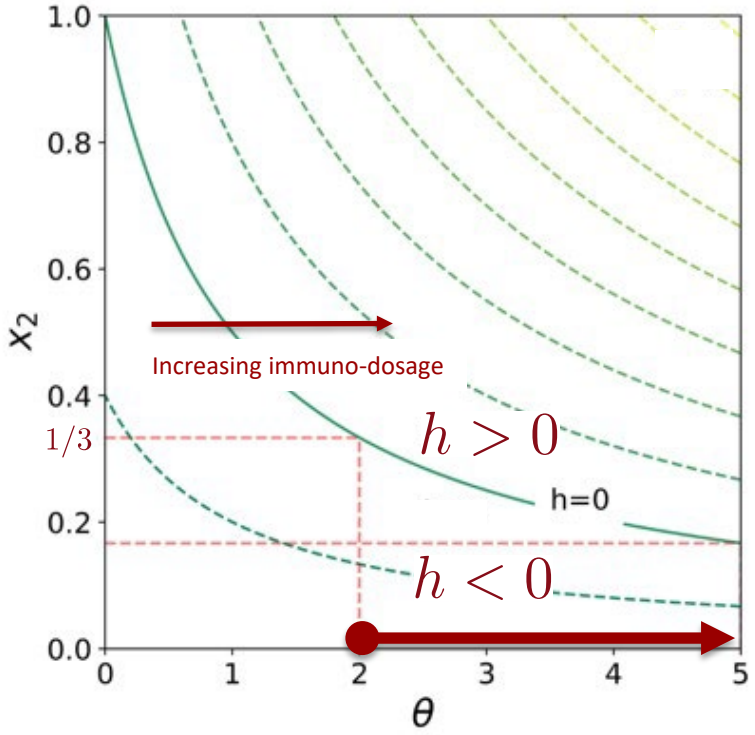


The model: Part 3
Control thresholds

$$\alpha_G \equiv f_2 - \langle f \rangle$$

$$x_2 = \frac{1}{1+\theta}$$





Chemotherapy thresholds

Immunotherapy thresholds

Fitting and forecasting challenges

Fitting parameters:

1. ϵ Immune response timescale
2. δ Volumetric growth/regression discrepancy parameter
3. δ_G Tumor growth timescale (payoff matrix)
4. δ_R Tumor regression timescale (payoff matrix)
5. σ Immune suppression strength
6. A_T Immune activation threshold
7. K Tumor carrying capacity

Key immune cycle timescale parameters:

1. Tumor growth/immune timescale ratio
2. P_{CIC} parameters