Mathematical challenges in the treatment of cancer.

Ami Radunskaya, Pomona College
Claremont Colleges, Claremont, California

MathFest2010
Pittsburgh - PA

August 6, 2010


MODEL INSTITUTIONS FOR EXCELLENCE PROGRAM
SPELMAN COLLEGE
NASA


WASHINGTON STATE
XXL
COUGAR ATHLETIC

Cancer Modeling is a Huge Field

2006 Falconer Lecture

Trachette Jackson:

"Cancer Modeling: From the Classical to the Contemporary"

Outline

Doctors **DO** read

- in their spare time!

M.O.M.

Charles Wiseman, M.D.
Los Angeles Institute of Oncology
St. Vincent's Hospital

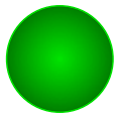
A tale of cooperation

Lisette dePillis

And so many more!

Dann Mallet	Kathe Todd-Brown
Seema Nanda	Allison Wise
Weiquing Gu	Hana Ueda
Shari Pilon-Thomas	Megan Hunter
Sarah Hook	Chris DuBois
Kasia Resniak	Sam Antill
Angela Gallegos	Rob Donnelly
Minaya Villasana	Liz Howe
	Chris DeBoever
	Helen Wu
	Katherine Belsky
	Ryan Handoko

What they learned in Medical School



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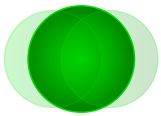

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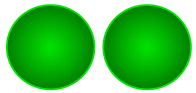

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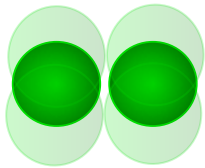

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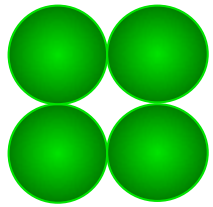

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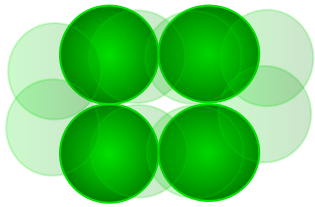

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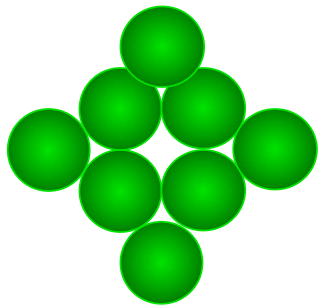

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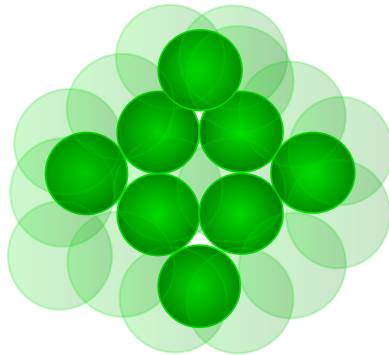

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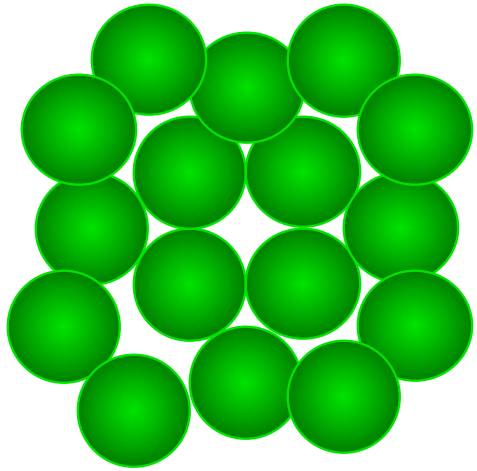
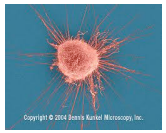


What they learned in Medical School

After k doublings: 2^k cells.

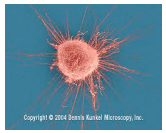
Implications of exponential growth:

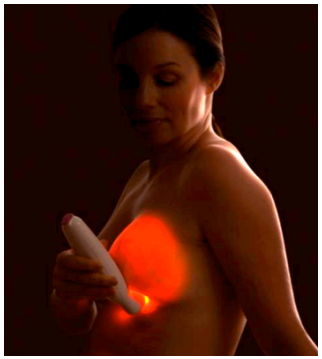
- If we start with one cell:



Implications of exponential growth:

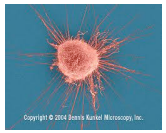
- If we start with one cell:
- then it takes 44 days to detect a 7mm tumor

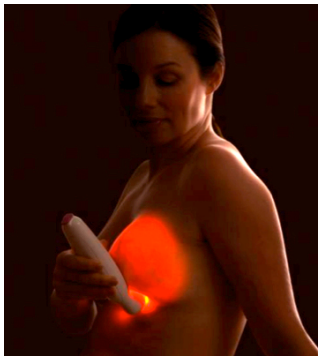




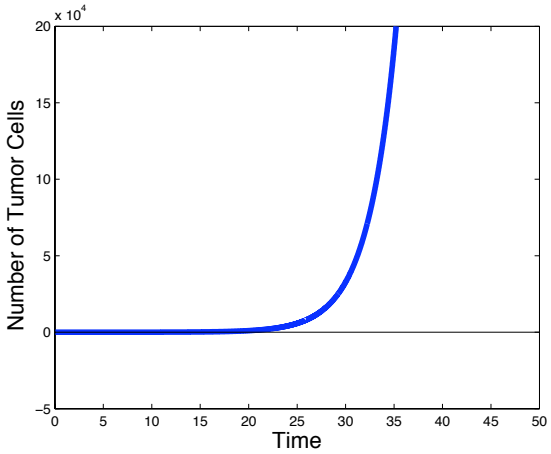
Implications of exponential growth:

- If we start with one cell:
- then it takes 44 days to detect a 7mm tumor
- and after 98 days the tumor will be the size of a beach ball





Exponential growth is not consistent with clinical observations



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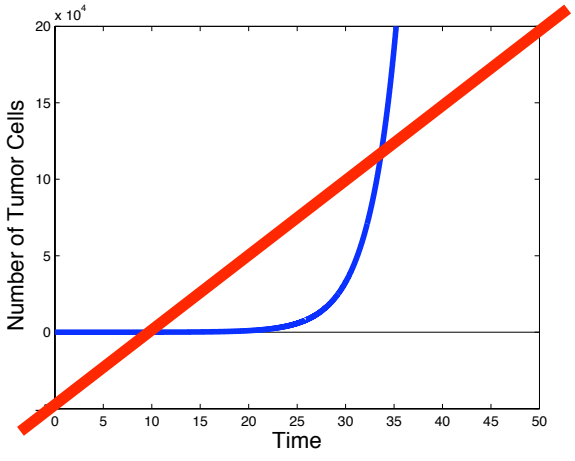

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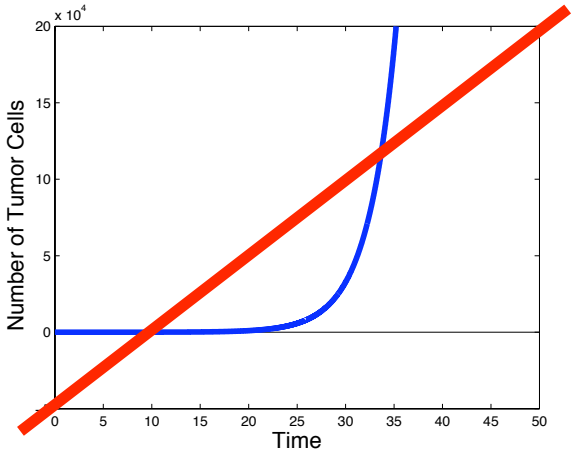

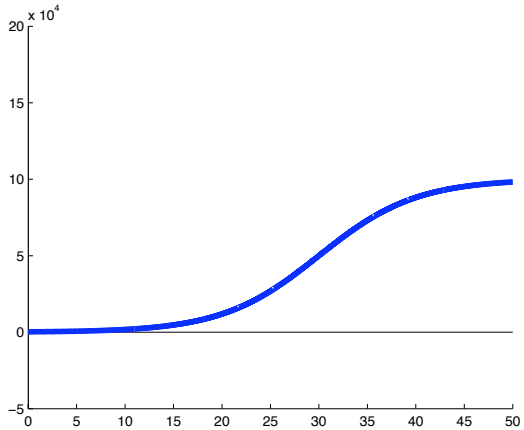

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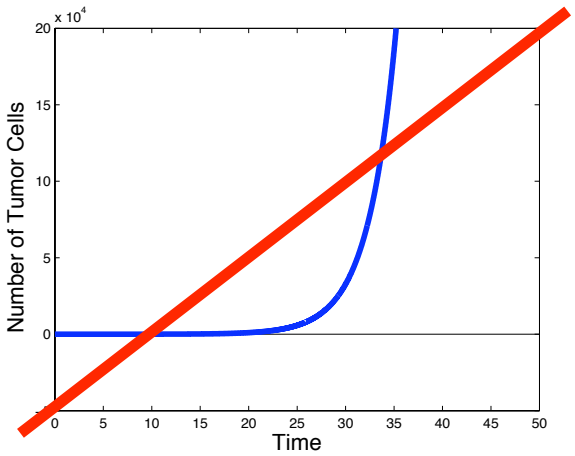

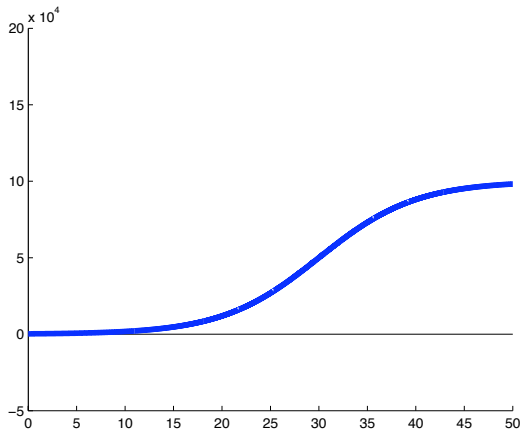

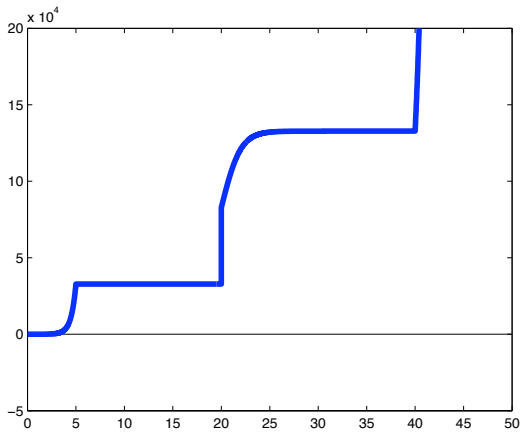

Predator-Prey Models

Example: The Canada Lynx and the Snow Hare

Equations:

$$\frac{dS}{dt} = rS(1-S) - c_1 SC$$

$$\frac{dC}{dt} = -dC + c_2 SC$$

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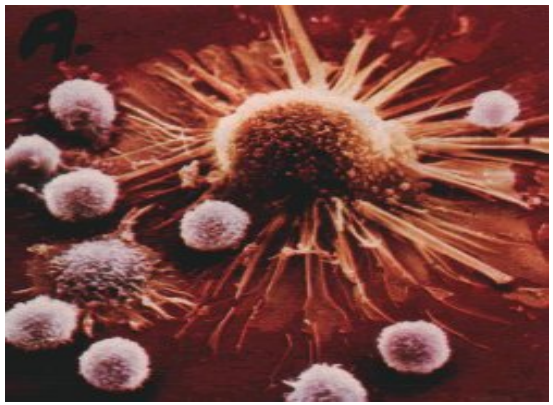
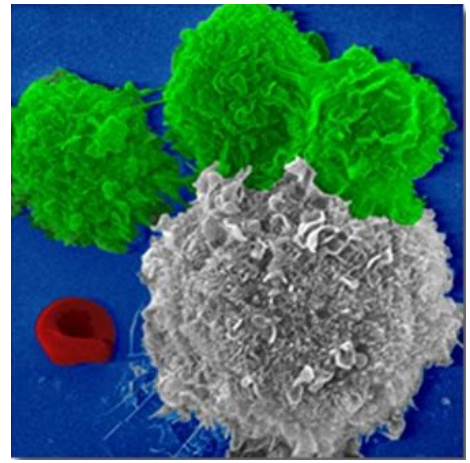
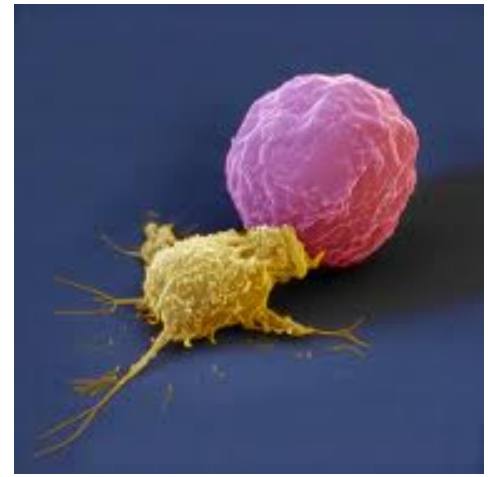
Predator-Prey Models

The predators in the immune system are the cytotoxic T-cells [1]





and the Natural Killer cells [2].



[1] http://www.alkalizeforhealth.net

[2] Prof. Dr. Rupert Handgretinger

A model of tumor-immune interactions

T: Tumor Cells

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N: Natural Killer Cells (innate response)

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$$\begin{aligned} \frac{dT}{dt} &= g_T(T) - c_N(T,N) - c_L(T,L) \\ \frac{dN}{dt} &= g_N(N) - c_{TN}(T,N) \end{aligned}$$

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The simplest interaction terms are of the form:

Power Kill Term

$$c_N(T,N) = kNT \quad \text{or} \quad kN^pT.$$

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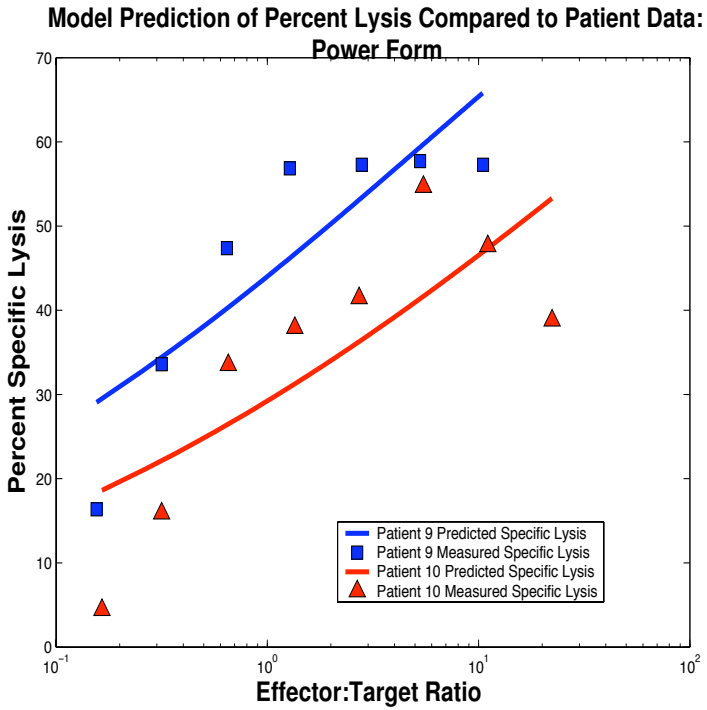
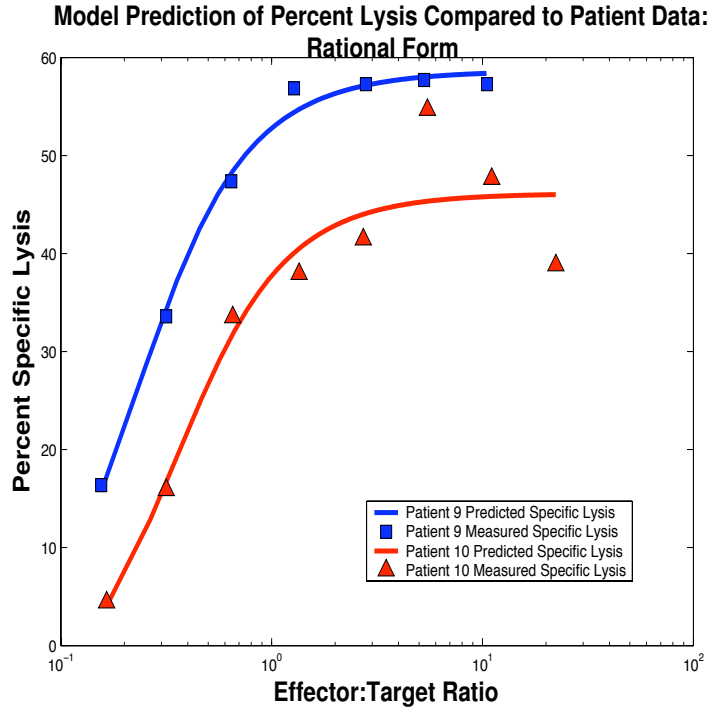
A power kill term could not be reconciled with data involving CTL's.

Comparison with data: patients [3]





$$\leftarrow C_L(T, L) = kTL^p$$

[3] Dudley et al. *Science* (2002); Graphs from dePillis, Radunskaya and Wiseman *Cancer Research* (2005)

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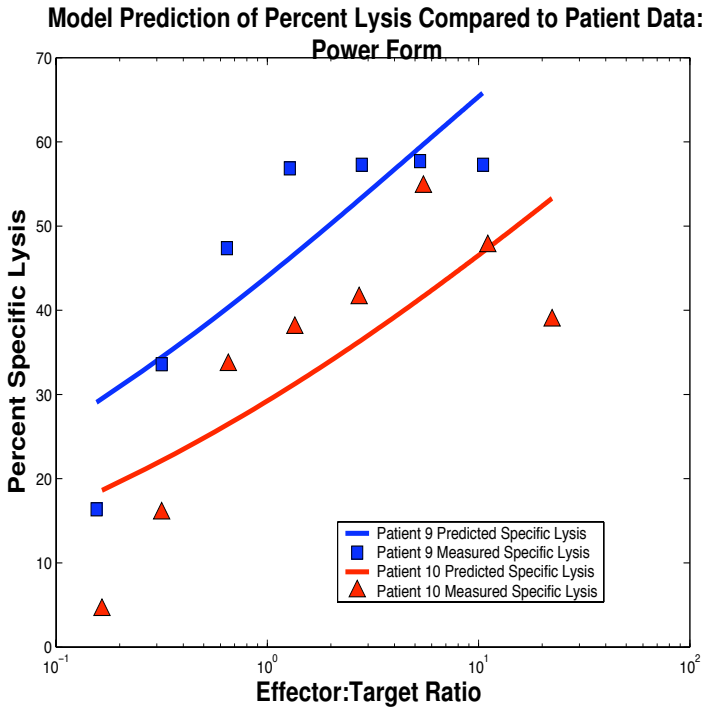

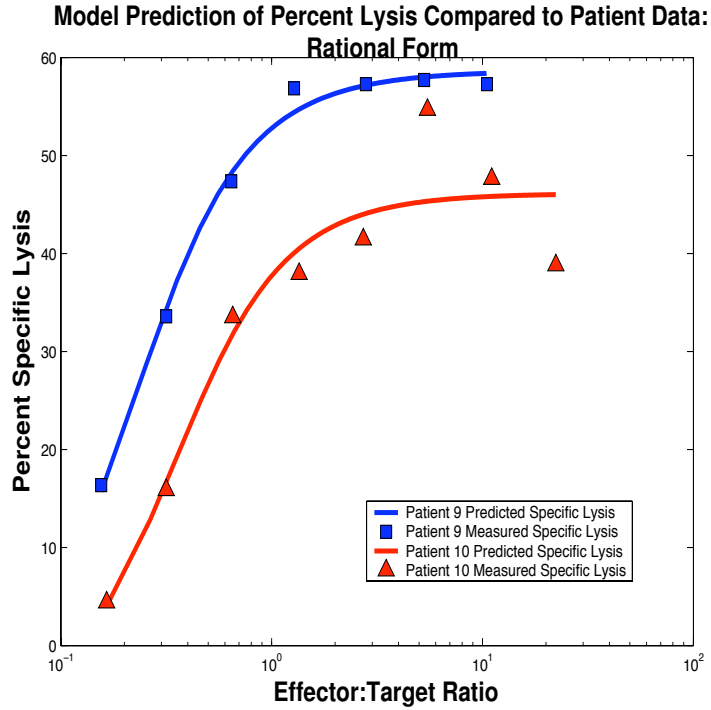

$$C_L(T,L) = \frac{k(L/T)^p}{s+(L/T)^p.} \rightarrow$$

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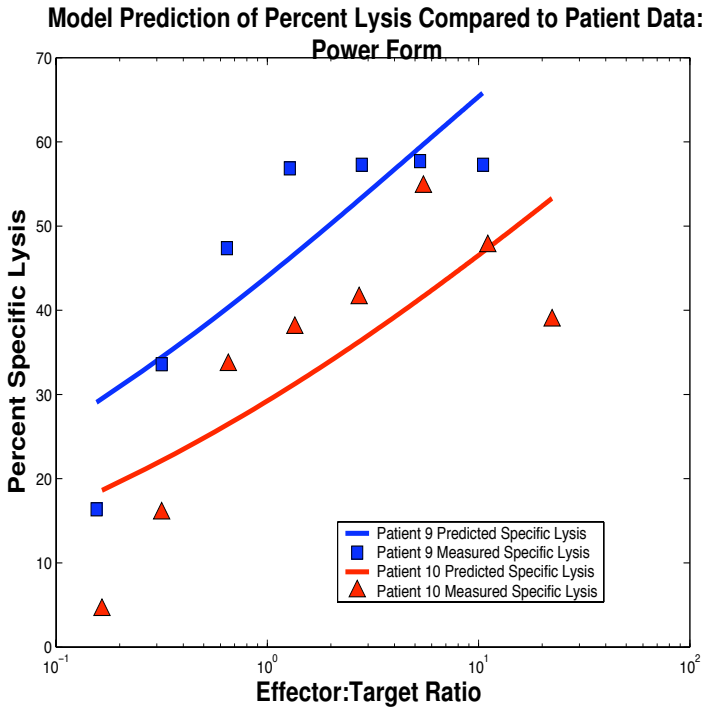

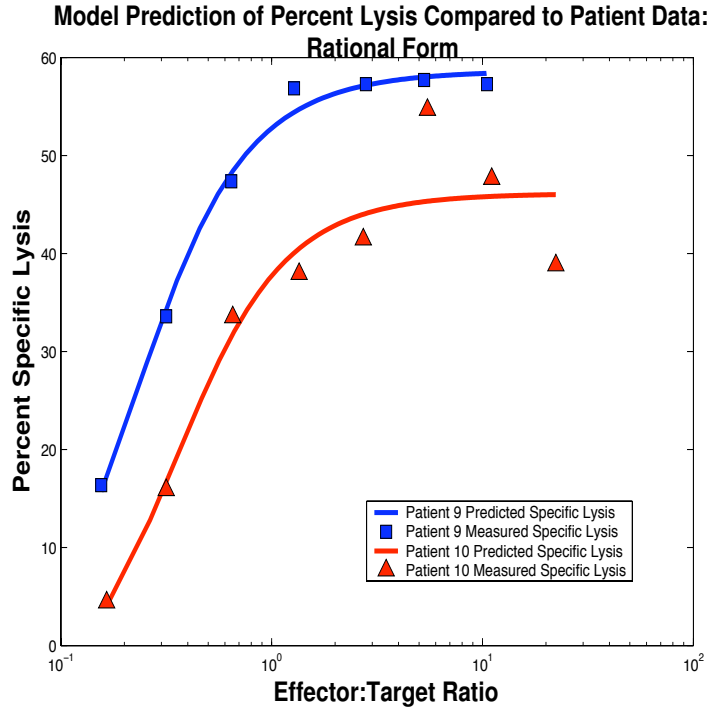

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Conclusion: The kill rates by activated, antigen specific cytotoxic immune cells obey a *ratio-dependent* law.

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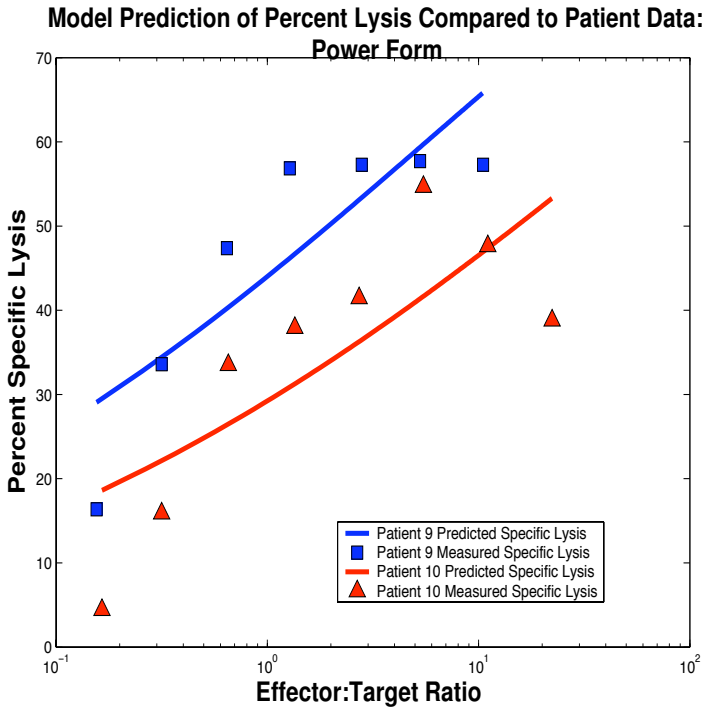

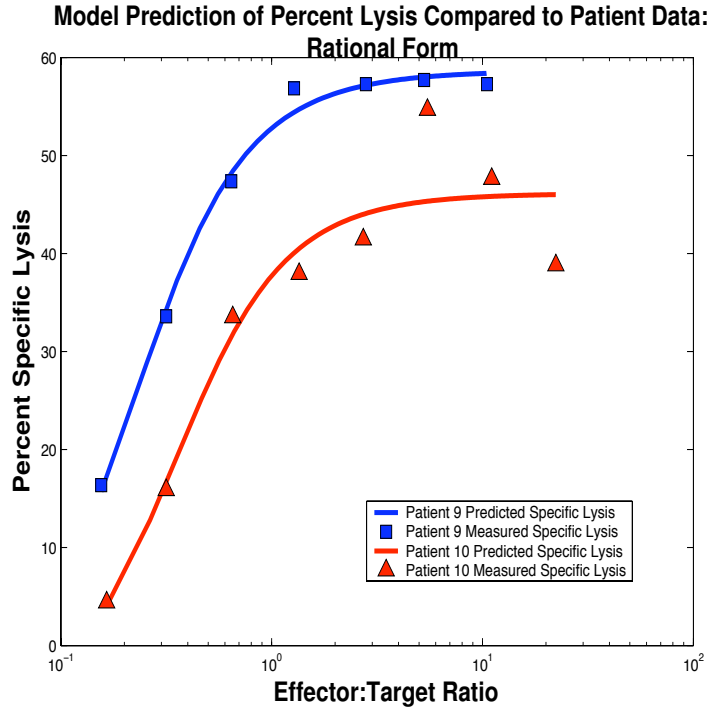

$$C_L(T,L) = \frac{k(L/T)^p}{s+(L/T)^p.}$$

Dr. Wiseman calls this the **dePillis-Radunskaya Law**

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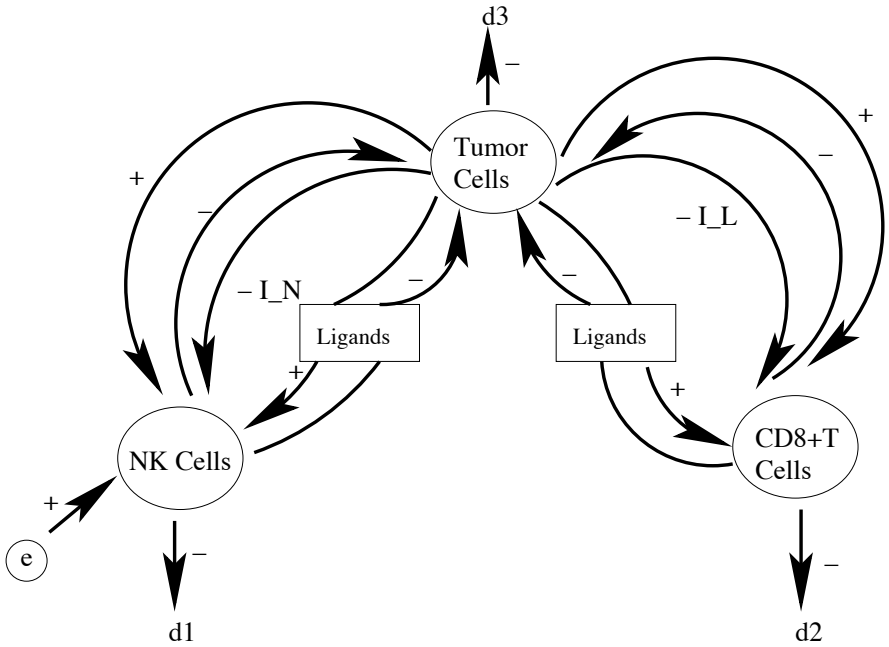
Population model with the dePillis-Radunskaya Law



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

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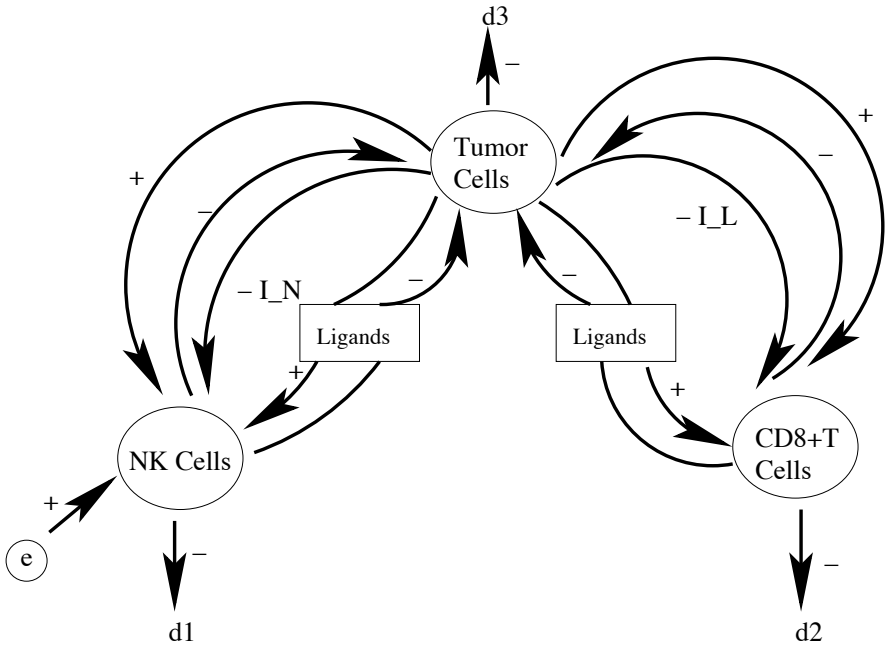
$$\frac{dL}{dt} = -mL + \frac{jD^2}{k+D^2}L - qLT + rNT$$

where $D = d\dfrac{\frac{L^p}{T}}{s+\frac{L^p}{T}}T.$

NOTE: The functional forms of the lysis terms distinguish NK -cells from CD8+ tumor specific cells.

Population model with the dePillis-Radunskaya Law



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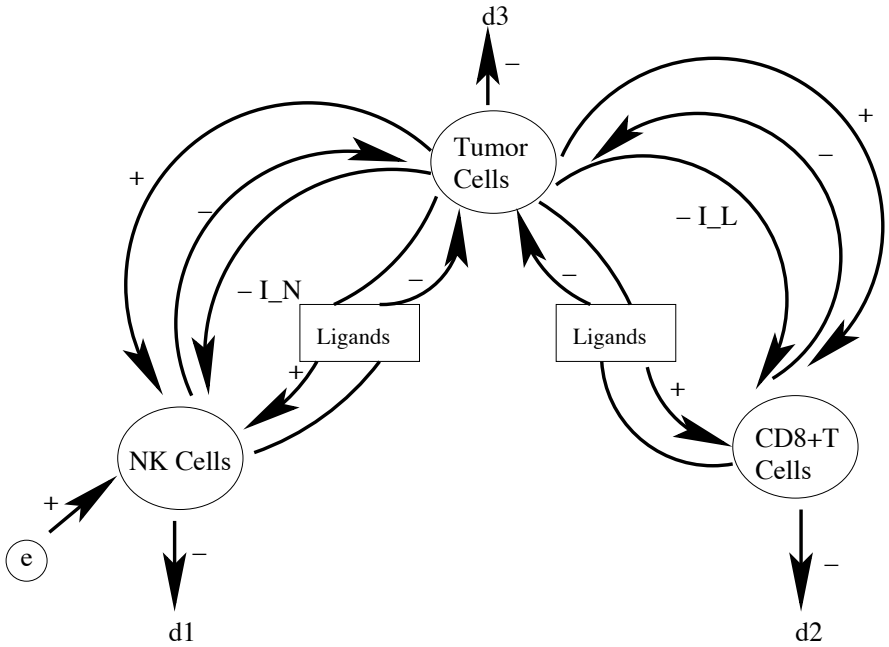

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NOTE: The functional forms of the lysis terms distinguish NK -cells from CD8+ (antigen specific) cells.

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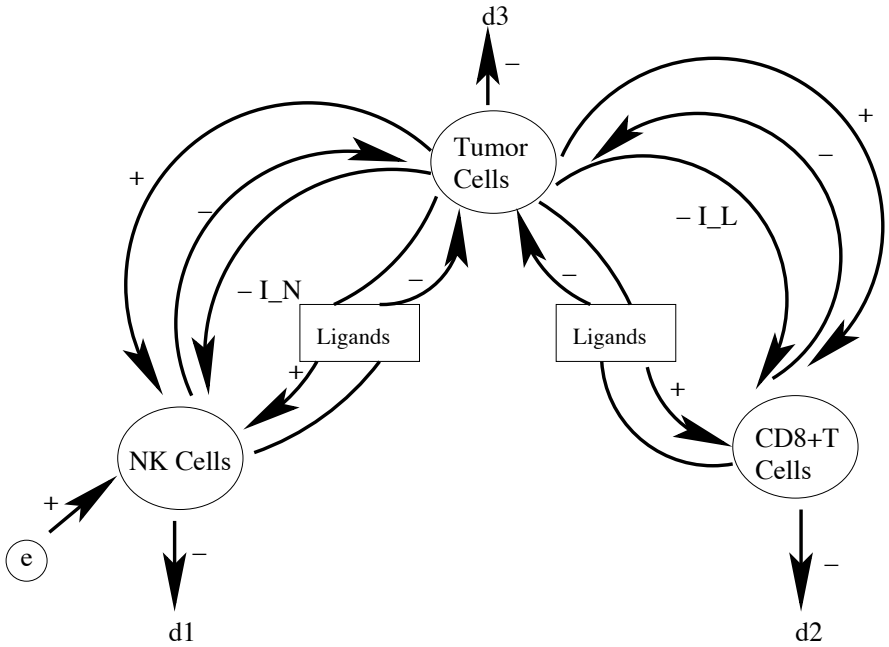

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NOTE: The functional forms of the lysis terms distinguish NK -cells from CD8T (tumor-specific) cells.

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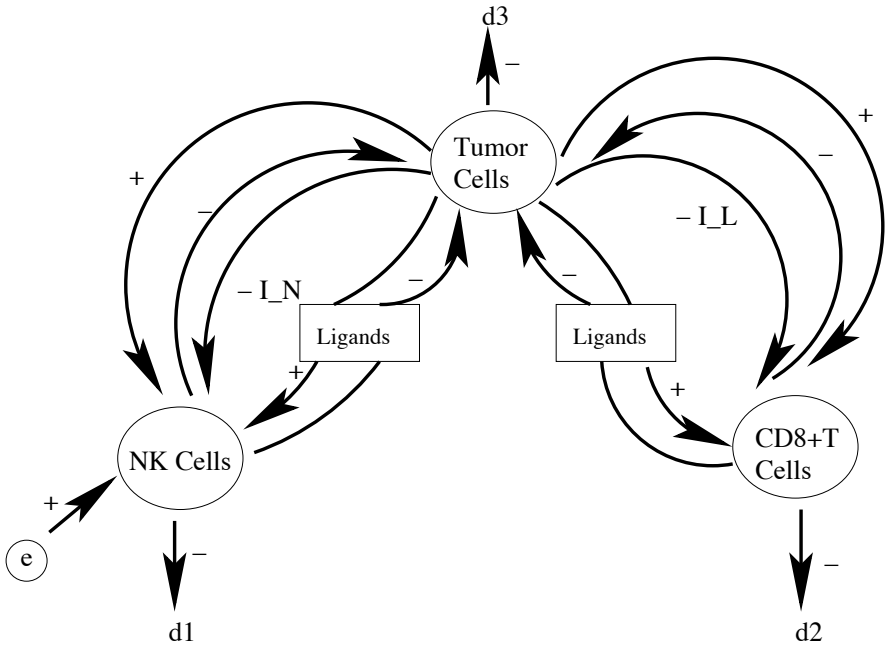

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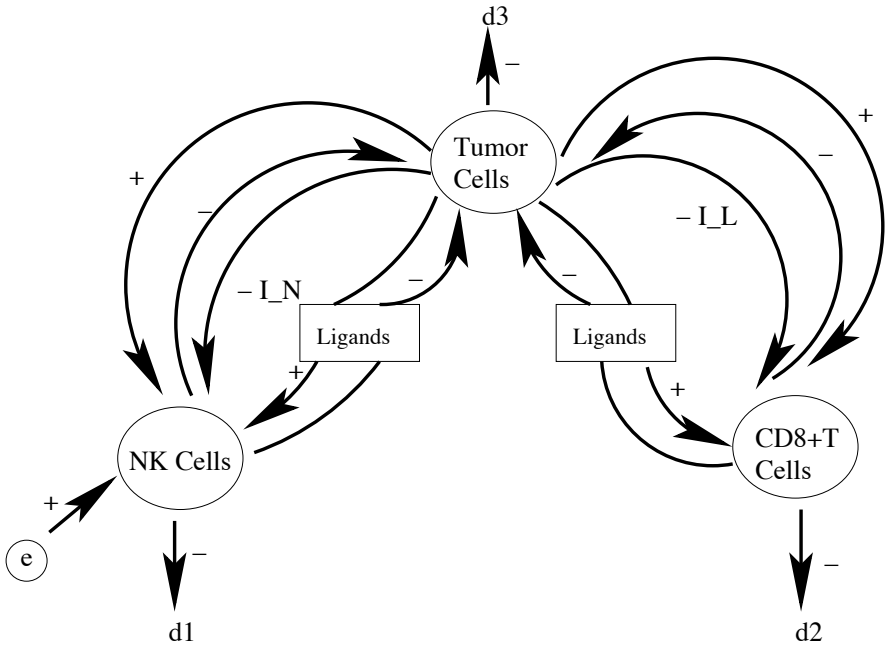

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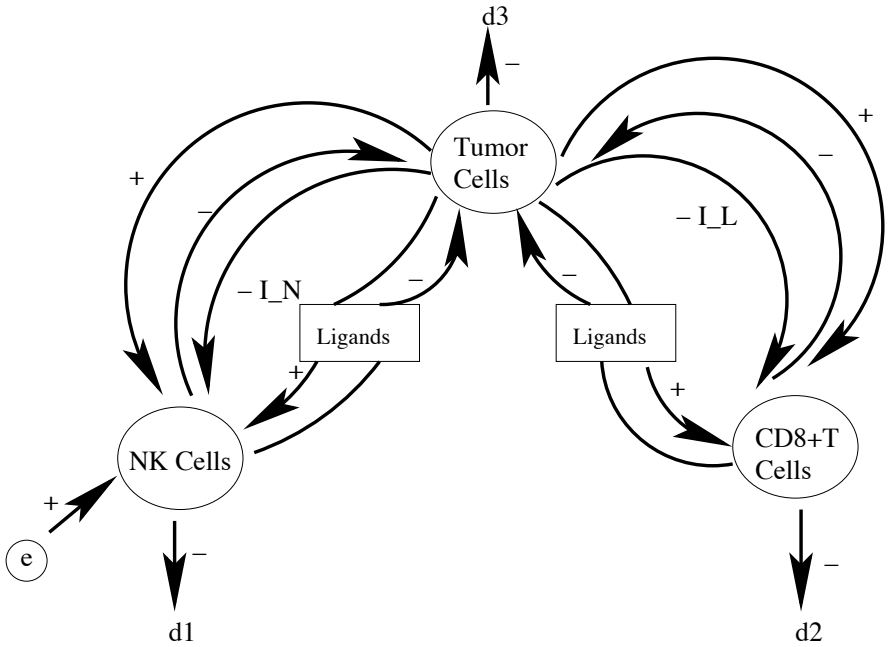
Population model with the dePillis-Radunskaya Law



$$\begin{aligned}
\frac{dT}{dt} &= aT(1-bT) - cNT - D \\
\frac{dN}{dt} &= e - fN + \frac{gT^2}{h+T^2}N - pNT \\
\frac{dL}{dt} &= -mL + \frac{jD^2}{k+D^2}L - qLT + rNT
\end{aligned}$$

where $D = d\dfrac{\frac{L}{T}^p}{s+\frac{L}{T}^p}T.$

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Mystery Remains !!

The mechanisms behind the dePillis-Radunskaya Law is still not understood.

Intuitively: Immune cell population density should influence average immune cell kill rate.

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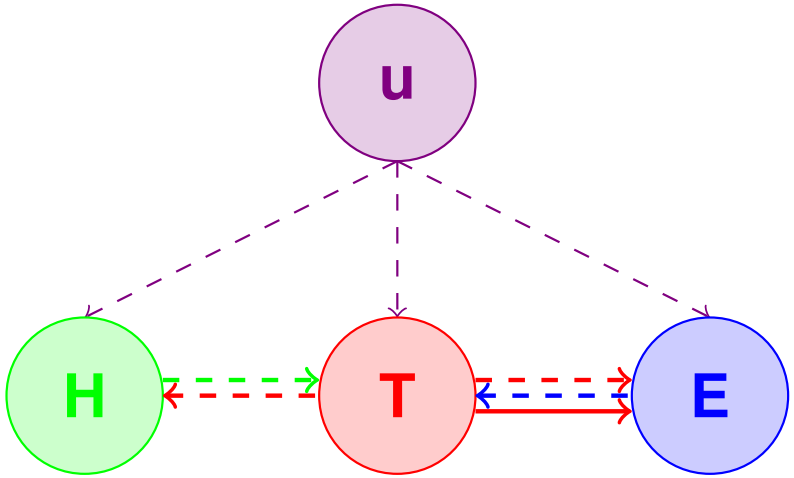

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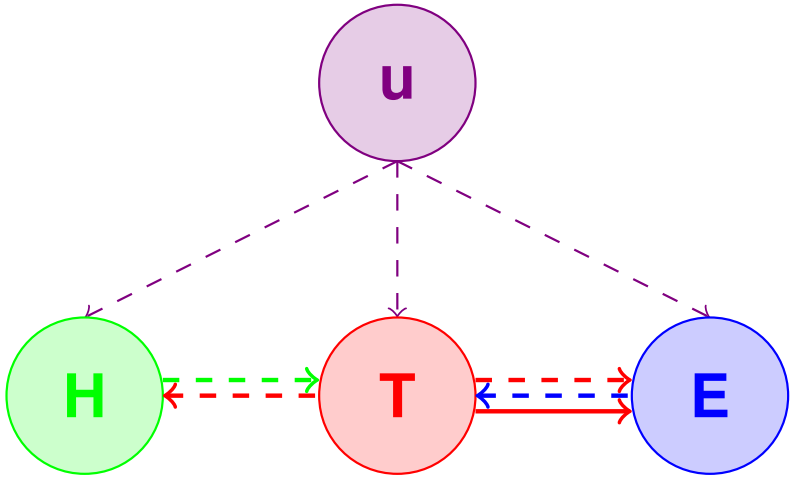

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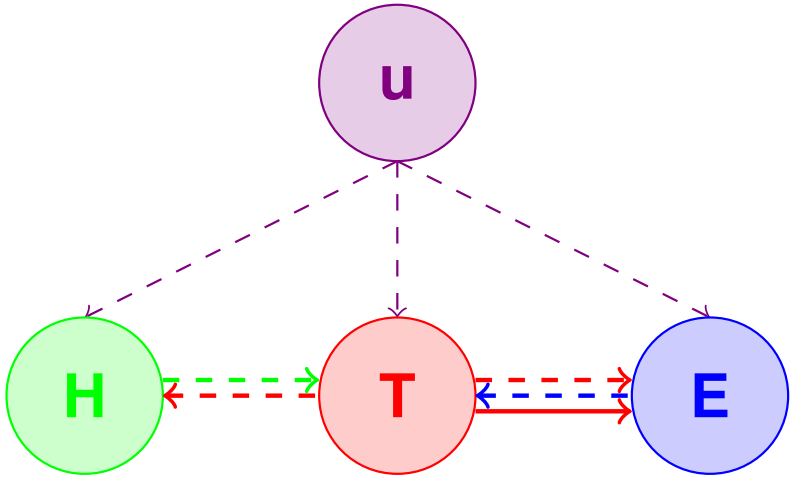

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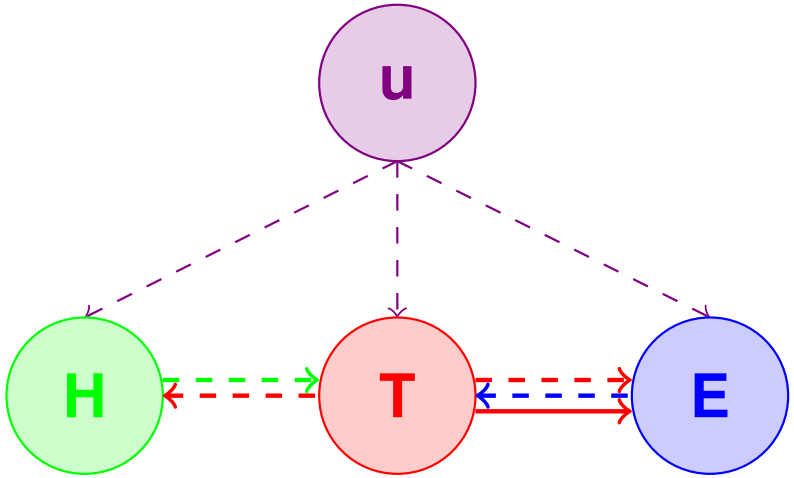

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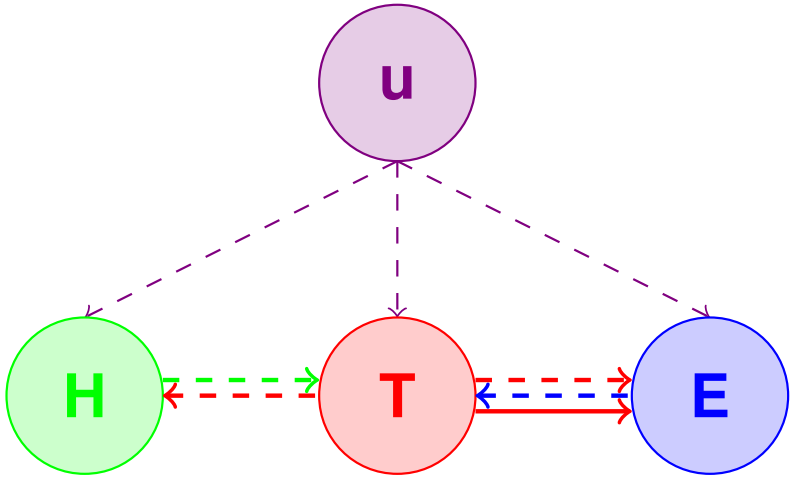

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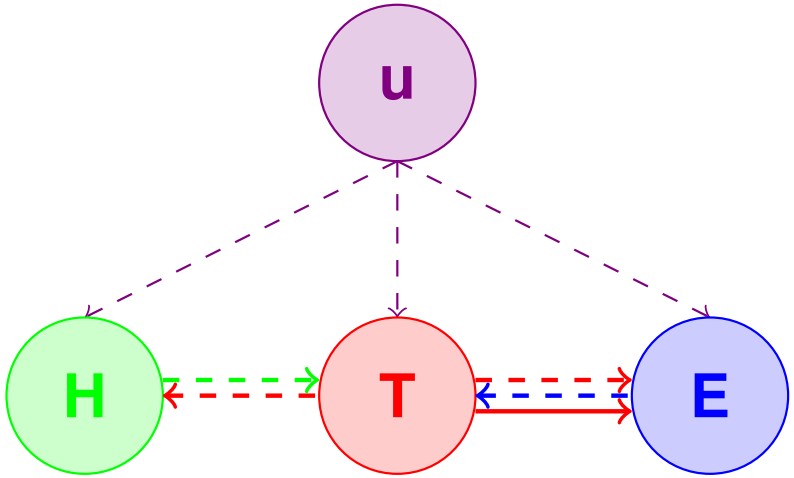

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Optimize Treatments

- Find the control variable $v(t)$ that minimizes the objective functional

$$J(v) = K_1 T(t_f) + K_2 \int_{t_0}^{t_f} T(t)\, dt$$

- subject to the differential equations with Initial Conditions
- and the inequality constraints

$$H(t) \geq .75 \times H_{normal}$$

$$\int_{t_0}^{t_f} v(t)\, dt \leq u_{Total}$$

This problem admits bang-bang solutions (on or off)

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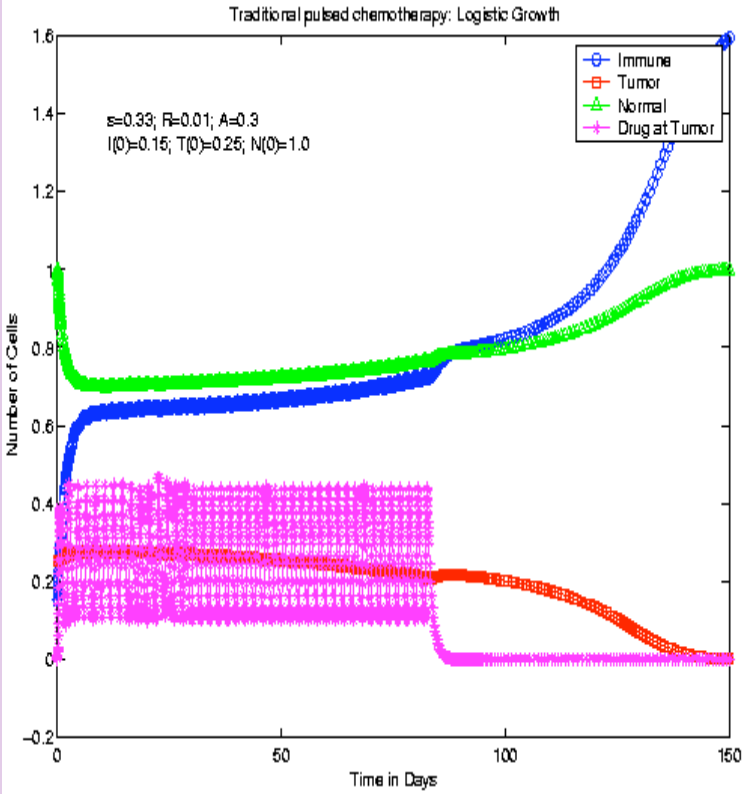
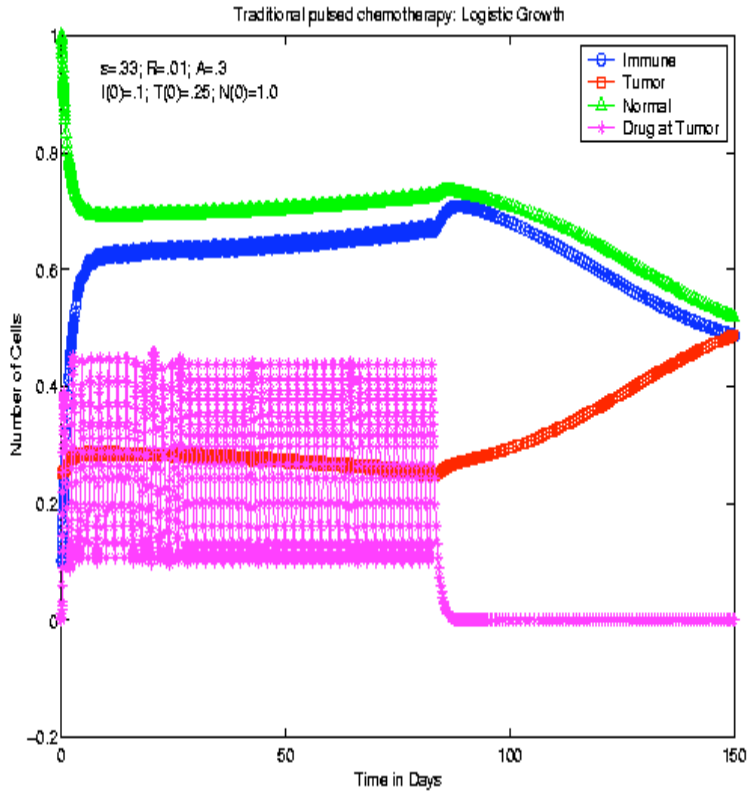
Tumor Growth - Traditional Pulsed Chemotherapy



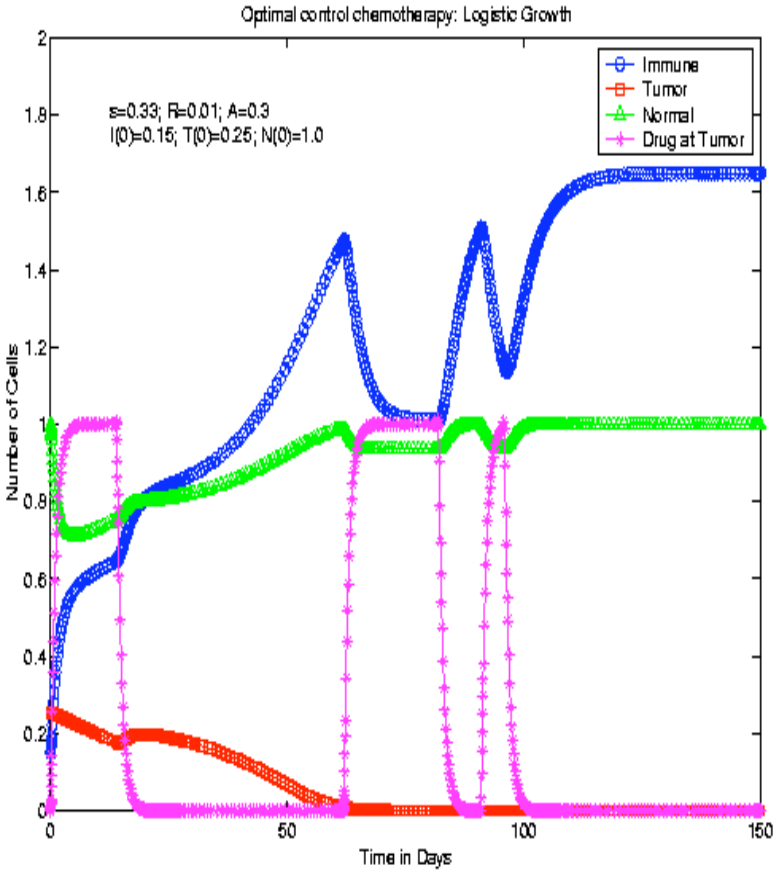
$I(0) = 0.15$



$I(0) = 0.1$

Red denotes tumor, Magenta denotes "shots" of drug.
Blue denotes immune cells, Green denotes normal cells.

Tumor Growth - Optimal Chemotherapy



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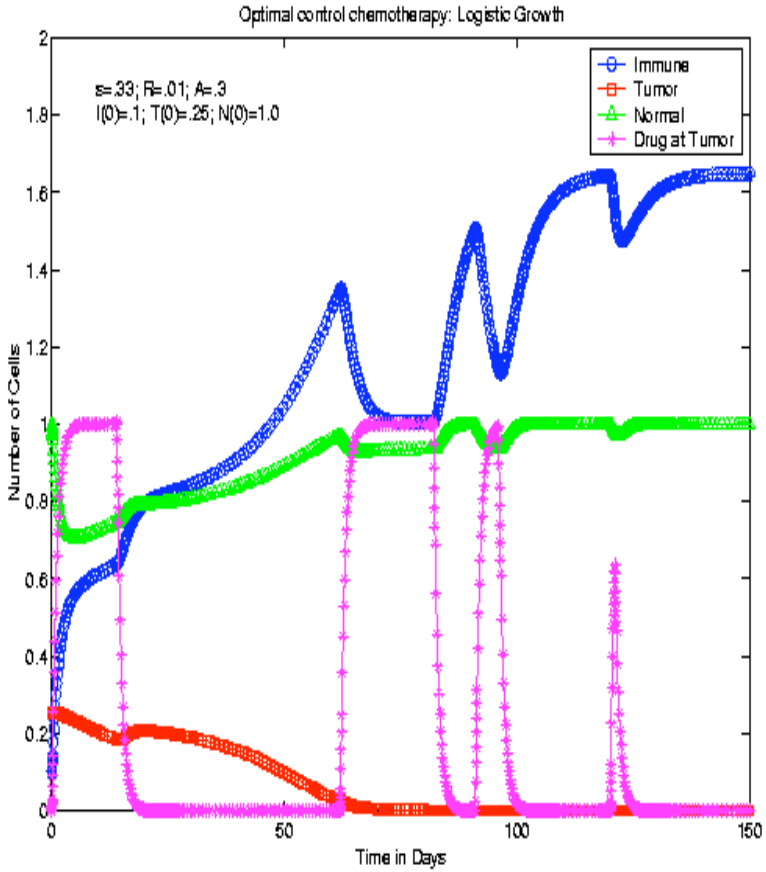

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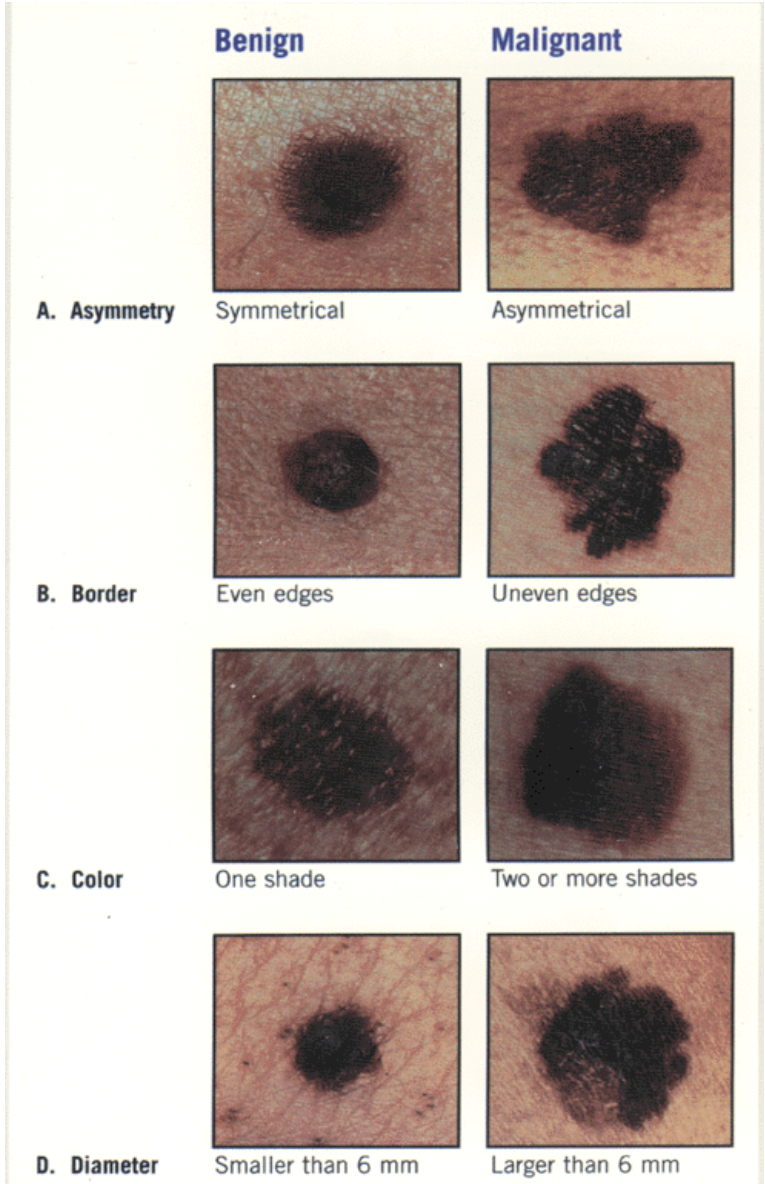
Morphology and Metastasis



This simple ABCD approach is a useful guide to help identify moles that should be evaluated. Photo courtesy of Schering Corporation.

Cellular Automaton (CA)

Add spatial variability $\Rightarrow$ need populations at each point in space as well as time.

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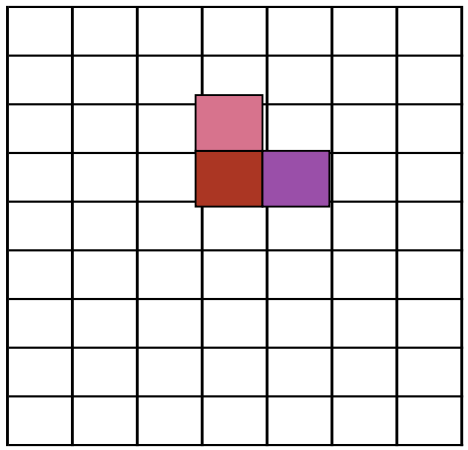
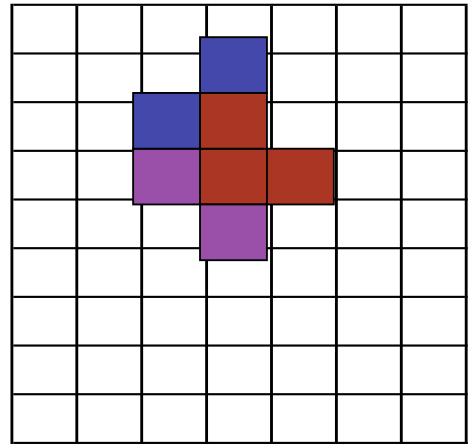


Sample RULE:

All cells divide

Max 100 per grid element - extras move to adjacent grid elements



= 100 = 75 = 50 = 25

Cellular Automaton Model [5]

- Includes Tumor cells (living and necrotic), Immune cells (NK and CTL), and normal Host cells.
- Two types of nutrients: one for maintenance, M, e.g. oxygen and one necessary for cell division N, e.g. glucose.

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A change in the relative consumption rates of the two nutrients causes a change in the morphology

$\lambda_m = 1.5, \quad \lambda_n = 1.5$ $\qquad$ $\lambda_m = 1.5, \quad \lambda_n = 45$

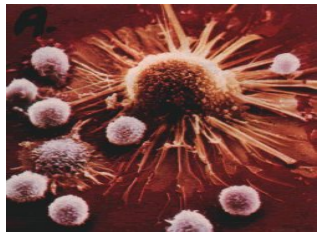
High innate immune level: $I_0 = .003$

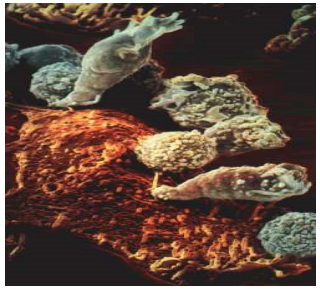
Low innate immune level: $I_0 = .0005$

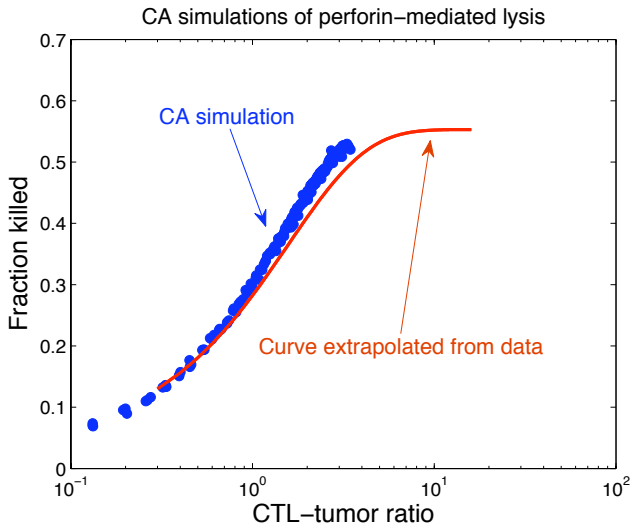
High CTL induction rate

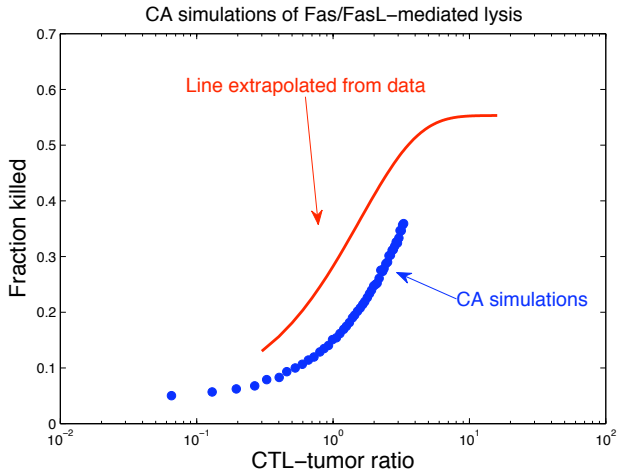
Low CTL induction rate

Use spatial model to test mechanisms behind the dePillis-Radunskaya Law.









Theory: “Ratio-dependency” comes from perforin-mediated lysis

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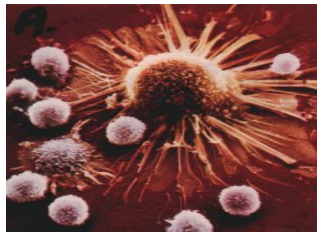

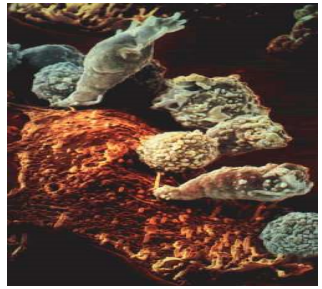

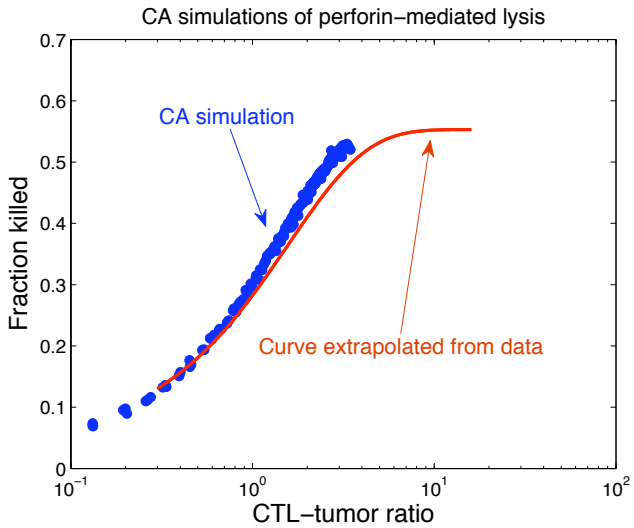

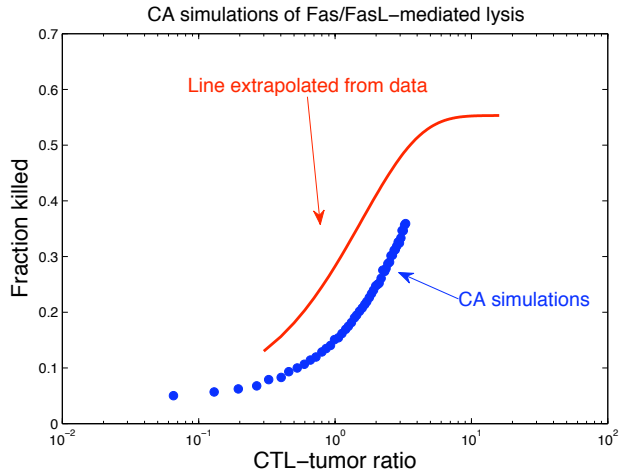

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First FDA Approval of Therapeutic Cancer Vaccine A Milestone Victory for Field of Cancer Immunotherapy

SHARE

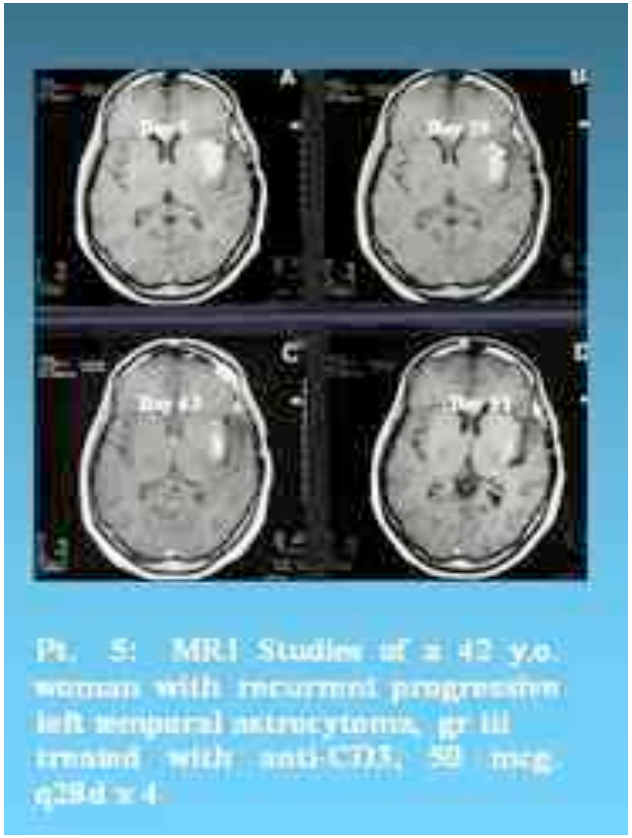
First FDA Approval of Therapeutic Cancer Vaccine A Milestone Victory for Field of Cancer Immunotherapy

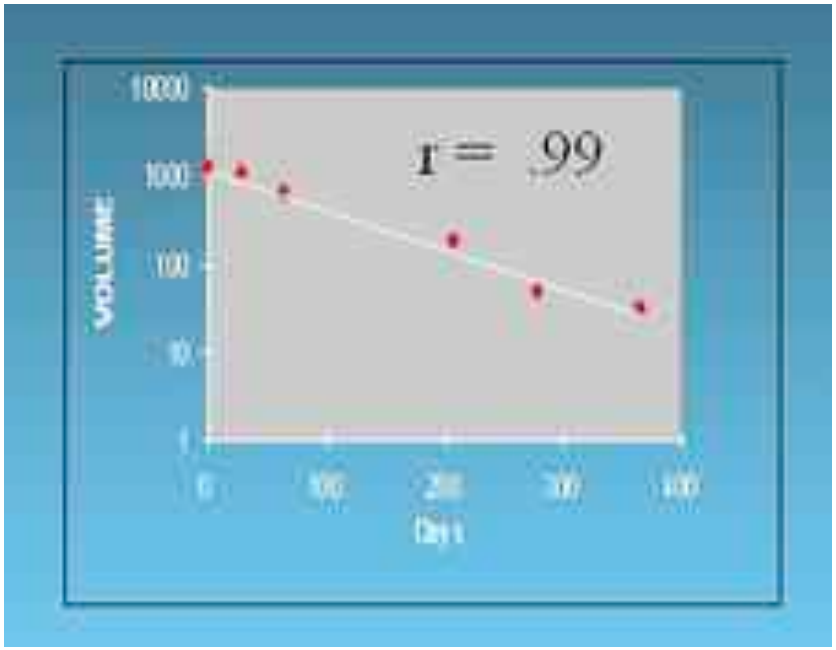
Released: 4/30/2010 7:00 PM EDT
Source: Cancer Research Institute

(April 30, 2010 – New York, NY) The Cancer Research Institute celebrates yesterday's announcement of the first therapeutic cancer vaccine to receive approval from the U.S. Food and Drug Administration. The vaccine, called Provenge, is produced by Seattle biotech company Dendreon (NASDAQ:DNDN) and is designed to treat certain forms of advanced prostate cancer.

"The approval of a vaccine to treat cancer is a victory in the history of cancer therapy, and signals the beginning of a new era in cancer medicine," said Jill O'Donnell-Tormey, Ph.D., executive director of the U.S.-based Cancer Research Institute (CRI), a nonprofit organization founded in 1953 that has provided decades of significant support to cancer immunology researchers around the world so that the development of cancer immunotherapies such as Dendreon's Provenge might one day be possible.

Cancer Immunotherapy: clinical response to anti-CD3 T-cell vaccine. [6]





Anti-CD3 vaccine given on Day 0, retreat on Day 28

[6] patient of Dr. Charles Wiseman

A collaborative effort

This project is in close collaboration with a laboratory immunologist, Dr. Sarah Hook, *University of Otago, NZ*

Measuring the immune response

- Two immune cell populations are measured in the laboratory that indicate antigen specific response: $CD4^+$ (helper T-cells) and $CD8^+$ (killer T-cells).
- The vaccine is a peptide recognized by Dendritic Cells (APC's).
- Immune response is self-regulatory: phases triggered by the presence of antigen (APC's).
- Self-regulating mechanisms play critical role in effectiveness of cancer vaccines, *limited success to date*.

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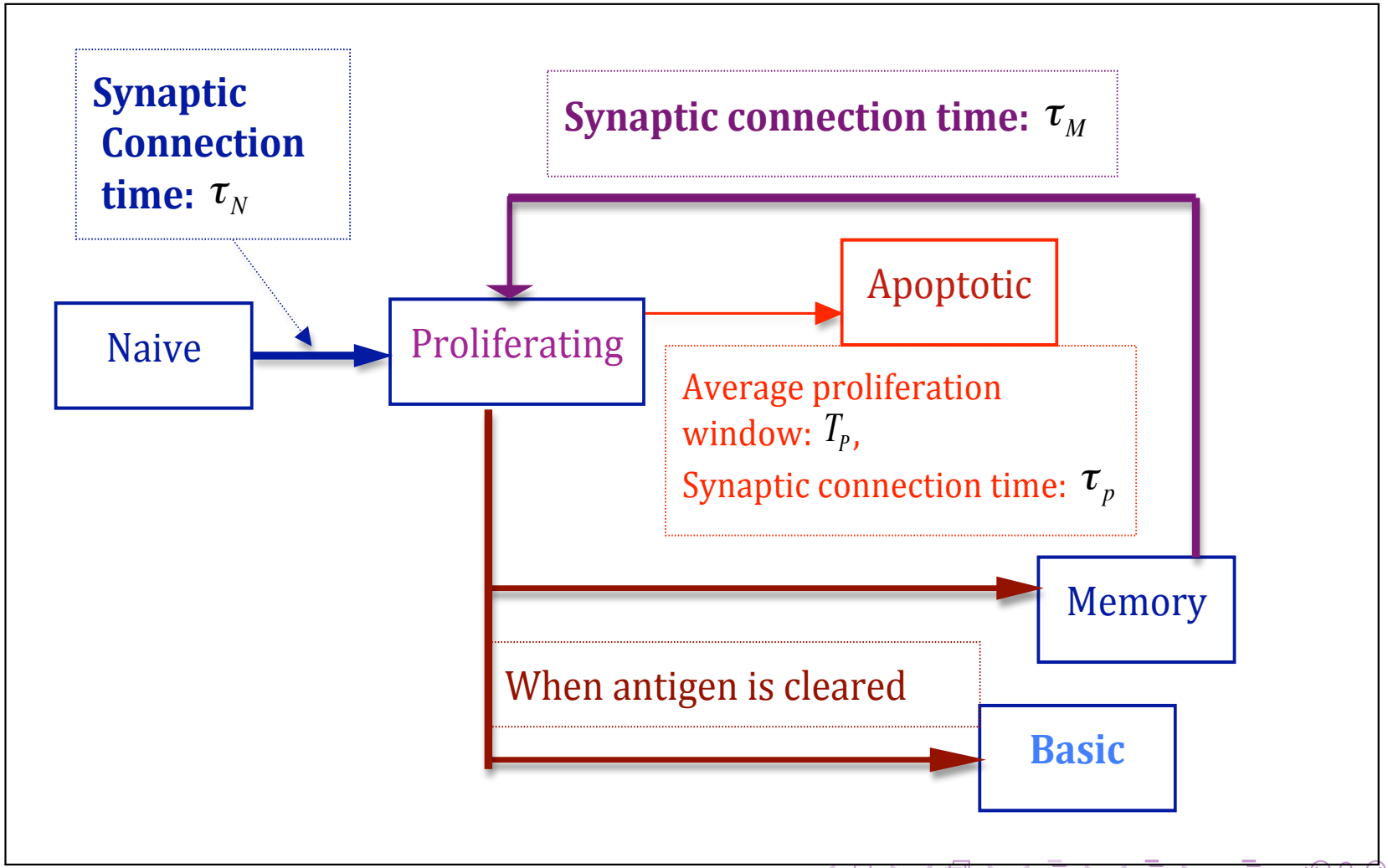
Model Flow: Each T-cell Type ($CD4^+$ and $CD8^+$)

5 sub-populations: **N**aive,**P**roliferating, **A**poptotic, **B**asic, **M**emory



Model DDE's *(for each T-cell Type)*

$$
\begin{aligned}
\dot{D} &= \mu D B(t) - d_D D \\
&\dots \\
\dot{N} &= s - d_N N - g N_{\tau_N} D_{\tau_N} \\
\dot{P} &= g N_{\tau_N} D_{\tau_N} + \rho \frac{D_{\tau_P}}{\theta + D_{\tau_P}} P_{\tau_P} + \lambda M_{\tau_M} D_{\tau_M} - d_P(D) P \\
\dot{A} &= \frac{1}{T_P} P - d_A A \\
\dot{B} &= r_B(D) P - d_B B \\
\dot{M} &= r_M(D) P - \lambda M_{\tau_M} D_{\tau_M}
\end{aligned}
$$

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\dot{N} &= s - d_N N - g N_{\tau_N} D_{\tau_N} \\
\dot{P} &= g N_{\tau_N} D_{\tau_N} + \rho \frac{D_{\tau_P}}{\theta + D_{\tau_P}} P_{\tau_P} + \lambda M_{\tau_M} D_{\tau_M} - d_P(D) P \\
\dot{A} &= \frac{1}{T_P} P - d_A A \\
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\end{aligned}
$$

where τ subscripts denote delayed variables: $N_\tau = N(t-\tau)$.

Model DDE's *(for each T-cell Type)*

$$
\begin{aligned}
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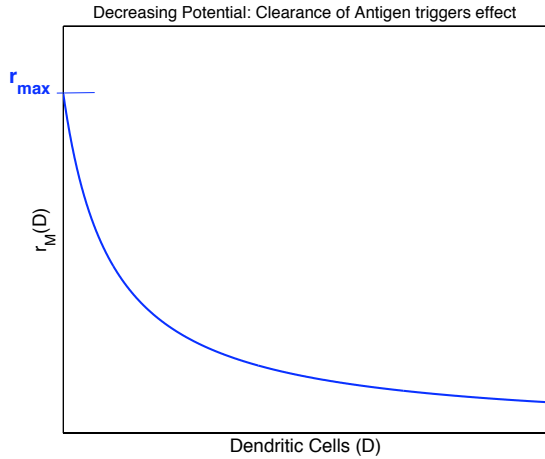
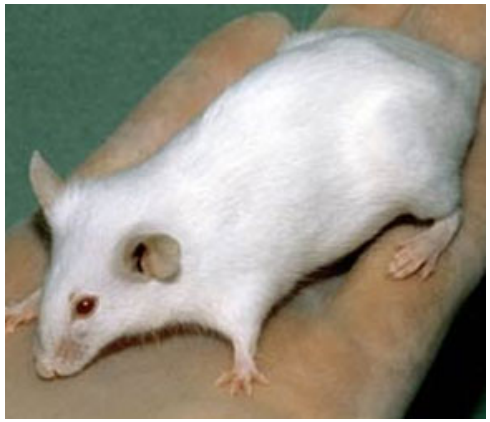
and functions of D reflect *antigen clearance*:



First Kinetics Experiments



- Mice were injected with OVA [7] after being injected with transgenic OVA-specific CD4 and CD8 cells.
- The numbers of cells were counted at various time points post-vaccination.

[7] Ovalbumin protein

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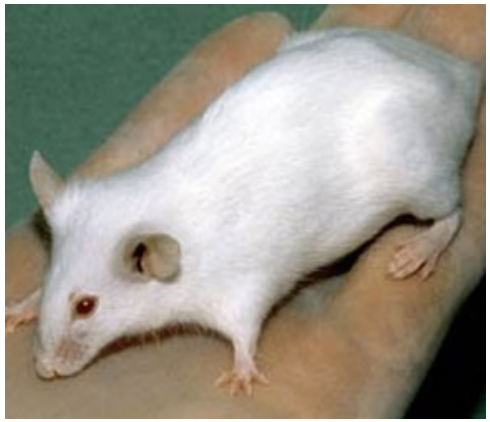

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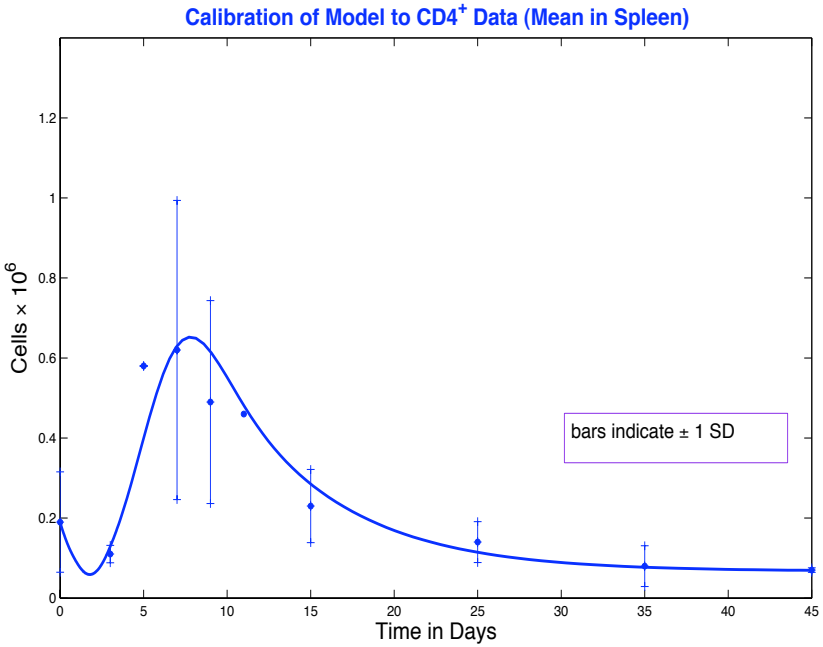
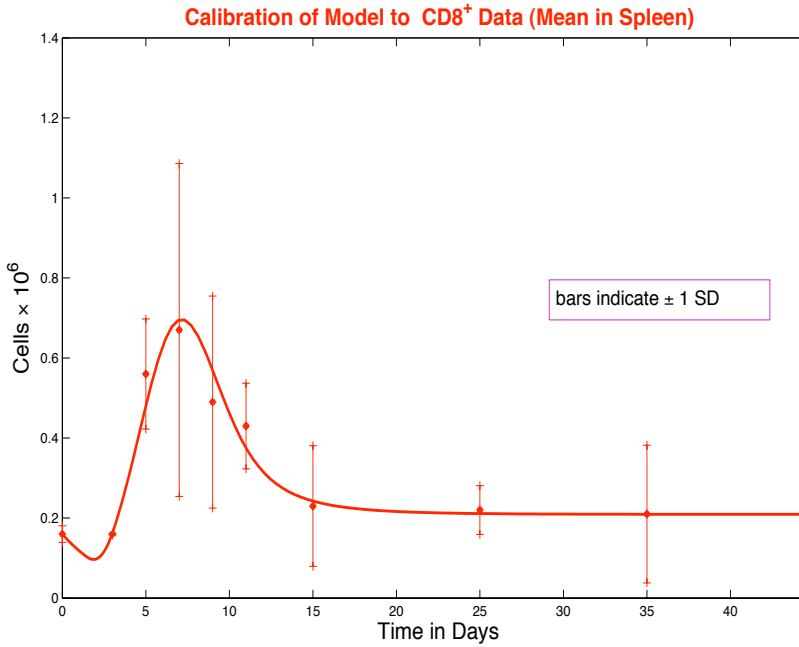
Calibrate the model to data





Note that the peak $CD4^+$ levels are slightly lower and come slightly later than the peak $CD8^+$ levels.

CD4 - Helper Cells

T-cells

CD8 - Killer

Optimization question: When to give the vaccines?

- Cancer vaccines are weak antigens.
- Repeated doses are needed to initiate an effective immune response.
- Immune cell production self-regulates: prolonged contact with antigen isn't always better.
- Find the optimal boosting schedule.

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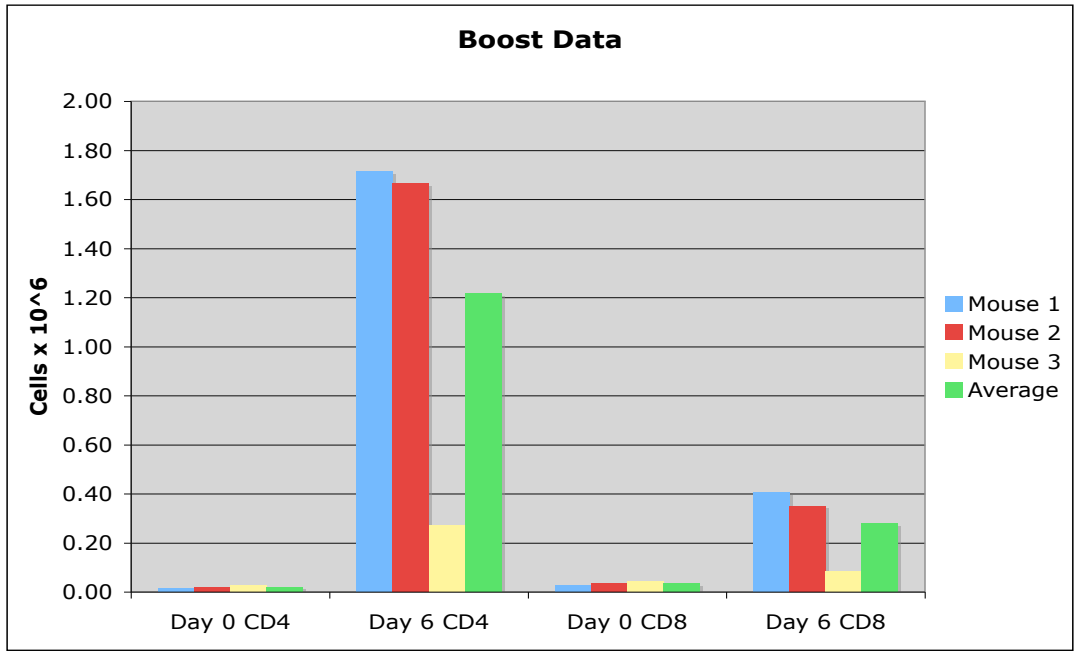
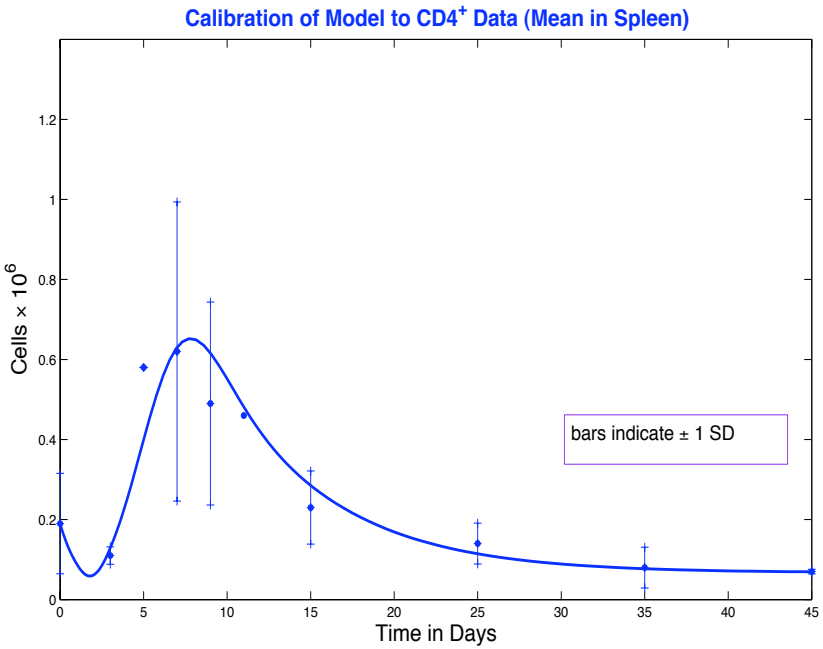
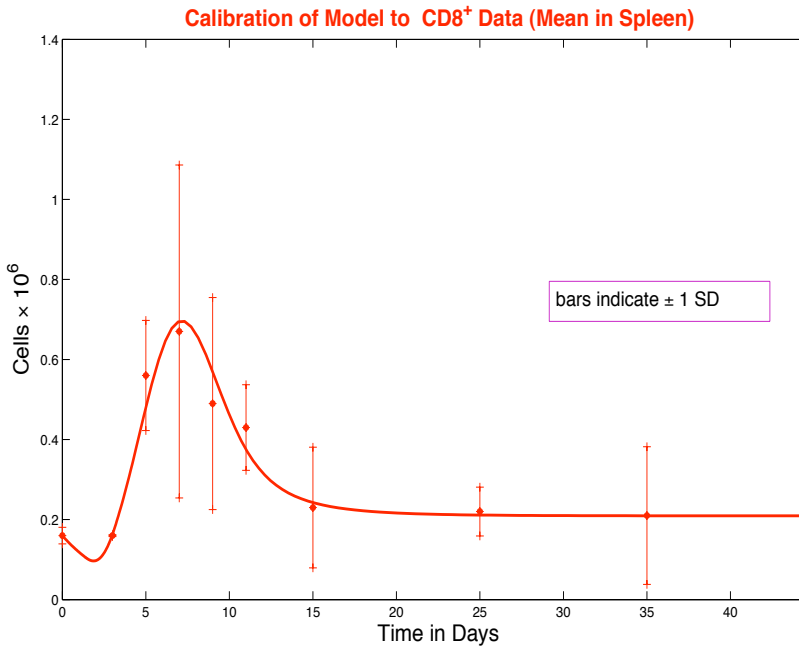
Preliminary Boosting Experiments Give Frustrating Results



$CD8^+$ expansion is much lower than expected. Where is the boosting effect?

Boost given at peak of data points:





Best Dosage Strategy

The number of antigen presenting cells in the spleen, $D(t)$, is directly affected by an input function, $u(t)$, that represents a controlled dose of weak antigen (vaccine) entering the blood stream.

Optimization goal: Find the control function, $u(t)$ (vaccine) that maximizes the immune response:
the number of effector T-cells in the **Blood** and/or the number of **Memory** cells.

Admissible controls: $0 \leq u \leq u_{max}$. *In practice: step functions.*

Maximize:

$$J(u) = k_1 \mathbf{v}^T \mathbf{x}(T_f) + k_2 \int_{T_0}^{T_f} \mathbf{w}^T \mathbf{x}(t)\, dt$$

where x is the vector of state variables, $k_1, k_2, \mathbf{v}, \mathbf{w}$ indicate relative weights.

In terms of a control problem, this is simple. However, due to the delays in the equations, the situation becomes complicated ...

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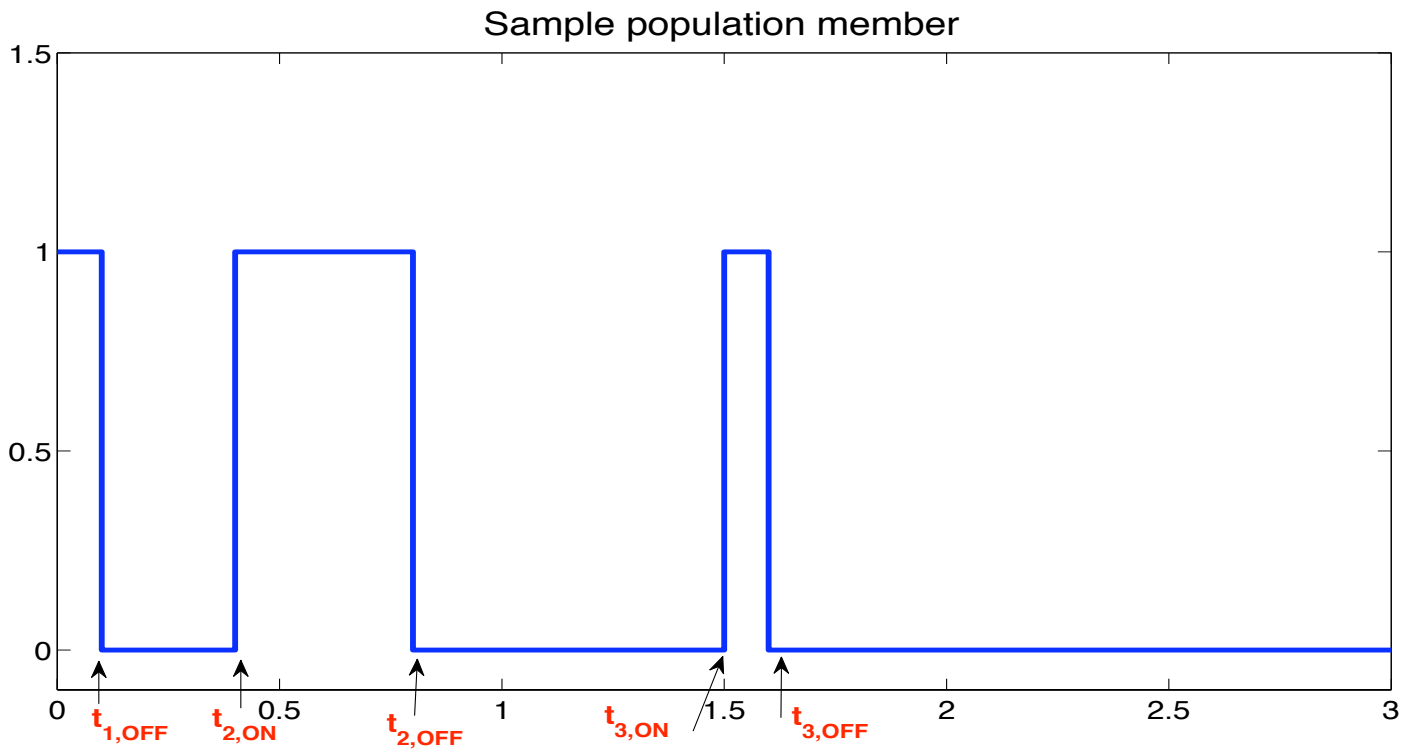
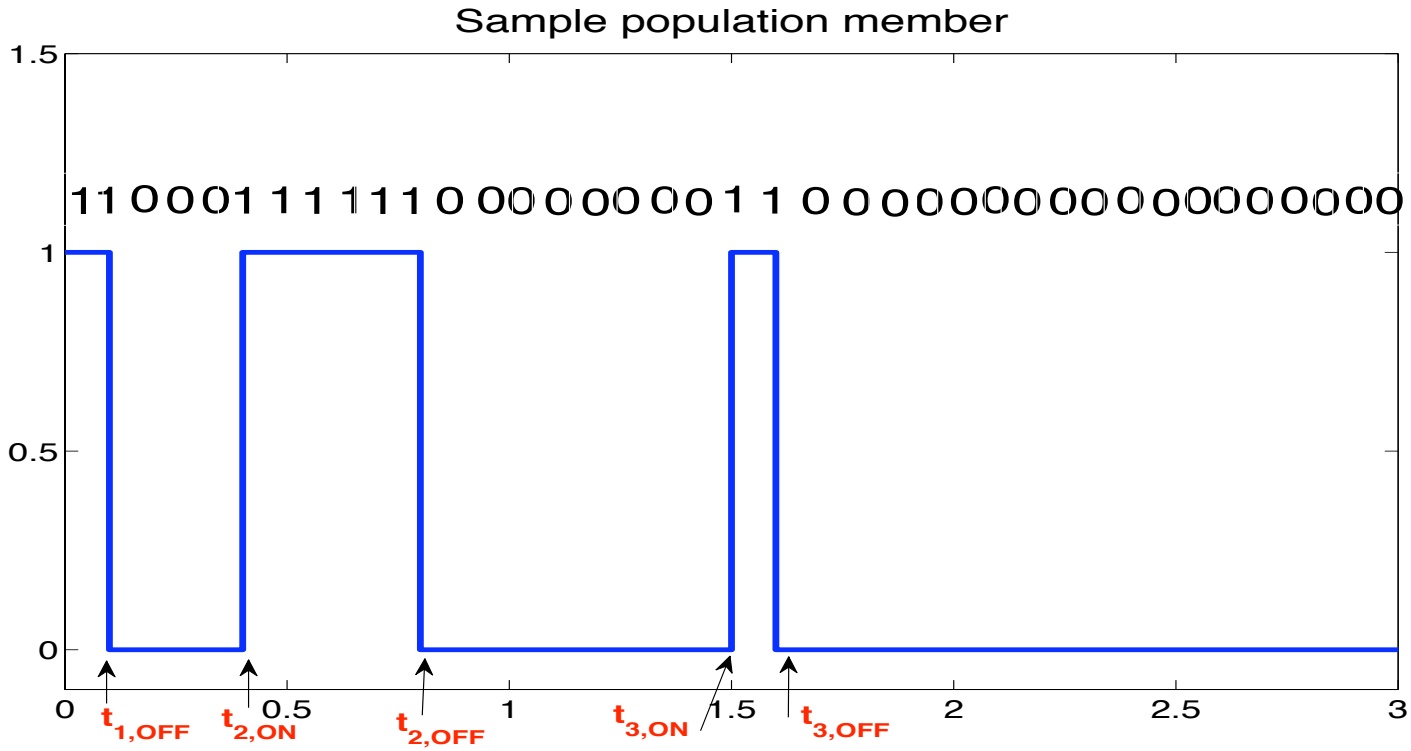
Heuristic Optimization of Dose Times

Search space: "populations" of dosage timings and durations.



Heuristic Optimization of Dose Times

Each “individual” is a sequence of “on”s and “off”s.



Optimization techniques: evolutionary algorithms, simulated annealing. [8]

- Example here: Genetic Algorithm.

$$1,1,0,0,0,1,1,1,1,1,1,0,0,0,0,0,0,0,0,1,1,0,0,0,0,0$$
$$\Rightarrow \quad 1,1,0,0,0,1,1,1,1,1,0,0,0,0,0,0,0,0,1,1,0,0,0,0,0$$

Restrict to one Boost with constant duration (mimics laboratory setup).

- Optimization choices: maximize peak response? Number of memory cells?

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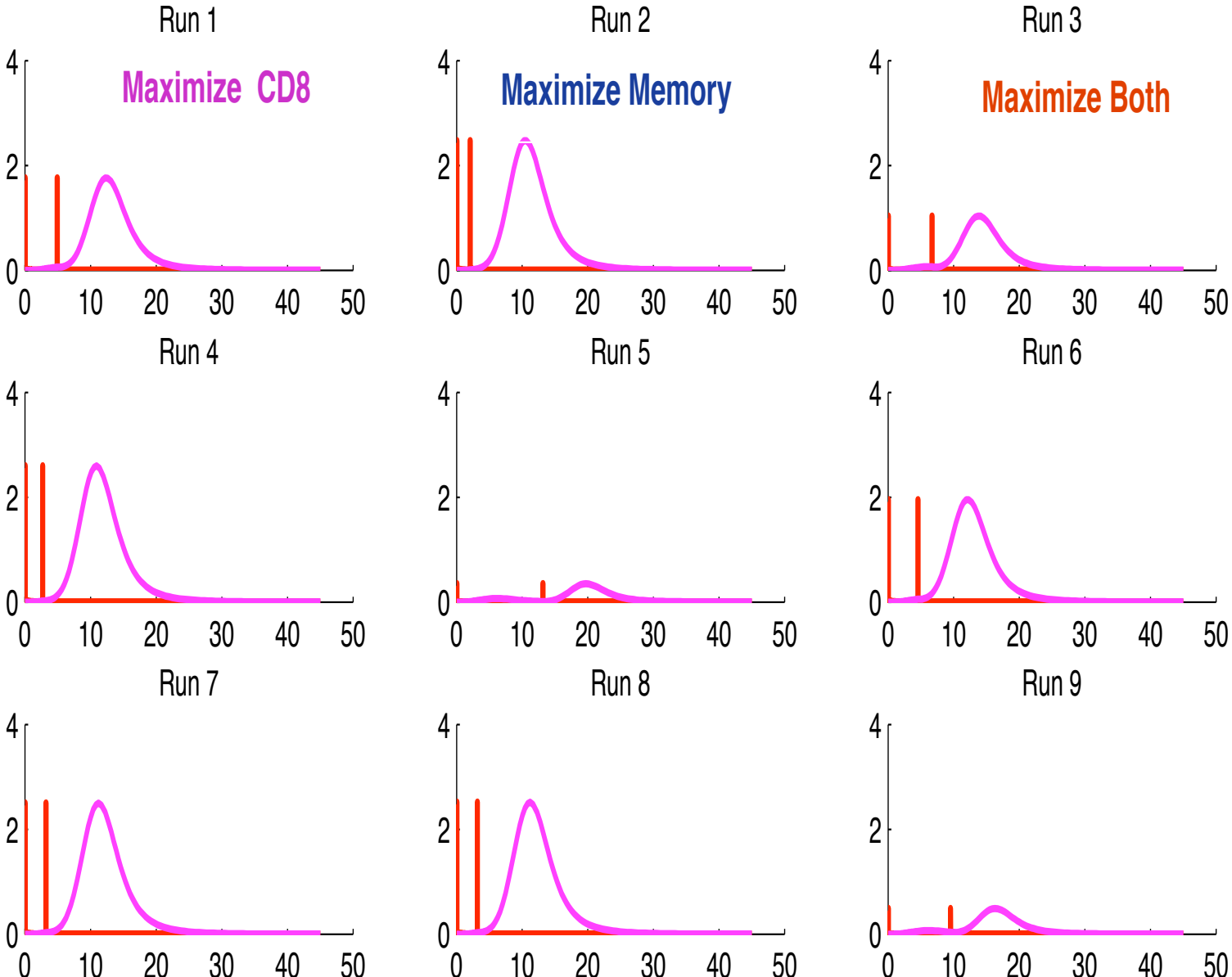
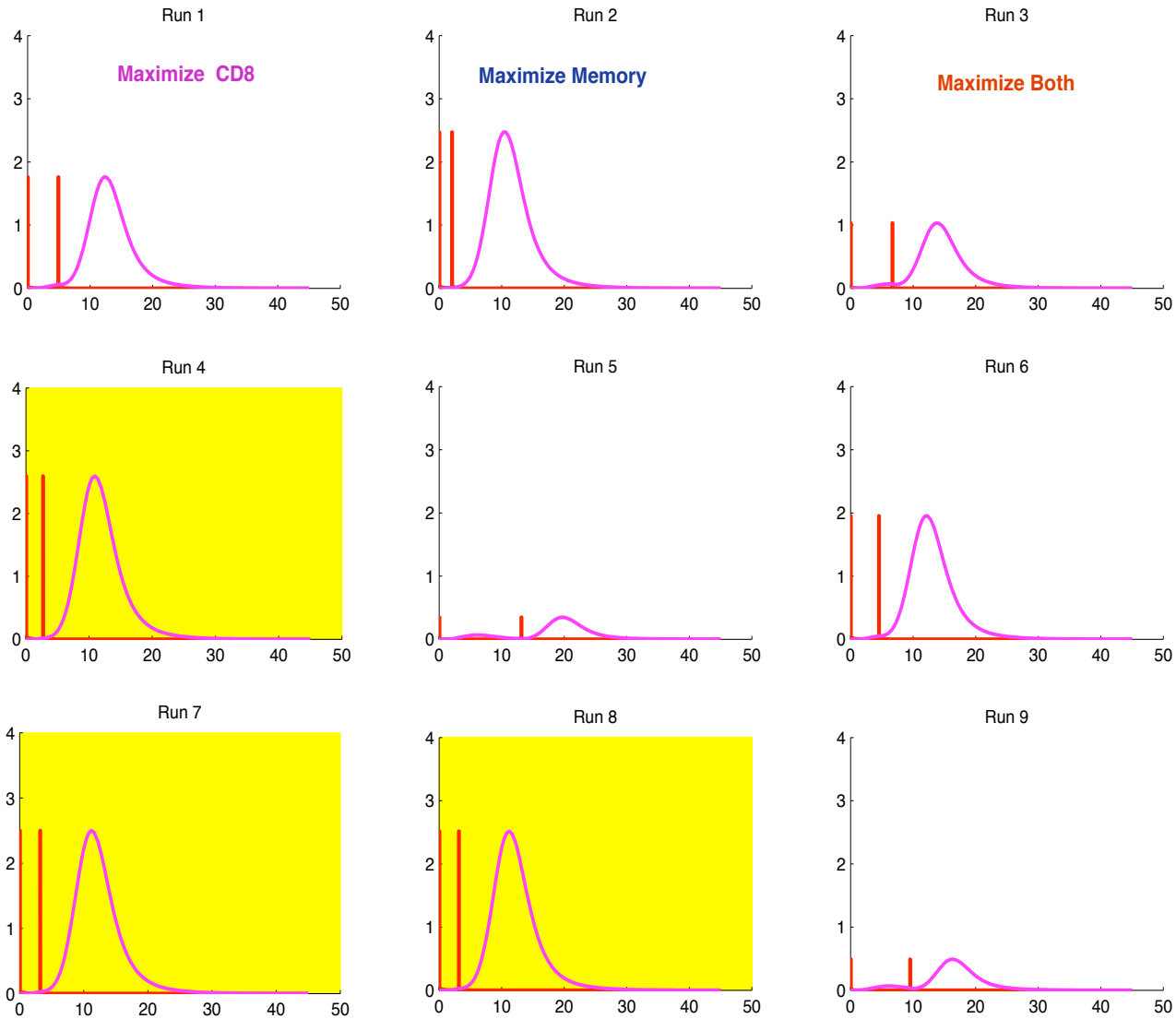
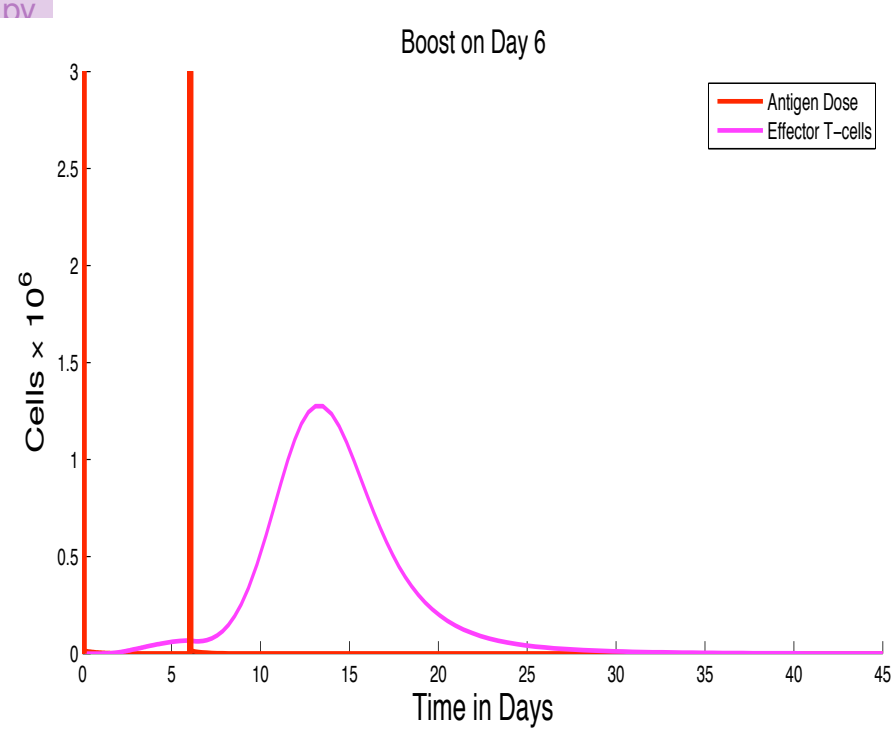
Genetic algorithms yield many optimal candidates

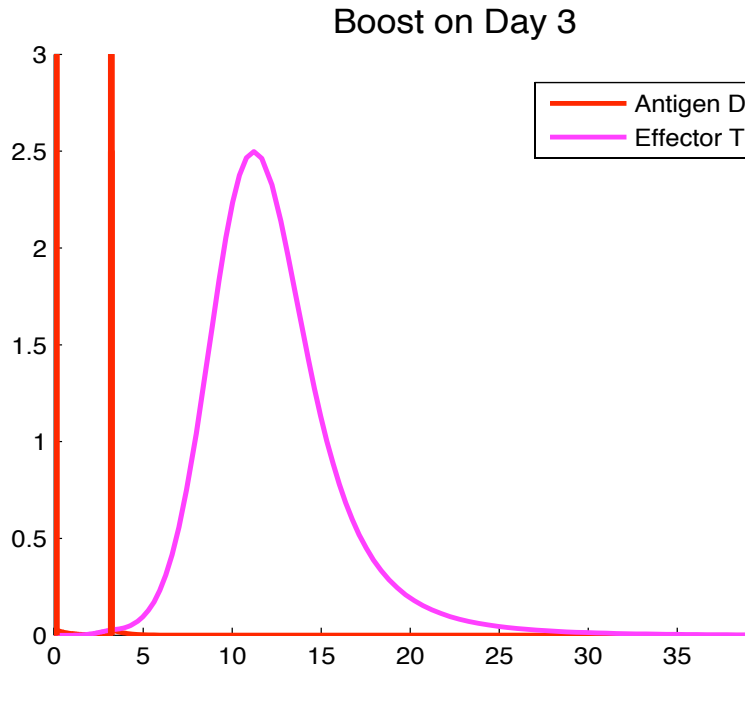


Select "Best of Bests"



Compare GA result to "Standard" Protocol





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- A sensitivity analysis can suggest which parameters are the best indicators of patient response.

Continuing Work:

- Dosage timings suggested by optimization results should be tested in the laboratory.
- A stability analysis suggests that adjuvants that decrease delays might sustain the production of effective T-cells. Confirm this theory with laboratory tests.
- Test theories of immune cell kill mechanisms in the laboratory.
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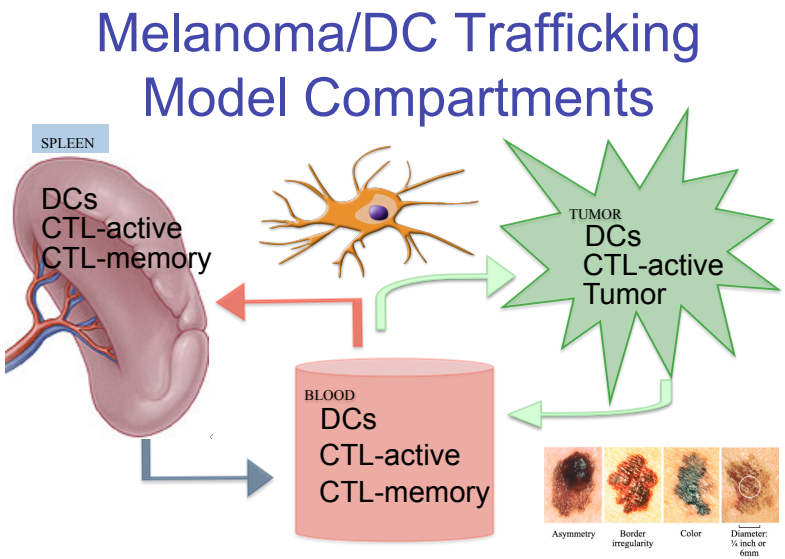

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Thanks to the organizers and . . .

thanks for listening!

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