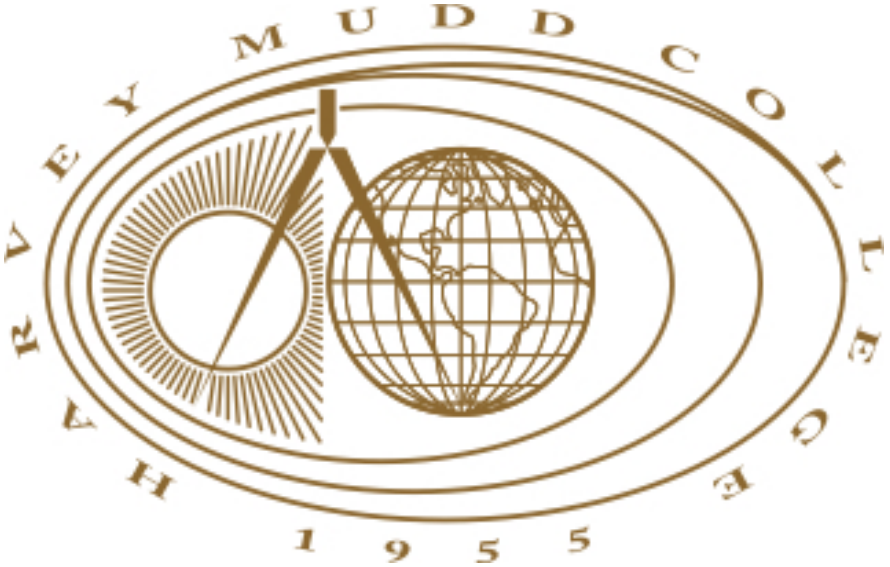
Modeling Cancer-Immunology Dynamics

L.G. de Pillis

Harvey Mudd College
Claremont, California, USA

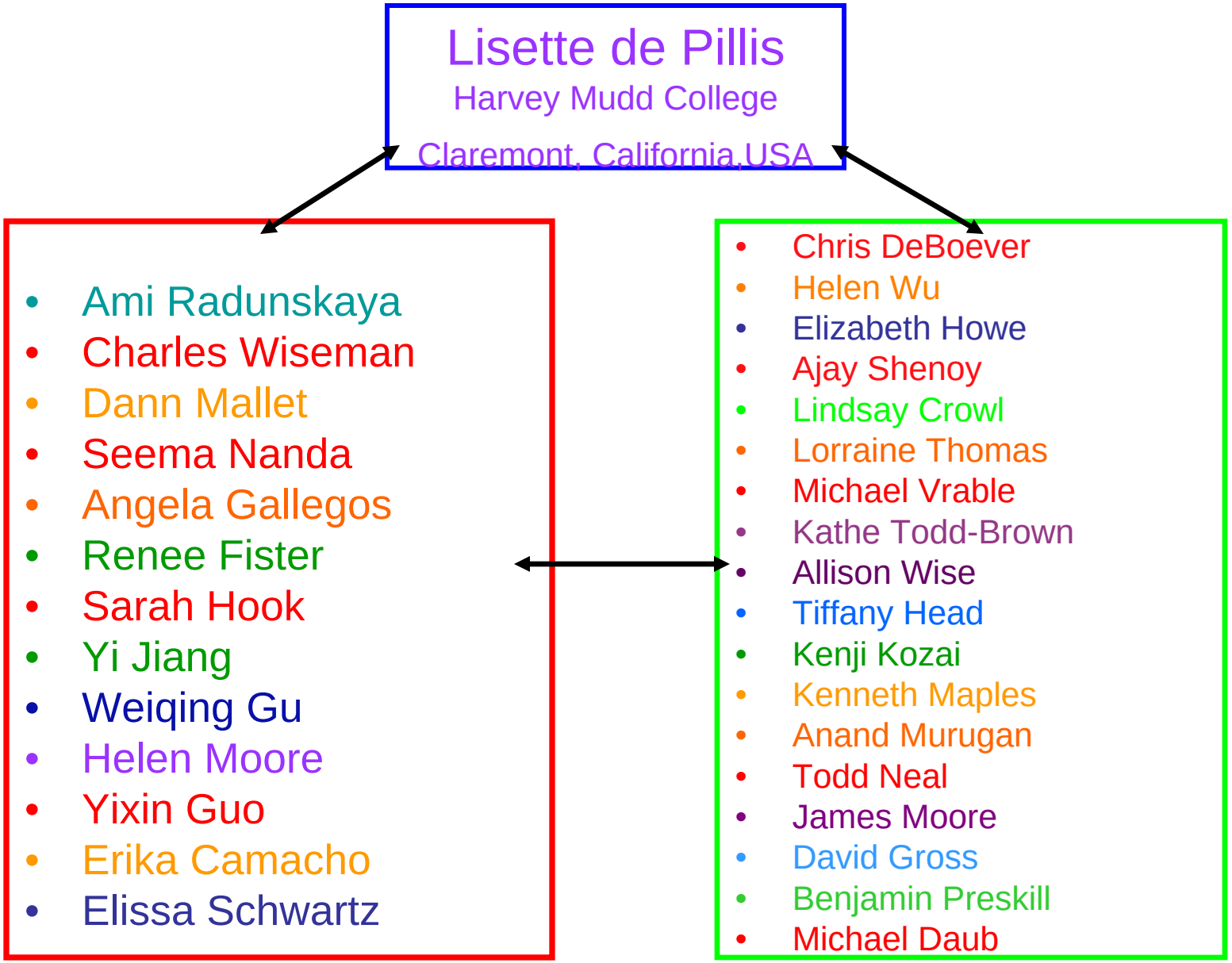


Modeling Cancer-Immunology Dynamics

L.G. de Pillis

Harvey Mudd College
Claremont, California, USA

A Cooperative Endeavor

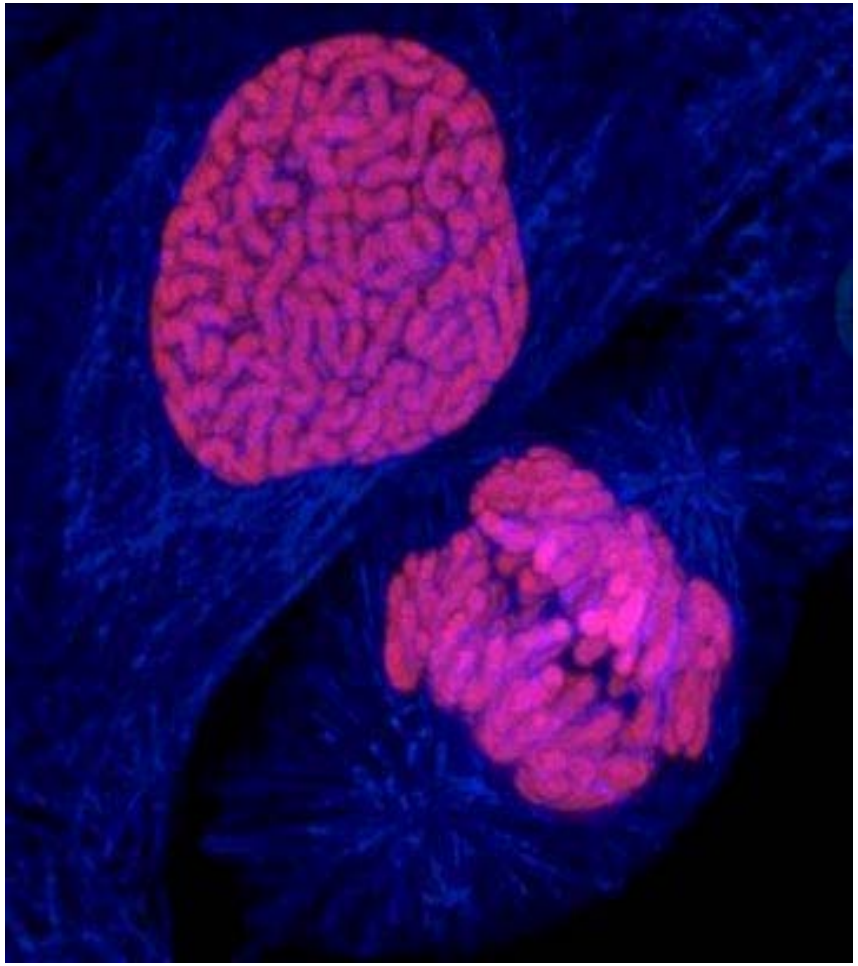


Outline

- Background: Cancer and genesis of this work
- The original motivating problem
- Controlling treatment
- Immunology of cancer
  - The Immune System Targets Cancer
  - Two Kinds of Immune Responses: Innate and Specific
- Extended model, include immune components
- Adding treatment
- Specific cancer: B-CLL
- Work in progress: Spatial tumor models
  - Hybrid CA models
  - 3D PDE models

What is Cancer?

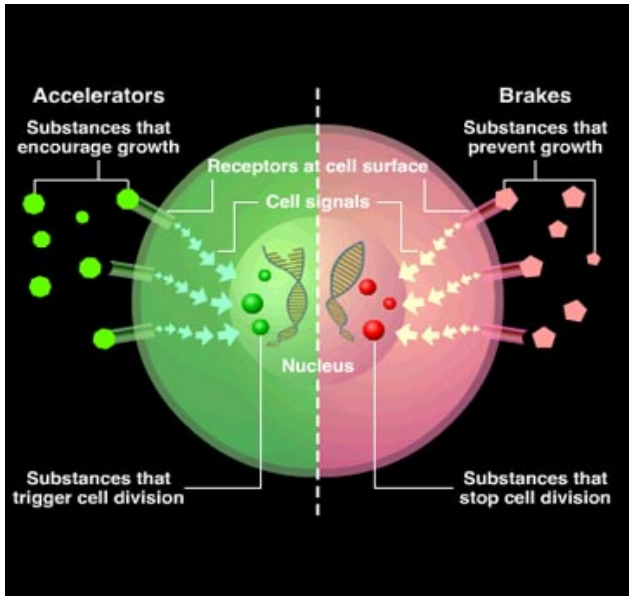
- Cancer is a cellular disorder.
- There are several hundred types of cancer, but all have some general characteristics in common.
- It can begin with just one cell gone awry...



Thanks: cancer-info.com

Cancer: Uncontrolled Growth

- Cancer cells experience *uncontrolled* and *disorganized* growth.
- Cancer cells can divide “forever” but never differentiate (vs normal cell 50x limit)



Thanks:www.sciencemuseum.org.uk

Our Mathematical Model: What and Why

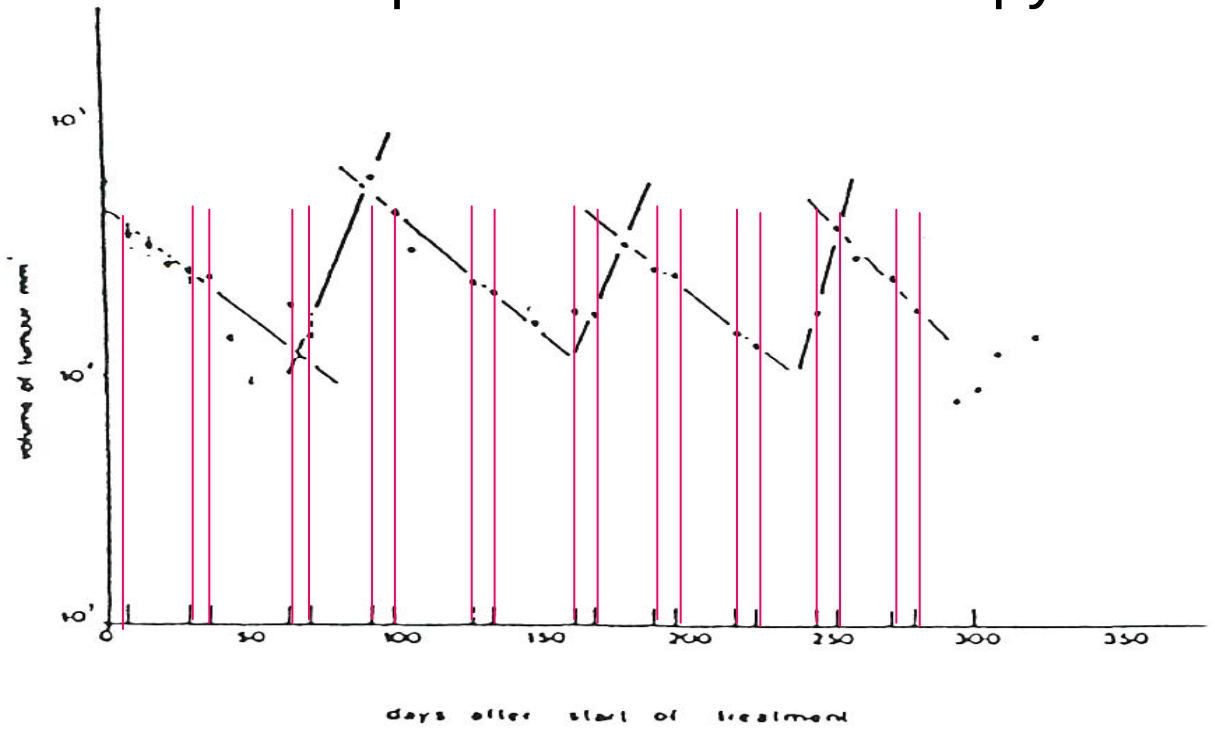
- **What:** Simulation of *tumor-immune dynamics*:
  - Provide low-cost prediction, explanation.
- **Why:** Dr. Wiseman's MoM group
- **Goals**:
  - Math model with *range* of dynamics, ability to simulate real laboratory and clinical data.
  - Focus on immune-tumor interactions and treatment modeling.
- **Process, Method and Analysis:**
  - Model with *differential equations* and *cellular automata*.
  - Choose/create functions with empirical/biological fit to existing experimental data.

Outline

- Background: Cancer and genesis of this work
- The original motivating problem
- Controlling treatment
- Immunology of cancer
  - The Immune System Targets Cancer
  - Two Kinds of Immune Responses: Innate and Specific
- Extended model, include immune components
- Adding treatment
- Specific cancer: B-CLL
- Work in progress: Spatial tumor models
  - Hybrid CA models
  - 3D PDE models

The first question we investigated…

- Why might a tumor grow when it is treated, and shrink when it is not? That is, In the clinic, what causes asynchronous response to chemotherapy?



- Note: The 2 population models of the time did not answer this question…We needed to extend the models.

Could competition for resources cause the asynchronous response?

- Develop a three then four population model (dePillis and Radunskaya, 2001, 2003): include normal cell competition and chemo
- Why: Gives more realistic response to chemotherapy treatments: allows for delayed response to chemotherapy

Three Population Mathematical Model

Population change in time	Stuff going in	Stuff going out

- Combine Effector (Immune), Tumor, Normal Cells

$$dE/dt = s + \rho ET/(a+T) - c_1 ET - d_1 E$$

$$dT/dt = r_1 T(1 - b_1 T) - c_2 ET - c_3 TN$$

$$dN/dt = r_2 N(1 - b_2 N) - c_4 TN$$

Note: There is always a tumor-free equilibrium at (s/d,0,1)

Analysis: Finding Null Surfaces

- Curved Surface:

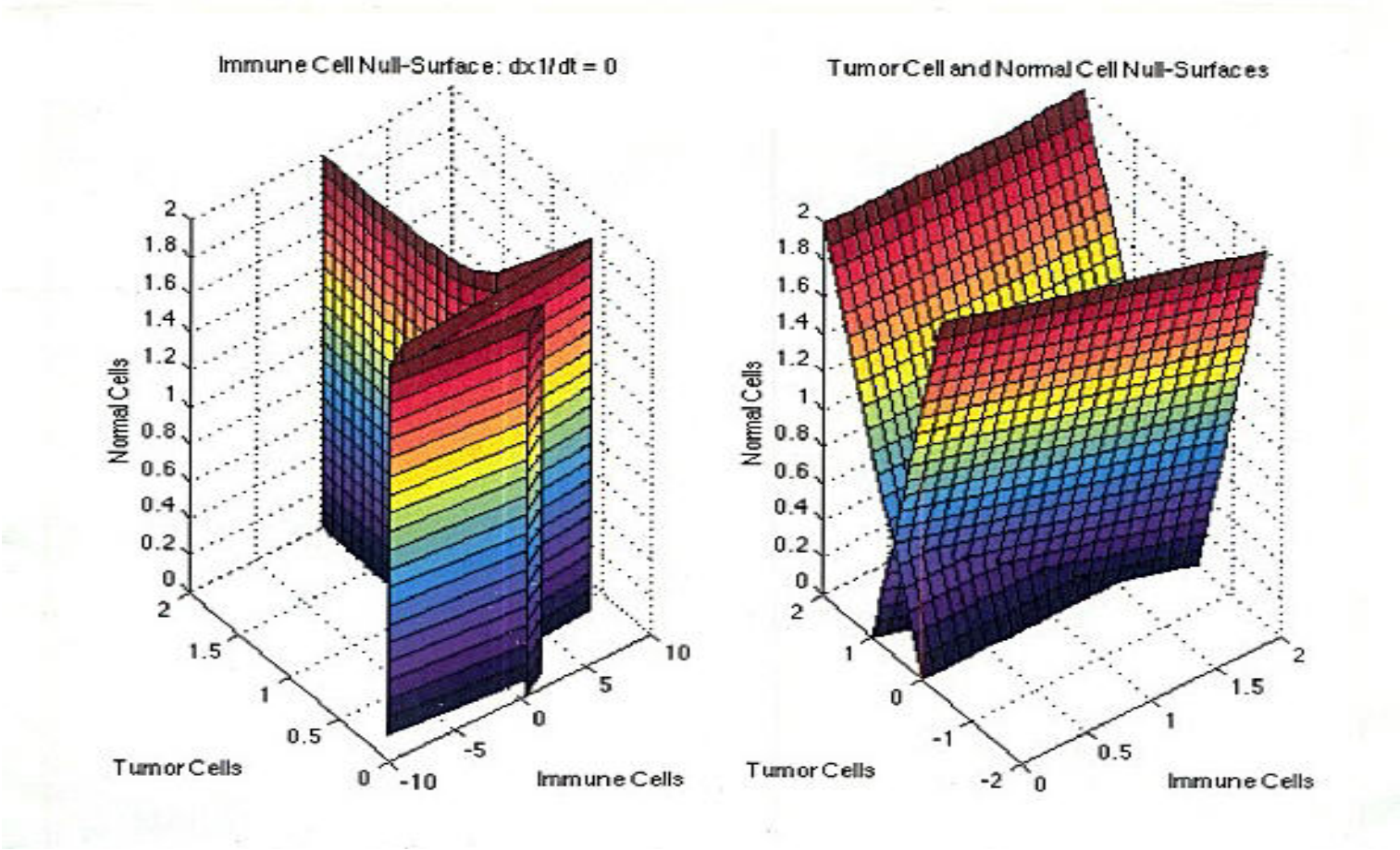
$$dE/dt = 0 \Rightarrow E = \frac{s(A+T)}{c_1 T(A+T) + d_1(A+T) - rT}$$

- Planes

$$dT/dt = 0 \Rightarrow T = 0 \quad \text{or} \quad T = \frac{1}{b_1} - \left(\frac{c_2}{b_1 r_1}\right) E - \left(\frac{c_3}{b_1 r_1}\right) N$$

$$dN/dt = 0 \Rightarrow N = 0 \quad or \quad N = \frac{1}{b_2} - \left(\frac{c_4}{b_2 r_2}\right) T$$

Null Surfaces: Immune, Tumor, Normal cells



Analysis: Determining Stability of Equilibrium Points

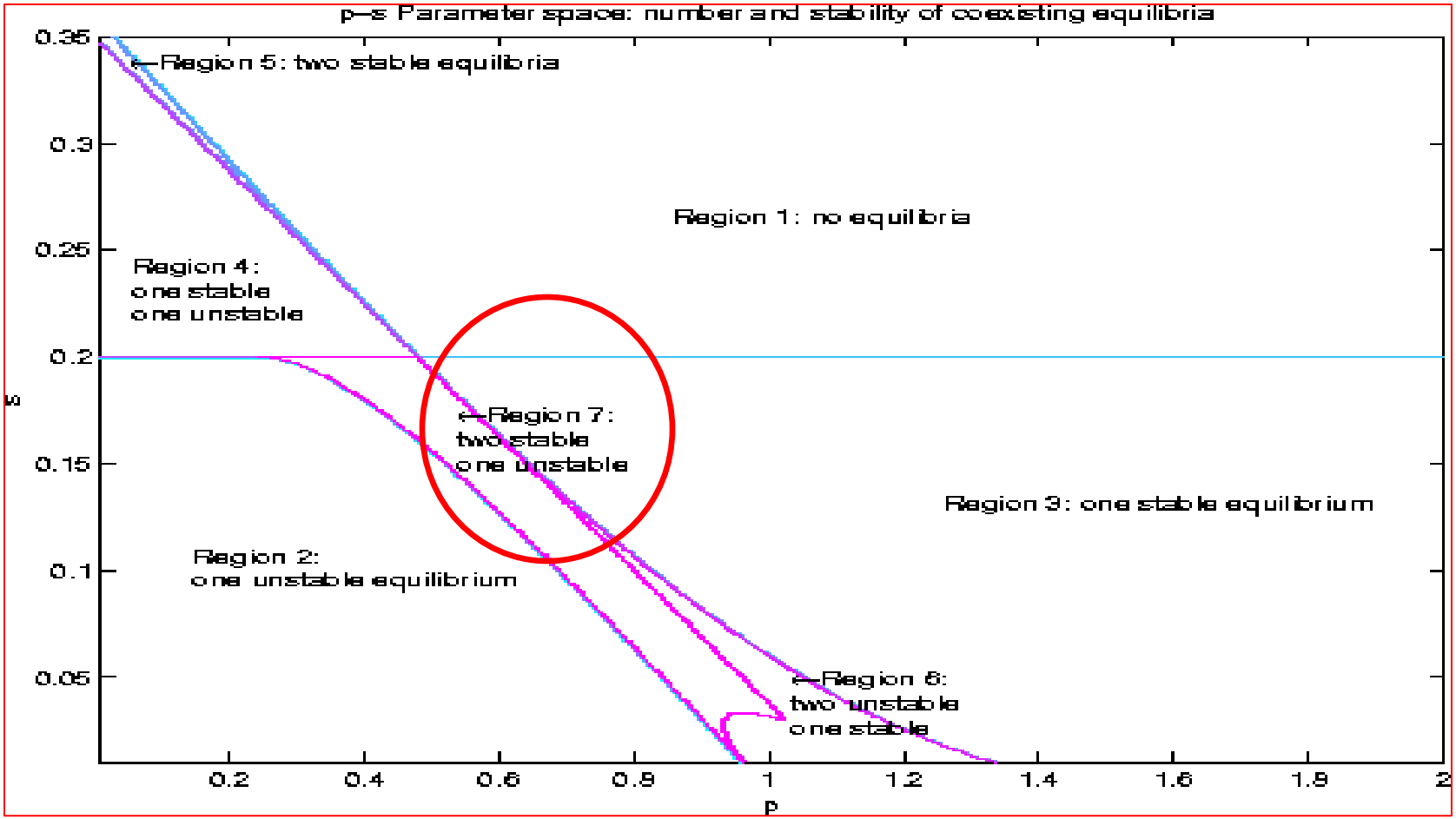
- Linearize ODE's about (eg, tumor-free) equilibrium point
- Solve for system eigenvalues:

$$\lambda_1 = -d_1 < 0 \qquad \text{Always Negative}$$

$$\lambda_2 = -r_2 - c_2/b_2 < 0 \qquad \text{Always Negative}$$

$$\lambda_3 = r_1 - c_3 s/d_1 - c_2/b_2 \qquad \text{Positive or Negative}$$

CoExisting Equilibria Map: $\rho - s$ Parameter Space

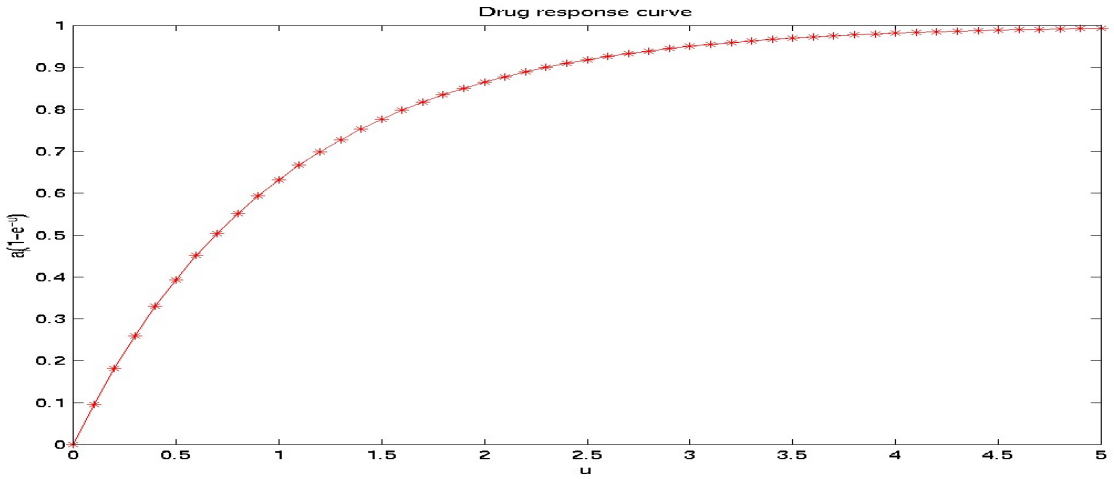


Cell Response to Chemotherapy

- To add drug response term to each DE, create new DE describing drug

  Amount of cell kill for given amount of drug ***u***:

$$F(u) = a_i(1 - e^{-ku})$$



Normal,Tumor & Immune Cells with Chemotherapy

- Four populations:

$$dE/dt = s + rET/(A+T) - c_1ET - d_1E - a_1(1-e^{-u})E$$

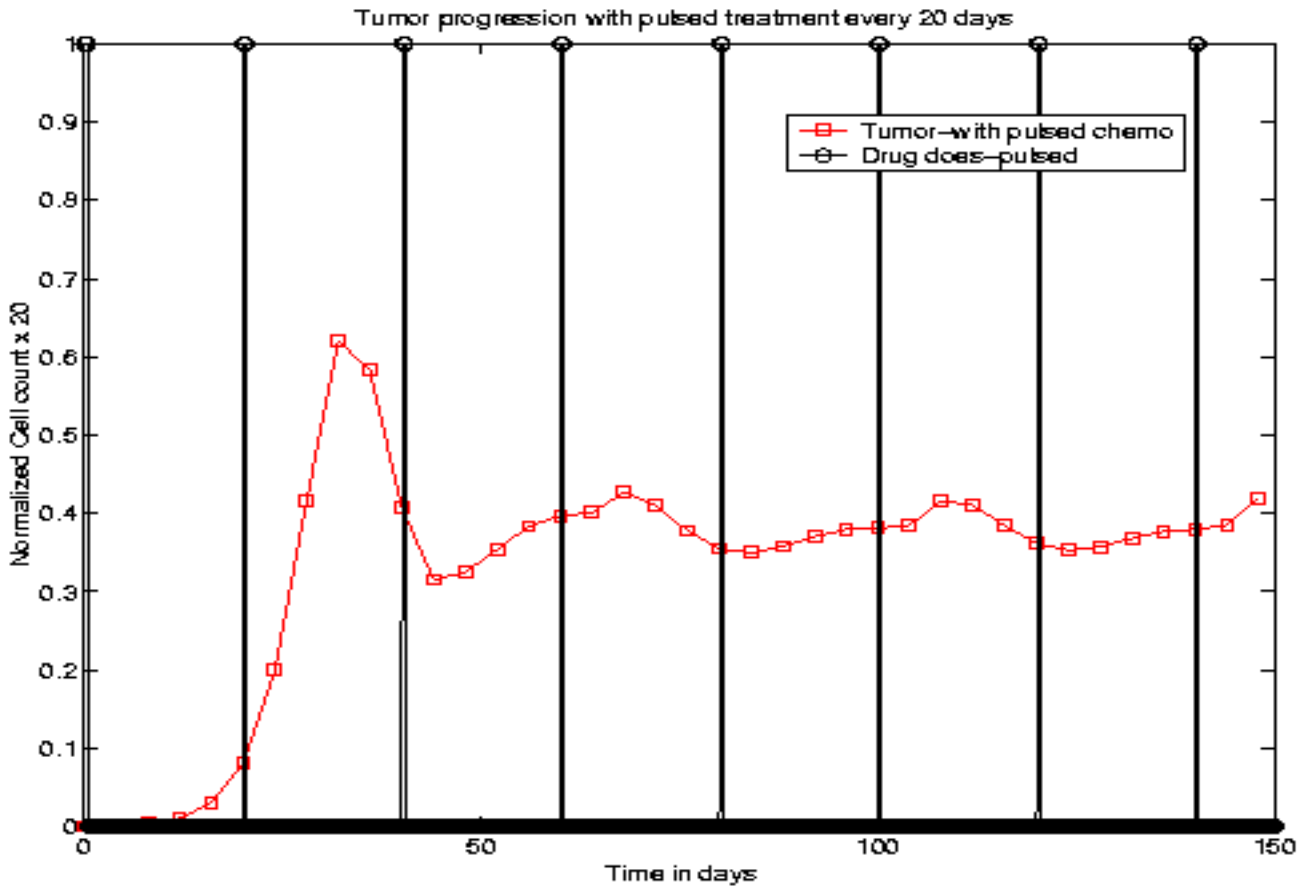
$$dT/dt = r_1T(1-b_1T) - c_2ET - c_3TN - a_2(1-e^{-u})T$$

$$dN/dt = r_2N(1-b_2N) - c_4TN - a_3(1-e^{-u})N$$

$$du/dt = v(t) - d_2u$$

- Chemotherapy dose $v(t)$ to treat tumor
- See: "A Mathematical Tumor Model with Immune Resistance and Drug Therapy: an Optimal Control Approach", *Journal of Theoretical Medicine, 2001*

Question Answered – Asynchronous (Delayed) Response happens with Immune System and Normal Cells



Outline

- Background: Cancer and genesis of this work
- The original motivating problem
- Controlling treatment
- Immunology of cancer
  - The Immune System Targets Cancer
  - Two Kinds of Immune Responses: Innate and Specific
- Extended model, include immune components
- Adding treatment
- Specific cancer: B-CLL
- Work in progress: Spatial tumor models
  - Hybrid CA models
  - 3D PDE models

Second Question: Can we find a better chemotherapy schedule?

- Four populations:

$$dE/dt = s + rET/(A+T) - c_1ET - d_1E - a_1(1-e^{-u})E$$

$$dT/dt = r_1T(1-b_1T) - c_2ET - c_3TN - a_2(1-e^{-u})T$$

$$dN/dt = r_2N(1-b_2N) - c_4TN - a_3(1-e^{-u})N$$

$$du/dt = v(t) - d_2u$$

- Goal: control dose $v(t)$ to minimize tumor
- See: "A Mathematical Tumor Model with Immune Resistance and Drug Therapy: an Optimal Control Approach", *Journal of Theoretical Medicine, 2001*

Optimal Control: Therapy Design

provides a theoretical framework to solve the problem: maximize or minimize **X (objective)** while making sure that **Y** is … **(constraint)**

- **Objective function options:**
  - Minimize a combination of total tumor and final tumor burden.
  - Minimize amount of drug given, maximize the number of effector cells.
- **Constraint options:**
  - Always keep circulating lymphocytes above a given threshold.
  - Treat only when circulating lymphocytes are above a threshold.
  - Fix total amount of drug given.

(Experiment with different options …)

Basic Optimal Control Problem:

- Let (Effector,Tumor,Normal)= $x = (x_1, x_2, x_3)$
- Find control variable *v(t)* that minimizes objective functional

$$J[x,v] = K_1 \cdot x_2(t_f) + K_2 \cdot \int_{t_0}^{t_f} x_2(t)\,dt$$

- subject to state equations with IC's

$$dx/dt = f(x(t), v(t), t), \qquad x(t_0) = x_0$$

- and inequality constraint

$$g(x(t), v(t)) = x_3(t) - .75 \geq 0 \qquad t \in [t_0, t_f]$$

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

Basic Optimal Control Solution

- Pontryagin's Max/Min Theorem: If Hamiltonian *H* is

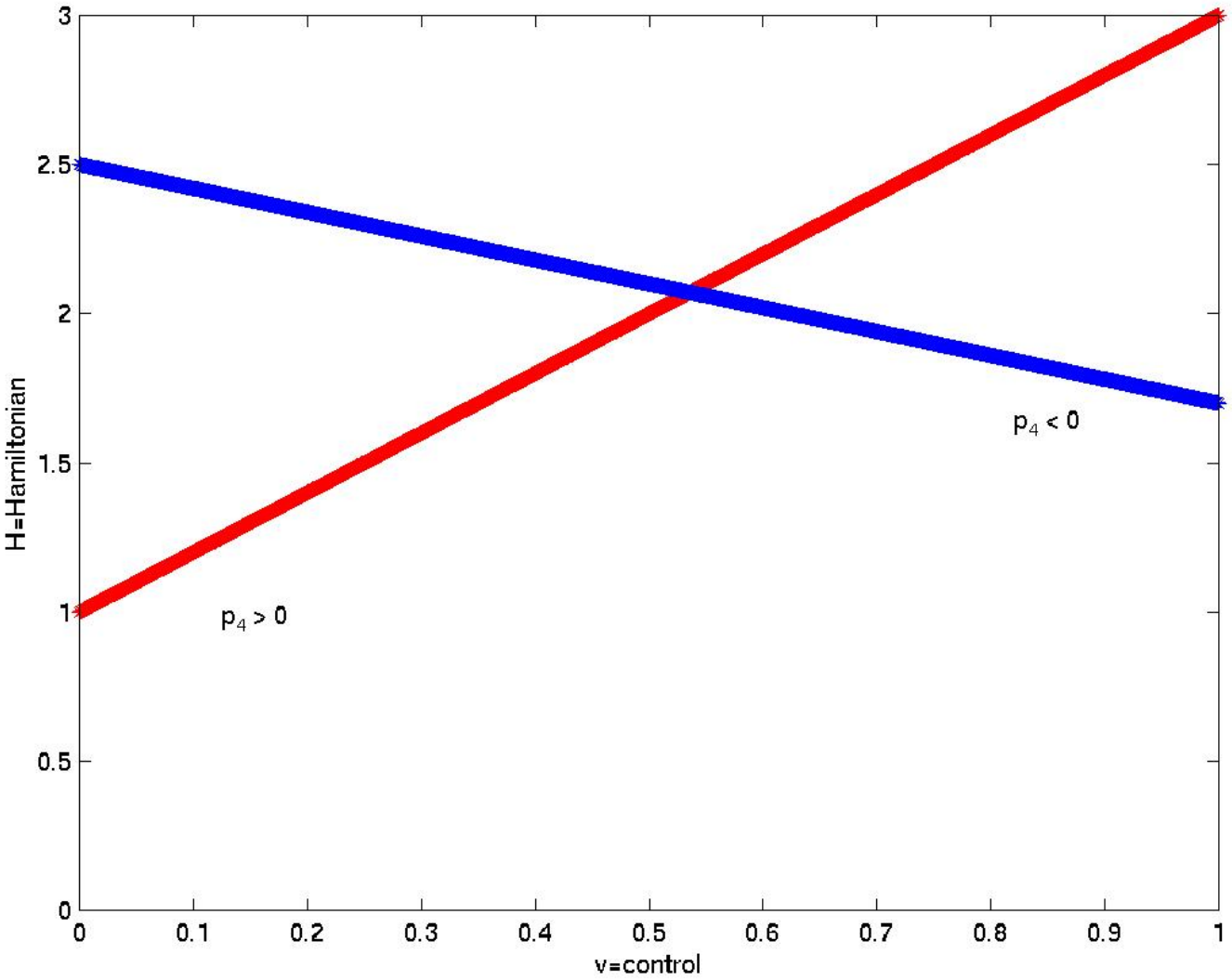
$$H = \theta + (p^T \cdot f) + \eta g$$

- where $\eta(t) > 0$ only when $g(x(t), v(t)) = 0$
- θ is the integrand of the objective *J*
- then *v(t)* is a candidate for a max/min of *J* if we can find co-state variables *p* satisfying

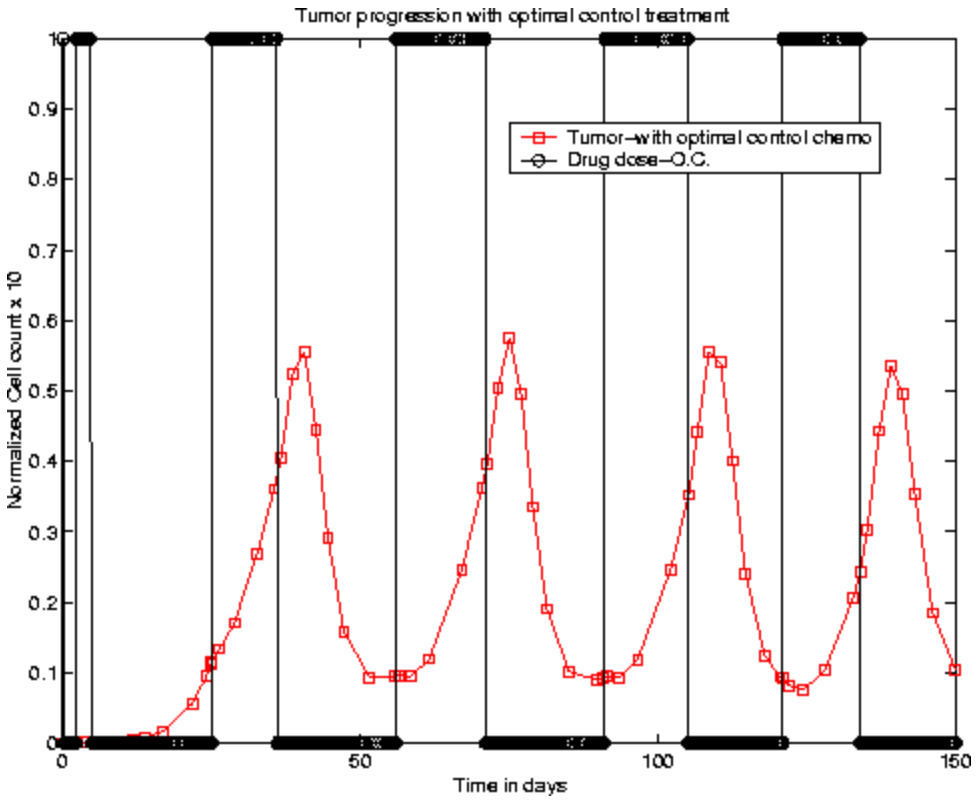
$$\frac{dp_i}{dt} = -\frac{\partial H}{\partial x_i}, \quad p_i(t_f) = \partial J / \partial x_i \mid_{t_f}$$

- and *v(t)* is such that $\partial H / \partial v = 0$

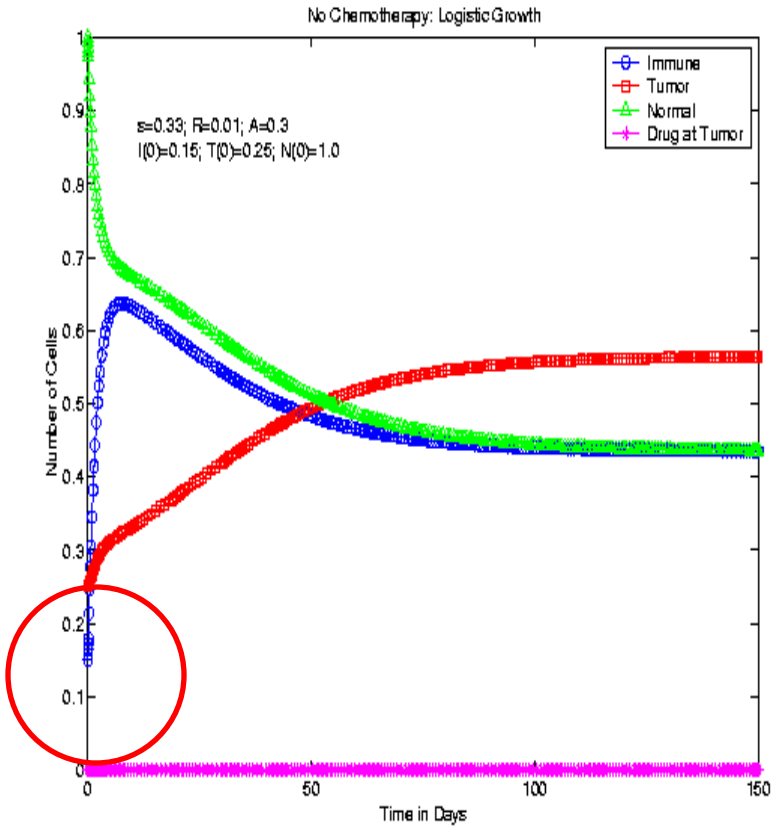
Bang-Bang Solutions



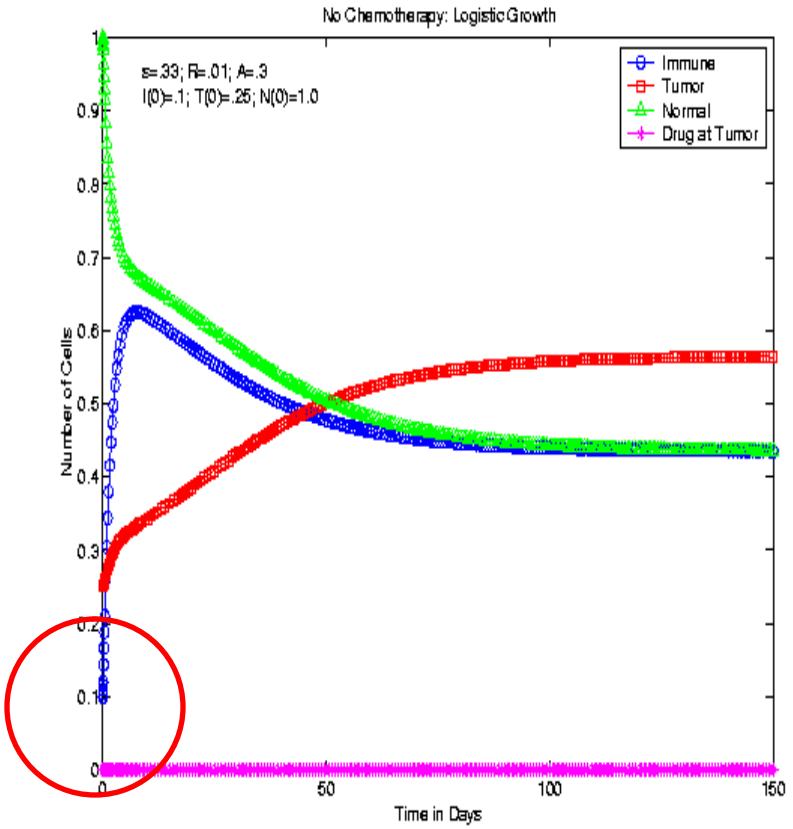
Optimal Control Solutions



Tumor Growth - No Medication

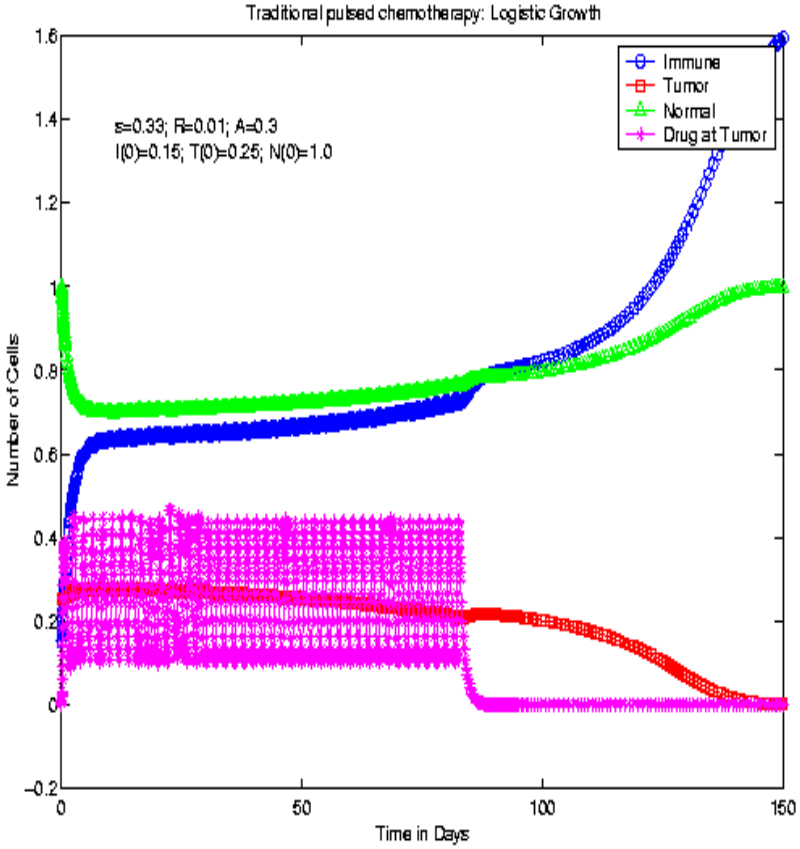


E(0) = 0.15

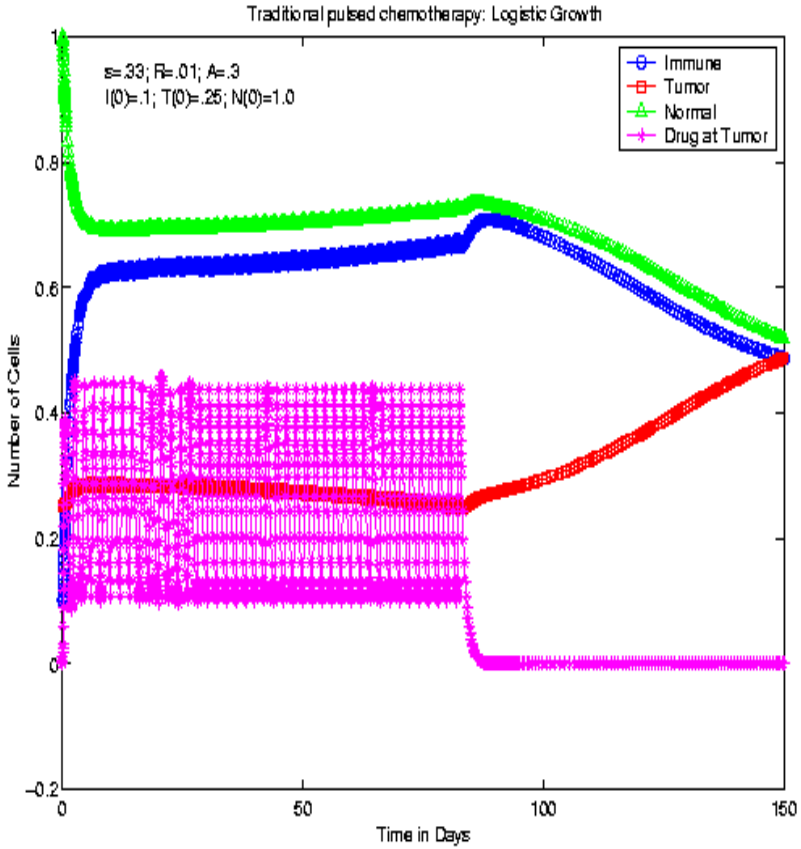


E(0) = 0.1

Tumor Growth - Pulsed Chemo

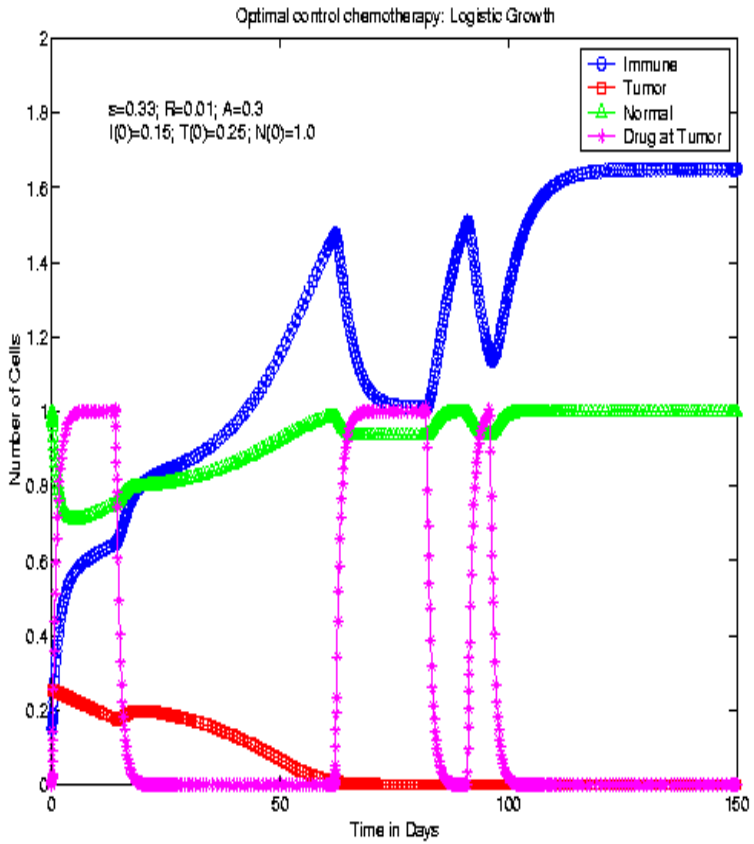


I(0) = 0.15

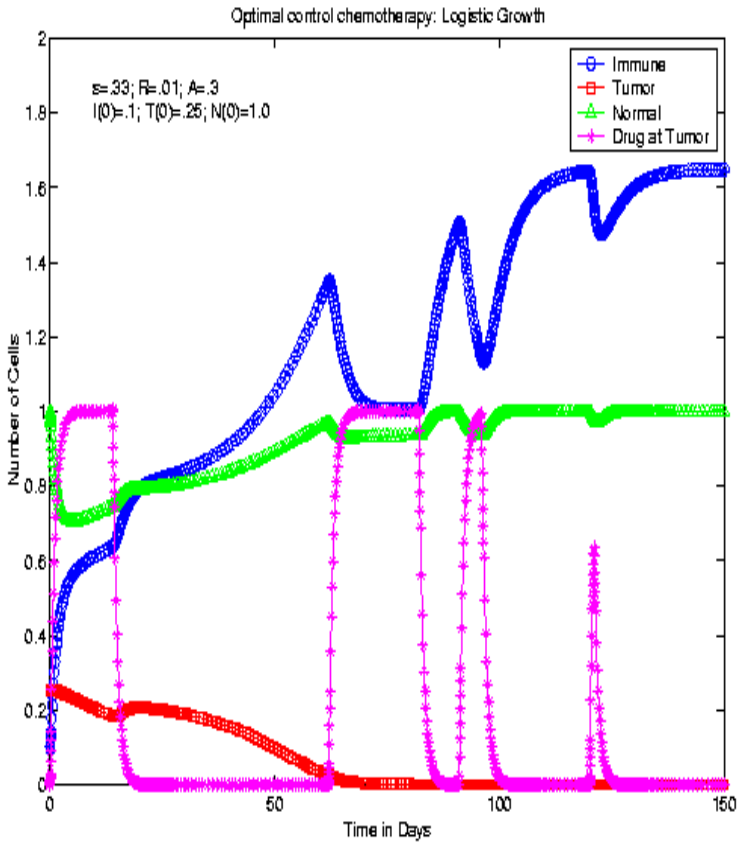


I(0) = 0.1

Tumor Growth - Optimal Control Chemo



I(0) = 0.15



I(0) = 0.1

Tumor Growth - Optimal Control Chemotherapy

Current work: New models with quadratic and linear Optimal control: Analysis

Tumor Growth - Optimal Control Chemotherapy

Single Quadratic Control: No Singularities

- T(t), tumor cells
- N(t), natural killer effector cells
- C(t), circulating lymphocytes
- M(t), chemotherapy in patient
- v_M(t), chemotherapy drug dose

$$J(V_M) = \int_0^{t_f} T(t) + \varepsilon_M \left(V_M^2(t)\right) dt$$

Tumor Growth - Optimal Control Chemotherapy

Single Quadratic Control: No Singularities

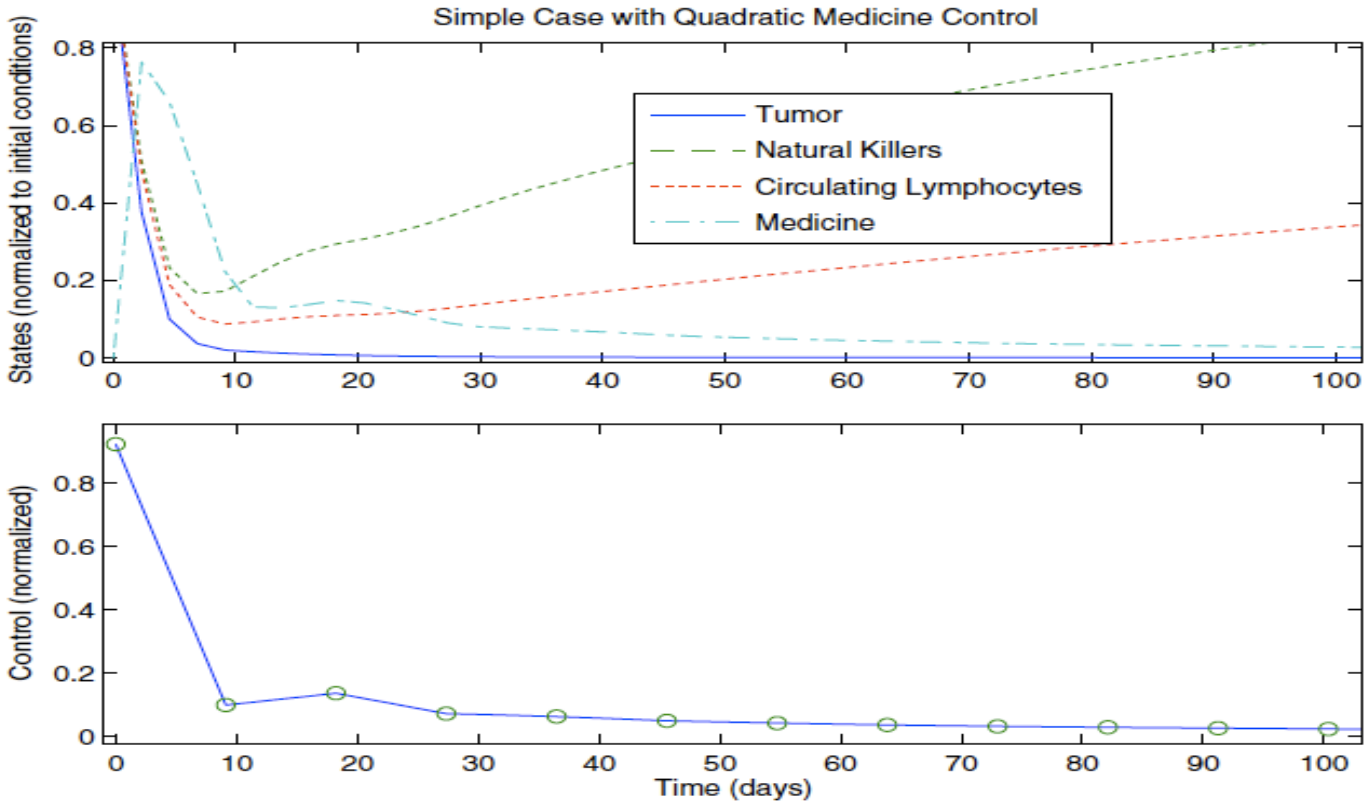
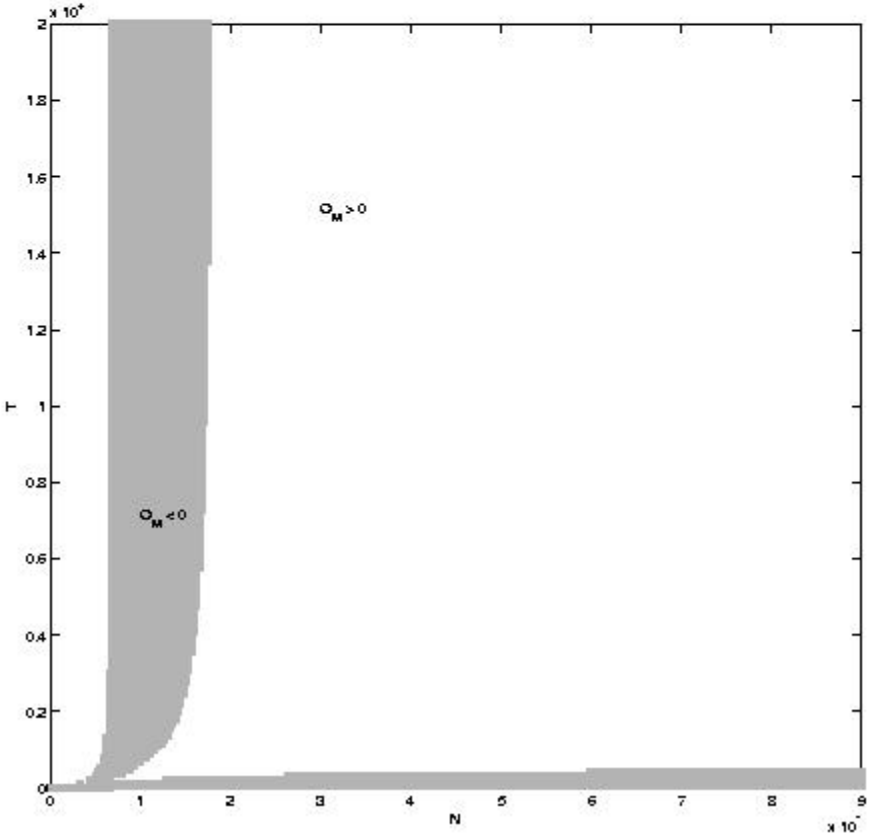


Fig. 1. Quadratic control situation. This is a 100 day view of optimal chemotherapy treatment for 365 days. One can see that the largest dose of (normalized) chemotherapy is administered at the beginning of the time period, and then is lowered to a small but non-zero and very slowly decreasing level for the remainder of the treatment period. The tumor is driven to near-zero, while the populations of immune cells are rising. Initial tumor size is 1×10^7 cells. Initial natural killer cell level is 3×10^5 and initial circulating lymphocyte level is 6.25×10^{10}.

$$J(V_M) = \int_0 T(t) + \varepsilon_M \left(V_M^2(t)\right) dt$$

Tumor Growth – Single Linear Optimal Control of Chemotherapy

Determining Singular Regions



$$J = \int_0^{t_f} (T(t) + \varepsilon_M \left(V_M(t)\right) dt$$

Tumor Growth – Single Linear Optimal Control of Chemotherapy

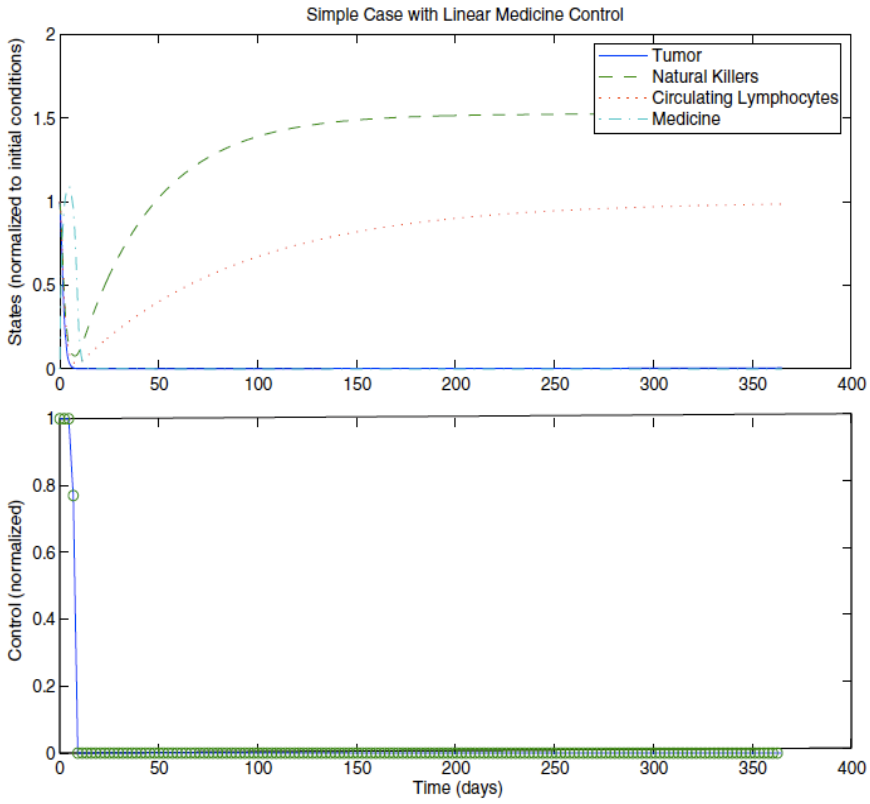


Fig. 3. These graphs represent the states and control for the linear case. There is an initial burst of chemotherapy at the start of the treatment period, after which the medicine is completely shut off and is never again turned on. The tumor is driven to a very low but non-zero level, while the immune cell populations increase over time. Initial tumor size is 1×10^{7} cells. Initial natural killer cell level is 3×10^{5} and initial circulating lymphocyte level is 6.25×10^{10}.

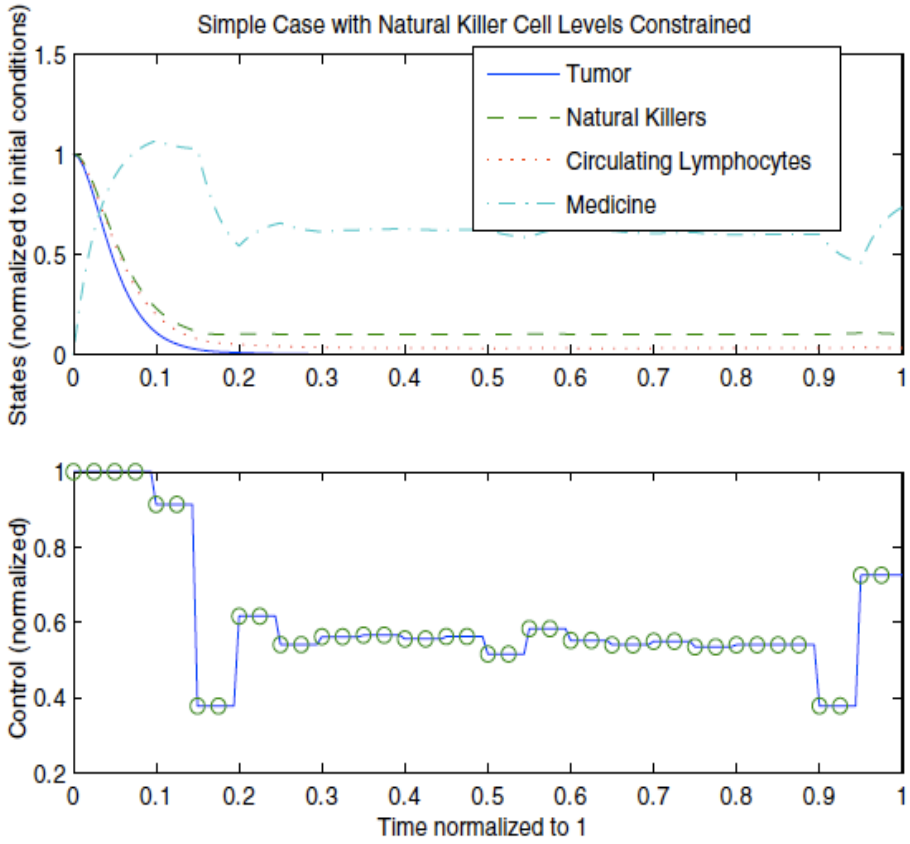


Fig. 5. In this run, the only value minimized was the tumor size. Additionally, the natural killer cells were required to be kept above 10% of their initial value and final time was not fixed. Miser chose 35.62 days to run this simulation. The medicine starts high and then lowers and adjusts to keep the natural killer cells at the appropriate level. Initial tumor size is 1×10^{7}cells. Initial natural killer cell level is 3×10^{5} and initial circulating lymphocyte level is 6.25×10^{10}.

$$J=\int_0^{t_f}\left(T(t)+\varepsilon_M\left(V_M(t)\right)\right)dt$$

$$J=\int_0^{t_f}T(t)\,dt,\quad \text{Constraint: } N>0.1N(0)$$

Outline

- Background: Cancer and genesis of this work
- The original motivating problem
- Controlling treatment
- Immunology of cancer
  - The Immune System Targets Cancer
  - Two Kinds of Immune Responses: Innate and Specific
- Extended model, include immune components
- Adding treatment
- Specific cancer: B-CLL
- Work in progress: Spatial tumor models
  - Hybrid CA models
  - 3D PDE models

The next question:

- What role can immunotherapy and vaccine therapy play in cancer treatment?

Cancer Immunology in the News

ScienceDaily

Your source for the latest research news

Web address:
http://www.sciencedaily.com/releases/2008/09/080925144758.htm

Lung Cancer: Radiation, Immunotherapy Gives Greater Effectiveness, Study Suggests

ScienceDaily (Sep. 27, 2008) — Oregon Health & Science University Cancer Institute researchers have found the right formula of rad
hope will translate to better tr

The study was presented Sept
Oncology conference in Bost

Principal investigator Marka
the effects of stereotactic bod
delivered in three large doses
normal, healthy tissue, more

"We studied the consequence
fewer of the cells that turn off
these radiation doses," said C
Medicine.

Researchers then selected a fo
with the immune response ge
immune system to attack tum
more effective at clearing the

Cancer Immunotherapy Reduces Risk Of Relapse After Surgery, Study Shows

ScienceDaily

Your source for the latest research news

Prostate Cancer Treatment
California residents learn how HIFU treats prostate cancer.
www.internationalhifu.com

Chemo? No Chemo?
For early stage breast cancer A te help with your decision
www.MyTreatmentDecision.com

News | Articles | Videos | Images | Books

Health & Medicine | Mind & Brain | Plants & Animals | Earth & Climate | Space & Time | Matter &

Science News

Share | Blog | Cite

Cancer Immunotherapy Reduces Risk Of Relapse After Surgery, Study Shows

ScienceDaily (Apr. 26, 2008) — New, long-term results from a clinical trial presented today at the 1st European Lung Cancer Conference jointly organized by the European Society for Medical

Ads by Google — Advertise here

Immunotherapy Treatments
Learn about immunotherapy treatment by chatting w/ an oncology expert.

Jobs | Cars.com |

LAT Home | My LATimes | Print Edition | All Sections

Los Angeles Times | Health

Medicine | Fitness & Nutrition | Policy | Opinion | Conditions A-Z

You are here: LAT Home > Health > Fitness

For cancer patients, personalized treatment offers a new range of options -- and hope

Jay L. Clendenin / Los Angeles Times

rs ago, a vaccine designed specifically for musician Kevin Carlberg, shown with his daughter, him beat back an aggressive type of brain cancer.

ng a therapy derived from the genetic information of a person's cancer is g to change today's standard medical approach -- and may help bring on a cure.

MSNBC.com

'Cancer vaccines' offer new way to fight disease

Treatment using immune system to battle 3 types of cancer shows promise

The Associated Press

updated 11:33 a.m. PT, Sun., May 31, 2009

ORLANDO, Fla. - First there was surgery, then chemotherapy and radiation. Now, doctors have overcome 30 years of false starts and found success with a fourth way to fight cancer: using the body's natural defender, the immune system.

The approach is called a cancer vaccine, although it treats the disease rather than prevents it.

At a cancer conference Sunday, researchers said one such vaccine kept a common form of lymphoma from worsening for more than a year. That's huge in this field, where progress is glacial and success with a new treatment is often measured in weeks or even days.

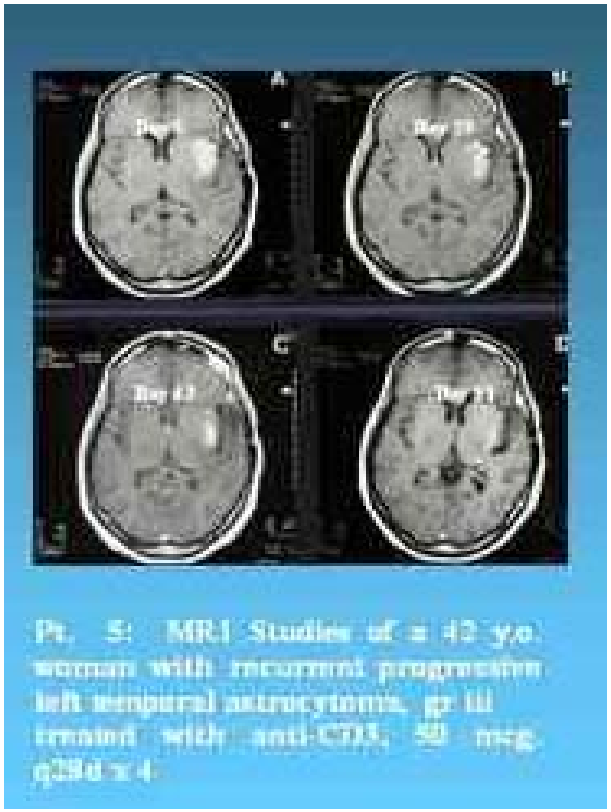
Experimental vaccines against three other cancers — prostate, the deadly skin disease melanoma and an often fatal childhood tumor called neuroblastoma — also gave positive results in late-stage testing in recent weeks, after decades of struggles in the lab.

"I don't know what we did differently to make the breakthrough," said Dr. Len Lichtenfeld of the American Cancer Society.

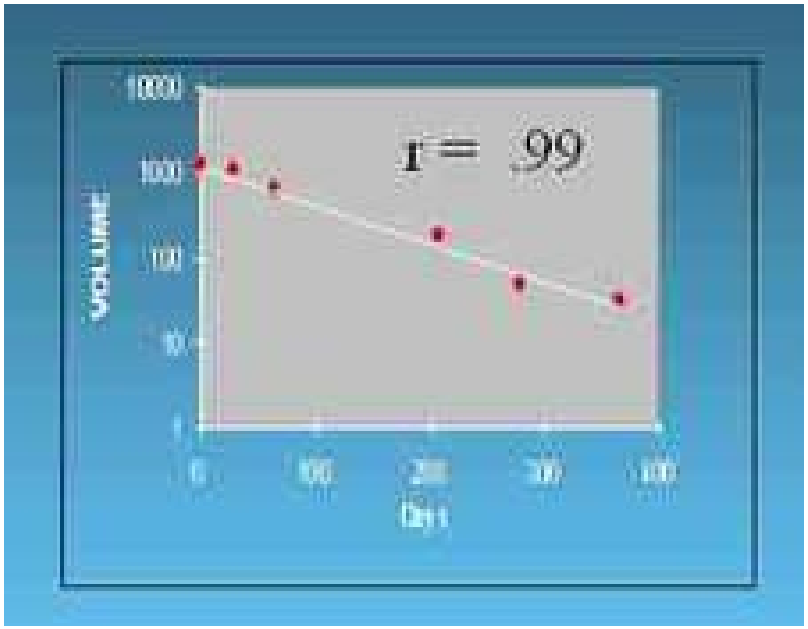
Instead of a single "A-Ha!" moment, there have been many "ah, so" discoveries about the immune system that now seem to be paying off, said Dr. John Niederhuber, director of the National Cancer Institute.

Cancer Immunotherapy

Immunotherpay: Clinical Response to Anti-CD3



Pt. 5: MRI Studies of a 42 y.o. woman with recurrent progressive left temporal astrocytoma, gr iii treated with anti-CD3, 50 mcg. q28d x 4



Treatment: Day 0 - Anti CD-3 10-75 mcg iv/60 min
Day 1 - Cyclophosphamide 300 mg/m^2
Day 28 - Re-evaluate, MRI, re-treat

[CANCER RESEARCH 51, 2127–2132, April 15, 1991]

Antitumor Effects of Interleukin 2 Liposomes and Anti-CD3-Stimulated T-Cells against Murine MCA-38 Hepatic Metastasis[1]

Cynthia M. Loeffler,[2] Jeffrey L. Platt, Peter M. Anderson, Emmanuel Katsanis, Juan B. Ochoa, Walter J. Urba, Dan L. Longo, Arnold S. Leonard, and Augusto C. Ochoa

Departments of Surgery [C. M. L., A. S. L.], and Pediatrics [J. L. P., P. M. A., E. K.], University of Minnesota, Minneapolis, Minnesota 55455; Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania 15261 [J. B. O.]; Immunotherapy Laboratory, Program Resources, Inc. [C. M. L., W. J. U., A. C. O.], and Biological Response Modifiers Program [D. L. L.], National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, Maryland 21702

ABSTRACT

The stimulation of murine splenocytes with the monoclonal antibody anti-CD3 and interleukin 2 (IL-2) results in the propagation of large

spleen (4). Several subpopulations of lymphocytes develop LAK activity, depending on the specific signals used to activate the cells. The addition of IL-2 alone generates cells with lytic

ASCO American Society of Clinical Oncology

www.asco.org

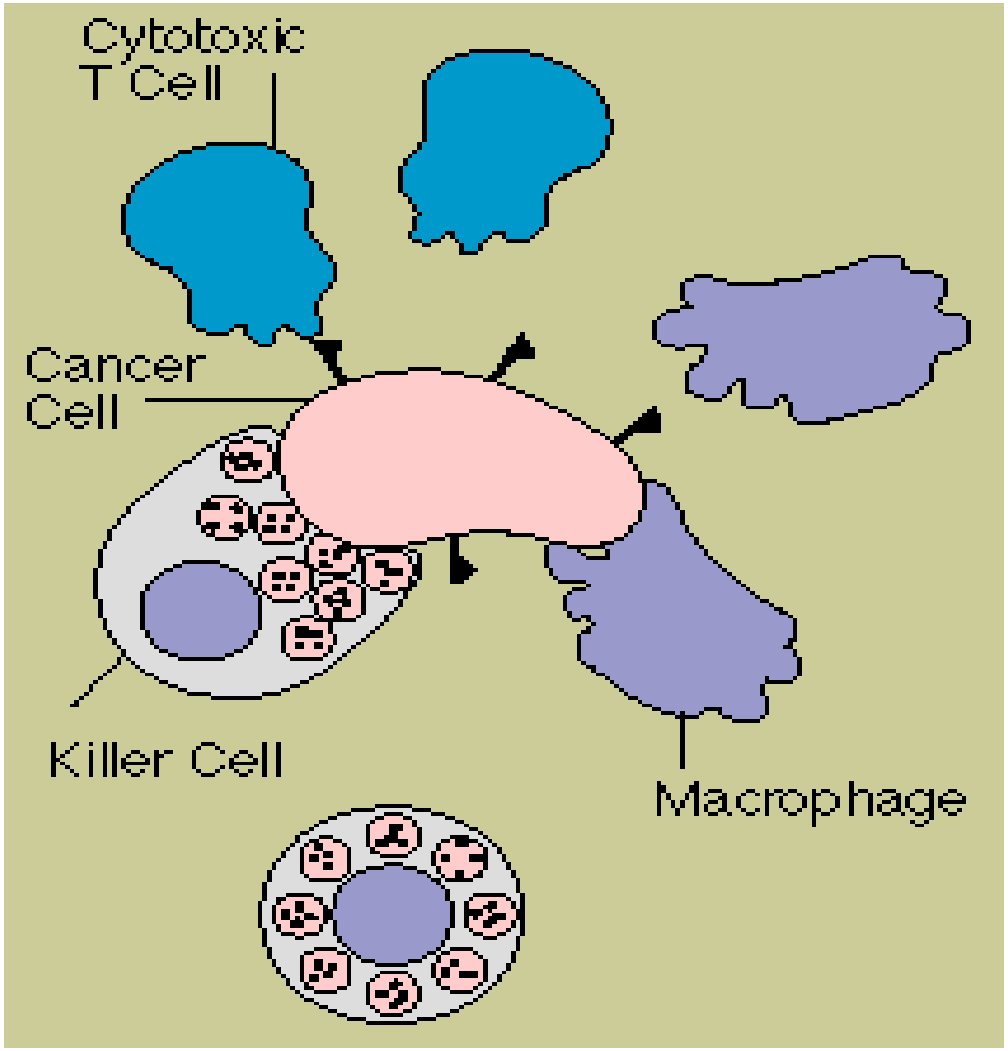
Salvage Monoclonal Antibody Therapy for Primary Brain Tumors.

Sub-category: Central Nervous System Tumors
Category: Central Nervous System Tumors
Meeting: 2000 ASCO Annual Meeting

VACCINES and IMMUNOTHERAPY

- **Immunotherapy** boosts immune resistance with biological response modifiers
- **Vaccine Therapy** (special case) boosts immune resistance with modified tumor challenge
- **Use**: Vaccines used mainly **therapeutically**, not yet preventatively.
- **Sometimes Only Option**: When chemo won't work. Certain cancers **good candidates**, eg, melanoma,glioma
- **Benefits**: Low toxicity, potentially high efficacy

Immune System Targets Cancer



Thanks: National Cancer Institute

Data Evidence

Experimental Data: Basis for ODE Models

Mouse Data: Basis for Preliminary Vaccine Therapy in Model.

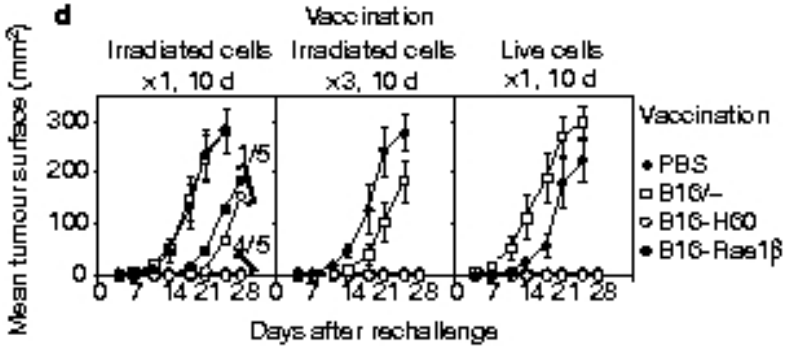
The Diefenbach et al.[2] study

Human Data: Basis for Immunotherapy in Model:

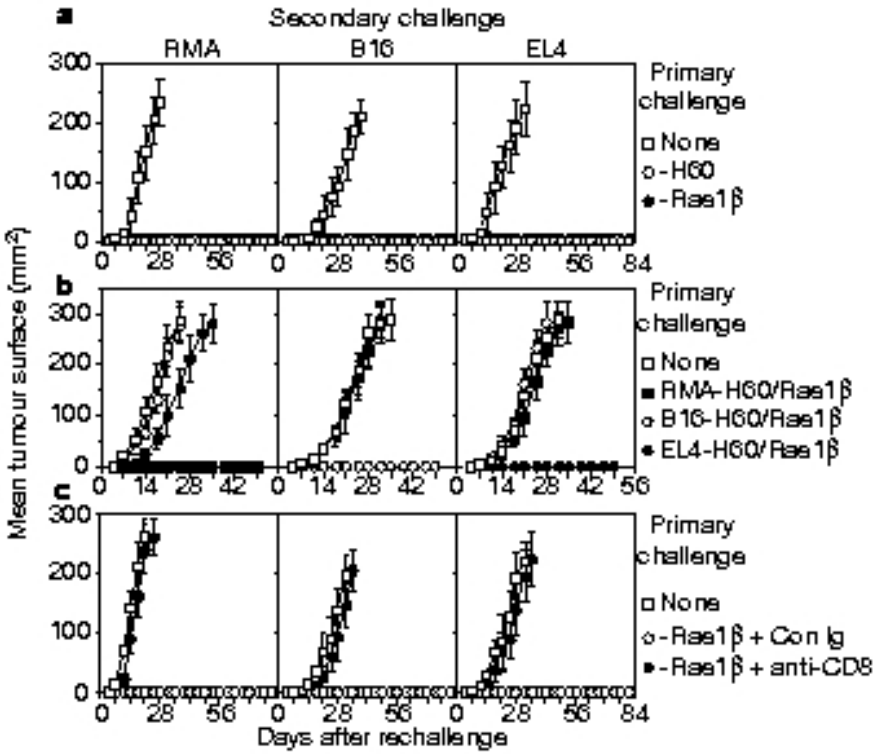
The Rosenberg et al. [4] study

Mouse Lab Data: Preventative Vaccination

Diefenbach mouse trials with various vaccination strategies.



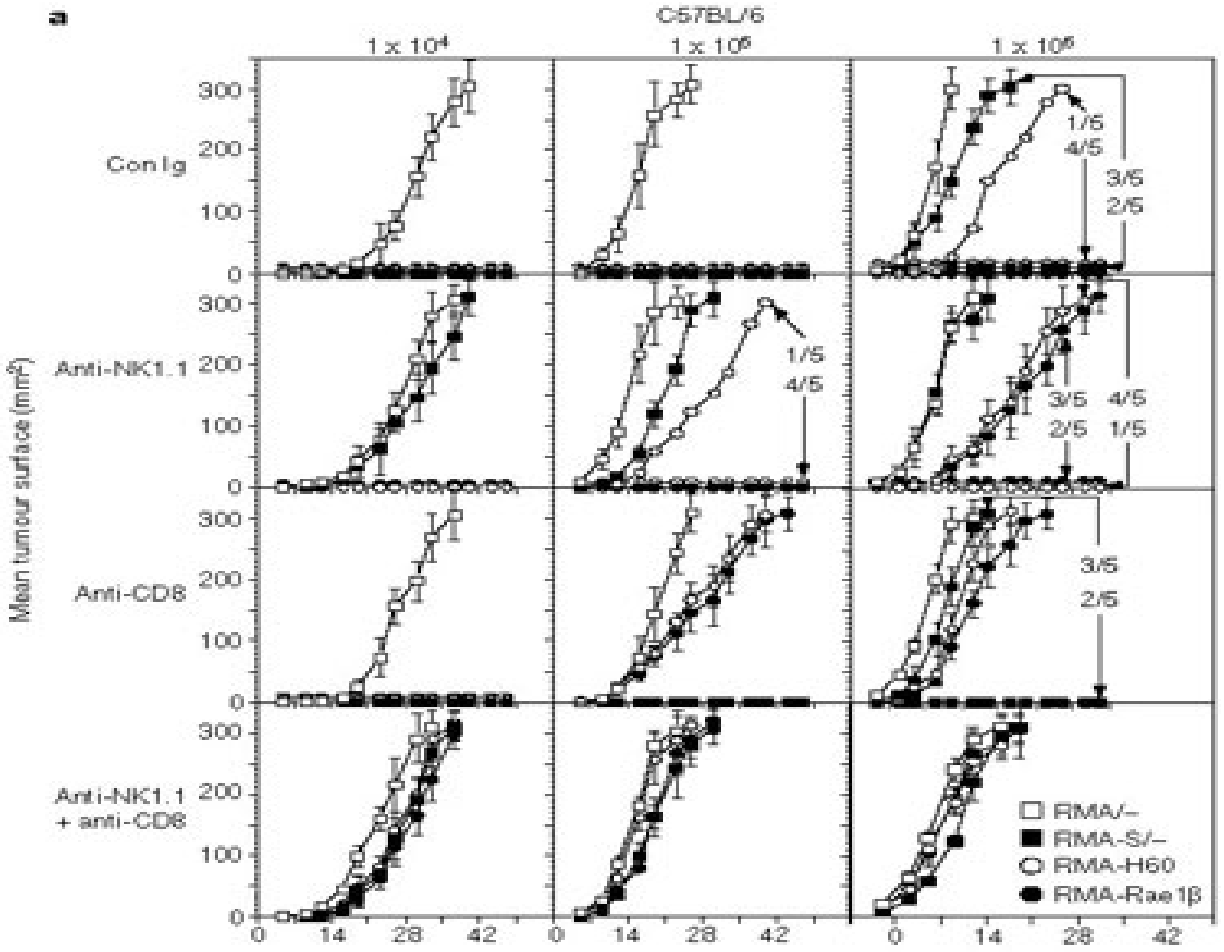
Mice "vaccinated" with ligand transduced cells, then rechallenged with control-transduced cells, were proteced.



reprinted from *Nature*, 2001;41:165-171

Mouse Lab Data: CD8 vs NK Protection

Diefenbach mouse trials with varying tumor challenge levels.



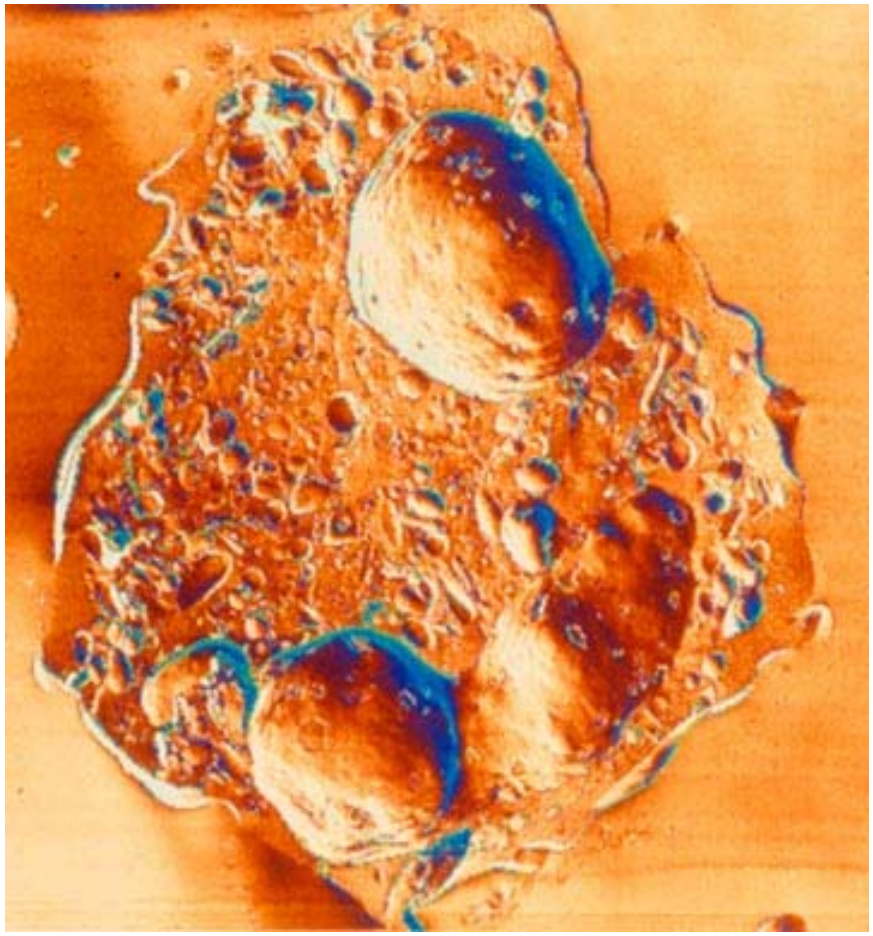
Black circles: RMA-Rae1b

Ligand Transduced Cells

reprinted from *Nature*, 2001;41:165-171

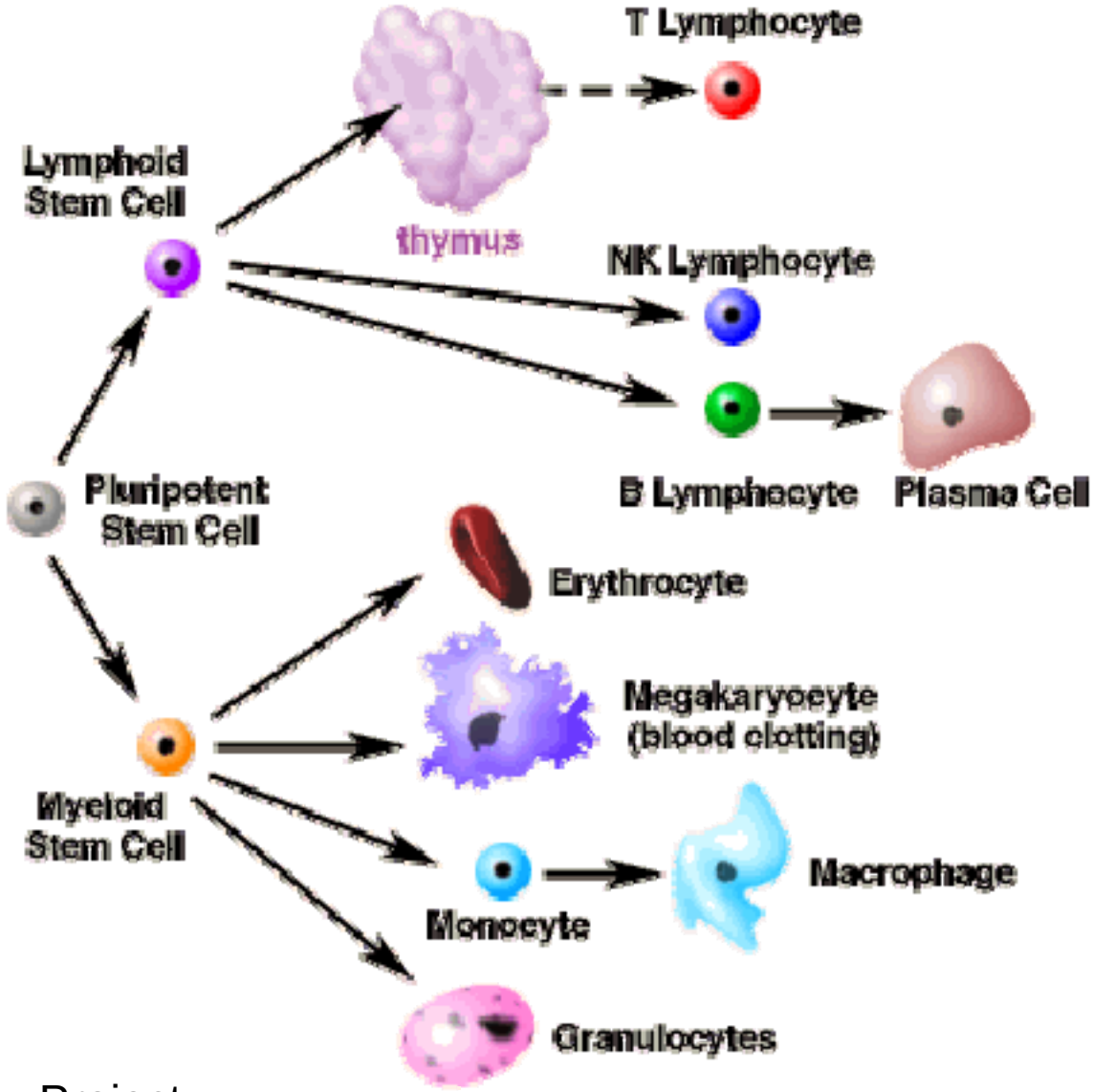
How the Immune System Works

- Huge army of “defender cells”: White Blood Cells
- Body creates about 1000 million per day
- Natural Immunity: Regular Patrols (“Secret handshake”)
- Specific Immunity: Activated After Invasion (“Glove sniffing dog”)



Coloured electron micrograph of a white blood cell.
National Medical Slide Bank/Wellcome Photo Library

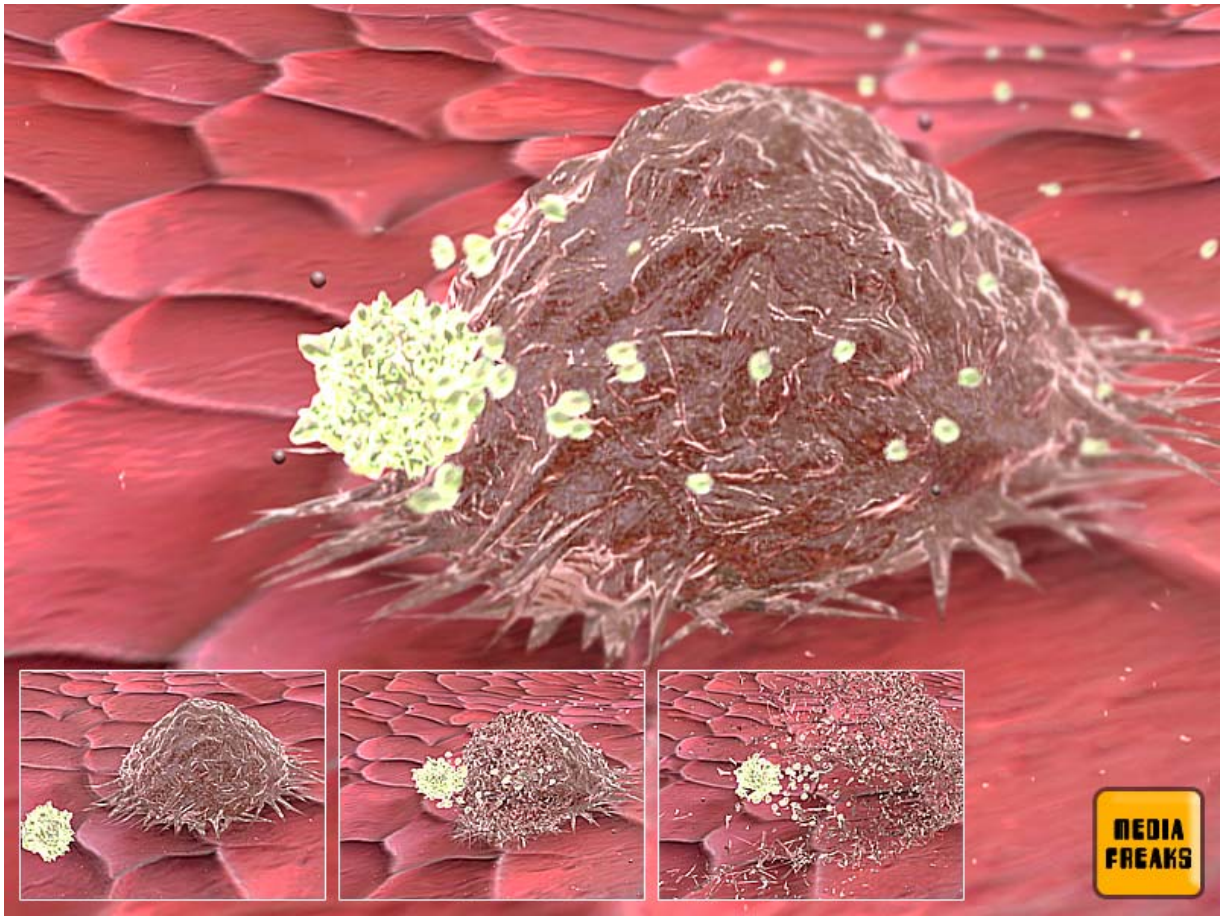
The Immune System



Thanks: The Biology Project

NK Cell Killing Cancer Cell

Aspects of Tumor Immune Response: NK cells

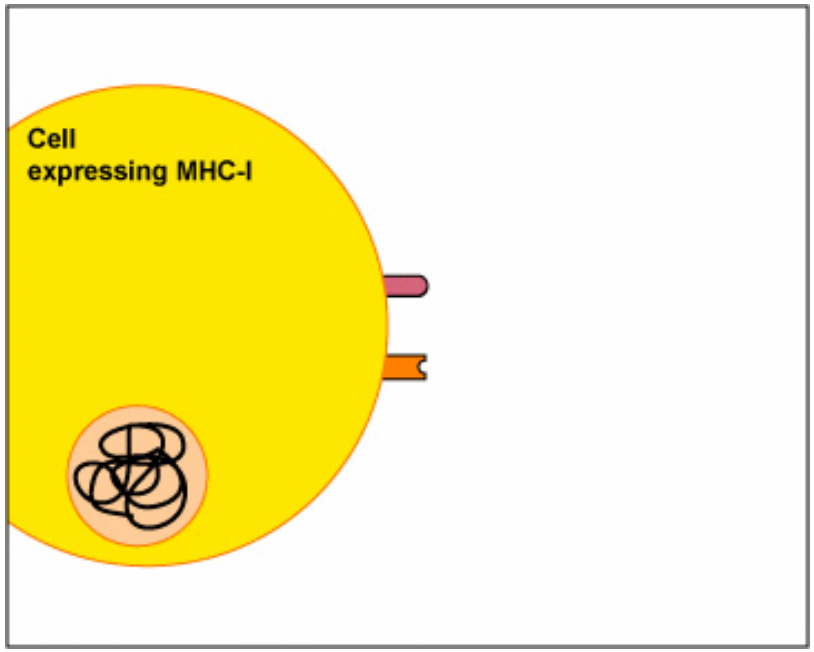


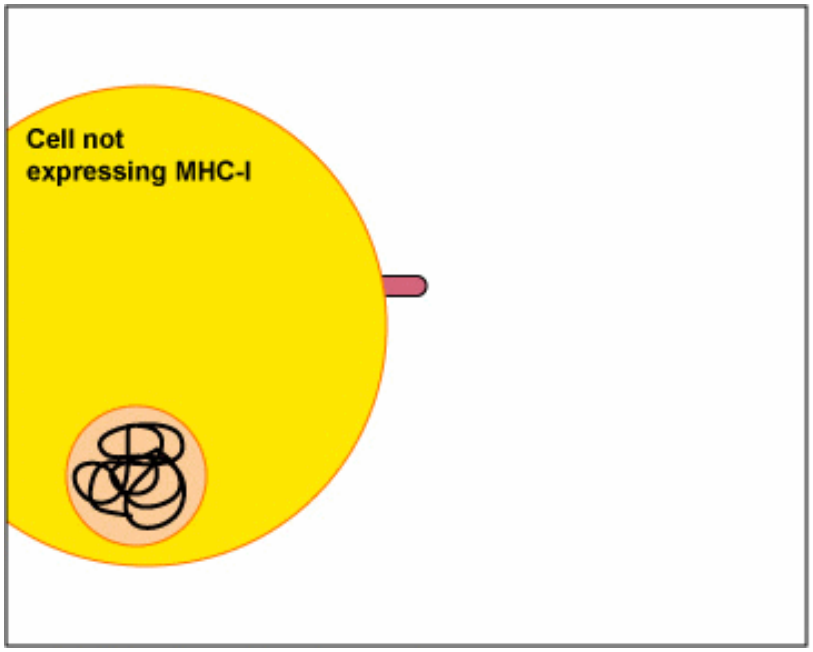
NKs recognize self (MHC-I expressed)

Down-reg of MHC-I (as with certain cancer cells) allows NK-tumor lysis

Thanks: http://www.media-freaks.com/casestudies/eexcel_cdrom/

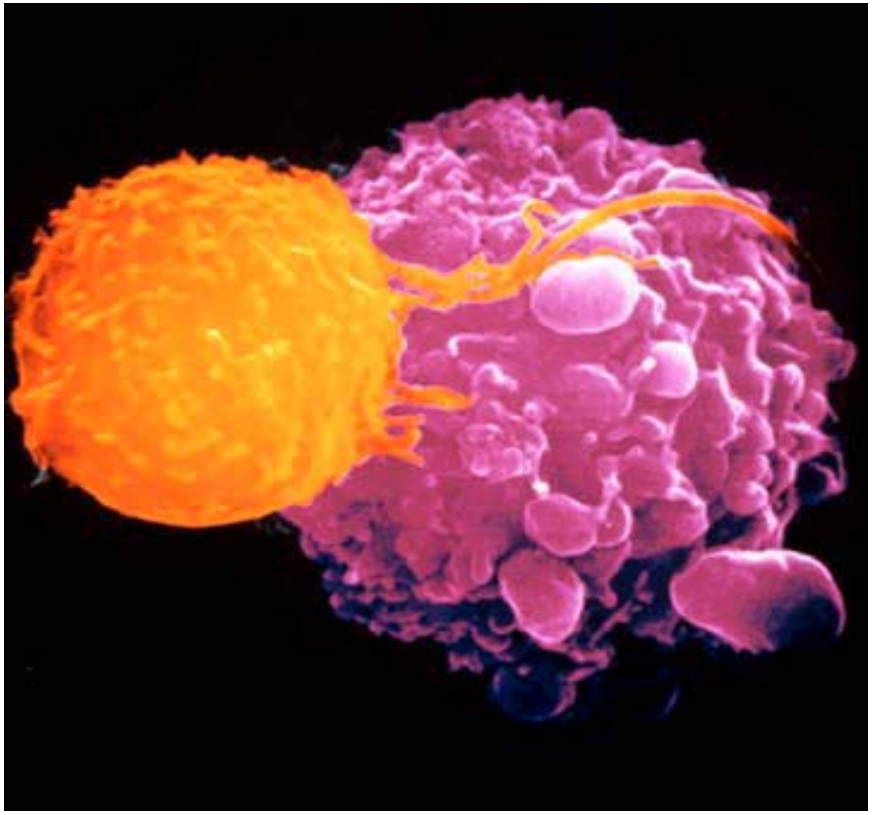
Innate Immune Response to Cancer
(Natural Killer Cell = NK)
NK recognizes "self" and attacks "non-self"
(the cancer): **Secret Handshake**

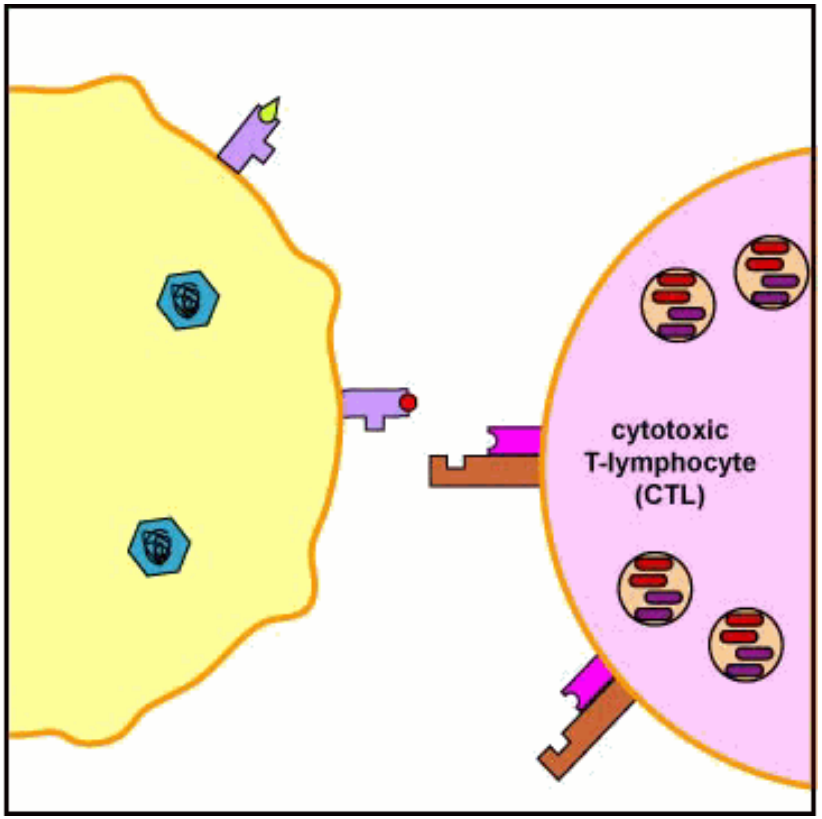




Specific Immune Response to Cancer

- T-cell (CTL, CD8+T-cell) recognizes and attacks cancer: "**Glove Sniffing Dog**"





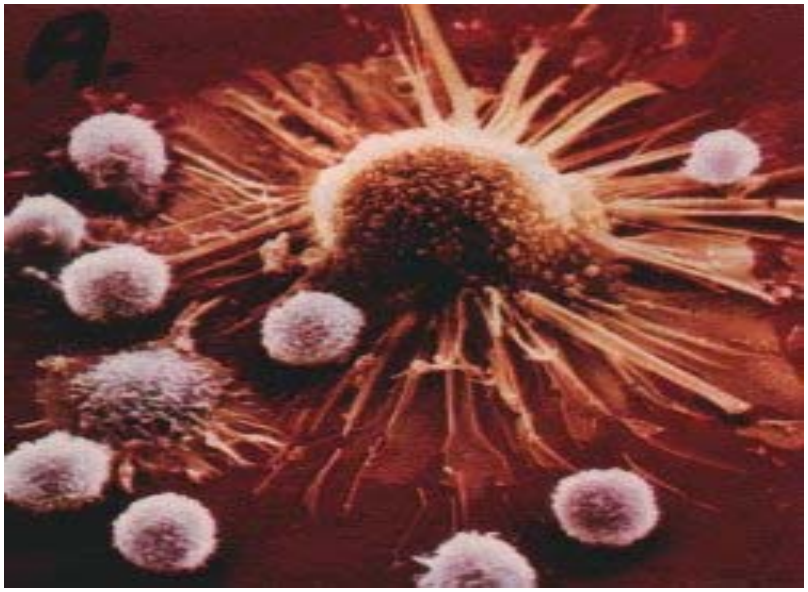
T-cell Attacking Cancer-cell Movie

QuickTime™ and a
Video decompressor
are needed to see this picture.

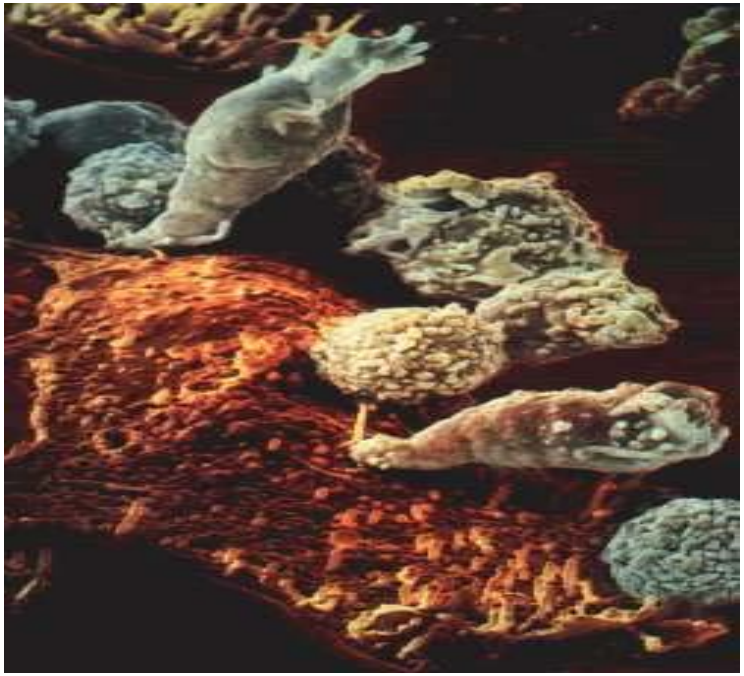
Thanks: CellsAlive.com

T-Cells Killing a Cancer Cell

- **Before**
  A fully intact cancer cell surrounded by the immune system's killer T-cells. Notice the tentacles of the cancer cell.



- **After**
  The cancer cell is completely flattened and totally destroyed.



Thanks: cancer-info.com

Outline

- Background: Cancer and genesis of this work
- The original motivating problem
- Controlling treatment
- Immunology of cancer
  - The Immune System Targets Cancer
  - Two Kinds of Immune Responses: Innate and Specific
- Extended model, include immune components
- Adding treatment
- Specific cancer: B-CLL
- Work in progress: Spatial tumor models
  - Hybrid CA models
  - 3D PDE models

New Mathematical Model Components

Cell Populations:

- Tumor Cells: ***T(t).***
- Natural Killer (NK) Cells: ***N(t).*** Nonspecific. Always present, stimulated by the presence of tumor cells.
- CD8+T Cells: ***L(t).*** Specific. Cytolytic activity and cell proliferation are increased by the presence of tumor cells.

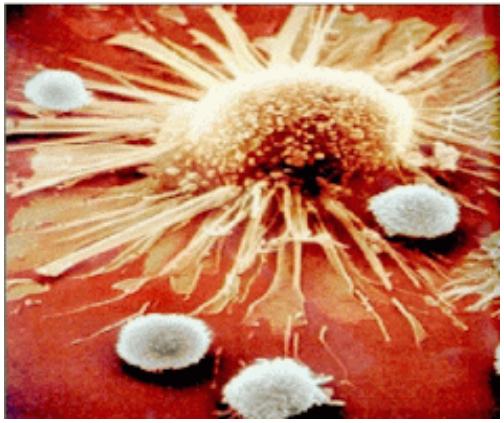


Image courtesy http://www.immuneresources.com/cancer.htm

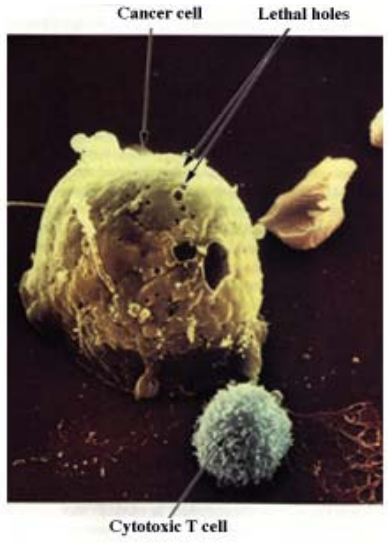
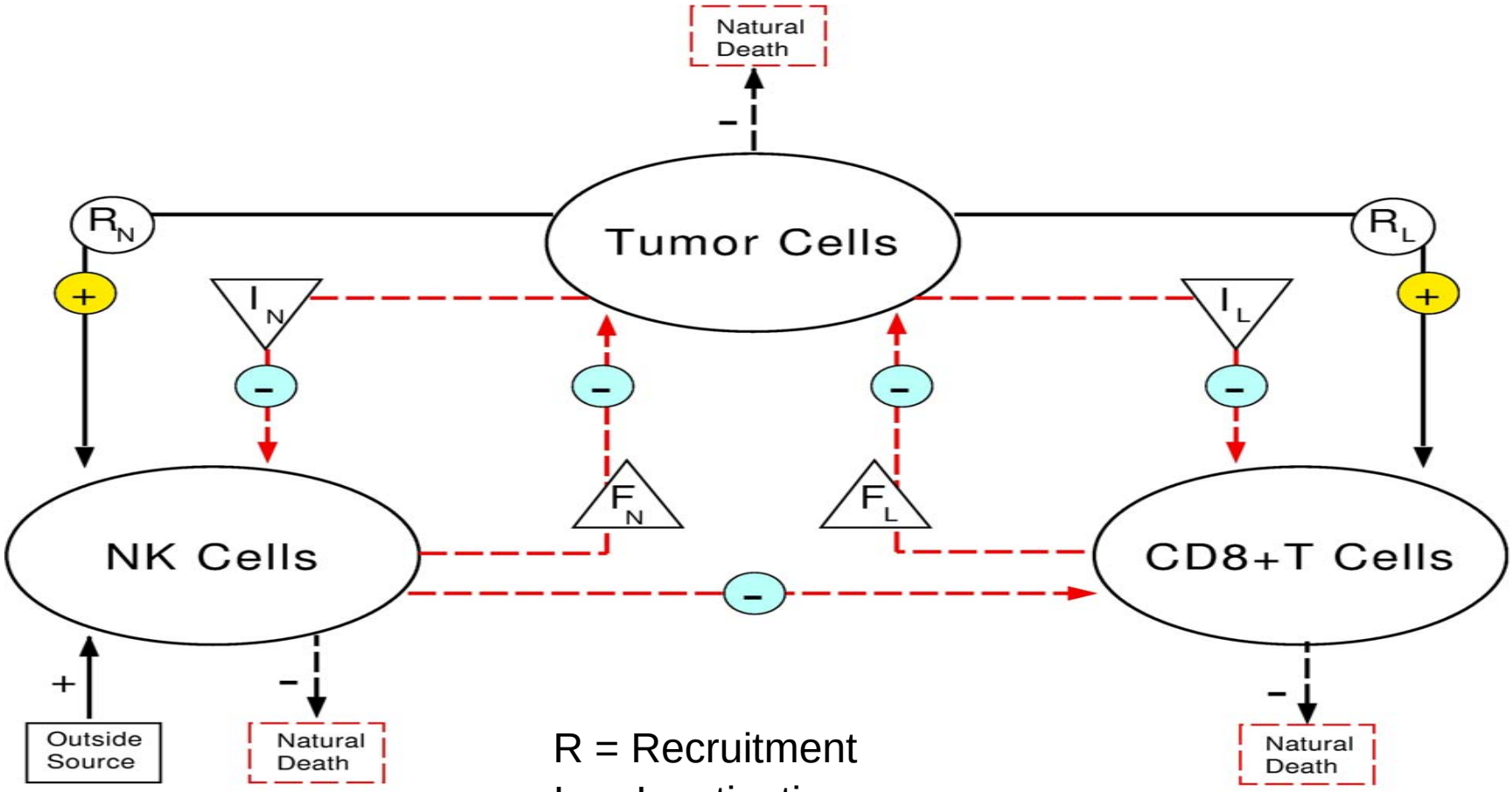


Image courtesy
http://www.wellesley.edu/Chemistry/Chem101/antibiotics/immune.html

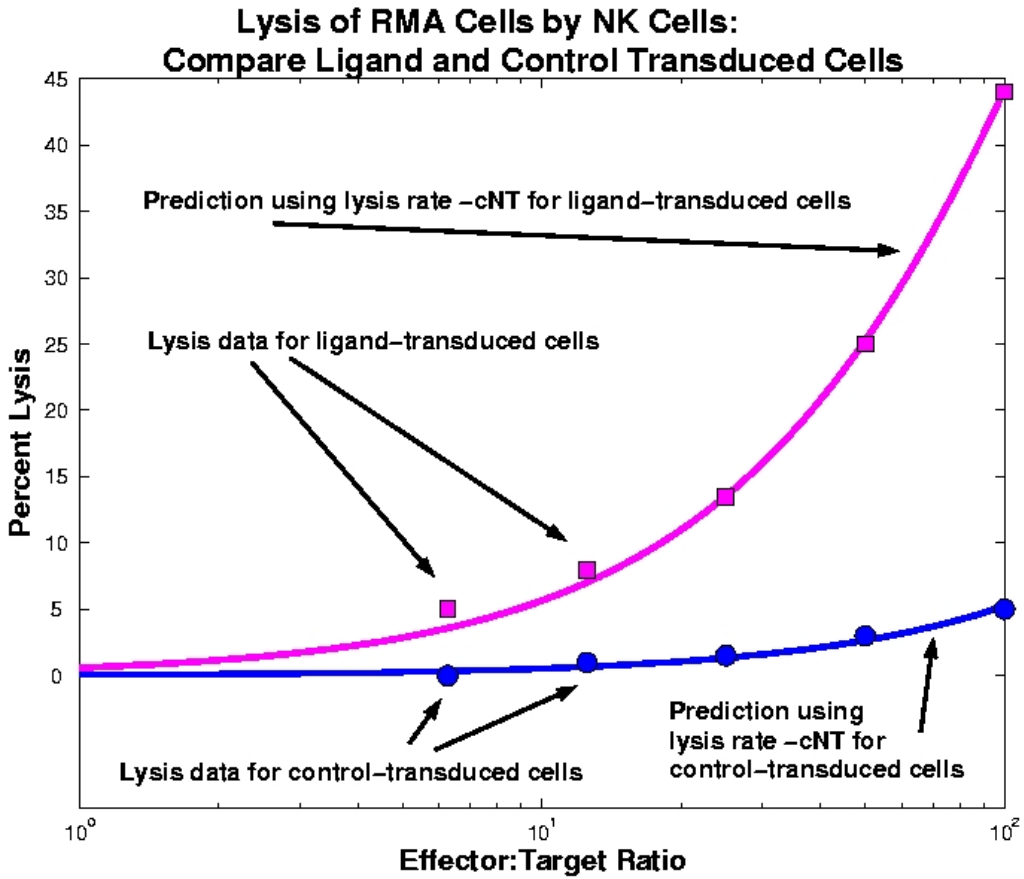
Mathematical Model Flow Diagram



R = Recruitment
I = Inactivation
F = Fractional Cell Kill

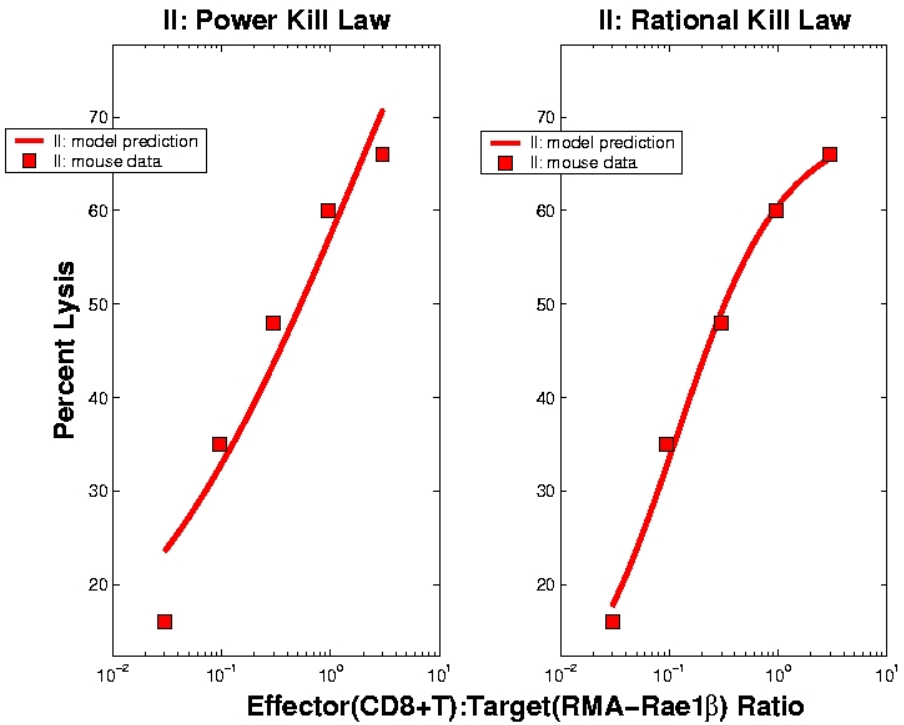
Mathematically Modeling the Innate Immune (Secret Handshake) Killing of Cancer Cells

$$\text{Rate of Target Cell Lysis by NK-cells} = cNT$$



Tumor Cell Lysis by NK-Cells: Fit to Mouse Data

Mathematically Modeling the Specific (Glove Sniffing) Killing of Cancer Cells: New "de Pillis-Radunskaya Law"



Rate of Target Cell Lysis by T-cells:

$$d\,\frac{(L/T)^{\nu}}{s+(L/T)^{\nu}}\,T$$

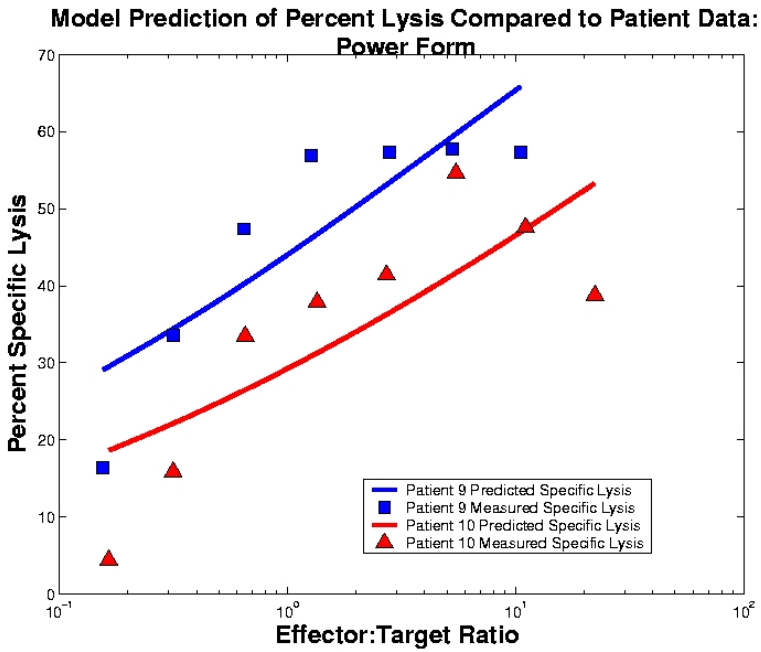
Conventional vs DePillis-Rad Laws

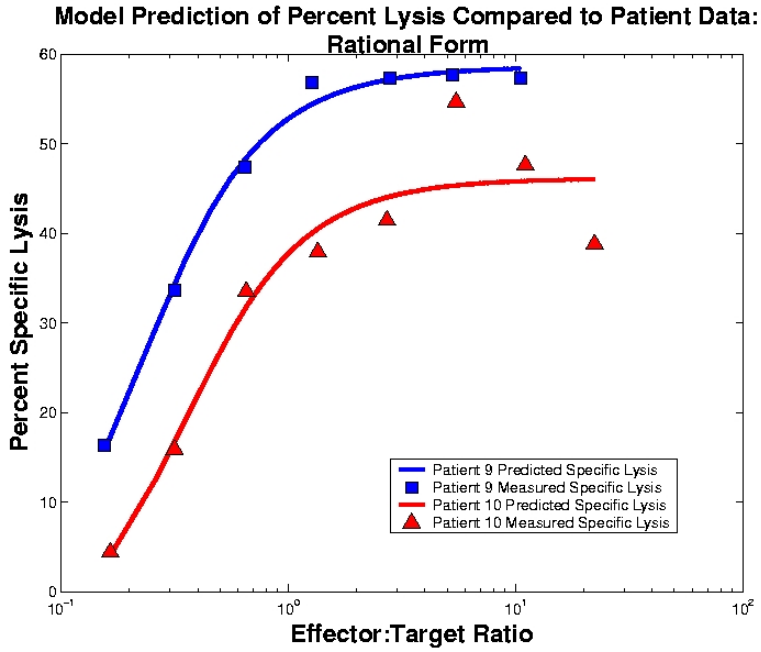
Tumor Cell Lysis by CD8+T-Cells: Fit to Mouse Data

Ligand-Transduced Cancer Cells

Specific (Glove Sniffing) Killing of Cancer Cells Follows New Mathematical Law De Pillis-Radunskaya Law

NEW DE PILLIS-RAD LAW also applies to HUMAN DATA:



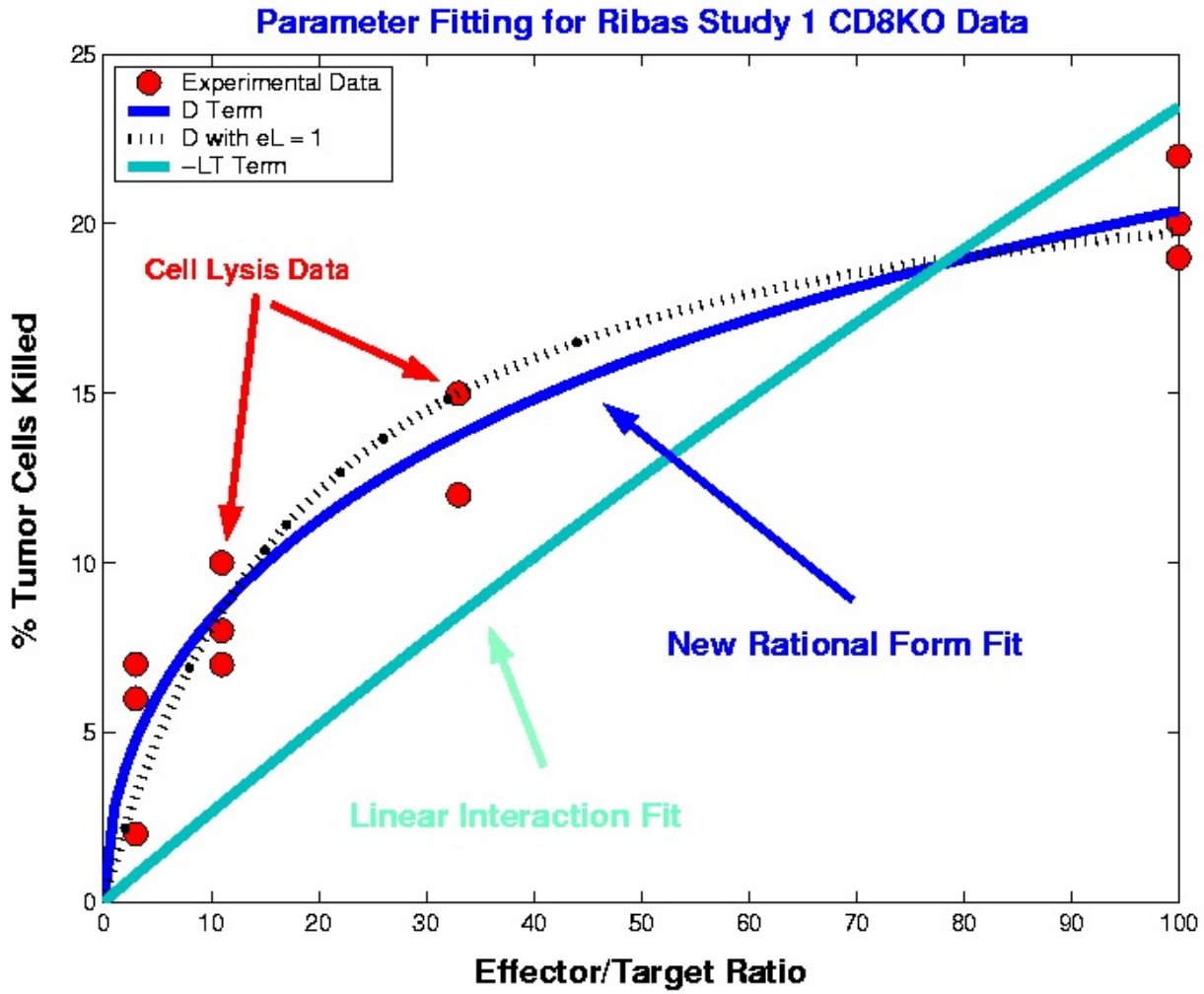


$$\text{Rate of Target Cell Lysis by T-cells} = d\,\frac{(L/T)^{\nu}}{s+(L/T)^{\nu}}\,T$$

Tumor Cell Lysis by CD8+T-Cells: Validated with Human Data

More Good Fit Evidence: Fit to Other Mouse Data

Data from Antoni Ribas, UCLA, fit to raw chromium release assay data.



Elements in Mathematical Model Equations

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

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

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

Where $D = \frac{\left(L/T\right)^l}{s + \left(L/T\right)^l}T$

Logistic Growth

NK-Tumor Kill: Power Law

CD8-Tumor Kill: Rational Law

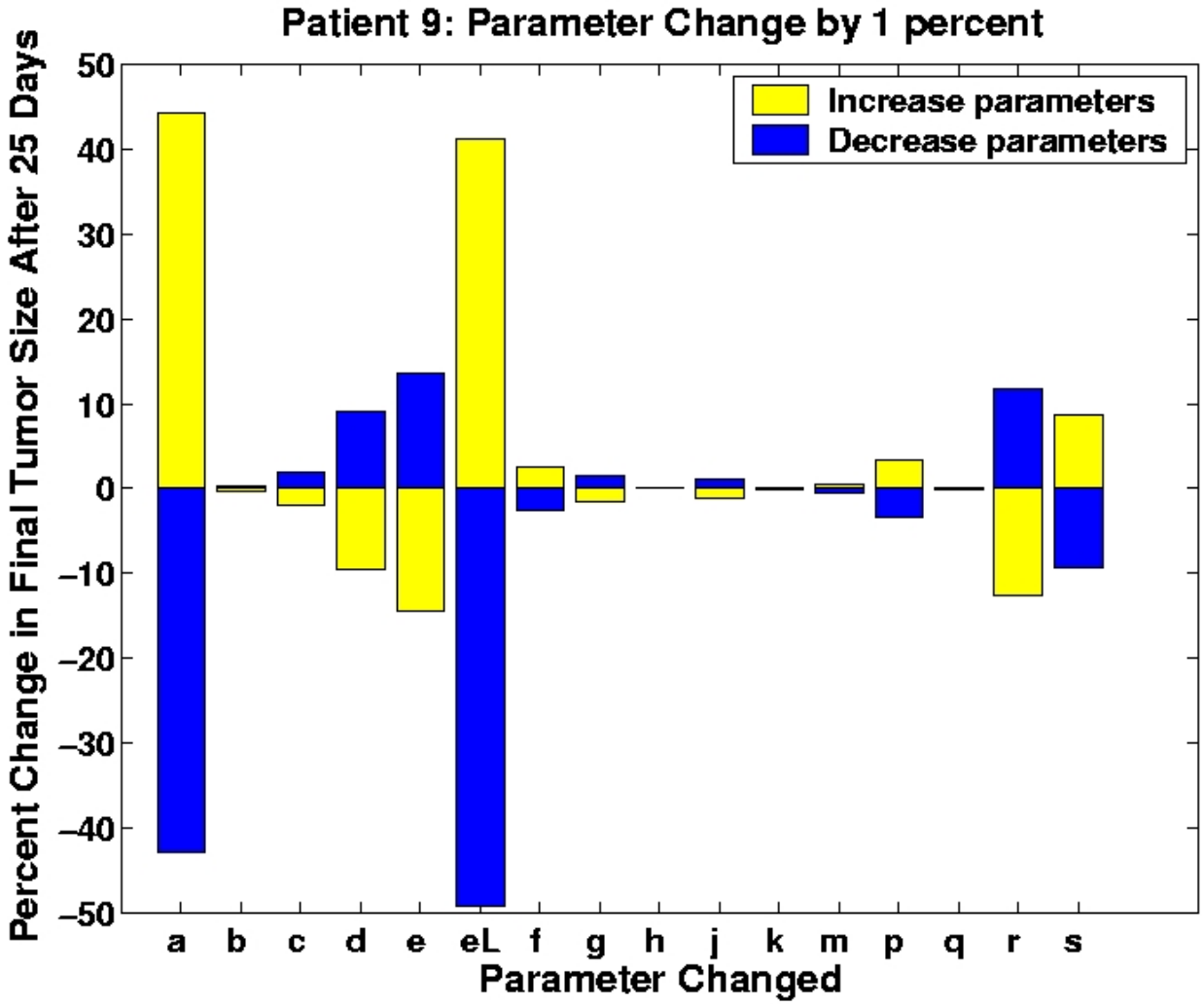
Immune Recruitment: Michaelis-Menten Kinetics

Are Some Parameters More Important than Others?

- Questions:
  - How do simulation outcomes vary as the parameters are varied?
  - Which parameters are the best predictors of successful outcomes?
- One Answer:
  - Need Sensitivity Analysis

Model Simulations: Traditional Sensitivity Analysis

one parameter is changed at a time



Simulation parameters: human, no chemo

Uncertainty Analysis: Latin Hypercube Sampling

all parameters are varied simultaneously

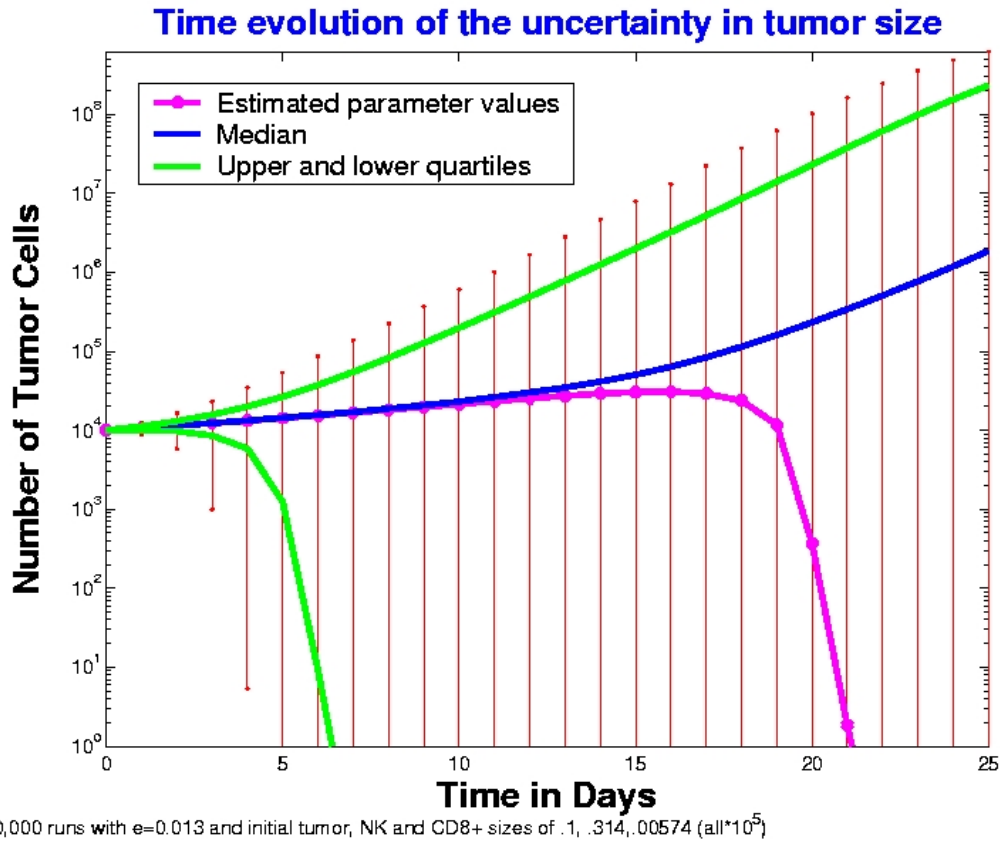
Sensitivity Analysis (LHS)

Method: **Latin Hypercube Sampling (LHS)** [3].

Outcome: the uncertainty in the predicted tumor size grows over time.

Details: 10,000 sample parameter sets were randomly selected in a range centered around the estimated values, and each parameter was varied independently over its own range. Median tumor size over time is depicted by the **solid blue line**. Upper and lower quartiles are shown by **green lines**. Full range of outcomes given by **red bars**.

Comment: While the uncertainty in the prediction grows over time, it is clear that the distribution of tumor sizes is not uniform, but rather is concentrated at the lower tumor levels.



[3] S.M. Blower and H. Dowlatabadi,
"Sensitivity and Uncertainty Analysis of Complex Models of Disease Transmission: an HIV Model, as an Example.
International Statistical Review (1994), **62**,2,pp.229-243.

Simulation parameters: human, no chemo, 5% range or reported ranges, truncated normal distribution

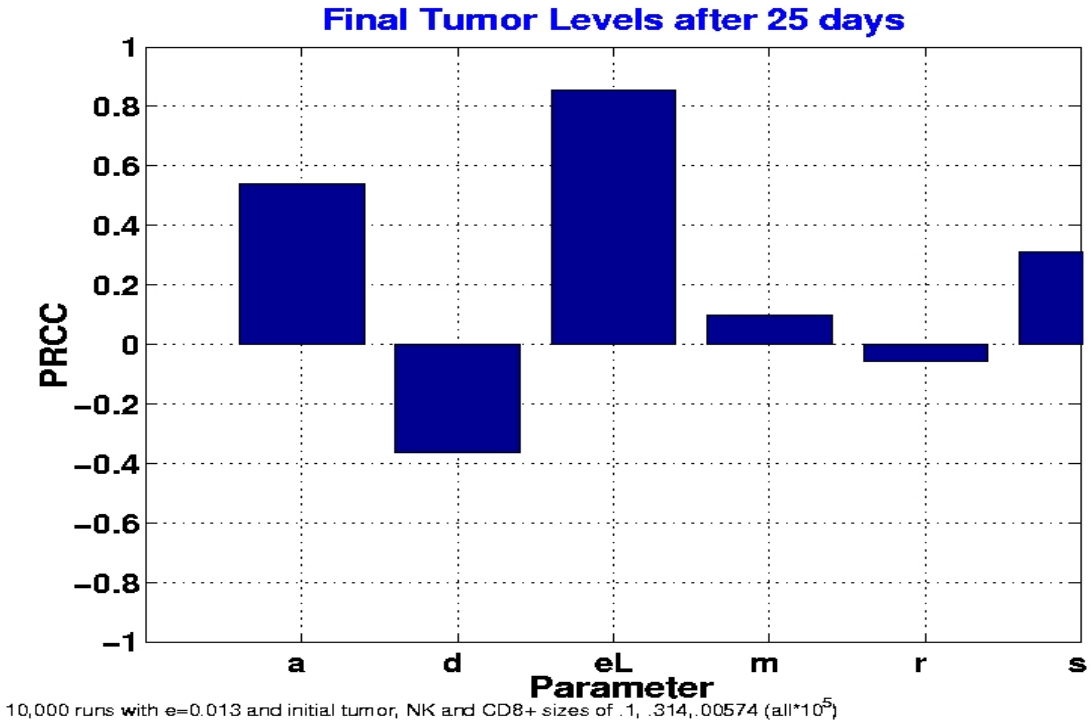
Model Simulations: Latin Hypercube Sampling

PRCC Results

• **PRCC**s (partially ranked correlation coefficients): measure outcome's sensitivity to each parameter. Bar graph: Relative ranking of the six most sensitive parameters with respect to tumor size.

• **Parameters *d*** and ***eL:*** represent overall tumor-cell lysis rate and the strength of the immune-tumor interaction, respectively. Both can be estimated from patient data, as in this example. Parameter ***a*** represents tumor growth rate

• **Predictions**: Tumor aggressiveness as well as patient specific immune strength may predict patient response to immunotherapy treatment.



Significance w/ Student's T:

P-values all less than 0.00001

Validation: Simulating Vaccine in Mouse Model

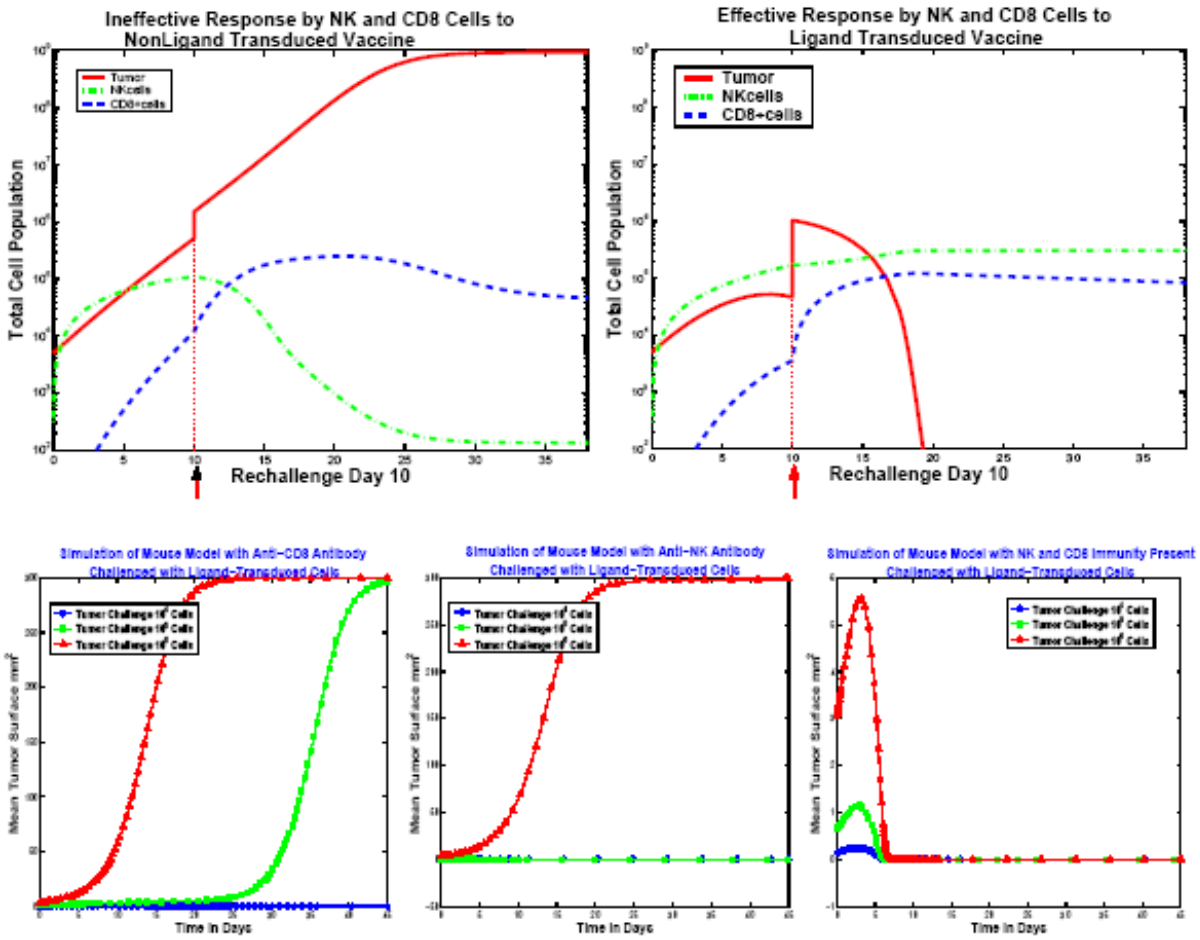


Figure 4: de Pillis

Validation: These *In Silico* Experiments Mirror *In Vivo* Mouse Experiments

See: dePillis et al, Cancer Res, 65(17), 2005

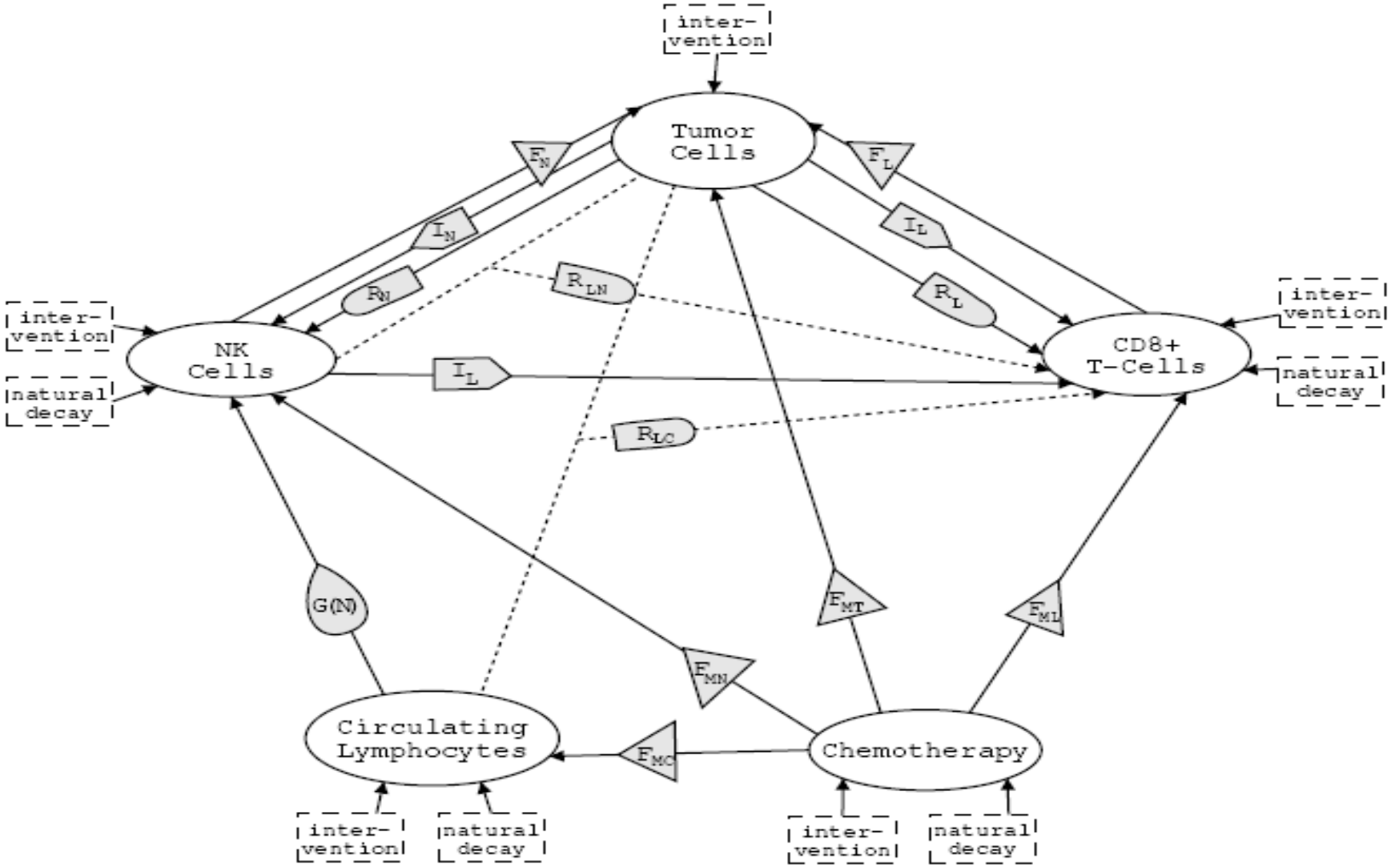
Outline

- Background: Cancer and genesis of this work
- The original motivating problem
- Controlling treatment
- Immunology of cancer
  - The Immune System Targets Cancer
  - Two Kinds of Immune Responses: Innate and Specific
- Extended model, include immune components
- Adding treatment
- Specific cancer: B-CLL
- Work in progress: Spatial tumor models
  - Hybrid CA models
  - 3D PDE models

Experimenting with Treatments

- Must Extend the Model to Examine:
  - Chemo Alone
  - Immunotherapy Alone
  - Combined Therapy
- To Simulate Dudley's Human Data
  - Add IL-2 immunotherapy
  - Add Circulating Lymphocytes to track "health"

Multi-Population Model Schematic



System of Model Equations: Additional Treatments Possible

Parameters *a*, *b*, *c*, *d*, *s*, and *eL* were fit from published experimental data. All other parameters were estimated or taken from the literature.

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T(1-e^{-M})T$$

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT - K_N(1-e^{-M})N$$

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T$$

$$- uNL^2 - K_L(1-e^{-M})L + \frac{p_I LI}{g_I + I} + v_L(t)$$

$$\frac{dC}{dt} = \alpha - \beta C - K_C(1-e^{-M})C$$ **Circulating lymphocytes**

$$\frac{dM}{dt} = -\gamma M + v_M(t)$$ **Rate of drug administration and decay**

$$\frac{dI}{dt} = -\mu_I I + v_I(t)$$ **IL-2 boost**

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

See dePillis et al, J. Theor. Biol., 2005

No IL2

Bifurcation diagram: the effect of varying the NK-kill rate, c.

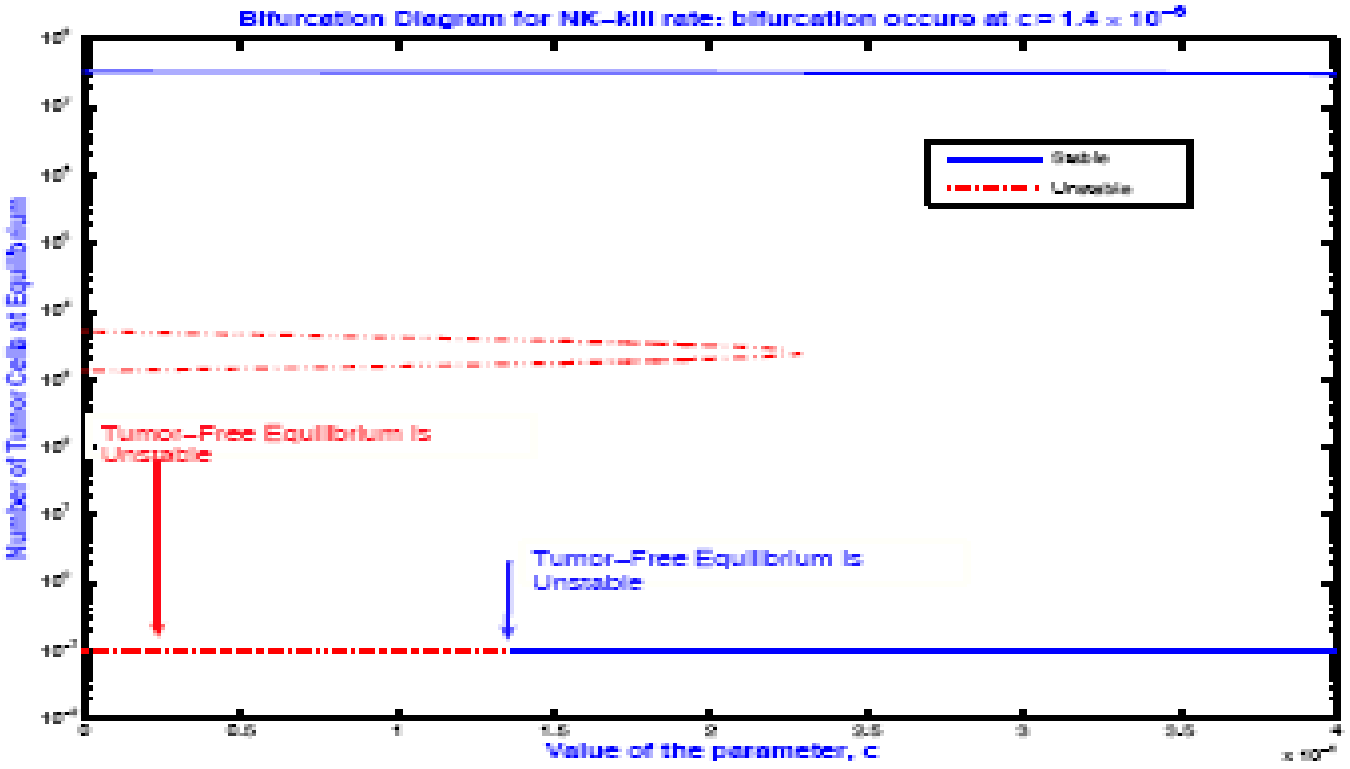


Fig. 2. Bifurcation diagram showing the effect of varying the NK-kill rate, c. Other parameters for this diagram are from Table 1.

See dePillis et al, J. Theor. Biol., 2005

Sensitivity to Initial Conditions after Bifurcation Point. C*=0.9763

Sensitive to ICs after bifurcation→

Before bif, 0 unstable ····

After bif, 0 stable ——

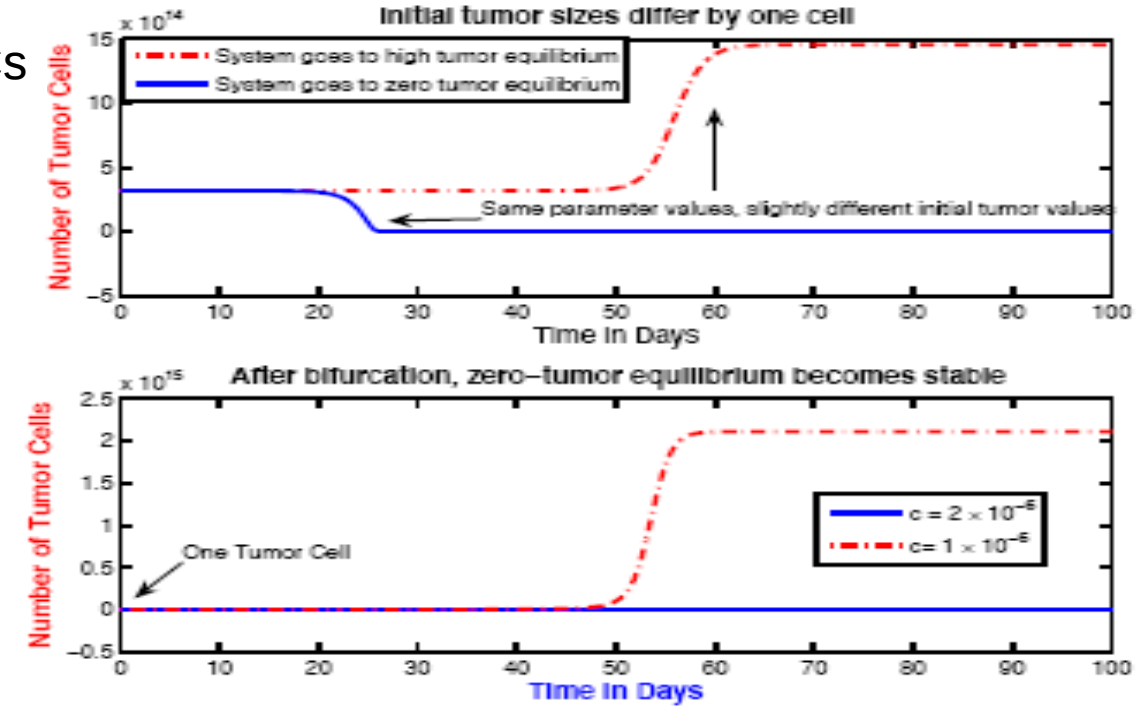
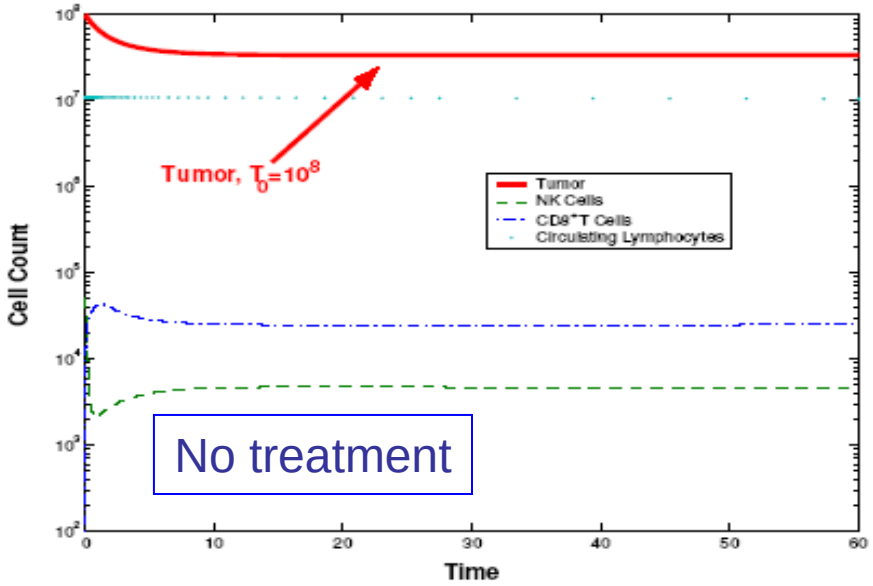
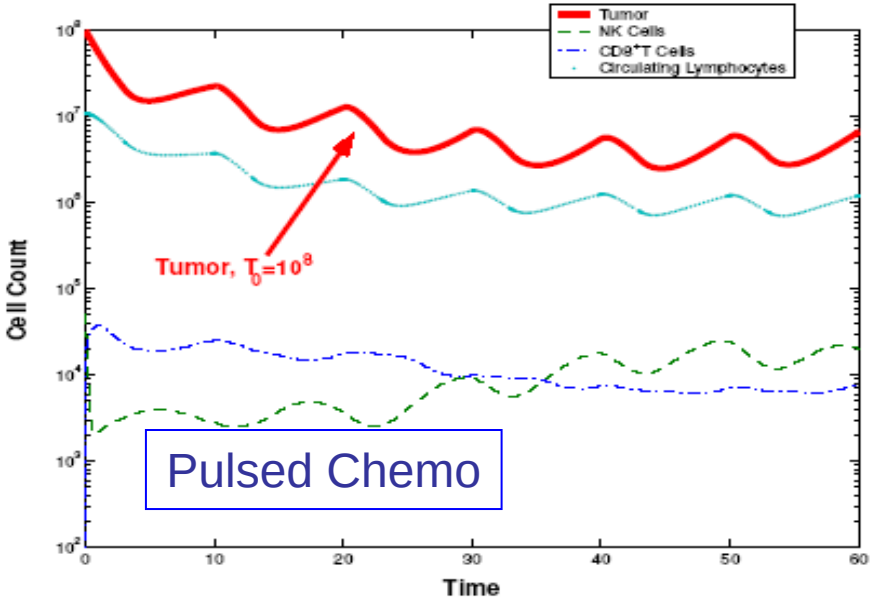


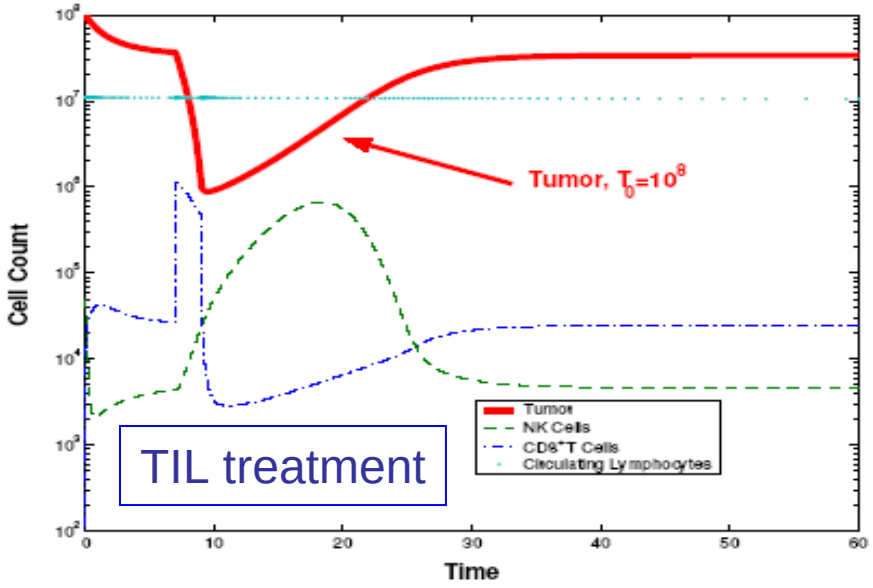
Fig. 3. Simulations illustrating system behavior for three values of parameter c. The bifurcation point is $c \approx 1.4\text{x}10^{-6}$. Top: After the bifurcation point, at $c = 4\text{x}10^{-6}$, the system shows sensitivity to initial conditions. In this simulation, a one cell difference in the initial number of tumor cells, T_0, results in very different outcomes. Initial values for the state variables are $T_0 \approx 6.89\text{x}10^6$, $N_0 \approx 3.97\text{x}10^9$, $L_0 \approx 7.15\text{x}10^3$, $C_0 \approx 1.65\text{x}10^9$. All parameters besides c are from Table 1. Bottom: Before the bifurcation, at $c = 1\text{x}10^{-6}$, one tumor cell grows to the high tumor equilibrium of approximately $2.1\text{x}10^{15}$ in 60 days. After the bifurcation, at $c = 2\text{x}10^{-6}$, an initial value of one tumor cell is drawn to the now stable zero tumor equilibrium. Immune recruitment parameters, g, j, r_1 and r_2 are set to zero. With the exception of the values for c and the immune recruitment parameters, all other parameters are from Table 1. Initial values for the state variables are $T_0 = 1$, $N_0 = 1.73\text{x}10^{10}$, $L_0 = 0$, $C_0 \approx 1.65\text{x}10^9$.

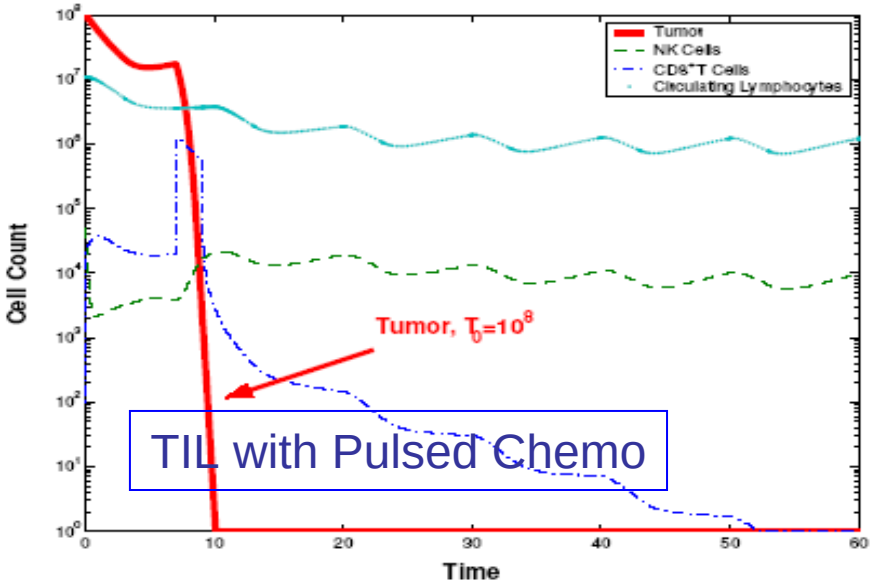
See dePillis et al, J. Theor. Biol., 2005

Mixed Therapy - Mouse Params

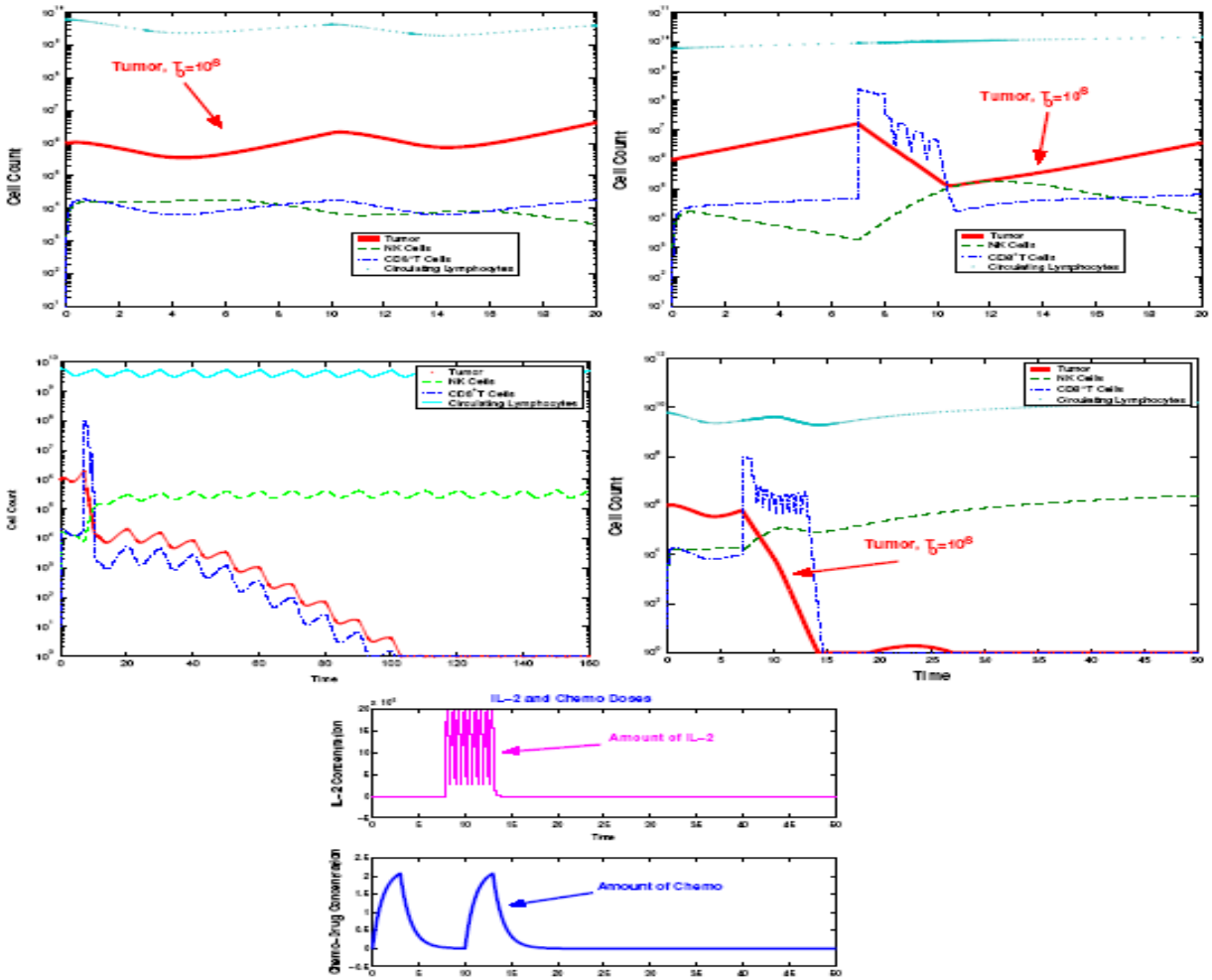








Mixed Therapy - Human Params



Top left: Pulsed chemo fails on 10^6 tumor (healthy immune).
Top right: TIL and IL2 fail. Middle left and right: Combo therapy kills tumor.
(Right has more aggressive immunotherapy)

Bifurcation Analysis: Basins of Attraction

(ODE model with IL-2)

- **Stable Zero Tumor Equilibrium:**
  - **Immune system keeps tumor under control**
- **Stable High Tumor Equilibrium:**
  - **Immune system too weak to control tumor**
- **Unstable Intermediate Tumor Equilibrium:**
  - **System wants to move toward high or zero**

Basin of Attraction of zero-tumor and high-tumor equilibria

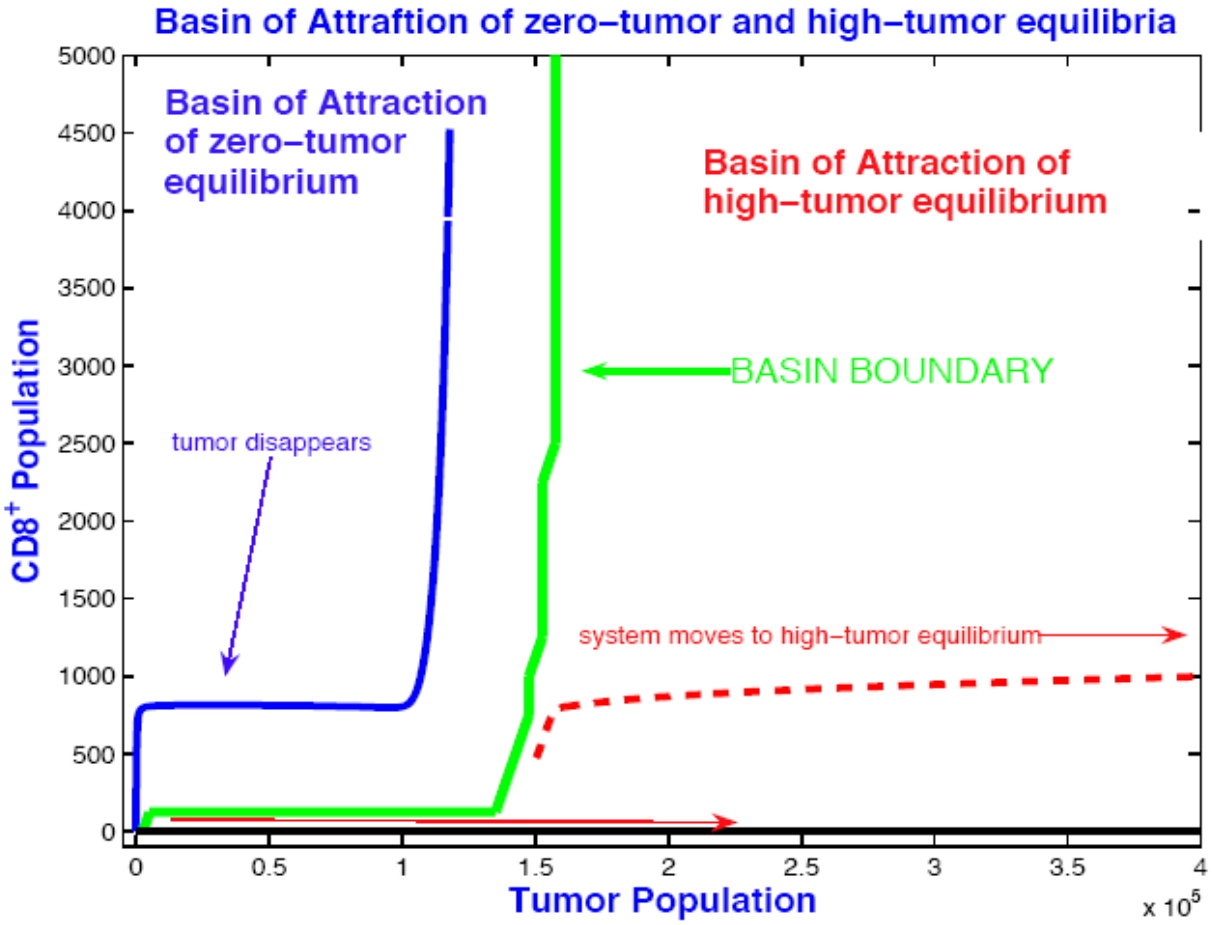
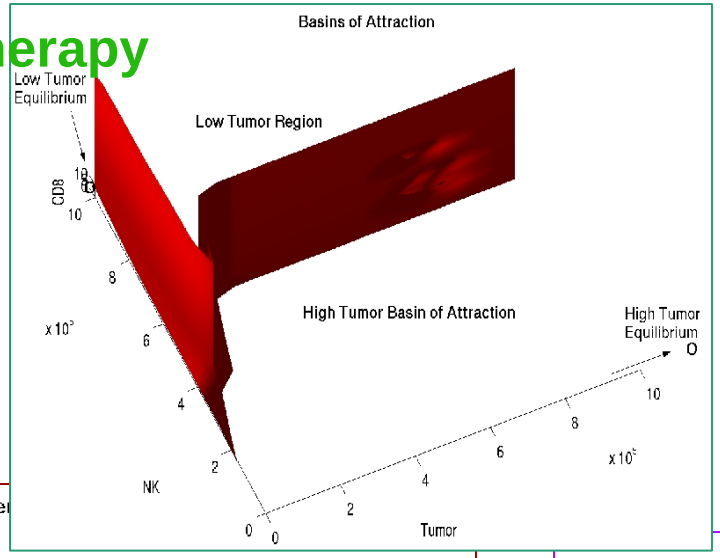


Fig. 5. Basins of attraction of the zero-tumor and high-tumor equilibria when the CD8+ T-cell recruitment parameter, $j = 4.5$.

See dePillis et al, J. Theor. Biol., 2005

Bifurcation Analysis: Basins of Attraction

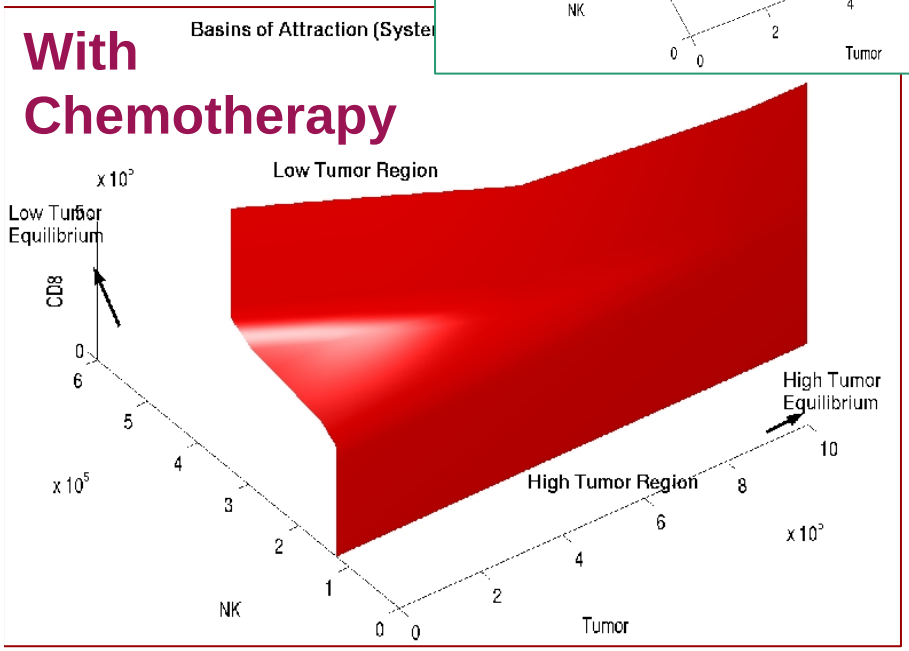
No therapy



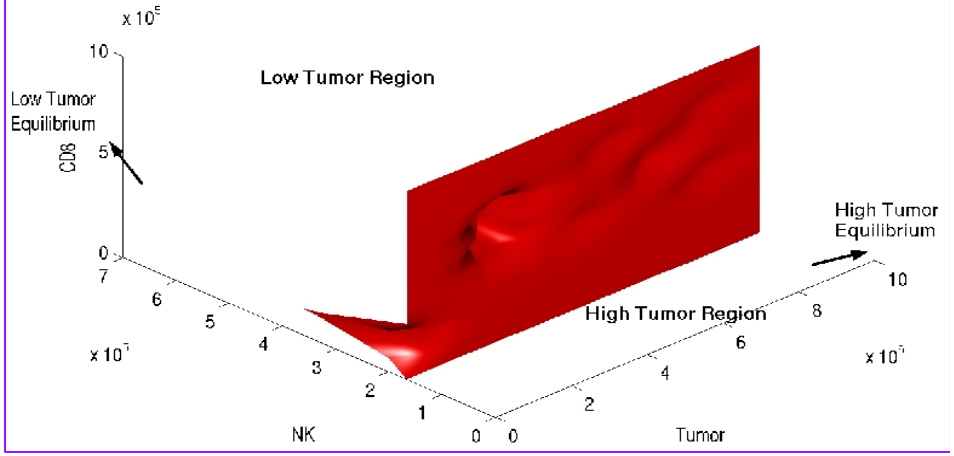
The barrier separates system-states which evolve toward the low-tumor equilibrium from those which evolve toward the high tumor state.

This barrier moves with therapy

With Chemotherapy



With Immunotherapy



Outline

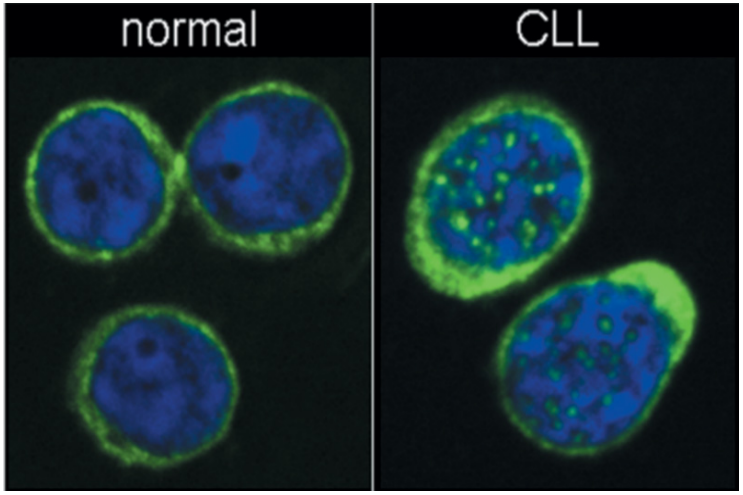
- Background: Cancer and genesis of this work
- The original motivating problem
- Controlling treatment
- Immunology of cancer
  - The Immune System Targets Cancer
  - Two Kinds of Immune Responses: Innate and Specific
- Extended model, include immune components
- Adding treatment
- Specific cancer: B-CLL
- Work in progress: Spatial tumor models
  - Hybrid CA models
  - 3D PDE models

B-CLL model:
A work in progress…

B-Cell Chronic Lymphocytic Leukemia (B-CLL)

- B-CLL: **Cancer of the immune system**. Characterized by the accumulation of large numbers of white blood cells (B cells) in the blood, bone marrow, spleen and lymph nodes.
- Current understanding: B-CLL cells derive from mature antigen-stimulated B-cells that are immunologically competent.

- Fuzzy characterization: over 5K cells / μ-liter one measure
- Precise cause unknown
- No cure
- High proliferation rate more serious than high numbers of cells
- NK cells, helper T cells and cytotoxic T cells may all play a role in stemming the growth of B-CLL



Subcellular localization of HS1 analyzed by confocal microscopy. HS1 is uniformly distribuited in the cytosol of normal B cells, while it shows a nuclear spotting distribution in B-CLL cells.

Image: http://www.vimm.it/research/images/semenzato_fig1.jpg

Example Model Equations

$$\frac{dB}{dt} = b_B + (r - d_B)B - d_{BN}BN - d_{BT}BT$$

$$\frac{dN}{dt} = b_N - d_N N - d_{NB}NB$$

$$\frac{dT}{dt} = \alpha - d_T T - d_{TB}TB + ka_T \frac{B^L}{s + B^L} T_H^p$$

$$\frac{dT_H}{dt} = b_{T_H} - d_{T_H}T_H + a_T \frac{B^L}{s + B^L} T_H^p$$

Growth or Source

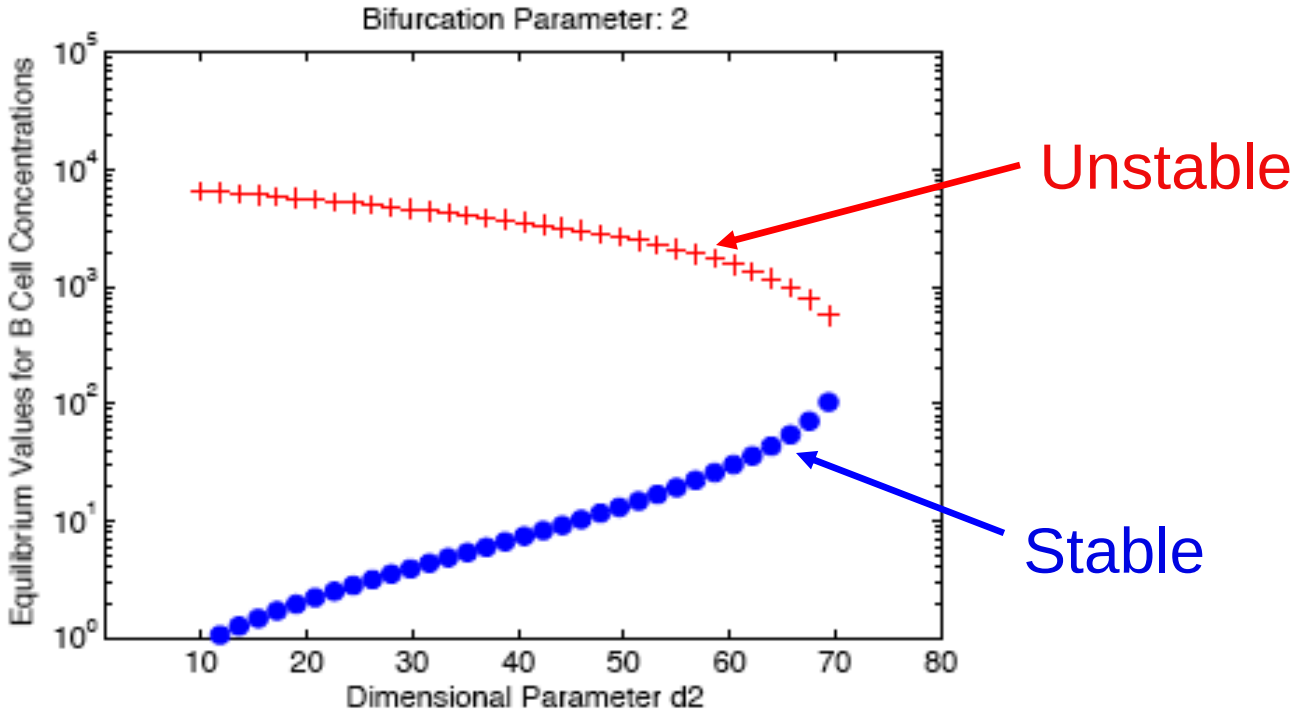
Death

Immune Cell Killing

Immune Recruitment

Parameter Choice: b_B

- Represents: B-CLL creation
  - A fraction of antigenically experieced immunologically competent B cells.
  - A constant source of **newly mutated cells.**
- Units: cells/μL per day
- Numerical value(s) used: 70 (range: [10,80])
- Source: Numerical Bifurcation Study

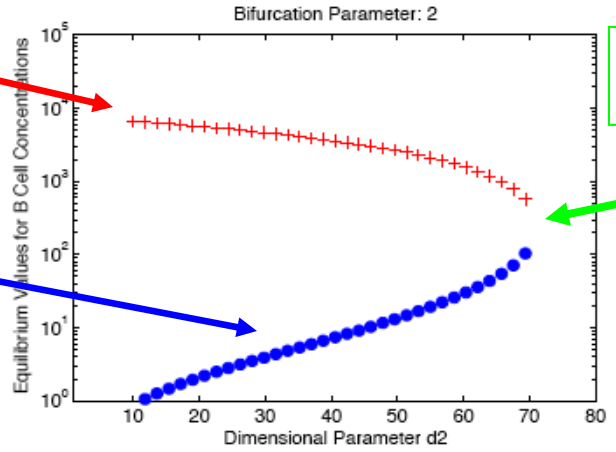


Numerical Simulations

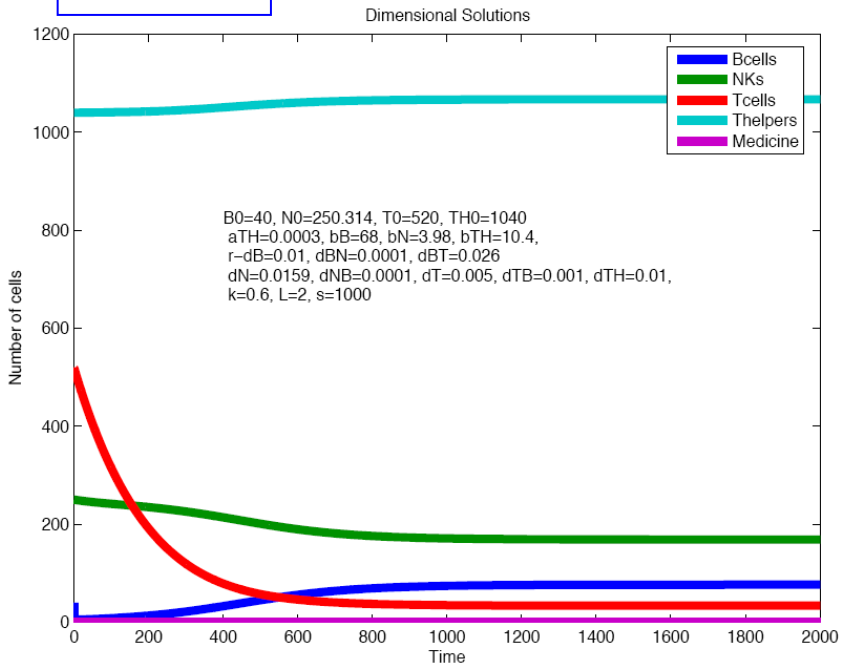
Unstable

Stable

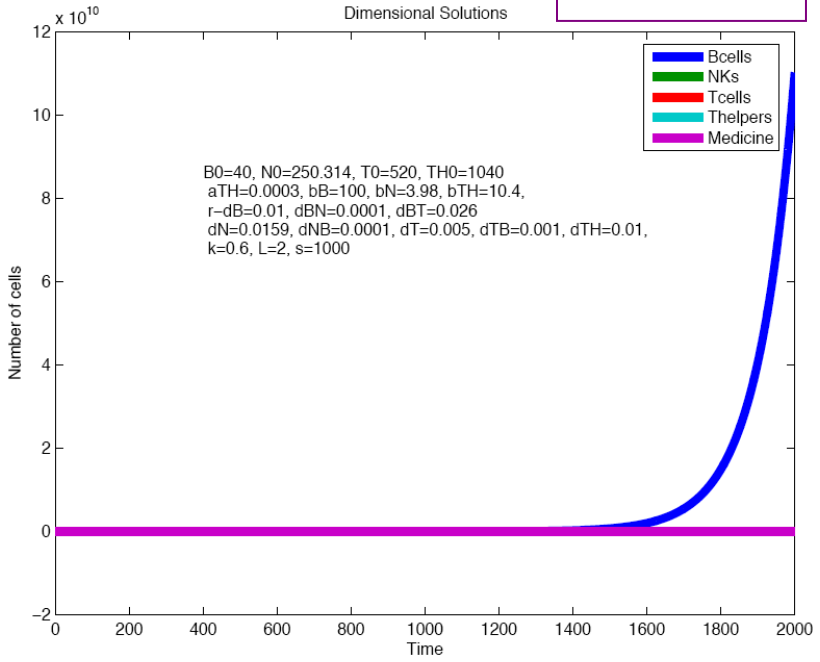
Bifurcation at $b_B = 70$



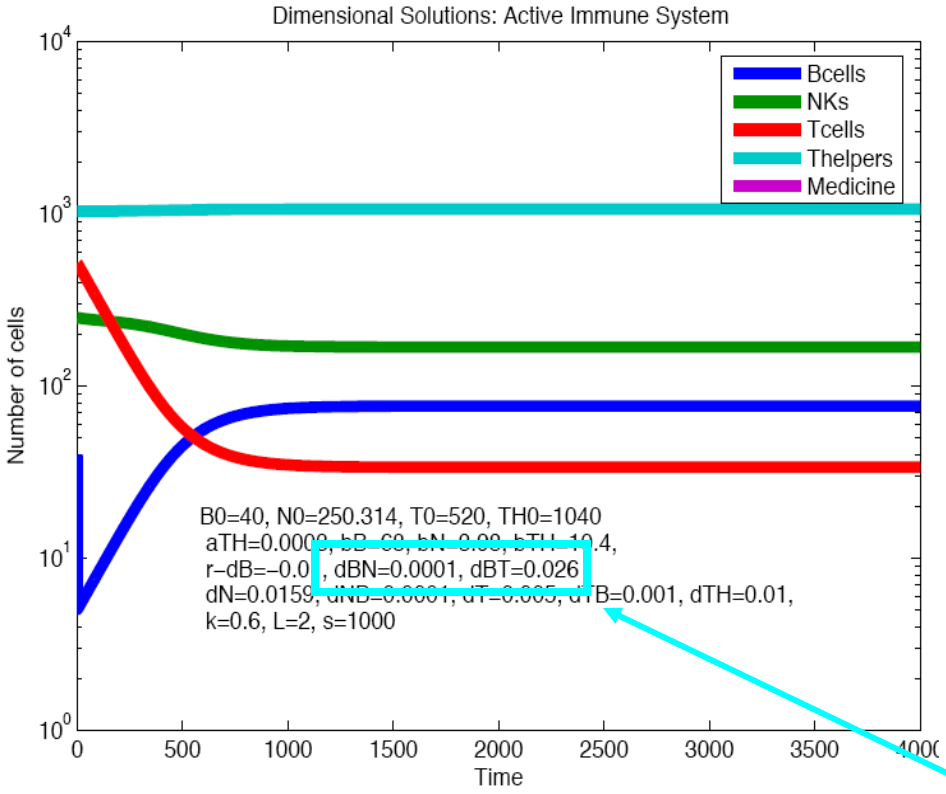
b_B=68

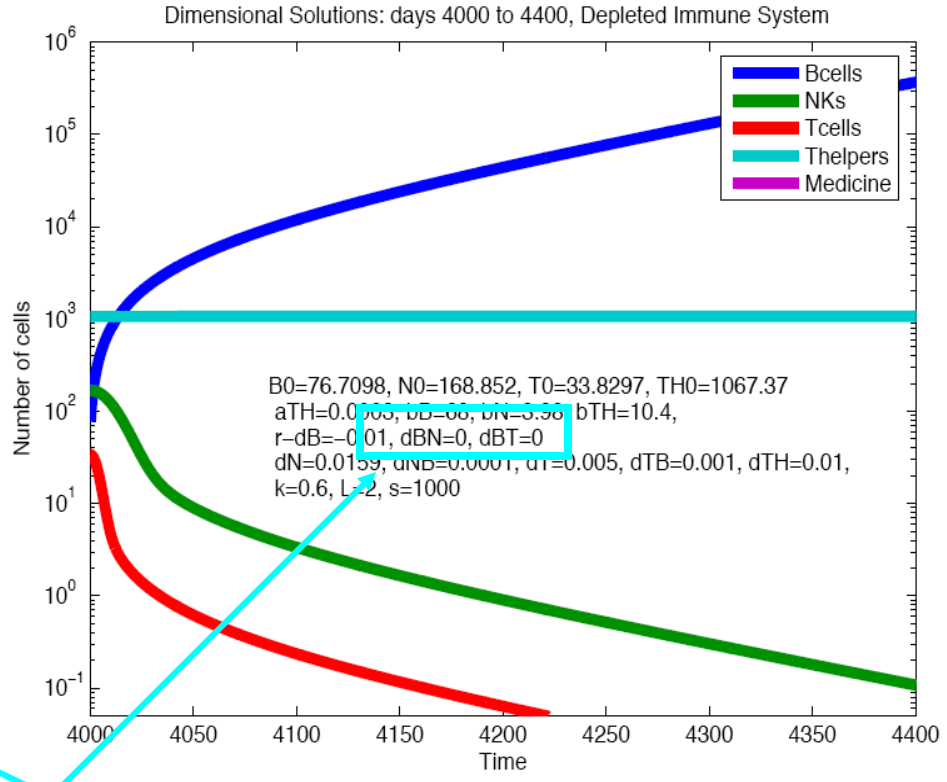


b_B=100



Numerical Simulations



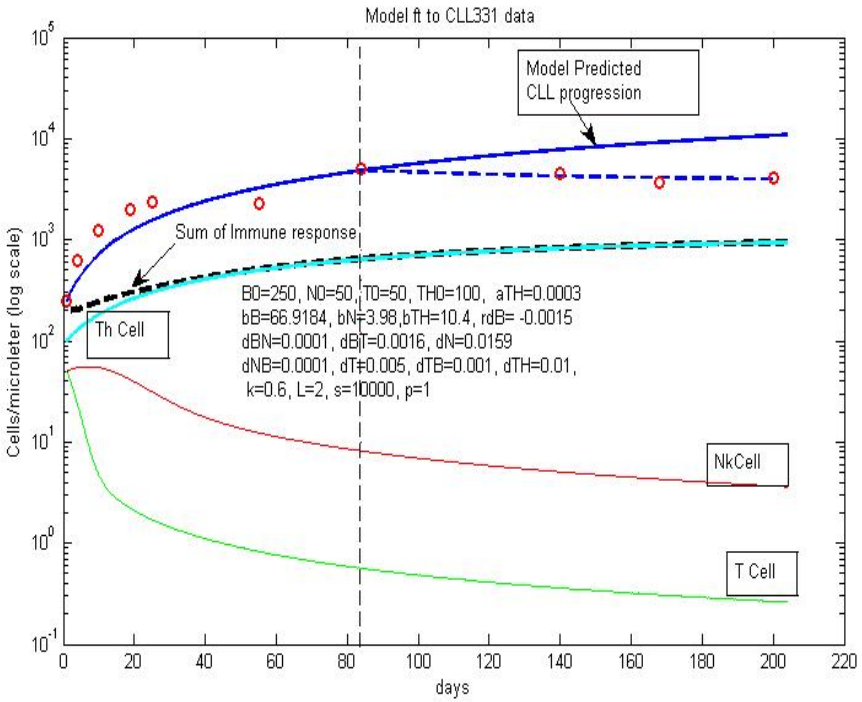


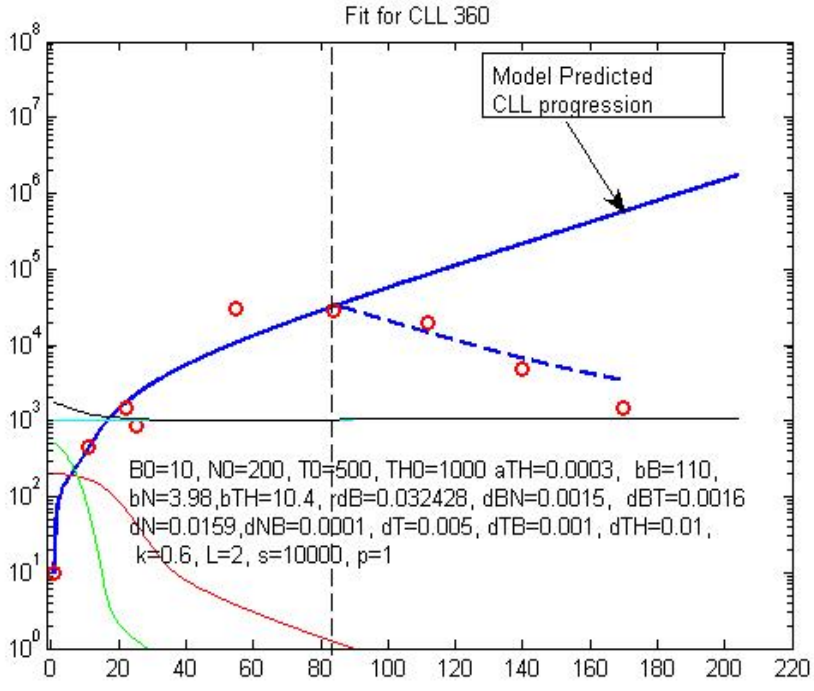
Solution at Steady State

Sudden Immune Depletion

$$\frac{dB}{dt} = b_B + (r - d_B)B - d_{BN}BN - d_{BT}BT$$

Fitting for parameters (-r+dB)
Patients 331 &360*





r range:[0.0011,0.0176], mean:0.004636

dB range:[-3.9e-3,2.14e-2]

* Messmer et al., J. Clin. Invest. 2005

Treatment Possibilities:

- Keating (2003) suggests:

Chemotherapy, Single and Combination

Regimen	Patients	%CR	%OR	Ref.
Chlorambucil alkylating agent	181	3	37	32
Fludarabine (Flu) purine analog	170	20	70	32
Flu+Cyclophosphamide (FC)	34	35	88	34
Flu+Rituximab (Concurrent)	51	77	90	37
(Sequential)	53	28	77	37
FC+Rituximab	202	69	95	38

Combination therapies

Figure 13: Final ODEs

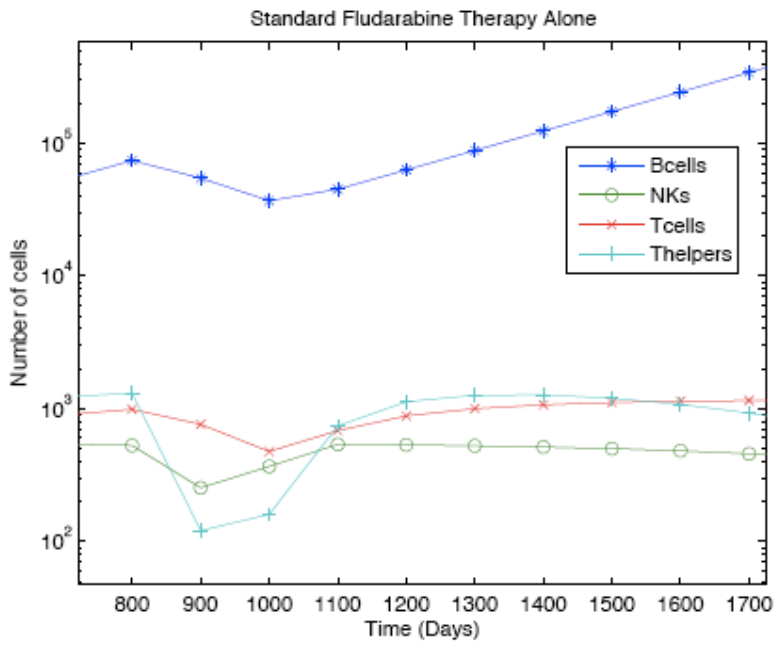
$$
\begin{aligned}
\frac{dB}{dt} &= (b_B - d_B - d_{BF}F - d_{BR}c\frac{R}{R+s_R})B - \\
&\quad d_{BN}B[(a_N + h_{RN}c\frac{R}{R+s_R})N] - d_{BT}B(a_T T + T_G) \\
\frac{dB_2}{dt} &= (b_B - d_B - d_{B2F}F - d_{BR}c\frac{R}{R+s_R})B_2 - \\
&\quad d_{BN}B_2[(a_N + h_{RN}c\frac{R}{R+s_R})N] - d_{BT}B_2(a_T T + T_G) \\
\frac{dN}{dt} &= b_N - (d_N + d_{NF}F)N - d_{NB}[(a_N + h_{RN}c\frac{R}{R+s_R})N](B + B_2) \\
\frac{dT}{dt} &= b_T - (d_T + d_{TF}F)T - d_{TB}(a_T T)(B + B_2) + \\
&\quad kM\frac{(B+B_2)^L}{s + (B+B_2)^L}(m_{TH}(a_{TH}T_H) + 1) \\
\frac{dT_H}{dt} &= b_{TH} - (d_{TH} + d_{THF}F)T_H - d_{THB}T_H(B + B_2) + \\
&\quad M\frac{(B+B_2)^L}{s + (B+B_2)^L}(m_{TH}(a_{TH}T_H) + 1) \\
\frac{dF}{dt} &= -d_F F \\
\frac{dR}{dt} &= -d_R R - cw_R(h_{RN}d_{BN}N + d_{BR})\frac{R}{R+s_R}(B + B_2) \\
\frac{dT_G}{dt} &= -(d_{TG} + d_{TF}F)T_G - d_{TB}T_G(B + B_2)
\end{aligned}
$$

Combination Therapy: Fludarabine & Rituximab

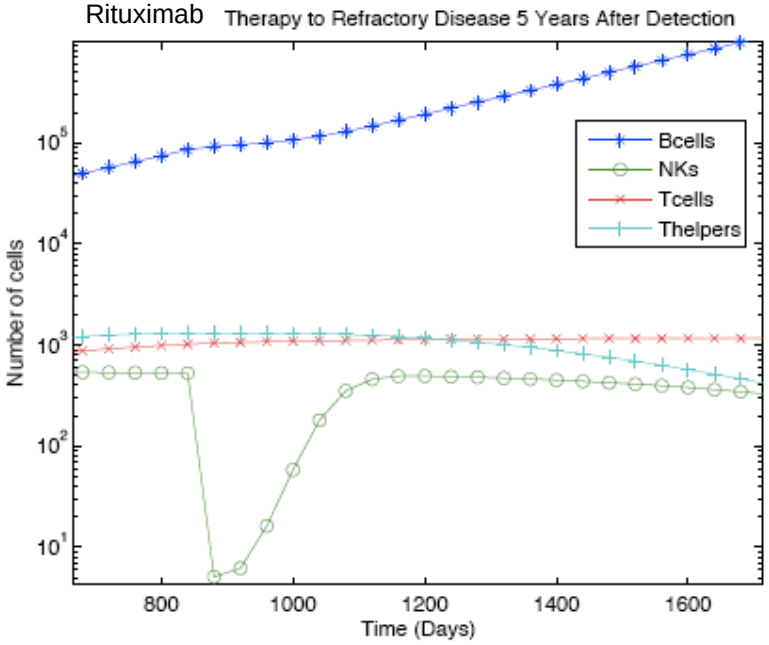
Making it tougher: bB=.5%, leukemic cell doubling time 205 days, 50% fludarabine resistant cells, low CD20 expression

Fludarabine vs Rituximab

a.



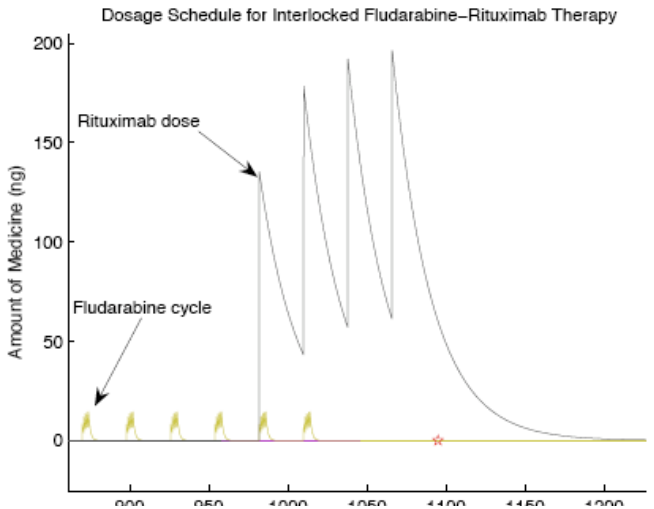
b.



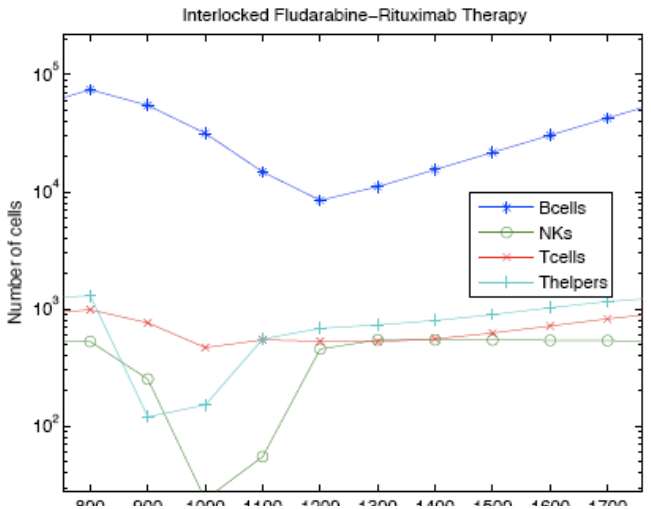
Fludarabine was administered at 25 $mg/m^2/day$ for the first five days of every 28-day cycle for six cycles [7], and rituximab was administered at 375 $mg/m^2/week$ for four weeks [10]. Both treatments prove rather pathetic. Although fludarabine manages to lyse roughly 63% of the leukemic cells (roughly 60000 $cells/\ L$), this nonetheless leaves over 34000 $cells/\mu L$ behind, capable of returning to pre-treatment levels in under a year and almost all of which are now fludarabine-resistent. Meanwhile, rituximab achieves less than 3% lysis (about 2500 cells/μL).

Combination Therapy

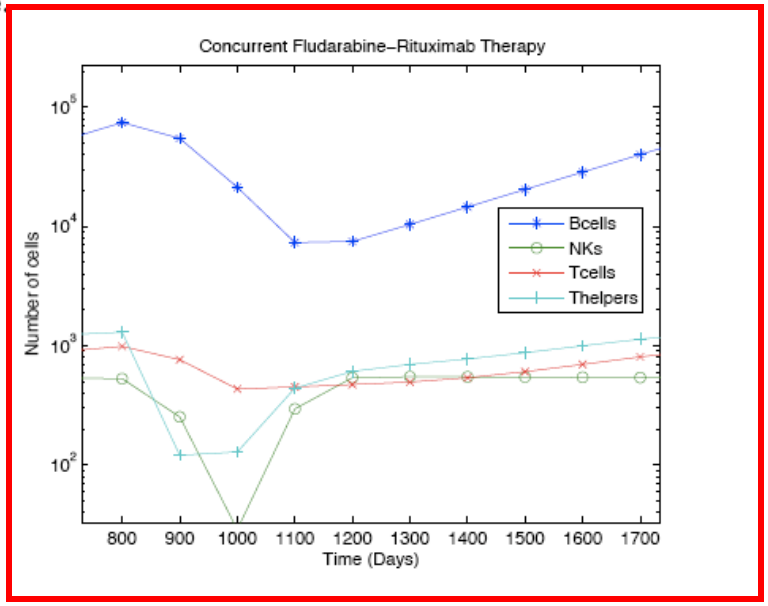
c.



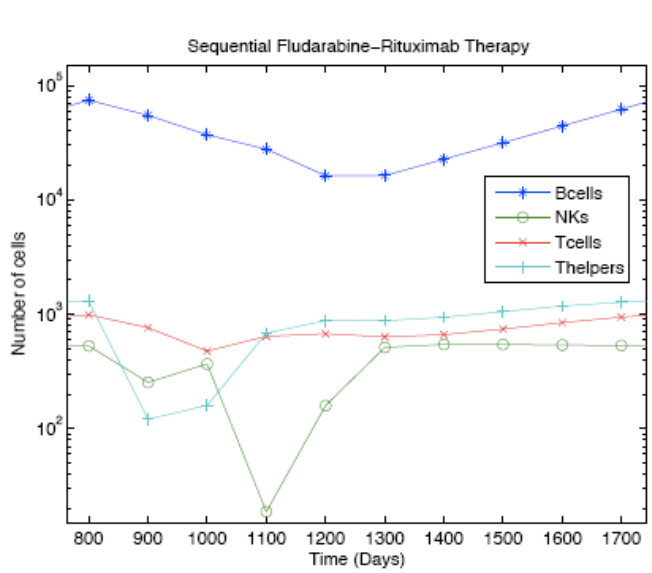
d.



e.



f.



Concurrent treatment best: 93% lysis, killed 87700 cells/microliter of blood. Still below pre-treatment levels after 5 years.

Outline

- Background: Cancer and genesis of this work
- The original motivating problem
- Controlling treatment
- Immunology of cancer
  - The Immune System Targets Cancer
  - Two Kinds of Immune Responses: Innate and Specific
- Extended model, include immune components
- Adding treatment
- Specific cancer: B-CLL
- Work in progress: Spatial tumor models
  - Hybrid CA models
  - 3D PDE models

Spatial Tumor Growth

Deterministic & Probabilistic:2D and 3D

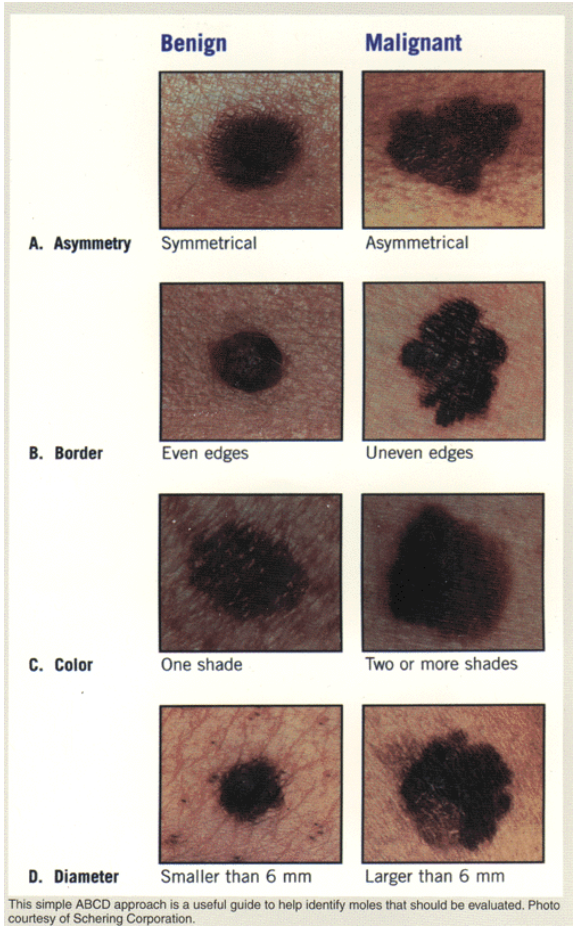
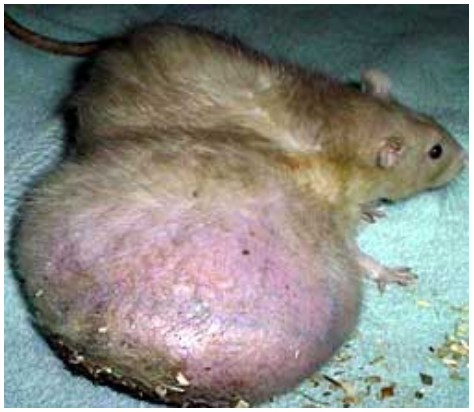
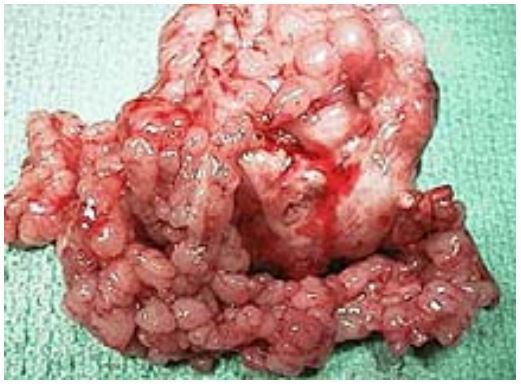


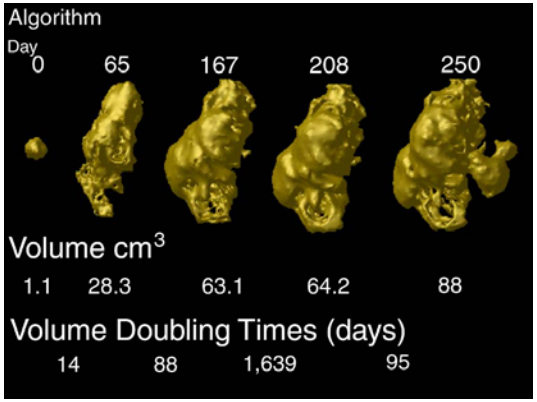
Image Courtesy http://www.ssainc.net/images/melanoma_pics.GIF



http://www.lbah.com/Rats/rat_mammary_tumor.htm



http://www.lbah.com/Rats/ovarian_tumor.htm



http://www.loni.ucla.edu/~thompson/HBM2000/sean_SNO2000abs.html

Goals for Spatial Modeling

- To model:
  - Nutrient dependent tumor growth in 2D
  - Immune system dynamics
- To explore:
  - Effects of the immune response
  - Effects of tumor “gluttony”
  - Effects of tumor adhesivity
  - Dynamic Energy Budget concept (DEB)
  - Effects of microenvironment
- Build from:
  - Immunology literature, ODE concepts

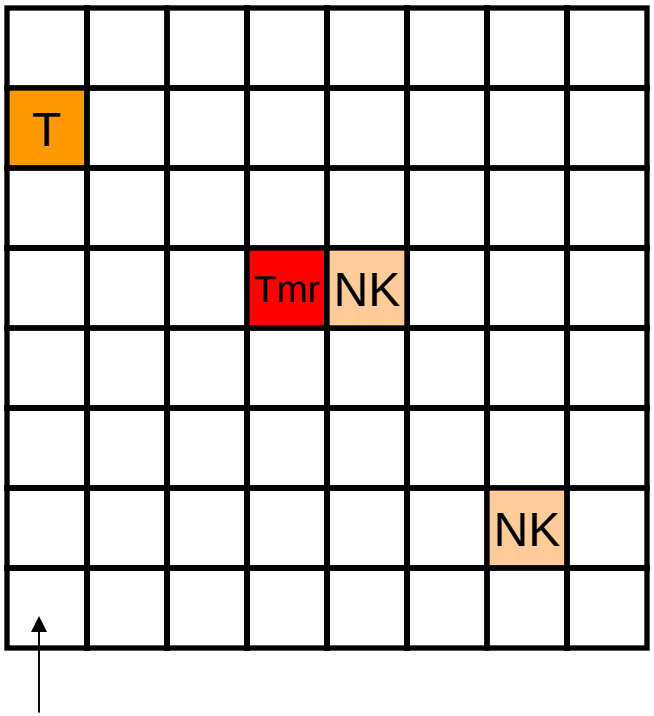
Approach: hybrid cellular automata

- Laws of evolution are written as partial differential equations or discrete rules, either stochastic or deterministic.
- Typically, all rules are eventually discretized for numerical solution.
- Inherent in these models: two time scales, one for the (fast) diffusion of small molecules, one for the evolution of cell populations.

In Particular…

- Include Tumor cells (living and necrotic), Immune cells (NK and CTL), and normal Host cells.
- Two types of nutrients: one for **M**aintenance and one necessary for cell division (**N**).
- Nutrients diffuse from a (constant) source: blood vessels at the upper and lower edge of the computational domain and are consumed by living cells.
- NK cells are constantly replenished in order to maintain relatively constant population.
- CTLs are recruited when tumor cells are lysed or recognized by the immune system.
- Tumor cells die, proliferate and migrate, affected by local nutrient concentrations.

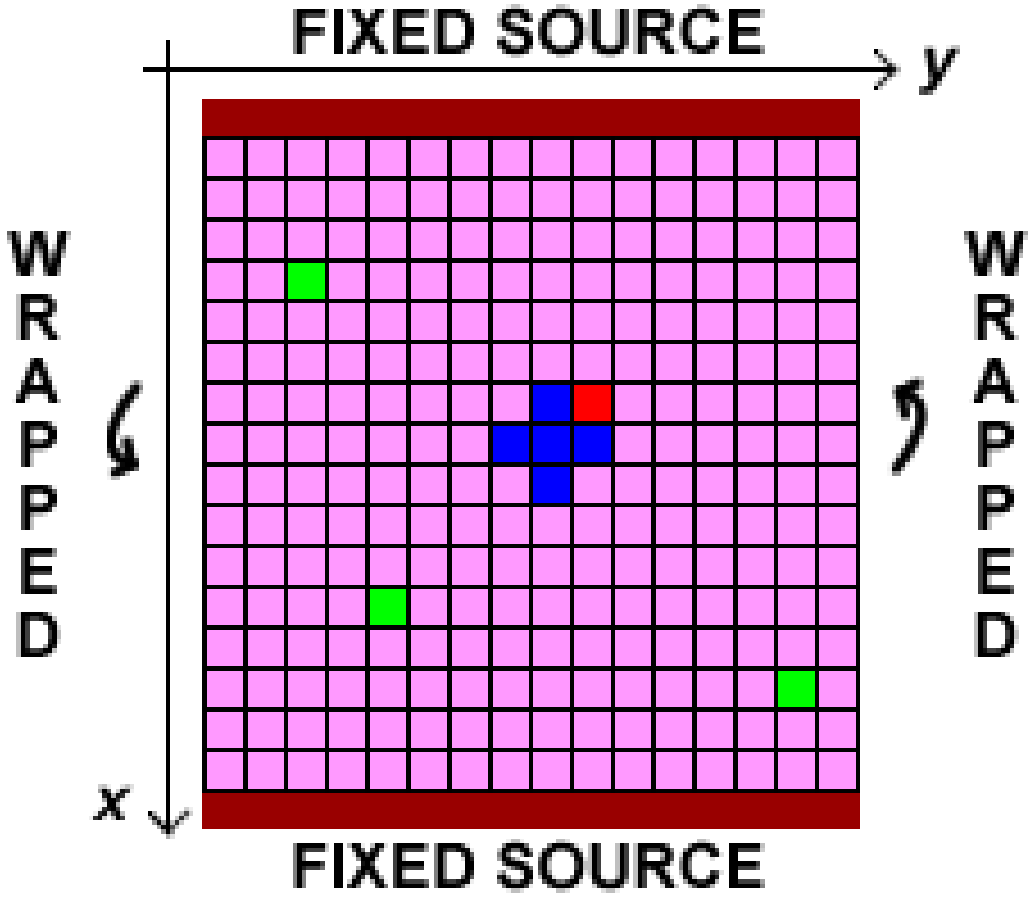
Cellular automata - the idea…



- DePillis/Mallet/Radunskaya models work w/ 2d, but can also be 3d
- Grid of elements where cells can be located
- Discrete time steps, cells:
  - Move
  - Divide
  - Interact
  - Die
  - Signal
  - Consume nutrients
  - etc

Model I

- Hybrid PDE/CA model
- 2D spatial domain
- Nutrient sources
- Initial cell scattering
- Stochastic cell rules
- Explore: Effect of varying nutrient consumption rates



Nondimensional Nutrient PDEs

$$\frac{\partial N}{\partial t} = \nabla^2 N - \alpha^2 (H + \mathrm{NK} + L) N - \lambda_N \alpha^2 T N,$$

Dimensionless rate of consumption

Tumor excess consumption factor

$$\frac{\partial M}{\partial t} = \nabla^2 M - \alpha^2 (H + \mathrm{NK} + L) M - \lambda_M \alpha^2 T M.$$

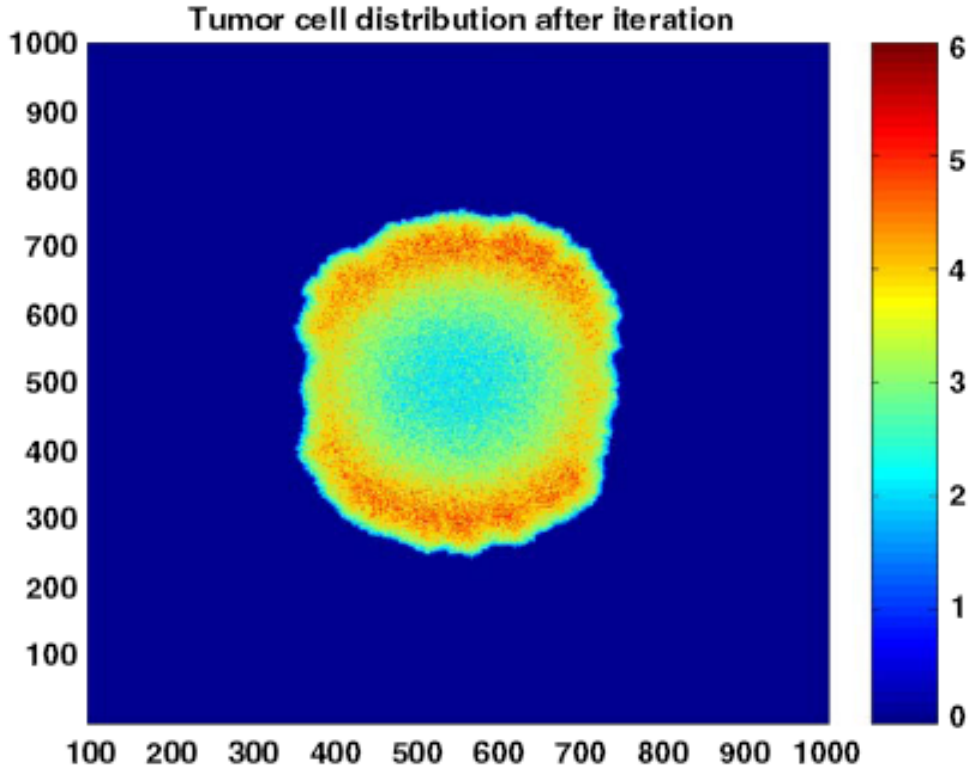
- *N*: nutrients required for proliferation
- *M*: nutrients required for survival
- *H*: host cells
- *T*: tumor cells
- *NK*: NK immune cells
- *L*: CD8+T lymphocytes

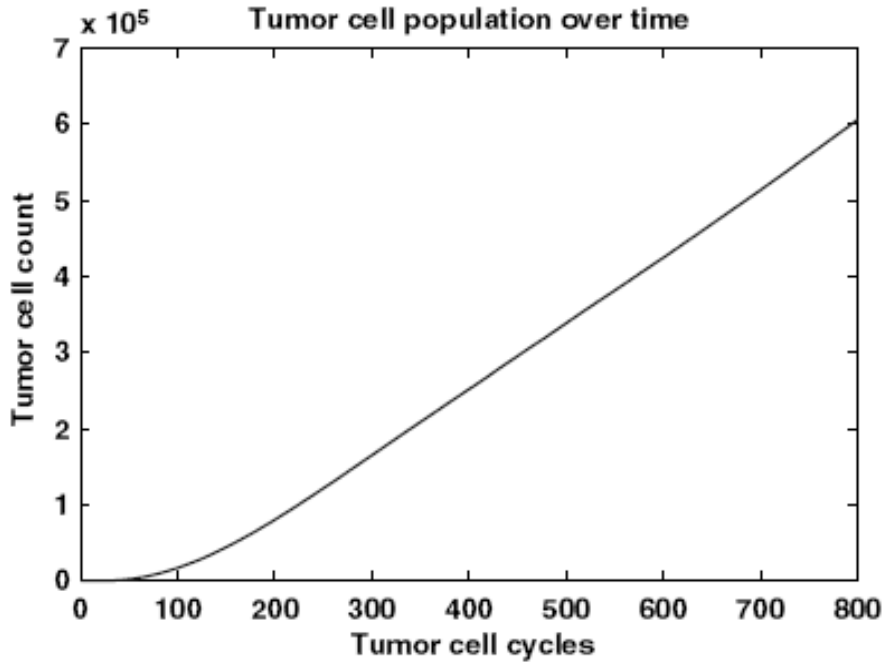
Cell rules

- Evolution: according to probabilistic rules
- All cells: consume nutrients
- Tumor cells: move, divide, die (from insufficient nutrient, or from immune cell attack)
- NK cells: move randomly, kill tumor, induce CTL recruitment; one tumor cell kill allowed.
- CTL cells: move preferentially toward tumor, kill tumor, induce further CTL recruitment; multiple tumor cell kills allowed.

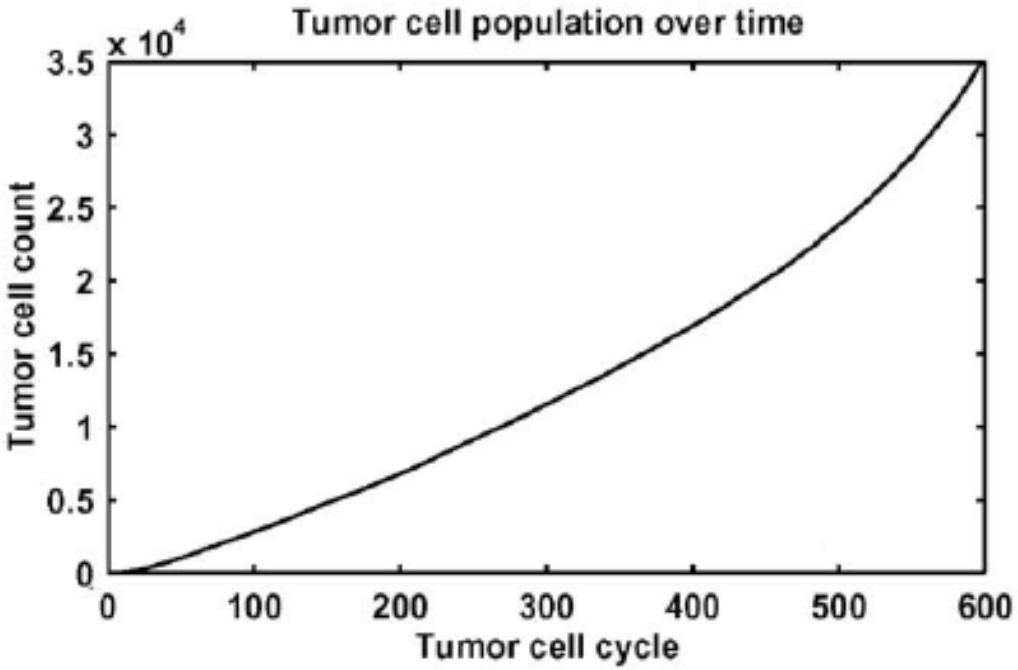
Spherical Growth: Lower nutrient consumption rates

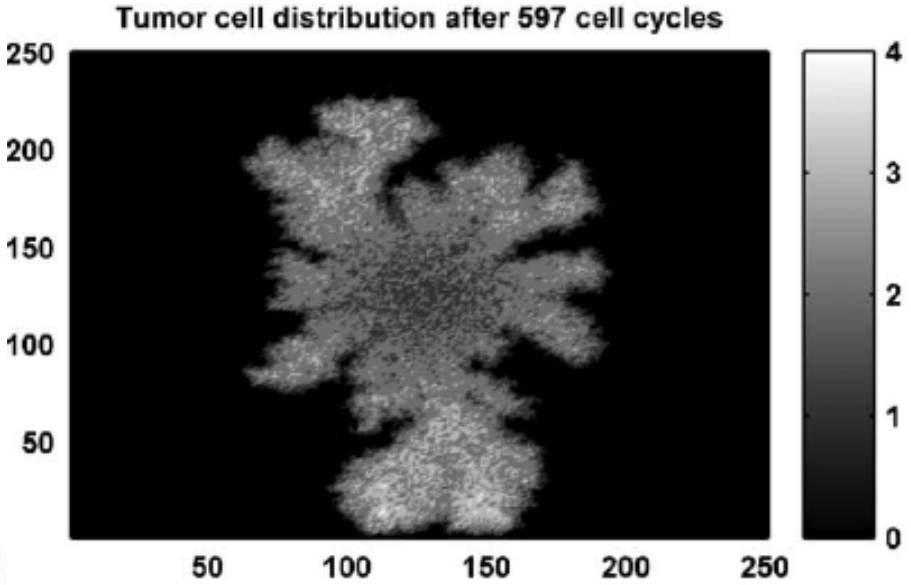
- No immune system…exp./lin. tumour growth





Papillary growth: Higher nutrient consumption rates

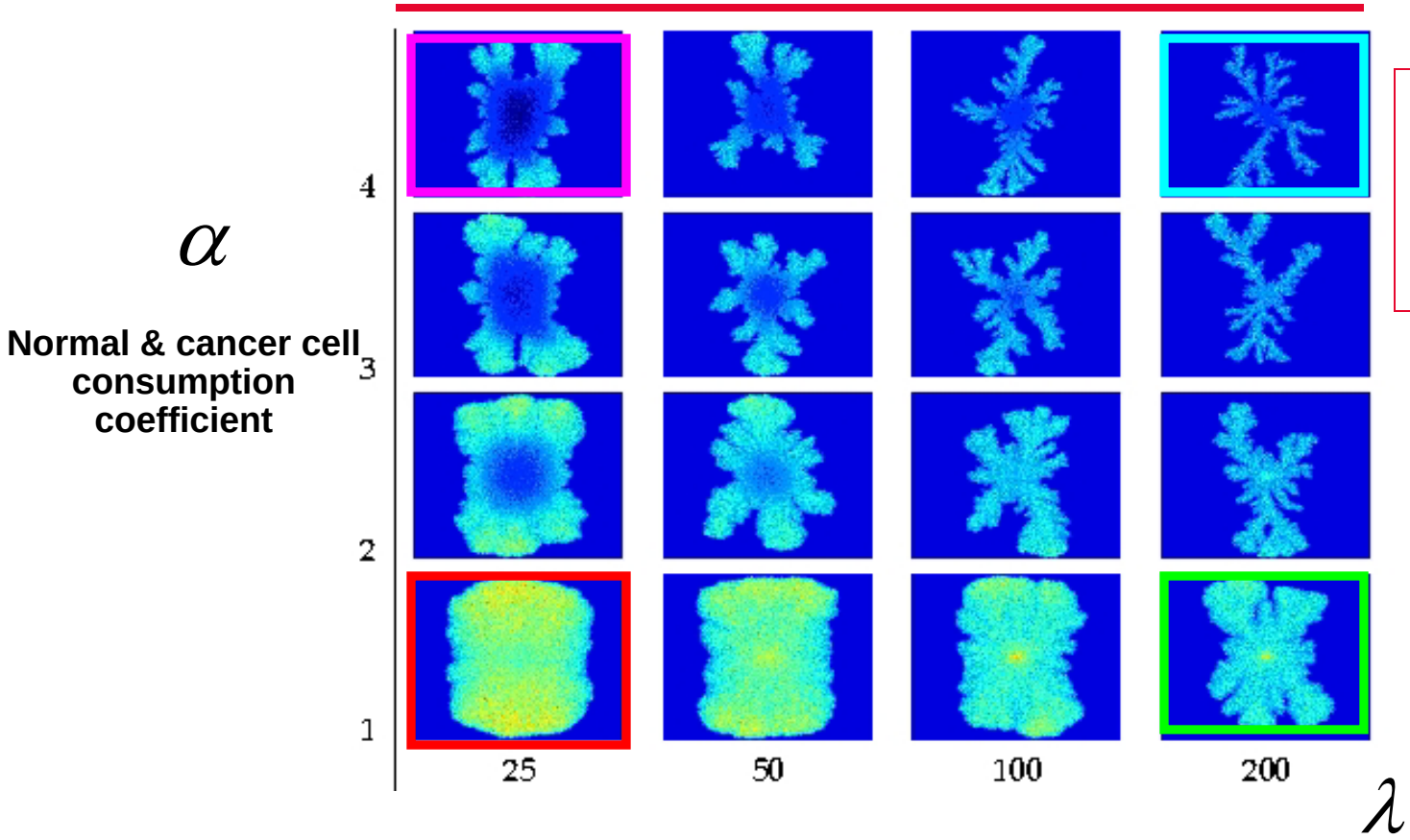




Papillary versus Spherical

Spatial Tumor Growth: one nutrient, one blood vessel

- **Nutrients diffuse from blood vessel (at top) in a continuous model (PDE).**
- **Cells proliferate according to a probabilistic model based on available nutrients.**

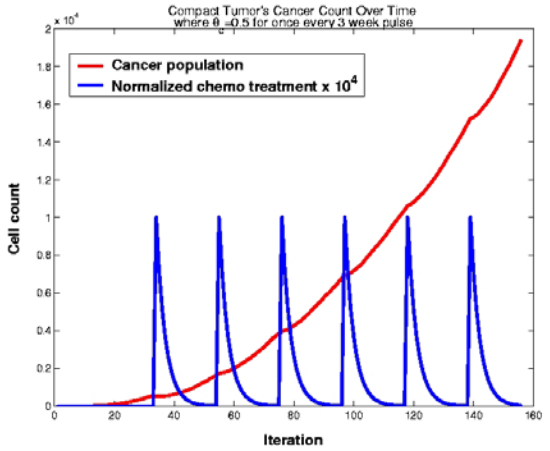


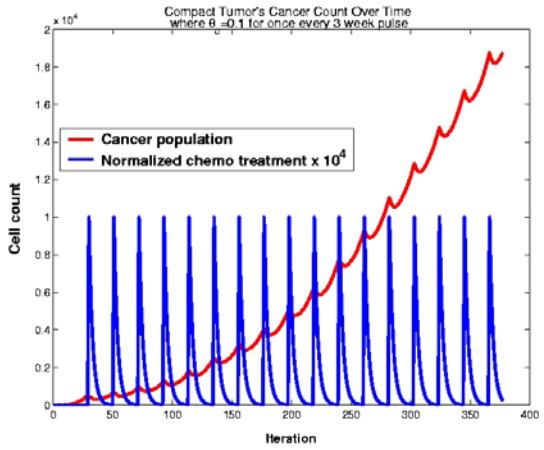
A blood vessel runs along the top of each square

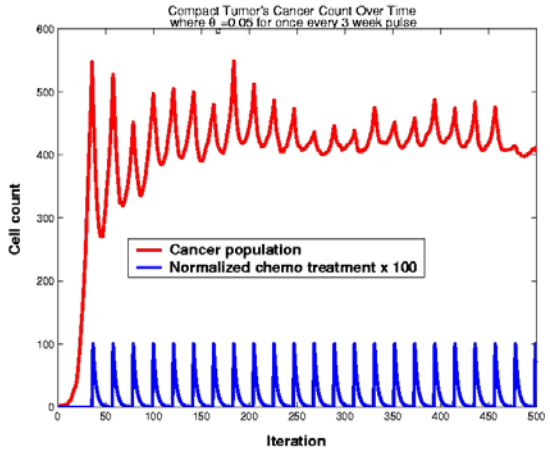
Spatial Features: Add Chemo

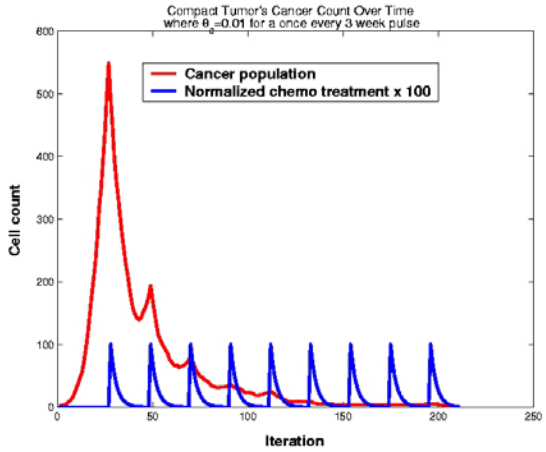
Spatial Tumor Growth

- **Chemotherapy Experiments: Every Three Weeks**





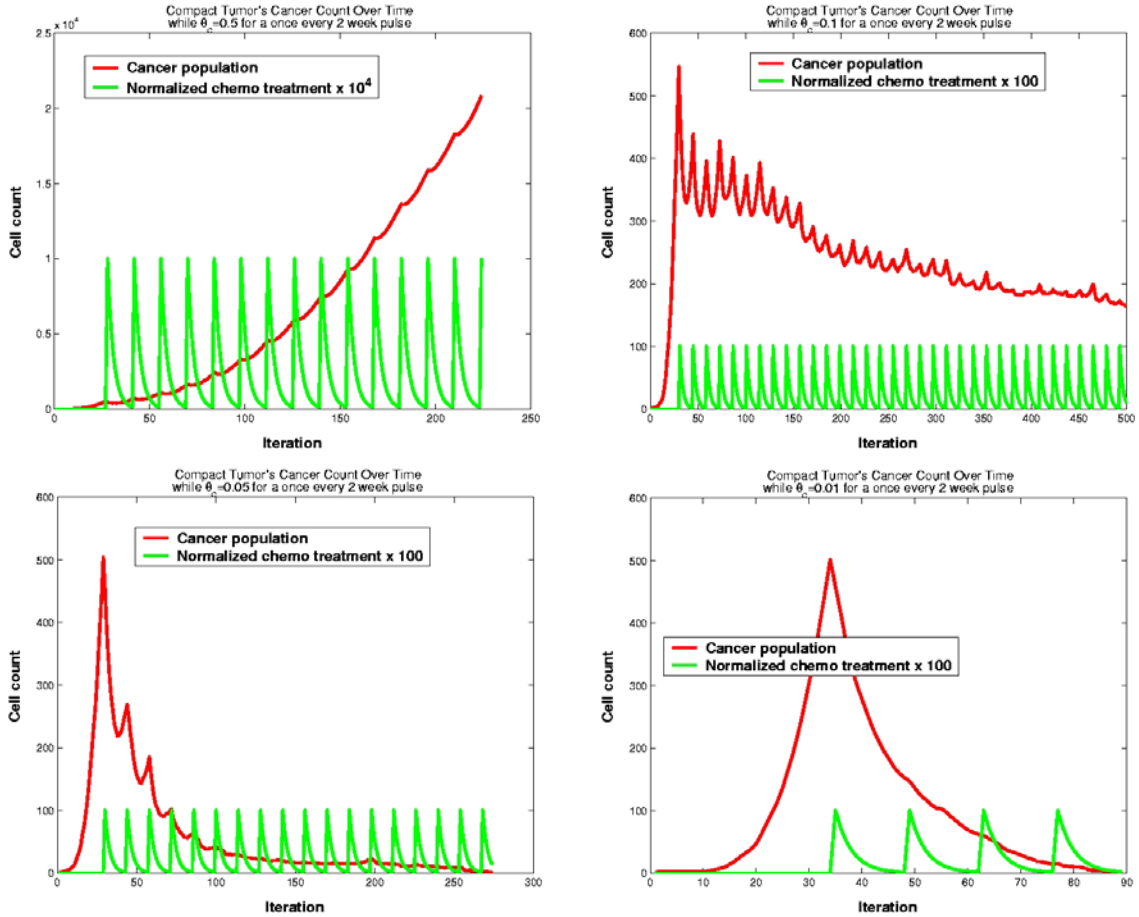




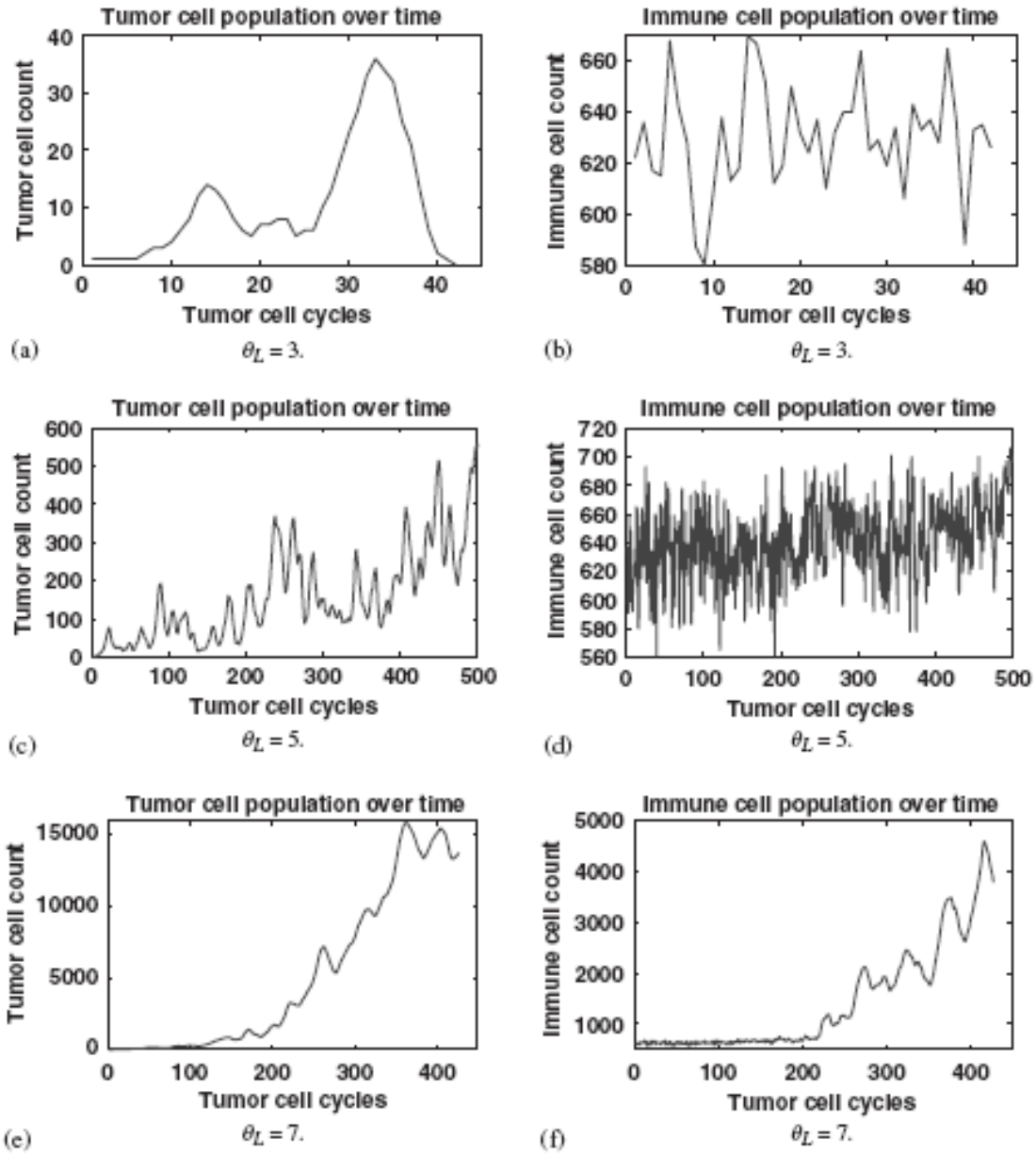
Spatial Features: Add Chemo

Spatial Tumor Growth

- **Chemotherapy Experiments: Every Two Weeks**



Add CTL recruitment to tumor



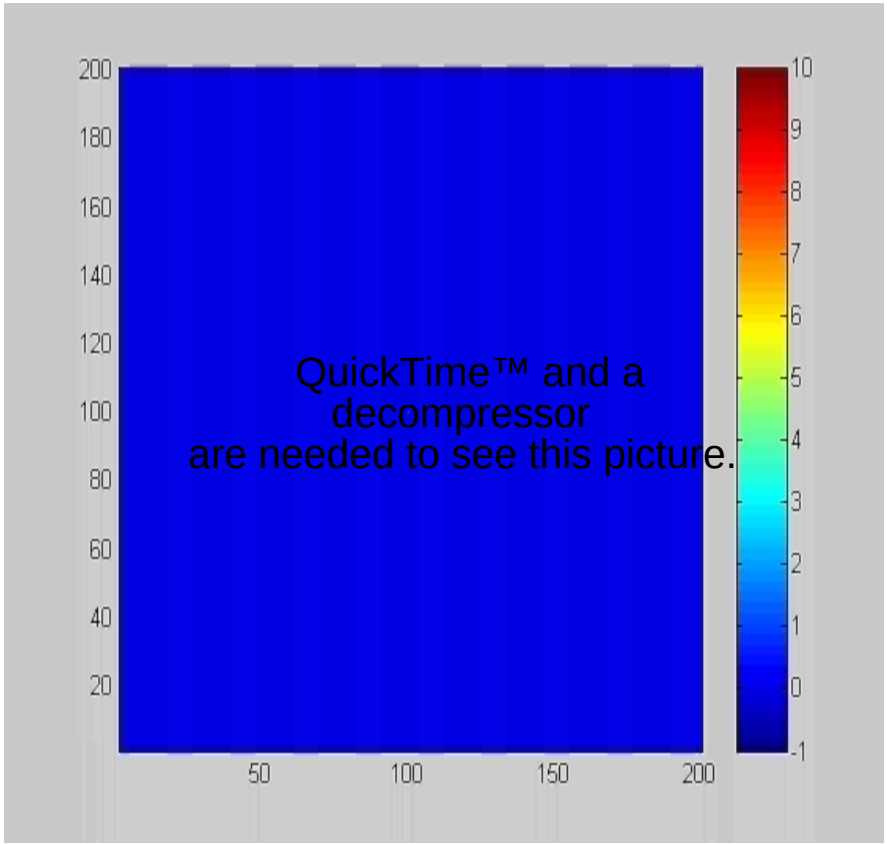
- High recruitment

Effects of CTL Recruitment to Tumour locations

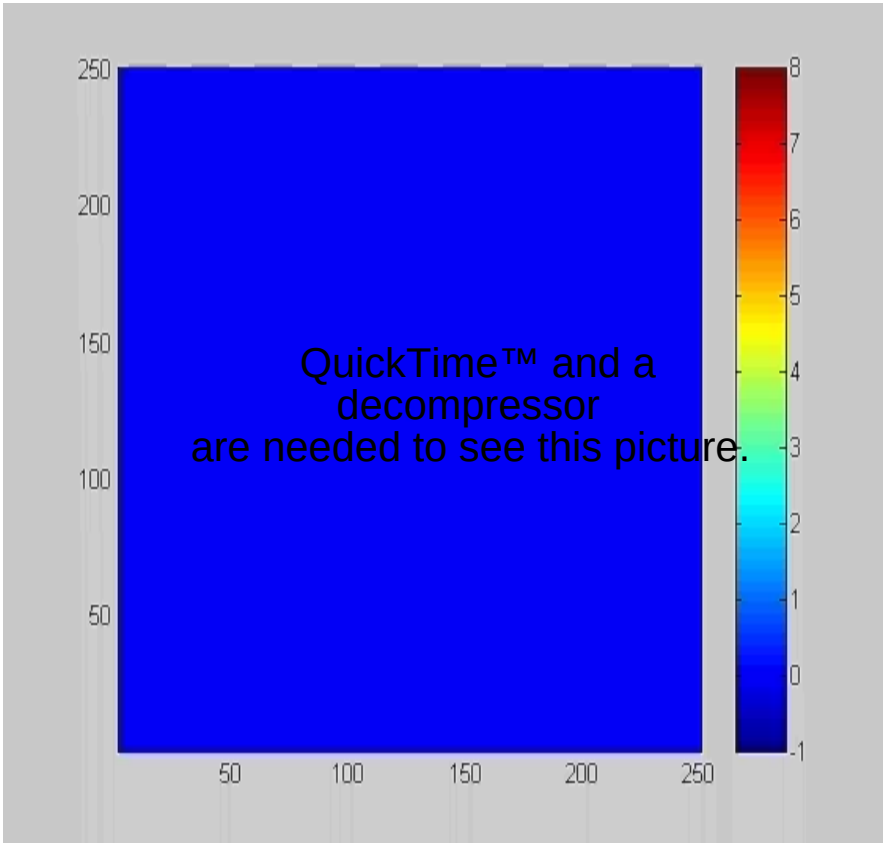
- Low recruitment

Spatial Tumor Growth

•NK and CD8 Immune Activity



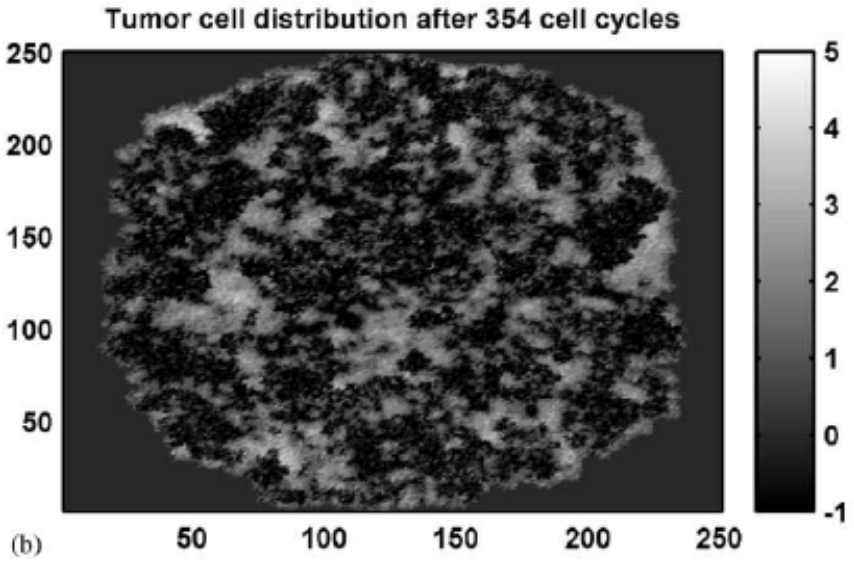
Simulation 1: Tumor



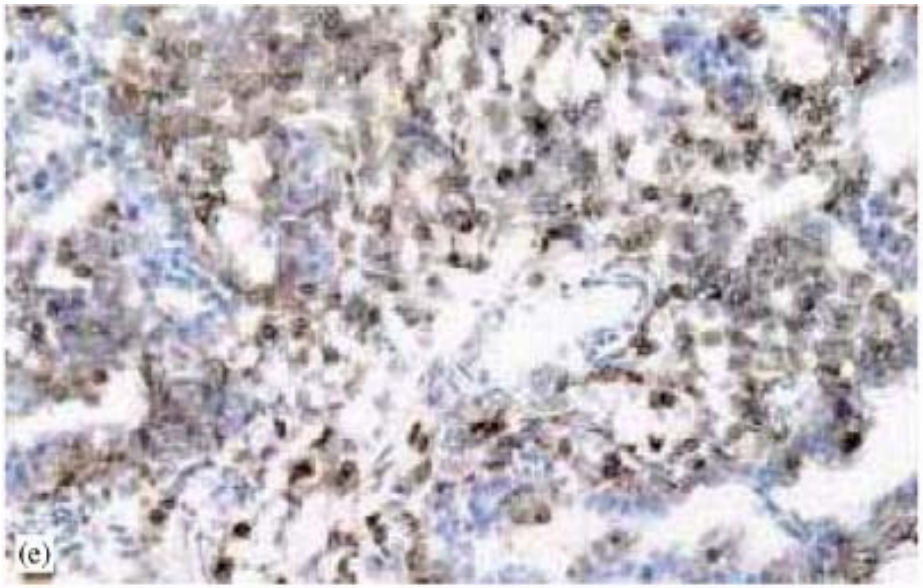
Simulation 2: Tumor

Thanks: Dann Mallet

Immune cell infiltration: Qualitative agreement with biological experiment



Simulation. Tumor cells (white) infiltrated by immune cells (black).



Ovarian carcinoma. Tumor cells (blue) infiltrated by immune cells (gray). Thanks: Zhang et al 2003

Mallet & de Pillis JTB 239, 2006

Radiation Treatment: in progress

- Goal of radiation: create enough DNA double-strand breaks to cause cell death.
- Standard model: Linear Quadratic (LQ)

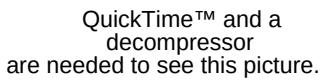
$$S = N/N_o = e^{-\alpha D - \beta D^2}$$

- LQ-modified with oxygenation effect - hypoxic cells less vulnerable to radiation: Need OER (oxygen enhancement ratio): standard is 2.5 to 3

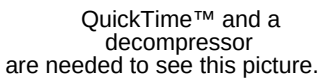
$$S(p) = e^{-\alpha_H \cdot OER_\alpha(p) \cdot \mathrm{Dose}_p - \beta_H \cdot (OE|R_\beta(p) \cdot \mathrm{Dose}_p)^2}$$

Radiation Treatment

No treatment

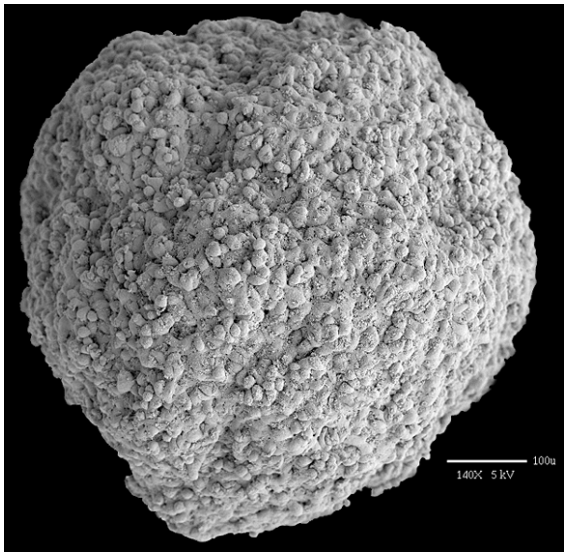


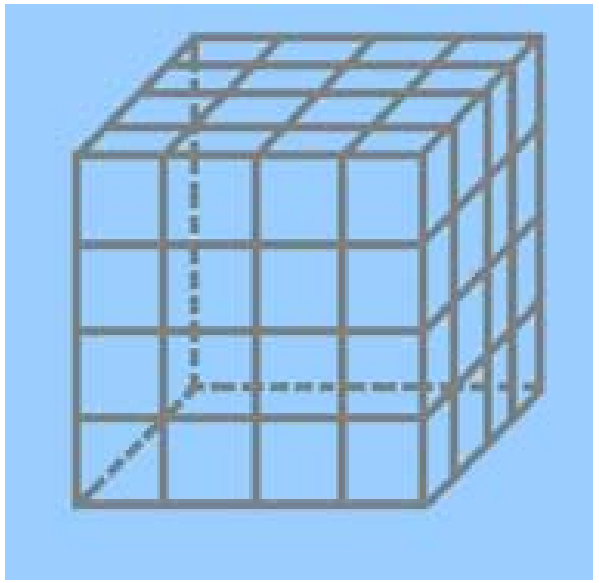
Radiation cycles 100-120



50x50 grid. Cycles 80 to 140. Radiation: Alternate Days (cycles 100-120), 3 Grays per dose.

HMC Mathematics Clinic: 5 Undergraduates and LANL

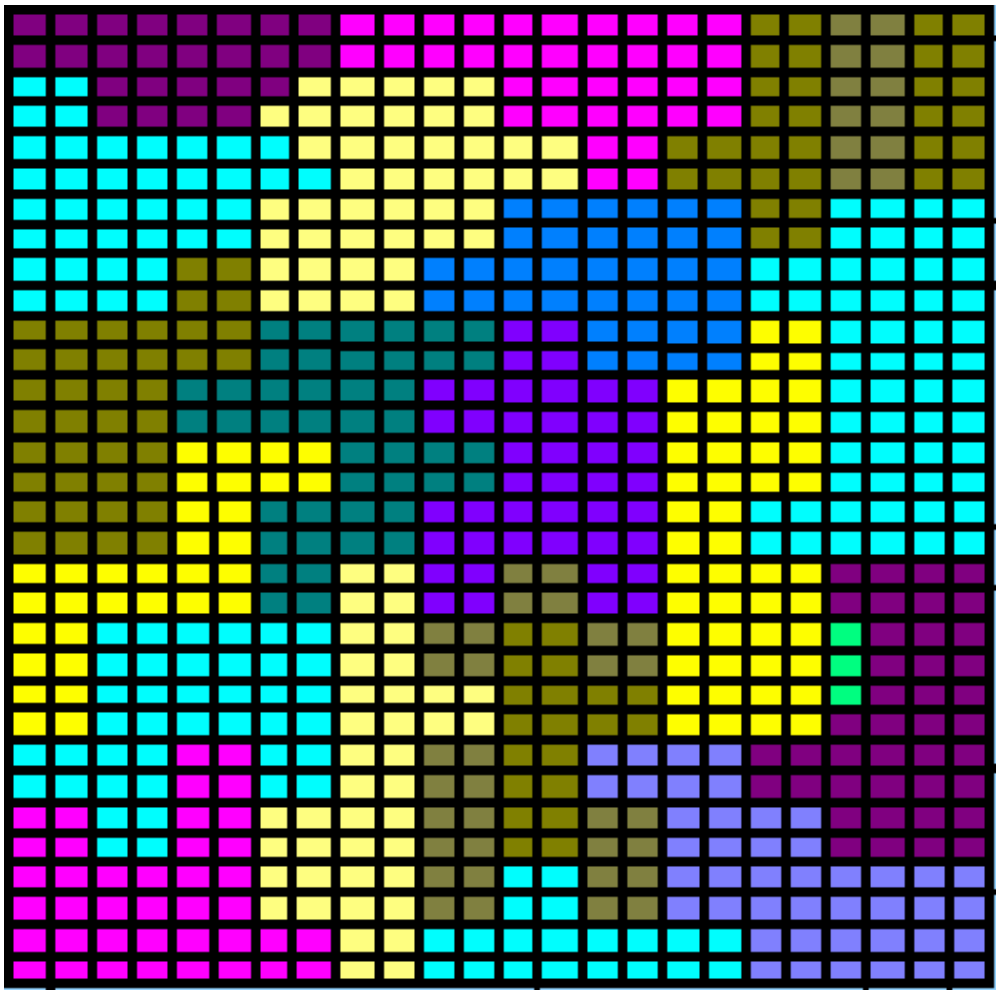




- **The three cell types within the model are:**
  - proliferating cells: alive, can divide and grow
  - quiescent cells: alive, but dormant
  - necrotic cells: dead

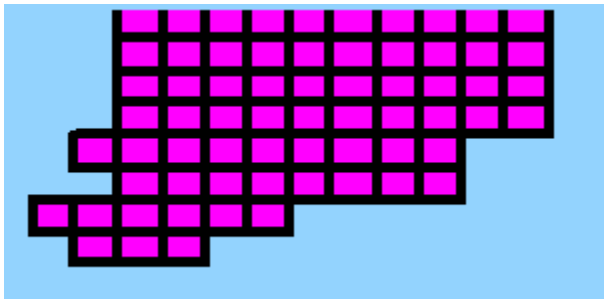
HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

Simulated Model Cross-Section



- Grid site

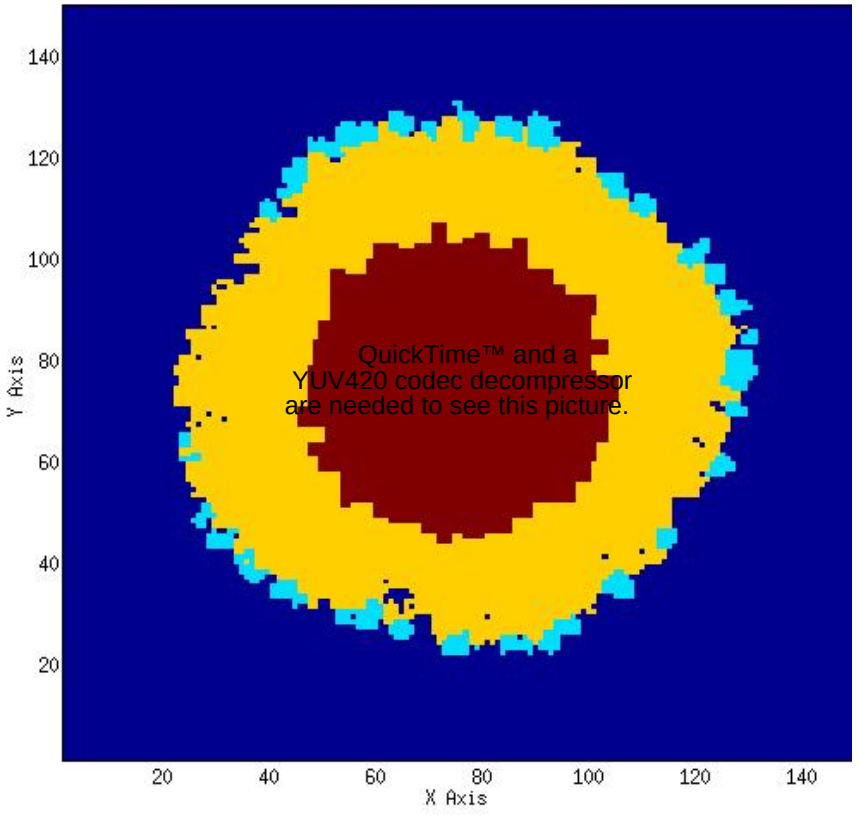
- Tumor cell



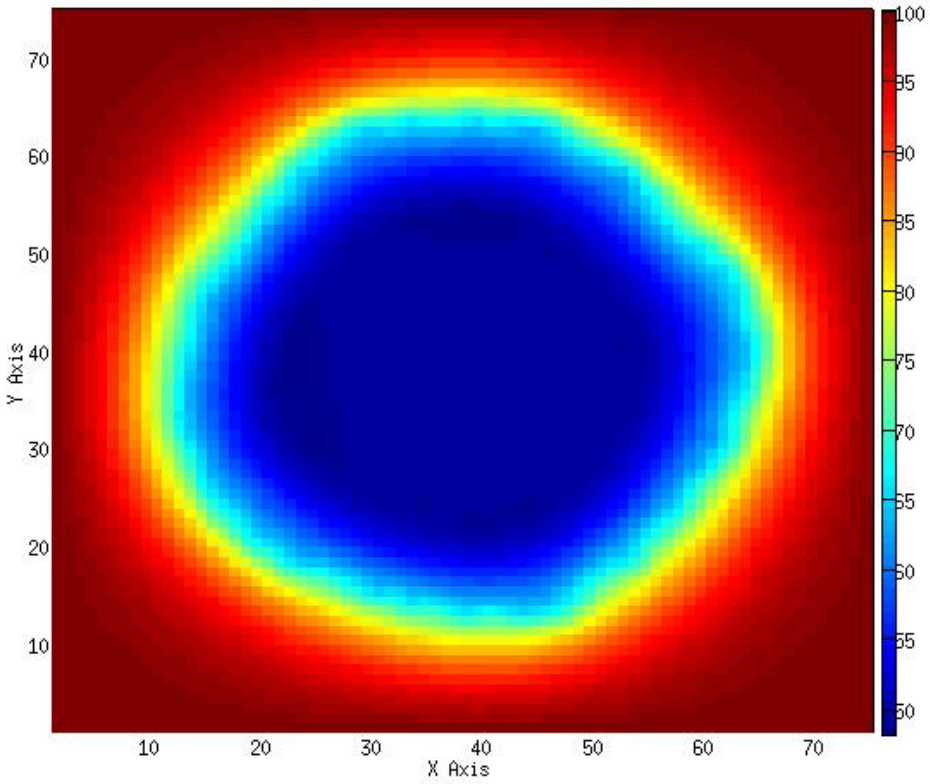
HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

Matlab Imaging – 2D Slices

Cell Types

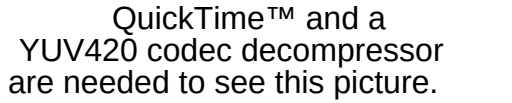


Growth Factor Concentration



HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

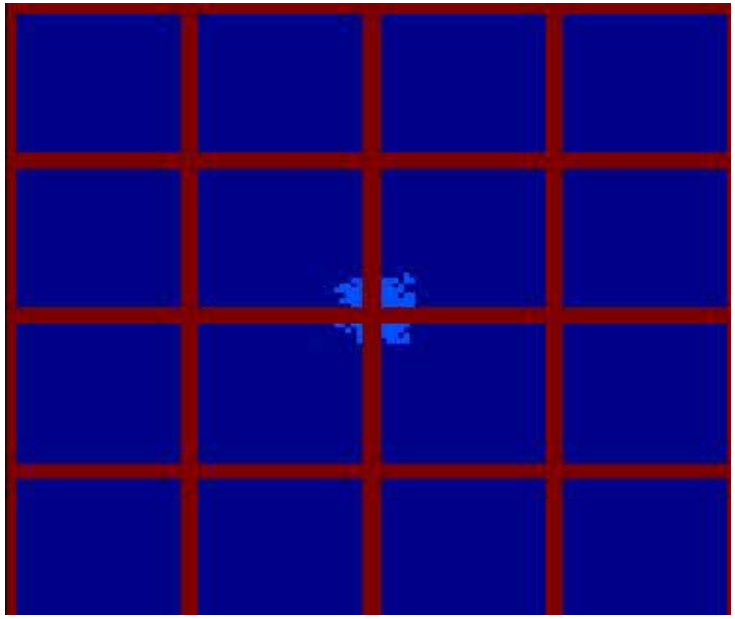
Linear Vasculature - Tumor Growth

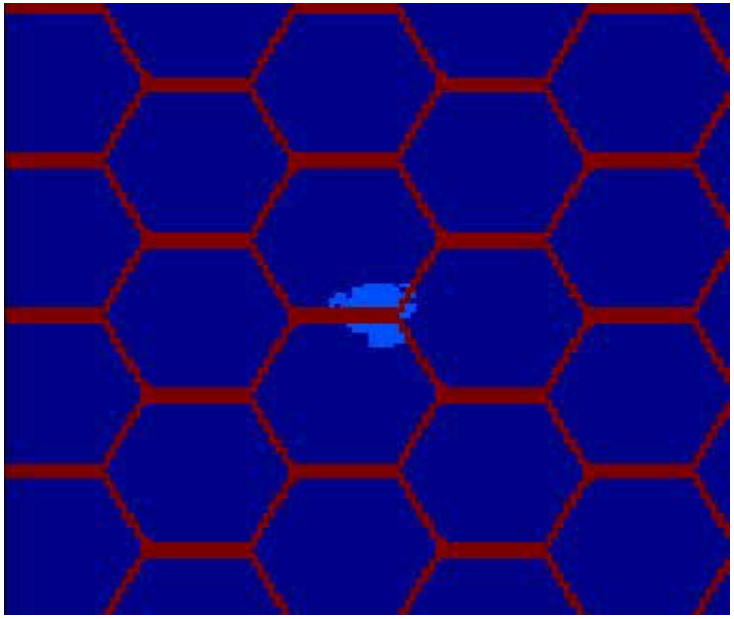


2D slice taken over several time steps

HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

Lattice Vasculature – Tumor Growth: 2D Slice of 3D Computation

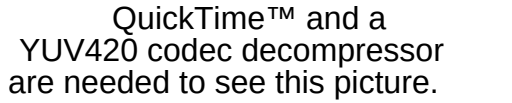




Series of fixed-depth 2D slices taken over several time steps

HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

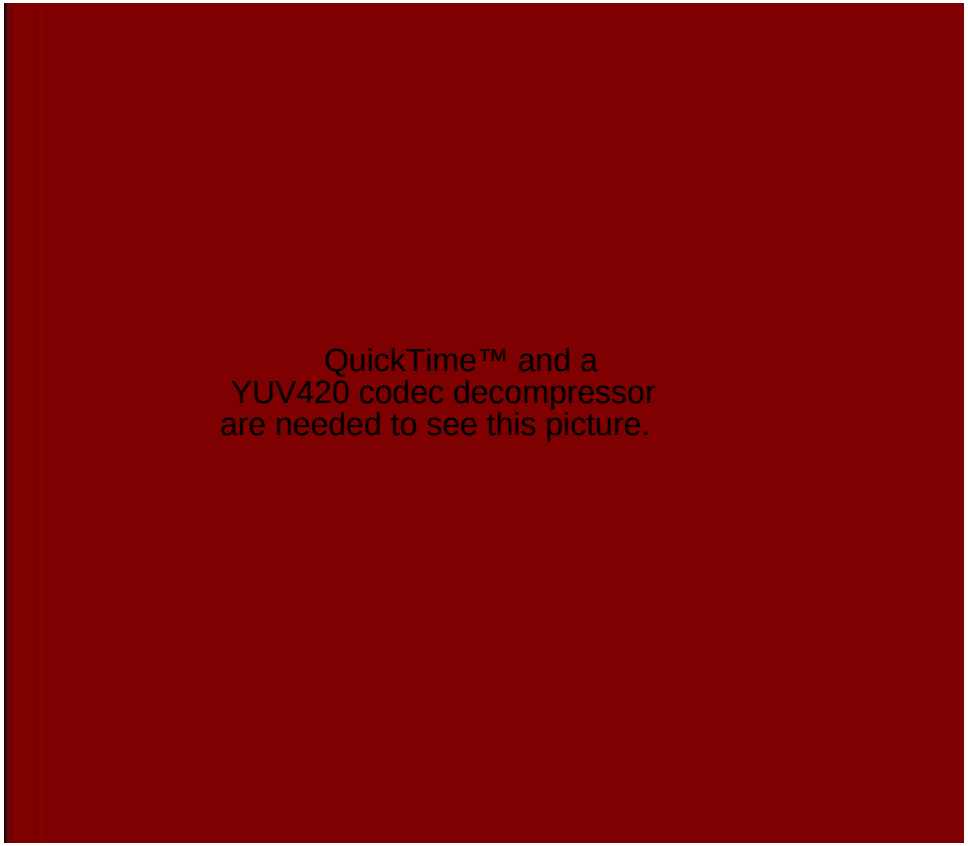
Hex Lattice Vasculature – Tumor Growth



2D slice taken over several time steps

HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

3D Vasculature – Fly-Through

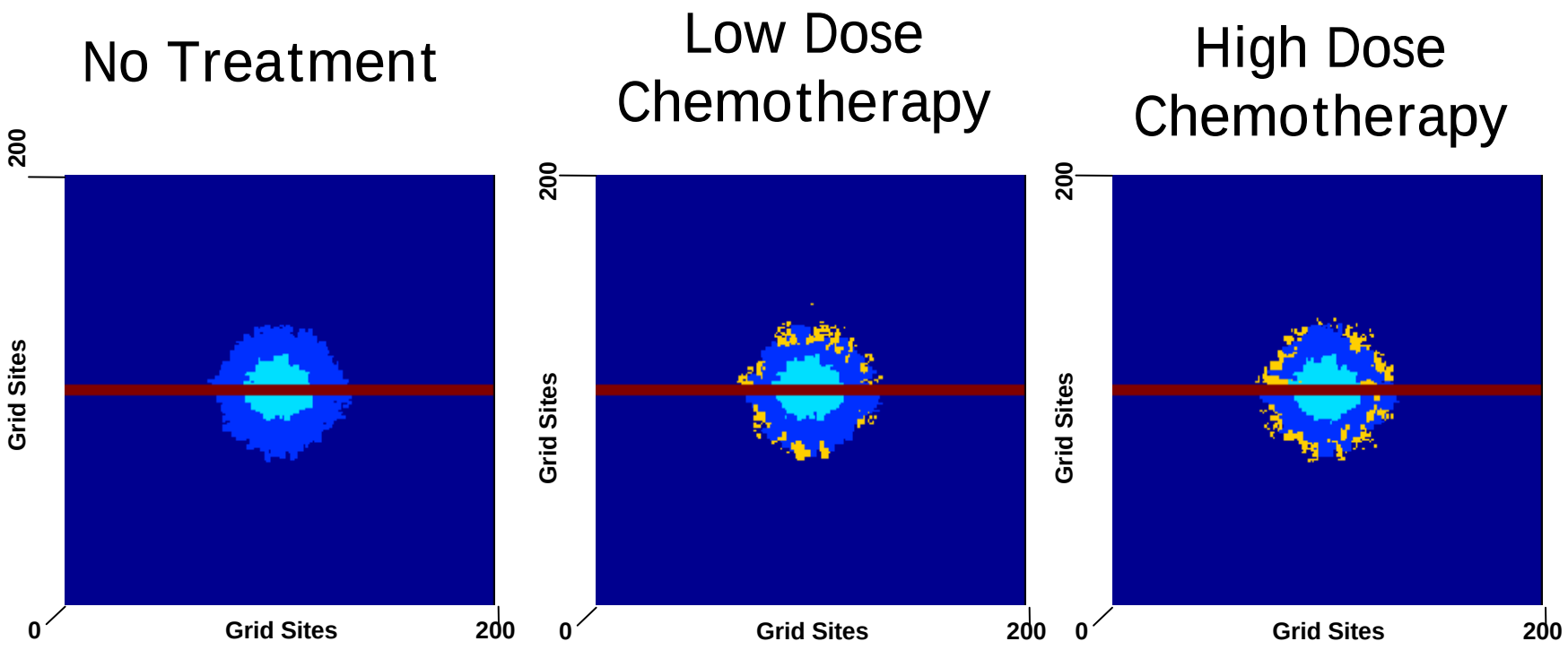


Series of fixed-depth 2D slices taken over several time steps

HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

Chemotherapy Treatments

37 MCS

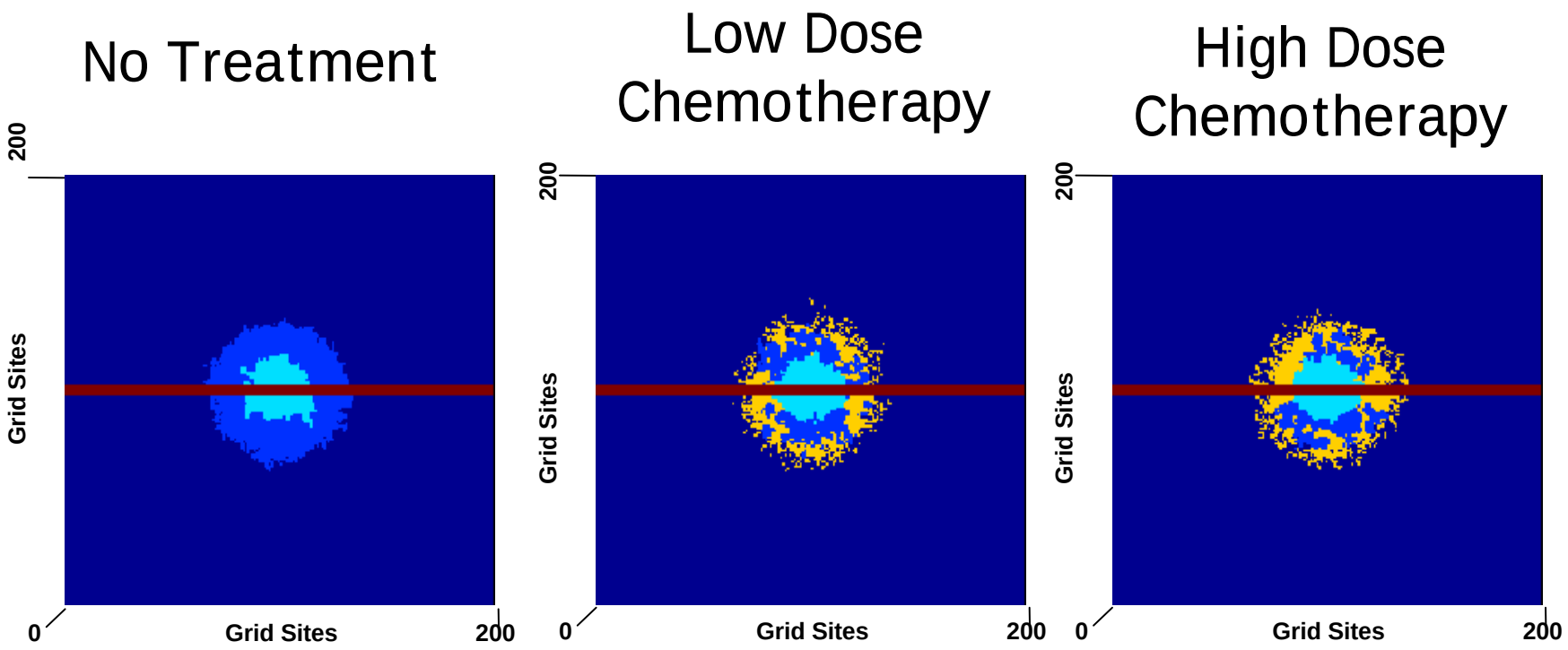


Red: Quiescent; Dark Yellow: Proliferating; Blue: Apoptotic;
Light yellow: Nutrient Medium; Light Blue Line: Blood Vessel

HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

Chemotherapy Treatments

40 MCS

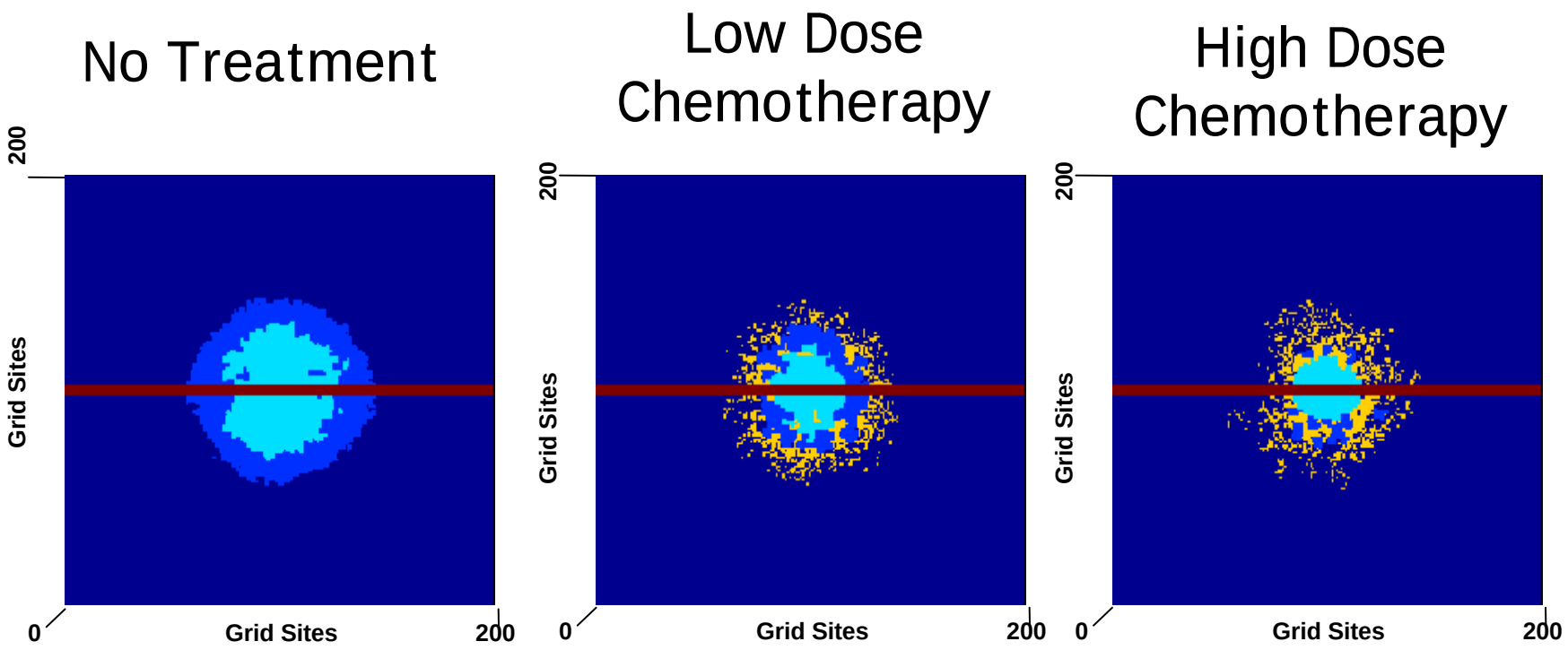


Red: Quiescent; Dark Yellow: Proliferating; Blue: Apoptotic;
Light yellow: Nutrient Medium; Light Blue Line: Blood Vessel

HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

Chemotherapy Treatments

50 MCS

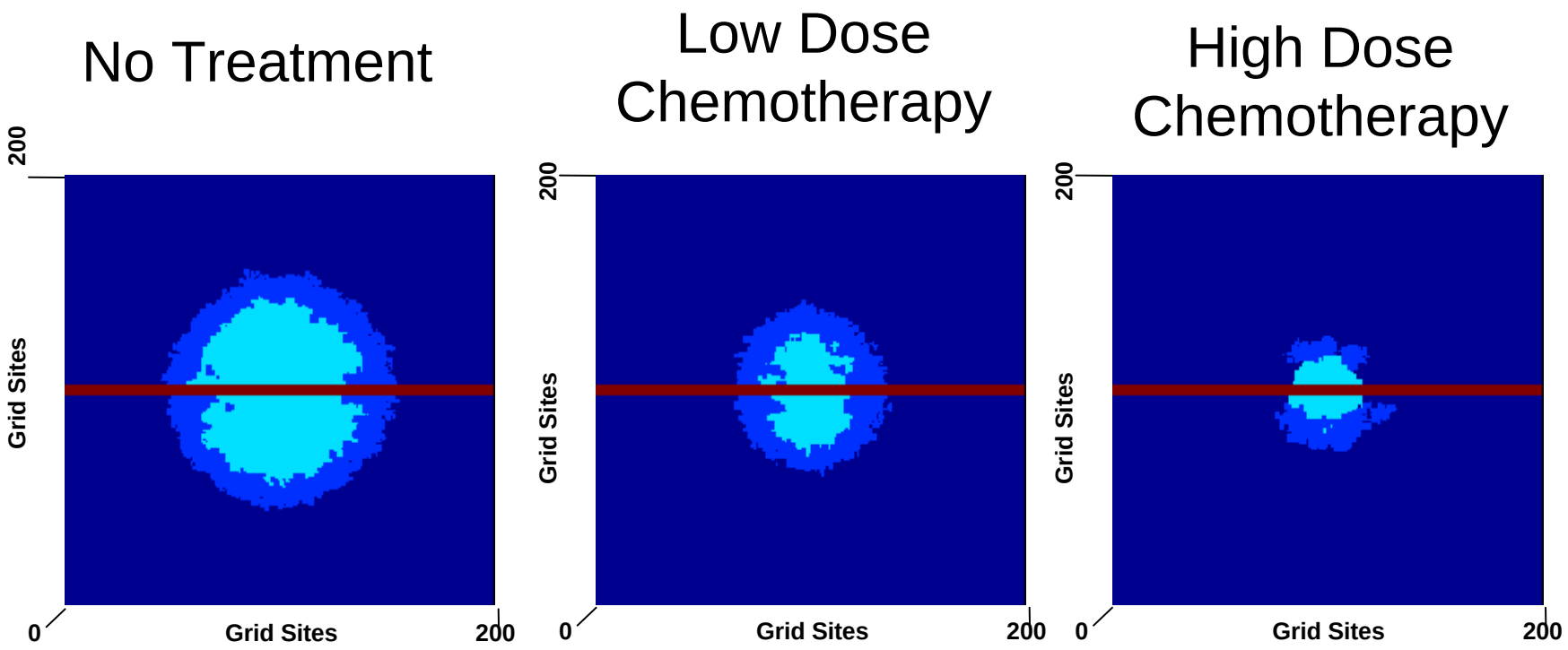


Red: Quiescent; Dark Yellow: Proliferating; Blue: Apoptotic;
Light yellow: Nutrient Medium; Light Blue Line: Blood Vessel

HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

Chemotherapy Treatments

60 MCS



Red: Quiescent; Dark Yellow: Proliferating; Blue: Apoptotic;
Light yellow: Nutrient Medium; Light Blue Line: Blood Vessel

HMC STUDENTS: Tiffany Head, Cris Cecka, Alan Davidson, Liam Robinson, Dana Mohamed
LANL Liason: Yi Jiang. Faculty Supervisor: L.G. de Pillis

3D Tumor Growth
Hybrid ODE-PDE Approach
with
Spherical Harmonics

Spherical Harmonics to Model 3D Tumor Growth

- Use knowledge from ODE models
- Incorporate spatial components to allow visualization of 3D tumor
- Spherical harmonics: Motivated by medical imaging techniques

$$Y_l^m(\theta,\varphi) = \sqrt{\frac{2l+1(l-m)!}{4\pi(l+m)!}} P_l^m(\cos\theta)\exp(im\varphi)$$

ODE/PDE Equations

$$
\begin{aligned}
T_t &= d_T \nabla^2 T + a\frac{U}{\theta + U} T(1 - bT) - cNT - DT - K_T(1 - e^{-\delta_T M})T \\
N_t &= d_N(\mathbf{x}, T)\nabla^2 N - pNT - K_N(1 - e^{-\delta_N M})N \\
L_t &= d_L(\mathbf{x}, T)\nabla^2 L - qLT - K_L(1 - e^{-\delta_L M})L \\
M_t &= d_M(\mathbf{x}, T)\nabla^2 M - \gamma M \\
U_t &= d_U(\mathbf{x}, T)\nabla^2 U - \Gamma\frac{U}{\zeta + U} \\
\frac{N_B}{dt} &= f(\frac{e}{f}C_B - N_B) + \frac{p_N N_B I_B}{g_N + I_B} - K_N(1 - e^{-\delta_N M_B})N_B \\
\frac{L_B}{dt} &= \frac{-m g_I I_B}{g_I + I_B} + r_1\langle NT\rangle + r_2 C_B\langle T\rangle + \frac{p_I L_B I_B}{g_I + I_B} - \frac{u_0 L_B^2 C_B I_B}{g_I + I_B} + \frac{j\langle LT\rangle}{k + \langle T\rangle} - K_L(1 - e^{-\delta_L M_B})L_B + \eta_1 V_L(t) \\
\frac{C_B}{dt} &= \beta(\frac{\alpha}{\beta} - C_B) - K_C(1 - e^{-\delta_C M_B})C_B \\
\frac{M_B}{dt} &= -\gamma_B M_B + \eta_2 V_M(t) \\
\frac{I_B}{dt} &= -\mu_I I_B + \phi C_B + \frac{\omega L_B I_B}{g_I + I_B} + \eta_3 V_I(t) \\
D &= d\frac{(\frac{L}{T})^\ell}{s + (\frac{L}{T})^\ell}.
\end{aligned}
$$

Variable	Description
$T(\mathbf{x}, t)$	Concentration () of tumor cells in tissue
$N(\mathbf{x}, t)$	Concentration () of natural killer (NK) cells in tissue
$L(\mathbf{x}, t)$	Concentration () of $CD8^+$ T cells in tissue
$M(\mathbf{x}, t)$	Concentration () of medicine in tissue
$U(\mathbf{x}, t)$	Concentration () of nutrient in tissue
$N_B(t)$	Concentration () of NK cells in the body
$L_B(t)$	Concentration () of $CD8^+$ T in the body
$C_B(t)$	Concentration () of circulating lymphocytes in the body
$M_B(t)$	Concentration () of medicine in the body
$I_B(t)$	Concentration () of interleukin-2 (IL2) in the body

PDE Types in Problem

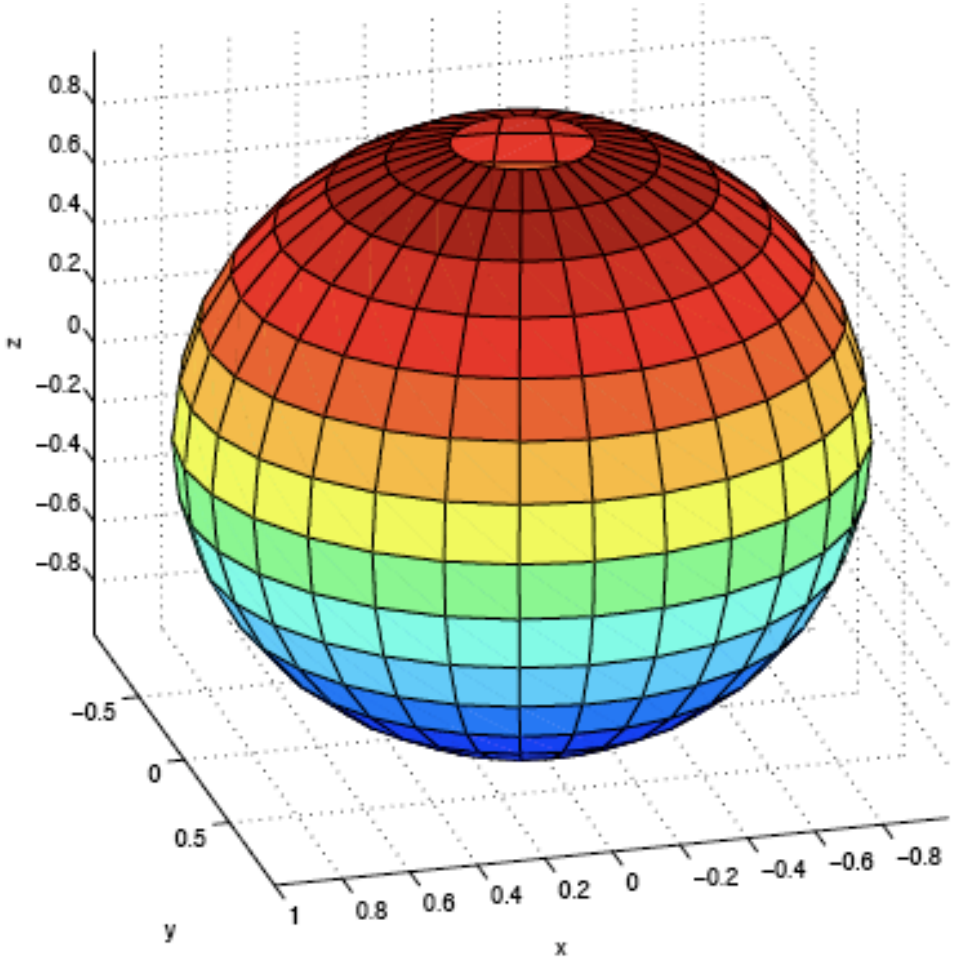
Hyperbolic Boundary

$$\frac{\partial \mathbb{Z}}{\partial t} \propto \nabla \mathbb{X}$$

Parabolic from Boundary to Interior

$$\mathbb{X}_t \propto \Delta \mathbb{X} + f(\mathbb{X})$$

Truncated Spherical Coordinates



Evolving Tumor Simulations

QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

Thoughts on Modeling

- "All models are wrong…some are useful", Box and Draper, 1987
- "All decisions are based on models…and all models are wrong", Sterman, 2002
- "Although knowledge is incomplete, nonetheless decisions have to be made. Modeling…takes place in the effort to plan clinical trials or understand their results. Formal modeling should improve that effort, but cautious consideration of the assumptions is demanded", Day, Shackness and Peters, 2005

Final Thoughts on Cooperation

- The more we cooperate, the more rapid progress we can make.
- The more we cooperate, the more interesting problems we can solve.
- The more we cooperate, the more relevant our contributions.

Sample References:

De Pillis, Radunskaya, "A Mathematical Tumor Model with Immune Resistance and Drug Therapy: an Optimal Control Approach", *J. Theor. Medicine, 2001*

De Pillis, Radunskaya, "The Dynamics of an Optially Controlled Tumor Model: A Case Study", *Math. Comp. Model., 2003*

De Pillis, Radunskaya, Wiseman "A Validated Mathematical Model of Cell Mediated Response to Tumor Growth",

Cancer Res., 2005

De Pillis, Gu, Radunskaya, "Mixed Immunotherapy and Chemotherapy of Tumors: Modeling, Applications and Biological Interpretations", *J. Theor. Biol., 2006*

Mallet, De Pillis, "A Cellular Automata Model of Tumor-immune System Interactions", *J. Theor. Biol., 2006*

De Pillis, Mallet, Radunskaya, "Spatial Tumor-immune Modeling ", *J. Comp. & Math. Methods in Med., 2006*

De Pillis, Fister, Gu, Head, Maples, Neal, Murugan, Yoshida, "Chemotherapy for tumors: An analysis of the dynamics and a study of quadratic and linear optimal controls ", *Math. Biosci., 2007*

De Pillis, Fister, Gu, Collins, Daub, Gross, Moore, Preskill, "Seeking Bang-Bang Solutions of Mixed Chemo-Immunotherapy of Tumors ", *EJDE., 2007*

De Pillis, Gu, Fister, Head, Maples, Neal, Murugan, Yoshida, "Optimal Control of Mixed Immunotherapy and Chemotherapy of Tumors ", *J. Biol. Systems 2008*

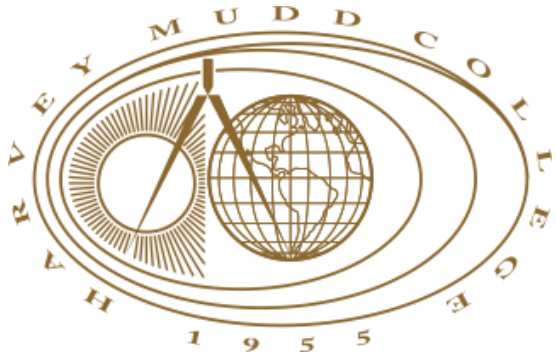
De Pillis, Gu, Fister, Collins, Daub, Gross, Moore, Preskill, "Mathematical model creation for Cancer Chemo-Immunotherapy ", *Comp. & Math. Methods in Med., 2009*

Thanks for listening!

Prof. L.G. de Pillis
http://www.math.hmc.edu/~depillis

Dept. of Mathematics

HARVEY MUDD COLLEGE



Claremont, CA, 91711

USA

depillis@hmc.edu