Introduction to Mathematical Oncology

January 22, 2019

Outline

What is Cancer?

A collection of diseases in which abnormal cells grow uncontrollably by ignoring the normal rules of cell division

- Healthy life requires **cooperation** to survive
- Cancer is the collapse of this cooperation (selfish)

A set of fundamental traits (more later):

- Grow independently from signals (activation of oncogenes, e.g. *ras*)
- Ignore stop signals (inactivation of tumor suppressor genes, e.g. p53)
- Ignore cell death signals (apoptosis)
- Become effectively immortal
- Induce angiogenesis (blood supply formation)
- Metastasize (invade other locations in the body)

Mutations and Clonal Expansion

Abnormal cells undergo **mutations** in their genetic material (DNA) to obtain traits

- Environmental - tobacco, radiation, chemicals, diet
- Genetic factors - i.e. inherited mutations, random events

Requires multiple mutations, and leads to **clonal expansion**

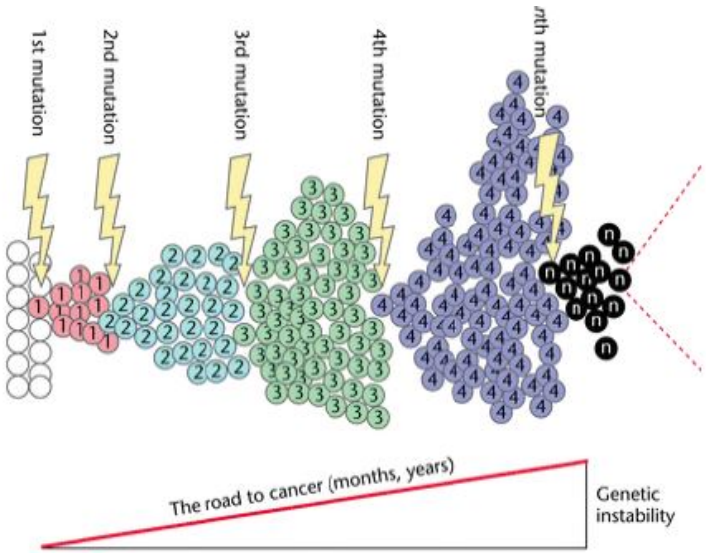


Figure 1.1 a: Clonal expansion. Cancer is a multi-gene, multi-step disease originating from single abnormal cell (clonal origin). Changes in DNA sequences result in the cell progressing slowly to the mildly aberrant stage. Successive rounds of mutation & natural selection leads to a mass of abnormal cells called tumours. Some cells in the tumour undergo further rounds of mutations leading to the formation of malignant cells which cause metastasis. (*Fig source: M Alison.* www.els.net)

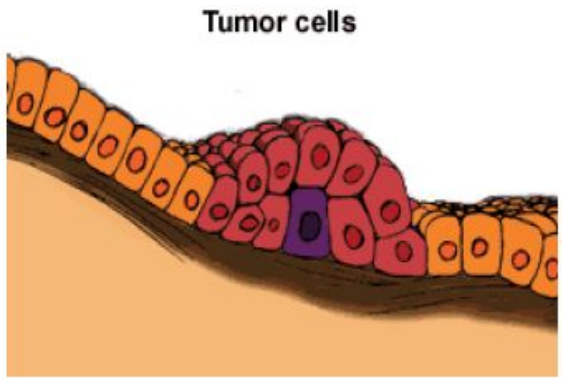


Figure 1.1b: Clonal expansion. Normal cells are subject to signals that regulate their proliferation and behaviour. All cancers disrupt normal controls of cell proliferation & for each cell there is a finite number of ways this disruption can occur. Cancer cells develop a degree of autonomy from external regulatory signals that are responsible for normal cellular homeostasis. Multiple mutations lead to a tumour mass. Subsequent mutations lead to malignant tumour which break through the basal membrane and spread to distant locations

Scientific Questions to Address

What would we like to know about disease (basic science, and clinically relevant)?

- How does cancer originate?
  - Time scales for multiple mutations
  - Oncogenes vs. tumor suppressor genes
  - Environment vs. genetic randomness
- How does a tumor grow?
- How does the immune system interact with cancer cells?
- What role does the physical environment play in growth and evolution?
- What is the "best" treatment strategy for chemotherapy or radiotherapy?
- When will a tumor metastasize?
- Why do treatments fail?
  - Interaction between sensitive (wild-type) and resistant clones

See how mathematics can help with some of these questions (and more!)

Mathematical Frameworks

Many different types of math in cancer modeling:

- Ordinary differential equations (ODEs)

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right)$$

or

$$\frac{dP}{dt} = (\beta - \mu_p - r_0(N))\,P + r_i(N)Q$$
$$\frac{dQ}{dt} = r_0(N)P - (r_i(N) + \mu_q)\,Q$$

- Partial Differential Equations (PDEs)

$$\frac{d\sigma}{dt} = \frac{D}{r}\frac{\partial}{\partial r}\left(r^2\frac{\partial \sigma}{\partial r}\right) - A\sigma$$

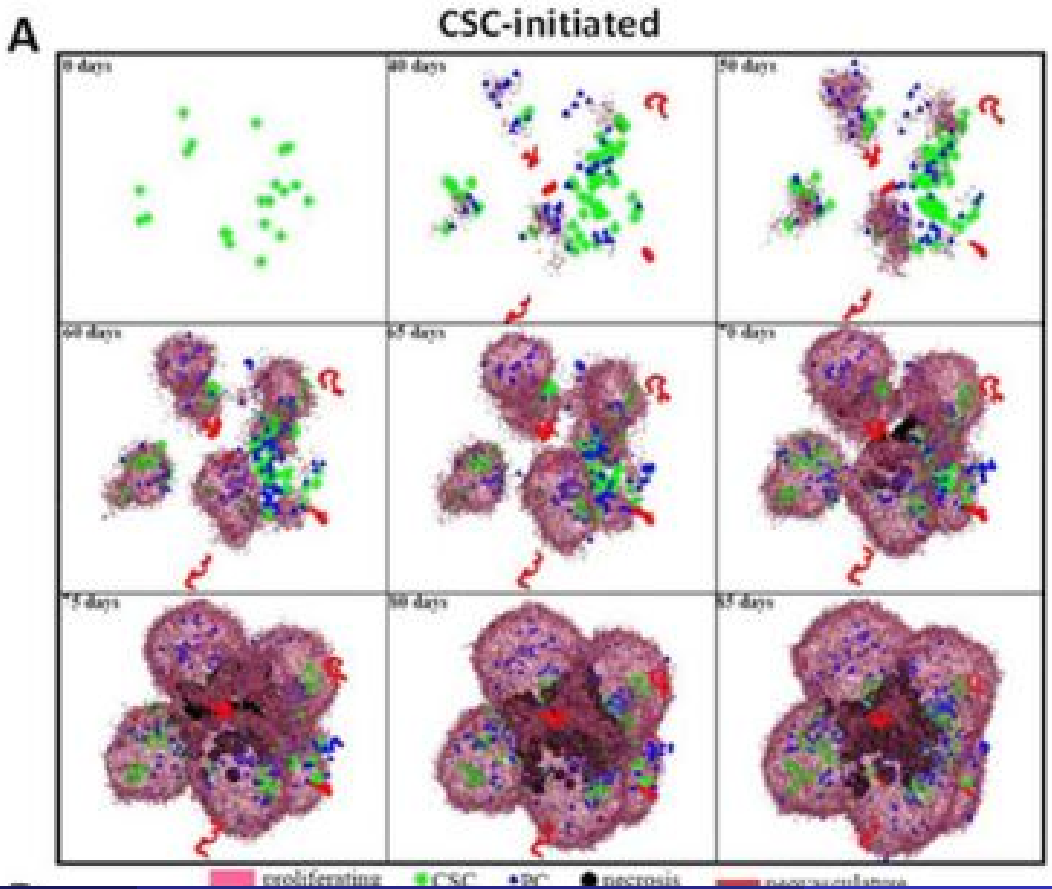
- Stochastic processes

$$\mathrm{A}_{(1)} \xrightarrow{u_1} \mathrm{B}_{(r)} \xrightarrow{u_2} \mathrm{C}_{(r_1)}$$

$$P_{ij} = \begin{cases} \frac{u_1(N-i)+(1-u_2)ri}{\mathcal{N}_i}\frac{N-i}{N}, & j = i+1, \\ \frac{(1-u_1)(N-i)}{\mathcal{N}_i}\frac{i}{N}, & j = i-1, \\ \frac{u_2 ri}{\mathcal{N}_i}, & j = E, \\ 1 - P_{i,i+1} - P_{i,i-1} - P_{i,E}, & j = i, \\ 0 & \text{otherwise,} \end{cases}$$

Mathematical Frameworks continued

- Hybrid/multiscale models (and cellular automaton)
  - Combine multiple frameworks to capture different scales
  - Cells as discrete entities (stochastic evolution)
  - Nutrients diffusing and consumed (PDEs)
  - Chemical networks internal to cell, maybe governing cell-cycle (ODEs)



Mathematical Modeling Applications

- Discuss some applications that use mathematics to address scientific questions
- Some will cover, some will not (dependent on time and student interest)

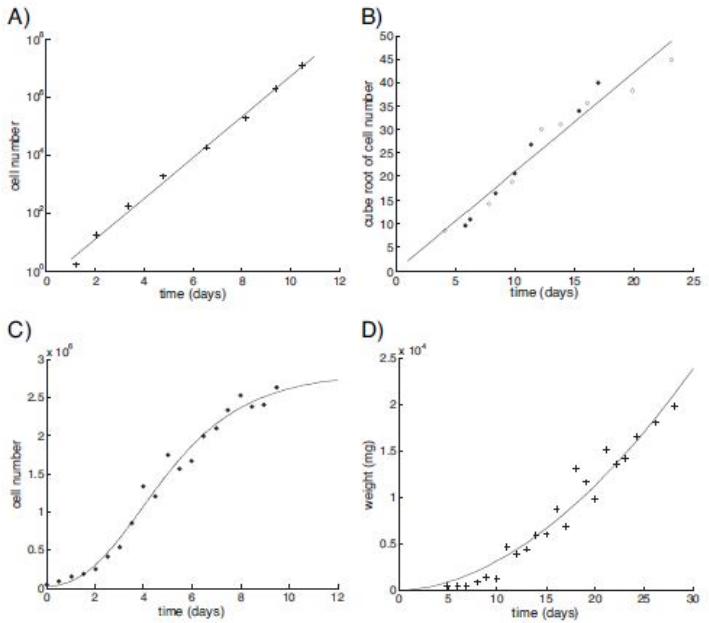
Growth Law of Cancer

Given a set of clinical measurements (volume, cell count, weight, PSA, etc), what type of growth law best describes it?

$$\frac{dN}{dt} = \lambda N, \qquad \frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right),$$

$$\frac{dN}{dt} = re^{-aN}N, \qquad \frac{dN}{dt} = aN^{2/3} - bN.$$

What does each type of model imply in regards to biological mechanisms?



Heterogeneous Populations and Competition

Cancer populations are heterogeneous in nature

- Genetic instability
- Environmental factors (location w.r.t. stroma, bloody supply, etc.)
- Processes with intrinsic variation (e.g. cell-cycle)

Can clonal variants coexist, or does competition imply the selection of only one phenotype?

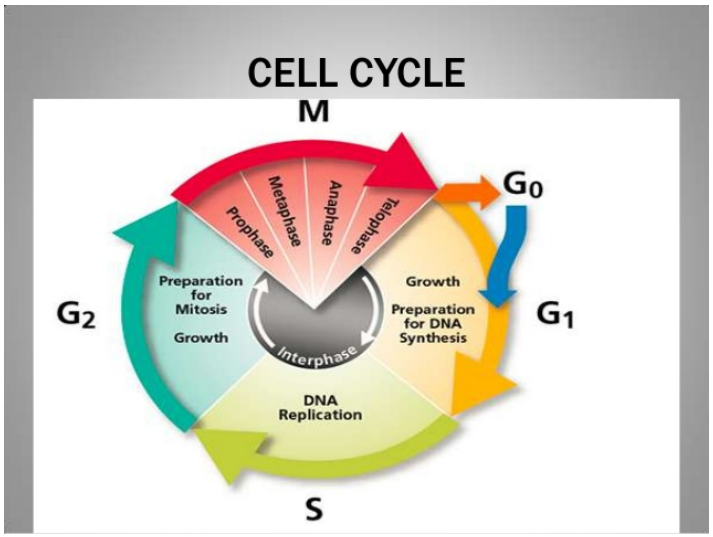
- Also understand competition between cancerous and healthy cells

$$\begin{aligned}
\frac{dx_1}{dt} &= \Phi(v)x_1 \\
\frac{dx_2}{dt} &= \Phi(v)x_2 \\
\frac{dy}{dt} &= (\alpha H(x_1, x_2, z) - \beta)y \\
\frac{dz}{dt} &= \gamma y - \delta v z \\
v(t) &= \frac{z}{x_1 + x_2}.
\end{aligned}$$

Heterogeneity continued

Cancer cells also differ based on progression through cell-cycle

- Proliferative (P) vs. Quiescent (Q) vs. Qpoptotic (A)
- More specifically at location of cell-cycle



$$\frac{\partial}{\partial t}n(t,a) + \frac{\partial}{\partial a}n(t,a) = -d(a)n(t,a),$$

$$n(t, a=0) = \int_{a\geq 0} b(a)n(t,a)\,da,$$

$$n(t=0,a) = n_0(a).$$

Models of Chemotherapy and Radiotherapy

Chemotherapy - any chemical agent used to decrease a tumor load

- How do we implement effect of chemotherapy into models?
- Clearly should depend on class of drug **AND** mutations present in cell
- Drug - alkylating agents vs. mitotic inhibitors
- Cell - phase of cell-cycle, mutations
- log-kill ($S = e^{-kD}$) and Norton-Simon hypothesis ($d(N) = kr(N)$)

Radiotherapy - treatment of cancer via X-rays

- Sufficient number of DNA "targets"" are "hit" by ionizing radiation $\Longrightarrow$ cell death (target-hit theory)
- Explain dose-response curves via underlying mechanisms (non-repair and repair)

$$S = 1 - (1 - e^{-D/D_0})^N$$

Computing Optimal Treatment Protocols

A central question: once we understand how chemotherapy effects our model, **what is the best protocol to apply?**

- Best is subjective:
  - Minimize tumor volume
  - Minimize resistant fraction of cells
  - Maximize survival time
- Subject to constraints (total amount of drug)

$$N' = \beta N(1 - N) - \gamma \frac{v(t)}{1 + v(t)} N$$

such that

$$\int_0^{t_f} v(t)\, dt \leq 1.$$

If we want to minimize $N(t_f)$, how should we apply $v(t)$?

Optimal Control continued

This is like a calculus problem, except instead of finding a number, we must find a **function** $v(t)$.

Use calculus of variations (i.e. optimal control theory) and solve a minimization (or maximization) problem

$$H(N, \lambda, v) = \lambda^T f(N, v) - L(N, v)$$

Sufficient to minimize Hamiltonian H pointwise (often)

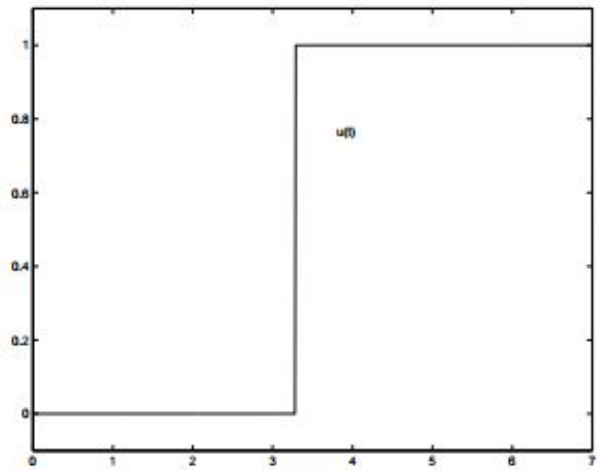


Figure 2: Killing agent

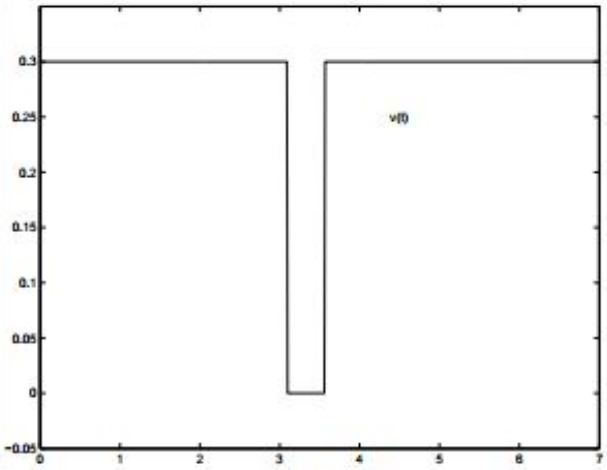
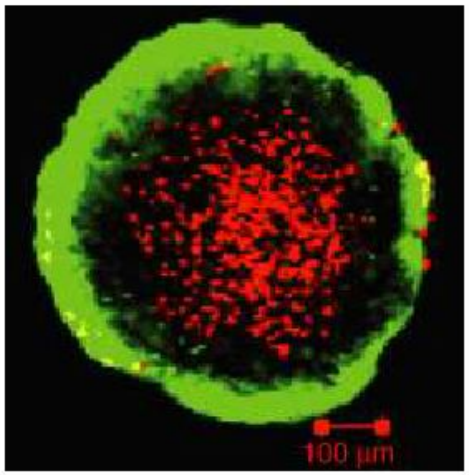


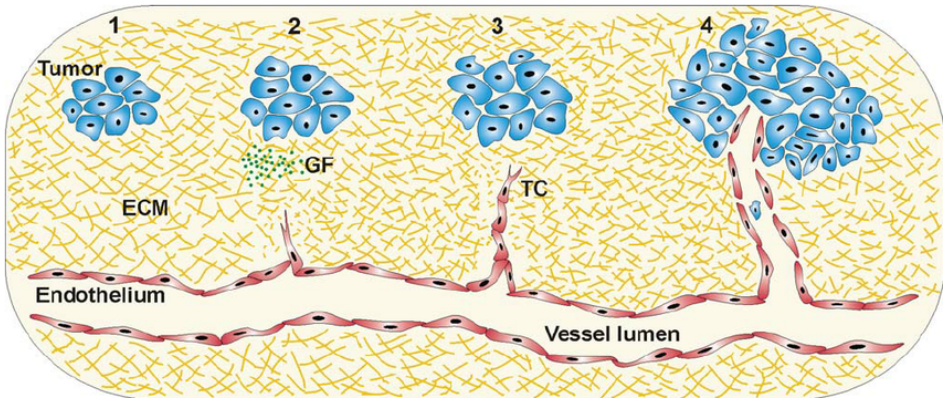
Figure 3: Blocking agent

The Environment and its Effect on Tumor Development

Understand physical tumor formation and the role of the environment

- Structure of tumor (proliferating rim, quiescent layer, necrotic core)
- Tumor growth into surrounding tissue (nutrients and ECM)
- Angiogenesis and metastasis





Geometry is fundamentally important (location of cells, location of blood vessels, etc.)

The Environment and PDEs continued

Thus, variables should depend on position $x \in \mathbb{R}^{1,2,3}$ and time t

- Partial differential equations (PDEs)
- Often view in fluid mechanics framework (Euler equations, Navier-Stokes)
- Also combine systems (hybrid modeling)
  - Cells as discrete units
  - Nutrients, drugs as fluids

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\mathbf{v}) = (k_m(c) - k_d(c))n,$$
$$\frac{\partial m}{\partial t} + \nabla \cdot (m\mathbf{v}) = k_d(c)n,$$
$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho\mathbf{v}) = 0,$$
$$\frac{\partial c}{\partial t} + \nabla \cdot (c\mathbf{v}) = D\nabla^2 c - \gamma k_m(c)n.$$

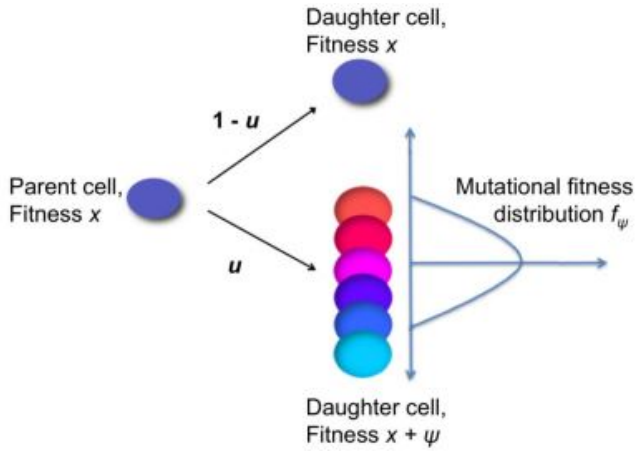
Example: understand **glycolytic phenotype** emerging from regions with low oxygen and high ECM density (and present even in cases of **high** oxygen)

Mutations and Carcinogenesis

Cancer initiation and progression is fundamentally stochastic

- Accumulation of multiple genetic and epigenetic alterations in a single cell, which eventually allow cell to escape homeostatic mechanisms
- What is the probability of developing cancer as a function of age?
- Expected time to cancer initiation
- Mutational profile of a given tumor

Thus, it is natural to model carcinogenesis via *random variables* (as opposed to deterministic quantities)

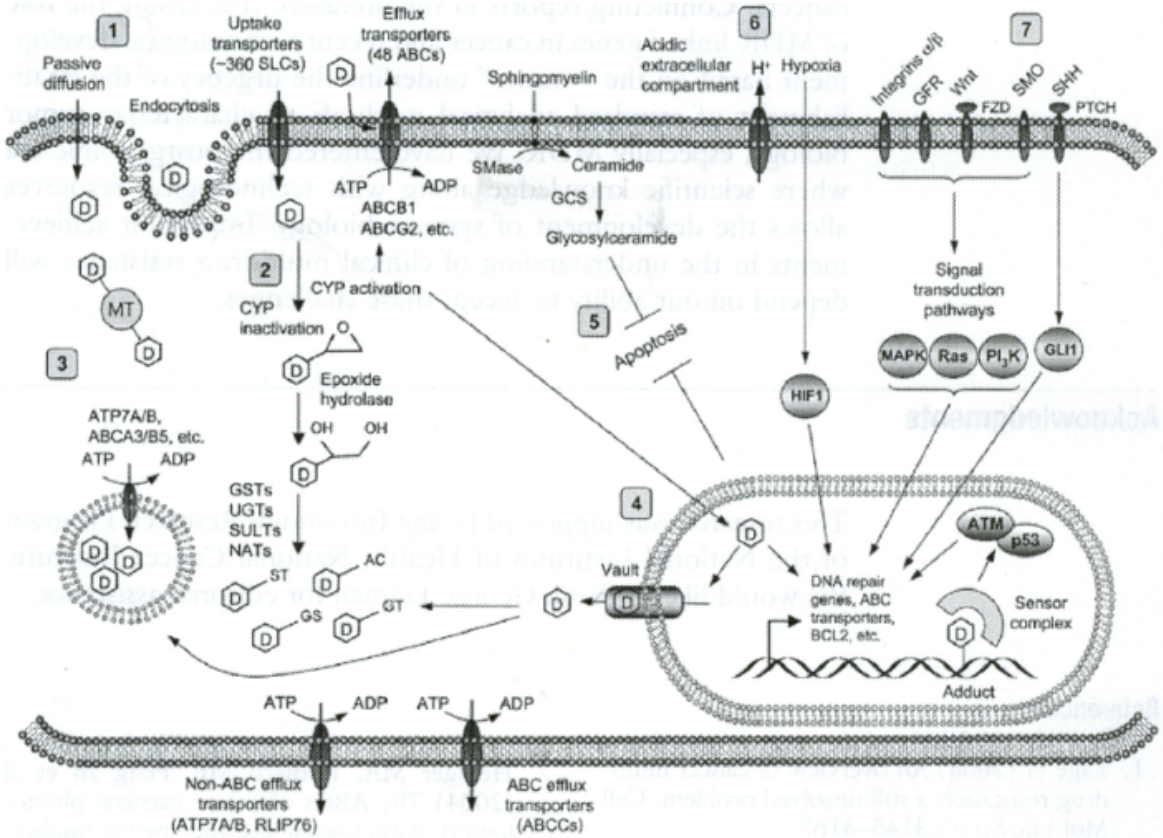


$$\rho_1 = \frac{1 - f_1/f_2}{1 - (f_1/f_2)^N}$$

Dynamics of Drug Resistance

Although we can kill some (or even most) cancer cells, we cannot usually kill them all

- Cancer populations are extraordinarily heterogeneous



- Heterogeneity $\iff$ drug resistance

Dynamics of Drug Resistance continued

Questions:

- Is resistance induced (by the drug) or random (and then selected)?
- Is there a qualitative and quantitative difference between induced vs. stochastic mutations (mathematically tractable, while experimentally subtle)?
- What is the optimal way to treat in presence of resistance?
  - Sensitive cells may be inhibiting growth of resistant cells
  - Not obvious what to do (kill too many sensitive, and resistant are free to grow)
- What is the probability resistance existed before treatment began?

$$P_R = 1 - \exp\left(-\frac{MuF}{1 - d/r}\right),$$

$$F = \int_0^1 \frac{1 - b/a}{1 - (b/a)y^{\alpha}}\, dy$$

Dynamics of Cancer and the Immune System

Why doesn't our immune system prevent (or eliminate) cancers?

- Can we induce an immune response?
- What is the best way to apply immunotherapies in conjunction with chemotherapies?
- Wave of the future (together with targeted therapies)
  - Guide development of combination therapies
  - Determine which patients will respond, and which won't
  - When are combinations needed (immunotherapy and chemotherapy)

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

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

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T - uNL^2 - K_L(1-e^{-M})L + \frac{p_I LI}{g_I + I} + v_L(t)$$

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

$$\frac{dM}{dt} = -\gamma M + v_M(t)$$

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

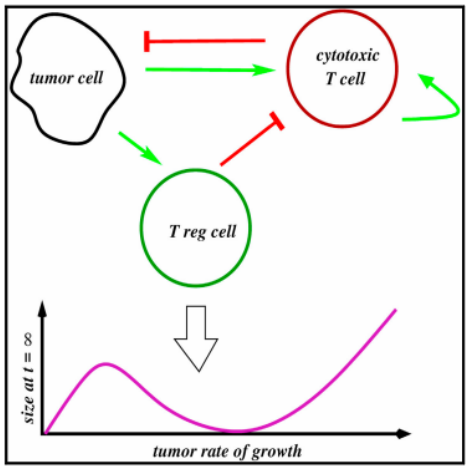
$$D = d\frac{(L/T)^\lambda}{s + (L/T)^\lambda}$$

Cancer/Immune Example 2

Mechanism by which immune system discriminates healthy (self) and disease (non-self)

- Immune activation and discrimination via **dynamics** (not just presentation)
- IFFL, negative feedback, and bistability

$$\dot{u} = (\lambda - \kappa y)u,$$
$$\dot{x} = -\delta_x x + \beta u,$$
$$\dot{y} = h(u/x) + f(y).$$



Prediction: specific tumor growth **rates** evade response despite presence of antigens

- "two-zone" tolerance

Sontag. A dynamic model of immune responses to antigen presentation predicts different regions of tumor or pathogen elimination, *Cell Systems*, 2017