The Mathematics of Cancer

Integrating Quantitative Models

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WPI

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Important Articles

Altrock , P. M., Liu, L. L., and Michor, F. (2015). The Mathematics of Cancer: Integrating Quantitative Models . Nature Reviews , 15, 730-745.

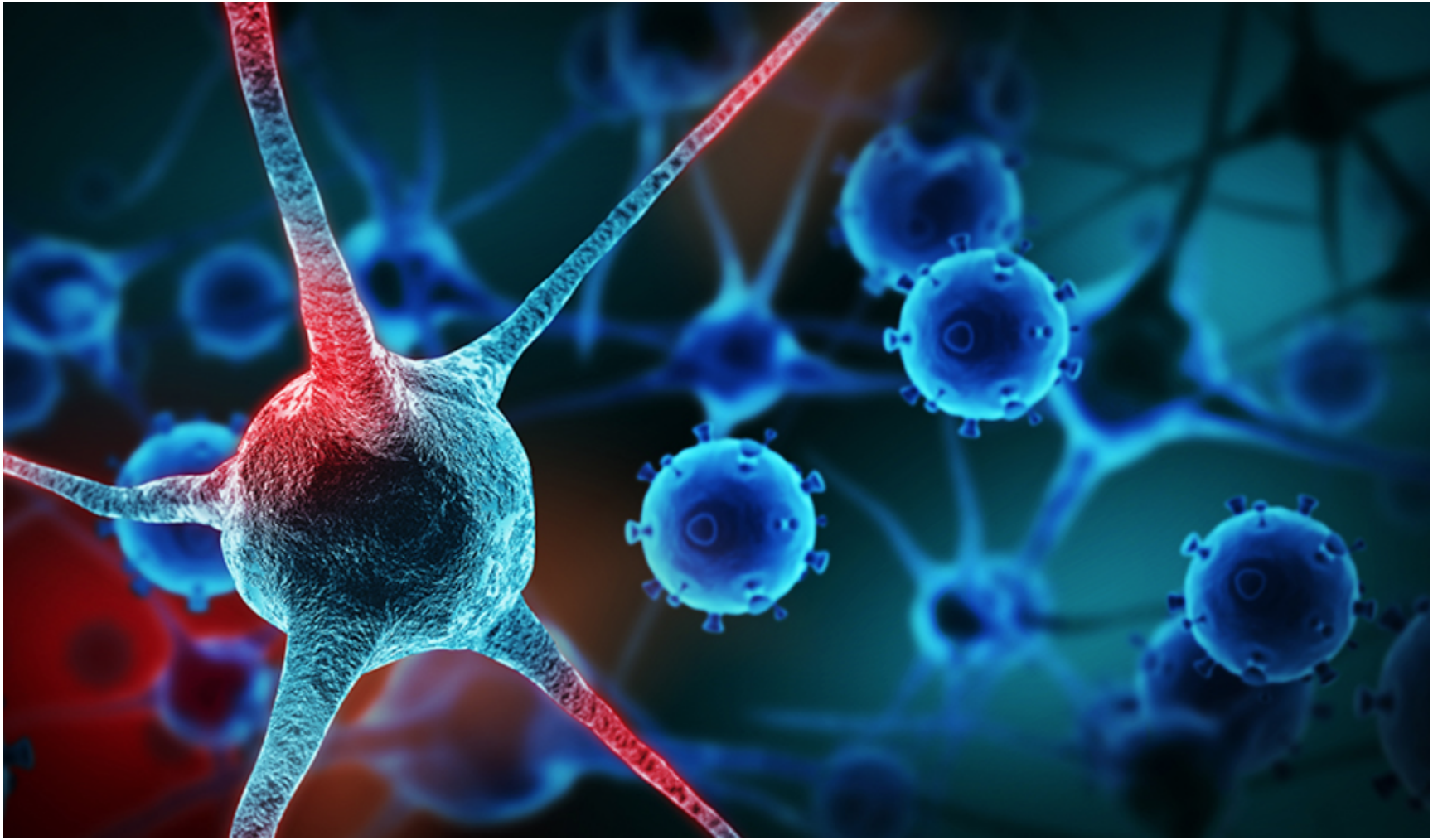
Anderson, A. R., and Quaranta, V. (2008). Integrative Mathematical Oncology . Nature Reviews Cancer , 8, 227-234.

Weekes, S. L., Barker, B., Bober, S., Cisneros, K., Cline, J., Thompson, A., Enderling, H. (2014). A Multi-Compartment Mathematical Model of Cancer Stem Cell Driven Tumor Growth Dynamics. Bulletin of Mathematical Biology, 76(7), 1762-1782.

Overview

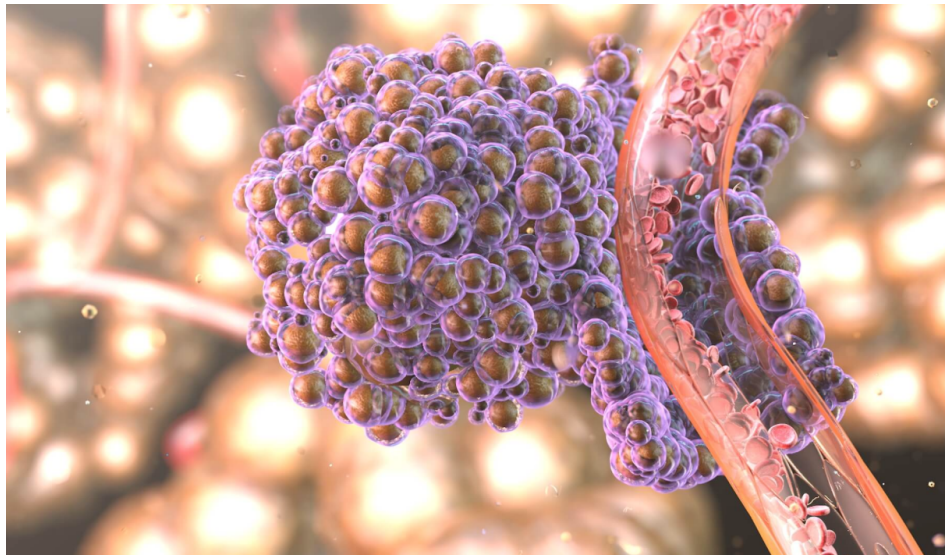
- Introduction
- The Dynamics of Mutation Accumulation
- Modeling the Tumor Microenvironment
- Treatment Response and Resistance
- Properties of Stem and Non-Stem Cells

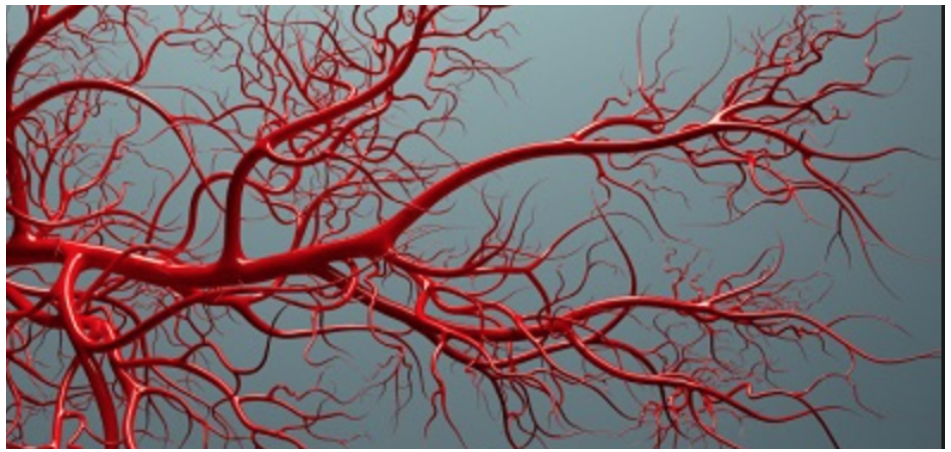
What is Cancer?



Hallmarks of Cancer

- Sustaining Proliferative Signaling
- Evading Growth Suppressors
- Resisting Cell Death
- Enabling Replicative Immortality
- Inducing Angiogenesis
- Activating Invasion and Metastasis





Where Mathematics Meets Biology

1. Validates biological mechanisms through quantitative means
2. Challenges current biological assumptions
3. Enables extrapolation beyond what we can originally analyze
4. Redefines our understanding of what drives tumorigenesis
5. Shapes future research in biology

Where Mathematics Meets Biology

"The power of mathematical modeling truly lies in its ability to reveal previously unknown physical principles that might have been missed by some of the more qualitative approaches that take place in biology"

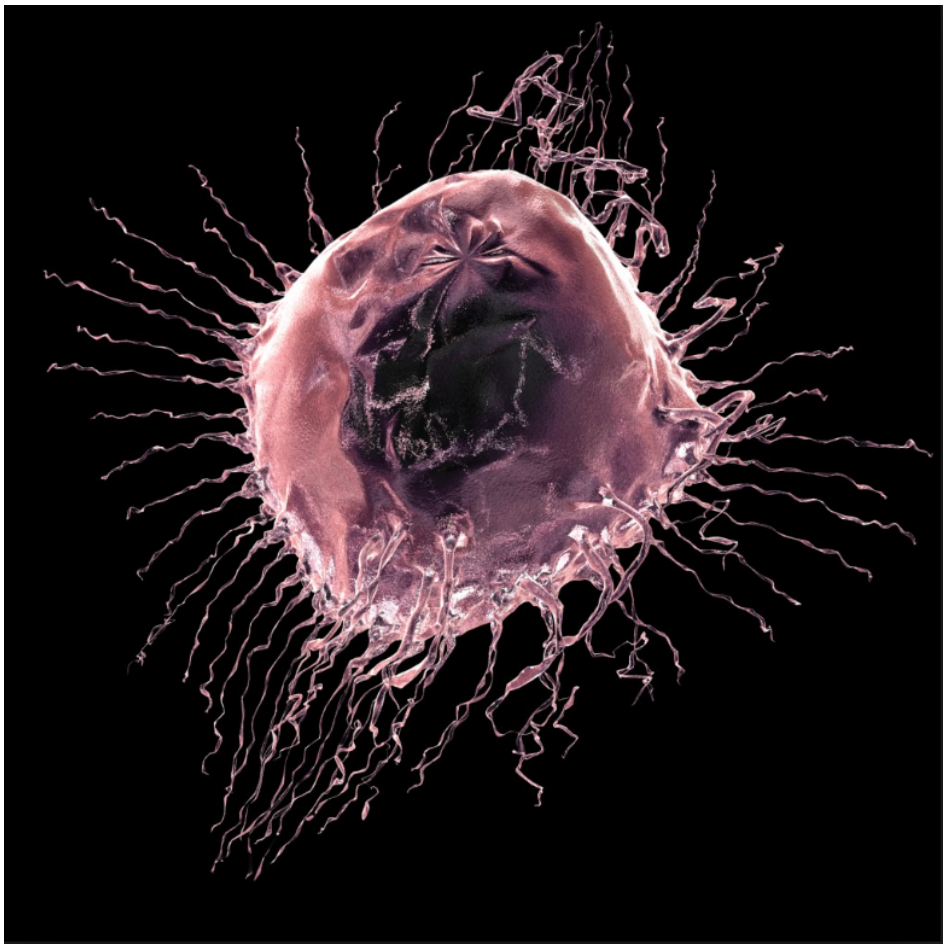
- Philipp M. Altrock

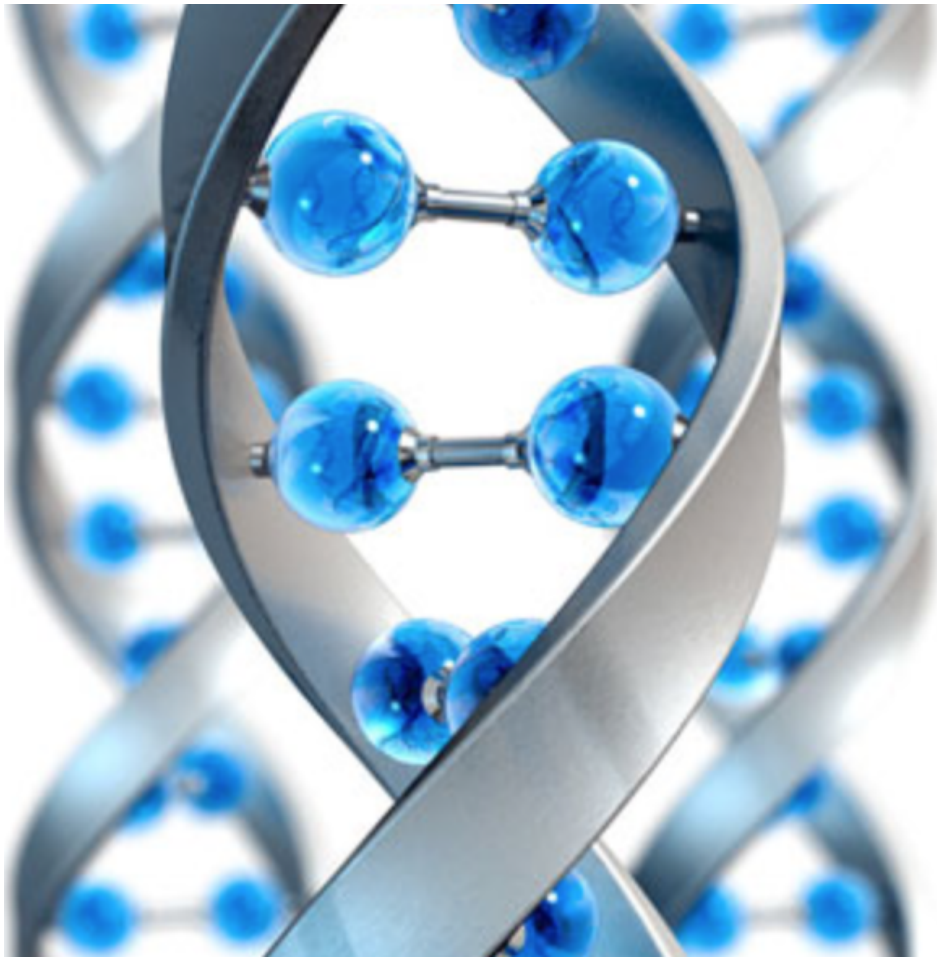
Where Mathematics Meets Biology

Cancer development and progression requires us to take into account a variety of biological factors, all of which can be understood further with the help of mathematics:

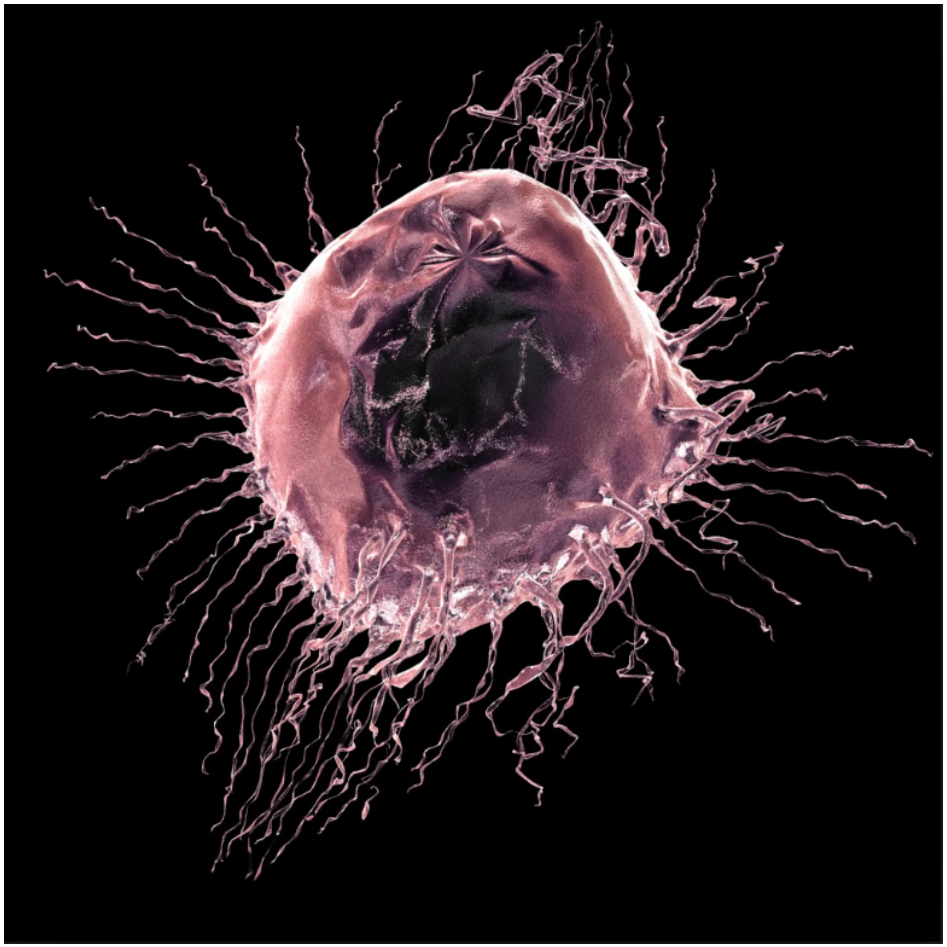
- Tumor initiation and probabilistic growth
- Mutation and metastasis dynamics
- Interactions within the microenvironment
- Responses to immunotherapy and other treatment options
- Properties of cancerous stem and non-stem cells

Where Mathematics Meets Biology





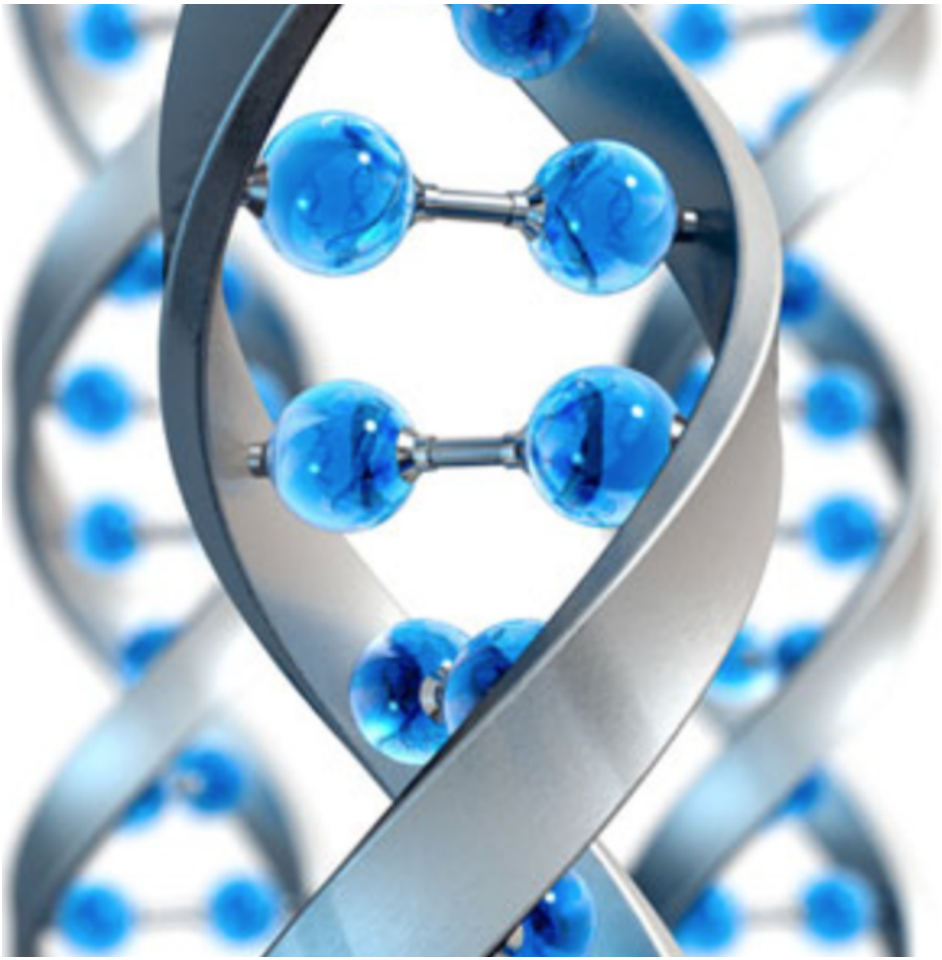
Where Mathematics Meets Biology



Descriptive Models

- discrete or categorical
- characteristics of tumor progression
- little emphasis on biology
  - cell population within a tumor
  - tumor size
  - tumor shape

Where Mathematics Meets Biology



Mechanistic

- complex model
- relationship between specific aspects of tumor progression
- focus on underlying biological principles
  - explanation of tumor growth based on chemical reactions between cells and their microenvironment

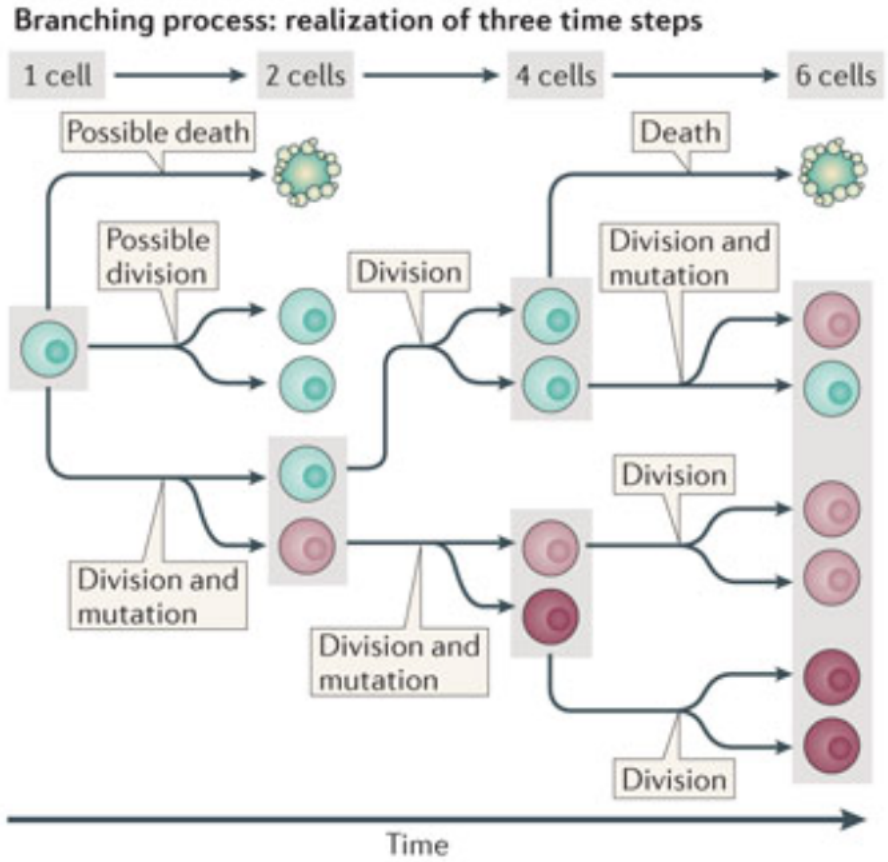
The Dynamics of Mutation Accumulation

The Branching Process

- A cell division model based on the assumption that each event (replication, replication with mutation, and death) occurs at given rates (λ_i, μ_i) dependent on cell type but independent of population size or time
- Markov process
  - the probability of a future event occurring does not depend on past events
  - transition probabilities are calculated

$$P(n_1(t+\Delta t)=i+1, n_2(t+\Delta t)=j \mid n_1(t)=i, n_2(t)=j) \approx \lambda_1(1-u)i\Delta t$$
$$P(n_1(t+\Delta t)=i-1, n_2(t+\Delta t)=j \mid n_1(t)=i, n_2(t)=j) \approx \mu_1 i\Delta t$$
$$P(n_1(t+\Delta t)=i, n_2(t+\Delta t)=j+1 \mid n_1(t)=i, n_2(t)=j) \approx (\lambda_2+\lambda_1 u)j\Delta t$$
$$P(n_1(t+\Delta t)=i, n_2(t+\Delta t)=j-1 \mid n_1(t)=i, n_2(t)=j) \approx \mu_2 j\Delta t$$

The Dynamics of Mutation Accumulation



Passenger Mutation: genetic changes that do NOT play a role in cancer development

Driver Mutation: genetic changes that play a large role in cancer development

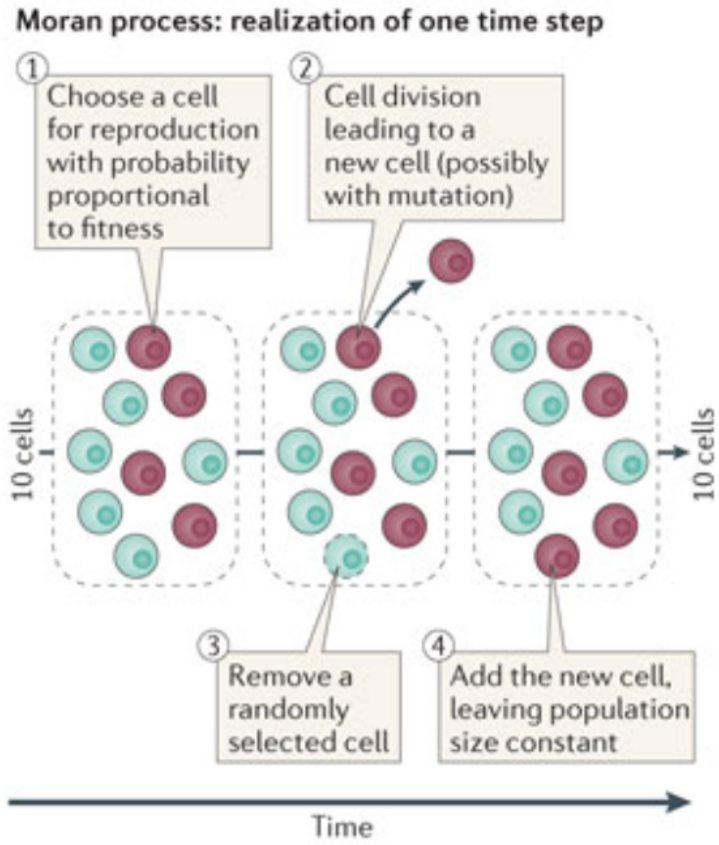
How does the Branching Process help us?

- Used to study accumulation of passenger and driver mutations in cell population
- Can study how various factors will affect this accumulation

The Dynamics of Mutation Accumulation

Moran Process

- Population is a constant size
- There are n types of individuals
- These types may have different fitness values f_i, $i = 1, 2, 3, \cdots, n$
- An individual of type i reproduces with probability proportional to f_i and subsequently, a random individual is chosen to die.



The Dynamics of Mutation Accumulation

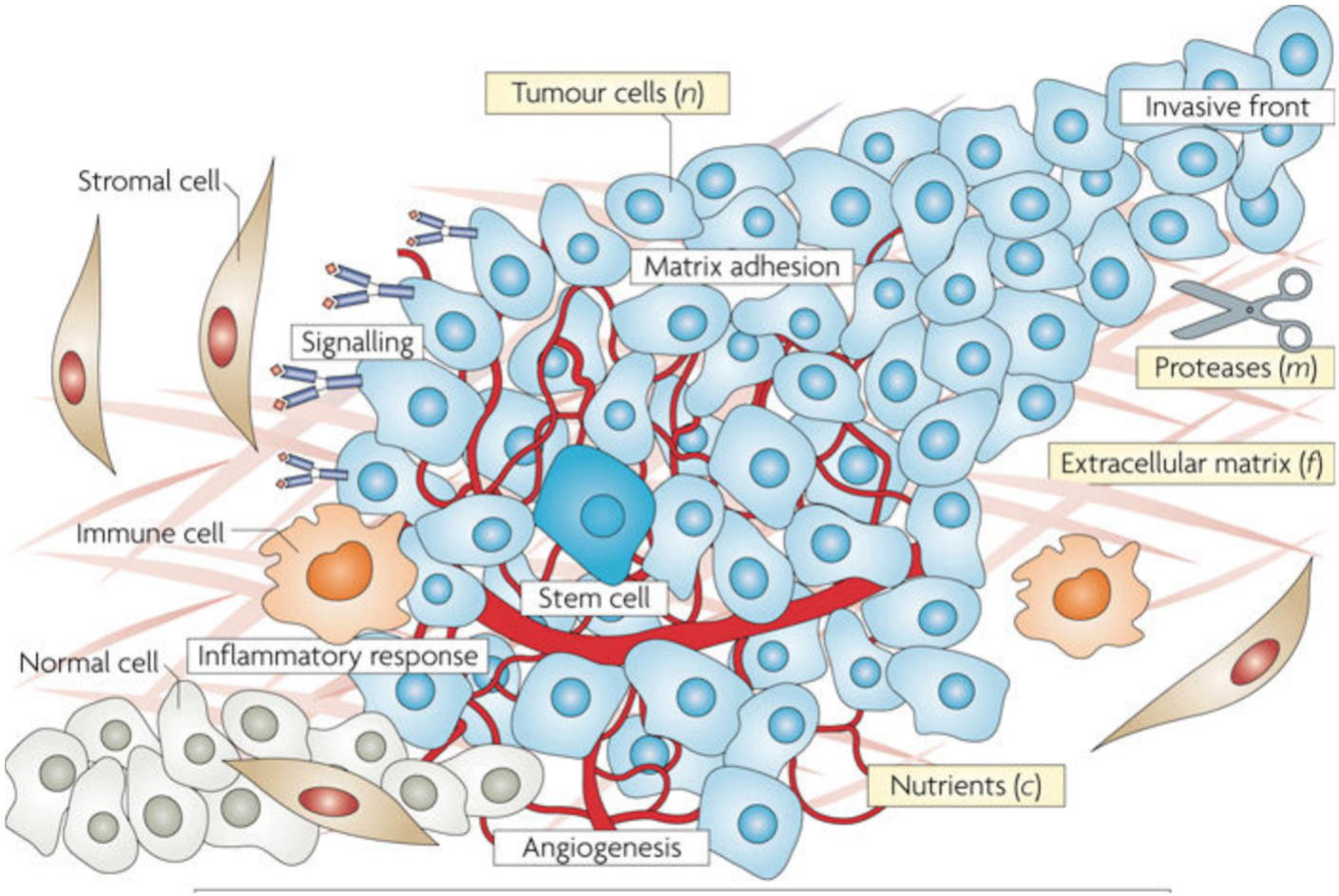
The Branching and Moran models of cancer cell evolution have allowed us to...

1. Understand the number of passenger and driver mutations in population
2. Find a positive correlation between patient age and diagnosis
3. Predict the probability of cancer and metastasis formation depending on size and concentration of mutations
4. Study how tumor composition depends on microenvironmental factors

Modeling the Tumor Microenvironment

Biophysical and environmental properties are considered

- diffusion of growth factors
- hormones
- nutrients and oxygen



Modeling the Tumor Microenvironment

This often requires complex model requirements:

- Dynamics might include space as well as time
- ODEs, PDEs

Examples:

1. Hybrid Model
2. Agent-Based Model
3. Predator-Prey Model

Hybrid Models

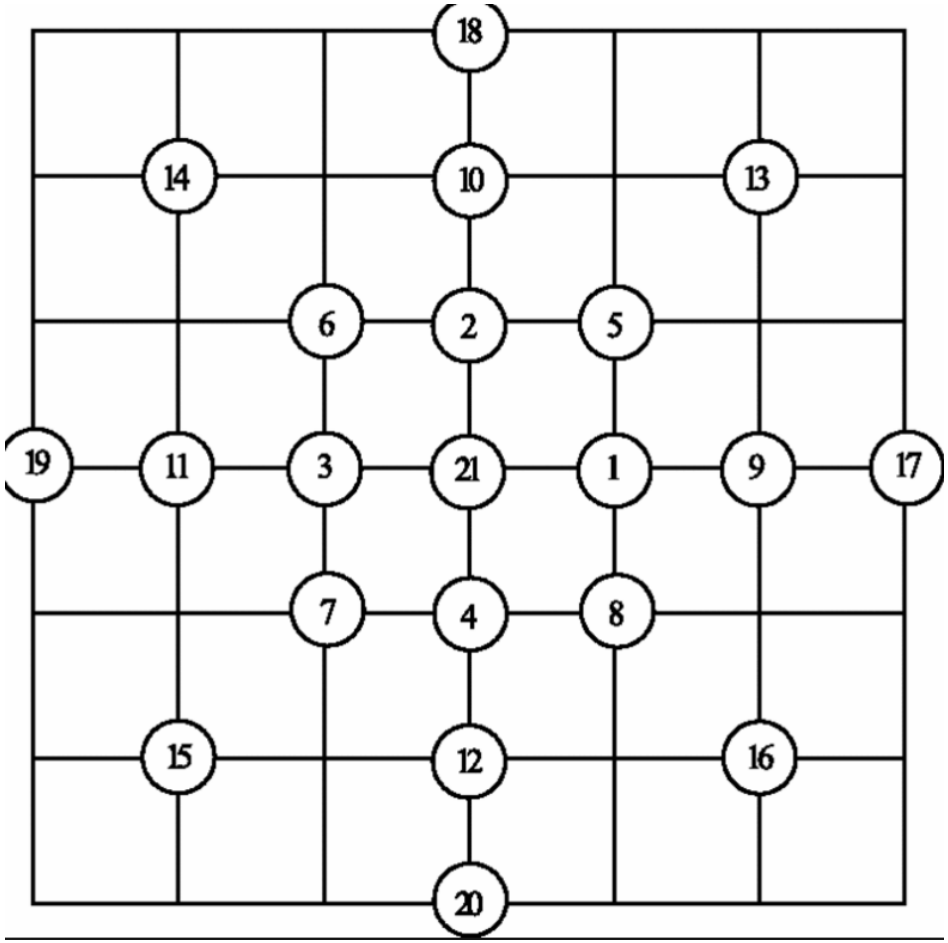
Hybrid Model: combine discrete and continuous modeling techniques to describe, in a single model, cell growth and motility

Key Characteristics:

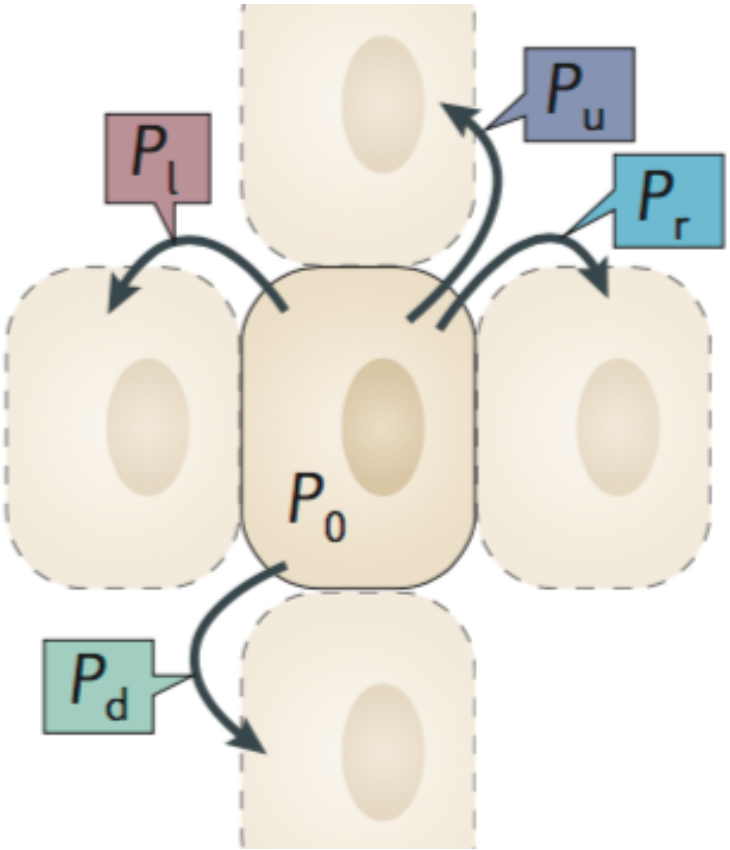
- On or Off-lattice structure to represent tissue microenvironment
- Cell phenotypes
- Supplemented with additional equations (ODEs and PDEs) to describe signaling, or mechanical details of life processes
- Environmental factors (e.g. density of extracellular matrix or nutrient concentration)

Hybrid Model

Agent-Based Simulation: a computational approach that models complex systems of interacting "agents". These agents often represent cells which can either mutate, divide, move into space, or die.

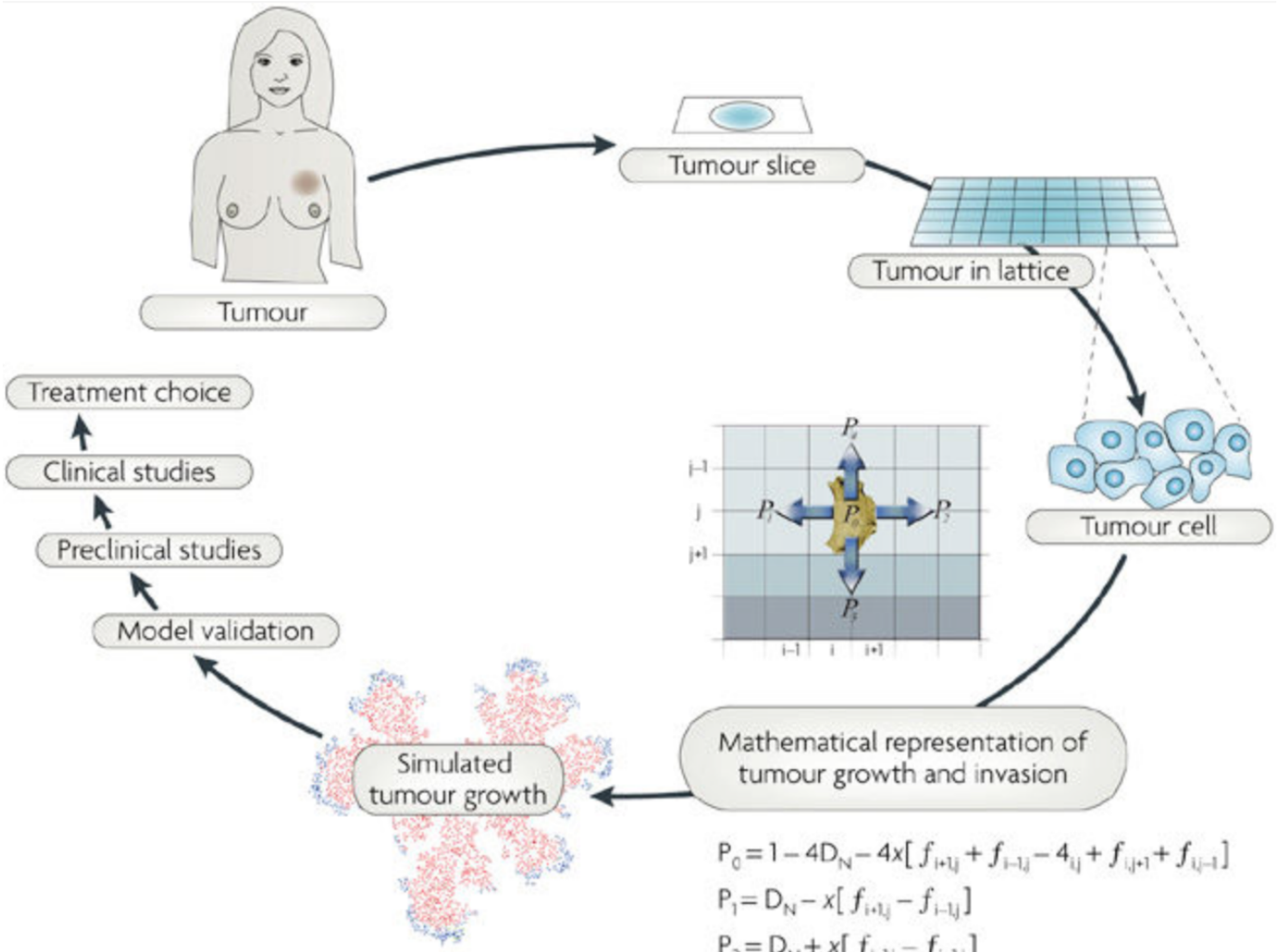


Agent-Based Model

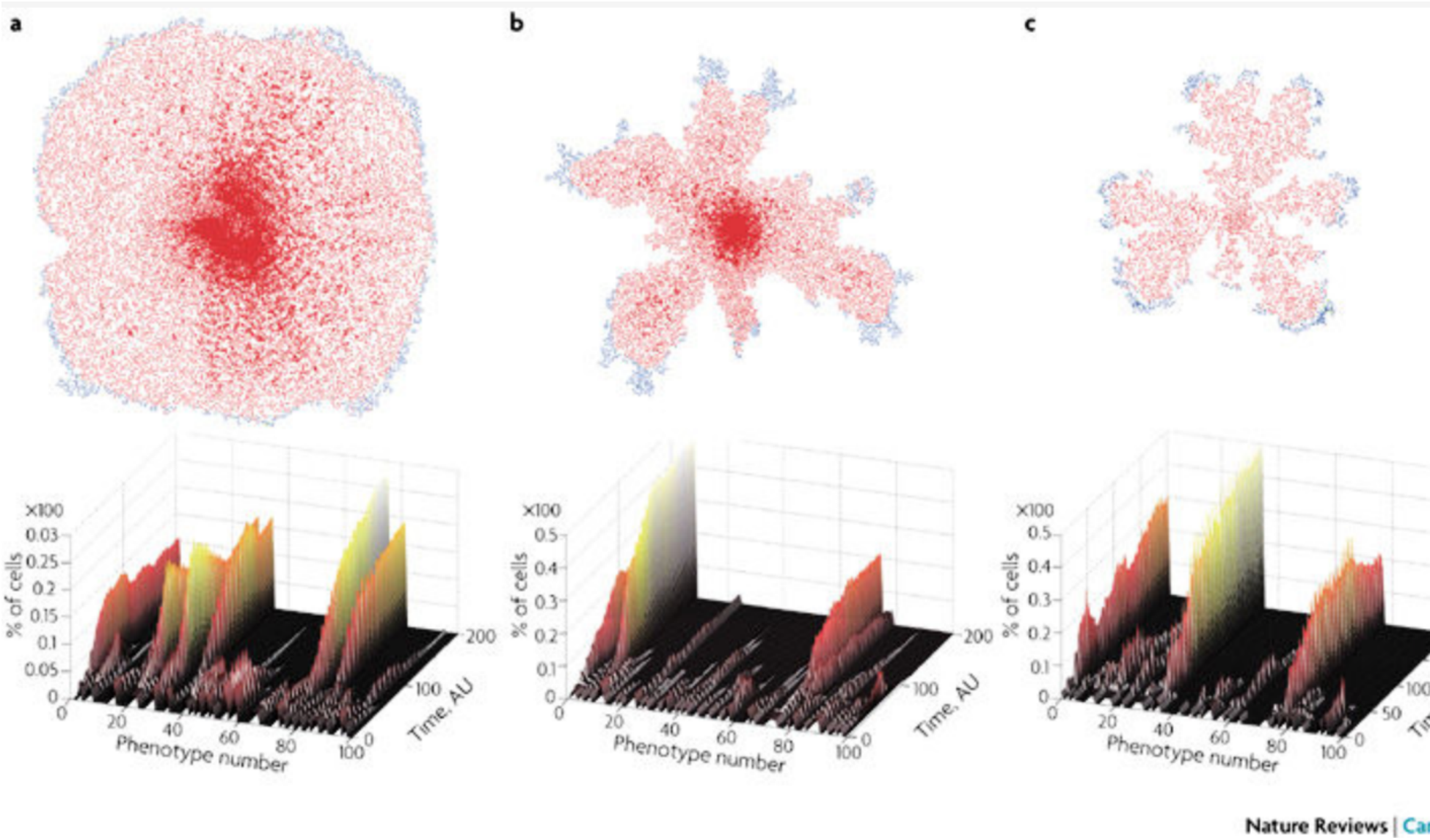


- P_u = prob. of moving up
- P_d = prob. of moving down
- P_r = prob. of moving right
- P_l = prob. of moving left
- P_o = prob. of not moving
- P_i depends on concentrations of continuous variables in model

The Hybrid Discrete Continuum Model



Hybrid Simulation



Modeling the Tumor Microenvironment

Phenotype: a cell's observable characteristics or traits

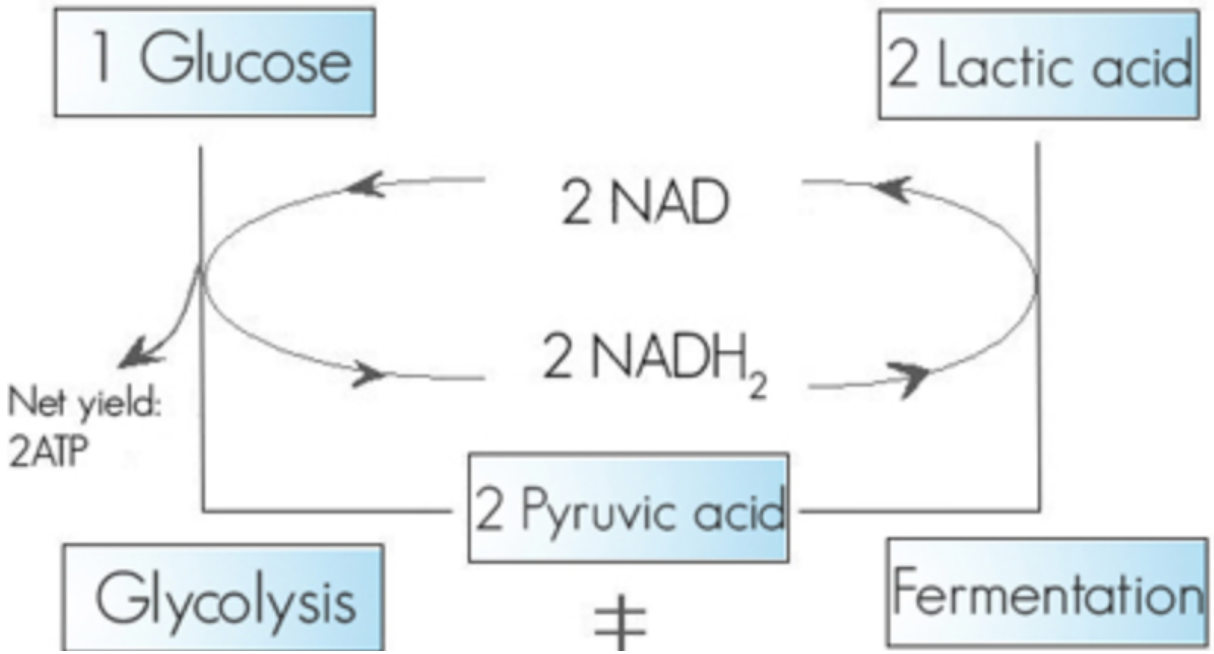
Biological Implications

- Cancer invasion is best explained in terms of the struggle between cell phenotypes
- A "harsh" microenvironment can lead to smaller number of more invasive cells
- A "mild" microenvironment leads to tumors that are less lively to invade adjacent tissue
- Emergence of metabolic states and their influence on tumor growth

Understanding the Glycolytic Phenotype

Glycolysis: cellular metabolic process in which glucose is broken down

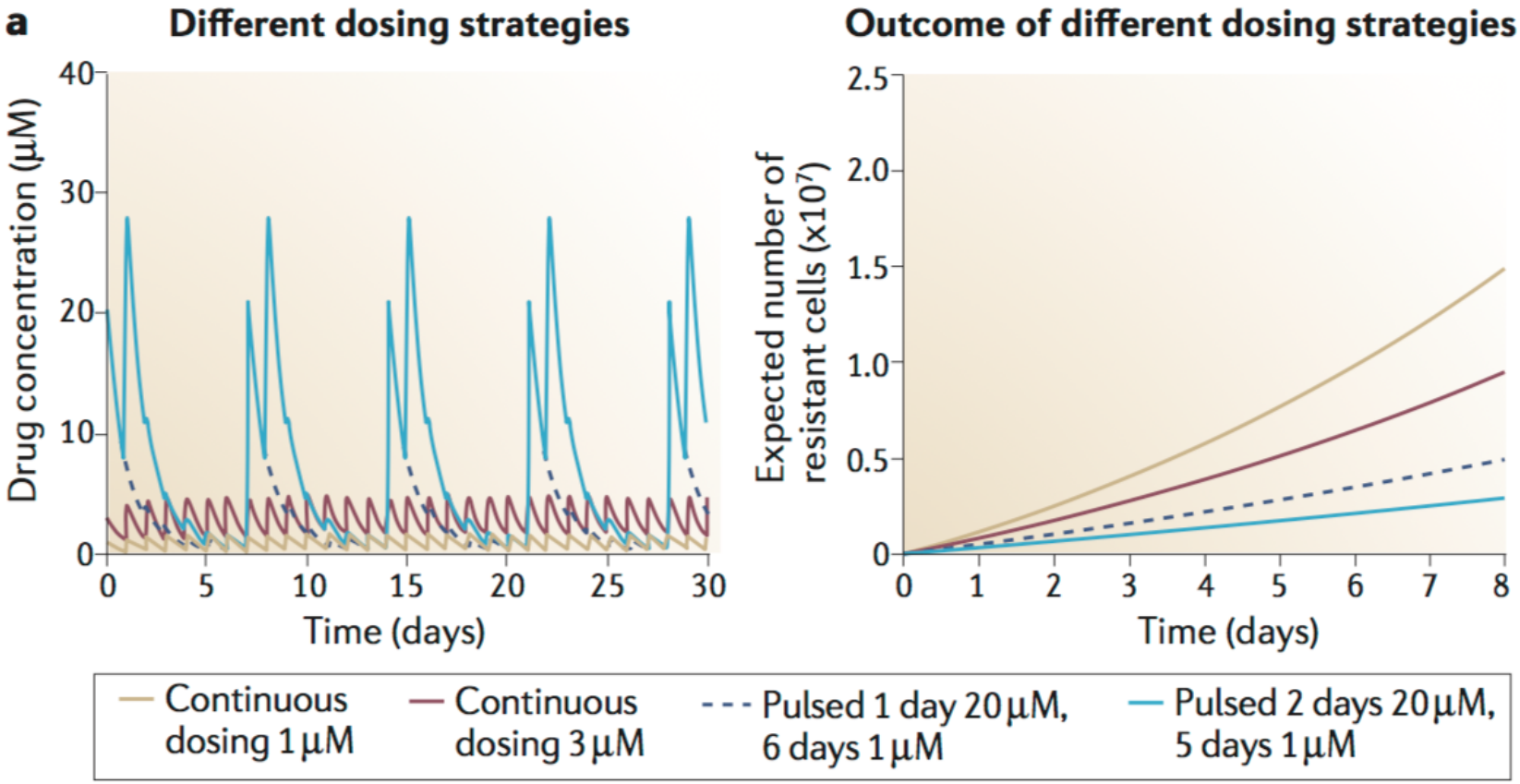
Warburg Effect: increased and sustained rates of glycolysis in the presence of oxygen in the microenvironment



Treatment Response and Resistance

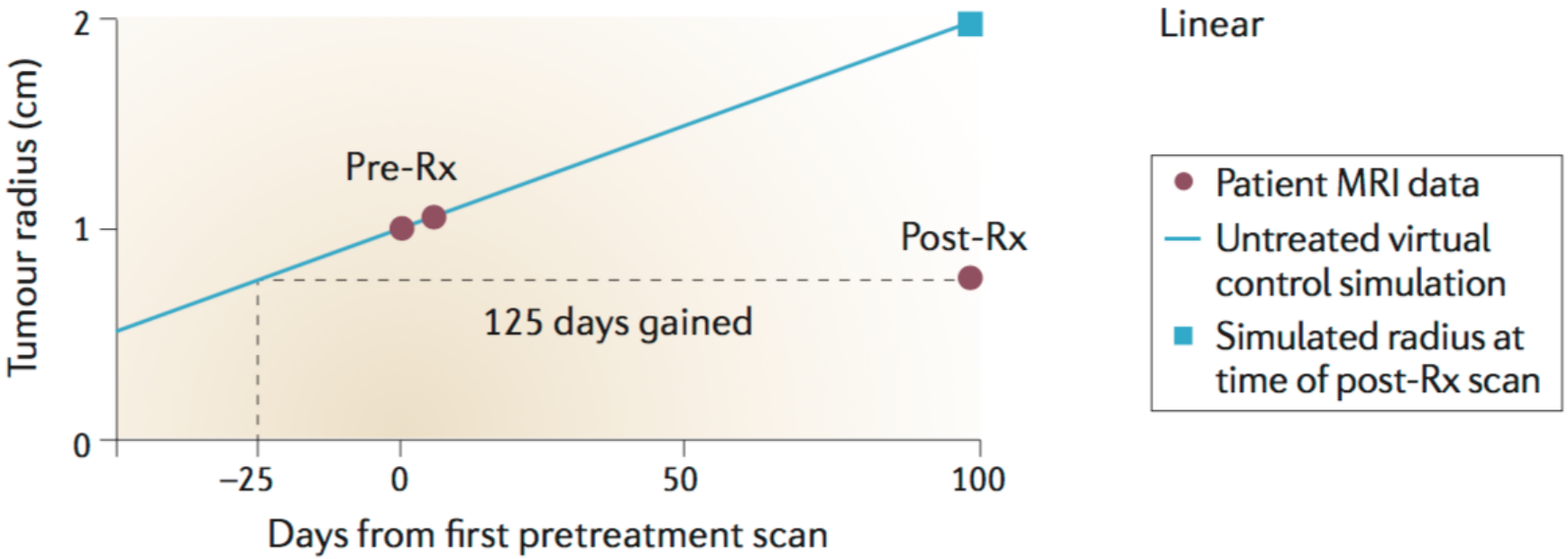
1. Investigate optimum administration schedules for various treatments
2. Branching process can model cell mutations under treatment schedules
3. Understand effects of radiotherapy
4. "Days Gained" metric and its relationship to patient survival

Treatment Response and Resistance



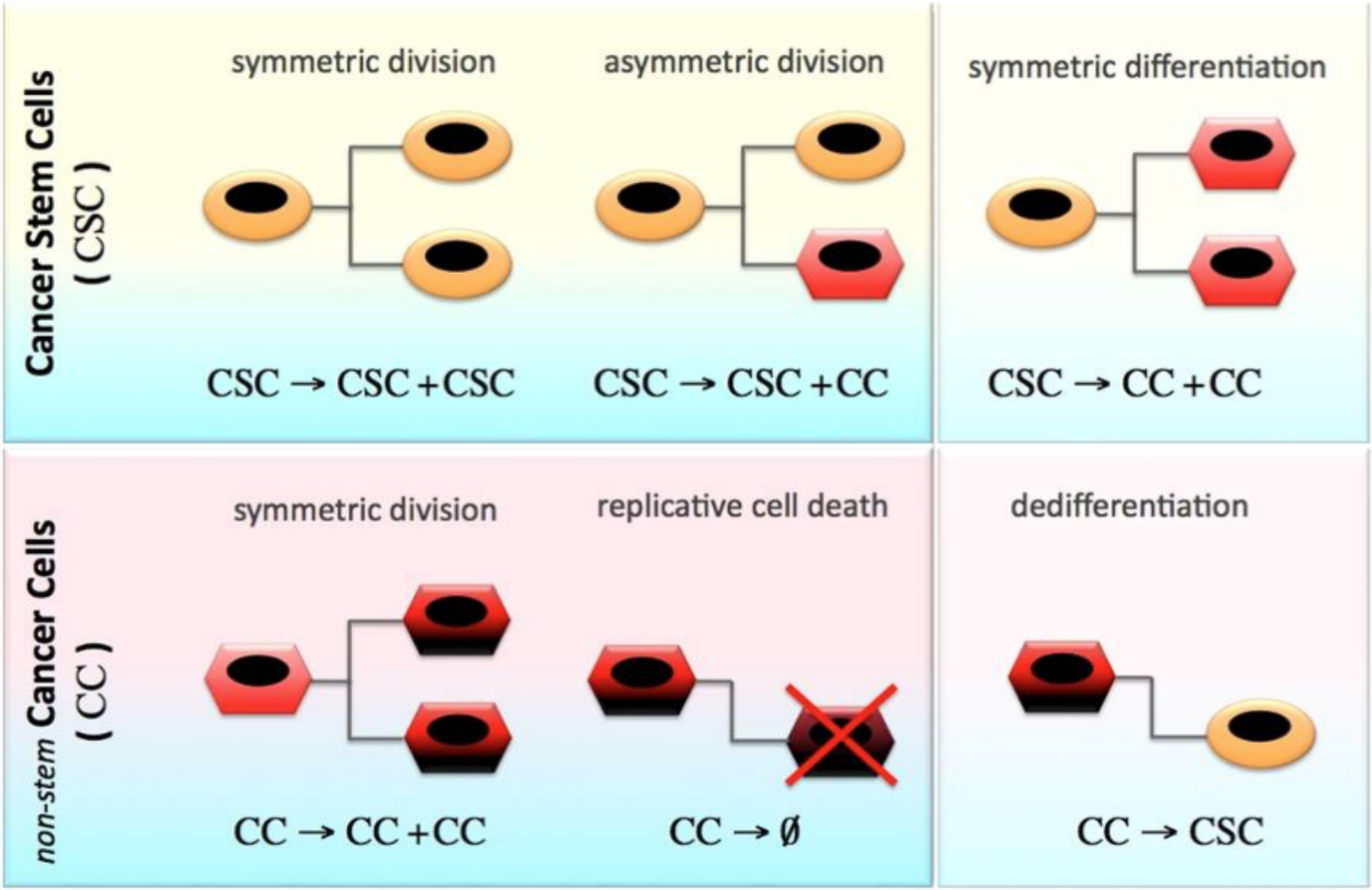
Treatment Response and Resistance

"Days Gained" metric: the difference in time between the post-treatment MRI scan and the predicted time for which the same tumor radius would be reached had the patient not been treated



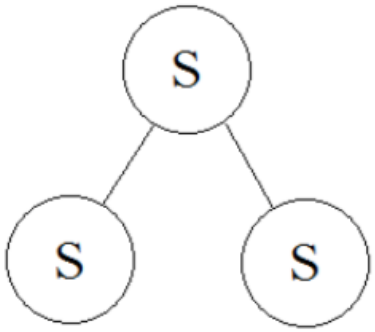
Linear Multi-compartment Models

Properties of Cancerous Stem and Non-Stem Cells

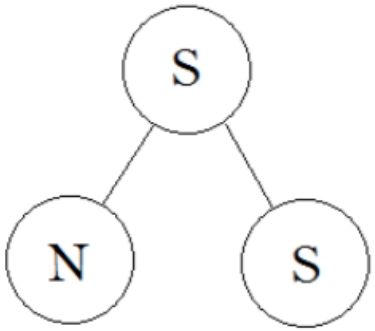


Assumptions: Stem Cells

- Can initiate tumors
- Indefinite proliferation
- Performs three types of proliferation:
  - Symmetric (p_1)
  - Asymmetric (p_2)
  - Symmetric differentiation (p_3) - actually 0
- Constant per capita proliferation rate λ
- Constant per capita death rate a.



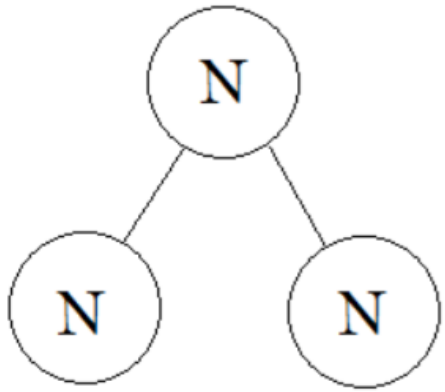
Symmetric



Asymmetric

Assumptions: Non-Stem Cells

- Cannot initiate tumors
- Have a proliferation capacity (m)
- Only perform symmetric proliferation



- Constant, generation-independent per capita proliferation rate γ
- Cells die at constant per capita rate b
- The last (mth) generation suffers *replicative cell death* as it tries to proliferate at rate γ

Linear Multi-compartment System

$$\frac{dC}{dt} = (p_1\lambda - p_3\lambda - a)C$$

$$\frac{dN_1}{dt} = (p_2 + 2p_3)\lambda C - \gamma N_1 - bN_1$$

$$\vdots$$

$$\frac{dN_k}{dt} = 2\gamma N_{k-1} - \gamma N_k - bN_k$$

$$\vdots$$

$$\frac{dN_m}{dt} = 2\gamma N_{m-1} - \gamma N_m - bN_m$$

- C – pop. of stem cells
- λ – proliferation rate of stem cells
- p_1 – prob. of symmetric division
- p_2 – prob. of asymmetric division
- a – death rate of stem cells

- N_k – pop. of kth gen. non-stem cells
- γ – prolif. rate of non-stem cells
- b – death rate of non-stem cells
- m – proliferation capacity

Analytic Solution to Multi-compartment Linear System

stem cell population

$$C(t) = C_0 e^{\beta t}$$

non-stem populations

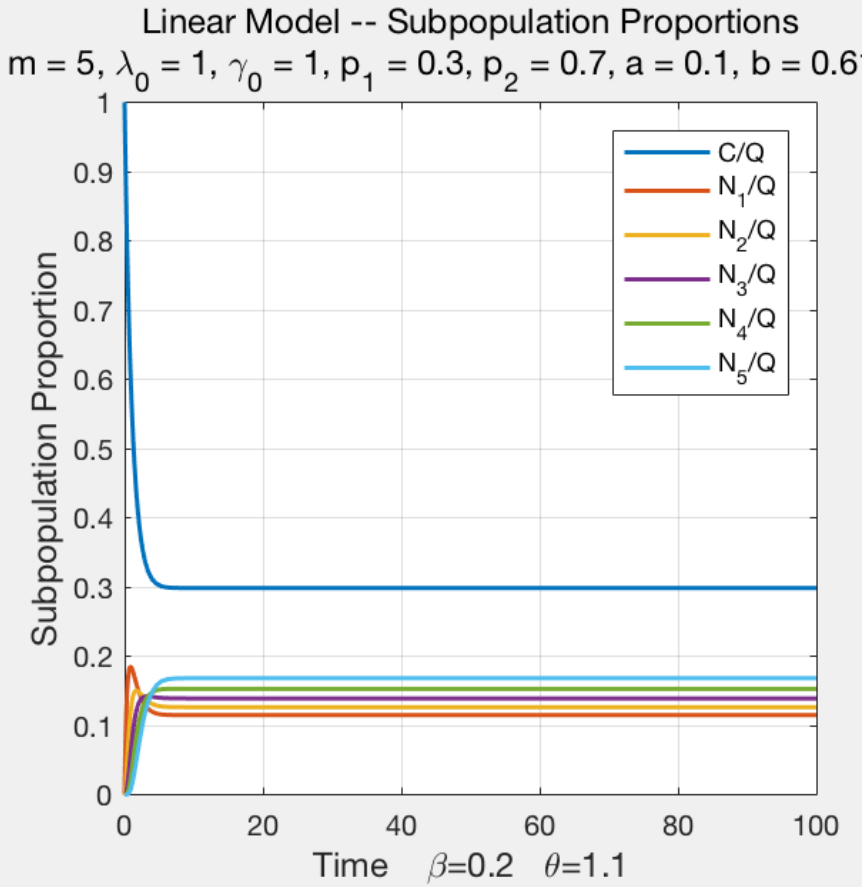
$$N_k(t) = \sum_{i=1}^{k} \frac{t^{i-1}(2\gamma)^{i-1}}{(i-1)!} N_{k+1-i}(0)\, e^{-(\gamma+b)t} + \frac{\theta^k (p_2 + 2p_3)\lambda C_0}{2\gamma} \left(e^{\beta t} - \sum_{i=1}^{k} \frac{t^{i-1}(2\gamma)^{i-1}}{\theta^{i-1}(i-1)!} e^{-(\gamma+b)t} \right).$$

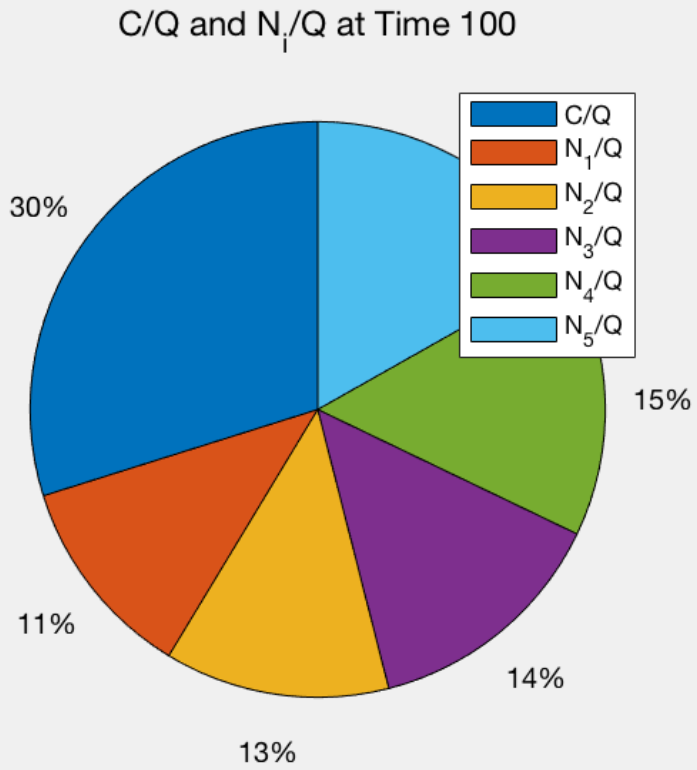
Key Parameters

$\beta = p_1\lambda - p_3\lambda - a$ is the net per capita growth rate of stem cells

$\theta = 2\gamma/(\gamma + b + \beta)$.

Graphing Linear Multi-compartment System





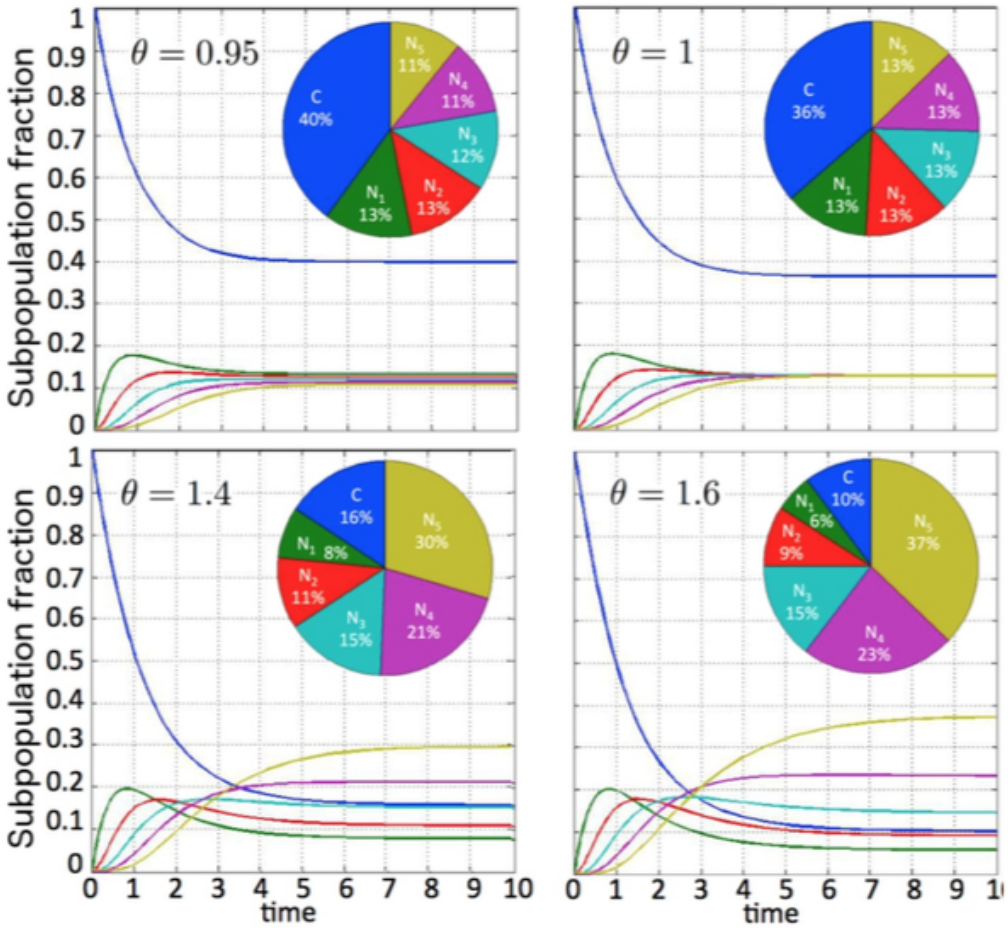
Linear Multi-compartment System

1. Understand population behavior of cancer cells
   - if $\beta > 0$, then C and H increase exponentially -tumor grows
   - if $\beta = 0$, then C and H remain constant -tumor size remains constant
   - if $\beta < 0$, then C and H decreases exponentially -tumor shrinks
2. Determine the dominant generation of cancer cells
   - If $\theta < 1$, then $N_{m-1} < ... < N_1 < C$
   - If $\theta > 1$, then $N_1 < N_2 < ...N_m$
   - If $\theta = 1$, then $N_1 = N_2... = N_{m-1} = N_m$ and $H_s = mN_1$
3. Understand important relationships between parameters
   - Dependence of b on θ and how this affects cell populations

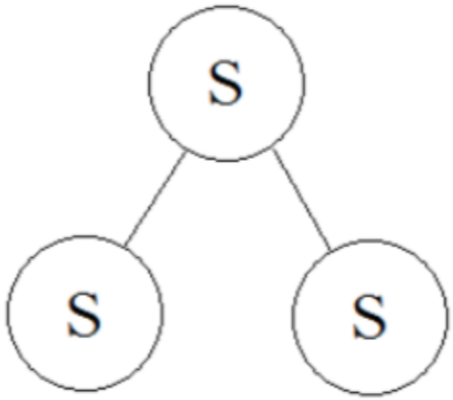
Linear Multi-compartment System

Time Evolution of Subpopulation Fractions

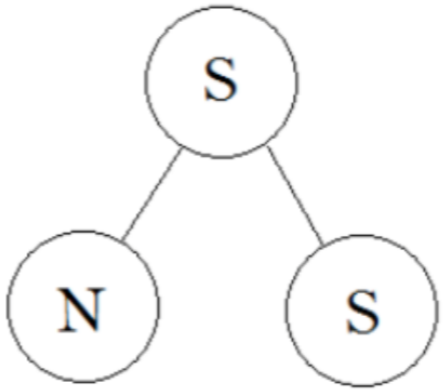
$$\theta = (2\gamma)/(\gamma + b + \beta) \tag{1}$$



My Work



Symmetric



Asymmetric

- Nature says that stem cells cannot exist without non stem cells. So why are non-stem cells even present in the first place?
- Too much glycolysis causes a build up of lactic acid (toxin)
- Lactic acid can cause cancer cells to commit "evolutionary suicide"
- Are non-stem produced to help neutralize glycolytic build up?

My Work

- Include 4 new parameters in Linear Multi-compartment Model:
  1. ω = the amount of active toxins at time t
  2. $\widetilde{\omega}^*$ = the amount of toxin per unit cell at time t
  3. τ = amount of toxins produced per unit stem cell
  4. η = amount of neutralizer produced per unit non-stem cell
- Stem cell divides with the purpose of making $\widetilde{\omega}^*$ value lower

$$\frac{d\omega}{dt} = \tau\frac{dC}{dt} - \eta\frac{dH}{dt}$$
$$\frac{dC}{dt} = (p_1\lambda - p_3\lambda - a(\omega))\,C$$
$$\frac{dN_1}{dt} = (p_2 + 2p_3)\lambda C - \gamma N_1 - b(\omega)N_1$$
$$\vdots$$
$$\frac{dN_k}{dt} = 2\gamma N_{k-1} - \gamma N_k - b(\omega)N_k$$
$$\vdots$$
$$\frac{dN_m}{dt} = 2\gamma N_{m-1} - \gamma N_m - b(\omega)N_m$$

Acknowledgements

Professor Suzanne Weekes, Clare Boothe Luce Scholarship Advisor

Works Cited

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