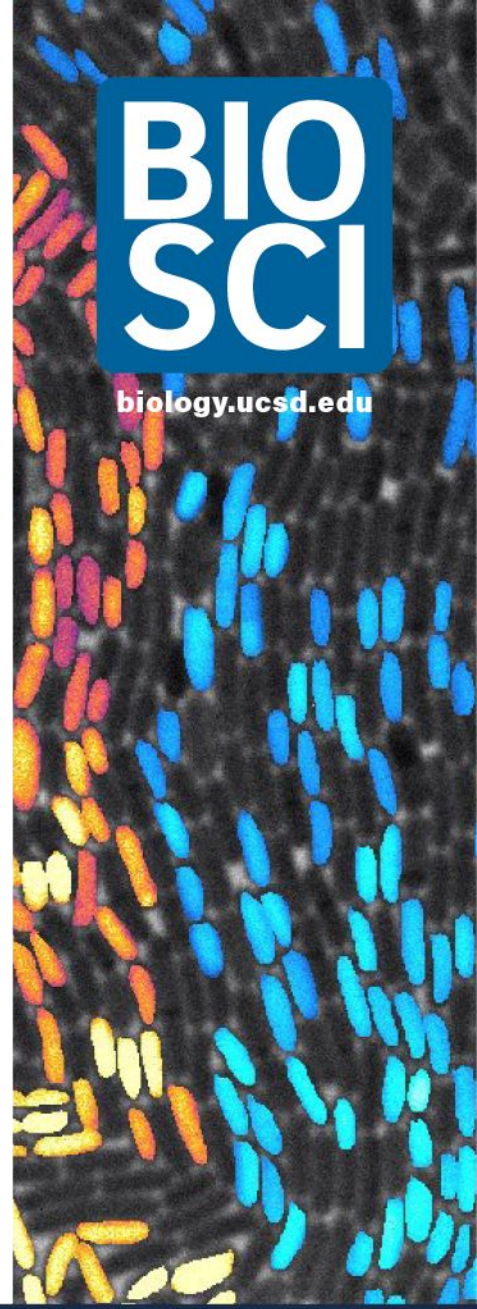
Cancer Dynamics, Evolution, and Spatial Structure

1. Basic concepts in cancer biology and cancer evolution

2. Modeling cell evolution in pre-malignant tissue

3. Evolutionary dynamics in spatially structured cell populations



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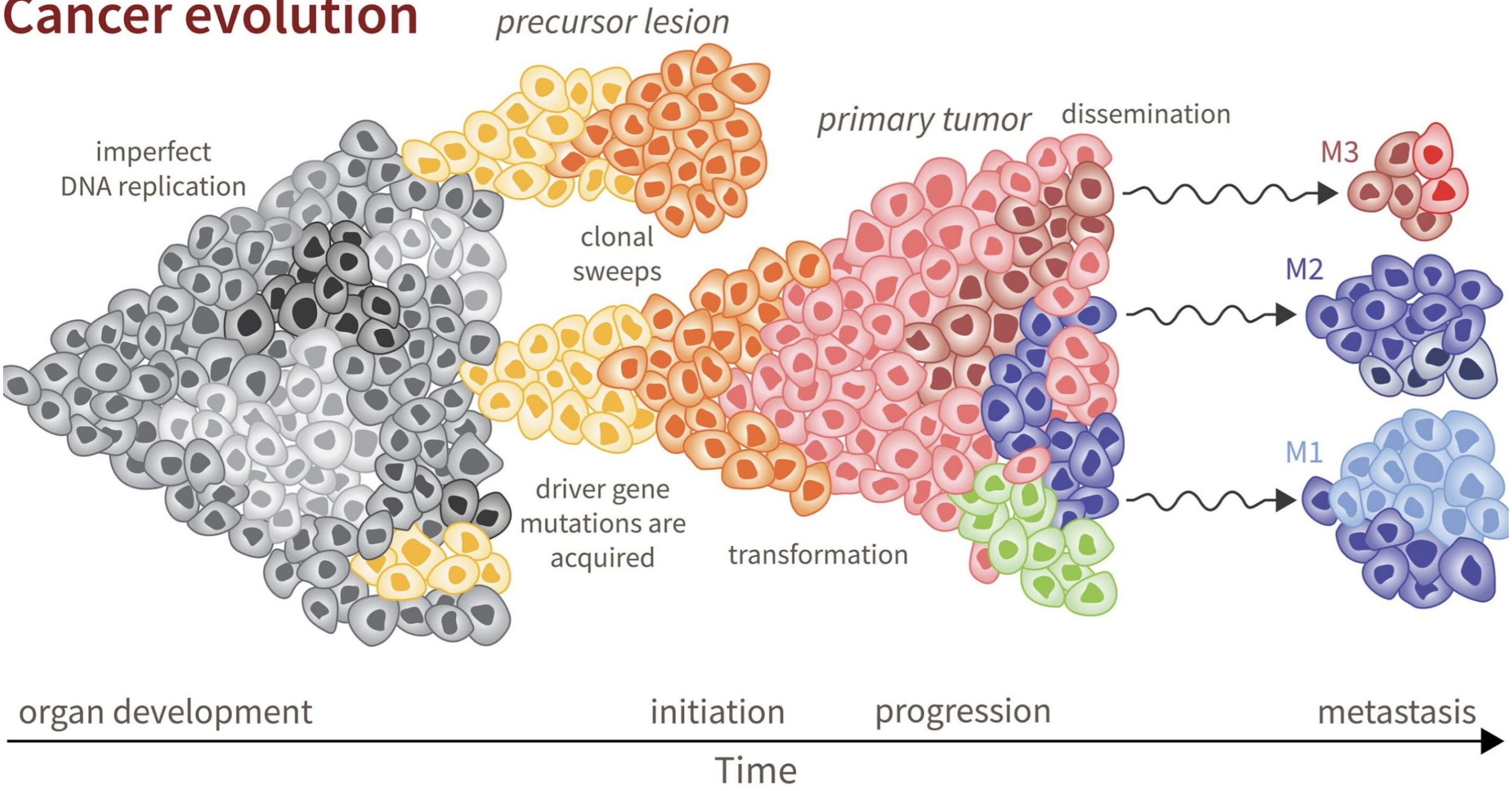
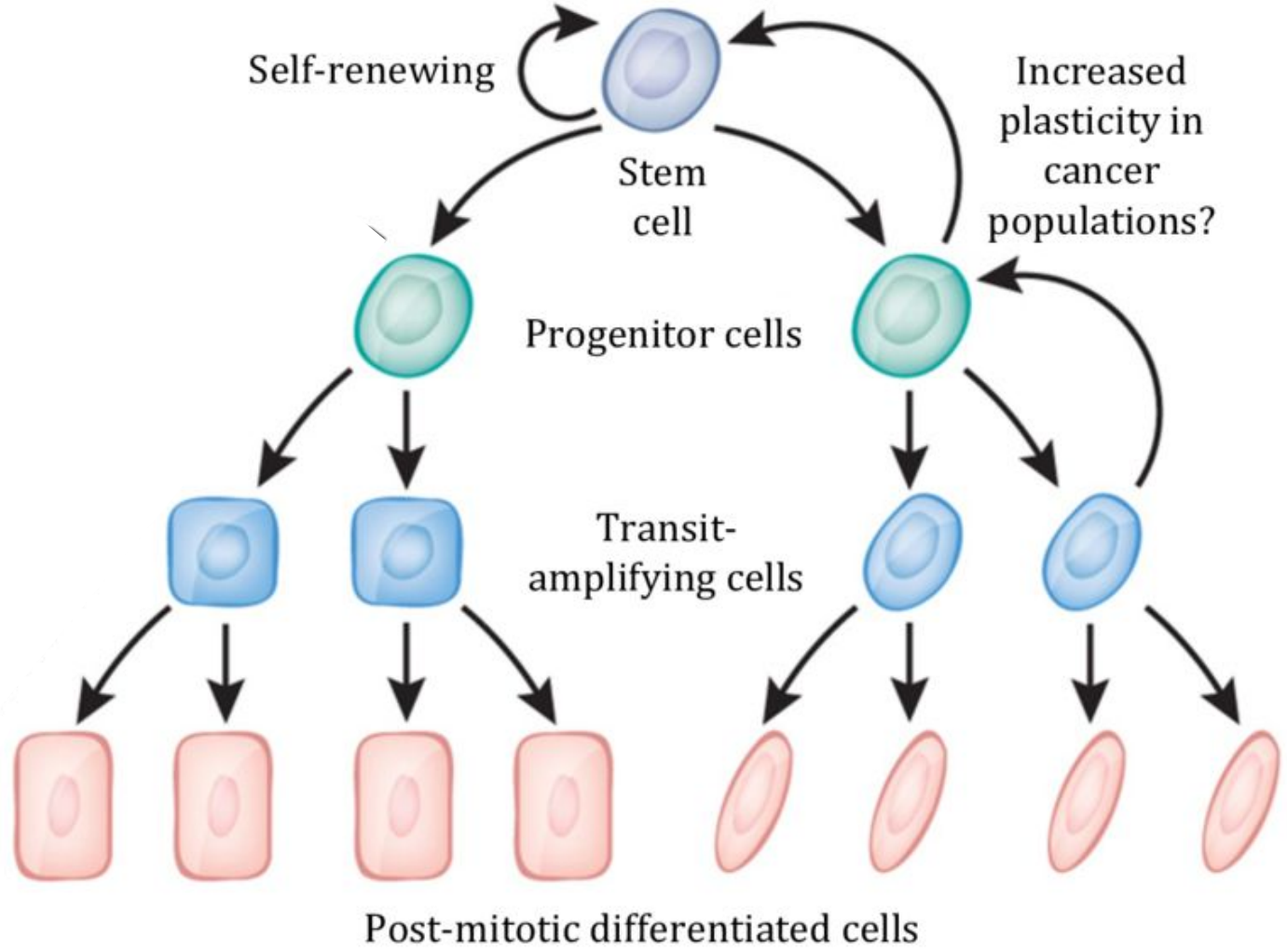
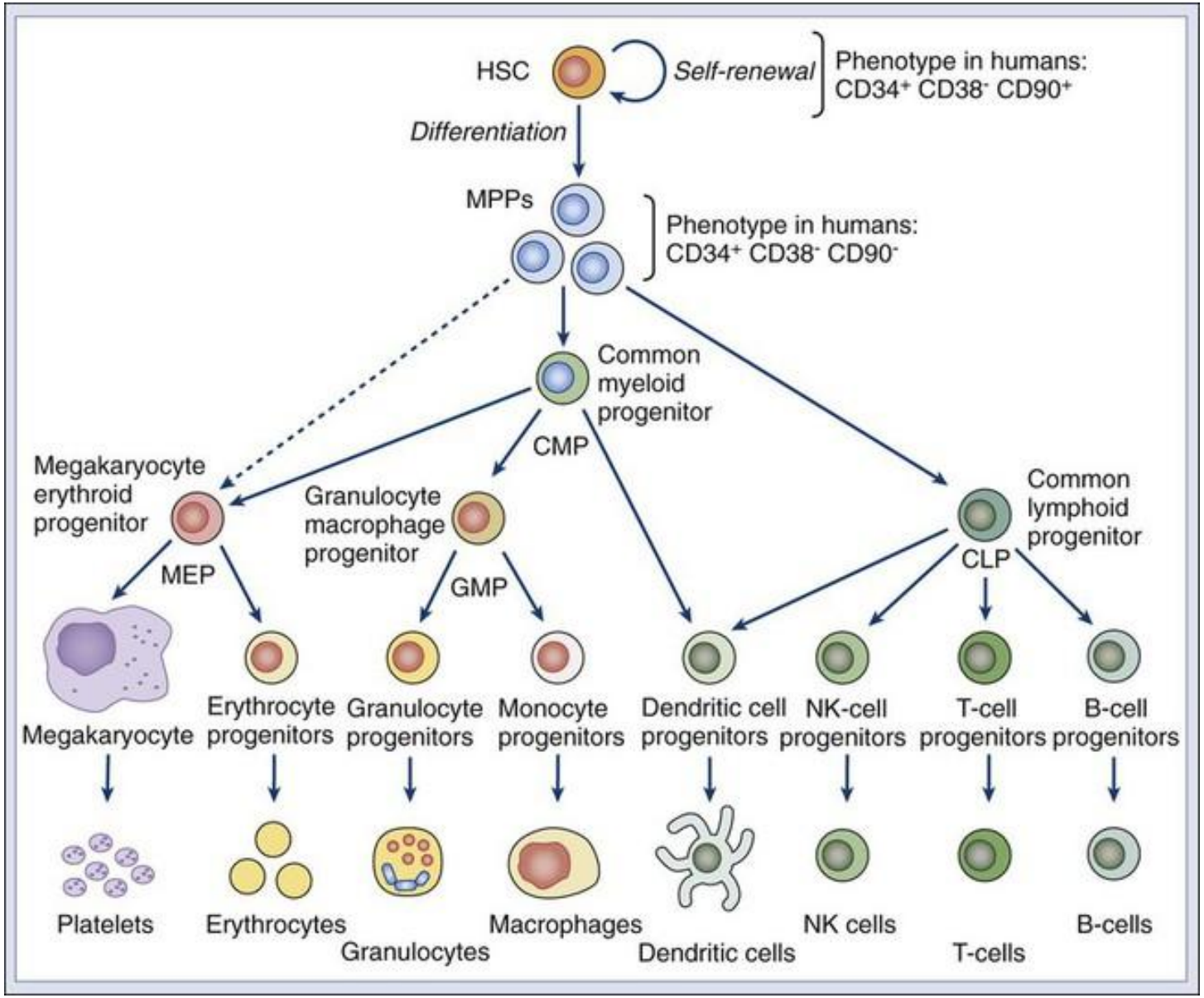
1. Cancer evolution



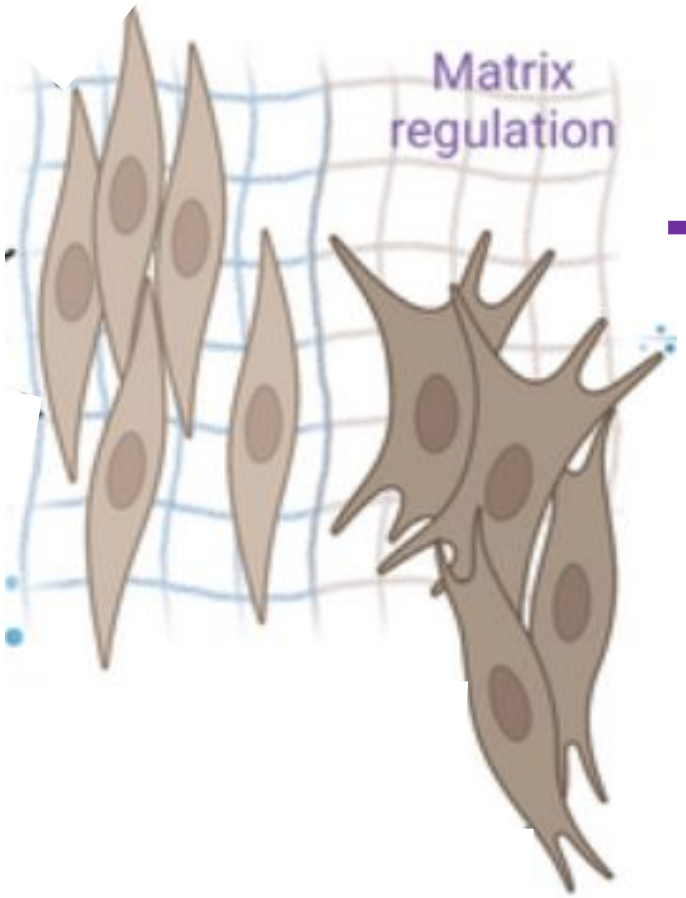
Healthy tissue architecture and homeostasis



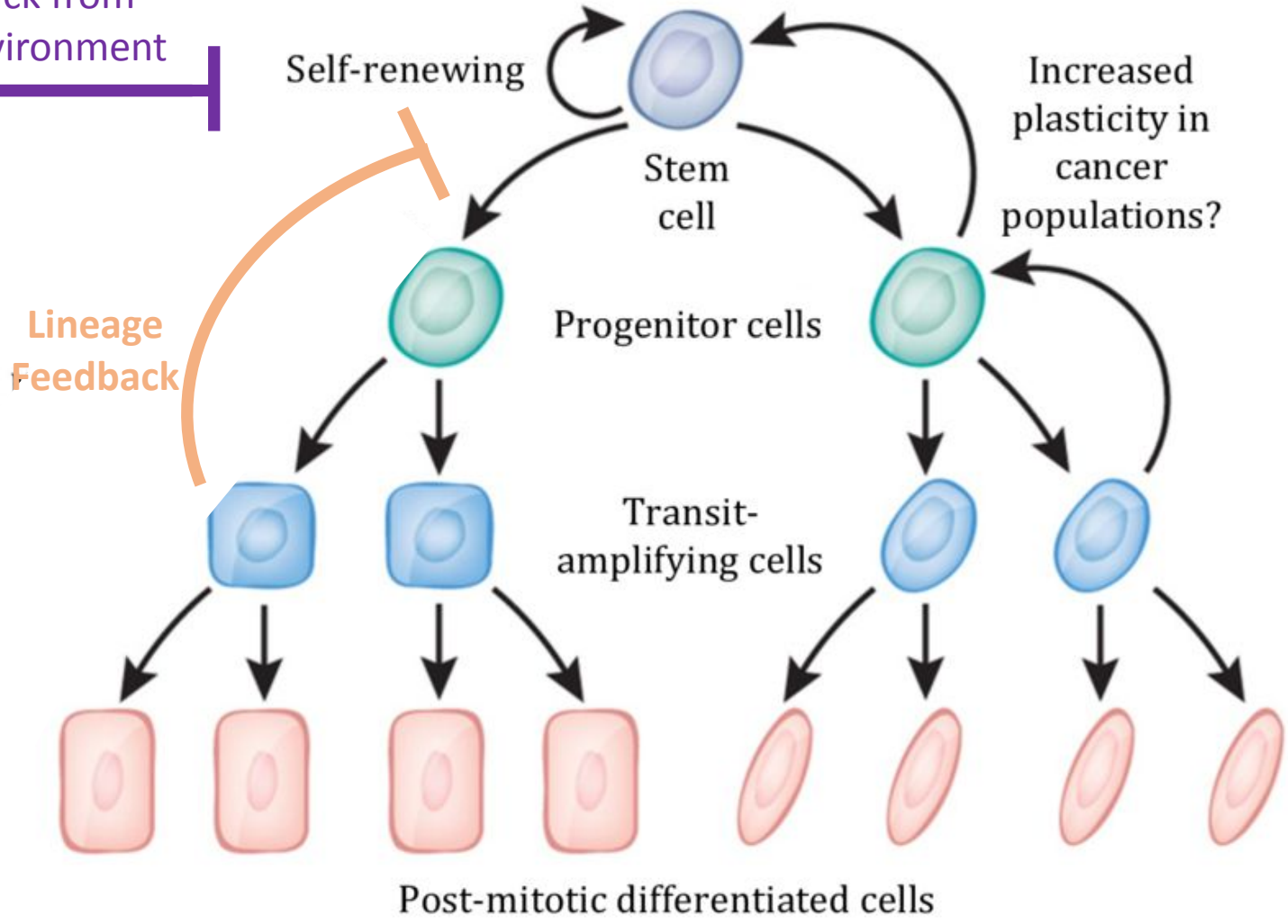
For example: Blood



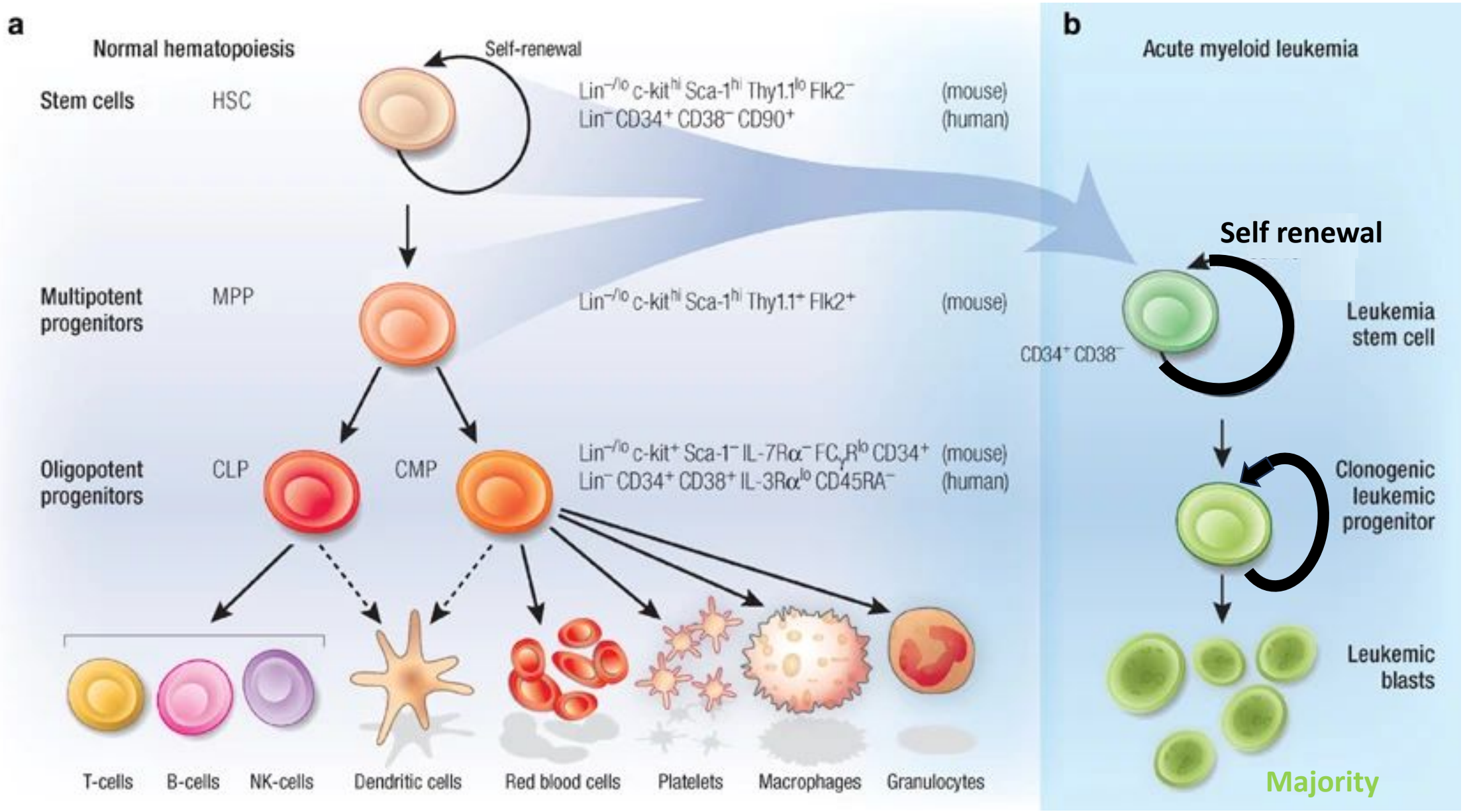
Homeostasis



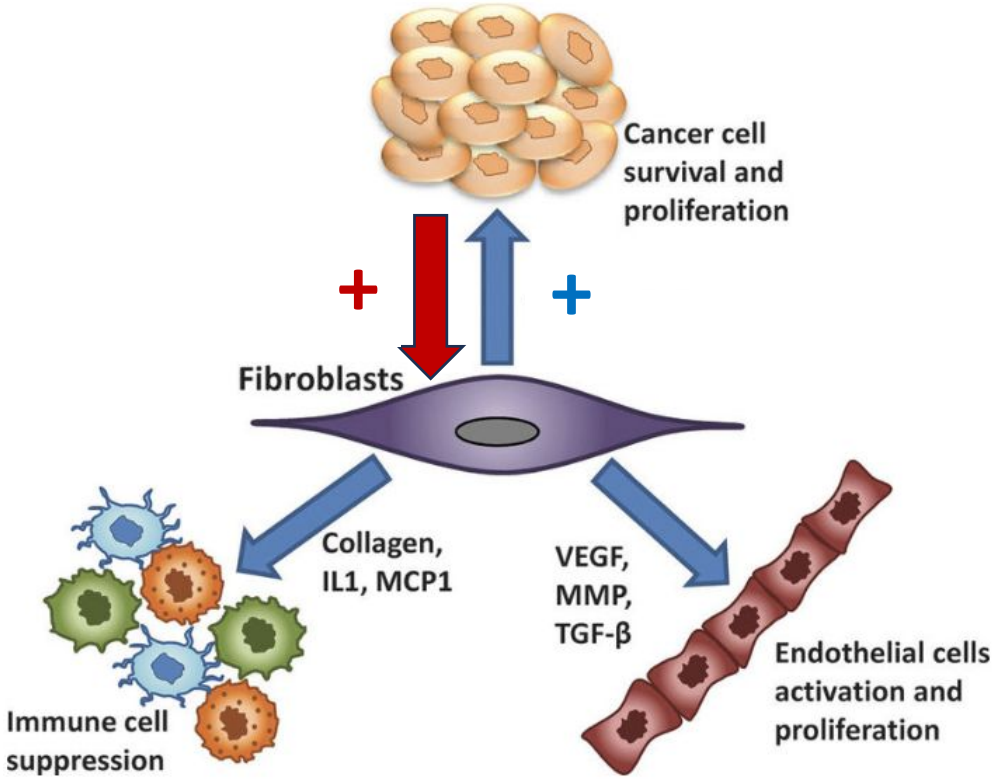
Feedback from microenvironment

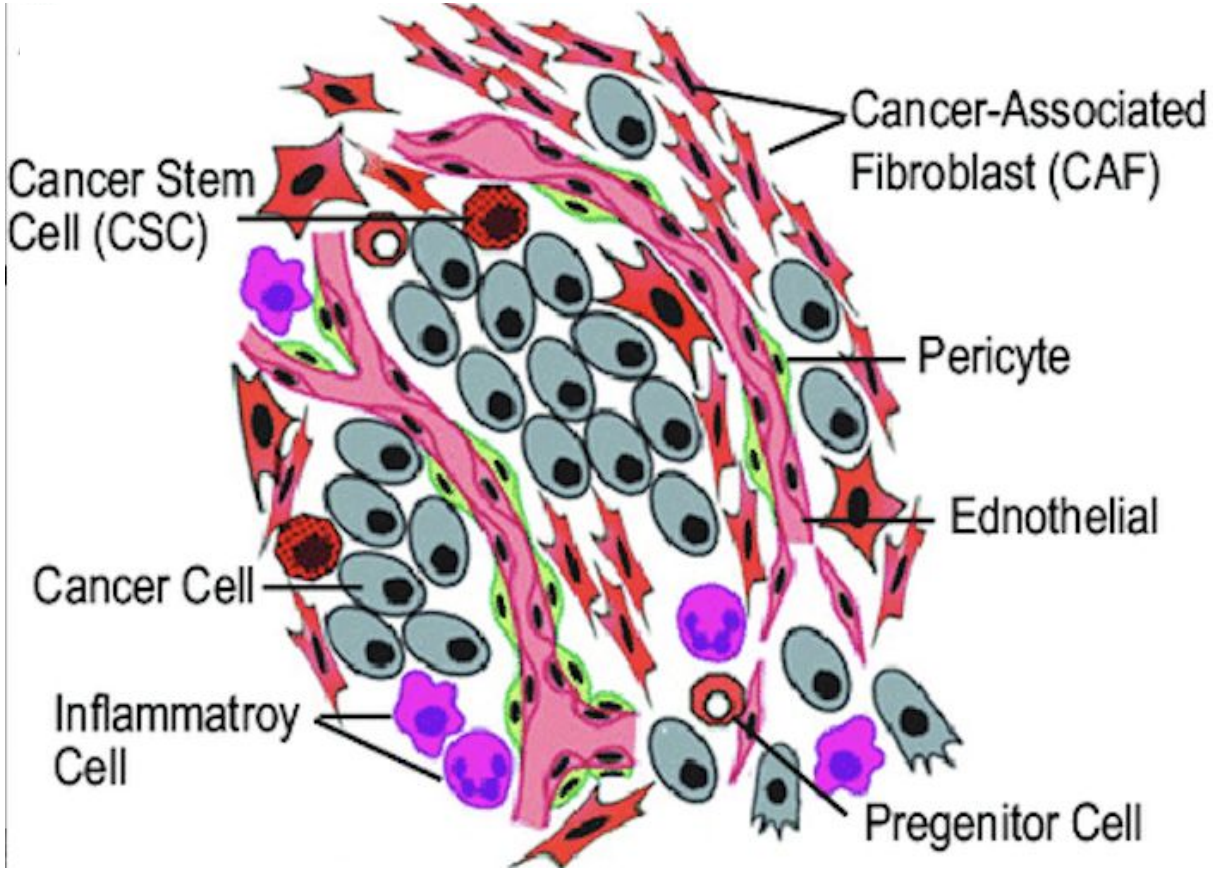


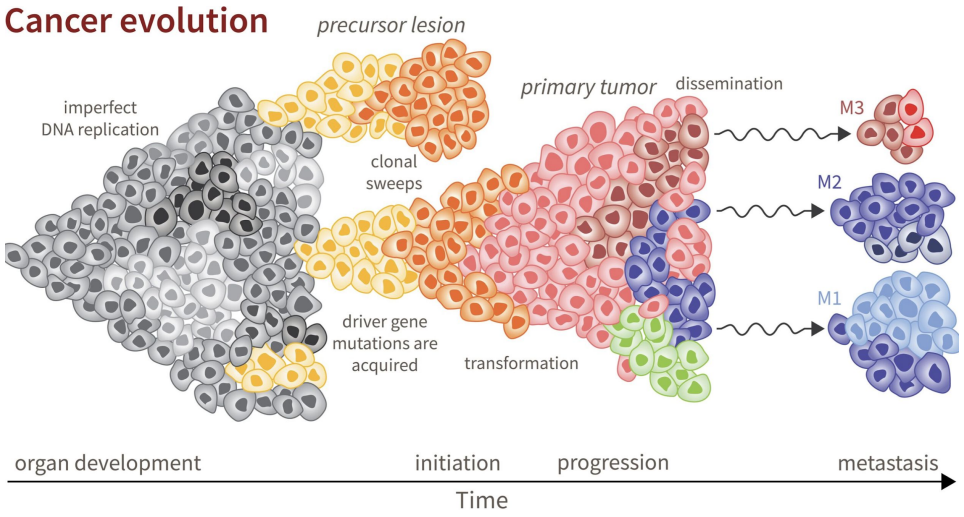
Cancer is a tissue gone wrong: characterized by the same issue architecture

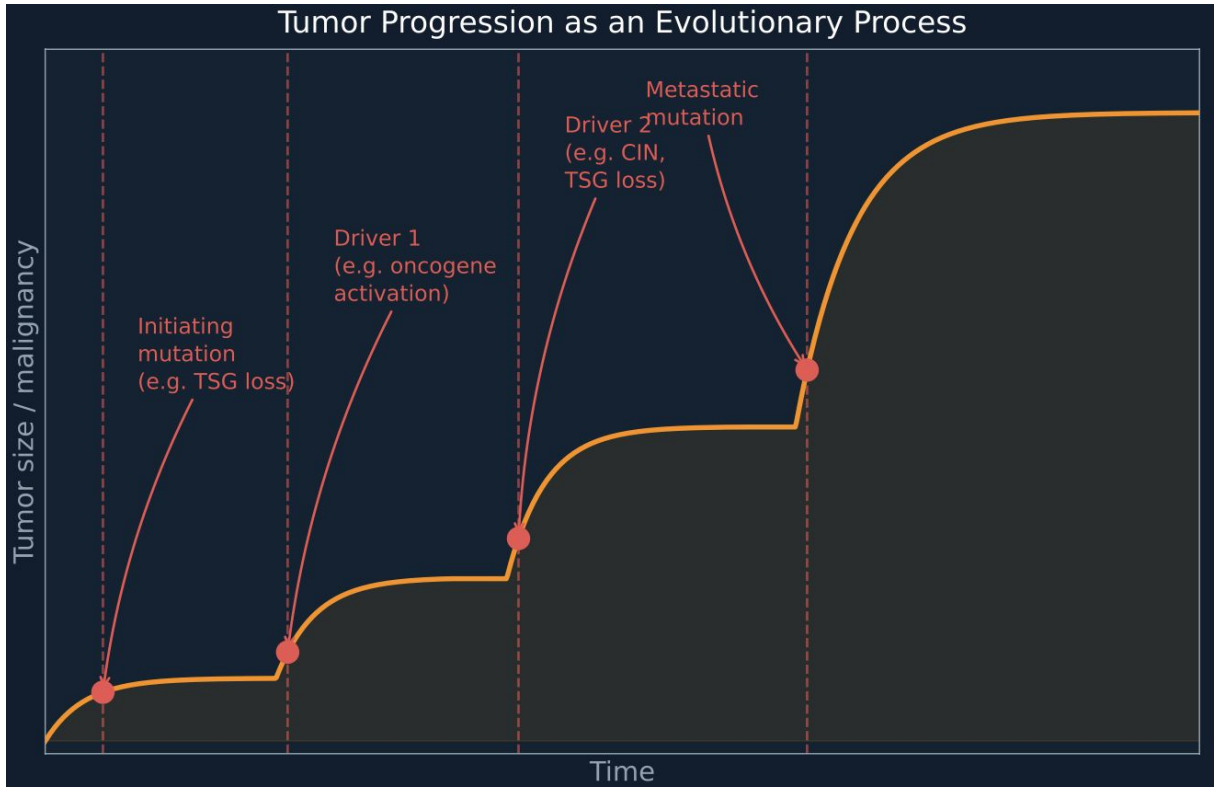


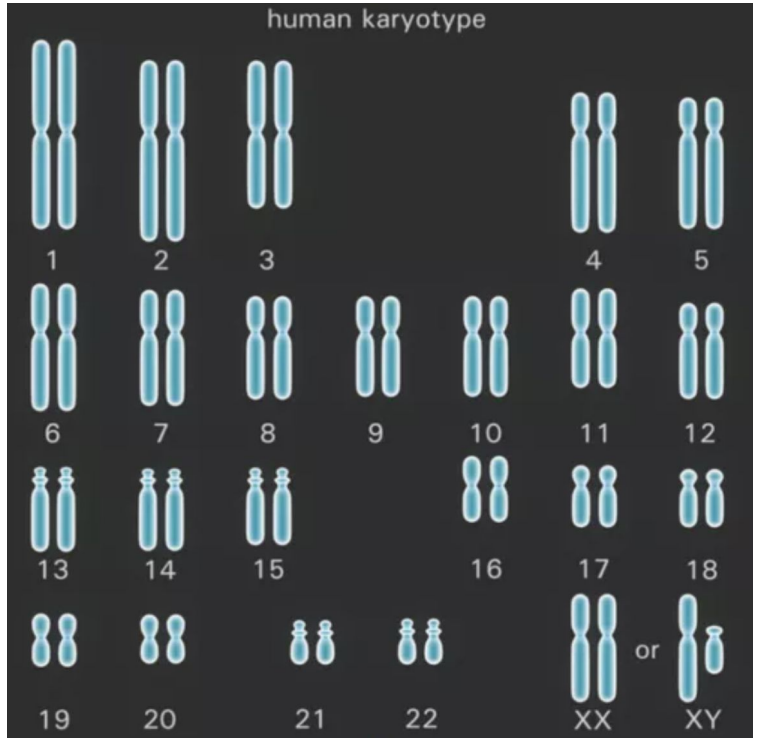
Cancer – Microenvironment interactions






Cancer evolution
precursor lesion
imperfect
DNA replication
clonal
sweeps
primary tumor
dissemination
M3
M2
M1
driver gene
mutations are
acquired
transformation
organ development
initiation
progression
metastasis
Time


Tumor Progression as an Evolutionary Process
Initiating
mutation
(e.g. TSG loss)
Driver 1
(e.g. oncogene
activation)
Driver 2
(e.g. CIN,
TSG loss)
Metastatic
mutation
Tumor size / malignancy
Time


human karyotype
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
XX
or
XY

Cancer Evolution: Driver Mutations & Gene Classes

Cancer is driven by mutations in three key gene classes

Oncogenes

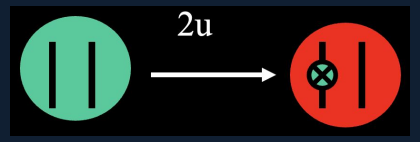
"Accelerator"

Normally promote cell growth

Gain-of-function mutations

One mutant copy sufficient

Examples: RAS, MYC, BCR-ABL



Stuck 'ON' -- uncontrolled growth

Tumor Suppressor Genes (TSGs)

"Brakes"

Normally inhibit cell growth

Loss-of-function mutations

Both copies often needed

Examples: TP53, RB, APC

Both brakes cut -- growth unchecked

DNA Repair Genes

"Caretakers"

Maintain genome integrity

Loss elevates mutation rate

Accelerates driver acquisition

Examples: BRCA1/2, MMR genes

More mutations -- faster evolution

Genetic Instability: Accelerating Evolution

Defective genome maintenance --> elevated mutation rate --> faster evolution

Chromosomal Instability (CIN)

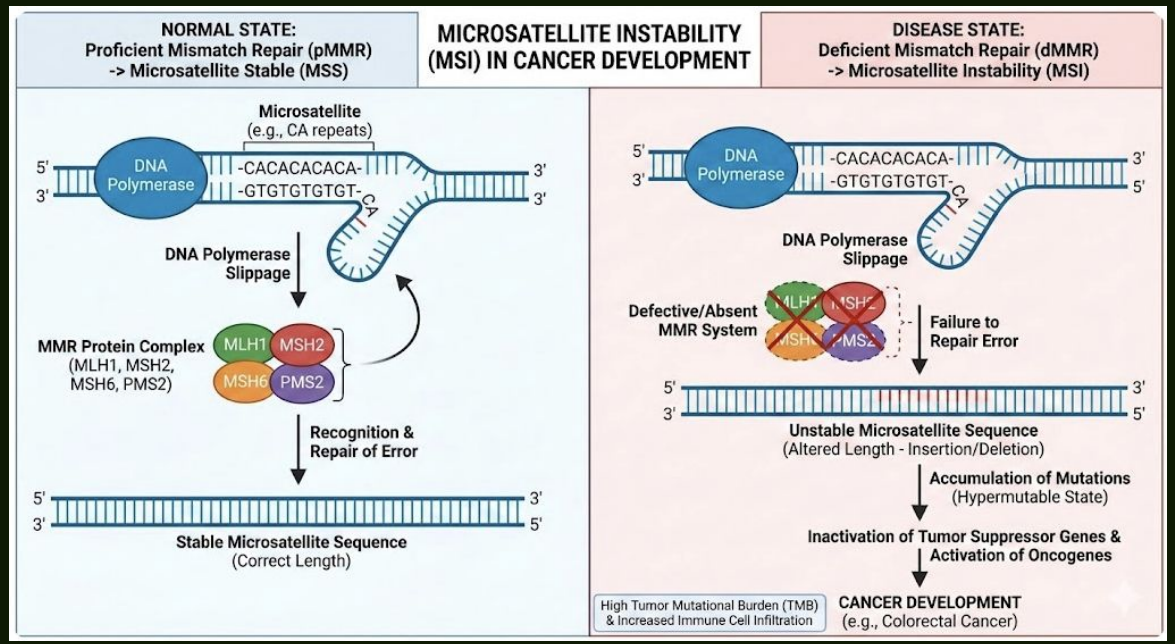
large-scale genetic changes

normal cell

cancer cell

Microsatellite Instability (MSI)

small-scale genetic changes



Key insight: Genetic instability is an 'enabler' -- it accelerates acquisition of driver mutations

Cancer Therapy: Major Approaches

Traditional Chemotherapy

Cytotoxic agents kill rapidly dividing cells

DNA-damaging agents
(cisplatin, doxorubicin)

Mitotic inhibitors
(taxanes, vinca alkaloids)

Antimetabolites
(5-FU, methotrexate)

Affects all dividing cells --> toxicity

Targeted Therapy (Small Molecules)

Inhibit specific molecular drivers of cancer

Tyrosine kinase inhibitors
(imatinib in CML, BCR-ABL)

EGFR inhibitors
(erlotinib, lung cancer)

BRAF inhibitors
(melanoma)

Higher specificity but resistance common

Immunotherapy

Harness the immune system against cancer

Immune checkpoint inhibitors
(PD-1, CTLA-4)

CAR-T cell therapy

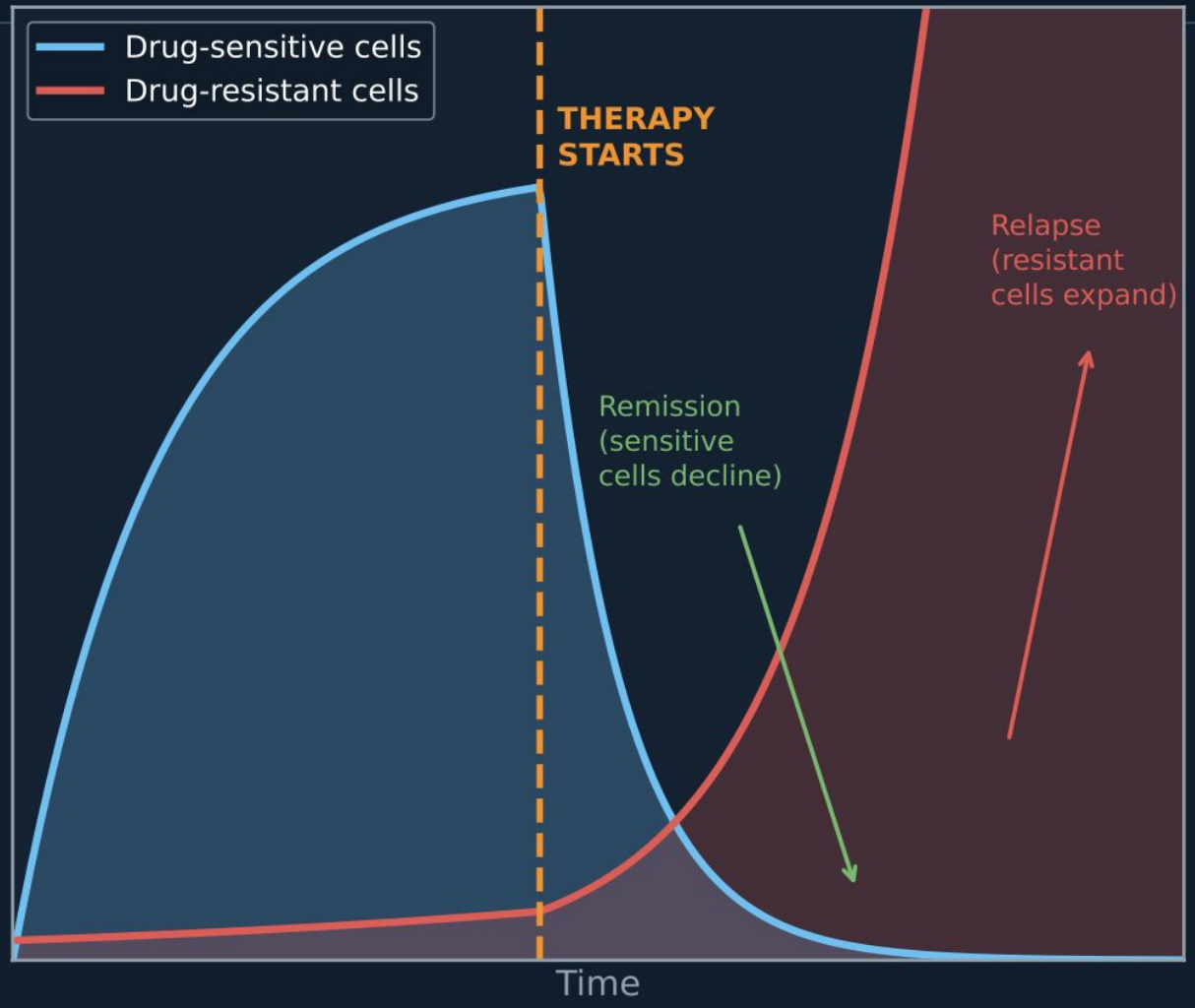
Cancer vaccines

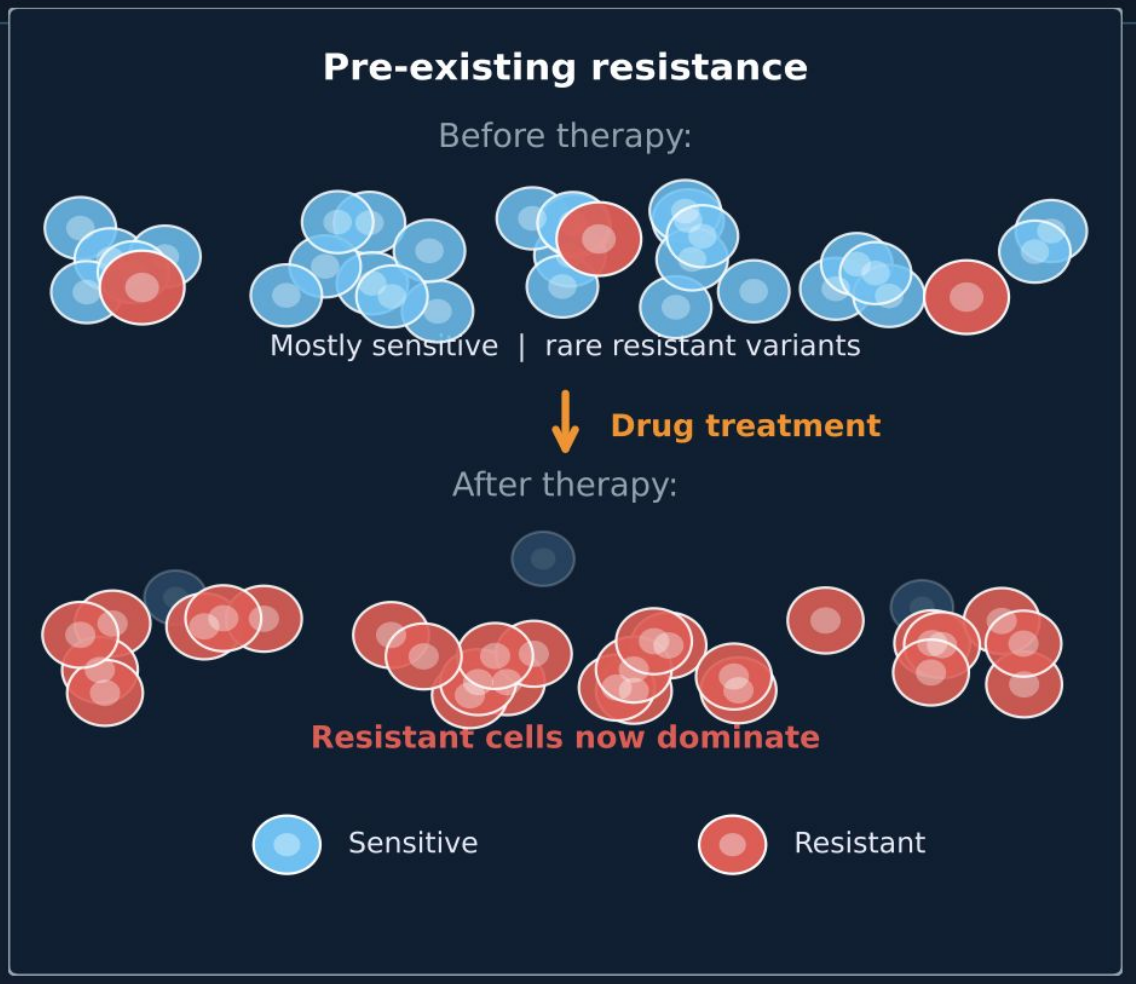
Bispecific antibodies

Durable responses in some patients

Landmark: Imatinib (Gleevec) targets BCR-ABL in CML -- transformed a lethal disease into a manageable chronic condition

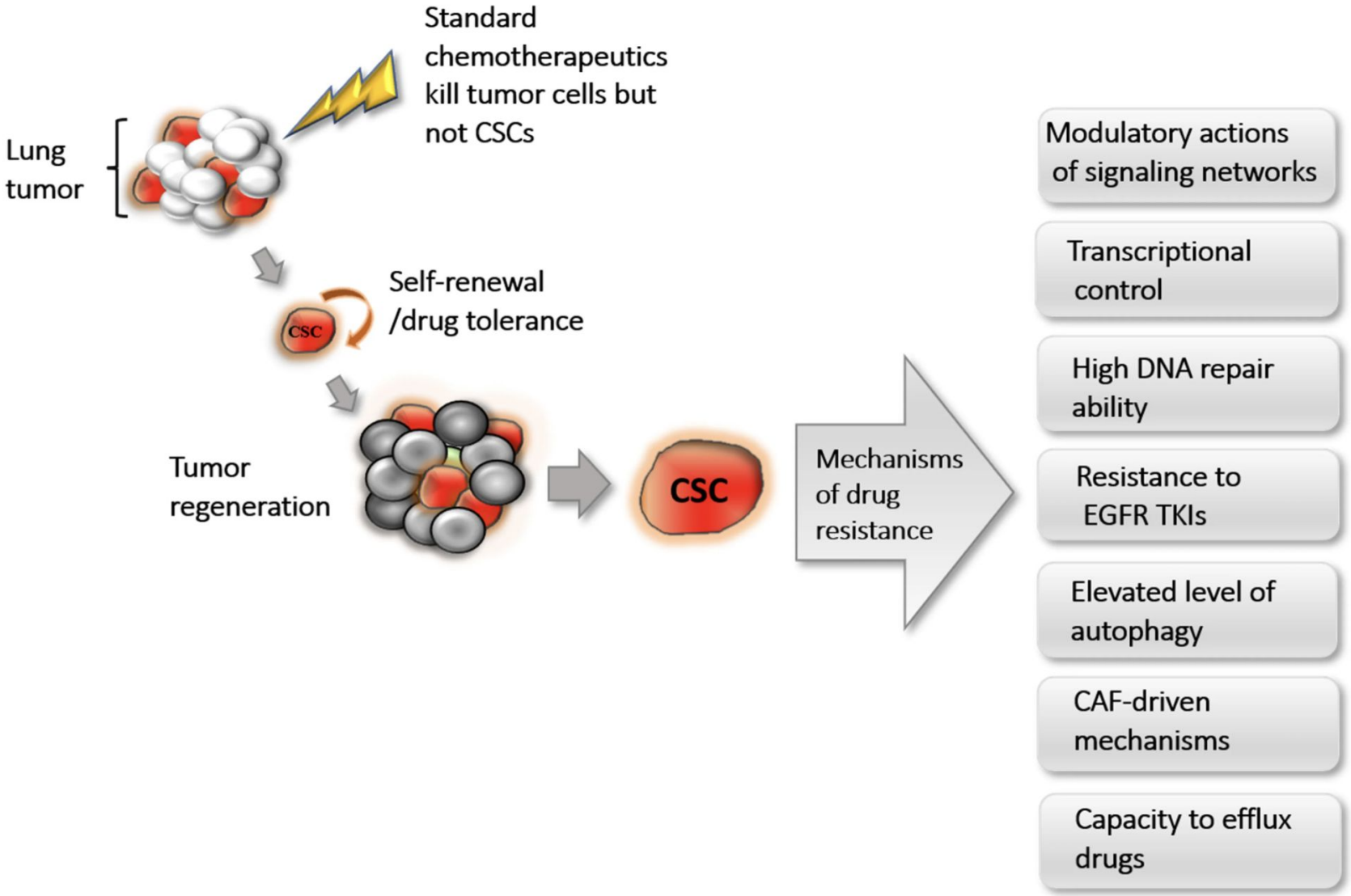
Drug Resistance: Evolution in Action





Key insight: Resistant cells PRE-EXIST as rare variants before therapy starts.
Therapy selects for them -- combination therapy targeting multiple pathways is more effective at preventing resistance.

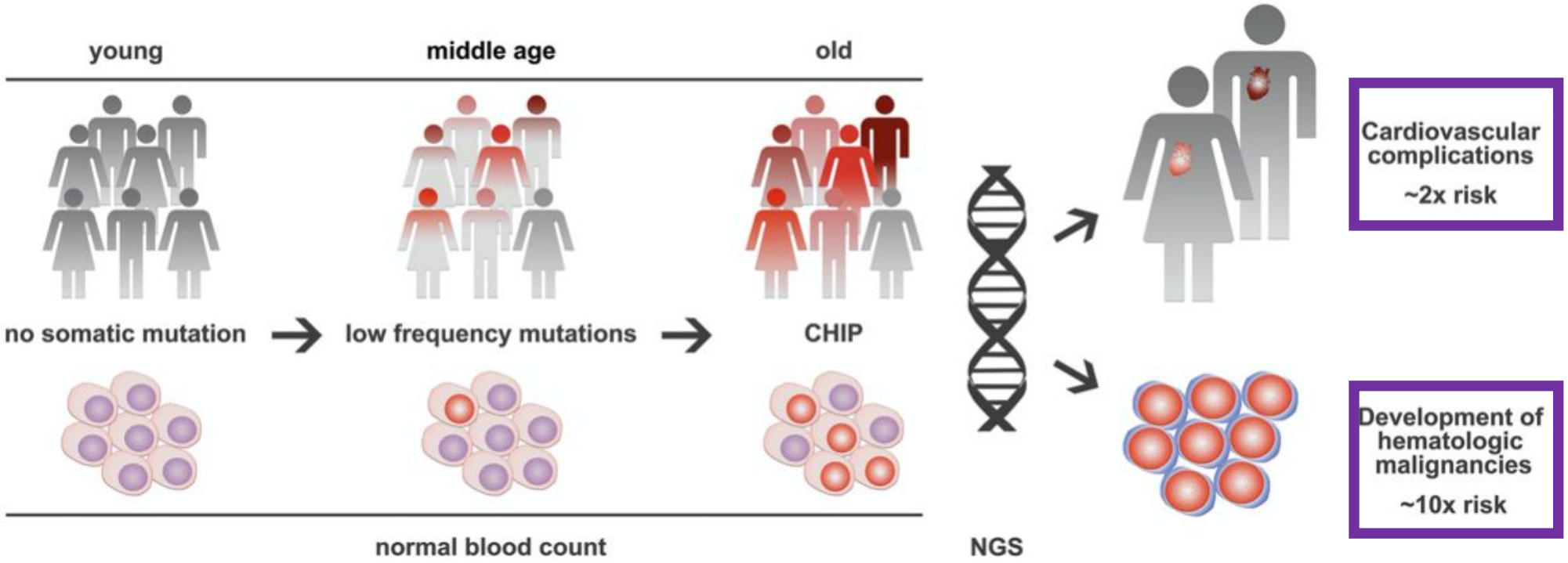
Drug resistance can also be based on cancer stem cell persistence (no resistant mutations)



2. Modeling tissue and tumor cell evolution

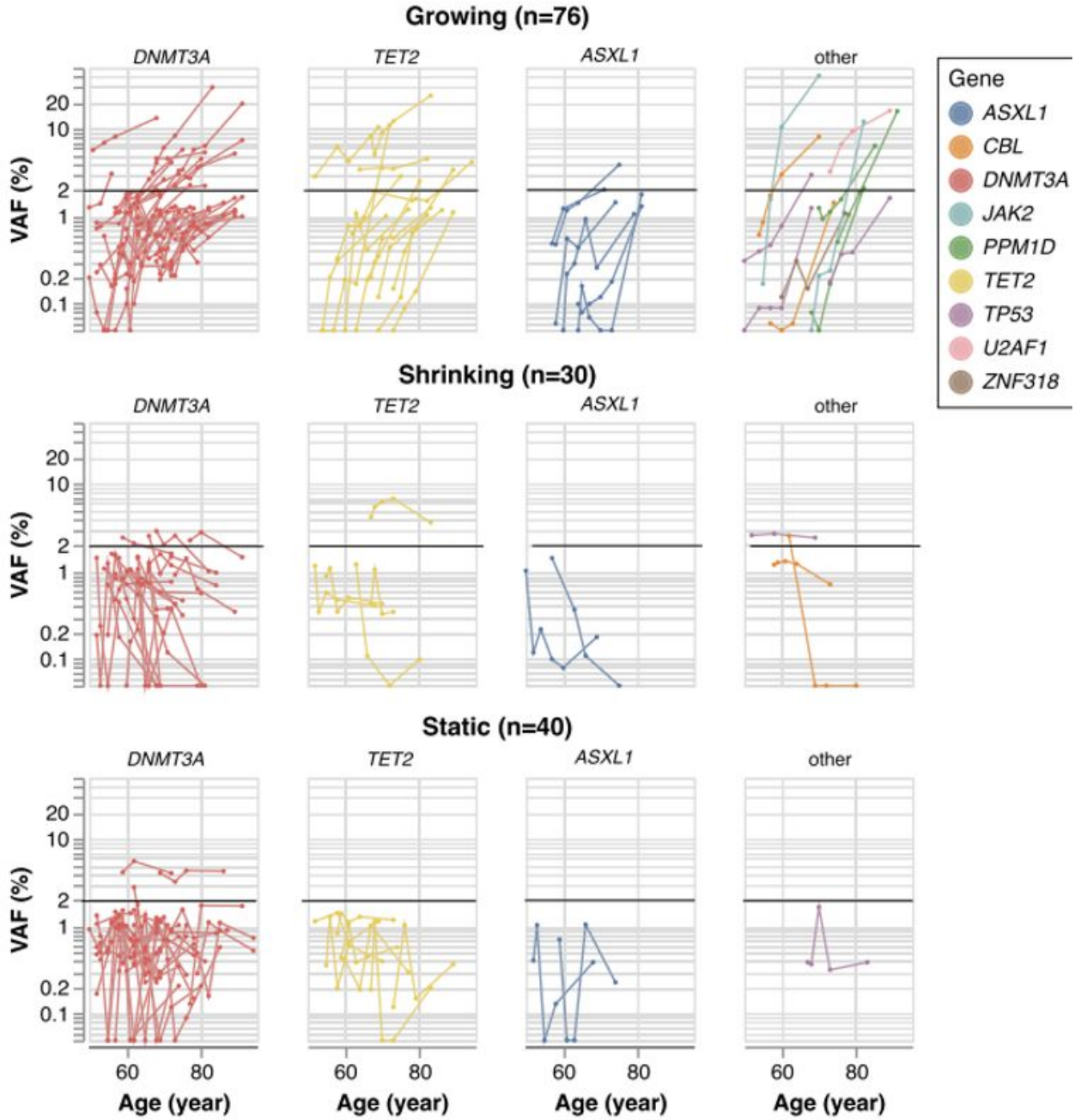
- Consider pre-malignant cell evolution in the blodd
- Show how simple ordinary differential equation models can provide biological insights

Pre-cancer evolution in healthy tissue:
Clonal hematopoiesis of indeterminate potential in the blood

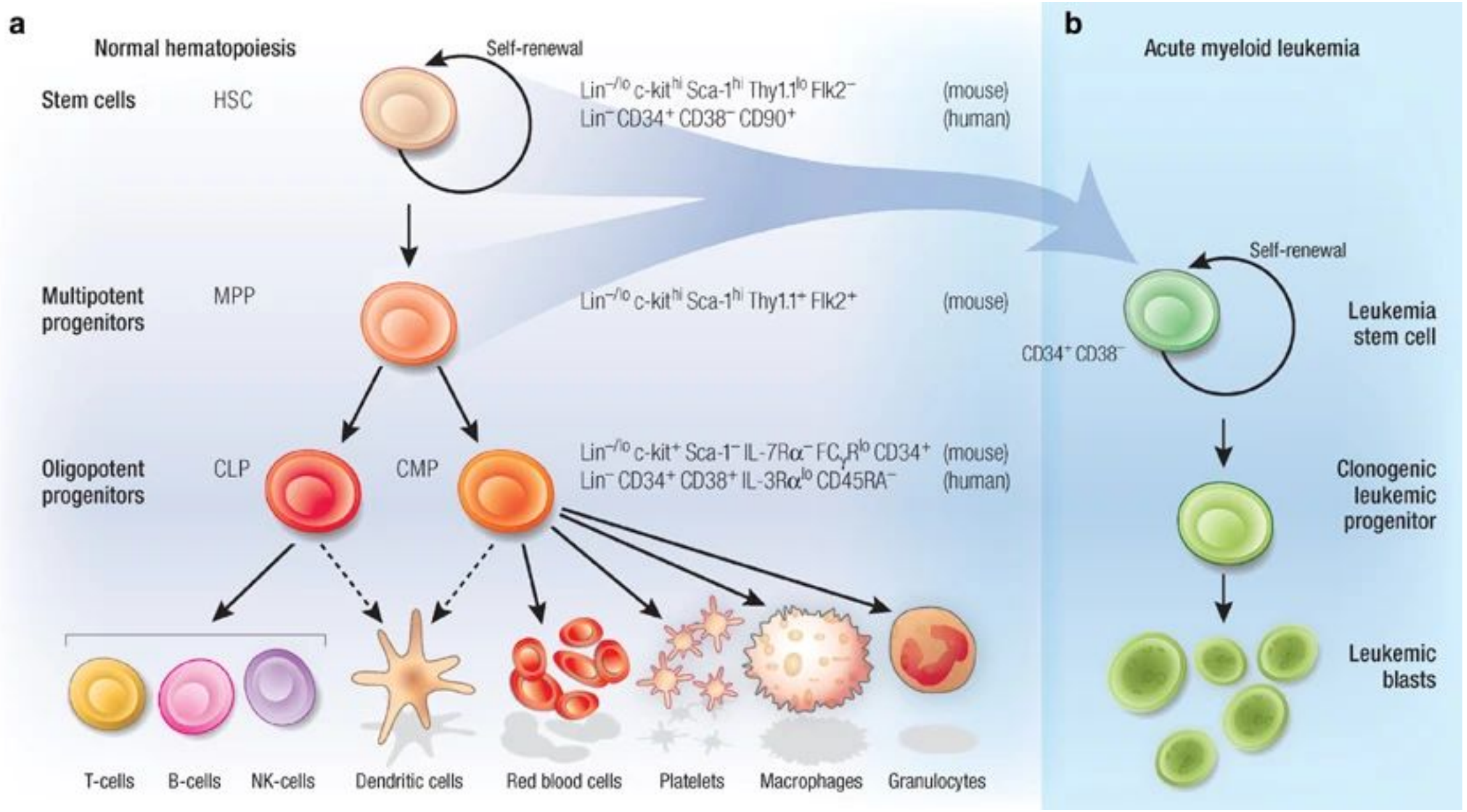


- How do CHIP mutants evolve?
- What are the selection pressures?
- Can we treat to create conditions that select against CHIP clones (evolutionary therapy)?

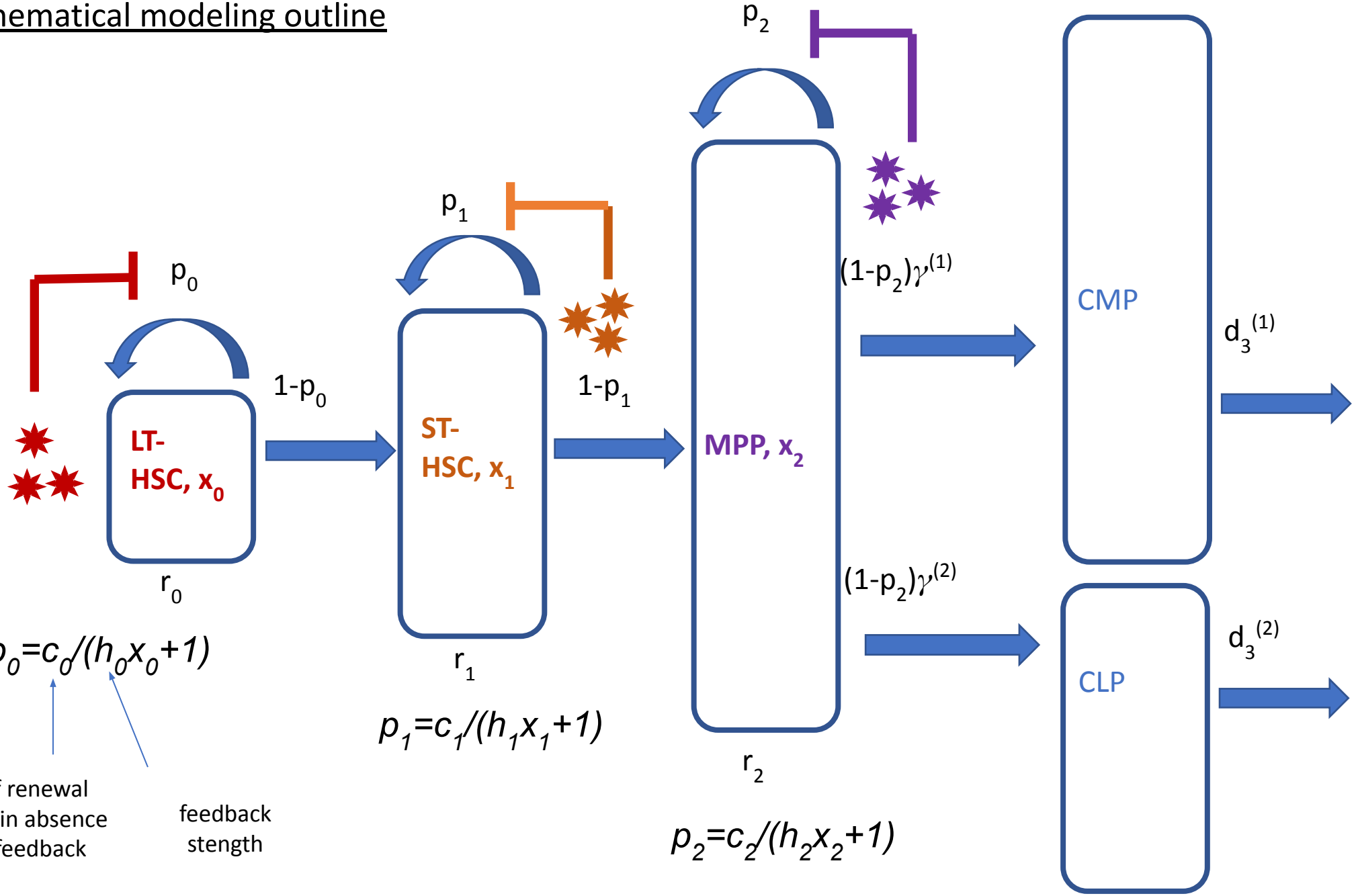
Lots of existing mathematical modeling work by e.g. Stiehl, Marciniak-Czochra , Mackey, Loeffler, Roeder


Growing (n=76)
Shrinking (n=30)
Static (n=40)
DNMT3A
TET2
ASXL1
other
VAF (%)
20
10
2
1
0.2
0.1
60
80
Age (year)
Gene
ASXL1
CBL
DNMT3A
JAK2
PPM1D
TET2
TP53
U2AF1
ZNF318

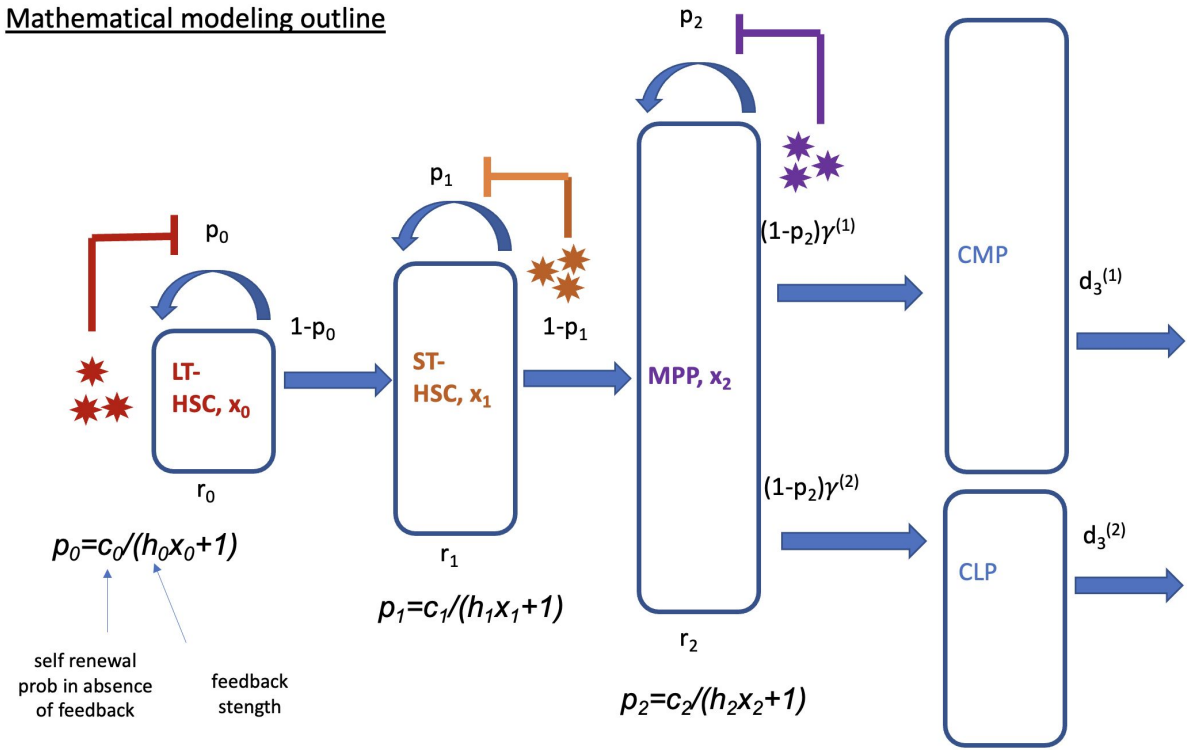
What is the fate of mutants arising in the different compartments?



Mathematical modeling outline



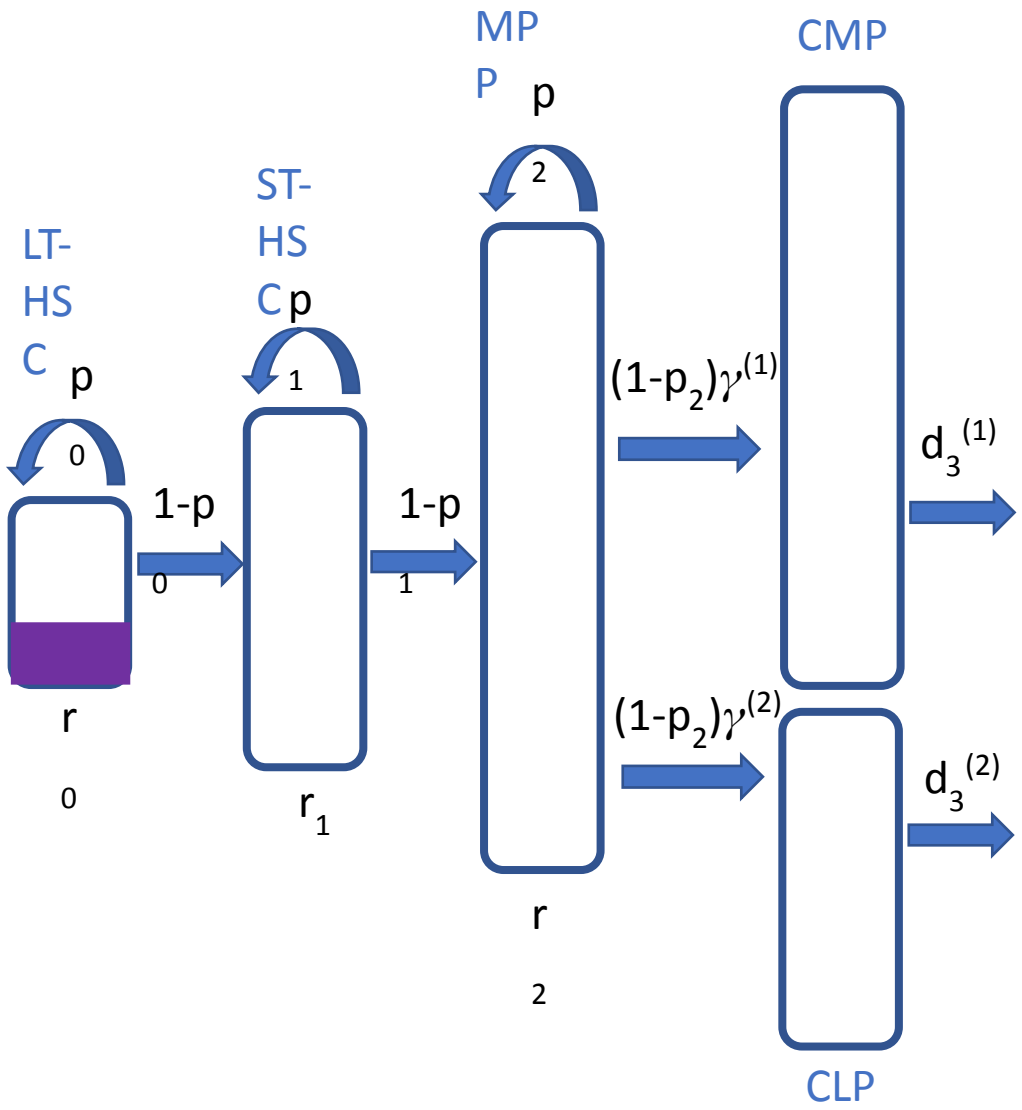
Mathematical modeling outline

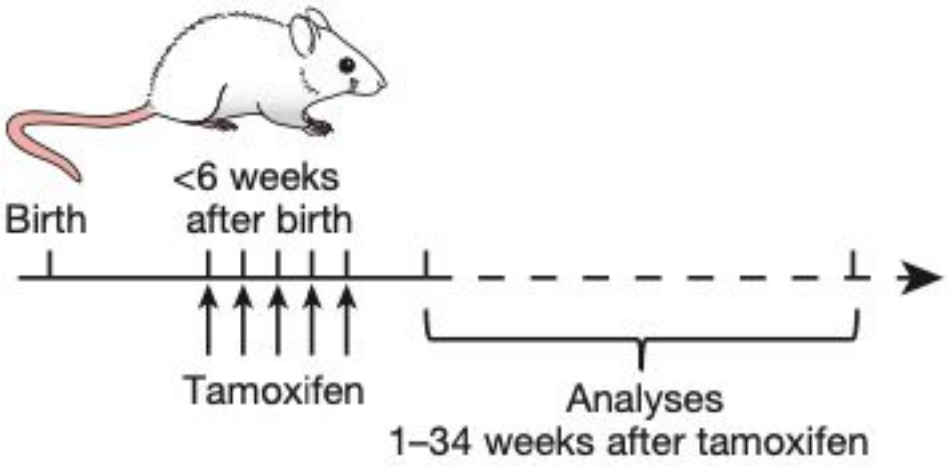


$$
\begin{aligned}
\frac{dx_0}{dt} &= r_0 x_0 (2p_0 - 1), \\
\frac{dx_1}{dt} &= 2r_0 x_0 (1 - p_0) + r_1 x_1 (2p_1 - 1), \\
\frac{dx_2}{dt} &= 2r_1 x_1 (1 - p_1) + r_2 x_2 (2p_2 - 1), \\
\frac{dx_3^{(1)}}{dt} &= 2r_2 x_2 (1 - p_2)\gamma^{(1)} - d_3^{(1)} x_3^{(1)}, \\
\frac{dx_3^{(2)}}{dt} &= 2r_2 x_2 (1 - p_2)\gamma^{(2)} - d_3^{(2)} x_3^{(2)},
\end{aligned}
$$

$$
p_i = p_i(x_0, x_1, x_2, x_3^{(1)}, x_3^{(2)}), \quad 0 \le i \le 2.
$$

Neutral label propagation





Busch, K., Klapproth, K., Barile, M., Flossdorf, M., Holland-Letz, T., Schlenner, S. M., ... & Rodewald, H. R. (2015). Fundamental properties of unperturbed haematopoiesis from stem cells in vivo. *Nature*, *518*(7540), 542-546.

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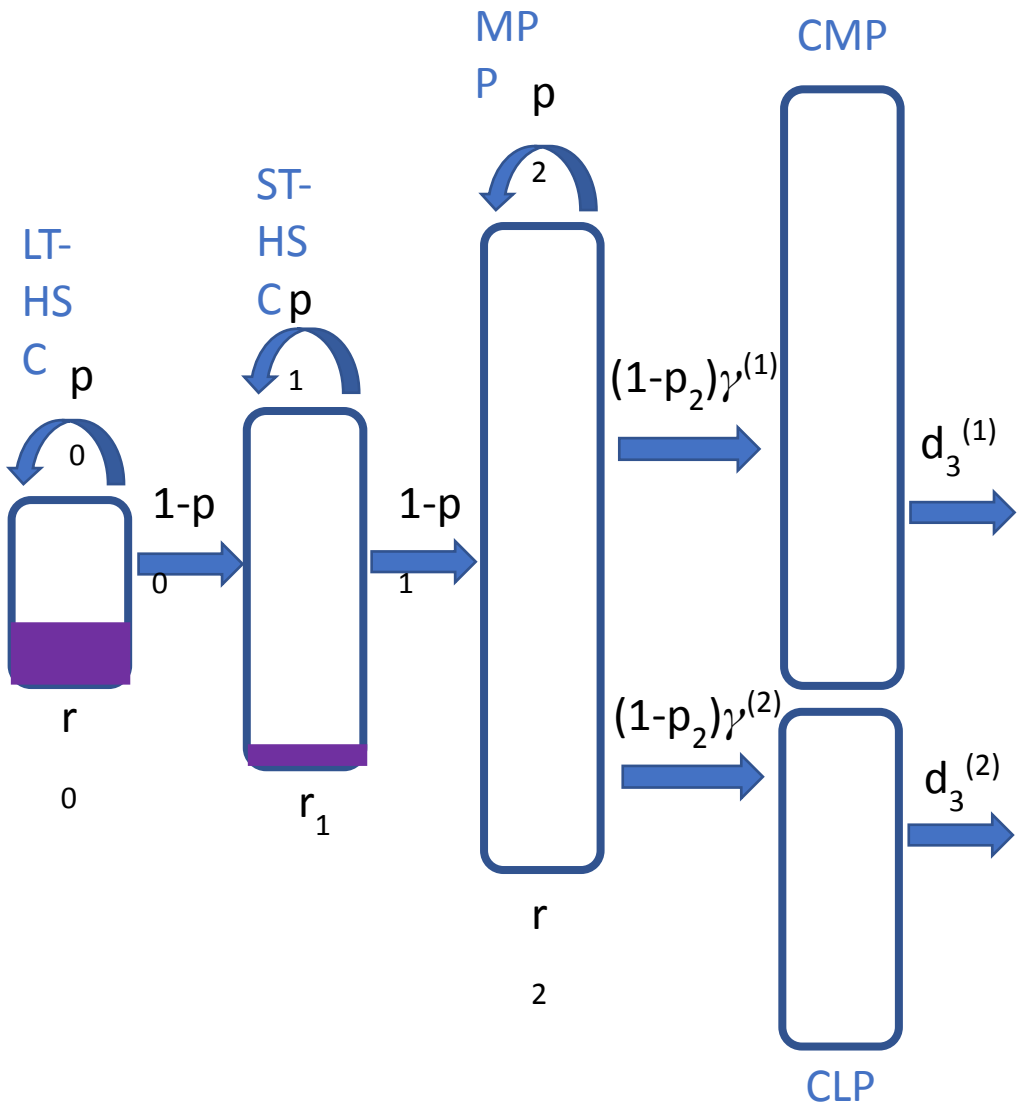

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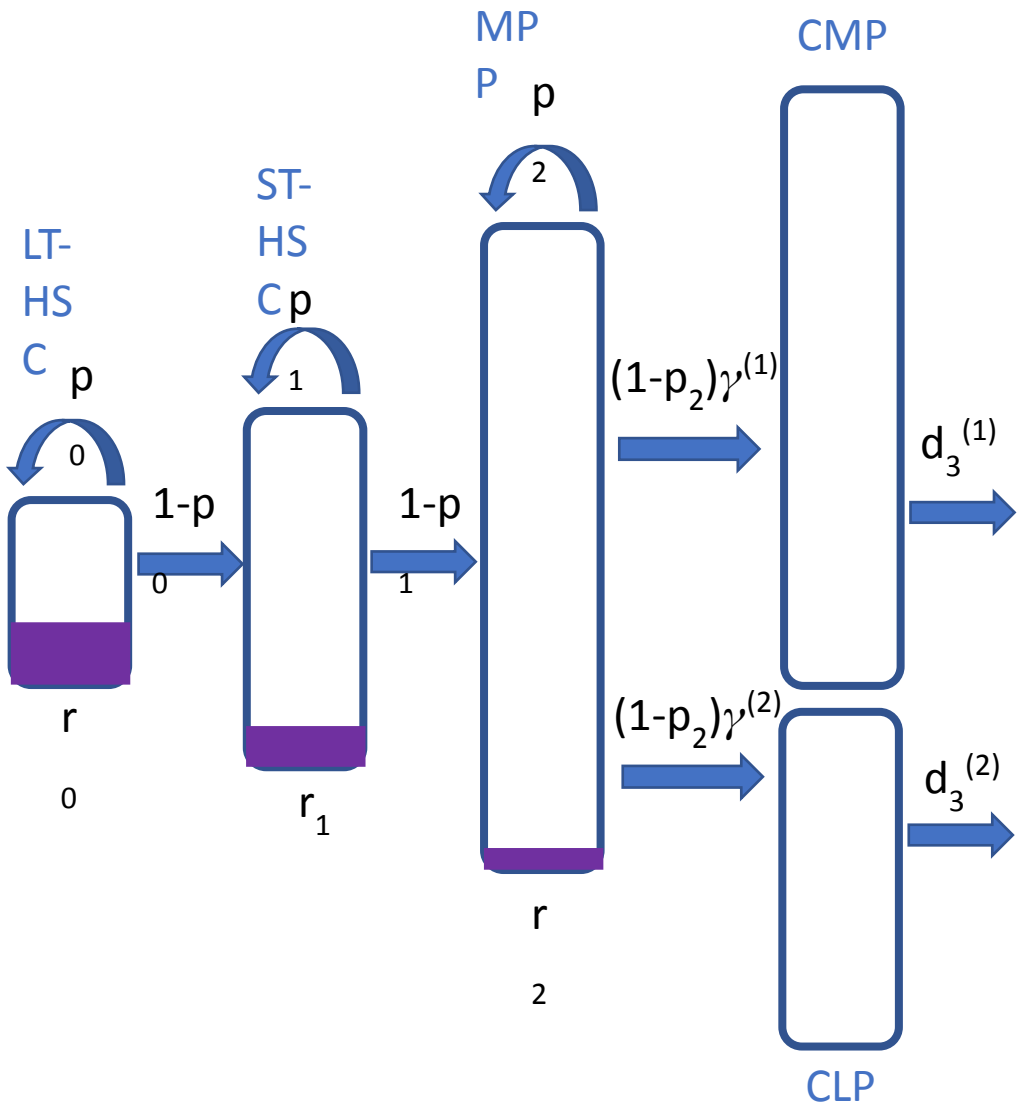

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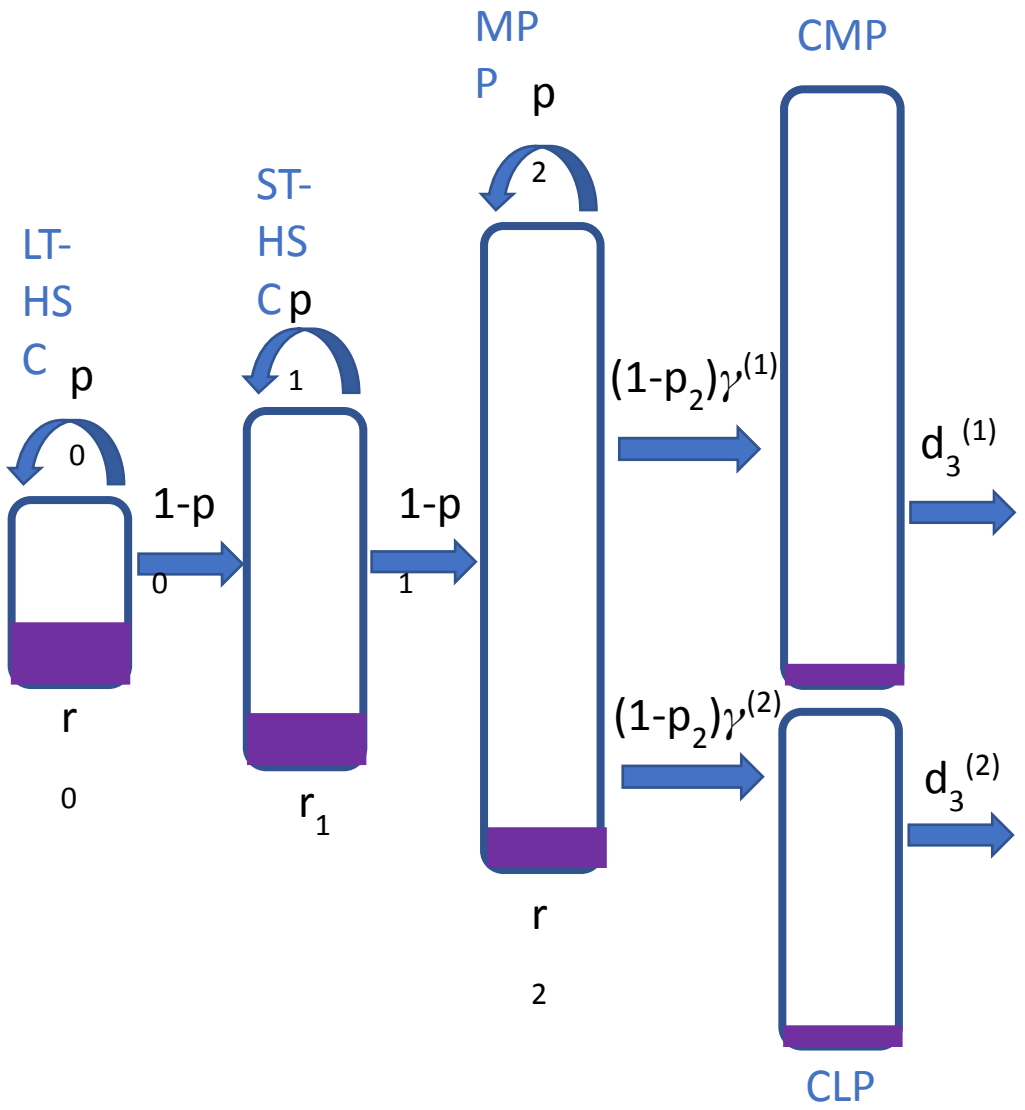

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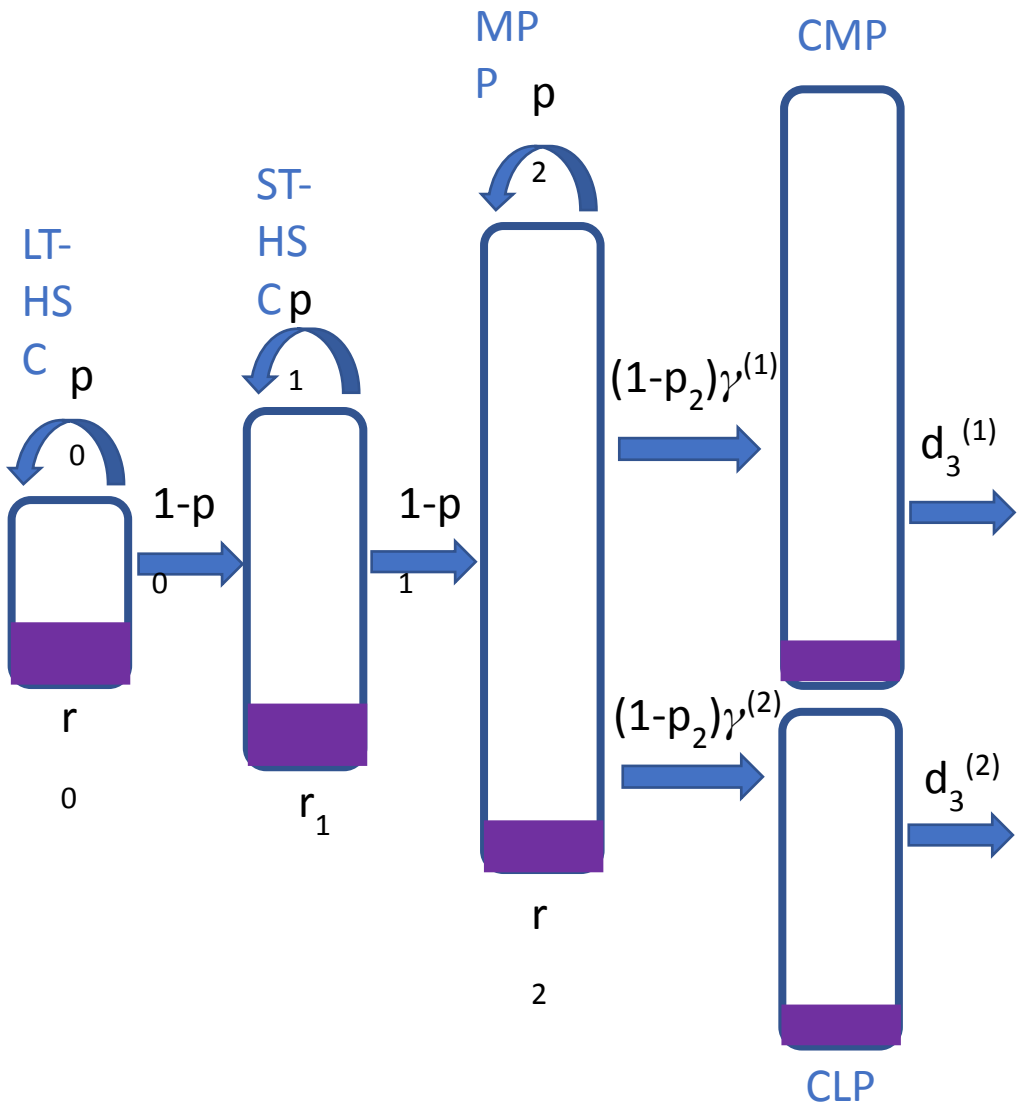

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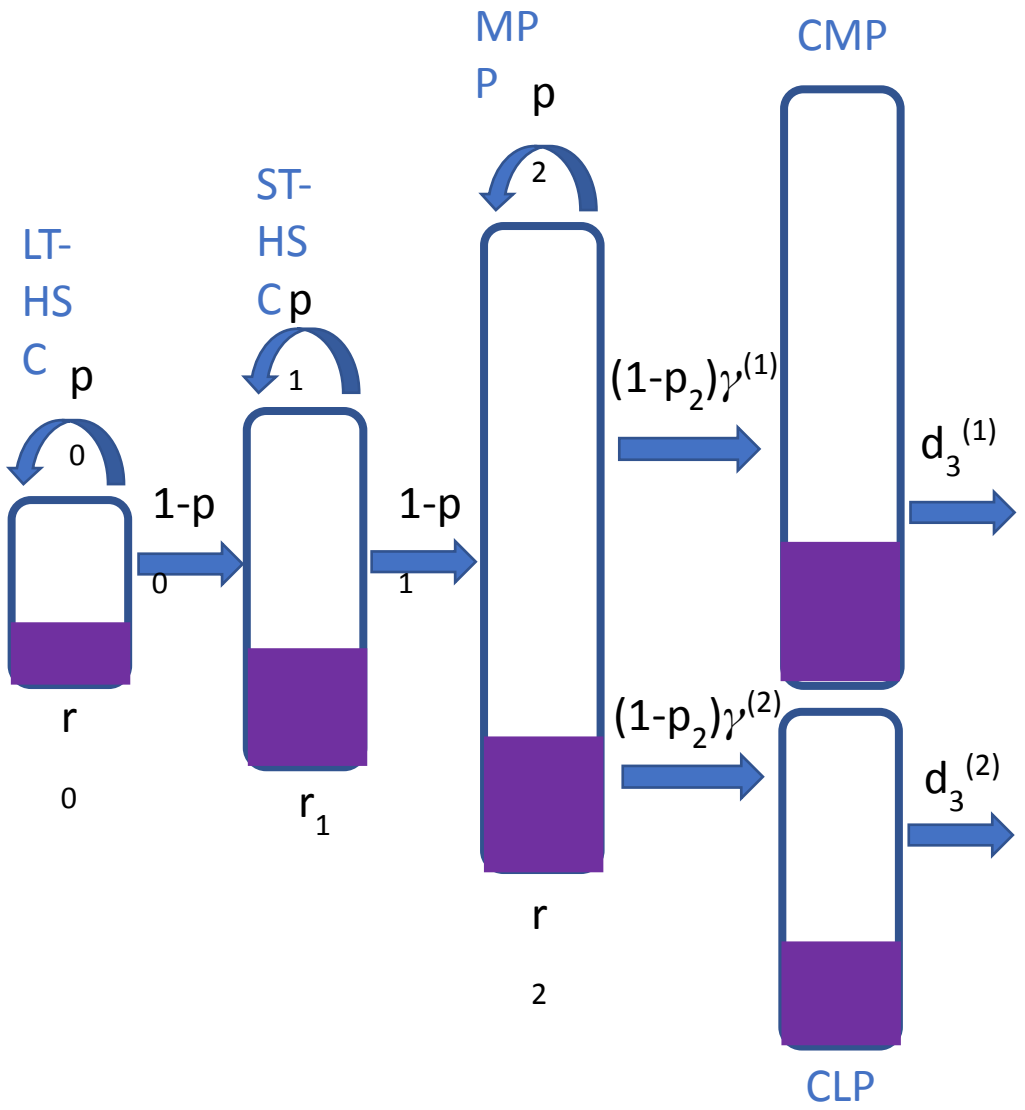

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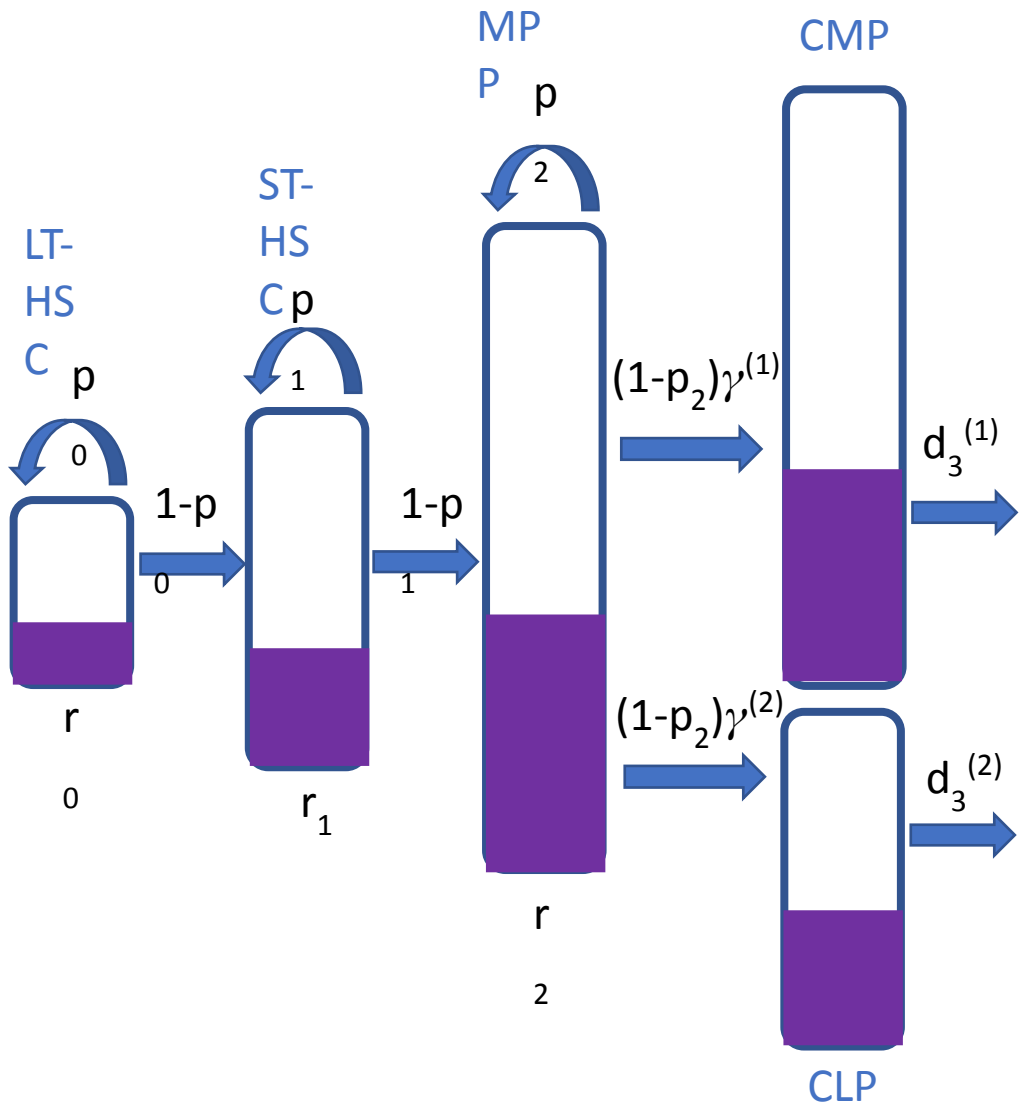

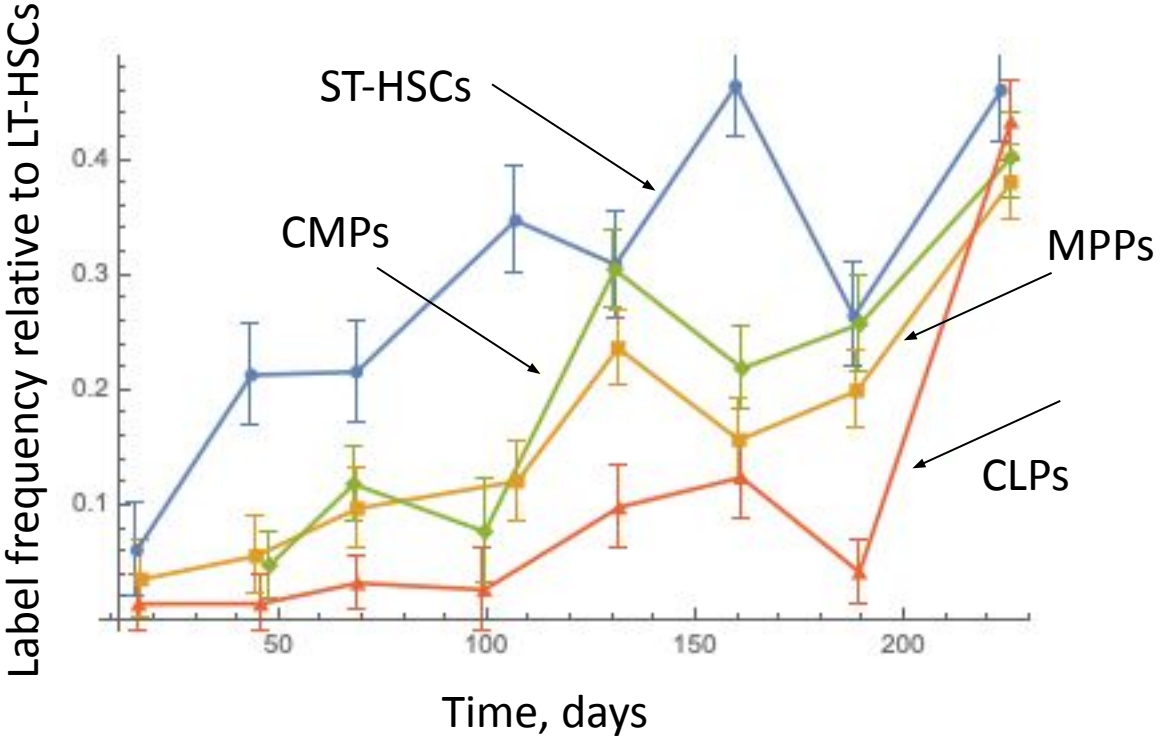

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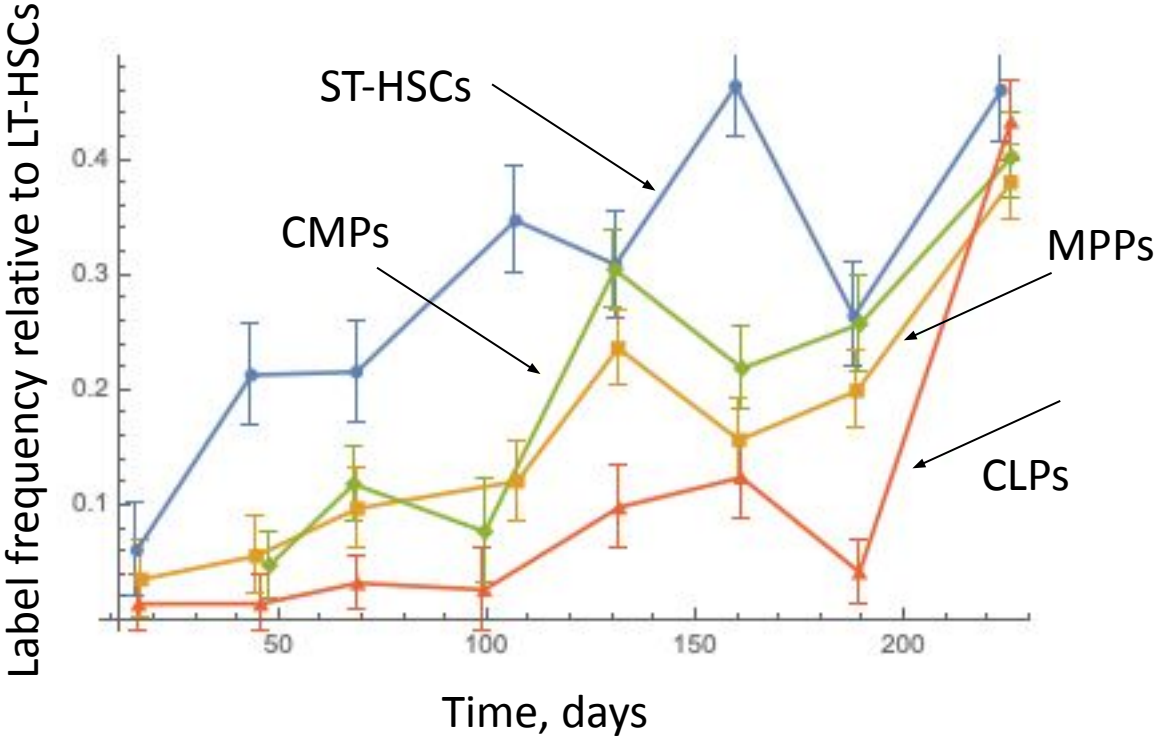
Model parameterization

Fraction of the neutral label in each compartment

$$\begin{aligned}
\dot{f}_0 &= 0, \\
\dot{f}_1 &= \frac{1}{\tau_1}(f_0 - f_1), \\
\dot{f}_2 &= \frac{1}{\tau_2}(f_1 - f_2), \\
\dot{f}_3^{(1)} &= \frac{1}{\tau_3^{(1)}}(f_2 - f_3^{(1)}), \quad \dot{f}_3^{(2)} = \frac{1}{\tau_3^{(2)}}(f_2 - f_3^{(2)}).
\end{aligned}$$

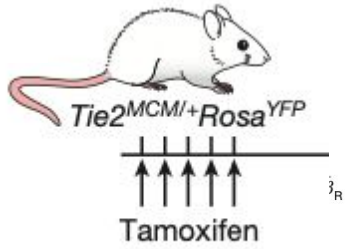


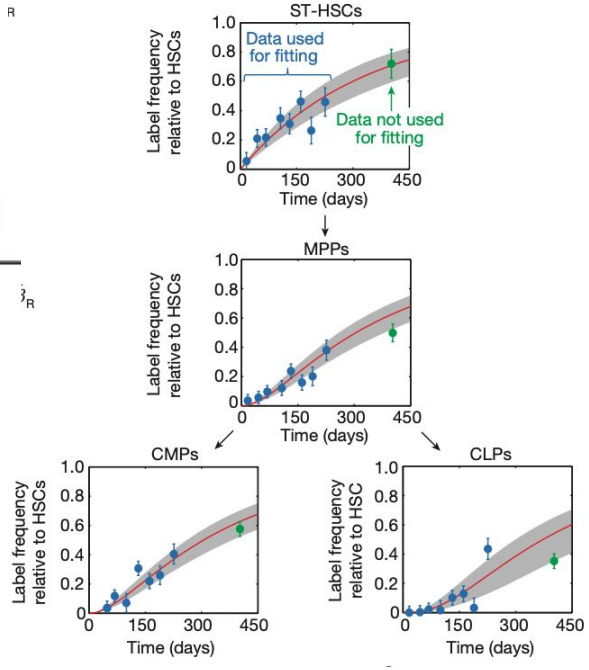
"Time to equilibirum"

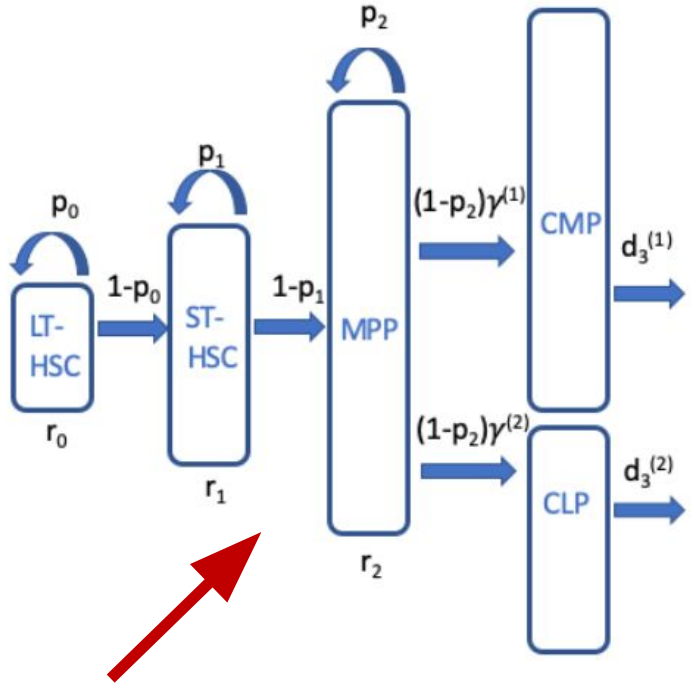
$$\tau_1 = \frac{1}{r_1(1-2p_1)}, \quad \tau_2 = \frac{1}{r_2(1-2p_2)}, \quad \tau_3^{(1)} = \frac{1}{d_3^{(1)}}, \quad \tau_3^{(2)} = \frac{1}{d_3^{(2)}}.$$

Compartment size ratios:

$$\frac{X_1}{X_0} = \frac{r_0}{r_1(1-2\bar{p}_1)}, \quad \frac{X_2}{X_1} = \frac{2r_1(1-\bar{p}_1)}{r_2(1-2\bar{p}_2)}, \quad \frac{X_3^{(1)}}{X_2} = \frac{2r_2\gamma_2^{(1)}}{d_3^{(1)}}, \quad \frac{X_3^{(2)}}{X_2} = \frac{2r_2\gamma_2^{(2)}}{d_3^{(2)}}.$$







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\frac{dx_3^{(1)}}{dt} &= 2r_2 x_2 (1 - p_2)\gamma^{(1)} - d_3^{(1)} x_3^{(1)}, \\
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\end{aligned}
$$

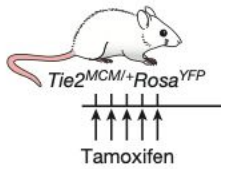
$$p_i = p_i(x_0, x_1, x_2, x_3^{(1)}, x_3^{(2)}), \quad 0 \le i \le 2.$$

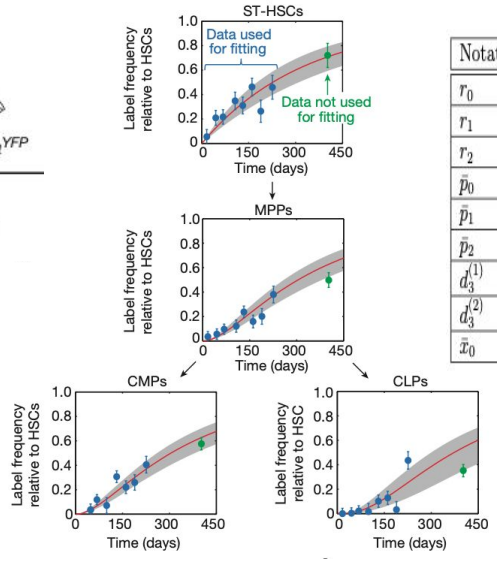
First, parameter estimation without feedback

Notation	Parameter definition	Value	95% C.I.	Units
r_0	Division rate of LT-HSCs	0.0107	(0.0084, 0.014)	days^{-1}
r_1	Division rate of ST-HSCs	0.067	(0.021, 0.10)	days^{-1}
r_2	Division rate of MPPs	0.136	(0.066, 0.95)	days^{-1}
$\bar{p}_0$	Self-renewal probability of LT-HSCs	0.5		1
$\bar{p}_1$	Self-renewal probability of ST-HSCs	0.473	(0.40, 0.48)	1
$\bar{p}_2$	Self-renewal probability of MPPs	0.416	(0.323, 0.49)	1
$d_3^{(1)}$	Removal rate of CMPs	0.034	(0.017,0.22)	days^{-1}
$d_3^{(2)}$	Removal rate of CLPs	0.007	(0.005,0.017)	days^{-1}
$\bar{x}_0$	Equilibrium number of LT-HSCs	17,000*		cells

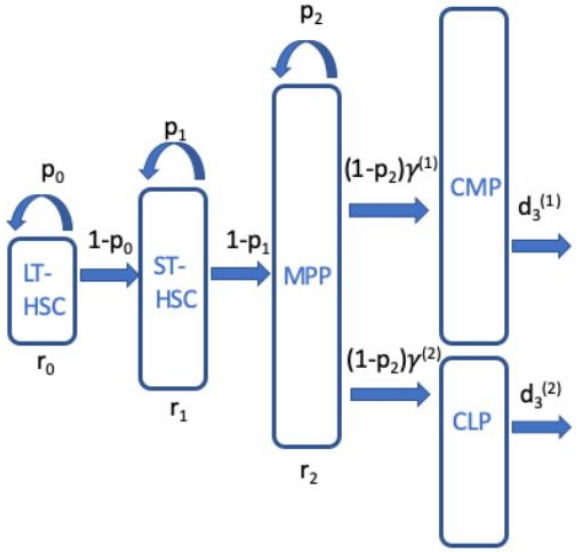
Introduce mutants:

Under what conditions do mutants invade and when do they fail?





Notation	Parameter definition	Value	95% C.I.	Units
r_0	Division rate of LT-HSCs	0.0107	(0.0084, 0.014)	$days^{-1}$
r_1	Division rate of ST-HSCs	0.067	(0.021, 0.10)	$days^{-1}$
r_2	Division rate of MPPs	0.136	(0.066, 0.95)	$days^{-1}$
$\bar{p}_0$	Self-renewal probability of LT-HSCs	0.5		1
$\bar{p}_1$	Self-renewal probability of ST-HSCs	0.473	(0.40, 0.48)	1
$\bar{p}_2$	Self-renewal probability of MPPs	0.416	(0.323, 0.49)	1
$d_3^{(1)}$	Removal rate of CMPs	0.034	(0.017,0.22)	$days^{-1}$
$d_3^{(2)}$	Removal rate of CLPs	0.007	(0.005,0.017)	$days^{-1}$
$\bar{x}_0$	Equilibrium number of LT-HSCs	17,000*		cells



$$
\begin{aligned}
\frac{dx_0}{dt} &= r_0 x_0 (2p_0 - 1), \\
\frac{dx_1}{dt} &= 2r_0 x_0 (1 - p_0) + r_1 x_1 (2p_1 - 1), \\
\frac{dx_2}{dt} &= 2r_1 x_1 (1 - p_1) + r_2 x_2 (2p_2 - 1), \\
\frac{dx_3^{(1)}}{dt} &= 2r_2 x_2 (1 - p_2)\gamma^{(1)} - d_3^{(1)} x_3^{(1)}, \\
\frac{dx_3^{(2)}}{dt} &= 2r_2 x_2 (1 - p_2)\gamma^{(2)} - d_3^{(2)} x_3^{(2)},
\end{aligned}
$$

$$
p_i = p_i(x_0, x_1, x_2, x_3^{(1)}, x_3^{(2)}), \quad 0 \le i \le 2.
$$

Evolution

Wild-type cell populations

$$
\begin{aligned}
\frac{dx_0}{dt} &= r_0 x_0 (2p_0 - 1), \\
\frac{dx_1}{dt} &= 2r_0 x_0 (1 - p_0) + r_1 x_1 (2p_1 - 1), \\
\frac{dx_2}{dt} &= 2r_1 x_1 (1 - p_1) + r_2 x_2 (2p_2 - 1), \\
\frac{dx_3^{(1)}}{dt} &= 2r_2 x_2 (1 - p_2)\gamma^{(1)} - d_3^{(1)} x_3^{(1)}, \\
\frac{dx_3^{(2)}}{dt} &= 2r_2 x_2 (1 - p_2)\gamma^{(2)} - d_3^{(2)} x_3^{(2)},
\end{aligned}
$$

Mutant cell populations

$$
\begin{aligned}
\frac{dy_0}{dt} &= r_0 y_0 (2p_0^{(m)} - 1), \\
\frac{dy_1}{dt} &= 2r_0 y_0 (1 - p_0^{(m)}) + r_1 y_1 (2p_1^{(m)} - 1), \\
\frac{dy_2}{dt} &= 2r_1 y_1 (1 - p_1^{(m)}) + r_2 y_2 (2p_2^{(m)} - 1), \\
\frac{dy_3^{(1)}}{dt} &= 2r_2 y_2 (1 - p_2^{(m)})\gamma^{(1)} - d_3^{(1)} y_3^{(1)}, \\
\frac{dy_3^{(2)}}{dt} &= 2r_2 y_2 (1 - p_2^{(m)})\gamma^{(2)} - d_3^{(2)} y_3^{(2)}
\end{aligned}
$$

Evolution - Modeling Mutant Spread

Wild-type cell populations

$$\frac{dx_0}{dt} = r_0 x_0 (2p_0 - 1),$$
$$\frac{dx_1}{dt} = 2r_0 x_0 (1 - p_0) + r_1 x_1 (2p_1 - 1),$$
$$\frac{dx_2}{dt} = 2r_1 x_1 (1 - p_1) + r_2 x_2 (2p_2 - 1),$$
$$\frac{dx_3^{(1)}}{dt} = 2r_2 x_2 (1 - p_2)\gamma^{(1)} - d_3^{(1)} x_3^{(1)},$$
$$\frac{dx_3^{(2)}}{dt} = 2r_2 x_2 (1 - p_2)\gamma^{(2)} - d_3^{(2)} x_3^{(2)},$$

Mutant cell populations

$$\frac{dy_0}{dt} = r_0 y_0 (2p_0^{(m)} - 1),$$
$$\frac{dy_1}{dt} = 2r_0 y_0 (1 - p_0^{(m)}) + r_1 y_1 (2p_1^{(m)} - 1),$$
$$\frac{dy_2}{dt} = 2r_1 y_1 (1 - p_1^{(m)}) + r_2 y_2 (2p_2^{(m)} - 1),$$
$$\frac{dy_3^{(1)}}{dt} = 2r_2 y_2 (1 - p_2^{(m)})\gamma^{(1)} - d_3^{(1)} y_3^{(1)},$$
$$\frac{dy_3^{(2)}}{dt} = 2r_2 y_2 (1 - p_2^{(m)})\gamma^{(2)} - d_3^{(2)} y_3^{(2)}$$

Competition through shared feedback:

$p_0 = c_0/(h_0 (x_0 + y_0) + 1)$

$p_0^{(m)} = c_0^{(m)}/(h_0 (x_0 + y_0) + 1)$

$p_1 = c_1/(h_1 (x_1 + y_1) + 1)$

$p_1^{(m)} = c_1^{(m)}/(h_1 (x_1 + y_1) + 1)$

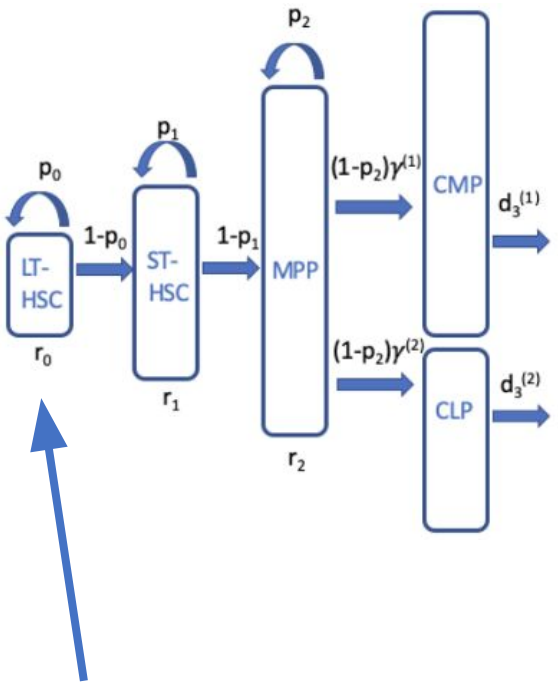
$p_2 = c_2/(h_2 (x_2 + y_{02}) + 1)$

$p_2^{(m)} = c_2^{(m)}/(h_2 (x_2 + y_2) + 1)$

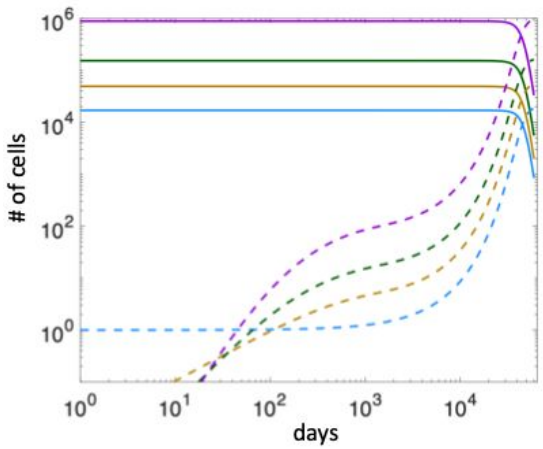
Advantageous mutants:

$$p_i^{(m)} = (1 + s)p_i > p_i$$

Insights from evolutionary computer simulations



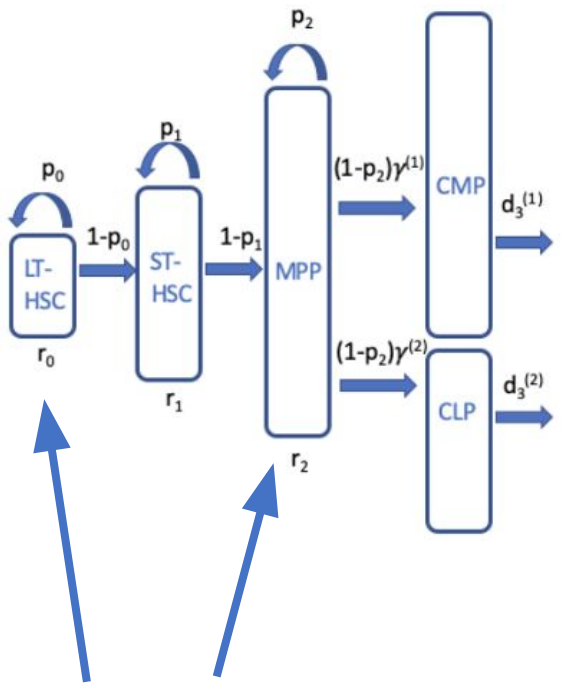
Mutant arises in **LT stem cells** (unlikely)
2% advantage



Where does the mutant arise?

Komarova, Rignot, Fleischman & Wodarz (2024) PNAS

Insights from evolutionary computer simulations



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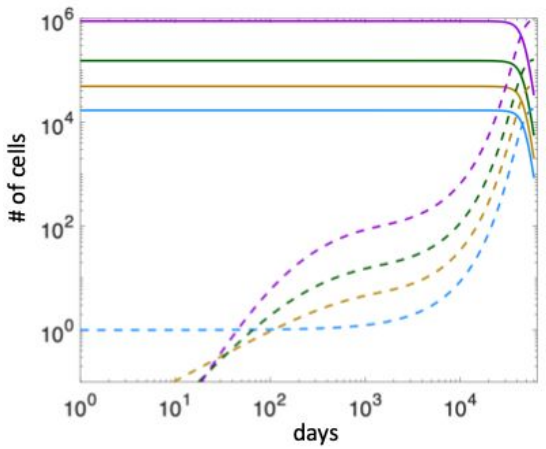
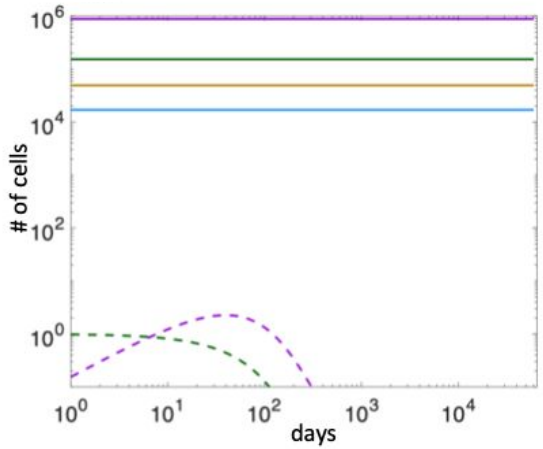
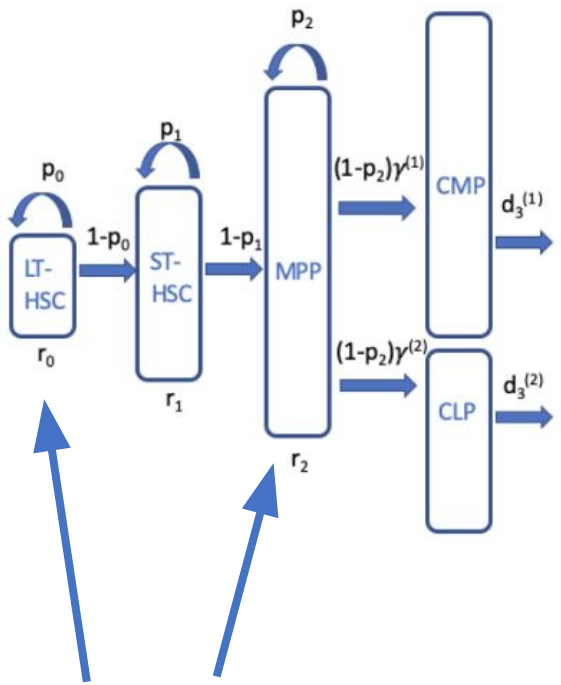


Mutant arises in **progenitors** (likely)
2% advantage

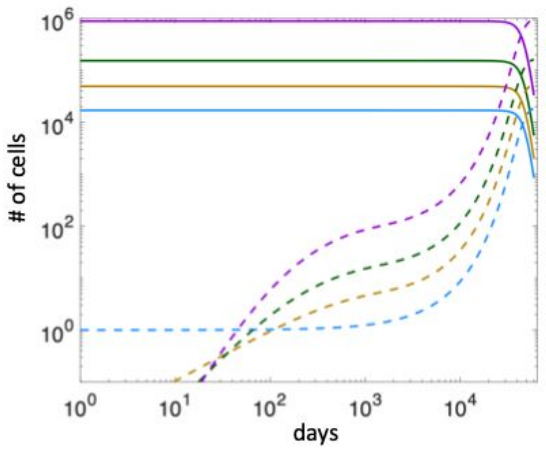


Insights from evolutionary computer simulations

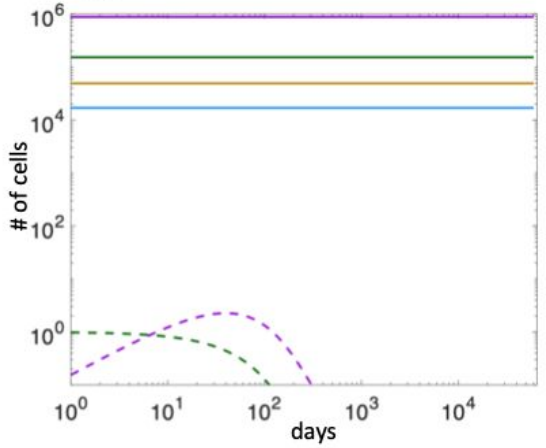


Where does the mutant arise?

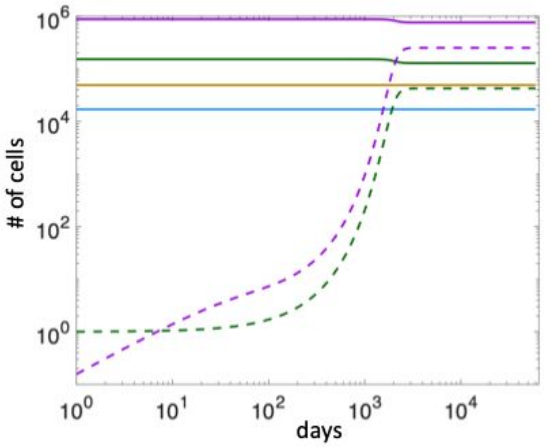
Mutant arises in **LT stem cells** (unlikely)
2% advantage



Mutant arises in **progenitors** (likely)
2% advantage



Mutant arises in **progenitors**
25% advantage

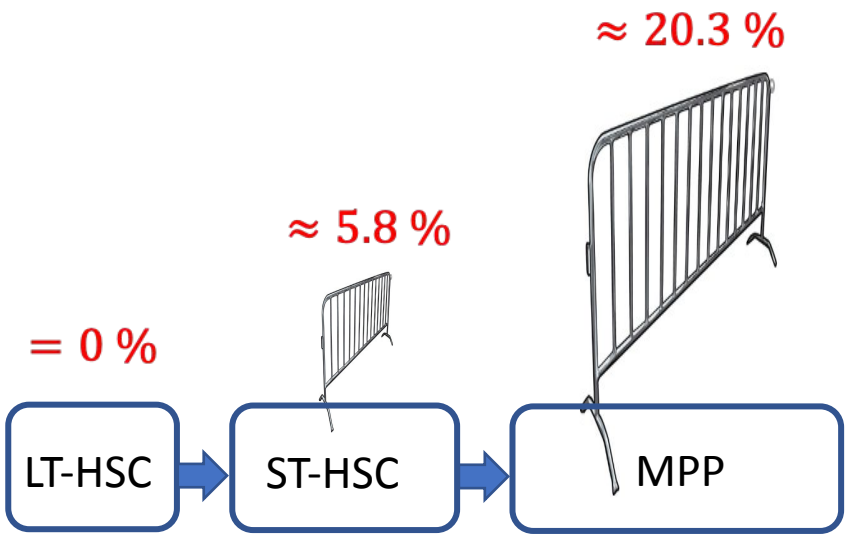


Mutants matter only when they arise in the downstream, progenitor compartments

But there, successful invasion requires a massive mutant advantage

⇒ Barrier to mutant invasion

Hematopoietic hierarchy protects against mutations



mutant production unlikely

mutant production more likely

mutant production most likely

Mutant invasion barrier:

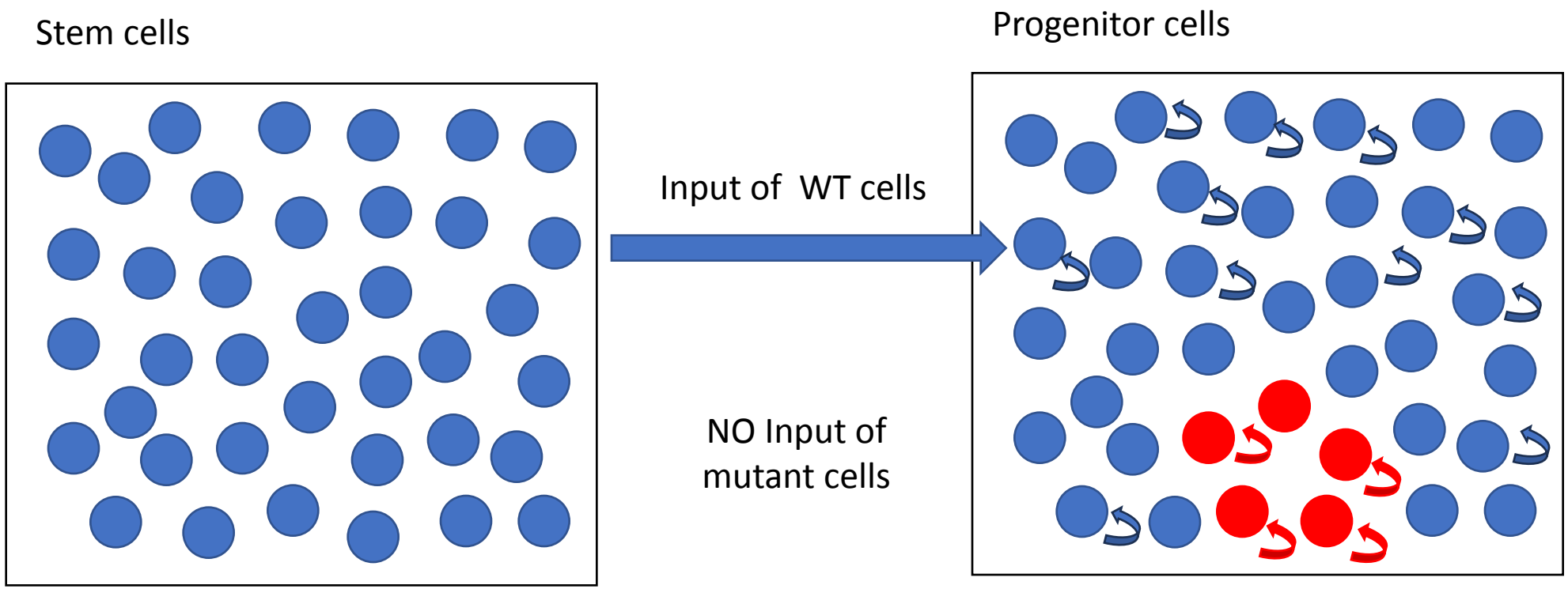
$$s > s_c = \frac{1}{2\bar{p}_i} - 1$$

Advantageous mutants:

$$p_i^{(m)} = (1+s)p_i > p_i$$

Evolutionary compromise between

- tissue amplification and
- invasion barrier

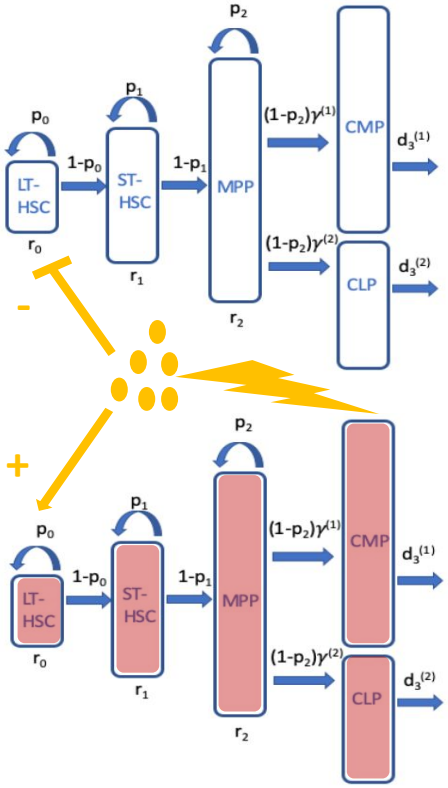


Fitness of cells in progenitor compartment:

WT cells: local division + input from upstream compartment

mutant cells: local division only
=> Hence advantage in division must be large to overcome WT fitness

What can facilitate mutant invasion?

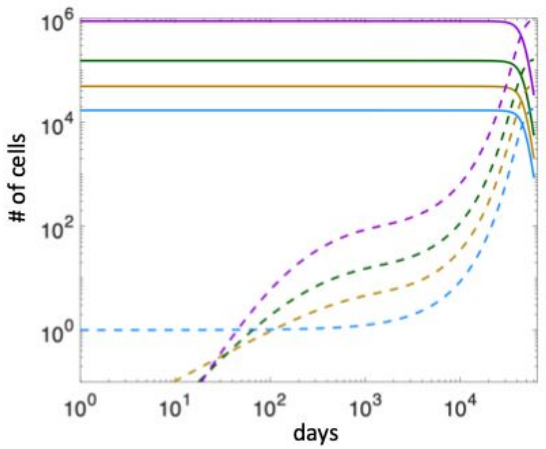


Mutants generate inflammation

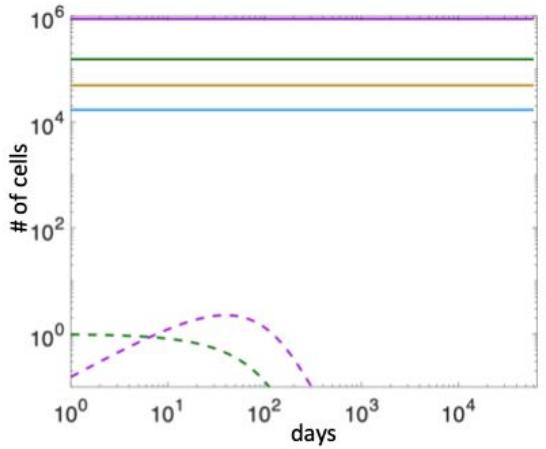
Inflammation creates environment that is beneficial for mutants

=> Evolutionary niche construction

Mutant arises in **LT stem cells** (unlikely)
2% advantage



Mutant arises in **progenitors** (likely)
2% advantage



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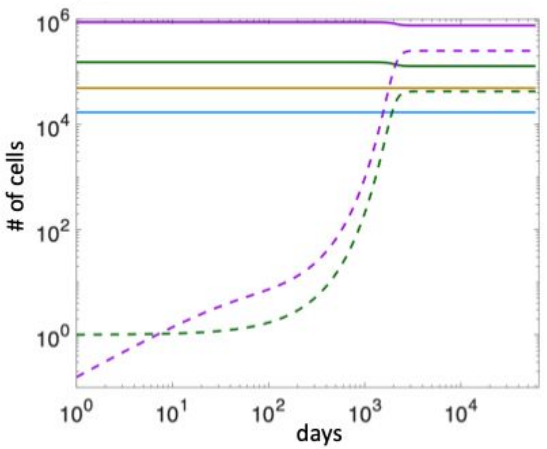
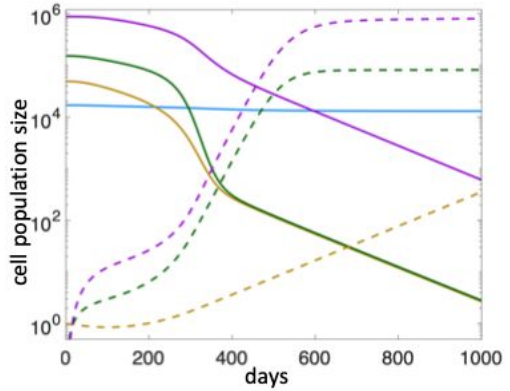
25% advantage

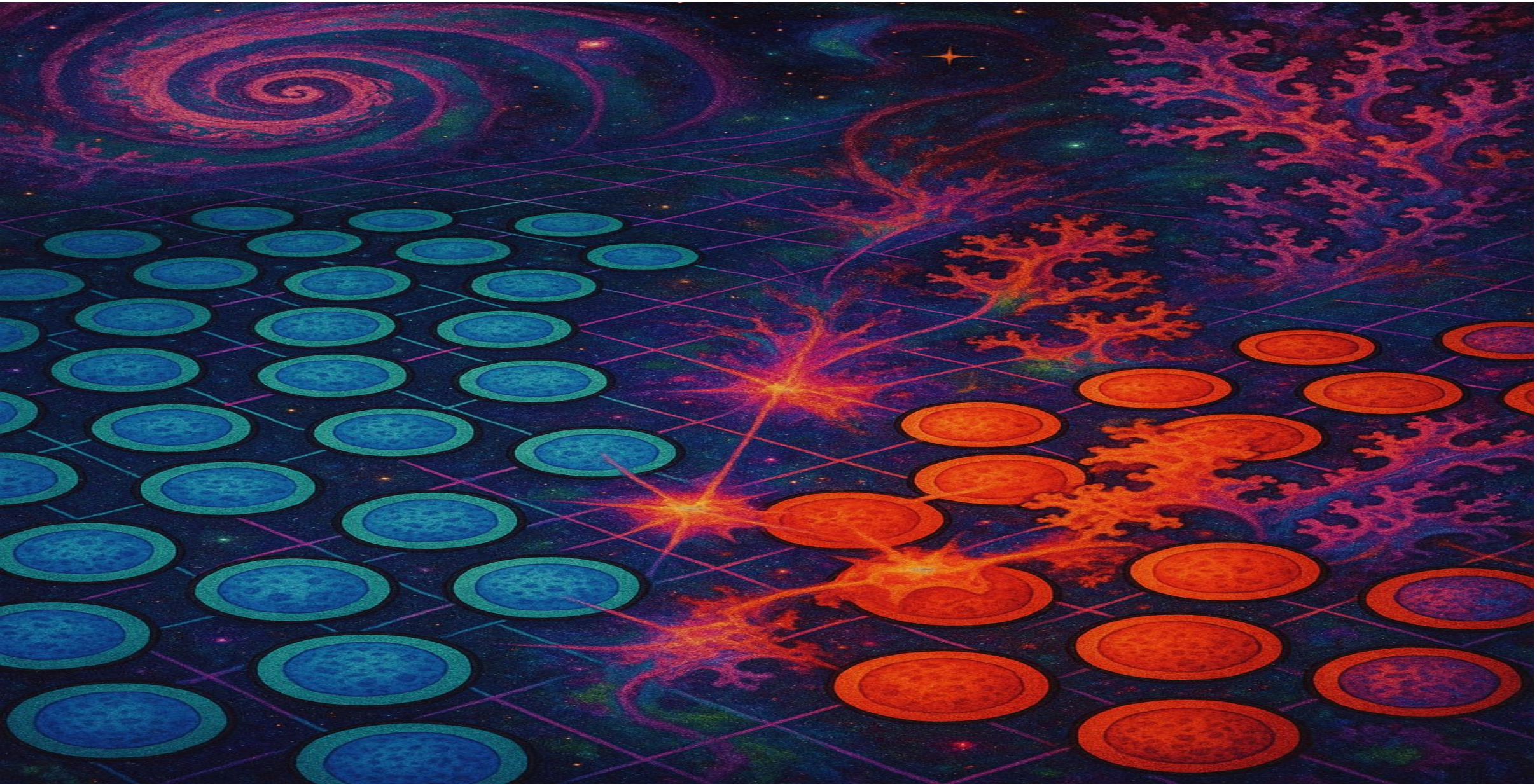


Mutant arises in progenitors
2% advantage



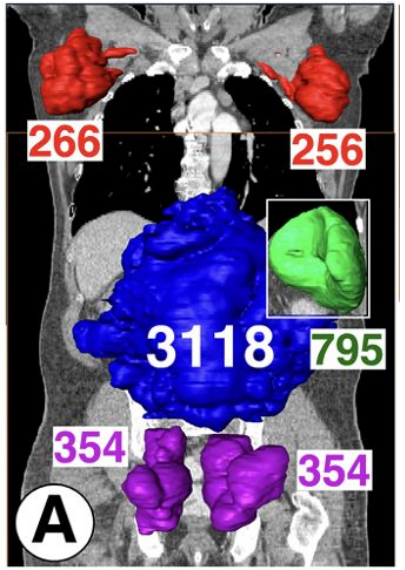
Fast mutant emergence

3. Cell evolution in spatially structured populations:

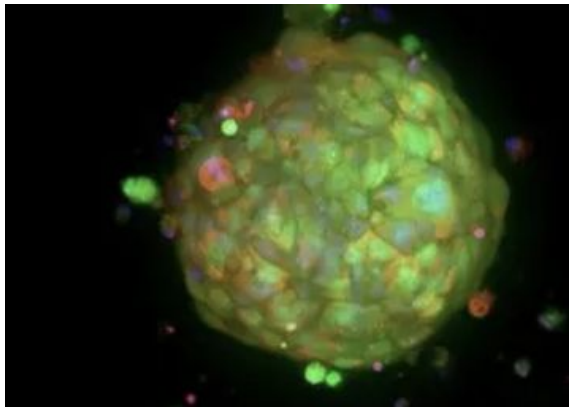


Everything is spatial

tumors arising in patients
are spatially structured



Lymph nodes packed
with leukemia cells



patient-derived tumor organoid

Some spatial modeling approaches

Partial Differential Equations (PDEs)

Continuous mathematical models using reaction-diffusion-taxis equations to describe cell populations and molecular concentrations across space and time.

- 📊 Continuous cell densities
- 🧱 Deterministic dynamics
- ⚡ Computationally efficient
- 📈 Analytical tractability

Agent-Based Models (ABMs) & Cellular Automata (CA)

Discrete models that simulate individual cells as autonomous agents with explicit behaviors and local interactions.

- 🔲 Lattice-based CA (fixed grid)
- 🎯 Off-lattice ABM (free movement)
- 🎲 Stochastic cell behaviors
- 👥 Cell heterogeneity

Cellular Potts Model (CPM)

Lattice-based, energy-minimization approach where cells are extended objects with explicit shapes spanning multiple lattice sites.

- 🔷 Multi-pixel cell representation
- 🧲 Adhesion & surface tension
- 📐 Explicit cell shapes & volumes
- 🔄 Monte Carlo dynamics

Lattice Gas Cellular Automata (LGCA)

Multiple cells can occupy a single lattice site, tracking cell movement through channels between sites rather than individual trajectories.

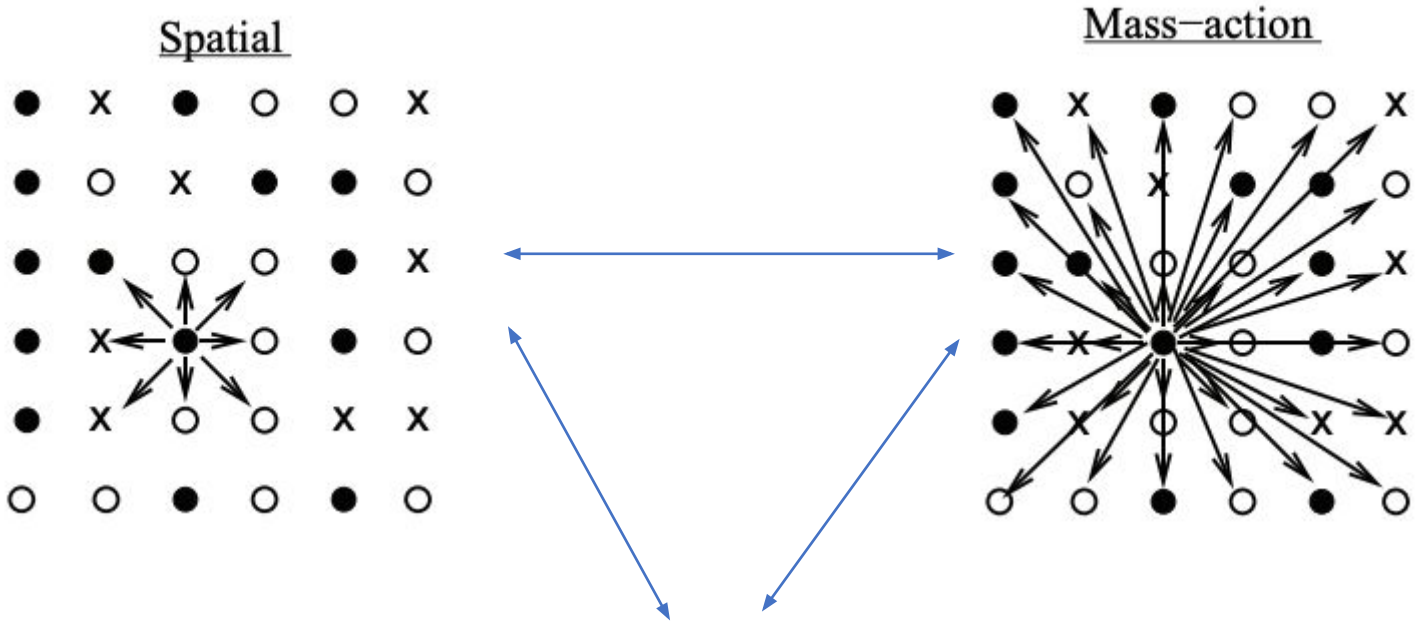
- 📦 Multiple cells per site
- ⚙️ Statistical mechanics framework
- ⏱️ Large-scale simulations
- 🔗 Links to continuum models

Hybrid & Multiscale Models

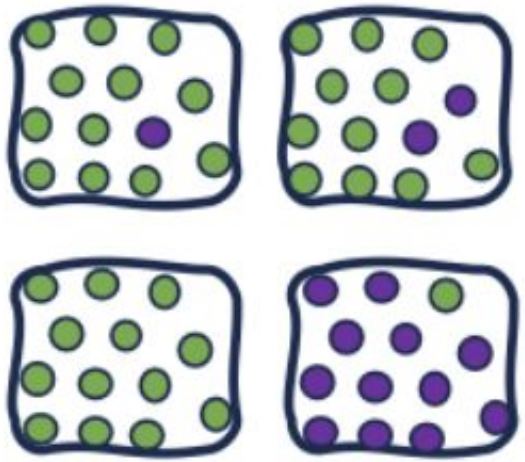
Combine multiple modeling approaches to span spatial and temporal scales—discrete cells coupled with continuous chemical fields.

- 🔀 PDE + ABM coupling
- 🧬 Intracellular signaling networks
- 🌐 Tissue-level phenomena
- 💊 Drug pharmacokinetics

Mixed vs ABM vs deme models – similarities and differences



Demes, e.g. lymph nodes



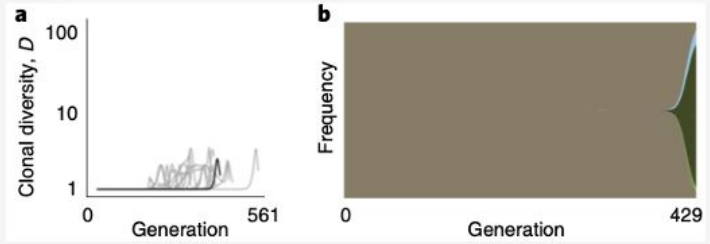
Study examples that show important roles of space for tumor evolution

Spatial structure governs tumor evolution – Noble et al (2022) Nat Eco. Evol.

1. Non-Spatial

Mode: Rapid Clonal Expansion

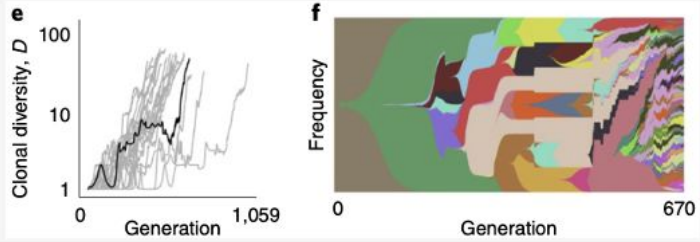
- Well-mixed population
- Fast selective sweeps
- Few dominant clones
- Low diversity (D < 10/3)



2. Gland Fission (Adenoma)

Mode: Progressive Diversification

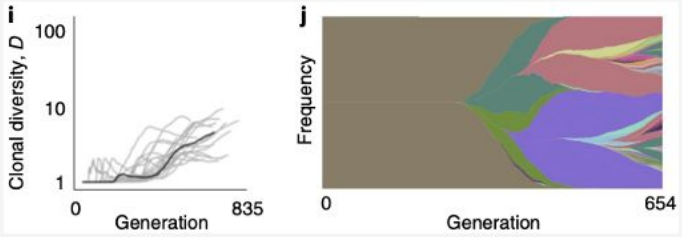
- Growth by bifurcation
- Localized sweeps
- Highly branched tree
- High diversity (D > 20)



3. Invasive Glandular

Mode: Branching Evolution

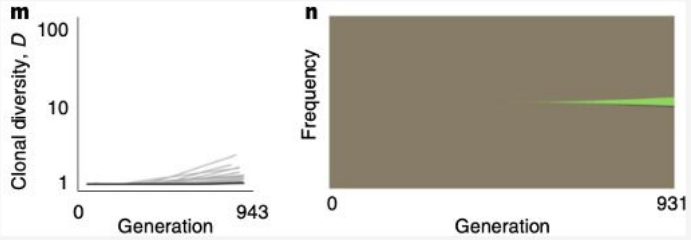
- Invades normal tissue
- Clonal interference
- Multiple long branches
- Moderate diversity (3 < D < 20)



4. Boundary Growth

Mode: Effectively Neutral

- Proliferation at edge only
- Genetic drift dominates
- Star-shaped tree
- Low drivers per cell (n < 2)



Noble et al., Nat Ecol Evol 6:207-217 (2022)

Boundary-Driven Growth in Hepatocellular Carcinoma

Lewinsohn et al 2023, Nature Ecology & Evolution

Tumor Architecture

🔴 **Edge:** High division rate

🔵 **Center:** Low division rate

🎯 Key Finding

Tumor 1

6.4×

faster division on edge vs center

Tumor 2

2.8×

faster division on edge vs center

📊 Data Used

- Multi-region sequencing from 2 HCC tumors
- 9-16 spatially-labeled biopsies per tumor
- Genetic sequences + spatial locations (edge/center)
- SDevo model links mutation rate to division rate

✓ Biological Interpretation

Boundary-driven growth confirmed in vivo:

- Cell divisions concentrated at tumor periphery
- Center cells division-limited (crowding, hypoxia, nutrient depletion)
- Spatial structure shapes tumor evolution

💡 **Conclusion: Clinical tumors exhibit strong boundary-driven growth with most proliferation occurring at the tumor surface, validating predictions from spatial models**

Lewinsohn et al., Nat Ecol Evol 7:581-596 (2023)

Spatial Sampling Determines Clonality Inference

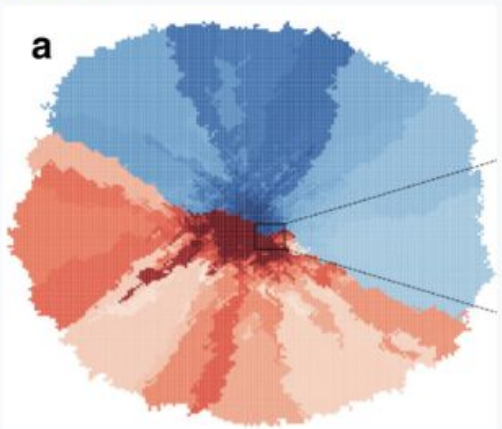
Opasic et al., BMC Cancer (2019)

Research Question: How many samples are needed to correctly identify truly clonal (truncal) mutations from spatially heterogeneous tumors?

📋 Methodology

1. Spatial Tumor Model (2D Lattice)

- Cells grow on 2D lattice
- Mutations create spatial heterogeneity
- First sub-clone (🟥) branches from ancestral (🟦)



2. Sampling & Analysis

- Take **n** biopsies (single-cell or bulk)
- Reconstruct mutational profiles
- 10,000 iterations per simulation
- Compare: random vs. pattern sampling

Key equation:

Probability of correct classification = $1 - f^n$

where f = proportion of largest sub-clone

🎯 Key Results

1. Samples Needed (98% confidence)

f = 0.1: ~2 samples ✓

f = 0.5: ~6 samples

f = 0.9: >38 samples

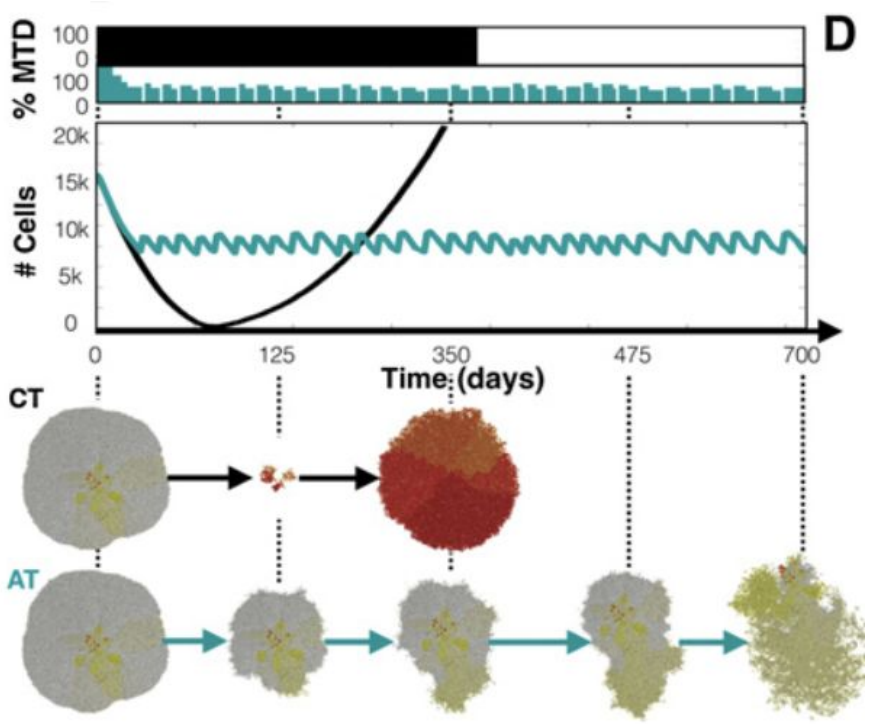
where f = proportion of largest sub-clone

2. Pattern Sampling > Random Sampling

Strategy: Sample from tumor periphery at equidistant locations (e.g., North, South, East, West positions)

Benefit: Maximizes spatial dispersion → increases probability of sampling different clonal regions → higher accuracy with fewer samples

Spatial structure can be important for the competition between resistant and sensitive cells



Convergence and Technologies

Cancer Research

Spatial Heterogeneity and Evolutionary Dynamics Modulate Time to Recurrence in Continuous and Adaptive Cancer Therapies

Jill A. Gallaher[1], Pedro M. Enriquez-Navas[2], Kimberly A. Luddy[2], Robert A. Gatenby[1], and Alexander R.A. Anderson[1]

nature COMMUNICATIONS

ARTICLE

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Excess of mutational jackpot events in expanding populations revealed by spatial Luria–Delbrück experiments

Diana Fusco[1,2], Matti Gralka[1], Jona Kayser[1,2], Alex Anderson[1] & Oskar Hallatschek[1,2]

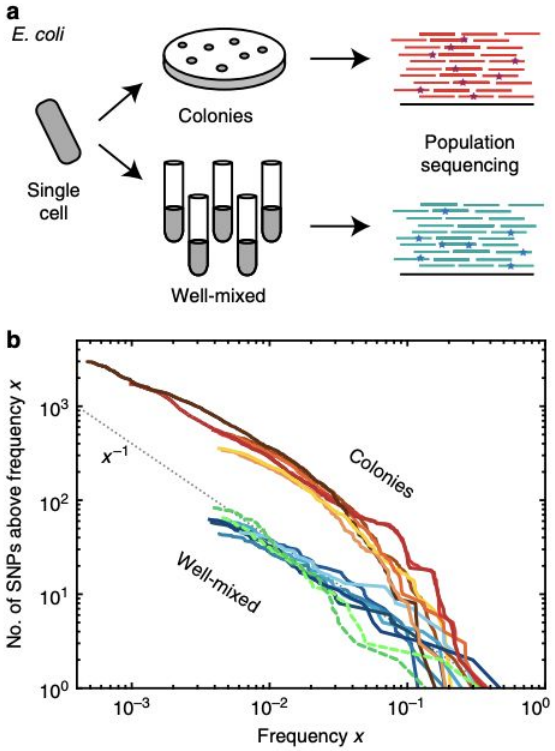
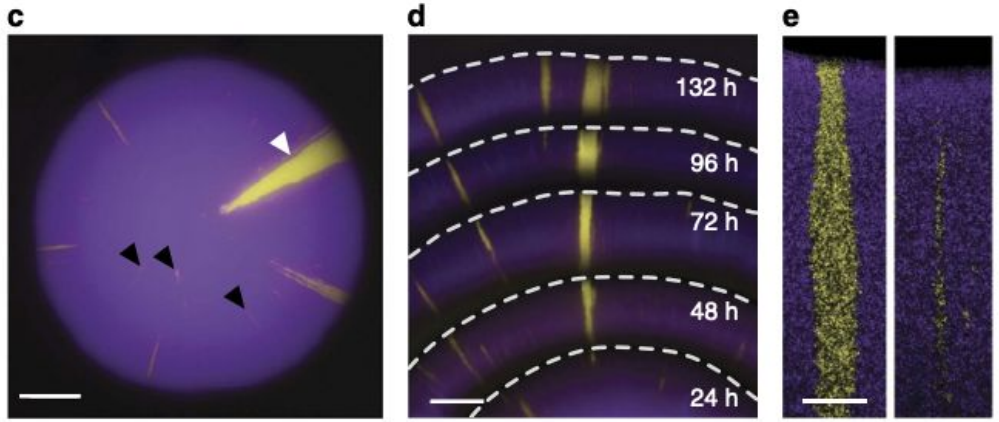
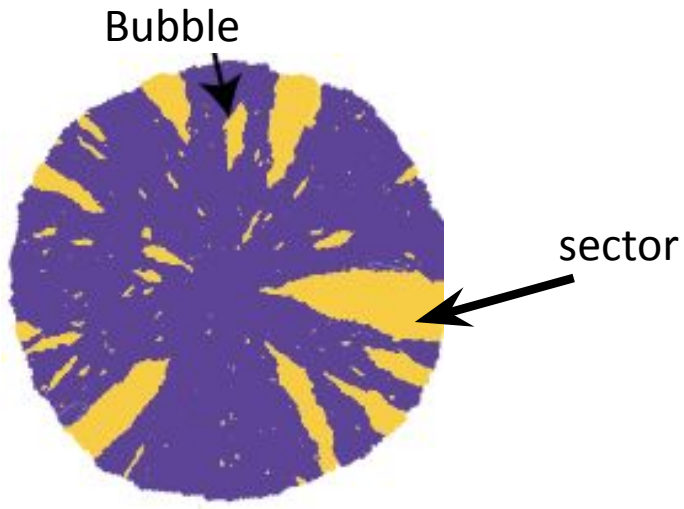


Figure 1 | Population sequencing reveals an excess of jackpot events in spatially growing populations. (**a**) Starting from few cells of a mutator

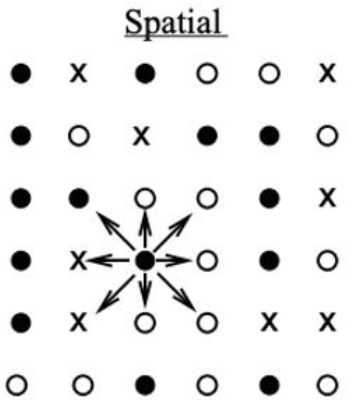
More mutants in spatially growing colonies compared to non-spatially growing colonies at the same population size



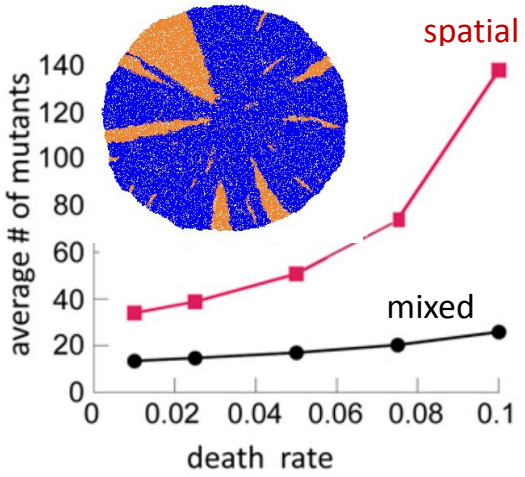


At population size N how many mutants? (crucial question for resistance evolution)

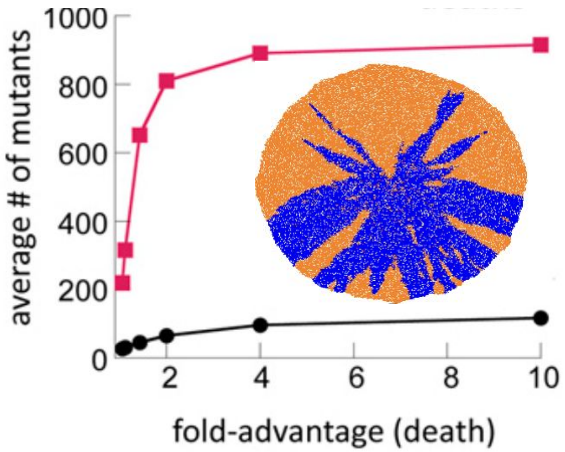
Wodarz & Komarova 2020, Genetics

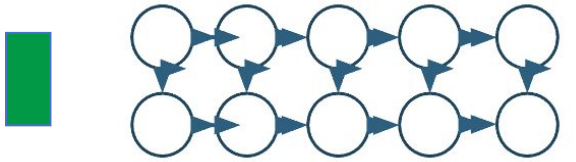


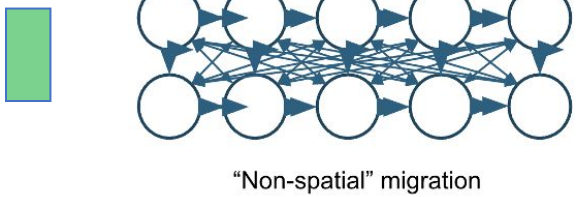
neutral mutants

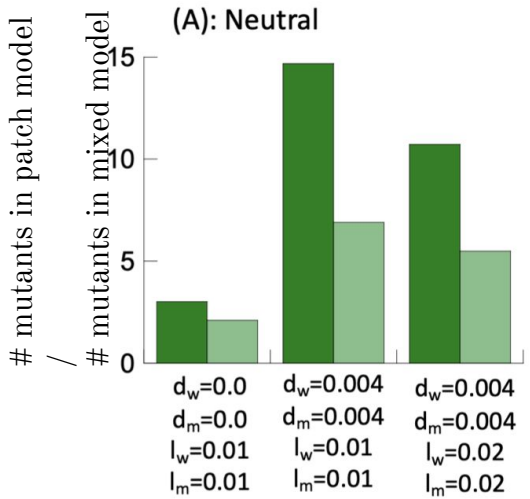


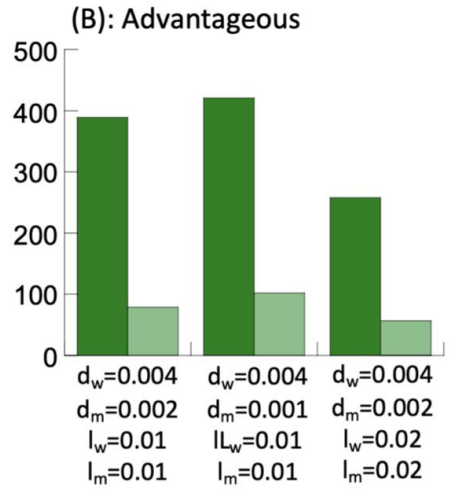
advantageous mutants



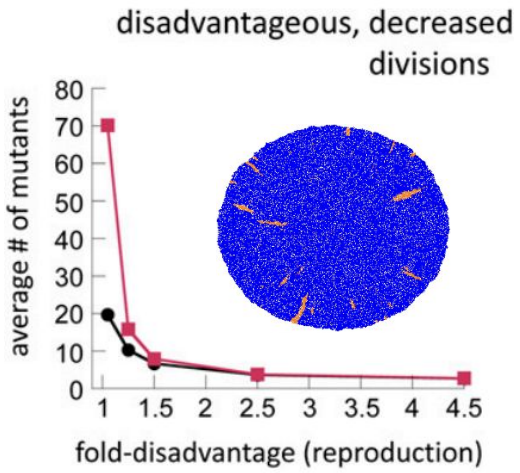


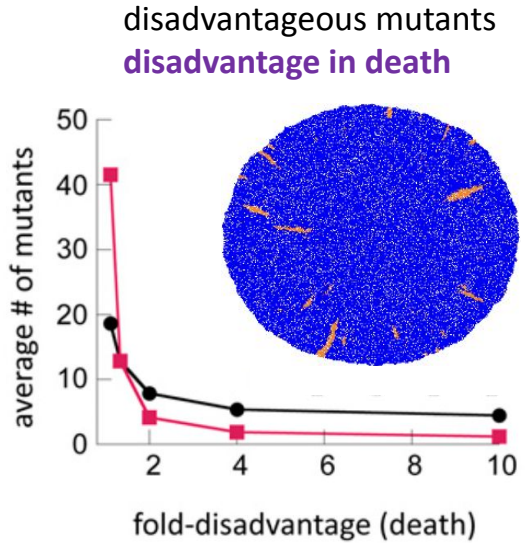


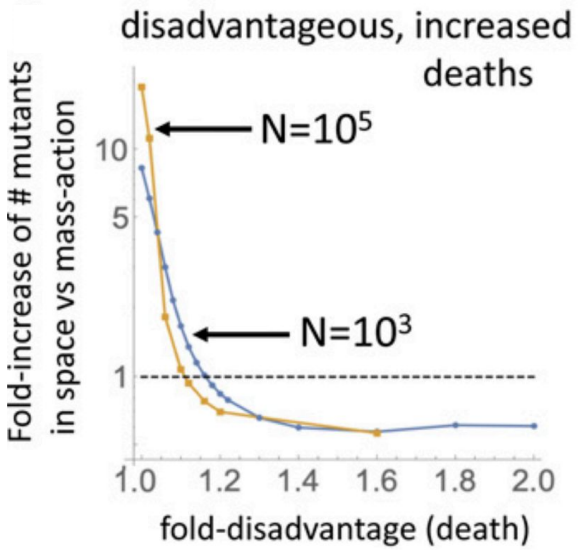




Complexity of Disadvantageous Mutants





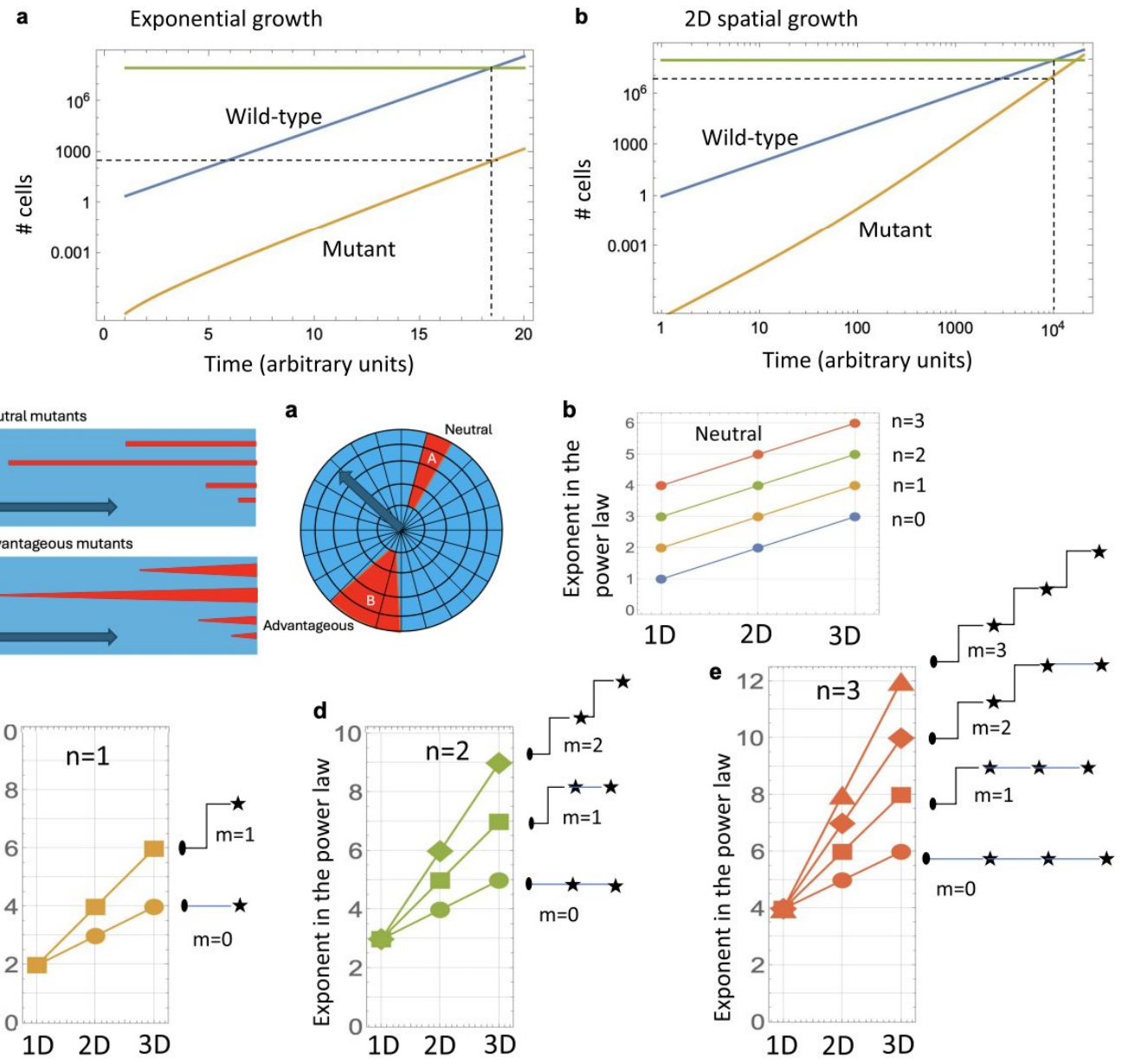


If mutant disadvantage is in less birth: more mutants in spatial compared to mixed system
If mutant disadvantage is in more death: less mutants in spatial compared to mixed system

Same patterns observed in

- ABM
- Deme model with **migration to nearest neighbors**
- Deme model with **non-spatial migration**

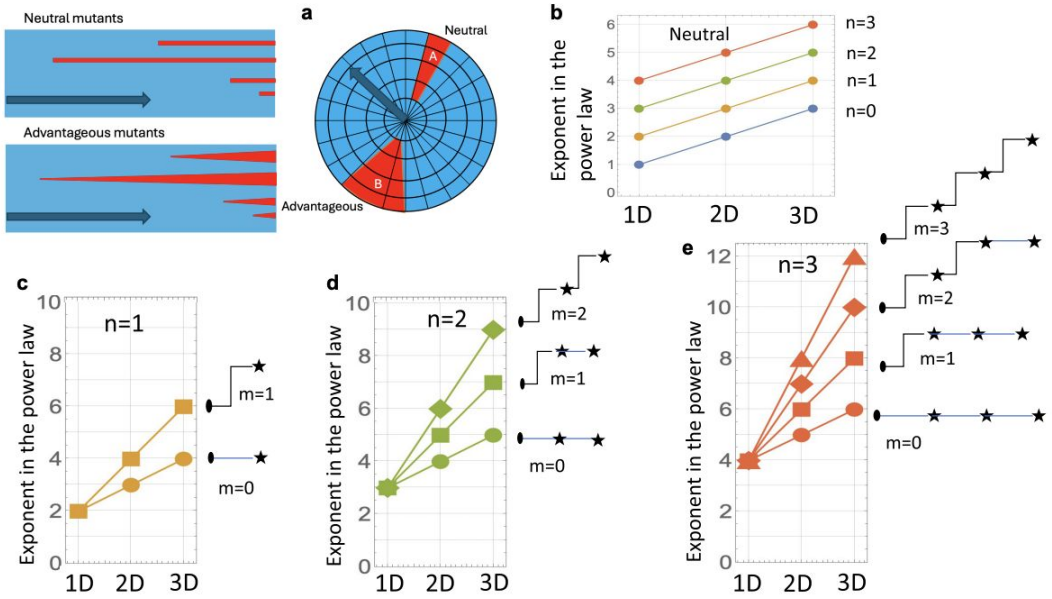
Scaling laws for n-hit mutants in 1, 2, and 3 dimensional spatial growth



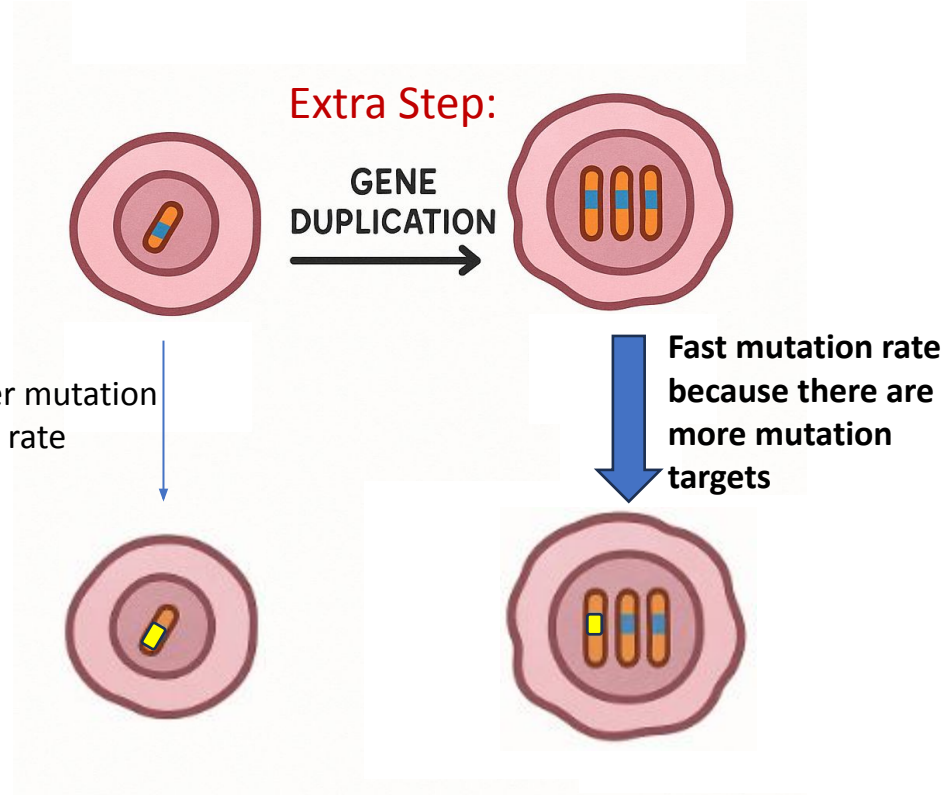
Komarova, Pritchard & Wodarz 2025, PNAS Nexus

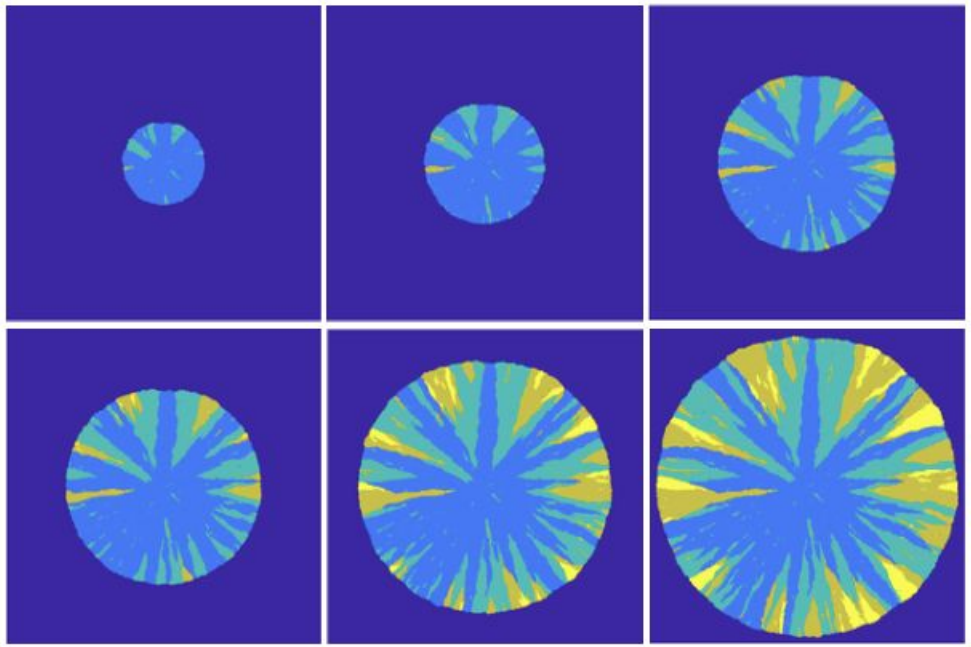
Why are mutant scaling laws useful?

- Tumors are large cell populations, up to 10^{12} or 10^{13} cells.
- Simulating growth to such sizes with stochastic ABMs to determine mutant burden is very slow
- With scaling laws, you can extrapolate mutant burden to large population sizes without the need to simulate up to these huge population sizes



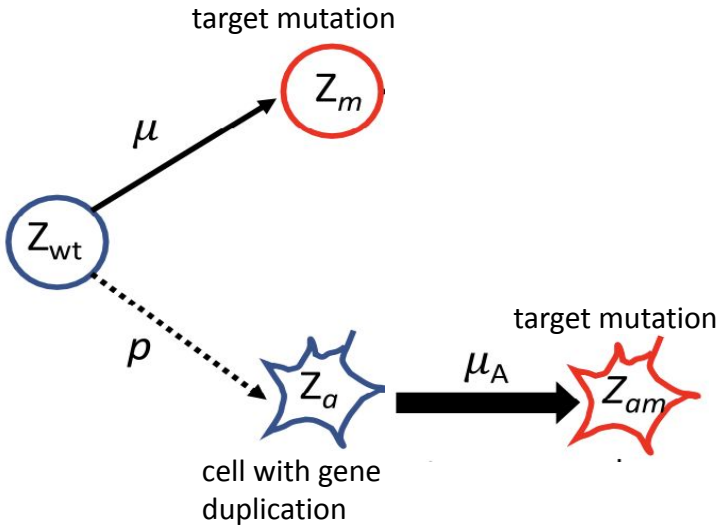
Application: Role of gene amplifications



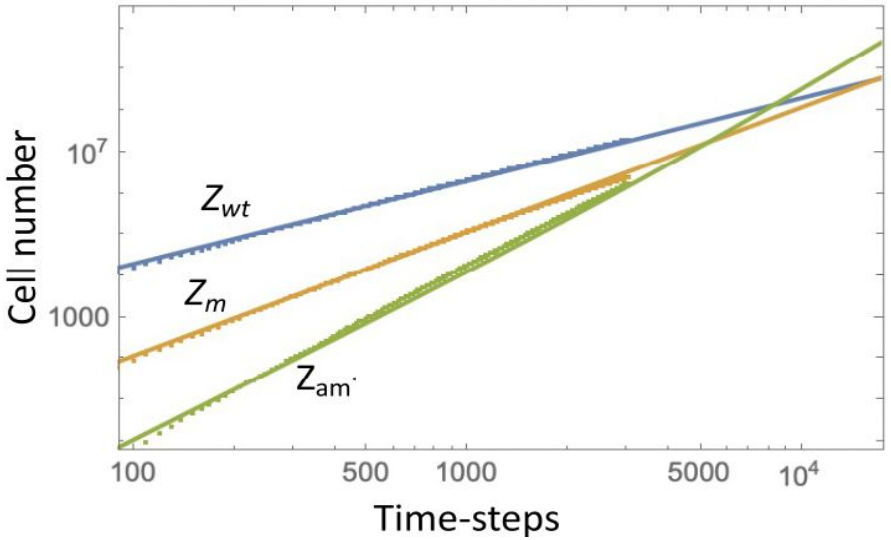


Komarova, Pritchard & Wodarz 2025, PNAS Nexus

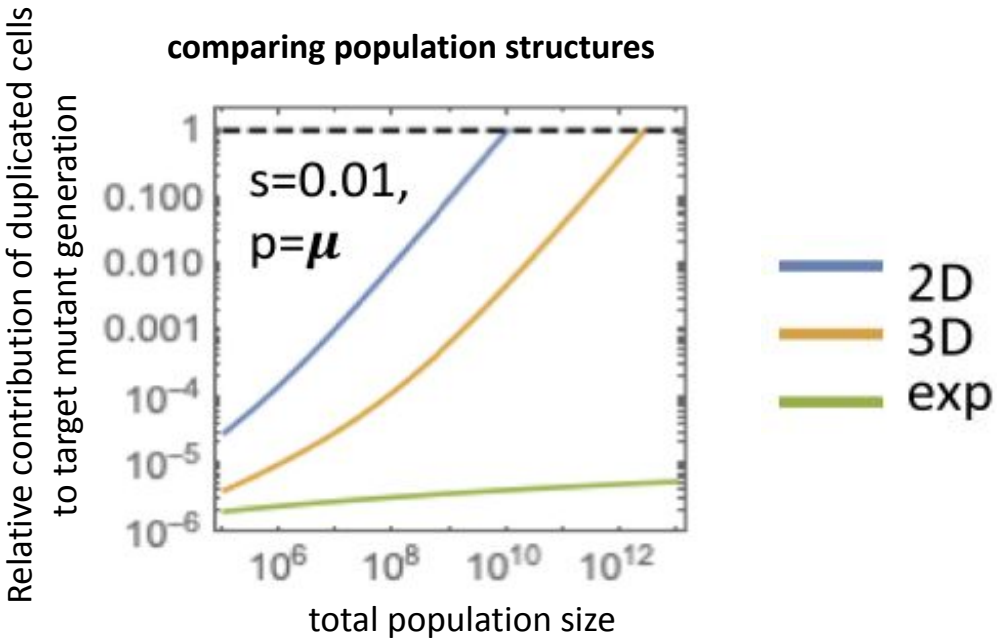
Spatial structure is required for cells with gene amplifications to contribute to mutant evolution



2D spatial simulation



comparing population structures



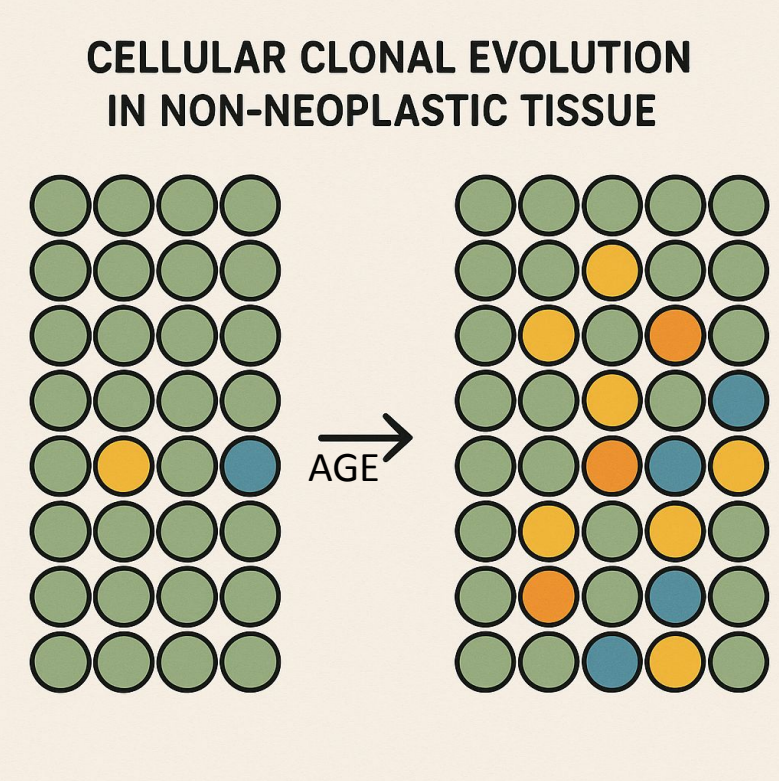
PNAS NEXUS

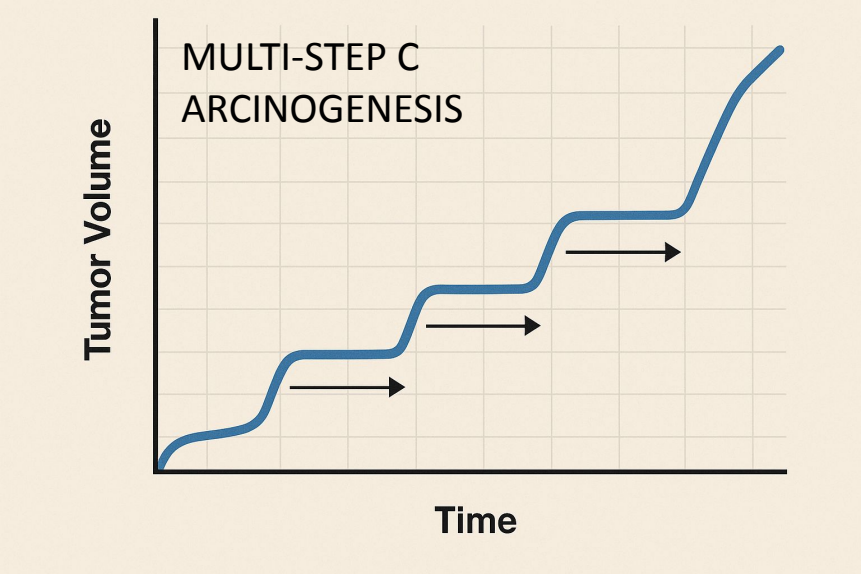
PNAS Nexus,
https://doi.org/10.1093/pn
Advance access publication 2

Efficient mathematical methodology to determine multistep mutant burden in spatially growing cell populations

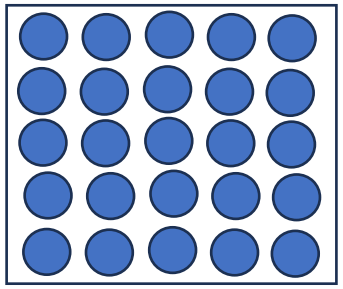
Natalia L. Komarova[a], Justin R. Pritchard[b] and Dominik Wodarz[c,*]

Spatial mutant evolution and selection at steady state



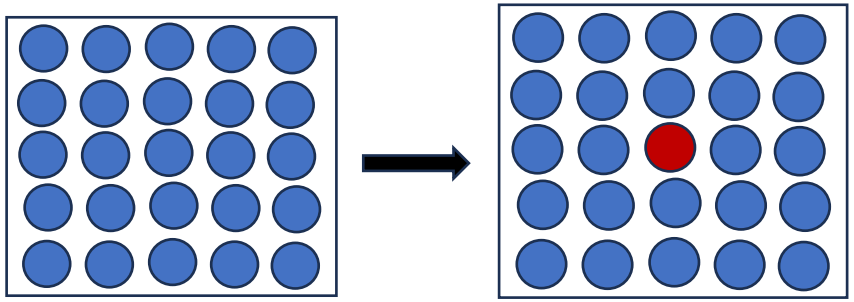


FIXATION PROBABILTY as a measure of fitness



WT population at equilibrium

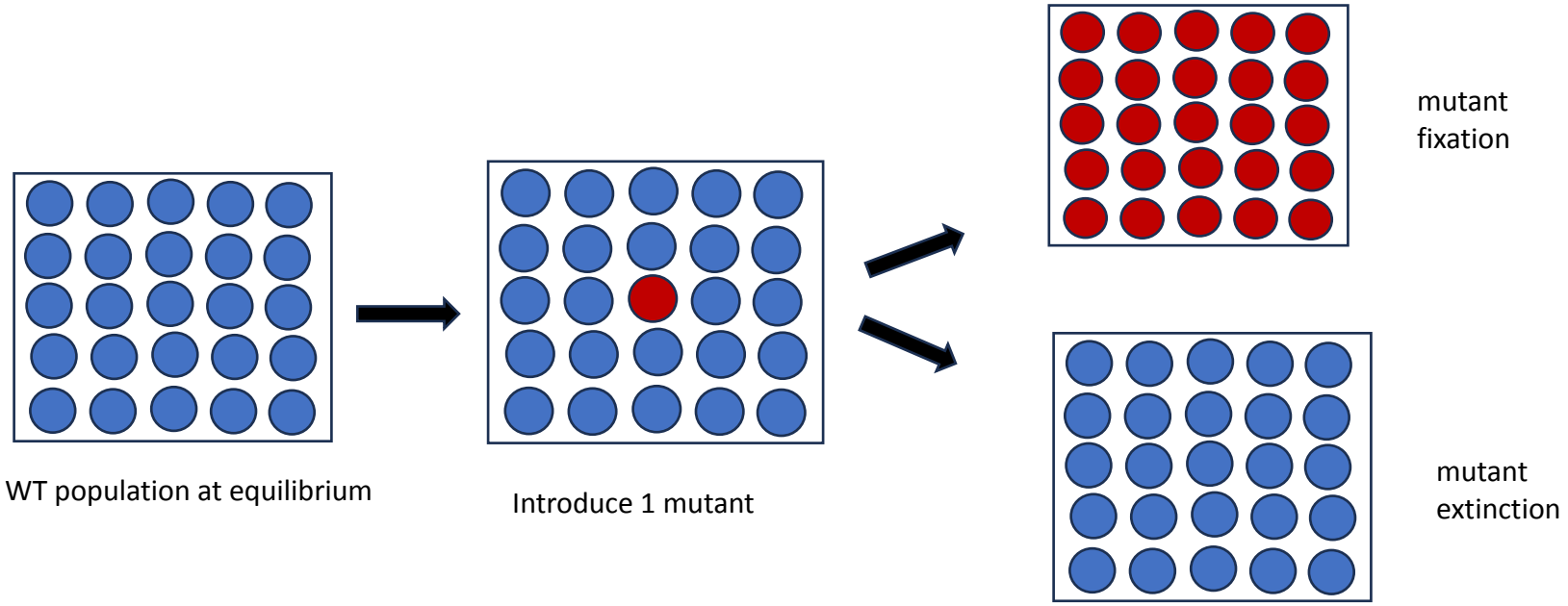
Fixation probability as a measure of fitness



WT population at equilibrium

Introduce 1 mutant

Fixation probability as a measure of fitness



WT population at equilibrium

Introduce 1 mutant

Mutants can be

- neutral
- disadvantageous
- advantageous

Fixation probability

p(fix) = 1/N

$$p(fix) = \frac{1-\left(\frac{1}{r}\right)^{i}}{1-\left(\frac{1}{r^{n}}\right)}$$

Moran process

Advantage or disadvantage typically expressed through the change of one parameter, such as a changed birth rate or a changed death rate

American Journal of Pathology, Vol. 142, No. 3, March 1993

Correlations Between Apoptotic and Proliferative Indices in Malignant Non-Hodgkin's Lymphomas

Faster cell division rates often correlate with faster cell death rates

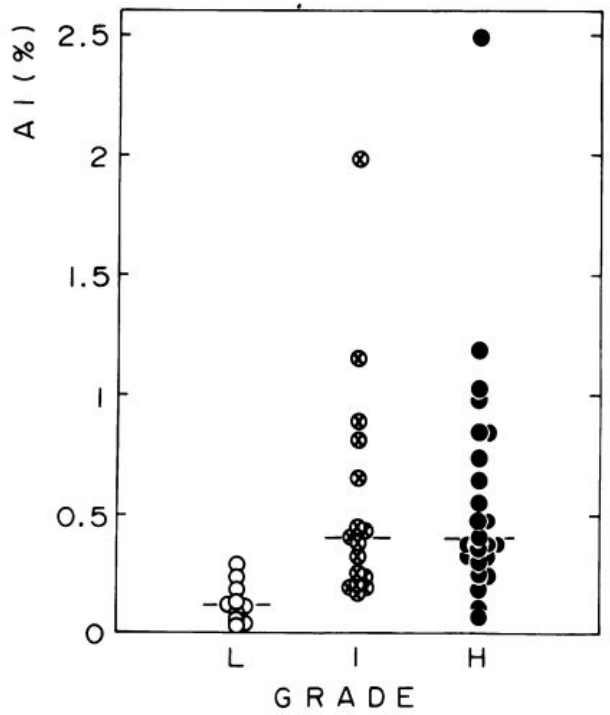


Figure 2. *Mean apoptotic indices per case (AI) of low (L, open circles), intermediate (I, crossed circles), and high (H, closed circles) malignancy grade NHLs according to the Working Formulation.[20] Bars represent median AIs per group.*

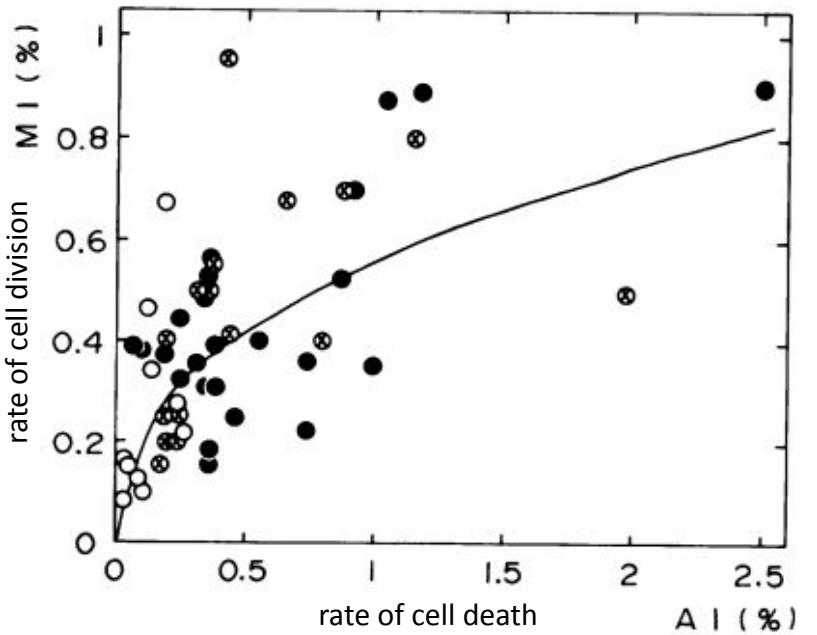


Figure 3. *Mean mitotic indices per case (MI) plotted against AIs of NHLs. Regression analysis: nonlinear model, $y=ax^b$. The correlation coefficient (CC) is 0.659. See also legend to Figure 2.*

The concept of Quasi-Neutral Mutants

JOURNAL ARTICLE

Some Consequences of Demographic Stochasticity in Population Genetics

Todd L Parsons, Christopher Quince, Joshua B Plotkin

Genetics, Volume 185, Issue 4, 1 August 2010, Pages 1345–1354,
https://doi.org/10.1534/genetics.110.115030

reproduction rate of mutant and WT

$$r_m = \tau r_w$$

death rate of mutant and WT

$$d_m = \tau\, d_w$$

MUTANT AND WT HAVE IDENTICAL LIFE-TIME REPRODUCTIVE SUCCESS

$\tau > 1$: higher turnover mutant

$\tau < 1$: lower turnover mutant

	reproduction rate r	death rate d	life-time repr. output r/d
wt	0.1	0.01	10
mutant	1.0	0.1	10

Fixation probability of quasi-neutral mutants in ***well-mixed populations***

WT cells $\frac{dx}{dt} = r_w x\left(1 - \frac{x+y}{K}\right) - d_w x$

Mutant cells $\frac{dy}{dt} = \tau\ r_w y\left(1 - \frac{x+y}{K}\right) - \tau\ d_w y$

stochastic process

Fixation probability of quasi-neutral mutants in ***well-mixed populations***

WT cells $\frac{dx}{dt} = r_w x\left(1 - \frac{x+y}{K}\right) - d_w x$

Mutant cells $\frac{dy}{dt} = \tau\ r_w y\left(1 - \frac{x+y}{K}\right) - \tau\ d_w y$

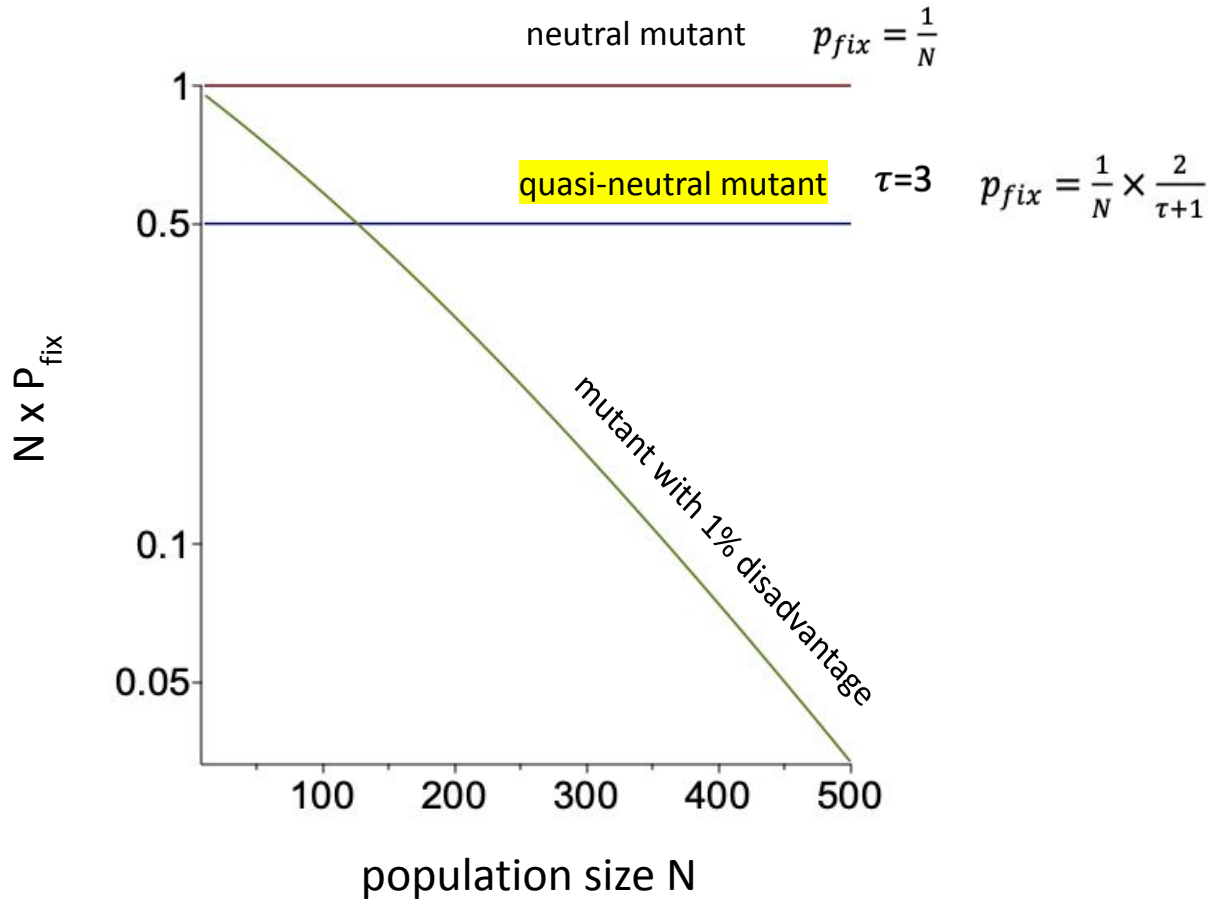
stochastic process

$$p_{fix} = \frac{1}{N} \times \frac{2}{\tau+1}$$

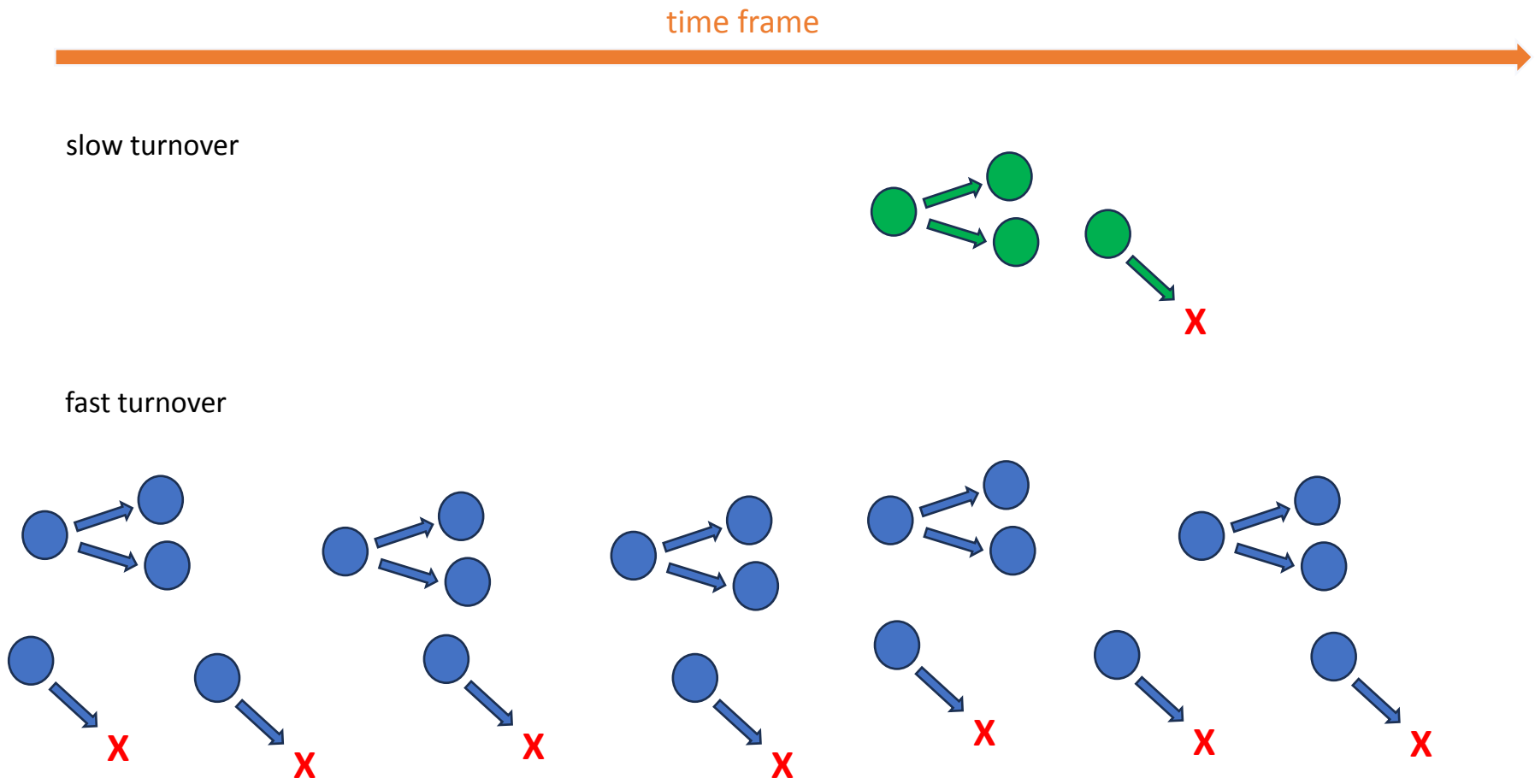
rather than

$$p_{fix} = \frac{1}{N}$$

Fixation probability of quasi-neutral mutants in ***well-mixed populations***



Reason for deviation from neutrality

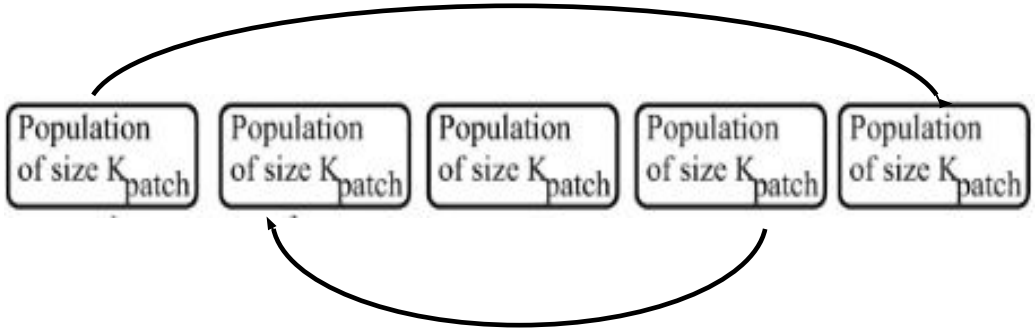


Spatial Dynamics

Dynamics of quasi-neutral mutants in **deme structured** populations

Komarova & Wodarz 2025, Nature Communications

Deme / patch model with non-spatial migration



In each deme, Gillespie simulations are performed for the ODE mode:

WT cells $$\frac{dx}{dt} = r_w x\left(1 - \frac{x+y}{K}\right) - d_w x$$

Mutant cells $$\frac{dy}{dt} = \tau\ r_w y\left(1 - \frac{x+y}{K}\right) - \tau\ d_w y$$

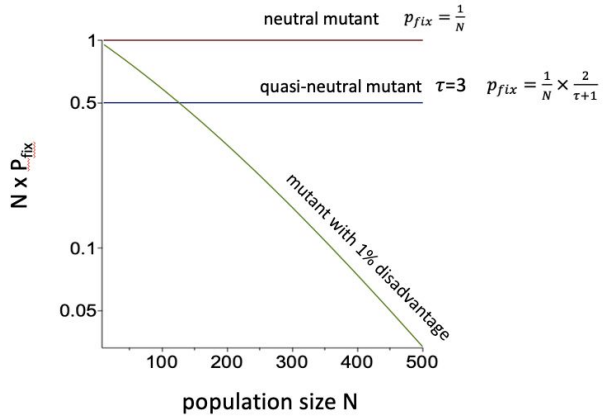
Reproduction can lead to the offspring being placed into a randomly chosen deme with a certain probability.
i.e. migration is coupled to reproduction.

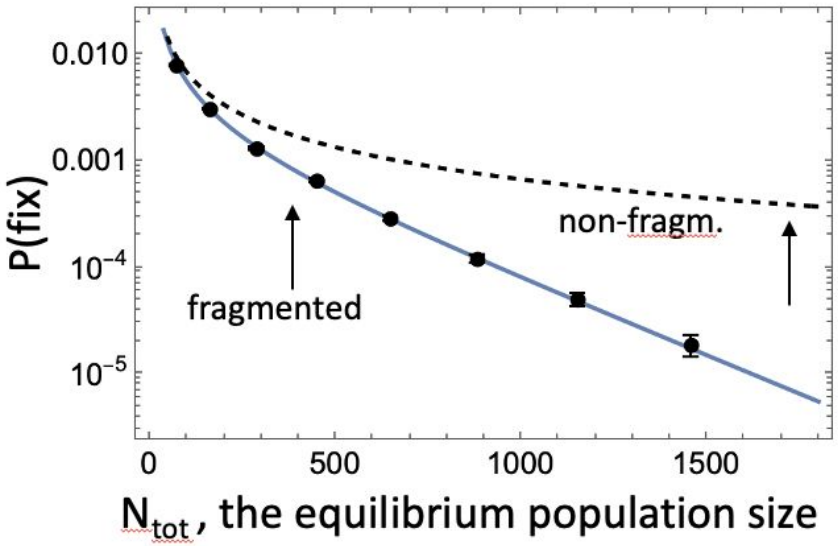
=> WT population is at equilibrium. Introduce 1 mutant into a randomly chosen deme

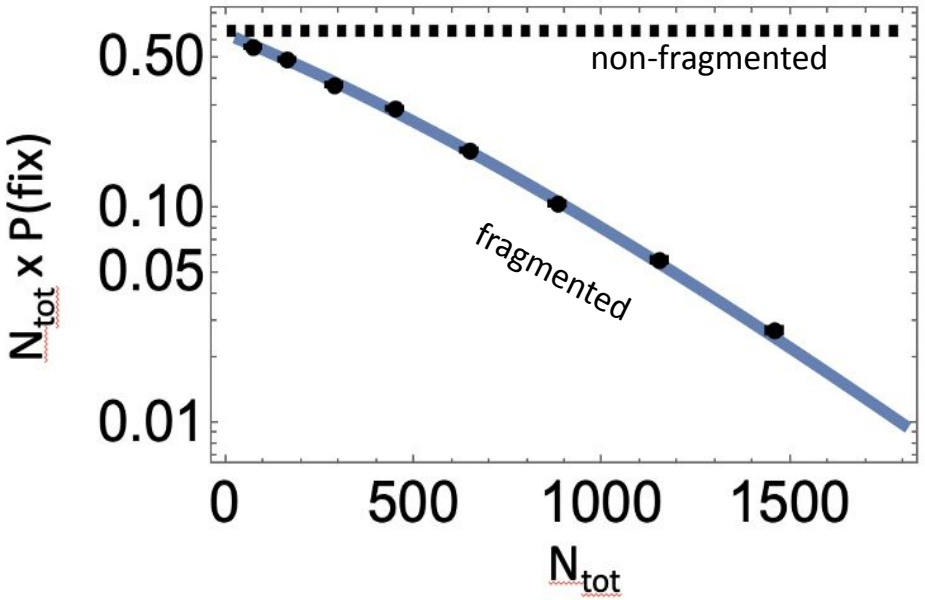
SPATIAL STRUCTURE MAKES A QUASI-NEUTRAL MUTANT **TRULY DISADVANTAGEOUS**

DESPITE IDENTICAL REPRODUCTIVE SUCCESS

non-spatial

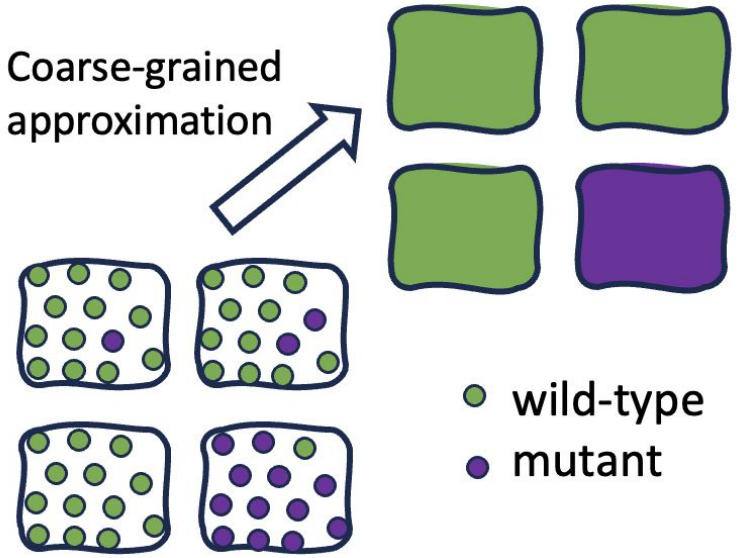






In a deme-structured model, the quasi-neutral mutant becomes truly disadvantageous, even though it has the same life-time reproductive success compared to WT

Calculating stuff



ρ_m probability of a single mutant to fixate in an isolated wild-type deme

ρ_w probability of a single wild-type individual to fixate in an isolated mutant deme

$$\Pi_1^{frag} \approx \rho_m \frac{1-\frac{1}{\mathcal{F}}}{1-\frac{1}{\mathcal{F}^D}},$$

$\mathcal{F} = \tau \frac{\rho_m}{\rho_w}$ = relative fitness of a mutant deme

defined by the ratio of the 2 deme conversion rates

assumptions:

1. mutation rate is sufficiently low such that individual demes are typically homogeneous with respect to the type
2. Small deme population size

For large populations, we have $\frac{\rho_m}{\rho_w} = \frac{1}{\tau}$ and hence $\mathcal{F}=1$

so the effect is lost

A BIOLOGICALLY MORE REALISTIC SCENARIO: A MUTANT WITH A CHANGED LIFE-TIME REPRODUCTIVE OUTPUT & ALSO PROPORTIONALLY SCALED BIRTH AND DEATH RATES

$$r_m = \tau\ (1+s) r_w$$

$$d_m = \tau\ d_w$$

s > 1: mutant has higher reproductive output than WT

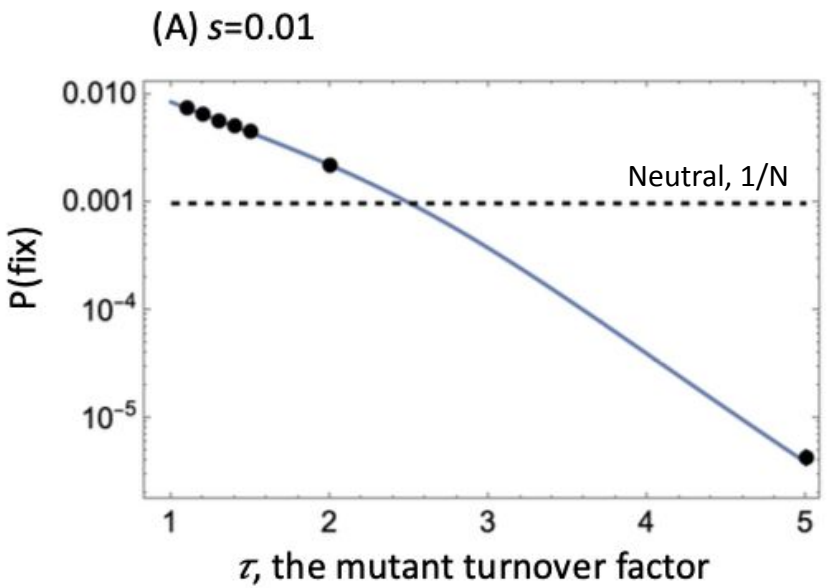
s < 1: mutant has lower reproductive output than WT

When the turnover parameter τ=1, a mutant is advantageous if s>1 and disadvantageous if s<1.

What happens if the turnover parameter, τ, deviates from 1?

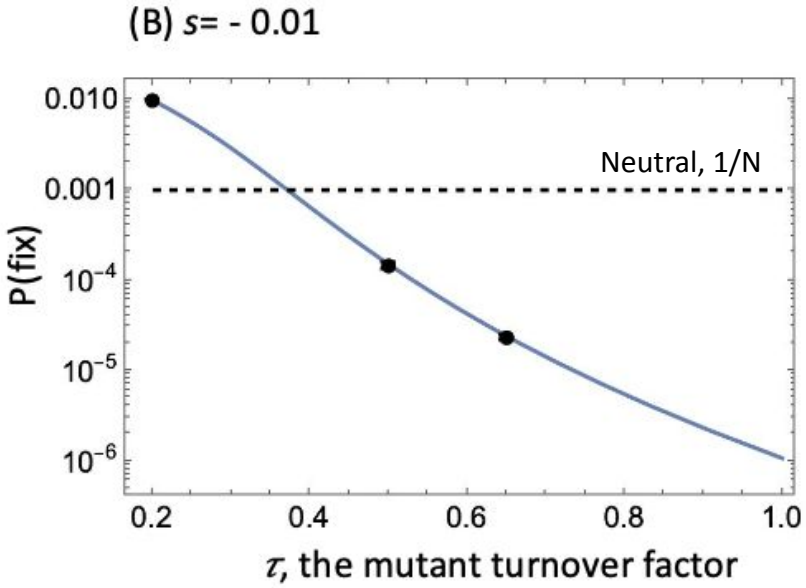
SPATIAL STRUCTURE REVERSES SELECTION

Mutant with higher reproductive output



A mutant with a **higher reproductive output** than WT can become **strongly disadvantageous** if it also has higher turnover

Mutant with lower reproductive output



A mutant with a **lower reproductive output** than WT can become **advantageous** if it also has lower turnover

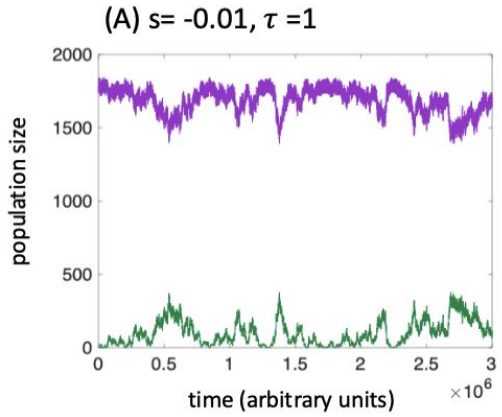
Relationship between life-time reproductive success and Darwinian fitness is more complex than previously appreciated

MOVE AWAY FROM FIXATION PROBABILITIES:

Mutant with lower life-time reproductive output

Assume that mutant is generated by WT a certain rate

mutant with **LOWER** life-time reproductive output than WT



WT wins for $\boldsymbol{\tau}$ =1 (identical turnover)

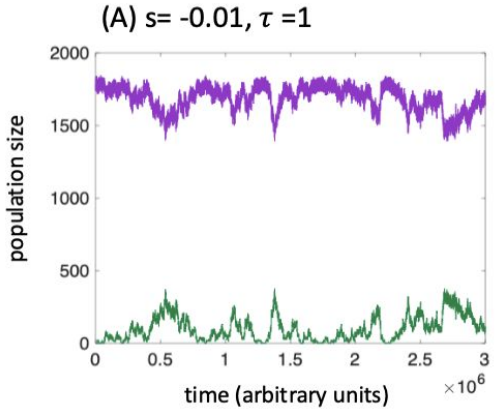
mutant persists at mutation-selection balance

MOVE AWAY FROM FIXATION PROBABILITIES:

Mutant with lower life-time reproductive output

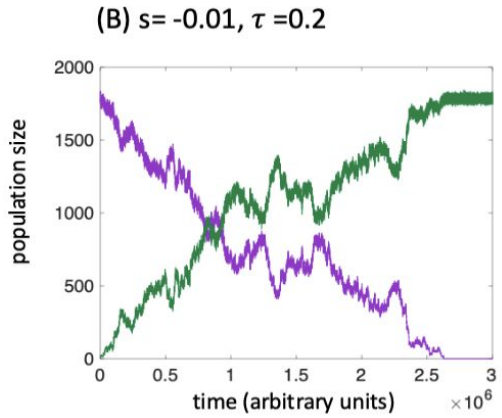
Assume that mutant is generated by WT a certain rate

mutant with **LOWER** life-time reproductive output than WT



WT wins

mutant persists at mutation-selection balance



mutant invades and takes over with reduced turnover ($\boldsymbol{\tau}$ <1)

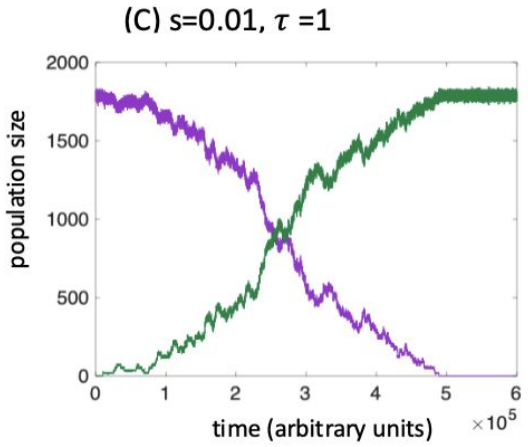
MOVE AWAY FROM FIXATION PROBABILITIES:

Mutant with higher life-time reproductive output

Assume that mutant is generated by WT a certain rate

mutant with **HIGHER** life-time reproductive output than WT

mutant takes over if it has identical turnover ($\boldsymbol{\tau}$ =1)



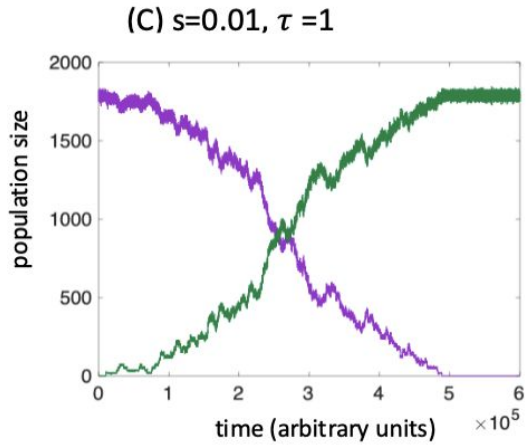
MOVE AWAY FROM FIXATION PROBABILITIES:

Mutant with higher life-time reproductive output

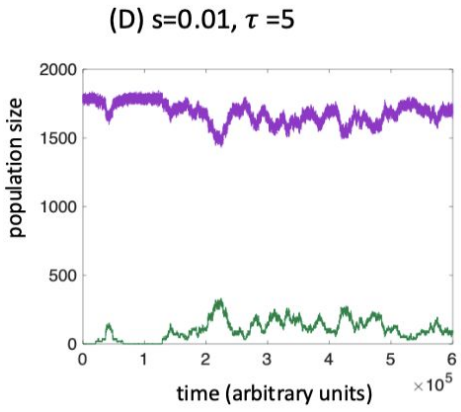
Assume that mutant is generated by WT a certain rate

mutant with **HIGHER** life-time reproductive output than WT

mutant takes over if it has identical turnover ($\boldsymbol{\tau}$ =1)

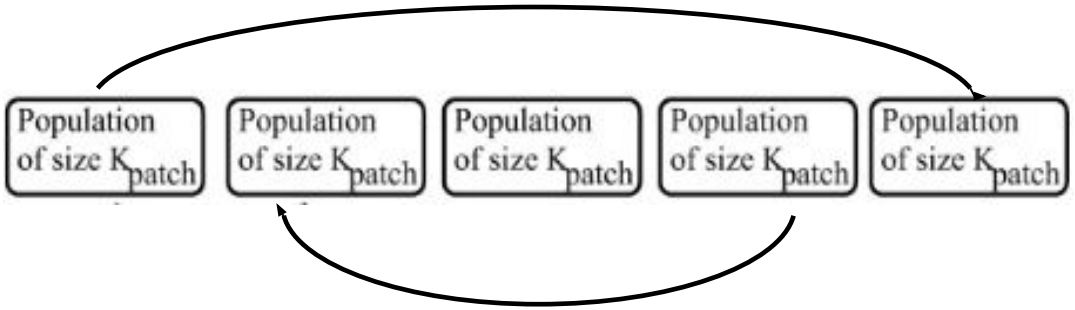


mutant becomes disadvantageous if it also has a higher turnover ($\boldsymbol{\tau}$ >1)

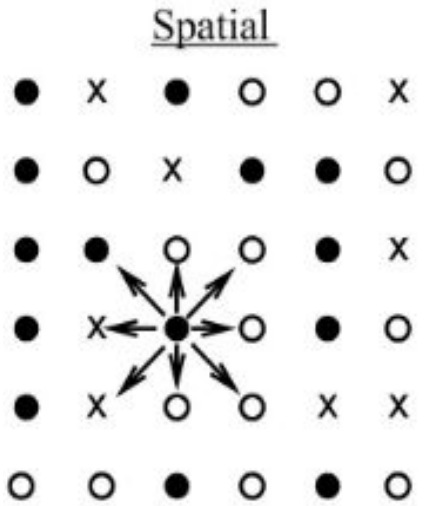


mutant persists at mutation-selection balance

deme model with non-spatial migration



Agent-based model

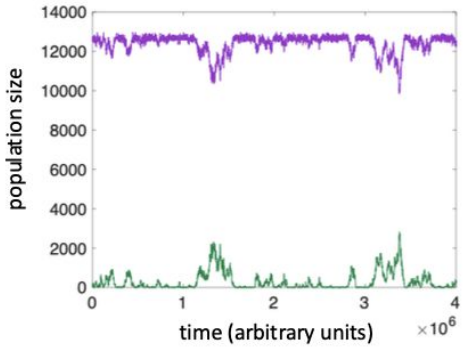


Spatial agent-based model has same basic properties as deme model with non-spatial migration

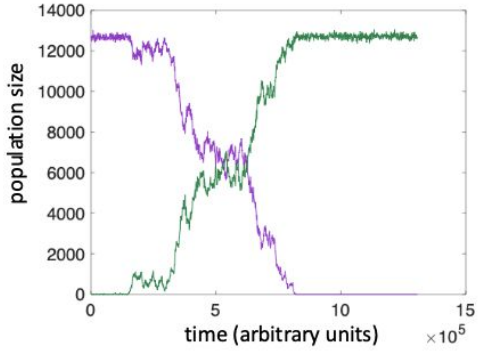
Mutant with LOWER reproductive output

Mutant with HIGHER reproductive output

(A) s= -0.001. τ=1

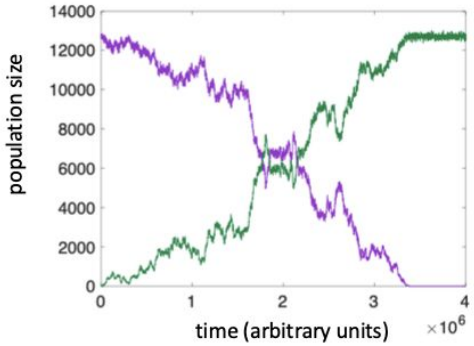


(C) s=0.001, τ=1

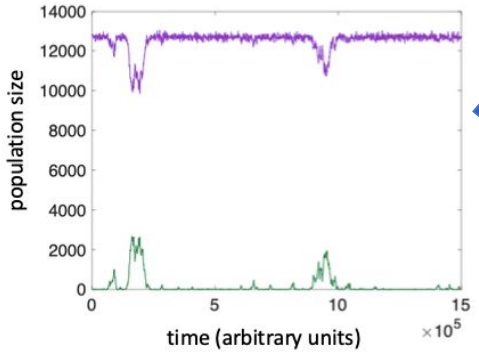


Mutant and WT have identical turnover

(B) s= -0.001. τ=0.1



(D) s=0.001, τ=3



Mutant has changed turnover

Takeaway messages

Spatial structure can have important consequence on evolutionary dynamics

These can be found in relatively simple models of spatial cell dynamics

Such insights inform computational models that describe specific cancers and take into account the higher biological complexities seen in the spatial organization of tumors (eg cancer stem cells, differentiated cells, microenvironment)

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