Tracking the Invisible

a probabilistic approach to field cancerization

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Collaborators

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Motivation

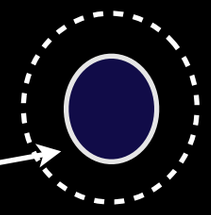
a clinical problem

Diagnosis

- Patient presents with tongue cancer

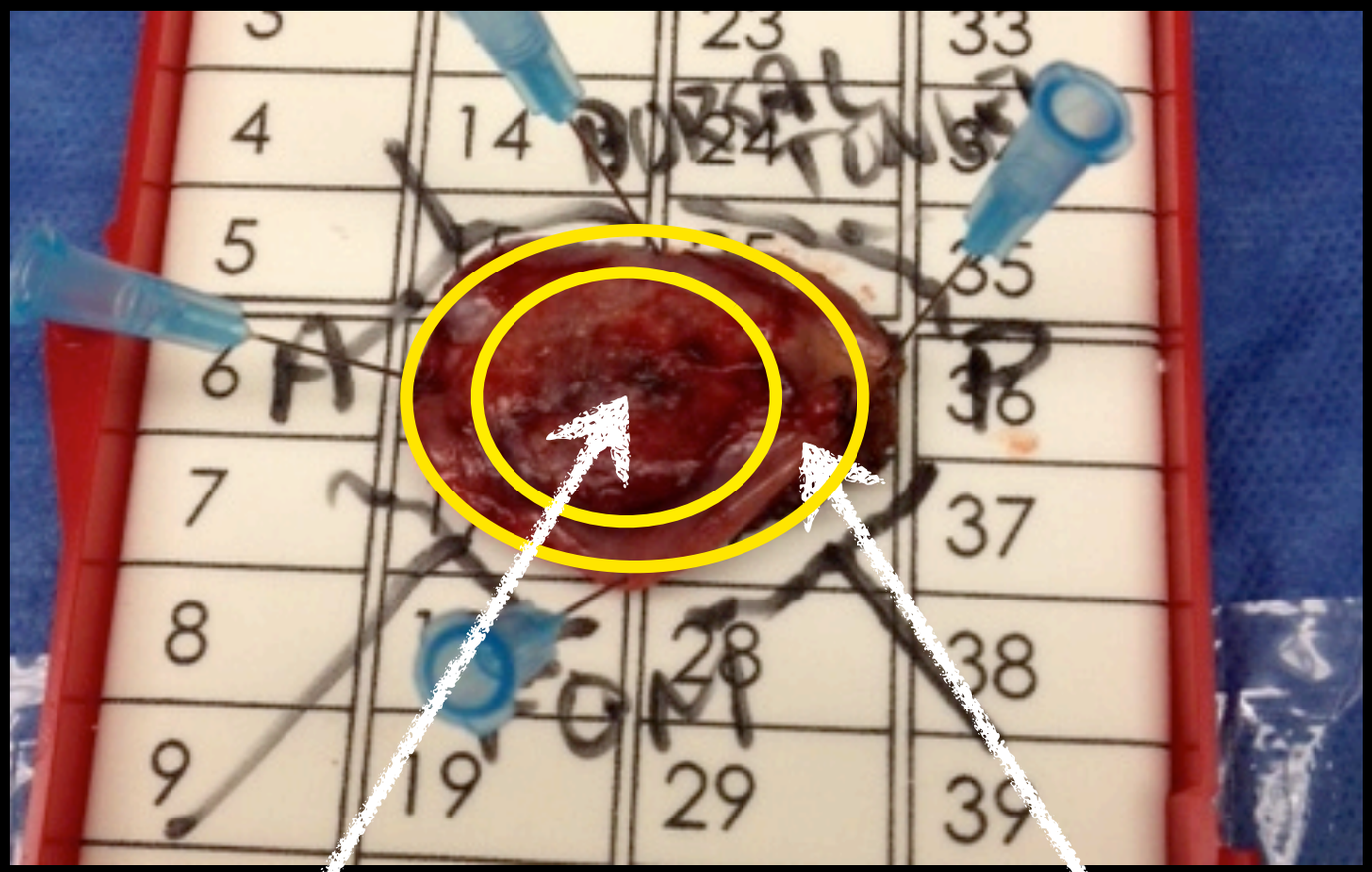
Treatment

1. Surgical resection
2. Check margin
3. Follow-up therapy: radiation and/or chemotherapy



Resected tongue cancer

Resected tongue cancer



Frequent recurrence of disease
(20-30%)...

… 1-5 years later

Resected portion

Local recurrence

… 1-5 years later

Resected portion

Local recurrence

But margin was tumor free…
why the new tumor?

precancer field

Resected portion

Local recurrence

precancer field

Resected portion

Local recurrence

precancer field

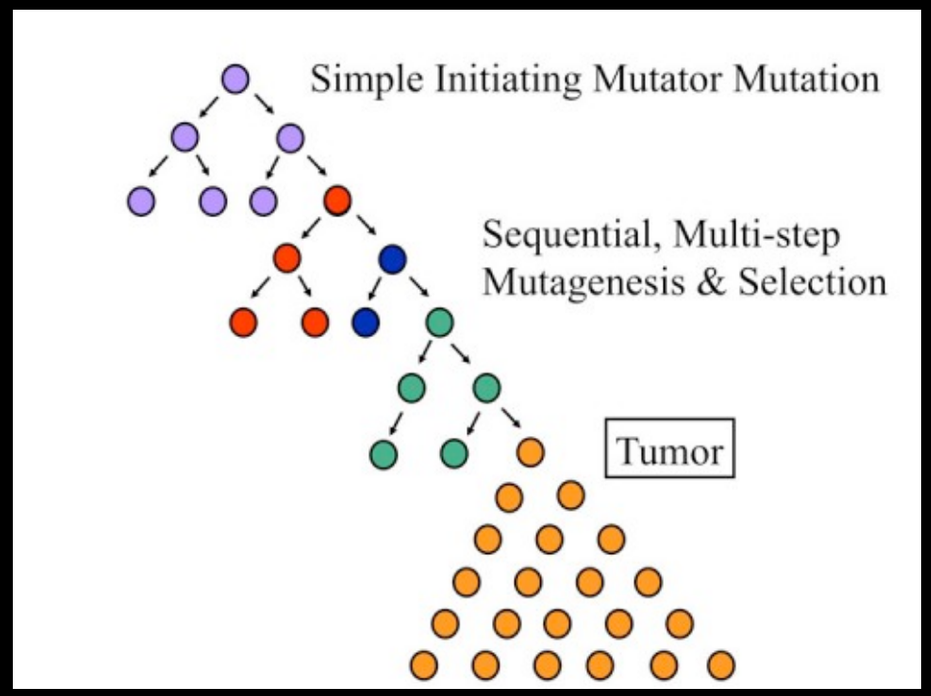
Resected portion

Local recurrence

precancer field

Resected portion

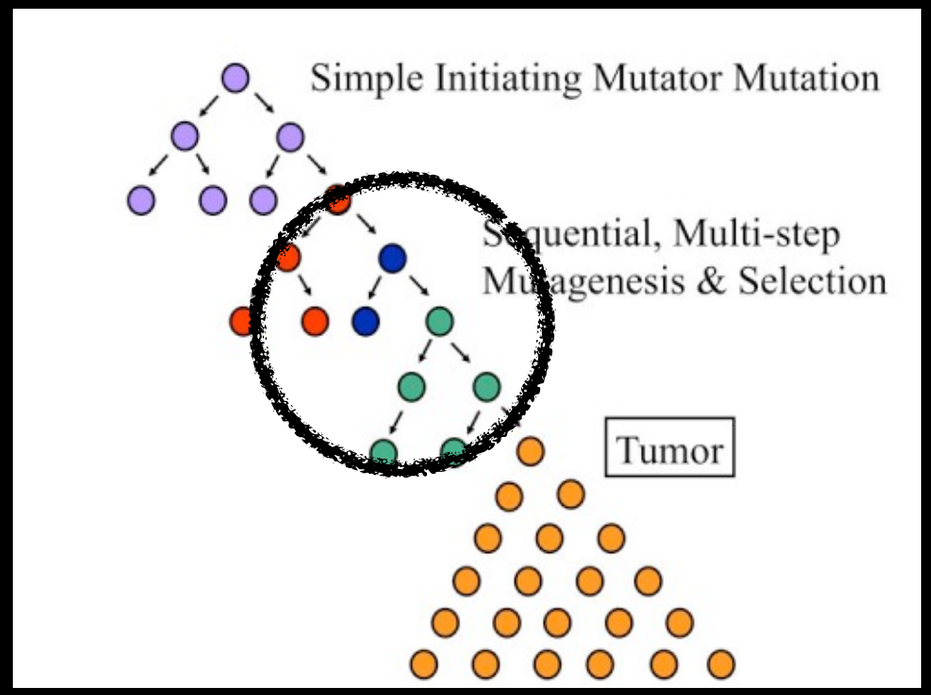
Local recurrence



precancer field

Resected portion

Local recurrence



The Problem

field cancerization

Field Cancerization

- Malignant tumor is surrounded by precancerous ‘field’
- Not visible to surgeon
- ‘Field’: high risk of progression

Field Cancerization

- Present in most skin-cancers (carcinomas)
- Head and neck, lung, bladder
- Also: breast, colon, cervix, etc

Invisibility = Uncertainty

- Surgeon: how much margin around tumor?
- Distant field present at diagnosis?
- Risk of progression - surveillance protocol?

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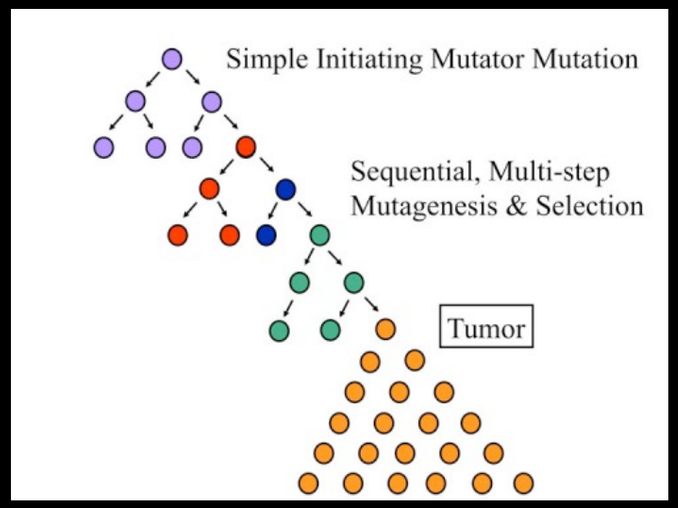
Can we develop a mechanistic, dynamic model to answer these questions?

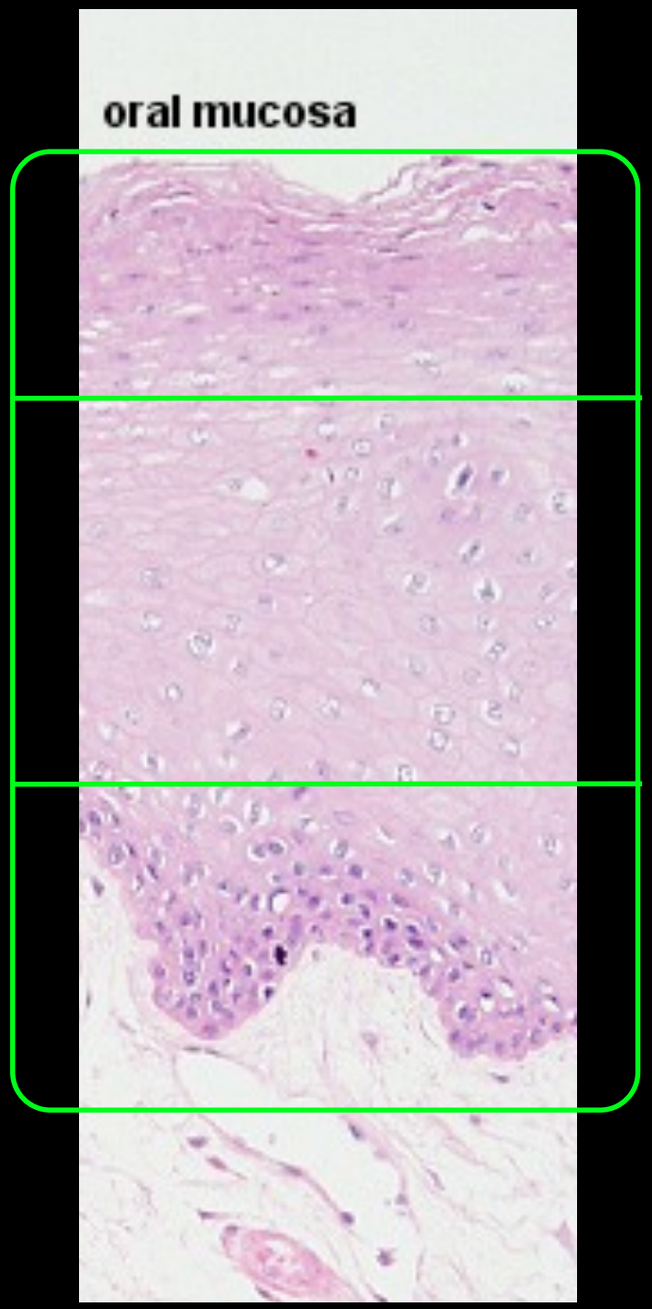
The Model

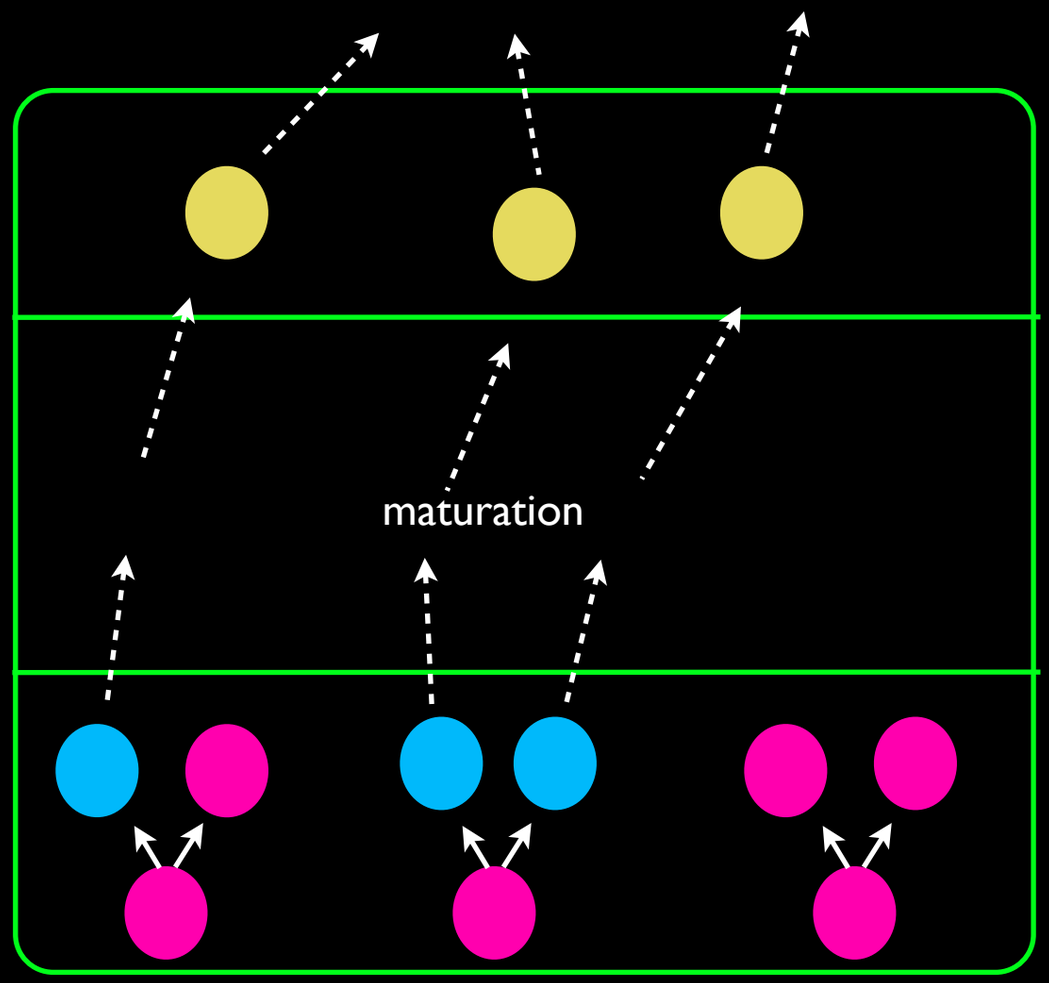


- Non-spatial model: branching process
- Here, geometry matters!

cross-section of epithelium

Cellular dynamics



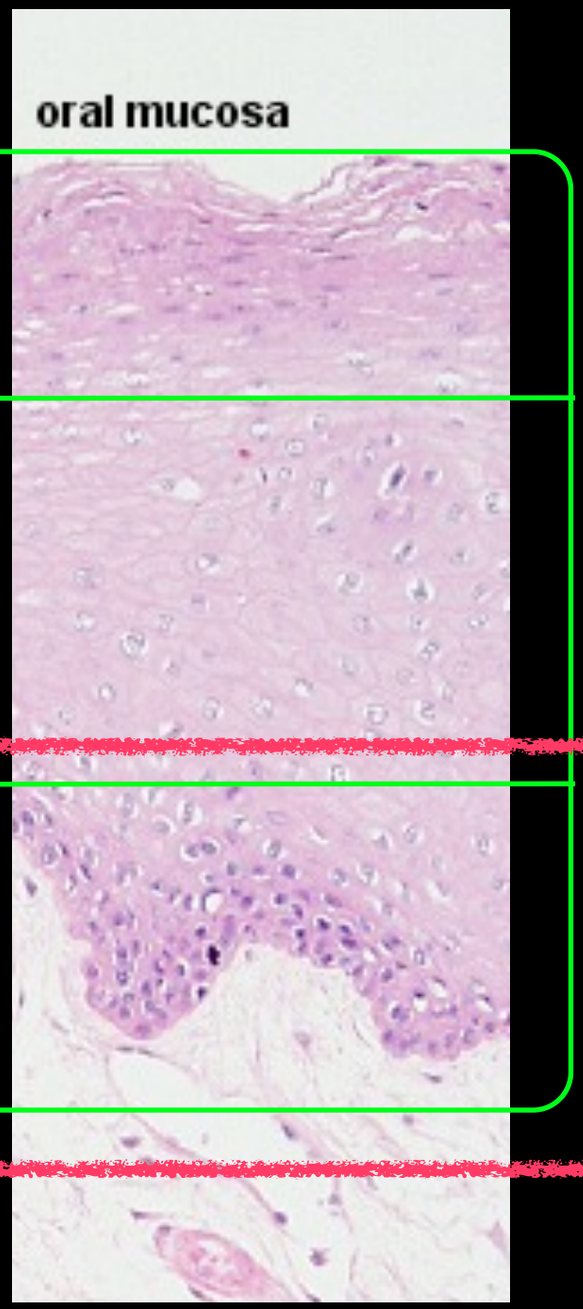


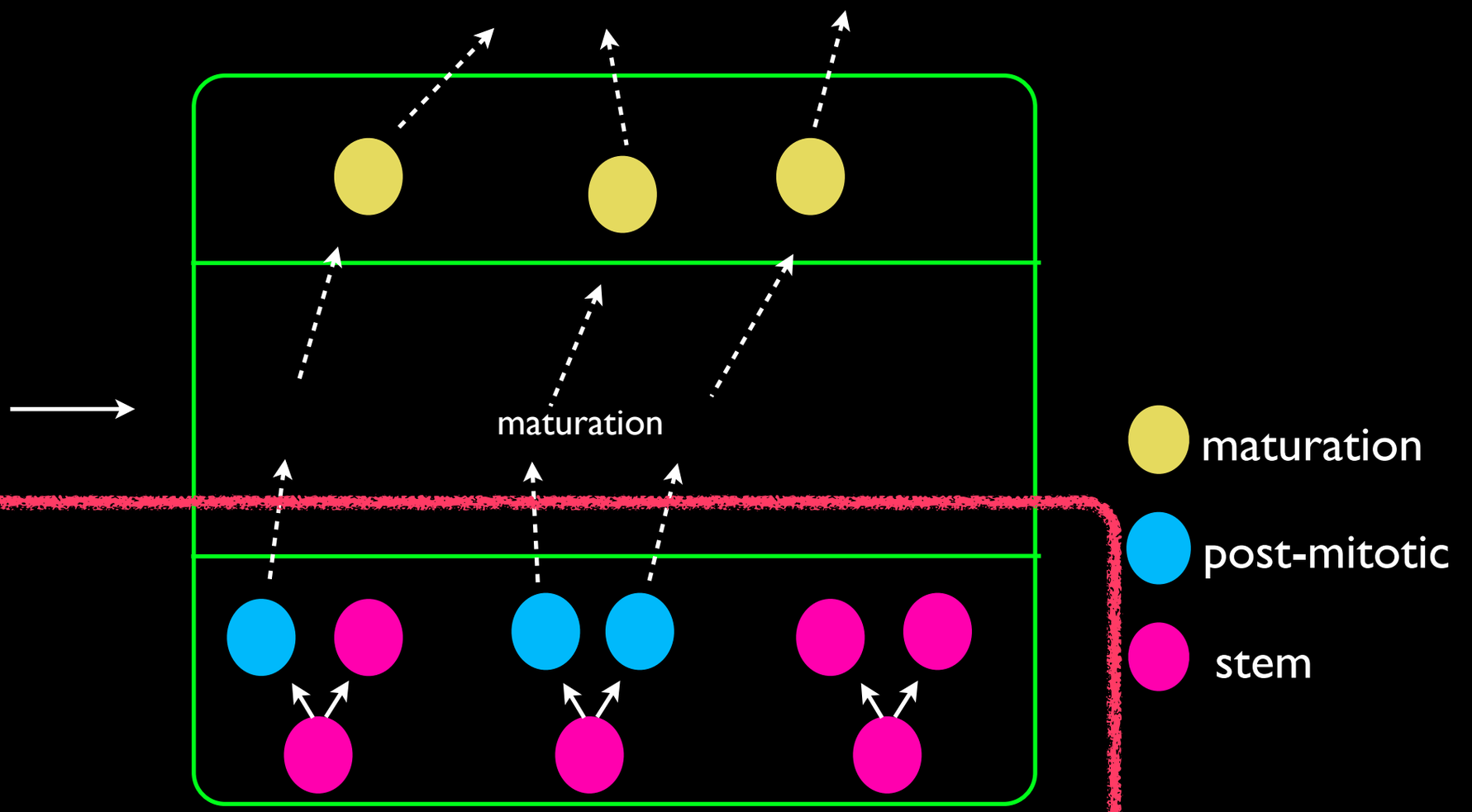
maturation

post-mitotic

stem

Cellular dynamics

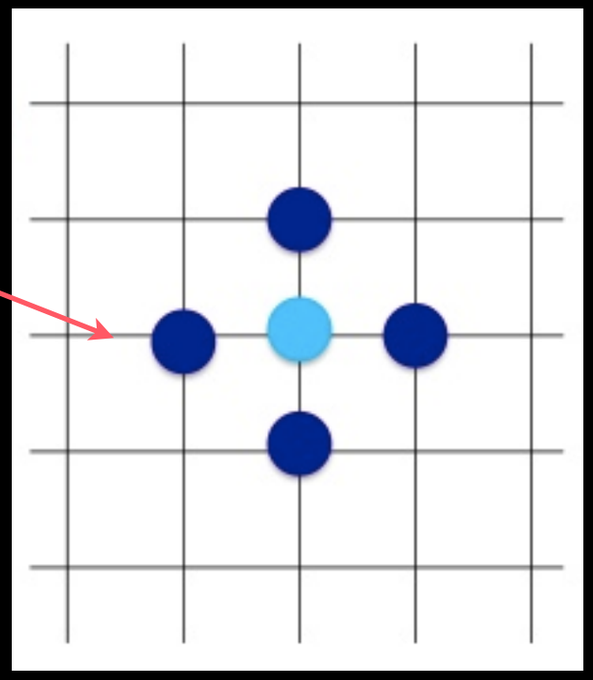




Focus on basal layer

Focus on basal layer

Cells



- Spatial evolutionary dynamics
- Cell of type i: stochastic division @ rate f_i
- Replace neighbor (unif. at random)

Growth dynamics of mutant progeny

Movie 1

sped-up process

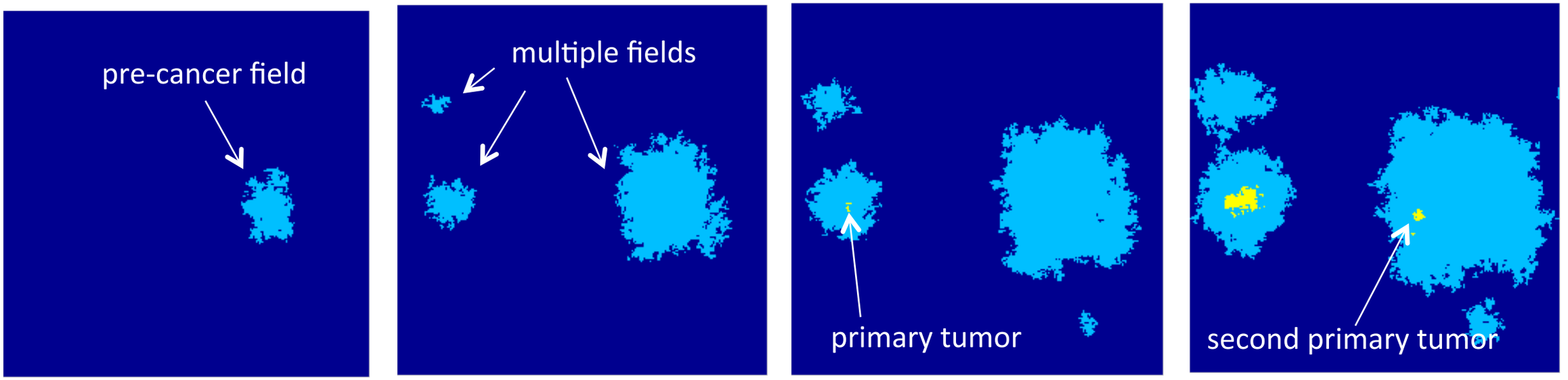
Movie 2

Add mutations

Movie 3

Movie 4

Add mutations: multistep carcinogenesis

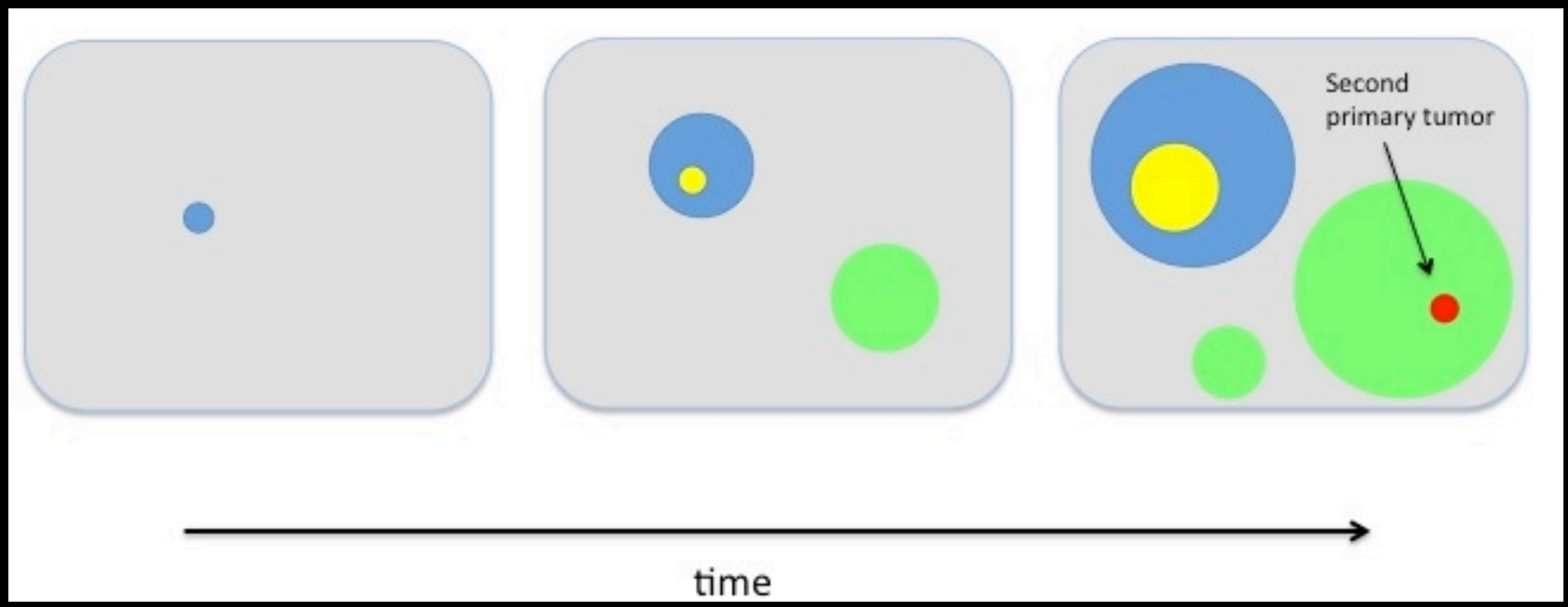


time

Biased voter model

Jasmine Foo's talk

Mesoscopic model



Model Analysis

Assumptions

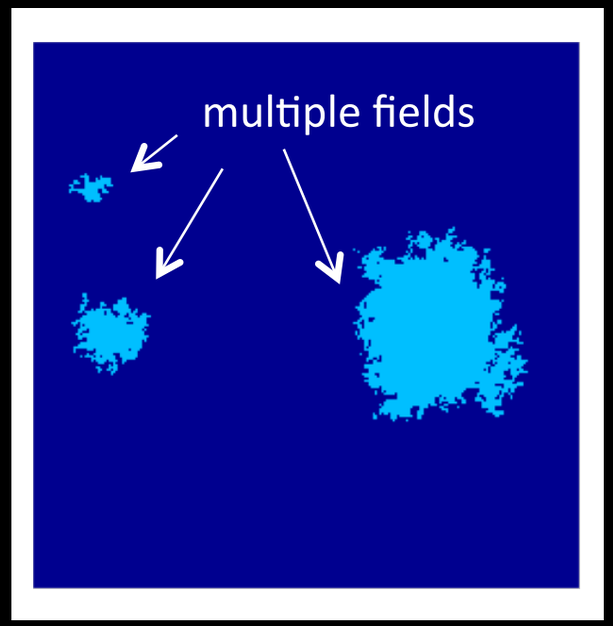
- 3 cell types: normal cells, precancerous cells and malignant cells
- General dimension $d \geq 1$

- New precancer fields: Poisson arrivals
- Fields grow at constant radial rate
- Each field: non-homogeneous Poisson process to yield a tumor clone

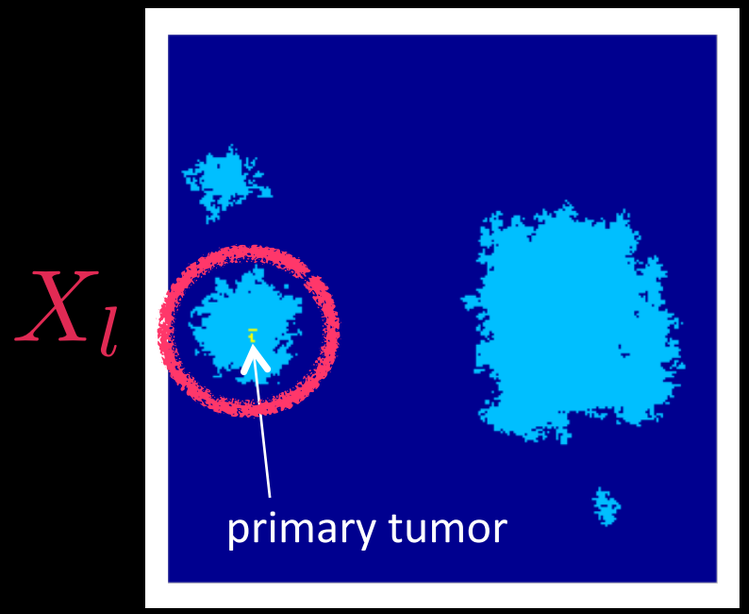
Important notion:
size-biased pick

Definition 3.1 (Size-biased pick). *Let $L_1, \ldots, L_n$ be a family of n random variables. A size-biased pick from $L_1, \ldots, L_n$ is defined as a random variable $L_{[1]}$ with conditional probability distribution*

$$P(L_{[1]} = L_i | L_1, \ldots, L_n) = L_i / \sum_{j=1}^{n} L_j.$$



Local field area

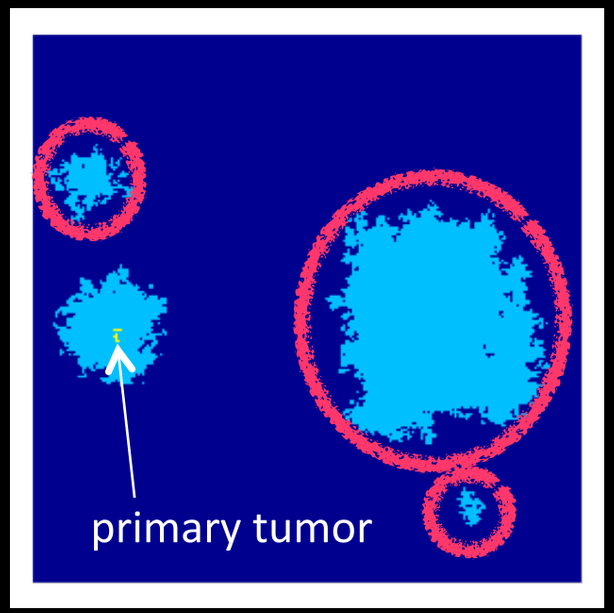


Theorem 0.1. *The distribution of the area of the local field at time of tumor initiation σ_2, conditioned on $\{\sigma_2 \in dt\}$, is given by*

$$\hat{P}\left(X_l(\sigma_2) \in dx\right) = \hat{P}\left(X_{[1]} \in dx\right) = \frac{u_2 \bar{s}_2 x^{1/d}}{d\gamma_d^{1/d} c_d(s_1)(1 - e^{-\theta t^{d+1}})} \exp\left[\frac{-u_2 \bar{s}_2 x^{\frac{d+1}{d}}}{(d+1)\gamma_d^{1/d} c_d(s_1)}\right],$$

for $x \in [0, \gamma_d c_d^d(s_1) t^d]$.

Distant field area



$\bar{X}_d$

Theorem 0.2. *The size-distribution of the distant field clones at time of tumor initiation σ_2, conditioned on $\{\sigma_2 = t\}$, is given by*

$$\mathcal{L}(\bar{X}_d | t \in dt) =_d \hat{P}(\tilde{X}_1 \in dx_1, \ldots, \tilde{X}_{M(t)-1} \in dx_{M(t)-1})$$
$$= \frac{1}{1 - e^{-\lambda t \phi(t)}} \sum_{m=1}^{\infty} \frac{(\lambda \phi(t) t)^m e^{-\lambda \phi(t) t}}{m!} \prod_{i=1}^{m-1} g_t(x_i),$$

where

$$g_t(x) \equiv \frac{x^{1/d-1}}{d \gamma_d^{1/d} c_d(s_1) t \phi(t)} \exp\left[\frac{-u_2 \bar{s}_2 x^{\frac{d+1}{d}}}{(d+1) \gamma_d^{1/d} c_d(s_1)} \right].$$

Key insight from these results:

How do microscopic parameters (cellular fitness, mutation rates etc) influence the geometry of the invisible precancer fields.

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How do microscopic parameters (cellular fitness, mutation rates etc) influence the geometry of the invisible precancer fields.

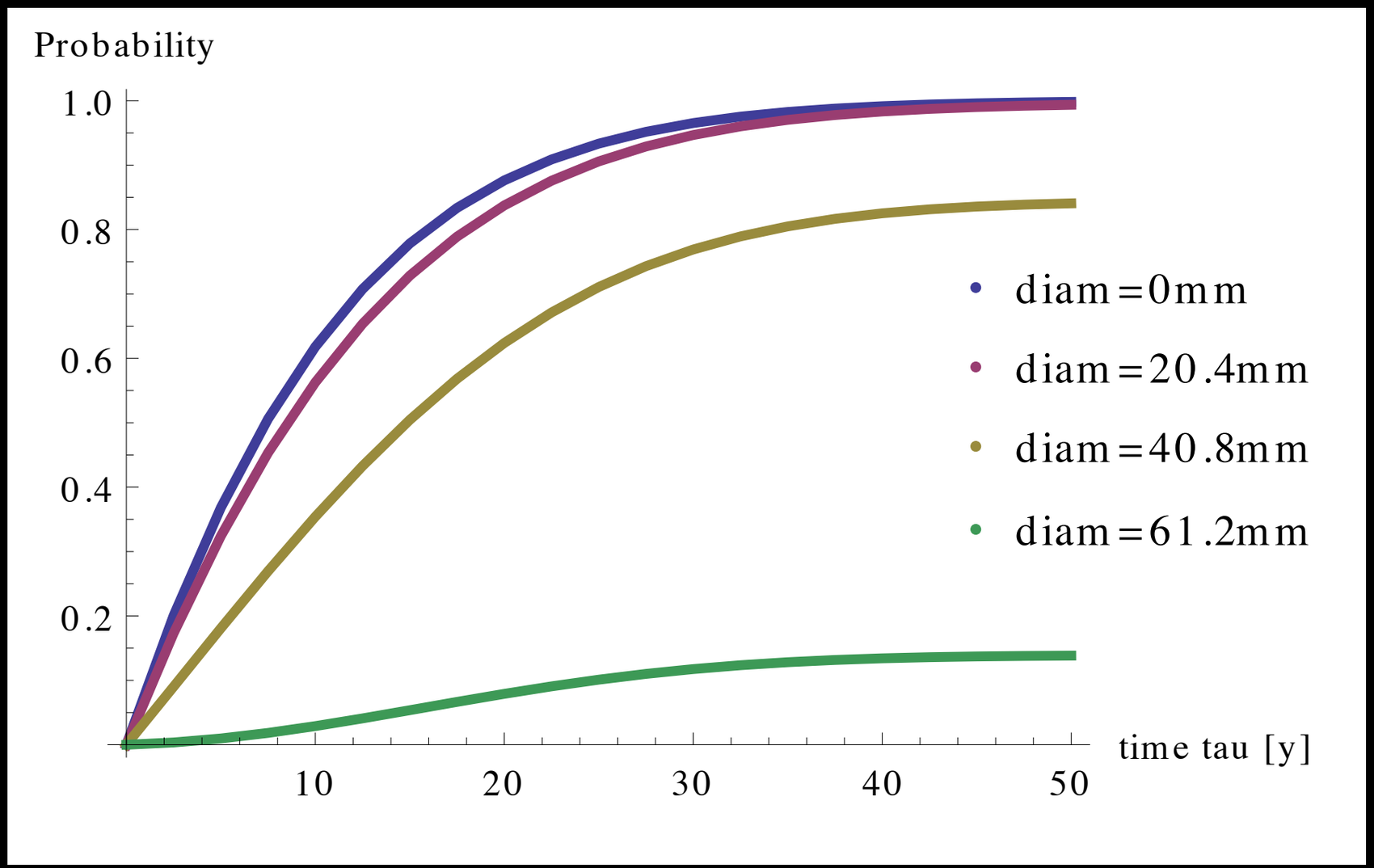
Now, let's go back to the clinical issues outlined in the beginning...

Excision Margin I

How big should the margin be
to avoid recurrence from unresected
portion of the field?

Excision Margin II

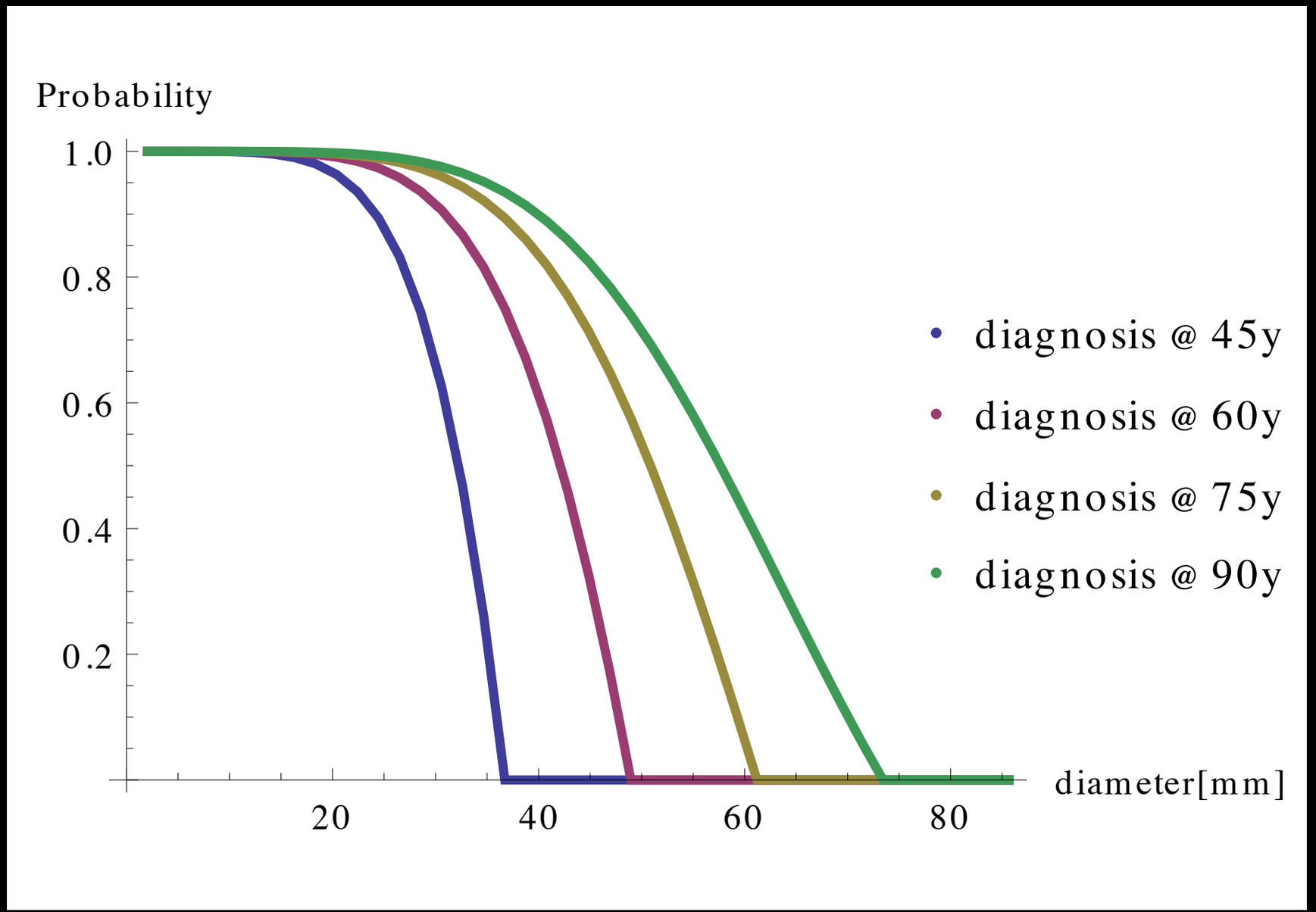
Cumulative incidence of second field tumor



diam=diameter of excised portion

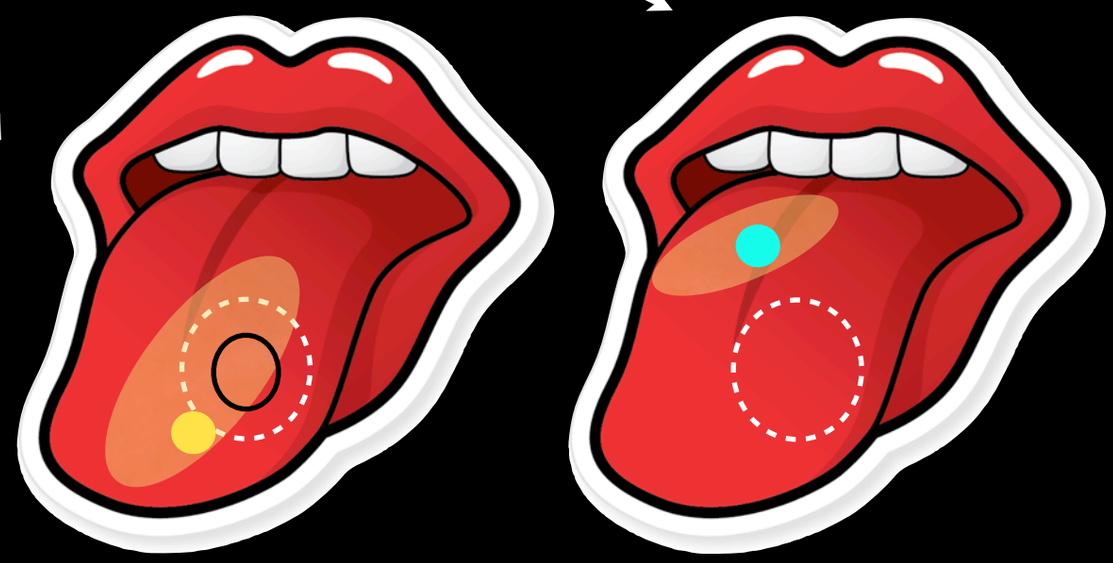
Excision Margin III

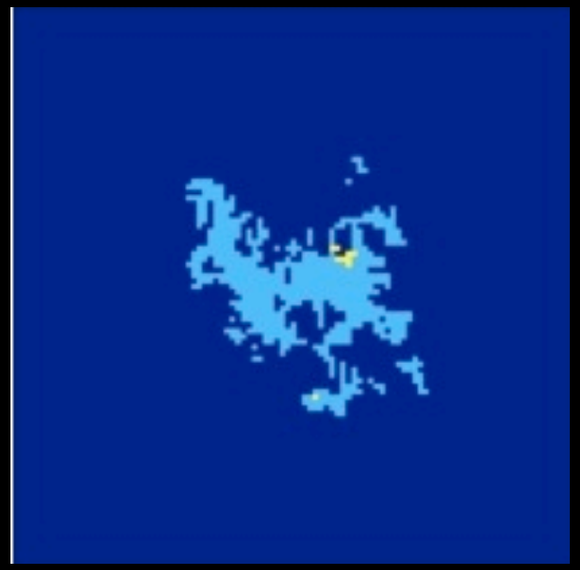
Probability of recurrence

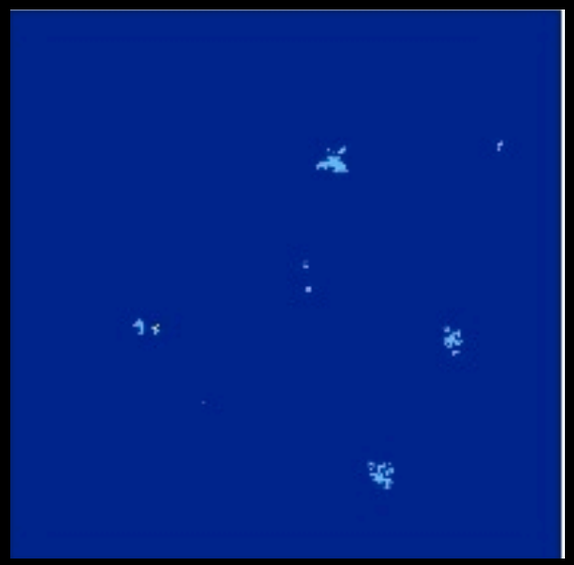


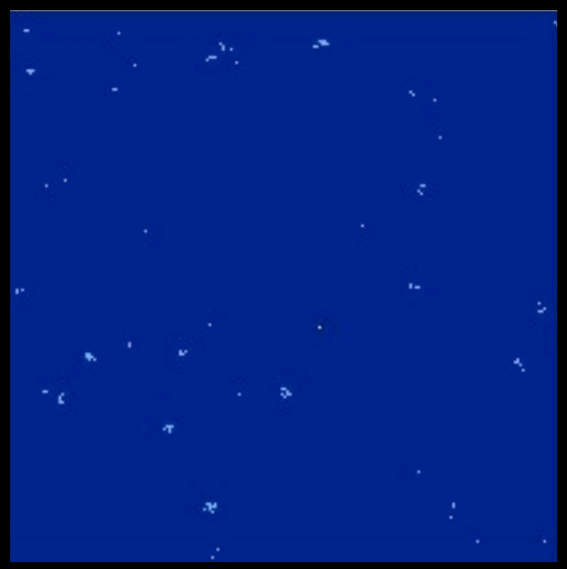
Recurrence: local vs distant

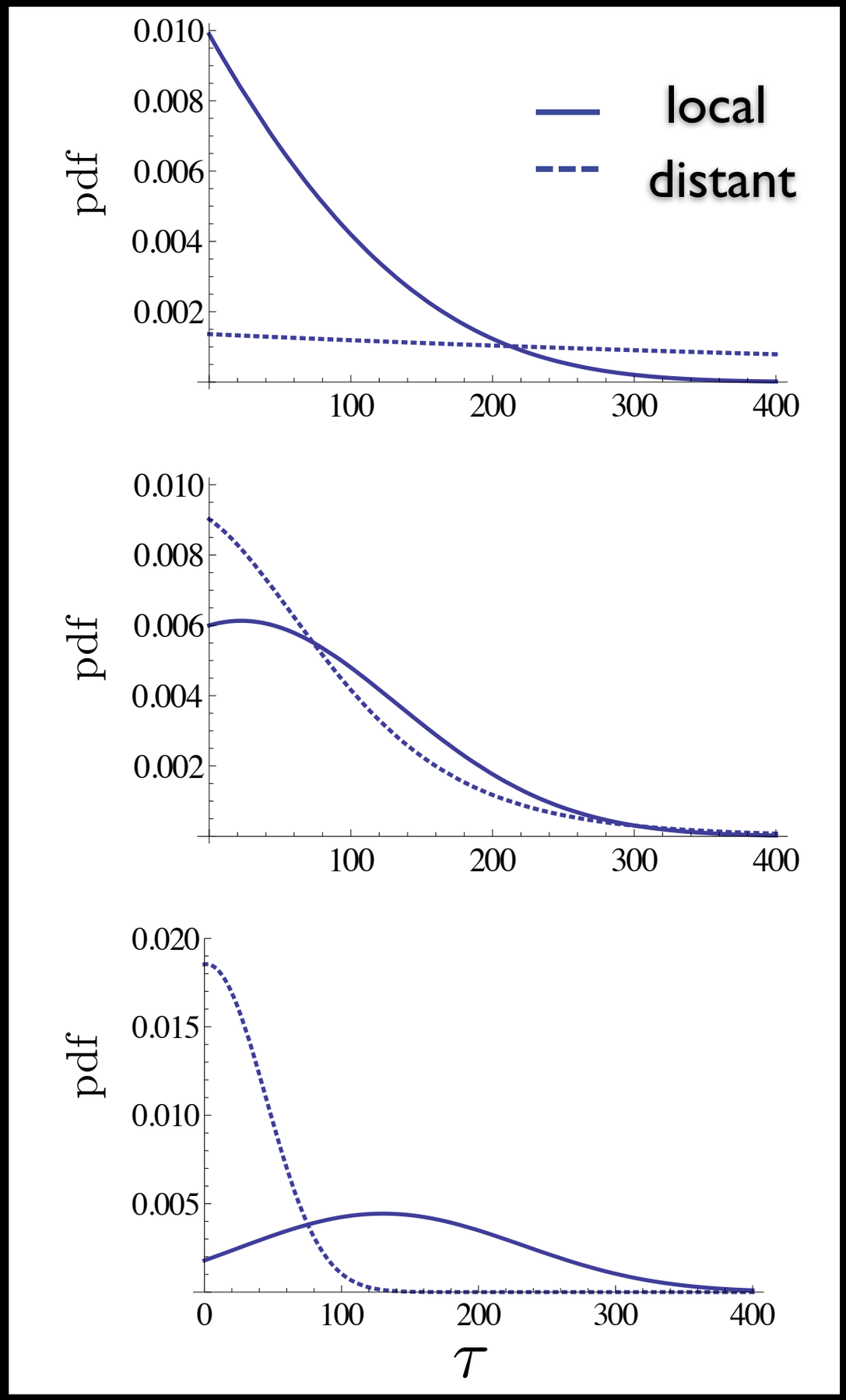
- At time T=0, remove the tumor
- Time to distant recurrence?
- Time to local recurrence?







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Reference

Foo, Leder, Ryser (2014)

Journal of Theoretical Biology

Ongoing Work

With Drs. Lee, Ready, and Shealy (Duke Medicine)

Added complexity

- Beyond the 2-step model
- Collect clinical data for validation/ refinement
- Goal: patient-specific predictions via integrated data-modeling framework

Patient data
spectroscopic probe
imaging
biopsies

Diagnosis → Treatment → Follow-up

Mathematical Model

That's all Folks!