Evolutionary dynamics of cancer: A spatial model of cancer initiation

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Collaborators

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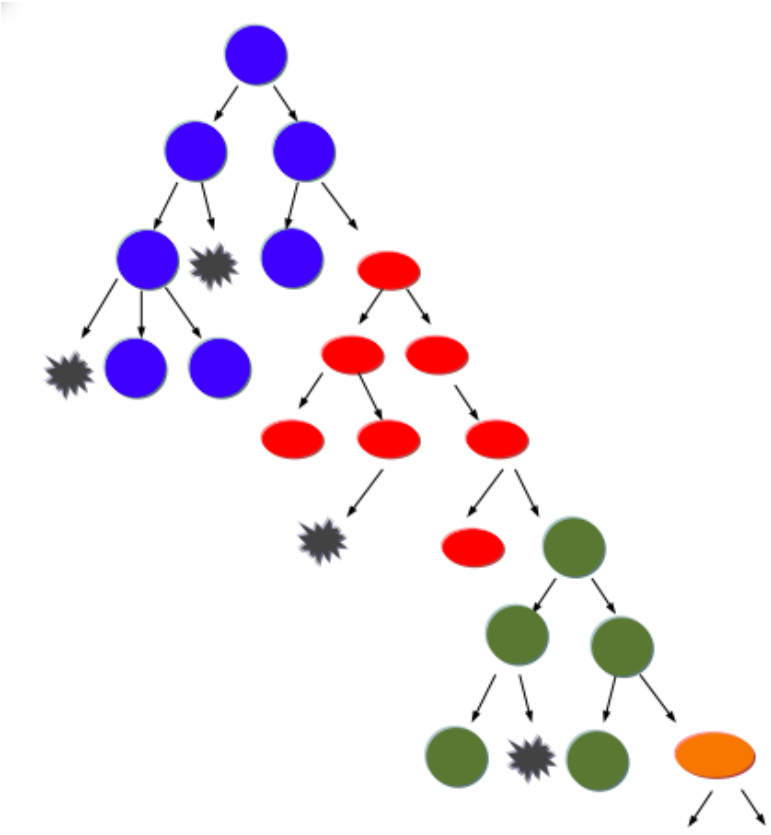
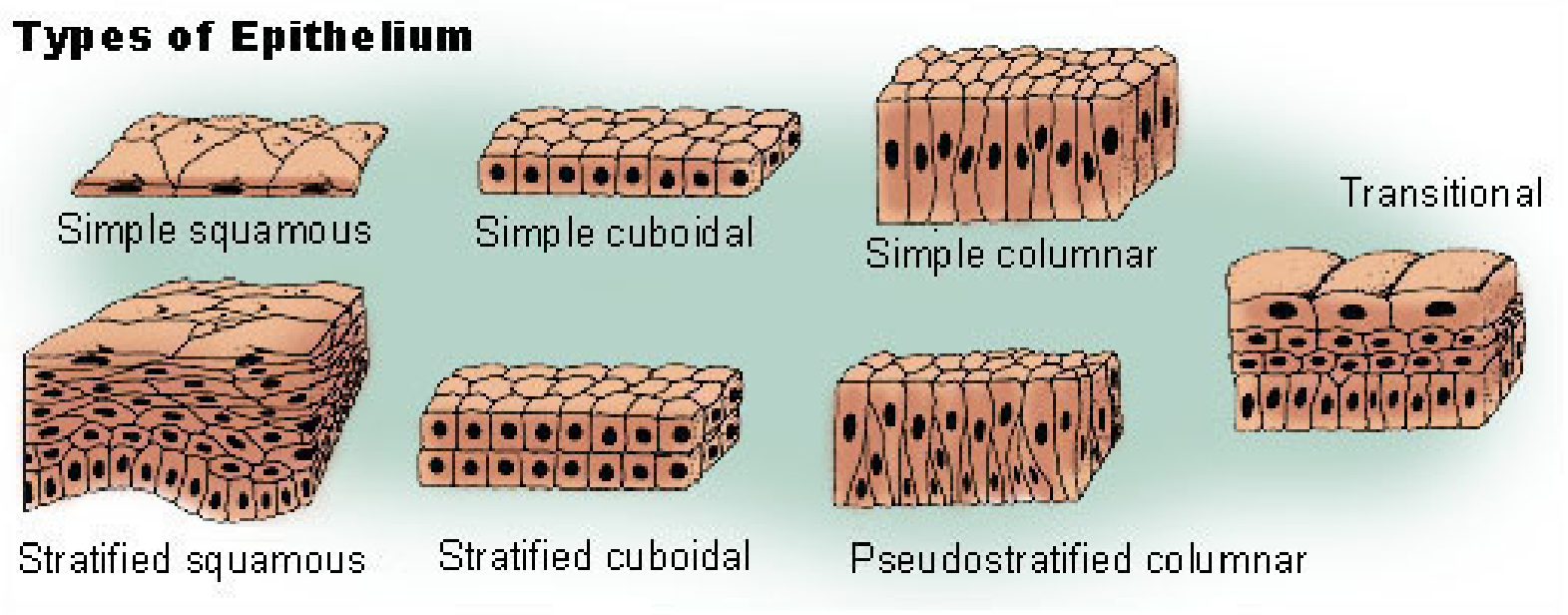
Next talk by Marc Ryser/Rick Durrett: Part II

Multi-step theory of carcinogenesis

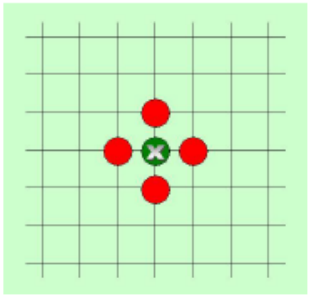
Cancer arises as a result of genetic alterations that occur in a stepwise fashion; these alterations can confer intermediate growth advantages and cause clonal expansion.



Cancer arises (mostly) from epithelial tissue (spatially structured).

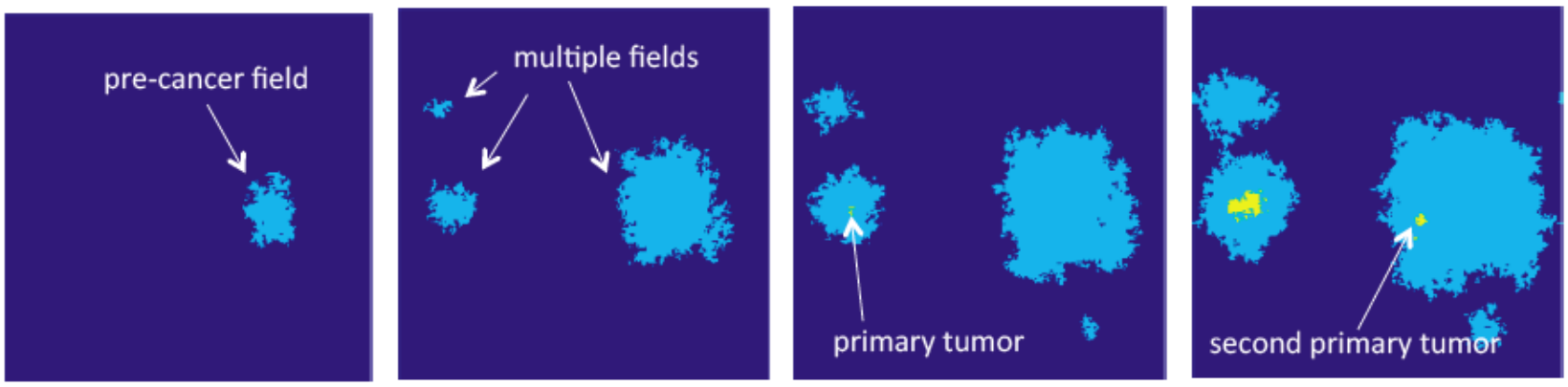

Types of Epithelium
Simple squamous
Simple cuboidal
Simple columnar
Transitional
Stratified squamous
Stratified cuboidal
Pseudostratified columnar

Model of carcinogenesis in epithelium



- Start with lattice $(\mathbb{Z} \mod L)^d$, each lattice site occupied by a cell $(N \doteq L^d)$
- Initially all cells are type-0 (normal) and reproduce at rate 1.
- Offspring replaces a randomly chosen neighbor cell
- Multi-step carcinogenesis process: type-0 (r=1) mutate at rate u_1 to become type-1 premalignant cells, which mutate at rate u_2 to become type-2 premalignant cells
- Type-i cells reproduce at rate $(1 + s_i)$ relative to type-$(i - 1)$ cells where $s_i \geq 0$.
- $u_i \leq u_{i+1}$ (genomic instability increases with malignant phenotype)

Model Dynamics



Consider a two-step initiation process (e.g. inactivation of tumor suppressor genes).

Would like to establish some basic properties as $s \to 0, N \to \infty, u_1, u_2 \to 0$: (1) how fast do premalignant clones grow? (2) how long to first 'successful' type-1? (3) type-2?

Biased voter process

Consider the growth of a family starting from a single type-1 cell, in domain $\mathbb{Z}^d$ otherwise filled with type-0s.

Type-0 (fitness 1) and type-1 (fitness $1 + s$) cells, selection dynamics only (mutations suppressed).

Biased voter model: considered by Williams and Bjerknes 1972 (tumor growth); Schwarz 1977 (interacting particle systems)

Define $\xi_t \equiv \{x \in \mathbb{Z}^d | \text{type-1 cell at } x \text{ at time } t\}$.

Basic result for biased voter process: survival probability of a single mutant clone

On $\mathbb{Z}^d$, $\xi_t \neq \emptyset$, $|\xi_t|$ jumps at rate proportional to $|\partial \xi_t|$.

Embedded discrete time process Z_n is a biased random walk:

At every edge between a 0 and 1, during the next event:
- 0 is replaced by 1 w.p. p, where $p = \frac{1+s}{2+s}$.
- 1 is replaced by 0 w.p. $1 - p$

Extinction time of the clone $T_0 = \inf\{t > 0 : |\xi_t| = 0\}$.

$$P(T_0 = \infty) = 1 - \frac{1-p}{p} = \frac{s}{1+s}$$

Results on expansion of premalignant clones in $\mathbb{Z}^d$

Starting from one premalignant cell initially with fitness advantage s, no mutations, and conditioned on nonextinction.

Case $d = 1$ (trivial): $\xi_t = [L_t, R_t]$, an interval. No holes

$\Rightarrow \frac{R_t}{t} \to s$ as $t \to \infty$. Growth is linear.

Case $d \geq 2$ (Bramson and Griffeath 1981): (voter process)

There is a set D such that for any $\epsilon > 0$, $\exists t_\epsilon$ such that for $t \geq t_\epsilon$,

$$(1 - \epsilon)tD \cap \mathbb{Z}^d \subseteq \xi_t \subseteq (1 + \epsilon)tD$$

Growth is linear with asymptotic shape D, where D is convex and symmetric.

Speed of expansion

Specifically, how does the (macroscopic) spread rate of a mutant clone depend on the (microscopic) fitness advantage?

Theorem *Let e_1 be the first unit vector and define the growth rate $c_d(s)$ such that the intersection of D with the x axis is $[-c_d(s)e_1, c_d(s)e_1]$. Then, as $s \to 0$ we have*

$$c_d(s) \sim \begin{cases} s & d = 1 \\ \sqrt{4\pi s/\log(1/s)} & d = 2 \\ \sqrt{4\beta_d s} & d = 3 \end{cases}$$

where β_d is the probability that two d-dimensional simple random walks started at the origin and (1,0,.., 0) never hit.

Defining success of clones on a finite domain

On $(\mathbb{Z} \mod L)^d$ we must define what we mean by 'success' of any mutant clone.

Define $T_i \equiv$ first time for Z_n to hit size i.

$$P_1(T_k < T_0) = \frac{1-(1+s)^{-1}}{1+(1+s)^{-k}} \text{ and } P_k(T_0 < \infty) = (1+s)^{-k}$$

When $s \to 0$ and $k \sim C/s$:

$$P_1(T_k < T_0) \sim \frac{s}{1-e^{-C}} \text{ and } P_k(T_0 < \infty) \to e^{-C}$$

To have success probability s as in infinite domain case, define success as reaching size C_s/s, where $C_s \to \infty$ as $s \to 0$.

Unsuccessful families behave like subcritical BV processes

Lemma Let ξ_t be the set of 1's in a supercritical BV model in $\mathbb{Z}^d$ starting from a single type-1 at the origin. Let T_0 be the time at which the process dies out. Let $\bar{\xi}_t$ be the same process with the fitnesses of type-1 and type-0 interchanged. Then

$$(\{|\xi_t|, t \leq T_0\} | T_0 < \infty) =_d \{|\bar{\xi}_t|, t \leq T_0\}$$

Boundary size of subcritical BV processes

Remark The size of the boundary of the subcritical BV process is (when $|\xi_t| = k$):

$$\partial(k) \sim q(k) = \begin{cases} 2d\beta_d k, & d \geq 3 \\ 4\beta_2 k / \log k, & d = 2. \end{cases}$$

Using (Cox, Durrett, Perkins 2002).

Upper bound on space-time volume of unsuccessful families

Recall that for a single mutant clone in $\mathbb{Z}^d$,

$$P(\text{extinction}) = \frac{1}{1+s}$$

Lemma: Space-time volume of unsuccessful premalignant clones

$$E\left(\int_0^{T_0} |\bar{\xi}_t| dt\right) = O(\ell(s))$$

$$\ell(s) = \begin{cases} s^{-2} & d = 1 \\ s^{-1}\log(1/s) & d = 2 \\ s^{-1} & d = 3 \end{cases}$$

Upper bound on space time volume of unsuccessful families

Let $\bar{Z}_n$ be the biased random walk conditioned to hit 0.

Note that $|\bar{\xi}_t|$ is a continuous time version of $\bar{Z}_n$ that jumps at approximately rate $(2+s)q(k)$ when in state k.

Define $\bar{T}_k^+ = \min\{n \geq 1 : \bar{Z}_n = k\}$ then

$$E_1\left(\int_0^{\bar{T}_0} |\bar{\xi}_t| dt\right) = O\left(\sum_{k=1}^{\infty} \frac{P_1(\bar{T}_k < \bar{T}_0)}{P_k(\bar{T}_k^+ = \infty)} \cdot \frac{k}{(2+s)q(k)}\right)$$

Unsuccessful families don't wander too far

Lemma Consider a BV process in $\mathbb{Z}^d$ with type-1s of fitness $1+s$ and type-0's of fitness 1, starting with a single type-1 at the origin and type-0s elsewhere. Let $\bar{\xi}_t$ be the set of 1's at time t in this process, conditioned to die out.

For $M > 0$, define the space time box

$$G_M = \left([-M\ell(s)^{1/2}/2, M\ell(s)^{1/2}/2]^d \times [0, M\ell(s)] \right).$$

For any $\delta > 0$ there exists $M(\delta)$ sufficiently large such that

$$P\left(\{\bar{\xi}_t : t \geq 0\} \cap G^c_{M(\delta)} \neq \emptyset \right) \leq \delta s.$$

Using result of (Merle 2008).

Arrival of first successful type-1 cell

Back to full model (on finite domain).

Initialize with all type-0 cells, and define σ_i: arrival time of first successful type-i cell. Define the function

$$\ell(s) = \begin{cases} s^{-2} & d = 1 \\ s^{-1}\log(1/s) & d = 2 \\ s^{-1} & d = 3 \end{cases}$$

and the assumptions

$$(A0): \quad (\ell(s))^{(d+2)/2} \ll 1/u_1$$
$$(A1): \quad N/\ell(s)^{d/2} \to \infty$$

Theorem *If (A0), (A1) hold,* $P(\sigma_1 > t/Nu_1 s) \to e^{-t}$. *as* $s, u_1 \to 0$.

Proof of arrival time - sketch

- Grid space-time, $(\mathbb{Z} \mod L)^d \times [0, \infty)$ into non overlapping boxes with time length $M_s \ell(s)$ and spatial volume $M_s^d \ell(s)^{d/2}$ where $M_s \to \infty$ sufficiently slowly such that $L \gg \ell(s)^{1/2} M_s$ and $u_1 \ell(s)^{(d+2)/2} M_s^{d+1} \to 0$.
- Previous result: probability of an unsuccessful family exiting its box (and neighboring boxes) is $o(s)$. We can approximately equate 'success' with exiting boxes.
- Probability that any box with ≥ 2 mutations, at least one which is successful goes to 0.
- Thus successful mutations arrive at rate $Nu_1 s$ and their fate is independent of any other mutations.

Simplified model with mesoscopic growth

We will only consider successful type-1 and type-2 families in spatial domain $D = [-L/2, L/2]^d \subset \mathbb{R}^d$

State. Specified by χ_t (space occupied by successful type-1 families iat time t). $D - \chi_t$ is filled by type-0s, from here on out we will refer to this set as χ_t^c.

Dynamics.

- Mutations to type-1: Poisson process Π_1 on on $D \times [0, \infty)$ with intensity $\lambda_1(x, t) = 1_{\{x \in \chi_t^c\}} u_1 s_1$.
- Each point in Π_1 initiates a ball with radius expanding as $c_d t$
- $B_{x,r} \equiv \{y : ||y - x|| \leq r\}$, where $|| \cdot ||$ is the ℓ_2 norm, then if $\Pi_1 \cap (D \times [0, t]) = \{(x_1, t_1), \ldots, (x_k, t_k)\}$,

$$\chi_t = \bigcup_{i=1}^{k} B_{x_i, c_d(t-t_i)}.$$

Simplified model with mesoscopic growth

- Mutations to type-2: Poisson process Π_2 with intensity

$$\lambda_2(x,t) = 1_{\{x\in\chi_t\}} u_2 s_2/(1+s_2) + 1_{\{x\in\chi_t^c\}} \frac{u_1 u_2 s_2 C(s_1)}{(1+s_2)}$$

  where $C(s_1)$ is the expected space-time volume of unsuccessful type-1 families in the biased voter model.

- Process is stopped at the time of arrival of the first successful type-2 mutant.

Results: regimes of initiation dynamics (simplified model)

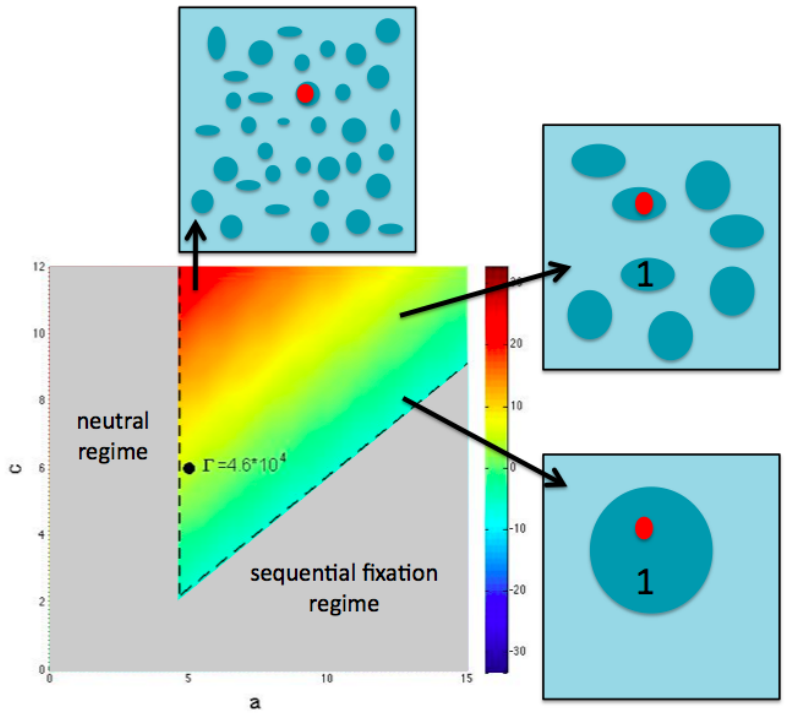
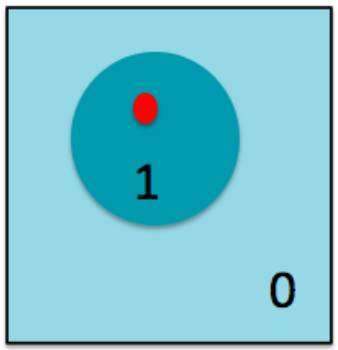


Figure : Color is log Γ, where $\Gamma = (Nu_1 s_1)^{d+1}(c_d (s_1)^d u_2 s_2)^{-1}$.

N = number of cells $= 10^c$, $u_1 = 10^{-a}$, $u_2 = 10^{-b}$, $b = a - 2$, $d = 2$, $s_1 = s_2 = s = .01$.

Distribution of initiation time in regime I ($\Gamma \to 0$)

Cancer initiation occurs within expanding clone of the first successful premalignant family.



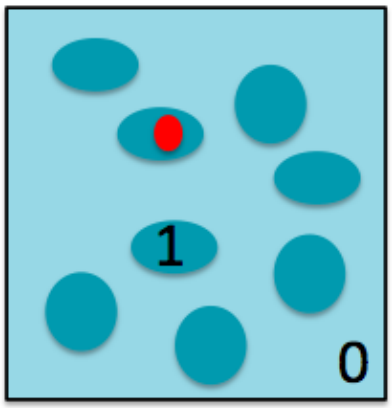
Theorem: Assume $(A3)$: $u_2 << 1/\ell(s)$

Then if $\Gamma \to 0$, $P(\sigma_2 > \frac{t}{Nu_1 s}) \to e^{-t}$ as $s, u_1, u_2 \to 0$.

Note that the assumptions used in the results to motivate the simplified model are in force throughout these results ((A0), (A1), (A2)).

Distribution of σ_2 in regime II ($\Gamma \to g \in (0, \infty)$)

Initiation occurs within one of several successful premalignant lesions.



Theorem: Assume $(A3)$ and $\Gamma \to g$

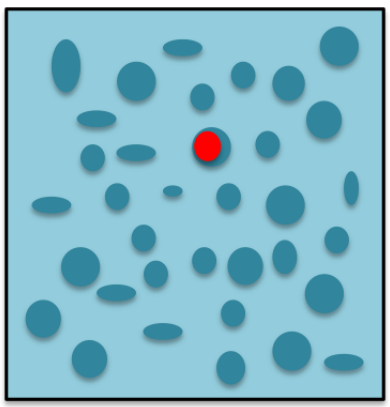
Then,

$$P(\sigma_2 > \frac{t}{Nu_1 s}) \to \exp\left(-t + \int_0^t \exp\left[-\frac{\gamma_d y^{d+1}}{(d+1)g}\right] dy\right).$$

where γ_d is the volume of unit ball in $d-$dimensions.

Distribution of σ_2 in regime III ($\Gamma \to \infty$)

Large number of premalignant lesions produced before cancer initiated from *either* a successful or unsuccessful premalignant clone.



Thm: Assume $(A3)$, $\Gamma \to \infty$.

Then, $P(\sigma_2 > t/Nu_1 s) \to \exp\left(-\frac{\gamma_d (t/K)^{d+2}}{(d+1)(d+2)} - \rho_2 \alpha_d t/J\right)$.
where α_d and ρ_2 are constants.

Distribution of σ_2 in regime $\Gamma \to \infty$

Approx. number of successful premalignant clones before cancer arises in

- an successful premalignant lesion ($K \equiv \Gamma^{1/(d+2)}$)
- an unsuccessful premalignant lesion ($J \equiv \frac{1}{u_2 \ell(s)}$)

For $J/K \to \infty$: arises in successful type-1 family

$$P(\sigma_2 > Kt/Nu_1 s) \to \exp\left(-\frac{\gamma_d t^{d+2}}{(d+1)(d+2)}\right).$$

For $J/K \to 0$: arises in unsuccessful type-1 family

$$P(\sigma_2 > Jt/Nu_1 s) \to \exp\left(-\rho_2 \alpha_d t\right).$$

For $J/(J+K) \to \theta \in (0,1)$: arises in either

$$P(\sigma_2 > (K+J)t/Nu_1 s) \to \exp\left(-\frac{\gamma_d (t/\theta)^{d+2}}{(d+1)(d+2)} - \rho_2 \alpha_d (t/(1-\theta))\right).$$

Summary

- Proposed/analyzed microscopic model of carcinogenesis (spatial evolution)
- Used results of analysis to propose approximating stochastic mesoscopic model
- Studied time of initiation of cancer in mesoscopic model, qualitative regimes of initiation behavior and dependence on tissue/pathway parameters.
- Ongoing work: spatial measures of diversity (+Katie Storey)

Next up: Understanding and predicting field cancerization with the mesoscopic model

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Previous comparisons with experimental data

- Process without mutations, beginning with just two cell types of equal fitness, is a voter model
- Previous comparisons between 2D voter model and clonal dynamics in mouse epithelial tissue
  - Klein et al, '*Mechanism of murine epidermal maintenance: Cell division and the voter model*' Phys. Rev. E 2007.
  - Doupe et. al. '*The Ordered Architecture of Murine Ear Epidermis is Maintained by Progenitor Cells with Random Fate*' Developmental Cell, 2012.'

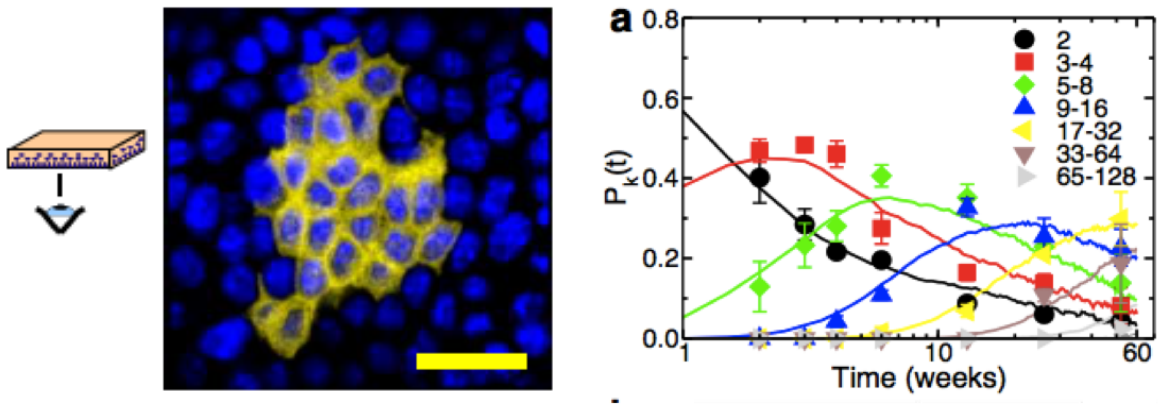

Figure : Klein et al, '*Mechanism of murine epidermal maintenance: Cell division and the voter model*' Phys. Rev. E 2007