Spatial evolution in cancer

Jasmine Foo

University of Minnesota - Twin Cities
School of Mathematics

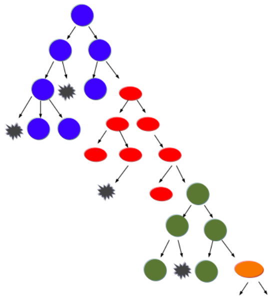
August 5, 2024

Outline

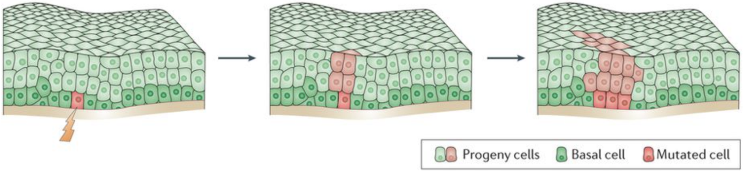
- Biased voter model of premalignant mutation spread in epithelial tissue
- Application to field cancerization
- Alternative models of tissue maintenance (death-birth process)

Cancer as an evolutionary process

- Variation: genetic alterations, epigenetic changes – stochastic or environmentally induced
- Fitness: avoidance of apoptosis signals, increases in proliferation signaling
- Heredity: permanent or transiently heritable (epi)genetic alterations

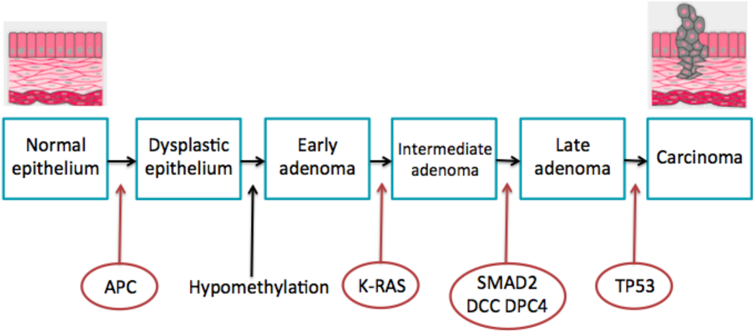


Spatial models of cancer initiation in epithelial tissues



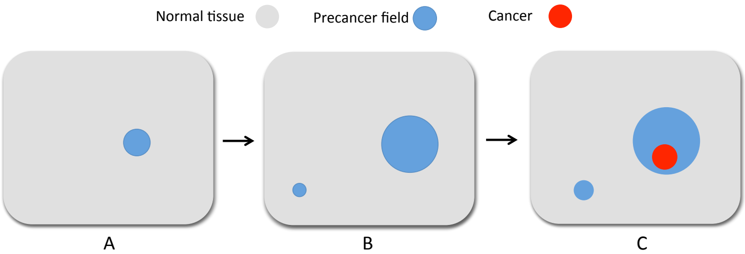
Curtius et. al. Nature Rev. Cancer 2017

Example: colorectal cancer initiation

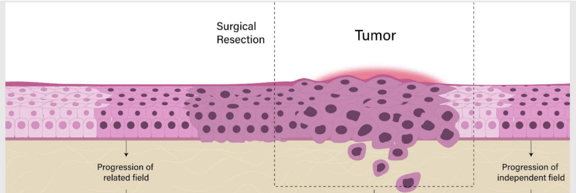


Vogelstein et al. 1988

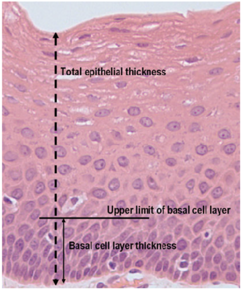
Field Cancerization



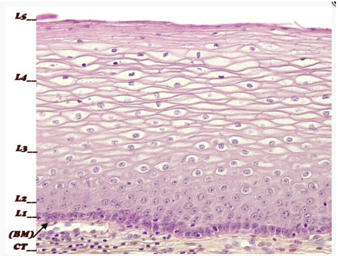
- Figure - example with two mutational hits to tumor initiation.
- 'Cancerized' fields (local and distant) likely to give rise to additional 'recurrent' tumors
- Fields often appear histologically normal (e.g TP53 mutation)



Basal layer width (w)

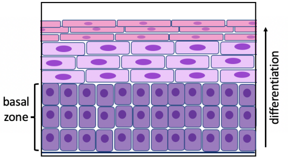


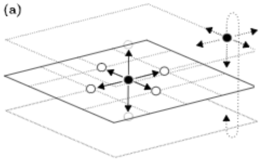
esophageal lining (w>1)



uterine cervix (w=1)

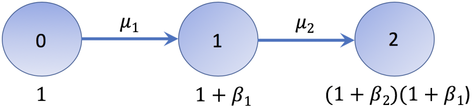
Model: carcinogenesis in epithelial basal layer





- $\mathbb{Z}^2 \times \mathbb{Z}_w$
- Cells reproduce at rate depending on fitness, daughter cell replaces neighboring cell at random.
- Initially all cells healthy (type-0)

Mutational pathway



- Type-i mutates to type-$i+1$ at rate μ_i.
- Mutations confer fitness increases $\beta_i > 0$
- Stop model when first successful type-k cell arises (time σ_k)
- Periodic boundary conditions

Biased voter model

ξ_t^A: set of sites in $\mathbb{Z}^2 \times \mathbb{Z}_w$ occupied by type-1 cells at time t, with initially type-1 occupied set A.

Set $A = \{0\}$ and $\mu_i = 0$.

ξ_t is a biased voter model with selection strength β

Survival probability (Maruyama '70, 74) via analysis of embedded random walk within $|\xi_t^A|$:

$$\frac{\beta}{1+\beta}$$

Asymptotic shape ($w = 1$): (Bramson and Griffeath 1981)

Conditioned on nonextinction, there is a set D such that for any $\epsilon > 0$ such that

$$P(\exists t^* : D(1-\epsilon)t \cap \mathbb{Z}^d \subseteq \xi_t^A \subseteq D(1+\epsilon)t \ \ \forall t > t^*) = 1$$

Biased voter model

ξ_t: set of sites in $\mathbb{Z}^2 \times \mathbb{Z}_w$ occupied by type-1 cells at time t, if $\xi_0(0) = \{0\}$.

ξ_t is a biased voter model with selection strength β

Survival probability (Maruyama '70, 74) via analysis of embedded random walk within $|\xi_t^A|$:

$$\frac{\beta}{1+\beta}$$

Asymptotic shape ($w = 1$): (Bramson and Griffeath 1981)

Conditioned on nonextinction, there is a set D such that for any $\epsilon > 0$ such that

$$P(\exists t^* : D(1-\epsilon)t \cap \mathbb{Z}^d \subseteq \xi_t^A \subseteq D(1+\epsilon)t \ \ \forall t > t^*) = 1$$

Extension to $\mathbb{Z}_2 \times \mathbb{Z}_w$

$$\mathbb{P}\Big(\exists t^* : (1-\varepsilon)tD \cap (\mathbb{Z}^2 \times \mathbb{Z}_w) \subseteq \xi_t^A \subseteq (1+\varepsilon)tD,\ \forall t \geq t^* \Big) = 1.$$

How fast do mutants spread?

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

$$c_w(\beta) \sim p_w \sqrt{\pi w} / \sqrt{h(\beta)}$$

where $h(\beta) = (1/\beta)\log(1/\beta)$ and

$$p_w = \begin{cases} 1 & w = 1 \\ 4/5 & w = 2 \\ 2/3 & w \geq 3 \end{cases}$$

(F., Gunnarsson, Leder, Storey. Ann App Prob, 2022)
(Durrett, F., Leder. J. Math Bio, 2016)

Proof sketch

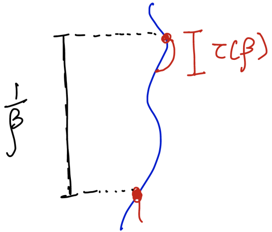
- Dual process is a coalescing branching random walk ζ_t with jump rate 1 and branching rate β:

$$P(\xi_t^A \cap B \neq \emptyset) = P(\zeta_t^B \cap A \neq \emptyset), \quad A, B \subset \mathbb{Z}^2 \times \mathbb{Z}_w$$

- Let T_0 be coalescence time between a parent and daughter particle in the dual process.

$$P(T_0 > \tau(\beta)) \sim \mu_w / \log(1/\beta),$$

where $\tau(\beta) \equiv 1/(\beta\sqrt{\log 1/\beta})$.



Proof sketch

- Ignore newborn particles that collide with parent before age $\tau(\beta)$.
- Assuming no other coalescences, resembles BRW with branching rate

$$\frac{\beta\mu_w}{\log(1/\beta)} = \mu_w/h(\beta)$$

- Effective time between branchings $\sim h(\beta)$, fluctuations of order $\sim \sqrt{h(\beta)}$:

$$\tilde{\zeta}_t^\beta = \zeta_{h(\beta)t}/\sqrt{h(\beta)}$$

- Show $\tilde{\zeta}_t^\beta$ approximates BRW with branching rate μ_w to obtain speed bounds:
  - Upper bound: couple $\tilde{\zeta}_t^\beta$ with approximating BRWs
  - Lower bound: compare $\tilde{\zeta}_t^\beta$ with oriented percolation process
- Expansion rate of BRW projection onto $\mathbb{Z}$ gives result.

Understanding cancer fields

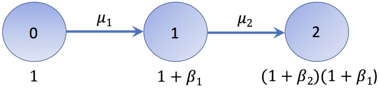
Goal: characterize the properties of the premalignant fields at the time of cancer initiation / diagnosis

Motivate a macroscopic model using properties of the microscopic model:

- Survival probability, shape of mutant clones conditioned on survival
- Expansion speed of mutant clones

Macroscopic model

k-step initiation process (type-k cells are malignant) in torus $[0, L]^d$ ($d = 2$ in epithelial tissue)



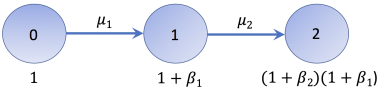
At time zero, all cells type-0.

Dynamics (k=2).

- Successful mutations to type-1: homogeneous Poisson process with rate $\mu_1 \frac{\beta_1}{\beta_1 + 1}$ per unit area
- Type-1 mutations initiate ball with expanding radius, rate $c_w(\beta_1)$.
- Type-1 individuals acquire second successful mutation at rate $\mu_2 \frac{\beta_2}{1+\beta_2}$ per unit area

Macroscopic model

k-step initiation process (type-k cells are malignant) in torus $[0, L]^d$ ($d = 2$ in epithelial tissue)



At time zero, all cells type-0.

Dynamics (k=2).

- Successful mutations to type-1: homogeneous Poisson process with rate μ_1 per unit area
- Type-1 mutations initiate ball with expanding radius, rate α.
- Type-1 individuals acquire second successful mutation at rate μ_2 per unit area
- Process is stopped at time σ_2, time of arrival of the first successful type-2 mutant.

Characterized waiting time to type-k mutation, σ_k (F., Leder, Schweinsberg. SPA 2020)

Determining local and distant field size distributions

What is the size of the local field at the time σ_2 when the first successful type-2 arises (cancer initiation)?

Conditioned on observing $\{\sigma_2 \in dt\}$, the size of the local field follows the distribution

$$\hat{P}\left(X_{[1]} \in dx\right) = \frac{u_2 \bar{\beta}_2 x^{1/d}}{d\gamma_d^{1/d} c_w(\beta_1)(1 - e^{-\theta t^{d+1}})} \exp\left[\frac{-u_2 \bar{\beta}_2 x^{\frac{d+1}{d}}}{(d+1)\gamma_d^{1/d} c_w(\beta_1)}\right],$$

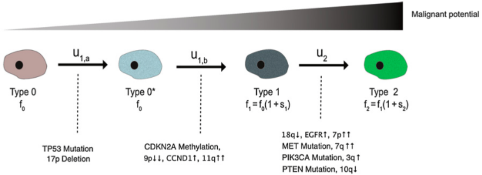
for $x \in [0, \gamma_d c_w^d(\beta_1) t^d]$, $\bar{\beta}_i = \frac{\beta_i}{1+\beta_i}$, $\theta = \frac{u_2 \bar{\beta}_2 \gamma_d c_w^d(\beta_1)}{d+1}$.

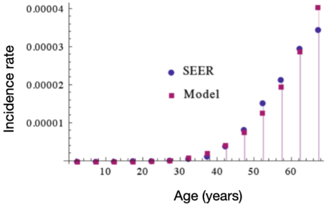
Analogous results can be obtained for the **distant field** (number and size of field patches).

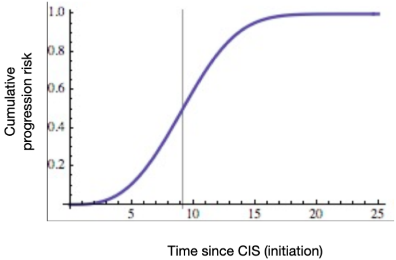
Field size distributions can be used to predict recurrence risk.

Application to HPV- Head and Neck Squamous Cell Carcinoma (HNSCC)

HNSCC arises in the epithelial lining of the oral cavity, pharynx, and larynx, associated with high recurrence rates due to field cancerization.



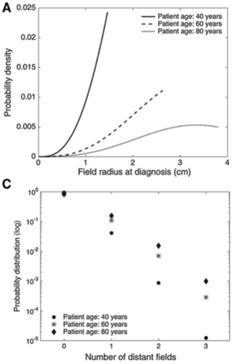




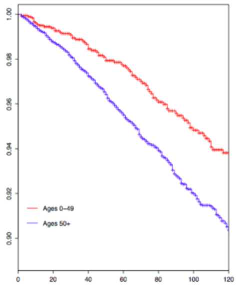
Field extent is dependent on age-at-diagnosis

Radius of local field surrounding primary tumor

Number of distant fields present at diagnosis



Age-stratified recurrence-free survival rate after surgery (SEER)



Time since treatment (months)

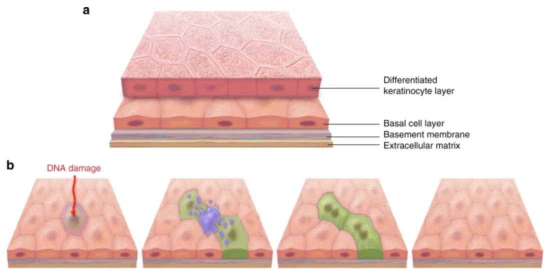
Ryser et al 2016, Cancer Research

Alternative models of tissue maintenance

Birth-death (biased voter) model: Cell division triggers death of a neighbor, thus maintaining homeostasis.

Death-birth model: Cell death triggers division of a neighbor.

Fig. 6



(Brock et. al., Nature Comm 2019) Damaged epithelial cells release apoptotic bodies, which are engulfed by neighboring cells and signal proliferation.

Death-birth model

- Each cell dies at rate 1.
- Upon death, a neighboring cell selected with probability proportional to fitness to divide and place offspring at dead cell position.
- We again assume that type-0 cells have fitness 1 and type-1 cells have fitness $1+\beta$. Let $\lambda = 1+\beta$.
- Denote the set of sites occupied by type-1 cells by ξ_t^A, where $\xi_0^A = A \subset \mathbb{Z}^d$.
- Define $\tau_\emptyset^A = \inf\{t \geq 0 : \xi_t^A = \emptyset\}$ time of extinction of type-1.

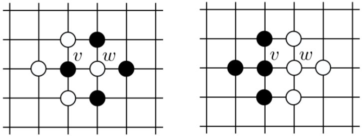
Note that fitness can be incorporated in the first or second stage (e.g. $B^f D$, BD^f, $D^f B$, DB^f). Here we consider $BD \equiv B^f D$ and $DB \equiv DB^f$.

Bias of 0-1 edges ($d > 1$)

- Birth-death: at 0-1 edges the rate of $0 \to 1$ is $(1+\beta)/(2d)$ independent of neighbors.
- Death-birth: at 0-1 edges flipping rates are configuration-dependent, i.e.

$$\frac{1}{k + (2d-k)\lambda}\ (1 \to 0) \quad \text{and} \quad \frac{\lambda}{(2d-m) + m\lambda}\ (0 \to 1)$$

  where k = number of type-0 neighbors of the 1, and m = number of type-1 neighbors of the 0.
- DB 0-1 edges have non-negative bias towards type-1, but can be zero (checkerboard).



minimal bias ($k = m = 2d$) maximal bias ($k = m = 1$)

Survival Probability

In $d = 1$, $P(\tau_\emptyset^0 = \infty) = 2\beta/(2+3\beta)$ ($\to \beta$ in weak selection limit).
For $d > 1$:

- Define S_n the jump process embedded in $(|\xi_t^{\{0\}}|)_{t\geq 0}$
- S_n acquires a non-negative drift from every 0-1 edge, configuration-dependent for $S_n \geq 2$.

Proposition

$$C_1(d)\beta \geq P(\xi_t^0 \neq \emptyset \text{ for all } t \geq 0) \geq C_2(d)\beta^{d/(d-1)}$$

where C_1, C_2 are positive constants.

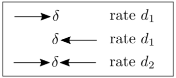
- Consider boundary of ξ_t^0 with unbounded component of complement, lower bound.
- Drift on boundary edges strictly nonzero.

F., Gunnarsson, Leder, Sivakoff (2023)

Graphical representation of DB process

- Let $\mathcal{N}(x) \subseteq 2^{\mathbb{Z}^d}$ be the set of neighbors of $x \in \mathbb{Z}^d$.
- For each subset $S \subseteq \mathcal{N}(x)$ of neighbors with $|S| = j$, draw δ-arrows from all sites in S to x at rate $d_j(\beta)$.
- δ kills the particle at x, and that x assumes state 1 if and only if at least one of the arrows connects x to a site in state 1.

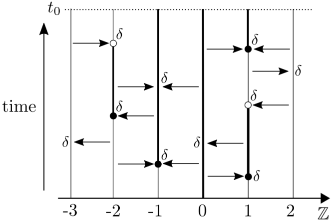
(a)



(b)

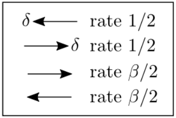
	$\to\delta$	$\delta\leftarrow$	$\to\delta\leftarrow$
$0-x-0$	0	0	0
$0-x-1$	0	1	1
$1-x-0$	1	0	1
$1-x-1$	1	1	1

(c)



Graphical representation of BD process

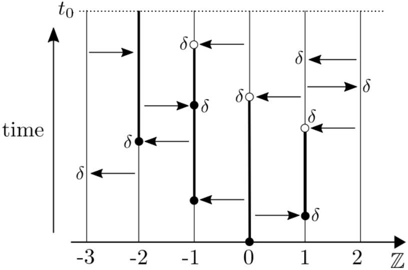
(a)



(b)

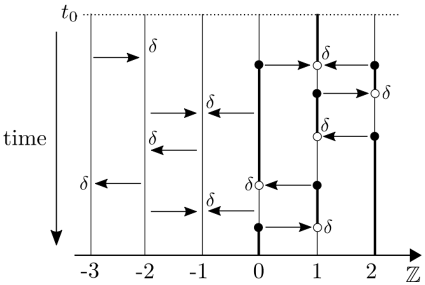
$x - y$	$\delta \leftarrow$	$\leftarrow$
$0 - 0$	0	0
$0 - 1$	1	1
$1 - 0$	0	1
$1 - 1$	1	1

(c)



Dual process $\hat{\xi}_t$

- Consider particle $x \in \hat{\xi}_t$. For each subset $S \subseteq \mathcal{N}(x)$ of neighbors with $|S| = j$, replace the particle at x with j offspring placed at the elements of S at rate d_j. Particles coalesce if they meet.
- Satisfies $P(\hat{\xi}_t^A \cap B \neq \emptyset) = P(\xi_t^B \cap A \neq \emptyset)$.



Shape theorem for DB

Theorem

Conditioned on nonextinction, there is a convex subset D of $\mathbb{R}^d$ *such that for every* $\varepsilon > 0$

$$\mathbb{P}\left(\exists t_* < \infty : (1-\varepsilon)tD \cap \mathbb{Z}^d \subseteq \xi_t^0 \subseteq (1+\varepsilon)tD,\ t \geq t_* \;\middle|\; \tau_\varnothing^0 = \infty\right) = 1.$$

Durrett, Griffeath (82) provide conditions for existence of shape theorems for growth models on $\mathbb{Z}^d$.

- Conditioned on extinction, process eventually contains a linearly expanding ball (modify techniques from Bramson Griffeath (81) BV analysis)

F., Gunnarsson, Leder, Sivakoff (2023)

Shape theorem

- Extinction probability decays approximately exponentially in initial size.

Lemma

There are constants $C, \gamma > 0$ so that

$$\sup_{A \in \overline{\mathcal{S}}, |A|=k} \mathbb{P}(\tau_{\varnothing}^{A} < \infty) \leq C \exp\left(-\gamma k^{(d-1)/d}\right), \quad k \geq 1.$$

- Probability that the death-birth process remains alive at a small size to time t decreases exponentially fast.

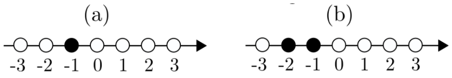
Lemma

For sufficiently small $\varepsilon > 0$, there are constants $C, \gamma > 0$ so that

$$\mathbb{P}\Big(|\xi_s^0| \in \left(0, \varepsilon t^{d/(d+1)}\right),\ s \leq t\Big) \leq C \exp\left(-\gamma t^{(d-1)/(d+1)}\right), \quad t \geq 0.$$

Note on other models of maintenance

- $D^f B$ model: type-0 particles die at rate 1, type-1 particles die at rate $1/\lambda$. ($\lambda = 1 + \beta$). When a particle dies at x, a neighboring particle is chosen uniformly at random to divide and place its offspring at x.
  - Run at speed λ, we obtain the $B^f D$ model.
- BD^f model: all particles divide at rate 1, a neighbor is selected to die with probability inversely proportional to its fitness. If there are i type-0 neighbors and j type-1 neighbors, a type-0 neighbor is selected to die with probability $i/(i + j(1/\lambda)) = i\lambda/(i\lambda + j)$, and a type-1 neighbor is selected to die with probability $j(1/\lambda)/(i + j(1/\lambda)) = j/(i\lambda + j)$.
  - Switching rate depends on neighbors of neighbors



Acknowledgements

- Einar Gunnarsson (Univ Iceland)
- Kevin Leder (Univ Minnesota)
- David Sivakoff (OSU)
- Katie Storey (Lafayette Coll.)
- Jason Schweinsberg (UCSD)
- Marc Ryser (Duke)
- Rick Durrett (Duke)

Funding from NSF, NIH, UMN