Spatial modeling of carcinogenesis

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November 1, 2019
Multi-step theory of carcinogenesis

Oncogenic mutations may confer increased fitness and mutation rate
Example: colorectal cancer initiation
Stratified epithelium

e.g. skin epithelia

- squame about to flake off from surface
- keratinized squames
- granular cell layer
- prickly cell layers
- basal cell layer
- basal lamina
- connective tissue of dermis

basal cell passing into prickly cell layer

30 μm
Expansion of premalignancy in epithelial tissues


Expansion of premalignancy in glandular tissues

Field Cancerization

- ‘Cancerized field’: a collection of cells that have gained some but not all the phenotypic alterations required for malignancy
- Fields likely to give rise to tumors
- Fields often appear histologically normal (e.g. TP53 mutation)
- Recurrences more likely when fields present
Clinical questions

Clinical observation: multiple independent (metachronous or synchronous) tumors occurring in same region of tissue, not metastases of primary tumors.

- Surgeon:
  - surgical margins
  - distant fields present at diagnosis/surgery

- Oncologist:
  - likely timing of recurrence
  - recurrence type: second primary or second field tumor
  - risk of progression, designing surveillance protocols
  - sampling guidelines for suspected premalignant lesions
Model: carcinogenesis in epithelial basal layer

- $\mathbb{Z}^2 \times \mathbb{Z}_w$ (stack of sheets)
- Initially all cells healthy (type-0)
- Reproduction rate depends on fitness.
- Daughter cell replaces neighboring cell at random.
- Type-$i$ mutates to type-$i+1$ at rate $\mu_i$.
- Mutations confer fitness increases $\beta_i > 0$
- Periodic boundary conditions
Survival probability and shape theorem

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

Consider \( A = \{0\}, \mu = 0 \). \( \xi_t^A \) a biased voter model with selection strength \( \beta \)

Survival probability (Maruyama ’70, 74)

\[
\frac{\beta}{1 + \beta}
\]

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

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

\[
P(\exists t^* : D(1 - \epsilon)t \cap \mathbb{Z}^d \subseteq \xi_t^A \subseteq D(1 + \epsilon)t \ \forall t > t^*) = 1
\]
Speed of advantageous mutation expansion through basal layer

**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

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

FGLS (2019); DFL (2016)
Boundary conditions: periodic vs. reflecting

K. Storey
Basal layer width \((w)\)

- esophageal lining \((w>1)\)
- uterine cervix \((w=1)\)
Other models

Understanding cancer fields: a simpler model

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

Motivate a simplified model using properties of the full model:

- Survival probability, shape of mutant clones conditioned on survival
- Expansion speed of mutant clones
- Arrival rate of ‘successful’ mutations
- Contribution of unsuccessful mutants to subsequent mutations
Simplified model: deterministic growth approximation

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

At time zero, all cells type-0.

Dynamics.

- 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
Simplified model: deterministic growth approximation

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

At time zero, all cells type-0.

Dynamics.

- Successful mutations to type-1: homogeneous Poisson process with rate $\mu_1$ per unit area
- Type-1 mutations initiate ball with expanding radius, rate $\alpha$.
- Type-1 individuals acquire second successful mutation at rate $\mu_2$ per unit area
- Process is stopped at time $\sigma_2$, time of arrival of the first successful type-2 mutant.
Waiting time $\sigma_2$

11 cases ($N = L^d$)

1. $\mu_1 \ll \frac{\alpha}{N^{(d+1)/d}}$ and $\mu_2 \gg \mu_1$
2. $\mu_1 \ll \frac{\alpha}{N^{(d+1)/d}}$ and $\mu_2 \ll \mu_1$
3. $\mu_1 \ll \frac{\alpha}{N^{(d+1)/d}}$ and $\frac{\mu_2}{\mu_1} \rightarrow c \in (0, \infty)$
4. $\mu_1 \gg \frac{\alpha}{N^{(d+1)/d}}$ and $\mu_2 \gg \frac{(N\mu_1)^{d+1}}{\alpha^d}$
5. $\mu_1 \gg \frac{\alpha}{N^{(d+1)/d}}$ and $\frac{\mu_2\alpha^d}{(N\mu_1)^{d+1}} \rightarrow c \in (0, \infty)$
6. $\mu_1 \gg \frac{\alpha}{N^{(d+1)/d}}$ and $\frac{(\mu_1\alpha^d)^{1/(d+1)}}{N} \ll \mu_2 \ll \frac{(N\mu_1)^{d+1}}{\alpha^d}$
7. $\mu_1 \gg \frac{\alpha}{N^{(d+1)/d}}$ and $\frac{N\mu_2}{(\mu_1\alpha^d)^{1/(d+1)}} \rightarrow c \in (0, \infty)$
8. $\mu_1 \gg \frac{\alpha}{N^{(d+1)/d}}$ and $\mu_2 \ll \frac{(\mu_1\alpha^d)^{1/(d+1)}}{N}$
9. $\mu_1 \gg \frac{\alpha}{N^{(d+1)/d}}$ and $\mu_2 \gg \frac{(N\mu_1)^{d+1}}{\alpha^d}$
10. $\mu_1 \gg \frac{\alpha}{N^{(d+1)/d}}$ and $\mu_2 \ll \frac{(N\mu_1)^{d+1}}{\alpha^d}$
11. $\mu_1 \gg \frac{\alpha}{N^{(d+1)/d}}$ and $\mu_2 \gg \frac{(N\mu_1)^{d+1}}{\alpha^d}$.

DFL 2016, FLS 2019
Case 5: \( \mu_1 \gg \frac{\alpha}{N(d+1)/d} \) and \( \frac{\mu_2 \alpha^d}{(N\mu_1)^{d+1}} \rightarrow c \in (0, \infty) \)

\[ P(N\mu_1 \sigma_2 > t) \]
\[ \rightarrow \exp \left( - \int_0^{t/N\mu_1} N\mu_1 \left( 1 - \exp \left( - \frac{\gamma_d}{d+1} \cdot \mu_2 \alpha^d (t/N\mu_1 - r)^{d+1} \right) \right) \, dr \right) \]

probability of 2nd mutation by time \( t' \) in type-1 ball initiated at time \( r \)

\[ = \exp \left( - \int_0^t \left( 1 - \exp \left( - \frac{c \gamma_d y^{d+1}}{d+1} \right) \right) \, dy \right). \]

where \( \gamma_d \) is volume of unit ball in \( d \) dimensions, \( c \) a constant
Case 6: \( \mu_1 \gg \frac{\alpha}{N(d+1)/d} \) and \( \frac{(\mu_1 \alpha^d)^{1/(d+1)}}{N} \ll \mu_2 \ll \frac{(N\mu_1)^{d+1}}{\alpha^d} \)

\[
q(t) = 1 - \exp\left(-\int_0^t \mu_1 \gamma_d (\alpha r)^d \, dr\right) = 1 - \exp\left(-\frac{\gamma_d}{d+1} \cdot \mu_1 \alpha^d t^{d+1}\right)
\]

probability a site occupied by type-1 or higher

\[
P(\sigma_2 > t) \approx \exp\left(-\int_0^t N\mu_2 q(r) \, dr\right) \approx \exp\left(-\frac{\gamma_d}{(d+1)(d+2)} \cdot N\mu_1 \mu_2 \alpha^d t^{d+2} \, dt\right).
\]

\[
P\left((N\mu_1 \mu_2 \alpha^d)^{1/(d+2)} \sigma_2 > t\right) \rightarrow \exp\left(-\frac{\gamma_d t^{d+2}}{(d+1)(d+2)}\right).
\]
$\sigma_2$ dependence on $w$
Local field sizes

What is the size of the local field at the time $\sigma_2$ when the first successful type-2 arises (cancer initiation)?

[FLR2014] Conditioned on observing $\{\sigma_2 \in dt\}$, the size of the local field follows the distribution

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

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).
Distant fields

The size-distribution of the distant field clones at time $\sigma_2$ of the first successful type-2 mutation, conditioned on \( \{ \sigma_2 = t \} \), is given by

$$
\mathcal{L}(\tilde{X}_d|\sigma_2 \in dt) \sim \tilde{P}(\tilde{X}_1 \in dx_1, \ldots, \tilde{X}_{M(t)-1} \in dx_{M(t)-1})
$$

$$
= \sum_{m=1}^{\infty} \frac{(\lambda \phi(t)t)^{m-1} e^{-\lambda \phi(t)t}}{(m-1)!} \prod_{i=1}^{m-1} g_t(x_i),
$$

where $g_t(x) = \frac{x^{1/d-1}}{d \gamma_d^{1/d} c_d(\beta_1) t \phi(t)} \exp \left[ -u_2 \beta_2 x^{d+1} d \gamma_d^{1/d} c_d(\beta_1) - \frac{-u_2 \beta_2 x^{d+1} d}{(d+1) \gamma_d^{1/d} c_d(\beta_1)} \right]$, 

$\phi(t) \equiv \frac{1}{t} \int_0^t \exp (-\theta r^{d+1}) \, dr$, and $\lambda = Nu_1 \beta_1 / (1 + \beta_1)$ (arrival rate of premalignant clones).
Field sizes depend on $w$
HPV- head and neck squamous cell carcinoma

- Head and neck squamous cell carcinoma (HNSCC) arises in the epithelial lining of the oral cavity, pharynx, and larynx.
- Annual incidence estimated to be around 600,000 new cases worldwide.
- High rates of local recurrence commonly attributed to unresected fields of precancerous tissue (not easily detectable at time of surgery).
- Modeling may allow for prediction of the extent and dynamics of these fields.
Neutral first step allows analysis of ‘effective’ $u_1$ (Durrett and Moseley, 2015).

$$u_{1,a} \pi^{−1/2} (u_{1,b} \bar{\beta}_1)^{1/2} \log^{1/2}(1/u_{1,b} \bar{\beta}_1)$$

Ryser et al 2016, Cancer Research
Model parameters

- Total population size (N)
- Cellular transition rates from normal to precancer ($u_1$), from precancer to carcinoma in situ ($u_2$)
- Relative proliferative advantage of precancer ($\beta_1$) and carcinoma in situ cells ($\beta_2$)
- Mean sojourn time from preclinical lesion to clinical diagnosis with cancer ($1/\Psi$).

Derive survival function under evolutionary model (define $\sigma_3$ as time to diagnosis with invasive cancer):

\[
S(t) = P(\sigma_3 \geq t) = e^{-\Psi(t)} + \Psi e^{-\Psi(t)} \int_0^t \exp \left( \frac{\lambda}{3\theta_1/3} \gamma(1/3, \theta \tau^3) - \lambda \tau + \Psi \tau \right) d\tau
\]

where $\lambda \equiv Nu_1 \beta_1$ (initiation rate of successful type 1 clones), $\theta \equiv \frac{u_2 \beta_2 \pi c_1^2}{3}(\beta_1)$ (related to time for successful type 1 to give rise to successful type 2).
Model calibration to age-specific incidence data

- Compare model-predicted hazard rate for cancer incidence to age-specific incidence rates from National Cancer Institute data
- Estimate posterior parameter group distributions using Bayesian framework, given observed age-specific incidence data
- Independently estimated parameters in agreement with posteriors
Model predictions

- Current clinical practice recommends an age-independent excision margin width of 1 cm.
- Model predicts higher recurrence risk in older patients treated with surgery only (larger amount of premalignant tissue left behind in primary field, secondary fields)
- For patients treated with adjuvant radiation after surgery, age-related difference should be reduced.
Observed population-level recurrence patterns

- Kaplan-Meier curves for recurrence-free survival
- Recurrence risk in older patients (≥ 50 yrs) 58% greater than in younger patients treated by surgery only
Field predictions

A. Probability density vs. field radius at diagnosis (cm) for different patient ages.

B. Relative mean field radius vs. age at diagnosis (years).

C. Probability distribution (log scale) vs. number of distant fields for different patient ages.

D. Probability of multiple fields vs. age at diagnosis (years).
Consider an alternative ‘death-birth’ model of basal layer epithelial dynamics:

- 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 $1 + \beta$.
- Denote the set of sites occupied by type-1 cells by $\xi_t^A$, where $\xi_0^A = A \subset \mathbb{Z}^d$.

(w/J. Foo and D. Sivakoff)
Survival Probability

- In birth-death dynamics originally studied survival probability is easily calculated using gambler’s ruin formula.
- This is because at each discordant edge the rate of 1 winning is always \((1 + \beta)/(2d)\), i.e., doesn’t depend on neighbors of particular site.
- In death-birth dynamics this is no longer the case. Rate of 1 losing at a discordant edge will depend on neighbors.
- This leads to the question, is probability of survival positive? If so, how does it depend on fitness advantage?
- Partial answer:

**Theorem**

*There exists a positive constant \(C\) such that*

\[
P(\xi_t^0 \neq \emptyset \text{ for all } t \geq 0) \geq C \beta^{(d-1)/d}.
\]
Shape theorem

- Had nice shape theorem for birth-death dynamics.
- A little bit of work and it is possible to extend the shape theorem to death-birth dynamics.

**Theorem**

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

$$P(\exists t^* < \infty : (1 - \varepsilon)U \subset t^{-1} \xi_t^0 \subset (1 + \varepsilon)U | \xi_t^0 \neq \emptyset \ \forall t > 0) = 1.$$*
Summary

- Carcinogenesis in epithelial tissue modeled with stochastic particle systems
- Simplified models based on microscopic model behaviors facilitate analysis of macroscopic, clinically relevant quantities
- Analytical results can drive statistical frameworks for interpreting clinical/experimental data, parametrizing models
- Many problems to do!