Evolutionary dynamics of cancer:  
A spatial model of cancer initiation

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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 $(N \div L^d)$
- 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)
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

\[ \Rightarrow \frac{R_t}{t} \to s \text{ as } t \to \infty. \text{ Growth is linear.} \]

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 $\beta_d$ 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 $i$.

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

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

\[ P_1(T_k < T_0) \sim \frac{s}{1 - e^{-c}} \quad \text{and} \quad P_k(T_0 < \infty) \to e^{-c} \]

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

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

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

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

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 $\sigma_i$: 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

$$(A0) : (\ell(s))^{(d+2)/2} \ll 1/u_1$$

$$(A1) : N/\ell(s)^{d/2} \to \infty$$

**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 \(\geq 2\) 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 \( \chi_t \) (space occupied by successful type-1 families at time \( t \)). \( D - \chi_t \) is filled by type-0s, from here on out we will refer to this set as \( \chi_t^c \).

**Dynamics.**

- Mutations to type-1: Poisson process \( \Pi_1 \) on \( D \times [0, \infty) \) with intensity
  \( \lambda_1(x, t) = 1_{\{x \in \chi_t^c\}} u_1 s_1 \).

- Each point in \( \Pi_1 \) initiates a ball with radius expanding as \( c_d t \)

- \( B_{x,r} = \{ y : \| y - x \| \leq r \} \), where \( \| \cdot \| \) is the \( \ell_2 \) 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 $\Pi_2$ with intensity

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

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 $\Gamma$, where $\Gamma = (Nu_1s_1)^{d+1}(c_d(s_1)^d u_2 s_2)^{-1}$.

$N =$ 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 $\Gamma \to 0$, $P(\sigma_2 > \frac{t}{Nu_1s}) \to e^{-t}$ 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 $\sigma_2$ in regime II ($\Gamma \rightarrow g \in (0, \infty)$)

Initiation occurs within one of several successful premalignant lesions.

**Theorem:** Assume (A3) and $\Gamma \rightarrow g$

Then,

$$P(\sigma_2 > \frac{t}{Nu_1s}) \rightarrow \exp \left( -t + \int_0^t \exp \left[ -\frac{\gamma_d y^{d+1}}{(d + 1)g} \right] dy \right).$$

where $\gamma_d$ is the volume of unit ball in $d$–dimensions.
Distribution of $\sigma_2$ 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 $\alpha_d$ and $\rho_2$ are constants.
Distribution of $\sigma_2$ 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

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

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

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