Cancer Evolution in Spatially Structured Tissues

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Evolution can be defined as the process of cumulative change in characteristics of populations over many generations [6]. At the heart of any evolutionary process lies a reproducing population whose dynamics generate the biological diversity and selection forces that drive change. These processes are strongly shaped by the spatial structure of the population, which can influence both the temporal dynamics and overall direction of evolutionary progression. Cancer initiation, driven by the stochastic accumulation of oncogenic mutations and their subsequent clonal expansion, is an evolutionary process that often occurs within the regulated spatial structure of an epithelial tissue. Since tissue spatial structure (i.e., geometry and reproduction/death dynamics) can vary between sites in the body and cancer types, some interesting and important questions arise: how does the spatial population structure of a tissue influence the process of carcinogenesis? Specifically, how does spatial structure affect the timing, survival, and spread of advantageous oncogenic mutations, and how do these variations materialize into clinically-relevant differences in incidence, recurrence rates, and resection guidelines?

The majority of human cancers originate from structured epithelial tissue, which covers the outer and inner surfaces of organs and blood vessels. In typical stratified epithelial tissue, stem cells proliferate along the bottom (basal) layers and continually replenish the upper layers with differentiated cells that lose their ability to proliferate (Figure 1(a)) [3, 10]. Since the accumulation and spread of mutations is driven by the proliferating basal cells, the spatial structure of the basal zone (which may be of varying cellular thickness) is the appropriate setting to study the process of carcinogenesis in the epithelial tissue. In 1977 Williams and Bjerknes proposed a two-dimensional model of clonal expansion of advantageous mutants, in which normal and faster-proliferating mutant cells reside on a regular lattice. Upon cell division, a daughter cell replaces a neighboring cell chosen uniformly at random. The same model also arose independently in the interacting particle systems community and is widely known as the biased voter model. Bramson and Griffeath [1, 2] showed in 1980–1981 that under the biased voter model, an advantageous mutant clone conditioned upon survival eventually assumes a convex, symmetric shape whose diameter grows linearly in time. More recently, using a one-dimensional lattice model, Komarova [11] analyzed the timing of cancer initiation, assuming that only two oncogenic mutations are required for cancer initiation. Durrett and Moseley [4] extended Komarova's work to two and three dimensions assuming a selectively neutral first step.

A key component of understanding the impact of spatial structure on carcinogenesis is characterizing the survival and expansion dynamics of a single advantageous mutant in a structured population. Although this problem is motivated by the study of cancer initiation, the theoretical results are more generally applicable to understanding invasion dynamics in spatially structured populations. In recent work with Einar Gunnarsson, Kevin Leder, and Kathleen Storey, we examined the effect of the basal zone geometry, in addition to proliferation and selection characteristics of the tissue and mutants, on the speed of advantageous mutation expansion in epithelial basal zones [7]. In particular the propagation speed of a premalignant mutant clone was determined as a function of a small mutant selective advantage and the number of layers in the basal zone, which enables comparison of cancer evolution between different types of epithelial cancer. These results were obtained using a spatially explicit model of cell division and replacement, where cells live on a set of stacked two-dimensional integer lattices representing a multilayered basal zone, and cellular birth and death dynamics follow biased voter rules (see Figure 1).

In particular, let $\mathbb{Z}_w := \mathbb{Z} \bmod w$ denote the additive group of integers modulo $w \geq 1$. The epithelial basal zone is represented as the set $\mathbb{Z}^2 \times \mathbb{Z}_w$ of w layers of two-dimensional integer lattices, with a periodic boundary condition along the third dimension. For each site $x \in \mathbb{Z}^2 \times \mathbb{Z}_w$, we define its *neighborhood* as $\mathcal{N}(x) := \{x \pm e_i : i = 1, 2, 3\}$, where e_i is the ith unit vector, and addition along the third dimension is carried out modulo w. To model the spread of premalignant fields, we define the biased voter model on $\mathbb{Z}^2 \times \mathbb{Z}_w$ as follows. Each site in $\mathbb{Z}^2 \times \mathbb{Z}_w$ is occupied by either a type-0 cell, representing a normal cell, or a type-1 cell, representing a premalignant mutant cell. Type-1 cells have fitness advantage $\beta > 0$ over type-0 cells, meaning that type-1 cells divide at exponential rate $1 + \beta$, while type-0 cells divide at rate 1. Upon cell division at site $x \in \mathbb{Z}^2 \times \mathbb{Z}_w$, one daughter cell stays at site x, while the other daughter cell replaces a neighboring cell at a site $y \in \mathcal{N}(x)$ chosen uniformly at random (Figure 1(b)).

Let ξ_t^A denote the set of sites in $\mathbb{Z}^2 \times \mathbb{Z}_w$ occupied by type-1 cells at time t, given the initial condition $\xi_0^A = A$ with

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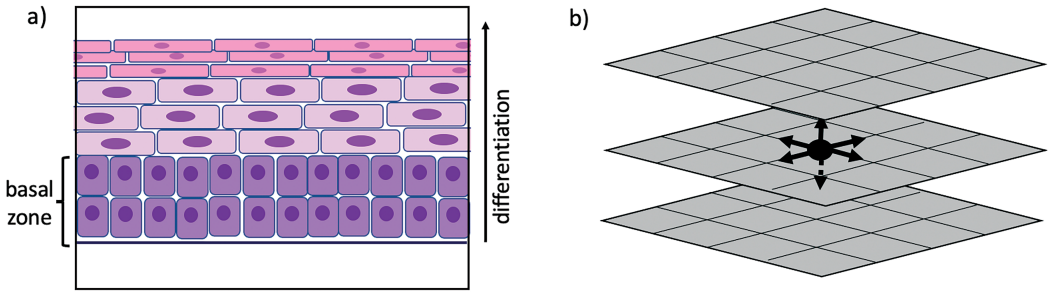


Figure 1. (a) Cross-section of the stratified squamous epithelium of the esophagus. A basal zone, which consists of several layers of stem and stem-like cells, continually replenishes the upper layers with more differentiated cells. Figure adapted from [7]. (b) Model dynamics for the $w = 3$ case (basal zone consists of three layers). When the black cell in the middle divides, one daughter cell remains at the site and the other replaces one of six neighboring cells chosen uniformly at random.

$A \subseteq \mathbb{Z}^2 \times \mathbb{Z}_w$. Suppose the system starts out with a single type-1 cell at the origin, i.e., $A = \{0\}$. If the mutant does not die out, it can be shown that the shape theorem [1, 2] extends to $\mathbb{Z}^2 \times \mathbb{Z}_w$, i.e., ξ_t^0 asymptotically assumes a shape $D(\beta)$. $D(\beta)$ is a stack of convex and symmetric sets defined in [1] as a unit ball under a norm induced by ξ_t^0, and it expands linearly in time along the first two dimensions. To determine the rate of expansion of the mutant clone ξ_t^0, we denote the radius of $D = D(\beta)$ by $c_w(\beta)$, and define it in terms of the projection of D onto the x-axis as

$$\{x \in \mathbb{R} : (x, y, z) \in D\} =: [-c_w(\beta), c_w(\beta)]\, e_1, \qquad (1)$$

where $e_1 = (1, 0, 0)$. We determine $c_w(\beta)$ as a function of a small selective advantage $\beta > 0$ and tissue thickness $w \geq 1$. In particular, let p_w be the probability that a cell giving birth on $\mathbb{Z}^2 \times \mathbb{Z}_w$ replaces a cell occupying the same layer. Then, as $\beta \to 0$,

$$c_w(\beta) \sim p_w \sqrt{\pi w \beta} \Big/ \sqrt{\log(1/\beta)}.$$

This core result can be leveraged to characterize the impact of tissue structure, geometry, and maintenance dynamics on cancer initiation and recurrence risks. To do this we append to the model the stochastic accumulation of oncogenic mutations following a spatial Poisson process. We utilize a model approximation in which mutant expansion, conditioned on nonextinction, proceeds deterministically based on the speed results obtained from the biased voter dynamics. This approximate model is analytically tractable enough to obtain results on the timing of cancer initiation, geometry and heterogeneity of premalignant fields, and recurrence risk after surgery [5, 8, 9, 12]. These analyses can also be extended to study the variations in tissue maintenance dynamics and their impact on the cancer initiation process.

References

[1] M. Bramson and D. Griffeath, *On the Williams-Bjerknes tumour growth model. II*, Math. Proc. Cambridge Philos. Soc. **88** (1980), no. 2, 339–357. MR578279

[2] M. Bramson and D. Griffeath, *On the Williams-Bjerknes tumour growth model. I*, Ann. Probab. **9** (1981), no. 2, 173–185. MR606980

[3] P. T. Chandrasoma, *Gerd: a new understanding of pathology, pathophysiology, and treatment*, Academic Press, 2017.

[4] R. Durrett and S. Moseley, *Spatial Moran models I. Stochastic tunneling in the neutral case*, Ann. Appl. Probab. **25** (2015), no. 1, 104–115, DOI 10.1214/13-AAP989. MR3297767

[5] R. Durrett, J. Foo, and K. Leder, *Spatial Moran models, II: cancer initiation in spatially structured tissue*, J. Math. Biol. **72** (2016), no. 5, 1369–1400, DOI 10.1007/s00285-015-0912-1. MR3464206

[6] J. Endler, *Natural selection in the wild*, Princeton University Press, New Jersey, 1986.

[7] J. Foo, E. Gunnarsson, K. Leder, and K. Storey, *Spread of premalignant mutant clones and cancer initiation in multilayered tissue*, submitted (2021).

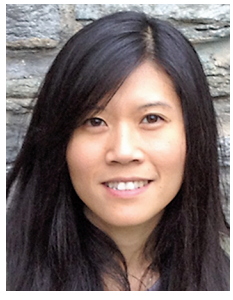
[8] J. Foo, K. Leder, and M. D. Ryser, *Multifocality and recurrence risk: a quantitative model of field cancerization*, J. Theoret. Biol. **355** (2014), 170–184, DOI 10.1016/j.jtbi.2014.02.042. MR3217192

[9] J. Foo, K. Leder, and J. Schweinsberg, *Mutation timing in a spatial model of evolution*, Stochastic Process. Appl. **130** (2020), no. 10, 6388–6413, DOI 10.1016/j.spa.2020.05.015. MR4140038

[10] K. Geboes, *Squamous mucosa and reflux*, OESO Knowledge, 1994.

[11] N. L. Komarova, *Spatial stochastic models for cancer initiation and progression*, Bull. Math. Biol. **68** (2006), no. 7, 1573–1599, DOI 10.1007/s11538-005-9046-8. MR2257717

[12] K. Storey, M. D. Ryser, K. Leder, and J. Foo, *Spatial measures of genetic heterogeneity during carcinogenesis*, Bull. Math. Biol. **79** (2017), no. 2, 237–276, DOI 10.1007/s11538-016-0234-5. MR3599691



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