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Survival probabilities at spherical frontiers

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ABSTRACT

Motivated by tumor growth and spatial population genetics, we study the interplay between evolutionary and spatial dynamics at the surfaces of three-dimensional, spherical range expansions. We consider range expansion radii that grow with an arbitrary power-law in time: $R(t) = R_0(1 + t/t^*)^{\Theta}$, where Θ is a growth exponent, R_0 is the initial radius, and t^* is a characteristic time for the growth, to be affected by the inflating geometry. We vary the parameters t^* and Θ to capture a variety of possible growth regimes. Guided by recent results for two-dimensional inflating range expansions, we identify key dimensionless parameters that describe the survival probability of a mutant cell with a small selective advantage arising at the population frontier. Using analytical techniques, we calculate this probability for arbitrary Θ. We compare our results to simulations of linearly inflating expansions ($\Theta = 1$ spherical Fisher–Kolmogorov–Petrovsky–Piscunov waves) and treadmilling populations ($\Theta = 0$, with cells in the interior removed by apoptosis or a similar process). We find that mutations at linearly inflating fronts have survival probabilities enhanced by factors of 100 or more relative to mutations at treadmilling population frontiers. We also discuss the special properties of "marginally inflating" ($\Theta = 1/2$) expansions.

1. Introduction

Early tumor evolution is driven by rare driver mutations that sweep the prevascular tumor population at the frontier and push the growing cell mass further down the path toward metastasis. Hence, an understanding of the evolutionary dynamics governing the survival of such mutations is crucial in cancer prevention (Merlo et al., 2006; Vogelstein et al., 2013). One significant, largely unexplored aspect of this evolution is the effect of tumor geometry. An important *in vitro* model of cancer is the multicellular tumor with an approximately spherical shape, or "spheroid". The spheroid captures many of the essential features of solid tumors *in vivo* and is a model for anti-cancer therapies (Kunz-Schughart, 1999; Santini and Rainaldi, 1999; Hirschhaeuser et al., 2010). Spheroids are especially useful for understanding small, avascular tumors. In the later stages of growth, in order for the tumor to survive, it requires a vascular system and undergoes angiogenesis (Weis and Cheresh, 2011). The growth then becomes more complicated, and more sophisticated modeling efforts are necessary (Shirinifard et al., 2009; Alarcón et al., 2005). We focus here on the earlier evolutionary dynamics of spheroidal range expansions in two and three dimensions. We assume that attractive cell–cell interactions keep such aggregates approximately spherical, i.e. that there is an effective surface tension, similar to that observed for yeast cell colonies (Nguyen et al., 2004). Although we are motivated by tumor evolution, our models are intended to be quite general. Two-dimensional and three-dimensional expansions may be realized in experiments, for example, using microbial or yeast populations in hard and soft agar, respectively (Korolev et al., 2012, 2011; Lavrentovich et al., 2013a).

We will be particularly interested in computing the survival probability of a mutation that occurs among the dividing cells at the surface of a spherical or circular population of initial radius $R(t = 0) = R_0$, which may or may not increase in time. In general, the radius $R(t)$ has a complicated time dependence, especially in tumor growth. At the early stages, cells divide everywhere inside the tumor, and the cluster radius grows exponentially in time. After the tumor reaches a size larger than a nutrient shielding length (Lavrentovich et al., 2013b), nutrients will no longer be able to diffuse into the tumor interior. This effect, combined with inward pressure from the surrounding non-cancerous tissue (Cheng et al., 2009; Montel et al., 2011, 2012), decreases the growth rate toward the center of the tumor. The radius $R(t)$ then grows more slowly. We will model the growth generally as

$$R(t) = R_0\left[1 + \frac{t}{t^*}\right]^{\Theta}, \tag{1}$$

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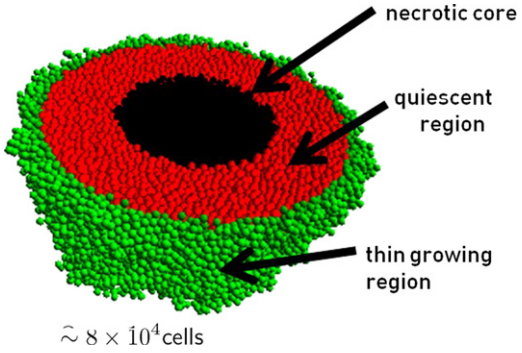

Fig. 1. A schematic of a treadmilling tumor. Due to nutrient shielding, cells divide in a thin green region at the frontier. In the red region, cells are in an arrested state and do not grow. In the necrotic core, cells undergo apoptosis and their contents are flushed out of the cluster, resulting in an overall volume loss. This volume loss can balance the gain of volume at the cluster periphery, resulting in a "treadmilling" effect and a cell mass with a constant radius (Cheng et al., 2009; Montel et al., 2011, 2012; Stott et al., 1999). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

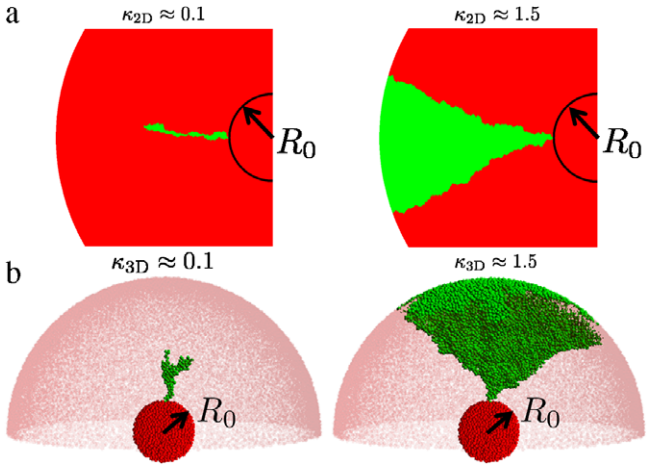

Fig. 2. Examples of simulated mutant clusters (green cells) in two- and three-dimensional range expansions (see Section 2), generated using two different values of the key dimensionless selection parameters $\kappa_{2D,3D}$ defined in Eq. (2). (a) Circular range expansions with a uniform front with an initial radius $R_0 = 50$ average cell diameters and a single initial mutant green cell at the population frontier. (b) Spherical range expansions with uniform fronts and a single green cell at the initial population frontier with radius $R_0 = 10$ cell diameters. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

where R_0 is the initial tumor radius, Θ is a (possibly time-dependent) growth exponent, and t^* is a characteristic time for the power-law growth in an inflating geometry. Both Θ and t^* may be tuned to model various growth regimes. For example, for a substantial portion of the growth in tumors, the radius grows linearly in time ($\Theta = 1$), and $t^* = R_0/v$, where v is the front speed (Brú et al., 2003). Linear growth and nutrient shielding are also present in microbial populations grown in Petri dishes (Korolev et al., 2012). Eq. (1) can also model an exponential growth regime $R(t) = R_0 e^{\lambda t}$ with rate λ if we let both $\Theta, t^* \to \infty$, such that $\lambda = \Theta/t^*$ is held constant.

Eventually, apoptosis may be induced at the tumor center, creating a necrotic region (Cheng et al., 2009; Montel et al., 2011, 2012), illustrated in Fig. 1. The cells at the tumor periphery continue to divide relatively rapidly. Thus, a "treadmilling" effect is created, and the tumor experiences a rapid turnover of cells at its surface while remaining the same size, a situation we represent by a growth exponent $\Theta = 0$ in Eq. (1). We will show that the different growth regimes captured by varying Θ have dramatically different consequences for the fate of mutations at the tumor frontier. We will focus on $\Theta = 0$, $\Theta = 1$, and $\Theta = 1/2$, capturing, respectively, treadmilling, linear inflation, and an intriguing borderline growth regime.

The actively growing region in a tumor mass or a spherical microbial population can be quite thin, with a width of just a few cell diameters (Folkman and Hochberg, 1973; Lavrentovich et al., 2013b). In this case, genetic drift is strong and can locally fix the mutation at the population frontier. This local fixation creates a mutant "sector", i.e., a region along the front that is entirely occupied by the mutant cells. Example sectors, marked in green, are shown in Fig. 2 for circular and spherical range expansions. Previous studies have focused on the deterministic movement of these mutant sectors: The sectors inflate or deflate due to a mutant selective advantage or disadvantage, respectively (Antal et al., 2013). However, genetic drift will introduce fluctuations in the sector motion at its boundaries that can drive the mutation to extinction, as illustrated on the left panels of Fig. 2(a) and (b). For example, in circular expansions (Fig. 2(a)), the sector has two boundaries which both perform random walks, as observed in microbial range expansions (Korolev et al., 2010, 2012). Selection introduces a bias to the sector boundary motion. Also, the increasing population radius $R(t)$ will deterministically increase the distance between the boundaries. If the sector boundaries collide, the sector vanishes, and the mutation goes extinct (left panel of Fig. 2(a)).

Because the two boundaries of mutant sectors in two-dimensional expansions perform random walks, the distance between the boundaries performs a random walk as well. The mutant survival probability, then, is the probability that this distance never vanishes, i.e., that the random walk it performs never reaches the origin. Such a probability is a well-studied first-passage property of a random walk (Redner, 2001). Previous studies, such as Hallatschek and Nelson (2010); Korolev et al. (2010) and Lavrentovich et al. (2013a), have exploited these known random walk results to calculate survival probabilities of mutations in two-dimensional populations. We will review some of these previous results for two-dimensional expansions and generalize them to arbitrary growth exponents Θ. We will then use them to motivate our discussion of three-dimensional expansions.

In three-dimensional populations, the focus of the present work, the mutant sector can have a complex, branched shape, as shown in Fig. 2(b). Characterizing the boundary positions with just two random walks is impossible in this case. Although we can still treat mutant cell lineages using random walks (see, e.g., Cox and Griffeath, 1986 or the chapter on voter models in Liggett, 1985), incorporating selection is more complicated than in the two-dimensional case (Bramson and Griffeath, 1981). Also, we know of no generalization to inflating frontiers. So, instead of mapping to random walks, we study the time evolution of the coarse-grained density of mutant cells along the population frontier of spherical range expansions. We then apply a field-theoretic analysis of the time evolution that allows us to treat genetic drift, selection, and inflation within a single theoretical framework.

By using random walk theory for two-dimensional range expansions and field-theoretic techniques for three-dimensional ones, we will show that the key dimensionless parameters for mutant survival are, respectively,

$$\kappa_{2D} = s\sqrt{\frac{t^*}{\tau_g}} \quad \text{and} \quad \kappa_{3D} = \frac{st^*}{\tau_g}, \tag{2}$$

where t^* is the characteristic time of the radius growth defined in Eq. (1), s is the selective advantage, and τ_g is a generation time. The mutant survival will also depend on the initial number of mutant cells and the growth exponent Θ. The mutant cluster shapes at different $\kappa_{2D,3D}$ for linearly inflating frontiers ($\Theta = 1$ in Eq. (1)) are illustrated in Fig. 2(a) and (b) for two- and three-dimensional