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Spatial invasion dynamics on random and unstructured meshes: Implications for heterogeneous tumor populations

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HIGHLIGHTS

- Studying phenotypic heterogeneity which appears to be highly prevalent during various stages of tumor growth.
- Understanding the effect of tissue geometry on the invasion probability by generating a random set of neighbors for each node on a regular grid in the presence of migration.
- Studying invasion dynamics of mutants using unstructured meshes in the presence of migration, which captures features of real tumors that structured meshes fail to do.
- Examining the effect of boundaries on the fixation probability.

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ABSTRACT

In this work we discuss a spatial evolutionary model for a heterogeneous cancer cell population. We consider the gain-of-function mutations that not only change the fitness potential of the mutant phenotypes against normal background cells but may also increase the relative motility of the mutant cells. The spatial modeling is implemented as a stochastic evolutionary system on a structured grid (a lattice, with random neighborhoods, which is not necessarily bi-directional) or on a two-dimensional unstructured mesh, i.e. a bi-directional graph with random numbers of neighbors. We present a computational approach to investigate the fixation probability of mutants in these spatial models. Additionally, we examine the effect of the migration potential on the spatial dynamics of mutants on unstructured meshes. Our results suggest that the probability of fixation is negatively correlated with the width of the distribution of the neighborhood size. Also, the fixation probability increases given a migration potential for mutants. We find that the fixation probability (of advantaged, disadvantaged and neutral mutants) on unstructured meshes is relatively smaller than the corresponding results on regular grids. More importantly, in the case of neutral mutants the introduction of a migration potential has a critical effect on the fixation probability and increases this by orders of magnitude. Further, we examine the effect of boundaries and as intuitively expected, the fixation probability is smaller on the boundary of regular grids when compared to its value in the bulk. Based on these computational results, we speculate on possible better therapeutic strategies that may delay tumor progression to some extent.

1. Introduction

Cancer can be viewed as an evolutionary process, where a collection of pre-neoplastic clones acquire genetic and epigenetic changes over a period of time (Nowell, 1976). During the process of carcinogenesis, it is commonly believed that mutant cells with a gain-of-function fitness advantage take over a small neighborhood of host cells through a selection process and initiate a clonal area, leading to invasion into the proximal tissue. The fitness rates of pre-neoplastic clones are effected by a mutation-selection mechanism and various micro-environmental factors, and as a result a growing tumor has a high level of heterogeneity at the cellular level. Both initiation and progression stages have been proposed to follow an evolutionary stochastic model and different authors have observed the effect of a fitness advantaged mutant introduced into the system and the probability that this takes over a finite compartment of the cellular tissue. In recent years (see Komarova et al., 2003; Nowak et al., 2004; Michor et al., 2004; Iwasa et al., 2004;

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Komarova, 2006, 2007; Thalhauser et al., 2010; Foo et al., 2011), these models have been successfully applied to both one-hit and two-hit mutation-selection processes. During the final stages of malignancy, the mutant phenotype gains a relative advantage through motility. The evolutionary theory of these complex phenomena has not yet been addressed in the literature.

For the past three decades, there have been several attempts to understand the process of fixation in spatially homogeneous systems. It was found that many spatially structured models such as lattices models have little or no effect on the selection process (Maruyama, 1970, 1974a, 1974b; Slatkin, 1981). More recently, Lieberman et al. (2005) generalized this to arbitrary graphs and found the exact symmetry conditions under which the fixation probability for an advantaged mutant, evolving on a graph, are the same as that for a mixed population model. Houchmandzadeh and Vallade (2011) demonstrated that fixation probability of a beneficial mutation in a geographically structured population is almost the same (or, slightly smaller) compared to the unstructured population for a Voter framework.

Many authors have studied the spatial dynamics of cancer invasion using cellular automata/agent based models, partial differential equation models, and hybrid models including multiscale modeling techniques (Deutsch and Dormann, 2005; Byrne et al., 2006; Anderson et al., 2008; Quaranta et al., 2008; Cristini and Lowengrub, 2010; De Pillis et al., 2006; Anderson and Chaplain, 1998; Anderson and Quaranta, 2008; Bartoszyński et al., 2001; Bellomo et al., 2008; Byrne and Chaplain, 1996; Chaplain et al., 2006; Enderling et al., 2006, 2007; Deisboeck et al., 2008; Gaffney, 2004; Gatenby and Maini, 2003; Gerlee and Anderson, 2007; Hinow et al., 2006; Lowengrub et al., 2009; Macklin et al., 2009). In these models, it is possible to incorporate progressively more complex cellular mechanisms and biological phenomena (Cristini and Lowengrub, 2010). In the current paper, we adopt a simpler approach. In an attempt to understand and analyze the dynamics of invasion, we focus on only two forces, namely, proliferative and migrative potentials that influence the inherited genetic behavior of mutants.

Our approach builds on spatial evolutionary modeling of cancer initiated in Komarova (2006), where the process was described as a linear chain (1D). In this spatial model, cells were placed linearly at different positions, and restricted to replicate only to a neighboring point after a cell death. In this model, the fixation probability of single hit and double hit mutants was investigated. In particular, it was found that in the spatial case, the probability of fixation of advantaged and disadvantaged single mutants is lower compared to that in the space-free model. An extension of this 1D model is presented in Thalhauser et al. (2010), where the spatial dynamics on a 2D lattice is analyzed. Two genetic factors are considered: replicative potential and cellular motility. The overall conclusion is that migration has a major impact on the probability of a single mutant cell's ability to invade an existing colony, something that had not been investigated in the previous modeling efforts to understand cancer progression.

The goal of the present study is to develop a better quantitative analysis of the invasion probability, by avoiding the rigid framework imposed by a regular grid. We introduce a stochastic death–birth model (i.e., the Moran process) for the spatial evolutionary system. In order to circumvent the rigidity of a regular grid, we use two different methods. In the first construction, we start with a regular square lattice and add/remove neighbors in a random way (the background lattice can be of Moore neighborhood type with 8 neighbors, or, von-Neumann neighborhood, with 4 neighbors). The important feature of this construction of the connectivity graph is the notion that we construct the number of neighbors for each of the nodes on the lattice (where each node is occupied by either a normal or a mutant cell). This construction is a mixture of both directed and undirected links, i.e., some nodes and their neighbors are bi-directional and some are uni-directional.

Broadly speaking, any regular grid assumes that the number of neighbors around each cell is homogeneous at every location in space. This is not a realistic assumption for modeling biological tissues. An unstructured mesh where the number of neighbors around each nodal position is a random variable can be a better approximation to reality. This suggests our second construction, where we consider an unstructured mesh which is defined as a random neighborhood graph with longer ranges of connectivities vs. the previous case. The distinguishing feature, however, is the main fact that the unstructured mesh does behave symmetrically between the two types of species in terms of the connectivity graph and the number of neighbors. The contrasting feature in the unstructured mesh construction is that every node and its corresponding neighbors are bi-directional compared to the previous scenario.

Here, we are mainly concerned with the question of fixation probability in the presence of a migration potential, or cellular motility for either only the mutant phenotype or for both the normal and mutant phenotypes. We address the effects of a random environment and migration potential on the fixation probability.

The paper is organized as follows. In Section 2, we review the background related to space free and spatial models and introduce our spatial model in the presence of a migration potential/motility. In Section 3, we investigate the two spatial models of structured grids with variable (static and dynamic) neighborhoods and observe the effect of varying the number of neighbors and/or migration potentials of both cell types. We subsequently turn to the unstructured mesh to investigate the effect of migration potential on the fixation probability. The effect of boundaries on the value of the fixation probability is briefly discussed at the end of Section 3. In Section 4, we discuss the biological relevance and connections to the known analytical limits of the models in the discussion part.

2. Methods

2.1. Background

The traditional Moran process is described as follows. Consider a population of N cells consisting of two phenotypes: A (host cells) and B (mutant cells). We also refer to type B cells as pre-cancerous or pre-malignant cells throughout the paper. Each cell type has a proliferative potential. At every time step, one cell is randomly chosen for death and is replaced by the progeny of another randomly chosen cell from the same population, such that the population size is constant at every time step. Cells are chosen for death with equal probabilities, and they are chosen to reproduce according to their relative fitness. We assume that the two cell types A and B have fitness rates $r_A=1$ and $r_B=r$ respectively. If the number of B cells is i, then the probability that B is chosen for reproduction is $P_{B+}=ri/(N-i+ri)$. The Moran process is a one-dimensional birth-death process which tracks the number of type B cells over time. Its properties in the context of invasion probability and other statistical features have been discussed in detail in Komarova et al. (2003), Nowak et al. (2004), Michor et al. (2004), Iwasa et al. (2004), Komarova (2006, 2007), Thalhauser et al. (2010), Foo et al. (2011), Maruyama (1970, 1974a, 1974b), Slatkin (1981), Lieberman et al. (2005), and Houchmandzadeh and Vallade (2011).

A spatial generalization of the above model is considered as a 1D model in Komarova (2006), in which a population of N cells are placed along a line at locations $1, 2, \ldots, N$. As before, at each time-