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Incomplete penetrance: The role of stochasticity in developmental cell colonization

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HIGHLIGHTS

- Developmental cell colonization is modeled with two Markovian processes.
- Models include cell proliferation and motility, and gut tissue growth mechanisms.
- Probability of cell colonization success is quantified.
- Propose a new mechanism for incomplete penetrance requiring no genetic differences.
- Variability in colonization attributed to stochastic interactions of cellular mechanisms.

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ABSTRACT

Cell colonization during embryonic development involves cells migrating and proliferating over growing tissues. Unsuccessful colonization, resulting from genetic causes, can result in various birth defects. However not all individuals with the same mutation show the disease. This is termed incomplete penetrance, and it even extends to discordancy in monozygotic (identical) twins. A one-dimensional agent-based model of cell migration and proliferation within a growing tissue is presented, where the position of every cell is recorded at any time. We develop a new model that approximates this agent-based process – rather than requiring the precise configuration of cells within the tissue, the new model records the total number of cells, the position of the most advanced cell, and then invokes an approximation for how the cells are distributed. The probability mass function (PMF) for the most advanced cell is obtained for both the agent-based model and its approximation. The two PMFs compare extremely well, but using the approximation is computationally faster. Success or failure of colonization is probabilistic. For example for sufficiently high proliferation rate the colonization is assured. However, if the proliferation rate is sufficiently low, there will be a lower, say 50%, chance of success. These results provide insights into the puzzle of incomplete penetrance of a disease phenotype, especially in monozygotic twins. Indeed, stochastic cell behavior (amplified by disease-causing mutations) within the colonization process may play a key role in incomplete penetrance, rather than differences in genes, their expression or environmental conditions.

1. Introduction

Cell colonization during embryonic development involves cells migrating and proliferating over growing tissues. Unsuccessful colonization can result in various birth defects. For example, in the case of the neural crest (Zhang et al., 2014), failure of colonization in the enteric nervous system may lead to Hirschsprung Disease (Newgreen and Young, 2002) and failure in cranial–facial development may lead to cleft lip and palate (Muhamad and Azzaldeen, 2012; Parsons et al., 2008). In these conditions the colonizing cell population fails to populate the entire field (which is itself growing), or fails to provide the normal number of cells.

There are many genetic causes of these diseases and these are often classed as dominant mutations. However not all individuals with the same mutation show the disease; this is termed incomplete penetrance. This incomplete penetrance extends even to discordancy in monozygotic (identical) twins.

Most explanations of incomplete penetrance in genetically identical individuals are made by assuming differences in gene

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expression between affected and unaffected individuals. The work presented here suggests a novel explanation of incomplete penetrance which is based on stochastic cell behavior, amplified by disease-causing mutations.

We investigate the success or otherwise of a colonization by considering two continuous-time one-dimensional Markovian models: one an agent-based model and the other an approximating model. The agent-based (cellular automata) model is based on a 2-dimensional discrete-time model which has been used previously to simulate the invasion of NC cells within the growing gut tissue (Binder et al., 2008; Binder and Landman, 2009; Simpson et al., 2007; Zhang et al., 2010). Here we use the continuous-time 1-D analog of that model.

Although the probability distribution of the state of this agent-based model is determined by a set of ordinary differential equations, the size of this system makes it impractical to solve. We therefore derive a second model which is a Markov chain approximation to quantify more efficiently the variability of the cell invasion front, providing a measure of colonization success.

The approximation is validated by comparison with averaged simulation data from the agent-based model of the overall process, demonstrating a high level of accuracy across a wide range of parameter space.

2. Agent-based model

We consider a continuous-time one-dimensional discrete-state agent-based model to simulate a cell colonization process. All quantities and variables are non-dimensional. The domain (tissue) is a single row of lattice sites whose positions are located at the discrete integer points $x = 1, 2, \ldots, L(t)$, where $L(t)$ is the length of the domain that elongates with time t. Each lattice site of the domain can be either occupied by a single agent or unoccupied. The total number of agents at any given time is $N(t) \in \{1, 2, \ldots, L(t)\}$. The local rules for domain growth, agent motility and agent proliferation events are similar to those described previously (Binder et al., 2008; Binder and Landman, 2009), and are shown in Fig. 1(a)–(c). If the target site is occupied for any motility or proliferation event, then that event is aborted. These events are volume exclusion processes (Chowdhury et al., 2005; Simpson et al., 2009). Note that if the chosen lattice site is occupied by an agent in the case of a domain growth event, then the agent is transported to the right with the moving lattice site.

The model is updated in continuous-time (Gillespie, 1977) with domain growth rate λ_g, agent motility rate λ_m, and proliferation rate λ_p. We define the propensity function as $\lambda = (\lambda_m + \lambda_p)N(t) + \lambda_g L(t)$, giving the total rate at which events occur at time t. Random numbers are drawn from the exponential distribution and standard discrete uniform distribution as $E[\lambda^{-1}]$ and $U[0, 1]$, respectively. The algorithm then proceeds as follows, being terminated at either a maximum chosen time $t_f > 0$ or maximum chosen domain length $L_f > L(0)$.

Step 1: Calculate the propensity function λ given the current state, and update the time with $t := t + E[\lambda^{-1}]$. If $t < t_f$ (or alternatively $L(t) < L_f$) go to *Step* 2; else stop.

Step 2: Generate a random number $R = \lambda U[0, 1]$.

Step 3: Decide which type of event to perform. If $R < \lambda_m N(t)$ then attempt to perform a motility event. If $\lambda_m N(t) \le R < (\lambda_m + \lambda_p)N(t)$ then attempt to perform a proliferation event. If $R \ge (\lambda_m + \lambda_p)N(t)$ then perform a domain growth event. Update the state as appropriate.

Step 4: If $t < t_f$ (or alternatively $L(t) < L_f$) repeat *Steps* 1–3; else stop.

We initialize a simulation by populating all the lattice sites to the left of and including the site z_0, where $1 \le z_0 \le L(0)$, and then record the position of the rightmost agent at later times. This provides a measure for the cell invasion front. Shown in Fig. 1(d)–(f) is a simulation that was terminated when $L_f = 12$, with $z_0 = 2$, $L(0) = 4$, $\lambda_m = \lambda_p = 0.5$ and $\lambda_g = 0.1$.

To quantify the success of the colonization, we record the counts (number of occurrences) of the positions $z(t)$, where $z_0 \le z(t) \le L(t)$ for $t > 0$ and $z(0) = z_0$, of the rightmost or leading agents from M realizations. Dividing the counts by the number of simulations M then produces an estimated probability mass function (PMF) $P(z)$, for the position of the rightmost agent or invasion front; that is, $P(z)$ is the probability that the right-most agent is in position z at the stopping time. Typical PMFs are shown in Figs. 2 and 3 (light gray). We delay the discussion of these curves to Section 4. In particular, we define a successful invasion as one in which the right-most (most advanced) cell occupies a site in the last fraction $(1-\beta)$ of sites. As such, we evaluate and report the *probability of success* by the sum, Q, of marginal probabilities of occupancy $P(z)$ in the last fraction $(1-\beta)$ of sites

$$Q = \sum_{z = \lfloor \beta L_f \rfloor}^{L_f} P(z).$$

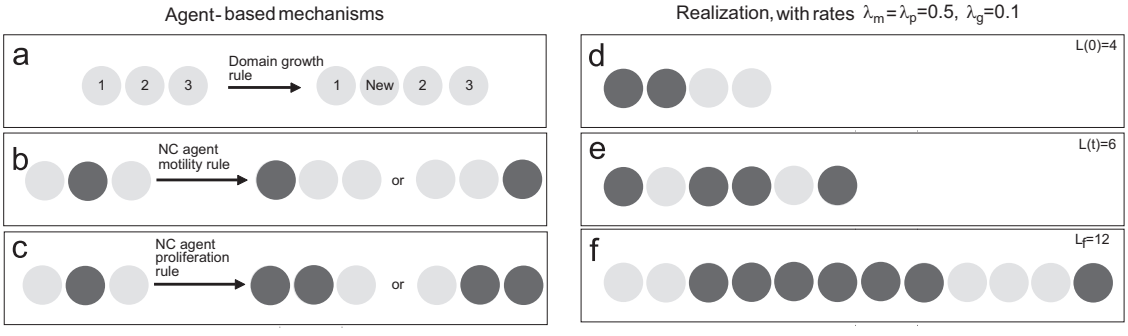

Fig. 1. Agent-based mechanisms and typical realization. (a)–(c) Agent-based mechanisms, domain agents (light gray) and agents (dark gray). (a) Domain growth rule. A domain agent is randomly selected to proliferate. After mitotic division the selected agent, and all the agents to its right, are transported one agent-length to the right. A new agent is inserted in the original position of the agent that was selected to proliferate. (b) Agent motility rule. The agent can move to one of the two configurations shown with equal probability. (c) Agent proliferation rule. The mother agent divides into two daughter agents. After mitotic division two possible configurations can occur with equal probability. (d)–(f) Typical realization, with $\lambda_m = \lambda_p = 0.5$ and $\lambda_g = 0.1$. (d) Initial condition, $z_0 = 2$ and $L(0) = 4$. (e) Snapshot at domain length $L(t) = 6$. (f) The simulation was terminated at the chosen domain length $L_f = 12$.

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