Physics Letters A 380 (2016) 1267–1278

Contents lists available at ScienceDirect

Physics Letters A

www.elsevier.com/locate/pla

Study of selected phenotype switching strategies in time varying environment

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ARTICLE INFO

Article history:
Received 19 October 2015
Received in revised form 23 January 2016
Accepted 25 January 2016
Available online 28 January 2016
Communicated by Z. Siwy

Keywords:
Phenotype switching strategies
Stochastic environment
Dynamic heterogeneity of cell populations
Markov model
Evolutionary simulations
Universality of the statistical characteristics

ABSTRACT

Population heterogeneity plays an important role across many research, as well as the real-world, problems. The population heterogeneity relates to the ability of a population to cope with an environment change (or uncertainty) preventing its extinction. However, this ability is not always desirable as can be exemplified by an intratumor heterogeneity which positively correlates with the development of resistance to therapy. Causation of population heterogeneity is therefore in biology and medicine an intensively studied topic. In this paper the evolution of a specific strategy of population diversification, the phenotype switching, is studied at a conceptual level. The presented simulation model studies evolution of a large population of asexual organisms in a time-varying environment represented by a stochastic Markov process. Each organism disposes with a stochastic or nonlinear deterministic switching strategy realized by discrete-time models with evolvable parameters. We demonstrate that under rapidly varying exogenous conditions organisms operate in the vicinity of the bet-hedging strategy, while the deterministic patterns become relevant as the environmental variations are less frequent. Statistical characterization of the steady state regimes of the populations is done using the Hellinger and Kullback–Leibler functional distances and the Hamming distance.

1. Introduction

The therapeutic experience indicates that intratumor heterogeneity is a key to understanding the treatment failure, as an extreme diversity of responses of cancer cells to applied therapy crucially complicates development of clinically efficient targeted therapies [1]. The cell-to-cell phenotypic variability is not bound exclusively to differences in the DNA sequences of the respective cells but to epigenetic differences as well [2]. The ability of isogenic cells to express different phenotypic characteristics, known as phenotype plasticity, confers to cellular tissues important properties such as the ability of cancer cells to escape a targeted therapy by switching into an alternative phenotype [3].

Evidence suggests that transitions between epithelial and mesenchymal states, which are the central regulators of cellular plasticity in carcinoma, play important roles in the therapeutic resistance, tumor recurrence and metastatic progression [4]. In [5], reversible stochastic state transitions between three different cell types (stem, basal, and luminal) in the population of breast cancer cells [5] was reported. Moreover, after cultivating single cell-type separately, the original phenotypic composition reestablished by generating appropriate number of the respective cell types [5]. As the rapidity of reestablishing equilibrium phenotypic proportions excludes its explanation by differential growth alone (as it would require implausibly high proliferation rate), the stochastic transitions between different cell-types were accepted as a responsible mechanism [5].

The fundamental role of phenotypic heterogeneity in cancer progression and therapy motivates an effort to stimulate (or prevent) the switch into a specific desirable phenotypic state purposefully as a therapeutic strategy [6,7]. Therefore, molecular mechanisms behind the respective phenotype switches are intensively studied anticipating their more or less straightforward therapeutic application. On the other hand, a range of studies suggests that phenotype heterogeneity results from the evolutionary pressure to keep gene expression in tune with physiological needs dictated by the tumor microenvironment [8]. It is well accepted that the phenotype switching is a general strategy enabling a population to maximize its survival probability in fluctuating environments. A series of disparate theoretical models of phenotype switching was constructed which use different parameterizations on different spatial scales [9–14]. An important example for gene network

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http://dx.doi.org/10.1016/j.physleta.2016.01.037
0375-9601/

with stochastically induced transitions between multiple phenotypic states on the cellular scale has been studied in [15].

In this paper, a causal relation between evolved phenotype switching strategy and a time-varying environment is conceived as an interaction of the time series corresponding to the environment and to the cell states, respectively. The presented conceptual-level study avoids biochemical details of underlying molecular mechanisms and focuses on universal aspects of the evolution of the switching strategy in a time-varying environment. Throughout the paper, we refer to cancer biology as a motivation, as well as an eventual application field for the obtained results, nevertheless, the scope of the approach is much broader. Below proposed discrete lattice models and their construction and application have much in common with the models applied in statistical physics. At a conceptual level, our work is influenced by the extensive class of optimization and computational techniques designed for a time-varying environment [16–18], where some of the elements of the problem domain which defines the fitness function, typically the target, changes over time. The time series corresponding to a changing environment is represented by the Markov process. The phenotypic variation and phenotypic equilibrium can be explained by different concepts of stabilities in different models [19]. To enable evolution of a broad range of possible behaviors, from stochastic to deterministic, the time series corresponding to the cell state dynamics were selected from the set of models with different properties, focusing on the Markov and nonlinear tent-map processes, respectively.

The simulation model of the relation between environmental exogenous conditions and evolution of a phenotype switching strategy is applied to the populations (or colonies) of asexual organisms – cells of stylized phenotypic structure, each defined by the evolutionarily refined parameters within the respective switching strategy, such as the Markov, tent map, etc., prescribed for the whole generation, see below. In the simulation, evolutionary algorithm with the *tournament selection* [20] was chosen instead of biologically less relevant fitness proportional selection. In distinction to the question of the best solution (in our case the switching strategy with its respective refined parameters) posed by optimization approaches, our motivation is to extract relevant statistical properties of the evolving populations. For that reason, we study averaged distance-based measures which evaluate how cells fit into environment. In our work, most simulations are carried out applying 1D lattice topology for orderings of populations. However, to capture the features of more realistic systems, 3D highly amorphous lattices with the alternating number of neighbors [21] seem to be the most appropriate candidates.

The paper is organized as it follows. Stochastic environment is introduced in Section 2. In Section 3 we describe three basic strategies which represent the micro-models in our approach. Particular strategies are described in Subsections 3.1, 3.2, and 3.3. The details of the one-dimensional population model of evolutionary dynamics are introduced in Section 4. Its two subsections discuss the issue of fitness definition (Subsection 4.1), selection and replication schemes (Subsection 4.2), and the rules that drive mutations (Subsection 4.3). The methods that allow us to evaluate simulation outputs and make conclusions are discussed in Section 5. The details of the simulation algorithm and simulation results are presented in Section 6. Finally, the discussion (7) and conclusions are presented. Additional statistical results demonstrating universality of the approach in dimensions two and three, as well as the results for alternative strategies, are presented in Appendix A.

2. Stochastic exogenous environment

Spatio-temporal model of evolutionary trajectories is formulated and studied within a stochastic simulation scheme. In the model, environmental dynamics is conceived as a stochastic switching between two environmental states, 0 and 1, represented by the binary variable $h(t) \in \{0, 1\}$ which follows the formula

$$h(t) = \begin{cases} 1 & \text{if } h(t-1) = 0 \\ & \text{and } W_{\mathrm{h},01} \geq u_{\mathrm{h}}(t) \\ 0 & \text{if } h(t-1) = 1 \\ & \text{and } W_{\mathrm{h},10} \geq u_{\mathrm{h}}(t) \\ h(t-1) & \text{otherwise} \end{cases}, \tag{1}$$

where $u_{\mathrm{h}}(t)$ is a random number drawn uniformly from $(0, 1)$ interval, $W_{\mathrm{h},01}$, $W_{\mathrm{h},10}$ are the elements of the stochastic matrix, $W_{\mathrm{h},01}$ denoting the probability of environment transition from the state described by $h(t) = 0$ to the state corresponding to $h(t) = 1$ and vice versa. The above formula for the stochastic discrete time dynamics of $h(t)$ represents an application of the Monte Carlo (MC) acceptance–rejection method. Here, the argument t in $u_{\mathrm{h}}(t)$ indicates that random numbers are generated independently for each particular t. The above transition probabilities uniquely determine the limit probability distribution

$$P_{h=0} = \frac{W_{\mathrm{h},10}}{W_{\mathrm{h},01} + W_{\mathrm{h},10}}, \quad P_{h=1} = 1 - P_{h=0}. \tag{2}$$

3. Population

Let environment with the above specified dynamics be a platform where the population of N cells – agents evolve. Each cell is located at a position in a one dimensional lattice space indicated by the respective position index $i \in \{1, 2, \ldots, N\}$. Each cell is in time t in one of the two phenotypic states represented by the binary $s(i, t) \in \{0, 1\}$ (see e.g. [22] for the motivation). The above elementary topology and the set of possible states are chosen for the sake of simplicity and consistency with the set of possible states of environment. If not stated otherwise, we hold the convention that it is beneficial for the cell to be in agreement with its environment, i.e. when $s(i, t) = h(t)$, which is reflected in the fitness definition, see below. The simplifying assumption made in our approach is, that any $h(t)$ is the same for all the sites and there is no feedback connecting $h(t)$ with the delayed $\{s(i)\}_{i=1}^{N}$, which is consistent with other models [23].

In the paper, we analyze three different strategies (Markov, tent-map and mixed) of the phenotype switching, each of them framed by the respective set of evolvable parameters (the additional strategies and their impacts on evolutionary equilibrium can be found in Appendix A.2). More formally, the cell at the position i in time t is represented by the time-varying phenotype tuple $C(i, t)$ of the general structure

$$C(i, t) \equiv [\text{evolving parameters}(i, t);\ \text{phenotypic state variables}(i, t)],$$

where t denotes the generation. The temporal discretization is constrained mainly by the need to provide adequate and sufficiently frequent sampling of the cell cycle. Three possible variants of $C(i, t)$ corresponding to the three main phenotype switching strategies are introduced in the following subsections.

3.1. Markov strategy of switching

Here, the above state variable $s(i, t) \in \{0, 1\}$, indicating in which of the two states the i-th cell currently is, represents a Markov binary stochastic variable switching accordingly to the rule