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Toward understanding of the role of reversibility of phenotypic switching in the evolution of resistance to therapy

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ABSTRACT

Reversibility of state transitions is intensively studied topic in many scientific disciplines over many years. In cell biology, it plays an important role in epigenetic variation of phenotypes, known as phenotypic plasticity. More interestingly, the cell state reversibility is probably crucial in the adaptation of population phenotypic heterogeneity to environmental fluctuations by evolving bet-hedging strategy, which might confer to cancer cells resistance to therapy. In this article, we propose a formalization of the evolution of highly reversible states in the environments of periodic variability. Two interrelated models of heterogeneous cell populations are proposed and their behavior is studied. The first model captures selection dynamics of the cell clones for the respective levels of phenotypic reversibility. The second model focuses on the interplay between reversibility and drug resistance in the particular case of cancer. Overall, our results show that the threshold dependencies are emergent features of the investigated model with eventual therapeutic relevance. Presented examples demonstrate importance of taking into account cell to cell heterogeneity within a system of clones with different reversibility quantified by appropriately chosen genetic and epigenetic entropy measures.

1. Introduction

Human diseases are typically caused by invading pathogenic microorganisms, such as viruses, bacteria, fungi, prions, etc. Despite immunity system is able to cope with the majority of pathogens, those escaping from innate immunity surveillance must be treated by therapy. The main obstacle to efficient therapy is the variability of the microorganisms within the population, such as strain or clone, conferring them resistance to therapy. Population variability flows from the evolutionary essence of population dynamics of microorganisms which equips evolving populations of pathogens with powerful adaptive capability. For example, evolutionary dynamics of carcinogenesis [1–3] is considered the main reason why targeted therapy does not work [4].

As it is known for a long time, intratumor heterogeneity is not bound exclusively to the differences in DNA sequences of the respective cells (genetic heterogeneity), but to the epigenetic differences as well [5]. It is broadly accepted that the epigenetic mechanisms for gene transcription regulation are usually reversible [6]. It has been found that the role of epigenetic mechanisms, such as DNA methylation, histone modifications, chromatin remodeling, and small RNA molecules, in cancer initiation and progression is causative [7,8]. In particular, variability in phenotypic characteristics of isogenic cells, known as phenotypic plasticity, is assumed to be an important cause of the therapeutic resilience of advanced cancers [9].

Recognizing tumor dynamics as evolutionary process, one can exploit known universal features of evolution to influence the evolution of the population in desirable direction in mathematically more purposeful way. While the role of genetic intratumor heterogeneity in tumor evolution was accepted long time ago, the role of epigenetic heterogeneity is much less obvious. To implement evolutionary principles into the therapy design, the interplay between genetic diversity and epigenetic plasticity [10] should be carefully studied at the model level within an evolutionary-based integrative conceptual framework. Recently, the concept of Waddington's epigenetic landscape was applied to formalize the relation between the cancer cell genome and epigenetic mechanisms [11] in mathematically instructive way. Therein, each point in the fitness landscape (i.e. genome) provides epigenetic landscape of unique topology. Due to their mathematical complexity, the epigenetic landscapes contain many areas (attractors) around the stable cell-states corresponding to the respective stable phenotypes of a cell. Straightforwardly, the phenotypic switching corresponds to the transition between two such attractors.

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Below we use the above conceptualization [11] as an instructive backbone for our considerations. As different cell states in the epigenetic landscape differ in their fitness-related properties, the cell states composition (or non-genetic heterogeneity) becomes, from the viewpoint of the clone, evolutionary important at the clone's respective timescale. It was observed that in the case of variable selective pressure, population of organisms evolve mechanisms to tune the phenotypic variability to the variability of the acting selective pressure [12]. In bacteria, the well known risk-diversification strategy evolved in the populations when facing uncertain future and/or environment [13–15] is the bet-hedging strategy [16,17,10]. Based on formal similarity of evolving cancer cells population with bacteria, viruses or yeast, it has been recently proposed that the structure of intratumor heterogeneity is evolutionary trait as well, evolving to maximize clonal fitness at a cancer-relevant timescale in changing (or uncertain) environment and that its structure corresponds to the bet-hedging strategy [18–22] which has been recently put into therapeutic context [23,24]. To sum up, the genome stays the main protagonist (i.e. selection unit) in the evolution of cancer cells, nevertheless with non-genetic heterogeneity of its eventual clone being the crucial adaptive trait at cancer-relevant, instead of proximate timescale.

Phenotypic plasticity confers to cellular tissues important properties, such as the ability of cancer cells to escape targeted therapy by switching to an alternative phenotype [25–30]. It motivates the effort to stimulate (or prevent) specific phenotype switching purposefully as a therapeutic strategy [31], which requires deep understanding of the phenotype switching causation.

As in classical evolutionary theory are random mutations, which cause phenotypic variation, independent of selective pressure, it seems probable that reversibility of phenotype switching can be underpinned exclusively by epigenetic modifications. Regarding the therapeutical perspectives, the difference between genetic and epigenetic changes is fundamental: while the genetic changes are, in principle, irreversible, the epigenetic modifications may be reversible at the therapy-relevant timescales [26,32,33].

To sum up, there are well-founded reasons for studying phenotypic switching using quasispecies or population dynamics models, which address the specific characteristics of cancer. In Section 2 we present the evolutionary based framework which assumes environmental dynamics shaping the evolution of reversible switching strategies. In the quasispecies framework (see Subsections 2.1, 2.3, A.1) the focus is placed on the phenotypic plasticity and reversibility. Studies of quasispecies models yielded important modelization ideas about how to implement the immunotherapy aspects. Most of our efforts in this area have focused on the construction of the population-based cancer models where evolution of phenotypic reversibility is incorporated together with immunotherapy. The resulting model of anti-cancer drug resistance are discussed in Section 3. In Subsection 3.1 we reassess the problem of intratumoral heterogeneity and related entropy measures. The corresponding simulation results are provided in Subsection 3.2. The results respond to specific questions concerning the evolutionary nature of the drug resistance. The threshold concept has emerged as natural outcome of the simulations. Its importance was underlined by providing a more detailed supplementary analysis in the Appendix A.2.

2. Quasispecies model of phenotypic changes

In this section we introduce the qualitative time-continuous evolutionary model based on the system of ordinary differential equations. The model is applied to nonequilibrium scenarios, where constrained populations of irreversible phenotypes are evolutionary drawn towards an attractor populated by reversible phenotypes.

Recently, mathematical modeling of phenotypic evolution in variable environment has received significant attention [34,20,35,36], which implicitly addresses the issue of eventual adaptivity of epigenetic modifications [37]. In particular, the formulation based on the quasispecies model [38] has been developed to clarify the role of mutations in the evolutionary process [39–42]. Owing to its versatility, the model has found applications in a broad range of scales – from molecular and virus scales [43] up to the cellular systems, such as the populations of heterogeneous cancer cells [44,45]. Investigation of heterogeneous malignant tissues within the context of variable environments [46] including local anti-cancer drug-induced environments [47] emerges as an interesting research area.

The entropic variable constraints imposed on the heterogeneity were studied in [48]. In [49], the elimination of heterogeneity in the system of replicating entities was conceived as an inverse problem, with an eventual potential in therapeutical applications.

Before going into details, we highlight three salient features of the model: (i) periodicity of the (micro)environmental variations; (ii) substantial genetic diversity underlying the switching rates between isogenic phenotypes (phenotypic states); (iii) competition between the clones adopting either reversible or irreversible phenotype switching under the constraint of constant total cell population size.

Below we study effects of the variation of evolutionary rate on the fractions $c^{(z)}(k,t)$, $k=0,1,\ldots,n_s-1$, of n_s clones (abstract "genotypes"), each of them allowed to occupy one of the two phenotypic states, indexed by $z\in\{0,1\}$. We assume that the k-th genotype responds to the environmental variation in two alternative ways depending on its respective phenotypic state, $[k;z=0]$ or $[k;z=1]$. The time-variability of environment can be indirectly represented by the time-variability of the reproduction rates of the respective phenotypic states, $r^{(z)}(t)$, $z\in\{0,1\}$, which are supposed to be of harmonic periodic form

$$r^{(z)}(t)=r_B+(-1)^z\Delta r\cos(2\pi t/T) \tag{2.1}$$

defined by the period T; Δr corresponds to the degree of diversification of the reproduction fitness and r_B to its basal level. It is worthy of noting that in [50] the oscillatory external (temperature) conditions are used to drive the evolution of the class of interacting information-carrying molecular replicators with the capability of reversible intermodal switches.

Presuming that the replication dynamics is restricted to the concentration plane $c^{(0)}(k,t)\simeq c^{(1)}(k,t)$, the parameter $r_B\simeq[r^{(0)}(t)+r^{(1)}(t)]/2$ may be interpreted as static effective replication rate. Many natural cycles may imply changes in the replication rate, which can be, within the context of cancer research, exemplified by the cyclic hypoxia-reoxygenation exposure within solid tumors [51].

To study quasispecies dynamics with purposefully specified the reversibility between the phenotypes $z=0$ and $z=1$ in the respective clones, we define the parameter $\varphi\in\langle 0,1\rangle$, via the linear relation

$$\varphi(k,n_s)=\frac{n_s-k-1}{n_s-2}\,,\quad k=1,\ldots,n_s-1\,, \tag{2.2}$$

which uniformly discretizes *commitment* of the cell to the respective phenotype. The labeling of the clones by the index k is introduced to make next formalization more feasible. Among the possible states we highlight the neutral (or "symmetric") case $\varphi(n_s/2,n_s)=1/2$ (equal commitment to either phenotype), as well as the "boundary" cases $\varphi(1,n_s)=1$ and $\varphi(n_s-1,n_s)=0$ corresponding to exclusive commitment to the respective phenotype, which implies complete irreversibility. In the following, the range