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Niche construction game cancer cells play*

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Abstract

Niche construction concept was originally defined in evolutionary biology as the continuous interplay between natural selection via environmental conditions and the modification of these conditions by the organism itself. Processes unraveling during cancer metastasis include construction of niches, which cancer cells use towards more efficient survival, transport into new environments and preparation of the remote sites for their arrival. Many elegant experiments were done lately illustrating, for example, the premetastatic niche construction, but there is practically no mathematical modeling done which would apply the *niche construction* framework. To create models useful for understanding niche construction role in cancer progression, we argue that a) genetic, b) phenotypic and c) ecological levels are to be included. While the model proposed here is phenomenological in its current form, it can be converted into a predictive outcome model via experimental measurement of the model parameters. Here we give an overview of an experimentally formulated problem in cancer metastasis and propose how niche construction framework can be utilized and broadened to model it. Other life science disciplines, such as host-parasite coevolution, may also benefit from niche construction framework adaptation, to satisfy growing need for theoretical considerations of data collected by experimental biology.

Introduction

Niche construction, as originally defined in evolutionary biology [1], is the interplay between natural selection via environmental conditions and the modification of these conditions by the organism itself. In this process, an organism modifies its environment, which in turns results in evolutionary or ecological consequences. While most organisms modify their own environment, *e.g.*, bacteria decompose the organic materials in their surroundings, such processes do not fall into *niche construction* unless the modification is upon their *evolutionary niche*. Additionally, niche construction is different from *adaptation*, as in adaptation process the environment stays independent while only individuals adapt, while in niche construction there is continuous interplay between the individual and the

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environment. Niche construction is most important in cases where the ecological effect spans multiple generations (vertically), where subsequent generations assimilate genetically inherited variation that benefits from the *constructed* niche. In addition, construction may be taken to be *modification* of the environment by other means such as migration, or dispersal, referred to as *relocational niche construction* [2].

Conceptual models of niche construction

Available conceptual and mathematical models of niche construction are formulated in the context of evolutionary population genetics and consider mostly genetic inheritance [2–4], sometimes also supplemented by cultural inheritance [5]. Such models generally involve the presence of large population and use differential or difference equation formalism. Two main classes of niche construction processes are covered by such models. First is *inceptive niche construction* [2], in which an organism imposing changes upon the environment by actively modifying it or by arriving into it from a different environment. Second, *counteractive niche construction* [2, 6], is a process in which the organism acts to negate deleterious environmental changes that occur by other physical or ecological means, conserving the beneficial environmental conditions, such as in the process of acquiring drug resistance [6].

The current understanding of niches in cancer biology

The *term niche* in cancer biology made its way from stem cell literature, where it was used to describe spatially defined tissue compartments with unique sets of properties. Stem cell niches allow for continuous maintenance of stem cell-rich pools by driving the balance of quiescence and proliferation. For example, the hematopoietic stem cell (HSC) niche within the bone marrow cavity is such a location. It was recently suggested that the HSC niche consists of smaller niches, such as sinusoidal vascular niche where stem cells are cycling and arteriolar vascular niche where stem cells are quiescent [7].

In the last decade, vast heterogeneity of cancer cells in primary tumors was revealed to be the cause of tumor progression and therapy failure, due to the variable capacity of cancer cells for tumor initiation, growth and metastasis [8]. This instigated development of two models of tumor progression- clonal evolution model, proposing that microenvironment pressure guides selection of dominant clones [9] and cancer stem cell (CSC) model, in which CSCs unidirectionally differentiate into daughter cells or self-renew. As definitive CSC markers are lacking, CSC model mostly uses tumor-initiating assays to provide functional definition for CSCs [10]. More recently, the concept of CSC niche has been utilized to unify tumor progression models [11]. Multipotency and self-renewal of CSCs, with addition to resistance to therapy, may be maintained by CSC localization to the niche, such as the localization of brain CSCs to the vascular niche [12]. In a bi-directional process driven by developmental factor Notch, CSCs also protect the niche by initiating additional recruitment of blood vessels. Attempts to break this internal niche communication by anti-angiogenic treatments cause hypoxia which results in cancer cell quiescence and hence resistance to cytotoxic drugs which kill dividing cells. In colorectal cancer, a non-vascular niche was described: going from top to bottom of the intestinal crypt, there is an increasing gradient of Wnt factor secreted by myofibroblasts. Transcriptional factor Wnt regulates

proliferation, differentiation and apoptosis and its high concentration colocalizes with the CSC niche in the bottom of the colorectal crypt [13].

Interestingly, it was also observed that by moving into the niche or being exposed to factors and cell types present in the niche, differentiated cancer cells may shift towards the CSC phenotype. This is just one of the examples of the cancer cell plasticity depending on their spatio-temporal context. In addition, cancer cells in the primary tumor go through epithelial-mesenchymal transition (EMT) during which they become detached from the tissue, motile and de-differentiated. A reverse process (MET) was shown to happen once cancer cells home inside the secondary organ, when they switch their state from motile to sessile [14]. A period of dormancy follows, which precedes formation of metastatic colonies.

Within the primary tumor, motile cancer cells also demonstrate spatial and temporal context dependency of different motility modes. One of these motility modes is fast-locomotion of cancer cells along collagen fibers, which eventually results in cells arriving to regions which do not allow further migration. In such regions, slow locomotion of cancer cells occurs, which includes formation of invadopodia, structures which enzymatically degrade extracellular matrix (ECM). Degradation of ECM in turn may result in cancer cell entry into blood vessels (intravasation) and/or create peptides which may serve as chemoattractants for other cancer cells in the primary tumors [15, 16].

All of these examples of cell plasticity argue towards high importance of the spatio-temporal context in which cells reside and direct us towards a closely related concept of tumor microenvironment.

Tumor microenvironment is the result of systemic changes that the host cells and ECM go through in the primary tumor, due to the continuous communication with cancer cells [17]. Throughout progression, education and adaptation processes of the host to cancer species lead to development of complex networks of signals which are exchanged via secreted factors, microvesicles (*e.g.* exosomes), direct contact or mechanical factors, inducing transient or permanent changes in either cell type or tissue structures. Host cell types such as fibroblasts, immune cells (macrophages, neutrophils, T cells, etc.), endothelial cells and others, as well as host ECM, have vastly different characteristics in primary tumors compared to that of the healthy host [18]. Within tumor microenvironment, several CSC and other types of niches can co-exist. The tumor microenvironment contribution to cancer phenotypes was demonstrated as essential even in late progression stages, where the cancer cells are known to have accumulated a number of mutations and epigenetic changes. Even in those cases, transfer of cancer cells into healthy hosts can reverse malignancy and transform tumors into differentiated and benign [19]. In contrast, addition of tumor-associated fibroblasts to grafts of non-tumorigenic cell lines can cause tumor formation in mice.

Recently, definition of the niche in cancer was broadened to describe construction of the *premetastatic niche*, inspired by the Paget's *seed-and-soil* hypothesis, which describes a process in which cancer cells prepare distant sites for the arrival of their descendants [19]. This process involves secretion of various chemokines (IL6, TGFβ, SDF1) and exosomes from the primary tumor, resulting in creation of the soil amenable for cancer cell homing,

survival and eventual outgrowth. While hematopoietic progenitor cells are recruited from the bone marrow, fibroblasts at the distant sites (lung, liver, bone) secrete high levels of ECM components tenascin and periostin, leading to cancer cell survival via Wnt and Notch signaling. Upon arrival to the secondary organ, it is likely that the process of the premetastatic niche construction continues, as tumor cells remain dormant for days to years prior to continuing proliferation [20]. When initiated, proliferation mainly occurs in perivascular space. This suggests that such space was either the niche of native stem cells or that it is a newly formed metastatic niche.

Cancer seems to reprogram every metabolic process within the host as it develops attempting to create a deterministic process without a chance of failure. However, each of the numerous steps in its progression and metastasis is rare, introducing stochastic nature to the process. As one example of the inefficiency of metastatic steps, when metastatic melanoma cells were introduced directly into blood circulation, only 0.02% survived the shear stress and migrated across blood vessel walls into the liver tissue [21].

Extending the existing mathematical models to include cancer progression

As presented above, several processes used in cancer biology can be applied to the *niche construction* framework initiated by population genetics. Continuous interplay between cancer cells and their environment results in EMT transition and cancer cell migration to new environments, degradation of ECM and cancer cell intravasation, preparation of remote location for cancer cell arrival, etc. (fig. 1). While many elegant experiments were done in the last decade and the need for theoretical considerations which would link the two concepts was recognized [22], there is practically no mathematical modeling done as of now towards predicting locations or time-frames of metastatic colonization under different conditions.

During metastasis, cancer cells prepare for arrival at the secondary site, most likely via a mutational process. Similarly, once they have arrived to secondary site, they enter dormancy, during which they go through self-adaptation to be able to initiate proliferation and colonization. Simultaneously, the eco-system is recruited towards site modification (ecologically driven niche construction). To this end, Yang *et al.* [23] have recently proposed a phenomenological model which describes niche construction as a reduction in tumor cell fitness which leads to increased mutation rate and dispersion. This model combines niche construction and the notion of *cancer diaspora* built on above mentioned principles of ecological dispersion. In addition, we propose niche construction mechanism should be augmented by addition of population dynamics behavior such as frequency-dependent selection.

Frequency-dependent selection carries a tacit assumption that as the population *frequency* increases, there is a monotonic decrease in viability due to the limiting resources. As a result, the more an individual has, the less the collective has; such an assumption is absent from the current theory of niche construction which assumes unlimited resource generation other than ecosystem destruction. One example of the need for including frequency-dependent selection is the construction of hypoxic environment in progressing cancer, which

may be deleterious or even lethal to cancer cells. Such an environment is commonly a function of cell proliferation, that is, the higher the proliferation the more hypoxic (or necrotic) the environment is, as a result of limiting resources. On the other hand, hypoxic environment may subsequently result in increased or reactive oxygen species (ROS) potentially increasing invasion and metastasis [24] or cancer dormancy and drug resistance, both of which are beneficial to cancer cells. Such an addition will aid in balancing therapeutic doses and predicting a tradeoff of different levels of hypoxia in the tumor microenvironment.

We propose that the niche construction in cancer should be studied across different levels of organization: a) genetic, b) phenotypic and c) ecological —where multiple cell types are involved in constructing the secondary organ conducive to colonization.

The model

Towards a dynamical model of cancer niche construction, we considered the following aspects as necessary (and possibly not sufficient): cellular genotypes, cellular phenotypes and ecological factors. Components of the system can be classified as:

1. Tumor cells, which possess number of *genotypes* adapted via mutations to different environmental, including site-specific, conditions.

   1a) Each genotype (clone) has its potentials for different *phenotypic* behaviors: proliferation, ECM degradation, cell migration, cell adhesion to ECM or other cells, autophagy, apoptosis, necrosis.

   1b) Phenotypic behaviors can be changed via i) phenotypic switching, where the regulation is horizontal and switch can be quickly reversed via changing extracellular conditions or ii) via slow, vertical transitions, where new generations are progressively shifting towards more pronounced phenotypes.

   1c) Cancer cells recruit *ecological community* both locally and remotely through autocrine, juxtacrine and paracrine communication signals such as ROS, chemokines, exosomes, extension of tunneling nanotubes, etc.

2. Immune cells, such as macrophages react to chemokines and other signals to enable cancer cell motility, survival, proliferation, as well as premetastatic niche preparation.

3. Fibroblast in primary and secondary sites are activated to produce increased amounts of modified ECM and remodel its components.

4. Endothelial cells are activated to form new blood vessels and branch existing ones in the process of angiogenesis.

5. Extracellular matrix, which varies in architecture, stiffness and adhesion ligand density, influences phenotypes of all cell types.

6. Extracellular matrix fragments, some of which are bioactive, are produced by remodeling activities of any of the cell types.

Listed elements are to be considered quantitatively rather than as present or absent (binary) and recognized as dynamic and continually modifying their own environment and adapting to new conditions both in direct surroundings, as well as on remote locations. Figure 1 illustrates a cartoon that incorporate some of the elements described above as essential for the metastatic progression from the primary to the secondary tumor sites, however, without the time dimension.

Based on these elements, we can develop a conceptual framework for the usage of population genetics niche construction theory to the study of cancer development and progression. Cancer cells will be considered individual *organisms* that construct their immediate *ecological* environment, *disperse* to distant organs and construct *relocational niches*. While the ecological niche construction may be transmitted horizontally (to cells of the same generation), the relocational niche construction process via metastasis is more likely to be vertically transmitted to daughter cells. The relocational niche construction can also be mediated through additional players, *e.g.*, recruitment of bone marrow-derived myeloid cells (*e.g.* macrophages) and activation of fibroblasts as described in the premetastatic niche [20].

For simplicity, we will start by introducing a skeleton model that describe both primary tumor site construction, as well as the construction of pre-metastatic niche, and for clarity, we will farther consider only the pre-metastatic niche construction which involves two of the factors, clonal cancer cells and tumor-associated macrophages.

Consider a di-allelic haploid model where the “genotype” is composed of three cassettes, A, C, and E, where A represent the cassette of the major genes associated with tumor cell fitness (this fitness is considered to be fixed and genotype-dependent only), C represents the communicative ability between clonal cancer cells and immune cells which results in premetastatic niche construction and E is associated with the ability to construct the immediate environment. For simplicity we will consider haploid di-allelic model (extensions to more elaborated genotypic arrangement is straightforward).

The following are the 8 possible genotypes: *ECA*, *ECa*, *EcA*, *Eca*, *eCA*, *eCa*, *ecA*, and *eca*; with fixed fitness associated with the major gene A, $w_1^*, w_2^*, w_3^*, w_4^*, w_5^*, w_6^*, w_7^*, w_8^*$, respectively. The time-dependent frequencies of the 8 genotypes are $u_{1,t}$, $u_{2,t}$, $u_{3,t}$, $u_{4,t}$, $u_{5,t}$, $u_{6,t}$, $u_{7,t}$, $u_{8,t}$, respectively.

At each cellular generation the level of local reconstruction, R, either positively of negatively, is assumed to be a function of the frequency of the E allele

$$x_t = u_{1,t} + u_{2,t} + u_{3,t} + u_{4,t}.$$

The level of interaction, Q, with tumor-associated macrophage depends on the frequency of the C allele in the population

$$y_t = u_{1,t} + u_{2,t} + u_{5,t} + u_{6,t}.$$

Finally, let the frequency of the A allele be

$$z_t = u_{1,t} + u_{3,t} + u_{5,t} + u_{7,t}.$$

We will assume that at time t the level of local reconstruction takes the following form:

$$R_t = \sum_{i=t-n+1}^{t} \pi_i x_i,$$

where π_i is the weight associated with the impact of the i-th generation on reconstruction, and n is the number of past generations affecting the local environment. Similarly, let

$$Q_t = \sum_{i=t-n+1}^{t} \mu_i y_i$$

be the time-dependent effect of immune cells on the secondary tumor site (relocational reconstruction), and μ_i is, again, the weight associated with the impact of the i-th generation.

The functional form of π_i and μ_i can take the form of having equal weight over time. Alternatively, they can have have recency effect where the most recent generation has the highest impact $\pi_t > \pi_{t-1} > \pi_{t-2} \ldots > \pi_{t-n+1}$ or primacy effect $\pi_t < \pi_{t-1} < \pi_{t-2} \ldots < \pi_{t-n+1}$ or any other functional form. Similar rules can be established for μ_i, the weights associated with immune cell-driven relocational reconstruction.

Next, for clarity, we will consider solely the time-dependent effect of immune cells on secondary tumor site in terms of the tumor cell viability. As defined above, w_j^* is the fixed part of the viability portion of genotype j.

The frequency-dependent contribution to the fitness of individuals with alleles A and a will take the simple form of Q and $(1 - Q)$, respectively. That is, it is favorable for individual to have allele A when Q is “common” and to have allele a when Q is “rare”. A widely used functional relation between the quantity Q and fitness is the power function parameterized by f, to be determined experimentally. Similarly for the local reconstruction element of the niche, R. Thus, the time-dependent two components of the fitness of genotype j takes the form:

$$w_{j,t}^{R}=w_{j}^{*}+\varepsilon R_{t}^{f} \text{ for } j=1,3,5,7 \text{ and}$$
$$w_{j,t}^{R}=w_{j}^{*}+\varepsilon(1-R)^{f} \text{ for } j=2,4,6,8$$
$$w_{j,t}^{Q}=w_{j}^{*}+\varepsilon Q_{t}^{f} \text{ for } j=1,3,5,7 \text{ and}$$
$$w_{j,t}^{Q}=w_{j}^{*}+\varepsilon(1-Q_{t})^{f} \text{ for } j=2,4,6,8,$$

where ε is the strength of the frequency-dependent component of selection relative to the fixed fitness component of genotype *j*. Positive value of ε represents positive cumulative effect while negative ε represents negative effect on genotype *j* when arriving at the secondary tumor site.

Finally, assuming, for example, a multiplicative fitness model will result in an overall fitness of genotype *j* as

$$w_{j,t}=w_{j,t}^{Q}w_{j,t}^{R}.$$

Positive value of ε represents positive cumulative effect while negative ε represents negative effect on genotype *j* when arriving at the secondary tumor site.

To introduce the cellular population dynamics, we evaluate the genotypic frequencies in the next generation of cell population, using a selection process based on the relative fitness of the different genotype in the previous time-step, *i.e.*,

$$Ku_{j,t+1}=\frac{w_{j,t}u_{j,t}}{\sum_{i=1}^{8}w_{i,t}u_{i,t}},$$

where

$$K=\sum_{j=1}^{8}\frac{w_{j,t}u_{j,t}}{\sum_{i=1}^{8}w_{i,t}u_{i,t}}.$$

Again, for illustration purposes and without a loss of generality, we assumed a phenomenological description of a single gene di-allelic haploid model, however, extensions to a more realistic model are relatively straightforward.

Please note that when $n = 1$, where n is the number of generations affecting Q, the above formulation is reduced to a simple frequency-dependent selection model.

When considering additional factors such as local environmental effects, *e.g.*, one may introduce a model where the form of interaction between the local reconstruction and relocational reconstruction are more complicated including some form of epistasis, the model become more cumbersome, however, the conceptual framework does not change.

The process of the construction of a mathematical model based on previously collected experimental data is illustrated by this phenomenological model, which can be converted into a predictive outcome model via measurement of parameters such as ε and f or broadened in form. Most experiments offering modulation of cell numbers, genotype and phenotype can be done by currently available methodologies in preclinical mouse models:

– Number of immune (immature myeloid) cells recruited towards premetastatic niche formation can be boosted by animal treatment with different doses of inflammatory chemokines (*e.g.* CCL17, CCL22 which act through CCR4) or inflammatory chemoattractants (S100A8, S100A9).

– Conversely, inhibitors of LOX or blocking antibodies for CCR4 can be used to reduce the immune cell recruitment [25].

– Number of tumor cells landing in the secondary organ (*e.g.* lungs) can be varied by experimental metastasis assay [21], in which tumor cells are introduced directly into the vasculature.

– Genotype of cancer cells injected into vasculature can easily be controlled by selection of various cell lines or by sorting subpopulations of cancer cells from tumors.

– Genotype of immature myeloid cells can be controlled via bone marrow transplants using knock-out and knock-in mice as donors while.

– Phenotypes of tumor or immune cells can be modulated by stimulating or inhibiting specific signaling pathways.

With each of the modulations of the system, the number of cancer cells at secondary sites would be measured at two different time points. This would provide ε, which can be presented as a function of the primary tumor growth *versus* secondary site growth. Number of cancer cells in secondary site as a function of immune cell number would provide f.

To test the model's capability for distinguishing among genotypes and providing dynamical profiles of frequency and fitness, we have created a simulation in Matlab, using 0.5 as values for both ε and f parameters and random choice for w_j^* and random initial values for u_j (fig. 2). Even in this simplistic, haploid version of the model, we can observe complex system dynamics, including oscillations and non-monotonic trends. This suggests that for a model with higher complexity that will hold some predictive power, a careful experimental design for the estimation of the model parameters is needed.

Conclusions

Here we give an overview of an experimentally formulated problem in cancer metastasis and propose how existing niche construction framework can be utilized to model it, with additional implementations of concepts from evolutionary biology. We propose one possible approach on utilizing existing data and suggesting new directions for future experiments in a niche construction-type framework, which should further be modified and broadened by parameters from the experimental data. Moreover, there are additional considerations that

may be taken into account, such as the stochastic nature of the metastatic process, which relies on one or few cells and as such is subjected to high rate of extinction.

An effort of establishing this and similar workflows of experiments-theory-experiments is likely not possible in a single laboratory but rather calls for an effort of the cancer research community as well as the recruitment of physicists, engineers and mathematicians.

Other life science disciplines may also benefit from niche construction framework adaptation. Fields of host-parasite coevolution, including microbiome, are looking for theoretical ways to investigate very similar phenomena [26]. Whereas parameter values may greatly vary between different applications, we believe models similar to the one proposed here may help advance the understanding of complex disease progression and continual interactions between the host and cancer (parasite) populations.

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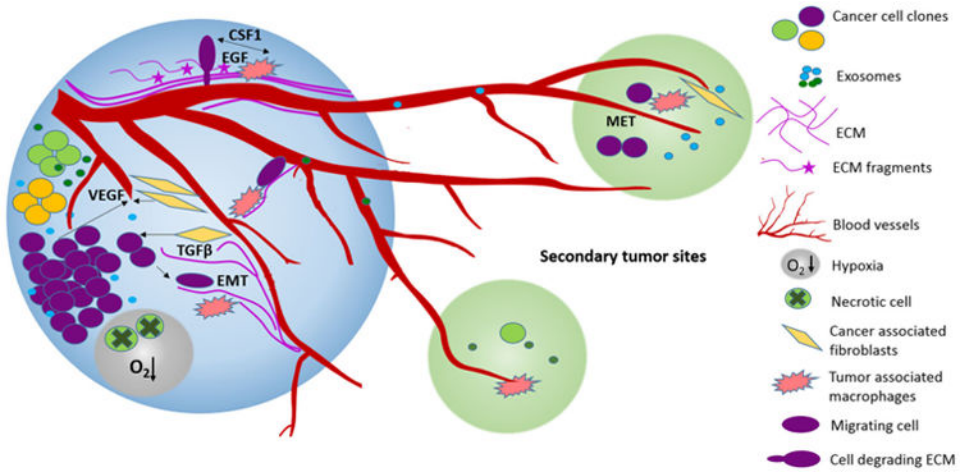

Fig. 1.

Schematic of major elements contributing towards niche construction in secondary tumor sites.

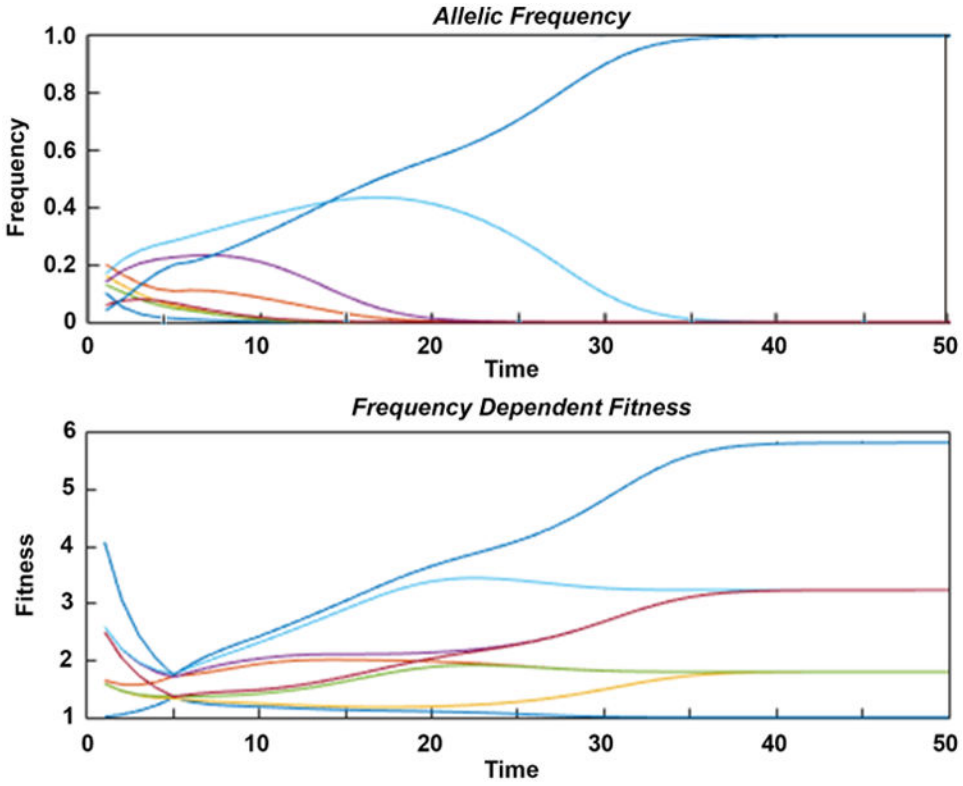

Fig. 2.

Model simulations illustrating complex dynamics of allelic frequencies ($u_{1,t} - u_{8,t}$) and frequency dependent fitness $(w_1^* - w_8^*)$, marked by different color lines.