WHEN RELAXATION MEETS ADAPTATION IN COMPLEX ADAPTIVE SYSTEMS: A COMPUTATIONAL STUDY OF TUMORIGENESIS

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Received 12 February 2017

Revised 9 October 2017

Accepted 10 November 2017

Published 28 December 2017

In complex adaptive systems (CASs), the relaxation based on intra-individual interactions and the adaptation based on sub-individual variations are two fundamental processes entangled to induce great complexity. We analyze the system evolution under multicellular homeostatic regulations coupled with various mutation strategies in computational tumorigenesis as a typical instance to clarify the coupling effect of relaxation and adaptation in CASs. Through visualizing the system dynamics on a synthesized fitness landscape which results from the superposition of the phase diagram and the individual fitness landscape, we entertain a simple theoretical framework that not only helps analyze our simulated multicellular dynamics but is potentially applicable to a broader class of problems in CASs where relaxation and adaptation intertwine. It is stressed that the nonadaptive relaxation process has the essential role in shaping the selective pressure of adaptation as well as in defining the final state of the evolution, whereas it is the rigidity of mutation strategy that determines the complexity of the dynamical process.

Keywords: Discrete receptor dynamics model; homeostasis; evolutionary cancer biology; mutation; fitness landscape.

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1. Introduction

Given limited resource and space, a system composed of many entities can undergo evolutions driven by either or both kinds of fundamental equilibrium dynamics [38]^a: relaxation and adaptation. The relaxation-driven evolution (RE), prevalent in physical systems, depends on such individual interactions that facilitate to reach a stable microscopic configuration under some mechanical and behavioral principles. The adaptation-driven evolution (AE), a bequeathed wisdom by C. Darwin and which is deemed as the essence of biology [12, 15, 23], depends on such autonomous variations of individual properties (hereafter mentioned as “mutation”) that facilitate the interspecies competitions under the law of “the survival of the fittest”. In brief, RE stabilizes the structure of inter-individual relationship in the system and AE shapes the individual properties that adapt to the environment by selective pressure. Notwithstanding that AE has long been treated in analogy to the RE of evolutionary dynamics with concepts and formulas borrowed from statistical physics [3, 19], they are essentially distinctive processes, governed by laws on disparate levels, yet they extensively intertwine in nature.

Very often, RE and AE have been studied separately for their incomparable characteristic spatiotemporal scales, under which one process with shorter characteristic scales predominantly controls the system evolution and the other leads solely to epiphenomena. For instance, in all many-body physical systems embracing fixed mechanical laws with nonmutable particles, the characteristic timescale of AE is infinitely long so that the system only equilibrates through RE, reaching a stable particle configuration; by contrast, for the living systems with frequent mutations, the timescale of AE is relatively short, hence the system equilibrates through AE to reach a configuration wherein no individual can gain more fitness through mutation.^b The concept of RE not only constitutes the physical relaxation in condensed matters and material sciences [13, 52], but also extends to pattern formations in diffusion-reaction systems [63, 65], the self-organization of homeostasis in biological organisms [32, 45, 57, 66], the Pareto optimization of resource allocation in neoclassical economics [14, 55], the emergence of behavioral patterns in macroscopic socioeconomics [20, 39] amongst others; meanwhile, studies of AE tackles mainly ecological and biological issues [53, 59], and can also be extended to cancer biology [11, 37, 49], game theory [58], sociobiology [33, 29], psychology [8], evolutionary economics [2, 17, 24, 36], and so forth.

For complex adaptive systems (CASs) [6, 31, 35], where relaxation and adaptation usually feature comparable characteristic scales, and the coupling of RE and AE is always concerned as a must [5, 16, 42, 48, 54, 56]. Mutation of individual properties

^aMost dynamics of relaxation and adaptation are nonequilibrium. “Equilibrium dynamics” here broadly refers to the process of dynamic optimization of some intrinsic functions (e.g., the minimization of energy for structural relaxation, the maximization of entropy for thermodynamic relaxation, or the maximization of fitness for biological adaptation) in a theoretical sense.

^bA well-spread concept is the Nash equilibrium in the game theory [51].

during AE changes the interaction laws underlying RE, and reciprocally, the ongoing stabilization of inter-individual relationship structure during RE will interfere with the way of mutation, selection, and adaptation. In the framework of Darwinian evolutionary theory, this complex and system-specific coupling of RE-AE can be realized by encapsulating the impact of both processes into the fitness function as two types of noises, which, nevertheless, is very difficult to formulate [3, 28, 41]. Game theory [60, 50] then addresses this problem via a paradigm in which the fitness of an individual genotype dynamically varies as a function of the composition of other individual genotypes, with a simplifying assumption of random phenotypic interactions.^c Yet, this simplification facilitates mathematical formulation at the sacrifice of nontrivial structures in the interactive dynamics that define the specified features of distinctive CASs. In this paper, we present an opposite paradigm, in which the coupling effect of RE-AE is studied on the basis of non-mutational phenotypic dynamics of local interactions but tailored by the impact of adaptive dynamics. In other words, we treat the CAS as a physical system composed of mutable particles, therefore many nontrivial structures of the inter-individual interactions can be designed for the study of some specific CAS.

To help the construction of our hypotheses and theory, we choose tumorigenesis in a computational multicellular system as a typical instance for obtaining contextualized empirical data. Tumorigenesis is extensively studied in the past few decades and ample evidence shows that tumor emerges from the interactions among multiple factors on multiple scales [1, 4, 47, 69].

On one hand, many biologists assert that Darwinian adaptation governs the cancer initiation and progression, in which cells with cancerous genes are advantageous and selected to survive [9–11, 22, 26, 27, 37, 49]; on the other hand, the multicellular system is constantly subject to the relaxation mechanism stemming from the biochemical negative feedbacks among different bio-entities to stabilize the multicellular culture for the maintenance of overall biological functions, i.e., a process called homeostasis [32, 45]. In the studies of multicellular homeostasis, cells are presumed to be homogeneously programmed automata without mutations because mutation rate is considered as too low to affect homeostasis. By contrast, in studies focusing on the genetic mutations and the evolutionary origin of cancer, those nonmutational factors (including the multicellular relaxation) can only be simplified as some “source of noise” [31, p. 269; 21, 40] added to the fitness function for the sake of theory formulation. How the two processes exactly couple in tumorigenesis is still obscure and the study oriented to practical uses is lacking.

Let us interpret the multicellular system in a simpler scheme, wherein each cell is supposed to be described by three phenotypic coordinates: (1) reproductivity,

^cA genotype is a replicable individual intrinsic trait that contributes to the phenotype, whereas a phenotype is the transient behavioral expression resulted from not only the genotypes but the local interactions and the environment as well.

Fig. 1. The conceptualization of AEs, REs, and their interplays in a multicellular biological system. (a) A schematic three-dimension phenotypic space upon which a cell is described. (b) System evolutions in the phenotypic space under AE (top) or RE (bottom). Note that there exists a diversity of homeostasis featuring distinctive phenotypic structures. (c) The AE and REs drive the system into different states marked as the circle, the diamond, and the triangle. The transitions among REs and AE and their impacts on the fate of the system are the subject of this study.

(2) susceptibility to death and (3) tendency of cell cycle arrest [corresponding to the three orthogonal axes in Fig. 1(a)]. From the adaptation perspective, the system will be gradually occupied by the “fitter” cells that acquire more hallmarks of cancer cells, such as high reproductivity, low death susceptibility and low cycle-arrest tendency [34], indicating that the final equilibrium of multicellular AE is tumorigenesis [top panel in Fig. 1(b)]; nonetheless, from the perspective of homeostatic relaxation, the nonmutating cells can form diverse stable structures of phenotype distributions, in which cells can keep diverse phenotypes rather than the fittest one [bottom panel in Fig. 1(b)] for keeping the system’s stability. Placing the same emphasis on both homeostasis (RE) and mutations (AE), we reiterated the question of RE–AE coupling in this specific context as how homeostatic relaxation and mutations are woven together to orchestrate the emergence of tumorigenesis (Fig. 1(c)). Is tumorigenesis a simple consequence of AE with RE having trivial impacts, or do tumorigenesis originate from a dynamical regime shift from normal homeostasis to abnormal homeostasis with the interference from AE? And is tumorigenesis the only equilibrium state of AE in the presence of RE?

In this paper, we will answer these biologically context-specified questions through computational simulations. A primary assumption is that tumorigenesis emerges from normal tissue, as a consequence of equilibrium dynamics (of either or both RE and AE), free from any pathological factors such as cancer-inducing

toxicants or physical damages.^d We choose the computational model that retain as many nontrivial details on both AE and RE sides as possible with proper computational efficiency. The model we adopt is the discrete receptor dynamics model (DRDM), which is capable of reproducing the formation of diverse homeostasis in nonmutational settings. Also, three new sub-models of mutations are invented and built into DRDM. In Sec. 2, we briefly elaborate the model construction and the major nonmutational results based on [45] before introducing three new mutation models. Section 3 displays the simulated system evolution measured by a phenotype structure index under various kinds of mutations. In Sec. 4, we further analyze system's evolution in terms of a mutational path on the phase diagram in the space of genotypic traits and draw a generic understanding of RE–AE coupling which is potentially applicable to a broader class of CAs. Section 5 concludes the whole studies.

2. Model

2.1. Basic model and the nonmutational result

DRDM is an on-grid cell-based model for homeostasis formation of epithelial tissues based on merely cell–cell and cell–extracellular matrix (ECM) interactions. The homeostasis in DRDM intrinsically evolves from normal states to diverse terminations over a large spectrum of timescales without intrinsic mutations or environmental perturbations. Cells in DRDM are accommodated in a two-dimensional (2D) regular lattice with a periodical boundary condition, given a constant amount of growth factor uniformly distributed in the space. These spatial conditions ensure that resource and space are limited in DRDM.

Each DRDM cell is equipped with five types of receptors, namely growth receptor, adhesion receptor, ECM receptor, arrest receptor, and death receptor. The cell behaviors including growing, adhering to the neighbors/ECM, polarization, proliferation, cell-cycle arrest, cell death, and cell movement are triggered (or muted) according to a comparison between the concentration of those five receptors with various thresholds (Fig. 2(a)). The transformation among five receptors occurs during each cell behavior at each computational time step. The discrete receptor dynamics are nearly deterministic, whereas the only stochastic behavior occurs in the *proliferate* function [refer to the right panel in Fig. 2(a)], in which the newly-born cell randomly occupies one of the vacant sites neighboring to the mother cell (see Appendix A for model parameters and detailed receptor dynamics rules).

The fluctuating receptor configurations of each cell cause heterogeneous but cooperative cell phenotypes dynamics and consequently lead to the self-organization of diverse homeostatic patterns. These diverse homeostatic states can be observed as

^dOf course, in reality, the pathological factors can deteriorate physiological environments of tissues, resulting in malicious mutations and the dysregulation of homeostasis; nevertheless, in this paper, we keep these factors irrelevant so as to focus on the role of RE and AE in tumorigenesis.

Fig. 2. (Color online) Schemes of DRDM and diverse homeostasis. (a) Left: The transformation among five kinds of receptors that govern cell behaviors. Right: the flow of cell behaviors, including cell growth, cell-cell adhesion, cell-ECM adhesion, apical polarization, cell division, cell cycle arrest, cell death and cell movement (see [45] for detailed model descriptions). The dichotomy of the arrows (e.g., after the *adhere* behavior, the arrow splits to two arrows, having two possible behaviors *proliferate* and *polarize* to ensue), requires a comparison between the receptor amounts and the thresholds. (b) Diverse evolutionary trajectories in terms of compositional percentage of arrested cells and the normalized total cell volume $N/N_{\max}$, where N is the total cell number and $N_{\max}$ is the space size. The arrows point to the direction of time evolution. Under different parameter settings, the DRDM system has divergent evolving patterns on the map (labeled in different colors) towards terminations with distinctive structures of cell phenotype distributions, as illustrated in the insets. Inset: cell phenotype distribution in a 3D phenotype space for four different homeostatic states, degenerate, inadequate, normal and tumorigenic. In reference to Fig. 1(a), the phenotype space has three dimensions: the horizontal axis is the summed amount of growth and adhesion receptor concentration indicating the reproductivity; the axis pointing perpendicular to the plane of the paper is the amount of death receptor concentration, indicating the susceptibility to death; the vertical axis is the amount of arrest receptor concentration indicating the tendency of cell cycle arrest. Two colored planes (perpendicular to each other) intersect respectively with x -axis and z -axis at the lines of $x = g$ (g : growth receptor threshold and $z = a$ (a : the arrest receptor threshold), i.e., the two planes visualize where the thresholds locate. The color of the dots represents cell density, and a darker color corresponds to a higher density. (c) Histogram (top) and corresponding probability distributions (bottom) of phenotypic structure index v evaluated at $t = 10^6$ steps in 3×10^4 sessions of simulation.

the various multicellular morphologies in real spaces (e.g., the morphocharts in [57]) and also be mapped to distinctive density distributions in the cell phenotype space. Figure 2(b) illustrates diverse evolutionary trajectories of the percentage of arrested cells versus the normalized total cells during the formation of distinctive cell phenotype distributions (degenerate, inadequate, normal and tumorigenic) in the receptor space [inset of Fig. 2(b)]. The description of homeostasis formation by cell phenotype distribution instead of multicellular morphology can facilitate the quantification of the system's homeostatic state. Therefore, the cell phenotypic structure index v , formulated as $v = 0.1N_a/N_{\max} + N_t/N_{\max}$, is proposed in [45] as a global quantity indicating the cell phenotype distribution, where N_a is the number of arrested cells, N_t is the number of tumorigenic cells (the proliferative cells having no space to divide, thus potentially inducing tumor), and $N_{\max}$ is the total number of lattice sites in the simulation space. Based on its formulation, the index v not only reflects the structures of cell phenotype distributions but also implies the global fitness of the system, with $v = 0$ corresponding to the extinctive degeneration (all cells dead) and $v = 1$ to a complete tumorigenic state (all cells proliferating).

By scanning three control parameters ECM receptor threshold e , death receptor threshold d and arrest receptor threshold a , we found three basic homeostatic states in 3×10^4 simulation sessions (one session for one set of parameter) over $t = 10^6$ time steps [three local peaks shown in the histogram, in the top panel of Fig. 2(c)]. The three peaks feature diverse phenotype structures: degeneration ($v < 0.08$), normal (v spanning from 0.3 to 0.7), and tumorigenesis ($v = 1$). By translating the frequency $f(v)$ [top panel in Fig. 2(c)] into a normalized probability $P(v)$ as:

$$P(v) = f(v) / \int_0^1 f(v) dv, \quad (1)$$

we can depict a “pseudo energy landscape” with $-\log P(v)$ serving as an effective energy function and the structure index v as the conformation coordinate^e (Fig. 3(b)). Two big valleys of the energy minima can be detected as degeneration and tumorigenesis, whereas a shallow and rugged valley spans the extensive region of medium v at a higher effective energy level. Note that the shallow valley at higher effective energy level indicates that the system states with *normal* phenotypic structure have an intrinsic potential to evolve towards degeneration or tumorigenesis as a relaxation process, and the ruggedness of the *normal* valley will arrest the system dynamics into many metastable states and prolong the relaxation processes.^f

The DRDM model enables an emergence of tumorigenesis from a nonmutational model setting. Through the past decades, accumulating discussions about the non-genetic origins of cancer has been documented [4, 47, 57, 69] and the DRDM results

^eIn a statistical sense, the conformations with the lower energy exist with the largest incidence in nature because it is the most stable among others.

^fHere, we borrow the concepts from physics of glass forming systems [64] to understand the process of homeostasis formation in DRDM.

Fig. 3. Three prototypes of mutations in the space of the genotypic trait p . The black ball marks the initial value of p before mutation. Each arrow represents an alteration in the value of p at each proliferation time.

suggest that one of those nongenetic origins might be the self-organization mechanism on the multicellular level.

2.2. Sub-models of mutation

The homeostatic dynamics in DRDM is formed through cell–cell interactions and cell–ECM interactions without considering mutations. Nonetheless, abundant experimental and theoretical works on cancer genomics show that the role of genetic instability and Darwinian selection [9–11, 25–27, 37, 49, 62] is indispensable in cancer progression and its therapeutic resistance. In this section, we will introduce the design of mutation modeling based on DRDM to scrutinize the system dynamics under the coupling of RE and AE in this computational multicellular organization.

2.2.1. General descriptions

As the entities like DNAs, genes, chromosomes, proteins are not explicitly modeled, a mutation event in DRDM is defined as a small amount of variation in one cell intrinsic parameter which measures a specific trait that emerges from underlying genotypes, and which can be altered continuously on a nonzero real field. These intrinsic parameters of cells are termed as “genotypic traits” hereafter. Thereby, in this model, the concept of mutation is not narrowly referred to the alterations of genes; instead, this mutation can be a complex result of genetic errors, epigenetic modifications, disordered regulation of the endogenous network [4], and so forth.

Subcellular abnormalities involved in the progression of cancer are accumulating slowly and steadily through the life of a living system [18, 46]. The genotypic properties can be inherited by descendant cells, therefore characterizing clonal expansion [22, 30]. Additionally, most mutations on genotypic levels are unnoticeable and harmless on the phenotypic level, whereas very few other ones may result in a remarkable phenotypic consequence due to the accumulation of alterations hitting

critical points. Based on this knowledge, three prototype mutation sub-models are considered, namely *monotonic*, *stochastic*, and *hereditary* as illustrated in Fig. 3. All of these sub-models follow two basic principles of mutation: the mutated genotypic traits are replicable and accumulating. The values of the genotypic traits can be passed upon to the next generation when the mother cell divides and the variations in the genotypic traits of the two new-born cells immediately occur, depending on the value of genotypic traits replicated from their mother.

The mathematical representations of three sub-models are as follows. For any chosen genotypic trait p , a cell at site i at each proliferation time t undergoes a mutation process as $p^i(t+1) = p^i(t)F(\mu)$, where $F(\mu)$ is the mutation function depending on a mutation rate μ . The function $F(\mu)$ in the *monotonic* model is formulated as $1 + \mu_m$ or $1 - \mu_m$, rendering an algebraic increase or decrease in p^i ; in the *stochastic* model, $F(\mu)$ is formulated as $\exp(\mu_s X)$, where $X \sim \mathcal{N}(0, 1)$ is a random variable with a standard Gaussian distribution, i.e., p^i varies by random drift. The last model, i.e., the *hereditary*, is a mixture of several *monotonic* mutations, where all cells inherit from their ancestor a clonal identity c that encodes one exclusive *monotonic* mutation strategy characterizing its ancestral lineage and therefore cells of different clonotypes feature disparate *monotonic* mutation strategies. Note that the mutation rate μ is a newly-introduced critical parameter that is associated with the timescale difference between RE and AE: a low μ indicates a trivial impact from AE, thus resulting in a leading role of RE, whereas a high μ will intensify the effect of AE in the system. It can be therefore inferred that a moderate μ could induce the interweaving of the two evolutions over comparable timescales.

Conventionally, genetic errors are considered to be random and occurring in all directions [23, 67], yet how these errors would influence the quantitative cellular traits through complex processes is unclear and is still the central subject of the ongoing studies in statistical genetics [7, 68]. Due to the absence of genetic details in our model and to the lack of the unanimous phenomenology of the way quantitative traits vary with time, we can only articulate the rules of the mutation in the genotypic traits for our model based on simple assumptions. Two extremal cases are considered: (1) the mutations in genotypic traits are algebraically accumulating in one direction or (2) they are totally isotropic and unpredictable. The *monotonic* mutation model belongs to the first extreme: a simple algebraic accumulation of mutations occurs to one genotypic trait at a predefined mutation rate with no heterogeneity. It idealizes a scenario where the mutation at each step is triggered by those at previous steps, which forms a positive feedback that can amplify the effect of mutation through the time. This amplification is usually seen in cancer where a small alteration in the tumor suppressor genes like p53 [43, 44, 61] causes a series of malfunctions in the cell cycle inhibition, self-repairing, apoptosis and even the activations of other oncogenes, rendering an incessant increase in the level of growth factors. By contrast, the *stochastic* model belongs to the second extreme: cells can randomly explore all possible mutations in all genotypic traits, showing the maximal

heterogeneity. Unlike the *monotonic* mutation, the *stochastic* model does not assume any positive feedback dynamics that define the relationship between all the errors on the genetic, epigenetic, or molecular levels and the changes in the genotypic traits; all the variations in the genotypic traits are random because of the multifactorial complexity. The third *hereditary* model, lying between the two extremes, realizes a constrained heterogeneity of mutations by equipping different clonotypes with disparate *monotonic* mutation strategies for all genotypic traits. The *hereditary* mutations are different linear combinations of the *monotonic* mutations, thus

Table 1. Mutation rules in DRDM for three sub-models.

Sub-model	Rules (for the cell at site i at any proliferation time t)	Characteristics
monotonic	$e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 + \mu_m)$ or $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 - \mu_m)$ or $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 + \mu_m)$ or $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 - \mu_m)$	homogeneous, deterministic
stochastic	$e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t) \exp(\mu_s X)$ and $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t) \exp(\mu_s X)$, where $X \sim \mathcal{N}(0, 1)$	heterogeneous, neutral, stochastic
hereditary	$c = 1$: $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 + \mu_{h,d})$ and if $d_{\text{scr}}^i(t+1) > d_{\text{scr}}^i(0)(1 + s)$, $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 - \mu_{h,e})$ $c = 2$: $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 - \mu_{h,d})$ and if $d_{\text{scr}}^i(t+1) < d_{\text{scr}}^i(0)(1 + s)^{-1}$, $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 + \mu_{h,e})$ $c = 3$: $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 + \mu_{h,d})$ and if $d_{\text{scr}}^i(t+1) > d_{\text{scr}}^i(0)(1 + s)$, $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 + \mu_{h,e})$ $c = 4$: $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 - \mu_{h,d})$ and if $d_{\text{scr}}^i(t+1) < d_{\text{scr}}^i(0)(1 + s)^{-1}$, $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 - \mu_{h,e})$ $c = 5$: $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 + \mu_{h,e})$ and if $e_{\text{scr}}^i(t+1) > e_{\text{scr}}^i(0)(1 + s)$, $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 - \mu_{h,d})$ $c = 6$: $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 - \mu_{h,e})$ and if $e_{\text{scr}}^i(t+1) < e_{\text{scr}}^i(0)(1 + s)^{-1}$, $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 + \mu_{h,d})$ $c = 7$: $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 + \mu_{h,e})$ and if $e_{\text{scr}}^i(t+1) > e_{\text{scr}}^i(0)(1 + s)$, $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 + \mu_{h,d})$ $c = 8$: $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 - \mu_{h,e})$ and if $e_{\text{scr}}^i(t+1) < e_{\text{scr}}^i(0)(1 + s)^{-1}$, $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 - \mu_{h,d})$	limited heterogeneity, clonal expansion, sequential mutation deterministic

Note: In the *hereditary* model, the parameter c represents the cell clonotype, which is inheritable during cell division. The parameter s is the coefficient controlling the significance of mutation sequence. The mutation rates for e_{scr} and d_{scr} are $\mu_{h,e}$ and $\mu_{h,d}$, respectively.

different types of positive feedbacks (labeled as the clonotype) can coexist in the system. Besides the mutation effect, the competition among multiple cell clonal lineages will also take place, resulting in clonal expansion; nevertheless, the cells within each clone still share the same *monotonic* mutation strategy along each dimension of the genotypic trait space so the *hereditary* mutations are less heterogeneous than the *stochastic* ones. In the last part of this section, we will further analyze a model integrating the *hereditary* with *stochastic* mutations, which exhibits the highest complexity yet has the most similar features to clonal expansions in reality.

2.2.2. Mutation rules in DRDM

In this study, we chose the ECM saturation fraction e_{scr} and the death receptor transforming rate d_{scr} as two mutable intrinsic parameters, which also play critical roles in controlling homeostatic states in DRDM. Hence, the variation of e_{scr} and d_{scr} affects both RE and AE. The ECM saturation fraction e_{scr} , which is the upper limit of the ECM amount secreted by per mass of its growth receptors, decides the sensitivity of a cell to its ECM. When e_{scr} is small, ECM concentration reaches saturation level very rapidly so that the growth receptors are quickly transformed to ECM receptors, and results in a higher tendency of polarization and subsequent cell cycle arrest. The death receptor transforming rate d_{scr} , as the term expresses, decides the susceptibility of a cell to death. In a simpler interpretation, the decrease in e_{scr} contributes to the cell cycle arrest and the increase in d_{scr} to the cell death.

The specific mutation rules for e_{scr} and d_{scr} are summarized in Table 1. Since two mutable parameters are involved in the *hereditary* model, the sequences of two mutations have been considered as well. For clonotype $c = 1$, for instance, the cell first mutates d_{scr} and then triggers the mutation of e_{scr} if d_{scr} has changed by a fraction s ($s \geq 0$) of the original value, where s is a sequence coefficient. If $s = 0$, the mutations of the two genotypic traits are simultaneous; otherwise, two mutations occur in a sequence. If s is sufficiently large, the mutation of a second genotypic trait will be postponed over so long a time that the 8-clone-hereditary model is reduced to a straightforward mixture of four *monotonic* mutations listed in Table 1 (row 2, column 2).

3. Simulation Results

The simulation results are divided into two parts. First, we examined the effect of different mutation models under a specific RE of the system: the normal-to-degeneration transitions which correspond to the life process of a healthy tissue (the majority of the cells remain in arrest and the total cell number is large. See Sec. 3.1) and in the second part, we investigated mutation trajectories of two genotypic traits to provide a unified explanation for the simulation results. Parameter settings are listed in Appendix A.

3.1. Tumorigenesis under different mutation models

3.1.1. Monotonic mutations

As shown in Fig. 4, mutations of e_{scr} and d_{scr} disturb the inadequate-to-degenerate RE in various ways. All black curves with v roughly persisting above 0.1 over 10^5 steps before crashing to below 0.02 represent the original nonmutational RE.

The mutations on e_{scr} affect the cell sensitivity to ECM, indirectly raising the tendency of cell cycle arrest. If e_{scr} is mutated as $e_{scr}^i(t+1) = e_{scr}^i(t)(1 + \mu_m)$, the sensitivity to ECM decreases and thus postpones cell cycle arrest; on the contrary, the mutation $e_{scr}^i(t+1) = e_{scr}^i(t)(1 - \mu_m)$ causes a higher propensity for cell cycle arrest. The role of the e_{scr} mutation is easy to interpret, as we observed in the simulation that when e_{scr} mutated upwards, the direction of the time evolution of v

Fig. 4. Time evolution of phenotype structure index v under four distinctive monotonic mutations with different mutation rate μ_m : (a) $e_{scr}^i(t+1) = e_{scr}^i(t)(1 + \mu_m)$, (b) $e_{scr}^i(t+1) = e_{scr}^i(t)(1 - \mu_m)$, (c) $d_{scr}^i(t+1) = d_{scr}^i(t)(1 + \mu_m)$, and (d) $d_{scr}^i(t+1) = d_{scr}^i(t)(1 - \mu_m)$, for any cell at site i at each proliferation time t . Zero value of μ_m corresponds to a typical nonmutational RE (black), which is a slow aging process with the phenotype structure shifting to degeneration over roughly 10^6 steps. The vertical axis v ranging from 0 to 1 is the phenotype structure index (see the definition in Sec. 2.1). Note that all figures are plotted in log-log scale.

was veered towards tumorigenesis from degeneration (Fig. 4(a)), whereas when e_{scr} mutated downwards, v crashed at an earlier time to a value closer to zero, indicating a severe degeneration (Fig. 4(b)).

The results of d_{scr} mutation are more complicated. When d_{scr} mutated upwards, indicating a higher synthesis rate of death receptors and thus a higher susceptibility to cell death, $v(t)$ first veered towards tumorigenesis and then crashed to extinctive degeneration (Fig. 4(c)). When d_{scr} mutated downwards, lowering the death rate, the “life span” of the homeostatic quasi-stable degenerative states before the crash were extended and the fluctuations in $v(t)$ were intensified when μ_m increases, without altering the trend of degenerating (Fig. 4(d)). Additionally, there exists a critical value of μ_m , exceeding which the regime transition of $v(t)$ from degeneration to tumorigenesis occurs for both e_{scr} and d_{scr} mutations, and a too low mutation rate did not induce tumorigenesis [the red curves in Figs. 4(a) and 4(c)].

To summarize, when μ_m is large enough to make the timescale of AE comparable to that of RE, the decrease in tendency of cell cycle arrest promotes the emergence of tumorigenesis, suggesting that the system transitions from a degeneration phase to a tumorigenesis phase; counterintuitively, the increase in cell death rate promotes tumorigenesis, as opposed to the decrease in death rate merely extending the lifetime of quasi-stable homeostasis without inducing a phase transition. Moreover, it was notable that the tumorigenesis caused by increasing d_{scr} eventually anneals to extinctive degeneration (v becoming 0), which terminates the dynamics. It could be expected that the combination of these simple mutations generates more complicated outcomes as will be demonstrated in the next section.

3.1.2. Stochastic and hereditary mutations

Under the *stochastic* mutations, there exists a critical value of μ_s around which the system undergoes a phase transition from degeneration to tumorigenesis; and in the tumorigenesis phase, a higher mutation rate μ_s induces an earlier advent of tumorigenesis as illustrated in Fig. 5(a), which confirmed that AE easily dominates the system with neutrally heterogeneous mutations.

Nevertheless, under the reality-mimetic *hereditary* mutations, the system evolutions exhibit a peculiar picture [Fig. 5(b)]. We observed three basic phases in terms of the evolutionary patterns of $v(t)$. For very small mutation rates $\mu_h = \mu_{h,d} = \mu_{h,e}$, wherein the timescale of AE (τ_{AE}) is far larger than that of RE (τ_{RE}), i.e., $\tau_{\text{AE}} \gg \tau_{\text{RE}}$ (*phase I*), the original degenerative RE resisted the mutations. For a medium range of μ_h ($\tau_{\text{AE}} \sim \tau_{\text{RE}}$, *phase II*), the evolution of v veered towards tumorigenesis at a late stage of the original RE process and finally plunged into an extinctive degeneration [similarly to the results of a *monotonic* increase in d_{scr} , in reference to Fig. 4(c)]. If mutation rates are even larger ($\tau_{\text{AE}} \ll \tau_{\text{RE}}$, *phase III*), the system will totally escape from the degenerative RE regime to reach acute tumorigenesis, yet later unexpectedly succeeded by a spontaneous regression to a normal state [$v(t)$ returns to over 0.3].

Fig. 5. Time evolution of phenotype structure index v under the *stochastic* mutations under varying μ_s (a) and the *hereditary* mutations with different mutation rates $\mu_h (= \mu_{h,d} = \mu_{h,e})$, and the sequence coefficient $s = 0.05$ (b).

3.1.3. Subpopulation dynamics under the hereditary mutations

The mechanism underlying the complexity of evolutions with *hereditary* mutations was revealed by examining the subpopulation dynamics. Figure 6(a) shows the snapshots of the entire cell population with eight clonotypes labeled in different colors (see Sec. 3.1 for the mutation rules of each clonotype). The ancestor cell of each clonotype was dispersedly seeded into the 2D space and then multiplied into eight patches of similar sizes with distinguishable boundaries at early stages [the top two panels in Fig. 6(a)]. After thousands of steps, the original boundaries blurred, followed by the invasion of advantageous clonotypes into the territory of the disadvantageous ones. Through longtime competition among advantageous clonotypes, only one of the eight clonotypes, as the “fittest” one that survived, finally occupied the whole space. We refer to the only surviving clonotype as the *winner* in the following demonstration.

Figure 6(b) shows the probability of each clonotype to become the *winner* under various mutation rate μ_h obtained from 200 sessions of simulation. The criteria for identifying a *winner* i ($i = 1, 2, \dots, 8$) is that there exists a time point t_0 , for all the time $t > t_0$, $N_i(t) > 0.8 \sum_i N_i(t)$, where N_i is the subpopulation size for the clonotype i . By varying the mutation rate μ_h , we observed different possibility distributions of *winner* corresponding to the three phases mentioned in Sec. 3.1.3. In the nonmutational case ($\mu_h = 0$), all clonotypes won with the same probability of nearly 12.5% as expected; when μ_h was slightly over zero ($< 0.01\%$, *phase I*), clonotype $c = 7$ and $c = 5$ won more frequently than others and the system exhibits an erratic evolution of v because of the unpredictable *winner* [refer to the curves of 0.0008%, 0.001%, 0.002% and 0.005% in Fig. 5(b)]; however, because the mutation rate is not high enough, the original RE regime strongly remains in the system and in most cases, degeneration reigns; for a medium range of μ_h (roughly from 0.01% to 0.3%, *phase II*), the system was most inclined to be occupied by the clonotype $c = 7$ or $c = 3$, corresponding to the extinction-inducing tumorigenesis in Fig. 5(b)

Fig. 6. Subpopulation dynamics in the *hereditary* mutation model. (a) Snapshots of the interspecies competition among eight clonal patches (a sample result of $\mu = 0.5\%$). (b) The probability of becoming the *winner* for eight *hereditary* clones calculated from one 200 rounds of simulation under various levels of mutation rate μ_h . The *winner* is defined as the clone occupy more than 80% of the total cells from a specific time to the end of system evolution. (c) Averaged phenotypic structure index v versus μ_h measured at the time t_0 when the *winner* appeared. (d) Example cases of the time evolution of the normalized cell number of the eight clonal lineages for three phases. In *Phase I*, the survivor clonotype is randomly chosen; in *Phase II*, $c = 3$ or 7 wins; in *Phase III*, $c = 2$ or 5 wins.

(refer to curves of 0.01%, 0.04%, 0.1%, and 0.2%); if μ_h becomes even larger ($> 0.2\%$, *phase III*), clonotype $c = 5$ or 2 defeats $c = 7$ and 3 , corresponding to a regression of v in Fig. 5(b) (refer to the curves of 0.4%, 1.6%, 3.2%, 6.4% and 12%). Figure 6(c) shows that averaged $v(t_0)$ intensely changes with μ_h as a continuous transition from *phase I* to *phase II* and *phase II* to *phase III*.

Besides, we can observe that clonotype $c = 7$ and $c = 5$ are more likely to win than $c = 3$ and $c = 2$. Mutation strategy of clonotype $c = 7$ (or $c = 5$) differs with $c = 3$ (or $c = 2$) merely by the mutation sequence of e_{scr} and d_{scr} (refer to Table 1), suggesting that the sequence of two degrees of mutation makes difference and the role of e_{scr} mutations in tumorigenesis is more effective in adaptation. Figure 6(d) shows the time evolution of normalized cell numbers of eight clones $N_i(t)/N_{\text{max}}$ for three phases. Note that in the bottom panel ($\mu_h = 1\%$), cells with clonotype $c = 7$ and $c = 3$ thrived at earlier stages, but soon defeated by cells with $c = 5$ and $c = 2$. The alternation of the dominant clonotypes accounts for the regime shift from the emergence to the regression of tumorigenesis in *phase III*.

3.2. Bridging hereditary and stochastic mutation

In the last section, the correlation between the *winner* clonotype and the evolutionary patterns of v was investigated. AE alone does not ensure the advent of malicious tumor despite the survival of the fittest clonotype, which is $c = 2$ or 5 that features low propensity for cell cycle arrest or apoptosis in our study. In fact, even without the competition among clonotypes, the existent eight clonotypes in the foregoing *hereditary* model cannot induce tumorigenesis under the intrinsic RE. Figure 7(a1) shows the time evolution of v with monoclonal cells ($c = 5$, or $6, 7, 8$, respectively, and their reversely-sequenced counterparts $c = 2$, or $4, 3, 1$ have similar evolutionary patterns).

In the foregoing *hereditary* model, the mutations rates of e_{scr} and d_{scr} are constant and equal. Therefore, giving plasticity to the *hereditary* mutation rules of eight clonotypes is supposed to bridge the gap between the *hereditary* and the *stochastic* model. We modified the *hereditary* mutation rules in Table 1 by multiplying a stochastic term $\exp(\mu_{\text{sh}}X)$. For instance, for $c = 1$, $d_{\text{scr}}^i(t+1) = d_{\text{scr}}^i(t)(1 + \mu_{h,d})\exp(\mu_{\text{sh}}X)$ and if $d_{\text{scr}}^i(t+1) > d_{\text{scr}}^i(0)(1 + s)$, $e_{\text{scr}}^i(t+1) = e_{\text{scr}}^i(t)(1 - \mu_{h,e})\exp(\mu_{\text{sh}}X)$, where $X \sim \mathcal{N}(0, 1)$ is a random variable with a standard Gaussian distribution and μ_{sh} scales the effect of stochasticity. The integration of the *hereditary* and *stochastic* mutations renders plastic *hereditary* mutations while keeping the feature of clonal expansion. Figure 7(a2) shows the results of the new *stochastic hereditary* model in *phase II* ($c = 3$ or 7 wins; top) and in *phase III* ($c = 2$ or 5 wins; bottom) with varying μ_{sh} . As we conjectured, the increase in plasticity of mutation rules altered the evolutionary trend of v towards the sustainable tumorigenesis followed by no extinction and no regression, very similar to the results of the *stochastic* models (Fig. 5(a)).

To reveal the mechanism underlying the emergence of sustainable tumorigenesis, we compare the time evolutions of e_{scr} and d_{scr} in the *hereditary*, *stochastic* and *stochastic hereditary* model. Figure 7(b1) illustrates the relationship between the ensemble average of the logarithmic d_{scr} , denoted as $\langle \log d_{\text{scr}} \rangle$, versus the ensemble average of the logarithmic e_{scr} , denoted as $\langle \log e_{\text{scr}} \rangle$, during the entire evolution in the *hereditary* (black) and the *stochastic* model (red). The two hereditary phases had divergent evolutionary trajectories which implicate the dominance of two different

Fig. 7. (Color online) Bridging the hereditary model and the stochastic model. (a) A comparison of $v(t)$ among the hereditary, the stochastic hereditary, and the biased hereditary model. Evolution of v (a1) with monoclonal population in four distinctive clonotypes $c = 5-8$ of the hereditary model, (a2) under the stochastic hereditary model ($\mu_{sh} = 0$ corresponding to the original hereditary model, and (a3) under the biased hereditary model ($\mu_{h,e}/\mu_{h,d} = 1$ corresponding to the original hereditary model). (b) Evolutionary trajectories of the ensemble average of $\log d_{scr}$ versus $\log e_{scr}$: (b1) a comparison between the hereditary model (black) and the stochastic model (red) and (b2) under the stochastic hereditary model with various μ_{sh} . The black arrow indicates the direction of time and the black star marks the initial values of d_{scr} and e_{scr} ; (b3) A comparison of averaged $\log d_{scr}(t)$ (red) and averaged $\log e_{scr}(t)$ (black) between the hereditary model (straight lines) and the stochastic hereditary model (dotted lines). (c) Subpopulation dynamics of eight clonal lineages: (c1) A comparison between the nonstochastic and stochastic hereditary model for phase II ($\mu_h = 0.002$, left) and phase III ($\mu_h = 0.008$, right); (c2) A comparison between two different values of $\mu_{h,e}/\mu_{h,d}$ in the biased hereditary model.

families of clonotypes ($c = 3$ or 7 leads to the increase in both e_{scr} and d_{scr} in phase II, whereas $c = 2$ or 5 leads to the decrease in d_{scr} in phase III). Moreover, the stochastic evolution partly resembled the hereditary one in phase III in that the red curve and the dotted black curve were almost paralleled. The only discrepancy between the two curves is that $\langle \log d_{scr} \rangle$ of the stochastic model was higher than that of the hereditary

model in the late stage. Figure 7(b2) shows that introducing stochasticity ($\mu_{sh} > 0$) to the *hereditary* model could raise the value of $\langle \log d_{scr} \rangle$. By observing the time evolutions of $\langle \log e_{scr} \rangle$ and $\langle \log d_{scr} \rangle$ in the *hereditary* model of *phase III* [the straight line in Fig. 7(b3)] and in the *stochastic hereditary* model [the dotted line in Fig. 7(b3)], we hypothesize that the stochasticity added to the *hereditary* mutation rules generates an effective mutation rate of e_{scr} higher than $\mu_{h,e}$ and an effective mutation rate of d_{scr} lower than $\mu_{h,d}$, which means that the sustainable tumorigenesis requires $\mu_{h,e} > \mu_{h,d}$.

To verify the hypothesis, we set up a *biased hereditary* model, in which a bias is preset to the two mutation rates as $\mu_{h,e}/\mu_{h,d} > 1$. Figure 7(A3) displays the results of *biased hereditary* mutations for *phase II* (top) and *phase III* (bottom). In *phase II* ($\mu_{h,d} = 0.001$), the plunge into extinctive degeneration was prevented by a larger ratio of $\mu_{h,e}/\mu_{h,d}$ (the blue and orange lines), and likewise in *phase III* ($\mu_{h,d} = 0.008$), the spontaneous tumor regression was impeded by the biased mutations, however, with a lower value of $\mu_{h,e}/\mu_{h,d}$. These data confirm that a larger mutation rate of e_{scr} promotes the sustainable tumorigenesis. Figure 7(c) exhibits the subpopulation dynamics of eight clonal lineages in the *stochastic hereditary* model (c1) and the *biased hereditary* model (c2), where we observe the clonotype $c = 2$ or 5, replacing $c = 3$ or 7, become dominant in the late stage. Therefore, mutation rules with plasticity can protect the clonotypes that better survive in the long run (which is $c = 2$ or 5 in our simulation) against the temporary dominance of “short-sighted” clonotypes (which is $c = 3$ or 7 in our simulation).

3.3. Mutation paths on the RE phase diagram

Figure 8(a) shows a nonmutational phase diagram in the space of e_{scr} and d_{scr} , exhibiting several phases distinguished by the value of $v(\bar{t})$ ($\bar{t} = 10^6$) with e_{scr} sampled within $10^{-3} < e_{scr} < 10^3$ and d_{scr} within $10^{-7} < e_{scr} < 10^2$ in 10^4 sessions of simulation. We should mention that $\bar{t} = 10^6$ is sufficiently long for the appearance of quasi-stable homeostasis which implicates the equilibrium state of REs, although the dynamics may have not yet be relaxed into a stable state. On the diagram, we identified four prominent phases: the extinctive degeneration phase (gray, marked as $E.D$ in the large d_{scr} region), the degeneration phase (red, marked as D in the small e_{scr} region), the inadequate-growth phase (orange, marked as I in the small d_{scr} with large e_{scr} region), and the tumorigenesis phase (blue, marked as T in the medium d_{scr} and large e_{scr} region). *Normal* homeostasis (yellow and green) narrowly sits between the boundary of T and D (or I).

From the perspective of individual adaptation, a larger e_{scr} or a smaller d_{scr} promotes the noninteractive fitness of one cell straightforwardly because of inducing a higher cell cycle activity (thus a higher possibility of proliferating) or a higher survival rate; nevertheless, the collective performance of interacting cells undergoing

Fig. 8. (Color online) Mutation paths of e_{scr} and d_{scr} distributions superposed on the phase diagram. (a) The phase diagram in the e_{scr} - d_{scr} space, with phases distinguished by phenotypic structure index v in different colors. ED is an abbreviation for extinctive degeneration (gray), D for degeneration (red), I for inadequate growth (orange), T for tumorigenesis (blue). Meanwhile, the increase in e_{scr} (or d_{scr}) is related to the increase in cell cycle activity (or survival rate) for each individual cell. (b) The mutation paths of $\{e_{scr}, d_{scr}\}$ distributions: in the *hereditary* model (*phase III*) (b1), in the *stochastic* model (b2), in the *stochastic hereditary* model with small stochasticity (b3), and in the *stochastic hereditary* model with huge stochasticity (b4).

RE can distort the individual cell fitness landscape[§] to hinder the AE or even veer the equilibrium of evolution towards a state with less individual fitness (the parameter region of T does not have the highest individual cell fitness). Now we can elaborate how REs significantly interfere with AEs and integrate all the results in Sec. 3 by examining the mutation paths of e_{scr} and d_{scr} on the phase diagram.

The star symbol on the phase diagram, located at $d_{\text{scr}} = 0.001$ and $e_{\text{scr}} = 0.18$, represents the uniformly distributed initial values of two parameters at $t = 0$. Under this parameter setting without mutations, the system will undergo the inadequate-to-degenerate homeostatic evolution as the star in the phase diagram is located on the boundary of phase D and I . The simple *monotonic* mutation rules can easily be interpreted on the phase diagram as the d_{scr} or e_{scr} of all cells shifting paralleled to the vertical or horizontal axes, and therefore, the star symbol simply moves along only four directions, i.e., upward, downward, leftward, and rightward (see four with white-edged arrows on the diagram). Obviously, the rightward shift corresponding to an endless increase in e_{scr} guarantees a dynamic phase transition from D to T (Fig. 4(a)), and the leftward shift corresponding to the decrease in e_{scr} drives the system into the phase of D , terminating the homeostatic dynamics earlier (Fig. 4(b)). The upward shift, corresponding to an increase in d_{scr} , first passes through the zone of *Normal* homeostasis before reaching the zone of ED , which demonstrates the appearance of a temporary rise of v towards tumorigenesis followed by a crash into extinction in Fig. 4(c); on the other hand, the downward shift, corresponding to the decrease in d_{scr} , drives the systems deep into the phase of I , extending the life spans of the quasi-stable homeostasis without a possibility of tumorigenesis as shown in Fig. 4(d).

The mutation paths of the eight *hereditary* clonotypes, which obey distinctive mutation rules (see Table 1), can also be explicitly marked on the phase diagram as the black arrows in Fig. 8(a). They shift along the two diagonal lines $\log d_{\text{scr}} \sim \pm \mu_{h,d}/\mu_{h,e} \log e_{\text{scr}}$, which is $\log d_{\text{scr}} \sim \pm \log e_{\text{scr}}$ if $\mu_{h,d} = \mu_{h,e}$ (the white dashed lines on the diagram). The four black arrows on the right side clockwise refer to the mutation paths of clonotype $c = 3, 7, 5$, and 2 .

Figure 8(b) shows four typical evolutionary snapshots of d_{scr} and e_{scr} distribution under various mutation models, where a set of $e_{\text{scr}}, d_{\text{scr}}$ for each cell was marked as a “+” plotted onto the schematic phase diagram. In the original *hereditary* model (b1), we can observe the mutation paths outreaching along two diagonal directions $\log d_{\text{scr}} \sim \pm \log e_{\text{scr}}$ at an early stage; moreover, cells with a clonotype $c = 3$ or 7 (right-upward) undergoes REs towards T , which mutated more frequently than any other lineages, and reached the phase of T more easily; however, the clonotype $c = 3$ or 7 are short-sighted without foreseeing the phase ED behind T , therefore all of them will be eventually eradicated. By contrast, cells with a clonotype $c = 2$ or 5 will mutate right-downward along the diagonal lines, which deviates from phase T thus

[§]In evolutionary theory, the fitness landscape (or adaptive landscape) visualizes the relationship between the genotype and its survival rate. It was first proposed by Wright [67] to illustrate the process of mutation and selection in the field of gene combination.

preventing the system from tumorigenesis. If μ_h is smaller, the clonotype $c = 3$ or 7 would advance more slowly and survive longer as the dominant clonotype before reaching *ED*, which corresponds to the *phase II* dynamics in Fig. 5(b) and Fig. 6(c) and 6(d); otherwise, if μ_h is large enough, the clonotype $c = 3$ or 7 would only dominate for a short time and cause a temporary tumorigenesis before extinction. After the extinction of clonotype $c = 3$ or 7 , the clonotype $c = 2$ or 5 could thrive, driving the system to *normal* and *inadequate* states. Hence, the spontaneous tumor regression of *Phase III* in Fig. 5 was caused by the alternation of underlying dominant clonotypes: from the short-lived ones to the long-lived ones.

Different from the rigid directions of mutation in the *hereditary* models, the *stochastic* mutations are isotropic thus efficiently navigating the system to find the phase *T* (Fig. 8(b2)). The marks on the diagram move first right-upwards then right-downwards exactly on the boundary between *I* and *T* as a perfect example of how the system is driven by coordinated RE and AE that always arrives at a stable tumorigenesis state (Fig. 5(a)). Similarly, for *stochastic hereditary* models [denoted as *S-hereditary* in Fig. 8(b3) and 8(b4)], the *stochastic hereditary* mutations can drag the *hereditary* mutation path towards the proximity of *T* if the intensity of stochasticity μ_{sh} is high enough.

Finally, from Fig. 8(a), we can understand why the *biased hereditary* model can give rise to sustainable tumorigenesis. The initial value of e_{scr} and d_{scr} determines that the mutation along the e_{scr} axis should be more rapid than that along the d_{scr} axis for the system progressing to the phase of *T*. Therefore, such *biased mutation* rates as $\mu_{h,e}/\mu_{h,d} > 1$ are more likely to induce tumorigenesis (Fig. 8(a3)), and if $\mu_{h,d} \ll 1$, i.e., the d_{scr} mutation is extremely slow, then a large bias $\mu_{h,e}/\mu_{h,d} \gg 1$ is necessary to guarantee a sufficient large $\mu_{h,e}$ for the system to evolve towards *T* [see the top panel in Fig. 7(a3)].

4. The Coupling Effect of RE and AE in General

4.1. The superposition of the phase diagram and the individual fitness landscape

The analysis of mutation paths in Sec. 3.3 can also be generalized to other genotypic traits and different mutation strategies in problems involving RE–AE coupling. Let us consider a 1D genotypic parameter x , uniformly encoded as an intrinsic property in each individual profile and x controls the several phases of relaxational equilibrium. The phases can feature distinctive values of fitness as shown in the schematic phase diagram in Fig. 9(a). Without mutations, the location of the ball, indicating the ensemble average of x , stays where it initially starts and the final fitness of the whole system, denoted as f_{sys} is then determined by the RE phase diagram [in Fig. 9, f_{sys} decreases with x as a schematic example]. The essential assumption is that phases of RE can be distinguished by an order parameter in terms of f_{sys} .

Fig. 9. Mutation paths visualized as the rolling ball on the schematic evolutionary landscape based on the one-dimensional phase diagram. The ball represents the final state of the system with a system fitness $f_{sys}(x)$. (a) Nonmutational fitness landscape solely under relaxational processes, which emerges from the interactions among individuals. Suppose there are three phases separated by two critical points x_1 and x_2 , around which the phase transition types could be either the first-order [$f_{sys}(x)$ jumps abruptly at x_1] or the second-order [$f_{sys}(x)$ is continuous but $df_{sys}(x)/dx$ jumps at x_2]. (b) The distorted fitness landscape under three different formulations of individual fitness function of $f_{in}(x)$.

Next, supposing that an individual fitness f_{in} also depends on x as a function of a noninteractive selective pressure along the space x , the RE phase diagram can be distorted by the noninteractive adaptation in a specific way according to the formulation of $f_{in}(x)$, and therefore the original $f_{sys}(x)$ resulted from RE is modified into a system fitness landscape synthesizing RE and AE [see the three examples shown in Figs. 9(b1)–9(b3)]. In Fig. 9(b1), $f_{in}(x)$ has the same trend with $f_{sys}(x)$, therefore the synthesized fitness landscape has the fittest state [with the highest $f_{sys}(x)$] at $x = 0$; and both the *stochastic* mutation and the *hereditary* mutation can easily find this global evolutionary optimum. By contrast, if $f_{in}(x)$ has the opposite trend to $f_{sys}(x)$ as depicted in Fig. 9(b2), the system may have disparate evolutionary patterns with various mutation models: under the *stochastic* mutations, the system can search freely within the proximity of $x(t = 0)$ and select the value of x with a larger

synthesized $f_{\text{sys}}(x)$, to finally reach the phase boundary which has the highest fitness; as for the *hereditary* mutations, which are more rigid, the subsystem whose strategy is temporarily advantageous may miss the fittest state by overreaching itself in a wrong mutation direction towards a state with extremely low f_{sys} . In a third case, as illustrated in Fig. 9(b3), $f_{\text{in}}(x)$ could also be more complicated (e.g., having multiple peaks), resulting in the paths to the fittest phase (P3) being blocked. From these schematic 1D phase diagrams, we can deduce that in a multi-dimensional genotypic trait space $\mathbf{x}$, the superposition of $f_{\text{sys}}(\mathbf{x})$ and $f_{\text{in}}(\mathbf{x})$ should present a fitness topology with unimaginable complexity, and the system may exhibit rich dynamical phenomena if mutation strategies are *hereditary*.

Given any genotypic trait, by analyzing the synthesized fitness landscape under the superposition of the phase diagram of RE and the individual fitness, we can predict the evolutionary processes with any initial values under arbitrary mutation strategies. Note that the system's initial condition (where the ball initially locates) can affect the final evolutionary destination. One can even expect a fluctuating landscape if the function of $f_{\text{in}}(\mathbf{x}, t)$ is dynamically updated because of the turbulent environment or the heterogeneous coevolution among the individuals. The speed of evolution (gradients of the landscape) depends on both the mutation rate μ of single reproduction events and the transient system fitness.

The phase diagram in DRDM simulations (Fig. 8(a)) is a vivid example of a two-dimensional landscape of system fitness with $\mathbf{x} = \{e_{\text{scr}}, d_{\text{scr}}\}$, where the system fitness $f_{\text{sys}}(\mathbf{x})$ is defined as v .^h In the range of $e_{\text{scr}} > 10^{-1}$ and $10^{-4} < d_{\text{scr}} < 10^{-2}$, the phase function of each coordinate, i.e., $v(e_{\text{scr}})$ or $v(d_{\text{scr}})$, is close to the schematic 1D phase diagram in Fig. 9(b2). This clarifies the reason why under the *stochastic* or the *stochastic hereditary* mutations, the center of the distribution of $\{e_{\text{scr}}, d_{\text{scr}}\}$ always sits exactly on the boundary between *I* and *T* [corresponding to the gray line separating P12 and P3 in Fig. 9(b2)] because the boundary has the highest fitness.

Finally, we should mention that although $f_{\text{in}}(\mathbf{x})$ and $f_{\text{sys}}(\mathbf{x})$ are two different representations of fitness, they can be positively correlated because $f_{\text{sys}}(\mathbf{x})$ by its definition is contributed by all the individuals' fitness under the effect of phenotypic interactions. For instance, v , indicating the percentage of proliferating cells in the system, is low at the left-top corner in Fig. 8 while the single cell vitality is also close to zero. Nevertheless, the system composed of individuals with a high $f_{\text{in}}(\mathbf{x})$ can have a low $f_{\text{sys}}(\mathbf{x})$ because the resources and space are limited (by whatever means), then the conflicts among those strong competitors may harm the interactive cooperation, diminishing the collective fitness of the system.

^h The phenotypic structure v is also a global quantity measuring how many cells are viable in the space; under the ergodicity assumption, a system with a viability v infers that each single cells, in a statistical sense, has a probability of v to be proliferative. In other words, v is the measurement for the single cell fitness under intercellular interactions, thus able to be superposed to the individual fitness f_{in} .

4.2. Implications for a broader class of problem

Based on Sec. 4.1, we can propose a simple method to help analyze the complicated dynamics of RE–AE coupling. For a set of genotypic traits $\mathbf{x}$, we can first study the nonmutational RE phase diagram with the order parameter indicative of the system fitness $f_{\text{sys}}(\mathbf{x})$, and the selective pressure in terms of the individual fitness $f_{\text{in}}(\mathbf{x})$ separately, and then reconstruct a synthesized fitness landscape $f_{\text{RE+AE}}(\mathbf{x})$ through the superposition of $f_{\text{sys}}(\mathbf{x})$ and $f_{\text{in}}(\mathbf{x})$ as below:

$$f_{\text{RE+AE}}(\mathbf{x}) = f_{\text{sys}}(\mathbf{x}) + \alpha f_{\text{in}}(\mathbf{x}), \quad (2)$$

where α is a coefficient weighing the scale difference between the two terms, and $f_{\text{sys}}(\mathbf{x})$ and $f_{\text{in}}(\mathbf{x})$ are the functions of genotypic traits $\mathbf{x}$ with compatible definitions on “fitness”. The coefficient α can also be interpreted as an effective mutation rate $\alpha = \mu G(f_{\text{sys}}(\mathbf{x}))$, in which the mutation rate for single mutation events μ is multiplied by a factor $G(f_{\text{sys}}(\mathbf{x}))$. In the case of tumorigenesis in the DRDM, $G(f_{\text{sys}}(\mathbf{x}))$ is a multiplier that adds a nonlinear dependence of α on $f_{\text{sys}}(\mathbf{x})$. $G(f_{\text{sys}}(\mathbf{x}))$ is a nonzero increasing function of $f_{\text{sys}}(\mathbf{x})$ because the mutation of cells only happens when the cell is dividing, and a system with a higher $f_{\text{sys}}(\mathbf{x})$ will have a higher frequency of cell division, thus a higher mutation frequency. For other CASs, the prerequisite of mutation could be different. For instance, in the free market systems, $G(f_{\text{sys}}(\mathbf{x}))$ can be a decreasing function of f_{sys} because the mutation of investment strategies of one company in the market may only happen when the current strategy becomes nonprofitable (inducing low fitness). Therefore, the formulation of α is context-specified.

Then, the system’s wandering path on topologically complicated fitness landscape through mutations involves five determinants:

- (i) $f_{\text{sys}}(\mathbf{x})$, which is also a phase function resulted from the nonmutational RE where all individuals have the same set of genotypic traits,
- (ii) $f_{\text{in}}(\mathbf{x})$,
- (iii) α , controlling the scale difference between RE and AE,
- (iv) the initial condition of $\mathbf{x}$,
- (v) mutation strategies, which define $d\mathbf{x}/dt$ for each individual.

In the framework of evolutionary theory, $f_{\text{RE+AE}}$ can correspond to the effective Wright evolutionary potential [3] that drives the cell distribution dynamics in the genotypic trait space. More precisely, the two components f_{in} and f_{sys} may correlate with the intrinsic noises and extrinsic noises of gene expression [21, 40], respectively.

Under *hereditary* mutations, the temporary tumorigenesis is succeeded by either extinction (for low mutation rate) or spontaneous regression (for high mutation rate) because different clones reign in different periods of time. The rigidity of the mutation strategy coupled with the rugged landscape of synthesized fitness fosters the complexity of clonal expansion in our computational multicellular organization.

In reality, especially for systems on larger scales like economic systems or social organizations, mutations can hardly be neutrally free since the mutation strategies tend to be inherited from one's families or imitated from the successful individuals in a constraint-ridden setting. Hence the evolutions in real CASs may exhibit huge complexities as in the computational tumorigenesis. If the synthesized fitness landscape can be approximated using the theoretical paradigm proposed in Eq. (2), we can, to some extent, foresee the evolutionary paths under rigid mutations and predict the system's evolution. The lesson from the *stochastic* mutation results tells us that given a high plasticity of mutation strategies, it is possible to predict the final state of the evolution through the system fitness alone because the system can efficiently find the fittest phase and tend to reside on the phase boundaries if the individual fitness and system fitness have opposite trends.

We hypothesize that this theoretical paradigm may also apply to other problems such as the free market competition in macroeconomics, the price formation with agents using learning techniques in finance, the knowledge transfer or opinion propagation among people frequently updating social network structure, and the emergence of cooperation in the multi-player prisoner's dilemma. Yet, these systems have distinctive interaction mechanics, mutation strategies, and specifically defined individual fitness. Whether and how Eq. (2) can be extended to other CASs needs further studies with the specific properties of those systems explicitly taken into account.

5. Summary

The coupling effect of relaxation and adaptation was investigated in the computational tumorigenesis as a typical instance of complex adaptive systems. We adopt a paradigm in which the simulation is based on cell phenotype dynamics tailored by some conceptual sub-models of mutation for preserving the nontrivial structures of local intercellular interactions. We found that tumorigenesis is the consequence of the system reaching the tumorigenic homeostatic phase (which is one of the relaxational equilibrium of the multicellular organization), implying that the relaxation process strongly interferes with adaptation. Mutation promotes tumorigenesis, however, in a way related to the mutation strategy: only the mutation with stochasticity helps the system find the tumorigenic states efficiently; by contrast, more rigid mutation strategies that mimic the realistic clonal expansion lead to bizarre phenomena such as the temporary tumorigenesis succeeded by either extinction (for low mutation rate) or spontaneous regression (for high mutation rate) due to an alternation of the dominant clonotype.

Through the superposition of phase diagram and individual fitness landscape in the genotypic trait space, we achieved a visualization of the evolutionary paths of genotypic traits on a synthesized fitness landscape and proposed a unified theory to explain and predict system dynamics under all sorts of mutation models. The reason why rigid mutations result in seemingly unpredictable complexity whereas neutrally

stochastic mutations drive the system into global optima is that the synthesized landscape features a nonlinearly complicated topology.

In other words, generic CAS evolutionary processes can be viewed as the individual adaptation under an effective selective pressure shaped by both interaction-based fitness and noninteractive fitness, and meanwhile the microscopic structure of local interactions and mutations that define the specific features of a system plays the key role in navigating the synthesized dynamics. Also, the initial condition and the effective mutation rate (the scale difference between relaxation and noninteractive adaptation, whose dependence on the interaction-based fitness is system-specific) can be decisive to the evolution of the system when the synthesized fitness landscape is complex and mutation strategies are rigid.

The profound implication is that in a real CAS such as the socioeconomic system where the candidates for mutation strategies are highly limited, any organizational schemes designed for an optimization process may be inefficient even shortsighted and probably resulting in the unexpected alternation of the dominant culture genes (which corresponds to the case of spontaneous tumor regression in our model with hereditary mutation strategies). Constructing the synthesized fitness may become one of the powerful approaches to the prediction and the regulation of the dynamics in such systems. In the future, we expect to validate this theory with many other CASs by computational methods and also to develop a standard approach to measuring the interaction-based fitness and noninteractive individual fitness along with the scale difference between them in real cases for potential applications.

Appendix A. DRDM Model Details

The dynamic cell profile for each site i includes the concentration of five kinds of receptors, the ECM concentration, genotypic traits and the clonotype (only in the *hereditary* model) as well as a Boolean index recording whether the cell enters arrest state, as listed in Table A.1.

The receptor transformation rules for the cell at any cite i at each time $t + 1$ are decided by the receptor configuration, the intrinsic condition of the cell, and the

Table A.1. Dynamic cell profiles for each site i .

Elements	Definition
R_g	Growth receptor concentration
R_h	Adhesion receptor concentration
R_E	ECM receptor concentration
R_a	Arrest receptor concentration
R_d	Death receptor concentration
E	ECM concentration
q	cell cycle arrest index (<i>true</i> = cell cycle arrest)
d_{scr}	The accumulation rate of death receptor
e_{scr}	The upper limit number ECM secreted by per mass of growth receptors
c	Clonotype

Table A.2. Receptor transformation rules in DRDM for the cell at any cite i .

Condition	Cell behavior	Receptor dynamics
$R_g(t) + R_h(t) \leq M$ AND $q(t) = false$	Grow	$R_g(t+1) = (1 + \gamma)R_g(t)$ $E(t+1) = s_1 R_g(t) - s_2 [R_h(t) + R_a(t) + R_d(t)]$
None	Adhere	$R_h(t+1) = R_h(t) + \Delta R_h(t)$ $R_E(t+1) = R_E(t) + \Delta R_E(t)$ $R_g(t+1) = R_g(t) - \Delta R_h(t) - \Delta R_E(t)$ See $\Delta R_h(t)$ and $\Delta R_E(t)$ in Appendices A and B of [45]
$R_h(t) > p$ AND $R_E(t) > e$	Polarize	$R_a(t+1) = R_a(t) + a_{scr} R_h(t)$ $R_h(t+1) = (1 - a_{scr})R_h(t)$
$R_h(t) \leq p$ OR $R_E(t) \leq e$	Not polarize	$R_d(t+1) = R_d(t) + d_{scr} [R_h(t) + R_a(t)]$ $R_h(t+1) = (1 - d_{scr})R_h(t)$ $R_a(t+1) = (1 - d_{scr})R_a(t)$
$R_a(t) > a$	Arrest	$q(t) = true$
$R_a(t) \leq a$ AND $R_g(t) > g$	Not arrest	$q(t) = false$
$R_g(t) + R_h(t) > M$ AND $q(t) = false$	Proliferate	choose one empty neighbor site j (if $j = \text{NULL}$, do nothing) $R_g^j(t+1) = R_g(t+1) = B$ Mutation : $[d_{scr}(t+1), e_{scr}(t+1)] = F[\mu, d_{scr}(t), e_{scr}(t)]$ $d_{scr}^j(t+1) = d_{scr}(t+1), e_{scr}^j(t+1) = e_{scr}(t+1)$ $c^j(t+1) = c(t+1) = c(t)$
$R_d(t) > d$	Suicide	Clear cell profile elements to zero
$R_h(t) + R_E(t) < h$	Move	See Appendix C in [45]

Note: The mutation of e_{scr} and d_{scr} within *Proliferate* has different formulations of $F(\mu)$ according to the mutation models (refer back to Table 1 in the main text).

Table A.3. Parameters of DRDM simulation.

Parameter	Definition	Baseline value
$N_{\max}$	The space size of the 2D normal lattice with periodical boundary condition	71×71
B	The concentration of basic growth receptor for a newly born cell	30
M	The concentration of total receptors required for mitosis	100
s_1	The secretion rate of ECM substance	0.01
s_2	The degradation rate of ECM substance	0.0005
g	Growth receptor threshold	$0.3M$
p	Polarization receptor threshold	$0.09M$
h	Adhesion receptor threshold	$0.2M$
d	Death receptor threshold	$3M$
e	ECM receptor threshold	$0.2M$
a	Arrest receptor threshold	$0.1M$
γ	Growth rate of growth receptor concentration (per iteration)	0.1
a_{scr}	The accumulation rate of arrest receptor (per iteration)	0.25
$d_{scr}(t=0)$	The initial accumulation rate of death receptor	0.001
$e_{scr}(t=0)$	The initial upper limit number ECM secreted by per mass of growth receptors	0.18

ECM amount at t . Table A.2 displays the basic discrete receptor dynamic details. For a complete demonstration, see [45].

The parameter setting used in our simulation is listed in Table A.3. The initial condition is to seed eight ancestor cells with growth receptor amount $R_g = B$ dispersedly in the space. In the *monotonic* and the *stochastic* model, the eight ancestor cells have the same profiles; whereas, in the *hereditary* model, these cells are assigned with eight different clonotypes $c = 1, 2, \dots, 8$.

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