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Simulating the multicellular homeostasis with a cell-based discrete receptor dynamics model: The non-mutational origin of cancer and aging

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ABSTRACT

The purpose of the study is to investigate the multicellular homeostasis in epithelial tissues over very large timescales. Inspired by the receptor dynamics of *IBCell* model proposed by Rejniak et al. an on-grid agent-based model for multicellular system is constructed. Instead of observing the multicellular architectural morphologies, the diversity of homeostatic states is quantitatively analyzed through a substantial number of simulations by measuring three new order parameters, the phenotypic population structure, the average proliferation age and the relaxation time to stable homeostasis. Nearby the interfaces of distinct homeostatic phases in 3D phase diagrams of the three order parameters, intermediate quasi-stable phases of slow dynamics that features quasi-stability with a large spectrum of relaxation timescales are found. A further exploration on the static and dynamic correlations among the three order parameters reveals that the quasi-stable phases evolve towards two terminations, tumorigenesis and degeneration, which are respectively accompanied by rejuvenation and aging. With the exclusion of the environmental impact and the mutational strategies, the results imply that cancer and aging may share the non-mutational origin in the intrinsic slow dynamics of the multicellular systems.

1. Introduction

There long exists a scientific conundrum on how cancer initiates. Despite the fact that many oncogenes or tumor suppressors have been revealed in a large amount of studies, accumulating evidences indicate that cancer initiation involves ingredients other than the genetic deficiency (Barillot, 2013). Cancer, as conventionally defined, is an uncontrolled cell growth, which could also be regarded as a large deviation of cell phenotypes from their homeostatic states. The dynamics of phenotypic structure is not driven merely by subcellular genetic mutations, but also by a heterogeneous influence from both the extracellular micro-environment and the intracellular interactions (Marusyk et al., 2012). In addition, cancer is a chronic disease featuring a very long period of incubation for the malignancy. In study of the origin of cancer, the multi-scale modeling and simulation of cancer *in silico* become a powerful approach, thanks to the tremendous computational power of modern supercomputers. Multi-scale simulations enabled us to understand the complicated intricacy of multi-scale factors and the emergent phenomena in many different biological systems (Deisboeck and Stamatakos, 2011). One of those multi-scale biological models is *IBcell* (Rejniak, 2007, 2012; Rejniak and Anderson, 2008a, 2008b; Rejniak et al., 2010), which is established for the simulation of acini formation through a receptor dynamics sensing ex-, intra- and sub-cellular cues during a cell cycle. *IBcell* can reproduce four self-organized acini morphologies, showing the existence of homeostatic diversity. An inspiring result is that the tumor-like morphology emerges from the cell cycle regulation without any predefined requisites, which indicates a causal relationship between the homeostatic diversity and tumorigenesis.

While the mainstream study on cancer initiation focused on the evolutionary picture of accumulating mutational damages due to environmental stress (Merlo et al., 2006; Attolini and Michor, 2009), the homeostatic diversity sheds light on a different scenario of cancer initiation: the shift from one homeostatic state to another and this shift could last a very long time period with the consideration that cancer is a chronic disease. To specify the mechanism underlying the shift of states, three questions are of great interest: (1) What are the differences among these homeostatic states? (2) What are the control parameters critical to the shift of state? (3) What roles does the genetic mutations play in the shift? Motivated by these questions, we think it essential to simulate the homeostasis formation on a much larger timescale (than that of *IBcell* simulations).

In *IBcell* simulations, the time duration is difficult to extend to a large enough scale, because it consumes a huge computational resource for the calculation of fluid mechanics. However, morphology is not the sole representation of homeostatic states; indeed the key property of homeostatic diversity could rather be the

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dynamically heterogeneous behaviors of cell phenotypes. Hence we propose, in this study, a new mesoscopic cell-based model (or usually called agent-based model) for the behaviors of different cell phenotypes to attain a higher computational efficiency at the sacrifice of morphological information.

To build the new model, we reform the continuously formulated receptor dynamics in *IBcell* to a set of the cell behaviors in a spatiotemporally discrete manner of agent-based model (ABM). ABMs have been applied to simulations of cancer development (reviewed in Wang et al. (2015)) because of the simplicity and flexibility when incorporating the multi-scale interaction for a multicellular system. Here we employ the ABM to simplify the fluid mechanics and receptor dynamics in *IBcell* in order to enable the large timescale simulations of diverse multicellular homeostases. In our model, the behaviors of an agent (or a cell), are executed in several sequenced cell cycle functions, which are triggered when various types of the receptors hit their thresholds. Cell behaviors will change the interactions between cell-extracellular matrix (ECM, the amount of extracellular matrix secreted by the cell during its growth) and local neighbors, through adjusting the configuration of cell receptors in a simplified discrete style. Due to the simplicity and flexibility of our model, all the information in the system could be tracked to facilitate reliable statistical analyses even under the multicellular heterogeneity through a large-timescale evolution.

Even without a detailed representation of cell morphologies, various kinds of homeostatic states can be observed in our model correspondently in terms of a new order parameters: the structure of phenotypic populations. Apart from the stable homeostatic states, many intermediate quasi-stable states also emerge in the simulation. In these quasi-stable states, the order parameter changes steadily but slowly, where the relaxation timescale could extend from 10^4 to over 10^8 time steps. It is worth mentioning that both tumorigenesis and aging process are found to originate from these quasi-stable states. Roles of the main factors such as growth signals, apoptosis, cell arrest, cell-cell adhesion, cell–ECM adhesion etc. in forming the diverse phenotypic population structures of homeostasis are discussed.

The details of the cell-based model will be elaborated in Section 2. The simulation results, the phase diagrams and the statistical analysis of each states will be presented in Section 3. We will have some discussions on the robustness and verification in Section 4. Section 5 summarizes the study and give some concluding remarks on the phase diagram and the effect of major parameters.

Table 1
Cell data structure. The receptor amount and ECM concentrations are dynamic variables, whereas the threshold T and profile P are parameters which are preset. The topological information of the network is decided by l, r, t, b in profile P, and they are fixed in all simulations in this study as long as the space is set to be a 2D regular lattice.

Cell data structure			
Receptor amount R	ECM E	Threshold T	Profile P
R_g Growth receptor	ECM	g Growth threshold	n Node number
R_h Adhesion receptor		p Polarization threshold	γ Growth factor
R_E ECM receptor		e ECM threshold	l Left neighboring node
R_a Arrest receptor		a Arrest threshold	r Right neighboring node
R_d Death receptor		g Growth threshold	t Top neighboring node
		h Adhesion threshold	b Bottom neighboring node

2. Model

2.1. Space and cell

The simulation space is a two dimensional (2D) normal lattice where each node has four neighbors under a periodic boundary condition. All nodes are distributed with environmental elements such as growth factors and nutrients. In the current stage, the environmental elements are set in a uniform and constant distribution. Each node can be occupied at most by one cell.

A cell is expressed in this model by a virtual data structure without visible cell membrane and subcellular organs. This data structure contains instant information of a cell from three level of

Table 2
Discrete receptor dynamics and cell behaviors. Refer to Appendices A and B for the detailed demonstration of *Adhere* functions for the cell-cell adhesion (**AD1** function) and the cell–ECM adhesion.

Conditions	**Cell behaviors**	**Receptor dynamics**
$R_g + R_h < M$ AND Not Arrested	Grow	$R_g[t+1] = (1+\gamma)R_g[t]$ $E[t+1] = sR_g[t] - c(R_h[t] + R_a[t] + R_d[t])$
None	Adhere	$R_a[t+1] = \mathbf{AD1}\{R_{neighbor}(R_g[t] + R_h[t])\}$ $R_E[t+1] = MIN(E[t]/e_{scr}, R_g)$ $\Delta R_g[t] = -\Delta R_h[t] - \Delta R_E[t]$ $(\Delta R_*[t] \equiv R_*[t+1] - R_*[t])$
$R_h > p$ AND $R_E > e$	Polarize	$R_a[t+1] = R_a[t] + a_{scr}R_h[t]$
$R_h < p$ OR $R_E < e$	Not polarize	$R_d[t+1] = R_d[t] + d_{scr}(R_h[t] + R_a[t])$ $R_h[t+1] = (1-d_{scr})\ R_h[t]$ $R_a[t+1] = (1-d_{scr})\ R_a[t]$
Not Arrest $R_a > a$	Restriction point	Entry into Arrest
Arrest $R_a < a$ AND $R_g > g$		Exit from Arrest
$R_g + R_h > M$ AND Not Arrested	Proliferate	
	Empty	Send a new cell with $R_g^{daughter}[t+1] = B$ $T^{daughter}[t+1] = T[t]$ $R_a[t+1] = B$
	No space	None
$R_d < d$	Suicide	$R[t+1] = 0,\ T[t+1] = 0$
$R_a + R_E < h$	Move	Appendix C