Intercellular competitive growth dynamics with microenvironmental feedback

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Normal life activities between cells rely crucially on the homeostasis of the cellular microenvironment, but aging and cancer will upset this balance. In this paper we introduce the microenvironmental feedback mechanism to the growth dynamics of multicellular organisms, which changes the cellular competitive ability and thereby regulates the growth of multicellular organisms. We show that the presence of microenvironmental feedback can effectively delay aging, but cancer cells may grow uncontrollably due to the emergence of the tumor microenvironment (TME). We study the effect of the fraction of cancer cells relative to that of senescent cells on the feedback rate of the microenvironment on the lifespan of multicellular organisms and find that the average lifespan shortened is close to the data for non-Hodgkin's lymphoma in Canada from 1980 to 2015. We also investigate how the competitive ability of cancer cells affects the lifespan of multicellular organisms and reveal that there is an optimal value of the competitive ability of cancer cells allowing the organism to survive longest. Interestingly, the proposed microenvironmental feedback mechanism can give rise to the phenomenon of Parrondo's paradox: When the competitive ability of cancer cells switches between a too-high and a too-low value, multicellular organisms are able to live longer than in each case individually. Our results may provide helpful clues for targeted therapies aimed at the TME.

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I. INTRODUCTION

Competitive behavior is a universal phenomenon existing in all levels of biological population. Animals compete with each other for territory, food, mates, and other resources [1,2]. The proliferation of root systems leads to competition within and between plants for nutrients and water in the surrounding environment [3]. Competition for nutrients or oxygen also occurs among microbial populations [4,5]. Generally, competitive behavior facilitates the selection of individuals better adapted to their environment and enhances the evolutionary fitness of the population. Specifically, competition exists between cells within multicellular organisms (especially cancer cells and their surrounding cells) by exerting changes on the microenvironment [6–9]. Intercellular competition is considered an efficient mechanism to combat aging during biological evolution [10,11], where low competitive senescent cells are outcompeted by those higher competitive cells [12]. Organisms can eliminate senescent cells through different apoptotic mechanisms (programmed cell death [13], mainly induced by intercellular competition) to avoid the accumulation of harmful substances in senescent cells.

However, endless competition may lead to the overexploitation of environmental resources and thus to the tragedy of the commons (TOC) [14]. Examples include uncontrolled population growth [14], climate problems [15], and groundwater depletion due to excessive irrigation [16]. In general, the TOC causes the system to enter a degraded state of shared resources, which adversely affects the evolution and ecological health of all individuals in the long term. The TOC also likely occurs in intercellular competition, where those cells with high competitive ability may attack functional cells, reflecting the ambition to reproduce indefinitely, which is usually considered a mechanism for the generation of cancer cells [17]. Taken together, organisms effectively remove part of the senescent cells through intercellular competition and slow down the rate of loss of functional cells, thus extending lifespan but with the risk of accelerating the production of cancer cells, making the aging of multicellular organisms inevitable [18,19].

We notice that real-world complex systems are typically characterized by bidirectional feedback between the environment and strategy interaction incentives [20]. For example, the temperature of the environment [21] and the status of environmental resources [22] are key factors that affect the lifespan of the organisms. Changing strategy behavior in terms of the environmental feedback can effectively avoid the TOC [23]. Thus, environmental feedback is an essential mechanism to resolve the TOC. Motivated by this point, in this work we ask whether there are similar environmental feedback mechanism in multicellular organisms that would balance aging and cancer to keep the organism alive for longer.

Homeostasis in multicellular organisms (that is, maintenance of the steady state that is essential for the survival of the organism) depends on a high degree of intercellular cooperation [24]. For each cell, dynamic equilibrium is widely present in the microenvironment in which it lives [25]. Organisms

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provide energy for cellular function and growth by consuming microenvironmental resources for metabolism [26]. Energy for the preservation of normal cellular functions, such as growth, survival, apoptosis, differentiation, and morphogenesis, is provided by the microenvironment [27,28]. However, aging and cancer are accompanied by changes in the state of the microenvironment. For instance, organisms suffering from metabolic diseases arising from aging can lead to microenvironmental imbalances [29]. Cancer cells have higher levels of glycolysis than normal cells [30], and rapid reproduction of cancer cells thus consumes a large amount of energy [31]. Immune cells and cancer cells compete intensely for nutrients in the tumor microenvironment (TME), which is unsuitable for the survival of most functional cells [32,33].

Based on the biological facts that the TME is not suitable for functional cell growth [32,33] and intercellular competition can remove senescent cells [19], we propose intercellular competitive growth dynamics with microenvironmental feedback. The work of Wen *et al.* manifested that cells in a state of alternating competitive and cooperative switching (by taking into account the effects due to periodic rhythms) can extend lifespan [24]. Their results inspired us to recognize that the growth dynamics of cells may be related to the microenvironment state they are living in. Since the microenvironment itself is determined by the composition of different types of cells, its state will be influenced directly by the changes of the fraction of the cells, resulting in a bidirectional feedback between the cell-to-cell interactions and the microenvironment. For instance, tumor progression is profoundly influenced by the interactions of cancer cells with their microenvironment [34]. Therefore, we let the microenvironmental state react to the competitive ability of functional cells according to the characteristics of functional cells in different microenvironmental states.

This paper is organized as follows. In Sec. II we introduce the cellular competitive ability, microenvironmental feedback mechanisms, dynamics, and production of all types of cells in our model. Numerical results and analysis are given in Sec. III, where we explain in detail the effect of the microenvironmental feedback parameters on the lifespan. We briefly summarize this work and discuss some relevant issues in Sec. IV.

II. MODEL

In order to describe the relationship between cell growth and the microenvironment in multicellular organisms, we extend the model proposed in Ref. [19] by including a microenvironmental feedback mechanism. As shown in Fig. 1, the model consists of two parts: multicellular growth dynamics and evolution of the state of the microenvironment. The composition of various types of cells in organisms constitutes the state of the microenvironment (aging, normal, or the TME), which in turn regulates the growth rate of functional cells.

A. Competitive ability of each cell type

To investigate the intercellular competition, we classify the cells in an organism into three types as in previous work

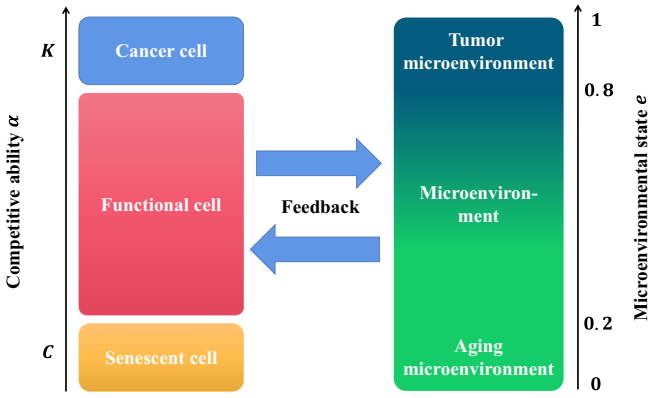

FIG. 1. Schematic diagram of the microenvironmental feedback. On the left are three types of cells divided according to their competitive ability, where the competitive ability of the functional cells is regulated by the state of the microenvironment. On the right are the senescent, normal, and tumor microenvironments, which are distinguished by the microenvironmental state parameter e. The fraction of cells in the multicellular organism can influence the state of the microenvironment.

[19], namely, cancer cells, functional cells, and senescent cells, whose competitive ability α is assumed to be from high to low: $\alpha_C > \alpha_F > \alpha_S$. For simplicity, we suppose that the competitive abilities of senescent and cancer cells are totally determined by the characteristics of the cells themselves, and microenvironment changes can hardly affect their competitive ability at the cellular level due to the low activity of senescent cells and the infinite reproduction capacity of cancer cells. Therefore, their competitive abilities are assumed to be independent of the microenvironmental state. Without loss of generality, we presume that senescent cells have low competitive ability ($\alpha_S = C$) whereas cancer cells have high competitive ability ($\alpha_C = K$), where $C \ll K$. By contrast, functional cells are presumed to be sensitive to the changes in the state of the microenvironment. Following common practice [23], we define the competitive ability of functional cells as

$$\alpha_F = e(C + \delta) + (1 - e)(K - \delta), \tag{1}$$

where $e \in [0, 1]$ measures the state of the microenvironment. The greater e is, the more the microenvironmental state tends toward to the TME. Conversely, the lower e is, the more the microenvironmental state tends toward to the aging microenvironment. The parameter δ is introduced to describe the competitive advantage of functional cells versus senescent cells, or cancer cells versus functional cells in extreme conditions. For example, the competitive ability of functional cells is $\alpha_F = C + \delta > \alpha_S$ and $\alpha_F = K - \delta < \alpha_C$ when $e = 1$ and 0, respectively. Therefore, the values of the parameter δ must satisfy $C + \delta < K - \delta$. To conveniently depict the specific states of the microenvironment at different stages, we choose $e \in \lfloor 0.8, 1 \rfloor$ as the TME and $e \in \lfloor 0, 0.2 \rfloor$ as the aging microenvironment. We have checked that other choices of the intervals of e do not change the qualitative properties of the results presented below.

B. Changes in the microenvironmental state

We define the fraction of each cell type in the organism as

$$f_a = \frac{n_a}{n_F + n_S + n_C}, \quad a \in \{F, S, C\}, \tag{2}$$

where n_F, n_S, and n_C are the number of functional, senescent, and cancer cells, respectively. Then the change in the microenvironmental state is determined by the variation of the fraction of each cell type. Functional cells ensure that the microenvironment is in homeostasis because the normal life activity of the organism cannot be separated from the dynamic balance of matter and energy within the microenvironment [35]. However, aging and cancer are often accompanied by changes in the microenvironment. For instance, cancer cells get a TME suitable for survival (for uncontrolled growth of cancer cells) [36,37].

Based on the above biological facts, we argue that when the fraction of senescent cells in the organism increases, it will degrade the normal microenvironment and lead to the emergence of an aging microenvironment. Similarly, when the fraction of cancer cells in the organisms increases, it deteriorates the normal microenvironment, resulting in the emergence of the TME. By taking these two factors into account, we assume that the microenvironmental state e is modified by the composition of the cellular population

$$e(t+1) = e(t) + \epsilon e(t)[1 - e(t)](\theta f_C - f_S), \tag{3}$$

where θ indicates the relative ratio of the feedback strength of cancer cells and senescent cells in the microenvironment. With large θ, one expects that the organism easily evolves to the TME state in the presence of cancer cells. Note that only for nonzero values of ϵ does the interplay between the microenvironmental state and the cells exist in our model, where the microenvironmental state affects the competitive ability of functional cells in terms of Eq. (1), which subsequently changes the composition of the cells and in turn the microenvironmental state itself. For $\epsilon = 0$, the microenvironmental feedback is absent in our studied dynamical system. As in [23,38], the dimensionless ϵ quantity satisfies $\epsilon \ll 1$ such that the changes in the microenvironment at the organismal level are much slower than those in the cellular fraction of the multicellular organism.

C. Growth dynamics with intercellular competition

The changes in the number of cells n_a within one developmental time step is described by a growth model with intercellular competition [19]

$$n_a(t+1) = r\left(p\frac{\alpha_a}{\bar{\alpha}} + (1-p)\right)n_a(t), \tag{4}$$

where $\bar{\alpha} = \sum_a \alpha_a n_a / \sum_a n_a$, r is the natural growth rate of the cell, and $r > 1$ stands for the intrinsic growth rate. When all types of cells grow in the absence of competition ($p = 0$), multicellular organisms exhibit cooperative growth. For $p \neq 0$, multicellular organisms exhibit competitive growth because α_a depends on the type of cells [refer to Eq. (1)].

In the initial stage, all cells are functional and there are no senescent or cancer cells [$n_S(0) = n_C(0) = 0$]. As growth and development progress, part of the functional cells inevitably start aging. In addition, external stimuli and/or genetic mutations may lead to the emergence of cancer cells. Accounting for these two points, we describe the dynamics of growth of each cell type with microenvironmental feedback by the following set of equations:

$$\begin{aligned}
n_F(t+1) =& r\left(p\frac{\alpha_F}{\bar{\alpha}} + (1-p)\right)n_F(t) \\
&- \mu_{FS} n_F(t) - \mu_{FC} n_F(t), \\
n_S(t+1) =& r\left(p\frac{\alpha_S}{\bar{\alpha}} + (1-p)\right)n_S(t) + \mu_{FS} n_F(t), \\
n_C(t+1) =& r\left(p\frac{\alpha_C}{\bar{\alpha}} + (1-p)\right)n_C(t) + \mu_{FC} n_F(t).
\end{aligned} \tag{5}$$

Here μ_{FS} is the probability that the functional cells are changed into senescent cells (including inevitable aging and mutation) and μ_{FC} is the probability that functional cells mutate to cancer cells.

Equations (3)–(5), together with Eq. (1) as the link between the microenvironmental state and the competitive ability of the functional cells, constitute the set of dynamical equations that mathematically describes the intercellular competitive growth dynamics with microenvironmental feedback. Solving these equations numerically, we are able to obtain how the number of each cell type evolves with the developmental time step.

III. RESULTS AND ANALYSIS

Aging is a process in which the function of various tissues and organs of the organism decrease comprehensively with the increase of age, which is shown to be inevitable due to the intercellular competition [19]. The main problem we are interested in is the effect of intercellular competition and microenvironmental feedback on the lifespan of multicellular organisms. To this end, we define the time at which the fraction of functional cells decreases to $\lambda = 1\%$ as the lifespan L of organisms, as done in [24]. We calculate the fitness (or competitive ability) of each cell type under different conditions, where the parameters are $C = 1$, $K = 10$, $\delta = 1$, $r = 1.001$, $\epsilon = 0.01$, $\mu_{FS} = 2 \times 10^{-3}$, and $\mu_{FC} = 5 \times 10^{-5}$ if not otherwise specified. In the initial stage of development, all cells are functional, so the initial numbers of each cell type are $n_F(0) = 10$ and $n_S(0) = n_C(0) = 0$. The results presented below are obtained for the initial state of the microenvironment with $e(0) = 0.5$. In Appendix A we also show the impact of λ and other initial values of the microenvironment state on the lifespan.

A. Intercellular competition can combat aging without microenvironmental feedback

We first discuss the situation without bidirectional feedback between the cells and their microenvironment. It refers to $\epsilon = 0$ in Eq. (3), i.e., $e(t) \equiv 0.5$ and $\alpha_F \equiv 5.5$ for $C = 1$ and $K = 10$. We present in Fig. 2 the effects of intercellular competition on the lifespan of the multicellular organism. Without intercellular competition ($p = 0$), the fraction of functional cells decreases to 1% at $t = 2248$, and senescent cells

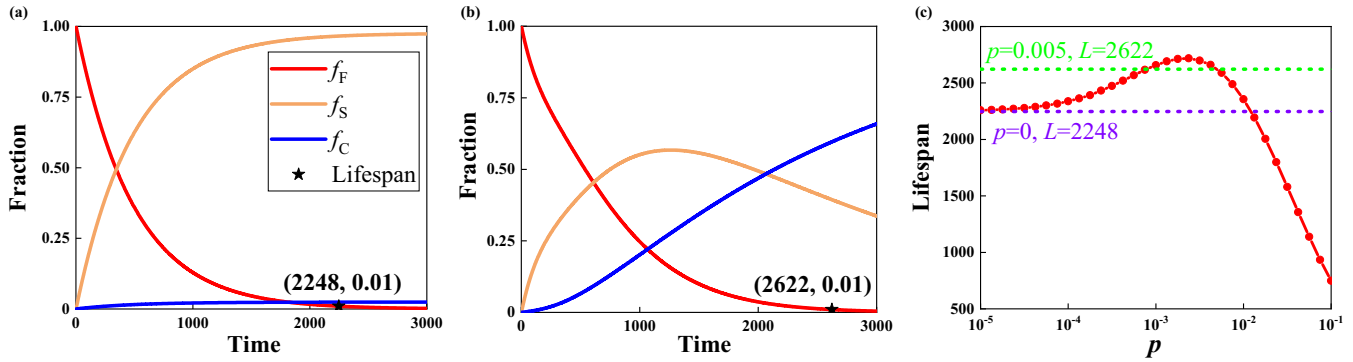

FIG. 2. Fraction of different types of cells as a function of time, where (a) without intercellular competition ($p = 0$ and $\epsilon = 0$) all cells grow under natural growth rate conditions and (b) with intercellular competition ($p = 0.005$ and $\epsilon = 0$) intercellular competition successfully delays the aging of the organism. (c) Lifespan L of the multicellular organism as a function of the competition parameter p.

dominate in the organism, as shown in Fig. 2(a). The increase in the fraction of senescent cells is inhibited by the growth of cancer cells when partial competitive growth ($p = 0.005$) is introduced in Fig. 2(b). According to our numerical results, we find that the lifespans of the multicellular organism are 2248 and 2622 for $p = 0$ and 0.005, respectively. By doing the algebra $(L_{p=0.005} - L_{p=0})/L_{p=0} \times 100\%$, we obtain that the lifespan is extended by 16.6% compared to the situation without intercellular competition. This suggests that intercellular competition can combat aging, but the decrease in the fraction of functional cells is not altered, since those highly competitive cancer cells have an evident growth advantage over both lowly competitive senescent cells and functional cells.

However, excessive competition among the cells is found to be detrimental for the multicellular organism. Figure 2(c) displays how the lifespan of the multicellular organism changes as the proportion of competition increases. When the percentage of competition p is too high, the lifespan of the multicellular organism is shortened compared to the case of without intercellular competition. Intercellular competition likely leads to the dominance of cancer cells in the organism, and the development of too many cancer cells gives rise to a shortened lifespan of the organism. This result is in accordance with the findings in [19], where intercellular competition creates an inescapable "double bind" that makes aging inevitable in multicellular organisms.

B. Microenvironmental feedback can extend lifespan

We now discuss how the introduction of microenvironmental feedback affects the lifespan of the organism. To do this, we fix the parameter $p = 0.005$ and check the dynamic behavior of the fraction of different types of cells as well as that of the microenvironment state for different choices of θ. Figure 3(a) features the time series of the fraction of functional cells for $\theta = 2$ and $\epsilon = 0$. By using the case without microenvironmental feedback ($p = 0.005$ and $\epsilon = 0$) as a baseline, we note that the lifespan is successfully extended by 14.6% due to the presence of microenvironmental feedback. As expected from our model, when the fraction of senescent cells in the organism increases, functional cells are affected by the changes in the microenvironmental state to increase their competitive ability to better delay aging. However, we find that for sufficiently large $\theta = 5$, the microenvironmental feedback accelerates aging instead, as shown in Fig. 3(b). This suggests that the existence of microenvironmental feedback has a nontrivial effect on the lifespan. We present in Fig. 3(c) the evolution of the microenvironmental state for $\theta = 1$, 2, and 5, respectively. We find that larger θ usually leads to faster evolution to the TME of the organism. Note that the competitive ability of functional cells is significantly reduced in the TME. Thus, although senescent cells are efficiently removed due to the presence of microenvironmental feedback, cancer cells and the TME dominate the multicellular organism, leading to the inevitable reduction in the fraction of functional cells.

By checking the evolution of the microenvironmental state, we can better understand how microenvironmental feedback extends lifespan. When intercellular competition exists [Fig. 2(b)], the fraction of senescent cells in the organisms is highest among the three types of cells at around $t \in \lfloor 600, 2000 \rfloor$, and eventually the fraction of cancer cells will dominate the organism. Consequently, the microenvironmental state will change from a normal to an aging microenvironment and finally to the TME. After introducing the microenvironmental feedback, we find that the case of $\theta = 2$ is in the best accordance with the above microenvironmental evolutionary rule.

The rate of decrease in the fraction of functional cells is almost the same under different conditions at $t < 300$ [see Fig. 3(a)]. The microenvironmental changes are smaller at this period, so it is difficult for the microenvironmental feedback mechanisms to play a role in the aging process of multicellular organisms. When the microenvironmental state changes to an aging microenvironment at $t \in \lfloor 629, 2200 \rfloor$, the competitive ability of the functional cells increases substantially and aging is delayed. As the fraction of cancer cells increases, the microenvironment eventually evolves to the TME ($t > 2708$) suitable for infinite growth of cancer cells.

C. Effect of microenvironmental feedback parameters on lifespan

We now study the influence of θ (the fraction of cancer cells relative to that of senescent cells) on the feedback rate

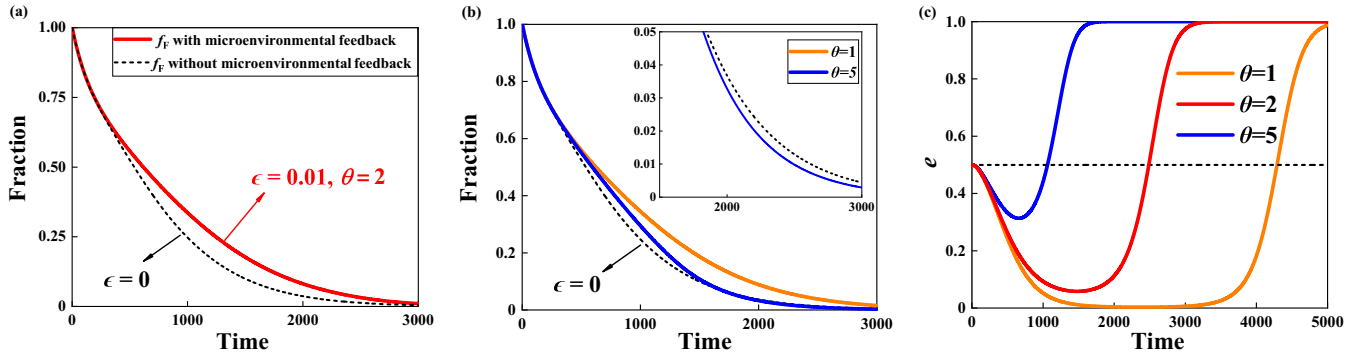

FIG. 3. Fraction of functional cells as a function of time, where (a) in the presence of intercellular competition with microenvironmental feedback ($\theta = 2$) we have $L_{\theta=2} = 3005$ and (b) for the cases of $\theta = 1$ and $\theta = 5$, we have $L_{\theta=1} = 3236$ and $L_{\theta=5} = 2493$, respectively. (c) Time evolution of the microenvironmental state $e(t)$ for the cases of $\theta = 1$, 2, and 5. The dashed line represents the case without microenvironmental feedback ($p = 0.005$ and $\epsilon = 0$), where $L_{\epsilon=0} = 2622$, as shown in Fig. 2(b).

of the microenvironment and the effect of the competitive ability of cancer cells K on the lifespan L of the multicellular organisms. The results summarized in Fig. 4(a) show that the lifespan L decreases monotonically with the parameter θ due to the enhanced feedback of cancer cells' fraction to the microenvironment (faster speed to reach to the state of the TME for larger θ). Using the case without microenvironmental feedback as a baseline, we observe a threshold phenomenon that the microenvironmental feedback can effectively extend the lifespan only for $\theta < 3.77$. The concrete threshold (here $\theta = 3.77$) depends on the percentage of competition p, the competitive ability of cancer cells K, and λ. We check that the threshold phenomenon is robust to different choices of λ in Appendix A. We notice that the increase or decrease of θ has a negligible effect on the lifespan provided that $\theta < 1$ [see Fig. 4(a)], as cancer is less influential than aging in such a situation. A too strong feedback rate of the fraction of cancer cells relative to the fraction of senescent cells to the microenvironment ($\theta > 3.77$) leads to the rapid development of the TME triggering malignant or acute tumors, which causes shortened lifespan instead.

When θ is between 0 and 2, we see that the microenvironmental feedback can extend properly the lifespan by about 20% as compared to the case without microenvironmental feedback. Time-restricted feeding (depend on circadian-regulated functions) is a potential antiaging treatment for organisms from *Drosophila* to humans [39–44]. Ulgherait *et al.* developed an intermittent time-restricted feeding dietary regimen that robustly extended fly lifespan [44]. Their work showed that, relative to animals on *ad libitum* diets, animals on this diet from days 10 to 40 had a mean lifespan increase of more than 18% (female flies) and 13% (male flies) [44]. An experimental study by Correia-Melo *et al.* established metabolite exchange interactions as a determinant of cellular aging and showed that metabolically cooperative cells can shape the metabolic environment to extend their lifespan [45]. Their work showed that the cells lived around 25% longer when they exchanged more metabolites with each other [45]. Thus, it seems that the magnitude of the extension of the

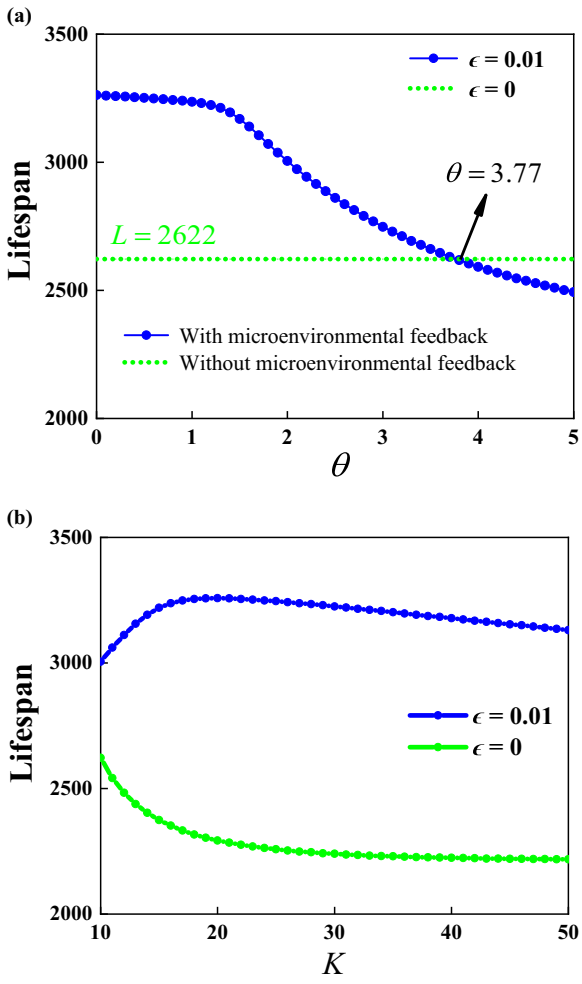

FIG. 4. Lifespan L for different parameters θ and K. (a) Lifespan L as a function of the feedback strength θ of the cancer cells' fraction to the microenvironment, with $K = 10$. (b) Lifespan L as a function of the competitive ability K of the cancer cells, with $\theta = 2$. The green dotted line is the case without microenvironmental feedback ($p = 0.005$ and $\epsilon = 0$).

lifespan predicted by our theoretical studies is in accordance with those from empirical investigations. For this reason, we are confident that our theoretical studies make sense.

In recent years, targeted therapies to address the TME have made rapid progress [46–49]. The shortened lifespan is a highly visual statistic in cancer treatment. Non-Hodgkin's lymphoma is a blood cancer generated by the hematopoietic system, such as the bone marrow or lymphatic system [50]. Pham *et al.* found that men with non-Hodgkin's lymphoma lost an average of 23.7% of their lifespan in 1980 versus 16.1% in 2015, while women with non-Hodgkin's lymphoma lost an average of 21.7% of their lifespan in 1980 versus 15.5% in 2015 [50]. From 1980 to 2015, improvements in medical care can be regarded as a key factor in the reduction in the shortened lifespan of cancer patients. We note that the decrease of θ can achieve a similar effect in our model, where θ is the feedback strength of the cancer cells regulating the microenvironment in Eq. (3), so that cutting off the positive feedback from the cancer cells to the TME ($\theta = 0$ or reducing θ) could be considered as a targeted treatment for the TME. It is reasonable for us to argue that completely cutting off the positive feedback from the cancer cells to the TME is the most optimal effect of therapies targeting the TME. Corresponding to the case of $\theta = 0$ in our model, $L_{\theta=0} = 3262$. The shortened lifespan κ can be quantitatively described as

$$\kappa_\theta = \frac{L_0 - L_\theta}{L_0} \times 100\%. \tag{6}$$

The shortened lifespans for $\theta = 3$ and 5 are 15.76% and 23.57%, respectively, according to Eq. (6). We note that the results for $\theta = 3$ and 5 on the two sides of the threshold ($\theta = 3.77$) are close to the data in the work of Pham *et al.* [50]. This suggests that reducing the feedback strength of the cancer cells regulating the microenvironment could theoretically achieve a longer lifespan of multicellular organisms. These results may provide helpful clues for targeted therapies aimed at the TME.

We next study the effect of the cancer cells' competitive ability on the lifespan of the multicellular organism [see Fig. 4(b)]. In the absence of microenvironmental feedback, the lifespan of the multicellular organism decreases as K increases. It is intuitive that the higher the competitive advantage of cancer cells, the faster the fraction of them increases in the multicellular organism. However, we obtain counterintuitive results with the presence of microenvironmental feedback. We find that increasing K extends the lifespan L with microenvironmental feedback when the cancer cell's competitive ability increases in $K \in \lfloor 10, 20 \rfloor$ [see Fig. 4(b)]. The reason for this phenomenon is that functional cells can dynamically adjust their competitive ability according to the state of the microenvironment and the competitiveness of cancer cells, as illuminated in Eq. (1). To clearly explain this phenomenon, we show the evolution of the fraction of functional cells and the microenvironmental state for $K = 10$ and 20 in Fig. 5. We find that the relative magnitude of the reduction rate of the functional cells for $K = 10$ and 20 changes on both sides of $t = 1795$. The rate of decline of functional cells for $K = 20$ is larger than that for $K = 10$ when $t < 1795$ in Fig. 5(a). During this period, the competitive ability of the cancer cells dominates the impact on functional cells. In addition, when $t > 1795$, the TME emerges faster for $K = 10$, which leads to a decrease in the competitive ability of functional cells and thus reduces the growth rate of the functional cells as shown in Fig. 5(b). Larger K gives those cancer cells a more evident competitive advantage during the microenvironmental feedback, despite the slow emergence of the TME. Therefore, there exists an optimal lifespan for the organism by adjusting the competitive ability of cancer cells.

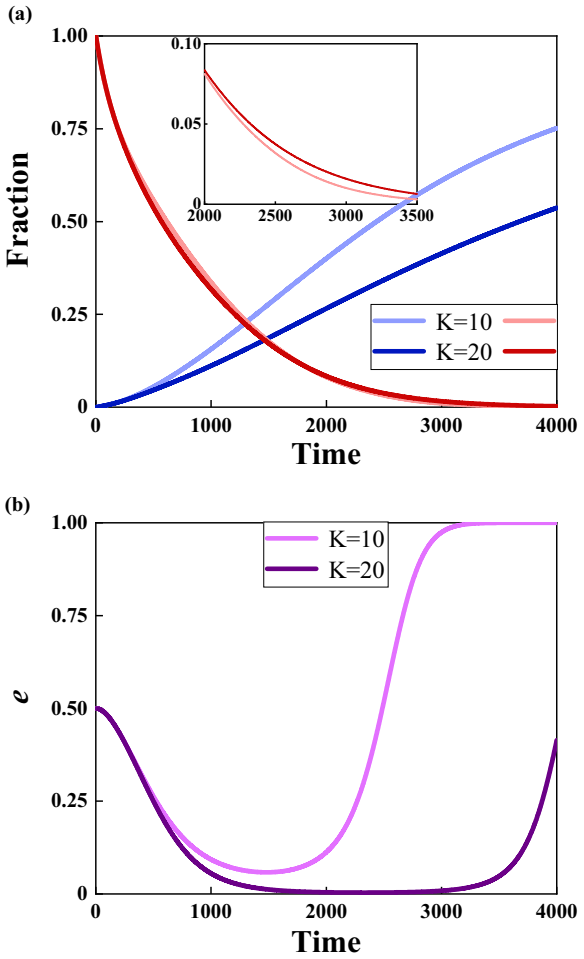

FIG. 5. Time series of the fraction of functional cells (red line) and the cancer cells (blue line) for two different choices of K, with $\theta = 2$. The relative magnitude of the reduction rate of the functional cells for $K = 10$ and 20 changes on both sides of $t = 1795$. (b) Time evolution of the microenvironment state for $K = 10$ and 20.

D. Parrondo's paradox of cancer cells' competitive ability

Recently, some counterintuitive phenomena are observed when organisms with different life history traits (strategies) compete with each other [17,24], which has been successfully explained by means of a game-theoretic framework known as Parrondo's paradox [51–53]. Basically, Parrondo's paradox describes an interesting, albeit counterintuitive at a first glance, situation that the periodic and/or random switching of two losing strategies can lead to a successful one [51–53].

In Sec. III C we saw that both too-low and too-high competitive abilities of cancer cells are losing strategies for the

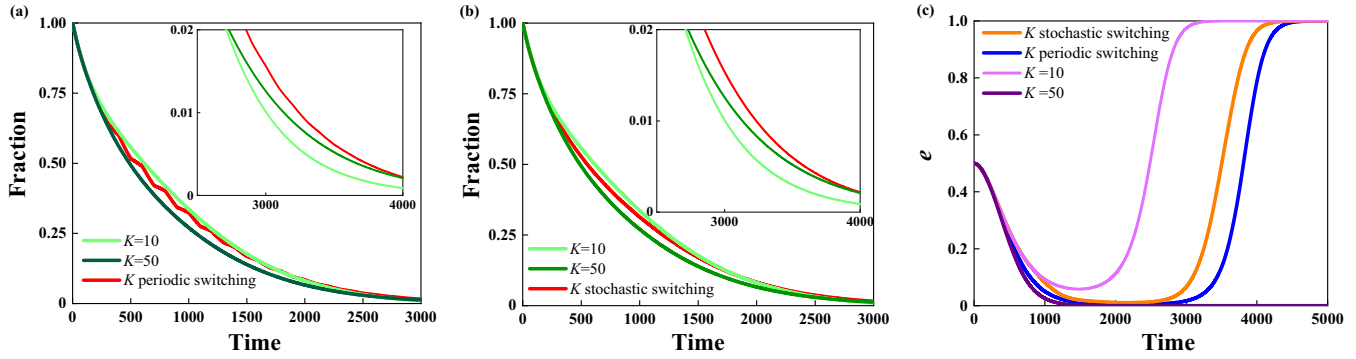

FIG. 6. Fraction of functional cells for different switching schemes: (a) periodic switching with $\xi = 100$ and $T = 200$ ($L_{\text{periodic}} = 3243$) and (b) stochastic switching with $\tau = 200$ and $\zeta = 50\%$ ($L_{\text{stochastic}} = 3234$). As a comparison, the lifespans for the separate $K = 10$ and 50 cases are 3005 and 3132, respectively. (c) Time evolution of the microenvironmental state for different switching schemes and the cases of $K = 10$ and 50 separately. The other parameters are $p = 0.005$ and $\theta = 2$.

lifespan of multicellular organisms, since there is an optimal selection of K for the multicellular organism to live the longest. It is possible that the competitive ability of cancer cell populations in multicellular organisms is periodically altered in clinical therapy. For example, when multicellular organisms develop malignant tumors, the competitive ability of the cancer cell populations will be too high; radiation therapy or new drug treatments may reduce the K value to a fairly low level. After clinical treatment, mutated or surviving cancer cells continue to multiply and spread, resulting in a high K value. Then, similar to what was done in [24], we wonder if a periodic or random switching between too-low and too-high competitive ability of the cancer cells could result in a greater lifespan than in each case alone, i.e., the emergence of Parrondo's paradox.

To answer this question, we first consider the case that the competitive ability of the cancer cells evolves as

$$K = \begin{cases} 10, & 0 \leqslant \mathrm{mod}(t, T) < \xi \\ 50, & \xi \leqslant \mathrm{mod}(t, T) < T. \end{cases} \tag{7}$$

Here the competitive ability of the cancer cells switches periodically, which is $K = 10$ during $[0, \xi)$ and $K = 50$ during $[\xi, T)$. Compared to the case of $K = 10$ or 50 alone, we find that a periodic switch of the competitive ability of the cancer cells can lead to a slower reduction of functional cells to 1% as shown in Fig. 6(a). This reveals clearly that with the microenvironmental feedback mechanism, a strategy of periodic switching in the competitive ability of the cancer cells can extend the lifespan of multicellular organisms.

As an alternative to the periodic switching scheme [24], we also check whether a similar phenomenon can occur when the competitive ability of the cancer cells switches randomly. To do this, we implement a stochastic switching scheme of the competitive ability of the cancer cells defined as

$$K = \begin{cases} 10, & \mathrm{mod}(t, \tau) = 0, \ \text{prob } \zeta \\ 50, & \mathrm{mod}(t, \tau) = 0, \ \text{prob } 1 - \zeta. \end{cases} \tag{8}$$

Specifically, the competitive ability of the cancer cells switches as 10 or 50 every τ time units, and the probability of choosing 10 is ζ. The decrease of the competitive ability of the cancer cells may be caused, for instance, by radiotherapy and chemotherapy. Figure 6(b) displays the fraction of functional cells for the stochastic switching scheme. Interestingly, the reduction in the fraction of functional cells to 1% is longer than that in the case of $K = 10$ and 50 separately. By performing some measurements, we have verified that the periodic switching scheme is more effective in promoting the lifespan L than the stochastic switching, i.e., $L_{\text{periodic}} > L_{\text{stochastic}}$. This is due to the faster appearance of the TME in the case of stochastic switching of K, as shown in Fig. 6(c).

Here we want to emphasize that the presence of the microenvironmental feedback is crucial in giving rise to the interesting phenomenon of Parrondo's paradox. We have checked that without the microenvironmental feedback mechanism, Parrondo's paradox is absent for the switching scheme of the competitive ability of the cancer cells (refer to the results in Appendix B).

On the one hand, in the framework of intercellular competition with microenvironmental feedback, a too-low competitive ability of the cancer cells is a losing strategy because it cannot reverse the tendency of senescent cells to accumulate. On the other hand, a too-high competitive ability for the cancer cells is also a losing strategy, because a too-high competitive ability makes it difficult for even functional cells to survive, leading to the cancerous transformation of the organisms. The emergence of Parrondo's paradox suggests that the multicellular organisms (or new medicine treatments) may combine these two strategies to achieve a longer lifespan in the presence of the microenvironmental feedback.

IV. CONCLUSION

In summary, we have studied the dynamical behavior of a mathematical model of intercellular competition, where a microenvironmental feedback mechanism is introduced to regulate the competitive ability of the different types of cells. In the absence of microenvironmental feedback, our model produces results consistent with those found in Ref. [19], i.e., intercellular competition can weed out senescent cells, but the unlimited proliferation of cancer cells leads to aging. With the involvement of the microenvironmental feedback, we found that the lifespan of the multicellular organisms can be effectively extended as long as the regulation rate of

cancer cells in the microenvironment is not so strong. The microenvironmental feedback mechanism plays a crucial role in maintaining a delicate balance between cancer and aging, thereby delaying the inevitable aging process in multicellular organisms.

It is well known that malignant tumors can greatly shorten the lifespan of organisms [54]. In recent years, the average lifespan shortened by cancer is decreasing owing to the improvement of medical treatments. Interestingly, the reduction in the lifespan revealed by our model matches quite well with the data for non-Hodgkin's lymphoma in Canada from 1980 to 2015 [50], which suggests that our proposed model might serves as a good candidate to treat the interactions of different types of cells in real organisms. Our results highlight the important role of the feedback rate of the fraction of cancer cells relative to the fraction of senescent cells in the microenvironment in extending the lifespan of the organism. In the presence of microenvironmental feedback, the development of the TME can be efficiently postponed. In this sense, we contend that the reduction of θ (i.e., the feedback strength of the cancer cells regulating the microenvironment, which could be characterized by the frequency and intensity of medical treatments in realistic situations) should be considered as a relevant therapeutic approach for targeting the inhibition of the TME.

Moreover, by exploring the effect of cancer cells' competitive ability on the lifespan of organisms, we have discovered a nonmonotonic phenomenon caused by the microenvironmental feedback. There is an optimal value of K (the competitive ability of cancer cells) that allows the multicellular organisms to achieve the longest lifespan, which is totally absent without the microenvironmental feedback mechanism. Of particular interest, we have found that either periodic or stochastic switching between too-high and too-low values of K can further extend the lifespan of the organism, compared to the cases of too-low or too-high K separately, which resembles the phenomenon of Parrondo's paradox [24]. Our work can be regarded as an important extension and advancement of the work by Wen *et al.* [24]. It is worth pointing out that microenvironmental feedback is a necessary factor for the emergence of Parrondo's paradox in our model, which is the difference between our present study and the work of Wen *et al.* Inspired by the phenomenon of Parrondo's paradox, we point out that periodic changes in the competitive ability of cancer cell populations (through cycles of radiotherapy or new drug treatments) may provide a possible treatment scheme.

Besides competitive interactions, complex cooperation among cells of multicellular organisms can further complicate the regulation of microenvironmental feedback [55]. Our present model describes just a homogenized microenvironment at the organismal level, which might be less significant for applications in realistic situations. In fact, it is very unlikely to reverse the microenvironment of the organism when it has already been dominated by the TME or the aging microenvironment [37]. Nevertheless, with the rapid development of modern medicine, we may expect at some future date that the microenvironment in real organism can be properly regulated in the procedure treating malignant tumors to achieve the most effective treatment. We thus hope that our theoretical work can inspire further experimental studies (such as *in vitro* experimental systems [56]) to better describe the relationship between the microenvironment and intercellular competition, providing valuable clues about tumor therapy.

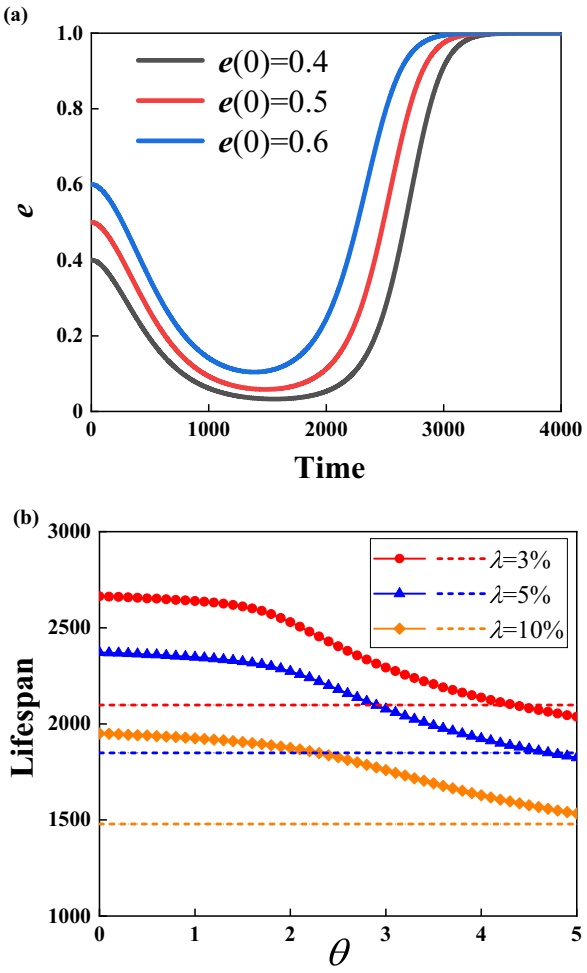

FIG. 7. (a) Time evolution of the microenvironmental state $e(t)$ starting from different initial values $e(0)$. The parameters are $p = 0.005$ and $\theta = 2$. (b) Lifespan L as a function of the parameter θ for $\lambda = 3\%, 5\%, 10\%$. The dotted lines mark the lifespan in the case of no microenvironmental feedback.

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APPENDIX A: IMPACT OF λ AND THE INITIAL STATE OF THE MICROENVIRONMENT ON THE LIFESPAN

Accounting for the fact that organisms would be in microenvironmental homeostasis without aging and cancer development, we also investigate the effect of different initial states of the microenvironment $[e(0) = 0.4, 0.5, 0.6]$ on

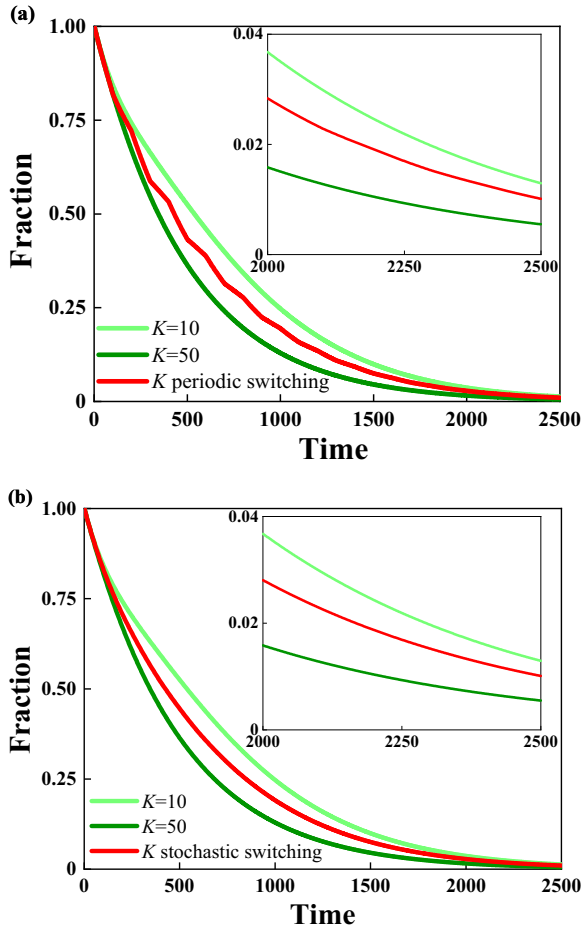

FIG. 8. Fraction of functional cells for different switching schemes without microenvironmental feedback. (a) Periodic switching with $\xi = 100$ and $T = 200$. (b) Stochastic switching with $\tau = 200$ and $\zeta = 50\%$. The parameters are $p = 0.005$ and $\epsilon = 0$.

its dynamical evolution in Fig. 7(a). We find that as the initial value increases, the microenvironmental state evolves more rapidly to the TME. Nonetheless, the evolutionary trend remains qualitatively the same, and for this reason we mainly focused on the results for $e(0) = 0.5$ in the main text.

To verify whether the threshold phenomenon (i.e., for sufficiently large θ, the lifespan L falls below the case where microenvironmental feedback is not taken into account) is robust to the other definition of the lifespan, we have calculated the lifespan L as a function of θ for different choices of $\lambda = \{3\%, 5\%, 10\%\}$. As λ increases [Fig. 7(b)], the observed threshold phenomenon always appears. This indicates that the threshold behavior of L versus θ originates from the microenvironmental feedback mechanism and is a robust phenomenon.

APPENDIX B: SWITCHING OF K WITHOUT MICROENVIRONMENTAL FEEDBACK

Here we complement the results when the competitive ability K of the cancer cells switches between 10 and 50 in the absence of microenvironmental feedback [$\alpha_F \equiv 5.5$ and $e(t) \equiv 0.5$]. Figure 8 shows the fraction of functional cells for periodic and stochastic switching. The parameters of the two switching schemes are consistent with those in Fig. 6. However, we find that without microenvironmental feedback, the lifespan is just monotonically shortened when the competitive ability of the cancer cells increases. This means that $K = 10$ is a failed strategy, $K = 50$ is an even more failed strategy, and there is no optimal situation in between. Specifically, either periodic or stochastic switching of K cannot lead to the emergence of Parrondo's paradox in the absence of the microenvironmental feedback mechanism.

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