Extending the Lifespan of Multicellular Organisms via Periodic and Stochastic Intercellular Competition

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Resolution of the intrinsic conflict between the reproduction of single cells and the homeostasis of a multicellular organism is central to animal biology and has direct impact on aging and cancer. Intercellular competition is indispensable in multicellular organisms because it weeds out senescent cells, thereby increasing the organism's fitness and delaying aging. In this Letter, we describe the growth dynamics of multicellular organisms in the presence of intercellular competition and show that the lifespan of organisms can be extended and the onset of cancer can be delayed if cells alternate between competition (a fair strategy) and noncompetitive growth, or cooperation (a losing strategy). This effect recapitulates the weak form of the game-theoretic Parrondo's paradox, whereby strategies that are individually fair or losing achieve a winning outcome when alternated. We show in a population model that periodic and stochastic switching between competitive and cooperative cellular strategies substantially extends the organism lifespan and reduces cancer incidence, which cannot be achieved simply by optimizing the competitive ability of the cells. These results indicate that cells could have evolved to optimally mix competitive and cooperative strategies, and that periodic intercellular competition could potentially be exploited and tuned to delay aging.

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All multicellular organisms face a fundamental conflict between the reproduction of individual cells and homeostasis at the organism level. Such conflicts across different levels of biological organization appear to be a key driver of the evolution of complexity [1]. Dynamic competition between neighboring cells is a prominent biological phenomenon [2], which promotes selective elimination of poorly functioning or senescent cells (and avoiding the accumulation of harmful substances from senescent cells), thus increasing organism fitness and delaying aging (onset of senescence) [3,4]. Moreover, it has been shown that the elimination of senescent cells is not limited to functional cells simply outgrowing the senescent ones, but rather, is an active process executed by distinct apoptotic mechanisms—programmed cell death [5]. Targeted apoptosis of senescent cells restores tissue homeostasis in aging mice [6]. However, intercellular competition can also result in the emergence of "cheater" cells, their uncontrolled proliferation, and ultimately, cancer, the second major cause of death in humans [7–10]. In general, the emergence of cheaters appears to be inescapable, due to the evolutionary instability of cooperator-only states [11]. Overall, the intrinsic trade-off between the vigor of individual cells and intercellular cooperation is likely to be one of the major factors affecting animal aging [12].

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. However, traits that are beneficial for the organism usually come at a high cost for an individual cell [13]. Thus, mutant cells that do not invest in the costly cooperative traits enjoy a selective advantage [14]. Under competition at the cell level, cheaters can replace other cells by rapidly evolving traits that are only beneficial to themselves, thereby improving their fitness, while the cooperative traits deteriorate [15]. Here, we show that the competition between cells is a key factor defining the trade-off between cell deterioration causing aging and cancer [14]. Such competition can slow down the loss of functional cells, thereby delaying aging, but increasing the incidence and accelerating the onset of cancer. As pointed out in the work of Nelson and Masel [14], the frustration between senescence and cancer creates a "double bind," making aging of multicellular organisms inevitable.

Recently, several counterintuitive phenomena occurring when organisms with different life history traits (strategies) compete against each other have been explained in terms of a game-theoretical concept known as Parrondo's paradox (PP) [16]. PP was conceived as an abstraction of flashing Brownian ratchets, wherein diffusive particles exhibit unexpected drift when exposed to alternating periodic potentials. Specifically, particles localize in the potential minima and undergo free diffusion when the potential is switched on and off respectively, but a directed motion (average drift) can be achieved through alternating the potential in order [17]. In general, in PP, a winning outcome can be achieved by switching between two losing strategies [18,19]. The paradox has been broadly useful in understanding various phenomena, such as drifts in granular flow [20] and unexpected quantum dynamical behavior [21,22]. In biology, PP has manifested in the competition between nomadic and colonial forms of organisms [23], predator dormancy in predator-prey systems [24], and competition between unicellular and multicellular phases of life [25].

Here, we ask what will occur if, in multicellular organisms, cells compete periodically, that is, switch between competitive and cooperative strategies. Motivated by previous studies on cell competition in multicellular organisms and the emerging field of Parrondo's games, we apply a population model to characterize the dynamics of growth of organisms with intercellular competition. In this model, cells with different traits can either (1) grow without interacting with other cells endowed with different traits (cooperation, for short), or (2) compete with other cells depending on differential fitness (competition, for short). Both of these cell growth regimes result in shorter average lifespans and lower fractions of functional cells in later times than mixed strategies, but competition markedly outperforms cooperation; we thus identify them as fair and losing strategies, respectively.

From the biological standpoint, our model is inspired by [14] and is designed to facilitate analysis of competitive dynamics and lifespan-extending effects. We show, counterintuitively, that cells in a multicellular organism can periodically or stochastically alternate between cooperation and competition to substantially extend the lifespan and delay the onset of cancer, thus achieving a winning outcome for the organism and recapitulating the weak form of PP [26,27]. Such a lifespan-extending outcome cannot be achieved by organisms that implement any of the individual strategies.

For the purpose of this Letter, cells in a multicellular organism are characterized by two key parameters on a 2D lattice (Fig. 1), namely, the ability of a cell to drive out of existence other intrinsically viable cells with different genotypes (cellular competitive ability α_i) [2], and the cell's contribution to the organism's vitality β_j, where vitality is regarded as the general health of the multicellular organism. Indices $i, j \in [1, K]$ enumerate the position of

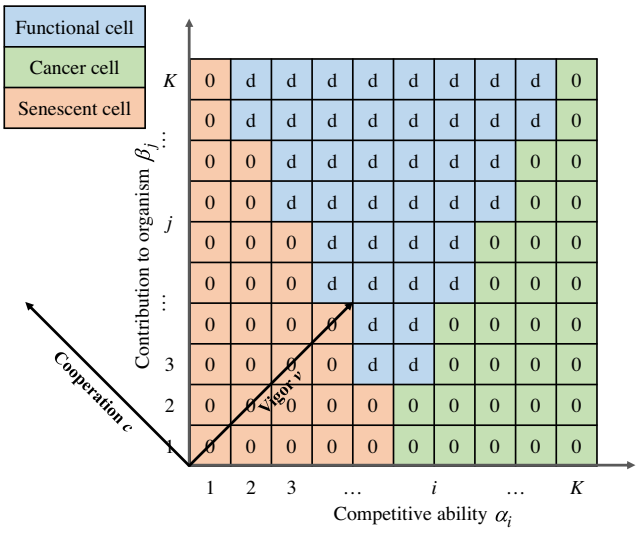

FIG. 1. Initial densities $n_{ij}(0)$ of cells in a multicellular organism, shown on a 2D lattice discretizing trait parameter space. Cellular competitive ability α_i (on x axis) and cooperative ability β_j (on y axis) are two parameters that characterize cell traits. Color shading of the lattice demarcates functional, cancer, and senescent cell types, according to their relative positions in the trait space.

cells with the specific trait in the parameter space. Vigor v (the total output of a cell) and cooperation c (the contribution of a cell to homeostasis of the organism) are both functions of α_i and β_j. As v and c are both positively correlated with β_j, but are, respectively, positively and negatively correlated with α_i, we adopt linear dependencies $v = f(\alpha_i, \beta_j) = \beta_j + \alpha_i$ and $c = g(\alpha_i, \beta_j) = \beta_j - \alpha_i$ [14]. Regular metabolic activities of cells are reflected by vigor v, such that cells with low vigor, for instance caused by cellular damage, are considered senescent and are eliminated in competition with cells of greater vigor [28]. Cells with high cooperation c invest in traits that are expensive for an individual cell but beneficial for the multicellular organism. In particular, low-cooperativity, competitive cells can manifest cancerlike behavior, where consumption of nutrients and growth become uncontrolled. Initially, all cells are functional, with no senescent ($1 \le i \le K/2$ and $1 \le j \le K - 2i + 2$) or cancer cells ($K/2 < i \le K$ and $1 \le j \le 2i - K$) present in the multicellular organism (Fig. 1); the number of functional cells is set uniformly at $n_{ij}(0) = d$ when $2 \le i \le K - 1$ and $\max(2i - K, K - 2i + 2) < j \le K$.

Inspired by the analysis of Nelson and Masel [14], the change of the number of cells n_{ij} in one developmental time step is described by a growth model with intercellular competition,

$$n_{ij}(t+1) = r\left[p\frac{\alpha_i}{\bar{\alpha}} + (1-p)\right] n_{ij}(t), \tag{1}$$

where r is the growth rate of cells, such that $r > 1$ corresponds to exponential growth. The somatic cells n_{ij} comprise two classes: (1) the fraction p competes with other cells based on competitive ability α_i, which evolves by selection of cells carrying somatic mutations that enhance competitiveness, and (2) the remaining fraction $(1-p)$ grows at the rate r independent of the genotype. The multicellular organism exhibits cooperative growth when all cells grow without competition ($p = 0$), and competitive growth when $p \neq 0$ due to the α_i-dependent intercellular competition. The average competitive ability $\bar{\alpha}$ of cells in a multicellular organism is defined as $(\sum_{i,j} \alpha_i n_{ij})/(\sum_{i,j} n_{ij})$.

Apart from cell growth and intercellular competition in the multicellular organism, genes can also mutate, leading to changes in traits. Here, we assume that the effect of mutations is deleterious, leading to cells losing cooperation ability c or vigor v, the values of which provide a natural categorization of cellular traits as discussed. Furthermore, cells in each state only degrade in one direction due to mutations, that is, either c or v, in each step [14]. The cooperation mutation model is then defined as

$$\begin{aligned} n_{ij}(t+1) &= n_{ij}(t) - \mu_c n_{ij}(t), \\ n_{i'j'}(t+1) &= n_{i'j'}(t) + \frac{1}{k}\mu_c n_{ij}(t), \end{aligned} \tag{2}$$

where μ_c is the probability of a mutation affecting cooperation. The impact of such a mutation is a transition from cell number n_{ij} to cells with the same vigor but lower cooperation $n_{i'j'}$. We assume the mutated cells are evenly redistributed between all such states (i', j'), such that the probability of a mutated cell landing in each state is $1/k$ for k total states. Explicitly, the indices $(i', j') = (i+\lambda, j-\lambda)$ and $k = \min(K-i, j-1)$ for $\lambda = \{1, 2, \ldots, k\}$. This evolution is shown as declining cooperation in Fig. 1. Likewise, the vigor mutation model is defined as

$$\begin{aligned} n_{ij}(t+1) &= n_{ij}(t) - \mu_v n_{ij}(t), \\ n_{i'j'}(t+1) &= n_{i'j'}(t) + \frac{1}{k}\mu_v n_{ij}(t), \\ (i', j') &= (i-\lambda, j-\lambda), \qquad k = \min(i-1, j-1), \end{aligned} \tag{3}$$

for $\lambda = \{1, 2, \ldots, k\}$, where μ_v is the probability of a mutation affecting vigor, and k is the number of states (i', j') with the same cooperation but lower vigor that can arise from n_{ij}. To evaluate the fitness of each cell type, we compute its fraction

$$\eta_a = \frac{N_a}{N_n + N_s + N_c}, \qquad a \in \{n, s, c\}, \tag{4}$$

where N_n, N_s, and N_c are the numbers of functional, senescent, and cancer cells, respectively.

We evaluate the fitness of each cell type under different conditions, to investigate the impact of the strategy the cells implement. We take parameters $K = 10$, $d = 10$, $r = 1.001$, $\mu_c = 5 \times 10^{-5}$, and $\mu_v = 5 \times 10^{-3}$ unless stated otherwise. Without intercellular competition, the fraction of functional cells diminishes and all cells become senescent quickly, due to the mutational ratchet. The decline in proportion of functional cells is decelerated when some cells compete, as lower-fitness senescent cells are competitively suppressed, whereas cancer cells, with high individual fitness, proliferate. In these cases, the lifespan is extended but all cells become cancerous (see discussion in Fig. S1 of Supplemental Material [29]), as expected and reported previously [14].

We then ask what will happen to the health of the organism if cells switch between regular growth and intercellular competition. The fractions of cell types obtained under permanent intercellular competition when $p = 0.005$ (dotted lines, η_n' and $\eta_n' + \eta_s'$, in Fig. 2) serve as a benchmark for comparison against different switching schemes. Motivated in part by the prominence of periodic and quasiperiodic processes in organismal physiology, such as circadian and other biological clocks [30], we explored a periodic scheme for cell behavior switching:

$$p = \begin{cases} 0.005, & 0 \leq \mathrm{mod}\,(t, T) < \xi, \\ 0, & \xi \leq \mathrm{mod}\,(t, T) < T. \end{cases} \tag{5}$$

Here, intercellular competition occurs periodically during growth, that is, cells compete during $[0, \xi)$ but do not compete during $[\xi, T)$. Compared with the case of permanent competition, the fraction of functional cells is larger at later stages ($\eta_n > \eta_n'$) under this switching scheme ($\xi = 150$, $T = 400$), suggesting a delay of senescence [Fig. 2(a)]. A larger proportion of functional cells improves the viability of the organism. Furthermore, several stepwise enhancements of fitness η_n occur during the growth process

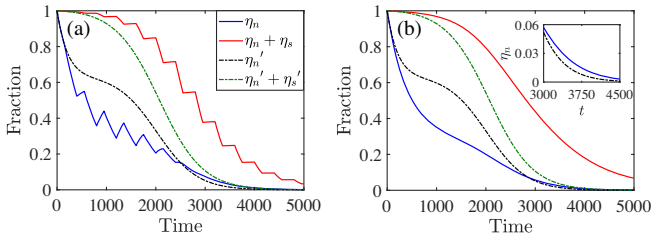

FIG. 2. Fraction of different types of cells under different switching schemes. Cell fractions under (a) the periodic switching scheme with $\xi = 150$ and $T = 400$ and (b) the stochastic switching scheme with $\theta = 200$ and $\zeta = 0.375$ are shown. The average fraction of time spent with competition is identical in both schemes. $\eta_n > \eta_n'$ in later times and $\eta_n + \eta_s > \eta_n' + \eta_s'$ throughout indicate an extension of the organism lifespan and delay of cancer onset, respectively. Results were averaged over 10^4 realizations.

[Fig. 2(a)], which does not occur for an organism that implements a pure strategy. Thus, a periodic switching strategy can enhance survival of functional cells, increasing fitness and delaying the apparent aging of the organism.

As an alternative to the periodic switching scheme, can the life of organisms also be prolonged when cells randomly "decide" whether to compete or not? The stochastic switching scheme is defined as

$$p = \begin{cases} 0.005, & \mathrm{mod}\ (t,\theta) = 0, \quad \mathrm{prob}\,\zeta, \\ 0, & \mathrm{mod}\ (t,\theta) = 0, \quad \mathrm{prob}\,(1-\zeta), \end{cases} \tag{6}$$

where cells decide whether to compete every θ time units, and the probability of choosing intercellular competition is ζ. As with periodic switching, $\eta_n > \eta_n'$ implies delayed onset of aging [segment enlarged in Fig. 2(b)]. Also notable, in both switching schemes, is that $\eta_n + \eta_s > \eta_n' + \eta_s'$ significantly at all times, implying a lower fraction of cancerous cells ($\eta_c < \eta_c'$). This observation suggests a reduction of cancer incidence, which is the principal drawback of the pure intercellular competition strategy. Notably, suppression of senescent cells, which is associated with the lifespan extension, is more pronounced under the periodic switching scheme, whereas the suppression of cancer cells is more pronounced under the stochastic switching scheme (Fig. 2).

The next major question is whether the switching period and probability affect the lifespan of the organism. To address this question, we explore the outcomes of the two switching strategies across a range of values of ξ and ζ. We define the lifespan κ of an organism as the time it takes for the fraction of functional cells to first reach $\gamma = 1\%$ (see Fig. S2 in Supplemental Material [29] for details), under the assumption that the loss of a sufficiently large fraction of functional cells renders the organism nonviable. A larger γ stipulates a larger required functional cell fraction for organism viability, resulting in decreases of lifespan regardless of the strategy the organism implements. The lifespan-extending effect conferred by switching schemes is naturally reduced at increasing γ (Fig. S2).

The lifespans $\bar{\kappa}$ and $\tilde{\kappa}$ of the organism with permanent intercellular competition and without competition serve as benchmarks that are independent of the ξ and ζ values (Fig. 3). We then explored periodic and stochastic switching schemes, with ξ and ζ, respectively, varied over the range $[0, T]$ and [0%,100%], for $T = 400$ and $\theta = 200$; the lifespans in the schemes are denoted κ_ξ and κ_ζ respectively. As shown in Fig. 3(a), $\kappa_\xi > \tilde{\kappa}$ throughout $\xi \in [0, T]$, clearly demonstrating a lifespan-extending effect. Furthermore, while $\kappa_\xi < \bar{\kappa}$ at small values of ξ, past a critical value of $\xi \approx 0.1T$, $\kappa_\xi > \bar{\kappa}$ takes over and persists for all larger ξ. This advantage diminishes as ξ approaches T, where $\kappa_\xi \approx \bar{\kappa}$. Thus, under periodic switching, the lifespan of the organism can be extended beyond what can be achieved by either pure strategies alone, and this effect is maximized when the times allocated to each of the strategies are comparable. This outcome is analogous to the weak form of PP. As expected, κ_ξ decreases and gets close to $\tilde{\kappa}$ and $\bar{\kappa}$ at extreme values of ξ because in those regimes, the organism implements almost a pure individual strategy.

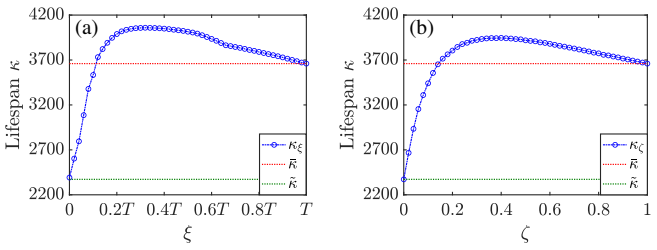

FIG. 3. Lifespan κ under different switching schemes. (a) Lifespan κ_ξ at varying ξ in the periodic switching scheme, and (b) lifespan κ_ζ at varying ζ in the stochastic switching scheme. Results were averaged over 5×10^3 realizations.

Under the stochastic switching scheme [Fig. 3(b)], the result is closely similar: the attained lifespan κ_ζ exceeds both $\bar{\kappa}$ or $\tilde{\kappa}$ for the majority of $\zeta \in [0\%, 100\%]$, and the lifespan-extending effect is most pronounced at intermediate ζ values. The effects of the switching period and probability at different T and θ (Fig. S3), and at different p (Fig. S4), are further examined in Supplemental Material [29]. We note the maximum increase of lifespan conferred by switching schemes compared to the individual strategies is ~50%. This magnitude of lifespan extension appears close to that attained in complex multicellular organisms, such as mice, through either dietary restriction or antiaging drugs and mutations, albeit smaller than that observed in simpler model organisms, such as yeast or worms [31].

We further explored the impact of lattice size $K \in \{10, 20, 50, 100\}$ under different switching schemes. The functional cell fractions η_n and η_n', and their difference $\Delta\eta_n = \eta_n - \eta_n'$, interpretable as the advantage conferred by switching, are presented in Fig. 4. We observe a larger

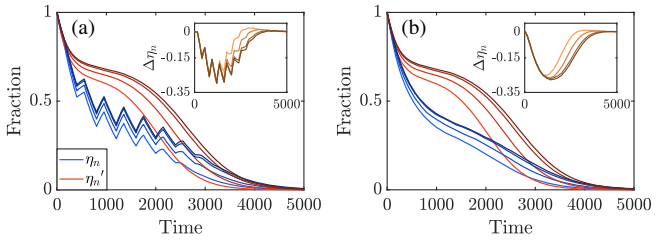

FIG. 4. Impact of K on the fraction of functional cells under different switching schemes. Functional cell fractions under (a) periodic switching scheme with $\xi = 150$ and $T = 400$ and (b) stochastic switching scheme with $\theta = 200$ and $\zeta = 0.375$. Darker line colors indicate larger values of K. Larger functional cell fractions η_n and η_n' are sustained with increasing K, but smaller K yield greater differences in max $\Delta\eta_n$ earlier, demonstrating stronger lifespan-extending effects in both switching schemes. Results were averaged over 10^3 realizations.

functional cell fraction (η_n, η_n') throughout T for larger values of K, regardless of the strategy the organisms implement, indicative of longer lifespans. At smaller K, the functional cell fraction η_n under switching surpasses that under permanent competition η_n' earlier than at larger K. This is most easily seen from $\Delta\eta_n$ in the inset of Fig. 4. Furthermore, $\max \Delta\eta_n > 0$ is greater at smaller K. Thus, the lifespan-extending effect of the switching schemes compared to the pure competition strategy appears most pronounced at smaller K. However, the principal result of our analysis, the extension of lifespan due to strategy switching, is robust to K. The effect of K on cancerous cell fraction is further examined in Fig. S5 in the Supplemental Material [29].

In this Letter, we demonstrate through a population model that switching between two cellular strategies can extend the lifespan of multicellular organisms. The lifespan of the organism is short without intercellular competition due to the accumulation of senescent cells, which has been specifically linked to the incidence of many age-related diseases in humans [32]. Competition between cells can slow down the decline of the fraction of functional cells, but at the cost of increased incidence and early onset of cancer. Alternating between the competitive and cooperative cellular strategies under two switching schemes (Fig. 2), such that the times allotted to each of the strategies are comparable (Fig. 3), extends the lifespan of the organism. This unexpected result is analogous to the weak form of PP [26].

Naive reasoning would suggest that in multicellular organisms, cells would be selected for cooperativity, whereas competition has deleterious effects and thus would be weeded out by selection. However, recent experimental and modeling results indicate that fitness and lifespan of a multicellular organism are more intricately defined by the fundamental trade-off between intercellular competition and cooperation [2,14]. Competition eliminates senescent cells and thus delays aging, but also promotes early onset of cancer. This frustration between competition and cooperativity [1] implies that, during the evolution of multicellular organisms, the balance between these cellular strategies could be optimized. The key result of this work is that the fitness of an organism can be increased by dynamically alternating competitive and cooperative strategies of individual cells, rather than by simply fine-tuning competitiveness or cooperativeness. Experimental signatures of such alternating behavior, for example, could manifest as oscillations in nutrient uptake or metabolic activity. If the ability of cells to alternate between the competitive and cooperative strategies could be manipulated, a degree of control over aging processes may be possible. For example, the antiaging effect of intermittent fasting that apparently exceeds that of simple calorie restriction [33] might stem from induced changes in cellular strategies. Investigation of the molecular mechanisms of this effect may yield evidence pertinent to the analysis made in this work. The conclusion of this Letter does not defy the inevitability of aging [14], but suggests that lifespan limits could be more flexible than currently appreciated.

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