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Programed Death is Favored by Natural Selection in Spatial Systems

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Standard evolutionary theories of aging and mortality, implicitly based on mean-field assumptions, hold that programed mortality is untenable, as it opposes direct individual benefit. We show that in spatial models with local reproduction, programed deaths instead robustly result in long-term benefit to a lineage, by reducing local environmental resource depletion via spatiotemporal patterns causing feedback over many generations. Results are robust to model variations, implying that direct selection for shorter life span may be quite widespread in nature.

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Life spans of different organisms in nature can vary over orders of magnitude, even among closely related species [1–4]. Why should otherwise self-repairing organisms eventually die without external causes, and what sets a species' characteristic life span? Standard evolutionary theory explains intrinsic mortality in the context of senescence as the result of two main effects, attendant on the decreasing strength of selection with increasing age: (1) mutations with late-appearing detrimental effects are not strongly selected against (*mutation accumulation* [5]); (2) genes that increase early-life reproductive success but contribute to later-life failures can be selected for (*antagonistic pleiotropy* [6] and its *disposable soma* formulation [7]). These effects are typically held to account for all senescent phenomena, and it is widely accepted in evolutionary theory and mainstream medicine that aging is a nonadaptive byproduct of the diminishing strength of age-specific selection, and not an adaptation for the explicit control of life span for its own sake [8,9]—indeed that life-span limitations cannot be directly adaptive. However, phenomena such as plasticity of life spans in response to genetic modification [10–13] and selective breeding [14,15], apparent programed death [16], and anomalous patterns of longevity [17] and senescence [3,18], which are difficult to reconcile with accepted frameworks [7], suggest that the classic theories may be incomplete.

We demonstrate here a mechanism for adaptive limitation of life span, using a spatial evolutionary model. The key to identifying this mechanism is the proper treatment of spatial symmetry breaking, a condition which violates mean-field assumptions commonly used in mathematical evolutionary biology. We find that spatial heterogeneity of limiting resources and self-organizing population structures result in robust selection for life-span limitation. In our model, intrinsic mortality leaves resources for descendants, which are more likely to be found in the same local region, increasing long-term strain success. The mechanism is fundamentally different from those underlying standard evolutionary theories. In contrast to the classic mechanisms, which are based on selection directly on the reproductive success of individual organisms, our mechanism predicts the evolution of traits that may become advantageous only for descendants after many generations. There is no compensating reproductive benefit to the individual of the shortened life span, as there would have to be in a mean-field model.

Simulations allow the identification of effects of symmetry breaking in spatial evolutionary dynamics including the short-term advantages but long-term disadvantages of overly exploitative variants [19,20]. "Selfish" variants that outcompete their neighbors, at the expense of depleting their local environment, have an advantage on short spatial and temporal scales. However, on longer scales, their descendants are left in impoverished environments and can be outcompeted by others in richer areas. This mechanism cannot occur in analytic models that rely on mean-field approximation and that examine the evolution of mutations affecting life span in homogenous populations. This clarifies why traditional theory discounts direct selection for shorter life span, while we find it dominates a wide range of spatial model conditions.

We consider an explicit spatial model of an interacting pair of organism types, in which one population relies on the second for survival, to the latter's detriment. Such spatial consumer-resource (e.g., predator-prey, pathogen-host, herbivore-plant) models have previously shed light on the evolutionary origins of phenomena such as reproductive restraint [20], sexual reproduction [21], limitations to pathogen virulence [20,22], and social altruism [19]; here we apply them to the evolution of life-span limits and intrinsic mortality.

The model uses a 2D stochastic cellular automaton to consider a population of abstract organisms ("consumers")

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with limited but self-renewing resources (e.g., prey or hosts). Sites represent empty space (E), available resources (R), or a consumer together with resources (C; a consumer cannot occupy a site in the absence of resources). Resources alone can reproduce into neighboring empty sites, with probability g per time step per such site; similarly, consumers can reproduce into neighboring resource-only sites, with probability p per time step per site. Additionally, consumers can exhaust resources in their site, leaving an empty site, with probability v per time step and c per reproduction; or they can die due to intrinsic mortality, leaving a resource-only site, with probability q per time step. A consumer's mean intrinsic life span is $L = 1/q$. Subscripts on p and q (i.e., p_i, q_i) may be used to indicate that p and q vary by consumer. If more than one consumer "tries" to reproduce into a given resource-only site in the same time step, one is chosen as the parent, with equal probability for each. Thus, at each time step, an empty site has probability

$$P_{E\to R} = 1 - (1-g)^{\mathcal{N}_R}$$

of transitioning to a resource-only site, where $\mathcal{N}_R$ is the number of resource-only sites in the empty site's four-cell neighborhood; a resource-only site has probability

$$P_{R\to C} = 1 - \prod_i^{\mathcal{N}_C}(1-p_i)$$

of transitioning to a consumer site, where $\mathcal{N}_C$ is the number of consumers among its four neighbors and the values p_i are the corresponding consumer reproduction probabilities; and a consumer site has probability $P_{C\to E} = v + kc$ of transitioning to an empty site, where k is the number of offspring the consumer produces in this time step, and probability $P_{C\to R} = q_i$ of transitioning to a resource-only site. Boundary conditions are periodic. Lattice updates are synchronous.

Consider a competition between two strains $C_1 \to \{p_1, q_1\}$ and $C_2 \to \{p_2, q_2\}$ in a mean-field analysis [23]. The fraction of sites in each of the four possible states $\{C_1, C_2, R, E\}$ at each time step can be expressed as a recurrence relation:

$$\begin{aligned}
n_{C1}(t+1) &= n_{C1}(t)[1 + n_R(t)\gamma p_1 - (v+q_1)/(1-c)],\\
n_{C2}(t+1) &= n_{C2}(t)[1 + n_R(t)\gamma p_2 - (v+q_2)/(1-c)],\\
n_R(t+1) &= n_R(t)[1 + n_E(t)\gamma g - \gamma(n_{C1}(t)p_1\\
&\quad + n_{C2}(t)p_2)] + n_{C1}(t)q_1 + n_{C2}(t)q_2,\\
n_E(t+1) &= n_E(t)[1 - n_R(t)\gamma g] + n_{C1}(t)(v+q_1c)/(1-c)\\
&\quad + n_{C2}(t)(v+q_2c)/(1-c),
\end{aligned}$$

where $\gamma = 4$ is the number of neighbors. These expressions are precise in the limit of low gn_R and pn_C; more exact expressions lead to nonlinear dependencies on g and p, but increasing p always increases the probability of reproduction in a given time step, and the conclusions are unaffected [23]. By inspection these equations state that higher reproduction probability p and lower intrinsic mortality probability q are always favored. If

$$\frac{v+q_1}{p_1} < \frac{v+q_2}{p_2},$$

then C_1 drives C_2 to extinction [23]. Lower q values will take over the entire consumer population [Figs. 1(a)–1(c), dashed lines]. This is the prediction of traditional theories of life span as well as simple intuition: a longer life means more opportunity to reproduce.

Critically, this mean-field prediction does not correctly describe the behavior of the spatial model, as revealed by numerical simulations. We performed three types of simulations, "competition," "ascendance," and "invasion," to investigate the evolution of life-span control. All tests show that, counter to the mean-field analysis, the evolutionarily optimal value of q in the simulated spatial model is nonzero.

"Competition" directly tests the dynamics of two competing strains. We introduce one consumer of the first type into a population of the second, and track the number of each over time. Longer-lived (smaller q) strains can have a temporary advantage that may last for hundreds of generations, but eventually be out-competed by shorter-lived types [Figs. 1(a)–1(c), solid lines]. The mean-field approximation fails because local resource availability quickly becomes characteristic of the local strain rather than of the population as a whole; longer-lived types have resource-impoverished environments [Figs. 1(d) and 1(e)].

"Ascendance" studies (Fig. 2) explore the evolution of life span in a consumer population undergoing mutation. We make the intrinsic death probability per time step q as well as the reproduction probability p heritable and independently subject to mutation. With probability μ_q (μ_p), a consumer offspring has a value of q (p) differing from that of the parent by $\pm\epsilon_q$ ($\pm\epsilon_p$); mutants with q (p) outside the range $[0, 1-v]$ ($[0,1]$) are set to the corresponding boundary value. Numerical simulations [Fig. 2(a)] show that after initialization [30], a transient is followed by a dynamic state with consistent mean values of q and p, with only small fluctuations in these average measures [Fig. (2b)], that persists as long as simulations are run in large enough lattices. Reported results use square lattices, with edge size equal to the smallest multiple of 250 for which a steady-state population with given g and v persists in all trials [23]; larger sizes do not affect the quantitative results. Results reported here use $\mu_q = \mu_p = 0.1275, c = 0$, and g and v as specified. To ensure that the bounds on q and p do not cause artifacts in their evolved steady-state values due to finite-size mutations, mutation sizes ϵ_q and ϵ_p were progressively reduced: after 10^5 time steps at $\epsilon_q = \epsilon_p = 0.005$ to achieve initial steady state, they were halved every 10^4 steps for an

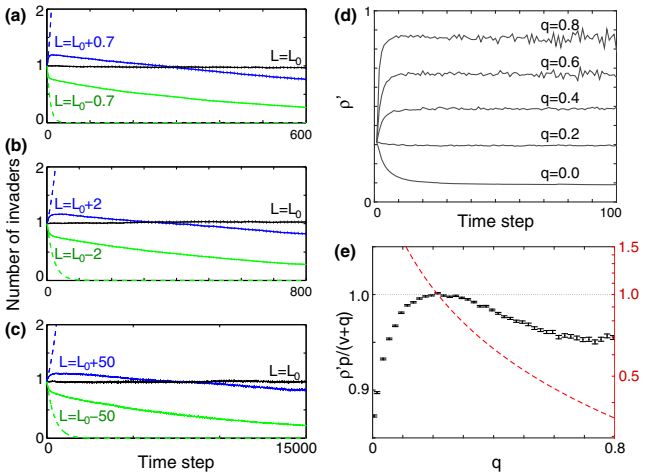

FIG. 1 (color online). Longer life span can give short-term advantage and long-term disadvantage in spatial models, in contrast to predictions based on mean-field approximation. (a)–(c) Plots show, for invaders with life span L introduced into a steady-state population with equilibrium life span $L = L_0$, reproductive success (average number of consumers of the introduced type present) as a function of time. (Dashed) Mean-field calculations give the incorrect prediction that longer life span is always favored. (Solid) Numerical results from the spatial model show that longer life span can be favored for periods of hundreds or thousands of time steps but outcompeted in the long term. The time scale of the simulated spatial dynamics is also much longer than the mean-field result [29]. Parameter values are (a) $g = 0.13, v = 0.2, L_0 = 2.7$, (b) $g = 0.17, v = 0.1, L_0 = 7.6$, (c) $g = 0.2, v = 0.005$, $L_0 = 170$, with resource growth g, consumption v, and reproduction cost $c = 0$. Error bars show the standard error of the mean among ten independent runs, each recording the mean for a set of 40 000 invasions. (d),(e) Longer-lived consumers deplete their local environment compared to shorter-lived ones. (d) Effective contact rate $\rho' = \sum_{j \in nn \text{ in state } R}[1/\mathcal{N}_C(j)]$, averaged over all invaders, as a function of time since introduction. A consumer's ρ' is the number of neighboring resource sites, corrected for the number of their neighbors that might consume them [23]. The local environment changes from a value characteristic of the invaded population to a value characteristic of the invader within a few dozen time steps. (Data for high q are more variable since the invaders are quickly outcompeted and so fewer samples are available.) (e) Expected lifetime reproduction $\rho' p/(v+q)$. (Solid) Numerical results, based on the simulated ρ' [(d), averaged over time steps 51–100] where the invader has transformed its local environment, show a disadvantage for invaders with life span longer or shorter than the equilibrium value of 0.215. Error bars show standard error of the mean. (Dashed) Mean-field calculations for invasion of an infinite population, with no local effect on environment, incorrectly predict an advantage for invaders with longer life span. Parameter values are $g = v = 0.1, c = 0, p = 0.9991$.

additional 10^5 steps, followed by 5×10^4 steps with ϵ_q and ϵ_p fixed [23]. The results showed that a self-limited life span was consistently favored, for all parameter values tested [Fig. 2(d)].

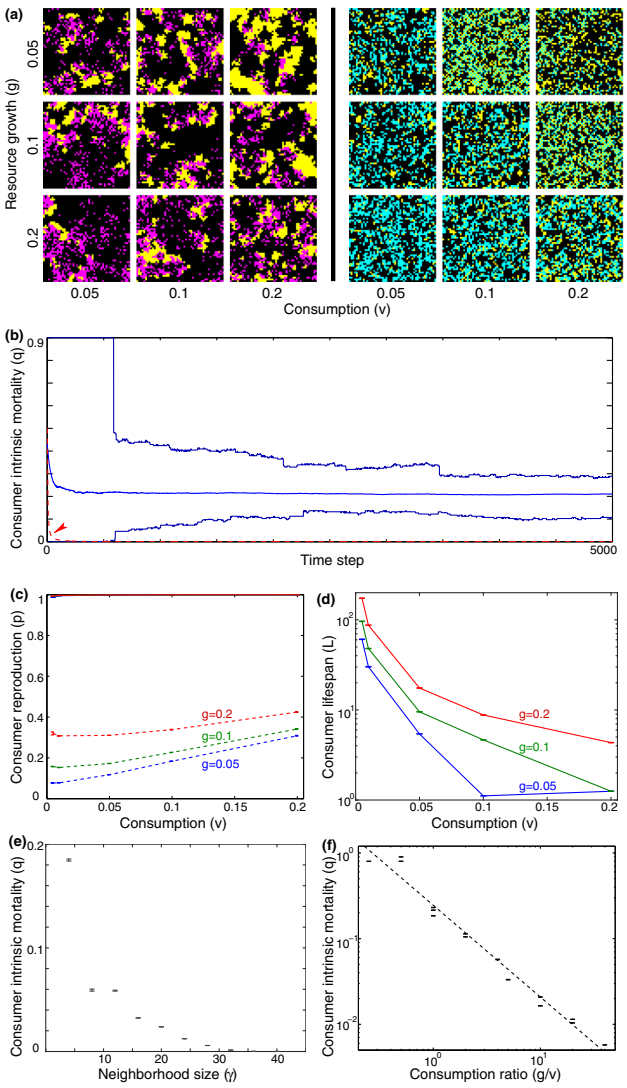

FIG. 2 (color online). Ascendance studies favor intrinsic mortality in numerical simulations with a spatial model. (a) Snapshots showing different spatial distributions of resources (yellow) and immortal (left, magenta) or mortal (right, cyan) consumers (50×50 subsets of 250×250 lattices). (b) History of evolving consumer intrinsic mortality q in one example trial ($g = v = 0.1, c = 0, \mu_p = \mu_q = 0.01$). Mean-field analysis (red, dashed; arrow) predicts mean q quickly goes to 0. Numerical simulations (blue, solid; population mean-maximum-minimum) show long-term stability of finite q and elimination of low-q strains from the population. (c),(d) Steady-state average values of (c) consumer reproduction probability p and (d) intrinsic life span $L = 1/q$, for different values of parameters g and v and for (c), (d) mortal (solid) and (c) immortal (dashed) populations. (e) Steady-state evolved q in mortal populations ($g = v = 0.05, c = 0$) for increasing neighborhood size γ. For high enough γ, consumers with $q = 0$ are not eliminated from the population. (f) Steady-state evolved q for the mortal populations of (d) approximately falls on a single curve [line is a power-law fit: $q = 0.245(g/v)^{-1.07}$] when plotted as a function of "consumption ratio" g/v, for all g and v tested. All error bars show the standard error of the mean from ten independent trials.

"Invasion" studies (Fig. 3; animation in the Supplemental Material [23]) explore the question of evolutionary origin and stability of the trait of intrinsic mortality: If a rare mutation could confer or remove the capacity for life-span control, would that mutant have an advantage or a disadvantage in its later spread through the population? These studies take a steady-state lattice configuration, randomly choose one consumer to convert to the invading type, and follow its lineage until fixation (extinction of either invaders or invaded), tracking the probability of successful invasion in 10^5 such trials (5×10^5 trials in cases where no successful invasions were observed). "Mortals" ($q = 0$ for the initial invader, but potentially nonzero for descendants through mutation) invading populations of "immortals" (q fixed at 0) had a success rate typically 2 to 3 orders of magnitude greater than that of immortals, while immortals managed no successful invasions of mortal populations in a total of several million trials [23,31].

Changing the values of the constant parameters g and v changes the population sizes and distributions of consumers and resources [Fig. 2(a)], evolved life span [Fig. 2(d)], and probability of invasion success (Table S1), but the key result—that life span self-limitation is favored—is consistently found, for both ascendance and invasion studies.

Because this result contrasts with the predictions of traditional theories, it is important to identify which model details are those relevant to limited life span being favored. We therefore explored a large number of variants [23,31] related to different real-world considerations in order to evaluate how that key result depends on model assumptions. In addition to robustness to changes in the values of parameters $(g, v, c, \mu_{\{p,q\}}, \epsilon_{\{p,q\}})$ in the base model as

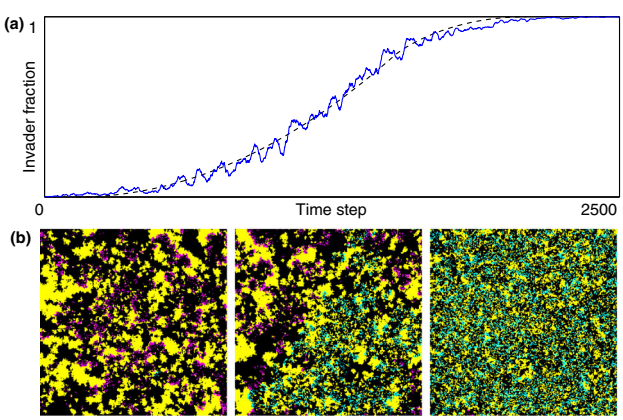

FIG. 3 (color online). A successful invasion of immortal consumers by mortal ones. (a) The fraction of invaders in the population (solid line) increases almost monotonically with time. The region dominated by mortals grows steadily: the dashed line shows the area of a circle (under periodic boundary conditions) whose radius increases at a constant rate (correlation $r = 0.997$). Resource growth $g = 0.05$, consumer consumption $v = 0.2$, consumer reproduction cost $c = 0$. (b) Snapshots at 50, 1350, and 2550 time steps [colors as in Fig. 2(a)].

described above, changes to the model that continue to result in life-span control include the following: (1) explicit deterministic life span (i.e., programed mortality or rapid senescence) or (2) increasing mortality with age (i.e., gradual senescence), rather than constant probability of death with time; (3) various forms of local consumer rearrangement and migration; (4) longer-range (but still limited) dispersal of consumers or resources during reproduction; (5) gradual, deterministic depletion of continuous-valued resources, rather than binary-valued resources stochastically depleted; (6) ability of consumers to adjust their "rate of living," lowering consumption, reproduction, and intrinsic mortality in response to low-resource conditions; (7) spontaneous resource generation, not requiring nearby resources to seed growth; (8) consumer offspring supplanting existing neighbors, so that the occupation of a site does not preclude reproduction there; (9) limited reproduction of exploited resources; and (10) sexual reproduction by consumers. The robustness of the finding that self-limited life span is favored across model variations provides evidence for its applicability to a variety of biological systems.

Intrinsic mortality is not favored for long-range spatial mixing or if resources are unlimited. Figure 2(e) shows that increasing consumer dispersal range for a fixed-size lattice results in increasing life spans. Figure 2(f) shows the evolved life span diverges with the "consumption ratio" g/v, a measure of the rate of resource replenishment. Note that in typical real-world systems, mixing and resources are both limited.

These results provide theoretical support for the idea that direct life-span control, and programed mortality and senescence as ways of achieving it, are consistent with natural selection. In contrast, it is widely reported that theory is incompatible with the evolution of explicit life-span control [7–9,23]. This perspective has guided and constrained the interpretation of empirical findings. Our results suggest that classic mechanisms relevant to the evolution of life span are incomplete. Direct selection for intrinsic mortality and senescence—not just selection for an individual benefit with senescence as a deleterious side effect—can be used to help understand empirical phenomena [31], particularly for cases that have posed problems for traditional theory [7] but are straightforward to explain with direct selection.

The idea that shorter life spans can be and are selected for directly goes back to at least 1870 [1]. It was later rejected based on theoretical arguments that the evolution of such a trait opposed to individual self-interest, like other altruistic behaviors, must require group selection, whose applicability should be accepted only as a last resort [6]. The theories developed consistently describe spatially averaged systems in mean-field analyses [23,31] and well-mixed experimental populations [32]. However, the real world possesses spatial extent, and spatial systems routinely demonstrate altruistic behaviors [19,20,33,34] which are not evolutionarily stable in mean-field models

[23,31] or well-mixed laboratory populations [34]. Previous models, some spatial, have demonstrated that selection for self-limited life span is not a theoretical impossibility, under assumptions such as the continual introduction of highly advantageous mutations [35], pre-existing senescence in the form of decreasing fecundity [36] or decreasing competitive fitness [37] with increasing age, or explicit group selection among nearly isolated subpopulations [38]. However, a generally applicable mechanism for the active selection of life-span control has not been previously demonstrated.

The robustness of our result that self-limited life span is favored, under many variations of model details and parameter values, suggests that genetically programed senescence may indeed be a quite general phenomenon, with strong implications for human medicine. If aging is programed, rather than a collection of secondary breakdowns or genetic tradeoffs, then effective health and life extensions through dietary, pharmacological, or genetic interventions [39,40] are likely to be possible, with the potential for significant impact (e.g., altering two genes extends nematode life span fivefold [11]). That the fundamental understanding of evolution can play a critical role in guiding health research should motivate a wider reevaluation of the evidence in relation to the theoretical frameworks.

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