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Research Article

THEORY

The Evolving Opportunistic Pathogen Communities on Host Individuals and the Evolution of Host Aging

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Abstract In the coevolution of host and the associated opportunistically pathogenic microbiota, the microbiota has an advantage of a smaller generation time and thereby faster evolution. Sexual reproduction by the host is hypothesized to be the hosts' evolutionary counter-strategy. We propose further that the ticking clock of the evolving microbiota influences the evolution of host aging. Modeling these dynamics shows that if transmission of microbes has a small to moderate vertical or kin-biased component, early aging can evolve in the host. Host genotypes with shorter longevity are more likely to escape pathogen evolution thereby getting a selective advantage for their progeny when risk of infection is high. As parasite communities are ecologically and evolutionarily dynamic, hosts can in response evolve plasticity in aging. The model shows that a genotype which activates aging or death pathways in response to threshold parasite colonization gets a selective advantage whenever there is a nonzero kin transmission bias. The hypothesis is compatible with classical hypotheses for aging. We make many predictions testable by epidemiological, comparative or experimental methods.

Keywords parasites transmission; evolution of lifespan; kin selection; lifespan; life history

1. Introduction

Whether aging is inevitable or is a trait specifically evolved under some kind of selection is an old debate. One school of thought assumes aging to be inevitable and beyond the reach of natural selection [1]. Many of the processes implicated in aging such as accumulation of somatic mutations, protein aggregation, oxidative damages or telomere shortening might be biochemically and thermodynamically inevitable [2]. However, since mechanisms of repair, replacement, throwing away or asymmetric segregation of damage exist, inevitability of mechanisms does not necessarily mean inevitability of the process. Germ line cells in higher organisms appear to perpetuate without any signs of aging [3,4,5,6,7]. Since every new generation begins with a single celled zygote, mutations in germ line cells are directly subject to natural selection, which prevents accumulation of deleterious mutations; therefore germ line cells do not seem to age. Organisms such as hydra and many plants that reproduce vegetatively do not show any obvious aging [4,5,8,9,10,11]. In some species, viability or reproductive capacity actually increases monotonically with age [11,12]. If decline in viability is not universal with aging, it is worth asking why and how it declines in some organisms including humans.

For a long time, bacteria that divide by binary fission were believed to be immune to aging. The demonstration of signs of aging in bacteria even during exponential growth [13] changed the perspective. However, asymmetric damage segregation, which is responsible for bacterial aging, has been shown to be both plastic and evolvable [14]. Bacterial aging provides many other grounds to doubt the inevitability of aging. Although some cells in a growing clone of bacteria undergo senescence, the clone as a whole grows with continued rejuvenation. A process that works for clones of bacteria should be possible, in principle, for multicellular organisms which are essentially clones of the zygote.

Is aging inevitable after a germ-soma division of cell lines? Even if one assumes that aging is inevitable for a somatic cell, it does not necessarily imply that it is inevitable for an organism. A multicellular organism may program the cell turnover so as to replace the old cells in a balanced manner and thus escape organismal senescence indefinitely if resource provisioning is adequate. On the other hand, senescence of a system is theoretically possible even if its components are individually nonaging but irreplaceable [15]. Therefore, cellular senescence is neither necessary nor sufficient to explain organismal senescence.

Since inevitability of aging is theoretically inadequate and empirically not universal, it can be said to have evolved to take different shapes in different species. The central logic of theories of evolution of aging is that the force of natural selection decreases with age of an individual [16,17,

18,19,20,21,22]. As a cumulative effect of age-independent death [23], progressively fewer organisms will survive until later ages. When the probability of surviving until a later age is progressively small, early reproduction will be selected and genes detrimental at a later age will experience weak negative selection [23,24,25]. In short, natural selection trades late survival for enhanced early fecundity [26].

The theory of antagonistic pleiotropy (AP), a term introduced in the early 1980s [27], can be applied to any genes or mechanisms that give a growth- or reproduction-related advantage early in life but have some detrimental effects later in life. Such genes would get selected due to stronger selection on early effects and weaker selection on late effects [18,25,26,28,29,30,31,32]. The concept of germ-soma trade-off implies that organisms with germ-soma division must invest differentially to reproduce and to maintain the soma [33,34,35,36]. Inadequate investment in the latter will lead to cumulative deterioration and aging [37,38,39,40]. There exists an optimal compromise between somatic maintenance and reproduction [41,42] that is demonstrable [43,44,45]. A debated idea in evolution of aging is programmed aging, which refers to the possible advantages of the aging process itself. The proposed advantages of aging are at supra-organismal level and involve kin selection, group selection [46,47,48] or greater evolvability for the population [47,49,50]. An inherent weakness of the programmed aging arguments is that the advantages of aging are indirect, slow, and weak whereas the loss due to aging for an individual is more direct and rapid [51].

Although AP and germ-soma trade-off are the most accepted theories for the evolution of aging, evolution of aging is likely to be more complex than what individual hypotheses attempt to capture. None of the classical models adequately explain the variation in age-related changes across the biome [12]. A good example is finite replacement of teeth in mammals. In the ancestral taxon of reptiles, such as lizards and snakes, teeth can be replaced indefinitely but mammals evolved finite replacement. Humans have only two sets of teeth. Elephants have six sets of molars that successively replace the former set [52]. Wearing out of the sixth set disables normal food intake in elephants and becomes a major contributor to senescence since they have fewer extrinsic causes of mortality. Fossil remains of human ancestors provide evidence for old age after wearing or losing teeth. The limited teeth replacement is hard wired and its evolution needs serious consideration. Such examples suggest that there is a need for theories of evolution of aging to evolve further. We suggest a previously unconsidered selective force in the evolution of aging, make a generalized model for selection, and examine conditions under which aging can evolve by this selective force. We discuss how this selection interacts with the classical hypotheses. We also suggest testable predictions of the new hypothesis.

1.1. Evolving microbiota and aging: a new possibility

The hypothesis stems from Hamilton's theory of the evolutionary advantages of sex [53]. Sexual reproduction is difficult to explain by natural selection since it has a considerable cost as compared to asexual reproduction. One of the promising hypotheses proposed by W. D. Hamilton for the evolution of sexual reproduction was that sex evolved under the pressure of a coevolutionary arms race between hosts and parasites [53]. Parasites here is an inclusive term covering subcellular, unicellular, and multicellular organisms parasitic in hosts with or without causing overt disease. Of particular interest here are those that can become pathogens opportunistically. The invasive mechanisms of the parasite and the resistance mechanisms of the host are always in a coevolutionary arms race. Host parasite coevolution takes complex paths with different possible outcomes [54]. However, this arms race is highly asymmetric. For complex multicellular hosts there lies an order of magnitude difference between the generation times of hosts and their parasites. Since the microbial parasites are fast growers, they undergo several generations of evolution in the lifetime of a single host. As a result, parasites always evolve faster than their hosts. Even if the host does not have any mechanisms of aging, the parasite evolutionary clock is ticking all the time during an individual's lifetime. Therefore, in an evolutionary arms race parasites would seem to have an upper hand all the time. How does the host genome cope up with the evolving virulent pathogens on an evolutionary scale?

Sexual reproduction offers a possible solution. Due to sexual reproduction, the host keeps on making different gene combinations in every generation which are difficult to track for the pathogen [55]. As some of the microorganisms evolve to overpower the specific resistance gene combination of one individual, the individual makes new combinations in the offspring. As a result, no single pathogen genotype can evolve to overpower the defence mechanisms of the host population or any host lineage. A possible corollary of the hypothesis is that as new combinations are being made, the old ones need to be demolished. The advantages of making new combinations are quite clear but we need to examine carefully whether there is any advantage in actively demolishing the old ones. We examine these possibilities with the help of a mathematical model here.

Microorganisms are speculated to have a role in host aging and their possible role is modeled by Otto and Michalakis [55]. However, their model starts with an assumption that the host has a pre-existing age structure with juvenile, reproductive, and senescent phases. They show that microorganisms that enhance death in the senescent phase offer a selective advantage to the host population. Our models do not assume any pre-existing age structure and we ask the question whether microbiota can lead to evolution of aging in the host.

Parasite life cycles are highly variable and the types of parasites relevant to this model are the ones that colonize some part of the host body chronically; they can exist as commensals but turn into opportunistic pathogens. This subgroup of parasites includes the opportunistic pathogens among the normal body flora but excludes ones with compulsory external life cycle such as helminths or obligates pathogens that have only a short-term association with the host body.

2. Method

2.1. The model description

Two host genotypes compete in a habitat where they share the resources as well as sources of parasite transmission. One genotype has a limited lifespan or age-dependent death and the other has only age-independent death. For simplicity, in the baseline model we do not assume crossbreeding between the two populations although both are assumed to be sexually reproducing and thereby combinatorially changing the parasite resistance gene composition of the genome. As we will see later, the assumption of non-crossbreeding is not crucial for the model but makes the model substantially simpler. Both populations are modeled in a Leslie matrix model. For the nonaging genotype, the rates of reproduction and mortality are kept constant across all age classes. This effectively means that there is no inherent aging. In the aging genotype, the reproduction rate and mortality follow a trend with age. The nature of this trend is variable and we ask the question whether any specific trend offers higher lifetime fitness advantage. For a given set of rate constants, the total population (including both host genotypes) and proportionately the ratio of the two genotypes and age classes are normalized at the end of every cycle as specified below.

In addition to the baseline mortality in the Leslie matrix model, the model incorporates parasite-induced mortality. For each of the host genotypes, the mean parasite populations for every class are modeled by considering growth and colonization of the parasite within individual hosts, a constant rate of death or removal of the parasites, and a rate of transmission. The rate of transmission and successful colonization of the host body is dependent on the sensitivity or resistance of individual hosts which has a heritable component.

Since the parasites evolve, we assume that their mean rate of colonizing the body increases with the age of the host. Evolution of the parasites in each individual host body is assumed to be independent and the main effect is increased probability of invading the host. Therefore, parasite evolution is captured by the model by increasing parasite colonization rates with age. Since this age-related difference is due to the parasite evolution, it is assumed to be independent of any intrinsic mechanisms of aging in the host. Therefore, it applies equally to the aging and nonaging host genotypes. We use linear, saturating sigmoid or exponential functions for this rise and examine whether the results are sensitive to any specific form of the curve. We normalize the parasite populations along with host populations at the end of every cycle in order to avoid large oscillations, chaos or extinctions which can commonly arise in host parasite dynamics [56]. Our main intention is to examine the effects of endemic and opportunistic parasites and for simplicity we avoid getting into the mechanisms that stabilize or destabilize host parasite dynamics. We assume that the parasites under consideration have a long-term endemic relationship with the host. This can be best achieved by normalizing the total parasite population along with normalizing the total host population at every cycle.

An important feature of parasite transmission in the model is that it considers differential probabilities of getting the infection from kin and getting it from the general parasite pool. Depending upon the reproductive biology, parental care, social structure, and dispersal patterns, there can be a kin bias in parasite transmission. Several factors can contribute to the kin bias. For example, there can be vertical transmission from mother to offspring through egg, placenta or milk [57]. Transmission probability is high during parental care, grand-parenting or nest helping if any. If the offspring have a small dispersal radius, spatial viscosity can cause a kin bias in transmission. The kin bias can be highly variable for species. We model it by assuming a kin bias k which ranges from 0 to 1 in different eco-behavioral settings. When k is zero all transmission is random from the total pool of organisms. When k is unity all transmission is only through kin and at intermediate values of k it is specifically from kin with a probability k and from the general parasite pool (to which kin also contribute) with a probability (1-k). We assume that the number of kin that can transmit infection to any individual is determined by the social and spatial structure and therefore it is independent of the total population or the frequency of the genotype and that is why it is constant. Therefore, the kin-biased component of infection transmission is a function of the mean parasite load per individual of the same genotype as the focal individual. The nonkin-biased transmission on the other hand is a function of the total parasite pool summed over the entire host population.

2.2. The formal model

The aging population in new born age class 1, H_1, is given by

$$H_{1(t+1)} = \sum H_{n(t)} \cdot R_n, \tag{1}$$

where R_n is the reproductive potential of the nth age class.

Populations in other classes are given by

$$H_{n(t+1)} = H_{(n-1)(t)} \cdot \left(S_{(n-1)} \cdot \left(1 - \frac{P_{(n-1)(t)}}{K + P_{(n-1)(t)}} \right) \right), \tag{2}$$

where S_n is the age specific survival rate independent of the pathogen. The formula $(P_{(n-1)}/K + P_{(n-1)})$ denotes the parasite-induced death rate which is assumed to follow a saturation curve with a half saturation constant K. Similar set of equations apply to the nonaging population H' but in that population the S'_n and R'_n will be constant for all ages:

$$H'_{1(t+1)} = \sum H'_{n(t)} \cdot R'_n, \tag{3}$$

$$H'_{n(t+1)} = H'_{(n-1)(t)} \cdot \left(S'_{(n-1)} \cdot \left(1 - \frac{P'_{(n-1)(t)}}{K + P'_{(n-1)(t)}} \right) \right). \tag{4}$$

In a Leslie matrix, if reproductive rates and survival rates are constant, the population reaches a stable age class distribution.

The age specific average parasite population P_n can be written as

$$\begin{aligned} P_{n(t+1)} = {} & C_{(n-1)} \cdot P_{(n-1)(t)} \\ & + \left(k \cdot I_1 \cdot P_{\text{kin}(t)} + (1-k) \cdot I_2 P_{\text{avg}(t)} \right) \end{aligned} \tag{5}$$

for the aging population and

$$\begin{aligned} P'_{n(t+1)} = {} & C_{(n-1)} \cdot P'_{(n-1)(t)} \\ & + \left(k \cdot I_1 \cdot P'_{\text{kin}(t)} + (1-k) \cdot I_2 P'_{\text{avg}(t)} \right) \end{aligned} \tag{6}$$

for the nonaging population, where C_n is the age specific rate of colonization by the parasite, k is the kin selection bias, P_{kin} is the average parasite load among the kin, that is the same genotype, and P_{avg} is the pooled weighted average parasite load of the entire population. I_1 and I_2 are infection rate constants for kin specific and generalized transmission, respectively. For $n = 1$ only the second term of the equation is applicable. Since the rate of parasite colonization C_n depended upon parasite evolution, it was assumed to increase with age similarly for both aging and nonaging host. We employed linear, saturating, exponential, and sigmoid increase in C_n with age.

2.3. Normalization

At the end of every cycle, the populations in each age class of both aging and nonaging genotypes are normalized proportionately to keep the total combined population of both genotypes constant. This was done by multiplying each calculated age class population by the ratio of the total population of both genotypes summed over all age classes to the target total normalized population H_T:

$$H_{n(t)} = H_n \left(\sum_{n=1}^{A} (H_n + H'_n) \right) / H_T. \tag{7}$$

This is the process during which the model incorporates competition between the two genotypes. The two genotypes interact with each other by two processes. Firstly they share the common (nonkin) parasite pool and secondly they compete for the environmental carrying capacity which acts during normalization of the combined populations.

The parasite populations were normalized similarly to keep the total parasite population constant. Normalizing host population alone was generally sufficient to avoid oscillations, chaos, and extinctions, but a specific advantage of separately normalizing the parasite population was that the steady state parasite population was in user control allowing us to study the effects of parasite density on evolution of host aging. In sensitivity analysis, we run the simulations without the normalizing steps to examine whether normalization brings in any artifacts.

2.4. Parameter space explored

Since the host and parasite populations are in arbitrary units, we fixed the total combined carrying capacity of the environment to 1,000 units. The results depend upon the relative growth rates of the two genotypes and therefore are independent of the carrying capacity used for host population normalization. The parameters that could potentially affect the results were explored in a range spanning at least three orders of magnitude as follows. The total parasite population used for normalization was varied between 1,000 to 1,000,000 units, that is 1 to 1,000 units per individual on an average. K for parasite-induced death varied in the same range as average parasites per individual but independent of it. C_n varied from 0.001 to 2 and increased with age linearly or nonlinearly. The kin transmission bias k ranged between 0 and 1 by definition.

We used only the normalized models to explore the entire parameter space specified above. In the absence of normalization, either the pathogen or the host frequently becomes extinct or the system becomes chaotic in considerable range of parameters making it difficult to get useful inferences throughout the parameter range.

3. Results

3.1. Conditions for evolution of aging

The model allows us to simulate competition between genotypes with and without intrinsic aging or between genotypes with shorter and longer intrinsic lifespans. With the parasite population or parasite-induced mortality set to zero, the aging genotype or the shorter generation genotype was at a fitness disadvantage and was driven to extinction demonstrating that aging exerted a significant negative selection (Figure 1(a)). This selection was operational and effective in spite of the mortality curve because of which the population living up to later age classes were a small fraction of the population in early age classes. In presence of the parasite but when parasite transmission was completely randomized in the population, the aging genotype became extinct for the same reason (Figure 1(b)).

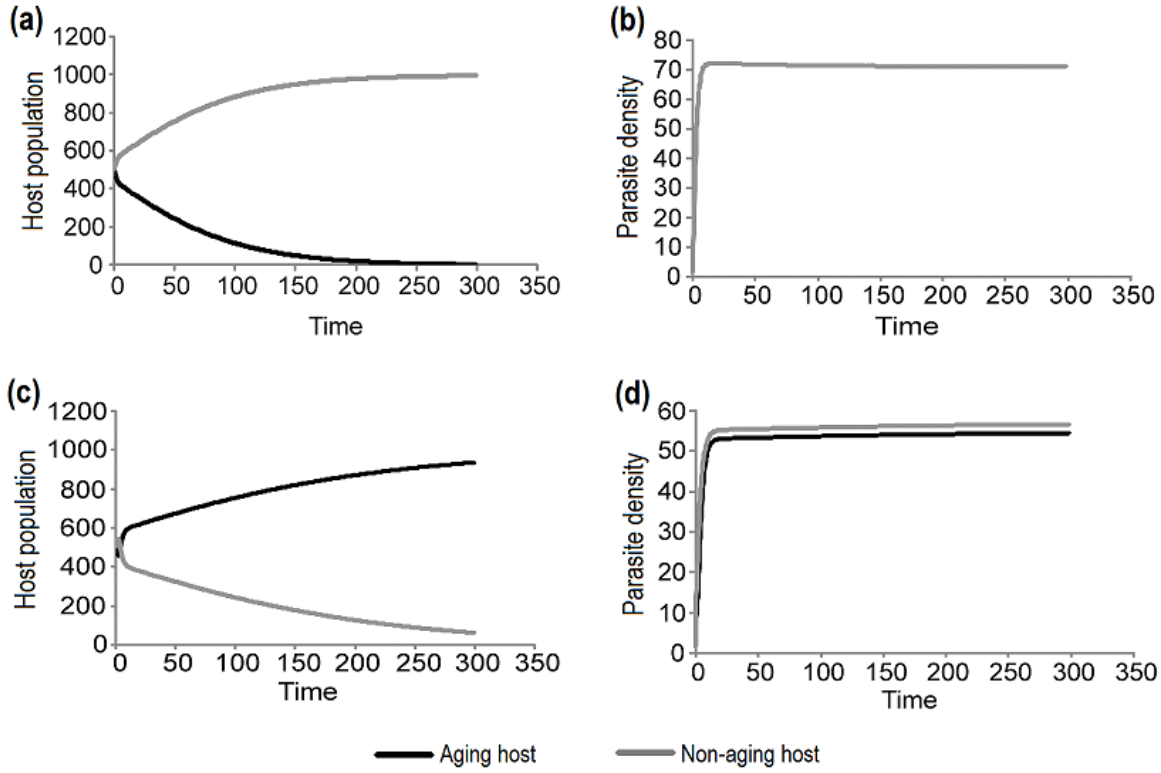

Figure 1: *Selection on the aging and nonaging population in presence of a parasite.* When transmission was random, the nonaging genotype replaced the aging genotype (a) and there was no difference in the mean parasite loads of the aging and nonaging population (b). However, when there was a kin bias in transmission (i.e., an infected individual was slightly more likely to transmit the infection to a kin than to a nonkin), the aging genotype got a selective advantage and replaced the nonaging genotype (c). This is mainly because the mean parasite burden of the aging population was lower than that of the nonaging population (d). The particular parameters used in the simulation were host population normalized to 1,000, parasite total population normalized to 10,000, $R_n = 0.2$ for all age classes, and age-independent mortality 0.1 for all age classes in the nonaging population. In the aging population, age-independent mortality was made 1 at age class 3 (i.e., the life span was suddenly ended after two years), C_n was increased exponentially starting from 0.004 and doubling every age class, and constant K for parasite-induced mortality was 5. Kin transmission bias was zero for (a) and (b) and 0.15 for (c) and (d).

Thus in the absence of differential parasite dynamics in the two genotypes, intrinsic aging even if weak and confined to later ages exerted a significant negative selection driving any intrinsic aging mechanism to extinction.

When there was a nonzero kin bias in parasite transmission, the intrinsic aging genotype had a fitness advantage above a threshold k (Figure 1(c)). Under this condition, the mean parasite load per individual was always smaller in the aging population than in the nonaging population (Figure 1(d)). The threshold kin bias needed for this fitness reversal was often very small; under some conditions it was even as small as 0.02. If 2% to 3% of parasite transmission was specific to kin, it was sufficient to give selective advantage to the aging phenotype after optimizing the aging parameters.

When the model was used to simulate competition between two aging genotypes with a shorter and longer lifespan and combinations of lifespans were tested against each other, it was revealed that there was always an optimum lifespan for a given set of parasite parameters which could not be invaded by any other lifespans. The optimum longevity was decided mainly by the contemporary parasite populations, transmission rate constants, parasite-induced mortality parameter and kin transmission bias (Figure 2).

The results show that it is possible, in principle, that evolution of opportunistic pathogens within the lifespan of a host can potentially drive the evolution of intrinsic aging in the host and further that at a given parasite-related parameters there is an optimum longevity for the host.

3.2. Sensitivity analysis

To examine whether the results were artifacts produced by some underlying assumptions, we relaxed the assumptions one by one to see whether the results were qualitatively sensitive to any of the relaxations.

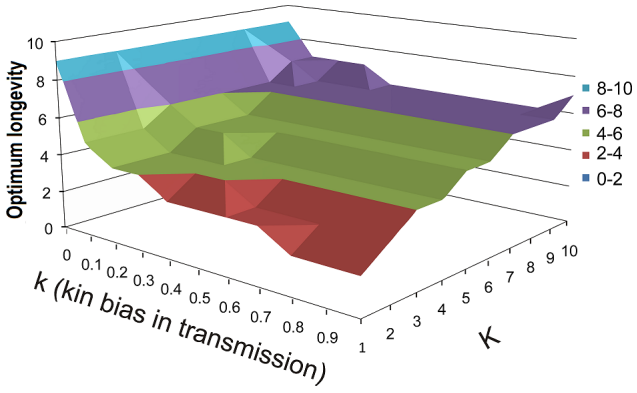

Figure 2: The optimum longevity as affected by k kin transmission bias and K, the half saturation constant for parasite-induced death. Other parameters are the same as in Figure 1. Shorter lifespans evolved at higher kin transmission bias and lower K which indicates greater parasite-induced mortality.

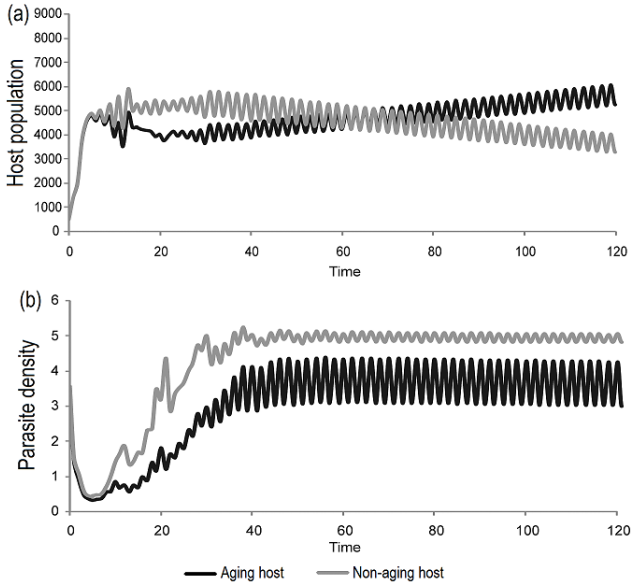

Figure 3: *Host and parasite population dynamics without normalization of either the host or parasite population.* In the absence of normalization, host or parasite populations become extinct frequently or oscillate with variable amplitudes and periodicities. Nevertheless, an advantage to the aging genotype owing to lower mean parasite loads could be seen. (Parameters used in this simulation were $R_n = 2.7$ for all age classes and age-independent mortality 0.1 for all age classes in the nonaging population. In the aging population, age-independent mortality was made 1 at age class 8, C_n was increased exponentially starting from 0.12 and increasing by 1.4 fold in every age class, constant K for parasite-induced mortality was 10, and kin transmission bias was 0.6.)

First, we removed the normalization of host population and parasite population one by one as well as jointly. With the removal of both populations' normalization, either the pathogen or the host (followed by pathogen) became extinct frequently. However, whenever a set of parameters allowed stability of the host-parasite dynamics, early aging phenotype showed an evolutionary advantage above a threshold k similar to the normalized model. Both the host and parasite populations oscillated with varying frequencies and amplitudes. Nevertheless, selection for intrinsic aging could be observed (Figure 3). Normalizing the host population gave substantial stability to the dynamics and reduced the conditions under which extinctions happened. In a narrow set of conditions an interesting dynamics was observed which allowed coexistance of long and short lifespan hosts. When the mean parasite loads were high, the short lifespan genotype had a distinct advantage and it increased substantially in frequency. However, as it increased the parasite population decreased. At a low parasite density, the longer lifespan genotype had a better fitness and it invaded back. This invasion made conditions more favorable for the parasite. This led to an oscillating dynamics that prevented extinction of the longer lifespan genotype which survived at low and oscillating densities. Normalization of parasite population removed the oscillations.

The baseline model assumes parasite-induced death. We examined the possibility that the parasite did not affect survival but suppressed reproduction to some degree. This was incorporated in the model by making the age specific reproductive rate a decreasing function of parasite load specific to that age class. Advantage to early aging genotype was observed in this model as well. Interestingly, the threshold k required to give advantage to early aging was an order of magnitude lower in this model than the one in which parasites affected survival. This is because the model allowed the elderly individuals with higher parasite loads to live and spread their parasites in the late aging population. In the early aging population, this class did not exist and therefore the net kin-biased transmission was substantially different in the two genotypes. When we allowed the parasite to affect both survival and reproduction the advantage to early aging genotype was retained and the threshold k remained similar to the survival alone model.

The Leslie matrix model is necessarily a discrete time model. We cannot consider continuous time in this framework. However, when we increased time resolution by making finer age classes and time cycles adjusting other parameters to retain the same net growth rates for hosts and parasites, the threshold k decreased more or less proportionately to the time resolution. That is doubling the number of classes reduced k by approximately one half. This indicates that the minimum kin bias needed was decided by the minimum

aging disadvantage experienced by the early aging genotype. Since the age structure was discrete, longevity could be reduced by minimum one age class at a time. This disadvantage to the early aging population could be overcome by the kin bias. This means that the actual kin bias required for the evolution of aging could be much smaller than what the model shows if time can be treated as continuous or fine grained.

The baseline model assumes no crossbreeding between the two genotypes. This simplifies the model substantially. Whether intrinsic aging mechanisms are governed by one or a few genes or by several small effect genes is debatable. We considered a simple case with one gene affecting longevity with one allele for longer lifespan and another for shorter lifespan. This increases the complexity of the model but it can be perceived that the results would be qualitatively similar. If we assume either the short or the long lifespan allele to be dominant, the homo and heterozygotes would be distributed by Hardy-Weinberg equation. The main model with two age structure matrices remains the same but the advantage to the diploid genotypes need to be converted back into allelic frequencies. Simulating for one gene two alleles crossbreeding model showed that qualitatively intrinsic aging still obtained an advantage above a threshold k.

If we assume the heterozygote, to have a mixed effect of the two alleles, that is an intermediate lifespan, we need a model with three different age structure matrices, one each for the two homozygotes and one for the heterozygote respectively followed by calculation of allelic frequencies and redistributing them in Hardy-Weinberg. Simulating this also gave an advantage to the shorter lifespan allele above a threshold kin bias. Thus our baseline simplifying assumption was not responsible for the observed selective advantage of early aging.

Evolution of aging and optimum lifespan was observed independent of the linear or nonlinear form of change in parasite colonization rate with age, provided it increased monotonically. Evolution of aging was also robust to whether the parasite colonization rate alone, transmission rate alone or both were made sensitive to age. It was also robust to whether the age-related decline in parasite independent survival reduced suddenly or gradually with different shapes of curves. All results were dependent on the parameters but were not sensitive to the starting population sizes.

3.3. Plasticity in aging

One potential problem in the evolving microbiota model is that since the pathogens are fast evolving entities the parasite-related parameters are likely to change from time to time and thereby the optimum lifespan might be an unstable characteristic. We therefore considered a plastic response from the host. Rather than having an evolved hardwired lifespan or aging mechanism, the aging mechanisms might be activated in response to the frequency of infections or some other parasite population parameter. We therefore modified the model with an assumption that the survival probability of the host reduced when a threshold parasite population was reached on the body of a given host individual. Simulations showed that above a threshold kin transmission bias a host that reduced its lifespan by activating intrinsic aging in response to parasite population on the body had a selective advantage over one that did not. The threshold required was small and comparable to the hardwired lifespan model. Thus, it is possible that a plastic lifespan in response to the composition of microbiota can evolve. Parasite responsive aging is different from getting killed by infection itself. In the former the host dies in anticipation of infection and thereby the total parasite population is kept in check whereas in the latter the parasites gain an advantage of maximum growth in an individual so that the total parasite population increases.

4. Discussion

The only critical conditions for evolution of aging in the model are that the parasite exerts substantial cost on the host and that there is some component of kin-biased transmission. A very small kin transmission bias is sufficient for aging to evolve in this model. In reality, there can be a number of reasons for having a kin selection bias in transmission. Genetic susceptibility is one possible reason. Since parasites evolve to overcome the resistance mechanisms of an individual host, individuals with greater genetic relatedness to that individual are likely to be more susceptible to that particular evolved lineage of parasites. There can be vertical transmission of parasites through egg, placenta or milk [56]. Feeding, nursing, and other acts of parental care enable transmission. Also if offspring dispersal is limited in space, they are more likely to receive infection from their parents or siblings. One or more of these processes can easily result into a minimum kin transmission bias required for the model which ranged from 0.003 to 0.6 over a wide range of simulation parameters. Molecular epidemiological studies of parasite lineages have given evidence for a substantial vertical or kin component in parasite transmission [58,59,60,61]. Therefore, the conditions needed for the evolution of aging in the model are well within the realistic range.

It is a common observation that old-age infections are frequently caused by opportunistic pathogens normally associated with human body [62,63,64]. One possible interpretation is that of a reduction in immunity with age. It is equally likely that it is due to evolved varieties of the microbes that can better overcome the individual's resistance genes. If it is the former, all infections should increase in frequency more or less similarly. If the proportion of opportunistic infections increases disproportionately

in old age, the latter hypothesis is better supported. The critical assumption of parasite evolution on host body is thus testable with epidemiological data.

The plastic aging response to parasite populations has strong evidence in literature and also makes important testable predictions. Infections have been shown to reduce the telomere length [65,66,67,68], increase oxidative stress [69], and upregulate the AGE-RAGE pathways [70]. Of particular interest is the finding that the host body does not give an oxidative response to a commensal organism but launches it when the same organism turns infectious [71]. RAGE and oxidative pathways are involved in the immune response. While the effects of oxidative damage on aging can be viewed as inevitable, RAGE pathways are specific receptor mediated pathways and therefore a product of evolution. It may not be a coincidence that the same receptor modulates immune mechanisms as well as aging pathways after sensing infections. This indicates that apart from death from infections other mechanisms determining lifespan are also altered by infection. The human lifespan increased dramatically after the wide-scale use of antibiotics. This may be a coincidence or there could be causal relationship. If broad spectrum antibiotics interrupt the evolving microbial community associated with a body, the evolution of opportunistic pathogens would be delayed allowing greater longevity. It is also possible that introduction of nonpathogenic organisms that compete with opportunistic pathogens to slow down their evolution would also increase lifespan. It should be possible to test whether periodic interruption of evolution of the microbiota by broad spectrum antibiotics or by introducing competing "probiotic" species increases lifespan in experimental animals.

Plasticity of lifespan in response to parasites also suggests why the microbiota shows diverse interactions with the host physiology. The composition of microbiota has been shown to affect host metabolic, endocrinal, neuronal, and behavioral responses [72,73,74]. So far, there are little insights into why and how the microbiota evolved to modulate host physiology or why does the host respond to the microbiota by altering its metabolic, endocrinal, neuronal, and behavioral processes. The microbiota responsive plasticity of the aging-related processes suggests at least a partial answer to the question.

The link between sex and senescence is also in a direction predicted by the hypothesis. In hydra and vegetatively reproducing plants, senescence may not be observed at all as long as the reproduction remains vegetative. If and when the organisms enter a sexual cycle, senescence sets in rapidly. Spectacular examples of the association between sexual reproduction and aging are hydra [8], soybean, agave, Madagascar palm, and many species of bamboo [50,75]. Organisms that can reproduce both vegetatively and sexually can be used to test that sexual reproduction is specifically traded-off with longevity and not any type of reproduction. A quantitative biome-wide analysis can test the prediction of the hypothesis that sexual reproduction and organismal aging will have a significant positive association across species and negative within species. Species that reproduce sexually should have evolved more elaborate mechanisms of intrinsic aging compared to ones reproducing asexually. On the other hand, species that have both modes of reproduction, intrinsic senescence should be coupled with sexual reproduction rather than asexual one. Another prediction of the model that can be tested in multispecies data is that species that have little kin transmission bias will show little or no decline in reproductive capacity with aging. For example, species without parental care and absence of viscosity in spatial dispersal of offspring should have viability and reproductive capacity independent of or increasing with age. Since kin transmission bias in such species is likely to be close to zero, aging may not evolve. An example is species of marine turtles that lay eggs gregariously in sandy beaches, where there is no parental care and the dispersal of offspring is independent of parental home range or movement [76,77]. Indeed, marine turtles do not show reduction in viability and reproduction with age as expected by the hypothesis [78]. Another possibility is that host species that have other means of interrupting parasite evolution on the body may show little aging. This is possible for tree species that shed most of the soft tissues which are likely to colonize microbes. Thus, the evolving microbiome hypothesis has the potential to at least partly explain the variability in aging patterns across life forms. Again a careful biome-wide comparative analysis is required to test such cross-species predictions of the model. It is likely that data needed for such analysis may become available in the near future [12].

The microbiota hypothesis of aging, particularly the plastic response model, is compatible with other hypotheses for the evolution of aging. It stands on the borderline of programmed and nonprogrammed aging dichotomy. It is not hard wired programmed since it is plastic and responds to the microbial environment. But there can be evolved anticipatory responses. Similar to programmed aging theories, our model depends upon kin selection but unlike other programmed aging hypothesis, our model quantitatively examines the extent of kin selection element required for the evolution of earlier aging and finds it to be very small and realistic.

The microbiota hypothesis holds a synergistic relationship with AP. If infections increase mortality, early reproduction and later aging trade-offs can evolve independent of microbiota evolution or kin transmission bias. The microbiota can contribute to aging by two alternative routes, by our hypothesis and by facilitating selection for AP. The two processes are mutually compatible and can

work independent of each other or in synergy, but they make differential predictions by which they can be differentially tested. Sexual organisms make new combinations of parasite resistance genes and therefore asexual populations should be more susceptible to infections. As a result, if the AP response to infections predominated, one should see rapid aging associated with asexual reproduction than with sexual reproduction. On the other hand, if evolving microbiota and kin-biased transmission predominate, then a positive association between sex and aging is expected for reasons discussed above. This can be used as a testable prediction and a biome-wide analysis for the association between sex and aging can be helpful.

Parasite resistance is a part of somatic maintenance which is theoretically sound with germ-soma division, but it adds a new dimension to the germ-soma theory. The maintenance efforts needed will increase or the effectivity of maintenance will decline with age owing to the evolution of microbiota. This dimension was not considered by the classical germ-soma theory. Further, the evolving microbiota offers a plausible and testable explanation for why caloric restriction increases longevity. The microbiota on a host body depends on the host as the sole or major nutrient source. In a rather simplistic way, the nutrients available to the microbiota can be considered a spill-over of host nutrition. When the host nutrition is restricted, nutrients available to the microbiota are also most likely to be restricted which would reduce the growth rate, increase generation time, and thereby reduce the rate of evolution. If the host aging response to microbiota is plastic, slower microbiota evolution would result into increased host lifespan. This hypothesis is testable by monitoring the longitudinal changes in microbiota in caloric restricted and unrestricted individuals.

In effect, the evolving microbiota hypothesis is not yet another alternative and competing hypothesis for the evolution of aging. It is not only compatible with the AP and germ-soma trade-off theories, it also adds certain new dimensions to them. It also offers an alternative set of explanations for the programmed like aging effects. It can prove to be the catalyst for amalgamating the different extant hypotheses and give rise to a new synthesis which will be more comprehensive, less fraught with flaws and paradoxes, and testable through its predictions.

Conflict of interest The authors declare that there are no conflict of interest.

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