Asexual and sexual replication in sporulating organisms

Bohyun Lee
School of Biology, Georgia Institute of Technology, Atlanta, Georgia 30332, USA

Emmanuel Tannenbaum*
Department of Chemistry, Ben-Gurion University of the Negev, Be'er-Sheva, Israel

(Received 30 November 2006; revised manuscript received 18 April 2007; published 8 August 2007)

Replication via sporulation is the replication strategy for all multicellular life, and may even be observed in unicellular life (such as with budding yeast). We consider diploid populations replicating via one of two possible sporulation mechanisms. (1) Asexual sporulation, whereby adult organisms produce single-celled diploid spores that grow into adults themselves. (2) Sexual sporulation, whereby adult organisms produce single-celled diploid spores that divide into haploid gametes. The haploid gametes enter a haploid "pool," where they may recombine with other haploids to form a diploid spore that then grows into an adult. We consider a haploid fusion rate given by second-order reaction kinetics. We work with a simplified model where the diploid genome consists of only two chromosomes, each of which may be rendered defective with a single point mutation of the wild-type. We find that the asexual strategy is favored when the rate of spore production is high compared to the characteristic growth rate from a spore to a reproducing adult. Conversely, the sexual strategy is favored when the rate of spore production is low compared to the characteristic growth rate from a spore to a reproducing adult. As the characteristic growth time increases, or as the population density increases, the critical ratio of spore production rate to organism growth rate at which the asexual strategy overtakes the sexual one is pushed to higher values. Therefore, the results of this model suggest that, for complex multicellular organisms, sexual replication is favored at high population densities and low growth and sporulation rates.

DOI: 10.1103/PhysRevE.76.021909 PACS number(s): 87.23.−n

I. INTRODUCTION

The emergence of sexual replication as the preferred replication strategy for complex multicellular organisms is one of the oldest and most important problems in evolutionary biology [1]. There are two broad theories for the selective advantage for sex [1–6], both of which have more than one specific version.

The first theory for the selective advantage for sex is the genetic repair theory, or, in the context of small populations, the Muller's Ratchet theory [4,6–10]. The genetic repair theory holds that sex evolved as a way to remove mutations from diploid genomes. By reproducing via a haploid intermediate, defective copies of genes can be discarded, and functional copies of genes can be brought together via haploid fusion.

In the context of finite populations, the genetic repair theory takes the form of the Muller's Ratchet theory [7–9]. Briefly, Muller's Ratchet is a phenomenon whereby a finite population will steadily accumulate mutations, and may eventually go extinct as a result. Sexual replication, by providing a mechanism to discard defective genes, can slow down or stop Muller's Ratchet, and thereby prevent small populations from going extinct.

The second theory for the selective advantage for sex is the adaptability theory [11]. This theory, which originates with Weismann, has two versions: The Vicar of Bray hypothesis, and the Red Queen hypothesis. The Vicar of Bray hypothesis argues that sex increases variability in small populations, making them more adaptable to changing circumstances. The name derives from an English cleric who was known for changing his religion according to circumstance [1]. Within the context of the idea that sex increases variation within a population, it is believed that host-parasite coevolutionary dynamics drove the emergence of sex [6,11]. This "arms race" argument for the existence of sex is termed the Red Queen hypothesis.

While the various theories for sex are not necessarily mutually contradictory, each of them is either incomplete or has difficulties. The Muller's Ratchet theory, for example, by relying on a small population size, suggests that sex should disappear in large populations. It is not immediately clear that this should be true, however, since many sexual organisms can attain seemingly fairly large population sizes.

The Vicar of Bray and the Red Queen hypotheses rely on a dynamic environment. However, there are a number of sexually replicating organisms, such as sharks, crocodiles, and certain fish such as the coelacanth, that have remained essentially unevolved over millions of years (or have not evolved very much when compared with other organismal lines), in what appear to be fairly stable environments. Therefore it is not immediately clear that a dynamic environment is the main selective pressure driving the emergence of sex [12–14] (it should be noted that it has recently been discovered that female sharks are capable of reproducing without a male, if necessary. However, this does not contradict the assertions of this paragraph, since it is believed that sharks will resort to asexual reproduction only if there is no alternative [12]).

The genetic repair theory is the theory with the broadest acceptance among evolutionary biologists. That being said, it could be argued that the theory is incomplete because it does

*emanuelt@bgu.ac.il

not explain why sexual replication is disadvantageous in organisms such as bacteria [15]. Furthermore, it does not explain why, among the organisms that replicate sexually, some employ sexual replication merely as a stress response (such as Baker's yeast), and why others replicate exclusively via the sexual pathway.

It should be noted here that the issue is not why recombination is beneficial, since genetic recombination occurs at all biological length scales [16]. The issue is why some organisms, such as bacteria, replicate asexually (and sometimes exchange genetic material with another), and why other organisms, such as humans, replicate via a haploid intermediate.

In two recent papers [17,18], Tannenbaum and Fontanari developed simple evolutionary dynamics models based on the sexual stress response in Baker's yeast. The first paper assumed a density-independent characteristic haploid fusion time, while the second assumed second-order haploid fusion kinetics. In both papers, the general result that emerged was that sex is favored when the characteristic haploid fusion time is small compared with the characteristic replication time. Therefore the results of the models suggested that sex is favored in slowly replicating organisms, and that, all other factors being equal, sex is favored at high population densities.

While the results of these models were broadly consistent with what is observed biologically, they are unsuitable for considering additional features of sexual replication, such as gamete differentiation into sperm and egg, and sex differentiation into male and female. Although many organisms replicate sexually, not all have distinct gametes, and, even among organisms that produce distinct gametes (the anisogamous organisms), not all have distinct male and female sexes. There are therefore presumably different regimes where the different types of sexual strategies will be advantageous.

The previous two models, because they consider a sexual pathway whereby a given diploid cell splits into two haploids, do not reflect the fact that most sexually replicating organisms may continually produce gametes that may recombine to produce new organisms. The analogous process for asexually replicating organisms is sporulation. Therefore before considering the regimes where asexual replication and various sexual replication strategies are advantageous, we first need to develop a formalism for describing the evolutionary dynamics of populations which replicate by producing either single-celled spores or gametes.

This paper is divided into four sections: In Sec. II, we develop a model describing asexual replication of organisms that replicate by producing single-celled spores. In Sec. III, we consider the analogous process for sexual replication, where we assume that the gametes fuse via second-order kinetics. In Sec. IV, we numerically solve for the steady-state mean fitnesses of the various populations, and determine the various regimes where the different strategies are advantageous. We find that sexual replication is favored in organisms that produce offspring at lower rates. The critical offspring production rate increases as the characteristic organismal maturation time increases, or as the density of adult organisms increases. Therefore the results of this paper appear to be broadly consistent with what is observed biologically. However, based on known scaling laws for organismal maturation times as a function of organism size, it is not clear that the results of our model imply that sexual replication will be favored in larger organisms. In Sec. V, we summarize our conclusions and discuss future research directions. In particular, we discuss additional modeling that could resolve this possible inconsistency between our predictions for the preferred sexual strategy as a function of organism size, and what is observed biologically.

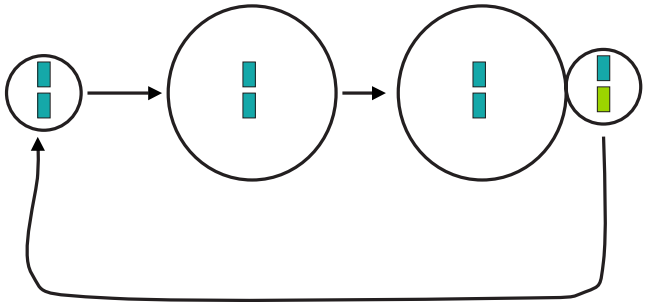

FIG. 1. (Color online) Illustration of asexual replication via sporulation. A newly formed, immature organism, grows to adult size, at which point it produces new immature cells through budding at some regular rate. The green (dark) rectangle represents a wild-type chromosome, while the yellow (light) rectangle represents a mutant chromosome.

We should note that the models we develop are quasispecies-type models. Quasispecies theory has found application in a wide range of problems in evolutionary dynamics, including molecular, viral, and bacterial evolution [19–33] , the immune response [34–36], and the emergence of cancer [37–46]. Furthermore, quasispecies theory has been used to study a number of general aspects of evolutionary dynamics that provide insight into a wide range of phenomena in evolutionary biology. These include the emergence of mutational robustness [47–50], dynamic fitness landscapes [51,52], punctuated equilibrium [53], and finite-size effects [54–57]. Therefore we believe that the quasispecies formalism is well-suited to studying the selective advantage for various types of replication strategies.

II. ASEXUAL REPLICATION VIA SPORULATION

In this section, we develop the evolutionary dynamics equations appropriate for describing asexual replication via sporulation. As discussed in the Introduction, while a model involving simple binary fission is appropriate for unicellular organisms, such an approach is inadequate for describing larger, multicellular organisms. The reason for this is that asexually replicating larger organisms begin their life cycle as a single cell. This cell develops into the adult organism, which then begins to produce single-celled spores at some rate (see Fig. 1).

Therefore in order to properly study the regimes where asexual and various sexual replication strategies are advantageous, we first need to develop equations more appropriate for the replication dynamics of multicelled organisms.

A. Definitions

The asexual replication of an organism (single or multicelled) by sporulation is illustrated in Fig. 1. An immature organism grows to adult size. The adult then produces single-celled spores by budding. Each of these spores are immature organisms that then repeat the process and develop into adults on their own.

For simplicity, we assume that the organisms have diploid genomes consisting of two chromosomes. The genome of each organism may then be denoted by $\{\sigma_1,\sigma_2\}$, where σ_1 and σ_2 denote the respective base sequences of each chromosome (we assume that each chromosome consists of a single strand of bases, so that a given chromosome σ may be written as $\sigma=s_1s_2\cdots s_L$. Here, L is the total sequence length, and each s_i is a base which is chosen from an alphabet of size S, where $S=4$ for terrestrial life).

Following standard practice in quasispecies theory, we make the simplifying assumption that there exists a single master sequence, denoted σ_0, for which a given chromosome is functional. In this single-fitness-peak approximation, any chromosome $\sigma\neq\sigma_0$ is nonfunctional. A given genome may therefore be classified by the number of functional chromosomes it has, namely zero, one, or two.

A genome with zero functional chromosomes is said to be of type (u,u), where u signifies that a chromosome is *unviable*. A genome with one functional chromosome is said to be of type (v,u), where v signifies that a chromosome is *viable*. A genome with two functional chromosomes is said to be of type (v,v).

We assume that the growth of an immature organism to adulthood is characterized by a first-order rate constant. We further assume that this rate constant is genome-dependent, since different organisms are differently suited to the given environment, and so will reach maturity at different rates. We therefore let κ_{vv}, κ_{vu}, and κ_{uu} denote the first-order spore-to-adult rate constants for the (v,v), (v,u), and (u,u) organisms, respectively. Presumably, the (v,v) organisms, since they are mutation-free, will have the highest growth rate constant. The (v,u) organisms, since they have one nondefective and one defective chromosome, will have an intermediate growth rate constant. Finally, the (u,u) organisms, since both of their chromosomes are defective, will have the lowest growth rate constant. It is therefore reasonable to assume that $\kappa_{vv}\geq\kappa_{vu}\geq\kappa_{uu}$.

We also assume that, once an organism reaches adulthood, it produces spores at some fixed rate, which is again genome-dependent. The rates of per-organism spore production for the various genome types are denoted ω_{vv}, ω_{vu}, and ω_{uu}. As with the first-order growth rate constants, it makes sense to assume that $\omega_{vv}\geq\omega_{vu}\geq\omega_{uu}$. We let $n_{ai,xy}$ denote the number of asexual, immature organisms with genome (x,y), and $n_{am,xy}$ denote the number of asexual, mature organisms with genome of type (x,y).

During the sporulation process itself, the adult organism replicates each of the chromosomes in the genome. It is assumed that the adult organism retains the original parent chromosomes, and only the two newly synthesized daughters (i.e., offspring) segregate into the budding spore. This "immortal strand" mechanism is believed to occur in the adult stem cells of vertebrates and in budding yeast [58–60]. Since the spores are being produced by stem cells in the adult, it is reasonable to assume that a similar mechanism is at work here as well.

Finally, the replication of each chromosome is not error-free. We let p denote the replication fidelity, defined as the probability that a v chromosome produces a v daughter (equivalently, offspring, as indicated before). If we neglect backmutations, then a v chromosome produces a u daughter with probability $1-p$, and a u chromosome produces a u daughter with probability 1.

B. Mutation-selection equations

The mutation-selection equations governing the evolutionary dynamics of the sporulating population are then given by

$$\frac{dn_{am,vv}}{dt}=\kappa_{vv}n_{ai,vv},$$

$$\frac{dn_{am,vu}}{dt}=\kappa_{vu}n_{ai,vu},$$

$$\frac{dn_{am,uu}}{dt}=\kappa_{uu}n_{ai,uu},$$

$$\frac{dn_{ai,vv}}{dt}=p^2\omega_{vv}n_{am,vv}-\kappa_{vv}n_{ai,vv},$$

$$\frac{dn_{ai,vu}}{dt}=2p(1-p)\omega_{vv}n_{am,vv}+p\omega_{vu}n_{am,vu}-\kappa_{vu}n_{ai,vu},$$

$$\frac{dn_{ai,uu}}{dt}=(1-p)^2\omega_{vv}n_{am,vv}+(1-p)\omega_{vu}n_{am,vu}+\omega_{uu}n_{am,uu}-\kappa_{uu}n_{ai,uu}. \quad (1)$$

We now define $n_{am}=n_{am,vv}+n_{am,vu}+n_{am,uu}$, so that n_{am} is simply the total population of mature adults. We then define all population fractions with respect to this population number. Specifically, we define the population fractions $x_{aq,rs}=n_{aq,rs}/n_{am}$, where $q=m,i$ and (r,s) is the genome type. Note that, in principle, some of the population fractions can be greater than 1, since they are not defined with respect to the total population, but rather with respect to the population of mature adults.

Changing variables, we obtain

$$\frac{dx_{am,vv}}{dt}=\kappa_{vv}x_{ai,vv}-\bar{\kappa}_a(t)x_{am,vv},$$

$$\frac{dx_{am,vu}}{dt}=\kappa_{vu}x_{ai,vu}-\bar{\kappa}_a(t)x_{am,vu},$$

$$\frac{dx_{am,uu}}{dt}=\kappa_{uu}x_{ai,uu}-\bar{\kappa}_a(t)x_{am,uu},$$

$$\frac{dx_{ai,vv}}{dt} = p^2\omega_{vv}x_{am,vv} - [\kappa_{vv} + \bar{\kappa}_a(t)]x_{ai,vv},$$

$$\frac{dx_{ai,vu}}{dt} = 2p(1-p)\omega_{vv}x_{am,vv} + p\omega_{vu}x_{am,vu} - [\kappa_{vu} + \bar{\kappa}_a(t)]x_{ai,vu},$$

$$\frac{dx_{ai,uu}}{dt} = (1-p)^2\omega_{vv}x_{am,vv} + (1-p)\omega_{vu}x_{am,vu} + \omega_{uu}x_{am,uu} - [\kappa_{uu} + \bar{\kappa}_a(t)]x_{ai,uu}, \quad (2)$$

where $\bar{\kappa}_a(t) = \kappa_{vv}x_{ai,vv} + \kappa_{vu}x_{ai,vu} + \kappa_{uu}x_{ai,uu}$ is simply the mean fitness of the population.

The change of variables from population number to population ratio is accomplished in the following manner: Starting with the variable $n_{am,vv}$, we have that $n_{am,vv} = n_{am}x_{am,vv}$. Therefore

$$\frac{dn_{am,vv}}{dt} = n_{am}\frac{dx_{am,vv}}{dt} + x_{am,vv}\frac{dn_{am}}{dt}$$

$$\Rightarrow \frac{dx_{am,vv}}{dt} = \frac{1}{n_{am}}\frac{dn_{am,vv}}{dt} - \left(\frac{1}{n_{am}}\frac{dn_{am}}{dt}\right)x_{am,vv}. \quad (3)$$

From the definition of n_{am}, it is readily shown that $(1/n_{am})dn_{am}/dt = \kappa_{vv}x_{am,vv} + \kappa_{vu}x_{am,vu} + \kappa_{uu}x_{am,uu} = \bar{\kappa}(t)$, from which the expression for $dx_{am,vv}/dt$ given in Eq. (2) immediately follows. The other population ratio equations are derived similarly.

C. Steady-state mean fitness

We may solve for the steady-state of this system of equations analytically. To begin, we first assume that $\kappa_{uu}=0$. This simplification derives from the logical assumption that an organism with two defective chromosomes cannot grow. Although it makes sense that an organism with two defective chromosomes cannot grow, we did not assume this explicitly in deriving the equations governing the evolutionary dynamics of the population. The reason for this is that, in the single-fitness-peak model often used in standard quasispecies theory, it is assumed that organisms with defective genomes can replicate, albeit more slowly than the wild-type organisms. If we wish our two-chromosome model to be analogous to the earlier single-chromosome models, then we must derive the dynamical equations without making any *a priori* assumptions about κ_{uu}. Nevertheless, as we have already stated, from now on we will work with the logical assumption that $\kappa_{uu}=0$.

With the assumption that $\kappa_{uu}=0$, the first three equations give, at steady state, that

$$x_{ai,vv} = \frac{\bar{\kappa}_a(t=\infty)}{\kappa_{vv}}x_{am,vv},$$

$$x_{ai,vu} = \frac{\bar{\kappa}_a(t=\infty)}{\kappa_{vu}}x_{am,vu},$$

$$x_{am,uu} = 0, \quad (4)$$

so that

$$0 = \{p^2\kappa_{vv}\omega_{vv} - [\kappa_{vv} + \bar{\kappa}_a(t=\infty)]\bar{\kappa}_a(t=\infty)\}x_{am,vv}. \quad (5)$$

If $x_{am,vv} > 0$, then we have

$$\bar{\kappa}_a(t=\infty)^2 + \kappa_{vv}\bar{\kappa}_a(t=\infty) - p^2\kappa_{vv}\omega_{vv} = 0, \quad (6)$$

so that

$$\bar{\kappa}_a(t=\infty) = \bar{\kappa}_{a,1}(t=\infty) = \frac{1}{2}[-\kappa_{vv} + \sqrt{\kappa_{vv}^2 + 4p^2\kappa_{vv}\omega_{vv}}]. \quad (7)$$

If $x_{am,vv}=0$, then we have

$$0 = \{p\kappa_{vu}\omega_{vu} - [\kappa_{vu} + \bar{\kappa}_a(t=\infty)]\bar{\kappa}_a(t=\infty)\}x_{am,vu}, \quad (8)$$

so, if $x_{am,vu} > 0$, then we have

$$\bar{\kappa}_a(t=\infty) = \bar{\kappa}_{a,2}(t=\infty) = \frac{1}{2}[-\kappa_{vu} + \sqrt{\kappa_{vu}^2 + 4p\kappa_{vu}\omega_{vu}}]. \quad (9)$$

Based on a stability analysis of the possible steady states, it is possible to show that the actual value of $\bar{\kappa}_a(t=\infty)$ is given by $\max\{\kappa_{a,1}(t=\infty), \kappa_{a,2}(t=\infty)\}$, where $\kappa_{a,1}$ and $\kappa_{a,2}$ are defined in Eqs. (7) and (9), respectively.

We now also assume that $\kappa_{vv} > \kappa_{vu}$ and that $\omega_{vv} > \omega_{vu}$, which makes sense, since we presume that an organism with no defective chromosomes grows more quickly and can produce spores more quickly than an organism with two defective chromosomes. Therefore, since by differentiating with respect to x and y we can see that $-x + \sqrt{x^2 + xy}$ is an increasing function of x and y, it is readily shown that $\bar{\kappa}(t=\infty) = \bar{\kappa}_{a,1}$ at $p=1$. The value of $\bar{\kappa}(t=\infty)$ becomes $\bar{\kappa}_{a,2}$ at $p = p_{crit}$ defined by the condition $\bar{\kappa}_{a,1}(t=\infty) = \bar{\kappa}_{a,2}(t=\infty)$. Below this replication fidelity, the effective growth rate of the (v,v) genomes is no longer competitive with that of the (v,u) genomes, and the result is the disappearance of the (v,v) genomes from the population (a phenomenon termed the error catastrophe) [19–34,37–45,50–52,54–57] .

III. SEXUAL REPLICATION

In this section we consider a sexual replication pathway, whereby a given diploid spore splits into two haploids, which may then fuse with other haploids in the population.

A. Definitions

In the sexual replication model being considered here, a mature diploid with genome (v,v) produces smaller diploid spores at a rate given by ω_{vv}. These diploid spores then divide into two haploid intermediates. The haploids of type v may then recombine with each other to form an immature diploid of type (v,v), which then grows to a mature diploid and begins the cycle again. This process is illustrated in Fig. 2. We should note that the haploids essentially enter a haploid pool where haploid fusion occurs. Therefore while it is

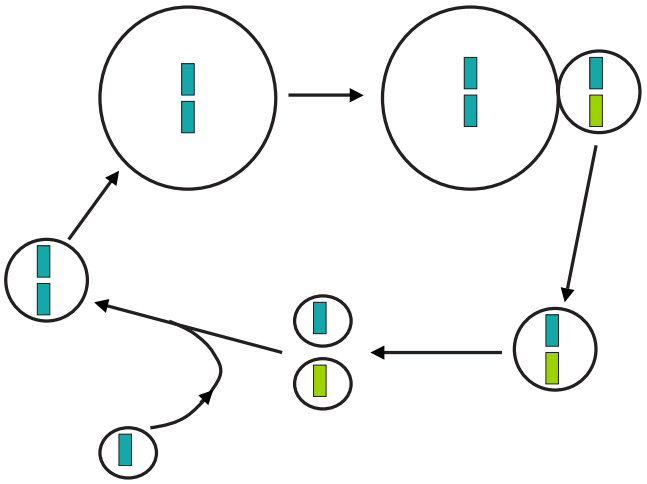

FIG. 2. (Color online) Illustration of sexual replication. A newly formed, immature organism, grows to adult size, at which point it produces new immature cells through budding at some regular rate. The immature cells immediately divide into haploid intermediates. The haploids may then recombine with other haploids to form new immature diploids, which then repeat the cycle. The green (dark) rectangles represent the wild-type chromosomes, while the yellow (light) rectangles represent the mutant chromosomes.

possible for a haploid to fuse with a haploid from the same parent, in general this is statistically unlikely in any sufficiently large population.

In this model, we assume that only the v haploids may recombine with one another. Essentially, the u haploids are defective and cannot participate further in the replication process. We assume that the haploid fusion rate is described by second-order kinetics characterized by a rate constant γ. We also assume that the haploids have a finite lifetime in the population, and decay with a first-order rate constant κ_h. The assumption of second-order kinetics for the haploid fusion rate comes from viewing the haploid fusion as a binary collision process. At the simplest level of modeling, chemical reaction rate theory then predicts a second-order rate expression.

The assumption of first-order kinetics for the haploid decay process is the simplest model possible given that the haploids decay independently of one another, and given that the haploids have an average lifetime within the population.

Because only viable haploids can recombine, the only diploids in the population are immature and mature diploids of type (v,v). We let $n_{si,vv}$, $n_{sm,vv}$ denote the number of immature and mature diploids of type (v,v), respectively. We also let n_v denote the number of viable haploids in the population.

B. Mutation-selection equations

For a haploid fusion rate governed by second-order reaction kinetics, the equations governing the evolutionary dynamics of the population are given by

$$\frac{dn_{sm,vv}}{dt} = \kappa_{vv} n_{si,vv},$$

$$\frac{dn_{si,vv}}{dt} = \frac{1}{2}\frac{\gamma}{V} n_v^2 - \kappa_{vv} n_{si,vv},$$

$$\frac{dn_v}{dt} = 2\omega_{vv} p n_{sm,vv} - \frac{\gamma}{V} n_v^2 - \kappa_h n_v, \tag{10}$$

where V denotes the system volume in which the organisms are present.

The factor of $1/2$ in the second equation comes from the fact that we take γ to be defined in such a way that $(\gamma/V)n_v^2$ is the rate of disappearance of haploids due to haploid fusion. Since two haploids produce one diploid spore, the result is that the rate of spore production is given by $1/2$ the rate of haploid disappearance due to haploid fusion.

As another point of clarification, the factor of 2 in the third equation comes from the fact that when a mature organism produces a diploid spore, the spore immediately divides to form two haploids. As a result, since $\omega_{vv} n_{sm,vv}$ is the rate of production of diploid spores from mature organisms, the rate of production of haploids is given by $2\omega_{vv} n_{sm,vv}$. Now, each haploid contains a single chromosome that is the daughter of a parent chromosome of type v in the mature organisms genome. Since the probability that a v parent produces a v daughter is p, the fraction of v haploids produced is simply p, and so the overall rate of production of v haploids is simply $2\omega_{vv} p n_{sm,vv}$.

In this model, we assume that the system volume changes in such a way as to maintain a constant density ρ of mature diploids (they are the fully grown organisms, so the total volume is dictated by the number of mature diploids present). We also define all population fractions with respect to the mature diploids, so that $x_{si,vv} \equiv n_{si,vv}/n_{sm,vv}$, and $x_v \equiv n_v/n_{sm,vv}$.

In terms of the population fractions, we have

$$\frac{dx_{si,vv}}{dt} = \frac{1}{2}\gamma\rho x_v^2 - [\kappa_{vv} + \bar{\kappa}_s(t)]x_{si,vv},$$

$$\frac{dx_v}{dt} = 2\omega_{vv} p - \gamma\rho x_v^2 - [\kappa_h + \bar{\kappa}_s(t)]x_v, \tag{11}$$

where the mean fitness $\bar{\kappa}_s(t) = (1/n_{sm,vv})dn_{sm,vv}/dt = \kappa_{vv} x_{si,vv}$. Note that we do not need to include an equation for $x_{sm,vv}$, since by definition $x_{sm,vv} = 1$. The change of variables from population number to population ratio is accomplished in a similar manner to the asexual case.

C. Steady-state mean fitness

Using the relationship between $\bar{\kappa}_s(t)$ and $x_{si,vv}$, we obtain the steady-state equations

$$0 = \frac{1}{2}\gamma\rho x_v^2 - \left(1 + \frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)\bar{\kappa}_s(t=\infty),$$

$$0 = 2\omega_{vv} p - \gamma\rho x_v^2 - [\kappa_h + \bar{\kappa}_s(t=\infty)]x_v. \tag{12}$$

The first equation may be solved for x_v, giving

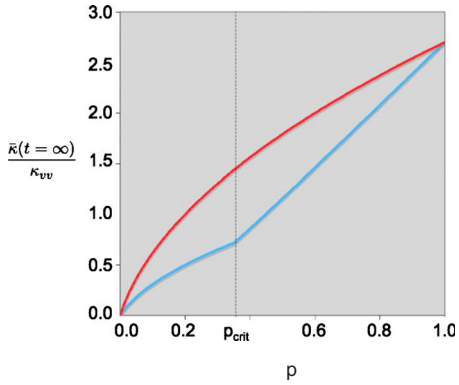

FIG. 3. (Color online) Comparison of the sexual (top line) versus asexual mean fitness (bottom line) in the limit $\rho \to \infty$. We chose $\kappa_{vv}=1$, $\kappa_{vu}=0.5$, $\omega_{vv}=10$, and $\omega_{vu}=5$.

$$x_v = \sqrt{\frac{2\left(1+\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}}{\frac{\gamma\rho}{\kappa_{vv}}}}. \tag{13}$$

Plugging into the second equation, and rearranging, we obtain

$$\frac{1}{2}\frac{\kappa_{vv}}{\gamma\rho} = \frac{\left[\frac{\omega_{vv}}{\kappa_{vv}}p - \left(1+\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right]^2}{\left(\frac{\kappa_h}{\kappa_{vv}}+\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)^2\left(1+\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}}. \tag{14}$$

If we assume that $\kappa_{vv}/(\gamma\rho)\to 0$, then we obtain

$$0 = \left(\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)^2 + \frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}} - p\frac{\omega_{vv}}{\kappa_{vv}}, \tag{15}$$

which may be solved to give

$$\bar{\kappa}_s(t=\infty) = \frac{1}{2}\left[-\kappa_{vv} + \sqrt{\kappa_{vv}^2 + 4p\kappa_{vv}\omega_{vv}}\right]. \tag{16}$$

Note that, at least in the limit of $\kappa_{vv}/\gamma\rho\to 0$, we have $\bar{\kappa}_s(t=\infty)\geq\bar{\kappa}_a(t=\infty)$, with equality only occurring at $p=0,1$, or if $\kappa_{vv}=\kappa_{vu}$ and $\omega_{vv}=\omega_{vu}$. Therefore in the model being considered here, sexual replication outcompetes asexual replication when the cost for sex (as measured by the ratio of the characteristic haploid fusion time to the characteristic growth time) is negligible. This is an encouraging result because it reveals a basic selective advantage due to sex even in a highly simplified model. For completeness, a comparison of sexual and asexual replication in the limit where the cost for sex is negligible is given in Fig. 3.

IV. COMPARISON OF THE VARIOUS REPLICATION MECHANISMS

The relative sizes of the steady-state mean fitnesses for the asexual and sexual populations dictate the dominant strategy for a given set of parameters. The reason for this is that the steady-state mean fitness is the first-order growth rate constant for a given population. Therefore given two populations employing two distinct replicative strategies, the population with the larger mean fitness will steadily increase its overall population fraction and eventually drive the other population to extinction.

We may numerically solve for the mean fitness of the sexual replication mechanism, and compare the values of $\bar{\kappa}_a(t=\infty)/\kappa_{vv}$ and $\bar{\kappa}_s(t=\infty)/\kappa_{vv}$. We choose to divide the mean fitnesses by κ_{vv}, since this corresponds to a transformation to a dimensionless system of units in which the first-order growth rate constant of the (v,v) organisms is simply 1.

For simplicity, we assume that $\kappa_h=0$. This means that we are assuming that the haploids do not decay. This is a simplifying assumption that facilitates an initial analysis of our model. It should be noted that because we assume that haploids do not disappear from the population except through fusion, the assumption that $\kappa_h=0$ maximizes the parameter regime for which sexual replication is advantageous.

In this case, the steady-state mean fitness of the sexual population is obtained by solving

$$\frac{1}{2}\frac{\kappa_{vv}}{\gamma\rho} = \frac{\left[\frac{\omega_{vv}}{\kappa_{vv}}p - \left(1+\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right]^2}{\left(\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)^3\left(1+\frac{\bar{\kappa}_s(t=\infty)}{\kappa_{vv}}\right)} \tag{17}$$

so that $\bar{\kappa}_s(t=\infty)/\kappa_{vv}$ depends only on $\kappa_{vv}/\gamma\rho$ and ω_{vv}/κ_{vv} for a given value of p.

It should be noted that $\kappa_{vv}/\gamma\rho$ measures the cost for sex in this model because this quantity measures the ratio of the characteristic haploid fusion time ($\propto 1/\gamma\rho$) to the characteristic maturation time ($\propto 1/\kappa_{vv}$).

The asexual mean fitness is given by Eqs. (7) and (9), which, when normalized by κ_{vv}, gives $\bar{\kappa}_a(t=\infty)/\kappa_{vv} = \max\{\bar{\kappa}(t=\infty)_{a,1}/\kappa_{vv}, \bar{\kappa}(t=\infty)_{a,2}/\kappa_{vv}\}$, where

$$\frac{\bar{\kappa}_{a,1}(t=\infty)}{\kappa_{vv}} = \frac{1}{2}\left[-1+\sqrt{1+4\frac{\omega_{vv}}{\kappa_{vv}}p^2}\right],$$

$$\frac{\bar{\kappa}_{a,2}(t=\infty)}{\kappa_{vv}} = \frac{1}{2}\alpha\left[-1+\sqrt{1+4\frac{\beta}{\alpha}\frac{\omega_{vv}}{\kappa_{vv}}p}\right], \tag{18}$$

where we have defined $\alpha=\kappa_{vu}/\kappa_{vv}$ and $\beta=\omega_{vu}/\omega_{vv}$.

For a given p we can determine, as a function of ω_{vv}/κ_{vv}, the value of $\kappa_{vv}/\gamma\rho$ at which the sexual and asexual mean fitnesses are equal. This curve defines the boundary separating the regimes of dominance for the two strategies. A sample curve is illustrated in Fig. 4.

We can analytically determine the behavior of this curve in both the low and high ω_{vv}/κ_{vv} regimes. First, when ω_{vv}/κ_{vv} is small, then we have

$$\frac{\bar{\kappa}_{a,1}(t=\infty)}{\kappa_{vv}} = \frac{\omega_{vv}}{\kappa_{vv}}p^2,$$

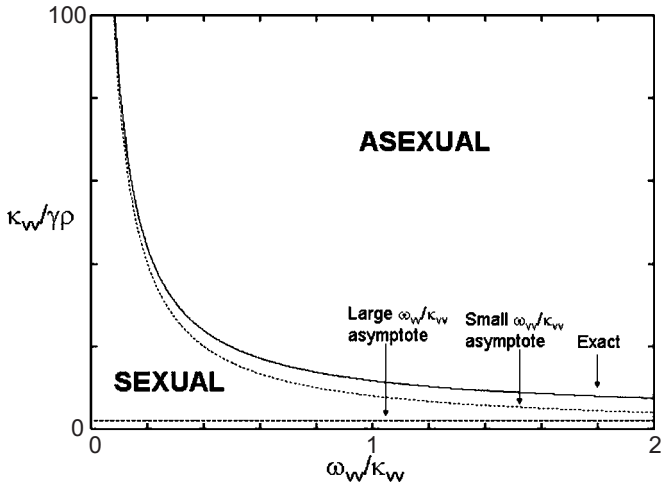

FIG. 4. Regimes for the selective advantage for asexual replication and sexual replication with second-order haploid fusion kinetics. The "Exact" curve shows the numerically computed boundary, the "Small ω_{vv}/κ_{vv} asymptote" curve shows the small ω_{vv}/κ_{vv} form of the boundary, and the "Large ω_{vv}/κ_{vv} asymptote" curve shows the large ω_{vv}/κ_{vv} form of the boundary (if we were to extend the curve all the way out to $\omega_{vv}/\kappa_{vv}=1000$, the large ω_{vv}/κ_{vv} curve and the numerically exact curve would be seen to more or less coincide). We took $\alpha=\beta=p=0.5$.

$$\frac{\bar{\kappa}_{a,2}(t=\infty)}{\kappa_{vv}}=\frac{\omega_{vv}}{\kappa_{vv}}\beta p, \tag{19}$$

and so, in any event, we have $\bar{\kappa}_a(t=\infty)/\kappa_{vv}=(\omega_{vv}/\kappa_{vv})\chi p$, where $\chi=\beta,p$.

Now, since we wish to determine the value of $\kappa_{vv}/(\gamma\rho)$ at which the sexual and asexual mean fitnesses are equal, we simply use the value of $\bar{\kappa}_a(t=\infty)/\kappa_{vv}$ for $\bar{\kappa}_s(t=\infty)/\kappa_{vv}$ in Eq. (17). Since we are assuming ω_{vv}/κ_{vv} is small, we can drop all higher-order terms in the numerator and denominator expressions, giving

$$\frac{\kappa_{vv}}{\gamma\rho}=2\frac{(1-\chi)^2}{\chi^3 p}\left(\frac{\omega_{vv}}{\kappa_{vv}}\right)^{-1}. \tag{20}$$

Now, when ω_{vv}/κ_{vv} is large, then we have

$$\frac{\bar{\kappa}_{a,1}(t=\infty)}{\kappa_{vv}}=p\sqrt{\frac{\omega_{vv}}{\kappa_{vv}}},$$

$$\frac{\bar{\kappa}_{a,2}(t=\infty)}{\kappa_{vv}}=(\alpha\beta)^{1/2}p^{1/2}\sqrt{\frac{\omega_{vv}}{\kappa_{vv}}}, \tag{21}$$

and so, in any event, we have $\bar{\kappa}_a(t=\infty)/\kappa_{vv}=p^{1/2}\chi(\omega_{vv}/\kappa_{vv})^{1/2}$, where $\chi=p^{1/2},\sqrt{\alpha\beta}$. Following a similar procedure to the one used for small ω_{vv}/κ_{vv} (only this time we drop the lowest-order terms since ω_{vv}/κ_{vv} is large), we obtain that the asexual and sexual mean fitnesses are equal when

$$\frac{\kappa_{vv}}{\gamma\rho}=2\left(\frac{1}{\chi^2}-1\right)^2. \tag{22}$$

We therefore find that, at low sporulation rates, the cost for sex, as measured by $\kappa_{vv}/\gamma\rho$, must be made steadily larger as ω_{vv}/κ_{vv} decreases in order for the asexual strategy to remain competitive with the sexual one. As illustrated in Fig. 4, this pattern indeed holds at all values of ω_{vv}/κ_{vv}. The large ω_{vv}/κ_{vv} behavior of this model also shows that, once the cost for sex drops below a critical value, given by $2(1/\chi^2-1)^2$, then sexual replication is the dominant strategy for all values of ω_{vv}/κ_{vv}.

These results may be understood as follows. As the sporulation rate ω_{vv} drops, the time interval between the production of diploid spores increases. Therefore the additional fitness penalty incurred by having the diploid spores split and pay a time cost in finding other haploids with which to fuse decreases. The result is that the cost for sex has to be pushed to higher values before the strategy becomes disadvantageous.

It is also interesting to note from the small ω_{vv}/κ_{vv} expression for the critical value of $\kappa_{vv}/\gamma\rho$ that, as p decreases, the critical cost for sex increases. This makes sense since, as the replication fidelity p drops, the benefit of sexual recombination increases as well.

Therefore the results of this model suggest that, in the case of multicellular organisms that replicate via the production of unicellular spores (or gametes, in the case of sexual organisms), sexual replication is favored in organisms that sporulate slowly. This is essentially equivalent to the statement that sexual replication is favored in organisms that produce few offspring. For such organisms, the time cost associated with haploid fusion is comparatively small, and so it makes sense to replicate via a mechanism that provides the few offspring produced with the highest possible survival probability.

Furthermore, as the maturation time of the organisms increases, or, as the population density ρ increases, the sexual strategy becomes advantageous as well. Again, this makes sense, since both an increased maturation time and an increased population density reduce the time cost associated with sex, thereby leading to a selective advantage for the sexual replication strategy.

V. CONCLUSIONS AND FUTURE RESEARCH

This paper developed models describing asexual and sexual replication in sporulating organisms. Such models are necessary for studying the selective advantages of asexual and sexual replication strategies in multicellular organisms.

Under the assumption of second-order haploid fusion kinetics, we found that sexual replication is favored at low sporulation rates, or equivalently, at low offspring numbers, long organism maturation times, and high population densities. These results make sense, since low offspring numbers, long organism maturation times, and high population densities all reduce the effective time cost associated with sex. In particular, for organisms that produce relatively few offspring, it makes sense to invest a comparatively small cost in sex and thereby maximize the survival probability of each child.

While the results of this paper appear to be consistent with actual behavior, a difficulty that arises is in correlating

preferred replication strategy with organism size. It is believed that the maturation time of an organism goes as $N^{1/4}$, where N is the number of cells in the adult organism [61,62] (there is some controversy as to whether the exponent is closer to 1/4 or 1/3 [63,64]. The argument that follows is unaffected in either case). Therefore as a function of N, we expect κ_{vv} to scale as $N^{-1/4}$. The population density of adults, however, should scale as $1/N$, giving $\kappa_{vv}/\gamma\rho \propto N^{3/4}$. Therefore the cost of sex goes to ∞ as $N \to \infty$, and so, from the small ω_{vv}/κ_{vv} criterion, we obtain that $\omega_{vv}/\kappa_{vv} \propto N^{-3/4}$ for large N, so that $\omega_{vv} \propto 1/N$. Therefore as organism size increases, the rate of sporulation must scale as the reciprocal of the organism size. This rate of decrease appears to be much too rapid to allow for the predominance of sex as the preferred replication strategy of larger organisms.

To hopefully resolve this issue, future research will study the effects of mobile gametes on haploid fusion rates. In this vein, gamete differentiation (sperm/egg) and sex differentiation (male/female) will be studied as well. It is possible that, as organism size increases, these replication strategies reduce the time cost for sex to a sufficient amount that sex does indeed emerge as the preferred replication strategy for larger organisms. While important work on gamete differentiation has been done by Dusenbery [65–67], a determination of the regimes where the various sexual replication strategies and asexual replication are advantageous has not yet been done.

Another important factor that will need to be considered is death. Thus far, our models do not assume that organisms eventually die. The neglect of this phenomenon could lead to an unrealistically large regime where asexual replication is dominant, though it is of course not yet clear if this is the case.

Finally, a key assumption of our model is that the sexual organisms release gametes continuously. In reality, sexually replicating organisms generally store up gametes for a certain period, and then, during a mating season, collectively release these gametes into the surroundings (we are considering organisms that replicate in aqueous environments for this analysis). Thus, although the gamete production rate may be low, during these brief periods when massive numbers of gametes are rapidly released, the rate of haploid fusion is fast, thereby reducing the time cost associated with sex. This reduction in time cost could be quite large, which could significantly increase the size of the regime where the sexual strategy is dominant. In this case, a weaker dependence of ω_{vv} on N may be necessary to ensure the selection for a sexual strategy, so that we do indeed obtain that sexual replication is preferred as organism size grows.

ACKNOWLEDGMENTS

The authors thank Jose F. Fontanari for helpful discussions leading to the completion of this work. This research was performed while E.T. was in the School of Biology at the Georgia Institute of Technology.

[1] G. Bell, *The Masterpiece of Nature: The Evolution and Genetics of Sexuality* (Croom Helm, London, 1982).
[2] G. C. Williams, *Sex and Evolution* (Princeton University Press, Princeton, 1975).
[3] J. Maynard-Smith, *The Evolution of Sex* (Cambridge University Press, Cambridge, UK, 1978).
[4] R. E. Michod, *Eros and Evolution: A Natural Philosophy of Sex* (Addison-Wesley, New York, 1995).
[5] L. D. Hurst and J. R. Peck, Trends Ecol. Evol. **11**, 46 (1996).
[6] D. Stauffer, P. M. C. de Olveira, S. Moss de Olveira, and R. M. Zorzenon, e-print arXiv:cond-mat/9605110.
[7] H. J. Muller, Mutat Res. **1**, 2 (1964).
[8] J. Felsenstein, Genetics **78**, 737 (1974).
[9] J. Haigh, Theor Popul. Biol. **14**, 737 (1974).
[10] H. Bernstein, H. C. Byerly, F. A. Hopf, and R. E. Michod, Science **229**, 1277 (1985).
[11] W. D. Hamilton, R. Axelrod, and R. Tanese, Proc. Natl. Acad. Sci. U.S.A. **87**, 3566 (1990).
[12] http://en.wikipedia.org/wiki/Shark.
[13] L. Kelly, *Crocodile: Evolution's Greatest Survivor* (Allen and Unwin, London, 2007).
[14] http://en.wikipedia.org/wiki/Coelacanth.
[15] J. F. Fontanari, A. Colato, and R. S. Howard, Phys. Rev. Lett. **91**, 218101 (2003).
[16] M. C. Boerlijst, S. Bonhoeer, and M. A. Nowak, Proc. R. Soc. London, Ser. B **263**, 1577 (1996).
[17] E. Tannenbaum, Phys. Rev. E **73**, 061925 (2006).
[18] E. Tannenbaum and J. F. Fontanari (unpublished).
[19] M. Eigen, Naturwiss. **58**, 465 (1971).
[20] M. Eigen, J. McCaskill, and P. Schuster, Adv. Chem. Phys. **75**, 149 (1989).
[21] D. Alves and J. F. Fontanari, J. Phys. A **30**, 2601 (1997).
[22] S. Galluccio, Phys. Rev. E **56**, 4526 (1997).
[23] P. Tarazona, Phys. Rev. A **45**, 6038 (1992).
[24] R. Pastor-Satorras and R. V. Sole, Phys. Rev. E **64**, 051909 (2001).
[25] S. Franz and L. Peliti, J. Phys. A **30**, 4481 (1997).
[26] J. Swetina and P. Schuster, Biophys. Chem. **16**, 329 (1982).
[27] S. Altmeyer and J. S. McCaskill, Phys. Rev. Lett. **86**, 5819 (2001).
[28] S. Crotty, C. E. Cameron, and R. Andino, Proc. Natl. Acad. Sci. U.S.A. **98**, 6895 (2001).
[29] D. Bonnaz and A. J. Koch, J. Phys. A **31**, 417 (1998).
[30] W. Ebeling and R. Feistel, Ann. Phys. (N.Y.) **34**, 81 (1977).
[31] P. Schuster and J. Swetina, Bull. Math. Biol. **50**, 635 (1988).
[32] S. Bonhoeffer and P. Stadler, J. Theor. Biol. **164**, 359 (1993).
[33] J. S. McCaskill, Biol. Cybern. **50**, 63 (1984).
[34] C. Kamp and S. Bornholdt, Phys. Rev. Lett. **88**, 068104 (2002).
[35] C. Kamp, C. O. Wilke, C. Adami, and S. Bornholdt, Complexity **8**, 28 (2002).
[36] C. Kamp and S. Bornholdt, Proc. R. Soc. London, Ser. B **269**, 2035 (2002).
[37] K. Negishi, D. Loakes, and R. M. Schaaper, Genetics **161**,

1363 (2002).
[38] D. A. Kessler and H. Levine, Phys. Rev. Lett. **80**, 2012 (1998).
[39] E. Tannenbaum, E. J. Deeds, and E. I. Shakhnovich, Phys. Rev. Lett. **91**, 138105 (2003).
[40] E. Tannenbaum and E. I. Shakhnovich, Phys. Rev. E **69**, 011902 (2004).
[41] A. Sasaki and M. A. Nowak, J. Theor. Biol. **224**, 241 (2003).
[42] E. Tannenbaum, E. J. Deeds, and E. I. Shakhnovich, Phys. Rev. E **69**, 061916 (2004).
[43] Y. Brumer and E. I. Shakhnovich, Phys. Rev. E **70**, 061912 (2004).
[44] E. Tannenbaum, J. L. Sherley, and E. I. Shakhnovich, Phys. Rev. E **70**, 061915 (2004).
[45] E. Tannenbaum, J. L. Sherley, and E. I. Shakhnovich, Phys. Rev. E **71**, 041914 (2005).
[46] R. V. Sole and T. S. Deisboeck, J. Theor. Biol. **228**, 47 (2004).
[47] E. van Nimwegen, J. P. Crutchfield, and Martijn Huynen, Proc. Natl. Acad. Sci. U.S.A. **96**, 9716 (1999).
[48] C. O. Wilke, J. Wang, C. Ofria, R. E. Lenski, and C. Adami, Nature (London) **412**, 331 (2001).
[49] C. O. Wilke and C. Adami, Mutat Res. **522**, 3 (2003).
[50] E. Tannenbaum and E. I. Shakhnovich, Phys. Rev. E **70**, 021903 (2004).
[51] M. Nilsson and N. Snoad, Phys. Rev. E **65**, 031901 (2002).
[52] M. Nilsson and N. Snoad, Phys. Rev. Lett. **84**, 191 (2000).
[53] J. Krug and C. Karl, Physica A **318**, 137 (2003).
[54] P. R. A. Campos and J. F. Fontanari, Phys. Rev. E **58**, 2664 (1998).
[55] D. Alves and J. F. Fontanari, Phys. Rev. E **57**, 7008 (1998).
[56] P. R. A. Campos and J. F. Fontanari, J. Phys. A **32**, L1 (1999).
[57] Y. C. Zhang, Phys. Rev. E **55**, R3817 (1997).
[58] J. Cairns, Nature (London) **255**, 197 (1975).
[59] J. R. Merok, J. A. Lansita, J. R. Tunstead, and J. L. Sherley, Cancer Res. **62**, 6791 (2002).
[60] C. S. Potten, G. Owen, and D. Booth, J. Cell. Sci. **115**, 2381 (2002).
[61] G. B. West *et al.*, Science **276**, 122 (1997).
[62] L. Demetrius, J. Theor. Biol. **243**, 455 (2006).
[63] P. S. Dodds, D. H. Rothman, and J. S. Weitz, J. Theor. Biol. **209**, 9 (2001).
[64] J. S. Weitz and S. A. Levin, Ecol. Lett. **9**, 548 (2006).
[65] D. B. Dusenbery, J. Theor. Biol. **202**, 1 (2000).
[66] D. B. Dusenbery, J. Theor. Biol. **219**, 1 (2002).
[67] D. B. Dusenbery, J. Theor. Biol. **241**, 33 (2006).