

The maintenance of sex: host–parasite coevolution with density-dependent virulence

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Keywords:

frequency-dependent selection;
host–parasite coevolution;
population dynamics;
Red Queen hypothesis;
virulence.

Abstract

Why don't asexual females replace sexual females in most natural populations of eukaryotes? One promising explanation is that parasites could counter the reproductive advantages of asexual reproduction by exerting frequency-dependent selection against common clones (the Red Queen hypothesis). One apparent limitation of the Red Queen theory, however, is that parasites would seem to be required by theory to be highly virulent. In the present study, I present a population-dynamic view of competition between sexual females and asexual females that interact with co-evolving parasites. The results show that asexual populations have higher carrying capacities, and more unstable population dynamics, than sexual populations. The results also suggest that the spread of a clone into a sexual population could increase the effective parasite virulence as population density increases. This combination of parasite-mediated frequency-dependent selection, and density-dependent virulence, could lead to the coexistence of sexual and asexual reproductive strategies and the long-term persistence of sex.

Introduction

Coevolutionary interactions with parasites have been invoked to explain the long-term maintenance of genetic diversity (Haldane, 1949; Clarke, 1976). Such interactions have also been invoked to explain the maintenance of sexual reproduction in species where asexual forms of reproduction are possible (Jaenike, 1978; Hamilton, 1980; Lloyd, 1980; Bell, 1982; Hamilton *et al.*, 1990). The logic is that sexual reproduction allows for the production of genetically variable progeny, which may be more successful on average than asexual progeny in escaping infection by coevolving parasites and pathogens. This idea is now known as the 'Red Queen hypothesis' (Bell, 1982). More specifically, under the Red Queen hypothesis, parasites are under strong selection to be able to infect the most common host genotypes. If parasites are also common, and sufficiently virulent, they could impose selection that at least temporarily favours sexual

individuals over asexual individuals (Hamilton, 1980; Hamilton *et al.*, 1990; Howard & Lively, 1994, 1998; Salathe *et al.*, 2008). The Red Queen hypotheses has been recently supported in field and laboratory studies on parthenogenetic freshwater invertebrates (Decaestecker *et al.*, 2007; Koskella & Lively, 2007, 2009; Jokela *et al.*, 2009; Wolinska & Spaak, 2009).

Although a role for parasites is not controversial with respect to the maintenance of genetic diversity, it is controversial for the maintenance of sex. The reason for the controversy, at least in part, is that the Red Queen theory for the maintenance of sex would seem to require that parasites are highly virulent. In fact, simulation studies of host–parasite coevolution suggest that parasites must be (1) common, and (2) that they must kill or sterilize infected hosts before they reproduce, in order to select for sexual reproduction (May & Anderson, 1983; Lively & Howard, 1994; Howard & Lively, 1998; Otto & Nuismer, 2004). Virulence in these models, however, tends to be a static parameter, rather than a property of the host's ecology. In the present study, I treat virulence as a function of host population density such that virulence increases monotonically with increasing host density.

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Previous theoretical results have suggested that avirulent parasites at low-host density can become highly virulent as host population size increases (Lively, 2006). The reason for this result is that infection becomes more debilitating when resources become limiting, as expected at the host's carrying capacity (Jokela *et al.*, 1999, 2005; Brown *et al.*, 2000; Ferguson & Read, 2002; Tseng, 2004; Bedhomme *et al.*, 2005). Moreover, the spread of a clone into a sexual population could lead to an increase in host density (Doncaster *et al.*, 2000). Thus, the spread of a clone into a sexual population could increase parasite virulence whenever virulence is density dependent. This coupling between the spread of asexual reproduction and parasite virulence could in turn increase the parameter space for which sex can persist under the Red Queen hypothesis. In addition, because asexuals have higher per-capita birth rates, the invasion of a sexual population by an asexual clone could lead to unstable population dynamics. In the present study, I test these ideas using analytical and computer-simulation models.

Models

Carrying capacity in sexual and asexual populations

I assume discrete, non-overlapping generations in the host population. I also assume that resources limit population size, rather than space (e.g. access to nest sites). I first show the standard solution for carrying capacity in an asexual population. I then show how carrying capacity is reduced in a sexual population, and how this stems from the cost of producing males. The implication here is that invasion by an asexual lineage will increase the population size, which may, in turn, increase virulence.

Using standard terminology, let b be the number of offspring produced by females in the absence of any competition. Let d be the death rate following reproduction, also in the absence of competition. Now let a represent the sensitivity of the birth rate to density, so that the actual birth rate, B , is equal to: $b - aN$, where N is in the number of hosts competing for resources in the relevant patch. Similarly, let c represent the sensitivity of the death rate to density, so that the actual death rate, D , is equal to: $d + cN$. Note that D is constrained to be less than or equal to one.

The recursion equation for the number of individuals at time $t + 1$, as a function of N_t is:

$$N_{t+1} = N_t + BN_t - DN_t. \quad (1)$$

The change in population size is calculated as:

$$N_{t+1} - N_t = N_t(B - D). \quad (2)$$

The equilibrium density, K_{asex} , is thus attained when $B = D$. Hence as reviewed by Gotelli (1995), the carrying capacity is:

$$K_{\text{asex}} = \frac{b - d}{a + c} \quad (3)$$

Using this value for K_{asex} , eqn 1 can be converted into the more familiar form of the discrete-time logistic equation:

$$N_{t+1} = N_t + rN_t \left(1 - \frac{N_t}{K_{\text{asex}}}\right), \quad (4)$$

where $r = b - d$. This formulation assumes that all individuals are reproducing (e.g. asexual). For a dioecious (or gonochoric) population, however, males are not directly producing offspring. Hence the calculation for equilibrium in a sexual population is attained when $(1 - s)B = D$, where s is the frequency of males in the population. It is easy to show that the carrying capacity for a sexual population, K_{sex} , is equal to:

$$K_{\text{sex}} = \frac{(1 - s)b - d}{(1 - s)a + c}. \quad (5)$$

Clearly, an asexual population would have a higher carrying capacity (see also Doncaster *et al.*, 2000). Assuming the death rate is density independent (i.e. $c = 0$), the ratio of the carrying capacity for an asexual population divided by the carrying capacity for a sexual population reduces to:

$$\frac{K_{\text{asex}}}{K_{\text{sex}}} = \frac{(1 - s)(b - d)}{(1 - s)b - d} \quad (6)$$

Note that for $d = 0$ (an immortal population), $K_{\text{asex}} = K_{\text{sex}}$ (see also Doncaster *et al.*, 2000). For $d > 0$ and $s = 1/2$, we get

$$\frac{K_{\text{asex}}}{K_{\text{sex}}} = \frac{b - d}{b - 2d}. \quad (7)$$

Therefore, the asexual population would be expected to be larger than the sexual population, and invasion of a sexual population by an asexual lineage would be expected to increase the population size. For example, for $b = 4$ and $d = 1$, the asexual population would be expected to be 1.5 times larger than the sexual population ($K_{\text{asex}}/K_{\text{sex}} = (4 - 1)/(4 - 2) = 1.5$).

This result seems counterintuitive at first. Why would an asexual population be more numerous on the same resource base than a sexual population? The result, however, makes more sense when one realizes that sexual females must, on average, produce two offspring at carrying capacity (K_{sex} , assuming a 1 : 1 sex ratio), whereas asexual females need to make only 1 offspring at carrying capacity (K_{asex}). Hence, asexual populations have a lower R^* (Tilman, 1982). And this is precisely why asexuals can invade a sexual population at its carrying capacity. Specifically, at K_{sex} , asexuals produce more offspring per capita than sexuals, which is what allows the clone to spread in the sexual population (Fig. 1).

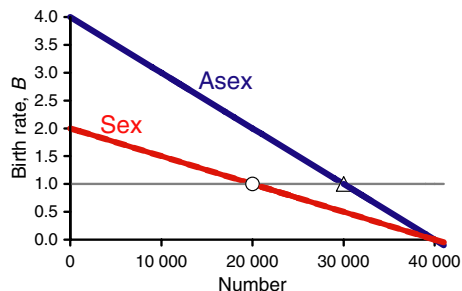


Fig. 1 Graphical representation of the cost of sex. The red line gives the per capita birth rate for the sexual population; the blue line gives the per capita birth rate for the asexual population. The horizontal black line gives the death rate (here assumed to be one for an annual). The open circle gives the carrying capacity for the sexual population ($n = 20\,000$), and the open triangle gives the carrying capacity for the asexual population ($n = 30\,000$). The carrying capacities were calculated from the equations for K_{sex} and K_{asex} in the text. Parameter values as follows: $b = 4$; $a = 0.0001$; $s = 0.5$. Note that the per capita birth rate for the asexual population is equal to two at the carrying capacity for the sexual population.

Simulation model

I constructed a computer-simulation model to determine the outcome of competition between sexual and asexual individuals in the presence of potentially coevolving parasites. The goal was to determine whether: (1) invasion of sexual populations by asexual clones increased population size, (2) whether such an increase in population size lead to increased parasite virulence and (3) whether parasites could prevent the fixation of clonal mutants.

I assumed an annual host population, so the death rate, D , was equal to one ($d = 1$, and $c = 0$). I also assumed two loci in a haploid host population, with three alleles at both loci (giving nine possible genotypes). Infection by parasites required that parasites match the host at both loci, which is the standard assumption for the matching alleles model for infection (Frank, 1993; Otto & Michalakis, 1998; Agrawal & Lively, 2002). I did not simulate the effects of infection as determined by gene-for-gene interactions; but elsewhere, we have found that the coevolutionary system behaves dynamically like a matching-alleles system over most of the continuum between matching alleles and gene-for-gene genetics (Agrawal & Lively, 2002). In general, the matching-alleles model is a good approximation for the genetic basis of infection when different parasite genotypes infect different host genotypes (for experimental evidence, see Carius *et al.*, 2001; Dybdahl *et al.*, 2008).

Under these assumptions, the recursion for the number of asexual individuals with genotype ij at time $t + 1$ is:

$$A'_{ij} = A_{ij(I)}(b_{(I)} - a_{(I)}N_t) + A_{ij(U)}(b_{(U)} - a_{(U)}N_t), \quad (8)$$

where A'_{ij} gives the total number of asexual individuals with the ij th genotype at time $t + 1$; $A_{ij(I)}$ gives the number of infected (I) asexual individuals with the ij th genotype at time t ; and $A_{ij(U)}$ gives the number of uninfected (U) asexual individuals for the ij th genotype at time t . In addition, $b_{(I)}$ gives the intrinsic birth rate of infected individuals, whereas $b_{(U)}$ gives the intrinsic birth rate of uninfected individuals. Finally, $a_{(I)}$ reflects the sensitivity to total density for infected individuals, and $a_{(U)}$ gives the sensitivity of uninfected individuals to total host density, where N_t is the total number of sexual and asexual individuals in the population. Similarly, the recursion for the number of sexual individuals with genotype ij at $t + 1$, assuming no recombination between resistance loci, is:

$$S'_{ij} = (1 - s)[S_{ij(I)}(b_{(I)} - a_{(I)}N_t) + S_{ij(U)}(b_{(U)} - a_{(U)}N_t)], \quad (9)$$

where S'_{ij} is the total number of sexual individuals with the ij th genotype at time $t+1$; s is the frequency of males in the sexual population; $S_{ij(I)}$ is the number of infected individuals of the ij th genotype in the sexual population at time t ; and $S_{ij(U)}$ is the number of uninfected individuals of the ij th genotype in the sexual population at time t . If there is recombination between loci, the number of sexual individuals of each genotype, after accounting for recombination is:

$$S''_{ij} = (1 - \rho)S'_{ij} + \rho S_i S_j, \quad (10)$$

where S_i is the number of individuals with allele i at the first locus; S_j is the number of individuals with allele j at the second locus; and ρ is the frequency of recombination (see Hartl & Clark, 1989). Finally, I used the standard assumption that the probability of infection for each host genotype depends on the frequency of the matching genotype in the parasite population. Hence, we get:

$$S'_{ij(I)} = S''_{ij}P_{ij} \text{ and } S'_{ij(U)} = S''_{ij}(1 - P_{ij}), \quad (11)$$

where P_{ij} gives the frequency of parasite genotype ij at time t . Similarly, the number of infected and uninfected asexual individuals at time t is:

$$\begin{aligned} A'_{ij(I)} &= A'_{ij}P_{ij}, \text{ and} \\ A'_{ij(U)} &= A'_{ij}(1 - P_{ij}). \end{aligned} \quad (12)$$

The simulation began with a sexual population at its carrying capacity (eqn 5). There were two haploid loci, each with three alleles that determined ‘self’ for the host; parasites that matched at both loci infected the host; otherwise the parasite was killed by the host’s self-nonsel self recognition system. Host-genotype frequencies began in linkage equilibrium, calculated from allele frequencies that were randomly assigned at the beginning of each run. Parasite-genotype frequencies were set as being equally common at the start of the simulation.

Migration into the sexual host population was allowed. In the results presented below, the probability that a

single, uninfected individual entered the population was set to 0.10 for each sexual genotype. Similarly, the probability that a single, infected individual entered the population was set to 0.02 for each sexual genotype; hence, the simulation also allowed for a low level of parasite immigration. A single clonal mutant entered the simulation at generation 1000. Clones did not immigrate into the population, and the clone was considered extinct if the number of clones dropped below one in any generation. The recombination rate, ρ , in the sexual population was set to 0.2, as intermediate values of recombination were favoured in similar models (Peters & Lively, 2007).

To test the generality of the results, I also ran the simulation for a haploid, two-locus, two-allele system, thereby reducing the number of possible genotypes from nine to four. I also ran the simulation for a diploid system, assuming two alleles at each of two loci, giving nine possible genotypes, as in the original haploid model. In the diploid model, I assumed that the clone had the same genotype as one of the double homozygotes in the sexual population. All other assumptions were retained as for the haploid, two-locus, three-allele model described above.

In all simulations, the effect of infection (virulence) emerged as the difference in per capita growth rates between infected and uninfected individuals within each reproductive mode. For the sake of calculating the effect of infection over time, virulence at time t (V_t) was calculated (assuming $D = 1$) for both sexual and asexual populations as,

$$V_t = 1 - \frac{b_{(I)} - a_{(I)}N_t}{b_{(U)} - a_{(U)}N_t}. \quad (13)$$

Thus, virulence depended on total host density (N_t), as well as on the birth rates of infected individuals relative to uninfected individuals (see also Lively, 2006).

Results

I first tested the analytical prediction that an asexual population would rapidly replace a sexual population in the absence of virulent parasites, and reach a higher carrying capacity. The simulation results are consistent with this idea (Fig. 2). Assuming that the intrinsic birth rates of sexual and asexual females are both equal to 3.0, and no effect of infection on competitive ability ($a_{(I)} = a_{(U)} = 0.0001$), the results show rapid replacement of the sexual population and an asymptotic approach to a higher carrying capacity by the asexual population (Fig. 2a), consistent with equation (3). In addition, the asexual population shows stable population dynamics (Fig. 2a). When the birth rates of both sexual and asexual females were increased to 3.5, a similar result was obtained, except that the asexual population was not

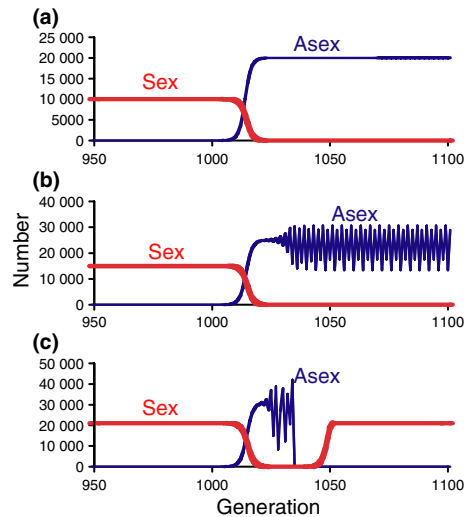


Fig. 2 Sex vs. asex assuming avirulent infection for different host birth rates for infected (b_I) and uninfected (b_U) individuals. (a) $b_I = b_U = 3$, (b) $b_I = b_U = 3.5$ and (c) $b_I = b_U = 4.1$. The labels are as follows: 'sex' for the sexual population, and 'asex' for the asexual population. For all three panels, $a_I = a_U = 0.0001$ (i.e. virulence = 0). The simulated carrying capacities for asexual and sexual populations converge on the analytical solutions in equations (3) and (5), respectively.

stable and showed oscillatory dynamics (Fig. 2b), as expected under theory (May, 1974). Finally, when the birth rates of both sexuals and asexuals was increased to 4.1, the asexual population rapidly replaced the sexual population; but the dynamics of the asexual population became chaotic, also an expected result (May, 1974), and the clone went extinct (Fig. 2c). The sexual population then reinvaded the unoccupied area, and quickly grew to a stable equilibrium density as given by eqn 5. Hence, sexual populations are more stable as a direct consequence of producing males, because males decrease the per-capita birth rate.

I then examined the effect of increasing parasite virulence on the competition between sexual and asexual populations. For these simulations, the intrinsic birth rates of sexual and asexual females were assumed to be the same ($b_{(I)} = b_{(U)} = 3.5$), which is conservative with respect to virulence. The competition coefficient for infected individuals ($a_{(I)}$) was, however, altered from 0.00016 to 0.00025, while holding the competition coefficient for uninfected individuals at a lower rate ($a_{(U)} = 0.00010$). Thus, virulence depended on host density. Starting with $a_{(I)} = 0.00016$, the results showed a stable sexual population prior to the introduction of the clonal mutant (Fig. 3a). In addition, virulence fluctuates slightly around 0.4 (Fig. 3b), which is too low to select for sexual reproduction given the standard two-fold cost of sex. Following the introduction of the clone at

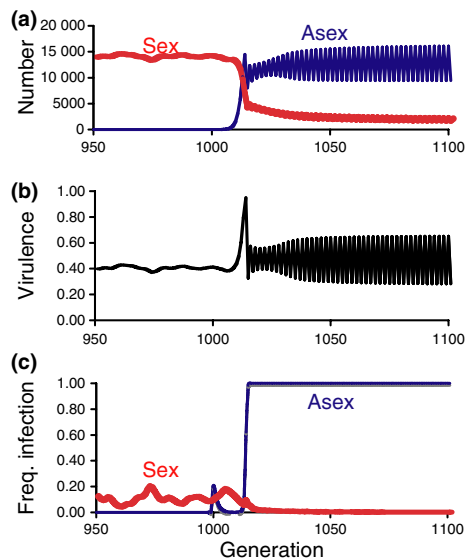


Fig. 3 Sex vs. asex with density-dependent virulence ($a_{(l)} = 0.00016$; $a_{(U)} = 0.0001$; $b_{(l)} = b_{(U)} = 3.5$). (a) numbers of sexual ('sex') individuals and asexual (asex) individuals over time, (b) virulence over time and (c) the frequency of infection in the sexual and asexual populations over time. The clone was introduced at generation 1000.

generation 1000, the asexual population rapidly increases, followed by a dramatic spike in virulence, as well as an equally dramatic increase in the total frequency of infection as the parasites begin to 'target' the common clone (Fig. 3c). At some point, the overall strength of selection becomes sufficient to prevent the further spread of the clone, and the population becomes a mixture of sexual and asexual individuals, wherein the frequency of asexual reproduction and virulence both oscillate.

Increasing the competition coefficient for infected individuals ($a_{(l)}$) to 0.00020 leads to more dynamically complex results (Fig. 4a). Here virulence oscillates at a high level (0.55–0.70) prior to the introduction of the clone at generation 1000. Nonetheless, both virulence and frequency of infection spike after the clone enters the population, followed by a dramatic decrease in the frequency of the clone (Fig. 4b). The clone then begins to oscillate numerically with the sexual population; and it is periodically driven to low levels, which would facilitate the operation of Muller's Ratchet (Howard & Lively, 1994). In addition, every time the clone increases in frequency, virulence and the frequency of infection both increase. As a result, the strength of selection against the clone is highly dynamic (Fig. 4b).

Finally, when the competition coefficient for infected individuals ($a_{(l)}$) was increased to 0.00025, the clone increased after its introduction (Fig. 5a), followed by an increase in the frequency of infection as well as an

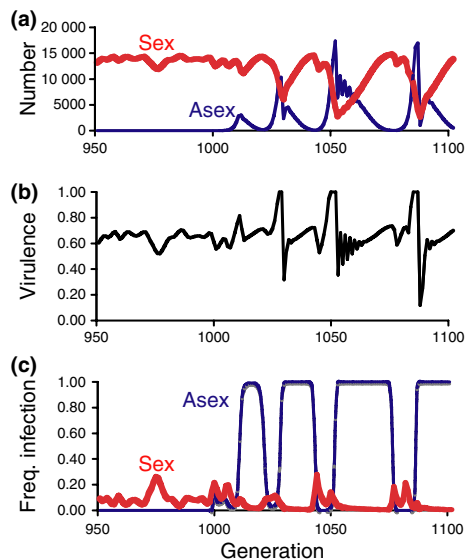


Fig. 4 Sex vs. asex with density-dependent virulence ($a_{(l)} = 0.0002$; $a_{(U)} = 0.0001$; $b_{(l)} = b_{(U)} = 3.5$). (a) numbers of sexual ('sex') individuals and asexual ('asex') individuals over time, (b) virulence over time and (c) the frequency of infection in the sexual and asexual populations over time. The clone was introduced at generation 1000.

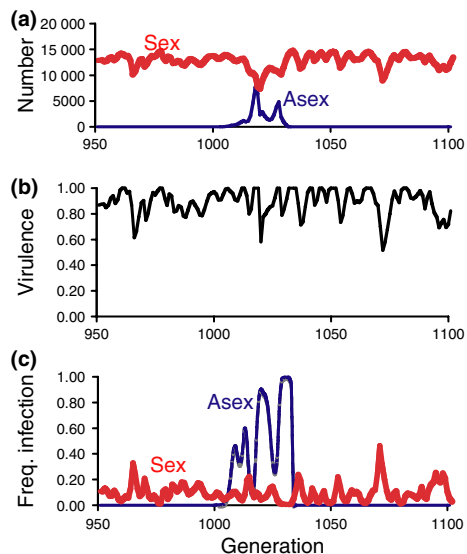


Fig. 5 Sex vs. asex with density-dependent virulence ($a_{(l)} = 0.00025$; $a_{(U)} = 0.0001$; $b_{(l)} = b_{(U)} = 3.5$). (a) numbers of sexual ('sex') individuals and asexual ('asex') individuals over time, (b) virulence over time and (c) the frequency of infection in the sexual and asexual populations over time. The clone was introduced at generation 1000.

increase in virulence, from very high to complete sterilization (Fig. 5b,c). The clone was rapidly driven to extinction (Fig. 5a). This result suggests that parasites

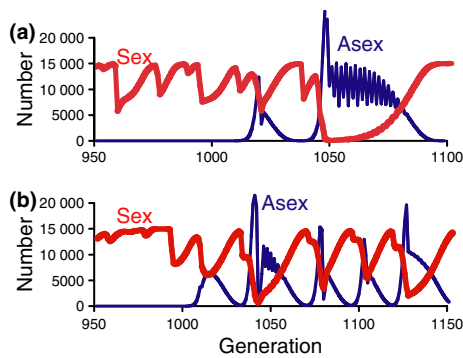


Fig. 6 Sex vs. asex with density-dependent virulence ($a_{(l)} = 0.00020$; $a_{(U)} = 0.0001$; $b_{(l)} = b_{(U)} = 3.5$). (a) numbers of sexual ('sex') individuals and asexual ('asex') individuals over time, assuming a haploid, two-locus, two-allele model (four possible genotypes) and (b) numbers of sexual ('sex') individuals and asexual ('asex') individuals over time, assuming a diploid, two-locus, two-allele model (nine possible genotypes). Compare to Fig. 4b, which gives a haploid, two-locus, three-allele model (nine possible genotypes). The clone was introduced at generation 1000.

could be sufficient, under some cases, to cause the extinction of clones without the aid of other forces (at least under the assumption made here of a linear effect of population density on host birth rates).

The results are robust to some of the specific assumptions of the model. For example, reducing the number of alleles from three to two per locus rendered qualitatively similar results (Fig. 6a). In addition, increasing or decreasing the rate of recombination (ρ) also generated similar results (not shown). Finally, shifting the model to a diploid, two-locus, two-allele model gave similar results, (Fig. 6b). In all cases, the frequency of infection in the asexual population greatly exceeded the frequency of infection in the sexual population as long as the clone was common (Figs 3–5).

Discussion

The results of the present study suggest that asexual populations would rapidly replace sexual populations in the absence of coevolving parasites, and that the asexual populations would reach a higher carrying capacity (Fig. 2) (see also Doncaster *et al.*, 2000). Higher carrying capacities are possible in asexual populations because asexual females require fewer resources to replace themselves than sexual females. In other words, asexual populations have a lower R^* (Tilman, 1982) than sexual populations. This prediction could be tested by examining the equilibrium densities of sexual and asexual populations living separately on the same resource base.

I also found that replacement of sexuals by asexuals could change the population dynamics, from stable, to oscillatory or even chaotic, because the introduction of

asexual reproduction increases the per-capita birth rate. If the asexual population experiences chaotic fluctuations, it could go extinct, simply as a consequence of extreme fluctuations in population size, and the patch could then be re-invaded by sexuals following migration. Therefore, it is possible that sex is evolutionarily stable in metapopulations because sexual populations are more dynamically stable. Phenotypic diversity also helps to stabilize population dynamics, which may also help promote stability in sexual populations (Doebeli & Koella, 1994; Doebeli, 1995; Ruxton, 1995; Doebeli & de Jong, 1999; Flatt *et al.*, 2001; Lively, 2006).

If the spread of asexuality into an otherwise sexual population increases the carrying capacity, then it could also increase parasite virulence, if virulence is density dependent (for experimental studies of density-dependent virulence see Lively *et al.*, 1995; Bell *et al.*, 2006; Bieger & Ebert, 2009; Yamazaki *et al.*, 2009). The present results suggest that sexual populations experiencing low levels of infection, and low virulence (resulting in a low strength of selection), would be invaded by asexuals. However, after an asexual clone becomes common in the population, both the frequency of infection and virulence increase, leading to stronger parasite-mediated selection against the clone, and to coexistence of sexual and asexual individuals (Fig. 3). Hence, the fact that parasites are not common or virulent in a sexual population cannot be taken to mean that they could not become sufficiently common and virulent in a mixed population to prevent the elimination of sexual females.

More generally, any factor that increases virulence would also increase the parasite-mediated selection against common clones. I have focused here on one ecological factor, population density, but additional ecological or evolutionary factors might lead to increased virulence [e.g. superinfection (Nowak & May, 1994), coinfection (Bremermann & Pickering, 1983; May & Nowak, 1995; Frank, 1996), spore longevity (Bonhoeffer *et al.*, 1996), and propagule interactions (Lively, 2001)]. In addition, factors that increase the number of parasite exposures per host would also increase the parasite-mediated selection against common host genotypes. Incorporation of more realistic ecological, genetic, and life-history details should give a more robust view of host–parasite interactions as a coevolutionary force in natural populations.

Finally, the results presented here do not seem to be an artefact of the haploid, two-locus, three-allele model chosen for most of the simulations. Similar results were obtained for two-loci, two-allele models that were either haploid or diploid. Thus, in general, the specific genetic system may not matter, as long as the sexual population has sufficient genotypic 'space' that it can evolve away from the clone as it becomes common, and thereby reduce the risk of infection. On the other hand, the results would not be robust to the assumption regarding the number of clones competing with the

sexual population (here only 1). As clonal diversity increases, any possible advantage to sexual reproduction (in avoiding infection) decreases (Lively & Howard, 1994). Similarly, modifiers that increase the amount of diploid sex may not increase in genetically diverse asexual populations (Agrawal, 2009). Nonetheless, an obligately sexual population might be stable to replacement by different obligately asexual genotypes when introduced one at a time, provided parasites prevent the fixation of clones in the short term, and that the clones are eliminated by Muller's ratchet in the longer term (Lively & Howard, 1994) or by the parasites themselves.

Acknowledgments

The author thanks Anil Agrawal, Lynda Delph, Steve Howard, Jukka Jokela, Kayla King, Maurine Neiman, and Aurelien Tellier for comments on the paper. This study was supported by the US National Science Foundation (DEB-0515832, DEB-0640639).

References

- Agrawal, A.F. 2009. Differences between selection on sex versus recombination in Red Queen models with diploid hosts. *Evolution* **63**: 2131–2141.
- Agrawal, A.F. & Lively, C.M. 2002. Infection genetics: gene-for-gene vs. matching-allele models, and all points in between. *Evol. Ecol. Res.* **4**: 79–90.
- Bedhomme, S., Agnew, P., Vital, Y., Sidobre, C. & Michalakis, Y. 2005. Prevalence-dependent costs of parasite virulence. *PLoS Biol.* **3**: 1403–1408.
- Bell, G. 1982. *The Masterpiece of Nature: The Evolution and Genetics of Sexuality*. University of California Press, Berkeley.
- Bell, T., Freckleton, R.P. & Lewis, O.T. 2006. Plant pathogens drive density-dependent seedling mortality in a tropical tree. *Ecol. Lett.* **9**: 569–574.
- Bieger, A. & Ebert, D. 2009. Expression of parasite virulence at different host population densities under natural conditions. *Oecologia* **160**: 247–255.
- Bonhoeffer, S., Lenski, R.E. & Ebert, D. 1996. The curse of the pharaoh: the evolution of virulence in pathogens with long living propagules. *Proc. R. Soc. Lond. B* **263**: 715–721.
- Bremermann, H.J. & Pickering, J. 1983. A game-theoretical model of parasite virulence. *J. Theor. Biol.* **100**: 411–426.
- Brown, M.J.F., Loosli, R. & Schmid-Hempel, P. 2000. Condition-dependent expression of virulence in a trypanosome infecting bumblebees. *Oikos* **91**: 421–427.
- Carius, H.-J., Little, T.J. & Ebert, D. 2001. Genetic variation in a host–parasite association: potential for coevolution and frequency dependent selection. *Evolution* **55**: 1136–1145.
- Clarke, B. 1976. The ecological relationships of host–parasite relationships. In: *Genetic Aspects of Host–Parasite Relationships* (A.E.R. Taylor & R. Muller, eds), pp. 87–103. Blackwell, Oxford.
- Decaestecker, E., Gaba, S., Raeymaekers, J.A.M., Stoks, R., Van Kerckhoven, L., Ebert, D. & De Meester, L. 2007. Host–parasite 'Red Queen' dynamics archived in pond sediment. *Nature* **450**: 870–873.
- Doebeli, M. 1995. Phenotypic variability, sexual reproduction, and evolutionary population dynamics. *J. Evol. Biol.* **8**: 173–194.
- Doebeli, M. & de Jong, G. 1999. Genetic variability in sensitivity to population density affects the dynamics of simple ecological models. *Theor. Popul. Biol.* **55**: 37–52.
- Doebeli, M. & Koella, J.C. 1994. Sex and population dynamics. *Proc. R. Soc. Lond. B* **257**: 17–23.
- Doncaster, C.P., Pound, G.E. & Cox, S.J. 2000. The ecological cost of sex. *Nature* **404**: 281–285.
- Dybdahl, M., Jokela, J., Delph, L.F., Koskella, B. & Lively, C.M. 2008. Hybrid fitness in a locally adapted parasite. *Am. Nat.* **172**: 772–782.
- Ferguson, H.M. & Read, A.F. 2002. Genetic and environmental determinants of malaria parasite virulence in mosquitoes. *Proc. R. Soc. Lond. B* **269**: 1217–1224.
- Flatt, T., Maire, N. & Doebeli, M. 2001. A bit of sex stabilizes host–parasite dynamics. *J. Theor. Biol.* **212**: 345–354.
- Frank, S.A. 1993. Specificity vs. detectable polymorphism in host–parasite genetics. *Proc. R. Soc. Lond. B* **254**: 191–197.
- Frank, S.A. 1996. Models of parasite virulence. *Quart. Rev. Biol.* **71**: 37–78.
- Gotelli, N.J. 1995. *A Primer of Ecology*. Sinauer Associates, Sunderland.
- Haldane, J.B.S. 1949. Disease and evolution. *La Ricerca Scientifica* **19**(Suppl.): 68–76.
- Hamilton, W.D. 1980. Sex vs. non-sex vs. parasite. *Oikos* **35**: 282–290.
- Hamilton, W.D., Axelrod, R. & Tanese, R. 1990. Sexual reproduction as an adaptation to resist parasites (a review). *Proc. Natl Acad. Sci. USA* **87**: 3566–3573.
- Hartl, D.L. & Clark, A.G. 1989. *Principles of Population Genetics*, 2nd edn. Sinauer Associates, Sunderland.
- Howard, R.S. & Lively, C.M. 1994. Parasitism, mutation accumulation and the maintenance of sex. *Nature* **367**: 554–557.
- Howard, R.S. & Lively, C.M. 1998. The maintenance of sex by parasitism and mutation accumulation under epistatic fitness functions. *Evolution* **52**: 604–610.
- Jaenike, J. 1978. An hypothesis to account for the maintenance of sex within populations. *Evol. Theory* **3**: 191–194.
- Jokela, J., Lively, C.M., Taskinen, J. & Peters, A.D. 1999. Effect of starvation on parasite-induced mortality in a freshwater snail (*Potamopyrgus antipodarum*). *Oecologia* **119**: 320–325.
- Jokela, J., Taskinen, J., Mutikainen, P. & Kopp, K. 2005. Virulence of parasites in hosts under environmental stress: experiments with anoxia and starvation. *Oikos* **108**: 156–164.
- Jokela, J., Dybdahl, M. & Lively, C.M. 2009. The maintenance of sex, clonal dynamics, and host–parasite coevolution in a mixed population of sexual and asexual snails. *Am. Nat.* **174**: S43–S53.
- Koskella, B. & Lively, C.M. 2007. Advice of the rose: experimental coevolution of a trematode parasite and its snail host. *Evolution* **61**: 152–159.
- Koskella, B. & Lively, C.M. 2009. Evidence for negative frequency-dependent selection during experimental coevolution of a freshwater snail and a sterilizing trematode. *Evolution* **63**: 2213–2221.
- Lively, C.M. 2001. Propagule interactions and the evolution of virulence. *J. Evol. Biol.* **14**: 317–324.
- Lively, C.M. 2006. The ecology of virulence. *Ecol. Lett.* **9**: 1089–1095.

- Lively, C.M. & Howard, R.S. 1994. Selection by parasites for clonal diversity and mixed mating. *Phil. Trans. Roy. Soc. Lond. B* **346**: 271–281.
- Lively, C.M., Johnson, S.G., Delph, L.F. & Clay, K. 1995. Thinning reduces the effect of rust infection on jewelweed (*Impatiens capensis*). *Ecology* **76**: 1859–1862.
- Lloyd, D.G. 1980. Benefits and handicaps of sexual reproduction. *Evol. Biol.* **13**: 69–111.
- May, R.M. 1974. Biological populations with non-overlapping generations: stable points, stable cycles, and chaos. *Science* **186**: 645–647.
- May, R.M. & Anderson, R.M. 1983. Epidemiology and genetics in the coevolution of parasites and hosts. *Proc. R. Soc. Lond. B* **219**: 281–313.
- May, R.M. & Nowak, M.A. 1995. Coinfection and the evolution of virulence. *Proc. R. Soc. Lond. B* **261**: 209–215.
- Nowak, M.A. & May, R.M. 1994. Superinfection and the evolution of parasite virulence. *Proc. R. Soc. Lond. B* **255**: 81–89.
- Otto, S.P. & Michalakis, Y. 1998. The evolution of recombination in changing environments. *Trends Ecol. Evol.* **13**: 145–151.
- Otto, S.P. & Nuismer, S.L. 2004. Species interactions and the evolution of sex. *Science* **304**: 1018–1020.
- Peters, A.D. & Lively, C.M. 2007. Short- and long-term benefits and detriments to recombination under antagonistic coevolution. *J. Evol. Biol.* **20**: 1206–1217.
- Ruxton, G.D. 1995. Population models with sexual reproduction show a reduced propensity to exhibit chaos. *J. Theor. Biol.* **175**: 595–601.
- Salathe, M., Kouyos, R.D. & Bonhoeffer, S. 2008. The state of affairs in the kingdom of the Red Queen. *Trends Ecol. Evol.* **23**: 439–445.
- Tilman, D. 1982. *Resource Competition and Community Structure*. Princeton University Press, Princeton.
- Tseng, M. 2004. Sex-specific response of a mosquito to parasites and crowding. *Proc. R. Soc. Lond. B* **271**: S186–S188.
- Wolinska, J. & Spaak, P. 2009. The cost of being common: evidence from natural *Daphnia* populations. *Evolution* **63**: 1893–1901.
- Yamazaki, M., Iwamoto, S. & Seiwa, K. 2009. Distance- and density-dependent seedling mortality caused by several diseases in eight tree species co-occurring in a temperate forest. *Plant Ecol.* **201**: 181–196.

Received 10 April 2009; revised 20 July 2009; accepted 21 July 2009