A Review of Red Queen Models for the Persistence of Obligate Sexual Reproduction

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Abstract

I present a historical review of coevolutionary models for the evolutionary persistence of sexual reproduction. The focus is on the fate of obligately sexual populations facing competition with one or more obligately asexual clones. An early simulation model by Hamilton (Hamilton WD. 1980. Sex versus non-sex versus parasite. Oikos. 35:282–290.) suggested that parasites could be an important force in selecting against asexual clones, leading to the persistence of sex. This result was consistent with a number of independent verbal models generated from 1975–1983. Conversely, the models by May and Anderson (May RM, Anderson RM. 1983. Epidemiology and genetics in the coevolution of parasites and hosts. Proc R Soc Lond B Biol Sci. 219:281–313.), which included more epidemiological detail, suggested that parasites were an unlikely source of selection to favor sexual over asexual reproduction. Thus began an oscillation of opinion regarding the role of parasites in selection for sex. It would seem at present that some of the differences of opinion over time stemmed from the different ways that models were constructed, including whether the sexual population was in competition with a genetically diverse asexual population or a single clonal genotype. On theoretical grounds, parasite-mediated selection for sex seems more likely if the sexual population has options in genotypic space that are not available to the clones. Models that incorporate more ecological realism also seem more favorable to the parasite theory of sex.

Key words: *evolution of sex, host–parasite coevolution, parthenogenesis*

As for so many issues in evolutionary biology, consideration of the conundrum presented by sexual reproduction goes back to Darwin. Darwin was interested in heterostyly in plants, a condition in which the anthers and pistil occupy different positions in different individual plants. In one morph, the anthers occur above the top of the pistil, and in the other morph the opposite is true: the anthers occur below the pistil. Through a series of elegant experiments, Darwin found unambiguous evidence that each morph could only cross with the other morph; crosses between different individuals of the same morph were unsuccessful (Darwin 1862). Darwin wondered why this should be true and suggested that the heterostylous condition evolved so as to ensure cross-fertilization and thereby avoid the fitness costs associated with close inbreeding. But then he took a step back and asked a more general question, illustrated in this quote:

> "... why new beings should be produced by the union of the two sexual elements, instead of by a process of parthenogenesis .... The whole subject is as yet hidden in darkness."

Why indeed? Why should reproduction so often require cross-fertilization between different reproductive morphs, especially when asexual reproduction is a known alternative? Evolutionary biologists are still grappling with the question. For example, Hamilton (1975b) remarked that, "... complete inbreeding abandons the obviously important advantages of sexual reproduction, whatever these are."

Darwin's (1862) question was considered by several of the great evolutionary biologists over the next 100 plus years (see Meirmans 2009), but it took on renewed force in the early 1970s when John Maynard Smith and G. C. Williams pointed out the large costs associated with cross-fertilization. Both biologists seem to have come to the question through their deliberations on group selection. In dismissing the logic of good-of-the-species reasoning, they realized that the previous explanations for the advantages of sex were, in fact, at the group level. For example, Maynard Smith (1978) stated that

> "My own active interest in the evolution of genetic systems dates from around 1964, when I realized that it was illogical

to reject Wynne-Edwards's (1962) views in ecology as group selectionist, if at the same time I accepted a group selectionist explanation of sex."

It is important to follow the thread of Maynard Smith's reasoning for suggesting that there must be a short-term advantage to sexual reproduction. The reasoning stems directly from the fact that obligately sexual, dioecious (separate sexes) populations produce males, which do not give birth; and hence males decrease the per capita birth rate of the population. For example, in a sexual population composed of 50% males, one half of the adult population is not giving birth. Why then would a parthenogenetic clone, for which all the adults give birth, not rapidly replace the sexual population? Surely a clone, in which all the females were fertile, would rapidly replace another clone in which half of the adult females were unable to reproduce. Thus Maynard Smith made a powerful case for the cost of producing males, which could be as high as 2-fold, and he pointed out that evolutionary biologists could not explain why sex persisted in the face of this cost.

Williams made a similar case for the anomaly provided to evolutionary biology by sex, as exemplified by this quote from the preface of his book (Williams 1975).

"... the prevalence of sexual reproduction in higher plants and animals is inconsistent with current evolutionary theory ... There is a kind of crisis at hand in evolutionary biology."

However, Williams framed the cost of sex in a different way. Williams framed the cost of sex as resulting from the reduction in relatedness between parent and offspring (the "cost of meiosis"). The cost of meiosis is not, as the name implies, that the cost of maintaining the machinery for meiosis but rather that offspring resulting from meiosis and cross-fertilization are only half as related to their mother as parthenogenetic offspring. This additional cost suggests that there may be 2 costs of sex, giving a greater than 2-fold total cost of sex, but elsewhere it has been shown that either one or the other (but not both) apply, depending on the type of uniparental offspring (Lively and Lloyd 1990). Here, I will stick with Maynard Smith's "cost of producing males," as it is the relevant cost of sex when considering a competition between a sexual population and one or more reproductively isolated asexual clones. I will also focus on the role that parasites might play in preventing the fixation of obligately asexual clones after their introduction into a dioecious, sexual host population.

Origin of the Red Queen Hypothesis

The parasite hypothesis for sex can be presented in surprisingly complicated terms, but the core idea is straightforward. The core idea is that parasites are generally under selection to infect the most common genotypes in the local host population, assuming that 1) they contact hosts at random and 2) that the different parasite genotypes are only able to infect a subset of the host-resistance genotypes. This parasite-mediated frequency-dependent selection can then lead to genetic polymorphism in both the host and parasite, as first recognized by Haldane (1949). Hence, if an asexual clone becomes the most common genotype in an otherwise sexual population, the parasites would be expected to quickly evolve to infect it. If the parasites evolve to disproportionately infect the clone, they may prevent, or help prevent, the clone from replacing the sexual population (e.g., Jokela et al. 2009). If so, parasites have contributed to the short-term maintenance of sex, even if they do not drive the clone to extinction. More recently, the parasite hypothesis for sex has been called the "Red Queen hypothesis," for reasons that I will now discuss.

The phrase "Red Queen hypothesis" comes from Chapter 2 in Through the Looking Glass (Carroll 1872). In Alice's dream about the looking-glass house, she first finds that things appear left-to-right, as if shown in a mirror. She then finds that the chess pieces are alive. She will later encounter several of these pieces (most notably the Red Queen), after she leaves the looking-glass house to see the garden.

Alice decides that it would be easier to see the garden if she first climbs the hill, to which there appears to be a very straight path. However, as she follows the path, she finds that it leads her back to the house. When she tries to speed up, she not only returns to the house but also crashes into it. Hence, forward movement takes Alice back to her starting point (Red Queen dynamics) and rapid movement causes abrupt stops (extinction).

Eventually, Alice finds herself in a patch of very vocal and opinionated flowers, of which the rose is especially abusive. The flowers tell Alice that someone like her (the Red Queen) often passes through, and she decides to seek this person, mostly as a way to escape more verbal abuse. When Alice spots the Red Queen, she begins moving toward her, but the Red Queen quickly disappears from sight. Alice decides to follow the advice of the rose and go the other way (I should advise you to walk the other way). Immediately she comes face-to-face with the Red Queen (see Lythgoe and Read 1998).

The Red Queen then leads Alice directly to the top of the hill. Along the way, the Red Queen explains that hills can become valleys, which confuses Alice. Already, in this world, straight can become curvy and progress can be made only by going the opposite direction; now, according to the Red Queen, hills can become valleys and valleys can become hills. (Adaptive landscapes can move under frequency-dependent selection.) At the top of the hill, the Red Queen begins to run, faster and faster. Alice runs after the Red Queen but is further perplexed to find that neither one seems to be moving. When they stop running, they are in exactly the same place. Alice remarks on this, to which the Red Queen responds: "Now, here, you see, it takes all the running you can do to keep in the same place." And so it may be with coevolution. Evolutionary change may be required to stay in the same place. Cessation of change may result in extinction.

Van Valen (1973) used this story as a metaphor for species interactions and suggested that the constant rates of

extinction observed over millions of years in many taxa might be due to species interactions, and he called his idea the Red Queen hypothesis. Bell (1982) later adopted the same name for a different hypothesis, namely that co-evolutionary interactions between hosts and parasites would lead to long-term fluctuations in their genotype frequencies (Red Queen dynamics) and that such interactions might also explain the maintenance of sex. Here, again, hosts and parasites are thought to be constantly evolving in response to each other; but the idea was now meant to capture the movement of genotypes through time rather than serve as an explanation for extinction rates. Specifically, genotype frequencies over time tend to oscillate in both hosts and parasites, at least in simulation models, in a way that suggests that both populations are running just to remain in the same place. And these kinds of dynamics could select for recombination and sex, if the parasites imposed strong selection on their hosts.

Possibly the first reference to the possibility that host–parasite interaction could lead to selection for sex (at least in host populations) came from Hamilton's (1975a) review of Ghiselin's (1974) and Williams' (1975) books on the evolution of sex. The review appeared in the Quarterly Review of Biology and contained this remarkable pair of sentences.

"... it seems to me that we need environmental fluctuations around a trend line of change."
"For the source of these we may look to fluctuations and periodicities ... generated by life itself."

Hamilton was clearly referring to species interactions leading to oscillations in selection; but, as he later states (Hamilton 2001), he was not specifically referring to host–parasite interactions. He does, however, become very focused later on the utility of parasites for generating periodicities in selection. Levin, in the same year, makes a similar, but much more explicit connection (Levin 1975):

"I propose that the persistent tracking of plant hosts by multiple pathogens and herbivores is a prime factor which prohibits the congealing of the genomes of species, especially those in closed communities."

Jaenike (1978) also explicitly incorporated parasites as a selective agent potentially causing selection for sexual reproduction. He borrowed heavily from the work of Bryan Clarke, who was among the first to recognize the possibility of genetical oscillations in species interactions (Clarke 1976). Jaenike realized that these kinds of genetical dynamics could be easily generated in host–parasite interactions and further that they could lead to the build up of linkage disequilibrium, which would negatively affect fitness in the near future. Thus sex and recombination would reduce linkage and might favor outcrossing over uniparental forms of reproduction. Parasites were then essentially creating the kind of environment that Maynard Smith (1978) had reasoned would select for recombination; that is, one that alternated predictably so that previously selected genotypes would be selected against. Just a few years later, Lloyd

(1980) was thinking about the differences between parasites and uncertain physical environments, concluding that the former were probably more important. For example, Lloyd wrote:

"... biological interactions are more likely than unpredictable physical conditions to provide the kind of relentless, repetitive change that is necessary for sexual parents to be selected because of the genetic diversity that sex engenders."

In the same year, Bremermann (1980) wrote:

"The function of sexual recombination, in our model, is the creation of ever novel random assortments of alleles in a polymorphic population. Kimura and Ohta (1971) have said that, "Sexual recombination speeds evolution, helping to produce man before the sun in our solar system burns out". We propose that this effect is secondary, a by-product of its primary function: immunological defense."

Rice (1983) latter added to the idea by suggesting, "... that pathogen transmission between parent and progeny may strongly select for sexual reproduction."

The early verbal models by Hamilton, Levin, Jaenike, Lloyd, Bremermann, and Rice were persuasive enough to motivate empirical studies, which were supportive of the basic ideas. For example, the large field studies by J. Antonovics and N. Ellstrand on sweet vernal grass lead to the following conclusions by the authors (Ellstrand and Antonovics 1985).

"The precise biological cause of the advantage to variable progeny has been difficult to pinpoint, but the evidence from both studies taken together suggests that biologically mediated frequency-dependent selection is a much more important mechanism for the maintenance of sex than is density-dependent selection."

This key result was quickly followed by similar conclusions from comparative studies (Burt and Bell 1987; Lively 1987). More recent empirical studies have also been supportive of the basic tenets of the theory (e.g., Decaestecker et al. 2007; Jokela et al. 2009; King et al. 2009; Koskella and Lively 2009; Wolinska and Spaak 2009), but more empirical systems in which coexisting sexual and asexual forms can be evaluated under natural conditions are needed before any general decisions can be made.

Sex/Asex Models

In 1980, Hamilton produced models that generated selection for sexual reproduction (Hamilton 1980). He considered 2 genetic systems: a one-locus diploid model and 2-locus haploid model (both systems assumed 2 alleles per locus in both hosts and parasites). He assumed that the parasite strains specialized on one of the host genotypes so that the fitnesses of the host genotypes were frequency dependent. However, host fitnesses were not directly dependent on the frequencies of the different genotypes in the parasite population. Rather host genotype fitnesses depended only on their own frequencies. For example, for the diploid model, the fitness of the ith asexual host

genotype was $w_i = r^{(1-3f_i)}$, where f_i is the frequency of the ith host genotype type and r is the maximum number of offspring that can be produced. Note that fitness can be greatly affected by small deviations from the equilibrium point ($f_i = 1/3$) for large values of r. The derivative of fitness with respect to f_i evaluated at the equilibrium point is

$$\left. \frac{\partial w_i}{\partial f_i} \right|_{f_i = 1/3} = -3\ln(r).$$

Hence for large values of r, small departures from the equilibrium lead to large changes in fitness (Hamilton used $r = 107$, so the slope at equilibrium is -14). Large values for r also tended to select for sexual reproduction over asexual reproduction, even when the maximum value for r was truncated to values less than 10. Thus the slope at equilibrium may be more important than the maximum number of offspring produced.

In the same paper, Hamilton also considered a haploid host with 2 loci at each of 2 alleles. The model was more complicated because now there could be recombination between loci; but Hamilton also felt that adding recombination made the model more useful for understanding sex, and it led to protection for sex under lower values for r (Hamilton 2001). For this situation, $w_i = r^{(1-4f_i)}$, because there are 4 possible genotypes; and the slope at equilibrium ($f_i = 1/4$) is $-4[\ln(r)]$. For free recombination, the geometric mean fitness (GMF) of a sexual population (having a 2-fold cost of sex) was greater than the GMF for the asexual population for maximum birth rates of greater than about 8, assuming free recombination. (However, as Hamilton realized, higher GMF for the sexual population over the long term does not necessarily mean that asexuals would not win in the short term.)

The results from Hamilton's simulation studies showed that frequency-dependent selection could lead to oscillations in genotype frequencies and to selection for sex in spite of a potential 2-fold reproductive advantage of asexuals in the absence of parasites. However, it was not clear that real parasites could generate strong enough selection to maintain sex or that selection would be so sensitive to small departures from equilibrium. It was also not clear how the time-lagged responses of parasites would affect the result. Nonetheless, Hamilton's model was a crucial first step.

May and Anderson (1983) took on these questions regarding the strength and nature of selection. First, they allowed host fitness to depend on the number of infected hosts of a particular genotype and the reproductive rates of the parasite strains that matched these genotypes (but not on the frequency of the parasite genotypes per se). On the epidemiological front, they assumed that all infected hosts either died or recovered; the frequency of deaths (s_i) for infected individuals was modeled as the death rate (α_i) divided by the death rate plus the recovery rate (v_i) ($s_i = \alpha_i/(\alpha_i + v_i)$; hence the strength of selection depended on s_i. They also included genotype-dependent threshold densities for the establishment of infection for each of the host

genotypes, where the threshold density $N_{T,i} = (\alpha_i + v_i)/\beta_i$ (where β_i gives the transmission rate). Thus, the spread of each of the different parasite strains depended on the density of the matching host type rather than on its frequency.

May and Anderson first considered the case where there was no density dependence in the host population, using the same one-locus, 2-allele model as Hamilton (1980). They found that sex (with a 2-fold cost) could be favored over asex only if s_i for all genotypes was equal to one. In other words, sex would win if none of the infected hosts recovered ($v_i = 0$). When they included host-density dependence in the model, asexual reproduction replaced sexual reproduction for all values of s, including $s = 1$. They concluded that: "These results severely undercut the generality of Hamilton's conclusions for one-locus models."

As a brief aside, May and Anderson (1983) assumed that one of the 2 alleles was dominant, giving only 2 possible phenotypes. Doebeli and Koella (1994) changed the assumption so that each of the 3 possible genotypes was susceptible to a different pathogen strain. They found that this change stabilized the numerical dynamics for the sexual population, whereas the asexual population remained chaotic. They also state (but did not show) that the same change leads to selection for sex over asex for the density-dependent case examined by May and Anderson. Nonetheless, Doebeli and Koella (1994) also assumed extremely strong selection ($s = 1$).

May and Anderson also studied a 2-locus model for haploid hosts similar to then one studied by Hamilton (1980). Using the same kinds of epidemiological considerations as in the one-locus diploid model, they found that the conditions for the maintenance of sex were somewhat less restrictive, but nonetheless required s values of 0.9 or greater; and even so, sex was only favored under a narrow range of values for the reproductive rate of the host (between 9.98 and 11.39). May and Anderson, concluded that:

"Our studies, in which the epidemiological details of the parasite–host interactions are treated more explicitly than in Hamilton's work, make this [the parasite] answer to 'the problem of sex (Ghiselin 1974; Williams 1975; Maynard Smith 1978) less likely."

On the other hand, May and Anderson (1983) also state that the epidemiological details of their model were not "brought down by Moses from Mt. Sinai" and that other models might revive the parasite theory. They added that:

"Whatever the status of the theoretical arguments, Hamilton's ideas have the merit of being empirically testable, and it is on such tests that they will ultimately stand or fall."

There have been a couple of attempts to deal with the problem on theory that May and Anderson so forcefully pointed out. The first one was by Hamilton et al. (1990). The idea here was that individual infections might have very little impact on host fitness in noncompetitive situations; but infection, especially by multiple species of parasites, might have severe effects in nature if competition for

resources were fierce. Specifically, they imaged that parasites might cause a rank-order truncation selection against the most infected hosts in competitive situations. In their model of an iteroparous host (humans) they simulated the situation where 7% of the hosts would fail to reproduce each year, where these individuals were those that were the most infected in the population at the time. Under less crowded conditions, these individuals might have done fine, but under restricted resources they simply failed to reproduce. The remaining 93% suffered no reduction in fitness, so selection was truncated (all or nothing). Hamilton et al. (1990) found that this kind of rank-order truncation selection could select for sex (with a 2-fold cost). The basic result fits with the May and Anderson's requirement for strong selection because the most infected individuals were effectively castrated.

Another attempt to deal with the apparent need for strong parasite-mediated selection came from an individual-based simulation model by Howard and Lively (1994). They employed a haploid 2-locus model with 2 alleles at each locus. The loci were assumed to be on separate chromosomes. Parasites that matched the host at both loci successfully infected the host; otherwise the host killed the parasite. The model did not have the epidemiological detail as in the May and Anderson model, but host fitness depended on the frequency of parasite strains in the population. Hence, time lags emerged naturally from the model. Howard and Lively (1994) found that parasites had to be extremely virulent in order to eliminate the asexuals (with a 2-fold advantage). However, for more moderate virulence (e.g., virulence = 0.6), parasite-mediated selection resulted in the coexistence of sexuals and asexuals, wherein the frequency of the sexuals fluctuated over time. Hence, importantly, parasite-mediated selection permitted the persistence of sexual individuals, even though they did not eliminate the asexual population. This coexistence seemed stable, unless additional clonal mutants were "spun off" in the computer simulation. In this case, clonal diversity increased, and the sexual population was eventually eliminated by a diverse assemblage of clones (Lively and Howard 1994). This latter result illustrates an important point. Parasites are simply a potential source of frequency-dependent selection, which could easily lead to the replacement of sexual individuals by a diverse clonal population, unless additional forces are acting against the asexuals.

This last point may be especially important for understanding the different results among the different simulation models of host–parasite coevolution and sex. In the simulation model by May and Anderson (1983), it would seem that the sexual population was competing with a "fully saturated" clonal population. By fully saturated I mean that every genotype in the sexual population was also initialized in the asexual population. As such, the sexual population cannot evolve into genotypic space that could not also be occupied by clonal genotypes. This is certainly true of the model by Hamilton et al. (1990). Their model started with a "burn-in" period in which all the individuals were asexual, and the asexual population was fully saturated. Then, at generation 70, half of the population was switched

from being asexual to sexual. In contrast, in the model by Howard and Lively (1994), a single clonal genotype was introduced into a genetically diverse sexual population by mutation. Hence, in their model, the clonal population was not fully saturated, and the sexual population could evolve into genotypic space that was not occupied by clones. This could partially explain why Howard and Lively (1994) observed coexistence of sexuals and asexual, even under moderate levels of virulence (virulence = 0.5), whereas May and Anderson (1983) observed the elimination of the sexual population over most of the parameter space, and Hamilton et al. (1990) observed discrete switches from sex to asex, depending on the number of loci involved in defense against infection. From my point of view, it seems more reasonable that clonal diversity might build up over time, rather than being initiated instantaneously. As such, even if sexual reproduction could persist in the face of competition with a single clone (which would be remarkable in itself), would it persist in the long term if different clonal genotypes were occasionally generated by mutation? Or could the clones be eliminated more rapidly than they originated?

Howard and Lively (1994) repeated their simulation allowing for the possibility that mutations would accumulate over time by Muller's ratchet. They found that for avirulent parasites, clones would go to fixation, thereby eliminating sex. The clones eventually accumulated enough mutations so that they also went extinct. However, for moderately virulent parasites, the combination of infection and mutation accumulation was sufficient to select for sexual reproduction and eliminate asexual reproduction. Here, the elimination of asex was caused by mutation accumulation. Parasites would drive clonal hosts through population bottlenecks (even though the host population itself was maintained at a constant density), which increased the rate of mutation accumulation by Muller's ratchet. Later models verified that the results were robust to the exact function (synergistic vs. multiplicative) relating mutation load to fitness (Howard and Lively 1998) and showed further that the same combination of coevolution and mutation accumulation could also select for sex in the parasite (Howard and Lively 2002). This later result is helpful in that parasites of parasites are not required to select for parasite sex (also see, Lythgoe 2000; Galvani et al. 2003).

Otto and Nuismer (2004) also presented a model of parasite-mediated selection for sex and recombination. Importantly, they considered multiple genetic interfaces for infectivity/resistance and different kinds of species interactions. Their model was primarily focused on the fate of modifiers for recombination, but they also included simulations to determine whether an obligately sexual population having different levels of recombination would resist invasion and replacement by obligately asexual clones (which is the focus here). As in the models by May and Anderson (1983) and Hamilton et al. (1990), the clonal population was introduced as being fully saturated. But their model was also different in some other important biological details from the previously discussed models: first, there was no cost of sex; and second, the parasites were not obligate

parasites, meaning that they could reproduce outside of hosts. For the matching genotypes model, the sexual population was able to resist invasion by the clonally diverse asexual population only when selection on both the host and parasite was "strong" (selection coefficient = 0.50), and recombination in the sexual population was low. However, as they state: "Including a cost of sex would have substantially increased the invasibility of the asexual clones." So, it would seem that the persistence of sex is very unlikely when sexuals are competing with fully saturated asexual populations, even when there is no cost of sex.

Much of the recent theoretical work on the parasite theory of sex has been appropriately focused on the genetic details of host resistance to infection, especially the differences in the results obtained under the gene-for-gene model and the matching alleles (or matching genotypes) model for infection (Agrawal and Lively 2002, 2003; Otto and Nuismer 2004; Engelstadter and Bonhoeffer 2009). It would seem at present that tight genetic specificity for infection is required if parasites are to contribute to selection for genetic polymorphism and sex. Empirical evidence for genetic specificity comes from the highly significant host-genotype by parasite-genotype interactions (Carius et al. 2001), strong host–parasite interaction effects in local adaptation studies (e.g., Thrall et al. 2002; Lively et al. 2004), and the breakdown of infectivity in hybrid parasites lines (Dybdahl et al. 2008). Less attention has been paid so far to the epidemiological details of disease spread (barring May and Anderson (1983)) or to the ecological aspects of virulence. Most models treat the probability of infection as depending only on the frequency of the matching parasite type. In addition, virulence is usually treated as a static parameter that cannot change over time. Finally, hosts are usually treated as annuals (barring Hamilton et al. 1990), meaning that the entire adult population is replaced every generation.

A recent model has incorporated some additional ecological details into parasite virulence (Lively 2009). In this model, the birth rates of infected individuals declined with host density at a faster rate than that for uninfected individuals. Hence, virulence increased gradually with host density, rather than in a stepwise fashion as in the model by Hamilton et al. (1990). In addition, the model showed that an asexual population would have a higher carrying capacity than a sexual population because asexual females can replace themselves with fewer resources than sexual females (see also Doncaster et al. 2000). Thus the initial spread of asexuals into a sexual population leads to a gradual increase in parasite virulence as total host population grows in number because virulence is positively density dependent. In runs of this model, parasites that were originally not virulent enough to prevent the fixation of a single asexual clone (virulence <0.5) became sufficiently virulent to select against asexual reproduction (virulence >0.5), but only after the clone spread into the population and increased the total host population size. After the parasite population evolved to disproportionately infect the clone, both the clone and the total host population size, decreased in number, thereby reducing virulence. The outcome of the numerical and gene-frequency dynamics was the oscillatory coexistence of sexual and asexual individuals. The simulation demonstrates that the spread of a clone into a sexual population can dramatically affect the host's ecology.

The model was later expanded to include some epidemiological realism (Lively CM, unpublished data). Specifically, the probability of infection for each host genotype depended on the number of infected individuals having the same genotype in the previous generation, as well as the frequency of the host genotype in the population (following Lively 2010b). This change means that the number of exposures per host, usually assumed to be one in population genetic models, could increase dramatically overtime as the clone spread into the population, and the parasites become better adapted to infecting it. Here, as in the previous model, it is not difficult to find parameter space in which asexuals are prevented from fixing by antagonistic coevolution with parasites, in part because the number of parasite exposures per host increases dramatically as the parasites adapt to the clone, greatly exceeding one exposure per host. The results also show that sexual reproduction can persist in the face of clonal competition, even though the sexual genotypes showed stable (rather than oscillatory dynamics) over most of the parameter space, prior to the introduction of the clone. Hence Red Queen dynamics are not essential to the parasite theory for sex (see also Howard and Lively 2003).

Another assumption of most host–parasite coevolution models is that the hosts are annuals. The parasites may have multiple generations for each host generation, but the entire host population is periodically replaced. Under this assumption, the cost of males per reproductive time step is 2-fold, assuming that half the sexual population is male. However, if only some portion, D (for death rate), of the population dies during each time step, the cost of males is $1 + D$ for each time step (Lively 2010a). Thus the cost of sex per time step increases with the death rate (see also Doncaster et al. 2000). If the parasites are attacking during each time step, it stands to reason that they only have to overcome the cost of sex per time step (not per generation) to select for sexual reproduction. In this case, the minimum virulence to select for sex becomes $V_{\min} = D/(1 + D)$, suggesting that parasite-mediated selection for sex may be more effective in long-lived species with overlapping generations (Lively 2010a).

Summary

I have focused this review on the subset of models that consider the potential effects of parasite-mediated selection on the persistence of sexual individuals in direct competition with one or more obligately asexual clones. I have not covered the much larger body of theory concerned with the evolution of recombination rates within a sexual population. However, as for the theory for recombination modifiers, the Red Queen model has oscillated in its appeal as an explanation for sexual reproduction (Salathe et al. 2008).

The early theory by Hamilton (1980) was supportive of the parasite model for sex, but the generality of the results were quickly questioned by the simulation results of May and Anderson (1983), which incorporated more epidemiological detail. Hamilton et al. followed in 1990 with a model that included additional ecological complexity in the form of rank-order truncation selection against the most infected individuals. This model thus generated the high levels of virulence that seemed to be required by the May and Anderson model in order to select for sexual reproduction over asexual mutants. On the other hand, the maximum strength of selection, which depends on prevalence as well as virulence, would not seem high enough in the Hamilton et al. model to overcome the 2-fold cost of sex as only 7% of the individuals were unable to reproduce as a consequence of infection. (However, the Hamilton et al. model also assumed overlapping generations, which might reduce the cost of sex per reproductive time step.)

The models by May and Anderson (1983) and Hamilton et al. (1990) both placed sexual populations in competition with "fully saturated" asexual populations, meaning that the asexual population was initiated with all the resistance genotypes present in the sexual population. This assumption might provide an interesting but overly stringent exploration of the problem. It would seem more biologically reasonable to introduce clonal genotypes one at a time. Under this scenario, extremely high virulence (death or castration) is not required for the persistence of sex (Howard and Lively 1994; Lively 2009) because the sexual population can evolve into genotypic space that is relatively free of infection, as well as free of competition with genetically similar clones. Similar reasoning might apply to "modifier models," which consider the fate of mutations that increase the frequency of outcrossed offspring within individuals that can make both outcrossed and asexual progeny, effectively leading to high levels of genetic diversity in the asexual cohort. In these models, parasites do not select for more sex (Agrawal and Otto 2006), unless parasites tend to be passed between a mother and her offspring (Agrawal 2006).

My own feeling is that there is still value in solving the original problem laid out so clearly by Maynard Smith (1978) concerning competition between ecologically similar but reproductively isolated sexual and asexual forms. I think we might set the bar too high by insisting on conditions where an asexual clone cannot increase when rare (evolutionary stability of sex). Indeed, the invasion of the clone should be expected under any model of sex relying on frequency-dependent selection. Rather, I think we should seek conditions where the clone does not replace the sexual population in the short term (evolutionary persistence of sex) and determine whether these conditions are commonly met in natural populations.

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