

Host-Parasite Coevolution and the Red Queen Hypothesis:
How did she come about and why is she still prevalent?

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To thrive in this world, organisms employ different strategies in order to maximize their fitness while minimizing the cost of survival. Organisms will attempt to take advantage of all available resources, at times exploiting specific niches or forming symbiotic interactions. Nature is fraught with mutually beneficial relationships, such as lichens, mycorrhizal symbiosis (Garbaye, 1994), dairy ants and aphids, orchids and hawkmoths, Egyptian plovers and rhinoceros, and sea anemone and the clown fish (Billet and Burchill 2004) just to name a few. Both organisms involved benefit within the relationship by being honest, however mutualisms are not stable evolutionary endpoints, they are inherently unstable, and can be disrupted by conflicts of interest between partners (Hibbert, 2002). Cheating to increase personal utility is an tempting prospect, the attitude of which has been captured in “The Tragedy of the Commons” (Hardin, 1968). Here, the deceiver would solely gain the benefits, while the losses would be equally distributed, therefore it is in the best interest each player to utilize as much of the resources as possible, which may lead to the desiccation of the commons. The delicate balance of maximizing fitness while exploiting resources can be a vital skill, and the breakdown of relationships initially existing as mutualistic can lead to parasitism (+/-) or the complete dissolution of the symbiosis. (Hibbert, 2002).

Parasitism is defined as a form of symbiosis in which the population of one species benefits at the expense of the population of another species. The parasite becomes physiologically dependent on the host, often possessing a higher reproductive potential capable of ultimately killing its host (such parasites are referred to as parasitoids). (Kahn, 2004; Lawrence, 2000; Kennedy, 1975). There are numerous ways in which parasites are

able to infect and manipulate hosts, from obligatory rearing of young to directly changing their behaviour. Intuitively, resistance to such attacks would increase fitness, nonetheless fixation does not occur and high levels of genetic variability are seen within host populations. Costs of resistance must be high enough to allow susceptibility to linger, however hosts must also possess alternative mechanisms to defend against potential parasites. With each defensive action expressed by the host, the parasite must produce a counter attack in order to continue taking advantage of its host. Recent work performed by researchers such as Lively, Jokela and Agrawal have shown that the presence and persistence of sex may be contributing to the coevolutionary arms race between host and parasite. The above topics will be discussed in further detail in this paper in order to investigate this life-or-death game in hopes of increasing awareness of these issues and developing new strategies for disease control.

As stated previously, there are numerous ways in which parasites have evolved to infect and manipulate their chosen host. A common method of infection has been ingestion, found in systems such as the Snail-trematode (Dybdahl and Lively, 1998), and Stickleback-tapeworm (Barber and Svensson, 2003). Other methods include laying eggs in the nests of hosts [Magpie and Cowbird (Soler, *et al*, 1998)], or directly inside the host [*Drosophila melanogaster* and parasitic wasps (Kraaijeveld, *et al*, 1999)]. Once inside, the parasite will utilize resources now available to it, such as internal organs. Trematodes are known to eat the gonads of their snail or fish hosts, completely destroying their ability to reproduce, possibly preventing the reallocation of resources to offspring that the parasite would not have access to (Webster, 2001.; Jokela and Lively, 1995; Barber and

Svensson, 2003). In extreme cases, parasitoid wasp larvae will devour the *Drosophila* host, and emerge when developed, killing the host in the process (Kraaijeveld, *et al*, 1997). Coevolving along side its host, *Asobara tabida* (a parasitoid wasp) have adapted to maximize the resources available to it by preferentially allocating female eggs to female hosts who have a higher resource value (Kraaijeveld, *et al*, 1999). Consequently, wasps emerging from female drosophila are shown to be larger in size than those emerging from male hosts (Kraaijeveld, *et al*, 1999).

Manipulation of the host to maximize available resources can take on different forms than exclusively differential allocation of offspring. In many instances, parasites have been shown to change the behaviour of their hosts in order to complete their life cycles, whether it be remaining in that host (Hughes, *et al*, 2004) or altering the host's behaviour to attract an intermediate or final host. For instance, when paper wasps (*Polistes dominulus*) are infected by the strepsipteran parasite *Xenos vesparium* Rossi, a dramatic behavioural change occurs. The parasitized females abandon the colony and form extranidal aggregations near prominent vegetation and male lek sites, often used by future Queens (Hughes, *et al*, 2004). Through artificial infections, parasitized "workers" were found to be more inactive, and deserted the nest 1-week after emergence from their cell. It is believed that this change in behaviour helps to promote the completion of the parasitic life cycle (Hughes, *et al*, 2004).

Tapeworms, *Schistocephalus solidus*, require more than one host to complete their life cycles. They infect three-spined sticklebacks (*Gasterosteus aculeatus*) in their larval stage, and must be ingested by fish-eating birds in order to advance to the adult stage

(Barber and Svensson, 2003). To increase the likelihood of this event, *S. solidus* dramatically alters the behaviour of *G. aculeatus*. The infected sticklebacks were found to spend less time sheltering and even fled less when “attacked” by predatory birds (simulation) (Barber and Svensson, 2003). One interesting and perplexing outcome of that study was the increase in ovary size of parasitized females.

Engineering of host behaviour also occurs in snail (*Potamopyrgus antipodarum*)-trematode (*Microphallus*) systems, similarly requiring final host ingestion of the parasitic larval stage (Levri, 1999). It was found that parasitized snails spent a disproportioned amount of time foraging on the tops of rocks, independent of the amount of food available. During the scarcity trials, *P. antipodarum* would hunt on the peaks of rocks despite the lack of food, greatly increasing the likelihood of its predation. Levri also discovered that *P. antipodarum* would forage on the upper portion of rocks during the early morning when the frequency of birds was higher, and shelter in the afternoon when fish predation was highest (organisms that could not be utilized as a final host for this particular trematode) (1999). In order to manipulate the host behaviour, the parasite must develop an inexpensive method of altering chemical pathways that would incur a fitness advantage.

Neuromodulators can modify neural circuits, giving an animal the behavioural flexibility it needs to survive in a complex changing world. This ability, however, provides parasites with a potential mechanism for manipulating host behaviour (Adamo, 2002). Parasites either release neuromodulators disrupting bodily functions, or manipulate the host’s production of such neuromodulators (Adamo, 2002).

Size of the parasite influences the method used to exploit its host. For the systems mentioned above, parasites dwell within the host, therefore must be substantially smaller than the host in order to subsist on its internal organs. However, examples exist where the parasite's size is considerably larger than its host, and an example of this is the Magpie-Cowbird system (Soler, *et al*, 1998). Here, the cowbird lays its eggs within the nest of the magpie, expecting the host to nurture its offspring. The method of enforcing this parasitic relationship is much more invasive; if the magpies remove the cowbird eggs, their nests and entire contents, including any eggs, are destroyed by the cowbirds, thus the magpies are forced to rear young that decrease their own fitness (Soler, *et al*, 1998).

It appears as if hosts are powerless to wage war against parasites, which have coevolved along side them, seemingly mastering the art of manipulation and exploitation. Despite all the hardships hosts endure, they too possess methods of warding off, and even destroying invading parasites. *Drosophila* have acquired a non-specific technique of sequestering parasitoid wasp larvae called encapsulation (Kraaijeveld, *et al*, 1997; Carton and Bouletreau.1985). Haemocytes aggregate around the parasitic egg creating a hemocytic capsule, which is then hardened by melanin, suffocating the parasitoid inside, resulting in a hard capsule that is visible on the outside, a badge of courage that will remain until it dies (Kraaijeveld, *et al*, 1997; Carton and Bouletreau.1985). This is not a parasite-specific mechanism; *drosophila* utilize this method for all invading entities.

A similar defence mechanism is found to occur in the snail *Biomphalaria glabrata* during a schistosome infection. The response is activated and mediated by

immune effector cells known as haemocytes (Raghavan, et al, 2003). These blood cells, found only in invertebrates, are associated with haemocoel and defend by phagocytosis (B.O., 2004; Lawrence, 2000). Though this is an effective method of defense, *B.glabrata* stave off parasites by causing their bodies to be less-susceptible to attack. In a study done by Webster and Woolhouse (1999), it was discovered that *B.glabrata* decrease the production of internal factors that may be essential for normal parasite development.

Given that parasites inflict bodily harm, deplete the host of valuable resources and even rob the host of the ability to reproduce, fixation of resistance to parasitism would appear to be a logical solution. Nevertheless, this is not the case found in nature. Several studies have shown that genetic diversity with respect to resistance and susceptibility within populations is exceptionally high (Da Silva, et al, 2004; Krist, et al, 2004; Jokela, et al, 2003; Webster and Woolhouse, 1999; Hoffman, et al, 1998.). In the same study done by Webster and Woolhouse (1999), the fitness of resistant and susceptible individuals in a population of *B.glabrata* was investigated. Lines of resistant and susceptible snails were reared over a period of time, and fecundity and mortality were compared. It was determined that in this species there existed a cost to being resistant as fecundity was shown to be significantly lower. To reduce the success rate of the parasite, *B.glabrata* diminishes the production of some factors associated with reproduction, as they are vital to the survival of that parasite. Allocation of resources towards mounting a defence can also be quite costly, and decreases the resources available for reproduction and growth. Carotenoid pigments that are produced by birds aid in immunofunctions and defending against parasites (Mahler, et al, 2003). However, the more allocated to

fighting off infections means less can be allocated to plumage, and therefore causing the organism to be less attractive to mates (decreasing fitness). This has shown to be the same in *Drosophila*, as Kraaijeveld, *et al* (1997) provided evidence that the genes for advantages to resistance are cancelled out by a negative correlation between encapsulation ability and other fitness components. Fellows *et al*, (1999) selected replicate lines of *D.melanogaster* for an increase in resistance against parasitoid wasps (*A.tabida* and *Leptopilina boulardi*). In both cases it was observed that an improved ability to mount a defence against these parasitoids was associated with reduced survival, lower competitive ability, and decreased rates of larval feeding. This shows a link between competition for resources and resistance to infection, and provides more evidence towards the cost of resistance (Kraaijeveld and Godfray, 1997). A decrease in fitness is observed when comparing resistant to susceptible individuals, indicating that an advantage exists for the susceptible lines when no parasite is present, conversely a benefit exists for the resistant individuals when parasites are prevalent.

In two independent studies performed in New Zealand, it was found that in a population housing both resistant and susceptible snails, there existed a cline in susceptibility of snails along a depth of water gradient; shallow-water snails were found to be more susceptible to infection than deep-water ones (Jokela and Lively 1995a; Krist *et al.* 2000). Two separate explanations were given for this given pattern: (i) that shallow-water snails are physiologically unfit, allowing them to be more susceptible, and (ii) that coevolutionary interactions are restricted to shallow water, making these snails more tractable. The latter may come about due to the foraging preferences of the final

host of the *Microphallus*, the duck. It forages exclusively in shallow waters; therefore coevolution may be stronger there.

Genetic diversity within the population is beneficial as resistant and susceptible individuals thrive with varying levels of parasite exposure. In addition to employing defensive mechanisms for halting attacks from parasites, hosts are able to utilize offensive techniques. The exact mechanism that allows either parasites to invade a host or a host being resistant to infection is not fully known or understood. The gene-for-gene model was developed by H.H. Flor (1942), who was the first to look at the variability of the pathogen (*Melampsora lini*) and host (flax) at the same time, studying the inheritance of both resistance and susceptibility. The main idea behind this concept is that the coexistence of host plant and its pathogens indicates that the two have been co-evolving, therefore changes in the virulence of the pathogen are continually balanced by changes in the host's resistance, and vice versa, causing a step-wise evolution. Since then, the genes have become known as corresponding genes, and resistance can only occur if specific recognition between the avirulence gene product and the corresponding resistance gene product occurs (Flor, 1942). This view has been partially adopted for other organisms and has been dubbed the "Matching Alleles Model" (Peters and Lively, 1999).

Within this model, the ability of a parasite to infect a haploid host is determined by the match between two diallelic "self" loci in the host and a complementary set of two diallelic "mimic" loci in the parasite (Peters and Lively, 1999). Infection can only occur if the parasite matches the host at every locus. If it fails to do so, it will be destroyed by the host's self/nonself recognition system. Conversely, the system may work if the

parasite does not match the host at any loci (the “Inverse Matching Alleles Model”). The host is then able to offensively elude parasitic attacks by increasing the variation in the population (Peters and Lively, 1999).

Interestingly enough, another study done by Jokela and Lively (1995b) showed that there are more sexual females in shallow water where the levels of infection are higher. The host, *P. antipodarum*, is able to reproduce both sexually and asexually, however there exists a cost to sexual reproduction. If a clonal population beginning with a single asexual female could replace a population of one million sexual individuals in less than 50 generations, then why is sex still prevalent? (Lively, 2004a; Lythgoe and Read, 1998). The same argument can be made for recombination, in that breaking up linkage disequilibria previously favoured by selection seems disadvantageous (Peters and Lively, 1999), yet it is still prevalent within the population.

For sexual reproduction and recombination to persist, there must be an advantage that will outweigh the two-fold cost of sex. Within a sexual population, ecological costs are ensued by the production of males. In order for a female in a dioecious population to replace herself, she must produce, on average, one male and one female (assuming a 1:1 sex ratio) (Lively, 2004b). In contrast to this, asexual females are able to produce many more daughters than the typical sexual female, as they reproduce clonally (i.e. after two generations, asexual females will have four times the progeny). The advantage in clonal production stems from the fact that sexual females must produce males, who do not produce any progeny on their own. This is not to say that males do not contribute anything to reproduction, but simply states that a cost results from 50% of the population

not able to bear offspring (Lively and Lloyd, 1990). In addition to this, there is a cost to meiosis as progeny are only half as related to their offspring as asexual females. (Lively and Lloyd, 1990). To further complicate the matter, an added cost of sex exists due to anisogamy, as both sexes contribute fifty percent of the genes to the progeny, yet the larger contribution to the zygote comes from the egg-producing females as compared with the small contribution from the male sperm (Agrawal, 2001). This provides conditions for sexual selection, a powerful evolutionary force not present in asexual populations (Agrawal, 2001).

Numerous hypotheses have been brought forth to explain the stability of sexual reproduction, most of which have focused on potential advantages gained by the production of variable offspring (Lively, 2004b), while others present evidence of clearing deleterious mutations, and demonstrate the advantages of sex in variable environments (Howard and Lively, 2002).

A widespread hypothesis was dubbed after a character in a popular children's novel:

"Well, in our country," said Alice, still panting a little, "you'd generally get to somewhere else -- if you run very fast for a long time, as we've been doing."

"A slow sort of country!" said the Queen. "Now, here, you see, ***it takes all the running you can do, to keep in the same place.*** If you want to get somewhere else, you must run at least twice as fast as that!" (emphasis added) (Carroll, 1872)

Antagonistic biotic interactions occurring between parasite and host are constantly underway, which can maintain genetic change in the players involved

(Lythgoe and Read, 1998). Val Valen proposed in 1973 that natural populations are not attaining the perfectly adapted phenotype, even in the absence of external environmental change, but are continually reacting to the surrounding populations who are also evolving. In the same way that the Red Queen in *Through the Looking Glass* must run in order to stay in the same place, organisms must persistently evolve to survive; hence the hypothesis was named after her.

The “Red Queen” is used to describe a couple of coevolutionary interactions where organisms respond to selection pressures they imposed on one another (Lively, 2004b; Lythgoe and Read, 1998). The first idea, proposed by Van Valen (1973), stated that extinction of a species could occur from the constant coevolution between two antagonistic species, the probability of such an event being independent of species age (Lively, 2004b; Van Valen, 1973). An analogy given by Lythgoe and Read (1998), explained this in the context of a fight between you and an enemy, both battling with bare fists, until one day your opponent draws a sword. You are no match to this weapon, until you invent the bow and arrow; now you are able to remain at a safe distance while still inflicting damage. Your enemy then ups the ante by revealing a gun, to which you develop nuclear fission. This arms race is characterized by repeated bouts of directional selection, which cannot be reversed; the sword will not bestow an advantage in the future. New methods must constantly be developed in order to surpass one’s opponent, however there is a coevolution between players so victory is short-lived.

A second concept proposed along the same lines is the idea that oscillations in genotype frequencies could be sustained by coevolution, particularly between host and

parasite (Lively and Dybdaul. 2000; Peters and Lively, 1999; Lythgoe and Read, 1998;), which is a leading hypothesis for the persistence of sexual reproduction (Lively, 2004b). Oddly enough, the oscillations were described quite clearly in *Through the Looking Glass*, as the Red Queen explains that hills become valleys, and valleys hills (Carrol, 1872). In the second chapter, we find Alice walking a straight path up a hill to reach the garden, however the path leads her back to the house. In frustration, she tries speeding up, which not only leads her right back to the house, but also causes her to crash into it. Her forward movement takes her back to her starting point (Red Queen dynamics) and rapid movement causes abrupt stops (extinction) (Lively, 2004b; Carrol, 1872). In order to progress, Alice is told to walk in the opposite direction, which leads her straight to her destination, a concept recently found in nature (Dybdahl and Lively, 1998).

Once more, Lively and Dybdaul (1998) give an excellent analogy for the cycling repetitive behaviour of the Red Queen Hypothesis. Instead of trying to kill one another, you and your opponent are playing to win all the lollipops you both possess. The rules are as follows: You both begin with five lollipops. If you possess more, then you must give your opponent four of yours, otherwise s/he gives you one of hers/his. In the first round, you both have the same amount, so s/he is forced to give you one; you now possess six, and your opponent four. Beginning the second round, you retain a higher number, and as a result you must relinquish four of your lollipops. Sadly, you look at your depleted supply, as you now retain only two lollipops, your opponent eight. Yet, after three rounds you both are back to the original five lollipops, and the Red Queen has just run

nowhere. The dynamics of this cycling will depend on the species involved and the rate at which they evolve together, but this illustrates the repetitive nature.

Lively and his groups have laid a solid foundation of both theoretical and empirical evidence for the Red Queen and the persistence of sexual reproduction. The snail-trematode system (specifically *P. antipodarum* – *Microphallus*) has been of special interest as it is able to reproduce sexually and asexually, both forms found to coexist in nature. Through the work, they have shown that the Red Queen' hypothesis makes several straightforward predictions about the prevalence of sexual individuals. In areas where the risk of infection is high, sexual individuals should be favoured (Lively, 2004b). This prediction was found to be true empirically (Jokela and Lively, 1995a,b), which suggests that asexual females have replaced sexual females where there is a low risk of infection (Lively, 2004b).

Over time, host genotypes should oscillate(Lively, 2004b). Dybdahl and Lively (1998) provide evidence that changes in frequencies of snails and later prevalence of infection oscillate over time. When rare, parasites are not able to readily infect the snails; therefore the snails are able to increase in abundance. As their numbers increased, so did the trematode's ability to infect, and the population became over-infected, leading to a crash in both populations.

If the past genotypes were readily infected, then there should be selection against these individuals(Lively, 2004b). In the same study done by Dybdahl and Lively (1998), they experimentally infected snails to test this hypothesis, and found mounting evidence in favour of it. In order to confirm that the outcome was not due to a fitness trade-off,

they performed an additional experiment (2002), this time exposing the snail to the local trematode, and a remote source. *B.glabrata* was only readily susceptible to the local trematode, indicating that it was in fact the Red Queen, and not a decrease in fitness due to trade-offs.

On the reverse of this last hypothesis, parasites should readily infect local populations of their hosts with whom they have coevolved (Lively, 2004b). Coevolving with the host, a parasite should be more adapted to infecting a local host than an invading/remote one (Lively, 2004b). This was also found to be true in their 2002 experiment, in that local parasites more readily infected hosts they adapted to.

Many factors are involved in the ability of hosts to evolve counter-attacks; linkage disequilibria and epistasis interact with one another to facilitate the persistence of recombination. It has been suggested that recombination can only increase under fluctuating epistasis when the sign of epistasis changes every two to five generations, and that antagonistic coevolution may produce such conditions (Barton, 1995; Peters and Lively, 1999). In other words, the combinations of alleles that were advantageous one generation must quickly become disadvantageous (Barton, 1995). In a study performed by Peters and Lively (1999), coevolution was broken down into four components: parasite linkage disequilibrium(LD), host epistasis, host LD, and parasite epistasis. Each stage affects the next, causing both the host and parasite sign to change every few generations, giving rise to recombination. The cycling (or Red Queen) happens in the following manor: (i) Negative parasite LD causes positive host epistasis (if a genotype is under represented in the parasite populations, then the host of that genotype will be under

infected, thus obtaining a disproportionately high level of fitness: the Matching Alleles Model). (ii) The positive host epistasis leads to positive host LD, after a time lag, determined by cycling rates. (iii) Host positive LD then causes positive parasite epistasis (as the host genotype increases in number, the parasites mimicking that genotype will increase in success, infecting more, therefore experiencing a disproportionately high fitness). (iv) Moving in the opposite direction, positive parasite LD causes a negative host epistasis, leading to a negative LD, which leads to a negative parasite epistasis (Peters and Lively, 1999).

This feedback loop reveals how antagonistic coevolution may lead to the conditions required for recombination and sexual reproduction. During step (ii), since LD is not developed immediately, a time lag exists between the moments in which both LD and epistasis change, giving them opposite signs (Peters and Lively, 1999). Fit genotypes are rare and common genotypes are unfit, consequently these LD are maladaptive, thus recombination provides an immediate benefit by breaking up the LD. If the periods are frequent enough, then recombination can increase in the population (Peters and Lively, 1999).

Within antagonistic coevolutionary systems, directional selection and fluctuating epistasis work together to maintain sexual recombination. It was found that the directional selection mechanism (advantage to recombination due to sustained directional selection) incurs a benefit because recombination increases additive genetic variance within a population for fitness (Peters and Lively, 1999). Recombination becomes associated with long-term high-fitness genotypes because it causes an increased response

to selection (Peters and Lively, 1999). Sexual reproduction reshuffles the alleles, creating both extremely advantageous and disadvantageous genotypes, and by natural selection, the more advantageous genotypes will survive. This consequently generates a decrease in fitness over the short term, however fluctuating epistasis accounts for that, presents evidence that within the context of antagonistic coevolution, such as the host-parasite system, sexual reproduction and recombination provides strong advantages, ergo its persistence in nature (Peters and Lively, 1999).

Further evidence for the advantages of sexual reproduction have focused on sexual selection on males due to anisogamy (Agrawal, 2001). It was established that deleterious alleles could be purged from an entire sexual population due to sexual selection. In addition to this, theoretical work indicates that an increase in the probability of fixation of new and beneficial mutations could arise from sexual selection (Agrawal, 2001). This may also explain the unexpected increase in ovary size in infected sticklebacks, as sexual reproduction may increase in hopes of recombining maladaptive genotypes (Barber and Svensson, 2003). Overcoming the costs of sex is quite attainable by combining the advantages of sexual reproduction caused by directional and sexual selection, as well as fluctuating epistasis. Hence, recombination is a valid and advantageous method of combating antagonistic coevolving species.

As can be seen, there has been much work done, both experimentally and theoretically in order to understand the coevolution between hosts and parasites, however the base of experimental evolution is quite thin, and the exact method of interactions is not known at the genotypic level. Very recently, amplification of the DNA by

RAPD-PCR was utilized to investigate the genetic variability between susceptible and resistant strains of *Biomphalaria tenagophila* to strains of *S.mansoni* (Da Silva, *et al*, 2004). The results provided more evidence that RAPD-PCR is adequate for investigating polymorphisms, aiding in our knowledge of genetic variability in these hosts, and will promote future identification of genomic sequences related to resistance and susceptibility. The relationship between *B. tenagophila*, *B. glabrata* and *S.mansoni* was explored employing RAPD-PCR in order to see if similarities existed and if polymorphisms were present (Spada, *et al*, 2002). The focus of this study was to understand the genetic polymorphisms associated to resistance in hopes of contributing to future identification of genes related to resistance in order to develop new control strategies for schistosomiasis. It is my hopes that these new findings will spark further interest into this genomic research in order to further our understanding of coevolution and to develop new techniques and strategies to battle disease.

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