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Catching the Red Queen? The advice of the Rose

Are natural populations like ducks on a river, with calm stasis on the surface being maintained by frantic paddling beneath the surface at the genetic level? In 1973, Van Valen[1] proposed that even in the absence of external environmental change, natural populations are not edging ever closer to that perfectly adapted phenotype, but are locked in a process of constant change, acting and reacting to the populations changing around them. He named this coevolutionary process after the Red Queen, who pointed out to Lewis Carroll's Alice the need to run constantly to stay in the same place[2].

Since then, a substantial body of theory has confirmed that antagonistic biotic interactions can indeed maintain genetic change in the players involved[3–7]. But what of reality? Evidence from wild populations is mostly indirect[3,8]. Now, Dybdahl and Lively[9] claim to have come face to face with the Red Queen. Evidently, they followed the advice of the rose:

> Having lost sight of the Red Queen, Alice asked the Rose how to catch her. 'I should advise you to walk the other way'. This sounded like nonsense to Alice, but after only occasional glimpses of the Queen in the distance, she thought she would try the plan, this time, of walking in the opposite direction. It succeeded beautifully. She had not been walking a minute before she found herself face to face with the Red Queen.

What does she look like?

The Red Queen is generally taken to be an ongoing process of reciprocal co-adaptation, in which the evolving parties continually respond and counter-respond to the selection pressures imposed by each other. But empirical tests of this notion require explicit details. There are different kinds of coevolution. Consider two extreme scenarios.

In the first, you are happily fighting your neighbour with bare fists, until one day she arrives armed with a sword. Your fist is no contest against her sword, but with a simple bow and arrow you can attack your neighbour whilst staying out of her reach. Your neighbour responds with a gun, but when you develop a nuclear fission device, you have the last laugh. Or do you? This type of arms-race is characterized by repeated bouts of directional selection, and there is no going back. Swords never again confer a fitness benefit.

At the other extreme, going back to the sword does provide an advantage. Instead of playing for world domination, let's play for lollipops. You and your opponent each have a bag containing five blue lollipops. The rules of the game are very simple. If you have more lollipops than her, you have to give her four of yours, otherwise she gives you one of hers. In the first round you have the same number and so get one of her lollipops, but that means in the next round you have six while she has only four. You are forced to give her four of yours, leaving your depleted supply at only two lollipops compared with her eight. But don't despair, after three further rounds you gradually restock your arsenal and you are both back to the original five lollipops each. The Red Queen just ran nowhere. This process is characterized by cycling repetitive behaviour.

The qualitative dynamics of any coevolutionary system will depend critically on the details of the game. This also applies to the quantitative dynamics. Important factors are the relative rates at which the players evolve (if you lose five lollipops instead of four, it will take longer to complete a full cycle), the repertoire of alternatives available to the different parties (how many types of weapons do you have, and how many colours of lollipops), and how exactly the coevolving parties interact with each other (by how much is a gun better than a sword?). Attributing fluctuations in gene frequencies to Red Queen processes thus requires an explicit and system-specific model that makes clear which of many possible dynamical outcomes should actually be occurring. In a new paper, Dybdahl and Lively[9] have done just that.

Is this her?

For five years, they have been tracking levels of infection of snails (*Potamopyrgus antipodarum*) by sterilizing trematodes (*Microphallus* spp.) found in one of New Zealand's spectacular glacial lakes. In their study population, the snails were wholly asexual and could be grouped into distinct clonal lineages using genetic markers. Of more than 40 lineages, only four were present in appreciable numbers. The frequency of these four fluctuated significantly during the study. Were these dynamics a consequence of frequency-dependent selection imposed by coevolving trematodes? At first glance, apparently not: there was no correlation between the frequency of these clones and the change in their level of infection in any particular year. But would we expect to see such a correlation even if coevolution was involved? Dybdahl and Lively[9] have developed a simple model that captures their understanding of the interaction between the snails and their trematodes. This showed that with relevant parameter values – in particular, estimated selection coefficients and generation times – correlations between changes in the level of infection and clonal frequency should not be measured between contemporary populations. Instead, the correlations should be between the change in infection levels in one year and the frequency of the host clone in the previous year. It is necessary to look backwards in time, and the model told Dybdahl and Lively how far back to look. The Rose had the answer all along.

As expected, change in clone frequencies in the population was correlated with the time-lagged change in clone-specific rates of trematode infection – rare clones had low levels of infestation but, as they became common, they became over-infected and declined in frequency. This significant over-infection of a clone following its peak abundance suggests a time-lagged overshoot driven by a delayed disadvantage to being common. In a laboratory experiment, Dybdahl and Lively further demonstrated that there is indeed an advantage to being rare: the rare clones were substantially less susceptible to infection by the parasites than the common clones.

In this case, the evidence for the existence of Red Queen dynamics is highly suggestive – the snail clones were not infected in proportion to their current frequencies, showing that snail genotype must be relevant to parasite infection success. But the case is by no means closed. For a start, longer time series consistent with the current data (four clones over five years) would be more comforting. Perhaps more importantly, the Red Queen describes a coevolutionary process, and so evolutionary change in both parties needs to be demonstrated. Even if genetic change is occurring in the trematode populations, a sceptic could argue that something else is causing the fluctuations in clone frequencies (chance? other parasites?) with these particular trematodes tracking the fluctuations.

The data also prompt another question. If being a rare snail clone is so good, why did only a small minority of the 40 or so clones that were rare throughout the study increase in frequency? A possible answer is that, for some reason, most of the rarer clones are on average less fit. Imagine the fate of a new clone that enters the population, say by mutation. This clone initially enjoys an advantage because few parasites have evolved means of successfully infecting them. However, as the clone becomes common, parasites capable of infecting that clone will spread, until eventually the clone is driven to low frequencies. Now, while at these low numbers, Muller's ratchet will start to click in our clonal lineage causing it to get less fit as deleterious mutations accumulate. So, although our clones should experience an advantage to being rare because there is less chance they will be infected by parasites, the deleterious mutations that have built up whilst being rare makes them unable to capitalize on this advantage. It will be very interesting to track the success of the four clones studied by Dybdahl and Lively[9] in the future. Can formerly common clones ever return to high frequencies? If they do not, the dynamics are being generated by more than antagonistic evolution, and this will not appear cyclical.

This combination of Red Queen dynamics and Muller's ratchet has been invoked to give an advantage to sex[10]. A sexual population will also be driven through cycles in a similar manner to the clonal lineages already mentioned, but at low numbers a sexual population is not subject to the ravages of Muller's ratchet, which, unlike its clonal counterpart, allows it to return to high frequency by virtue of its rare advantage. It is important to note that here the advantage to sex does not come from creating rare host genotypes out of common ones – that is, the Red Queen theory of sex[11]. Instead, sex is allowing the hosts to avoid the accumulation of deleterious mutations caused by the cranking of Muller's ratchet. Here, the role of the Red Queen is to drive the snail genotypes to very low frequency where the ratchet clicks the fastest.

Is she everywhere?

In evolutionary biology, the Red Queen is relevant to areas as disparate as the evolution of sex[6], palaeontology[1], the maintenance of genetic variation and signalling[12]. Despite this, there remains little direct evidence of her existence. Why are highly dynamical gene frequency fluctuations not ubiquitous? Actually, they might be, but the few studies gathering temporal data on gene frequencies in natural populations might not be looking at the right genes. On the one hand, working with clonal snails meant that Dybdahl and Lively did not need to specify or study the particular (and still unknown) host loci driving the dynamics. On the other hand, the trematodes involved are sexual, so the most direct way to study any Red Queen dynamics in the parasites is to look directly at the loci involved. Those have not yet been identified, but it is not difficult to envisage a time when they will be – in biomedical circles, there is great interest in snail–trematode interactions. Hopefully, longitudinal samples of trematodes from the snails in Dybdahl and Lively's population are accumulating in a freezer.

Biomedical science has already revealed the potential ubiquity of the Red Queen. The within-host dynamics and evolution of HIV and trypanosome infections, for instance, have been exceptionally well characterized at a genetic level; the wild fluctuations in the frequency of pathogen surface antigens in response to the somatic evolution of the immune response reeks of Red Queen dynamics. In these circumstances, the relevant pathogen and T- and B-cell lineages can be recognized. Such sophistication is almost certainly required to detect the Red Queen in the habitats more conventionally studied by evolutionary biologists. A key issue is the existence of really good time series data on relevant genetic variants. Like Alice, we need to be able to look backwards.

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