Review

Time-shift experiments as a tool to study antagonistic coevolution

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Although understanding natural selection in antagonistic host–parasite interactions has been a challenge for many years, direct evidence for the coevolutionary process is still scarce, particularly in relation to changes in antagonist populations over time. The underlying processes of coevolution thus remain difficult to characterise. Time-shift experiments can be used to test the performance of an antagonist population from a moment in time against the other from the same and different moments in time, revealing reciprocal adaptation in host–parasite relationships. Here we discuss how time-shift experiments together with modelling can shed new insights on the underlying processes of antagonistic coevolution.

Experiments to detect temporal coevolutionary dynamics

The term 'coevolution' describes reciprocal evolutionary interactions between populations that lead to adaptive changes in those populations [1]. Given that hosts and parasites are often characterised by strong selection and rapid evolutionary change, their response to selection imposed by a biotic environment has received particular attention in the study of antagonistic interactions (see Glossary) [2]. However, studying host–parasite coevolution is difficult, because a change in one antagonist might quickly be countered by the other antagonist. Following the evolution of both species over time requires multigenerational studies, which is often not possible. Thus, many empirical studies have focussed on analysing spatial patterns of host–parasite interactions rather than temporal patterns. For example, several studies have investigated whether parasites are locally adapted to their host populations (reviewed in Ref. [3]). However, detecting a pattern of local adaptation does not provide direct evidence of an ongoing coevolution process in local populations [1,4,5] (Box 1). Another way to follow the evolution of two interacting species is to examine temporal variations of antagonistic populations. By looking at populations over time, one might compare the performance of the host (parasite) population from a moment in time against the parasite (host) population from the same, past and/or future moments in time. Such time-shift experiments are possible when the genotypes of either host, parasite or both can be preserved, and have been shown to be a promising tool for research on coevolution [6–8].

Here we demonstrate that time-shift experiments, combined with mathematical modelling, can advance our understanding of the processes underlying coevolution. To this end, we explain how to monitor coevolution throughout time-shift experiments and highlight the importance of different experimental designs. We describe how modelling can help differentiate among the mechanisms underlying host–parasite coevolution. Finally, we review empirical evidence of coevolution using time-shift experiments and conclude that there is still more potential in using these experiments to understand coevolution.

Monitoring coevolution through time-shift experiments

Measuring coevolutionary changes in host–parasite interactions is difficult because both antagonist populations might change simultaneously, leading to a pattern where the overall picture (e.g. average resistance or average infectivity) remains apparently unchanged. Underlying changes in the frequencies of the relevant gene variants are only visible when disease loci or linked loci can be followed directly [9]. One solution is to keep one antagonist constant (preventing it from evolving) while observing changes in the other antagonist. Time-shift experiments have recently been developed specifically to overcome this problem [6,10].

In time-shift experiments, samples of host (or parasite) populations from different time points are tested in combination with samples of parasite (or host) populations from other particular moments in time. For example, parasite (host) populations might be exposed to contemporary, past and future host (parasite) populations. Figure 1 illustrates this idea with samples of host

Glossary

Antagonistic interaction: negative reciprocal interaction between two species, that is the two antagonists benefit at the expense of the other.
Gene-for-gene: a universally infective parasite genotype can infect all host genotypes, whereas the other parasite genotypes can infect fewer or even only one host genotype.
Matching allele model: the infection is successful when parasite and host genes match.
Negative frequency-dependent selection: the relative fitness of an allele declines with its frequency.
Selection coefficients: relative measure of fitness.
Selective sweeps: a new mutant genotype arises in the population and increases in frequency owing to a fitness advantage relative to other members of the population.
Time-shift experiments: experiments that test the performance of one antagonist population from a moment in time against the other population from the same and different moments in time.

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Box 1. Temporal versus spatial experiments in detecting coevolutionary patterns

Many studies have examined coevolutionary dynamics using spatial variation of antagonistic interactions by determining whether the parasites were locally adapted to their sympatric hosts. Most of the studies relied on the geographical mosaic theory of coevolution, which examines the role of evolutionary and ecological processes in determining coevolutionary patterns across geographical localities [34]. On a geographical mosaic, coevolutionary dynamics are likely to be out of phase because of slight variations in initial genotype frequencies [35]. Under this assumption, comparing the performance of host and parasite populations from different geographical localities can provide insights into coevolutionary dynamics. However, under realistic conditions, other factors might have a role in shaping local evolutionary processes, such as variation in gene flow (between antagonists and localities), asymmetry in gene flow, founder effects and genetic drift and local difference in host and/or parasite communities. Consequently, coevolution in spatially diverse landscapes (i.e. geographical mosaics) can lead to almost any pattern of host–parasite interactions [5].

Time-shift experiments can be seen as temporal adaptation experiments. Although they might appear to have the same drawbacks as local adaptation studies in their use for coevolutionary inference, time-shift experiments differ in a key aspect. Both types of experiment assume that coevolutionary dynamics are placed in the same genetic and ecological settings (e.g. the same underlying genetic systems, constant migration rates in space and time or similar habitats [abiotic and biotic]). Although these assumptions are rarely met across spatial conditions (i.e. geographical mosaic), they are much more likely to hold true within a population across a period of time. In other words, environmental variation introduced by a geographical mosaic is likely to be larger than variation introduced by a temporal mosaic. Moreover, if time-shift studies are conducted with samples from experimental evolution, they do not suffer from this temporal mosaic effect.

and parasite populations from nine successive generations (P1–P9 and H1–H9, with larger numbers representing more recent samples). Such samples can be collected from natural coevolving populations or from experimental populations and stored for later analysis. The sampling process and the experimental design must be carefully thought through, as they can have a direct effect on the observed adaptation pattern (Box 2).

Using host and parasite samples from the same population but from different moments in time enables several tests concerning evolutionary change to be done. First, one can test for general trends over time, either by testing all contemporary combinations (Figure 1a) or by testing all parasites (or hosts) in combination with one particular host (or parasite) (Figure 1b). These two experimental designs lead to different outcomes: testing all contemporary com-

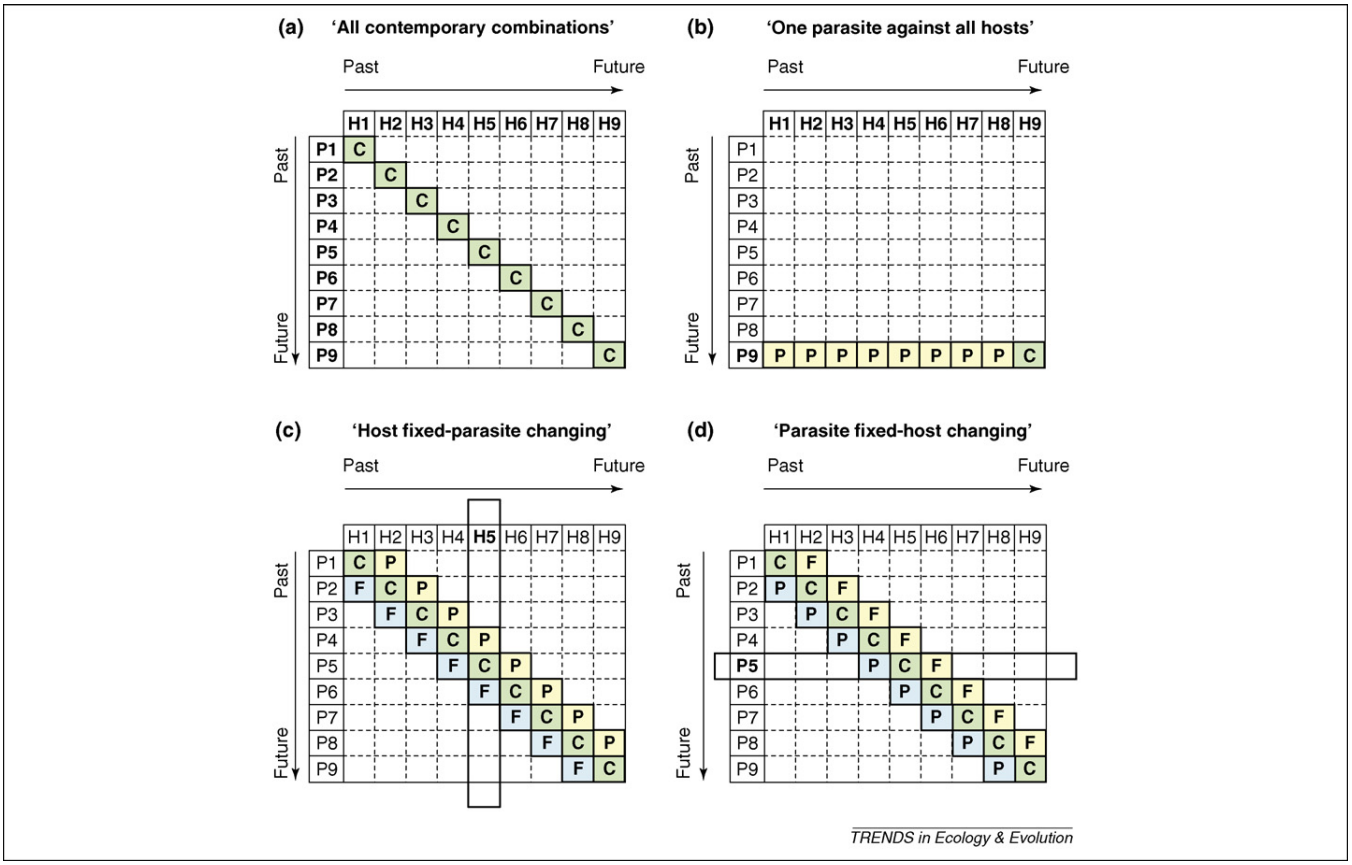

Figure 1. Different designs to test for host–parasite coevolution. H and P denote host and parasite populations, respectively. H9 and P9 are the most recent samples, whereas H1 and P1 are the oldest samples from the same populations. C, P and F indicate cross-infections: C = with a contemporary population; P = with a population from the past; and F = with a population from the future. **(a)** Cross-infection between all contemporary combinations. **(b)** A time-shift experiment in which all hosts are tested in combination with one particular parasite (the reverse is also possible, but is not shown). When only the most recent population of one antagonist is available, this design is the only option. **(c)** Cross-infection experiments with a 'host fixed–parasite changing' design. **(d)** Cross-infection experiments with a 'parasite fixed–host changing' design. In (c) and (d), the same combinations are used in the experiment, but the comparisons differ for the analysis of the data (as shown by the boxes). In (a)–(d), host and parasite populations 1–9 correspond to one generation each; thus, there is a time lag of one generation between contemporary and past or future populations.

Box 2. Experimental design and pattern of adaptation

Demonstrating antagonistic coevolution with time-shift experiments relies on the sampling strategy. First, it is important that host and parasite samples are independent from each other to avoid confounding effects. For example, infected hosts should not be discarded from the host sample because this would reduce the average susceptibility of the sample. Second, depending on the biological system, the number of samples from different time points might be limited. More sets of combinations (past, contemporary and future samples) would increase the statistical power of the analysis and hence the likelihood of detecting a general pattern. By contrast, more time points into the past and/or future would increase the temporal resolution and would be necessary to differentiate among possible mechanisms (Figure 3). Finally, the pattern obtained with time-shift experiments can reflect an interaction between population dynamics and sampling, as Ref. [8] has shown. In this study, parasite infectivity was lower when host populations were exposed to parasite populations from the recent future than to contemporary parasite populations, which is contrary to what a simple model would predict (Figure 3a). Whereas the predictions in Figure 3a are based on a generation-by-generation time shift, the experimental pattern was based on sediment slices, each containing the archived propagules of several generations, that is each sediment layer (each population sample) included material from several generations. Taking this into account in a model of coevolution by NFDS, the predictions properly fit the data [8].

In addition to sampling strategy, the design of cross-infection can affect the observed experimental pattern, as illustrated by Figure 3.

binations can confound host and parasite changes, as opposed to testing against one of the two antagonists. Second, one can test for patterns that repeat themselves over time. Evidence for recurrent events is essential for demonstrating repeated reciprocal adaptations and can be tested for in two ways. One can compare parasite populations from different generations to a fixed-host population (host fixed–parasite changing design). This demonstrates changes in the parasite population relative to the host (Figure 1c). Similarly, the same tests can be done with a fixed-parasite population, which would monitor host changes relative to the parasite (Figure 1d). These comparisons are repeated for each contemporary combination (P1 with H1, P2 with H2) and their respective past and future samples. The number of past and future samples included depends on the experimental possibilities (only one shown each in Figure 1c,d; Box 2).

Mechanisms underlying host–parasite coevolution and adaptation patterns

Antagonistic host–parasite coevolution can occur under a range of conditions. The two most discussed models are selective sweeps (arms-race dynamics; Figure 2a) and negative frequency-dependent selection (NFDS; Figure 2b) [1,11]. Antagonistic coevolution by selective sweeps occurs when new alleles that appear either by mutation or migration spread to fixation in the host or parasite population [12–15]. Changes in populations owing to selective sweeps are slow, unless the selection coefficients of the spreading mutant or migrant are high, because the sweeping genotype is initially rare and takes a long time to reach a detectable level [16].

By contrast, genotypic changes are assumed to be faster under antagonistic coevolution driven by NFDS [12,17–19]. NFDS is often described as Red Queen dynamics, although this term has been used for an entire family of mathematical and verbal models that include some form of fluctuating selection [20–22]. This model is based on the idea that selection will favour rare host genotypes, as parasites track the common host genotypes [9,23]. In the ideal case, selection against common host genotypes gives rise to cyclical oscillations of genotype frequencies that continue over time [17,23]. Such oscillations are not seen in selective sweep dynamics. Therefore, mathematical models predict that time-shift experiments should produce different outcomes for coevolution by selective sweeps and by NFDS [24].

Depending on the mechanism underlying antagonistic coevolution, different predictions can be made by mathematical modelling for the outcome of the time-shift experiments suggested in Figure 1. Under coevolution driven by selective sweeps, outcomes depend on the moment during a sweep of a new mutant in which the samples were collected (Figure 3c,d). During a sweep of a new parasite mutant, parasites from the past population should, in general, be

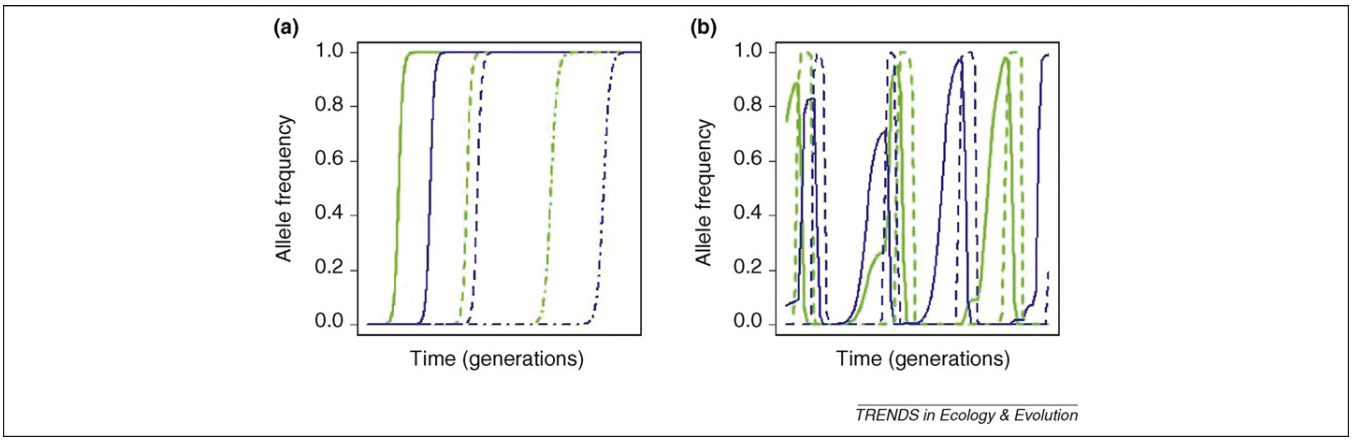

Figure 2. Two models for antagonistic coevolution. This figure shows the change in allele frequencies (green for parasite alleles and blue for host alleles) under two models of coevolution. Different types of line represent different alleles. **(a)** A conceptual model of coevolution by selective sweep. A new genotype that has arisen either by mutation or by migration has a higher fitness (higher resistance or infectivity) than the previously dominant genotype. This figure shows the successive spread of three new alleles in the host and in the parasite. **(b)** Allele frequency changes for coevolution by NFDS. The allele frequencies of the two antagonists oscillate in time as rare genotypes are favoured and common genotypes are selected against. For each antagonist, we present only the changes of two alleles. (b) was modified, with permission, from Ref. [8].

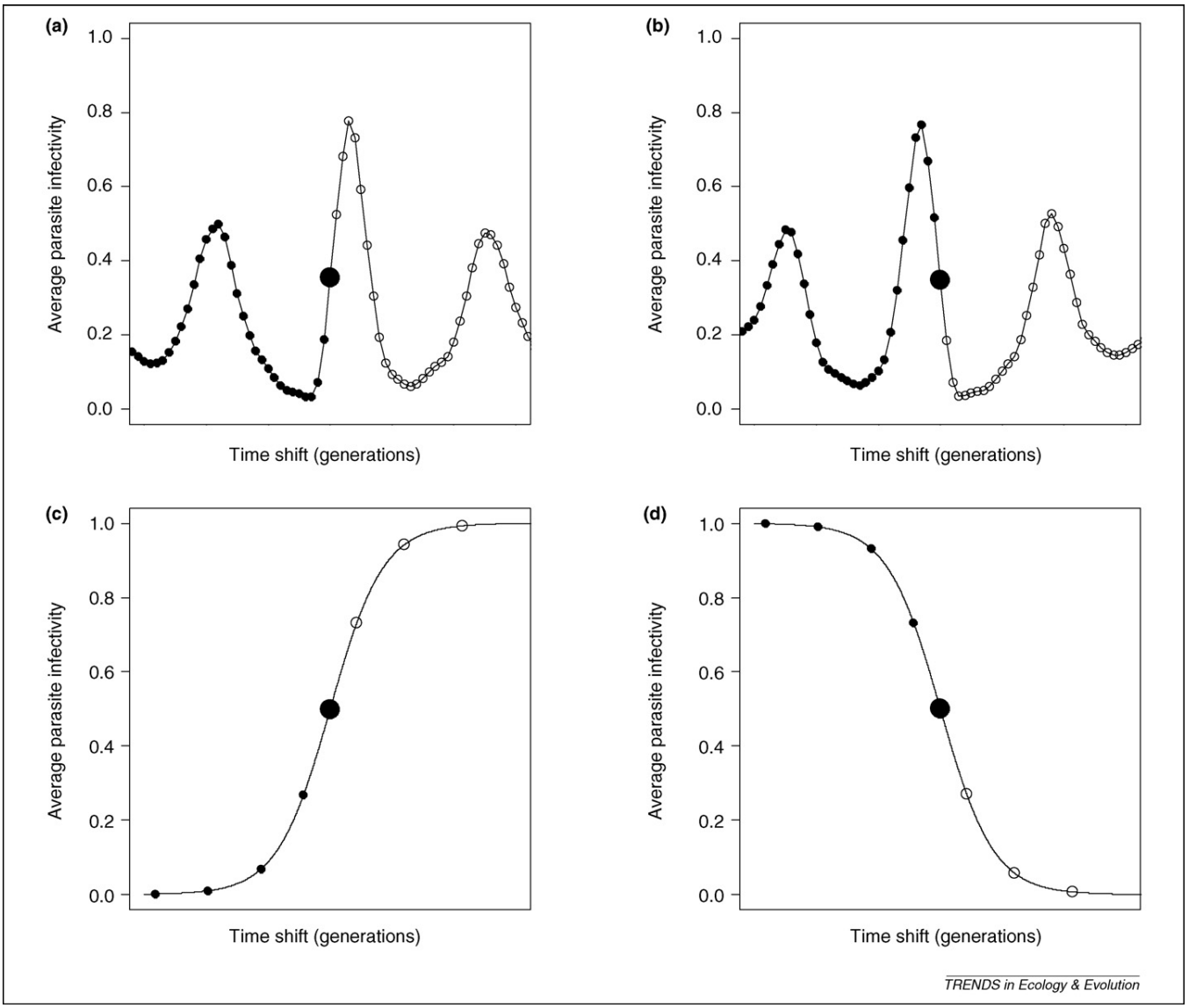

Figure 3. Predicted pattern of coevolution driven by either selective sweeps or negative frequency-dependent selection with different experimental designs. **(a–d)** The average parasite infectivity for different time shifts with two different experimental designs: 'host fixed–parasite changing' ([a] and [c]) and 'parasite fixed–host changing' ([b] and [d]). The response of the host and the parasite is measured by levels of parasite infectivity. The large solid black dot represents the contemporary cross between host and parasite, whereas the smaller solid black dots represent crosses from past generations of either parasites ([a] and [c]) or hosts ([b] and [d]); open dots represent crosses from future generations of parasites ([a] and [c]) or hosts ([b] and [d]). (a) and (b) show patterns of coevolution by NFDS based on a simple coevolutionary model [8]. The compatibility matrix of parasite and host genotypes is defined by a matching allele model (definition in Box 3), with one locus and four alleles for each antagonist. This prediction is the same for every set of past, contemporary and future samples. (c) and (d) show patterns of coevolution by selective sweep. Parasite infectivity increases when the allele of the new genotype introduced either by mutation or by migration into the population increases in frequency. The individual carrying this new allele can infect all the genotypes until a resistant allele appears. Under coevolution by NFDS with a host fixed–parasite changing design, similar patterns to those detailed in (c) will emerge when the time shift is small. Therefore, a cross-infection experiment within a small time shift is not enough to distinguish between coevolution by NFDS (a) and by selective sweep (c). Only a multigeneration time-shift experiment, as performed in Refs [6,8], can provide enough information to distinguish the mechanisms underlying host–parasite coevolution. (a) and (b) were modified, with permission, from Ref. [8].

less able to infect a contemporary host, whereas parasites from the future would generally be more capable of infecting the host (design, Figures 1c,3c). During the spread of a new host mutant, hosts from the past would be less resistant when tested with contemporary parasites, and hosts from the future would be more resistant (design, Figures 1d,3d). For samples collected in between sweeps, no changes are expected.

If coevolution is driven by time-lagged NFDS, the predictions depend on the study design. We illustrate this in the case of a host fixed–parasite changing design (Figure 1c). The cyclic pattern observed during NFDS (Figure 2b) is also readily seen in time-shift plots (Figure 3a,b). With parasite samples from the past, infectivity first declines and then increases as the time shift becomes larger. With parasite samples from the future, infectivity first increases for a few generations and then sharply drops.

In comparing the predicted patterns of time-shift experiments for coevolution by selective sweep and NFDS, we observe two points. First, the overall pattern is strikingly different. Second, if we consider only the time shifts of a few generations close to the contemporary one, the same adaptation pattern is predicted in both mechanisms, namely,

Box 3. Modification of predicted adaptation patterns by characteristics of antagonistic interactions

Antagonistic interactions increase fitness in a parasite but decrease fitness in a host. The fitness effect of antagonist interaction varies with the (genetics) mechanisms underlying the interaction. Among the possible genetic interaction matrixes, the gene-for-gene model (GFG) and the matching-allele model (MA) are usually used to represent the genetics underlying host–parasite antagonism [36]. The key feature of these models is a specific match between parasite traits (infectivity and/or virulence) and host traits (resistance). These models can be empirically tested with cross-infection experiments in which parasite infection ability is measured in parasite genotype × host genotype interaction. Under the GFG model, a universally infective parasite genotype can infect all host genotypes, whereas the other parasite genotypes can infect fewer or even only one host genotype. A fitness cost for the host can be assumed to be associated with its ability to be infected (resistance) [37].

GFG interactions have been well demonstrated in plant–pathogen interactions [38,39] and, recently, in the bacteriophage Φ2 bacteria *Pseudomonas fluorescens* SBW25 system [40]. By contrast, under the MA model, a match between parasite and host genes is needed for a successful infection, such that a parasite genotype can only infect a 'matching' host genotype. Such genotype-specific interactions have not yet been shown. No overall superior genotype was found for *Daphnia magna* and its parasite the bacterium *Pasteuria ramosa* [28,29], nor for the soil nematode *Caenorhabditis elegans* and the pathogenic soil bacterium *Serratia marcescens* [41]. These data are inconsistent with a GFG model and consistent with an MA or a hybrid GFG-MA model as defined by Ref. [36].

infectivity increases over time. Thus, to distinguish between these two mechanisms, larger time shifts are necessary. The same is true for parasite fixed-host changing designs (Figure 1d).

Using time-shift experiments and modelling to differentiate between possible mechanisms

The appropriate data to carry out time-shift experiments are available for only a few biological systems. Phage–microbe systems have become a commonly used model for experimental evolution [6,14]. In comparison to systems with eukaryote hosts, they are characterised by large population sizes and high mutation rates, both of which provide a sufficiently high supply of new mutations. New mutations could be an important factor in driving reciprocal adaptation and, hence, a coevolution by selective sweep is often assumed. By contrast, evolution in eukaryote systems might, to a larger extent, rely on standing genetic variation. Several experiments have used eukaryote host systems to investigate coevolution (e.g. plant–pathogen systems [25,26], a snail–schistosome–rodent system [27], a snail–trematode system [9] and a crustacean–bacteria system [28,29]), some of which used time-shift experiments to test for coevolutionary dynamics.

The first direct evidence of long-term antagonistic coevolution in a eukaryote host system came from the freshwater snail *Potamopyrgus antipodarum* and the sterilising trematode *Microphallus* spp. [9]. Evidence for time lags in parasite infectivity was later tested with laboratory populations of both the host and the parasite [7] with a 'parasite fixed–host changing' experimental design (Figure 1d). The authors compared the infection rates of contemporary hosts that were exposed to contemporary parasites with those of hosts that were lagged one generation behind the parasite (past hosts). The cross-infection experiment showed that contemporary hosts were less infected than hosts from the previous generation. Although the use of this one-generation time-shift experiment in one direction (backward in time) revealed an adaptation of the host to the parasite, it does not, on its own, provide enough information to distinguish between coevolution by NFDS and selective sweeps (Figure 3). However, together with previous work on this system [9], the results of the time-shift experiment suggest that coevolution is induced by NFDS rather than by selective sweeps.

Using multiple time points increases the power of time-shift experiments

Increasing the number of time points (i.e. larger time shifts) can help to determine the mechanisms underlying coevolution. The first experiment that was carried out over multiple generations and that revealed multiple cycles of defence and counterdefence involved the bacterium *Pseudomonas fluorescens* SBW25 and its phage SBW25Φ2 [6]. Starting without any genetic variation, the experiment was forced (at least initially) to evolve by selective sweeps. The authors observed that bacteria resistant to their contemporary phages were always resistant to ancestral phages and that phage populations from all time points were able to infect ancestral bacteria. Moreover, on average, bacterial resistance and phage infectivity increased with time [6]. The importance of mutations in this system was recently highlighted when it was shown that coevolving bacteria evolved at higher mutation rates than did non-coevolving experimental lines [30]. Using the same biological system but starting with standing genetic variation (a prerequisite for NFDS), a long-term coevolution experiment was performed with a host fixed–parasite changing design [30]. The results revealed an increase in both host resistance and parasite infectivity, with no consistent change over time of average infectivity in contemporary infections [30]. This pattern is consistent with coevolution by NFDS and with other studies on the same host–parasite system [31,32]. These results show that the specific details of an experiment determine which evolutionary process will occur. The observed pattern and the characterisation of the underlying processes directly depended on the genetic structure of populations tested (with or without standing genetic variation).

A two-direction time-shift experiment with natural populations

In another recent study, a two-direction time-shift experiment was conducted over several time points in *Daphnia magna* and its bacterium *Pasteuria ramosa* and revealed the temporal dynamics of antagonistic coevolution in a natural population [8]. In this system, both the host and the parasite produce resting stages that accumulate in lake sediments, providing an archive of gene pools from the past [33]. Host and parasite populations from different generations were restored by reactivating host and parasite resting stages from two sediment cores [8]. The process of long-term coevolution was tested with a parasite fixed–host changing design: the infectivity of the parasite was measured by exposing it to the host from the same sedi-

ment layer (contemporary), and from the sediment layer below (past) and above (future). As predicted by a coevolution model based on NFDS, parasite infectivity was higher when host populations were exposed to contemporary parasite populations than to parasite populations from the recent past (Figure 3a). The analysis of the temporal response of the host and the parasite showed that the parasite continuously adapts to the evolving host population. The interpretation of these results was supported with a simple mathematical model [24]. Restored populations of *Daphnia* and its parasite were also exposed to contemporary combinations (Figure 2a) to test for changes in parasite infectivity and virulence over time. A low temporal variation of parasite infectivity was revealed. In parallel, an increase in parasite virulence over time associated with an increase in parasite fitness was observed. Both results suggest that the antagonists continually respond and counter-respond to the selection pressures imposed by each other. The fact that the underlying coevolutionary dynamics are not visible when both antagonists are seen together highlights the utility of time-shift experiments to reveal such dynamics.

Conclusions and future research

Here we have highlighted the use of time-shift experiments in the study of antagonistic coevolution. Such experiments illustrate the evolution of hosts and parasites in isolation without losing the coevolutionary aspect. Combining time-shift experiments with mathematical models is a relatively new but promising tool in coevolutionary research. Although a few examples have been used to highlight its power, more must be understood about its value for different types of study. Its strength is the generation of testable predictions based on different types of mathematical models. Streamlining models for specific systems can greatly aid in the interpretation of the results.

A weakness of time-shift experiments is that not every system is equally suitable for these types of experiments. This is because in many host–parasite systems, one or both of the antagonists cannot be stored without genetic changes. However, we believe that there are many systems where time-shift experiments can be used. Bacteria, viruses, dormant (resting) eggs, dauer larvae, clonal organisms and plant seeds are examples of taxa and life stages that can be preserved over time. If it is not possible to keep lasting stages of both antagonists, time-shift experiments can also be done with a time series of one antagonist (Figure 1b) tested against the current population of the other antagonist. The predictions for such cases can be seen in the left part (negative time shifts) in Figure 3c (coevolution by selective sweeps) and Figure 3a (coevolution by NFDS). To characterise the underlying processes of coevolution, we need to better understand the context in which each antagonist has been evolving. Conducting time-shift experiments over a wide range of systems might not only confirm predicted patterns of adaptation but also reveal novel patterns. Combined with modelling [8,24], this would help to clarify the types of process (NFDS versus selective sweep) and their interaction with the underlying genetics (e.g. gene-for-gene model and the matching-allele model).

In summary, time-shift experiments are a powerful but still underused tool by which to gain a better understanding of host–parasite coevolution. Although far from comprehensive, we have introduced here the basic concept of time-shift experiments in the hope that the method will be used and adapted to further systems. The complexity of time-shift experiments is a challenge for the experimenter and the modeller, but they are a rewarding and rich source of insights into the tangled dynamics of nature.

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Evolution Annual Meeting, held jointly by the Society for the Study of Evolution, the American Society of Naturalists and the Society of Systematic Biologists, Moscow, ID, USA
http://www.evolutionsociety.org/meetings.asp

21–26 June 2009
30th Annual Meeting Society of Wetland Scientists, Madison, WI, USA
http://www.sws.org/2009_meeting/

28 June– 1 July 2009
SEB Annual Meeting, Glasgow, UK
http://www.sebiology.org/meetings/Glasgow/glasgow.html

30 June–3 July 2009
International Human Ecology Conference, Manchester, UK
http://www.societyforhumanecology.org/