

SHORT COMMUNICATION

Host–parasite coevolution and patterns of adaptation across time and space

S. GANDON,* A. BUCKLING,† E. DECAESTECKER‡ & T. DAYS§

*Centre d'Ecologie Fonctionnelle et Evolutive, Montpellier, France

†Department of Zoology, Oxford, UK

‡Laboratory of Aquatic Ecology and Evolutionary Biology, Leuven, Belgium

§Departments of Mathematics, Statistics and Biology, Queen's University, Kingston, ON, Canada

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The description of coevolutionary dynamics requires a characterization of the evolutionary dynamics of both the parasite and its host. However, a thorough description of the underlying genetics of the coevolutionary process is often extremely difficult to carry out. We propose that measures of adaptation (mean population fitness) across time or space may represent a feasible alternative approach for characterizing important features of the coevolutionary process. We discuss recent experimental work in the light of simple mathematical models of coevolution to demonstrate the potential power of this phenotypic experimental approach.

Introduction

The study of host–parasite coevolution raises many experimental challenges. In particular, demonstrating evolutionary change of a focal species requires measurements of the phenotypes against a reference genotype of the interacting species. For example, the evolutionary change of the virulence of myxoma virus has been demonstrated by evaluating the case mortality of virus strains sampled at different points in time, with the same reference line of rabbits (Fenner & Fantini, 1999). Reciprocally, the coevolution of the rabbit population has been tracked by measuring the resistance of wild caught individuals at different points in time against reference virus strains (Fenner & Fantini, 1999).

Most coevolution studies therefore work with microbial organisms in the laboratory, taking advantage of their short generation times and cryopreservation (Levin & Lenski, 1983; Buckling & Rainey, 2002). In particular, this allows one to measure the performance of the parasite against hosts sampled in contemporaneous

populations, in populations from the past and populations from the future. For example, Buckling & Rainey (2002) and Brockhurst *et al.* (2003) conducted cross-infection experiments across time to detect and measure the speed of coevolution between the bacteria *Pseudomonas fluorescens* and its phage $\phi 2$. Specifically, they measured the ability of phage populations from different time points to infect focal bacteria populations. They found that (i) the infectivity of phages from two transfers in the past was lower than the infectivity of contemporaneous phages and (ii) that the infectivity of phages from two transfers in the future was higher than the infectivity of contemporaneous phages (Fig. 1a).

In another recent experimental study, Decaestecker *et al.* (2007) used samples of dormant stages of *Daphnia* and their bacterial parasites archived in pond sediments to analyse, in the field, the emerging pattern of parasite adaptation across time. In contrast with the results obtained on the coevolution between bacteria and phage (Buckling & Rainey, 2002; Brockhurst *et al.*, 2003; Lopez Pascua & Buckling, 2008) they showed that, over approximately 30 years of coevolution, parasites were better able to infect contemporary hosts than hosts from either past or future generations (Fig. 1b).

Here we point out that simple mathematical arguments can (i) explain the contrasting patterns of adaptation

Correspondence: S. Gandon, Centre d'Ecologie Fonctionnelle et Evolutive, UMR 5175, 1919 route de Mende, F-34293 Montpellier cedex 5, France. Tel.: +33 467 613423; fax: 33 467 412138; e-mail: sylvain.gandon@cefe.cnrs.fr

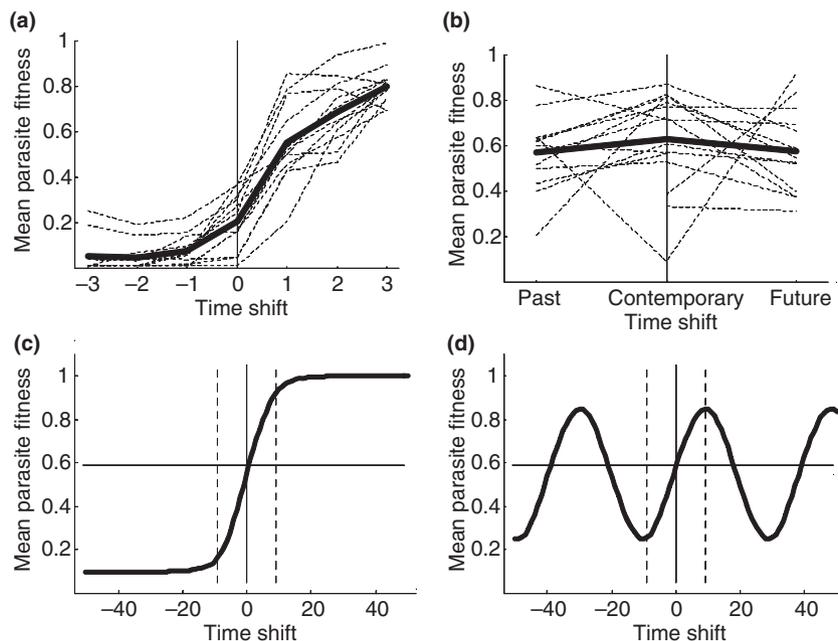


Fig. 1 In (a) and (b) we plot measures of mean parasite fitness of replicate populations (dotted lines), and average pattern of adaptation (bold line), in two cross-infection studies looking at patterns of adaptation across time. In (a) we plot the mean infectivity of phages on bacteria populations (the proportion of bacteria infected by a given phage population) from the past and the future, where time shift is measured in units of 10 transfers (modified from Buckling & Rainey, 2002). In (b) we plot the infectivity of bacteria on daphnia from the past and the future (modified from Decaestecker *et al.*, 2007). In (c) and (d) we plot mean parasite fitness across time under (c) the arms race dynamics (ARD) and (d) the fluctuating selection dynamics (FSD) obtained from numerical discrete time simulations (modified from Gandon & Day, in press). Note that for small time shifts (for time shifts within the vertical dashed lines), both the ARD and the FSD yield the same predicted pattern of adaptation.

across time obtained in these two studies and (ii) illustrate how one can use the observed pattern of adaptation across time to obtain important insights into the dynamics of coevolution.

Fluctuating selection vs. arms race dynamics

Coevolution is often described using the metaphor of the 'Red Queen' (van Valen 1973), where the constant degradation of the environment (e.g. the evolution of interacting species) explains why 'it takes all the running you can do, to keep in the same place'. Yet, very different coevolutionary processes may drive 'Red Queen' dynamics. Two different coevolutionary models are often distinguished (Woolhouse *et al.*, 2002). First, the arms race dynamics (ARD), with no frequency-dependent selection, where both species continually accumulate adaptive mutations. Second, the fluctuating selection dynamics (FSD), where host and parasite genotype frequencies oscillate over time because of negative frequency-dependent selection. Interestingly, numerical simulations can be used to show that these two coevolutionary dynamics yield very different patterns of adaptation over time (Gandon & Day, in press). Of

course, these two dynamics are likely to represent two extremes in a continuum of more complex models of interactions (Agrawal & Lively, 2002). Furthermore, when multiple loci are involved in the interaction, some loci may evolve according to the FSD whereas others follow the ARD. Yet, the analysis of these two extreme cases is a necessary first step towards a better understanding of general coevolutionary scenarios.

Under the ARD, one expects the level of parasite adaptation to increase monotonically with the *time shift* (the time interval between the sampling of the parasite and the host). Indeed a larger time shift between the parasite and its host allows the parasite to have accumulated a larger number of adaptive mutations (Fig. 1c). In contrast, the FSD yields fluctuations of genotype frequencies and, consequently, generates patterns of adaptation that fluctuate with time shift (Fig. 1d). Note, however, that both ARD and FSD yield similar increasing patterns of adaptation with time shift, when the time shift is small (between the vertical dashed lines in Fig. 1c, d). Thus, distinguishing between these two alternative coevolutionary models require measures of adaptation across relatively long periods of time.

Unlike the other studies on the bacteria–phage system discussed above, which measured the time shift over

approximately 14 bacterial generation intervals (or two experimental 'transfers'), Buckling & Rainey (2002) measured interactions between bacteria and phage over a range of longer time intervals. The data are shown in Fig. 1a and the observed pattern is consistent with the ARD scenario. The pattern of coevolution between *Daphnia* and bacteria obtained by Decaestecker *et al.* (2007), however, is inconsistent with ARD (compare Fig. 1b and Fig. 1d). Decaestecker *et al.* (2007) conducted numerical simulations of FSD and showed that many patterns can be obtained, including some fitting the observed one. Broadly speaking, their simulation results demonstrate that coevolution in this system might be due to FSD, but below we illustrate that much more can be inferred about this system through the analysis of a simple mathematical model of coevolution leading to FSD.

A simple coevolution model for the fluctuating selection dynamics

Suppose coevolution is governed by a single diallelic locus in both species. The dynamics of allele frequency oscillations in the host, h and the parasite, p are approximately (Gandon, 2002; Gandon & Otto, 2007):

$$\begin{aligned} h(t) &= \frac{1}{2} + A \sin(Bt) \\ p(t) &= \frac{1}{2} + A' \sin(Bt - C) \end{aligned} \quad (1)$$

where A and A' are the amplitudes, B is the frequency (period is $T = 2\pi/B$ and C measures the lag between host and parasite genotype frequency oscillations. In this model, the parasite lags $CT/2\pi$ time steps behind the host (Fig. 2a).

Under these assumptions, the mean fitness of a parasite population sampled D time steps away (i.e. D is the time shift between host and parasite populations) from the host population, where host and parasite samples are pooled from time windows of size G , is (Fig. 2b):

$$\begin{aligned} W_{A,A',B,C}(D, G) &= \frac{\int_{t=0}^T 2 \left(\int_{\tau=-G/2}^{G/2} (h(t+\tau)) d\tau \right) \left(\int_{\tau=-G/2}^{G/2} (p(t+\tau+D)) d\tau \right) dt}{TG^2} \\ &= \frac{1}{2} + AA' \cos(C - BD) \left(\frac{\sin(BG/2)}{(BG/2)} \right)^2. \end{aligned} \quad (2)$$

Equation 2 can be used to clarify the simulation results obtained by Decaestecker *et al.* (2007). They point out that averaging over several generations of parasites can affect the pattern of adaptation across time (Fig. 2 in Decaestecker *et al.*, 2007). In the experiment and the simulations of Decaestecker *et al.* (2007), however, it is assumed that $D = G$. Equation 2 allows one to analyse the influence of D and G independently, and to see that there are two effects hidden in the simulation results presented in Fig. 2 of Decaestecker *et al.* (2007). First, the

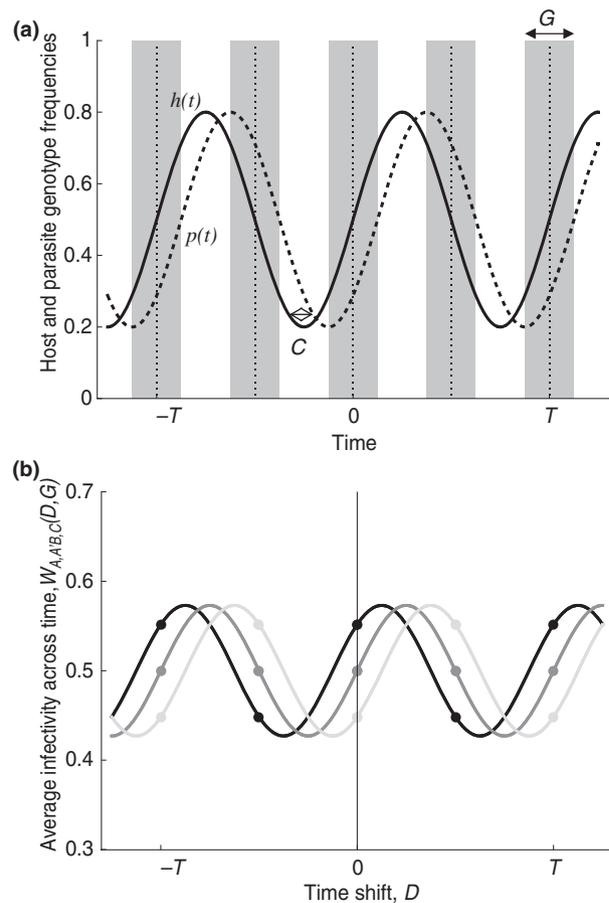


Fig. 2 Coevolutionary dynamics in a simple coevolution model of fluctuating selection dynamics governed by a single diallelic locus (eqns 1 and 2). In (a) we plot the fluctuations of host genotype frequency, $h(t)$ (full line) and parasite genotype frequency, $p(t)$ (dotted line) across time, as in eqn 1. In this specific case, the oscillation period is $T = 2$ time steps and the parasite lags $C = \pi/4$ behind the host. In (b) we plot the average parasite infectivity (mean parasite fitness in this model, eqn 2) on hosts sampled D time steps away, and when hosts and parasites are sampled in time windows of size $G = T/2$ time steps. Three patterns of adaptation across time are presented differing only in the duration of the lag C between host and parasite dynamics: $C = \pi/2$ (dark gray), $C = \pi/4$ (black), $C = 3\pi/4$ (light gray). In each case, the dots refer to an experiment in which the time shift would be $D = \pm T, \pm T/2$ and 0. The sampling times and the width of the time windows, $G = T/2$, of each sample are depicted in (a) with a vertical dashed line and a gray area, respectively. The typical pattern observed in Decaestecker *et al.* study, where the middle dot (mean parasite fitness on contemporaneous hosts) has the highest infectivity, only emerges when $C = \pi/2$ (black dots) and for $D = \pm T/2$. This figure illustrates the fact that the shape of the pattern of adaptation across time is governed by parameters C, D and TC [see conditions (3)]. Other parameter values: $A = A' = 0.3$.

effect of increasing G only dampens the oscillations of the pattern of adaptation across time, without affecting its qualitative shape. Second, variations in D , can affect

qualitatively the pattern of adaptation. For example, in Fig. 2b we show that the pattern observed by Decaestecker *et al.* (2007) is obtained when $D = \pm T/2$ but not when $D = \pm T$. We suspect that it is this latter effect that explains the change in the qualitative pattern presented in their Fig. 2. We also note that eqn 2 allows one to explore the effects of other factors as well, including virulence, mutation, number of alleles and migration rates, through their effects on A , A' , B and C (Gandon, 2002; Gandon & Otto, 2007).

More importantly, this simple model can be used to infer other important aspects of the coevolutionary process. In particular, the pattern observed in the data of Decaestecker *et al.* (2007), where the parasite is better able to infect contemporary hosts than hosts from either past or future generations (Fig. 1d), is expected to emerge only if $W_{A,A',B,C}(0, G) > W_{A,A',B,C}(\pm D, G)$. Using eqn 2, this inequality reduces to the conditions:

$$\frac{C}{\pi} < \frac{D}{T} < 1 - \frac{C}{\pi}. \quad (3)$$

Conditions (3) can be satisfied only if (i) $C < \pi/2$ and (ii) D falls within the appropriate time interval. The condition $C < \pi/2$ means that the parasite population tracks host evolution very closely (Fig. 2). Several factors can produce such an outcome, but all involve increasing the relative strength of selection on the parasite (larger selection coefficients, shorter generation times, larger number of alleles in the matching-allele model), and/or increasing the genetic variance in the parasite population (higher mutation, recombination or migration rates than the host). This suggests that the pattern observed by Decaestecker *et al.* (2007) is generated by an asymmetry in favour of the parasite in one of the above factors.

Discussion

Adaptation across time

The examination of patterns of adaptation across time in the light of simple mathematical models allows one to infer important information regarding the underlying coevolutionary dynamics in these systems. The pattern obtained by Buckling & Rainey (2002) is indicative of an ARD whereas the pattern obtained by Decaestecker *et al.* (2007) supports the FSD in which the parasite has a greater evolutionary potential than its host.

Interestingly, similar experiments have been carried out to monitor the 'coevolution' of human pathogens with the host immune system at the scale of an infected host. For example, it is possible to measure the ability of antibodies that bind to virions of hepatitis C virus (HCV). Shimizu *et al.* (1994) used this assay to measure the neutralization potential of the antibody in serial serum samples obtained from the same chronically infected patient, against samples of the virus at different time points over 14 years following onset of his hepatitis.

Plasma collected from this patient in 1990, 13 years after onset of hepatitis, and which contained HCV that had diverged genetically from the 1977 strain, did not contain antibody capable of neutralizing either the 1977 or the 1990 strain of HCV. However, plasma collected a year later contained neutralizing antibody to the 1990, but not the 1977, strain of HCV. These results suggest that HCV chronic infections induce a 'coevolution' between specific antiviral antibodies, and immune escape variants of the virus. Moreover, the fact that the antibodies present in the serum of recent samples (from 1990 onwards) lost the ability to neutralize the 1977 strain is similar to the wave-like pattern of Fig. 1b indicative of the FSD hypothesis.

Similarly, the antigenic evolution of influenza can be monitored by various binding assays of antibodies to the viral surface glycoprotein hemagglutinin (Smith *et al.*, 2004) using virus from different time points. The antibody response and the cross-specificity to various antigens are obtained using hemagglutination inhibition (HI) assay. The higher the HI value, the greater efficacy the antiserum of the host to neutralize a focal virus strain. These tests reveal that the antigenic distance between strains increases monotonically with time. Whether the mean fitness of the virus population measured across different time points is also decreasing with time depends on the ability of the immune system of recovered hosts to retain a memory of previous exposure. Measuring mean fitness across time points after sampling serum from several individuals might be a way to test alternative hypotheses regarding the generation and the maintenance of immunity in human host populations.

Adaptation across space

Comparisons across time points is not always feasible. In many host-parasite systems, the organisms cannot be stored in suspended animation for later experimental tests. An interesting alternative to measurements of mean fitness across time are measurements across space. Under the hypothesis that the coevolutionary processes occurring in various populations are not synchronized, the dynamics over space is often very similar to the dynamics over time (Frank, 1991; Gandon, 2002). Mean fitness measurements across space involve cross-infection and transplant experiments which are feasible in most host-parasite systems. Many such studies have been realized in the last 20 years using several different biological systems (Lively, 1989; Ebert, 1994; Kaltz *et al.*, 1999; Lively & Dybdhal, 2000; Morgan *et al.*, 2005). These studies typically yield measures of adaptation to local environmental conditions (Gandon *et al.*, 1996; Kaltz & Shykoff, 1998; Kawecki & Ebert, 2004; Nuismer, 2006). As for mean fitness measured across time, the examination of the pattern of mean fitness across space (e.g. parasite local adaptation) can be used to infer some information regarding the coevolutionary process. In

particular, those models show that local adaptation is partially governed by the relative rates of gene flow of the host and the parasite (Gandon *et al.*, 1996; Gandon, 2002; Nuismer, 2006; Greischar & Koskella, 2007). Significant levels of parasite local adaptation (or maladaptation) could thus be indicative of higher (or lower) rates of parasite gene flow.

The analysis of simple FSD scenarios, such as the one formalized in eqn 1, can also be used to show that factors affecting patterns of local adaptation are the same as those affecting patterns of adaptation across time. Therefore, in principle, one should expect a relationship between patterns across space and across time. For example, the conditions leading to the pattern obtained by Decaestecker *et al.* (2007) (i.e. asymmetries in selection pressures and/or local genetic variance) should also lead to parasite local adaptation. Interestingly, a cross-infection experiment using *Daphnia magna* and *Pasteuria ramosa* from distant populations nevertheless did not reveal such local adaptation, in spite of substantial genetic variation for host resistance within populations, and some genetic differentiation among host populations (Ebert *et al.*, 1998). One mitigating factor in this study, however, is that the populations examined were geographically very distant from one another. As a result, the kind of meta-population analyses that are used in much of the theory on local adaptation might not, in fact, be applicable. It would thus be interesting to look for a pattern of local adaptation at a smaller spatial scale in this system.

The link between expected patterns of adaptation across time and across space is less clear under the ARD scenario. The emergence of local adaptation requires some divergence among populations. Under the ARD scenario presented above, evolution is directional: parasite infectivity and host resistance keep increasing within each population. Yet, different populations may achieve adaptation through different routes (i.e. different genes may be involved in adaptation) which could result in some differentiation among these populations. This mechanism could explain the patterns of local adaptation emerging in long-term coevolution experiments using the bacteria–phage system discussed above (Morgan *et al.*, 2005). An alternative explanation would be that, after some time, the host–parasite system shifts from the ARD to the FSD, where local adaptation is known to emerge more readily. A potential explanation for such a shift would be that the first adaptive mutations are associated with a general fitness gain in very different environments (i.e. directional selection and ARD). Later on, when all those general adaptive mutants are fixed, evolution may involve mutants with a more narrow niche breadth because of costs associated with increasing resistance and infectivity ranges (Buckling *et al.*, 2006; Poullain *et al.*, 2007; Lopez Pascua & Buckling, 2008) which could be maintained in a dynamic polymorphism through negative frequency dependence (i.e.

FSD). A cross-infection experiment across time after long-term coevolution would allow one to detect such FSD, and would thus help to distinguish between these two alternatives. This illustrates the fact that patterns of adaptation across time and across space shed different lights on coevolution and are thus complementary. In general, we believe that combining the information gathered from both patterns can help characterize the details of underlying coevolutionary process.

Conclusion

The importance of spatial structure on coevolutionary dynamics has been pointed by several authors (Thompson, 1994, 2005; Gomulkiewicz *et al.*, 2000; Lively & Dybdhal, 2000; Thompson & Cunningham, 2002). In particular, the study of spatial patterns of adaptation (i.e. local adaptation) has led to a better understanding of the coevolutionary process in many host–parasite systems (Dybdhal & Lively, 1996; Kaltz *et al.*, 1999; Hanifin *et al.*, 2008). Here we point out that the examination of patterns of adaptation across time in the light of numerical simulation (Fig. 1) and simple analytical models of coevolution (Fig. 2 and eqn 2) can be used to infer important information about: (i) the underlying model of coevolution (FSD vs. ARD), (ii) the asymmetry in selection pressures acting on the host and the parasite, and (iii) the asymmetry in the evolutionary potential of the host and the parasite. Hence, looking for patterns of adaptation across space and across time could help meet the challenges that often arise in the study of coevolution between parasites and their hosts. It might also be useful in the broader context of the coevolution between males and females (Rice, 1996), nuclear–cytoplasmic conflicts (Gigord *et al.*, 1998) or mutualistic interactions (Day *et al.*, 2008). Such phenotypic approaches cannot, however, answer all the questions about coevolutionary dynamics, and a thorough description of the underlying genetics of the host–parasite interaction (e.g. number of loci and alleles involved in the interaction) is required to complete the picture.

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