# Local adaptation, evolutionary potential and host–parasite coevolution: interactions between migration, mutation, population size and generation time

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## Abstract

Local adaptation of parasites to their sympatric hosts has been investigated on different biological systems through reciprocal transplant experiments. Most of these studies revealed a local adaptation of the parasite. In several cases, however, parasites were found to be locally maladapted or neither adapted nor maladapted. In the present paper, we try to determine the causes of such variability in these results. We analyse a host–parasite metapopulation model and study the effect of several factors on the emergence of local adaptation: population sizes, mutation rates and migration rates for both the host and the parasite, and parasite generation time. We show that all these factors may act on local adaptation through their effects on the evolutionary potential of each species. In particular, we find that higher numbers of mutants or migrants do, in general, promote local adaptation. Interestingly, shorter parasite generation time does not always favour parasite local adaptation. When genetic variability is limiting, shorter generation time, via an increase of the strength of selection, decreases the capacity of the parasite to adapt to an evolving host.

## Introduction

Host–parasite interactions constitute one of the best settings in which adaptation in spatially and temporally heterogeneous environments can be studied. Indeed, the effects of parasitism are likely to be highly variable in time and among different host populations. The recognition of such a geographical mosaic view of coevolution (Thompson, 1994, 1999) has stimulated several empirical, experimental and theoretical studies of species interactions.

In spatially heterogeneous environments evolution may lead to the adaptation of populations to their local environmental conditions. Local adaptation occurs when the mean fitness of a population is higher on its own habitat than on a remote habitat (but see Gandon *et al.*, 1998 for other definitions of local adaptation). When the mean quality of the habitat of different populations is identical across time one may use an averaged measure of local adaptation in the metapopulation (average over the different measures of local adaptation of each population). In this case, local adaptation is a property of the metapopulation as a whole and, assuming that adaptation has a genetic basis, it measures the adequacy between spatial variability of the environment and the distribution of adaptive genetic variation.

The use of the above definition is particularly appropriate to study local adaptation in coevolving host–parasite systems because, as stated above, such systems are often characterized by important variations in space and time. In coevolutionary host–parasite systems each species constitutes an ever changing environment to which its opponent has to adapt. In such a variable environment adaptation depends on both the strength of selection and the evolutionary potential which is the ability to incorporate genotypes able to overcome the weaponry put forward by the opponent. The evolutionary potential thus depends on three processes: (1) mutation, (2) migration and (3) recombination. Moreover, what really matters is not just the rates but the

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numbers of new genotypes entering a population; the evolutionary potential hence depends also on population size.

It is conventional wisdom that parasites have greater evolutionary potential than their hosts because they often have larger population sizes, shorter generation times and higher rates of mutation and migration than their hosts, and therefore parasites are expected to be locally adapted. Several experiments support this view. Indeed, most transplant experiments showed that parasites perform better on sympatric than on allopatric hosts (Parker, 1985; Lively, 1989; Ebert, 1994; Manning *et al.*, 1995; Morand *et al.*, 1996; Koskela *et al.* 2000; Lively & Dybdahl 2000; see Kaltz & Shykoff, 1998 for a review). However, some other experiments did not find any evidence of parasite local adaptation (Dufva, 1996; Morand *et al.*, 1996; Mutikainen *et al.*, 2000) or even, found a local maladaptation of the parasite (Imhoof & Schmid-Hempel, 1998; Kaltz *et al.*, 1999; Oppliger *et al.*, 1999). These results suggest that the parasite might not always be ahead in the coevolutionary arms race.

Gandon *et al.* (1996, 1998) showed how all these coevolutionary outcomes may arise within the same context. Using a matching-alleles model of host–parasite coevolution (negative-frequency dependant selection) in a metapopulation, they showed that the ratio of host and parasite migration rates strongly affects local adaptation: if parasites (hosts) migrate much more than hosts (parasites), parasites (hosts) are locally adapted, whereas if both species have similar or high migration rates there is no differential response (i.e. equal performance in sympatry or allopatry).

In the present paper, we investigate the robustness of the above result to the effects of, and interaction with, other factors that influence the evolutionary potential of each species, namely mutation rates, population sizes and generation time. Whereas overall the previous result is quite robust, the number of migrants (which depends on both migration rates and population size) having a strong influence on local adaptation, we further found an interesting interaction between incoming genetic variation (which in the present model depends on the number of mutants and the number of migrants) and generation times.

The aim of this analysis is to identify the qualitative impact of various factors more or less independently, although some factors might be actually linked (e.g. migration and population sizes). These factors can be characterized by their effects on (i) the generation of genetic variation and (ii) the intensity of selection. Variation and selection are of paramount importance in the process of adaptation because variation generates the types that can be potentially favoured by selection and, ultimately, lead to adaptation.

## The model

### Host and parasite life cycles

The habitat consists of 20 sites disposed on a circle (circular stepping stone model). Each site supports a host population and a parasite population of fixed sizes $N_h$ and $N_p$, respectively. Each population sends migrants to the two neighbouring ones with probability $m_h$ and $m_p$ for hosts and parasites, respectively. We assume no variation in the quality of the sites (i.e. no spatial variation of the abiotic environment).

Both hosts and parasites are haploid and reproduce asexually. The genetic determinism of infectivity (and resistance) follows the assumptions of a Matching Allele Model (MAM) of interaction (Frank, 1991, 1994; Gandon *et al.*, 1996). Under this model, hosts resist when, at least, one matching between alleles in the host and in the parasite occurs. We further assume that two loci and four alleles per locus are involved in the interaction. This yields 16 different genotypes in each species (see Table 1).

Parasites reproduce before the host. Within each site infection occurs randomly as in an air-borne disease (i.e. parasites encounter hosts at a rate proportional to their frequency). We further assume that parasites reproduce $g$ times before host reproduction. In other words, when $g > 1$, parasites have shorter generation times than their hosts. These multiple generations occur at the scale of the host population and not at the within individual host level. The change in parasite genotype frequencies depends only on differential reproduction while facing the local host population. Genotypes that can infect more hosts reproduce more and, consequently, increase in frequency. The fitness of parasite genotype $i$ in population $x$ is:

$$wp_{i,x} = \sum_{j=1}^{16} I(i,j)h_{j,x}, \qquad (1)$$

where $h_{j,x}$ is the frequency of host genotype $j$ in the population $x$, $I(i, j)$ is the infectivity (i.e. the probability of infection) of parasite $i$ on host $j$ (see Table 1). After selection, some genotype frequencies might be very low. We assume that in each generation, a particular genotype goes extinct if its frequency falls below $1/N_p$. After each reproduction event the parasites mutate. For each mutation event, the actual number of mutants is randomly chosen in a Poisson distribution with mean $2N_p\mu_p$ (the factor 2 stands for the fact that two loci may mutate), where $\mu_p$ is a per locus mutation rate. These mutants yield a new genotype after mutation took place on one of their two loci.

After the $g$ reproduction events of the parasites some infected hosts die. We assume that parasites only affect the survival rate of the hosts (no effect on fecundity). Therefore, selection on the host population depends only

**Table 1** Matching Allele Model with two loci and four alleles. The first row (column) shows the genotype of the parasite (host), where the first and the second number refer to the first and the second locus, respectively. The other cells give the infectivity, *I*, for each interaction. In black cells the parasite infects successfully, while in white cells the host resists.

| | 1 : 1 | 1 : 2 | 1 : 3 | 1 : 4 | 2 : 1 | 2 : 2 | 2 : 3 | 2 : 4 | 3 : 1 | 3 : 2 | 3 : 3 | 3 : 4 | 4 : 1 | 4 : 2 | 4 : 3 | 4 : 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 : 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| 1 : 2 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 |
| 1 : 3 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 |
| 1 : 4 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| 2 : 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| 2 : 2 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 |
| 2 : 3 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 |
| 2 : 4 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| 3 : 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| 3 : 2 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 3 : 3 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 |
| 3 : 4 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 |
| 4 : 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 4 : 2 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 4 : 3 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| 4 : 4 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

on the differential mortality of each type of host. The fitness of host genotype $j$ in population $x$ is:

$$wh_{i,x} = 1 - V\sum_{j=1}^{16} I(i,j)p_{i,x} \qquad (2)$$

where $p_{i,x}$ is the frequency of parasite genotypes $i$ in the population $x$, $V$ is parasite virulence (disease induced mortality). Again, we assumed that a particular host genotype goes extinct if its frequency falls below $1/N_h$. After each reproduction event the host population mutates, where $\mu_h$ is the host per locus mutation rate. The mutation process follows the one described above for the parasite population.

Local dynamics are followed by migration. As mutation, the migration process is stochastic. For each migration event the number of migrants is randomly chosen in a Poisson distribution with mean $N_h m_h$ and $N_p m_p$, for the host and the parasite, respectively. Migration does not occur after each parasite reproduction event but after host reproduction and, consequently, the number of parasite migrants does not depend on the number, $g$, of parasite generations per host generation. It is also important to note that the above life cycles assume that parasite population size does not affect virulence and therefore the selection pressure imposed on the host population. Finally, note that neither host nor parasite populations can go to extinction. This follows from the constant population size assumption. Whereas this assumption is very useful in making the analysis much more convenient, it also excludes epidemiological feedbacks (in contrast with the model by Gandon *et al.*, 1996).

## Simulations

At the beginning of a simulation each population is founded by 10 randomly chosen individuals among the 16 potential genotypes. Foundation is immediately followed by a reproduction event which allows host and parasite populations to reach their respective fixed population sizes, $N_h$ and $N_p$. This initialization introduces some within population diversity which enables hosts and parasites to coevolve. It also introduces between populations variation in host and parasite genotypic frequencies, which results in spatial heterogeneity in the direction and strength of selection for each organism. Because initialization may also introduce considerable noise on the coevolutionary outcome, we started to collect statistics after 5000 host generations.

The antagonistic coevolution follows deterministic equations (equations 1 and 2). In particular, there is no genetic drift in this model. However, stochasticity emerges at three different steps of the life cycle: (1) the initialization of each simulation, (2) mutation, (3) migration. Because of this stochasticity, we ran five replicates for each set of parameter values. Unless specified, the results presented below are averaged over these five replicate simulation runs.

We studied the coevolutionary dynamics by looking at various measures of adaptation and variation. There are different ways to look at this system. First, one can focus at the local population's scale (Fig. 1) and, secondly, it is possible to search for spatial patterns at the metapopulation level to see if the host is more resistant to sympatric or to allopatric parasites. These different scales yield different measures of adaptation in both the host and the parasite populations.

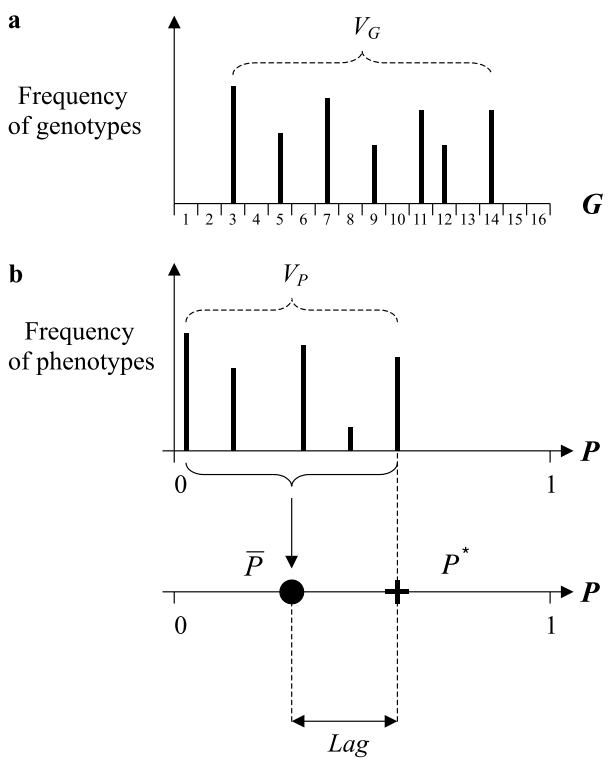


**Fig. 1** Different measures of variation and adaptation at the scale of the population. A first way to look at a population is to plot the frequency distribution of genotypes (a). The genetic variance $V_G$ measures the average amount of genetic diversity at the population scale (see Appendix 2). This distribution of genotypes affects the phenotype and, consequently, the fitness of the interacting species. A second way to look at the population is to plot the frequency of the different phenotypes (b). The distribution is characterized by its variance, $V_P$ (see Appendix 2), and its mean, $\bar{P}$. The difference between this mean and the optimal phenotype, $P^*$, measures the evolutionary lag. Note these measures of variation and adaptation can be taken for both parasite and host populations where the phenotypes are infectivity and resistance, respectively.

### *Measures of adaptation*

Different measures of adaptation can be used to describe the coevolutionary race between the host and the parasite. These measures can either focus on the coevolutionary outcome (the first two measures) or on the coevolutionary process (the evolutionary lags).

*Mean phenotype* An obvious measure of adaptation in host–parasite systems is to look at the level of resistance of the host or, reciprocally, the level of infectivity of the parasite at the population level (Fig. 1). This yields:

$$\bar{R}_{\mathrm{loc}} \equiv 1 - \bar{I}_{\mathrm{loc}} \equiv 1 - \sum_{x}^{20}\sum_{i}^{16}\sum_{j}^{16} p_{i,x} h_{j,x} I(i,j)/20 \qquad (3)$$

where $\bar{R}_{\mathrm{loc}}$ and $\bar{I}_{\mathrm{loc}}$ are the average levels of local resistance and, respectively, local infectivity. Note that $\bar{R}_{\mathrm{loc}}$ is equivalent to the measure $P_{\mathrm{loc}}$ used in Gandon *et al.* (1996).

*Differential adaptation* The mean phenotype yields measures of the level of host resistance (parasite infectivity) to sympatric parasites (hosts). It is also possible to look at the level of resistance, and infectivity, to allopatric populations. Differential adaptation may reveal whether the host or the parasite is locally adapted. We can either examine the shape of the resistance gradient across distance, or use a more synthetic measure of differential adaptation, which compares the local performance to the averaged performance in all the other populations of the metapopulation:

$$\Delta_{\mathrm{h}} \equiv -\Delta_{\mathrm{p}} \equiv \sum_{\mathrm{loc}}^{20}(R_{\mathrm{loc}})/20 - \sum_{\mathrm{loc}}^{20}\left(\sum_{x\neq \mathrm{loc}}^{20} R_x/19\right)/20 \qquad (4)$$

where $\Delta_{\mathrm{h}}$ and $\Delta_{\mathrm{p}}$ measure differential adaptation of hosts and parasites, respectively. To calculate $\Delta_{\mathrm{h}}$, each site is considered as the focal site in turn. We calculate the resistance of the local host population to the local parasite population ($R_{\mathrm{loc}}$), and the resistance of the local host population to each of the nonlocal parasite populations ($R_x$ ). These two quantities are averaged over all sites, to yield the two terms in the right side of the above equation.

*Evolutionary lags* The above measures of adaptation consider different levels of performance of the host and the parasite against sympatric or allopatric organisms. It is also possible to look in a different way at the process of adaptation. In both host and parasite populations, at every particular point in time and space, there is (are) one (or several) genotype(s) which has (have) a higher fitness. In other words, this genotype has maximal performance against its coevolving opponent. In the present model, the optimal phenotype of the host is the phenotype which maximizes resistance against its sympatric parasite population. Similarly, the optimal phenotype of the parasite is the phenotype which maximizes infectivity against its sympatric host population. At every place and time there is directional selection towards such optimal phenotypes. Negative frequency-dependent selection and spatial variation of genotypic frequencies ensure an ever changing optimal genotype in each site. An interesting measure of adaptation would be the distance between the average phenotype of the population to the optimal phenotype (Fig. 1):

$$Lag_{\mathrm{p}} \equiv \sum_{x=1}^{20}(P_x^* - \bar{P}_x)/20 \qquad (5)$$

where $Lag_{\mathrm{p}}$ is the evolutionary lag on the phenotype $P$ ($P$ can either be host resistance, $R$, or parasite infectivity, $I$), $P_x$* is the optimal phenotype at site $x$ and $\bar{P}_x$ is the average phenotype at site $x$. This evolutionary lag is a

well-known measure of adaptation in classical models of quantitative genetics (Lande & Shannon, 1996). It is a complementary measure of adaptation because, unlike mean phenotypes and differential adaptation, the evolutionary lags of the host and the parasite are not intrinsically linked. The host lag can be very low although the parasite lag can be either high or low.

All the above measures of adaptation are descriptions at a particular point in time. Unless specified, we measured these variables just after host reproduction and mutation. The results we present in the following section are averaged over the last 1000 host generations of each run.

## Results

### Effects of migrants

We first consider the case where the host and the parasite do not mutate (i.e. $\mu_h = \mu_p = 0$). Figure 2 shows the effects of migration rates on different measures of adaptation. The first graph gives the average measures of resistance against sympatric parasites. Three main cases can be distinguished. (1) When there is little or no host migration, parasite migration has a nonmonotonous effect on host resistance. It first decreases the level of resistance but, above a certain value, too much parasite migration increases the host resistance. (2) When there is little or no parasite migration, higher host migration allows the host population to reach higher levels of resistance. As for the parasites, above a certain threshold, too much host migration reduces resistance. (3) When both the host and parasite have high migration rates the level of resistance tends to reach a plateau. Indeed, large migration rates tend to maintain all the genotypes in all the populations in equal frequencies yielding an average level of resistance equal $R_{loc} = 0.4375$ (see Appendix 1). These results are mostly in agreement with the one discussed in Gandon *et al.* (1996) using an epidemiological model. The main difference occurs for the case where host and parasite do not migrate. In the previous model, the parameter values that have been used led to a full susceptibility of the host population in the absence of migration.

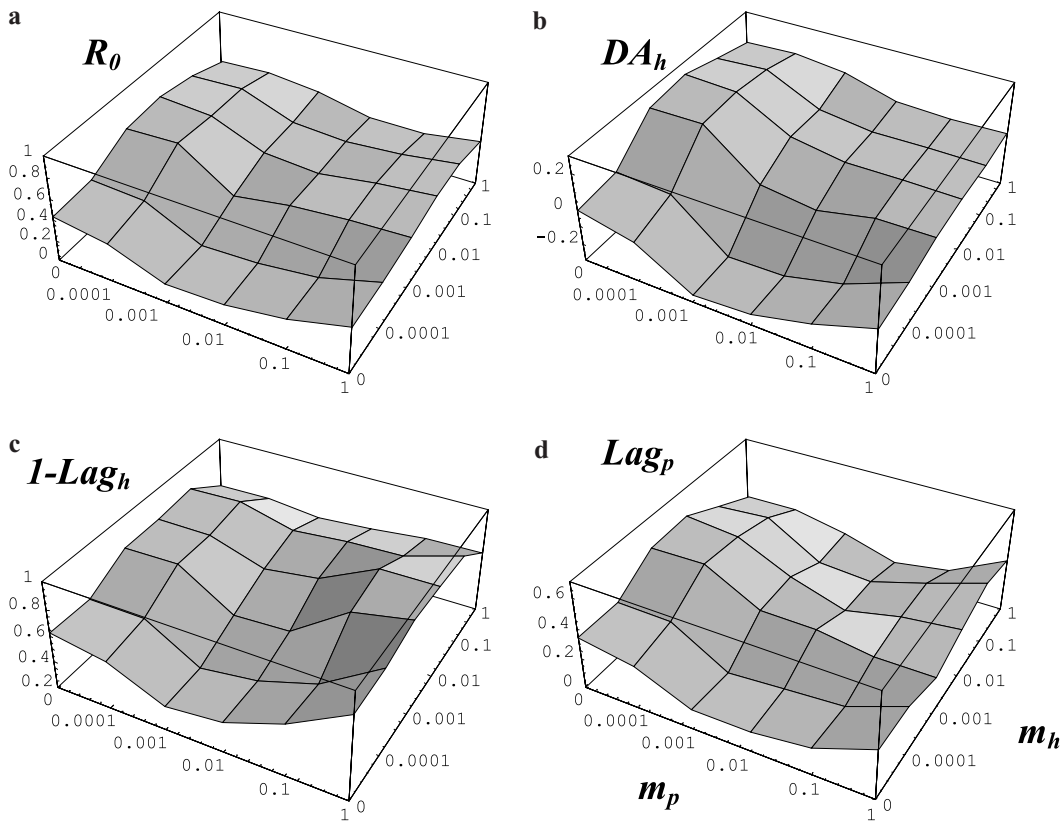


**Fig. 2** Effects of host and parasite migration on different measures of adaptation. (a) Average level of host resistance to sympatric parasites. (b) Differential adaptation of the host. (c) 1-Evolutionary lag of the host. (d) Evolutionary lag of the parasite. Note the similarity between the four graphics. The first three graphics (a, b and c) give different measures of host adaptation. The last graphic (d) gives a measure of parasite maladaptation (obviously, these figures show that parasite maladaptation is correlated with measures of host adaptation). Other parameter values: $N_h = N_p = 100$, $V = 0.5$, $g = 1$.

The two other measures of adaptation that we proposed all give a very similar picture. Interestingly, the maladaptation ($Lag_p$) of the parasite follows a similar pattern. In other words, whatever the measure of adaptation, host and parasite migration rates have a strong effect on the pattern of adaptation. Given the similarities between these different measures of adaptation, in the rest of this paper, we will focus on the analysis of the measure of differential adaptation. Our choice is guided by empirical considerations. It is very difficult to measure evolutionary lags in the field because these measures require some knowledge of the optimal phenotype. Besides, differential adaptation is the only measure which gives information on the spatial pattern emerging at the metapopulation scale.

The number of migrants depends also on population sizes. The level of adaptation is strongly affected by the host and parasite population sizes (Fig. 3). Larger populations always increase the level of adaptation (here measured by differential adaptation) as the number of migrants is directly proportional to population sizes.

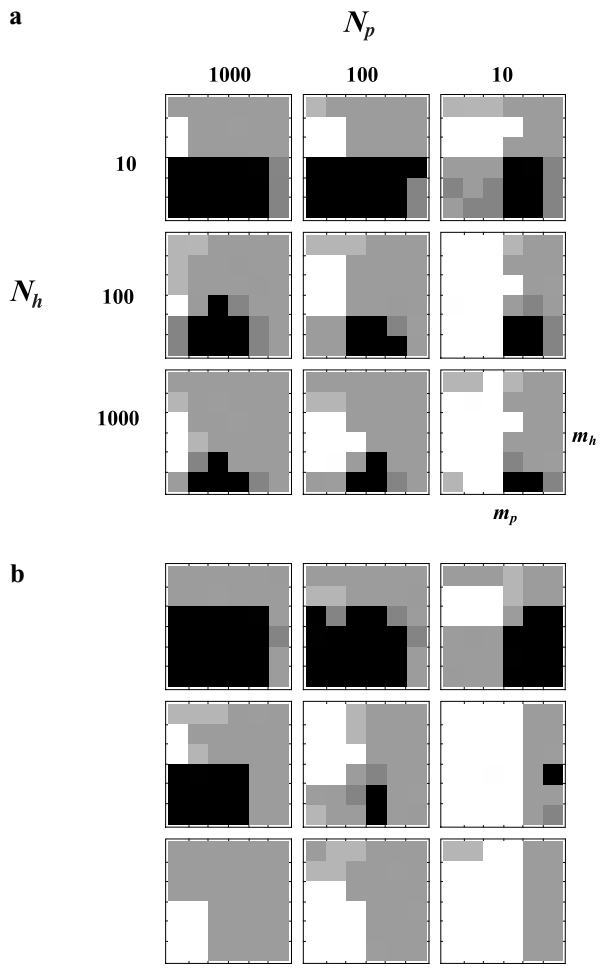


**Fig. 3** Interactions between migration and population sizes on differential adaptation. The top panel (a) shows the results in the absence of mutation ($\mu_h = \mu_p = 0$). The lower panel (b) shows the results when some mutation occurs ($\mu_h = \mu_p = 10^{-4}$). Host and parasite migration rates vary, as in Fig. 2, between 0 and 1 (see the lower right square of the panel A for the disposition of the migration axes). The five levels of grey indicate different levels of adaptation. Darker colours correspond to higher levels of parasite local adaptation: black ($DA_h < -0.15$); dark grey ($-0.15 \leq DA_h \leq -0.075$); medium grey ($-0.075 \leq DA_h \leq 0.075$); light grey ($0.075 \leq DA_h \leq 0.15$); white ($DA_h > 0.15$).Other parameter values: $V = 0.5$, $g = 1$.

### Effects of mutants

Next, we analyse the effect of mutation rates on host–parasite coevolution. Mutation introduces new genotypes in the population and allows the species to track the temporally variable optimal phenotype. As soon as migration is a limiting factor mutation becomes a critical parameter allowing adaptation and higher mutation rates than the coevolving species favours local adaptation (Fig. 4).

Like migration, mutation rates strongly interact with population sizes. Larger populations produce more mutants which allows local adaptation. Note the difference between Fig. 3a and b. The effects of population sizes are more contrasted (either host or parasite local adaptation) because a bias in population size acts on both the number of migrants and mutants.

### Effects of parasite generation time

Figure 5 illustrates the typical temporal dynamics of parasite adaptation if parasites have shorter generation time than their hosts. Just after host reproduction the parasite adaptation to its host population leads to an increase of infectivity until the next host reproduction event. Host selection favours more resistant genotypes and, consequently, parasite infectivity drops after host reproduction. This results in saw-like dynamics of parasite infectivity (Fig. 5a). A similar pattern is observed for measures of parasite differential adaptation (Fig. 5b). Figure 5c shows that selection occurring within the parasite population affects strongly the parasite genetic variance (see Appendix 2 for definitions of genetic and phenotypic measures of variance in each taxon). Host–parasite coevolution induces a negative-frequency-dependent selection, which favours, in general, rare genotypes. When these genotypes increase in frequency the genetic variance first increases but, when these genotypes tend to invade the parasite population the genetic variance tends to decrease again. This results typically in bell-shape dynamics of the genetic variance between two successive host reproduction events (similar patterns are observed for the phenotypic variance, not shown).

As illustrated on Fig. 5, parasite generations between host reproduction events increase the strength

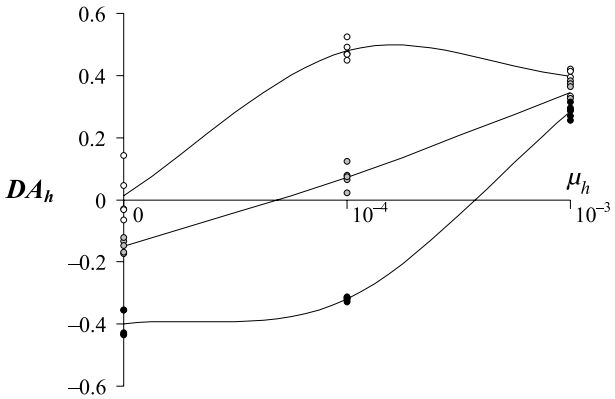


**Fig. 4** Differential adaptation of the host against host mutation rate for three parasite mutation rates: $\mu_p = 0$ (white), $\mu_p = 10^{-4}$ (grey), $\mu_p = 10^{-3}$ (black). For each set of parameters we plot the results of five simulations. Other parameter values: $N_h = N_p = 100$, $m_h = m_p = 0$, $V = 0.5$, $g = 1$.

of selection on the parasite population and lead to parasite adaptation. It is important to realize, however, that strong selection pressures on the parasite populations may ultimately lead to a drastic reduction of both genetic and phenotypic variabilities. Such reductions may jeopardize the ability of the population to coevolve against its temporally variable host. The latter effect is likely to be negligible when sufficient genetic variation is provided by large parasite mutation rates, population sizes and/or migration rates. The interactions of generation time with some of these processes are illustrated on Fig. 6. In the absence of mutation (Fig. 6, top panel) shorter generation times may either select for higher or lower parasite local adaptation. The coevolutionary outcome mainly depends on parasite migration rates: below a certain threshold, genetic variability is limiting and shorter generation time always leads to host local adaptation. Above this threshold, shorter generation time may either lead to parasite local adaptation or no local adaptation, depending on host and parasite migration rates.

With mutation, the coevolutionary outcome depends mainly on host migration. Below a certain threshold value of host migration, shorter generation times (larger $g$) always enhance parasite local adaptation (whatever parasite migration) because mutation provides enough variability for the parasites. Above this threshold the host population is a moving target which moves too fast for the parasite and this yields host local adaptation or no local adaptation, depending on parasite migration rates.

The effects of parasite generation time on the coevolutionary process is analysed in Fig. 7, where we plot the effect of generation time on a measure of local adaptation (differential adaptation) and the ratios of parasite to host phenotypic and genetic variation (see Appendix 2 for definitions of genetic and phenotypic variation in each taxon). We present ratios because we can thus compare changes in genotypic and phenotypic variation. We chose migration rate values for which mutation strongly interacts with generation time. Indeed, for $mig_h = mig_p = 0.0001$, larger $g$ can either favour host (no mutation) or parasite (mutation) local adaptation (see Figs 6 and 7a). The analysis of these cases reveals several interesting points.

Larger $g$ strongly decreases the phenotypic variance of the parasite (Fig. 7b). This is because of the fact that larger $g$ increases the selection intensity imposed on the parasite, which in turn decreases the parasite's phenotypic variance. The effect of $g$ on the genotypic variance is different (Fig. 7c) and depends on whether mutation occurs or not. In the absence of mutation genetic variance follows the same qualitative pattern as phenotypic variance, i.e. decreases with $g$, though at a slower rate. The difference in rate can be explained by the fact that genetic variance can be neutral. When there is mutation, the genetic variance of both hosts and parasites is minimal for intermediate values of $g$, here 10 (Fig. 7c). This nonmonotonic behaviour illustrates the balance between selection and mutation. In the initial phase, i.e. from $g = 1$–$10$, mutation allows the parasite population to incorporate one (or a few) of the genotypes which maximize infectivity on local hosts. This leads to the decrease of both $V_G$ and $V_P$ as $g$ increases, for both hosts and parasites. A further increase of $g$, allows the parasite populations to incorporate more genotypes with the same phenotypic effects. As a result, while the phenotypic variance still decreases the genetic variance increases.

## Discussion

The results presented here support those obtained previously showing that the migration rates are major components of the evolutionary potential of interacting species. High migration rates (but not too high) promote the emergence of local adaptation. Therefore, the present model yields similar predictions as the model studied by Gandon *et al.* (1996) despite several different assumptions: (1) the Matching Allele Model of coevolution used here is determined by two loci (instead of just one); (2) the population sizes are fixed (i.e. no epidemiological feedback); (3) the environment is a linear stepping stone model; (4) host and parasite generation times may differ. These different assumptions suggest that the effects of migration rates are very robust.

These effects are consistent whatever the measure of adaptation that we use (Fig. 2). The similarity between the measure of the mean phenotype at the population level, for example, for the host the average resistance of the local host population to the local parasite population ($\bar{R}_{loc}$), and for differential adaptation the average difference between the resistance of the local host population to the local parasite population and the resistance of the local host population to all nonlocal parasite populations

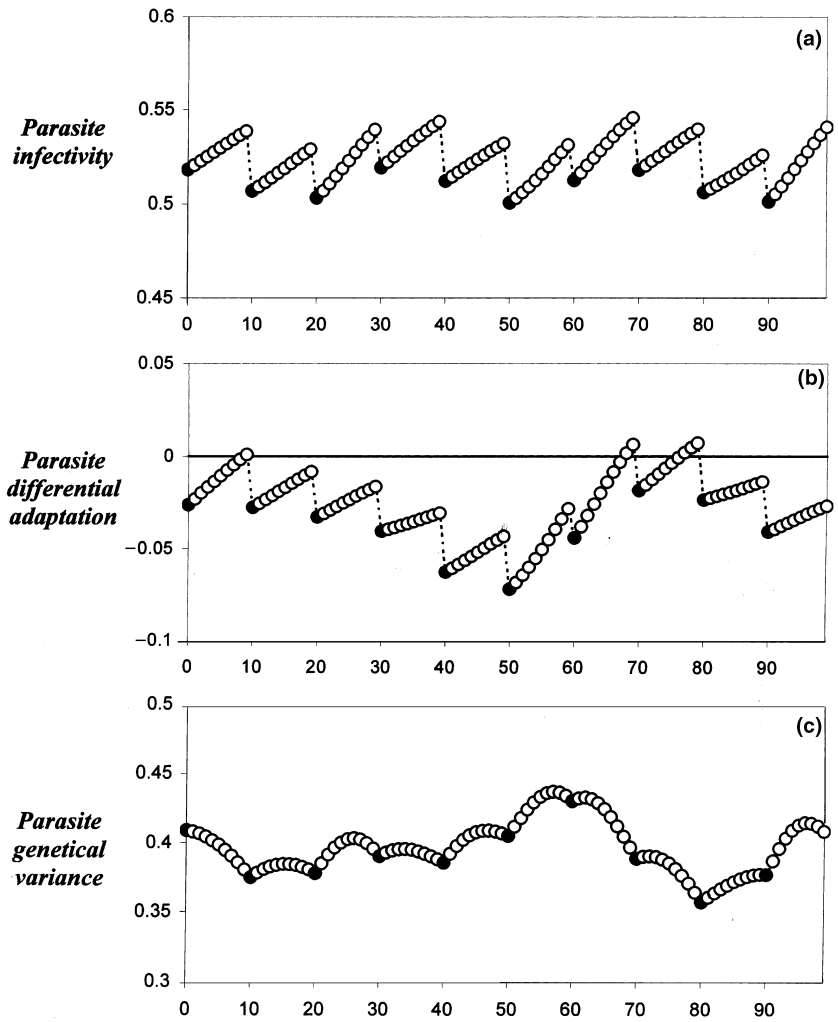


**Fig. 5** Temporal dynamics of (a) parasite infectivity (b) parasite differential adaptation and (c) parasite genetic variance in a situation where neither the parasite nor the host are locally adapted. Each point represents an averaged value over the whole parasite metapopulation. The filled symbols indicate that variables are measured just after host reproduction (empty symbols indicate measures after parasite reproduction events). Parameter values: $N_h = N_p = 100$, $m_h = m_p = 0.0001$, $V = 0.5$, $\mu_h = \mu_P = 0$, $g = 10$.

($\Delta_h$) (compare Fig. 2a and b) can be explained by the fact that the probability of resistance to allopatric parasites can be approximated by the probability of resistance to a parasite population where all genotypes are present and equi-frequent (Appendix 1). This is because of the negative frequency dependence which maintains each genotype at similar frequencies at the scale of the metapopulation even if genotype frequencies are likely to differ between populations. Since, the probability of resistance to allopatric hosts does not depend on migration rates, the variation of differential adaptation reflects directly the variation in the mean phenotype at the population level. The analogy between the evolutionary lags and each species' local adaptation (compare Fig. 2a, c, d) was first pointed out by Nee (1989). Here, we show that this result still holds in a metapopulation context.

The absence of epidemiology (fixed population sizes) in the present model allowed us to show the interaction between migration rates and population sizes. Figure 3 shows clearly that the number of migrants is a critical parameter. A similar pattern is obtained when we consider different host and parasite mutation rates: larger numbers of mutants promote local adaptation. The interaction between mutation rate and population size on the rate of adaptation has already been illustrated both experimentally (Giraud *et al.*, 2001) and theoretically (Tenaillon *et al.*, 1999) in the context of the evolution of mutation rates. Our results indicate that the coevolutionary outcome depends critically on the number of new genotypes introduced per host generation. For the host this will be equal to the number of migrants and the number of mutants per generation, each of these numbers being equal to the product of host population size, $N_h$, and the respective rate, $m_h$ for migration and $\mu_h$ for mutation, yielding $N_h\ (m_h + \mu_h)$. To obtain the number of mutants for the parasite, the mutation rate, $\mu_p$, should be multiplied by the number of parasite generations per host generation, $g$, yielding an overall number of new genotypes introduced per host generation equal to:

$$N_p(m_p + g\,\mu_p)$$

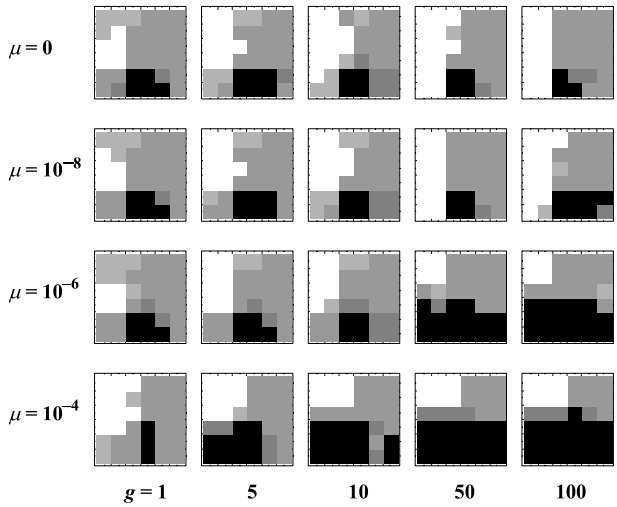


**Fig. 6** Interactions between generation time, mutation and migration on differential adaptation. The five levels of grey indicate different levels of adaptation. Darker colours correspond to higher levels of parasite local adaptation (see legend of Fig. 3). Five different generation times are presented ($g = 1$, 5, 10, 50, 100) and four subcases are considered depending on mutation rates (from top: no mutation; to low: mutation = $10^{-4}$ for both the host and the parasite). Other parameter values: $N_h = N_p = 100$, $V = 0.5$, $g = 1$.

(other symbols as for the host, subscript $p$ replacing $h$). The number of new genotypes gives a measure of the evolutionary potential of each species or, to recall the Red Queen metaphor, the speed at which each opponent can run. It will determine which of the two species will be ahead in the coevolutionary race.

However, some parameters involved in the evolutionary potential may also erode genetic variation. For instance, contrary to conventional wisdom, we show that the often shorter generation of parasites (higher $g$) may not always favour their local adaptation. This point was anticipated by Hamilton (1993, p. 334): 'Tentatively, the pattern as a whole may be understood as arising from the capability that intercurrency [i.e. number of parasite generations per host generation] gives parasites to 'overtake' and to 'head off' trends of the hosts to approach fixation planes. However, it has to be remembered that while the host is static, the parasite centroid is also heading for boundary planes and not to the host centroid itself: it too runs the risk of going extreme'. Indeed, parasite generation time arbitrates the balance between selection, which removes genetic variation and hence the potential to adapt in a temporally variable environment, and the factors which introduce genetic variation in the population (number of mutants and migrants). When mutation and/or migration are not limiting, shorter parasite generation time increases parasite local adaptation. On the contrary, when mutation and migration are limiting, repeated selection over the short parasite generation time exhausts parasite genetic variance which would allow adaptation to the variability of the environment (the coevolving host).

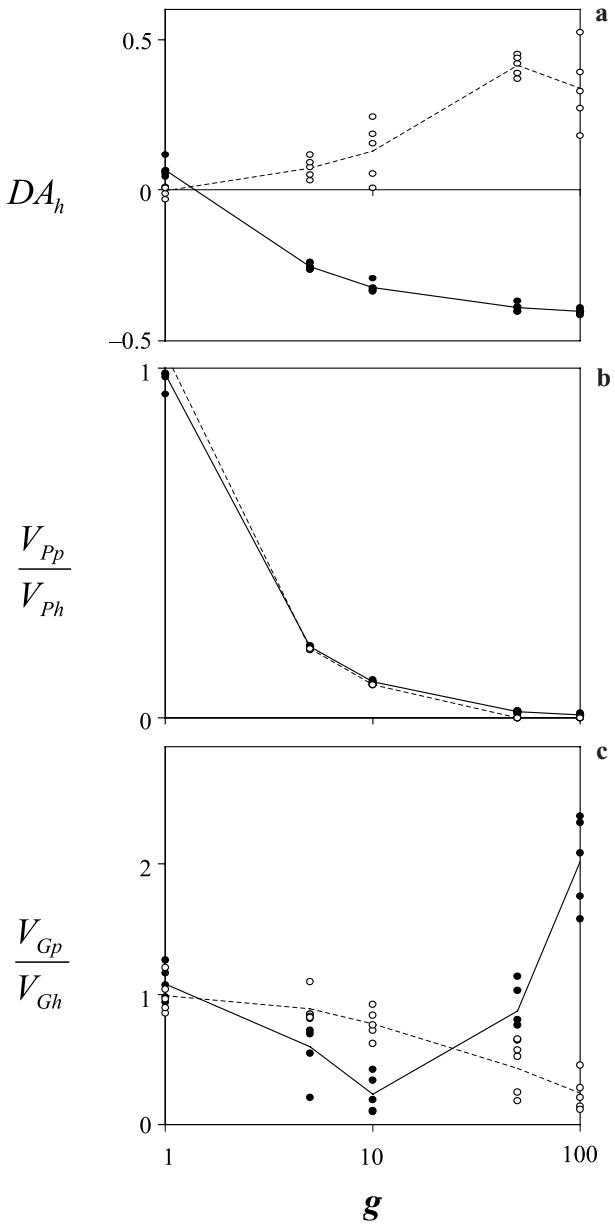


**Fig. 7** Effect of the number of parasite generations per host generation ($g = 1$, 5, 10, 100) on (a) differential adaptation of the host (b) ratio of parasite phenotypic variance on host phenotypic variance and (c) ratio of parasite genetical variance on host genetical variance. On each figure, we plot the results when there is no mutation (open symbols and dashed line) and when mutation rates of both the host and the parasite are equal to $10^{-4}$ (closed symbols and full line). Each symbol indicates the results of one simulation run. The lines follow the mean of the five runs of each set of parameter. Parameter values: $N_h = N_p = 100$, $V = 0.5$, $m_h = m_p = 0.0001$.

Some cautionary remarks and comments, however, are called upon here. Indeed, it should be noted that the number of new parasite genotypes per host generation is rather unlikely to be limiting in short generation time parasites. First, shorter parasite generation time will increase the number of parasite mutants per host reproduction and, secondly, will also increase the growth rate of the parasite population which should result in larger parasite population sizes and thus indirectly affect the number of migrants and mutants. Although our model fully considers the former effect, it does not take into account the latter, and therefore our results should be viewed as liberal in that respect.

Another important point we need to raise is that the relevant mutation rates here are of a very restrictive type, specifically those concerning changes in host–parasite recognition systems. Thus, although the per locus mutation rates above which the genetic variability erosion effect due to short generation times is no longer observed might be rather low, i.e. of the order of $10^{-8}$ to $10^{-6}$ as suggested by Fig. 6, such low mutation rates could still be realistic.

Obviously, this will not be the case for organisms such as RNA viruses, already known for their high mutation rates. For example, Schrag *et al*. (1999) report that the spontaneous mutation rate conferring resistance of the measles virus to a monoclonal antibody is $1.2 \times 10^{-4}$. This effect could occur, however, in some fungal plant pathogens, where some of the measured spontaneous mutation rates for virulence fall close to the threshold values. Indeed, Flor (1958) reported mutation rates of $\sim 10^{-5}$ to $10^{-6}$ for virulence in *Melampsora lini*, whereas Watson (1957) found a frequency of $10^{-5}$ for virulence mutants in *Puccinia coronata* var. *tritici*. Finally, Zimmer *et al*. (1963) reported a much higher mutation rate for virulence ($1–4 \times 10^{-4}$) in *P. coronata*.

The above results point out the importance of taking into account the availability of genetic variation in order to understand host–parasite coevolutionary processes. This bears a clear analogy to those obtained with models of quantitative genetics. Indeed, Lande & Shannon (1996) showed the importance of the within population genetic variance for the adaptation of a population living in a temporally variable environment. Using similar models, Bürger & Lynch (1995) showed that the viability of the population (another measure of adaptation) increased with the intensity of selection in stable environments. In temporally variable environments, however, they showed that stronger selection decreases the viability of the population. This result is due to the effect of selection on the amount of genetic variance: strong selection reduces the genetic variance and thus impedes adaptation to a temporally variable environment. In our model, the variability of the parasite's environment is under the control of the host (in particular the parameters which affect host's evolutionary potential: number of mutants, number of migrants) whereas the intensity of selection depends on the generation time of the parasite (shorter generation time increases the strength of selection on parasite population).

An empirically important point revealed in the present study is that when the parasite has a short generation time relative to the host, the time at which local adaptation is assessed may be very important (Fig. 5b). In Fig. 5b, we present an example where an assessment of local adaptation just after host reproduction always reveals host local adaptation (i.e. $\Delta_p < 0$), whereas an assessment after several parasite reproductions and before host reproduction often reveals no differential response (i.e. $\Delta_p \approx 0$). It is also possible to obtain cases where assessment right after host reproduction leads to no differential response, whereas an assessment after several parasite reproductions and before host reproduction often reveals parasite local adaptation. In all cases an assessment before host reproduction is favourable to the parasite, and an assessment right after host reproduction is favourable to the host. This makes intuitive sense because host reproduction modifies the genetic environment of the parasite.

These predictions can be tested via local adaptation experiments involving a tree–herbivore interaction, the paradigm of an interaction where parasites have much shorter generation times than their hosts. Most of these experiments consisted of 'transplantations' of insects across mature trees and revealed either parasite local adaptation or no differential response (Van Zandt & Mopper, 1998). Mopper *et al*. (2000), however, followed the level of local adaptation of *Stilbosis quadricustatella* leafminers after recolonization events of young sand-live oak trees. This long-term study did reveal an increase of the level of local adaptation over time, as expected (see Fig. 5b). In another study, Sork *et al*. (1993) measured resistance to leaf herbivores of subsequent populations of red oak (*Quercus rubra*) by transplanting seedlings. They found that seedlings transplanted in the site of their mother exhibited the least damage. This is also consistent with the prediction that a measure of local adaptation just after host reproduction should favour the host.

Evolutionary potential components such as mutation and migration, in interaction with population sizes and generation times do indeed determine local adaptation in host–parasite interactions. In general, these components interact synergistically, although exception may arise if genetic variability becomes extremely limiting. Future studies should incorporate recombination in order to verify the intuitive prediction that it, as well, should increase evolutionary potential and thus enhance local adaptation.

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## References

Bürger, R. & Lynch, M. 1995. Evolution and extinction in a changing environment. *Evolution* **49**: 151–163.

Dufva, R. 1996. Sympatric and allopatric combinations of hen fleas and great tits: a test of local adaptation hypothesis. *J. Evol. Biol.* **9**: 505–510.

Ebert, D. 1994. Virulence and local adaptation of a horizontally transmitted parasite. *Science* **265**: 1084–1086.

Flor, H.H. 1958. Mutation to wider virulence in *Melampsora lini*. *Phytopathology* **48**: 297–301.

Frank, S.A. 1991. Ecological and genetic models of host-pathogen coevolution. *Heredity* **67**: 73–83.

Frank, S.A. 1994. Recognition and polymorphism in host-parasite genetics. *Phil. Trans. R. Soc. Lond. B* **346**: 283–293.

Gandon, S., Capowiez, Y., Dubois, Y., Michalakis, Y. & Olivieri, I. 1996. Local adaptation and gene-for-gene coevolution in a metapopulation model. *Proceedings R. Soc. Lond B* **263**: 1003–1009.

Gandon, S., Ebert, D., Olivieri, I. & Michalakis, Y. 1998. Differential adaptation in spatially heterogeneous environments and Host-Parasite coevolution. In: *Genetic Structure and Local Adaptation in Natural Insect Populations* (S. Mopper & S. Strauss, eds), pp. 325–340. Chapman & Hall, London.

Giraud, A., Matic, I., Tenaillon, O., Clara, A., Radman, M., Fons, M. & Taddei, F. 2001. Costs and benefits of high mutation rates: adaptive evolution of bacteria in the mouse gut. *Science* **291**: 2606–2608.

Hamilton, W.D. 1993. Haploid dynamic polymorphism in host with matching parasites: effects of mutation/subdivision, linkage, and patterns of selection. *J. Hered.* **84**: 328–338.

Imhoof, B. & Schmid-Hempel, P. 1998. Patterns of local adaptation of a protozoan parasite o its bumblebee host. *Oikos* **82**: 59–66.

Kaltz, O. & Shykoff, J. 1998. Local adaptation in host-parasite systems. *Heredity* **81**: 361–370.

Kaltz, O., Gandon, S., Michalakis, Y. & Shykoff, J. 1999. Local maladaptation in the anther-smut fungus *Microbotryum violaceum* to its host plant *Silene latifolia:* evidence from a cross-inoculation experiment. *Evolution* **53**: 395–407.

Koskela, T., Salonen, V. & Mutikainen, P. 2000. Local adaptation of a holoparasitic plant, *Cuscuta europea*: variation among populations. *J. Evol. Biol.* **13**: 749–755.

Lande, R. & Shannon, S. 1996. The role of genetic variation in adaptation and population persistence in a changing environment. *Evolution* **50**: 434–437.

Lively, C.M. 1989. Adaptation by a parasitic trematode to local populations of its snail host. *Evolution* **43**: 1663–1671.

Lively, C.M. & Dybdahl, M.F. 2000. Parasite adaptation to locally common host genotypes. *Nature* **405**: 679–681.

Manning, S.D., Woolhouse, M.E.J. & Ndamba, J. 1995. Geographic compatibility of the freshwater snail *Bulinus globosus* and schistosomes from the zimbabwean highveld. *Int. J. Parasit.* **25**: 37–42.

Mopper, S., Stiling, P., Landau, K., Simberloff, D. & Van Zandt, P. 2000. Spatiotemporal variation in leafminer population structure and adaptation to individual oak trees. *Ecology* **81**: 1577–1587.

Morand, S., Manning, S.D. & Woolhouse, M.E.J. 1996. Parasite-host coevolution and geographic patterns of parasite infectivity and host susceptibility. *Proc. R. Soc. Lond. B* **263**: 119–128.

Mutikainen, P., Salonen, V., Puustinen, S. & Koskela, T. 2000. Local adaptation, resistance, and virulence in a hemiparasitic plant-host plant interaction. *Evolution* **54**: 433–440.

Nee, S. 1989. Antagonistic co-evolution and the evolution of genotypic randomization. *J. Theor. Biol.* **140**: 499–518.

Oppliger, A., Vernet, R. & Baez, M. 1999. Parasite local maladaptation in the Canarian lizard *Gallotia galloti* (Reptilia: Lacertidae) parasitized by haemogregarian blood parasite. *J. Evol. Biol.* **12**: 951–955.

Parker, M.A. 1985. Local population differentiation for compatibility in an annual legume and its host-specific pathogen. *Evolution* **39**: 713–723.

Schrag, S.J., Rota, P.A. & Bellini, W.J. 1999. Spontaneous mutation rate of measles virus: direct estimation based on mutations conferring monoclonal antibody resistance. *J. Virol.* **73**: 51–54.

Sork, V.L., Stowe, K.A. & Hochwender, C. 1993. Evidence for local adaptation in closely adjacent subpopulations of northern red oak (*Quercus rubra* L.) expressed as resistance to leaf herbivores. *Am. Nat.* **142**: 928–936.

Tenaillon, O., Toupance, B., Le Nagard, H., Taddei, F. & Godelle, B. 1999. Mutators, population size, adaptive landscape and the adaptation of asexual populations of bacteria. *Genetics* **152**: 485–493.

Thompson, J.N. 1994. *The Coevolutionary Process*. University of Chicago Press, Chicago, IL.

Thompson, J.N. 1999. Specific hypotheses on the geographic mosaic of coevolution. *Am. Nat.* **153**: S1–S14.

Van Zandt, P.A. & Mopper, S. 1998. A meta-analysis of adaptive deme formation in phytophagous insect populations. *Am. Nat.* **152**: 595–604.

Watson, I.A. 1957. Mutation for increased pathogenicity in *Puccinia graminis* var. *Tritici. Phytopathol.* **47**: 507–509.

Zimmer, D.E., Schafer, J.F. & Patterson, F.L. 1963. Mutations for virulence in *Puccinia coronata*. *Phytopathology* **53**: 171–176.

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## Appendix 1

### Probability of resistance under equi-frequency assumption

Let us assume that hosts and parasites are involved in a MAM coevolution with $L$ loci and $n$ alleles per locus. Here, we focus on the simple case where the $n^L$ different genotypes are present in both host and parasite populations in equal frequencies. The probability, $r(M)$, that a randomly chosen host and a randomly chosen parasite have exactly $M$ matching loci is:

$$r(M) = \frac{(n-1)^{L-M}\binom{L}{L-M}}{n^L}$$

where the numerator gives the number of parasite genotypes which have exactly $M$ matching loci with a randomly chosen host.

As a single matching locus is assumed to induce resistance, the probability of resistance of a randomly chosen host under the above assumptions (equifrequencies of the genotypes) is:

$$R_{\mathrm{loc}} = 1 - r(0) = 1 - \left(\frac{n-1}{n}\right)^{L},$$

which, under the assumptions used in our simulations ($L = 2$, $n = 4$) yields: $R_{\mathrm{loc}} = 0.4375$.

## Appendix 2

### Measures of variation

*Genetic variation*

First, it is possible to measure the frequency of each genotype in the population (Fig. 1a). A measure of genetic variation, $V_{\mathrm{G}}$, can be obtained from the distribution of genotype frequencies:

$$V_{\mathrm{G}} \equiv 1 - \sum_{x=1}^{20} \sum_{i}^{16} G_{i,x}^{2}/20$$

where $G_{i,\,x}$ is the frequency of the genotype $i$ in the population $x$. This measure of genetic variance is a genotypic analogue of gene diversity. We preferred a genotypic measure because of the strong epistatic interactions governing the host–parasite interaction and the asexual mode of reproduction of both organisms in our model.

*Phenotypic variation*

The phenotype (resistance of the host or infectivity of the parasite) of each genotype can be measured in a particular biotic environment (the population of the interacting species). This yields a distribution of phenotypes for both the host and the parasite (Fig. 1B). The variance, $V_{\mathrm{P}}$, of this distribution is the phenotypic variance of the population:

$$V_{\mathrm{P}} \equiv 1 - \sum_{x=1}^{20} \sum_{i}^{16} G_{i,x}^{2}(P_{i,x} - \bar{P}_{x})^{2}/20$$

where $P_{i,\,x}$ is the phenotype of the genotype $i$ in the population $x$ and $P_x$ is the average phenotype of the population $x$.

At first sight both measures of variation may seem redundant. There is, indeed, an obvious link between the two measures of variation because in the absence of any genetic variation, there is no phenotypic variation. However, it is interesting to note that the point where genetic variance is maximized (equi-frequency of all the 16 potential genotypes in both host and parasite populations, yielding a $V_{\mathrm{G}}$ ~ 0.996) corresponds to a case where there is no phenotypic variance. Therefore, both these measures of variation will provide complementary pieces of information concerning the quantity and the quality of variation.