Migration, Virulence, and the Geographic Mosaic of Adaptation by Parasites

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ABSTRACT: The geographic mosaic theory of coevolution is predicated on structured populations of interacting species where gene flow and the force of selection can vary among populations, leading to a mosaic of traits in space. Here, I briefly review some recent studies of adaptation by a sterilizing parasite to structured populations of a freshwater snail. The results show geographic structure as expected under the geographic mosaic model. I then consider the effects of virulence and migration on local adaptation by parasites using a computer simulation. The results suggest that high virulence and low migration contribute to the strength of local adaptation by parasites. Highly virulent parasites showed adaptation to local hosts for migration rates of up to 10% of the population per generation. In addition, because of the dynamic nature of host-parasite coevolution, the magnitude of local adaptation fluctuates over time. During some points in the cycle, parasites may be no more effective at infecting individuals from local host populations, even though they would be shown to be locally adapted if examined over enough generations. Contrary to expectation, parasite local adaptation was not affected by giving the parasite a longer generation time than the host, but differences in local selection intensities had a dramatic effect.

Keywords: coevolution, local adaptation, migration, parasites, sex, virulence.

The geographic mosaic theory of coevolution is based on the idea that structured populations of interacting species experience local differences in the intensity of selection they impose on each other (Thompson 1994, 1999). This can lead to a geographic patchwork for traits involved in the interaction. Mosaics can also occur if selection is fluctuating, rather than directional, and the fluctuations among populations are out of phase with each other. Mosaics of this kind may be particularly common for structured populations of hosts interacting with a variable community of obligate parasites.

Theoretical work in this area has suggested that, depending on the rates of migration by hosts and parasites, host-parasite coevolution can generate local adaptation by parasites. Local adaptation by parasites is generally expected if host migration is low, and parasites disperse at the same rate (or slightly more) than their hosts (see Ladle et al. 1993; Judson 1995; Gandon et al. 1996). Even under these conditions, however, the degree of local adaptation may vary in time, and even occasionally disappear or be reversed, due to the dynamical nature of host-parasite interactions (Gandon et al. 1996; Morand et al. 1996). Here, I review the pattern of adaptation in a highly virulent trematode parasite of a freshwater snail. I then present a model that evaluates the combined effects of parasite migration and parasite virulence as factors affecting the patterns of adaptation by parasites.

Experimental Studies of Local Adaptation by a Digenetic Trematode

Among-Population Results

The first rigorous experimental study of local adaptation by natural populations of parasites/pathogens was conducted by Parker (1985). He showed that isolates from geographically separate populations of a fungal pathogen were more infective to host plants (*Amphicarpaea bracteata*) drawn from the same geographic region. I modeled my initial studies of parasite differentiation on Parker's pioneering study and gained similar results. These studies involved infectability of the digenetic trematode (*Microphallus* sp.) to different lake populations of its snail host (*Potamopyrgus antipodarum*) that are separated by various distances and geographical barriers on New Zealand's South Island (Lively 1989). The parasite is highly virulent, causing complete sterilization of infected individuals. Successful infection (by a single egg) produces hundreds of encysted larvae in the snail that "hatch" when ingested by the final hosts, usually waterfowl. In the original experiment, I used two populations that were separated by New

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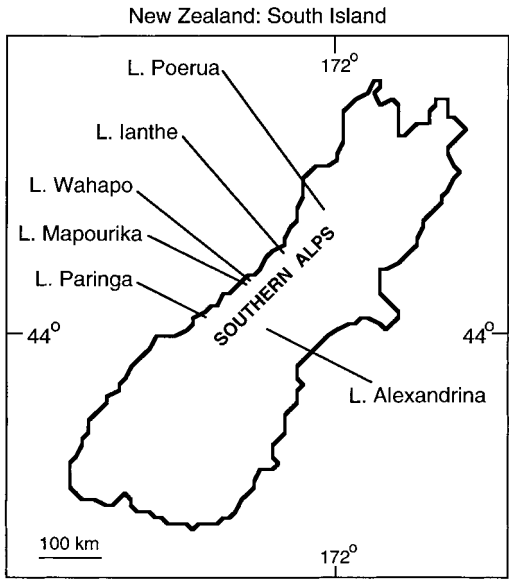

Figure 1: Locator map showing host and parasite source populations (on New Zealand's South Island) used in the reciprocal cross-infection experiments. Genetic distances and migration estimates for host and parasite populations can be found in Dybdahl and Lively (1996). Local adaptation is found in reciprocal, cross-infection experiments involving Lake Alexandrina and Lake Mapourika; Lake Mapourika, Lake Wahapo, and Lake Paringa (Lively 1989); and, more recently, Lake Poerua and Lake Ianthe (M. Dybdahl and C. M. Lively, unpublished data). In a nonreciprocal cross, Lake Alexandrina parasites were found to be more infective to Lake Alexandrina snails than to Lake Paringa snails (Lively and McKenzie 1991). In addition, for Lake Alexandrina, shallow-water parasites are more infective to shallow-water hosts, but the converse is not true for deep-water parasites, suggesting a coevolutionary hot spot in the shallow water in this lake. Finally, shallow-water parasites in Lake Poerua show evidence of time-lagged selection against common snail clones in the shallow water of the same lake (Dybdahl and Lively 1998). All lakes shown here have mixed (sexual and asexual) populations of the snail, except Lake Poerua, which is composed solely of asexual snails. Multiple clonal lineages exist in all the lakes shown, and the composition of these clonal lineages does not overlap among lakes (Dybdahl and Lively 1995*a*).

Zealand's Southern Alps. One lake on the west side of the Alps (Lake Mapourika) and one lake on the east side of the Alps (Lake Alexandrina) were selected as the experimental populations (fig. 1). Both of these lakes have large, stable populations of the snail. The working assumption was that the host populations do not exchange migrants, and thus they might be divergent with respect to the alleles involved in host defense. Using a reciprocal cross-infection design, I exposed snails from both lake populations to parasites collected from both populations in a common garden setting; all the snails were collected from the shallow-water margins of the lakes. The results showed strong evidence for local adaptation: parasites from Lake Mapourika were more infective to Lake Mapourika snails, and Lake Alexandrina parasites were more infective to Lake Alexandrina snails. This result suggests that there is a genetic basis to the host-parasite interaction, and that both parasites and hosts have diverged with respect to the alleles that were currently common in two respective populations.

I then repeated the experiment to ask a slightly more refined question: what is the role of geographic distance in generating the pattern of local adaptation seen in the previous experiment? Was it necessary, for example, to select populations on either side of the formidable barrier to gene flow provided by the Southern Alps? For this experiment, I selected lakes that were not separated by mountains but rather varied in their distances from each other (Lively 1989). I used Lake Mapourika again as an anchor for the experiment and then selected a near lake (Lake Wahapo, 7 km to the north) and a far lake (Lake Paringa, 80 km to the south; see fig. 1). I expected to find additional evidence for local parasite adaptation in the comparisons of far lakes (Mapourika-Paringa, Wahapo-Paringa) but no such differentiation in the comparison of the near lakes (Mapourika-Wahapo). Instead, I found strong local adaptation in all three parasite populations. In other words, all three parasite populations were most infective to sympatric snails ($P < .001$ for all comparisons). In addition, there was no consistent trend suggesting that distance affected the infectivity of the parasite to allopatric hosts. Mapourika parasites were significantly better at infecting snails from the near lake (Wahapo) than from the far lake (Paringa; $P = .031$), but there was no hint of a difference in the other possible comparison: Wahapo parasites were no better at infecting snails from the near lake (Mapourika) than from the far lake (Paringa; $P = .689$). I think this combination of results suggests that local coevolutionary dynamics are outstripping gene flow between the adjacent lakes due to the high virulence of the parasite. This guess forms part of the motivation for the model in the next section.

As indicated above, these results are consistent with Parker's work on population differentiation in fungal pathogens of legumes. They are also consistent with more recent studies of local adaptation by microsporidians of *Daphnia* (Ebert 1994) and trematode worms of fish (Ballabeni and Ward 1993) and pulmonate snails (Manning et al. 1995). One minor inconsistency among results is that Ebert (1994) found that geographic distance negatively affected infectivity by parasites, whereas I found no consistent difference in my experiments. In any case, one question that emerges from these studies is, Why do the parasites seem to be ahead, especially when the host populations are sexual?

In contrast to these and other studies (e.g., Karban 1989; Hanks and Denno 1994; Mopper et al. 1995) that show

local adaptation by parasites, a recent study shows that the fungal parasites of *Silene latifolia* are maladapted to infecting local hosts (Kaltz et al. 1999). Similarly, Parker (1989) found no evidence for local adaptation for a fungal parasite of mayapple (*Podophyllum peltatum*), and Imhoof and Schmid-Hempel (1998) found no evidence to suggest that a parasitic trypanosome is locally adapted to infecting its bumblebee host. Again it is worth wondering, why? Why do some parasites show strong population differentiation and local adaptation, while other parasites do not? These questions form a secondary motivation for the model that follows.

Within-Population Results

If the scale is changed and we examine the pattern of parasite adaptation within a lake instead of among lakes, a different pattern emerges. A few years ago, we estimated the relative infectivity of parasites drawn from shallow and deep sections of a lake (Lake Alexandrina) on shallow and deep host snails in a reciprocal cross-infection experiment (Lively and Jokela 1996). We were motivated to conduct the study based on some striking observations. First, there are more males and more sexual females in the shallow near-shore section of this lake (Jokela and Lively 1995*a*; Fox et al 1996). There is also a higher age-specific risk of infection in the shallow-water regions of the lake (Jokela and Lively 1995*a*, 1995*b*). In addition, snails in the shallow water mature at a smaller size (Jokela and Lively 1995*a*), and different clonal genotypes occupy different depth-stratified vegetation zones (Fox et al. 1996). These observations suggest that the snails do not migrate among vegetation zones and that parasites might be selecting for sex and early reproduction in the shallow water regions of the where the prevalence (and, by inference, risk) of infection at a small size is greatest.

Risk of infection is a difficult parameter to estimate in the field, but the natural history of the parasite would be consistent with the field data showing a higher age-specific rate of infection in the shallow water, by the most common parasite (*Microphallus* sp.). The final hosts for this trematode worm are water birds, and in Lake Alexandrina dabbling ducks are likely to be the most common final host. These ducks forage in the shallow water, and presumably, most of the infected snails they ingest come from the shallow water. This would mean that the coevolutionary cycle between the snails and worms would be restricted to shallow water. Nonetheless, the ducks do move out over deeper water, where they surely deposit eggs, thereby generating the infections we see in deep-water (4-6 m) snails. If this scenario is right, we would expect to see an asymmetric pattern in a reciprocal cross-infection experiment. Parasites taken from the shallow water should be much better at infecting shallow-water snails than snails from the deeper vegetation zones, but parasites taken from the deep should not show such a strong asymmetry because they are only one generation from being in shallow-water hosts. We did indeed find such an asymmetry in a reciprocal cross-infection experiment: parasites from the shallow water were significantly better at infecting shallow water snails, but parasites from the deep were not significantly better at infecting deep water snails (Lively and Jokela 1996). Hence it appears that shallow water is a source of infections, and deep water is a sink for infections.

This is an important result because it suggests an explanation for our discovery of more sexual individuals in the shallow water. The explanation is that sex is favored in the source population (shallow water) where coevolutionary dynamics occur and that clones are favored in the sink population (deep water) where coevolutionary dynamics do not occur. In other words, only coevolving parasites are capable of selecting for sex and the production of genetically diverse progeny (the Red Queen hypothesis). This raises an important question, which I will return to later: do coevolutionary dynamics occur in the shallow water? For now it is important to address alternative explanations for the experimental results. One possible explanation is that male snails are more easily infected than females; hence shallow-water snails are more infectable because there are more males (and more sexual females) in the shallow water. Note that this explanation by itself would not explain the asymmetry in the infection results, but it could be a contributing factor. However, there is no evidence from infection experiments (Lively 1989) or field data (Lively 1987) to suggest that males are more easily infected than females. Similarly, it might be that the deep-water snails, which are 80% clonal, are more resistant to infection by this parasite. Again this would not explain the asymmetric nature of the results, and it appears to be incorrect. Using field data, we found no hint of difference in infection between sexual (diploid) and asexual (triploid) individuals; hence ploidy or reproductive mode per se does not seem to have any explanatory power (Jokela et al. 1997*a*, 1997*b*). One further possibility is that the experimental results are incorrect. We, therefore, repeated the experiment using a much more powerful experimental design and obtained the same result (C. Lively, A. Krist, and E. Levri, unpublished data). The simplest explanation for the results at present is that coevolutionary interactions are restricted to the shallow water due to the foraging patterns of the definitive host.

Now I want to return to the issue of whether coevolutionary dynamics occur in the shallow-water margins of lakes. This is a difficult question to answer in sexual populations because there are no existing markers for the relevant genotypes (i.e., those that are directly involved in

Table 1: Models for susceptibility/infectivity given two haploid, diallelic loci

	Pathogen genotype			
Host genotype	*AB*	*Ab*	*aB*	*ab*
Matching-alleles model:				
AB	I	…	…	…
Ab	…	I	…	…
aB	…	…	I	…
ab	…	…	…	I
	vv	*vV*	*Vv*	*VV*
GFG model:				
rr	I	I	I	I
rR	I	…	I	…
Rr	I	I	…	…
RR	I	…	…	…

Note: I = infection. GFG model: *R*, resistant; *r*, susceptible in host; and *v*, virulent; *V*, avirulent in parasite (following Otto and Michalakis 1998)

the host-parasite interaction). To overcome this problem we selected a different lake on the west coast of the South Island (Lake Poerua) in which all the individuals are asexual. In these clonal lines, the genotypes for resistance in the snails are inextricably linked with their multilocus allozyme genotypes. In an initial survey of this lake, we found four relatively common clones (defined by their allozyme genotypes), and we also found that the most common clone was significantly over infected (Dybdahl and Lively 1995*b*). If parasites are driving coevolutionary cycles, then we would expect this most-common clone to be driven down in frequency and a different clone become the most common in the population. Furthermore, we would expect that any changes between years in clone frequency would be correlated with changes in the frequency of infections in that clone at some future point. We found striking support for both of these ideas in a 5-yr study of clonal dynamics in Lale Poerua (Dybdahl and Lively 1998). Hence, the parasites seem to be driving oscillatory dynamics in the host population.

If indeed the parasites are driving dynamics, then there must be an advantage to possessing a rare host genotype, provided this genotype was also rare in the recent past. We were able to test this idea experimentally in an infection experiment in 1996. We knew which clones had been rare (<5%) in the population for the previous 4 yr. We then compared the infectability of these clones to the four clones that had been common (>20%) at some point in the previous 4 yr. The results showed strong evidence for rare advantage: rare clones were significantly less infected than common clones in a laboratory infection experiment (Dybdahl and Lively 1998). Hence, the combination of results from this study show strong evidence for a rare advantage, as well as evidence for time-lagged selection in the field. Both of these results are consistent with the Red Queen hypothesis.

Simulation Models of Host-Parasite Coevolution

The brief sketch of results given above leads naturally to several interesting questions. One of these is, Why, when there is local adaptation, does the parasite seem to be ahead (and what does it mean to be ahead)? Why are hosts not more resistant to local parasites than foreign parasites? Another question is, Why, in some studies, is there no evidence for local adaptation by either the host or parasite, even for geographically distinct populations? It seems reasonable that part of the answer to both of these questions depends in part on the genetic basis underlying the interaction between host and parasite, as well as on the

Table 2: Expected fitnesses of host (W_{ij}) and parasite (w_{ij}) genotypes in population 1

Genotype	Host (W_{ij})	Parasite (w_{ij})
AB	$(1 - m)P_1Q_1(1 - Vp_1q_1) + mP_1Q_1(1 - Vp_2q_2)$	$P_1Q_1[(1 - m)p_1q_1 + mp_2q_2]$
Ab	$(1 - m)P_1(1 - Q_1)[1 - Vp_1(1 - q_1)]$ $+ mP_1(1 - Q_1)[1 - Vp_2(1 - q_2)]$	$P_1(1 - Q_1)$ $\times [(1 - m)p_1(1 - q_1) + mp_2(1 - q_2)]$
aB	$(1 - m)(1 - P_1)Q_1[1 - V(1 - p_1)q_1]$ $+ m(1 - P_1)Q_1[1 - V(1 - p_2)q_2]$	$(1 - P_1)Q_1$ $\times [(1 - m)(1 - p_1)q_1 + m(1 - p_2)q_2]$
ab	$(1 - m)(1 - P_1)(1 - Q_1)$ $\times [1 - V(1 - p_1)(1 - q_1)]$ $+ m(1 - P_1)(1 - Q_1)$ $\times [1 - V(1 - p_2)(1 - q_2)]$	$(1 - P_1)(1 - Q_1)$ $\times [(1 - m)(1 - p_1)(1 - q_1) + m(1 - p_2)(1 - q_2)]$

Note: The variable P_1 is the frequency of the *A* allele in host population 1 (the a allele has frequency $[1 - P_1]$); Q_1 is the frequency of the *B* allele in host population 1 (the *b* allele has frequency $[1 - Q_1]$); p_1 is the frequency of the *A* allele in parasite population 1 (the *a* allele has frequency $[1 - p_1]$), and q_1 is the frequency of the *B* allele in parasite population 1 (the *b* allele has frequency $[1 - q_1]$); m is the proportion of migrants for each population. Genotype frequencies for host and parasite in population 2 are obtained by switching all 1 subscripts to 2s, and all 2 subscripts to 1s. The variable V is the virulence of the parasite; hence the fitness of an infected host is $(1 - V)$. Mutation to alternative parasite alleles was set in the simulation to 10^{-5}.

degree of parasite migration between host populations. The answer might also be expected to depend on the virulence of parasites, as virulence affects the strength of selection on hosts. In what follows, I examine the interacting effects of parasite virulence and migration in a matching-alleles model, which is based on the idea that there is a self/nonself recognition system in hosts (which seems to be common in invertebrate animals; see Grosberg 1988; Grosberg et al. 1996). The matching-alleles model (table 1) has been used in most simulation models of host-parasite interactions where the interest has been in gene-frequency dynamics (Frank 1993, 1994; Hamilton 1993; Howard and Lively 1994; Lively and Howard 1994; Otto and Michalakis 1998).

The models presented here assume two large, haploid sexual populations of both the host and the parasite. Contact between host and parasite occurs at random within populations with respect to genotypes, and each host is exposed to one parasite propagule. Infection is determined by two, diallelic loci in both host and parasite.

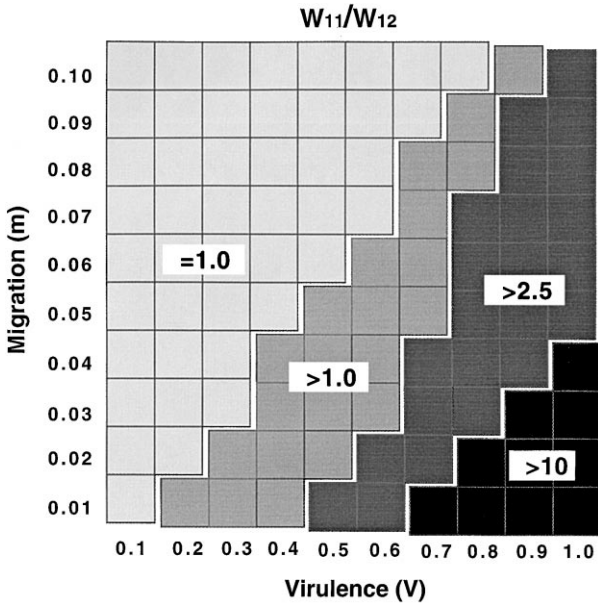

Figure 2: Parameter space for local adaptation, given the migration rate (m) between two populations and the virulence (V) of the parasite. Four different regions are shown for the mean fitness over 50 generations of the sympatric parasite (w_{11}) divided by the allopatric parasite (w_{12}): approximately equal to 1 = no local adaptation); >1.0 = weak local adaptation; >2.5 = strong local adaptation; and >10 = very strong local adaptation. The reciprocal results (w_{22}/w_{21}) are the same and therefore not shown.

Definition of Variables

Let P_1 be the frequency of the A allele in location 1, and let $1 - P_1$ be the frequency of the only alternative form of the allele a in location 1. The frequency of the A allele in location 2 is then P_2. Similarly, let Q_1 be the frequency of the B allele in location 1, and let $1 - Q_1$ be the frequency of the alternative form, b, in location 1. The frequency of the B allele in location 2 is Q_2.

An individual host is infected by any parasite that has an exact match for genotype. For example, a host with genotype Ab is infected by a parasite with genotype Ab. Any mismatch in genotype does not result in infection. Thus, there will be selection on the host to avoid matches. Let p_1 (note the lowercase) be the frequency of the A allele for parasites in location 1, and let $1 - p_1$ be the frequency of the alternative form of the allele, a, in location 1; p_2 is then the frequency of the parasite's A allele in location 2. Similarly, let q_1 be the frequency of the B allele for parasites in location 1, and let $1 - q_1$ be the frequency of a in location 1; q_2 is the frequency of the B allele for parasites in location 2.

Parasites migrate between the two large stable populations of hosts. Let m be the proportion of the parasite populations in both locations that migrate every generation. I assume that the population sizes of both parasite populations are the same, and hence the number of individuals in the migrant pool for the two populations is also the same. Hosts do not migrate in this model. I also allow mutation in the parasite populations at the interaction loci; I set this value equal to 10^{-5}. Finally, let V be the virulence of the parasite; hence $1 - V$ is the fitness of an infected host.

Recursion Equations

I assume that the life histories of the host and parasite are reproduction, parasite migration, and selection. The frequencies of the host and parasite populations after reproduction, parasite migration, and selection are given in table 2. The frequency of A in host population 1, at generation $t + 1$, is

$$P_1' = \frac{W_{AB1} + W_{Ab1}}{W_{AB1} + W_{Ab1} + W_{aB1} + W_{ab1}},$$

and the frequency of B in host population 1 at the same time is

$$Q_1' = \frac{W_{AB1} + W_{aB1}}{W_{AB1} + W_{Ab1} + W_{aB1} + W_{ab1}}.$$

The frequencies for A and B, respectively, in host population 2 are

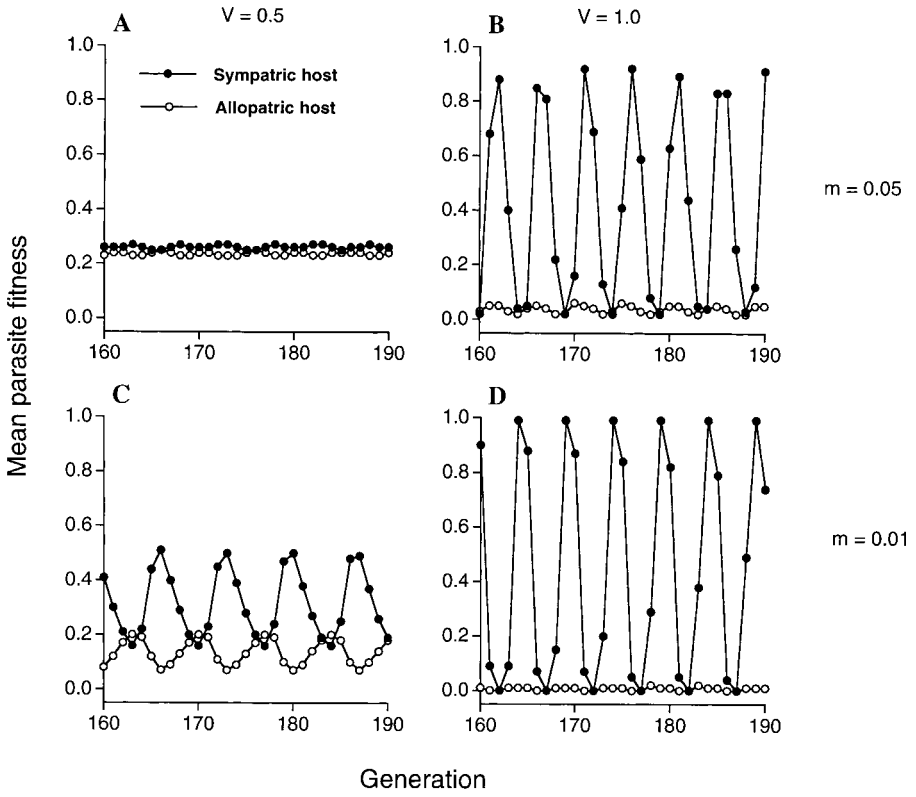

Figure 3: Representative runs of the model showing mean fitness in parasite population 1 when exposed to sympatric (*closed circles*) and allopatric (*open circles*) hosts. In these simulations, hosts from both populations were exposed to one parasite propagule from population 1. (The results for population 2 are similar, except that the oscillations are out of phase with those shown.) Note that increasing virulence increases the amplitude and decreases the period of oscillations. Increasing migration decreases the amplitude of the oscillations and reduces the degree of local adaptation. In this simulations, hosts and parasites had the same generation time.

$$P_2' = \frac{W_{AB2} + W_{Ab2}}{W_{AB2} + W_{Ab2} + W_{aB2} + W_{ab2}},$$

$$Q_2' = \frac{W_{AB2} + W_{aB2}}{W_{AB2} + W_{Ab2} + W_{aB2} + W_{ab2}}.$$

Similarly, the frequency of allele A in parasite population 1 at generation $t + 1$ is

$$p_1' = \frac{w_{AB1} + w_{Ab1}}{w_{AB1} + w_{Ab1} + w_{aB1} + w_{ab1}},$$

and the frequency of B in parasite population 1 at the same time is

$$q_1' = \frac{w_{AB1} + w_{aB1}}{w_{AB1} + w_{Ab1} + w_{aB1} + w_{ab1}}.$$

The frequencies for A and B, respectively, in parasite population two are

$$p_2' = \frac{w_{AB2} + w_{Ab2}}{w_{AB2} + w_{Ab2} + w_{aB2} + w_{ab2}},$$

$$q_2' = \frac{w_{AB2} + w_{aB2}}{w_{AB2} + w_{Ab2} + w_{aB2} + w_{ab2}}.$$

I iterated these equations for at least 200 generations. The allele frequencies in the two populations were initiated so that they would initially begin oscillating out of phase with each other. Specifically, $P_1 = 0.8$; $Q_1 = 0.1$; $P_2 = 0.2$; $Q_2 = 0.9$; $p_1 = 0.5$; $q_1 = 0.5$; $p_2 = 0.5$; $q_2 = 0.5$. To determine the degree of local adaptation, I calculated the ratio of the mean fitness of parasites in population 1, given hosts from population 1, relative to the mean fitness of parasites in population 1, given hosts in population 2 (i.e., w_{11}/w_{12}), where

$$w_{11} = w_{AB1} + w_{Ab1} + w_{aB1} + w_{ab1},$$

as given in table 2, and

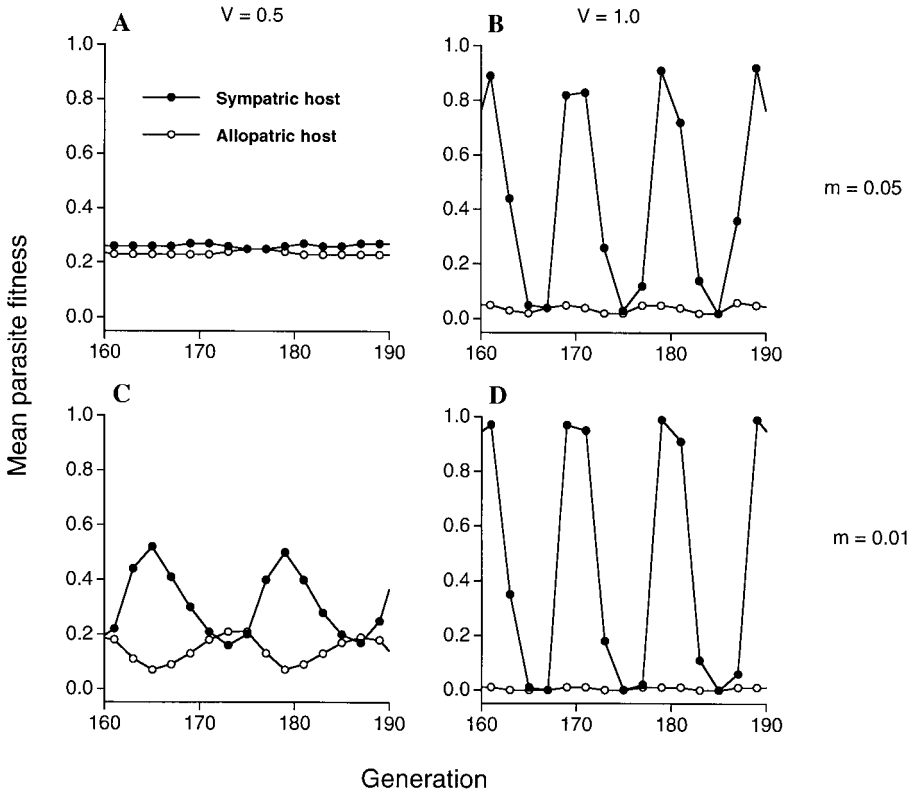

Figure 4: Representative runs of the model showing mean fitness in parasite population 1 when exposed to sympatric (*closed circles*) and allopatric (*open circles*) hosts. In this simulation, hosts went through two generations for each parasite generation. Note that increasing the parasite generation time increased the period of the oscillations (cf. fig. 3) but did not change basic pattern of local adaptation by the parasite.

$$\begin{aligned} w_{12} = {} & P_2Q_2[(1-m)p_1q_1 + mp_2q_2] + P_2(1-Q_2) \\ & \times [(1-m)p_1(1-q_1) + mp_2(1-q_2)] \\ & + (1-P_2)Q_2[(1-m)(1-p_1)q_1 \\ & \qquad + m(1-p_2)q_2] \\ & + (1-P_2)(1-Q_2) \\ & \times [(1-m)(1-p_1)(1-q_1) \\ & \quad + m(1-p_2)(1-q_2)]. \end{aligned}$$

To determine the effects of parasite migration and virulence on the degree of local adaptation shown by parasites, I ran all possible combinations of migration (m) from 0.01 to 0.10 (in steps of 0.01) against all possible combinations of virulence (V) from 0.1 to 1.0 (in steps of 0.1). This gives 100 combinations of parameters. For each combination I calculated the average ratio of w_{11}/w_{12} for the last 50 generations of the run. A high average ratio would indicate strong local adaptation by the parasite, and a low ratio would indicate little difference in the ability of parasites from population 1 to infect hosts from either population. The results are presented in figure 2.

Simulation Results

Parasite migration and virulence interact to affect the degree of local adaptation by parasites. Parasites having high virulence and low migration tend to be greater than 10 times more fit on sympatric host populations than on allopatric host populations. In addition, parasites with very high virulence ($V > 0.8$) show high degrees of local adaptation, even in the face of high rates of migration ($m > 0.07$). However, parasites with low virulence did not to show enhanced average fitness on sympatric host populations.

Average fitness needs to be emphasized here because of the dynamic nature of the host-parasite interaction. To illustrate this point, I have chosen four combinations of parameters and graphed the output of the simulation in figure 3. These four combinations of parameters represent some important boundary locations in figure 2. For example, figure 3*A* shows the situation where 5% of the

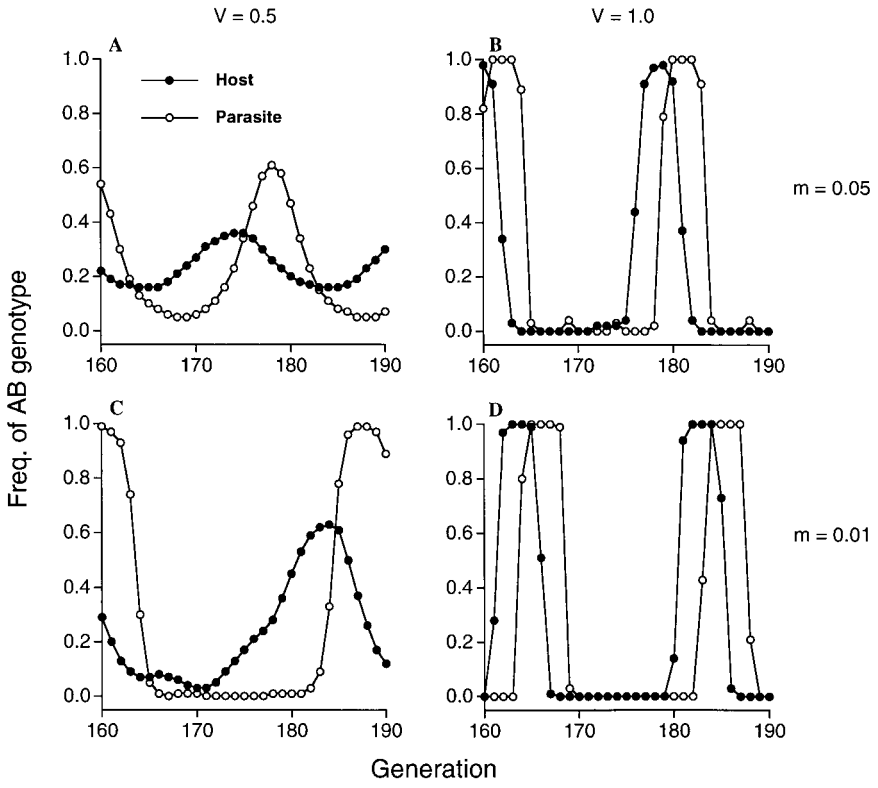

Figure 5: The effects of virulence and migration on gene frequency dynamics in both hosts and parasites. Note that parasites are 90° out of phase with their hosts, independent of migration rate and virulence as predicted by Nee (1989). Also note that increasing migration decreases the period of the oscillations (cf. *A* and *C*) because the higher migration rate more quickly restores the variation that is lost during periods in which the parasite "overshoots" the host.

parasite population migrates each generation and parasites reduce host fitness by 50%. The ratio of mean fitness of parasites in population 1 relative to parasites in population 2 (when both are exposed to hosts in population 1) is $w_{11}/w_{12} = 1.1$. To detect such a small difference with a reciprocal transplant experiment, an extremely powerful experimental design would be needed. Note that the mean fitnesses oscillate and that during about 25% of the cycle, the ratio of fitness is much less than 1.1; thus, even a very powerful experiment would not detect local adaptation part of the time. If migration rate is reduced to 1% of the population per generation (holding virulence at 50%), then the ratio of mean fitness of the parasite populations is equal to 3.02 (fig. 3*C*). Such a difference would be easier to detect with a reciprocal cross-infection experiment. Note that, as before, the ratio of mean fitness does not differ during part of the cycle; hence, reciprocal cross-infection experiments could give no sign of local adaptation by the parasite, even though there is strong local adaptation most of the time. This latter point is made even clearer by examination of figure 3*B* and *D*. In these panels, the virulence of the parasite (V) was increased to 1.0 (hence infected hosts are killed or castrated by the parasite) for migration rates of $m = 0.05$ (fig. 3*B*) and $m = 0.01$ (fig. 3*D*). The oscillations in mean fitnesses are extreme, but nonetheless, there is no difference in mean fitness during part of the cycles. On the whole, however, strong local adaptation should be detected most of the time ($w_{11}/w_{12} = 9.7$ for $m = 0.05$; and $w_{11}/w_{12} = 51.3$ for $m = 0.01$). In general, the strength of local adaptation by parasites should tend to increase as migration decreases and, as virulence increases, at least over part of the cycle.

In the simulations presented here, the parasite and host had the same generation times. Normally, parasites have faster generation times than their hosts, and this has been invoked as the reason for local adaptation on the part of parasites. I examined this idea by modifying the simulation to allow two host generations for each parasite generation. In other words, the hosts had a faster generation time. The results are presented in figure 4, and they are in direct conflict with the presently accepted wisdom. Parasites still show strong local adaptation to host populations, even

though they have fewer generations per cycle. Comparisons of figures 3 and 4 indicate that the main effect of changing the number of parasite generations per cycle was to lengthen the period of oscillations; the amplitude did not seem to be affected. The main point, however, is that parasites remain adapted to infecting local populations without a generation-time advantage.

Discussion

In this article, I have reviewed the spatial patterns of adaptation by a parasitic trematode worm to its intermediate host, the freshwater snail *Potamopyrgus antipodarum*. This snail is widely distributed in the freshwater habitats throughout New Zealand, but most studies have focused on the large populations that exist in lakes. These lakes were formed by glaciers during the Pleistocene, and they vary tremendously in size, depth, surface area, elevation, pH, seasonality, and degree of isolation. Perhaps as a result, the trematode communities vary among lakes and so does the expected force of selection on the snail. Over a dozen different species of these worms infect the snail, all of which mature and reproduce sexually in a final, vertebrate host. The larvae of these worms attack snails, and successful infections result in sterilization of both males and females.

The isolated nature of the lake populations, the differences in abiotic factors, and the resulting variation among lakes in the trematode community make this parasite-host interaction ideal for evaluating many of the ideas generated by Thompson's recent book (Thompson 1994). We have focused our experimental studies on the most common of the parasites (*Microphallus* sp.), which has a two-host life cycle: adults mature and reproduce sexually in the intestines of waterfowl, and the larvae reproduce asexually in the snails, producing cysts that are infective to the final host. As a consequence of the life cycle, the abundance of the worm is expected to covary to some degree with the presence of waterfowl, both within and among lakes. We have found that the parasite is consistently and significantly more infective to local populations of the snail host than to remote populations of the host (see legend to fig. 1). This result suggests that parasites are successfully tracking common host genotypes in their local populations. Tracking of this kind by such a virulent parasite should cause selection for rare host genotypes, thereby resulting

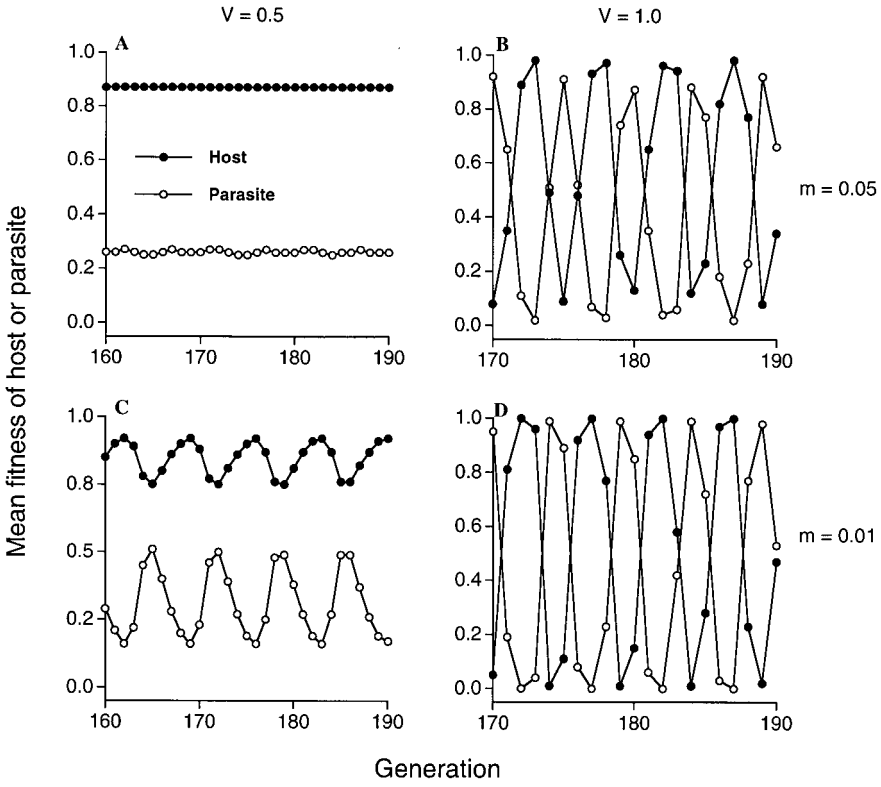

Figure 6: Mean fitness for both host and parasite in population 1. Note that the fitnesses oscillate at 180° out of phase, and that the oscillations are extreme when virulence is high. Where virulence is high, it is especially clear that neither the parasite or the host is ahead.

in oscillations in parasite and host gene frequencies. We have seen evidence for such oscillations in a natural population of clonal snails and have found a significant advantage of rare host genotypes in laboratory infection experiments (Dybdahl and Lively 1998). These latter results hint at the genetic foundation for local adaptation: sympatric parasites are better at infecting locally common host genotypes than remote parasites, which are likely to be tracking different host genotypes.

We also have found evidence for coevolutionary hot spots. The prevalence of infection varies from <1% to >40% among populations, and sexual reproduction in the snail is correlated with parasite prevalence (Lively 1987, 1992). This result is consistent with the parasite (or Red Queen) hypothesis for sex because it suggests that sexual reproduction is favored as a way to produce genetically variable offspring where the risk of infection is high (Jaenike 1978; Hamilton 1980; Bell 1982; Hamilton 1982). While these results are merely suggestive, there is no indication at present that the distribution of sex in these snails can be completely explained by any of the alternative models for sex (Lively 1987, 1992; Lively et al. 1998). Combinations of models, however, remain a possibility (West et al. 1999).

Additional evidence for coevolutionary hot spots comes from our cross-infection experiments across a steep cline in depth within a single lake. Parasites taken from shallow water are more infective to shallow-water snails than deep-water snails, but the converse is not true (Lively and Jokela 1996). This makes sense given that the final hosts (dabbling ducks) forage in the shallow water and that infection requires ingestion of the encysted larvae living in infected snails. It is worth noting that sexual reproduction is also more common in the shallow water (Jokela and Lively 1995*a*; Fox et al. 1996), which is consistent with the broader geographic association between sex and parasite prevalence. In addition, the shallow-water population of snails mature at a smaller size, which is consistent with the expectations of life-history theory (Jokela and Lively 1995*a*; see also Lafferty 1993) Hence, the shallow-water margins of the lake, where the final hosts forage most intensively, is a coevolutionary hot spot, and associated with this region, we find more sexual females and earlier reproduction. While it is difficult to be certain that coevolution is responsible for the observed trait differences, we can find no evidence to suggest that the patterns are due to inherent differences in the infectivity of the triploid asexual individuals (Jokela et al. 1997*b*). In addition, age at maturity is associated with habitat, rather than reproductive mode per se, so early reproduction in shallow water cannot be due to inherent physiological differences that might exist between sexual and asexual individuals (Jokela et al. 1997*a*).

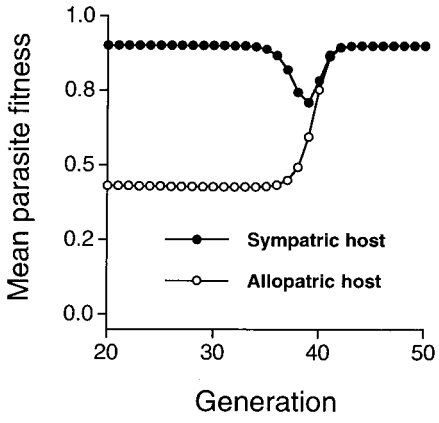

Figure 7: Simulation results for the gene-for-gene model (table 1). Host population 1 was initiated as fixed for genotype *rR*, while host population 2 was initiated as fixed for *Rr*. Parasites in both populations were initiated at $vv = vV = Vv = VV = 0.025$. Parasite virulence was set at 0.8; and the cost of virulence was set at 0.05. The cost of resistance was also set at 0.05. Parasite migration was set at 0.001, and mutation between alternative parasite alleles at both loci was set at 10^{-5}. At generation 30, I introduced the missing host alleles in both host populations at a frequency of 0.001. Note that the parasites are locally adapted before generation 30 (the results are identical for both parasite populations, although only one is shown). Following introduction of the new host alleles, local adaptation by the parasite has disappeared by generation 40. The basic result is robust to the combination of parameters chosen here.

Although the assumptions differ, the simulation results presented here are consistent with previous simulation models that examine host-parasite coevolution in stable, structured populations (Gandon et al. 1996; Morand et al. 1996). In addition, the present simulations suggest that local adaptation should be more common in parasites that have severe fitness effects on their hosts (fig. 2). This result leads to the prediction that local adaptation will be most easily detected, all else equal, where parasites are highly virulent. Some of the more striking examples of local adaptation by parasites do indeed concern virulent parasites, but the present core of studies is insufficient to evaluate the prediction in any meaningful way. Nonetheless, the prediction makes sense because the strength of selection on the host is positively related to parasite virulence, and stronger selection is more likely to lead to population differentiation in the face of gene flow (Wright 1931). The main difference between the simulation results in fig. 2 and classical population genetics theory is that the parasite-mediated effects of selection oscillate over time. In general, higher parasite virulence increases the amplitude of the oscillations (cf. fig. 5*C* and *D*) as well as the amplitude of mean fitness differences on local hosts (cf. fig. 3*C* and *D*). The oscillations also indicate that the outcome of an experiment could vary, depending on when the ex-

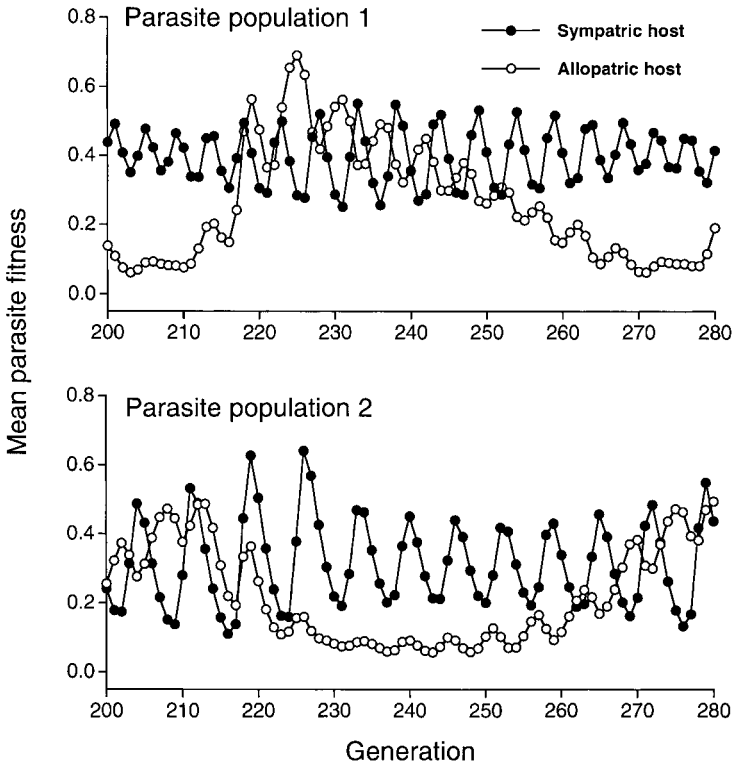

Figure 8: Selected results for the situation where the hosts in population 1 are exposed to two parasite propagules, while the hosts in population 2 are exposed to only one propagule. In this simulation $V = 0.5$ and $m = 0.01$ (parasite mutation rate = 10^{-5} in all figures). Note that there are periods where parasites from one or both populations have a higher fitness on the allopatric host (local maladaptation). Also note that the oscillations on the sympatric host have a shorter period in population 1, where the rate of exposure to parasite eggs is greater. These tighter oscillations in parasite population 1 apparently pass through the slower oscillations in parasite population 2, giving periods of no local adaptation in both populations.

periment is conducted. Thus, unfortunately, negative evidence regarding local adaptation, even from well-designed and statistically powerful experiments, cannot be taken as definitive, unless the experiments are repeated on a relevant temporal scale.

One surprising result of this study is that parasites can be locally adapted, even though they have slower generation times than their hosts (fig. 4). Why is it that parasites seem to remain ahead in the game, even without the advantage that was expected to come from faster generation times? This should be more formally modeled, but the answer is, perhaps, straightforward: parasites are driving local host dynamics. In the matching-alleles model, parasites track common host genotypes independent of whether they have more or fewer generations per year than hosts. As a result, parasites are only 90° out of phase with their local host populations (fig. 5; Nee 1989), and on average, 90° out of phase is probably better than the phase relationships among randomly drawn host populations. Of course, the phase relationship between any two host populations might, by chance, be <90°, but the probability of this fortuitous result might also be expected to diminish with increasingly complicated genetics (e.g., more loci and more alleles per locus and perhaps diploidy with dominance). The main point for our present purpose is that parasites are probably not locally adapted because they have faster generation times. In addition, reciprocal cross-infection experiments are probably not useful for determining who is ahead. They simply indicate whether parasites are adapted to infecting their local populations of hosts.

Who, then, is ahead? To address the question, I have graphed mean fitness for both hosts and parasites in figure 6 for four combinations of migration and virulence in the simulation model. The results show that mean fitness is affected by both migration and virulence and that it oscillates over time for both host and parasite (fig. 6*B* and *D*). Thus would be difficult to say who is ahead; both species are running as fast as they can to stay in the same place. In more formal terms, parasites create positive epistasis for host fitness (rare advantage), which results in linkage disequilibrium in the host. This linkage disequi-

librium in the host then causes positive epistasis for fitness in the parasite, which results in selection for host sex and recombination to break up the linkage and create rare genotypes; the fitness advantage thus continuously changes hands (Peters and Lively 1999). Thinking of the problem in this way allows us to address one additional question. The question can be phrased as, Since the parasites are locally adapted, the host has apparently lost; so how can parasites select for sexual reproduction in host populations if the host has already lost? The point of the previous paragraph is that the host has not lost; the mean fitnesses in both the host and parasite populations are simply oscillating over time. The more useful question would be to ask, What would happen to a rare clonal mutant introduced into a population with locally adapted parasites?

To my way of thinking, local adaptation implies that local coevolutionary dynamics are taking place, and that there would be some selection against clonal host mutants. Consider, for example, that local adaptation (in the face of parasite gene flow) requires moderate-to-high parasite virulence (figs. 3 and 4). Similarly, selection for sex/recombination also requires moderate-to-high parasite virulence (see Howard and Lively 1994, 1998; Peters and Lively 1999). Thus, local adaptation might imply that there is also local selection for sex. Unfortunately, the connection is not that straightforward; the predictions regarding selection for sex also depend on the deleterious mutation rate, population size, and the function that maps mutation number onto fitness (Howard and Lively 1998). Nonetheless, if parasites migrate more than their hosts, local adaptation would imply that parasites are tracking locally common host genotypes, which would impose selection against clonal host mutants as they spread in a population.

Local parasite adaptation and selection for host sex also depend on the genetic basis for infection. As Parker (1994) has shown, gene-for-gene models of infection will not result in parasite-mediated selection for host sex, and the oscillations expected under the microevolutionary Red Queen will not exist. He also presents a compelling case that the present data from plant-pathogen interactions are most consistent with a gene-for-gene model of infection (Parker 1994, 1996). It remains possible, however, that local adaptation by the parasites of large, stable host populations is at least suggestive of something reasonably similar to the matching-alleles model. My reason for this view is that local adaptation, while easily generated by matching-alleles models, would not be expected from the simple forms of the gene-for-gene model, provided any degree of host and parasite migration among populations. Figure 7 shows the results of a computer simulation in which two host populations are "stocked" with different resistance genotypes using the gene-for-gene model for infection in table 1. The parasites are seen to be adapted to infecting local host populations until a small fraction of hosts are exchanged at generation 30 (mutation would have the same effect). As the newly introduced host alleles spread, the two host populations converge, and the parasites become equally able to infect sympatric and allopatric populations; neither of the parasite populations are locally adapted.

It remains to be seen whether this result is general and whether local adaptation is indeed suggestive of some (perhaps messy) form of a matching-alleles model, at least for interactions involving large, stable host populations. (I include this caveat regarding population stability because gene-for-gene models could also result in local adaptation by parasites in host populations that are characterized by repeated bouts of colonization and extinction; see Thompson and Burdon 1992.) In any case, Frank (1996*a*, 1996*b*) has argued that the present data cannot be unambiguously interpreted as being consistent with gene-for-gene genetics. As such, it would seem that direct experimental tests are needed.

One factor that has not yet been addressed in models of host-parasite coevolution in structured populations is the notion that the intensity of selection due to the interaction varies among populations. This, however, is the one of the core ideas in the geographic mosaic theory of coevolution (Thompson 1994, 1999). Some insight into this question can be gained through the use of a minor variation of the model presented, which allows the exposure to parasites to vary among populations. I did this by increasing the exposure from one to two parasite propagules in one of the host populations. The results are presented in figure 8 for $V = 0.5$ and $m = 0.01$, and they hint at many complications to come as models become increasingly sophisticated. In general, this simple asymmetry in parasite exposure suggests the possibility of cycles on top of cycles, and that local adaptation by parasites may be a temporary phenomenon that depends on the phase relationships among populations (which changes due to an asymmetry in local periodicities). It would seem that there is much to learn about the patterns of host-parasite coevolution in space and time. But one thing seems especially clear: there is a need for estimates of parasite migration and virulence in the wild. These parameters are crucial in determining when, and if, local adaptation is expected, and whether locally adapted parasites can select for sex and recombination in their hosts.

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