Note

Rethinking Conventional Wisdom: Are Locally Adapted Parasites Ahead in the Coevolutionary Race?

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abstract: The metaphors of the Red Queen and the arms race have inspired a large amount of research aimed at understanding the process of antagonistic coevolution between hosts and parasites. One approach that has been heavily used is to estimate the strength of parasite local adaptation using a reciprocal cross infection or transplant study. These studies frequently conclude that the locally adapted species is ahead in the coevolutionary race. Here, I use mathematical models to decompose parasite infectivity into components attributable to local versus global adaptation and to develop a robust index of which species is ahead in the coevolutionary race, which I term coevolutionary advantage. Computer simulations of coevolving host-parasite interactions demonstrate that because the magnitudes of local and global adaptation are largely independent, the link between the sign of local adaptation and coevolutionary advantage is tenuous. A consequence of the weak coupling between local adaptation and coevolutionary advantage is that the bulk of existing empirical studies do not sample enough populations for any reliable conclusions to be drawn. Together, these results suggest that the long-standing conventional wisdom holding that locally adapted parasites are ahead in the coevolutionary race should be reconsidered.

Keywords: Red Queen, coevolution, local adaptation.

Coevolution between hosts and parasites has far-reaching ecological and evolutionary impacts. Although the best studied of these is coevolution's role in maintaining sexual reproduction (Jaenike 1978; Hamilton 1980; Salathe et al. 2008; Lively 2010), we now know that coevolution can also influence ploidy levels (Nuismer and Otto 2004), mating systems (Agrawal and Lively 2001; Nuismer et al. 2008), mutation rates (M'Gonigle et al. 2009), and epidemiological dynamics (Lion and Gandon. 2015). A diverse set of approaches have been used to study coevolution between hosts and parasites, with one of the most commonly employed being the estimation of parasite local adaptation from a reciprocal cross infection or transplant experiment (reviewed in Kaltz and Shykoff 1998; Greischar and Koskella 2007; Hoeksema and Forde 2008). Early studies of parasite local adaptation focused on demonstrating that infectivity and resistance have a genetic basis and that parasite populations evolve to infect their local host populations (Lively 1989; Ballabeni and Ward 1993; Ebert 1994; Hanks and Denno 1994). By establishing that parasites do indeed adapt to local host populations, these early studies were used to support the Red Queen hypothesis (Lively 1989), inform virulence theory (Ebert 1994), and implicate parasites in sexual selection (Ballabeni and Ward 1993).

Since this early pioneering work, studies of local adaptation in host-parasite interactions have proliferated, resulting in estimates for the strength and sign of local adaptation derived from a broad range of study systems and experimental designs (reviewed in Kaltz and Shykoff 1998; Greischar and Koskella 2007; Hoeksema and Forde 2008). These studies demonstrate that although the parasite is often locally adapted to the host (e.g., Ballabeni and Ward 1993; Ebert 1994; Imhoof and Schmid-Hempel 1998; DeClerck et al. 2001; McCoy et al. 2002; Thrall et al. 2002; Lively et al. 2004; Capelle and Neema 2005; Saarinen and Taskinen 2005; Schulte et al. 2011), in a number of cases, it is instead the host that is locally adapted to the parasite (e.g., Kaltz et al. 1999; Oppliger et al. 1999; Adiba et al. 2010). Theoretical efforts to explain the variable outcomes observed in these studies have identified a number of factors that influence the identity of the locally adapted species (Gandon et al. 1996; Lively 1999; Gandon and Michalakis 2002; Gavrilets and Michalakis 2008; Gandon and Nuismer 2009). For instance, it is now known that relative rates of gene flow, relative selective impacts, and patterns of selection mosaics all contribute to the observed pattern of local adaptation (Gandon and Nuismer 2009).

Although we now have a relatively good understanding of the forces that cause one or the other species to be locally adapted, little effort has been devoted to understanding what we can learn about the process and outcome of coevolution from estimates of local adaptation. Put differently, can stud-

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ies of parasite local adaptation demonstrate more than a genetic basis for infectivity and resistance and evolutionary tracking of local host populations by parasites? Answering this question rigorously is important because it can enrich our understanding of coevolution and help to glean more from existing studies. In addition, answering this question allows us to evaluate whether the locally adapted species is ahead in the coevolutionary race, as is held by conventional wisdom (e.g., Kawecki and Ebert 2004; Greischar and Koskella 2007; Schulte et al. 2011; Lemoine et al. 2012; Roth et al. 2012; Koskella 2014; Perez-Jvostov 2015), or whether this connection is actually much more tenuous (e.g., Lively 1999; Morran et al. 2014).

My goal with this note is to use simple mathematical models and computer simulations to decompose overall levels of parasite infectivity into components corresponding to local and global adaptation. Local adaptation quantifies the spatial association between frequencies of host and parasite genotypes that result in infection and can be measured as the difference between average parasite infectivity on local hosts and average parasite infectivity on all hosts, irrespective of origin. In contrast, global adaptation quantifies the average infectivity of parasites on hosts when individuals are sampled at random from the entire metapopulation without considering population of origin. Decomposing parasite infectivity into these two easily measurable quantities provides insight into the conditions that determine the relative contributions of local and global adaptation to expected levels of parasite infectivity. In addition, decomposing infectivity in this way allows us to determine when, if ever, local adaptation can be used to decipher which species has the upper hand in a coevolutionary interaction.

Analytical Model and Results

To understand how local and global adaptation contribute to infectivity and resistance in a coevolving host-parasite interaction, we need a model capable of predicting the outcome of encounters between individuals across an entire metapopulation. At a minimum, such a model must include multiple populations, genetically variable hosts and parasites, and rules for determining the outcome of encounters between individuals. The model considered here focuses on the interaction between a host (species X) and parasite (species Y) that occurs across a collection of N discrete habitats. Within each habitat, the host and parasite encounter one another at random, with the outcome of an interaction (infection or resistance) between an individual host and parasite determined by the genotypes of the interacting individuals. Specifically, we assume that the probability that a host with genotype i is infected by a parasite with genotype j is given by

$$P_{i,j} = \alpha_{i,j}, \tag{1}$$

where the infection matrix $\boldsymbol{\alpha}$ can take the form of any of the infection matrices commonly used in coevolutionary biology, such as the matching-alleles model, gene-for-gene model, or even models that depend on quantitative traits (Agrawal and Lively 2002; Nuismer et al. 2005, 2007; Dybdahl et al. 2014; Engelstaedter 2015). Because infection and resistance are assumed to be the only possible outcomes of an encounter between host and parasite, the probability of resistance is equal to $1 - P_{i,j}$. As a consequence, when the parasite is performing well (infecting most hosts), the host must be performing poorly (resisting few parasites) and vice versa. Thus, the probability of infection provides a natural currency for evaluating the relative performance of host and parasite within a coevolutionary interaction.

Expectations for Infectivity and Resistance

In order to partition infectivity into local and global components, we must first calculate the average infectivity of parasites sampled from population k when confronted with hosts sampled from population l, $\bar{P}_{k,l}$. Assuming random encounters between individuals within populations, this quantity is given by

$$\bar{P}_{k,l} = \sum_{i=1}^{n_X} \sum_{j=1}^{n_Y} \alpha_{i,j} x_{i,l} y_{j,k}, \tag{2}$$

where $x_{i,l}$ and $y_{j,k}$ are the frequencies of host genotype i in habitat l and parasite genotype j in habitat k, respectively, and n_X and n_Y are the number of host and parasite genotypes, respectively.

The next step in our partitioning of infectivity involves calculating the expected infectivity of parasites on local hosts over the entire metapopulation, $\hat{P}$. This expectation could be estimated experimentally by averaging the infectivity of parasites on their local hosts over the entire metapopulation. Taking this expectation is straightforward and results in the following expression:

$$\hat{P} = E_k[\bar{P}_{k,k}] = \sum_{i=1}^{n_X} \sum_{j=1}^{n_Y} \alpha_{i,j} (\bar{x}_i \bar{y}_j + \mathrm{cov}[x_i, y_j]), \tag{3}$$

where $\bar{x}_i$ is the average frequency of host genotype i over the metapopulation, $\bar{y}_j$ is the average frequency of parasite genotype j over the metapopulation, and $\mathrm{cov}[x_i, y_j]$ is the spatial covariance between host and parasite genotype frequencies over the metapopulation. Results derived in appendix, part A (appendix, pts. A–C, available online), show that the first term in equation (3) quantifies the contribution of global parasite adaptation, G, to infectivity, whereas the second term quantifies the contribution local parasite adaptation, $\mathcal{L}$, makes to infectivity. Using this shorthand, the expected

level of parasite infectivity across the metapopulation can be expressed as a simple sum of local and global adaptation:

$$\hat{P} = \mathcal{L} + G. \tag{4}$$

Biologically, if $\hat{P} > 1/2$, the majority of encounters between host and parasite lead to infection, whereas if $\hat{P} < 1/2$, most encounters between host and parasite result in resistance. An obvious consequence of equation (4) is that local adaptation need not reflect overall levels of parasite infectivity, such that it is possible for a strongly locally adapted parasite to be quite poor at infecting hosts at the metapopulation scale. The converse, of course, is also true.

Quantifying Coevolutionary Advantage

In order to evaluate the conventional wisdom that the locally adapted species is the one that is ahead in the coevolutionary race, we must first develop a rigorous and general definition of what it means to be "ahead." Although there are many possible definitions that have been used, perhaps the most influential has relied on the idea of phase differences in coevolutionary cycles (Nee 1989; Gandon 2002). Specifically, for a simple diallelic matching-alleles model of coevolution, it is possible to derive approximate solutions for the dynamics of coevolution under the assumption of weak selection and continuous time. These approximate solutions show that coevolutionary dynamics follow regular, periodic cycles, with host and parasite cycles offset by some phase difference, ϕ (Gandon 2002). When this phase difference equals zero, parasite allele frequency tracks host allele frequency perfectly, but as the phase difference increases, parasite allele frequency begins to lag behind host allele frequency, reaching a maximum lag when the phase difference reaches π. Thus, the closer the phase difference comes to π, the less well adapted the parasite is to its host population. Although mathematically elegant, these results were derived under highly idealized scenarios and are impossible to extend, or even to conceptualize, for more realistic scenarios where multiple genotypes segregate within each species, population sizes are finite, selection is strong, or time is discrete. In these latter cases, coevolutionary cycles are no longer strictly periodic (e.g., Seger 1988).

A more general way to identify which species is ahead in the coevolutionary race is to ask whether expected infectivity is above or below the value we expect from random genetic drift alone. In other words, does infectivity differ from the value we expect if host and parasite exert no selection on one another such that allele frequencies evolve independently and at random? The reasoning here is that genetic drift should form a logical null expectation for infectivity and that deviations from this expectation should correspond to scenarios where one or the other species is evolving/adapting more rapidly than the other. Thus, if the host is evolving more rapidly than the parasite and thus adapting more quickly, we would expect the level of infectivity to fall below the level expected under the pure drift model. In contrast, if it is the parasite that is evolving and adapting more rapidly, we would expect the level of infectivity to rise above the level expected under the pure drift model. Conveniently, calculating the neutral expectation for infectivity is straightforward if we know the underlying genetic basis of infection and assume drift has caused alleles to fix at random and with equal probability. Specifically, the neutral expectation for infectivity is equal to

$$\hat{P}_{\text{neutral}} = \sum_{i=1}^{n_X} \sum_{j=1}^{n_Y} \frac{\alpha_{i,j}}{n_X n_Y}, \tag{5}$$

which allows us to define an index of parasite coevolutionary advantage, $\mathcal{A}$, for a wide range of scenarios,

$$\mathcal{A} = \hat{P} - \hat{P}_{\text{neutral}}, \tag{6}$$

where $\hat{P}$ is the average level of parasite infectivity on local hosts observed within the metapopulation. Results derived in appendix, part B, using the model studied by Gandon (2002), demonstrate that the sign of $\mathcal{A}$, when averaged over time, depends only on the phase difference between host and parasite cycles. Thus, definition (6) is consistent with previous work but allows a much greater range of coevolutionary scenarios to be studied, including those that do not lead to periodic cycles.

Simulation Model and Results

The results derived in the previous section demonstrate that average infectivity depends on the contributions of both local and global adaptation. We do not yet know, however, how large the contributions made by each of these quantities are likely to be under various coevolutionary scenarios. In addition, the results we have derived so far do not predict whether the magnitudes of these quantities are correlated with one another or whether they rise and fall independently. If these two quantities are independent of one another, or negatively correlated, local adaptation may become decoupled from infectivity and thus become an inaccurate predictor of coevolutionary advantage, $\mathcal{A}$ (fig. 1). To investigate the relative magnitudes of these two components of infectivity over a range of coevolutionary scenarios, and their consequences for the connection between local adaptation and coevolutionary advantage, I developed and analyzed coevolutionary simulations.

Simulation Model

Simulations tracked the coevolution of a host and parasite distributed over a metapopulation consisting of N popula-

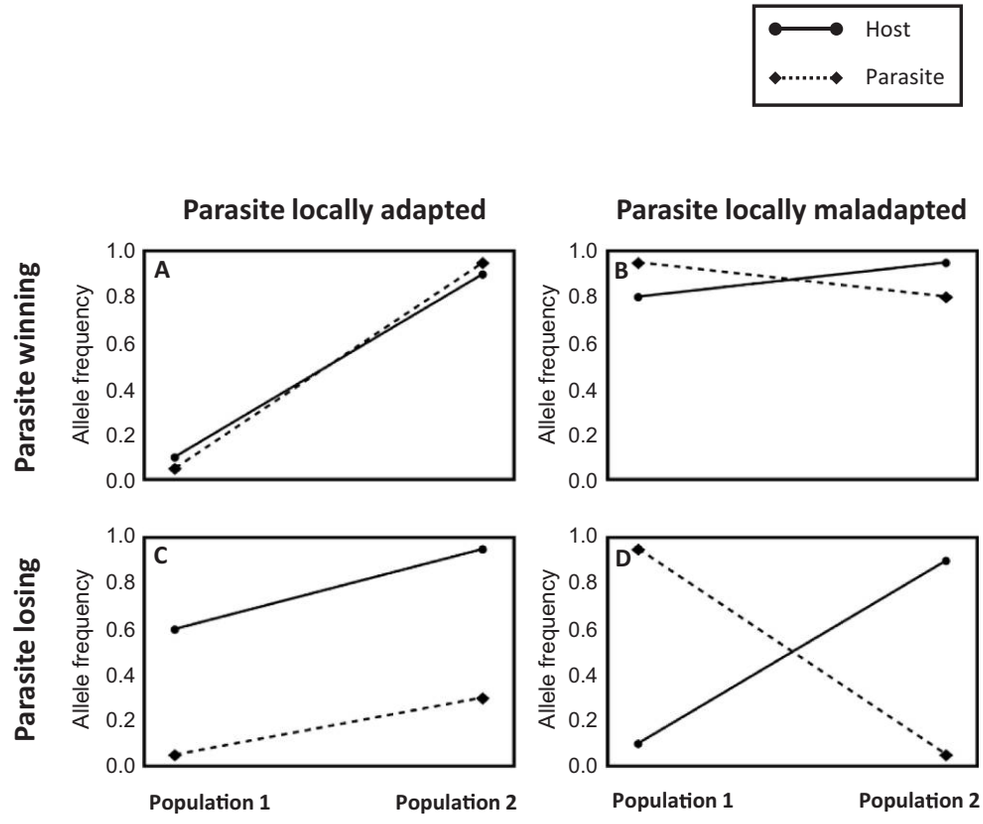


Figure 1: Host and parasite allele frequencies (p_X and p_Y) across two populations. The left-hand column shows allele frequencies that result in parasite local adaptation, whereas the right-hand column shows allele frequencies that result in parasite local maladaptation. In the top row, the parasite is winning the coevolutionary race ($\mathcal{A} > 0$), whereas in the bottom row the parasite is losing ($\mathcal{A} < 0$). In *A*, parasite local adaptation is equal to $\mathcal{L} = 0.36$, parasite global adaptation is equal to $G = 0.5$, and the overall rate of parasite infection is equal to $\hat{P} = 0.86$. In *B*, parasite local adaptation is equal to $\mathcal{L} = -0.36$, global adaptation is equal to $G = 0.5$, and the overall rate of parasite infection is equal to $\hat{P} = 0.14$. In *C*, parasite local adaptation is equal to $\mathcal{L} = 0.04$, parasite global adaptation is equal to $G = 0.32$, and the overall rate of parasite infection is equal to $\hat{P} = 0.36$. In *D*, parasite local adaptation is equal to $\mathcal{L} = -0.01$, parasite global adaptation is equal to $G = 0.78$, and the overall rate of parasite infection is equal to $\hat{P} = 0.77$.

tions, each of which contained η_X and η_Y individual hosts and parasites. Individuals were assumed to move among populations at rates m_X and m_Y in host and parasite, and successful infection was assumed to reduce host fitness by an amount ξ_X, whereas unsuccessful infection was assumed to reduce parasite fitness by an amount ξ_Y. Whether random encounters between host and parasite individuals resulted in infection or resistance was assumed to depend on a haploid, single-locus matching-alleles or inverse matching-alleles model with n possible alleles in host and parasite. Specifically, when compatible genetic combinations of host and parasite encountered one another, the probability of successful infection was greater than when incompatible combinations encountered one another. These models of infection genetics were chosen because they correspond to two fundamental mechanisms involved in immune reactions (Dybdahl et al. 2014). Mutation from one allele to any other occurred at rates μ_X and μ_Y in host and parasite, respectively. Simulations were initiated from random allele frequencies and run for 1,000 generations. In each generation, deterministic changes in allele frequencies caused by selection, gene flow, and mutation were calculated using standard population genetic recursions; random genetic drift was simulated by sampling alleles from a multinomial distribution. Infection rate and its components, coevolutionary advantage, and allele frequencies were recorded for both species in each generation.

The Relative Contributions of Local and Global Adaptation

In the broadest sense, simulations revealed important contributions of both global and local adaptation to overall levels of infectivity. Not surprisingly, the relative importance of global and local adaptation depends on rates of gene flow in the interacting species. Specifically, local adaptation is, in general,

substantial only when rates of gene flow are low. In contrast, global adaptation is insensitive to rates of gene flow. Thus, only when gene flow is weak do global and local components of adaptation both make substantial contributions to infectivity and interact in an interesting way. In these cases, the relative magnitude of local and global adaptation can fluctuate substantially and rapidly over time, such that most of parasite infectivity is explained by local adaptation at some time points but by global adaptation at others (fig. 2, top row). Of crucial importance for the conventional wisdom linking local adaptation to coevolutionary advantage, local and global adaptation do not always evolve in concert (fig. 2, top row). This result is quite robust, holding true as genetic dimensionality increases (fig. 3, top row) and across alternative models of infection such as the inverse matching-alleles model (appendix, pt. C).

Is the Locally Adapted Species Ahead in the Coevolutionary Race?

Simulations conducted over a large range of parameter values were used to explore the validity of the conventional wisdom holding that the locally adapted species is the one that is ahead in the coevolutionary race. Specifically, for each parameter combination, coevolutionary advantage was plotted against local and global adaptation in each generation. In addition, the predictive power of local and global adaptation was assessed by (1) calculating the temporal correlation between these measures of adaptation and coevolutionary advantage and (2) calculating the percentage of generations in which these measures of adaptation accurately predicted the species with the coevolutionary advantage. The results of these simulations demonstrate that local adaptation predicts which species has the coevolutionary advantage only under some circumstances and at particular points in time. For instance, in the pair of simulations shown in figure 2, local adaptation predicts the sign of coevolutionary advantage accurately in only 79% of generations when parasite gene flow exceeded host gene flow and in only 82% of generations when host gene flow exceeded parasite gene flow. Even less impressive is the association between the quantitative values of local adaptation and coevolutionary advantage, with the simulations shown in figure 2 having correlations between these quantities of only 0.59 and 0.73, respectively. Similar results are shown in figure 3 for a case where coevolution involves five alleles and appendix, part C, shows similar results for the inverse matching-alleles model.

Although local adaptation is not a reliable indicator of which species has the coevolutionary advantage in all cases, its accuracy does improve as the magnitude of local adaptation increases. This general trend can be seen in figures 2 and 3 by noticing that the gray points, which indicate erroneous predictions, are concentrated in generations where local adaptation is not too strong ($|\mathcal{L}| < 0.1$). To further explore the relationship between the magnitude of local adaptation and its ability to predict coevolutionary advantage, I ran additional, and more extensive, simulations. Specifically, I performed 1,000 replicate simulations over a range of randomly selected parameter combinations within a metapopulation consisting of 20 populations. In the final generation of each simulation, coevolutionary advantage was calculated for the entire metapopulation and local adaptation was estimated using a reciprocal cross infection study among a random sample of between two and 10 populations. The results of these simulations suggest that local adaptation is a reasonable predictor of coevolutionary advantage when its magnitude is very large (i.e., $|\mathcal{L}| > 0.2$) and a sufficient number (i.e., $\approx$10) of populations has been sampled (fig. 4). This suggests that most published studies of parasite local adaptation rely on far too few populations for inference about coevolutionary advantage.

Discussion

The results of mathematical models and computer simulations demonstrate that parasite infectivity can be partitioned into components corresponding to local and global adaptation and that the magnitudes of these components are highly variable across ecological conditions, genetic systems, and even generations. Because the magnitudes of local and global adaptation need not be positively correlated, information on both is required to predict infectivity. An important consequence of this result is that local adaptation is not an accurate and reliable predictor of how well a parasite is performing at the scale of the entire metapopulation or of which species has the coevolutionary advantage. This suggests that it may be time to abandon conventional wisdom holding that locally adapted parasites are ahead in the coevolutionary race (e.g., Kawecki and Ebert 2004; Greischar and Koskella 2007; Schulte et al. 2011; Lemoine et al. 2012; Roth et al. 2012; Koskella 2014; Perez-Jvostov 2015) and think more critically about what we can—and cannot—learn from studies of parasite local adaptation.

Although local adaptation is not a reliable predictor of coevolutionary advantage in general, its performance does improve as the magnitude of local adaptation increases (fig. 4). As a crude rule of thumb, local adaptation begins to be a reasonable indicator of coevolutionary advantage when its magnitude exceeds 0.2 and 10 or more populations have been included in a fully reciprocal cross infection design. Unfortunately, comparing this approximate threshold to published data is difficult because direct comparison requires that local adaptation is measured using a reciprocal cross infection study. The reason this comparison requires studies focused on infection proportions or probabilities (as opposed to, say, virulence) is that local adaptation has units and, as such, comparing

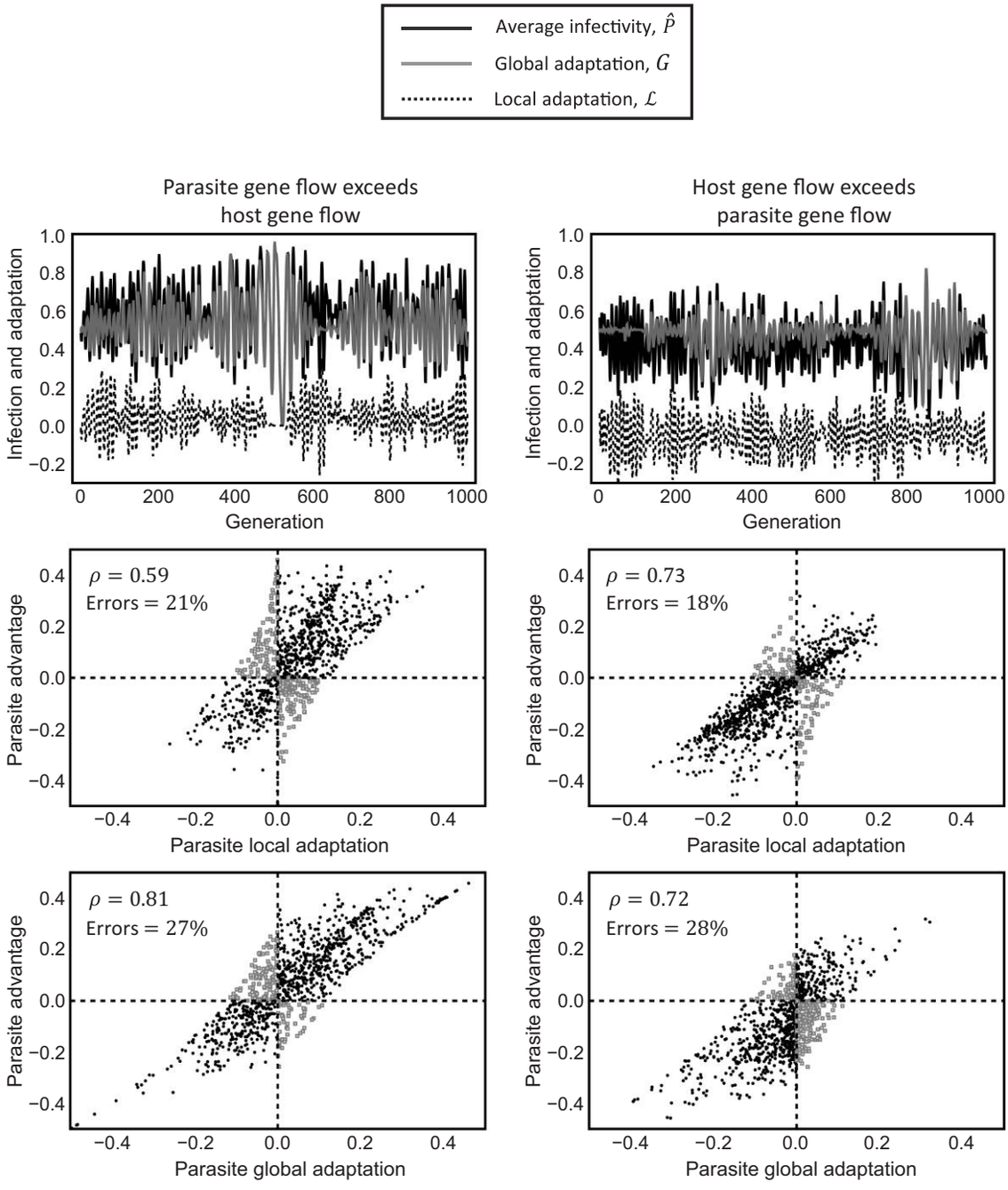


Figure 2: Results of coevolutionary simulations mediated by a matching-alleles model where each species has only two alternative alleles. The first row shows parasite infectivity, $\hat{P}$; parasite local adaptation, $\mathcal{L}$; and parasite global adaptation, G, over 1,000 generations of host-parasite coevolution. The second row shows bivariate scatterplots of parasite local adaptation, $\mathcal{L}$, against parasite coevolutionary advantage, $\mathcal{A}$, for the simulated data. The dashed lines indicate the neutral expectations for local adaptation and coevolutionary advantage for a pure drift model. Points shown in gray are those for which local adaptation fails to predict the sign of coevolutionary advantage, and the proportion of gray points is the error rate. The third row shows bivariate scatterplots of parasite global adaptation, G, against parasite coevolutionary advantage, $\mathcal{A}$, for the simulated data. The dashed lines indicate the neutral expectations for global adaptation and coevolutionary advantage for a pure drift model. Points shown in gray are those for which global adaptation fails to predict the sign of coevolutionary advantage, and the proportion of gray points is the error rate. Each column of the figure corresponds to a different combination of host and parasite gene flow rates. In the left-hand column, the parasite moves more than the host: $m_X = 0.001$ and $m_Y = 0.005$. In the right-hand column, the host moves more than the parasite: $m_X = 0.005$ and $m_Y = 0.001$. The correlations between adaptation component and coevolutionary advantage, ρ, are presented for each scatterplot. Remaining parameter values were constant across rows and were given by $N = 10$, $\eta_X = \eta_Y = 250$, $\mu_X = \mu_Y = 5.0 \times 10^{-5}$, $\xi_X = 0.8$, and $\xi_Y = 0.8$.

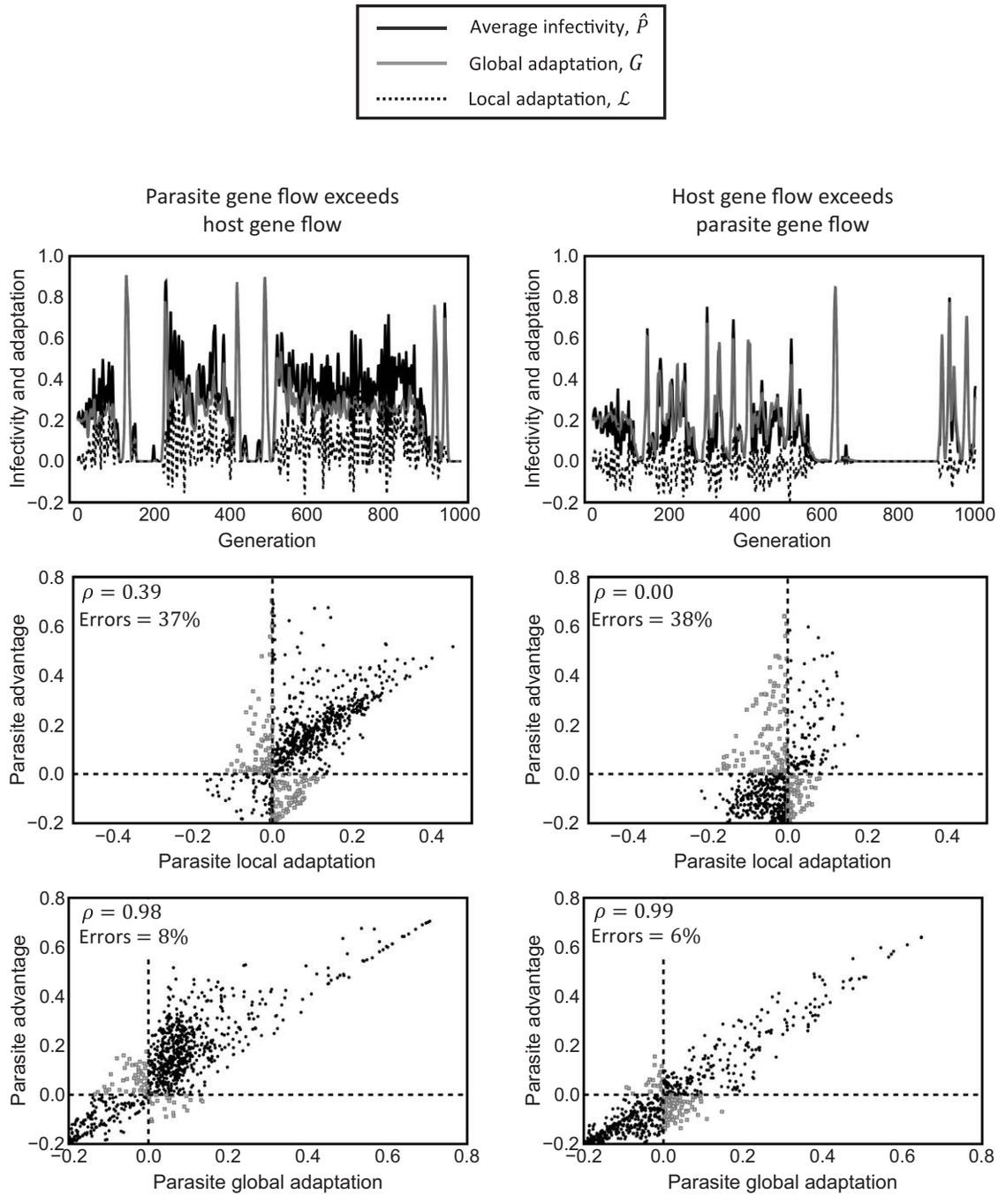
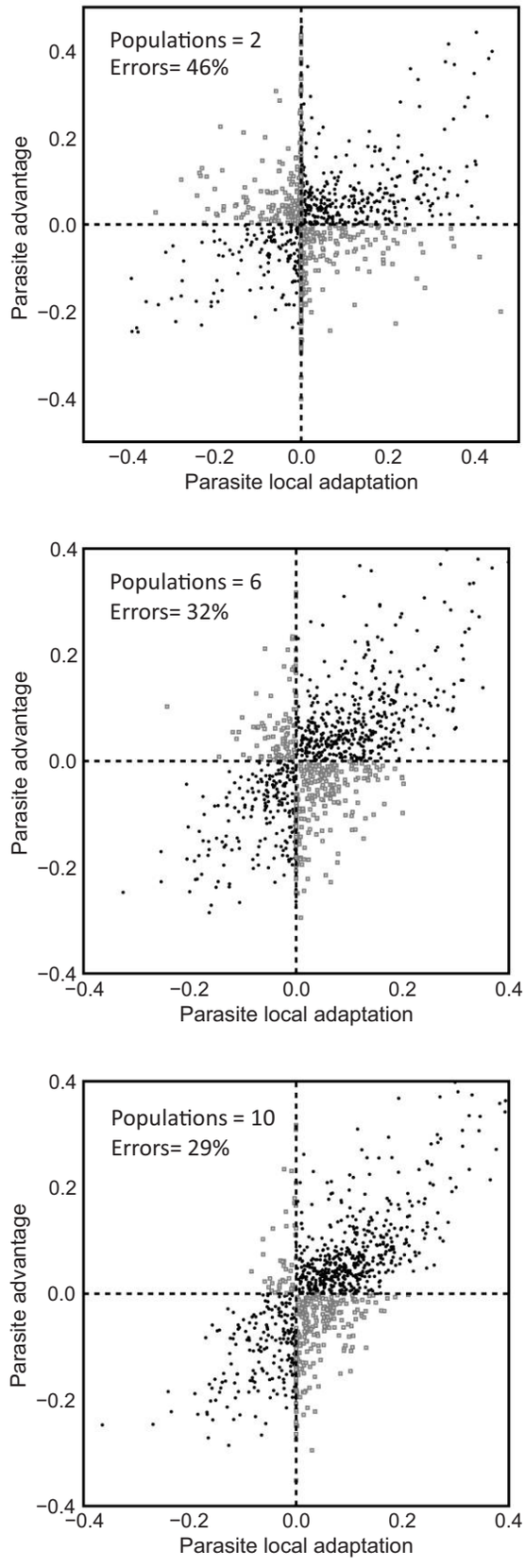


Figure 3: Results of coevolutionary simulations mediated by a matching-alleles model where each species has five alternative alleles. The first row shows parasite infectivity, $\hat{P}$; parasite local adaptation, $\mathcal{L}$; and parasite global adaptation, G, over 1,000 generations of host-parasite coevolution. The second row shows bivariate scatterplots of parasite local adaptation, $\mathcal{L}$, against parasite coevolutionary advantage, $\mathcal{A}$, for the simulated data. The dashed lines indicate the neutral expectations for local adaptation and coevolutionary advantage for a pure drift model. Points shown in gray are those for which local adaptation fails to predict the sign of coevolutionary advantage, and the proportion of gray points is the error rate. The third row shows bivariate scatterplots of parasite global adaptation, G, against parasite coevolutionary advantage, $\mathcal{A}$, for the simulated data. The dashed lines indicate the neutral expectations for global adaptation and coevolutionary advantage for a pure drift model. Points shown in gray are those for which global adaptation fails to predict the sign of coevolutionary advantage, and the proportion of gray points is the error rate. Each column of the figure corresponds to a different combination of host and parasite gene flow rates. In the left-hand column, the parasite moves more than the host: $m_X = 0.001$ and $m_Y = 0.005$. In the right-hand column, the host moves more than the parasite: $m_X = 0.005$ and $m_Y = 0.001$. The correlations between adaptation component and coevolutionary advantage, ρ, are presented for each scatterplot. Remaining parameter values were constant across rows and were given by $N = 10$, $\eta_X = \eta_Y = 250$, $\mu_X = \mu_Y = 5.0 \times 10^{-5}$, $\xi_X = 0.8$, and $\xi_Y = 0.8$.



across studies is meaningful only if identical units are used. An informal sampling of published studies that meet this criterion (Lively 1989; Kaltz et al. 1999; Lively and Dybdahl 2000; Jackson and Tinsley 2005; Niemi et al. 2006; Jenkins et al. 2015; Weber et al. 2017) suggests empirical estimates of local adaptation straddle the rule of thumb with respect to the magnitude of local adaptation. The number of populations included in these studies, however, is generally much smaller (e.g., two to four) than what the results presented here suggest would be the minimum required for reliable inference.

In addition to undermining conventional wisdom, simulations demonstrated interesting consequences of genetic dimensionality. Specifically, increasing the number of alleles has a strong impact on average infectivity although the direction of the effect depends on the genetic mechanism. For the matching-alleles model, as the number of alleles increases, the average level of parasite infectivity decreases (cf. top rows of figs. 2, 3). In contrast, for the inverse matching-alleles model, as the number of alleles increases, so too does the average level of parasite infectivity (cf. top rows of figures in appendix, pt. C). The reason for this effect may be that it becomes increasingly difficult for the species that needs to match alleles (the parasite in the matching-alleles model, the host in the inverse matching-alleles model) to track its opponent evolutionarily as the number of alleles (genetic dimensionality) increases (Lively 2016). This phenomenon has been previously demonstrated theoretically for quantitative traits (Gilman et al. 2012; Debarre et al. 2014) and may help to explain the relationship between genetic diversity and the spread of infectious disease (reviewed in King and Lively 2012). In contrast to these strong and interesting impacts of genetic complexity on average infectivity, no similar patterns were observed for local adaptation, further demonstrating the substantial disconnect between local adaptation, parasite infectivity, and coevolutionary advantage.

Although the results presented here demonstrate that local adaptation is not a reliable predictor of overall infectivity or

Figure 4: The relationship between coevolutionary advantage and local adaptation for cases where local adaptation was estimated from a reciprocal cross infection experiment conducted among two populations (top row), six populations (middle row), and 10 populations (bottom row). Each point in the figure represents the values of coevolutionary advantage and local adaptation calculated from a single simulation. Gray points indicate simulations where the signs of local adaptation and coevolutionary advantage to do not agree, whereas black points indicate simulations where they do agree. The predictive power of local adaptation improves with sample size and the magnitude of local adaptation. Each replicate simulation considered a metapopulation consisting of 20 populations and was run for 500 generations. Remaining parameters were selected at random in each run from the following uniform distributions: $\eta_X[100, 500]$, $\eta_Y[100, 500]$, $\mu_X[1.0 \times 10^{-5}, 5.0 \times 10^{-5}]$, $\mu_Y[1.0 \times 10^{-5}, 5.0 \times 10^{-5}]$, $\xi_X[0.7, 1.0]$, $\xi_Y[0.7, 1.0]$, $m_X[0, 0.005]$, and $m_Y[0, 0.005]$.

coevolutionary advantage, estimates of local adaptation can provide a huge wealth of valuable and important information if a large number of populations are included in a reciprocal design (Blanquart et al. 2013). Most importantly and precisely, estimates of local adaptation measure the spatial covariance between frequencies of host and parasite genotypes that result in infection (Nuismer and Gandon 2008). Thus, studies of parasite local adaptation quantify parasite and host spatial genetic variation and the extent to which parasite genotype frequencies track the frequencies of local host genotypes they can infect (Lively 1989; Dybdahl and Lively 1998). An interesting opportunity presented by this result is the possibility that studies of parasite local adaptation, when coupled with emerging genomic techniques, could be used to identify candidate coevolving genes in host and parasite by searching for spatially correlated marker frequencies (Nuismer et al. 2017). In addition, quantifying the magnitude of parasite local adaptation may shed light on the likelihood of parasite range expansion and the potential consequences of introducing parasites beyond their native range.

In conclusion, the results presented here show that local adaptation is only loosely tethered to parasite infectivity and coevolutionary advantage. Consequently, only those studies that include a large number of populations in a reciprocal design and demonstrate very strong local adaptation have any real chance of reliably identifying which species is winning the coevolutionary race. No matter how many populations are sampled, however, an absence of local adaptation never reliably indicates a coevolutionary "draw." Although it is possible that new approaches may emerge that allow coevolutionary advantage to be more reliably assessed, a more important realization may be that focusing on identifying which species is "winning" is distracting us from a broad range of more interesting and relevant questions. By using more powerful experimental designs that integrate larger numbers of populations (Blanquart et al. 2013), future studies of local adaptation will likely be able to answer a wealth of more interesting questions than who is ahead in the coevolutionary race.

Acknowledgments

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Literature Cited

Adiba, S., M. Huet, and O. Kaltz. 2010. Experimental evolution of local parasite maladaptation. Journal of Evolutionary Biology 23:1195–1205.

Agrawal, A. F., and C. M. Lively. 2001. Parasites and the evolution of self-fertilization. Evolution 55:869–879.

———. 2002. Infection genetics: gene-for-gene versus matching-alleles models and all points in between. Evolutionary Ecology Research 4:79–90.

Ballabeni, P., and P. I. Ward. 1993. Local adaptation of the trematode *Diplostomum phoxini* to the European minnow *Phoxinus*, its second intermediate host. Functional Ecology 7:84–90.

Blanquart, F., O. Kaltz, S. L. Nuismer, and S. Gandon. 2013. A practical guide to measuring local adaptation. Ecology Letters 16:1195–1205.

Capelle, J., and C. Neema. 2005. Local adaptation and population structure at a micro-geographical scale of a fungal parasite on its host plant. Journal of Evolutionary Biology 18:1445–1454.

Debarre, F., S. L. Nuismer, and M. Doebeli. 2014. Multidimensional (co)evolutionary stability. American Naturalist 184:158–171.

DeClerck, S., C. Cousyn, and L. De Meester. 2001. Evidence for local adaptation in neighbouring *Daphnia* populations: a laboratory transplant experiment. Freshwater Biology 46:187–198.

Dybdahl, M. F., C. E. Jenkins, and S. L. Nuismer. 2014. Identifying the molecular basis of host-parasite coevolution: merging models and mechanisms. American Naturalist 184:1–13.

Dybdahl, M. F., and C. M. Lively. 1998. Host-parasite coevolution: evidence for rare advantage and time-lagged selection in a natural population. Evolution 52:1057–1066.

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

Engelstaedter, J. 2015. Host-parasite coevolutionary dynamics with generalized success/failure infection genetics. American Naturalist 185:E117–E129.

Gandon, S. 2002. Local adaptation and the geometry of host-parasite coevolution. Ecology Letters 5:246–256.

Gandon, S., Y. Capowiez, Y. Dubois, Y. Michalakis, and I. Olivieri. 1996. Local adaptation and gene-for-gene coevolution in a metapopulation model. Proceedings of the Royal Society B 263:1003–1009.

Gandon, S., and Y. Michalakis. 2002. Local adaptation, evolutionary potential and host-parasite coevolution: interactions between migration, mutation, population size and generation time. Journal of Evolutionary Biology 15:451–462.

Gandon, S., and S. L. Nuismer. 2009. Interactions between genetic drift, gene flow, and selection mosaics drive parasite local adaptation. American Naturalist 173:212–224.

Gavrilets, S., and Y. Michalakis. 2008. Effects of environmental heterogeneity on victim-exploiter coevolution. Evolution 62:3100–3116.

Gilman, R. T., S. L. Nuismer, and D.-C. Jhwueng. 2012. Coevolution in multidimensional trait space favours escape from parasites and pathogens. Nature 483:328–330.

Greischar, M. A., and B. Koskella. 2007. A synthesis of experimental work on parasite local adaptation. Ecology Letters 10:418–434.

Hamilton, W. D. 1980. Sex vs. non-sex vs. parasite. Oikos 35:282–290.

Hanks, L. M., and R. F. Denno. 1994. Local adaptation in the armored scale insect *Pseudaulacaspis pentagona* (Homoptera: Diaspididae). Ecology 75:2301–2310.

Hoeksema, J. D., and S. E. Forde. 2008. A meta-analysis of factors affecting local adaptation between interacting species. American Naturalist 171:275–290.

Imhoof, B., and P. Schmid-Hempel. 1998. Patterns of local adaptation of a protozoan parasite to its bumblebee host. Oikos 82:59–65.

Jackson, J. A., and R. C. Tinsley. 2005. Geographic and within-population structure in variable resistance to parasite species and strains in a vertebrate host. International Journal of Parasitology 35:29–37.

Jaenike, J. 1978. An hypothesis to account for the maintenance of sex within populations. Evolutionary Theory 3:191–194.

Jenkins, T., J. Delhaye, and P. Christe. 2015. Testing local adaptation in a natural great tit–malaria system: an experimental approach. PLoS ONE 10:e0141391.

Kaltz, O., S. Gandon, Y. Michalakis, and J. A. Shykoff. 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.

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

Kawecki, T. J., and D. Ebert. 2004. Conceptual issues in local adaptation. Ecology Letters 7:1225–1241.

King, K. C., and C. M. Lively. 2012. Does genetic diversity limit disease spread in natural host populations? Heredity 109:199–203.

Koskella, B. 2014. Bacteria-phage interactions across time and space: merging local adaptation and time-shift experiments to understand phage evolution. American Naturalist 184(suppl.):S9–S21.

Lemoine, M., B. Doligez, and H. Richner. 2012. On the equivalence of host local adaptation and parasite maladaptation: an experimental test. American Naturalist 179:270–281.

Lion, S., and S. Gandon. 2015. Evolution of spatially structured host-parasite interactions. Journal of Evolutionary Biology 28:10–28.

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

———. 1999. Migration, virulence, and the geographic mosaic of adaptation by parasites. American Naturalist 153(suppl.):S34–S47.

———. 2010. A review of Red Queen models for the persistence of obligate sexual reproduction. Journal of Heredity 101:S13–S20.

———. 2016. Coevolutionary epidemiology: disease spread, local adaptation, and sex. American Naturalist 187:E77–E82.

Lively, C. M., M. E. Dybdahl, J. Jokela, E. E. Osnas, and L. E. Delph. 2004. Host sex and local adaptation by parasites in a snail-trematode interaction. American Naturalist 164(suppl.):S6–S18.

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

McCoy, K. D., T. Boulinier, S. Schjorring, and Y. Michalakis. 2002. Local adaptation of the ectoparasite *Ixodes uriae* to its seabird host. Evolutionary Ecology Research 4:441–456.

M'Gonigle, L. K., J. J. Shen, and S. P. Otto. 2009. Mutating away from your enemies: the evolution of mutation rate in a host-parasite system. Theoretical Population Biology 75:301–311.

Morran, L. T., R. C. Parrish, I. A. Gelarden, M. B. Allen, and C. M. Lively. 2014. Experimental coevolution: rapid local adaptation by parasites depends on host mating system. American Naturalist 184(suppl.): S91–S100.

Nee, S. 1989. Antagonistic coevolution and the evolution of genotypic randomization. Journal of Theoretical Biology 140:499–518.

Niemi, L., A. Wennström, J. Hjältén, P. Waldmann, and L. Ericson. 2006. Spatial variation in resistance and virulence in the host-pathogen system *Salix triandra–Melampsora amygdalinae*. Journal of Ecology 94: 915–921.

Nuismer, S. L., M. Doebeli, and D. Browning. 2005. The coevolutionary dynamics of antagonistic interactions mediated by quantitative traits with evolving variances. Evolution 59:2073–2082.

Nuismer, S. L., and S. Gandon. 2008. Moving beyond common-garden and transplant designs: insight into the causes of local adaptation in species interactions. American Naturalist 171:658–668.

Nuismer, S. L., C. E. Jenkins, and M. Dybdahl. 2017. Identifying coevolving loci using interspecific genetic correlations. Ecology and Evolution. https://doi.org/10.1002/ece3.3107.

Nuismer, S. L., and S. P. Otto. 2004. Host-parasite interactions and the evolution of ploidy. Proceedings of the National Academy of Sciences of the USA 101:11036–11039.

Nuismer, S. L., S. P. Otto, and F. Blanquart. 2008. When do host-parasite interactions drive the evolution of non-random mating? Ecology Letters 11:937–946.

Nuismer, S. L., B. J. Ridenhour, and B. P. Oswald. 2007. Antagonistic coevolution mediated by phenotypic differences between quantitative traits. Evolution 61:1823–1834.

Oppliger, A., R. Vernet, and M. Baez. 1999. Parasite local maladaptation in the Canarian lizard *Gallotia galloti* (Reptilia: Lacertidae) parasitized by haemogregarian blood parasite. Journal of Evolutionary Biology 12:951–955.

Perez-Jvostov, F., A. P. Hendry, G. F. Fussmann, and M. E. Scott. 2015. Testing for local host-parasite adaptation: an experiment with *Gyrodactylus* ectoparasites and guppy hosts. International Journal of Parasitology 45:409–417.

Roth, O., I. Keller, S. H. Landis, W. Salzburger, and T. B. H. Reusch. 2012. Hosts are ahead in a marine host-parasite coevolutionary arms race: innate immune system adaptation in pipefish *Syngnathus typhle* against *Vibrio* phylotypes. Evolution 66:2528–2539.

Saarinen, M., and J. Taskinen. 2005. Local adaptation in a crustacean parasite-molluscan host interaction: a field experiment. Evolutionary Ecology Research 7:1191–1199.

Salathe, M., R. D. Kouyos, and S. Bonhoeffer. 2008. The state of affairs in the kingdom of the Red Queen. Trends in Ecology and Evolution 23:439–445.

Schulte, R. D., C. Makus, B. Hasert, N. K. Michiels, and H. Schulenburg. 2011. Host-parasite local adaptation after experimental coevolution of *Caenorhabditis elegans* and its microparasite *Bacillus thuringiensis*. Proceedings of the Royal Society B 278:2832–2839.

Seger, J. 1988. Dynamics of some simple host-parasite models with more than two genotypes in each species. Philosophical Transactions of the Royal Society B 319:541–555.

Thrall, P. H., J. J. Burdon, and J. D. Bever. 2002. Local adaptation in the *Linum marginale–Melampsora lini* host-pathogen interaction. Evolution 56:1340–1351.

Weber, J. N., M. Kalbe, K. C. Shim, N. I. Erin, N. C. Steinel, L. Ma, and D. I. Bolnick. 2017. Resist globally, infect locally: a transcontinental test of adaptation by stickleback and their tapeworm parasite. American Naturalist 189:43–57.

References Cited Only in the Online Appendixes

Morgan, A. D., S. Gandon, and A. Buckling. 2005. The effect of migration on local adaptation in a coevolving host-parasite system. Nature 437:253–256.

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