

# Coevolutionary Epidemiology: Disease Spread, Local Adaptation, and Sex

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Submitted May 14, 2015; Accepted August 18, 2015; Electronically published January 8, 2016

Online enhancements: appendix.

**ABSTRACT:** How does evolution in parasite populations affect the rate of disease spread? In the present study, I derived the mean reproductive rate ( $\bar{R}_0$ ) for a genetically diverse parasite population that is evolving with a similarly diverse host population. Assuming a matching-alleles model, I found that  $\bar{R}_0$  is a positive function of the covariance between the frequencies of “matching” host and parasite genotypes. Computer simulations further showed that evolution in the parasite population tends to increase the covariance, which can lead to epidemiological feedbacks. However, the covariances can also become negative during counteradaptation by the host, leading to oscillatory dynamics in host and parasite fitness. Nonetheless, when parasite-mediated selection is strong, the covariance is positive on average, which facilitates the spread of disease. Positive covariances may also underlie patterns of local adaptation in parasite populations and increase the selective advantage of cross-fertilization in host populations.

**Keywords:** disease spread, evolution, epidemiological feedbacks, Red Queen dynamics.

## Introduction

Data from both agricultural (e.g., Zhu et al. 2000; Mundt 2002) and natural (e.g., Baer and Schmid-Hempel 1999; Seeley and Tarpay 2007; Altermatt and Ebert 2008) systems suggest that genetic diversity in host populations can reduce the spread of infectious disease (reviewed in King and Lively 2012). There are two reasons that could underlie the effect. One is that increasing genetic diversity in the host population reduces the number of susceptible hosts for each parasite strain, thereby reducing  $R_0$ . The second is that increasing host genetic diversity reduces the probability of infection for each parasite strain, which would reduce  $R_0$  even in infinitely large host populations. In a previous study, I found theoretical support for the latter idea

(Lively 2010a). Specifically, the results showed that the mean number of secondary infections (i.e.,  $\bar{R}_0$ ) is inversely proportional to the number of resistance genotypes in large host populations. The model assumed that hosts employ self/nonsel self recognition systems as a defense against infection, which requires that the parasite match the host's definition of “self,” an idea that has garnered recent empirical support (Dybdahl et al. 2008; Luijckx et al. 2013).

In the present study, I extend this work by allowing for the possibility that evolution in the parasite population leads to a positive covariance between the frequency of parasite genotypes and the frequency of host genotypes that they can infect. The analytical results show how  $\bar{R}_0$  is positively related to this covariance, and the simulation results demonstrate that the covariance can fluctuate over time. The model was then extended to cover a different kind of genetic architecture for infection, such that hosts must match parasite genotypes to resist infection. The two genetic models represent two ends of a continuum with respect to the specificity required for infection (Gandon and Day 2009). The results are interpreted in terms of disease spread, local adaptation by parasites, and parasite-mediated selection for cross-fertilization as envisioned under the Red Queen hypothesis (Levin 1975; Jaenike 1978; Hamilton 1980; Lloyd 1980; Hamilton et al. 1990).

## Models

### Matching-Alleles Model

I first assume that parasite genotypes must match their host's genotypes to evade the host's immune response (table 1, pt. A). This kind of model is known as the matching-alleles model (MAM, following Frank 1993), and it has been widely used in models of coevolution (e.g., Hamilton 1980; May and Anderson 1983; Hamilton et al. 1990; Howard and Lively 1994; Otto and Nuismer 2004). Another way that we might think of the MAM is “parasites match to infect” (PMI), as it is based on the idea that hosts have self/nonsel self recognition

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**Table 1:** Infection matrices for the matching-alleles model (MAM; pt. A) and the inverse matching-alleles model (IMAM; pt. B)

	Parasite fitness on host genotype $i$					
Parasite genotype	1	2	3	4	$R_{0i}$	$p_i(R_{0i})$
A. MAM:						
1	$B$	...	...	...	$Bh_1$	$Bh_1p_1$
2	...	$B$	...	...	$Bh_2$	$Bh_2p_2$
3	...	...	$B$	...	$Bh_3$	$Bh_3p_3$
4	...	...	...	$B$	$Bh_4$	$Bh_4p_4$
B. IMAM:						
1	...	$B$	$B$	$B$	$B(1 - h_1)$	$B(1 - h_1)p_1$
2	$B$	...	$B$	$B$	$B(1 - h_2)$	$B(1 - h_2)p_2$
3	$B$	$B$	...	$B$	$B(1 - h_3)$	$B(1 - h_3)p_3$
4	$B$	$B$	$B$	...	$B(1 - h_4)$	$B(1 - h_4)p_4$

Note: The matrices assume four host and four parasite genotypes. The variable  $p_i$  gives the frequency of the matching  $i$ th parasite genotype, and  $h_i$  gives the frequency of the matching host genotype. The variable  $B$  gives the maximum number of secondary infections. The sum of the last column in part A gives a special case of equation (5). The sum of the last column in part B gives a special case of equation (14).

systems as part of their immune responses to pathogens or competitors (Grosberg and Hart 2000).

Following a previous model (Lively 2010a), I use here a discrete-time formulation for the number of new infections in the  $i$ th host genotype in the next time step ( $I_{i(t+1)}$ ), such that

$$I_{i(t+1)} = h_{i(t+1)} N_{(t+1)} \left( 1 - e^{-BI_{i(t)}/N_{(t+1)}} \right). \quad (1)$$

Here,  $h_i$  is the frequency of the matching (and, hence, infectable) genotype in the host population (I used  $g_i$  for this variable in the previous study);  $N$  is the total number of hosts in the population, and  $B$  is the number of parasite propagules produced by each parasite strain that make contact with hosts. In the limit, as  $N$  goes to infinity, the number of new infections for the  $i$ th parasite genotype becomes

$$I_{i(t+1)} = h_{i(t+1)} BI_{i(t)}. \quad (2)$$

The number of secondary infections produced by a single infected individual of type ( $i$ ) gives  $R_{0i}$  (still assuming large host populations):

$$R_{0i} = h_{i(t+1)} B. \quad (3)$$

The expected fitness of parasite genotype ( $i$ ) is simply

$$W_i = \frac{I_{i(t+1)}}{I_{i(t)}} = h_{i(t+1)} B. \quad (4)$$

Hence,  $R_{0i} = W_i$ ; I will use them interchangeably. The average value for  $R_0$  taken over all the different parasite strains is then

$$\bar{R}_0 = \bar{W} = B \sum_{i=1}^P p_i h_i, \quad (5)$$

where  $p_i$  is the frequency of the  $i$ th parasite genotype and  $P$  is the number of parasite genotypes. Dividing both sides by  $BP$ , we get

$$\frac{\bar{R}_0}{B} \frac{1}{P} = \frac{1}{P} \sum_{i=1}^P p_i h_i, \quad (6)$$

$$= E[ph],$$

where  $E[ph]$  gives the mean of the products for host and matching parasite frequencies. Subtracting the product of the means from both sides then gives

$$\frac{\bar{R}_0}{B} \frac{1}{P} - \bar{p} \bar{h} = E[ph - \bar{p} \bar{h}], \quad (7)$$

which in turn gives

$$\frac{\bar{R}_0}{B} \frac{1}{P} - \bar{p} \bar{h} = \text{cov}(p, h), \quad (8)$$

as the right-hand side of equation (7) is the covariance between  $p_i$  and  $h_i$  (see Lynch and Walsh 1998; Otto and Day 2007). Given that  $\bar{p} = 1/P$  and  $\bar{h} = 1/H$ , equation (8) becomes

$$\frac{\bar{R}_0}{B} \frac{1}{P} = \text{cov}(p, h) + \frac{1}{PH}. \quad (9)$$

Finally, multiplying both sides by  $B \times P$  gives

$$\bar{R}_0 = B \cdot P \cdot \text{cov}(p, h) + \frac{1}{H}. \quad (10)$$

Hence, the average number of secondary infections over all parasite strains depends positively on the covariance be-

tween the frequency of matching genotypes as well as the number of host ( $H$ ) and parasite ( $P$ ) genotypes. Note that, if the covariance term is 0 ( $\text{cov}(p, h) = 0$ ), the result simplifies to

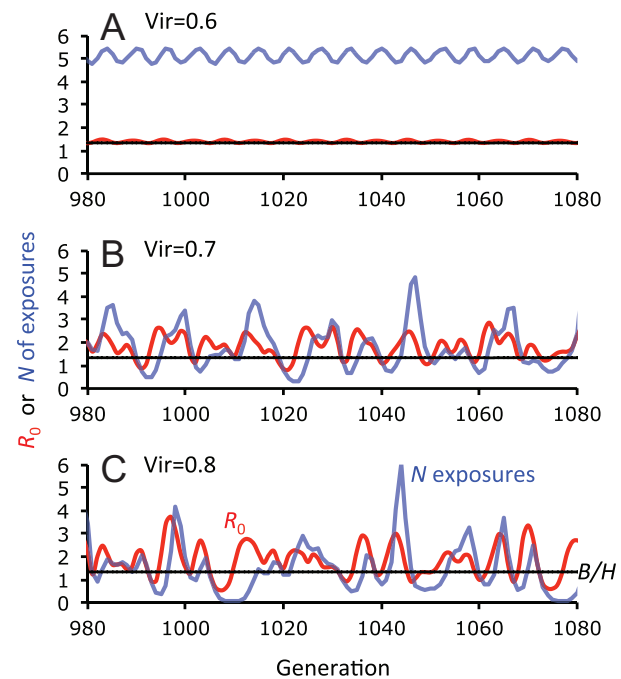
$$\bar{R}_0 = \frac{B}{H}, \quad (11)$$

which converges on my previous result (Lively 2010a) and suggests that increasing host genetic diversity should reduce disease spread (see also Ashby and King 2015). I henceforth refer to this value ( $B/H$ ) as the baseline value, which is the expected value for randomly selected distributions of parasite genotype frequencies.

The result in equation (10) suggests that the number of secondary infections depends on the covariance between the frequencies of matching host and parasite genotypes. Coevolution would be expected to periodically produce positive covariances whenever parasites are successfully “tracking” common host genotypes and to produce negative covariances whenever common host genotypes have not yet been tracked. Hence,  $\bar{R}_0$  could fluctuate such that it is periodically greater than  $B/H$  and periodically less than  $B/H$ .

This idea was confirmed by computer simulations of a previously published epidemiological model of host-parasite coevolution (methods are given in Lively 2010b). In brief, the model assumes a haploid, sexual host population that interacts with a haploid, asexual parasite population. Both hosts and parasites have three alleles at each of two loci, giving nine possible genotypes. For the MAM, an exact genotypic match is required for infection. Both hosts and parasites are assumed to be annuals, and hence they had the same generation times. Finally, host birth rates are density dependent, but they are also dependent on whether they were infected or uninfected. The effect of infection on host fitness (i.e., virulence) was determined by the standardized difference between the birth rates of uninfected hosts and infected hosts. The simulation results show that for high levels of parasite virulence, both average  $\bar{R}_0$  and the number of exposures per host oscillated strongly due to changes in the covariance over time (fig. 1B, 1C). Nonetheless, the covariances were positive, on average, resulting in a larger average  $\bar{R}_0$  over time relative to the case with no parasite evolution (e.g.,  $\bar{R}_0 = B/H$ ). For lower levels of virulence, the oscillations in  $\bar{R}_0$  were dampened; the covariances were still generally positive but were near zero (fig. 1A). This excess of positive covariances might be due to the fact that selection was stronger on the parasite than the host, as the MAM assumes that mismatched parasites are killed.

The excess of positive covariances would also be expected to contribute to local parasite adaptation (Gandon and Nuismer 2009), as revealed by reciprocal cross-infection ex-



**Figure 1:** Representative runs of the matching-alleles simulation model from Lively (2010b) for an outcrossing host population. The red line gives  $\bar{R}_0$  for the parasite, and the blue line gives the average number of host exposures to parasites. Note that the number of exposures tracks  $\bar{R}_0$ . The flat black line gives  $B/H$ . The  $\text{cov}(p, h)$  is positive when the red line is above the black line and is negative when the red line is below the black line. Parameters for the run were as follows: A, virulence = 0.6,  $b_u = 10$ ,  $b_i = 4$ ,  $a_i = a_u = 0.001$ ,  $B = 12$ ,  $H = 9$ ; B, virulence = 0.7,  $b_i = 3$  (all other parameters are as in A); C, virulence = 0.8,  $b_i = 2$  (all other parameters are as in A).

periments (e.g., Parker 1985; Lively 1989; Ebert 1994). In such experiments, the infectivity of sympatric parasite-host combinations is compared with allopatric parasite-host combinations (reviewed in Kawecki and Ebert 2004; Greischar and Koskella 2007). A rough estimate of the strength of parasite local adaptation under the MAM could be gained by dividing equation (10) by the baseline expectation for the allopatric (nonlocal) parasite population, where the covariance is assumed to be 0 ( $B/H$ ). Dividing equation (10) by the baseline value in equation (11), we get

$$\frac{\bar{W}_{\text{sympatric}}}{\bar{W}_{\text{allopatric}}} = 1 + PH \text{cov}(p, h). \quad (12)$$

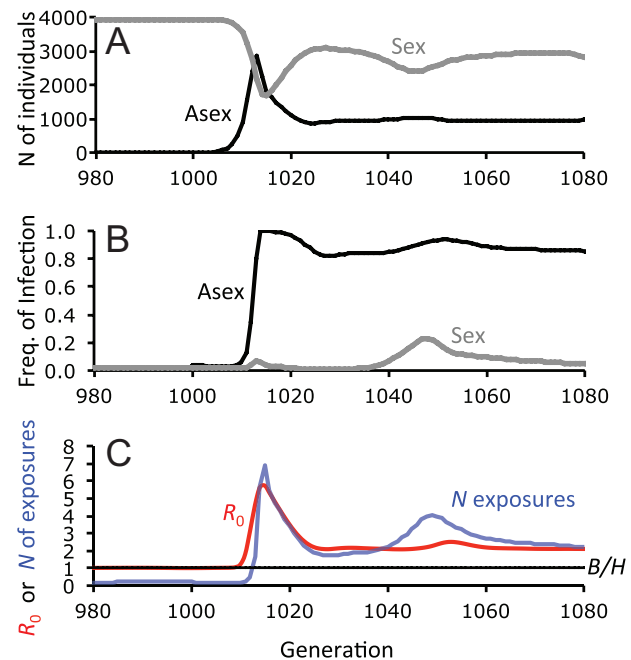
Thus, the strength of local adaptation should increase with the number of host and parasite genotypes as well as with the covariance between the frequencies of matching types in the sympatric population (see also Gandon and Nuismer 2009). It is worth noting, however, that the covariance term may be negatively related to  $P$  and  $H$ , as increasing the number of matching genotypes would reduce the probability of a

successful match, and it reduces the oscillations in genotype frequencies over time (e.g., Howard and Lively 2004). Nonetheless, equation (12) is likely to be a very conservative measure of the strength of local adaptation, as it assumes that the allopatric parasite population has the same complement of genotypes as the sympatric parasite population but that the parasite genotype frequencies in the allopatric population do not covary with the genotype frequencies in the sympatric host population. In reality, however, we might expect allopatric parasite populations to differ in both the complement and the frequency of genotypes, which would tend to increase the relative strength of parasite adaptation to sympatric host populations (see the appendix).

The covariance formulation can be further examined by considering asymmetries in the production of female offspring. Such an asymmetry would arise, for example, following the introduction of a reproductively isolated clonal lineage into a genetically variable, outcrossing host population. Assuming all else equal, the clone would have a twofold reproductive advantage, which stems from the “cost of males” in the sexual subpopulation (Maynard Smith 1978). To study the effect of reproductive asymmetry, I again used the simulation from Lively (2010b). In brief, a single clonal genotype was introduced into a sexually reproducing host population at generation 1,000. The clone was assigned the same genotype as one of the genotypes in the sexual host population, but, unlike the sexual females, the clone reproduced asexually and produced only daughters, giving a twofold reproductive advantage. The simulation results show that, prior to the introduction of the clone, the sexual host genotypes were oscillating mildly, and the  $\text{cov}(p, h)$  was very small (as in fig. 1A). In addition, average  $R_0$  was holding steady at just above 1 ( $B/H = 1.011$ ). Following the spread of the clone into the population,  $R_0$  increased more than sixfold, and the mean number of parasite exposures per host increased from 0.2 to 8.5 (fig. 2). The clone then decreased in frequency, followed by a decrease in  $R_0$  and the number of exposures per host. The population eventually became a stable mixture of sexual and asexual hosts, and  $R_0$  remained twice as high as that observed before the spread of the clone. The main point here is that evolution in the parasite population results in epidemiological feedbacks, thereby increasing parasite-mediated selection against asexual reproduction.

#### *Inverse Matching-Alleles Model*

The MAM represents the situation where parasites must match host genotypes to infect (PMI: “parasites match to infect”). At the other end of the continuum is the situation where hosts must match the parasite’s genotype to resist infection (HMR: “hosts match to resist”), which is known as the inverse MAM (table 1, pt. B). Neither model is likely to



**Figure 2:** Sexual versus asexual reproduction in an epidemiological model of coevolution (following Lively 2010b). A, Number of sexual and asexual individuals over time. A single asexual genotype was introduced at generation 1,000. B, Frequency of infection of sexual and asexual individuals over time. C, Mean  $R_0$  (red line), number of parasite exposures per host (blue line), and the baseline level for mean  $R_0$  (black line:  $B/H$ ). Parameters values are as in figure 1A, except that  $B = 9.1$ . Note that the disease is maintained at a very low level until after the clone becomes established. Note also that both the mean  $R_0$  and the number of exposures per host increase dramatically as the clone spreads, which illustrates the feedback between parasite evolution and epidemiology.

be strictly true, but they do represent useful ends of a continuum for heuristic purposes (see Gandon and Day 2009). Under the inverse matching-alleles scenario, the number of new infections produced by parasite strain ( $i$ ) is

$$I_{i(t+1)} = (1 - h_{i(t+1)})N_{(t+1)}(1 - e^{-BI_{i0}/N_{(t+1)}}). \quad (13)$$

Following the same steps as above, it can be shown that the mean value for  $R_0$  in large host populations is

$$\bar{R}_0 = B \sum_{i=1}^P p_i (1 - h_i), \quad (14)$$

which in turn leads to

$$\bar{R}_0 = B \left( 1 - P \text{cov}(p, h) - \frac{1}{H} \right). \quad (15)$$

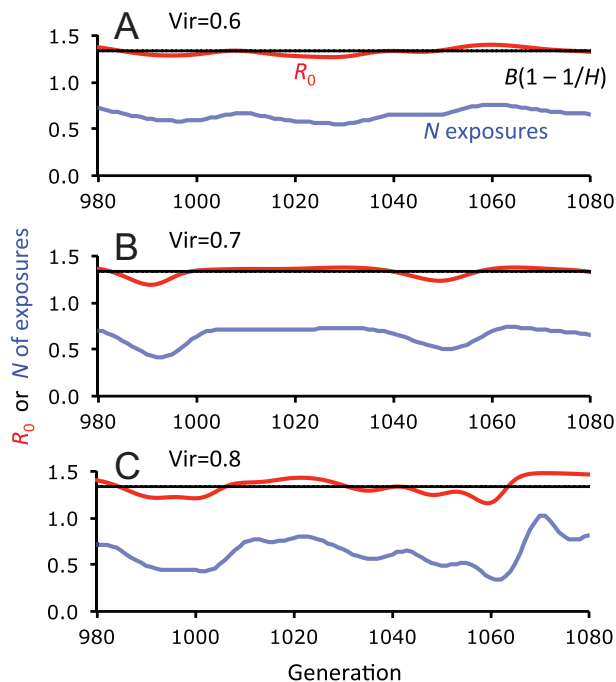
Note that, in the absence of coevolution ( $\text{cov}(p, h) = 0$ ), we get



$$\bar{R}_0 = B \left( 1 - \frac{1}{H} \right). \quad (16)$$

Hence, all else equal, increasing the number of host genotypes causes an increase in the mean number of secondary infections under the IMAM, whereas the opposite result was observed for the MAM. It is also interesting to note in equation (15) that a positive covariance has a negative, rather than positive, effect on  $\bar{R}_0$ .

In runs of the simulation model using similar parameters as for the MAM, I found no conditions under which the IMAM prevented the fixation of a single clonal genotype in a sexual population. This is consistent with the prevailing view that, to select for obligate cross-fertilization, parasite genotypes must be restricted to infecting a small subset of host genotypes (Engelstädter 2015). In addition, the temporal oscillations in  $\bar{R}_0$  were much less extreme (fig. 3) than those observed under similar parameters in the MAM



**Figure 3:** Representative simulation runs of the inverse matching-alleles model (IMAM) for an outcrossing host population. The simulation was adapted from Lively (2010b) using the IMAM of infection genetics (table 1, pt. B). The red line gives  $\bar{R}_0$  for the parasite, and the blue line gives the average number of host exposures to parasites. The flat black line gives  $B/H$ . The  $\text{cov}(p, h)$  is positive when the red line is above the black line, and the covariance is negative when the red line is below the black line. Parameters for the run were as follows: A, virulence = 0.6,  $b_u = 10$ ,  $b_i = 4$ ,  $a_i = a_u = 0.001$ ,  $B = 1.5$ ,  $H = 9$ ; B, virulence = 0.7,  $b_i = 3$  (all other parameters are as in A); C, virulence = 0.8,  $b_i = 2$  (all other parameters are as in A). The variable  $B$  was set to give the same baseline level for mean  $\bar{R}_0$  as in figure 1.

(fig. 1). This result makes sense, as the variance in fitness for parasites is likely to be much reduced when every parasite genotype can infect multiple host genotypes.

## Discussion

In a previous study, I found that in the MAM the number of secondary infections was inversely proportional to the number of genotypes in the host population (Lively 2010a). This previous model assumed that parasite genotypes were introduced into an uninfected host population and that the covariance between matching host and parasite genotypes was 0. However, even though the mean number of secondary infections produced by each parasite strain might be below the threshold required for disease spread ( $\bar{R}_0 < 1$ ), the strains that infect the common host genotypes might still increase (i.e.,  $R_{0i} > 1$  for some parasite genotypes). This spread could then produce a positive covariance between matching host and parasite genotypes, at least temporarily, which would lead to an increase in  $\bar{R}_0$ .

The present model therefore considers the possibility that evolutionary change in the parasite increases the covariance between matching host and parasite genotypes. The analytical results show how this covariance affects  $\bar{R}_0$  for the MAM (eq. [10]) and how the covariance might be expected to affect the strength of adaptation in the local parasite population (eq. [12]). In addition, counterevolution in the host could lead to negative covariances, which would reduce  $\bar{R}_0$ . Hence, there should be feedbacks between epidemiology and coevolution that are driven by the covariance between matching host and parasite genotypes (fig. 1).

In simulation runs of the MAM, I found that the sign of the covariance between the matching host and parasite genotype frequencies did, in fact, fluctuate; however, on average the covariance was positive. This finding may reflect the fact that selection was stronger in the parasite population, as hosts were assumed to kill nonmatching parasite genotypes. The positive average covariances also suggest that parasites would be adapted to infecting their sympatric host populations most of the time, as observed in long-term studies of local adaptation by a trematode parasite of snails (Lively et al. 2004). I also found that the covariance and  $\bar{R}_0$  increased dramatically following the introduction of an obligately asexual clone into a sexual host population (with a twofold cost of producing males). The increase in  $\bar{R}_0$  under these conditions led to epidemiological feedbacks, which resulted in stronger short-term selection against the clone than in a strict population genetic model in which feedbacks are prevented (fig. 2).

The opposite result was observed for the IMAM. Increasing the number of host genotypes tends to increase  $\bar{R}_0$  and, hence, the risk of spread of infectious disease. This is likely due to the fact that each host can defend itself against only

one parasite genotype, so increasing the number of host genotypes tends to increase the fraction of individuals that each parasite strain can infect. The current literature, although sparse, tends to suggest that increasing host genetic diversity tends to reduce disease spread (reviewed in King and Lively 2012), which is consistent with the results for the matching-alleles end of the continuum for specificity.

Taken together, the results show how mean parasite fitness depends on the covariance between matching host-parasite genotypes. They also suggest that this covariance can lead to local adaptation (or maladaptation) by parasites. Finally, the results demonstrate that evolutionary change can lead to epidemiological feedbacks that increase the strength of selection against common host genotypes.

### Acknowledgments

I thank L. Delph, D. Drown, and M. Gibson for helpful comments on the manuscript and the Lively-Hall laboratories for helpful discussions.

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Associate Editor: Jeff Leips  
Editor: Susan Kalisz

## Appendix from C. M. Lively, “Coevolutionary Epidemiology: Disease Spread, Local Adaptation, and Sex” (Am. Nat., vol. 187, no. 3, p. E77)

### Partial Overlap of Parasite Genotypes

What if the complement of parasite genotypes does not overlap between sympatric and allopatric populations? Here I let the frequency of overlapping parasite genotypes in the sympatric and allopatric parasite populations be represented by the variable  $q$ .

#### Matching-Alleles Model (MAM)

From equation (10) we have

$$\bar{R}_0 = B - P \operatorname{cov}(p, h) + \frac{1}{H}.$$

Given that average  $R_0$  is equal to mean parasite fitness, we can rewrite the equation for sympatric parasites as

$$\bar{W}_{\text{sympatric}} = B - P_1 \operatorname{cov}(p_{i1}, h_{i1}) + \frac{1}{H_1},$$

where  $\bar{W}_{\text{sympatric}}$  indicates the fitness of the sympatric parasite population and the subscript 1 indicates association with the sympatric population. For example,  $P_1$  is the number of parasites in the sympatric population (i.e., population 1).

Conversely,

$$\bar{W}_{\text{allopatric}} = qB - P_2 \operatorname{cov}(p_{i2}, h_{i1}) + \frac{1}{H_1} + (1 - q)B(0),$$

where  $\bar{W}_{\text{allopatric}}$  indicates the mean fitness of the allopatric parasite population (i.e., population 2) and  $q$  gives the frequency of genotypes in the allopatric parasite population that can infect one of the host genotypes in the sympatric population.

Assuming that (1)  $P_1 = H_1$  and (2) the covariance between the frequency of parasite genotypes in parasite population 2 (allopatric population) and the frequency of host genotypes in population 1 (sympatric population) is equal to 0 ( $\operatorname{cov}(p_1, h_1) = 0$ ), we get

$$\frac{\bar{W}_{\text{sympatric}}}{\bar{W}_{\text{allopatric}}} = \frac{H_1^2 \operatorname{cov}(p_{i1}, h_{i1}) + 1}{q}$$

as a measure of the degree of relative adaptation of the sympatric and allopatric host populations. Thus, the measure of local adaptation should increase as the overlap in the complement of parasite genotypes ( $q$ ) goes to 0. Note that, if the covariance term in the numerator is equal to 0, the sympatric parasite populations would still show local adaptation, provided the frequency of matching genotypes in the allopatric population ( $q$ ) is less than 1.

#### Inverse Matching-Alleles Model

From equation (15) we have

$$\bar{R}_0 = B - 1 - P \operatorname{cov}(p, h) - \frac{1}{H}.$$

Working as above, we can rewrite the equation as

$$\bar{W}_{\text{sympatric}} = B - 1 - P_1 \operatorname{cov}(p_{i1}, h_{i1}) - \frac{1}{H_1}$$

for the mean fitness of the sympatric parasite population, given the assumption that hosts must match parasite genotypes to resist infection. For the mean fitness of an allopatric population, we get

$$\bar{W}_{\text{allopatric}} = qB \left[ 1 - P_2 \text{cov}(p_{i2}, h_{i1}) - \frac{1}{H_1} \right] + (1 - q)(B).$$

Assuming that  $\text{cov}(p_{i2}, h_{i1})$  is equal to 0 and that the number of matching host and parasite genotypes are equal ( $P_1 = H_1$ ), the ratio of mean fitnesses for sympatric and allopatric populations becomes

$$\frac{\bar{W}_{\text{sympatric}}}{\bar{W}_{\text{allopatric}}} = \frac{H_1 - H_1^2 \text{cov}(p_{i1}, h_{i1}) - 1}{H_1 - q}.$$

Local adaptation by the sympatric population requires that the right-hand side is greater than 1, which is when

$$q > H_1^2 \text{cov}(p_{i1}, h_{i1}) + 1,$$

which requires that the covariance term is negative. If the covariance is equal to 0, then the sympatric parasite population would seem to be locally maladapted for all  $q < 1$ . Hence, in contrast to the MAM, reducing the overlap in the genotypic compositions of the sympatric and allopatric parasite population leads to local maladaptation, rather than local adaptation, by the parasite population.