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THE DYNAMICS OF RECIPROCAL SELECTIVE SWEEPS OF HOST RESISTANCE AND A PARASITE COUNTER-ADAPTATION IN *DROSOPHILA*

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Host–parasite coevolution can result in consecutive selective sweeps of host resistance alleles and parasite counter-adaptations. To illustrate the dynamics of this important but little studied form of coevolution, we have modeled an ongoing arms race between *Drosophila melanogaster* and the vertically transmitted sigma virus, using parameters we estimated in the field. We integrate these results with previous work showing that the spread of a resistance allele of the *ref(2)P* gene in the host was followed by the spread of a virus genotype, which overcomes this resistance. In line with these observations, our model predicts that there can be rapid selective sweeps in both the host and parasite, which can drive large changes in the prevalence of infection. The virus will tend to be ahead in the arms race, as incomplete dominance slows down host adaptation and selection for host resistance is weaker than selection for parasites to overcome resistance—the "life-dinner" principle. This asymmetry in the adaptation rates results in a partial sweep of the host resistance allele, as it loses its advantage part way through the selective sweep. This well-understood natural system illustrates how the outcome of host–parasite coevolution is determined by different population genetic parameters in the field.

KEY WORDS: **Cost of infection, dominance, life dinner principle, partial sweep, speed, selective sweep.**

The fitness of hosts and their parasites is intimately linked—the parasite's fitness relies on it being able to infect a host, whereas the host's fitness is reduced by the presence of the parasite. This conflict of interest may result in antagonistic coevolution, where the host evolves resistance to the parasite who in turn may develop counter-adaptations to overcome this resistance. This process can result in a range of evolutionary scenarios, including stable, cyclical, or chaotic polymorphisms (as reviewed in May and Anderson 1983). Alternatively, alleles may be fixed through a selective sweep, where an advantageous allele is driven to fixation through directional selection.

When coevolution occurs through reciprocal selective sweeps, the spread of a resistance allele in the host population is followed by the spread of a parasite allele that overcomes this resistance (or vice versa). In the literature on plants, the parasite alleles are conventionally referred to as virulent and avirulent. The virulent parasites can infect all hosts, but the avirulent parasites can only infect susceptible ones, as originally described by Flor (1956). In this situation, we expect the resistance and virulence alleles to spread to fixation under directional selection in a selective sweep, unless either allele is sufficiently costly to prevent its fixation.

EVOLUTION
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Selective sweeps are clearly of great importance in the plant kingdom. In agriculture (reviewed in Thompson 1994), crop breeding for resistance has led to dramatic "boom and bust" cycles of selective sweeps in crop pathogens (Suneson 1960; Mcdonald and Linde 2002). For example, the introduction of resistance genes to powdery mildew (*Erysiphe graminis*) in barley (*Hordeum vulgare*) only provided resistance for 2–5 years, before virulent clones took over (Brown et al. 1997). Patterns of sequence diversity at virulence loci (Barrett et al. 2009) and local adaptation (Thrall et al. 2002) suggest that selective sweeps may also play a role in a natural system, wild flax (*Linum marginale*) and flax rust (*Melampsora lini)*. Selective sweeps are also often observed in experiments where microbes and viruses coevolve in the test tube and changes in allele frequencies can be directly observed (e.g., Chao et al. 1977; Buckling and Rainey 2002). Indeed, directional selection and frequency-dependent processes such as balancing selection are not mutually exclusive but rather can frequently co-occur in the same system, as has recently been shown in work on phage–bacteria interactions (Paterson et al. 2010; Gomez and Buckling 2011; Hall et al. 2011).

In invertebrates, evidence for persistent directional selection, rather than fluctuating or balancing selection, has come from work on the molecular evolution of genes in the immune system (Jiggins and Kim 2007; Lazzaro 2008; Obbard et al. 2009a, 2011). These genes are commonly under intense directional selection in insects such as *Drosophila melanogaster* and *D. simulans* (Obbard et al. 2009b), whereas evidence of the long-term balancing selection seen in some plant immune genes (Tiffin and Moeller 2006) and vertebrate major histocompatibility complex (MHC) genes (Hughes and Yeager 1998) is rare. However, compared to frequency-dependent dynamics (Little 2002; Decaestecker et al. 2007; Salathe et al. 2008; Jokela et al. 2009), there are very few case studies of selective sweeps in animal host–parasite interactions. Notable exceptions are the butterfly *Hypolimnas bolina,* in which the invasion of a male-killing bacterium was followed by a selective sweep in the host population of a resistance gene that prevents *Wolbachia* killing males (Charlat et al. 2007; Hornett et al. 2009), and *Drosophila* and the sigma virus, which is the focus of this study. Because there is so little work on these systems, their behavior is poorly understood. Our aim in this study is therefore to understand the factors that control the dynamics of genes in the host and parasite populations by modeling the interaction and measuring key parameters in the field.

Overall, there appears to be the implicit notion in this field that recurrent selective sweeps may be less important in shaping coevolution or less rewarding to study then frequency-dependent selection. For example, in a review of one of the most influential model systems, *Daphnia* and its parasites, Ebert (2008) states that selective sweeps are unlikely to be a mode of rapid coevolution in multicellular hosts. The reason for this view is that selective sweeps rely on new mutations that increase or overcome host resistance, and the rate at which such mutations arise may be low. Furthermore, new mutations will be rare, and even under strong selection it can take many generations for these new alleles to reach an appreciable frequency.

The aim of this study is to illustrate the dynamics of an arms race consisting of successive selective sweeps in a natural insect virus system, *D. melanogaster* and the sigma virus. A powerful and unusual feature of this interaction is that we can estimate many of the important parameters in the wild. This has allowed us to combine a model of coevolution between the host and virus with measurements of epidemiological parameters from the field and laboratory and genetic data, to illustrate how population genetic principles determine the outcome of host–parasite evolution in this system. For example, we can examine the relative speed of adaptation in the host and parasite populations, and the impact that the coevolutionary process can have on the prevalence of infection.

SELECTIVE SWEEPS IN *DROSOPHILA* AND THE SIGMA VIRUS

The sigma virus is a parasite of *D. melanogaster* that reduces the egg viability and overwintering survival of infected flies (Fleuriet 1981a,b). It is exclusively vertically transmitted through both eggs and sperm, and is therefore completely host-specific. This also means that, unlike parasites that are only vertically transmitted via the maternal lineage, it can still invade populations even if it harms its host (Fine 1975; Wayne et al. 2011). A polymorphism in the host gene *ref(2)P*—where a complex mutation has transformed a glutamine-asparagine group to a single glycine—reduces the viral replication rate (Brun and Plus 1980; Contamine et al. 1989; Dru et al. 1993; Wayne et al. 1996; Bangham et al. 2007). The mechanisms of this resistance are unclear, although the ref(2)P protein is known to physically interact with the viral P protein (Wyers et al. 1993). The *ref(2)P* polymorphism greatly reduces the rate of vertical transmission, both when the virus is transmitted by the mother through the egg and by the father through sperm (Bangham et al. 2008a). All of the genetic variation in maternal transmission can be explained by this polymorphism, whereas other unidentified host genes also affect paternal transmission (Bangham et al. 2008a,b).

Field isolates of the virus fall into two categories—a virulent (infective) type that infects flies irrespective of their *ref(2)P* genotype and an avirulent type that infects only susceptible flies (Fleuriet 1988). This interaction of a host resistance allele and a parasite virulence allele is an example of the classical gene-for-gene model. Note that virulence is defined here as the capacity to overcome host resistance, in line with literature on gene-for-gene systems.

We have a clear picture of how natural selection has acted on these host and parasite polymorphisms. Based on comparative

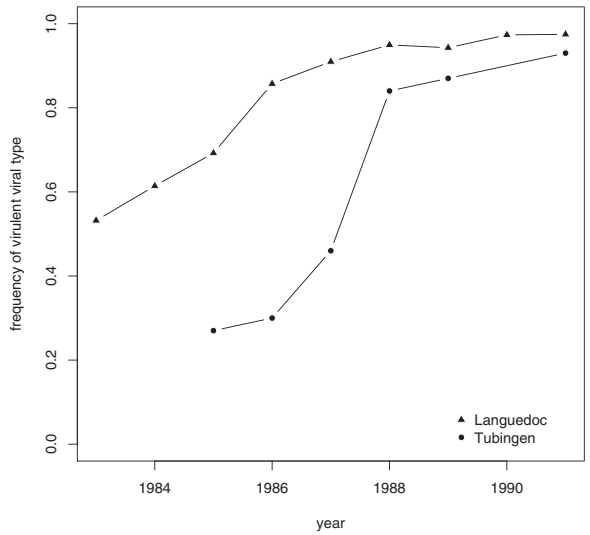

Figure 1. Relative frequency of virulent sigma virus isolates that are not affected by the host resistance gene *ref(2)P* in two wild populations (data from Fleuriet and Sperlich 1992; Fleuriet and Periquet 1993).

sequence analysis, it is clear that the resistant allele of *ref(2)P* arose by mutations in the susceptible allele (Wayne et al. 1996; Bangham et al. 2007). There is very little variation in the nucleotide sequence of the resistant alleles relative to the susceptible alleles, which provides strong evidence that the resistant allele has recently increased in frequency under directional selection (Wayne et al. 1996; Bangham et al. 2007). Direct observations of the frequencies of the virulent and avirulent types of the sigma virus also suggest directional selection. As shown in Figure 1, populations in Germany and France both experienced a large increase in the frequency of the virulent viral type in the 1980s, suggesting an ongoing selective sweep (Fleuriet and Sperlich 1992; Fleuriet and Periquet 1993). These resistance and virulence polymorphisms therefore appear to be engaged in an arms race, with both mutations increasing in frequency under strong directional selection.

To understand the epidemiology and evolutionary dynamics of this arms race, we constructed an epidemiological model that describes the spread of the virus through host populations. We measured key parameters—prevalence and transmission frequencies—in the field. We then tested whether our model could explain the patterns observed in the field.

Materials and Methods

VIRAL PREVALENCE AND TRANSMISSION RATE

The prevalence of sigma virus, and its transmission rate in male and female hosts, was estimated in a field population in Athens, Greece. Flies were collected over a 5-day period in October 2007 from fruit baits placed in an urban area ca. 300 m in diameter. To measure transmission frequencies under field conditions, we placed flies individually in food vials and allowed them to reproduce, as described in detail in Wilfert and Jiggins (2010). For male transmission, we added two virgin females from an uninfected outbred laboratory population originally collected in Athens to each male, whereas females were assumed to have mated in the field. The wild flies and their offspring vials were transferred to the laboratory and tested for sigma virus infection by exposing them to pure CO_2 at 12°C for 15 min. Although uninfected flies quickly recover from the CO_2-induced anesthesia, it causes paralysis or death in infected flies (Brun and Plus 1980). The infection rate of offspring was used to estimate the rate of vertical transmission. Infected field-caught flies that failed to produce offspring (six females and one male out of 900 flies) were therefore included in the estimate of prevalence but not transmission.

To exclude false positives, we confirmed the presence of sigma virus in wild flies where the results of the CO_2 assay were not clear (either in CO_2 paralyzed flies where we did not obtain infected offspring to verify the infection status of the parent, or occasional flies where the paralysis phenotype was unclear); detailed methods are provided in the Appendix S1. Of the 39 individuals assayed, 11 were negative for sigma virus RNA. We genotyped all flies for the *ref(2)P* gene and used a length polymorphism in the *drosomycin* gene to discriminate between *D. melanogaster* and *D. simulans* females as described in Wilfert and Jiggins (2010).

The mean rate at which infected males and females transmit the virus to their offspring was estimated using a general linear model with a quasibinomial error distribution, as this allows us to correctly weight the estimates by the number of offspring produced by each parent. Confidence intervals of these estimates were obtained by bootstrapping. We resampled infected individuals with replacement 1000 times and from each of these resampled datasets, we estimated the mean transmission using the general linear model. The limits of the 95% confidence interval were taken as the 2.5 and the 97.5 percentiles of the bootstrap distribution. Males and females were analyzed separately.

POPULATION GENETIC MODEL OF *DROSOPHILA MELANOGASTER* AND SIGMA

We have constructed a deterministic population genetics model of the inheritance of the vertically transmitted sigma virus, assuming an infinite population size, a haploid virus, and discrete generations (Fig. 2; a simpler version of the model was used to simulate the invasion of a related virus into populations of *D. obscura* [Longdon et al. 2011]). In this model, the proportion of infected male and female adults in generation i is P_i. The fertility of an infected individual is determined relative to an uninfected individual. Infected flies may suffer a reduction in fertility as compared to uninfected flies by a factor $(1 - C)$ $(C \leq 1)$. The

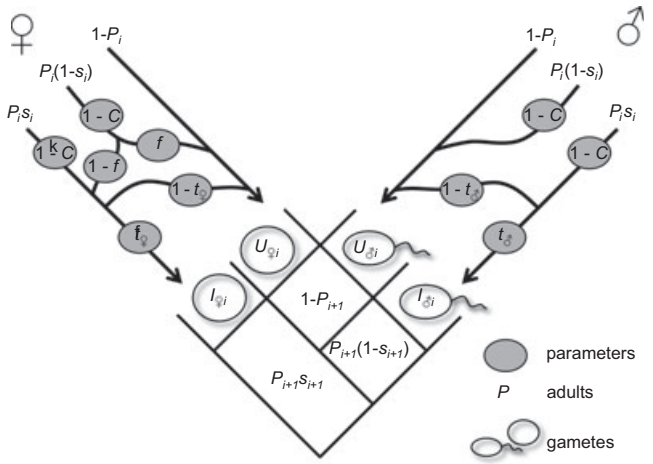

Figure 2. Schematic representation of the model of sigma virus transmission. In the parental generation *i*, infected (frequency P_i) and uninfected (frequency $1 - P_i$) adults produce infected (I_i) and uninfected (U_i) gametes depending on the relative fertility of infected individuals ($1 - C$) and the sex-specific transmission rate ($t_♀$ and $t_♂$). The combination of these gametes results in the next generation of infected adults (frequency P_{i+1}) and uninfected adults ($1 - P_{i+1}$). An added complexity is that when an individual is infected by its father rather than its mother, it transmits the virus at a lower rate. Flies infected from their mother are "stabilized" and occur at a frequency s_i among infected flies. Males that were infected by their father (i.e., not stabilized) never transmit the virus, and females have a reduced transmission rate of $t_♀$ multiplied by the factor $1 - f$.

frequency at which females transmit the sigma virus is greater than the frequency at which males transmit it to their offspring (Brun and Plus 1980), which is reflected in the model by separate male and female transmission frequencies. Furthermore, the frequency at which a fly transmits the virus is altered if the fly inherited the sigma virus from its father rather than its mother. Males that inherited the virus from their father do not transmit it to any of their offspring, whereas females that inherited the virus from their father transmit it at a reduced frequency of $t_♀$ multiplied by a factor $(1 - f)$ $(f \leq 1)$ (L'héritier 1970, but see Wayne et al. 2011). To account for these differences, we split the infected population in generation i into a fraction s_i (the "stabilized" individuals) that inherited the virus from their mother (or both parents) and a fraction $(1 - s_i)$ that inherited the virus only from their father. For simplicity, we have ignored that ~6% of flies that inherit the virus from their maternal grandfather also have reduced frequencies of transmission (Fleuriet 1982). The proportions of infected and uninfected eggs ($I_{♀i}$ and $U_{♀i}$) in generation i is given by the following equations, in which we divide by the sum of the numerators, w (note that $w_♀ = w_♂ = 1 - P_i C$):

$$I_♀ i = \frac{(P_i s_i + P_i(1 - s_i)(1 - f))(1 - C)t_♀}{w} \quad (1)$$

$$U_♀ i = \frac{1}{w}\big((1 - P_i) + P_i(1 - s_i) f(1 - C) + P_i(s_i + (1 - s_i)(1 - f))(1 - C)(1 - t_♀)\big). \quad (2)$$

The proportions of infected and uninfected sperm in generation i ($I_{♂i}$ and $U_{♂i}$) is obtained in a similar fashion:

$$I_♂ i = \frac{P_i s_i (1 - C) t_♂}{w} \quad (3)$$

$$U_{i♂} = \frac{(1 - P_i) + P_i(1 - s_i)(1 - C) + P_i s_i (1 - C)(1 - t_♂)}{w}. \quad (4)$$

With this, the proportion of infected individuals in generation $i + 1$, P_{i+1}, is calculated based on the proportion of infected and uninfected gametes:

$$P_{i+1} = I_{♀i} + I_{♂i} U_{♀i}. \quad (5)$$

At equilibrium, the proportion of infected and stabilized flies will not change between generations, that is, $P_{i+1} = P_i$ and $s_{i+1} = s_i$. To determine these equilibrium values a system of two equations for P and s has to be solved:

$$Ps = I_♀ \quad (6)$$

$$P(1 - s) = I_♂ U_♀. \quad (7)$$

From (6) and (1), the equilibrium proportion of infected flies that are stabilized, s^*, can be written as a function of P as:

$$s^* = \frac{I_♀}{P} = \frac{t_♀(1 - C)(1 - f)}{1 - PC - f t_♀(1 - C)}. \quad (8)$$

We can derive an equation for the equilibrium prevalence P^* by substituting equation (8) into equation (5), which is based on equations (1)–(4). With this, the analytic solution for the equilibrium prevalence P^* is a cubic function of the form

$$aP^{*3} + bP^{*2} + cP^* + d = 0. \quad (9)$$

The polynomial does not have a trivial symbolic solution, but can readily be solved numerically (see Appendix S1 for polynomic terms). To examine whether the equilibria are stable, we used simulations in which the initial prevalence was 10^{-6} either side of the equilibrium. We examined the change in prevalence after 10^4 generations. This allowed us to determine the invasion conditions (for the equilibrium of $P^* = 0$) and the stability of any internal equilibria ($0 < P^* \leq 1$). We found that across the parameter space shown in the figures, when there was one internal equilibrium it was always stable, but when there were two internal equilibria the upper one was stable, and the lower one was unstable.

ESTIMATION OF TRANSMISSION RATES AND THE COST OF INFECTION

In the field, we cannot directly measure the proportion of nonstabilized individuals s, nor the reduced rate $1-f$ at which nonstabilized females transmit the virus. Instead, the transmission frequencies, $T_{♀obs}$ and $T_{♂obs}$, which we measure in the field, include transmission from both stabilized and unstabilized individuals. We can calculate the expected $T_{♀obs}$ and $T_{♂obs}$ from our model by averaging over transmission from stabilized and unstabilized individuals:

$$T_{♀} = \frac{t_{♀}P_i s_i + t_{♀}(1-f)P_i(1-s_i)}{P_i} = t_{♀}s_i + t_{♀}(1-f)(1-s_i) \tag{10}$$

$$T_{♂} = \frac{t_{♂}P_i s_i}{P_i} = t_{♂}s_i. \tag{11}$$

At equilibrium, the transmission frequencies of stabilized flies, $t_{♀}$ and $t_{♂}$ can be derived from $T_{♀obs}$ and $T_{♂obs}$ by substituting s^* as in equation (8) into equations (10) and (11) solving them for $t_{♀}$ and $t_{♂}$.

$$t_{♀} = \frac{T_{♀}(1-P_iC)}{T_{♀}f(1-C)+(1-f)(1_i-P_iC)} \tag{12}$$

$$t_{♂} = \frac{T_{♂}(1-CP_i)}{T_{♀}(1-C)}. \tag{13}$$

We measured P, $T_{♀}$, and $T_{♂}$ in the field. For the stabilization parameter $1-f$, we have used Fleuriet's (1988) measure of $1-f=0.8$.

The reduction in fertility of infected flies, $1-C$, can only be exactly estimated when the population is at equilibrium. At equilibrium it is possible to simplify the model by fixing $s=1$ and replacing $t_{♀}$ and $t_{♂}$ with $T_{♀obs}$ and $T_{♂obs}$. Therefore, at equilibrium the proportions of infected and uninfected eggs ($I_{♀i}$ and $U_{♀i}$) eggs and sperm ($I_{♂i}$ and $U_{♂i}$) in generation i is given by the following equations:

$$I_{♀i} = \frac{P_i(1-C)T_{♀}}{w} \tag{14}$$

$$U_{♀i} = \frac{(1-P_i)+P_i(1-C)(1-T_{♀})}{w} \tag{15}$$

$$I_{♂i} = \frac{P_i(1-C)T_{♂}}{w} \tag{16}$$

$$U_{♂i} = \frac{(1-P_i)+P_i(1-C)(1-T_{♂})}{w}. \tag{17}$$

This is equivalent to our earlier model, as at equilibrium the proportion of stabilized individuals s_i does not change between generations, so the field measures of $T_{♀obs}$ and $T_{♂obs}$ account for the effect of stabilization. At equilibrium, the relative fertility of infected flies, $1-C$, can thus be estimated from these field estimates by solving the recursion equation $\Delta P = I_i + I_iU_i - P_i$, for C using equations (14–17). C is described by the quadratic equation

$$\begin{aligned}&\left(P_i^2 - P_it_{♀} - P_it_{♂} + P_it_{♀}t_{♂}\right)C^2\\&+(-2P_it_{♀}t_{♂} - 2P_i + P_it_{♀} + t_{♀} + P_it_{♂} + t_{♂})C\\&+P_it_{♀}t_{♂} - t_{♀} - t_{♂} + 1 = 0.\end{aligned} \tag{18}$$

which, with $aC^2+bC+c=0$, has the solution

$$C = \frac{-b \pm \sqrt{b^2-4ac}}{2a}. \tag{19}$$

When prevalence is not at equilibrium, we can calculate C by introducing a factor x, so that $P_{i+1} = xP_i$, to adjust for changes in prevalence as the virus increases or decreases in frequency. With this, we can calculate C outside of equilibrium by the quadratic equation

$$\begin{aligned}&\left(xP_i^2 - P_it_{♀} - P_it_{♂} + P_it_{♀}t_{♂}\right)C^2\\&+(-2P_it_{♀}t_{♂} - 2xP_i + P_it_{♀} + t_{♀} + P_it_{♂} + t_{♂})C\\&+P_it_{♀}t_{♂} - t_{♀} - t_{♂} + x = 0.\end{aligned} \tag{20}$$

This equation can be solved as shown for (18). At equilibrium, x equals 1 and (20) is equivalent to (18). We have not estimated x in the field, but the simulations of sigma virus coevolution described in the Results section below suggest that prevalence changes little from generation to generation around the observed value of $P_{obs}=0.103$, with x ranging from 0.98 to 1.05. Therefore, if we assume $x=1$, this approach gives a crude approximation of the cost of infection outside of equilibrium that can be compared with laboratory estimates.

Results

INVASION CONDITIONS

The model allows us to investigate the circumstances under which sigma virus can invade a population. The lowest transmission frequencies that allow the virus to invade can be obtained by assuming that the virus does not reduce the fertility of infected flies ($1-C=1$) and that stabilized and nonstabilized females transmit the virus at the same rate ($1-f=1$). Under these favorable conditions, the virus can invade a population whenever

$$0 < \frac{t_{♀}t_{♂} + t_{♀} - 1}{t_{♀}^2 t_{♂}}. \tag{21}$$

Therefore, for the virus to invade an uninfected population, both sexes must transmit the virus, even though male transmission can be close to zero if female transmission is close to 1, as the virus

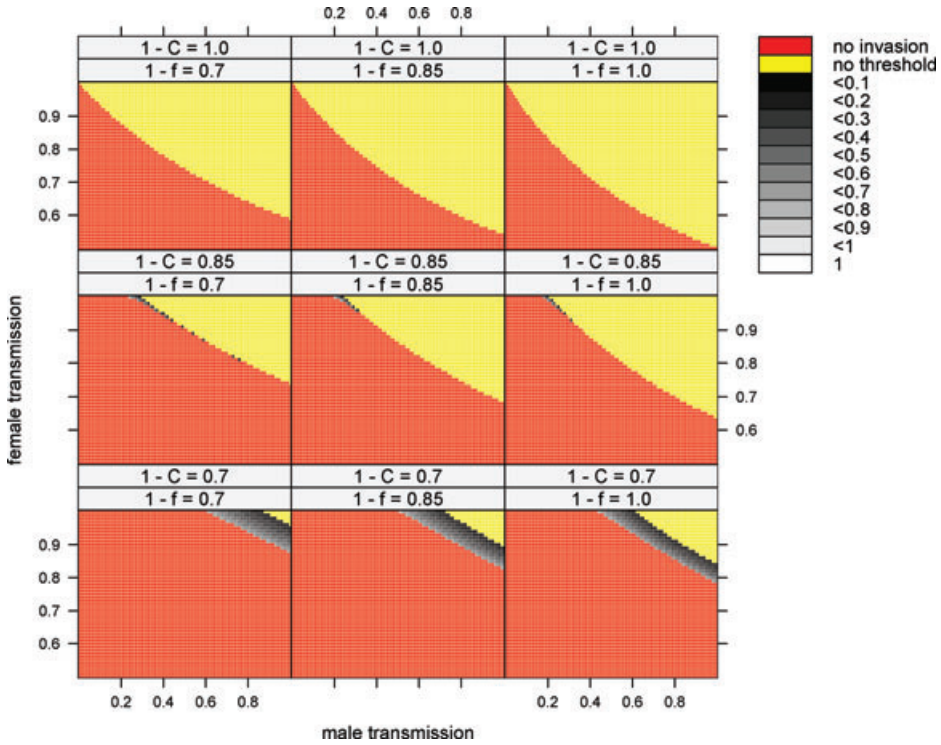

Figure 3. **Invasion threshold. In the combinations of parameters shown in gray, the virus must exceed a threshold prevalence to invade the population. In the region shown in yellow, the virus will invade irrespective of the starting prevalence. In the region shown in red, it will never invade. In the top panel the virus does not affect the fertility of infected flies, and in the bottom panel it causes a 30% reduction in fertility ($1 - C = 0.7$, 0.85, and 1). In the left hand panel, transmission drops by 30% in nonstabilized flies, and in the right hand panel there is no reduction ($1 - f = 0.7$, 0.85, and 1).**

invades if $t_{♂} > (1 - t_{♀})/t_{♀}$. Female transmission on the other hand has to be larger than 0.5, even if males transmit the virus to all their offspring (the virus invades if $t_{♀} > 1/(t_{♂} + 1)$).

Without this simplification, the results of an analytical invasion analysis have no simple interpretation as the equilibrium prevalence is described by a cubic equation. Instead, we performed a numerical invasion analysis by simulation as shown in Figure 3. The reduced fertility of infected flies, $(1 - C)$, plays a crucial role, with the virus only being able to establish if it causes small fitness reductions. A reduction in the rate at which nonstabilized females transmit the virus $(1 - f)$ also reduces the parameter space in which sigma can invade—transmission frequencies have to be higher for the virus to invade the population.

There are three equilibria for prevalence in this system, the trivial equilibrium of 0 as well as two internal ones. The equilibrium prevalence $P*$ and 0 are locally stable, whereas the lower internal equilibrium is unstable. The lower unstable internal equilibrium represents a threshold prevalence that the virus must exceed to invade the population, and if the virus is introduced below this threshold it declines in prevalence to extinction. If the virus has no effect on the fertility of flies ($1 - C = 1$), then there is no invasion threshold (Fig. 3). However, as the fertility of infected flies declines ($1 - C < 1$), there is a region of parameter space where the virus can only establish if it is introduced at a high enough initial prevalence (Fig. 3). It should be noted that both transmission rates and the harm inflicted by the virus, that is, the relative fertility of infected flies, may change over time. This means that invasion may have occurred under a different set of conditions ($t_{♀}$, $t_{♂}$, $1 - C$, and $1 - f$) then the ones observable in the field at any one time.

This invasion threshold arises because the virus is vertically transmitted by both sexes, and the transmission rate is lower if a fly was infected by its father. This results in the mean rate at which an infected fly produces infected gametes being dependent on the prevalence of the virus in the previous generation. As the prevalence increases, a larger proportion of the infected flies in the population are stabilized because infected males are more often mating with infected females. As stabilized flies transmit the virus at a higher rate, this results in infected flies having a higher average transmission rate when the prevalence is higher. In other words the transmission rate from a parent to its gametes is positively frequency dependent. Thus, if the virus is introduced into a naïve population at a prevalence below the threshold for its given transmission values, the virus goes extinct as the production of infected gametes cannot outweigh the reduction in fertility of infected individuals. However, if the same virus is introduced at

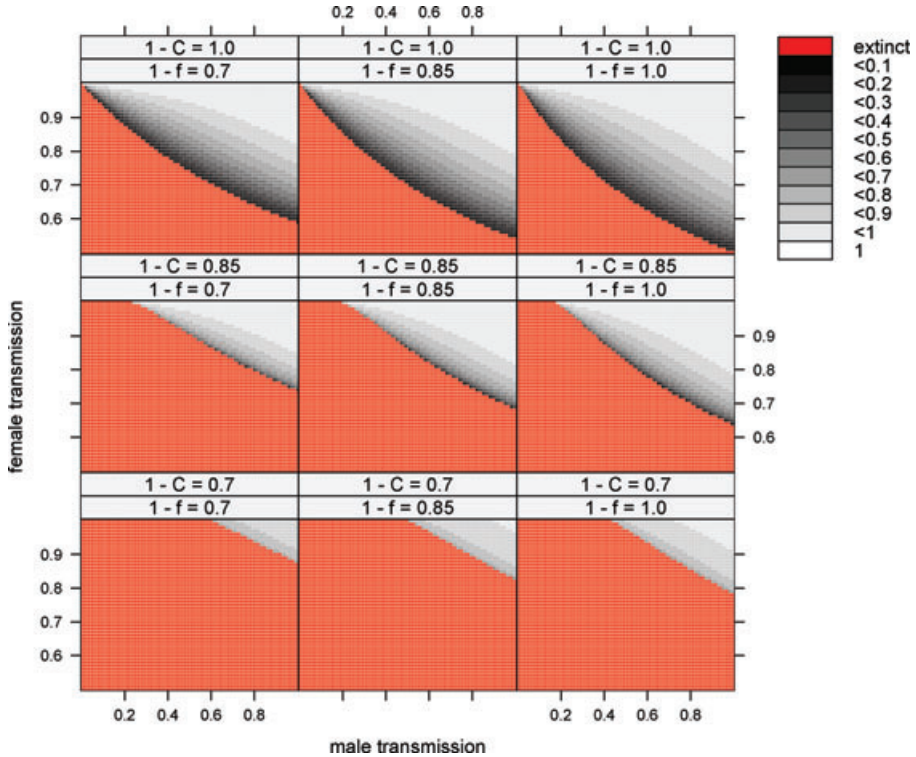

Figure 4. The equilibrium prevalence, *P, of the sigma virus as a function of female and male transmission frequencies. The range of parameters is described in Figure 3.**

a prevalence equal or higher than the threshold, more infected individuals are produced every generation and virus prevalence increases. It should be emphasized that the invasion threshold only exists for a narrow range of parameters.

EQUILIBRIUM PREVALENCE

To examine how different parameters affect the prevalence of the sigma virus, we calculated the equilibrium prevalence (P^*). As expected, increasing the transmission frequency or reducing the cost of the infection leads to an increase in prevalence (Fig. 4). Interestingly, unless the cost of infection is very low, in nearly the whole parameter space the virus either cannot invade or spreads to infect nearly 100% of the population (Fig. 4). This is also the case if infected individuals have a fertility advantage ($1 - C > 1$) (data not shown). We used simulations to explore the effects of genetic drift on the equilibrium prevalence, and the results show that this deterministic model is expected to provide a good approximation of *D. melanogaster* populations (see Appendix S1; Table S2).

FIELD MEASURES OF PREVALENCE AND TRANSMISSION

We measured the prevalence, P_{obs}, and the sex-specific transmission frequencies, $T_{♀obs}$ and $T_{♂obs}$, in a population of *D. melanogaster* in Athens, Greece. In the field, we cannot directly measure the proportion of nonstabilized individuals *s,* nor the reduced rate $1 - f$ at which nonstabilized females transmit the virus. Instead, the field measured transmission frequencies $T_{♀obs}$ and $T_{♂obs}$ are averaged over stabilized and nonstabilized individuals. As reported in Wilfert and Jiggins (2010), the prevalence P_{obs} was 10.3% ($n = 900$, 95% CI = 8.3–12.3%), and was the same between sexes ($\chi^2 = 0.33$, df = 1, $P = 0.57$, $n_{♀} = 456$, $n_{♂} = 444$). The mean female transmission rate $T_{♀obs}$ was 83.3% (95% CI = 71.2–93.1%), and mean male transmission was significantly lower with $T_{♂obs} = 46.9\%$ (95% CI = 35.0–59.0%; generalized linear model with quasi-binomial error structure, $t_{79} = 3.975$, $n_{♀} = 39$, $n_{♂} = 48$, $P < 0.001$) (Wilfert and Jiggins 2010).

If we assume our field population were at equilibrium, the fertility of infected flies relative to uninfected flies, $1 - C$, would be 0.77 (95% CI: 0.69–0.89). Based on our simulations, the fertility $1 - C$ will be in the range of 0.75–0.81 in this population if it is not at equilibrium (see section Methods for details). The true cost that infected flies pay will be overestimated while the virus is invading and underestimated if the virus prevalence is declining.

The field measured transmission frequencies, $T_{♀obs}$ and $T_{♂obs}$, are averaged over stabilized and nonstabilized individuals. Based on field measures, the transmission rates of stabilized flies are $t_{♀} = 89.4\%$ and $t_{♂} = 71.4\%$ in this population at equilibrium and may typically range from 88.8% to 89.7% and 68.0% to 73.0%, respectively, based on simulations. To compare these values to transmission rates measured under controlled conditions

in the laboratory in flies homozygous for the susceptible allele of the *ref(2)P* resistance gene, we calculated transmission rates for a subset of flies with this genotype. We found that the values thus estimated from the field are nearly identical to those measured in the laboratory with $t_{♀Sus} = 0.998$ and $t_{♂Sus} = 0.702$ being almost identical to Bangham et al.'s (2008a) laboratory estimates (maternal rate = 0.99, paternal rate = 0.67).

IS THE SIGMA VIRUS AT EQUILIBRIUM?

In most parameter combinations, the virus either cannot invade or spreads to high levels of prevalence close to fixation (Fig. 3). Therefore, it is surprising that only 10.3% of flies are infected in the field population that we studied, a value typical for this virus (Carpenter et al. 2007). This can be explained if the population is below the equilibrium prevalence.

To examine this hypothesis, we tested whether the observed parameters are compatible with the population being at equilibrium. This is possible because for each observed value of P_{obs}, $T_{♀obs}$, and $T_{♂obs}$ there is only one possible equilibrium, and this can be either stable or unstable (this arises because $T_♀$ and $T_♂$, which combine transmission from stabilized and unstabilized individuals, change with the prevalence of infection). Equations (12) and (13) allow us to solve equation (10) using the field parameters under the assumption that this population is at equilibrium. We found that, with the parameters we measured in the field ($T_{♀obs} = 83.3\%$, $T_{♂obs} = 46.9\%$) as well as $1 - f = 0.8$ (Fleuriet 1988), the equilibrium prevalence should be much higher than the observed field prevalence ($P^* = 0.85$). Therefore, our field estimates of transmission are not compatible with this population being at a stable equilibrium prevalence.

We used nonparametric bootstrapping to assess the robustness of this result. For each bootstrap replicate, we resampled with replacement from all the flies we collected to recalculate P, resampled from the infected males to recalculate $T_♂$, and resampled from the infected females to recalculate $T_♀$. We then checked whether these estimates were compatible with a stable equilibrium as described above. Out of 10,000 bootstrap replicates, 3.55% resulted in biologically irrelevant parameter estimates of vertical transmission frequencies > 1. Of the remainder, 9.88% were compatible with a stable equilibrium. Therefore, the data suggest that this population is probably not at stable equilibrium prevalence, but we cannot formally reject this hypothesis. This suggests that parameters which affect viral prevalence vary through time or space, which could be due to abiotic influences such as temperature or due to the recent evolutionary changes that we know have changed viral transmission rates (Fig. 1).

MODELLING THE REF(2)P ARMS RACE

We extended our model to simulate an arms race between the fly gene *ref(2)P* and the sigma virus. As described in the Introduction, sequence diversity data suggest that a mutation in *ref(2)P* that makes flies resistant to the virus swept through fly populations (Bangham et al. 2007). Recently, this was followed by the spread of a viral genotype that overcomes this resistance based on field data (Fleuriet and Sperlich 1992; Fleuriet and Periquet 1993). This was modeled by a straightforward extension of equations (5) and (6) that included the two *ref(2)P* alleles and the two viral types (details in Appendix S1). We also repeated the simulations including the effects of genetic drift (see Appendix S1; Fig. S1), which produced similar results to the deterministic model described below.

The susceptible and resistant alleles of the *ref(2)P* gene cause the virus to have a high or low frequency of transmission ($t_{♀/♂Sus}$ and $t_{♀/♂Res}$, respectively, in homozygous flies). Flies that are heterozygous have an intermediate frequency of transmission depending on the dominance, d, of the resistant allele (ranging from $d = 0$ if recessive and to $d = 1$ if dominant). We assume that a mutation arose in the viral population that produced a virulent viral type that is not affected by *ref(2)P* (it is transmitted at the higher rate $t_{♀/♂Sus}$ in all flies). Offspring are modeled to inherit the maternal viral type as Ohanessian-Guilleman (1959, 1963) has shown that, when both the mother and father are infected, the maternal viral type is inherited with rare exceptions. We assume that there is no cost associated with the host carrying the resistance or the pathogen carrying the virulence allele.

In our simulations we used field estimates of transmission (based on a subset of data from homozygous susceptible flies and eqs. 12 and 13, $t_{♀Sus} = 0.998$, $t_{♂Sus} = 0.702$), which are strikingly close to Bangham et al.'s (2008a) experimental results (maternal rate = 0.99, paternal rate = 0.67). We are unable to estimate the effect of the resistance gene on transmission from our field data, so we used the laboratory estimate of a 90% reduction in the transmission rate in homozygous resistant flies relative to susceptible flies (Bangham et al. 2008a). The resistance allele is largely recessive ($d = 0.24$) in females, and we assumed that dominance is the same in males (Bangham et al. 2008a).

Starting with a population at equilibrium, we first introduced only the resistance mutation at a frequency of 10^{-6} (this is equivalent to a single mutation assuming an effective population size of one million for *D. melanogaster* [Andolfatto and Przeworski 2000]). The host allele experiences only a partial sweep. Under these conditions, the resistant allele reaches an equilibrium frequency of 48.7%, as it loses its selective advantage once the avirulent virus has gone to extinction. Genotyping the Athens field population, we found that the resistant allele of *ref(2)P* was at a frequency of 24.0% ($n = 835$) (Wilfert and Jiggins 2010).

Once resistance is common, the virulent viral type can invade extremely fast. In our simulations we introduced this viral type at the same time as the resistant mutation, but the results are very similar if it is introduced at a later time point. For example, the

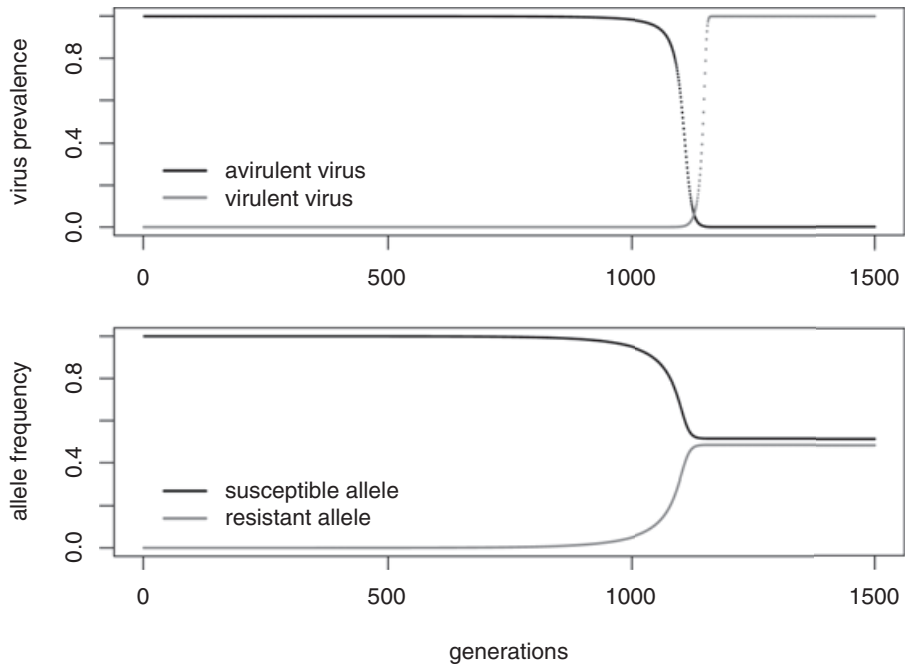

Figure 5. Simulation of the coevolution of the virus and host. The virus prevalences (virus sensitive to host resistance = black, virus insensitive to host resistance = gray) are shown in panel (A) and the allele frequencies of the host (susceptible = black, resistant = gray) are shown in panel (B). Relative fertility $1 - C = 0.8$ and stabilization parameter $1 - f = 0.8$.

maximum change in prevalence in one generation is 6.14%, both when the virulent viral type is introduced at the start (Fig. 5) and when it is introduced after the avirulent type has already gone to extinction (data not shown).

We found that the prevalence of the virus can change dramatically when a coevolutionary arms race is in progress (Fig. 5). When the virulent virus is introduced before the avirulent virus has gone to extinction, the avirulent virus decreases in prevalence due to the spread of resistant hosts while the virulent type increases. However, the time lag while the virulent virus spreads means that the total prevalence can be considerably below the equilibrium for many generations (Fig. 5).

There are rapid changes in allele frequencies in both the host and parasite populations (Fig. 5). However, the speed of adaptation in the host and parasite populations is different (Fig. 5). In the first phase of the arms race, the host resistance allele is increasing in frequency faster than the virulence allele in the viral population, despite introducing the host and viral mutations simultaneously. However, this pattern is then reversed as an increasingly resistant host population selects more strongly for the virulent viruses (Fig. 5, after 1136 generations). The maximum rate of the viral sweep is nearly a magnitude higher than that of the host sweep (the maximum relative increase in allele frequency was 14.3% in the virus and 2.5% in the host population). This pattern is not specific to this simulation, but is found across a wide range of parameters. Therefore, the spread of the host allele tends to be slow and prolonged, and as soon as the host population evolves significant levels of resistance, the virus swiftly counter-adapts.

Why is the virus able to adapt much faster than the host? To explore this, we tested how the selective sweeps are affected by the model's parameters. For these simulations, we used the upper and lower quartiles of the transmission rates ($t_{♀Sus} = 0.98$–1.0, $t_{♂Sus} = 0.55$–0.77; reduction in resistant individuals: 0.88–0.95) and dominance ($d = 0.01$–0.28) reported in Bangham et al. 2008a. For the relative fertility of infected individuals, we used our estimate of $1 - C = 0.75$–0.81. These simulations showed that the difference in speed and strength of selection depends both on the degree of dominance of the resistance allele and the asymmetric fitness benefits gained by resistant hosts and virulent parasites, that is, the "life-dinner" principle (Dawkins and Krebs 1979; see Table S3 for detailed results).

As expected, the host resistance allele sweeps through the population faster and reaches a lower equilibrium frequency when its dominance is higher (Table S3). But even if the resistance mutation where fully dominant ($d = 1$), the maximum relative change in allele frequency in the virus would be higher than in the host (14.8% vs. 5.9% change in allele frequency/generation, respectively). This illustrates the importance of differential fitness gains for host and parasite in this coevolving system. We can measure this effect by calculating the selective advantage of homozygous resistant hosts and virulent viruses. Using our estimated parameter values, the maximum selection coefficient acting on the virulent viral genotype is 14.3% compared to an advantage of 5.1% for

the homozygous resistant flies (the selection coefficient being the advantage of homozygous resistant flies over homozygous susceptible flies).

There are two main factors that affect the "life-dinner" balance in this system: the fertility reduction suffered by infected hosts ($1 - C$) and the parasite transmission rates. Lower transmission rates curb the speed of the viral sweep as compared to the host sweep, whereas an increased cost of infection increases the selection for host resistance (see Table S3). In this system, when combining all the parameter values in these simulations that would favor the host (dominance, transmission, and cost of infection), it would be possible for the host to be "ahead" in the arms race for a prolonged period (Table S3, Fig. S2).

Discussion

Reciprocal selective sweeps are clearly an important mode for antagonistic coevolution in animals and plants. The evidence for this comes mainly from studies of sequence evolution, which have shown that selective sweeps can occur frequently in nature (e.g., Obbard et al. 2006; Bangham et al. 2007; Stukenbrock and Mcdonald 2009). Although these studies have produced clear evidence for the occurrence of selective sweeps, they cannot provide information on the population genetics of this process. Knowledge of population genetic properties, such as the selection coefficients and dominance, is necessary to understand and predict the dynamics of coevolution, such as how fast sweeps may occur or what their impact on parasite prevalence may be. These are empirical questions that need to be addressed in biological systems. To illustrate how these factors determine the outcome of an arms race, we have measured key parameters of a coevolving system and produced a model to show how they determine the outcome of an arms race.

The question of whether it will be the parasite or the host that will be faster to adapt, and thereby "win" the arms race, is one that has inspired many debates (Dawkins and Krebs 1979). Many parasites have a shorter generation time than their hosts, which will often allow them to evolve faster than their hosts (Kaltz and Shykoff 1998), although sometimes it may have no or even the opposite effect (Lively 1999; Gandon and Michalakis 2002). As a vertically transmitted parasite, the generation time of the sigma virus is effectively the same as its host's when considering the spread of an allele through the population. Despite this, it is clear that it has a faster maximum rate of adaption than its host *D. melanogaster*. Our model shows that the maximum rate of spread of the virulent virus, which carries a viral counter-adaptation that allows it to overcome host resistance, is nearly a magnitude faster than that of host resistance, although this advantage can be reduced under extreme parameter values. This agrees with the available molecular data and field surveys. The virulent type of the sigma virus spread from intermediate frequencies to fixation within a decade in two populations in Europe as recently as the 1980s (Fig. 1) (Fleuriet and Sperlich 1992; Fleuriet and Periquet 1993). The speed of viral adaptation predicted by our model and observed in the field by Fleuriet and colleagues is strikingly similar (10–20 years), assuming about 12 host generations per year. A rapid selective sweep or invasion on the same order of magnitude has been demonstrated for a closely related host–parasite system, *D. obscura* and its sigma virus DobsSV (Longdon et al. 2011). We lack direct observations of the change in allele frequencies in the host, but it appears to be much older than the viral counter-mutation. Based on linkage disequilibrium around the *ref(2)P* gene, the resistant allele is between 1000 and 7000 years old (Bangham et al. 2007). Although the virulence mutation in the virus has not been isolated, Carpenter et al. (2007) have estimated that all European samples of the sigma virus shared a common ancestor 214 years ago. As this group contains both the virulent and the avirulent viral type (L. Wilfert, unpubl. data), the virulent mutation is expected to be very recent.

Two well-understood factors that may cause the parasite to adapt faster than the host are dominance and the selective advantage conveyed by the novel allele. As described by the "life-dinner principle" (Dawkins and Krebs 1979), the host and parasite are in an asymmetric arms race. When a virus finds itself in a resistant host, its fitness is dramatically reduced. However, the benefits of resistance for the host are smaller, because not all hosts are infected and the infection only causes a small reduction in host fitness. In the case of *D. melanogaster* and the sigma virus, the parasite suffers a 90% reduction in transmission—directly equivalent to its fitness—when it cannot overcome the resistant allele of the *ref(2)P* gene. The host on the other hand pays a much lower fitness cost when it is infected—by comparing the viral prevalences in the field with those reached under relaxed selection in the laboratory, Yampolsky et al. (1999) estimated that the fitness of flies is reduced by 20–30% when they are infected. This is in close agreement with our estimate of the cost of infection, that is, the relative fertility of infected flies $1 - C = 0.77$, despite this estimate being imprecise with a range of 0.75–0.81 based on simulations.

With few exceptions (Kimura 1980; Sibly and Curnow 1993), an advantageous dominant allele is expected to spread much faster than a recessive allele when it is uncommon (Fisher 1930). In the haploid sigma virus, the virulence allele is fully expressed when present. In heterozygous hosts, the resistant allele of *ref(2)P* only has about a quarter of the effect seen in homozygotes (Bangham et al. 2008a). If the allele was instead dominant, the number of generations that the allele needs to spread to its equilibrium prevalence would be more than halved. Independent of generation time, the sigma virus thus fulfils two criteria that will allow it to adapt faster than its host.

Another consequence of the parasite facing stronger selective pressure than the host is that the host allele only experiences a partial sweep, whereas the virulent viral type is swept to fixation. The sweep of the resistant allele is halted as it loses its selective advantage when the avirulent viral type disappears from the population. This results in a partial sweep, where the resistant allele remains as a neutral variant at an intermediate frequency in the population (Hudson et al. 1997). This is compatible with observations in the field, where the virulent viral type is sweeping to fixation (Fig. 1), whereas the resistant allele is only at a frequency of 24.0% in Athens and was found to be at similar low values in France ($31 \pm 2\%$) and the rest of Europe ($26 \pm 11\%$) in the 1980s (Fleuriet 1986).

The new resistance mutations that are required for a selective sweep to occur may appear only rarely, and when they do appear they will be at a very low frequency for many generations. This has led to the common—if not always explicit—notion in the community studying animal host–parasite coevolution that recurrent selective sweeps will occur relatively infrequently and that negative frequency-dependent selection is more likely to result in measurable short-term phenotypic changes (Ebert 2008). However, our model shows that selective sweeps may produce rapid and strong changes in allele frequencies in *D. melanogaster*. The viral sweep can be especially fast, with our model predicting that the virulent viral type can increase in relative frequency by 23.5% in a single host generation, in accordance with the rapid spread observed in the field (Fleuriet and Sperlich 1992; Fleuriet and Periquet 1993). In the host, evolution appears to be slower, although there can still be a relative change of 5.1% in allele frequency in a single generation. Assuming a generation time of one month for the host, the frequency of the resistant allele could rise by 9.3% within one year at the peak of the sweep according to our model, a change that could readily be picked up with the relevant phenotypic assay.

Drosophila and the sigma virus are not unusual in showing such rapid sweeps—to the contrary they seem to be the norm in agricultural and microbial systems (Buckling and Rainey 2002; Mcdonald and Linde 2002). In animals, Charlat et al. (2007) observed an even faster sweep, where a host gene blocking the male-killing function of *Wolbachia* spread to fixation in populations of the butterfly *H. bolina* in less than 10 generations. Is it just serendipity that researchers have stumbled across these examples of selective sweeps, or are they continually occurring in many host and parasite populations? The rate at which selective sweeps occur will depend on the frequency with which mutants that increase resistance or virulence arise. This in turn rests on the population size, the per-nucleotide mutation rate and the size of the mutational target, that is, the number of potential changes in the genome that would increase resistance or virulence. Little is known about these factors, but mutation rates can be high in parasites such as RNA viruses, and animals like *Drosophila* have large population sizes and many genes that interact with parasites, so new mutations that increase both resistance and virulence may arise at a high rate. In *D. melanogaster* we know of other polymorphisms that control resistance to the sigma virus (Bangham et al. 2008a), which suggests that the input of mutations that confer resistance into populations may be high. Selective sweeps may thus be on-going in many host and parasite populations, causing rapid changes in host resistance, and parasite infectivity and prevalence.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. Supplementary methods.

Table S1. The proportions of infected and uninfected gametes. The denominator is $w = 1 - P_i C$

Table S2. Equilibrium viral prevalence in model including genetic drift.

Table S3. Effect of dominance and relative fitness on the simulations of the co-evolutionary dynamics of the *ref(2)P* mutations and the sigma virus.

Figure S1. Simulation of the co-evolution of the virus and host including genetic drift.

Figure S2. Simulation of the co-evolution of the virus and host under extreme parameter values.