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Asymmetric gene flow and constraints on adaptation caused by sex ratio distorters

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Abstract

Asymmetric gene flow is generally believed to oppose natural selection and potentially impede adaptation. Whilst the cause of asymmetric gene flow has been seen largely in terms of variation in population density over space, asymmetric gene flow can also result from varying sex ratios across subpopulations with similar population sizes. We model the process of adaptation in a scenario in which two adjacent subpopulations have different sex ratios, associated with different levels of infection with maternally inherited endosymbionts that selectively kill male hosts. Two models are analyzed in detail. First, we consider one host locus with two alleles, each of which possesses a selective advantage in one of the subpopulations. We found that local adaptation can strongly be impeded in the subpopulation with the more female biased population sex ratio. Second, we analyze host alleles that provide resistance against the male-killing (MK) endosymbionts and show that asymmetric gene flow can prevent the spread of such alleles under certain conditions. These results might have important implications for the coevolution of MK bacteria and their hosts.

Introduction

Natural selection clearly is a major force that shapes the evolution of organisms. However, other factors such as mutation, genetic drift and gene flow can counteract natural selection and impede adaptation (Barton & Partridge, 2000). Gene flow – caused by the movement of organisms or gametes – can constrain the process of adaptation when traits are differentially selected in different areas. The effect may be particularly strong when gene flow is asymmetric. For example, it has been shown theoretically that asymmetric gene flow from the centre to the edge of a population can prevent adaptation at the periphery and thereby stop the population from growing in space (Kirkpatrick & Barton, 1997). Asymmetric gene flow has also been evoked as the cause of geographic distributions of sexual and asexual populations of a species (Peck *et al.*, 1998) and plays a major role in the geographic mosaic theory of coevolution (Thompson, 1994).

In most previous theoretical work, asymmetric gene flow has been assumed to stem from varying population densities over space. However, asymmetric gene flow may also be the result of variation in sex ratio between subpopulations. This is because both sexes contribute equally to the gene pools of subsequent generations, so that immigration of an individual into a subpopulation in which the sex ratio is skewed against it can have a much larger genetic impact than the same immigration to a subpopulation with an even sex ratio.

In arthropods, distorted sex ratios are often caused by selfish genetic elements, nuclear genes or cytoplasmically inherited endosymbionts that enhance their own transmission to the disadvantage of the rest of the genome (Werren *et al.*, 1988; Hurst & Werren, 2001). A case in point is the butterfly *Hypolimnas bolina*. This species is infected by maternally inherited bacteria of the genus

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Wolbachia that kill male offspring at an early stage of their development (Dyson *et al.*, 2002). Variation in the frequency of the infection between island populations of *H. bolina* is associated with population sex ratio variation from 50% to almost 100% females (Dyson, 2002; Dyson & Hurst, 2004). Given the common incidence in arthropods of cytoplasmic sex ratio distorters such as male-killers (Hurst *et al.*, 2003) and feminizing endosymbionts (Terry *et al.*, 2004), as well as sex chromosome drive elements (Jaenike, 2001), asymmetric gene flow caused by variation in population sex ratio might play an important role for adaptation in many species.

Here, we investigate theoretically the effect of cytoplasmic sex ratio distorters on rates of nuclear gene flow of their host, and the consequences of this for the process of adaptation. In particular, we focus on maternally inherited bacteria that selectively kill male offspring. We consider the fate of favourable alleles in two populations linked by migration, where one of the populations carries a male-killing (MK) bacterium at high prevalence, whereas the adjacent population carries a low prevalence of infection. In the first treatment, we study the effect of varying male-killer prevalence on the dynamics of locally adaptive alleles. We show that the spread of such alleles can be impeded strongly in the population with high prevalence of MK endosymbionts and elucidate this effect by means of the recently developed concept of the 'effective migration rate' (Telschow *et al.*, 2002a,b).

With a second model, we try to ascertain to what extent these results also apply to the spread of resistance alleles to the male-killer. This is interesting especially in that it might explain why in some host populations with very high infection frequencies of male-killers no resistance against MK has evolved (Jiggins *et al.*, 2002; Dyson & Hurst, 2004). We found that the spread of a resistance allele can again be impeded. However, the strength of the effect depends on the population structure and is most pronounced in a mainland-island model with unidirectional migration.

Model 1: effect on local adaptations

The model

In the first model we investigate the co-dynamics of MK bacteria and alleles at a selected locus in two populations with migration between them. In what follows, we give a verbal description of our model, for the mathematical description see Appendix A. For simplicity, we assume haploid sexual organisms, an assumption that often has been made for theoretical analyses (e.g. Hartl & Clark, 1989). Further, it makes our results comparable to previous studies (e.g. Telschow *et al.*, 2002a,2005).

Selection occurs at a single locus with two alleles (g and G). The g allele has a selection advantage of s_1 in population 1 compared with G, whereas the G allele has a selection advantage of s_2 in population 2 compared with g. Migration occurs in each generation. Migration rates m_1 and m_2 are defined as the fraction of populations 1 and 2, respectively, that are replaced by migrants from the other population (Fig. 1). Individuals reproduce sexually with a primary sex ratio of 1 : 1. We assume the following order of events for each generation: migration, selection, and reproduction. The generations are discrete and nonoverlapping.

Individuals can either be infected with a MK bacterium or uninfected (0). MK acts in an early stage of the embryogenesis and causes the death of all infected males. The transmission of the bacteria is strictly maternal. Following Hurst (1991) and Hurst *et al.* (1997), we use two parameters to describe MK dynamics, transmission rate and fitness compensation. The transmission rate t is defined as the fraction of offspring that inherit the infection from their mother. Further, all offspring of uninfected mothers are uninfected. The second parameter of the MK dynamics describes the benefit sisters get if their brothers die due to MK. We assume that this fitness compensation grows linearly with the number of dead siblings. The maximum increase is given by the parameter b, so that if all males die in a brood, the surviving sisters have a $(1+b)$-times higher chance to reproduce than offspring coming from an uninfected brood. The parameter b effectively corresponds to the selective advantage of the male-killer infection. As shown by Hurst *et al.* (1997), a male-killer can invade a panmictic host population if $(1 + b)t > 1$.

The basic question addressed here is how the presence of male-killer infections affects gene flow between populations under different levels of selection, migration, and fitness compensation, and the degree to which this impedes adaptation. To investigate the effect of a male-killer, two scenarios are considered, either without MK or with MK (Fig. 1). For the latter scenario we assume that the level of fitness compensation differs between the populations. To investigate the effect of MK we first determine the frequencies at the g–G locus under different parameter sets in absence of the male-killer and then compare the results with the corresponding equilibrium frequencies in the scenario with male-killers. As we will demonstrate in the next section, equilibrium frequencies at the g–G locus further allow us to determine gene flow between the populations by calculating effective migration rates.

Effective migration rate

To investigate the impact of MK infections on gene flow we compare the two scenarios with and without a male-killer and define an 'effective migration rate' as a measurement for gene flow. Verbally, the effective migration rate between two populations infected with MK bacteria is defined as the migration rate that causes the same equilibrium frequencies at the g/G locus in the scenario without male-killers as observed in the scenario with male-killers.

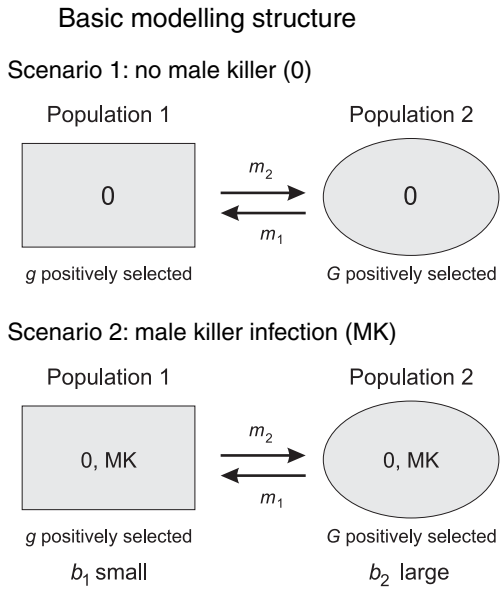

Fig. 1 Basic model structure. Two scenarios are considered, either both populations uninfected or both infected. In the latter scenario individuals can be either infected (MK) or uninfected (0). Model parameters are: selection coefficients s_1, s_2 describing selection at the *g*–*G* locus, migration rates m_1, m_2, and fitness compensation levels b_1, b_2. Generally, fitness compensation b_1 in population 1 is small compared to the fitness compensation b_2 in the other population.

In what follows we will derive a mathematically precise definition of the effective migration rate. Our starting point is the simple migration-selection model without MK. Let p and q be the frequencies of the g allele in populations 1 and 2. The frequencies of g in the next generation (p',q') are then given by the following equations:

$$p\prime = \frac{(1+s_1)[(1-m_1)p + m_1 q]}{1+s_1[(1-m_1)p + m_1 q]}, \qquad (1)$$

$$q\prime = \frac{[(1-m_2)q + m_2 p]}{1+s_2[(1-m_2)(1-q) + m_2(1-p)]}. \qquad (2)$$

Usually such equations are analyzed by calculating equilibrium frequencies (p^*, q^*) for given parameter sets (s_1, s_2, m_1, m_2). We will show these kinds of results below (Fig. 2a). However, eqns 1 and 2 also allow us to calculate parameter values if the equilibrium frequencies (p^*, q^*) are known. With simple algebraic transformations we get for $p^* \neq q^*$:

$$m_1 = \frac{p^*(1-p^*)\cdot s_1}{(p^*-q^*)\cdot[1+s_1(1-p^*)]}, \qquad (3)$$

$$m_2 = \frac{q^*(1-q^*)\cdot s_2}{(p^*-q^*)\cdot(1+s_2 q^*)}. \qquad (4)$$

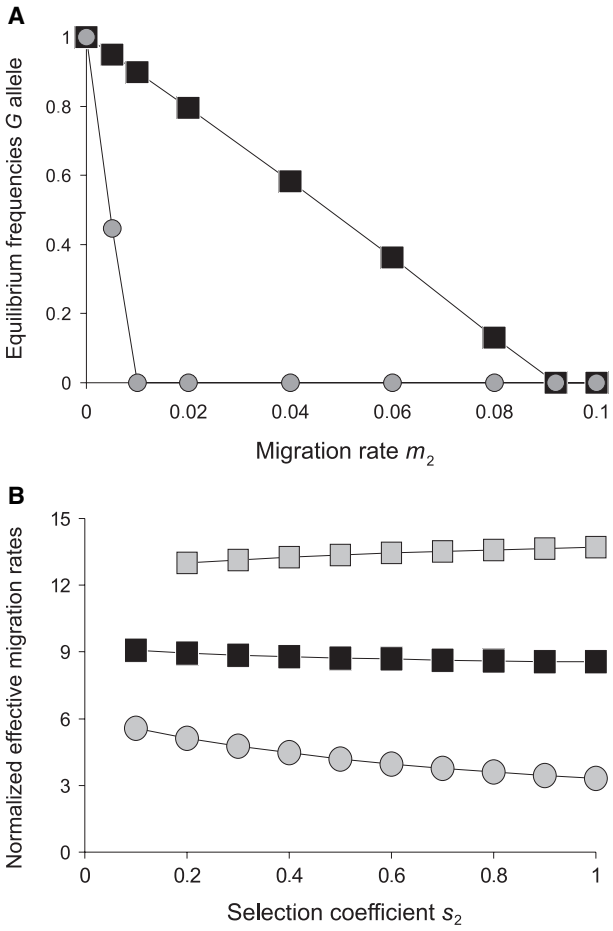

Fig. 2 Mainland-island model (m_1=0). Graph A shows the equilibrium frequencies of the *G*-allele in the island population 2 as a function of the migration rate m_2. Black squares indicate the scenario without MK, grey circles the scenario where the island population 2 is infected with MK but the mainland population 1 is not. Graph B shows normalized effective migration rates ($m_{2,\mathrm{eff}}/m_2$) as a function of the selection coefficient s_2. Grey squares indicate the situation where only males migrate, grey circles the situation where only females migrate, and black squares the situation where both males and females migrate. Note that effective migration rates cannot be calculated for low values of s_2 because the *G*-allele is lost under these circumstances. Parameters are: $t = 0.99$, $s_1 = 0.1$, $b_1 = 0$, $b_2 = 0.5$ for both graphs; $s_2 = 0.1$ for graph A; $m_2 = 0.01$ for graph B.

Equations (3) and (4) show that migration rates (in the model without the male-killer) can be calculated if equilibrium frequencies of g and selection coefficients are known. This relationship allows us to define the effective migration rate for the model with MK. Let x_g^* and y_g^* be the equilibrium frequencies of the g allele in populations 1 and 2 for the model with MK for given parameter set (s_1, s_2, m_1, m_2). Then the effective migration rates are defined as follows:

$$m_{1,\mathrm{eff}} := \frac{x_g^*(1-x_g^*)\cdot s_1}{(x_g^*-y_g^*)\cdot[1+s_1(1-x_g^*)]}, \quad (5)$$

$$m_{2,\mathrm{eff}} := \frac{y_g^*(1-y_g^*)\cdot s_2}{(x_g^*-y_g^*)\cdot(1+s_2 y_g^*)}. \quad (6)$$

With the help of eqns 5 and 6 it is possible to calculate the exact effective migration rates if the equilibrium frequencies of the scenario with MK are known. Note that the effective migration rates for the model without MK equal the real migration rates because in this case eqns 3 and 4 equal eqns 5 and 6. The effective migration rates shown below are determined in a two-step process. First, we obtained the equilibrium frequencies of g by numerical iteration of model (A1)–(A6). Second, equilibrium frequencies of the g-allele are used to calculate the effective migration rates with eqns 5 and 6.

Mainland-island scenario

We first discuss a scenario where migration occurs in one direction only, from the mainland population 1 to the island population 2. Throughout this section we consider a situation with fitness compensation only on the island but not on the mainland ($b_2 > b_1 = 0$). A MK infection can persist under these circumstances only on the island (and cause a sex ratio distortion there), whereas the mainland remains uninfected with an equal sex ratio. This scenario is motivated by observations in *H. bolina* where some island populations in the south pacific show strong female biased sex-ratios due to MK, whereas observations from the mainland population of Australia indicate absence of the male-killer in this area (Kemp & Charlat, pers. comm.). Levels of fitness compensation were not measured in this system. A more detailed discussion on fitness compensation is given (see section discussion).

To investigate the impact of a male-killer infection we compare two situations. In the first the island is infected, in the second it is uninfected. Fig 2a shows the equilibrium frequencies of the G-allele in the island for both scenarios. Note that this allele is positively selected on the island. As can be seen, the frequency of the G-allele for both scenarios decreases with increasing migration. Interestingly this decrease is much more profound if the island is infected than when it is uninfected. At a migration rate of 0.01 for example the G-allele is lost if the island is infected but it stays at allele frequencies over 90% if the island is not infected. Further, the G-allele can persist up to migration rates of 0.09 if both mainland and island are not infected.

The findings of Fig. 2a shows that migrants have a larger impact on the island gene pool if the island is infected. This arises because MK infections cause a shortage of males, and each male migrant has a higher reproductive success. Note that in each generation both sexes contribute the same amount to the gene pool of the next generation. In Fig. 2b we illustrate this reasoning using the framework of effective migration rates. Three cases are shown. In each case, the rate of migration is the same. However, the cases differ with respect to the percentage of males amongst the migrants. We first discuss the case where migrants consist of 50% males and females. As can be seen in Fig. 2b effective migration rates can be nine times higher than real migration rates for biologically reasonable values. In the second case only females migrate resulting in the much lower normalized effective migration rates of five. The reason for this finding is that female migrants have a lower reproductive success than male migrants. This view is further supported by the third situation where only males migrate. Here, high normalized effective migration rates of 13 are seen. We therefore conclude that enhanced effective migration rates are mainly caused by the sex ratio bias due to the MK infection.

Scenario with two-way migration

In the next section we analyze the scenario where migration between populations is bidirectional. This situation parallels migration between islands within the Pacific, where islands on which *H. bolina* carries the male-killer lie adjacent to islands where there is no MK in *H. bolina* (Dyson & Hurst, 2004; Charlat *et al.*, 2005). Again, the effect of MK on the effective migration rates is calculated. In preliminary simulations we demonstrated that the effective migration rate equals the real migration rates when fitness compensation in the two populations is equal in magnitude. However, this picture changes drastically if one of the populations is more 'suitable' for MK than the other.

As in the previous section, the populations differ with respect to the level of fitness compensation. We assume that only in population 2 do sisters get a fitness compensation following death of their brothers ($b_2 > 0$), with no compensation in population 1 ($b_1 = 0$). Fig 3a details the normalized effective migration rates as a function of the fitness compensation b_2 in population 2. Two properties are evident from the graph. First, we see an increase in the effective migration rates from population 1 to 2. This is mainly due to different sex-ratios between these populations. Whilst the percentage of females in population 1 is around 67%, population 2 consists of 96% females. Note that these values differ slightly for varying b_2. The second finding is a decrease in the effective migration rates from population 2 to 1. The reason for this is that female migrants are mostly infected and therefore bear a disadvantage compared to resident females.

The combination of these two effects can drastically alter the gene flow between the two populations as can be seen in Fig. 3b. We calculated $m_{2,\mathrm{eff}}/m_{1,\mathrm{eff}}$ to

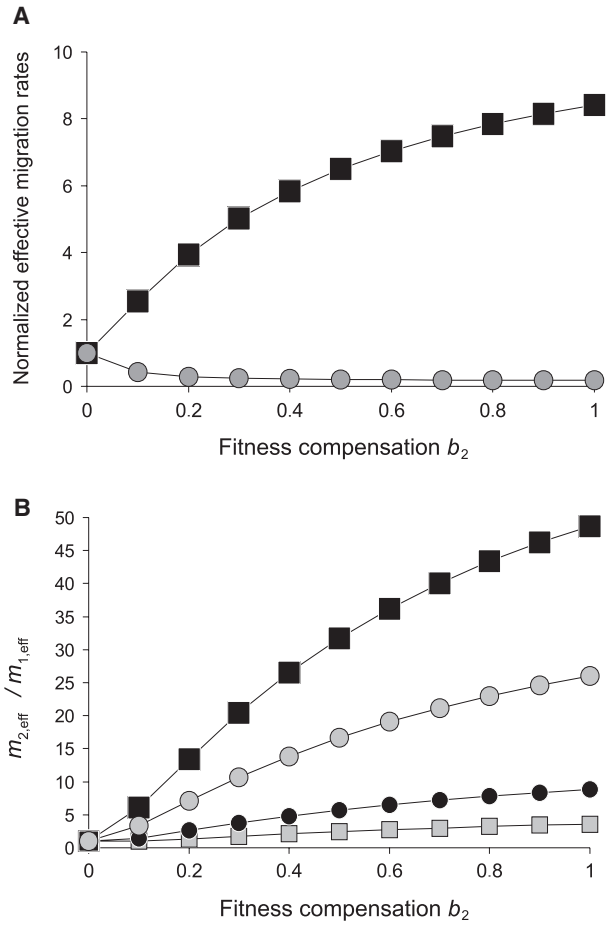

Fig. 3 Model with two-way migration. Graph A shows the normalized effective migration rates as a function of the fitness compensation b_2. Black squares indicate $m_{2,\text{eff}}/m_2$ grey circles $m_{1,\text{eff}}/m_1$. Graph B shows the gene flow alterations ($m_{2,\text{eff}}/m_{1,\text{eff}}$) for different transmission rates. Black squares indicate $t = 0.99$, grey circles $t = 0.98$, black circles $t = 0.95$, and grey squares $t = 0.9$. Parameters are: $m_1 = m_2 = 0.01$, $s_1 = s_2 = 0.1$, $b_1 = 0$ for both graphs; $t = 0.99$ for graph A.

measure gene flow asymmetries between the populations. As can be seen in the figure, gene flow can be over 40 times greater in one direction than the other. This is interesting because migration rates are equal ($m_1 = m_2$). Fig 3b shows further that this effect strongly depends upon the transmission rate of the male-killer. For a high transmission rate, 99%, and $b_2 = 0.2$ the gene flow is 15 times greater in one direction than in the other. But if the transmission rate is 95% this reduces to a fivefold difference. In summary, the results show that MK bacteria can strongly alter the gene flow between two infected populations if these populations are not equally suitable for the bacteria.

Model 2: resistance against male-killing

The model

In our second model, we investigate the extent to which the results from the previous model apply to a resistance allele that prevents the transmission of the male-killer, rather than an allele for a local adaptation. We make the same assumptions concerning population structure, MK and nuclear inheritance as in the previous section. We consider one nuclear locus with two alleles. While the wild-type allele has no phenotypic effect, an infected female that bears the resistance allele is assumed to transmit the male-killers to only $(1-\rho)\times t$ of her offspring, i.e. transmission is reduced by the factor ρ ('resistance efficiency', $0 \le \rho \le 1$). However, bearing the resistance allele may reduce the survival rate by the factor c ('cost of resistance', $0 \le c \le 1$). The mathematical description of the model is set out in Appendix B.

Again, this model could not be solved analytically; all results were obtained by computer simulation. Since resistance alleles are selected for only when male-killers exist within the population, the effective migration rate cannot be defined in a way similar to (5) and (6). Preliminary simulations revealed that when a single subpopulation is considered, the resistance allele always spreads in a population infected with male-killers when it does not involve a cost of resistance ($c = 0$). This leads to a decline of the equilibrium frequency of the MK endosymbionts and possibly to their extinction. If there is a cost to resistance ($c > 0$), damped oscillations occurred with some parameter values in the frequency of both resistance allele and male-killer frequency, before a polymorphic equilibrium is reached. All these findings are in accordance with the results of an earlier model on MK and resistance to it (Randerson *et al.*, 2000b).

Mainland-island scenario

As in model 1, we first consider the scenario when migration occurs in one direction only. Throughout, we assume that the island-population is infected with MK endosymbionts. As an indicator for the effect of gene flow on the spread of the newly arisen resistance allele in this subpopulation, we used the minimal value of the resistance efficiency ρ at which the resistance allele can spread in the population. In the case of no migration into the island and no cost of resistance ($c = 0$), the minimal ρ equals zero and the resistance allele spreads in the population until it is fixed or the male-killer has become extinct.

However, if there is migration of individuals from the mainland, the selective advantage of the resistance allele might be too weak for it to overcome the influx of wildtype alleles. Therefore a minimal resistance efficiency is necessary for resistance alleles to spread.

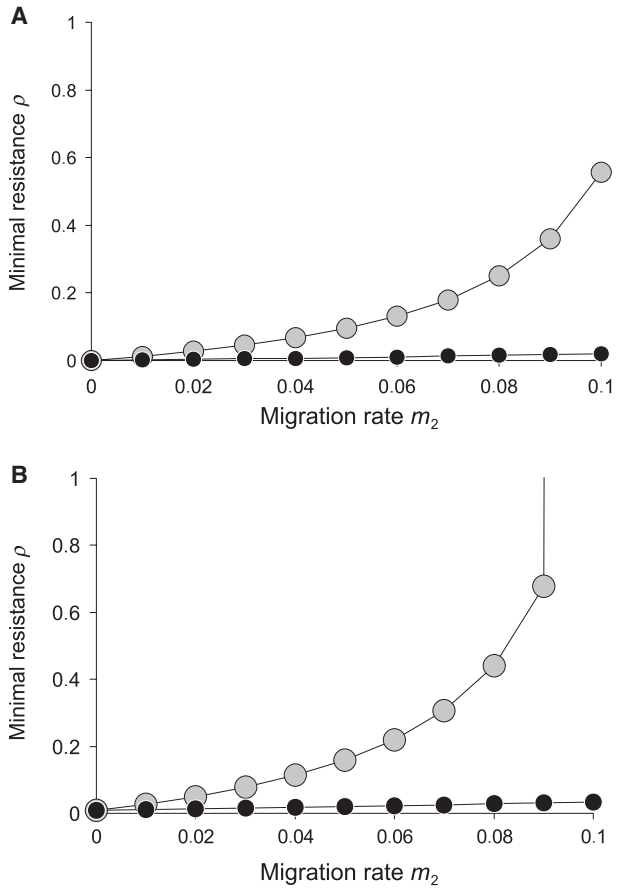

Fig. 4 Minimal values of the resistance efficiency ρ that allows spread of a resistance allele in the mainland-island model ($m_1 = 0$). Two scenarios are considered. Black circles indicate infection on the mainland and the island, grey circles that the island is infected but the mainland not. Parameters are: $t = 0.99$, $b_1 = b_2 = 0.2$ for both graphs; $c = 0$ for graph A; $c = 0.05$ for graph B.

Such minimal ρ values are shown for both no cost of resistance (Fig. 4a) and cost of resistance (Fig. 4b). In both graphs we compare the situation where mainland and island are infected with the situation where only the island is infected but the mainland not. In general, when the mainland is infected, the minimal ρ was found to increase only moderately with increasing migration rate. However, when the mainland is uninfected, this increase was much more pronounced. This derives from two effects. First, influx of uninfected females leads to a decreased equilibrium frequency of infected females on the island. Therefore, the selective advantage of the resistance allele reduces with increasing migration rate. Second, the migration of wild-type individuals in an even sex ratio to the female-biased island population leads to increased influx of the wild-type allele to the island that counteracts the positive selection of the resistance allele.

Scenario with two-way migration

We will now consider the scenario when there is migration in both directions. First, we consider the case where the rate of migration is symmetric ($m = m_1 = m_2$). Again, we analyze the spread of the resistance allele via calculation of the minimal value of the resistance efficiency ρ that allows spread of the allele. We compare two situations, when MK leads to fitness compensation for the surviving siblings in both populations equally ($b_1 = b_2$), and when there is fitness compensation in one population only ($b_2 > b_1 = 0$).

We first analyzed the case where resistance causes no costs ($c = 0$). We found that the resistance allele can always spread to fixation or until the male-killer has become extinct. This is because infected females occur in both populations due to migration. The resistance allele is therefore positively selected for even if MK is not favoured in one population. We note that this result is in contrast to the mainland-island scenario, where even resistance alleles without costs need a minimal value of ρ to spread (Fig. 4a).

Next, we investigated the case where resistance causes costs ($c > 0$). Fig 5 shows minimal values of ρ necessary for the resistance allele to spread. As can be seen, this spread is impeded when MK is not selected for in population 1 ($b_1 = 0$) compared to the case when MK is selected for in both populations ($b_1 = b_2$). The minimal values of ρ are twice as high in the first scenario compared to the latter. However, for both scenarios the minimal values of ρ are small compared to the mainland-island scenario (Fig. 4b).

To explain the initial increase in the minimal ρ with increasing migration rate and their subsequent decrease, again the combined effects of nuclear and cytoplasmic gene flow must be taken into account. Assuming that the infection prevalence in the two populations does not change, the influx of wild-type alleles into population 2 (where MK is selected for) increases with increasing migration rate. Therefore, for low levels of migration the minimal ρ values increase with increasing migration rate. However, at the same time the infection frequencies in the two populations increasingly approach each other with increasing migration rate. This has two consequences. First, the population sex ratio in the populations differs less and less, so that the impact of the migrating males bearing the wild-type allele decreases with increasing migration rate. Second, the infection frequency in population 2 decreases with increasing migration rate, and selection for the resistance allele becomes weaker. These two effects of increasing cytoplasmic gene flow eventually offset the effect of increased influx of wild-type alleles and lead to a drop in minimal ρ values.

In summary, the analysis of model 2 shows that migration from an uninfected mainland into an infected island can prevent the spread of resistance alleles for a wide range of parameters (Fig. 4) whereas such an effect

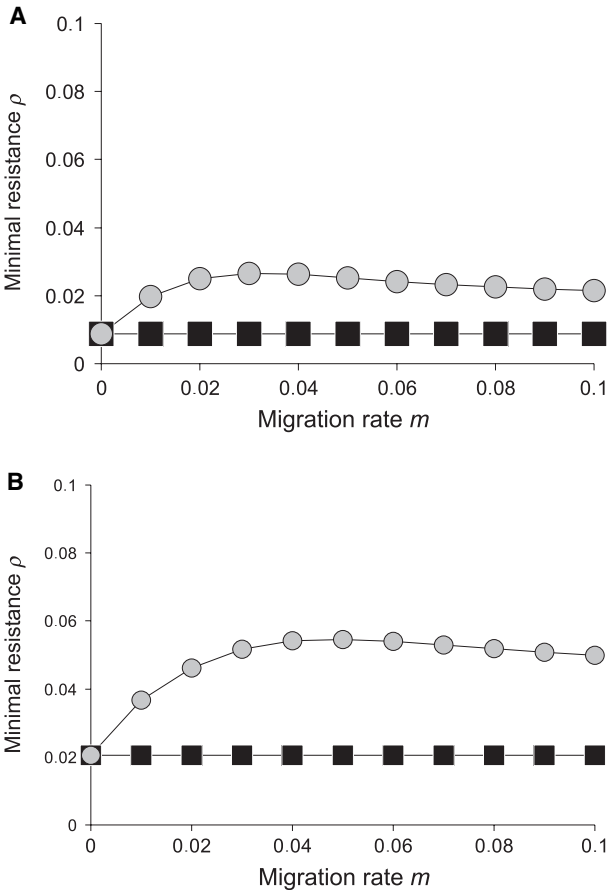

Fig. 5 Minimal values of the resistance efficiency ρ that allows spread of a resistance allele in the model with two-way migration ($m = m_1 = m_2$). Black squares indicate the scenario where both populations are suitable for the male killer infection ($b_1 = b_2 = 0.2$), grey circles the scenario where one population is suitable and the other not ($b_1 = 0$, $b_2 = 0.2$). Other parameters are: $t = 0.99$ for both graphs; $c = 0.05$ for graph A; $c = 0.1$ for graph B.

is much weaker if migration is bidirectional and equal in both directions (Fig. 5). In order to estimate the importance of the results of the mainland-island model we further analyzed the situation where migration is bidirectional but asymmetric ($m_1 < m_2$). We found that transitions from no migration from the island to the mainland ($m_1 = 0$) to a low rate of migration caused only minor changes in minimal values of ρ if MK is not positive selected on the mainland (results not shown). These findings imply that the mainland-island model is structurally stable with respect to migration and argue for their biological relevance.

Discussion

In this article we have shown that MK infections can strongly alter the gene flow between host populations. To measure gene flow we defined an 'effective migration rate' and presented a new way to calculate it. In the first part of this article we analyzed the gene flow of locally adaptive alleles. We demonstrated that MK induced gene flow alteration has two effects: (1) local adaptation is strongly impeded in populations where MK is favoured, due to excess influx of maladapted alleles and (2) reciprocally, local adaptation is more easily attained where MK is disfavoured, due to lowered influx of maladapted alleles. In the second part of this article we analyzed suppressor genes in the host that act against MK. These genes are also strongly affected by the alteration in gene flow. We demonstrated that this may prevent suppressors from spreading in mainland-island population structures, whilst this effect is weaker in models with two way migration.

To discuss these results, it is convenient to interpret them in terms of genetic sinks and sources (Pulliam, 1988). The term genetic sink is used in the context of a structured population and denotes subpopulations with a larger gene influx than gene outflux. The opposite is true for genetic sources. Here, outflux is bigger than influx. The findings of our study demonstrate that MK infections generate genetic sinks (and sources) if MK prevalence is heterogeneous within a structured population, despite the numerical movement of individuals being unchanged. Genetic sinks are generated in populations where selection favours MK, genetic sources in populations where MK is disfavoured or absent.

Intuitively, the genetic sink/source effect can also be explained in terms of Kimura's effective population size. It is well known that a sex ratio bias reduces the effective population size (Kimura, 1983). A MK infection should therefore reduce the effective size of a population. This reduction is greater for more profound population sex ratio bias. The genetic sink/source effect can now be explained by the fact that the population that is more suitable for MK has a smaller effective population size than its neighbour and is therefore converted into a genetic sink.

The ubiquity of MK bacteria in insects led to a discussion about their potential role in the evolutionary design of their hosts (Hurst & Werren, 2001). For example, Hurst & McVean (1998) argued that MK infections impose a strong selection pressure on host clutch size because half of the eggs fail to hatch. Much more debated is whether the evolution of host mating behaviour is affected. Here, the basic argument is that MK causes a sex ratio shift in host populations that lessens the strength of male–male competition, and also weakens the selection pressure for female mating preference. Some authors go a step further and claim that MK even causes the evolution of male mating preferences (Randerson *et al.*, 2000a). Our results suggest that for both scenarios host population structure may play a crucial role. Because MK generates a genetic sink in

populations where it is favoured, we expect hosts to be maladapted with regard to both clutch size and mating behaviour compared to single population models. Genetic sink/source effects might therefore strongly reduce the impact of MK on host evolution.

The genetic sink/source effect might also be crucial to understand the evolution of male-killer virulence. Some MK infections show an extreme level of virulence causing the death of all male offspring (reviewed in Hurst *et al.*, 2003). At the population level, this typically results in extreme female biased sex ratios. For example, in the butterfly *H. bolina* populations are known (in Independent Samoa) that consist to 99% of adult females (Dyson *et al.*, 2002; Dyson & Hurst, 2004). These data suggest strong selection pressure on the host against the presence of MK bacteria. Surprisingly, MK infections in *H. bolina* seem to have been present in these populations for at least 100 years without any sign of MK suppression (Hopkins, 1927; Dyson & Hurst, 2004). The genetic sink/source effect could help explain the evolution and persistence of such extreme male-killer infections. Our results show that asymmetric gene flow from an uninfected into an infected population acts against the spread of male-killer suppressor genes. In an evolutionary arms race the MK bacteria might therefore easily evolve high virulence because its coevolutionary 'corrective' is missing.

In our models, migration is described by a constant migration rate. However, in many organisms, migration is known to have a genetic basis (see Drake & Gatehouse, 1995; Gatehouse, 1997 for reviews). An interesting question is therefore how the genetic basis of migration itself evolves in presence of MK infections. Because of the sink/source effect we expect the genetic basis of migration to adapt to the optimum of uninfected rather than infected populations. A possible outcome of this might be that the tendency to migrate is selected for in males because male have a high reproductive success in infected populations. However, we have not analyzed this is detail.

A crucial assumption in our models is that MK endosymbionts can be disfavoured in one of the subpopulation due to different levels of fitness compensation. Fitness compensation has not been measured so far experimentally. However, different levels of fitness compensation are biologically reasonable under various circumstances and could, for example, derive from variation in population density or habitats that lead to different egg laying behaviour. Indeed, whilst eggs in *H. bolina* are generally laid in clutches within Polynesia (where the male-killer is locally present), records from Australia (where the male-killer is absent) indicate eggs are laid singly here (Kemp, 1998). Thus, whilst fitness compensation deriving from reduced sibling competition is possible in Polynesia, it will be weak or absent in Australia. Other possible reasons for different infection levels in different subpopulations are diverging environmental conditions such as different temperatures or naturally occurring antibiotics in one habitat, but not in the other one. Finally, uninfected subpopulations might result from infections with endosymbionts not inducing a sex ratio distortion. Previous theoretical work has shown that the infection of a subpopulation with vertically transmitted endosymbionts that induce cytoplasmic incompatibility can be expected to prevent the invasion of male-killers (Engelstädter *et al.*, 2004). The report of populations of *H. bolina* that are infected with *Wolbachia* inducing cytoplasmic incompatibility (S. Charlat, unpublished results) supports this view. However, future empirical and theoretical work has yet to determine how nuclear gene flow is affected when some subpopulations of the host species are infected with MK and others with cytoplasmic incompatibility inducing *Wolbachia*.

Our analysis was based on the concept of the effective migration rate. We presented a new way to calculate effective migration rates by comparing allele frequencies at weakly selected loci for the scenarios with and without MK bacteria. However, this is not the first attempt to describe effective migration rate mathematically. Barton & Bengtsson (1986) analyzed the flow of alleles at a neutral marker locus through a hybrid zone. They showed that this flow can be impeded if the neutral locus is linked to selected loci which cause lower hybrid fitness. Ingvarsson & Whitlock (2000) analyzed the effect of heterosis on gene flow between large and small populations. Using methods of multi-locus genetics, they demonstrated that the migration rate from larger populations into smaller ones is effectively higher if deleterious recessive mutations occur more often in the smaller population. Although both approaches are shown by the authors to have practical applications, both bear the disadvantage of a mathematically rather complicated definition of the effective migration rate. The advantage of our approach is its simple definition that allows a straightforward way to calculate effective migration rates.

In summary, our results show that MK infections can strongly alter the gene flow within a structured host population by generating genetic sinks in populations where MK is most favoured. This might have important implications for the coevolution of MK bacteria with their host and may help explain the evolution and persistence of extreme MK.

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Appendix A: model 1

In what follows, we give the mathematical description of the model with local adaptations. The frequencies of the different classes of individuals in populations 1 and 2 are denoted by x_{ijk} and y_{ijk}. Individuals are characterized by their sex i (0 = female, 1 = male), their cytotype j (0 = not infected, 1 = infected), and their genotype k (0 = g-allele, 1 = G-allele). In the first step of each generation, migration takes place as described by the following equations:

$$x^{+}_{ijk} = (1 - m_1)x_{ijk} + m_1 y_{ijk}, \tag{A1}$$

$$y^{+}_{ijk} = (1 - m_2)y_{ijk} + m_2 x_{ijk}. \tag{A2}$$

In the second step, the individuals are subject to selection at the *g/G* locus. This is described by eqns A3 and A4. Thereby W_1 denotes the sum of all numerators of (A3), and W_2 the sum of all numerators in (A4).

$$x^{++}_{ij0} = \frac{(1 + s_1)x^{+}_{ij0}}{\overline{W_1}} \quad \text{and} \quad x^{++}_{ij1} = \frac{x^{+}_{ij}}{\overline{W_1}}, \tag{A3}$$

$$y_{ij1}^{++} = \frac{y_{ij1}^{+}}{\overline{W_2}} \quad \text{and} \quad y_{ij1}^{++} = \frac{(1+s_2)y_{ij1}^{+}}{\overline{W_2}}. \qquad \text{(A4)}$$

The third step describes reproduction of the individuals. This includes the inheritance of the nuclear and cytoplasmic genome, and the killing of infected male offspring. The inheritance of the MK endosymbionts can be described by the matrix

$$T = \begin{pmatrix} 1 & 1-t \\ 0 & t \end{pmatrix},$$

in which $T_{j\alpha}$ denotes the fraction of offspring with cytotype j that a mother with cytotype α has. Inheritance of the genotype occurs according to the to matrices

$$H_0 := \begin{pmatrix} 1 & 0.5 \\ 0.5 & 0 \end{pmatrix} \quad \text{and} \quad H_1 := \begin{pmatrix} 0 & 0.5 \\ 0.5 & 1 \end{pmatrix},$$

where $H_{k,\mu\pi}$ is the fraction of offspring with genotype k which have a mother with genotype μ and a father with genotype π. After reproduction and selection, the frequencies of individuals of the different classes are then given by:

$$x\prime_{ijk} = \frac{1-ij}{\overline{W_3}} \sum_{\alpha,\mu,\lambda,\pi=0}^{1} x_{0\alpha\mu}^{++} x_{1\lambda\pi}^{++} T_{j\alpha} H_{k,\mu\pi}(1+\alpha t b_1), \qquad \text{(A5)}$$

$$y\prime_{ijk} = \frac{1-ij}{\overline{W_4}} \sum_{\alpha,\mu,\lambda,\pi=0}^{1} y_{0\alpha\mu}^{++} y_{1\lambda\pi}^{++} T_{j\alpha} H_{k,\mu\pi}(1+\alpha t b_2) \qquad \text{(A6)}.$$

Here, W_3 and W_4 denote the average fitness's of the individuals in the two populations and are defined as the sum of all terms in the two equations, respectively.

Appendix B: model 2

In this appendix we give the mathematical description of the model with repressor alleles against MK endosymbionts. We consider two panmictic populations whose individuals reproduce in discrete, nonoverlapping generations. The frequencies of the different classes of individuals in populations 1 and 2 are denoted by x_{ijk} and y_{ijk}. Individuals are characterized by their sex i (0 = female, 1 = male), their cytotype j (0 = not infected, 1 = infected) and their genotype k (0 = wildtype, 1 = resistance allele). In each generation, two events take place. First, migration takes place according to the following equations:

$$x_{ijk}^{+} = (1-m_1)x_{ijk} + m_1 y_{ijk}, \qquad \text{(B1)}$$

$$y_{ijk}^{+} = (1-m_2)y_{ijk} + m_2 x_{ijk}. \qquad \text{(B2)}$$

The second step describes reproduction of the individuals. This includes the inheritance of the nuclear and cytoplasmic genome, and the killing of infected male offspring. We first define the following matrices in order to present the recursion equations in a concise way:

$$T_0 := \begin{pmatrix} 1 & 1 \\ 1-t & 1-(1-\rho)t \end{pmatrix}, \quad T_1 := \begin{pmatrix} 0 & 0 \\ t & (1-\rho)t \end{pmatrix}$$

. Here, $T_{k,\mu\pi}$ is the fraction of offspring with cytotype j which were given birth by a mother with cytotype α and genotype π. The inheritance of genotypes is described by the matrices

$$H_0 := \begin{pmatrix} 1 & 0.5 \\ 0.5 & 0 \end{pmatrix}, \quad H_1 := \begin{pmatrix} 0 & 0.5 \\ 0.5 & 1 \end{pmatrix},$$

where $T_{k,\mu\pi}$ is the fraction of offspring with cytotype k that have a mother with genotype μ and a father with genotype π. We are now in a position to define the recursion equations for the reproduction step of a generation as follows:

$$x\prime_{ijk} = \frac{(1-kc)(1-ij)}{\overline{W_1}} \sum_{\alpha,\mu,\lambda,\pi=0}^{1} x_{0\alpha\mu}^{+} x_{1\lambda\pi}^{+} T_{j,\alpha\pi} H_{k,\mu\pi}[1+\alpha T_{1,1\mu} b_1], \qquad \text{(B3)}$$

$$y\prime_{ijk} = \frac{(1-kc)(1-ij)}{\overline{W_2}} \sum_{\alpha,\mu,\lambda,\pi=0}^{1} y_{0\alpha\mu}^{+} y_{1\lambda\pi}^{+} T_{j,\alpha\pi} H_{k,\mu\pi}[1+\alpha T_{1,1\mu} b_2], \qquad \text{(B4)}$$

W_1andW_2 denote the average fitness's of the individuals in the two populations and are defined as the sum of all terms in the two equations, respectively.

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