JOURNAL OF Evolutionary Biology

doi: 10.1111/j.1420-9101.2010.02106.x

Mobile DNA can drive lineage extinction in prokaryotic populations

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Keywords:

bacteria;
epidemiology;
evolutionary suicide;
plasmids;
population ecology;
tragedy of the commons.

Abstract

Natural selection ultimately acts on genes and other DNA sequences. Adaptations that are good for the gene can have adverse effects at higher levels of organization, including the individual or the population. Mobile genetic elements illustrate this principle well, because they can self-replicate within a genome at a cost to their host. As they are costly and can be transmitted horizontally, mobile elements can be seen as genomic parasites. It has been suggested that mobile elements may cause the extinction of their host populations. In organisms with very large populations, such as most bacteria, individual selection is highly effective in purging genomes of deleterious elements, suggesting that extinction is unlikely. Here we investigate the conditions under which mobile DNA can drive bacterial lineages to extinction. We use a range of epidemiological and ecological models to show that harmful mobile DNA can invade, and drive populations to extinction, provided their transmission rate is high and that mobile element-induced mortality is not too high. Population extinction becomes more likely when there are more elements in the population. Even if elements are costly, extinction can still occur because of the combined effect of horizontal gene transfer, a mortality induced by mobile elements. Our study highlights the potential of mobile DNA to be selected at the population level, as well as at the individual level.

Introduction

Mobile genetic elements (MEs) are DNA sequences that can move to different positions in a genome. Although MEs can occasionally cause beneficial mutations within hosts (e.g. Blot, 1994; Brookfield & Sharp, 1994; Capy *et al.*, 2000; Dunham *et al.*, 2002; Koszul *et al.*, 2003), they often have deleterious effects on the host (Charlesworth & Langley, 1989; Charlesworth *et al.*, 1994; Bartolome *et al.*, 2002; Arkhipova, 2005; Touchon & Rocha, 2007; Rankin *et al.*, 2010). MEs may spread rapidly through a population either through horizontal gene transfer (Ochman *et al.*, 2000) or through sexual reproduction (Hickey, 1982). As such, MEs are genomic parasites, acting in their own selfish interests at the cost of their host genome: they replicate themselves within a genome, spread rapidly through host populations and have deleterious effects on the fitness of their hosts (Doolittle & Sapienza, 1980; Orgel & Crick, 1980; Wagner, 2009). This has led to many studies that address the question of how costly MEs can persist in host genomes. These studies find that, if MEs inflict costs on the host (and thus do not code for any beneficial traits), they can only persist through sexual reproduction or horizontal gene transfer (e.g. Brookfield, 1986; Brookfield & Badge, 1997; Bestor, 1999; Burt & Trivers, 2006; Lili *et al.*, 2007).

The well-known tragedy of the commons is an example of where a trait that is beneficial at the individual level can be detriment at the group, or population, level (Hardin, 1968). The tragedy of the commons manifests itself in many dilemmas within evolutionary biology (Rankin *et al.*, 2007a), such as sexual conflict (Rankin & Kokko, 2006), worker production in social insects (Martin *et al.*, 2002; Wenseleers & Ratnieks, 2004), plant

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competition (Gersani *et al.*, 2001) and bacterial virulence (Griffin *et al.*, 2004). The evolution of virulence in parasites (Frank, 1994; 1996; Kerr *et al.*, 2006) is a particularly striking example for the tragedy of the commons where it is in the interest of each individual parasite to exploit the host as much as possible, potentially leading to higher host mortality and a reduction in collective fitness. In addition to reducing the fitness of other parasites in a host, parasites may also evolve to drive populations extinct (Boots & Sasaki, 2002; 2003; Gandon & Day, 2009), a phenomenon known as evolutionary suicide (Parvinen, 2005; Rankin & López-Sepulcre, 2005).

It has been speculated that, because of their high transmission rate and deleterious effect on host fitness, selfish DNA could drive host lineages extinct (Vinogradov, 2003; 2004a,b; Arkhipova & Meselson, 2005; Dolgin & Charlesworth, 2006; Wagner, 2006b). Genome size, which is correlated with the amount of selfish DNA within a genome (Vinogradov, 2004a; Touchon & Rocha, 2007), increases extinction risk, both in vertebrates (Vinogradov, 2004b) and in plants (Vinogradov, 2003). A comparative study of insertion sequences within 400 fully sequenced bacterial genomes revealed that most genomes contained few insertion sequences (the majority of genomes contained no, or only a single, insertion sequence). In addition, this study found that insertion sequences *within* a genome are very similar, whereas they are often highly divergent *between* genomes (Wagner, 2006b). These patterns suggest that insertion sequences within a genome are of recent shared descent and may thus have been acquired recently. It is therefore possible that insertion sequences may have periodically driven local host populations extinct and therefore persist in local populations through colonization–extinction dynamics. This pattern is consistent with their parasitic nature (Doolittle & Sapienza, 1980; Orgel & Crick, 1980). Here we present a number of models illustrating the conditions under which MEs may bring about the extinction of whole populations of prokaryotes. We start with simple models of mobile elements, based on models of parasite-driven extinction (e.g. Boots & Sasaki, 2003), and extend our model to apply more specifically to prokaryotic MEs. We refer to our selfish genetic elements as 'mobile elements' (MEs), but our model is sufficiently general to address a broad class of mobile elements, from insertion sequences and transposable elements, to plasmids and bacteriophages, all of which may have deleterious effects on their prokaryotic hosts.

Model and results

Simple model for mobile element-mediated extinction

We start with a simple analytical model to describe how MEs may drive the host population extinct. We first assume that there is a population of bacteria, where cells are either completely free of mobile elements (MEs) or are 'infected' with an undefined number of MEs. We denote the density of bacteria without any MEs as n_S and the density of bacteria that have at least one ME in their genome as n_I, where the subscripts S and I refer to 'susceptible' and 'infected' hosts, respectively, in line with models of epidemiology (Anderson & May, 1979; May & Anderson, 1979; Lipsitch *et al.*, 1995). So-called 'SI' models have been well used to study the persistence of mobile DNA such as plasmids (e.g. Bergstrom *et al.*, 2000; Smith, 2001; Lili *et al.*, 2007; Mc Ginty *et al.*, in press). Our initial model is based on previous models of parasite dynamics (e.g. Boots & Sasaki, 2003), extending these basic models to apply to mobile DNA in bacterial populations. Assuming logistic growth, we can write the dynamics of n_S and n_I as:

$$\frac{dn_S}{dt} = n_S\left(r\left(1-\frac{N_T}{k}\right) - \frac{\beta n_I}{s+(1-s)N_T} - \theta\right) + xn_I \quad (1)$$

$$\frac{dn_I}{dt} = n_I\left(r\left(1-\frac{N_T}{k}\right) + \frac{\beta n_S}{s+(1-s)N_T} - x - \mu - \theta\right) \quad (2)$$

where $N_T = n_S + n_I$. Full details of parameters used are given in Table 1. The base-line growth rate is given by r, θ is the base-line density-independent mortality and k scales the carrying capacity. The rate of full ME loss (where all MEs are lost from a genome, such as through excision) is given by x. The rate of horizontal gene transfer is given by β, and the rate of ME-induced mortality on an infected host is given by μ. In our

Table 1 Notation used in the model.

Notation	Definition
n_S	Density of cells uninfected with a mobile element
n_I	Density of cells infected with a single mobile element
q	Proportion of infected cells in the population (n_I/N_T)
n_z	Density of cells infected with z mobile elements
N_T	Total density of cells in the population
N_I	Total density of infected cells in the population
r	Logistic *per capita* birth rate
K	Carrying capacity
β	Transmission rate of a mobile element
x	Excision rate of a mobile element
a	Copy rate of a mobile element
θ	Density-independent death rate
s	Mode of transmission of a mobile element. Transmission is density-dependent (proportional to $n_I - s = 1$) or density-independent (proportional to $n_I/N_T - s = 0$)
μ	Mobile-element induced death rate
v	Shape of mobile genetic element mortality curve (where the death rate of a host infected with z mobile elements is μz^v)
γ	Shape of duplication curve (where the duplication rate of a host infected with z mobile elements is az^γ)
M	Maximum number of mobile elements within a genome

analysis, we assume that all of these rates are less than the primary growth rate r, meaning that any given event (e.g. HGT, excision) takes place less than once per cell division (i.e. we assume that $r > \theta$, $r > \beta$, $r > x$ and $r > \mu$). We introduce the binary parameter s (where $s \in \{0,1\}$) to describe whether infection is density-dependent ($s = 1$), in which case the infection of a given host is proportional to the density of cells n_I that are infected with a mobile element, or whether infection is frequency-dependent ($s = 0$), and is thus proportional to the probability of encountering an infected cell n_I/N_T, in the population. As little is known about the actual mode of ME transmission, we use s to compare the two most prominent mechanisms of parasite transmission.

As we are interested in the effect of MEs on the persistence of the whole population, we can write the dynamics of the total population density N_T as $dN_T/dt = dn_S/dt + dn_I/dt$, and also, from the quotient rule, we can find the rate of change in the proportion of hosts q that are infected by MEs $dq/dt = d(n_I/N_T)/dt = (N_T dn_I/dt - n_I dN_T/dt)/N_T^2$. For frequency-dependent transmission ($s = 0$), the system can now be described by the following dynamics:

$$\frac{dN_T}{dt} = N_T\left(r\left(1 - \frac{N_T}{k}\right) - q\mu - \theta\right) \quad (3)$$

$$\frac{dq}{dt} = q((1-q)(\beta - \mu) - x) \quad (4)$$

In the absence of any MEs (i.e when $q = 0$), the equilibrium population density is $N_T^* = k(1 - \theta/r)$. This equilibrium point represents the density of an ME-free population and is asymptotically stable if the growth rate exceeds the base-line mortality ($r > \theta$). MEs will be able to invade an ME-free population if $\beta > \mu + x$, that is, if the rate of horizontal gene transfer exceeds the sum of ME-induced mortality and the rate of ME loss. This can be interpreted in the context of the basic reproductive number, R_0, which is $R_0 = \beta/(\mu + x)$. If this number is greater than one, mobile elements will be able to invade the population. Figure 1a illustrates the invasion and persistence of MEs in a host population.

There is a single equilibrium of eqns 3 and 4 where the population cannot persist, which is when $N_T^* = 0$ and $q^* = 1 - x/(\beta - \mu)$. We determined the eigenvalues of the Jacobian matrix of eqns 3 and 4, which must be negative for any equilibrium to be stable. This stability criterion will be satisfied, and hence MEs will drive the entire population extinct, if

$$r > \theta > \frac{r(\beta - \mu) - \mu(\beta - \mu - x)}{\beta - \mu} \quad (5)$$

This additionally requires that $\mu > r - \theta$, which means that the rate of ME-induced mortality must be greater than the net per capita growth rate $r - \theta$. If the growth rate is low, or if the base-line mortality θ of cells is high, i.e. when there is high cell mortality in addition to that caused by MEs, the presence of MEs will greatly act to the detriment of the population. Figure 1b shows an example where MEs bring about the extinction of the entire population. In general, if the rate of horizontal gene transfer, β, is high, and if mortality because of MEs is low, then the population will be driven extinct. This is because, if the transmission rate is high, but the mortality rate is lower than the transmission rate (i.e. $\beta > \mu$), MEs will spread through the population, while inflicting a cost (μ) on their hosts. If MEs inflict sufficiently high mortality on their host (i.e. $\mu > r - \theta$), then the population will go extinct: in other words, the MEs over-exploit the very resource (the host) that they need to persist. Quantitative criteria for ME-mediated extinction are presented in Fig. 2. It can be seen that higher values of horizontal gene transfer favour ME-mediated extinction, as do higher ME costs.

For density-dependent transmission ($s = 1$), β is no longer divided by N_T and transmission can be said to be density-dependent. Using the quotient rule to calculate

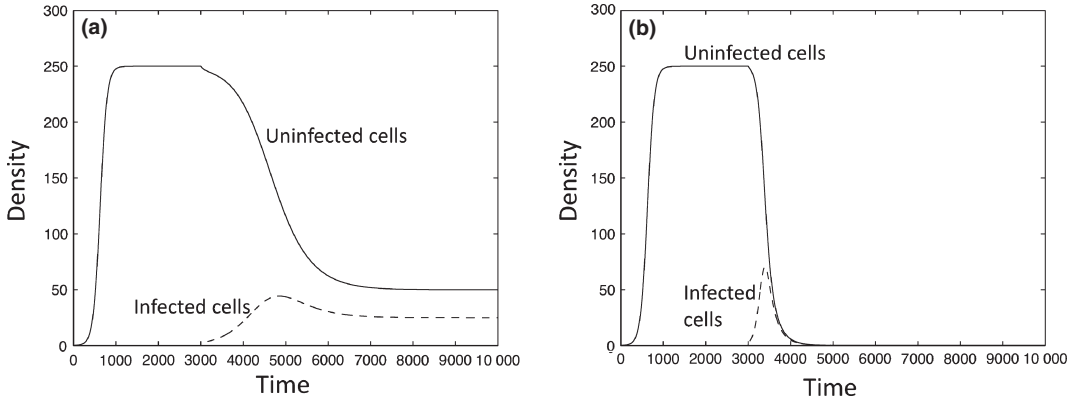

Fig. 1 The population dynamics of a deleterious mobile genetic element when it invades and persists in a bacterial host population (a) ($\beta = 0.5$) and invades and drives the population to extinction (b) ($\beta = 0.7$). Other parameters used are $r = 1$, $\theta = 0.75$, $x = 0.05$, $k = 1000$, $\mu = 0.4$.

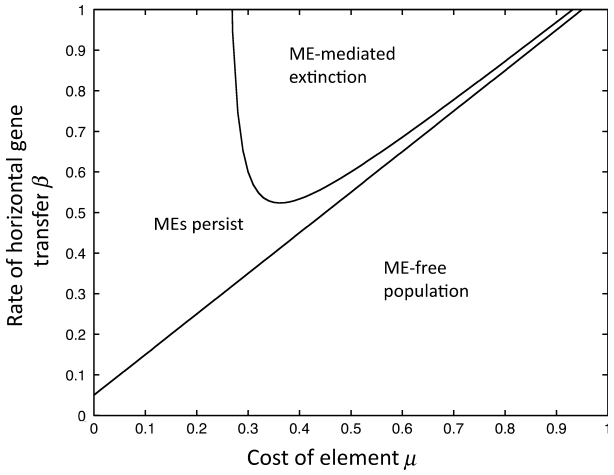

Fig. 2 The conditions under which mobile genetic elements persist or drive a population extinct. Other parameters used are $r = 1$, $\theta = 0.25$, $x = 0.05$, $k = 1000$.

the proportion of cells q infected with MEs, as in section 1, we now obtain from (1):

$$\frac{dN_T}{dt} = N_T\left(r\left(1 - \frac{N_T}{k}\right) - q\mu - \theta\right) \quad (6)$$

$$\frac{dq}{dt} = q((1-q)(N_T\beta - \mu) - x) \quad (7)$$

An ME will therefore invade when rare i.e. if $N_T\beta > x + \mu$, which – when N_T is at equilibrium – is $k\beta > x + \mu$. The equilibrium associated with extinction is $N^* = 0$ and $q^* = 1 + x/\mu$, and this equilibrium will be stable (i.e. the population will be driven extinct) if $r < x + \theta + \mu$ and $x < -\mu$. However, as both the loss rate x and the ME-induced mortality μ are positive, this cannot occur, and the equilibrium remains unstable. In other words, MEs will never force the population to the point where the population is exactly $N_T = 0$. However, this is not to say that mobile elements will not have a substantial effect on population density. Figure S1 (in the Supporting Information) plots the effect of transmission and element cost on the density of elements. In the case of density-dependent transmission, the extinction risk increases with both the rate of horizontal gene transfer β and the cost of carrying a mobile element μ (Fig. S1c,d). For example, for a rate $\beta = 0.15$ of horizontal gene transfer and a cost $\mu = 0.1$ of carrying an element, the population density is reduced to less than 1% of an uninfected population (Fig. 3c). We also checked the robustness of this simpler analytical model with a more complex analytical model (Appendix S2), incorporating cells that are infected with more than one mobile element. We found our results qualitatively similar to our basic model with only infected and uninfected cells (Fig. S2). We have additionally considered the case where transmission can evolve, as a result of a trade-off between transmission of MEs and the cost they inflict on their host (i.e. the virulence), and we include this in the Supporting Information (Appendix S1). This demonstrates that it is possible that the evolution of transmission of MEs can result in the population being driven extinct, highlighting the generality of the epidemiological models presented here.

Multiple MEs

The above model assumes that the cost of bearing an ME is the same, regardless of its copy number within the genome. However, some genomes may harbour multiple copies of MEs (Sawyer *et al.*, 1987; Wagner, 2006b; Touchon & Rocha, 2007). We now extend the above model to incorporate a variable number of MEs within genomes and to check the robustness of our results when there is a continuum of MEs within a given host. To this end, we define the density of individuals within the population that harbour z MEs in their genome as n_z (where $0 \le z \le M$). The transitions between the densities of cells in a given state are shown in Fig. S3 in the Supporting Information. Density-dependent growth and density-independent death is modelled as before.

We assume that the death rate because of mobile elements is μz^{ν}, where ν determines the shape of the relationship. The rate of ME duplication within a genome is given by az^{γ}, where a is the duplication rate and γ scales the shape of duplication. As we deal with a numerical model, we must impose an upper boundary condition for the number of MEs per genome, which we denote M. We use such a boundary for numerical convenience and choose a sufficiently high value ($M = 500$). However, insertion sequences are rarely as high as this, so we feel that this is a sufficient boundary condition. Here we assume that, regardless of how many mobile elements a donor cell carries, only a single mobile element is transferred during horizontal gene transfer. This would be the case if a genome contains few and unlinked mobile elements, which appears to be the case in bacterial insertion sequences (Wagner, 2006a), and thus the rate β can be interpreted as the per element transfer rate. Although this mode of transfer differs from our analytical model, our results remain qualitatively similar (as can be seen from Figs 3 and S1). As mentioned earlier, we additionally assume that the transfer rate is either proportional to the total number of infected cells N_I (i.e. transmission is density-dependent, and $s = 1$) or transfer is proportional to the overall proportion of infected cells N_I (i.e. transmission is density-independent, $s = 0$).

Making the assumptions mentioned earlier, and furthermore assuming a fixed excision rate per genome x, the overall population dynamics of the system can be written as:

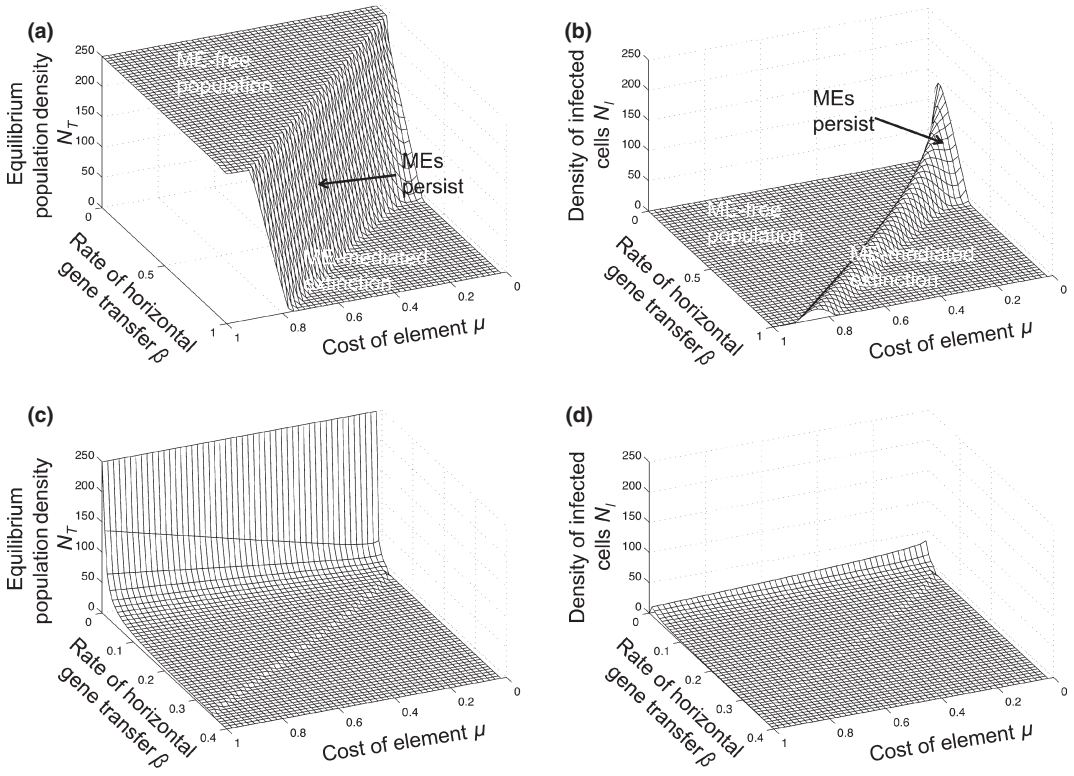

Fig. 3 The effect of horizontal gene transfer β and the cost of an additional mobile genetic element (ME) μ on the equilibrium density of the host population (a, c) and the equilibrium density of MEs in the population (b, d) for the numerical model. Results in (a) and (b) are for frequency-dependent transmission (i.e. $s = 0$), and results in (c) and (d) are for density-dependent transmission (i.e. $s = 1$). Parameters used are $r = 1$, $\theta = 0.75$, $k = 1000$, $a = 0.1$, $M = 500$, $v = 1$, $x = 0.05$, $\gamma = 1/2$.

$$\frac{dn_0}{dt} = n_0\left(r\left(1-\frac{N_T}{k}\right) - \frac{\beta N_I}{s+(1-s)N_T} - \theta\right) + xn_1 \quad (8)$$

$$\frac{dn_1}{dt} = n_1\left(r\left(1-\frac{N_T}{k}\right) - \mu - x - az^\gamma - \frac{\beta N_I}{s+(1-s)N_T} - \theta\right) + \frac{n_0\beta N_I}{s+(1-s)N_T} + xn_2 \quad (9)$$

$$\frac{dn_z}{dt} = n_z\left(r\left(1-\frac{N_T}{k}\right) - \mu z^\gamma - x - az^\gamma - \frac{\beta N_I}{s+(1-s)N_T} - \theta\right) + \frac{n_{z-1}\beta N_I}{s+(1-s)N_T} + xn_{z+1} + a(z-1)^\gamma n_{z-1} \quad (10)$$

$$\frac{dn_M}{dt} = n_M\left(r\left(1-\frac{N_T}{k}\right) - \mu M^\gamma - x - aM^\gamma - \theta\right) + \frac{n_{M-1}\beta N_I}{s+(1-s)N_T} + a(M-1)^\gamma n_{M-1} \quad (11)$$

Figure 3 shows the overall population density (Figs 3a,c) and the number of cells infected with at least one ME ($z \geq 1$, Fig. 3b,d). In the absence of horizontal gene transfer (i.e. when $\beta = 0$), extinction cannot occur, as elements will not be able to invade the population, even when the rate of duplication, a, is large (results not shown). The results are qualitatively similar to the basic model described in the previous sections: low rates of horizontal gene transfer are unfavourable for MEs to invade an ME-free population, whereas too high rates of transfer result in the extinction of the entire population. Similarly, whereas high costs of MEs (μ) inhibit their establishment in the population, intermediate costs will result in MEs being able to invade and drive the population extinct. Figure 3 shows that incorporating a variable number of MEs in the model leads to ME-mediated extinction under a much wider range of conditions: if there are multiple elements, the population can still be driven extinct, even if the overall population growth rate is high (i.e. $r > \mu + \theta$). This is indicated by the observation that extinction can occur even when the cost of a given element is close to zero (Fig. 3).

We performed a number of robustness checks on our numerical model. While we analyse a situation where the cost of an additional ME increases linearly (i.e. $v = 1$), costs may not necessarily be based on a linear relationship with ME copy number (Langley *et al.*, 1988). We therefore also examined the case where costs are

nonlinear, but found the results to be qualitatively similar (Figs S4 and S5, where $v = 2$ and $v = 1/2$, respectively). We additionally looked at the case where duplication did not depend on copy number and again found our results to be qualitatively similar (Figs S4–S6 in the Supporting Information, where $\gamma = 0$).

Metapopulation model

If MEs can bring about the collapse of an entire population, the question arises as to how MEs can persist over longer timescales. The above results assume a single, well-mixed population. In reality, populations are often divided into small sub-populations that inhabit small patches of a suitable environment. Such a population structure may affect the persistence of MEs. In particular, if MEs drive a local population extinct, they may still persist in a wider metapopulation if the cells they infect are able to colonize empty patches or patches with ME-free bacteria. Here we assume that the within-patch dynamics occur on a much faster timescale than the between-patch dynamics. If so, we can describe the transitions between patches containing a population of ME-free bacteria, denoted p_F, and patches containing ME-infected bacteria, denoted p_T. We assume that MEs will always be able to infect ME-free bacteria and that bacteria infected with MEs will invade a patch of ME-free cells with rate α. Bacteria are able to colonize empty patches at rate m. ME-free patches go extinct at rate e_F, whereas ME-containing patches go extinct at rate e_T. In this model, the cost caused by an ME to its host comes in the form of an increased extinction risk, that is, $e_T > e_F$. The dynamics of MEs in a metapopulation now becomes:

$$\frac{dP_F}{dt} = P_F(m(1 - P_F - P_T) - e_F - \alpha P_T) \quad (12)$$

$$\frac{dP_T}{dt} = P_T(m(1 - P_F - P_T) - e_T + \alpha P_F) \quad (13)$$

In the absence of any ME-infected individuals in the metapopulation, the proportion of patches occupied by ME-free bacteria at equilibrium is given by $P_F^* = 1 - e_F/m$. We can now examine the conditions under which MEs will be able to successfully invade a metapopulation consisting of entirely ME-free patches, when ME patches are rare (i.e. $P_T \rightarrow 0$). This will occur when

$$m > \frac{\alpha e_F}{\alpha + e_F - e_T} \quad (14)$$

This relationship shows that greater rates of ME invasion, and colonization, of ME-free patches will help to sustain MEs, as will an increase in the overall migration rate of bacteria between metapopulations. Additionally, greater extinction risk of either ME-free patches, or lower extinction risk of ME-colonized patches, will both favour MEs.

We next examine the criteria under which MEs will persist in a fully saturated environment with no empty patches, i.e. where all patches are colonized by bacteria. Dividing the colonization term α by the total number of patches in the environment, $M = P_F + P_T$, and then by rescaling eqn (15), we can obtain the proportion p of patches with ME-infected bacteria from the equation $dp/dt = d(P_T/N)/dt$. Using the quotient rule, this relationship becomes

$$\frac{dp}{dt} = p(1 - p)(e_T - e_T - \alpha), \quad (15)$$

which shows that, in a fully saturated environment, MEs will be able to persist if $\alpha > e_T - e_F$. In other words, ME-infected bacteria can persist in a saturated metapopulation if their rate of invasion into ME-free patches is higher than the difference in extinction rate between ME-colonized and ME-free patches, i.e. the rate of invasion of ME-infected cells into ME-free patches must outweigh the extinction risk of patches containing ME-infected bacteria. Thus, even though MEs may drive their host lineages extinct in the short-term, they can persist in structured environments over longer timescales.

Discussion

Our results identify the conditions under which mobile elements (MEs) can drive a population extinct. Importantly, horizontal gene transfer is the key, both to the persistence of MEs and to ME-mediated extinction (Figs 1–3): at low transfer rates, MEs will not be able to persist; whereas at high rates, they will drive populations extinct. The finding that horizontal gene transfer is required for element persistence is well established (e.g. Lili *et al.*, 2007), especially in sexually reproducing species (e.g. Bestor, 1999; Burt & Trivers, 2006). Our results also show that while higher rates of horizontal gene transfer facilitate extinction, ME-induced mortality needs to remain at a rate less than that of horizontal gene transfer to be able to both invade and facilitate extinction – too much mortality and an ME cannot invade; too little mortality and it cannot kill off the population (Figs 2 and 3).

While our results support the idea of ME-mediated extinction, it is important to note that they only apply if horizontal gene transfer occurs: in large populations, in the absence of horizontal gene transfer, deleterious mobile elements will not be able to persist unless they confer a benefit to the host (e.g. Edwards & Brookfield, 2003). Although for true extinction to occur (i.e. when $N_T = 0$), transmission must be frequency-dependent (i.e. proportional to the frequency N_I/N_T of infected cells in the population), our numerical results show that density-dependent transmission can also drive populations to

dangerously low levels where the population will then be driven extinct because of stochastic effects (Figs 3c and S1c). Once the population is reduced to such a low level, other effects on demography, such as demographic or environmental stochasticity (e.g. Lande, 1993), can cause complete population extinction. Similar arguments have been made for 'evolutionary suicide', where a population evolves to extinction: extinction can be abrupt (e.g. Gyllenberg & Parvinen, 2001; Parvinen, 2005) or gradual (e.g. Matsuda & Abrams, 1994; Rankin, 2007). In the latter case, a low threshold, below which the population is driven extinct, is often assumed to occur, because of demographic stochasticity (Dieckmann & Ferrière, 2004; Rankin & López-Sepulcre, 2005). In our model, we investigate only one class of mobile element, but many genomes contain more than one element (Sawyer *et al.*, 1987; Wagner, 2006b; Touchon & Rocha, 2007). A build-up of multiple species of MEs may cause the population to go extinct much faster: different species of costly MEs may build up within the genome, either through transposition or through horizontal gene transfer. This could weaken the resilience of individuals to environmental fluctuations and increase the likelihood that the population is driven extinct through stochastic effects.

Although there has been much debate about frequency-dependent and density-dependent transmission of parasites (e.g. de Jong *et al.*, 1995; McCallum *et al.*, 2001), little is known about actual transmission rates of MEs, but data suggests that transmission is rampant among closely related species (Wagner & de la Chaux, 2008). A key result of our model is that mobile elements can cause deterministic extinction only if transmission is frequency-dependent. In this case, the per capita infection rate of uninfected cells is βq, where the proportion of infected individuals is $q = N_I/N_T$. This means that if cells encounter each other at a rate β, there is a probability q that a potential donor will bear a mobile element. This is in contrast to density-dependent transmission, where the per capita infection rate of uninfected cells is $\beta q N_T$ and is thus proportional to the total number of cells N_T in the population. However, under density-dependent transmission, the population is also reduced to near-extinction (Figs 3c,d) so that extinction is likely because of demographic stochasticity. Furthermore, extinction occurs over a much wider parameter space under density-dependent transmission, because of the greater transfer rates of MEs at high population density. All three of our models use different assumptions about how individual mobile elements are transmitted: the model in section 2 allows all elements in a genome (either one element or many) to be transferred to an uninfected host, whereas the numerical model allows only one element to be transferred, regardless of how many elements the infected host genome contains. Despite these differences, the models all yield similar results with respect to the criteria for element persistence and for ME-induced extinction (Figs 3, S1 and S2). This suggests that our results are robust to changes in the mode of transmission of an individual ME and that the most important factor influencing ME-induced extinction is the rate of transmission β.

We would expect a trade-off between the transmission rate and an ME's effect on host fitness, as is the case for other parasites (Ewald, 1983; Alizon *et al.*, 2009). Transmission could be correlated with greater cell mortality if transmission imposed a cost to the cell, such as cell lysis in the case of virus transmission, or costs of conjugation, which would apply to MEs transmitted by plasmids. In this case, any increase in transmission of a given ME element would have a negative effect on the host. Thus, if there is a mild trade-off between transmission and host mortality, then mobile elements will be able to evolve high transmission rates, while still inflicting a modest mortality cost on the host, provided sufficient variation in transmission rate exists in the population (Appendix S1). A combination of high transmission and intermediate mortality can then drive the population extinct (see Appendix S1 in the Supporting Information). There is some evidence showing that bacterial genomes have mechanisms which help to confer resistance to parasitic elements such as phages and plasmids (Horvath & Barrangou, 2010), and there is evidence that other forms of MEs could face resistance from the host (e.g. Johnson, 2007). Under such mechanisms, we would expect extinction to be prevented if hosts could evade harmful elements.

An important condition for population extinction is that the overall *per capita* growth rate of the population is low. As the basal growth rate of bacteria in our model is $r - \theta$, which must be positive, this suggests that ME-mediated extinction will be more likely to occur if the host bacteria are subject to high rates of external mortality. This could occur if there was high environmental stress, or if the bacteria were subject to antibiotics in the environment. As θ represents any additional *per capita* host mortality, and is therefore independent of the mobile element in question, it is possible that a build-up of multiple types of different MEs could increase the *per capita* death rate. In our simple analytical model, which tracked only infected or uninfected hosts, the ME-induced mortality μ had to be greater than the net *per capita* growth rate $r - \theta$. Explicitly taking into account multiple elements within each genome revealed a broader region where mobile elements would drive the population extinct (Fig. S1 in Supporting Information). In fact, even when the cost μ was close to zero, the population could still go extinct, providing the level of horizontal gene transfer was great enough.

While our models have dealt only with the dynamics in sub-populations, any process that will increase the extinction risk of local populations will affect higher levels of biological organization, such as at the epidemiological or metapopulation level (Kokko *et al.*, 2008)

or the species-level (Rankin *et al.*, 2007b; Jablonski, 2008). The results of our metapopulation model show that, even if mobile elements drive populations extinct, they can still persist if they can successfully colonize new patches in a structured environment. As long as MEs can invade ME-free patches at a rate that exceeds their extinction from patches that they have already invaded, they will be able to persist in the metapopulation. MEs will be able to invade into patches of ME-free cells if the rate of horizontal gene transfer of MEs β exceeds the costs they inflict on their host. Similar arguments have been proposed for the evolution of sex, where sex has a disadvantage over asexual reproduction because of the two-fold cost of sex, but can be maintained if asexuals have a higher extinction rate (van Valen, 1975; Maynard Smith, 1978; Nunney, 1989; Kokko *et al.*, 2008). Applying multi-level selection thinking to mobile DNA highlights the hierarchical nature of selection's effects: selection can act both within and between genomes, as well as at the population level. MEs may spread easily between genomes, but if their transmission results in the extinction of the local population, there will be selection against them, which may affect their distribution and diversity (Sawyer *et al.*, 1987; Wagner, 2006b).

We specifically set out to test the idea that MEs could cause the extinction of populations, and our initial model was based on generic models of parasite-induced extinction (Boots & Sasaki, 2003). Thus, our results are sufficiently general to apply to a broad class of genomic parasites, from simple insertion sequences to bacteriophages and plasmids. Furthermore, our model incorporates explicit details of mobile elements, such as duplication and excision, and allows for a genome to be infected by multiple MEs. We show that, generally, the results of the simpler models hold, and that, even in large prokaryotic populations, it remains plausible that mobile elements could drive their host population extinct if they impose a sufficiently high cost on the host genome while retaining their ability to transfer horizontally. Our results have wider implications for evolutionary biology, such as evolution on multiple levels of organization (Lewontin, 1970; Okasha, 2006; Rankin *et al.*, 2007b; Jablonski, 2008). The extinction of populations or lineages by genes that are ultimately selected for at the individual level may occur in a wide range of systems (Rankin & López-Sepulcre, 2005). Any trait that affects fitness at the individual level will ultimately have effects at the population level. Our study has shown that mobile DNA can provide an excellent system to study the effect of selection at different levels, most notably at the population or lineage level. Such extinctions at the lineage level should additionally affect the diversity of traits we observe in nature. As such, our study illustrates that mobile elements may have dramatically detrimental consequences for the hosts and populations that harbour them.

Acknowledgments

DJR is funded by the University of Zürich *Forschungskredit*, the *SNF Ambizione* programme (grant PZ00P3-121800) and SNF grant 31003A-125457. AW and MB would like to acknowledge support through SNF grants 315200-116814 and 315200-119697, as well as through the YeastX project of SystemsX.ch. We thank Andrew Barbour for helpful discussions.

References

Alizon, S., Hurford, A., Mideo, N. & van Baalen, M. 2009. Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *J. Evol. Biol.* **22**: 245–259.

Anderson, R.M. & May, R.M. 1979. Population biology of infectious diseases: Part I. *Nature* **280**: 361–367.

Arkhipova, I.R. 2005. Mobile genetic elements and sexual reproduction. *Cytogenet. Genome Res.* **110**: 372–382.

Arkhipova, I.R. & Meselson, M. 2005. Deleterious transposable elements and the extinction of asexuals. *Bioessays* **27**: 76–85.

Bartolome, C., Maside, X. & Charlesworth, B. 2002. On the abundance and distribution of transposable elements in the genome of Drosophila melanogaster. *Mol. Biol. Evol.* **19**: 926–937.

Bergstrom, C.T., Lipsitch, M. & Levin, B.R. 2000. Natural selection, infectious transfer and the existence conditions for bacterial plasmids. *Genetics* **155**: 1505–1519.

Bestor, T.H. 1999. Sex brings transposons and genomes into conflict. *Genetica* **107**: 289–295.

Blot, M. 1994. Transposable elements and adaptation of host bacteria. *Genetica* **93**: 5–12.

Boots, M. & Sasaki, A. 2002. Extinctions in spatially structured host-pathogen populations. *Am. Nat.* **159**: 706–713.

Boots, M. & Sasaki, A. 2003. Parasite evolution and extinctions. *Ecol. Lett.* **6**: 176–182.

Brookfield, J.F.Y. 1986. The population biology of transposable elements. *Phil. Trans. Roy. Soc. Lond. B Biol. Sci.* **312**: 217–226.

Brookfield, J.F.Y. & Badge, R.M. 1997. Population genetics models of transposable elements. *Genetica* **100**: 281–294.

Brookfield, J.F.Y. & Sharp, P.M. 1994. Neutralism and selectionism face up to DNA data. *Trends Genet.* **10**: 109–111.

Burt, A. & Trivers, R. 2006. *Genes in Conflict*. Harvard University Press, Cambridge, MA.

Capy, P., Gasperi, G., Biemont, C. & Bazin, C. 2000. Stress and transposable elements: co-evolution or useful parasites? *Heredity* **85**: 101–106.

Charlesworth, B. & Langley, C.H. 1989. The population genetics of *Drosophila* transposable elements. *Annu. Rev. Genet.* **23**: 251–287.

Charlesworth, B., Sniegowski, P. & Stephan, W. 1994. The evolutionary dynamics of repetitive DNA in eukaryotes. *Nature* **371**: 215–220.

Dieckmann, U. & Ferrière, R. 2004. Adaptive dynamics and evolving biodiversity. In: *Evolutionary Conservation Biology* (R. Ferriere, U. Dieckmann & D. Couvet, eds), pp. 188–224. Cambridge University Press, Cambridge.

Dolgin, E.S. & Charlesworth, B. 2006. The fate of transposable elements in asexual populations. *Genetics* **174**: 817–827.

Doolittle, W.F. & Sapienza, C. 1980. Selfish genes, the phenotypic paradigm and genome evolution. *Nature* **284**: 601–607.

Dunham, M.J., Badrane, H., Ferea, T., Adams, J., Brown, P.O., Rosenzweig, F. & Botstein, D. 2002. Characteristic genome rearrangements in experimental evolution of Saccharomyces cerevisiae. *Proc. Natl Acad. Sci. USA* **99**: 16144–16149.

Edwards, R.J. & Brookfield, J.F.Y. 2003. Transiently beneficial insertions could maintain mobile DNA sequences in variable environments. *Mol. Biol. Evol.* **20**: 30–37.

Ewald, P.W. 1983. Host-parasite relations, vectors, and the evolution of disease severity. *Annu. Rev. Ecol. Syst.* **14**: 465–485.

Frank, S.A. 1994. Kin selection and virulence in the evolution of protocells and parasites. *Proc. Roy. Soc. Lond. B* **258**: 152–161.

Frank, S.A. 1996. Models of parasite virulence. *Q. Rev. Biol.* **71**: 37–78.

Gandon, S. & Day, T. 2009. Evolutionary epidemiology and the dyamics of adaptation. *Evolution* **63**: 826–838.

Gersani, M., Brown, J.S., O'Brien, E.E., Maina, G.M. & Abramsky, Z. 2001. Tragedy of the commons as a result of root competition. *J. Ecol.* **89**: 660–669.

Griffin, A.S., West, S.A. & Buckling, A. 2004. Cooperation and competition in pathogenic bacteria. *Nature* **430**: 1024–1027.

Gyllenberg, M. & Parvinen, K. 2001. Necessary and sufficient conditions for evolutionary suicide. *Bull. Math. Biol.* **63**: 981–993.

Hardin, G. 1968. The tragedy of the commons. *Science* **162**: 1243–1248.

Hickey, D.A. 1982. Selfish DNA - a sexually-transmitted nuclear parasite. *Genetics* **101**: 519–531.

Horvath, P. & Barrangou, R. 2010. CRISPR/Cas, the immune system of bacteria and archaea. *Science* **327**: 167–170.

Jablonski, D. 2008. Species selection: theory and data. *Ann. Rev. Ecol. Evol. Syst.* **39**: 501–524.

Johnson, L.J. 2007. The genome strikes back: the evolutionary importance of defence against mobile elements. *Evo Biology* **34**: 121–129.

de Jong, M.C.M., Diekmann, O. & Heesterbeek, H. 1995. How does transmission of infection depend on population size? In: *Epidemic Models: Their Structure and Relation to Data* (D. Mollison, ed.), pp. 84–94. Cambridge University Press, Cambridge.

Kerr, B., Neuhauser, C., Bohannanm, B.J.M. & Dean, A.M. 2006. Local migration promoted competitive restraint in a host-pathogen ''tragedy of the commons''. *Nature* **442**: 75–78.

Kokko, H., Heubel, K. & Rankin, D.J. 2008. How populations persist when asexuality requires sex: the spatial dynamics of coping with sperm parasites. *Proc. Roy. Soc. Lond. B* **275**: 817–825.

Koszul, R., Caburet, S., Dujon, B. & Fischer, G. 2004. Eucaryotic genome evolution through the spontaneous duplication of large chromosomal segments. *EMBO J.* **23**: 234–243.

Lande, R. 1993. Risks of population extinction from demographic and environmental stochasticity and random catastrophes. *Am. Nat.* **142**: 911–972.

Langley, C.H., Montgomery, E., Hudson, R., Kaplan, N. & Charlesworth, B. 1988. On the role of unequal exchange in the containment of transposable element copy number. *Genet. Res.* **52**: 223–235.

Lewontin, R.C. 1970. The units of selection. *Annu. Rev. Ecol. Syst.* **1**: 1–18.

Lili, L.N., Britton, N.F. & Feil, E.J. 2007. The persistence of parasitic plasmids. *Genetics* **177**: 399–405.

Lipsitch, M., Nowak, M.A., Ebert, D. & May, R.M. 1995. The population dynamics of vertically and horizontally transmitted parasites. *Proc. Roy. Soc. B Biol. Sci.* **260**: 321–327.

Martin, S.J., Beekman, M., Wossler, T.C. & Ratnieks, F.L.W. 2002. Parasitic Cape honeybee workers, *Apis mellifera capensis*, evade policing. *Nature* **415**: 163–165.

Matsuda, H. & Abrams, P.A. 1994. Runaway evolution to self-extinction under asymmetrical competition. *Evolution* **48**: 1764–1772.

May, R.M. & Anderson, R.M. 1979. Population biology of infectious diseases: Part II. *Nature* **280**: 455–461.

Maynard Smith, J. 1978. *The Evolution of Sex*. Cambridge University Press, Cambridge.

Mc Ginty, S., Rankin, D.J. & Brown, S.P. (in press) Horizontal gene transfer and the evolution of bacterial cooperation. *Evolution*.

McCallum, H., Barlow, N. & Hone, J. 2001. How should pathogen transmission be modelled? *Trends Ecol. Evol.* **16**: 295–300.

Nunney, L. 1989. The maintenance of sex by group selection. *Evolution* **43**: 245–257.

Ochman, H., Lawrence, J.G. & Groisman, E.A. 2000. Lateral gene transfer and the nature of bacterial innovation. *Nature* **405**: 299–304.

Okasha, S. 2006. *Evolution and the Levels of Selection*. Oxford University Press, Oxford.

Orgel, L.E. & Crick, F.H.C. 1980. Selfish DNA: the ultimte parasite. *Nature* **284**: 604–607.

Parvinen, K. 2005. Evolutionary suicide. *Acta Biotheor.* **53**: 241–264.

Rankin, D.J. 2007. Resolving the tragedy of the commons: the feedback between population density and intraspecific conflict. *J. Evol. Biol.* **20**: 173–180.

Rankin, D.J. & Kokko, H. 2006. Sex, death and tragedy. *Trends Ecol. Evol.* **21**: 225–226.

Rankin, D.J. & López-Sepulcre, A. 2005. Can adaptation lead to extinction? *Oikos* **111**: 616–619.

Rankin, D.J., Bargum, K. & Kokko, H. 2007a. The tragedy of the commons in evolutionary biology. *Trends Ecol. Evol.* **22**: 643–651.

Rankin, D.J., Lopez-Sepulcre, A., Foster, K.R. & Kokko, H. 2007b. Species-level selection reduces selfishness through competitive exclusion. *J. Evol. Biol.* **20**: 1459–1468.

Rankin, D.J., Rocha, E.P.C. & Brown, S.P. 2010. What traits are carried on mobile elements, and why? *Heredity*, doi 10.1038/hdy.2010.24.

Sawyer, S.A., Dykhuizen, D.E., DuBose, R.F., Green, L., Mutangadura-Mhlanga, T., Wolczyk, D.F. & Hartl, D.L. 1987. Distribution and abundance of insertion sequences among natural isolates of *Escherichia coli*. *Genetics* **115**: 51–63.

Smith, J. 2001. The social evolution of bacterial pathogenesis. *Proc. Roy. Soc. Lond. Series B Biol. Sci.* **268**: 61–69.

Touchon, M. & Rocha, E.P.C. 2007. Causes of insertion sequences abundance in prokaryotic genomes. *Mol. Biol. Evol.* **24**: 969–981.

van Valen, L. 1975. Group selection, sex and fossils. *Evolution* **29**: 87–94.

Vinogradov, A.E. 2003. Selfish DNA is maladaptive: evidence from the plant Red List. *Trends Genet.* **19**: 609–614.

Vinogradov, A.E. 2004a. Evolution of genome size: multilevel selection, mutation bias or dynamical chaos? *Curr. Opin. Genet. Dev.* **14**: 620–626.

Vinogradov, A.E. 2004b. Genome size and extinction risk in vertebrates. *Proc. Roy. Soc. Lond. B* **271**: 1701–1705.

Wagner, A. 2006a. Cooperation is fleeting in the world of transposable elements. *Plos Comput. Biol.* **2**: 1522–1529.
Wagner, A. 2006b. Periodic extinctions of transposable elements in bacterial lineages: evidence from intragenomic variation in multiple genomes. *Mol. Biol. Evol.* **23**: 723–733.
Wagner, A. 2009. Transposable elements as genomic diseases. *Mol. Biosyst.* **5**: 32–35.
Wagner, A. & de la Chaux, N. 2008. Distant horizontal gene transfer is rare for multiple families of prokaryotic insertion sequences. *Mol. Gen. Genomics.* **280**: 397–408.
Wenseleers, T. & Ratnieks, F.L.W. 2004. Tragedy of the commons in *Melipona* bees. *Proc. Roy. Soc. Lond. B* **271**: S310–S312.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Evolution of transmission and virulence.

Appendix S2 Analytical model of multiple mobile elements.

Figure S1 The effect of horizontal gene transfer β and the cost of mobile element infection μ on the equilibrium density of the host population (a,c) and the equilibrium density of MEs in the population (b,d) for the simple two-state analytical model.

Figure S2 The effect of horizontal gene transfer β and the cost of an additional ME μ on the equilibrium density of the host population (a,c) and the equilibrium density of MEs in the population (b,d) for the analytical three-state model described in section 2 of the model and results the main text.

Figure S3 Diagram showing the transition dynamics for the multi-state numerical model.

Figure S4 The effect of horizontal gene transfer β and the cost of an additional ME μ on the equilibrium density of the host population (a,c) and the equilibrium density of MEs in the population (b,d) for the numerical model described in Fig. S3.

Figure S5 The effect of horizontal gene transfer β and the cost of an additional ME μ on the equilibrium density of the host population (a,c) and the equilibrium density of MEs in the population (b,d) for the numerical model described in Fig. S3.

Figure S6 The effect of horizontal gene transfer β and the cost of an additional ME μ on the equilibrium density of the host population (a,c) and the equilibrium density of MEs in the population (b,d) for the numerical model.

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Received 28 May 2010; revised 30 July 2010; accepted 5 August 2010