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LETTER

Do-or-die life cycles and diverse post-infection resistance mechanisms limit the evolution of parasite host ranges

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Abstract

In light of the dynamic nature of parasite host ranges and documented potential for rapid host shifts, the observed high host specificity of most parasites remains an ecological paradox. Different variants of host-use trade-offs have become a mainstay of theoretical explanations of the prevalence of host specialism, but empirical evidence for such trade-offs is rare. We propose an alternative theory based on basic features of the parasite life cycle: host selection and subsequent intrahost replication. We introduce a new concept of effective burst size that accounts for the fact that successful host selection does not guarantee intrahost replication. Our theory makes a general prediction that a parasite will expand its host range if its effective burst size is positive. An *in silico* model of bacteria-phage coevolution verifies our predictions and demonstrates that the tendency for relatively narrow host ranges in parasites can be explained even in the absence of trade-offs.

Keywords

Bacteria-phage, coevolution, host range, host–parasite, mathematical model, mathematical theory, post-infection resistance, specialism.

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INTRODUCTION

Parasites shape the composition and dynamics of ecological communities across all biological scales (Price 1980) and together with their hosts they form dynamic coevolutionary systems (Thompson 1998). The potential of parasites to switch from one host to another is the key to major ecological issues, such as emerging infectious diseases (Woolhouse *et al*. 2005) and biological control (van Klinken & Edwards 2002).

Rapid host shifts have been documented for a wide array of host–parasite systems, suggesting that parasite host ranges are a dynamic ecological trait. Evidence comes from insects quickly adding introduced plants to their host ranges (Tabashnik 1983; Singer *et al*. 1993) and parasites switching from native to invading non-indigenous animals (Kelly *et al*. 2009). Another example is bacteriophages or phages, the viral parasitoids of bacteria, some of whom use special tail fibres to attach to receptors on bacterial cells. Tailed phage can quickly evolve to adsorb to previously unused receptors on bacterial cells (Meyer *et al*. 2012) which potentially confers a vastly increased host range. Some phages in fact possess tail fibres resembling 'Swiss army knifes', allowing attachment to a variety of host cells (Schwarzer *et al*. 2012).

Surprisingly, the flexibility in host usage is not generally associated with extended host ranges and, in fact, extreme specialisation is common in most parasitic taxa (Thompson 1994), including phages (Koskella & Meaden 2013). Why, despite the apparent advantages of a broad host range, should this be the case?

The most common rationale explaining the observed narrow host ranges assumes the existence of trade-offs: increased performance on one host is associated with decreased performance on others, so that the 'jack of all trades is a master of none' (MacArthur 1972). However, the search for such evolutionary trade-offs suggests that they are far from universal and when parasites are faced with heterogeneous host populations, generalism can indeed come without costs (see Elena *et al*. 2009 and references therein). Despite the inconclusiveness of empirical results and repeated criticism of the trade-off hypothesis (Fry 1996), surprisingly little theoretical work has been done to investigate how well-established life-history features (e.g. diet, dispersal and life-cycle complexity) in the absence of trade-offs may favour the evolution of ecological specialisation (Poisot *et al*. 2011).

In this article, we show that in the absence of host-use trade-offs, two basic features of the parasite life cycle are sufficient to limit host ranges. First, the life cycle of most obligate parasites follows a distinctive two-step pattern, with host selection and subsequent infection preceding intrahost parasite replication and/or maturation (Yao & Allen 2006; Spence *et al*. 2008). Second, for most parasites infection is a 'do-or-die' moment as they rely completely on the hosts metabolic and replicative machinery, while at the same time they must evade a wide array of intrahost resistance mechanisms (Labrie *et al*. 2010; Dangl & Jones 2001). Failure to replicate or evade post-infection resistance is generally fatal for the infecting parasite or its offspring, making it inherently more costly than failure to detect and infect the host in the first place. This asymmetry had not been considered in previous models with two-step infection mechanisms (Agrawal & Lively 2002; Fenton *et al*. 2012) and we show here that this crucial life-history feature by itself has the potential to limit host range evolution.

We focus on the interaction of bacteria and phages, which however does not impede the generality of our results. The parasitoid life cycle of phages involves steps that are analogous to those of most obligate parasites, and many bacteria

possess intracellular defence mechanisms resembling animal and/or plant innate and adaptive immune systems (Abedon 2012). In addition, their rapid coevolutionary turnover makes bacteria-phage systems amenable to direct experimental tests of theoretical predictions, making them ideal model organisms to study the ecology and evolution of host range.

We start by deriving a simple model of phage growth which explicitly takes into account the distinctive two-step nature of the parasite life cycle. In a generalisation of optimality theory (Bull & Wang 2010), this gives rise to a new concept of the dynamic 'value' or profitability of a particular host in terms of the likelihood of post-infection failure of replication. We call this the *effective burst size* and generate a simple and testable prediction that a pathogen will expand its host range if its effective burst size is positive. We then test this theory *in silico* with a fully dynamical model of bacteria-phage coevolution and demonstrate that it can successfully predict the evolution of specialist viruses. Our theory sheds light on the enigmatic observation that there is an inherent tendency of evolution to favour relatively narrow host ranges in parasitic taxa.

MATERIAL AND METHODS

A mathematical model of phage growth with post-adsorption resistance

Assumptions

Before we describe the model, we introduce the following assumptions regarding phage growth and replication. The phage replication process can roughly be broken down into two major steps: irreversible *adsorption* to the host cell and intracellular *replication* (Fig. 1). We assume that the rate of adsorption of phages to bacteria is proportional to bacterial density with rate constant ϕ. Completion of the initial adsorption step has the distinctive feature that it necessarily leads to the inactivation of the infecting phage by removing them from the environment. But despite paying this ultimate price, the success of the intracellular replication is not guaranteed. Completion of the replication process leads to bacterial lysis and death and the subsequent release of β new phages, which for simplicity we assume to occur instantaneously. This clearly poses a strong selection pressure on bacteria to devise specific strategies to interrupt the replication cycle. One such strategy is recognition and cleavage of the phage genome by intracellular resistance mechanisms, such as restriction/modification (Wilson & Murray 1991) and CRISPR systems (Horvath & Barrangou 2010). The collection of post-adsorption resistance mechanisms available to a host has been termed the phage *resistome*.

To ensure that our results do not depend on pleiotropic costs and associated trade-offs between different host phenotypes, we assume that neither the burst size nor the adsorption rate constant depends on the specific host resistome or phage phenotype respectively.

The model

We now derive a simple model for the *per capita* growth rate of phages, which takes into account the inactivation of phage following adsorption and the possibility of post-adsorption failure of replication. Consider a phage population P which can adsorb to a specific range of bacterial host cells. This bacterial population will be called the *adsorption range* of phage P and we will denote the total density of cells within this range as B_a. While to the phages appearing as indistinguishable cells, this bacterial population may actually represent a genetically diverse collection of post-adsorption resistance mechanisms or resistomes. Thus, it is not at all clear that a cell that is 'visible' to the phages by presenting the right receptor is necessarily also suitable for replication.

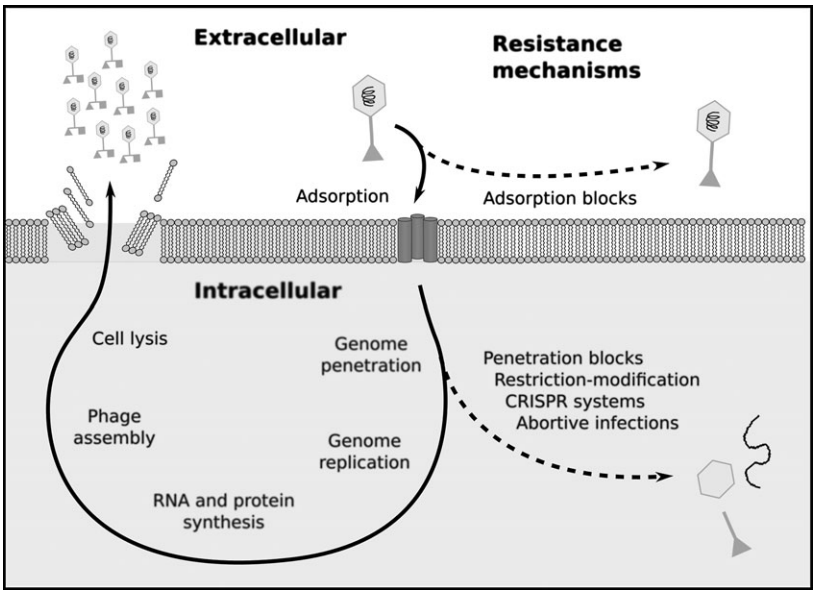

Figure 1 Sketch of the generalised life cycle of a tailed phage, involving extracellular adsorption to the host and intracellular replication. Adsorption blocks prevent infection, but do not destroy the phage particle. Intracellular resistance mechanisms on the other hand result in an inactivated phage particle.

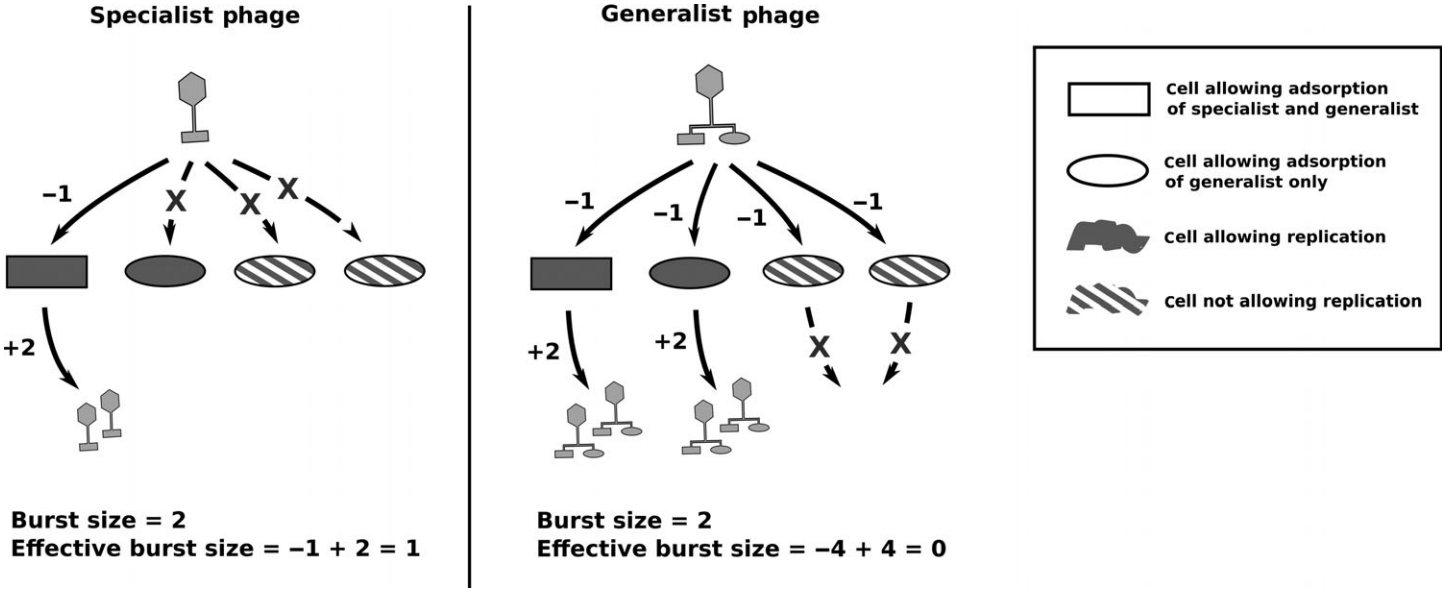

Figure 2 An example of the adsorption (B_a) and replication (B_r) range of a specialist phage (left panel) and a generalist phage (right panel) which have the same burst size $\beta = 2$ and are exposed to four bacterial types. In the specialist case (left panel), $B_a = B_r = 1$, which means that the removal of one specialist phage virion from the environment through adsorption, gives rise to two new phage virions. Therefore, the effective burst size of the specialist is 1. In the generalist case (right panel), $B_a = 2$ and $B_r = 4$, so that the removal of four generalist phage virions from the environment through adsorption gives rise to four new phage virions. Therefore, the effective burst size of the generalist phage is 0.

To account for this, the subset of hosts within the adsorption range which actually lead to the release of phage progeny will be called the *replication range*, with the total cell density within this range denoted by B_r. It is important to observe that the replication range may in general be strictly narrower than the adsorption range, namely $B_r < B_a$ (for an illustration, see Fig. 2). Note that this nomenclature is similar to terms that have been coined for plasmid transfer and replication (Filutowicz 2009), which is not surprising given the related nature of phages and plasmids as foreign genetic elements.

Subsequently, the *per capita* growth rate of the phage population is given as the difference between the rate of phage progeny release following successful replication and the rate of phage loss due to adsorption. The replication rate depends on the density B_r of host phenotypes which are in the replication range of P, whereas the loss rate is mediated by all hosts in the adsorption range. We thus obtain

$$\frac{1}{P}\frac{\mathrm{d}P}{\mathrm{d}t} = \underbrace{\beta\phi B_r}_{\text{gain through replication}} - \underbrace{\phi B_a}_{\text{loss through adsorption}} = \underbrace{\left[\beta\frac{B_r}{B_a} - 1\right]}_{\text{effective burst size}} \phi B_a, \quad (1)$$

for the *per capita* growth rate of the phage population P. The first factor in the rightmost expression emphasises that one phage particle is inactivated during adsorption to a host cell and that with a probability of B_r/B_a, this cell actually allows for replication. This effectively diminishes the use of the traditional *per capita* burst size β and introduces instead a new concept of the *effective burst size* (cf. Fig. 2).

RESULTS

Expansion of adsorption range

In general, the bacterial host B in growth model (1) will form part of a larger microbial community, which opens the possibility for host range expansions of the phage P. We now ask, under what conditions does a potential expansion of the adsorption range actually confer a higher phage fitness?

Specifically, imagine that P^* is an adsorption range mutant of P, which has developed the ability to adsorb to a new bacterial host B^*. As we explicitly exclude pleiotropic costs from our considerations, we assume that the mutation conferring the increased adsorption range does not impede the ability to replicate on the original host. As a consequence, the adsorption and replication range of the mutant P^* is potentially broader than that of its ancestor, but will always include the ancestral range of bacterial phenotypes (see Fig. 2 with specialist phage representing P and the generalist phage representing P^*).

To address the question whether the adsorption range mutant (P^*) has a higher fitness than the more specialist ancestor (P), we compare their growth rates. The *per capita* growth rate of the ancestor depends only on the bacterial species B and is given by eqn 1. The *per capita* growth rate of the mutant, on the other hand, is determined by the combined population densities of the two bacterial species and consequently it is given as the sum of the ancestral growth rate and the additional growth mediated by the new host species B^*:

$$\frac{1}{P^*}\frac{\mathrm{d}P^*}{\mathrm{d}t} = \underbrace{\left[\beta\frac{B_r}{B_a} - 1\right]\phi B_a}_{\text{growth rate on } B} + \underbrace{\left[\beta\frac{B_r^*}{B_a^*} - 1\right]\phi B_a^*}_{\text{growth rate on } B^*}. \quad (2)$$

Clearly, whenever this combined growth rate is positive, the adsorption range mutant can persist in an environment not containing the specialist ancestor. However, for this generalist mutant to have an actual fitness advantage over the specialist, it needs to have a higher instantaneous growth rate than the specialist, i.e.

$$\frac{1}{P^*}\frac{\mathrm{d}P^*}{\mathrm{d}t} > \frac{1}{P}\frac{\mathrm{d}P}{\mathrm{d}t}.$$

As the generalist mutant is assumed to have exactly the same growth rate on the shared host B as the ancestor, it will have a fitness advantage over the specialist if and only if its effective burst size on the new host B^* is positive, namely

$$\beta\frac{B_r^*}{B_a^*} > 1. \quad (3)$$

In general, the ratio between the replication and adsorption range associated with the new host will typically change dynamically in response to phage attack, bacterial coevolution and abiotic factors. As a consequence, unless the coevolutionary system is at equilibrium, a specific host range mutant may be favoured at one time and disfavoured at another depending on the current structure of the new host population. To illustrate the point consider a single cell of the new host B^* which allows for both adsorption and replication. Then $B_r^* = B_a^* = 1$, so that $B_r^*/B_a^* = 1$ and the effective burst size is $\beta-1$. Now assume that, after a division, a mutant arises that still allows adsorption but precludes replication of the phage. Consequently, the adsorption range of the phage expands to $B_a^* = 2$ but the replication range remains the same $B_r^* = 1$, leading to the new ratio $B_r^*/B_a^* = 1/2$ and thus lowering the effective burst size to $\beta/2-1$. We explore the transient and long-term dynamics highlighted by this example in more detail in the next section.

In silico test of the theory: bacteria-phage coevolution model

We test our general condition (3) *in silico* using a computational model of bacteria-phage coevolution incorporating CRISPR-mediated post-adsorption resistance, similar to the model presented by Childs *et al.* (2012) (see Supporting Information S1 for details).

We consider a microbial community consisting of two distinct bacterial hosts B and B^* and two phage populations. The first phage type P can only adsorb to host B, whereas the host range mutant P^* can adsorb to both B and B^*. For simplicity, we assume that both bacterial hosts have the same growth rate, both possess competent post-adsorption resistance mechanisms and they differ only in the number of distinct post-adsorption phenotypes. Specifically, we assume that population B consists of M distinct types differing in post-adsorption resistance, whereas population B^* is composed of up to $N > M$ genetically distinct phenotypes. Hence, adsorption to either host results in successful replication of the adsorbing phage only if the infecting phages genome is not recognised and cleaved by the specific host cell. To make the model as simple as possible, we represent the second infection step by a simple matching alleles infection mechanism (Frank 2002) while phage loci involved in the infection of either host are completely independent of loci involved in infection of the other.

Although this fully dynamic computational model allows for complex coevolutionary dynamics, as all host phenotypes have the same growth rate, the system will eventually reach an equilibrium where all host phenotypes are present in the population at the following frequencies: $1/M$ for host B phenotypes and $1/N$ for host B^* phenotypes. From eqn 3 our theory then predicts that the generalist phage P^* outcompetes the specialist P in the long run only if its burst size exceeds the number of phenotypes in the host population B^* at equilibrium, i.e. $\beta > N$ (for derivation see Supporting Information S2). This particular diversity threshold is the simplest special case of the general condition (3) and a similar result has been obtained by Lively (2010) in the limit of infinite population size.

For our simulations we set $N = 128$, which is on the order of genetically distinct CRISPR types observed for some bacterial species (Horvath *et al.* 2008). For host B to be distinct from host B^*, we need $M < N$ and for computational simplicity we set $M = 16$. Note, that our values for N and M are probably still conservatively low, given the reported tremendous diversity of the bacterial resistome (Hoskisson & Smith 2007; Andersson & Banfield 2008). According to our prediction, the specialist prevails if the phage burst size is less than N (but still large enough for the phage to persist on host B alone, i.e. $\beta>M$), whereas the generalist persists if the burst size is larger than N. This can be easily verified with our simulations by choosing two representative burst sizes, one below and one above the predicted diversity threshold N, but both being well within the range of typically observed burst sizes (De Paepe & Taddei 2006). Our simulations show precisely what the theory predicts and the results are given in Fig. 3, Figs S2 and S3. Note that each simulation is initiated with a homogeneous population of B and B^* in the presence of the specialist phage P. The host range mutant P^* is introduced after an initial lag phase ($t = 500$) to avoid any confounding effects of the initial coevolutionary adaptation of the ancestral phage to its host.

In the first scenario with burst size $\beta = 100$ (i.e. $\beta < N$), the broad host range phage is initially able to achieve a high growth rate and high population densities because it has to adapt to only a small number of distinct resistome phenotypes and losses due to adsorption to non-matching hosts are easily outweighed by replication on suitable cells (Fig. 3a/c). However, as soon as the broad host range phenotype makes up approximately half of the total phage population, the bacterial host B^* begins to diversify rapidly. At this stage the coevolutionary dynamics are characterised by a rapid turnover of host and phage phenotypes; cf. Fig. S2 for more detailed allele dynamics. After several rounds of diversification and once a critical level of host diversity is reached, host B^* has effectively become a sink for the host range mutant. While ongoing frequency-dependent selection still promotes considerable variation in the composition of the host and phage populations, the replication range of each phage phenotype has become so narrow relative to its adsorption range that on average more phages are lost than gained. This turns the coevolutionary process on its head, by rendering the initial

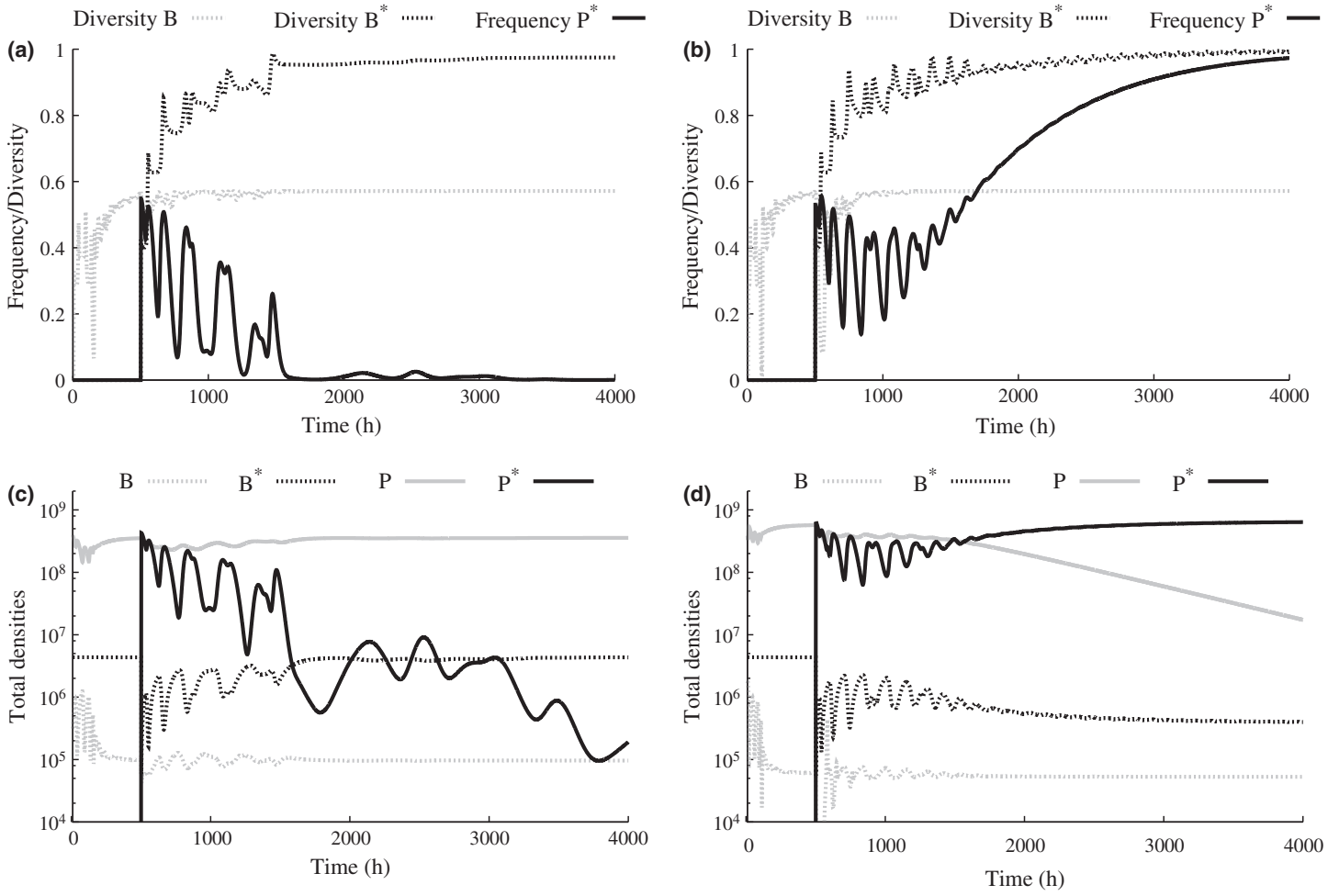

Figure 3 Generalist phage frequency (solid black line) with (a) burst size $\beta = 100$ and (b) burst size $\beta = 130$. Normalised Shannon–Wiener index shows the increase in diversity of host B (dashed grey line) and B^* (dashed black line). Corresponding total population densities over time of the bacterial hosts B (dashed grey line) and B^* (dashed black line) and the two phage types specialist P (solid grey line) and generalist P^* (solid black line) in the case of (c) burst size $\beta = 100$; (d) burst size $\beta = 130$.

advantage of the host range expansion into a selective disadvantage. Consequently, the phage community starts to shift back in favour of the host specialist. Eventually, the broad host range phenotype is lost from the phage population, its transient dominance brought to an end by the rapid diversification of one of its bacterial hosts.

A burst size of $\beta = 130$ (i.e. $\beta > N$) on the other hand should allow the generalist to permanently replace the specialist phage. This is indeed what is observed, as the host generalist is maintained even after the bacterial resistome has reached its maximal diversity (Fig. 3b/d). For population and allele dynamics in this case, see Fig. S3.

Our results are independent of the particular level of post-adsorption diversity (provided $M < N$) as illustrated in Supporting Information S4 where qualitatively similar results were obtained for the case where the shared host B does not possess a competent post-adsorption resistance mechanism and thus does not diversify ($M = 1$). Moreover, our findings are also robust to changes in the mechanism that confers post-adsorption resistance (Supporting Information S5).

DISCUSSION

In our study, we considered how the interplay of the 'do-or-die' nature of the parasite life cycle and diverse host defences can promote host specificity in parasites. Using bacteria and their viruses (phages) as model organisms we developed a mathematical framework that takes into account two distinctive stages in the host–parasite life cycle. Stage 1 involves the parasite's adsorption to a particular host and the subsequent deployment of host defences preventing the adsorption from taking place. Stage 2 follows successful adsorption and involves parasite intracellular replication and the subsequent deployment of host resistance preventing parasite replication inside the host. Although adsorption resistance mechanisms have been studied extensively, mechanisms preventing intracellular replication remain an underappreciated avenue of bacterial resistance to phage attack (Hyman & Abedon 2010).

Taking into account emerging insights into the diverse array of intracellular defence mechanisms (Labrie *et al.* 2010) and placing them in the context of the classical fields of ecological specialisation and diversity, our mathematical framework gen-

erated a simple but general condition for specialist parasites to be favoured over generalists. This condition utilises a new concept of *dynamic host profitability* defined as the effective number of parasites produced per infective host and states that a parasite will expand its host range if profitability of a new host is greater than zero. We verified this prediction using an *in silico* bacteria-phage system.

Our approach synthesises and extends several previous theories as we now discuss. While previous two-step infection models (Agrawal & Lively 2002; Fenton *et al*. 2012) also considered two distinct infection mechanisms to determine the outcome of a host–parasite interaction, they did not make the crucial distinction between the qualitatively different effects of failure at the first step (host finding/selection), which precludes host–parasite interaction altogether, vs. failure at the second step (intrahost replication), which leads to the death of the parasite or its offspring. As such these previous models are effectively based on a one-step process in disguise and therefore trade-offs were still necessary to maintain parasite diversity.

We further emphasise that it is not the total number of traits or alleles involved in the infection process that constrains host range evolution in our model. While in line with previous studies the probability of a successful host infection decreases with increasing number of host resistance loci (Gilman *et al*. 2012), this by itself would not render a broader host range unprofitable if infection and replication were mediated by a simple one-step process. This is because even marginal numbers of additional successful infections provide a fitness advantage for the parasite if failure of infection does not carry an intrinsic cost, as is typical for one-step host–parasite models. In fact, in a variant of our *in silico* model where the two-step infection process is replaced by a simple one-step interaction, the generalist always outcompetes the specialist irrespective of its burst size and the total number of traits or alleles involved in the host–parasite interaction (Fig. S6a). Only accounting for the consequences of intrahost replication failure allows us to derive condition (3) for the probability of infection success, thereby providing a limit on host range evolution by tying in life-history parameters of the parasite with the structure of the host population.

Our model is also related to classical optimal foraging theory, as adapted to host–parasite systems (Bull & Wang 2010). However, classical optimality theory is limited by its assumption of an essentially static host environment and constant host profitability, which could be the reason why it fails to explain certain aspects of host range evolution (Guyader & Burch 2008). In contrast, in our theory, host profitability is itself a fully dynamical variable, which is determined by the adsorption and replication ranges of the parasite, which are in turn related to the diversity of the host population. In particular, the dynamic nature of the host profitability and the specific form of condition (3) imply that the success of broad host range parasites may be transient. This is demonstrated by our *in silico* model, where at low burst sizes the initial success of the generalist phage is brought to an end by the diversifying host population (Fig. 3a/c). This theoretical result mirrors experimental evidence suggesting that the emergence of more generalist phages during the early arms race stages of coevolution is transient and short lived (Hall *et al*. 2011a).

Although the above findings are consistent with evidence suggesting that genetically diverse populations are more resistant to parasites (Altermatt & Ebert 2008), our results further suggest that the precise source of diversity is crucial for its potential to reduce parasite loads. For example, in our bacteria-phage system, while phage receptors on bacterial cells can be just as diverse as post-adsorption resistance mechanisms, they have a very different effect on phage fitness. Adsorption blocks effectively make the cell 'invisible' to the phages and while this reduces the availability of potential hosts, it does not directly lead to the loss of phage from the environment. Resistance conferred through post-adsorption mechanisms on the other hand leads to a direct reduction in free virions in the environment, making post-adsorption failure of replication inherently more costly than failure to infect the host in the first place. The effect of this dichotomy between an almost fitness-neutral and a severely fitness-reducing resistance mechanism has been experimentally demonstrated in the context of ecological traps (Dennehy *et al*. 2007; Heineman *et al*. 2008), where non-suitable hosts precluding replication are disguised as high-quality hosts. However, in contrast to those experimental systems, no host in our *in silico* system qualifies as a true ecological trap because at no point does a host completely preclude phage replication as there is no universally resistant phenotype in our model.

It is important to note that the central condition (3) was derived without assuming any particular infection genetics at either step of the infection process, implying that in general our results are independent of the specific mechanism that confers post-adsorption resistance. Thus, while the underlying infection genetics of course determine the interplay of adsorption and replication range, and as such can influence the potential of parasites to expand their host ranges (Poullain & Nuismer 2012), the general predictions of our model remain valid if, for example, the matching alleles mechanism at the second infection step is replaced by a modified gene-for-gene mechanism, cf. Supporting Information S5.

A large adsorption but small replication range is likely to result in a substantial reduction in phage fitness. As our coevolutionary model has shown, parasites can close this costly gap by excluding a host from their adsorption range. This phenotypically corresponds to a potentially simple and relatively quick loss of function. That phages actually use this option has been demonstrated by Heineman *et al*. (2008), suggesting that T7 phage can rapidly evolve to specifically avoid *Escherichia coli* strains which do not allow for replication. This observed rapid narrowing of the adsorption range moreover suggests that adaptation to post-infection resistance mechanisms imposes a relatively strong time constraint on the coevolutionary response of a parasite, as maladapted parasites are actively killed or inactivated by resistant hosts. This is consistent with genomic studies suggesting extremely rapid coevolution of bacterial CRISPR loci and corresponding phage proto-spacer motifs (Andersson & Banfield 2008; Levin *et al*. 2013; Sun *et al*. 2013).

A close association between adsorption and replication also suggests that a parasite's host range should closely match the

current host environment, which should be reflected in phylogenetic conservatism, i.e. decreased potential to infect phylogenetically distant hosts. This is consistent with recent experimental studies reporting that host phylogeny can explain most variation in viral fitness on different host species (Longdon *et al*. 2011) and that bacteria-phage coevolution does not extend host ranges to related, but previously unencountered hosts (Scanlan *et al*. 2013). In a way, the two-step nature of the parasite life cycle renders host shifts to genuinely novel hosts somewhat of an evolutionary 'chicken-and-egg' problem. Successful replication requires the parasite to succeed at every post-infection step of the replication cycle, but as long as a parasite is not properly adapted to the internal workings and resistance mechanisms of the new host, the ability to infect a new host may in fact confer a fitness cost.

This problem is alleviated in the case of host range expansions where continued replication on the original host can provide a supply of beneficial mutations (Dennehy *et al*. 2010), thereby enabling the long-term coevolution necessary for the adaptation to the new host (Hall *et al*. 2011b) even if effectively it is a sink for the parasite. Our model can easily emulate this scenario by taking the specialist out of the picture, in which case even if the effective burst size on the new host is negative and condition (3) is violated, the generalist can still persist as long as the generalist's combined growth rate (2) on both hosts is positive. This is illustrated in Fig. S6b, showing the persistence of the generalist at low burst sizes in the absence of the specialist.

While our theory was developed on the basis of bacteria–phage interactions, it is not exclusive to any specific resistance mechanism or host–parasite system. The 'do-or-die' two-step nature of the phage replication cycle (Fig. 1) is typical for many host–parasite interactions and choosing an unsuitable host is always associated with a direct reduction in parasite fitness, thereby promoting conservatism in host choice. For example, insects have evolved numerous post-infection defence mechanisms to disrupt parasitoid replication processes and, in line with our predictions, endoparasitoids that face the full arsenal of their hosts' immune system tend to have narrower host ranges than ectoparasitoids (Strand & Pech 1995).

We stress again that we have deliberately excluded all forms of genetic mechanisms depending on pleiotropic and/or epistatic interactions (Remold 2012) from our study. We have thus shown that the dynamic interplay of key features of the parasite life cycle and diversification of post-infection resistance mechanisms are sufficient to explain the apparent lack of generalists in natural environments. However, we want to emphasise that we do not claim that pleiotropic costs and associated host-use trade-offs do not exist at all. On the contrary, the search for and understanding of trade-offs remains key to many ecological and evolutionary questions (Gudelj *et al*. 2010) and they tend to reinforce our results by further diminishing the potential benefit of being too generalist.

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AUTHORSHIP

MS and IG conceived the idea; MS and IG developed and analysed mathematical models; MS and IG wrote the manuscript.

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