Adaptation and the evolution of parasite virulence in a connected world

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Adaptation is conventionally regarded as occurring at the level of the individual organism, where it functions to maximise the individual's inclusive fitness[1-3]. However, it has recently been argued that empirical studies on the evolution of parasite virulence in spatial populations show otherwise[4-7]. In particular, it has been claimed that the evolution of lower virulence in response to limited parasite dispersal[8,9] provides proof of Wynne-Edwards'[10] idea of adaptation at the group level. Although previous theoretical work has shown that limited dispersal can favour lower virulence, it has not clarified why, with five different suggestions having been given[6,8,11-15]. Here we show that the effect of dispersal on parasite virulence can be understood entirely within the framework of inclusive fitness theory. Limited parasite dispersal favours lower parasite growth rates and hence reduced virulence because it: (1) decreases the direct benefit of producing offspring (dispersers are worth more than non-dispersers, because they can go to patches with no or less parasites), and (2) increases the competition for hosts experienced by both the focal individual ('self shading') and their relatives ('kin shading'). This demonstrates that reduced virulence can be understood as an

individual-level adaptation by the parasite to maximize its inclusive fitness, and clarifies the links with virulence theory more generally[16].

Darwin's theory of natural selection explains both the process and the purpose of adaptation[17,18]. The process of adaptation occurs through the action of natural selection, which is mediated by differential reproductive success of individual organisms, and resulting changes in gene frequency[17]. This process leads individual organisms to appear designed as if for the purpose of maximising their inclusive fitness, which is defined as the effect of one individual's actions on her genetic contribution to future generations via her direct descendants and those of her relatives[1,2]. The inclusive fitness approach to adaptation has been extremely successful, especially in the fields of behavioural and evolutionary ecology, providing explanations for a huge range of traits[19,20].

Despite the success of inclusive fitness theory, a number of recent papers by E.O. Wilson and others have challenged this idea, arguing that natural selection can favour group adaptations in cases where inclusive fitness is not maximised[4-7]. This suggestion is analogous to Wynne-Edwards' original idea of group selection[10], where adaptations occur for the benefit of the group. The primary empirical evidence upon which this challenge is based[4-7], is the experimental observation that parasites (viruses) of both moths and bacteria evolve to cause less damage to their hosts (lower virulence) in spatially structured populations, when dispersal is limited[8,9]. The argument here is that the parasites become more prudent to prevent overexploitation and hence to avoid causing the extinction of the local host population. However, it seems plausible that this effect of limited dispersal could also be explained by inclusive fitness theory, because it will lead to a higher relatedness between interacting parasites, which has long been known to favour a more prudent exploitation of host resources and hence a lower virulence[16] (see supplementary information). The only way to resolve this debate is to

move away from verbal arguments and towards formal theoretical models, that incorporate explicit spatial dynamics such as variable patch sizes and within patch demography, and to use such models to determine the underlying evolutionary mechanisms[21].

Here, we address this problem, by using a standard epidemiological model [16,22], placed in the context of a geographically structured population, to determine why limited parasite dispersal selects for lower levels of virulence. We assume the simplest possible scenario to make the underlying selective forces explicit, and to allow comparison with previous models, which have shown that dispersal influences virulence, but have failed to clarify why[11-15]. More general discussion of the various ways in which virulence theory has been expanded, to examine the consequences of a range of potentially important biological factors, are provided elsewhere[16,23]. In addition to its role in the debate over the process of adaptation, this effect of dispersal may be particularly important for the evolution of parasites, because it suggests that as human-activity makes the world more connected, natural selection will favour more virulent and dangerous parasites[12].

We assume an "island model" with an infinite number of patches (subpopulations) each of which may contain up to N host individuals. In this model, an individual (host or parasite) either remains on its natal patch, or disperses. In the latter case, each of the other patches in the population is an equally likely destination. The island model is a standard tool for examining the effect of population structure, while allowing analytical simplifications by dividing interactions into "local" (same patch) or "global" (different patch)[21,24]. We assume that hosts reproduce at a constant per capita rate, b. A newborn host will attempt to settle either on its natal patch (local dispersal) with probability $1–d_h$, or on a randomly chosen, non-natal patch (global dispersal) with probability d_h. A newborn host successfully settles on a patch only when the patch in question supports

fewer than N individuals. If successful, the newborn host is assumed, for convenience, to mature instantaneously. If unsuccessful, the newborn dies. We assume also that adult hosts are not capable of dispersal—each adult remains on the patch it settled as a newborn.

We classify hosts as either infected by the parasite, or uninfected. We ignore the possibility of multiple infections[16], and so infected and uninfected hosts might also be called non-susceptible and susceptible, respectively. In our model, uninfected hosts die at constant per capita rate, μ. Infected hosts, on the other hand, suffer a greater risk of mortality, dying at rate $\mu + z$. Here, z describes the disease-induced mortality (parasite virulence) that arises as a consequence of the parasite's exploitation of its host.

We assume that parasite transmissibility, $\beta(z)$, is positively correlated with parasite virulence (z), to reflect the standard assumption that increased parasite growth leads not only to greater transmission, but also greater host mortality[16,22]. We allow only horizontal transmission of the parasite, from infected adult to uninfected adult, and hence vertical transmission from host parent to its unborn offspring is not possible. Transmission, itself, is assumed to occur locally (within patch) at a rate proportional to $(1 - d_p)\beta(z)$ and globally (to other patches) at a rate proportional to $d_p\beta(z)$. In both cases parasite transmission is assumed to follow a law of mass action. The parameter d_p is a proportion and is interpreted as the rate at which parasite offspring "disperse" to new, randomly-chosen patches.

We classify patches, and the parasites on those patches, according to the local number of uninfected (i) and infected (j) hosts. Naturally, parasite fitness depends upon the class to which its patch belongs, and the distribution of the different classes of patch in the population. In order to determine the evolutionarily stable (ES) level of parasite virulence, z^*, we consider a rare mutant parasite (the focal individual) belonging to

class (k,l)—i.e. on a patch with k uninfected hosts and l infected hosts. Note that while the *global* frequency of the mutant parasite is negligible, the probability that parasite neighbour of a mutant is, itself, a mutant is not necessarily negligible. Thus, it is reasonable to expect that the social effects of mutant virulence are felt by other mutants as well.

In the supplementary information we show that, if the focal mutant parasite increases its virulence phenotype by a small amount ($\delta > 0$), the resulting change in its inclusive fitness, $\Delta W_{(k,l)}$ is given by

$$\Delta W_{(k,l)} = -\delta v_{(k,l)} + \delta\beta'(z)[(1 - d_p)k v_{(k-1,l+1)} + d_p \Sigma_{(i,j)} v_{(i,j)}(i + 1)p_{(i+1,\,j-1)}]$$

$$-\delta\beta'(z)(1 - d_p)k(v_{(k,l)} - v_{(k-1,l+1)})$$

$$-\delta\beta'(z)(1 - d_p)k(v_{(k,l)} - v_{(k-1,l+1)})r_{(k,l)}(l - 1) + \delta(v_{(k,l-1)} - v_{(k,l)})\, r_{(k,l)}(l - 1), \qquad (1)$$

where $p_{(i,j)}$ is the equilibrium frequency of class-(i,j) patches, $r_{(k,l)} = r$ (see supplementary material) is the relatedness between two different parasites on the same class-(k,l) patch, and $v_{(k,l)}$ is the reproductive value[17] of a class-(k,l) parasite (the long-term genetic contribution made by such a parasite). Put verbally, equation (1) shows that the inclusive fitness effects of increased virulence are: the cost of killing one's host, the benefits of enhanced transmission, the costs of increased competition for self, the costs of increased competition for relatives, and the benefit to relatives due to killing one's host. In the supplementary material we show how equation (1) is used to determine the ES level of virulence z^*.

In clear contrast to recent claims[4-7], analysis of equation (1) shows that the effect of parasite dispersal on virulence can be explained entirely with inclusive fitness theory (Fig. 1). Equation (1) is divided into the direct (personal) fitness consequences of increased virulence (first and second lines), and the indirect consequences for relatives

(third line). The first line of equation 1 reflects the assumed trade-off between host survival and parasite transmission: the host exploited by the mutant parasite suffers increased mortality (captured by the term, $-\delta v_{(k,l)}$), while the parasite itself is able to produce new infections – both locally and globally – at a slightly higher rate (captured by the "fecundity change" term, $\delta\beta'(z)[(1-d_p)kv_{(k-1,l+1)} + d_p\Sigma_{(i,j)}v_{(i,j)}(i+1)p_{(i+1,j-1)}]$). For the special case of a well-mixed parasite population ($d_p = 1$), all but the first line of equation (1) vanishes (see supplementary information), giving us the standard result that virulence evolves to maximize the basic reproductive number of the parasite[16,22].

The second line of equation 1 describes the direct (personal) fitness consequences, for the mutant, of increased local competition for fewer uninfected hosts. The increased transmissibility of the mutant increases the rate at which uninfected hosts become infected on the mutant's patch: class-(k,l) mutants move to class-$(k-1,l+1)$ at a higher rate. Numerical results indicate that $v_{(k,l)} - v_{(k-1,l+1)} > 0$, and so this change in the local host population represents an additional direct fitness cost of increased virulence that occurs in structured populations (Fig. 1d). Put simply, if parasite offspring do not disperse, then they decrease the local availability of uninfected hosts, and increase the number of parasites competing for them. Consequently, increased parasite dispersal favours higher virulence because it reduces the direct cost of producing offspring with which the focal individual will have to compete (a reduction in both the difference in reproductive values and in $1-d_p$ in the second line of equation 1; Fig. 1a,d). This effect on direct fitness appears to be what is described as self-shading[12], and so this can be thought of as parasite dispersal reducing self-shading, but is also analogous to the tragedy of the commons[8].

The third line of equation 1 describes how the increased virulence exhibited by a mutant also has indirect fitness consequences, through changes to the competitive environment experienced by relatives. The major effect is that the increased

transmission that results from the higher virulence of the mutant means that the relatives of the mutant also suffer increased competition for fewer locally available, uninfected hosts. The first term of the third line of equation 1 is simply the second line multiplied by both the number of parasites (other than the mutant actor) on the patch ($l - 1$), and the mean relatedness of those other parasites to the mutant ($r_{(k,l)}$). This indirect cost of increased virulence is reduced by parasite dispersal, through making relatives less likely to interact (Fig. 1b), and by decreasing the extent to which an increased virulence reduces the availability of uninfected hosts to relatives (a reduction in $1 - d_p$, $r_{(k,l)}$, and the difference in reproductive values in the first part of line 3, equation 1; Fig. 1a,b,d). Consequently, increased parasite dispersal favours higher virulence, because it reduces competition between relatives, and hence reduces the indirect cost of higher virulence. This is analogous to self-shading, but applied to the relatives of the mutant actor, and so it could be thought of as "kin-shading." Kin shading is a between host equivalent to the previous result that a lower relatedness (higher strain diversity) within hosts favours higher parasite virulence because it selects for faster growth rates, to obtain a higher proportion of the host resources[16].

The third line of equation 1 also shows that the increased host mortality due to increased virulence affects the competitive environment experienced by the relatives of the mutant (second term of line 3, equation 1). Increased host mortality benefits relatives, because it leads to a reduction in the number of locally competing parasites (a parasite dies along with its host), and because it clears a space that can later be filled by newborn (uninfected) hosts. Increased host mortality is also potentially costly to relatives, because it reduces the number of local hosts (a source of newborn, uninfected hosts). In many cases, numerical results indicate that $v_{(k,l-1)} - v_{(k,l)} > 0$, and so the increased host mortality that results from increased mutant virulence provides a net benefit to the mutant's relatives (see top lines in Fig. 1d). In these same cases, reduced parasite dispersal leads to a decrease in the competition experienced by relatives, and

hence an indirect benefit to higher virulence. In other cases, $v_{(k,l)} > v_{(k,\,l\text{-}1)}$ and the term, $\delta(v_{(k,l\text{-}1)} - v_{(k,l)})r_{(k,l)}\,(l-1)$ of equation (1) counts as a cost in increased virulence. These latter cases are characterized by low host dispersal rates, and so the cost of increased virulence, here, stems from the depletion of the main source of new, uninfected hosts. We must emphasize that even when $\delta(v_{(k,l\text{-}1)} - v_{(k,l)})r_{(k,l)}\,(l-1)$ counts as an inclusive fitness benefit, its size at equilibrium appears to be insufficient to raise ES virulence level above that found in well-mixed populations.

More generally, as well as clarifying why the parasite dispersal rate should influence virulence, our model also shows how and why the parasite dispersal rate will interact with other parameters such as the maximum transmissibility of the parasite ($\beta_{\max}$), reproductive rate of the host, and host dispersal rate (Fig. 2). Increased host dispersal would favour increased virulence, through decreasing the extent to which increased virulence leads to self-shading and kin-competition, as well as through any influence on parasite dispersal by moving parasites within hosts.

The reason why the parasite dispersal rate should influence virulence has proved controversial. Previous studies have offered four different explanations: virulent strains being surrounded by other infected individuals ("self-shading")[12]; over-exploitation of the local availability of hosts ("tragedy of the commons")[8]; competition between related strains ("kin selection")[15]; the over-exploitation of local hosts and hence extinction of parasite groups (the original Wynne-Edwards theory of 'group selection')[6,11]. It has also been suggested that the relationship between parasite dispersal and virulence is beyond the scope of existing evolutionary theory[25].

Our results show that an increase in parasite dispersal rate leads to selection for increased growth, and hence higher virulence, for three reasons (Fig. 1). Increased dispersal provides a direct benefit to greater virulence, because it (1) increases the

relative value of producing offspring (dispersers are worth more than non-dispersers), and (2) reduces the extent to which producing offspring will lead to the focal individual experiencing an increase in competition for available hosts (self shading[12]). Increased dispersal provides an indirect benefit to greater virulence, because it (3) reduces the extent to which producing offspring will lead to relatives experiencing an increase in competition for available hosts ("kin shading"). The previous verbal explanations can be linked to these causal forces, in that self-shading[12] is our reason 1, the tragedy of the commons[8] involves our reasons 2 & 3, competition between relatives[15] is our reason 3, and the extinction of parasite groups[6,11] is linked to reasons 2 & 3 - if an individual causes harm to their patch, then this cost is paid by both the focal individual and their relatives on the patch (i.e. the group selection components can always be partitioned into offspring and non-offspring components). There is also a fourth effect that works in the opposite direction, favouring a lower virulence with increased parasite dispersal, due to the indirect benefit of reduced competition due to relatives dying being greater at lower dispersal rates, but this is outweighed by the other three factors.

To conclude, we have shown that selection on rare mutant virulence phenotypes in structured populations of parasites can be explained by inclusive fitness theory. This is the latest of numerous examples that have accumulated over the last 30 years, where it has been claimed that group selection and not kin selection are acting in a particular scenario, only for explicit analyses to show otherwise[26,27]. Future confusion could be avoided if such claims are backed by formal analyses that actually examine the underlying selective forces, rather than just verbal arguments[26]. More generally, our results emphasise the difference between levels of adaptation and levels of selection[28]. The multilevel (group) selection and kin selection (inclusive fitness) approaches to social evolution have long been known to be mathematically equivalent and, if the analyses are performed correctly, do not lead to conflicting predictions[29,30]. Thus, irrespective of the relative strengths of within-group versus between-group selection,

individuals are predicted to maximise their inclusive fitness. In contrast, groups are only predicted to evolve traits that function to maximise their fitness in extreme scenarios where there is no conflict of interest between the members of the group[28]. Put another way, the presence of group selection does not invalidate the idea that the individual is an adaptive unit, and it does not validate the idea that the group is an adaptive unit[28].

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Figure Titles and Legends

Fig. 1. Increasing parasite dispersal affects equation 1 in different ways.

Fig. 1. Increasing d_p **a** decreases parasite philopatry; **b** decreases the relatedness between parasite neighbours ($r_{(i,j)}$= r for all i and j > 2, see Supplementary Information); **c** reduces the variation in parasite "fecundity" change across patch types; **d** reduces variation in reproductive value across parasite classes. The net effect of changes **a**-**d** is illustrated on the far right. Increasing d_p increases both the ES level virulence, z^* and the fraction of hosts infected by the parasite. Results were generated by numerical simulation with μ = 1, d_h = 0.9, b = 3, N = 5 and $\beta(x) = 5x/(1+x)$.

Fig. 2. The relationship between ES virulence and parasite dispersal rate is affected by the life history parameters of both host and parasite.

Fig. 2. Relationship between z^* and d_p as host life-history parameters vary (**a** and **b**), and as maximum disease transmissibility, a parasite life-history trait, varies (**c**). **a** From top to bottom, d_h =0.9, 0.6, and 0.3 (b=3). **b** From top to bottom, b =9, 6, and 3 (d_h =0.3). Remaining parameters in **a** and **b** were μ =1, N =5 and $\beta(x) = 5x/(1+x)$. **c** From top to bottom, β_{max} =5, 7.5, and 20; remaining parameters were μ = 1, d_h = 0.3, b =3, N =5 and $\beta(x) = \beta_{max}x/(1+x)$. Additional, qualitatively similar results are presented in the Supplementary Information.

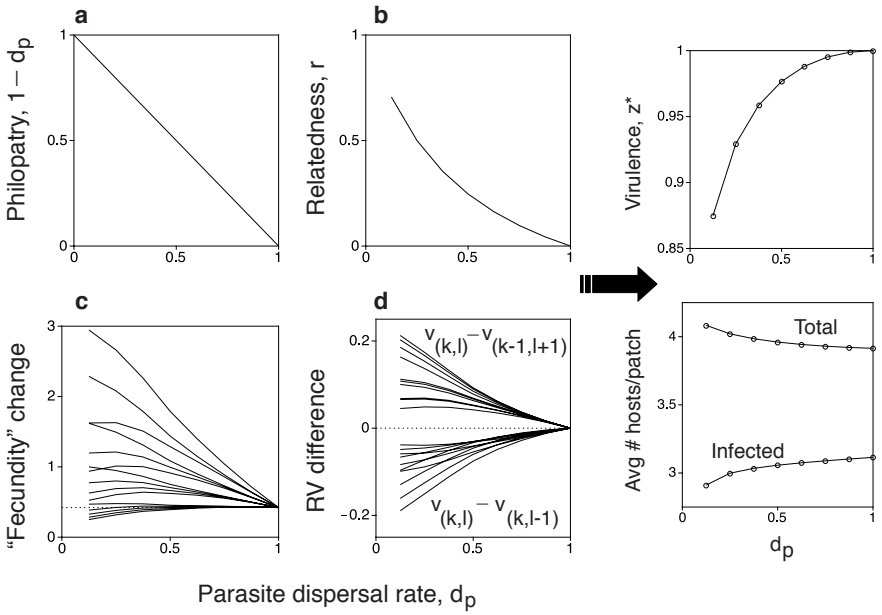

Fig. 1 (120 mm width)

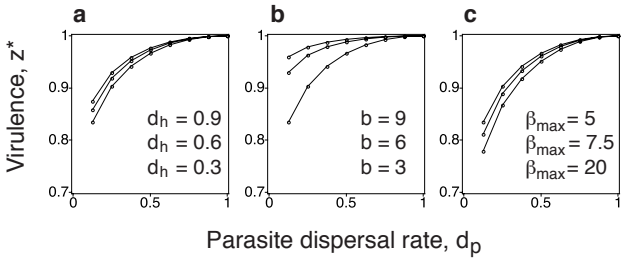

Fig. 2 (89 mm width)