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The evolution of resistance through costly acquired immunity

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We examine the evolutionary dynamics of resistance to parasites through acquired immunity. Resistance can be achieved through the innate mechanisms of avoidance of infection and reduced pathogenicity once infected, through recovery from infection and through remaining immune to infection: acquired immunity. We assume that each of these mechanisms is costly to the host and find that the evolutionary dynamics of innate immunity in hosts that also have acquired immunity are quantitatively the same as in hosts that possess only innate immunity. However, compared with resistance through avoidance or recovery, there is less likely to be polymorphism in the length of acquired immunity within populations. Long-lived organisms that can recover at intermediate rates faced with fast-transmitting pathogens that cause intermediate pathogenicity (mortality of infected individuals) are most likely to evolve long-lived acquired immunity. Our work emphasizes that because whether or not acquired immunity is beneficial depends on the characteristics of the disease, organisms may be selected to only develop acquired immunity to some of the diseases that they encounter.

Keywords: modelling; invasion analysis; adaptive dynamics; pathogens; disease; immune system

1. INTRODUCTION

Because individuals are likely to be subject to attack by an array of diverse parasitic organisms throughout their lifespan, the benefits of resistance mechanisms are clear. Resistance mechanisms are, however, unlikely to be cost free. The level of resistance that evolves is therefore a cost–benefit trade-off in terms of evolutionary fitness and as maximal acquired immunity is not necessarily optimal, evolutionary theory on the evolution of resistance is therefore important. Population-genetics-based theory tracking resistance gene frequencies in populations of a fixed size has been successfully applied to the 'gene for gene' interactions commonly found in plant pathogen systems (e.g. Frank 1993). However, in many systems resistance is likely to be a quantitative trait where we have little information on the underlying genetic structure. In this context, previous optimality work (Antonovics & Thrall 1994; Bowers *et al.* 1994; Boots & Bowers 1999; Boots & Haraguchi 1999; Roy & Kirchner 2000; Restif & Koella 2003) has considered the evolution of simple innate immunity where recovery from infection, when it occurs, leads to a return to complete susceptibility to subsequent infection. Here, we develop theory to establish the evolutionary dynamics of resistance to parasites that includes acquired immunity. We take an evolutionary rather than a coevolutionary approach in which the parasite is also able to evolve, as this approach has the advantage of providing a baseline for understanding the evolutionary dynamics of resistance through acquired immunity that can be developed into more complex models in the future.

The basis of this work is that immunity—including acquired immunity—is costly. There are two fundamental reasons to expect this. First, the development and maintenance of the resistance mechanisms are bound to involve energetic requirements, energy that cannot then be used on reproduction and survival. In the present context, acquired immunity in vertebrates has obvious benefits to the organism, but the complex array of cellular and other mechanisms that make up the immune system will require energy to develop, turn on and maintain. Second, there are obvious benefits to individuals in acquired immunity; if they are cost free, selection would be expected to fix all individuals and indeed species at the highest resistance. The existence of variation—including the fact that there are species without acquired immunity—suggests that there are costs.

Moreover, substantial costs of resistance have been demonstrated in a wide variety of organisms including both invertebrates with simple innate immune systems and vertebrates with acquired immunity (see Zuk & Stoehr 2002). For example, selection experiments have demonstrated directly costs in strains selected for higher investment in resistance in both insect (Boots & Begon 1993; Kraaijeveld & Godfray 1997) and vertebrate systems (Verhulst *et al.* 1999). Selection on correlated life-history traits has also demonstrated trade-offs with resistance (Hosken *et al.* 2001). In addition there is a considerable body of work where the costs of mounting an immune response are measured experimentally either by eliciting an immune response by challenging with a non-pathogenic substance (Ilmonen *et al.* 2000; Siva-Jothy *et al.* 2001) or by manipulating the host biology and measuring the immune response (Deerenberg *et al.* 1997; Siva-Jothy *et al.* 1998). Although experiments on genetic 'knockout' organisms (Råberg *et al.* 2002) have also been

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used to examine costs to resistance, caution should be used in implying the ancestral state from such 'knockouts'. The weight of evidence therefore (reviewed in Zuk & Stoehr 2002) along with the expectation of costs from basic life-history theory (Stearns 1992), provide a clear basis for an optimality approach to studying the evolution of resistance.

We can consider acquired immunity as having two distinct processes that may have differing cost structures. There are mechanisms that fight off the disease and allow the recovery of an individual to the immune state. In addition, there are the costs associated with the maintenance of immunity to the parasite. Recovery back to a susceptible state may also occur in organisms that possess only innate immunity and, as mentioned above, the evolutionary dynamics of this type of recovery without acquired immunity have previously been examined in an equivalent context to the one we will take here (Boots & Bowers 1999). A key result of this work on innate immunity was that polymorphism is most likely to occur between very dissimilar strains with very high and low levels of resistance. Importantly, it was also shown that for coexistence between such diverse strains to occur, correspondingly extreme costs were not necessary. Rather, highly resistant strains that paid little cost for their higher recovery rates are unable to exclude the susceptible strains as the resistant strain would not be able to support the parasite alone and in its absence would be at a disadvantage. Hence, rather counterintuitively, extreme dimorphism in resistance might be expected in nature with practically undetectable costs. The first purpose of the present paper is to examine whether these inferences relating to the evolution of resistance through from the work on innate immunity may be relevant to organisms—including man—with a developed acquired immunity.

Unique to acquired, as opposed to innate immunity, is the immunological memory that allows the recovered individual to remain immune to the disease. In some diseases there is lifetime immunity such that recovered individuals are effectively removed from the susceptible population. However, it is also common that immunity wanes through time. Again it is likely that immunological memory is costly to the individual and that there is an evolutionarily optimal period to remain immune based on a cost–benefit analysis of relative risks and costs. As yet there has been little theory on the optimal period spent removed from the susceptible population. The second and key purpose of this paper is to investigate this problem in general terms so as to examine questions of optimal immune response and polymorphisms in the length of immunological memory.

In addition to recovering from infection quickly and remaining immune to infection for a long time, there are two other general routes to resistance to parasites: innate avoidance and tolerance (Boots & Bowers 1999). The first of these are mechanisms that avoid infection in the first place. Forms of avoidance resistance may include mechanical barriers as well as behavioural mechanisms. Clearly this form of avoidance resistance is common to organisms with only innate immunity as well as those with additional acquired immunity. As part of an innate resistance mechanism, the evolutionary implications of avoidance resistance have also been extensively examined (Antonovics & Thrall 1994; Bowers *et al.* 1994; Boots & Bowers 1999; Boots & Haraguchi 1999). In general terms, the evolutionary dynamics of innate avoidance resistance and innate resistance through recovery are equivalent. We again find the polymorphism of extreme types without correspondingly extreme costs.

Another key route by which an organism may evolve resistance to a parasite is by tolerating infection and thereby reducing its death rate once infected. If such an individual is able to reproduce while infected, or recover and then reproduce, such tolerance is also a route to resistance (Boots & Bowers 1999). The evolutionary dynamics of tolerance resistance are quite different from avoidance and recovery in that there is no chance of polymorphism (see Roy & Kirchner 2000). The third and final purpose of this paper is to examine the evolutionary dynamics of both these other routes to resistance—avoidance and tolerance—once there is the possibility of acquired immunity. It is important not only to see whether the inferences of the work on innate resistance apply to organisms with acquired immunity, but also to determine whether there are emergent interactions between the different routes to resistance.

Here, we examine the evolution of acquired immunity and compare and contrast the evolutionary dynamics with those of innate immunity mechanisms. We start by determining the invasion criteria of resistant and susceptible morphs. Next, we present reciprocal invasion plots that show the role of the host life history in determining the chance of resistance and polymorphism developing. Finally, we use a novel graphical technical that presents our results in the context of adaptive dynamics with complex cost-structures and evolutionary branching.

2. MODELLING

Consider a generic susceptible, infectious, recovered (SIR) model based ultimately on the framework of May & Anderson (1983). We assume that there are two strains (susceptible (S) and resistant (R)) of the host that differ through various mechanisms in their resistance to a shared parasite or pathogen. These may involve a reduced transmission rate (β_R), an increased rate of recovery (γ_R), a reduced rate of loss of acquired immunity (δ_R) or a slower rate of death owing to infection (α_R). We therefore consider only the evolution of the host and develop a model without specific genetic mechanisms. As such the model is very general and pragmatic in that we wish to understand one part of a coevolutionary host–parasite interaction in the situation where the genetic basis of the interaction is not well understood. Our approach ignores heterozygotes of the two strains and may therefore strictly apply only to haploid hosts. Theory suggests, however, that haploid models can be strictly applied to diploid systems when the heterozyotes have characteristics that fall midway between those of the homozygotes (Crow & Kimura 1970; May & Anderson 1983). Additional work has also shown that evolutionarily stable strategies derived from haploid models prove at the least to be evolutionary attractors in diploid equivalents (Maynard Smith 1981).

We have

$$\frac{dX_S}{dt} = a_S H_S - bX_S - q_S H H_S - \beta_S X_S (Y_S + Y_R) + \delta_S Z_S,$$

$$\frac{dX_R}{dt} = a_R H_R - bX_R - q_R H H_R - \beta_R X_R (Y_S + Y_R) + \delta_R Z_R,$$

$$\frac{dY_S}{dt} = \beta_S X_S (Y_S + Y_R) - (\alpha_S + \gamma_S + b) Y_S,$$

$$\frac{dY_R}{dt} = \beta_R X_R (Y_S + Y_R) - (\alpha_R + \gamma_R + b) Y_R,$$

$$\frac{dZ_S}{dt} = \gamma_S Y_S - (b + \delta_S) Z_S,$$

$$\frac{dZ_R}{dt} = \gamma_R Y_R - (b + \delta_R) Z_R.$$

Here, X_S and X_R are the densities of uninfected susceptible and resistant individuals whereas Y_S (Z_S) and Y_R (Z_R) are the densities of the corresponding infected (immune) individuals and b is the shared disease-free mortality rate. Furthermore,

$$H_S = X_S + Y_S + Z_S,\ H_R = X_R + Y_R + Z_R,\ H = H_S + H_R.$$

Additionally ($i = \mathrm{R}, \mathrm{S}$), a_i is the intrinsic (that is, limiting low density) birth rate whereas q_i is the intraspecific density-dependent parameter that represents susceptibility to crowding. Notice that the first two equations imply a density-dependent birth rate that depends on the total host density H. We assume density dependence acts on birth rate for simplicity and to allow direct comparison with previous models (Antonovics & Thrall 1994; Bowers *et al.* 1994) where the results were not found to be dependent on whether density dependence acts on birth or death rates. Infection of either strain is related to the combined density ($Y_S + Y_R$) of both infected classes.

Here, we are concerned with the behaviour when at least one of the strains can support the pathogen. We suppose therefore that for the susceptible strain the carrying capacity exceeds the threshold density: $K_S > H_{T,S}$ ($K_i = r_i/q_i$ and $H_{T,i} = (\alpha_i + \gamma_i + b)/\beta_i$, where r is the intrinsic growth rate $a - b$). First, we use a biologically focused invasion analysis (Boots & Bowers 1999) to derive criteria that allow the invasion of each of the strains. We find (Appendix A) that the resistant strain can invade the susceptible strain when it is at equilibrium with the pathogen at densities H_S^*, Y_S^* essentially if and only if

$$r_R - q_R H_S^* + \frac{\beta_R Y_S^*}{(\alpha_R + \gamma_R + b)}(r_R - q_R H_S^* - \alpha_R) + \frac{\beta_R Y_S^*}{(\alpha_R + \gamma_R + b)} \frac{\gamma_R}{(b + \delta_R)}(r_R - q_R H_S^*) > 0.$$

Equivalently the susceptible strain can invade the resistant strain when it is at equilibrium with the pathogen at densities H_R^*, Y_R^* essentially if and only if

$$r_S - q_S H_R^* + \frac{\beta_S Y_R^*}{(\alpha_S + \gamma_S + b)}(r_S - q_S H_R^* - \alpha_S) + \frac{\beta_S Y_R^*}{(\alpha_S + \gamma_S + b)} \frac{\gamma_S}{(b + \delta_S)}(r_S - q_S H_R^*) > 0.$$

If only the first of these is met, the resistant strain will be favoured, whereas conversely if only the second is met the susceptible strain will be favoured. If both conditions are met, we expect stable coexistence of both strains with the pathogen to occur. Simulation was used to confirm this. From the invasion criteria we can produce diagrams in the resistant strain's parameter space that shows the conditions under which we get the susceptible strain, the resistant strain or coexistence of the two (figures 1–3). There is also a useful relation between the reciprocal invasion plots used here and elsewhere (Antonovics & Thrall 1994; Bowers *et al.* 1994; Boots & Bowers 1999) and the pairwise invadability plots (PIPs) of adaptive dynamics (Dieckmann *et al.* 2002). This emerges when we explicitly include the trade-off. We will use this analysis to examine the relative chance of polymorphism due to evolutionary branching.

3. RESULTS

Figure 1 shows a reciprocal invasion plot that summarizes the evolutionary dynamics of a resistant and susceptible strain, when resistance is through maintaining acquired immunity. This maintenance is a costly activity such that there is a reduced infection-free intrinsic population growth rate (resistant individuals reproduce less or survive less well). The characteristics of the susceptible strain are fixed in the top right-hand corner of the figure and the two solid lines correspond to the boundaries between the different outcomes. Whether a resistant strain (with a lower δ) invades or not can be viewed as a measure of whether there is a benefit to acquired immunity. The outcome is as expected dependent on the benefits and costs of acquired immunity, but this cost–benefit analysis is not a simple linear one. In particular there is an increased possibility of coexistence when the strains are very different; one with relatively long-lived and the other relatively short-lived acquired immunity. However, it is important to notice that coexistence does not occur when highly resistant strains with long-lived immunity suffer low costs.

The fact that correspondingly high costs are needed to maintain the coexistence of strains with very different levels of resistance seems intuitive, but contrasts with the situation when resistance is through avoidance of infection or rapid recovery (figure 3; Bowers *et al.* 1994; Boots & Bowers 1999). In these later cases, 'super-strains' that pay little cost for their extreme resistance nevertheless coexist with highly susceptible strains owing to the fact that the 'super-strains' cannot support the pathogen alone. By contrast, the length of time that individuals are immune does not affect the resistant strain's threshold density and therefore highly resistant strains can support the pathogen. In this case, therefore, 'super-strains' with very long-lived immunity that has little cost will outcompete rather than coexist with susceptible strains.

Figures 1 and 2 show how the evolutionary outcome and therefore cost–benefit analysis of possessing long-lived acquired immunity is affected by the life-history characteristics of the host and the features of the infection. Long-lived organisms are more likely to benefit from acquired immunity (compare figure 1*a–c*). This makes intuitive sense and is well understood as organisms that live a long time will re-encounter parasites more often and are therefore more likely to gain benefits from long-lived acquired immunity. However, it should be noted that the difference between figure 1*a* and 1*b* is mostly in a reduction in the coexistence region rather than in the parameter region in which the individuals with longer-lived acquired immunity

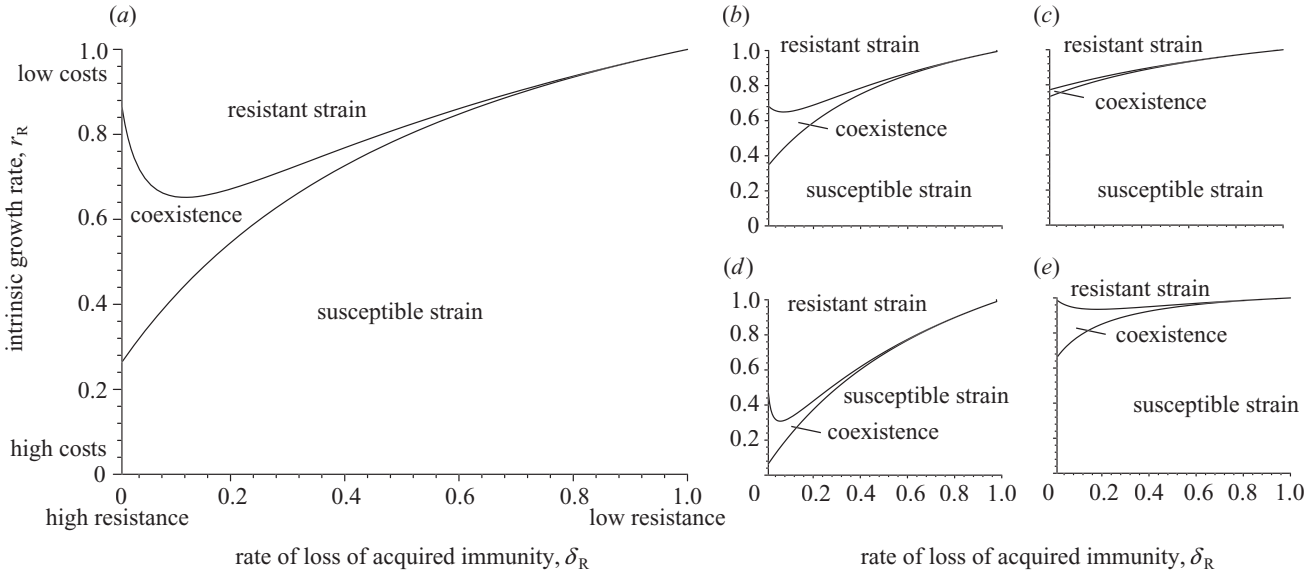

Figure 1. Reciprocal invasion plots in which the susceptible strain is fixed at the top right-hand corner with the lowest resistance (high rate of loss of acquired immunity) and the correspondingly lowest costs (highest growth rate). The outcome of invasion with possible resistant strains is then plotted in the resistant strain parameter space. Either the resistant strain with longer-lived acquired immunity or the susceptible strain with shorter-lived acquired immunity or coexistence between the two can occur. In (*a*) the other parameters are $q_S = q_R = 0.1$, $\beta_S = \beta_R = 5$, $\delta_S = 1.0$, $r_S = 1.0$, $\alpha_S = \alpha_R = 3$, $\gamma_S = \gamma_R = 1.5$, $b = 0.0005$. In (*b*) the hosts are less long lived ($b = 0.05$) and even less long lived in (*c*) ($b = 0.5$). In (*d*) there is less susceptibility to crowding in the host ($q = 0.01$) whereas in (*e*) there is more self-limitation ($q = 0.5$).

outcompete the others. Only when the lifespan is much shorter in figure 1*c* do we see a marked reduction in this second region, and again this is associated with a reduction in the coexistence region. Organisms with low susceptibility to crowding (low q) and therefore generally high carrying capacities are more likely to evolve acquired immunity (figure 1*a*,*d*,*e*). Acquired immunity is more likely to evolve against pathogens with high transmission rates (compare figure 2*a*,*b*,*c*), intermediate pathogenicity (compare figure 2*d–f*) and when there are intermediate rates of recovery to the immune state (compare figure 2*d*,*g*,*h*).

We now turn our attention to the evolution of three other routes to resistance: recovery, avoidance and tolerance. Figure 3*a–c* shows the evolutionary dynamics where resistance is through increased recovery rate (this time the most susceptible strain is at the top left). The dynamics are qualitatively the same as in susceptible, infectious, susceptible (SIS) models where there is no acquired immunity and therefore many of the predictions of these models can also be applied whether recovery is to an immune state or back to the susceptible state. The effect of the length of the immune period on resistance through recovery is intuitive (figure 3*a–c*): the longer the period spent in the immune stage the more beneficial recovery to the immune state becomes. There is also an equivalence in the evolutionary outcomes of resistance through reduced susceptibility and tolerance (reduced pathogenicity) between theory where there is no acquired immunity (SIS) and the present context with acquired immunity (SIR) (figure 3*d–f*,*g–i*). The inferences from the simpler models therefore follow in the more complex SIR case. Again, it is clear that in both cases there is more likely to be the evolution of resistance through both of these mechanisms if there is a longer period spent in the immune state.

Our analysis of reciprocal invasion plots thus far has been directed towards just considering two strains (resistant and susceptible). In this way, by presenting typical plots, we get a clear picture of the cost–benefit analysis of the different resistance mechanisms and can therefore predict when we would expect resistance to evolve and when coexistence is possible.

However, our method is not restricted to two strains. We can extend it so as to consider the case where there are many strains that differ in their resistance and costs in a manner determined by a trade-off relationship. We can then analyse the evolutionary dynamics of a monomorphic population that is allowed to evolve by local mutation. We do this in the following way. We start with the reciprocal invasion plot (such as figures 1, 2 or 3). This has two invasion boundaries plotted in the parameter space of the resistant (or mutant) strain with the values of the parameters relating to the susceptible (or resident) strain fixed. We then add a plot of the trade-off function to our diagram. We call the resulting diagram (figure 4) a trade-off and invasion plot (TIP). By sliding the point representing the resident along the trade-off curve and constructing a series of TIPs (while keeping the directions of the parameter axes for the mutant fixed), we can represent the invadability properties of all resident or mutant pairs in a way that allows explicit connection with the geometry of the trade-off function. Our novel approach finds parallels in the techniques employed in adaptive dynamics (Metz *et al.* 1995; Geritz *et al.* 1996, 1998, 1999; Dieckmann *et al.* 2002). However, the PIPs used there tend to represent the resident and mutant by one parameter. In the present context, this means that the trade-off function is applied before the figure is plotted (Boots & Haraguchi 1999). There are advantages in the present approach that result from the ability to relate evolutionary outcomes to the

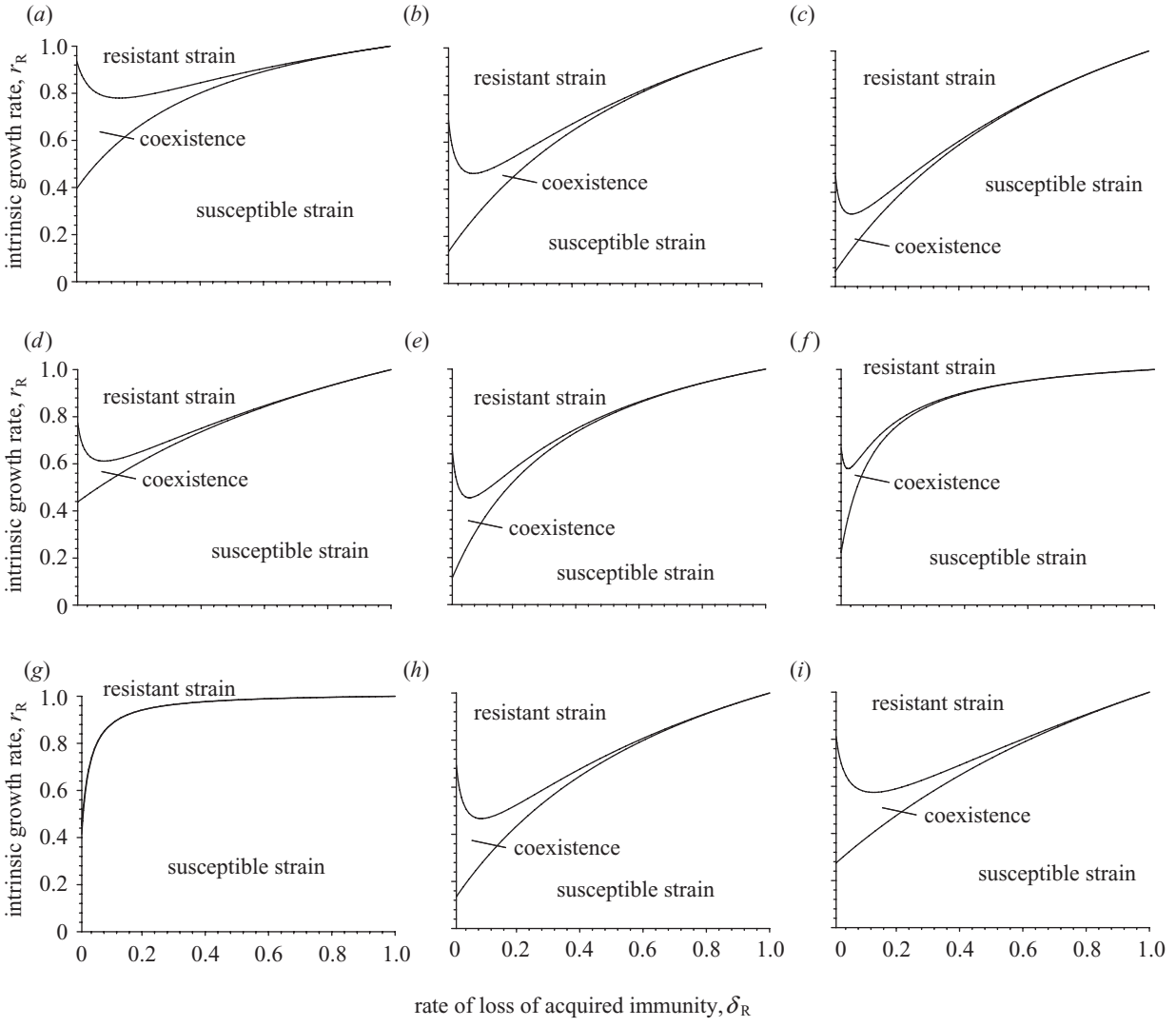

Figure 2. Reciprocal invasion plots in which the susceptible strain is fixed at the top right-hand corner with the lowest resistance (high rate of reversion to susceptibility) and the correspondingly lowest costs (highest growth rate). The outcome of invasion with possible resistant strains is then plotted in the resistant strain parameter space. Either the resistant strain with longer-lived acquired immunity or the susceptible strain with shorter-lived acquired immunity or coexistence between the two can occur. (*a–c*) show the effect of changing the transmission rate on the outcome: ($\beta_R = \beta_S = 2.5$ in (*a*) (low transmission), 15 in (*b*) (medium transmission) and 50 in (*c*) (high transmission)); whereas in (*d–f*) the pathogenicity of the parasite is varied ($\alpha_R = \alpha_S = 1.5$ in (*d*) (low pathogenicity), 5 in (*e*) (medium pathogenicity) and 15 in (*f*) (high pathogenicity)). In (*g–i*) the recovery rate is varied such that $\gamma_R = \gamma_S = 0.05$ in (*g*) (low recovery), 1.5 in (*h*) (medium recovery) and 2.5 in (*i*) (high recovery). When not varied, the other parameters are $q_S = q_R = 0.1$, $\beta_S = \beta_R = 15$, $\delta_S = 1.0$, $r_S = 1.0$, $\alpha_S = \alpha_R = 3$, $\gamma_S = \gamma_R = 1.5$, $b = 0.0005$.

geometry of the trade-off in an explicit manner. In particular, we can discuss in a geometrical fashion when we would expect evolutionary branching to lead to polymorphism in resistance.

A detailed general treatment of the relation between TIPs and PIPs—and more generally between our methods and those of adaptive dynamics—will be given elsewhere. For our purposes the following suffices. In a TIP, all three curves intersect at values of the mutant parameters that equal those of the resident. Because the strains are identical it means that they are on the invasion boundary for each other. Furthermore, because the resident is at a viable parameter combination, it must lie on the trade-off curve. An argument that has general validity (see Appendix A) shows that the two invasion boundaries are mutually tangential at the intersection point. The slope of the trade-off curve at this point will, in general, differ from this common value. A direct geometrical characterization of the location of evolutionary singularities can be given: they occur precisely when the trade-off curve is tangential to the two invasion curves at the intersection point. Notice that this criterion is a local one: it is the behaviour at the tip of the TIP that determines the outcome. Our geometrical picture indicates that the relative curvatures of the invasion boundaries and the trade-off at the tip (of the TIP) are implicated in determining the evolutionary behaviour near the singularity. The stable coexistence of neighbouring strains in a dimorphism occurs when, near the tip (figure 4), the trade-off curve is constrained to the region of mutual invadability (given that mutual invadability implies coexistence). Thus such dimorphism—which in the adaptive dynamics perspective corresponds

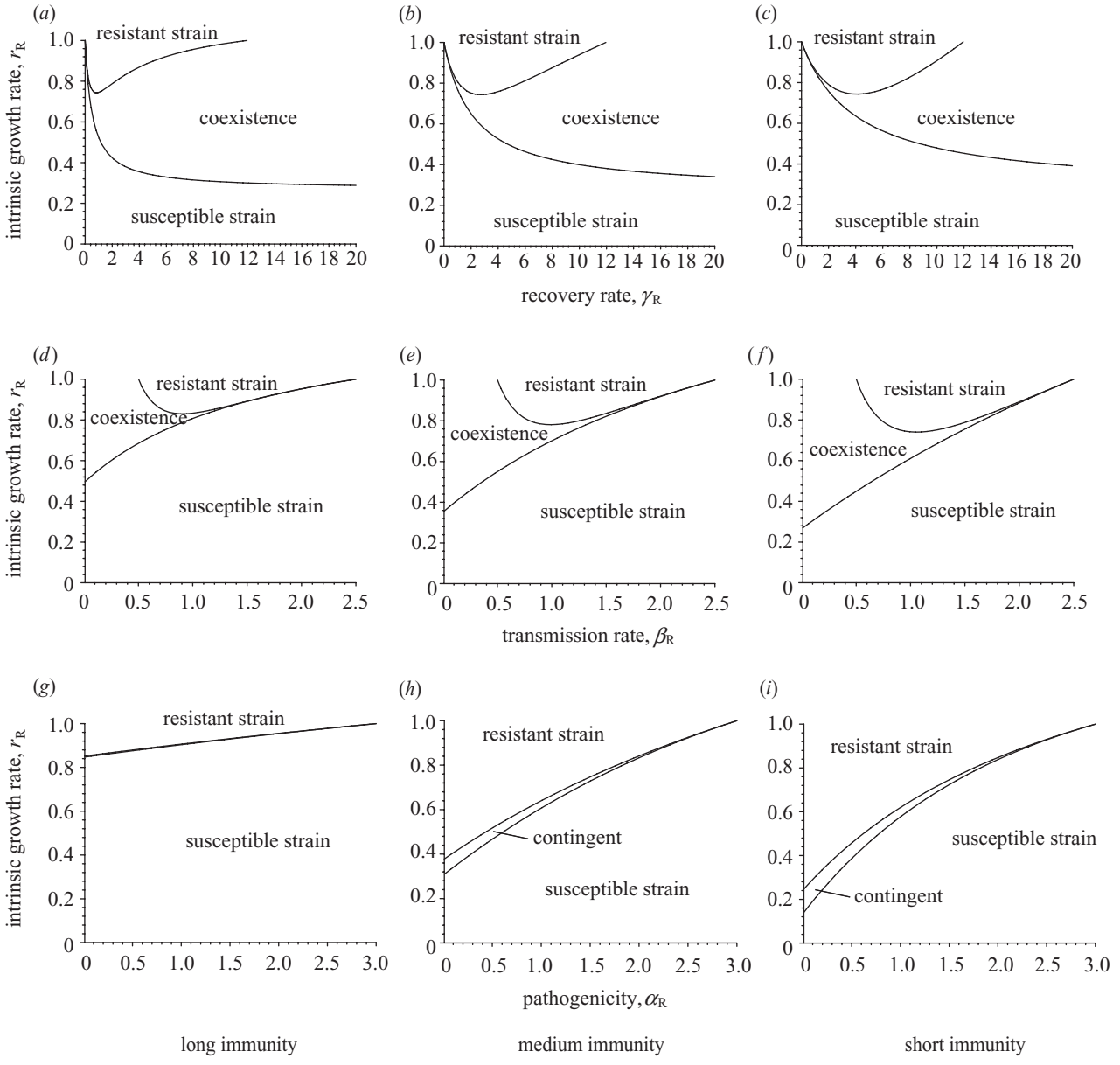

Figure 3. Reciprocal invasion plots where the resistance is either through recovery ((*a*), (*b*) and (*c*)), avoidance ((*d*), (*e*) and (*f*)) or tolerance ((*g*), (*h*) and (*i*)). Again the costs are through lower growth rate. The most susceptible strain is fixed at the top right corner for avoidance and tolerance resistance, whereas it is fixed at the top left for recovery resistance. For each form of resistance the effect of longer periods of acquired immunity is shown by varying $\delta_S = \delta_R$ such that in (*a*), (*d*) and (*g*) $\delta_S = \delta_R = 0.1$, whereas in (*b*), (*e*) and (*h*) $\delta_S = \delta_R = 1.0$ and in (*c*), (*f*) and (*i*) $\delta_S = \delta_R = 100$. With tolerance there is no coexistence but a small region of contingent behaviour. The other parameters are: $q_S = q_R = 0.1$, $\beta_S = \beta_R = 15$, $r_S = 1.0$, $\alpha_S = \alpha_R = 1.5$, $\gamma_S = 0.0005$, $b = 0.05$ in (*a*), (*b*) and (*c*); $q_S = q_R = 0.1$, $\beta_S = 2.5$, $r_S = 1.0$, $\alpha_S = \alpha_R = 1.5$, $\gamma_S = \gamma_R = 1.5$, $b = 0.5$ in (*d*), (*e*) and (*f*); and $q_S = q_R = 0.1$, $\beta_S = \beta_R = 15$, $r_S = 1.0$, $\alpha_S = \alpha_R = 3$, $\gamma_S = \gamma_R = 1.5$, $b = 0.0005$ in (*g*), (*h*) and (*i*).

to the singularity being a branching point and is taken as a possible model for speciation—is more likely the greater the degree that the invasion boundaries curve away from each other. In general in our plots, the invasion curves increase the degree to which they curve away from each other as the coexistence region increases. As such our general inferences on the relative likelihood of the coexistence from the direct analysis of reciprocal invasion plots still hold for the evolutionary dynamics of a monomorphic population subject to a trade-off and evolving by local mutation.

In addition, the cost structure required for polymorphism, is one where the costs of resistance are sufficiently mildly decelerating for acquired immunity in the same way as they were previously shown for avoidance resistance in Boots & Haraguchi (1999). This can been seen intuitively from the shapes of the invasion curve and the curvature of a trade-off curve that would be needed to emerge between them (figure 4).

4. DISCUSSION

By including acquired immunity into a theoretical framework that has previously examined innate immunity, we have shown that the evolutionary dynamics of innate immunity mechanisms are broadly equivalent in organisms that also possess acquired immunity. More importantly, our work has demonstrated that the evolution

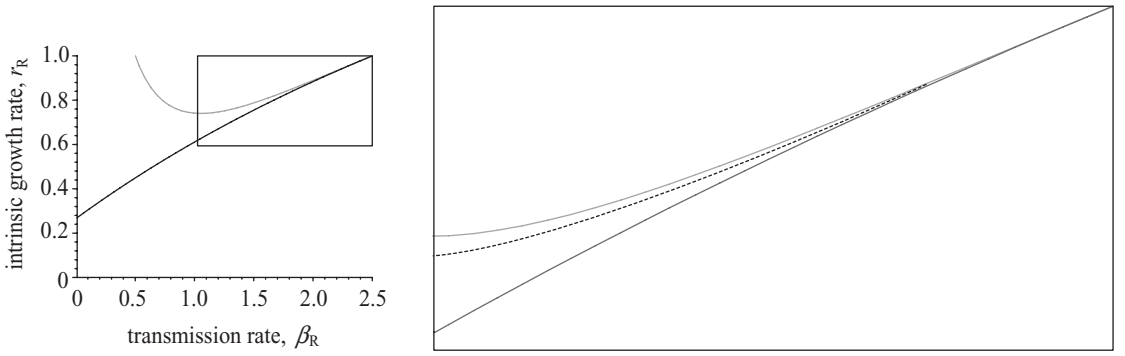

Figure 4. (*a*) The diagrammatic representation of a trade-off invasion plot (TIP)—corresponding to an evolutionary singularity—with (*b*) the crucial tip of the TIP enlarged.

of resistance through longer-lived immunity has different evolutionary dynamics to resistance through recovery or avoidance.

The formal optimality analysis presented here allows us to make some general predictions about when it would pay organisms to maintain long-lived immunity to infections. It is encouraging that many of these correspond to what might be expected. Longer-lived hosts are more likely to be infected several times in their lifespan and therefore are more likely to pay the costs of long-lived immunity. This well-known intuition has been formalized here. It should be noted that clonal invertebrates may also have evolved acquired immunity owing to the fact that the clone has a long lifespan even if individuals do not (Little *et al.* 2003). Acquired immunity is also rather intuitively selected for when the transmission rate of the parasite is high, because this directly increases the chance of re-infection. Less intuitively perhaps, we have shown that long-lived acquired immunity should be particularly selected for against parasites with intermediate levels of pathogenicity. If a pathogen kills its host very quickly, it is less likely that the infected individual will recover to become immune and therefore the costs of the acquired immunity are not worth paying. Equally, very little pathogenicity means there is less fixed cost to being infected and therefore less reason to pay the costs of an acquired immunity. Acquired immunity is also most likely to occur when the rate of recovery to the immune state is neither too high, nor too low. If the recovery rate is very low, there is little benefit from the acquired immunity as there is a relatively low chance of entering the immune state. When recovery is very fast, recovering rapidly back to the susceptible state may be cost-effective as the individual is only infected for a short time even if it is subsequently infected. Therefore long-lived acquired immunity is most likely when the recovery process takes an intermediate length of time.

An important implication of the understanding that the benefits of acquired immunity are dependent on both host and parasite biology is that a particular host may be selected to produce a long-lasting immune response to some to diseases and not to others. For example, whereas long-lived organisms may always be selected to produce immune responses and short-lived ones never find it selected for, intermediately long-lived animals may often find themselves with a different cost–benefit outcome based on the transmission rates and pathogenicities of particular diseases. An example where this may be occurring is in the responses of rodents to their various diseases where immune responses are only made to particular diseases (Cavanagh *et al.* 2002; Telfer *et al.* 2002). This might be viewed as a failure of the immune response in the host, but our work suggests that it may in fact be an adaptive response to different diseases. More attention should perhaps be given to the possibility that a lack of an immune response may be an adaptation of the host rather than a failure to adapt to the parasite.

Another important result of our work is that resistance to parasites through acquired immunity is not a 'self-limiting trait' in the way that resistance through avoidance of the parasite or increased recovery from infection are. Self-limited traits are 'limited' in that when they are particularly effective with little cost, they decrease the selective pressure to which they have successfully responded. Even low costs therefore give an advantage to seemingly poor strains, and coexistence rather than exclusion occurs despite a high advantage being gained with minimal costs. This occurs when resistance is through avoidance (reduced transmission β) or increased recovery because as resistance becomes very high, the resistant strain is no longer capable of supporting the parasite. Therefore strains with high resistance and little cost coexist with rather than outcompete with seemingly poor strains. This does not occur with acquired immunity. The implication of this is that coexistence and polymorphism between strains with very different degrees of acquired immunity are much less likely than such polymorphisms with resistance mechanisms based on avoidance or recovery. Polymorphism of this type in acquired immunity will only occur if there are correspondingly high costs associated with very long-term acquired immunity. Organisms tend to be thought of as either possessing just innate or innate and acquired immunity whereas polymorphic species in terms of acquired immunity are not seen. This may reflect the relatively low chance of polymorphism that we have found here. There is evidence of polymorphism in resistance through innate avoidance mechanisms (Ferrari *et al.* 2001), and therefore although our work suggests such polymorphism is less likely in terms of acquired immunity, it is a possibility in particular organisms to particular diseases. When it occurs it will tend to be between widely different strains and therefore it should be relatively easy to determine experimentally.

Following on from this, we have demonstrated that resistance through avoidance and faster recovery have the

same evolutionary dynamics whether or not the organism has acquired immunity or not. They are both self-limited traits and as such there is a significantly higher probability of highly dimorphic resistance patterns within populations. In addition, highly resistant strains may have barely detectable costs. There is evidence of this type of extreme resistance in innate immunity in insects (Ferrari *et al.* 2001), our work demonstrates that this pattern of innate resistance can also be expected in mammals and other organisms with acquired in addition to innate resistance. By linking the approach of examining the reciprocal invasion of two strains (Antonovics & Thrall 1994; Bowers *et al.* 1994; Boots & Bowers 1999) with the multi-strain adaptive dynamical approach, we have also shown how this polymorphism will come about through evolutionary branching under particular constraints between resistance and its costs. The probability of branching increases as the initial rate at which the angle between the invasion lines increases and therefore in general branching is more likely for avoidance and recovery resistance than it is for long-lived immunity. This provides a mechanism for the sympatric development of polymorphism and potentially speciation in terms of resistance to parasites.

Clearly our model is very general and therefore excludes several important processes, in particular stochasticity, which will have important implications. Stochasticity and cyclic host population dynamics are likely to affect the chance of coexistence and polymorphism. However, our approach gives clear general predictions and provides a baseline from which the effect of many different complexities can be examined in the future.

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APPENDIX A

We first establish the invasion criteria of the main text.

Consider an attempted invasion, by a resistant strain, of a resident susceptible strain characterized by an alone density $H_S^* = X_S^* + Y_S^* + Z_S^*$. We need to find the average increase in the resistant population per invader. Only if this is positive will the invasion prosper. Take the invader to be uninfected and suppose it remains so for an average time T_X and becomes infected (immune) for an average time T_Y (T_Z).

During the susceptible and immune periods the average rate of increase *per capita* is

$$\rho_X = \rho_Z = r_R - q_R H_S^*; \tag{A 1}$$

during the infected period it is

$$\rho_Y = r_R - q_R H_S^* - \alpha_R. \tag{A 2}$$

On average the number of offspring per invader represents a population increase of

$$I_R = \rho_X T_X + \rho_Y T_Y + \rho_Z T_Z \tag{A 3}$$

individuals. To find T_X we note that the probability of our invader dying while uninfected is bT_X whereas the probability of it becoming infected is $\beta_R Y_S^* T_X$. Because this exhausts the possibilities

$$(b + \beta_R Y_S^*) T_X = 1. \tag{A 4}$$

Similarly we have

$$bT_X + (\alpha_R + b + \gamma_R) T_Y = 1,$$
$$bT_X + (\alpha_R + b) T_Y + (b + \delta_R) T_Z = 1. \tag{A 5}$$

Equations (A 4) and (A 5) yield

$$T_X = \frac{1}{(b + \beta_R Y_S^*)},$$
$$T_Y = \frac{\beta_R Y_S^*}{(\alpha_R + b + \gamma_R)(b + \beta_R Y_S^*)},$$
$$T_Z = \frac{\gamma_R \beta_R Y_S^*}{(b + \delta_R)(\alpha_R + b + \gamma_R)(b + \beta_R Y_S^*)}. \tag{A 6}$$

Using equations (A 1), (A 2) and (A 6) in (A 3) gives

$$I_R = \frac{1}{(b + \beta_R Y_S^*)}\left(r_R - q_R H_S^* + \frac{\beta_R Y_S^*}{(\alpha_R + \gamma_R + b)}(r_R - q_R H_S^* - \alpha_R) + \frac{\beta_R Y_S^*}{(\alpha_R + \gamma_R + b)} \frac{\gamma_R}{(b + \delta_R)}(r_R - q_R H_S^*)\right). \tag{A 7}$$

Neglecting a positive common factor in (A 7) gives the result of the main text.

Two comments should be made. First, given that the rates of recovery and loss of immunity are not zero, successive periods of uninfected, infected and immune are possible. Including these scales our results by a positive factor and thus can be ignored. Second, invasion by infecteds or immunes can be included. Before any recovery, an invasion by an infected yields a contribution

$$\frac{1}{(\alpha_R + \gamma_R + b)}(r_R - q_R H_S^* - \alpha_R) + \frac{1}{(\alpha_R + \gamma_R + b)} \frac{\gamma_R}{(b + \delta_R)}(r_R - q_R H_S^*) \tag{A 8}$$

to the increase we have been calculating. If (A 7) fails to be positive, then this contribution cannot be positive and hence, as is obvious biologically, infecteds cannot prosper unless susceptibles do. A similar analysis accounts for invasion by immunes. For these reasons attention can be restricted to equation (A 7).

We now show that the two invadability curves leave the point of identity of the two strains tangentially to each other. This means that the probability of coexistence of two nearly identical strains is 'vanishingly small'. It is convenient to denote the fitnesses that we have been calculating in the form $I(\boldsymbol{x},\boldsymbol{y})$, where $\boldsymbol{x}$ is the vector of resident parameters and $\boldsymbol{y}$ is the vector of invader parameters. We can use the property $I(u,u) = 0$ to generate information near to strain equality as follows. Linear approximation gives

$$I(x + h, x + k) = I(x,x) + I_1(x,x)h + I_2(x,x)k + \ldots = I_1(x,x)h + I_2(x,x)k + \ldots,$$

and in particular

$$I(x + h, x + h) = I_1(x,x)h + I_2(x,x)h + \ldots = 0,$$

which yields the result $I_1(x,x) + I_2(x,x) = 0$. Now close to strain equality one invadability curve has the linearized equation

$$I(x + h, x) = I_1(x,x)h = 0,$$

and the other has the linearized equation

$$I(x,x+h) = I_2(x,x)h = -I_1(x,x)h = 0.$$

Because these are identical we have the promised result.

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