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An epidemiological context for the consequences of phenotypic plasticity in host–pathogen interactions

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ABSTRACT

Questions: What effect do different forms of strategic plasticity have on the co-evolution of host and pathogen? We focus on the co-evolution of pathogen exploitation strategies (virulence) and the rate at which the host immune system clears the pathogen (clearance rate).

Mathematical methods: Evolutionary game theory; computer simulations of host–pathogen pairs negotiating strategies using linear response rules.

Key assumptions: A trade-off exists between virulence and transmission rate for pathogens, and between fecundity while infected and recovery (clearance) rate for hosts. Disease dynamics are described by a standard susceptible–infected–susceptible epidemiological model. Transmission of the pathogen is exclusively horizontal, and random mixing of the host population is assumed.

Conclusions: All forms of plasticity promote the co-evolution of virulence and clearance rates that are lower than those predicted in the absence of plasticity. Plasticity promotes increased disease incidence rate (higher than those predicted in the absence of plasticity), but the way it affects case mortality depends critically on the assumed mode of plasticity.

Keywords: co-evolution, host–pathogen, infection, negotiation, plasticity, virulence.

INTRODUCTION

Game theory provides a natural framework in which to discuss the co-evolution of pathogen life histories and the immunological defences employed by their hosts. In this framework, host and pathogen are treated as 'strategists' with competing interests. Pathogens exploit their hosts to establish new infections, whereas hosts attempt to avoid exploitation by establishing an immune response. In game-theoretic terms, pathogens adopt an 'exploitation strategy' (i.e. virulence strategy) that is countered by the 'immunological strategy' of the host (i.e. clearance strategy).

Most game theory models of host–pathogen co-evolution suppose individuals adopt their strategies in ignorance of the strategies adopted by their opponents (e.g. van Baalen, 1998;

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Day and Burns, 2003). In such instances, we expect the co-evolutionary process to yield strategy pairs from which neither party (unilaterally) is willing to deviate. In other words, we expect the result of co-evolution to be a Nash equilibrium.

Despite standard assumptions of game theory models, the so-called strategies of host and pathogen do have the potential to be plastic. Hosts are often capable of responding plastically to an infectious pathogen. For example, different subsets of T-helper cells contribute to an immune system in humans that is capable of responding to different infections in different ways (see Graham, 2002, and references therein). Similarly, an invading pathogen can adjust its expression of virulence factors in response to features of intracellular micro-environments (Guo *et al.*, 1997), or adjust life-history traits in response to various transmission opportunities (Poulin, 2003). In short, it is reasonable to assume that a host and/or pathogen is able to ascertain some information about the strategy adopted by its opponent, and adjust its own strategy accordingly.

Cases in which only one player has information about the strategy of the other can be modelled as extensive form games. In such games, the informed player always chooses the (presumably unique) best reply to the strategy used by its uninformed opponent. The uninformed player, on the other hand, chooses the strategy that yields the highest pay-off under the assumption that its informed opponent always uses the best reply. The optimal informed and uninformed strategies form a pair known as a 'Stackelberg equilibrium' (Sjerps and Haccou, 1993; Taylor *et al.*, 2006). Although the concept of a Stackelberg equilibrium is relatively new to evolutionary biology, it has appeared in the literature in connection with the evolution of sex ratios (Abe *et al.*, 2003; Pen and Taylor, 2005), the evolution of mating systems (Kokko, 1999), and the evolution of clutch size (Sjerps and Haccou, 1993).

In many instances, interspecific interactions are characterized by reciprocal change in ecological time (Agrawal, 2001; see also Wellnitz, 2005). Instead of assuming that each player adopts a specific action in advance to respond to its counterpart, joint plasticity of host and pathogen can be considered by assuming that both host and pathogen have reaction norms that completely determine their response to any action chosen by their counterpart. As long as the appropriate mathematical conditions are met, these reaction norms then result in asymptotic convergence of the actions of each player to a steady state, and the focus is on the evolution of these reaction norms (and, thereby, the resultant steady-state actions of each player). This process has been referred to as 'negotiation' (and so the steady-state actions are often called 'negotiated outcomes'), and is modelled by using rules of response for both players (McNamara *et al.*, 1999; Taylor and Day, 2004).

The effect of plasticity on host–pathogen co-evolution has recently been studied by Taylor *et al.* (2006), who found that plasticity leads to both reduced host clearance and reduced pathogen virulence (what they called a more 'peaceful' or more cooperative outcome). These conclusions were based on a very simple epidemiological model, however, in which every juvenile host is infected by the pathogen. This assumption simplified the analysis, but the lack of a proper underlying epidemiological model meant that they were not able to determine how such plasticity affects important epidemiological quantities of interest [e.g. case mortality, incidence rate (Diekmann and Heesterbeek, 2000)].

In this paper, we examine the effects of plasticity on host–pathogen co-evolution by comparing Nash equilibria, Stackelberg equilibria, and negotiated outcomes within a standard epidemiological framework. We show that the conclusions of Taylor *et al.* (2006) – namely, that plasticity results in reduced host clearance and reduced pathogen virulence – continue to hold in this more realistic setting, and we then examine how this plasticity

affects case mortality (i.e. probability of a host dying, given that it is infected) and disease incidence (i.e. rate of production of new infections, per susceptible individual). Numerical and simulation results show that the effect of plasticity on case mortality is strongly influenced by whether the host or the pathogen (or both) is capable of plastic responses, whereas disease incidence always increases as a result of plasticity in either the host or the pathogen.

THE MODEL

A simple epidemiological model will be used to study host–pathogen interactions. We suppose that the host population is divided into two classes: individuals susceptible to the pathogen but uninfected (S) and individuals infected with the pathogen (I). Susceptible individuals become infected according to the law of mass action with rate parameter β. Conversely, infected hosts recover at a rate c (this is the immunological 'strategy' adopted by the host) and return to the susceptible class. The fecundity of susceptible individuals is constant and given by b_S, whereas the fecundity while infected is given by b_I, and is assumed to be a decreasing function of clearance rate, c. This captures the idea that immune system upregulation uses resources that would otherwise have been devoted to reproduction. For simplicity, we use the non-linear relationship $b_I(c) = b_S - \gamma c^2$, where γ is a positive constant representing cost [see Day and Burns (2003) for outcomes where a linear relationship is assumed]. Finally, we suppose that all hosts suffer a constant per capita background mortality rate μ.

We suppose transmission of the pathogen is exclusively horizontal, and hence offspring of infected hosts are born uninfected. To incorporate a virulence–transmission trade-off, we assume that infected hosts suffer an increase in mortality rate, v (this is the virulence or exploitation 'strategy' adopted by the pathogen), and that pathogen transmission from infected hosts is an increasing function of v. In particular, we use $\beta(v) = \frac{\beta_{\max} v}{\alpha + v}$ ($\alpha > 0$) as a simple function that displays diminishing returns, and approaches a maximum transmission rate of $\beta_{\max}$ asymptotically when virulence becomes large. Similar results were also obtained using the function $\beta(v) = mv^n$ ($0 < n < 1$) (G. Costain, unpublished results).

With the above assumptions, the dynamics of susceptible and infected hosts in the population over time can be modelled using the following pair of differential equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = b_S S + b_I(c)I - \mu S + cI - \beta(v)SI \tag{1a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta(v)SI - (\mu + v + c)I \tag{1b}$$

The non-trivial (i.e. endemic) equilibrium of system (1) is:

$$\hat{S} = \frac{(\mu + v + c)}{\beta(v)}$$

$$\hat{I} = \frac{(b_S - \mu)(\mu + v + c)}{\beta(v)[\mu + v - b_I(c)]}$$

Since we are interested in co-evolutionary dynamics, we assume hosts and pathogens co-exist over the long term. Mathematically, we assume that the endemic equilibrium above is locally stable, which requires $b_S > \mu$ and $\mu + v > b_I(c)$. The latter inequality, together with the requirement that $b_I(c)$ itself be positive, limits the possible c and v that we consider in this paper to a set of 'feasible pairs' (Fig. 1).

Using a standard invasion analysis, Day and Burns (2003) have demonstrated that natural selection maximizes

$$H(v,c) = \frac{\mu + v + c}{\mu + v - b_I(c)}$$

during host evolution, and maximizes

$$P(v,c) = \frac{\beta(v)}{\mu + v + c}$$

during pathogen evolution. In other words, host evolution acts to maximize the density of infected hosts (in the variable c) at the endemic equilibrium, and pathogen evolution acts to minimize the density of susceptible hosts (in the variable v) at this equilibrium. We will use $H(v, c)$ and $P(v, c)$ in our game theoretic analysis to describe the pay-off to host and pathogen, respectively.

ANALYSIS

No plasticity

In the absence of plasticity, the direction of evolutionary change in v and c is determined by the signs of $P_v \stackrel{\text{def}}{=} \partial P/\partial v$ and $H_c \stackrel{\text{def}}{=} \partial H/\partial c$, respectively (Roughgarden, 1983). Selection favours an

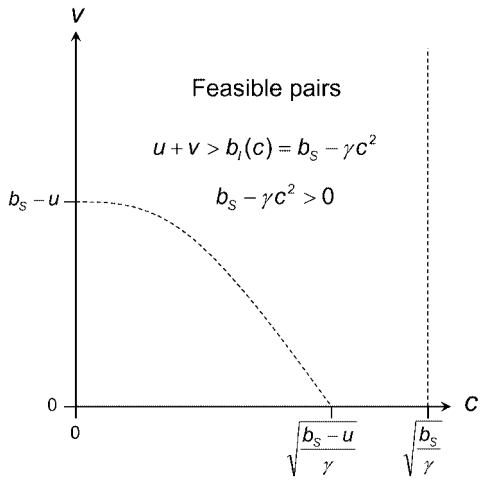

Fig. 1. Feasible pairs of clearance c and virulence v. For pairs (c,v) inside the region enclosed by both dashed lines, we are guaranteed the local stability of the endemic equilibrium of susceptible–infected–susceptible equations (1).

increased c (or v) when the corresponding partial derivative is positive; conversely, selection favours decreased c (or v) when the corresponding partial derivative is negative. At a joint c,v-equilibrium – henceforth called the Nash equilibrium, (v^*,c^*) – both partial derivatives vanish, i.e.

$$P_v(v^*,c^*) = 0 \tag{2a}$$

$$H_c(v^*,c^*) = 0 \tag{2b}$$

The Nash equilibrium will be used as a benchmark for comparison with results when there are plastic interactions.

Figure 2 illustrates the co-evolutionary dynamics of v and c in the absence of plasticity. Only in the case $b_S - u < \sqrt{\alpha u}$ do we find a globally stable, internal Nash equilibrium (Fig. 2A). We may also find a locally stable, internal Nash equilibrium when $b_S - u \geq \sqrt{\alpha u}$ (Fig. 2B). Of course, the existence of an internal Nash equilibrium is also contingent upon the pair (v^*,c^*) lying in the feasible set illustrated in Fig. 1. We can guarantee that an internal Nash equilibrium (v^*,c^*) is feasible by requiring that $1/2\gamma$ (the distance between the

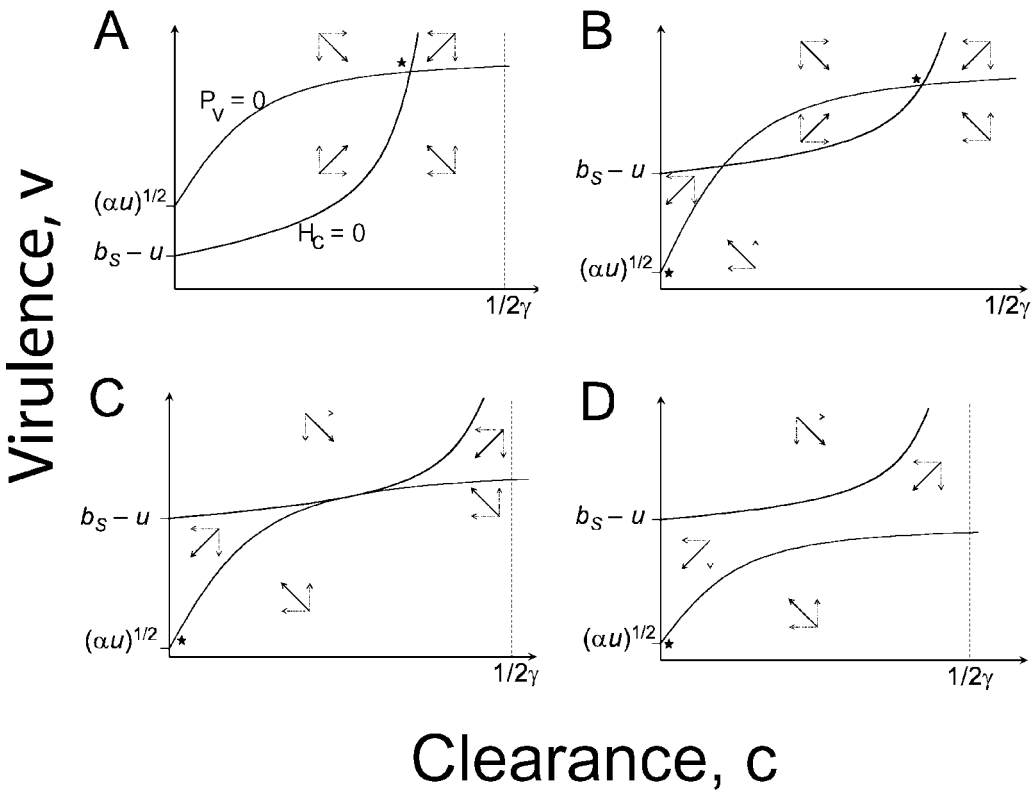

Fig. 2. Co-evolutionary dynamics of host clearance and pathogen virulence under the assumption of no plasticity. Minor arrows show direction of movement through c,v-space with respect to particular axes, whereas major arrows show net direction of movement. Nash equilibria are indicated with a star.

vertical line, in Fig. 2, and the origin) be less than $\sqrt{b_S/\gamma}$ (the position of the vertical boundary of the set of feasible c,v in Fig. 1), an assumption we now make.

When $b_S - u \geq \sqrt{\alpha u}$, another candidate Nash equilibrium occurs along the v-axis, where host clearance is zero (Figs. 2B–D). However, this candidate equilibrium is non-feasible (see Fig. 1).

Host or pathogen plasticity (but not both)

Conditions for evolutionary stability in host–pathogen interactions when only one of the two interactants displays plasticity are derived in Taylor *et al.* (2006). Specifically, when the pathogen displays plasticity, such that the host effectively chooses its strategy c first and the pathogen correctly adopts the corresponding optimal virulence plastically, the evolutionarily stable levels of pathogen virulence and host clearance ($\tilde{v}$ and $\tilde{c}$) must satisfy the equations:

$$P_v(\tilde{v},\tilde{c}) = 0 \tag{3a}$$

$$H_c(\tilde{v},\tilde{c})P_{vv}(\tilde{v},\tilde{c}) = H_v(\tilde{v},\tilde{c})P_{vc}(\tilde{v},\tilde{c}) \tag{3b}$$

where double subscripts denote second partial derivatives. Conversely, when the host displays plasticity, such that the pathogen effectively chooses its strategy v first and the host then correctly adopts the corresponding optimal level of clearance, the evolutionarily stable levels of pathogen virulence and host clearance must satisfy the equations:

$$H_c(\tilde{v},\tilde{c}) = 0 \tag{4a}$$

$$P_v(\tilde{v},\tilde{c})H_{cc}(\tilde{v},\tilde{c}) = P_c(\tilde{v},\tilde{c})H_{cv}(\tilde{v},\tilde{c}) \tag{4b}$$

It is difficult to determine when a feasible solution to system (3) or system (4) exists; and when a solution does exist, it is difficult to obtain it, analytically. Nevertheless, in cases where a feasible solution $(\tilde{v},\tilde{c})$ does exist, there are two important observations that can be made:

1. A feasible Stackelberg equilibrium $(\tilde{v},\tilde{c})$ is always accompanied by a feasible internal Nash equilibrium (v^*,c^*), and so there is always a benchmark against which the Stackelberg equilibrium can be compared. Formally, if a feasible solution to (3) or (4) exists, then there also exists a feasible solution (v^*,c^*) to equations (2).
2. The Stackelberg equilibrium $(\tilde{v},\tilde{c})$ always corresponds to levels of virulence and clearance that are lower than its 'sister' Nash equilibrium (v^*,c^*) (Fig. 3).

Both observations 1 and 2 are explained in the Appendix. When the host clearance rate changes plastically, the marginal change in fitness experienced by a mutant pathogen strain with an increased virulence will be lower than that in the absence of host plasticity, because such mutants will induce a higher clearance rate in their hosts. In other words, the induced change in the host results in an additional fitness cost of virulence (i.e. the host attempting to clear the infection more rapidly). Consequently, the costs and benefits of increased virulence equalize at lower values of virulence. The clearance rate is also then lower at this equilibrium because lowered virulence selects for lowered clearance (van Baalen, 1998; Day and Burns, 2003). An analogous argument explains why pathogen plasticity leads to lower virulence and clearance as well.

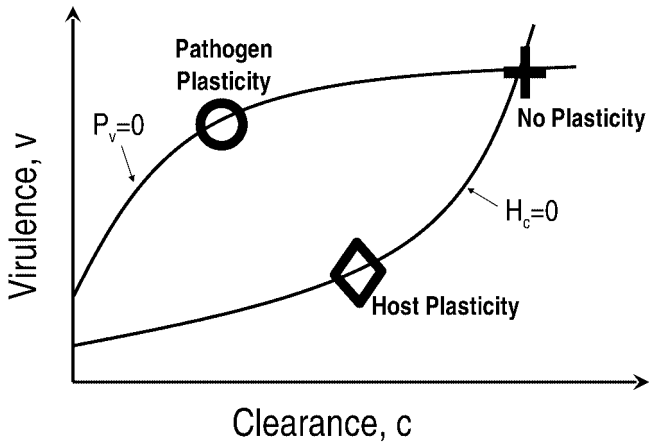

Fig. 3. Host or pathogen plasticity leads to 'more cooperative' outcomes. The Stackelberg equilibrium for the case in which only the host's strategy is plastic lies on the isocline $H_c(c,v) = \partial H/\partial c = 0$ and is indicated with a diamond. The Stackelberg equilibrium for the case in which only the pathogen's strategy is plastic lies on the isocline $P_v(c,v) = \partial P/\partial v = 0$ and is indicated with a circle. For comparison, the Nash equilibrium (i.e. no plasticity) is indicated with a cross.

We are now ready to consider the effect of plasticity on incidence rate and case mortality by using the optimal virulence and clearance rates given by the solutions of systems (3) and (4). Case mortality (χ) is the probability of a host dying once infected, and for the present model is given by $\chi = v/(\mu + v + c)$. This is generally considered to be a useful quantitative measure of pathogen-induced mortality and is one of the most common measures of virulence for human infectious diseases (Day, 2002). Plasticity on the part of the host or the pathogen was observed to have conflicting effects on case mortality: decreasing it in the former and increasing it in the latter, relative to the Nash equilibrium case (Fig. 4).

Incidence is defined to be the rate at which new infections are generated per susceptible individual in the population. Letting δ denote per capita incidence rate, we have

$$\delta = \beta \hat{I} = \frac{(b_S - \mu)(\mu + v + c)}{(\mu + v - b_S + \gamma c^2)}$$

Relative to the case of no plasticity, the assumption of plasticity on the part of the host or the pathogen typically results in an increased incidence rate (Fig. 5). Furthermore, plasticity has the potential to alter the relationship between incidence at the evolutionarily stable strategy (ESS) and various parameters of the model. Figure 5B presents an example in which plasticity in the host results in the incidence decreasing as the cost of host clearance increases as opposed to the positive relationship that exists in the absence of plasticity.

Joint plasticity

To investigate the consequences of joint plasticity we suppose that hosts and pathogens negotiate outcomes using linear response rules (McNamara *et al.*, 1999; Taylor and Day, 2004).

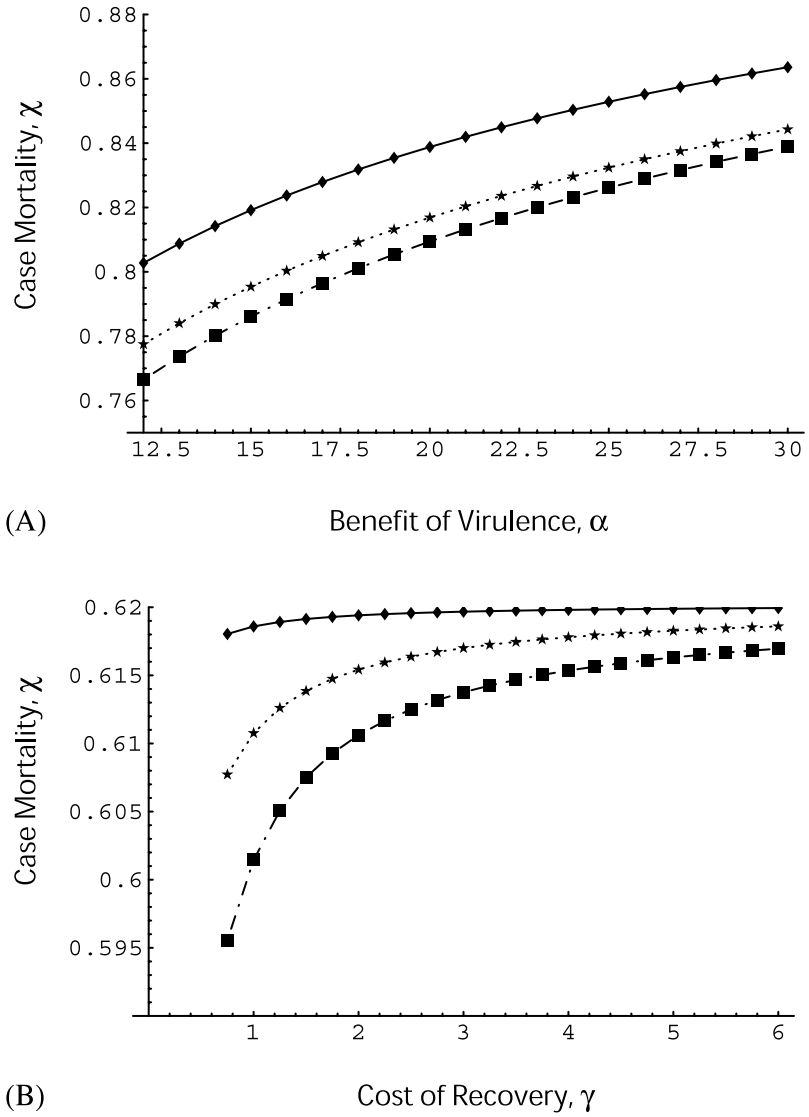

Fig. 4. A comparison of case mortality at equilibrium with host plasticity (squares), parasite plasticity (diamonds), and without plasticity (asterisks) as α and γ are varied (panels A and B, respectively). In A, $\beta_{max} = 2$, $b_S = 0.8$, $\gamma = 1$, and $\mu = 0.6$; in B, $\beta_{max} = 2$, $b_S = 4$, $\alpha = 8$, and $\mu = 3$. The numerical results presented in this figure suggest that pathogen plasticity can lead to case mortality rates that are higher than those found under either host plasticity alone or under no plasticity. Note, however, that the differences among the three cases are sometimes relatively small.

That is, hosts and pathogens respond to the actions of their counterparts according to the rules

$$c = \rho_{host} - \lambda_{host} v \tag{5a}$$

$$v = \rho_{path} - \lambda_{path} c \tag{5b}$$

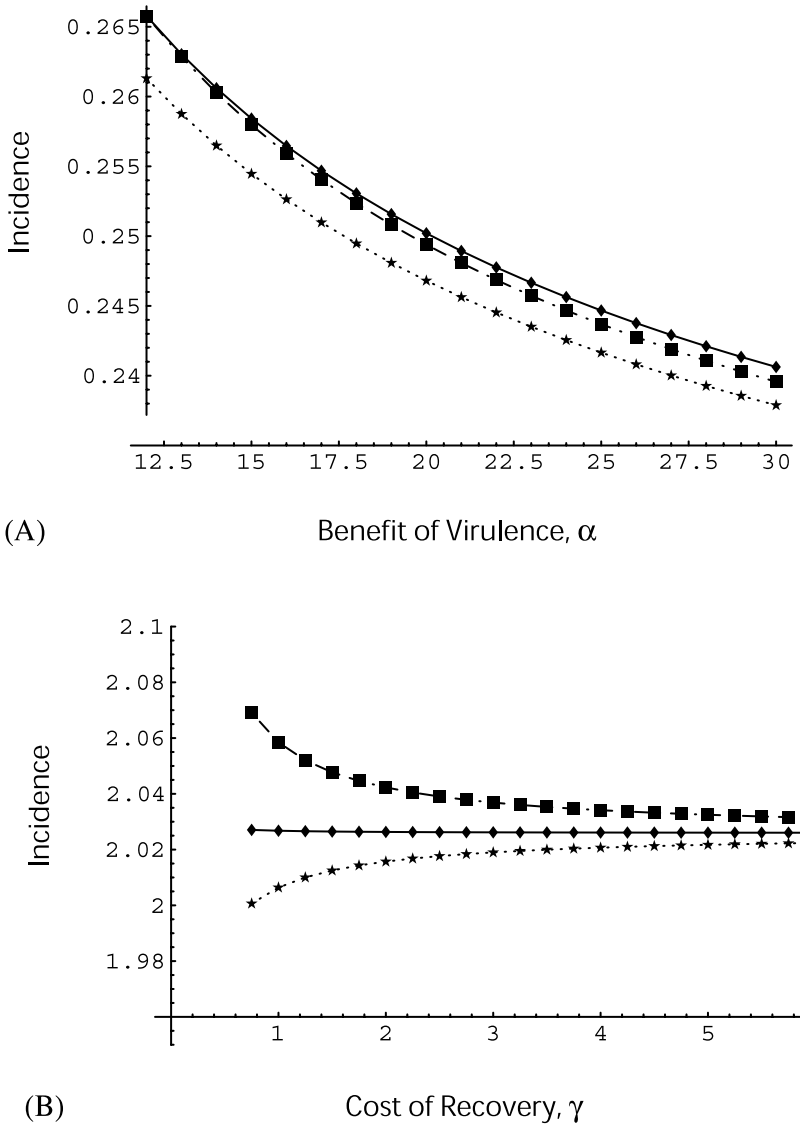

Fig. 5. A comparison of incidence rates at equilibrium with host plasticity (squares), parasite plasticity (diamonds), and without plasticity (asterisks) as α and γ are varied (panels A and B, respectively). In A, $\beta_{max} = 2$, $b_S = 0.8$, $\gamma = 1$, and $\mu = 0.6$; in B, $\beta_{max} = 2$, $b_S = 4$, $\alpha = 8$, and $\mu = 3$. The numerical results presented in this figure suggest that host plasticity can lead to incidence rates that are higher than those found under either pathogen plasticity alone or under no plasticity. Note, however, that the differences among the three cases are sometimes relatively small.

where λ_{path} and λ_{host} are measures of the responsiveness of the pathogen and the host to actions adopted by the other player, respectively.

Equations (5a) and (5b) describe the dynamics of negotiation, i.e. how strategic 'offers' and 'counter-offers' change over time (Fig. 6). It is possible to show that these offers and counter-offers eventually converge to the negotiated outcomes

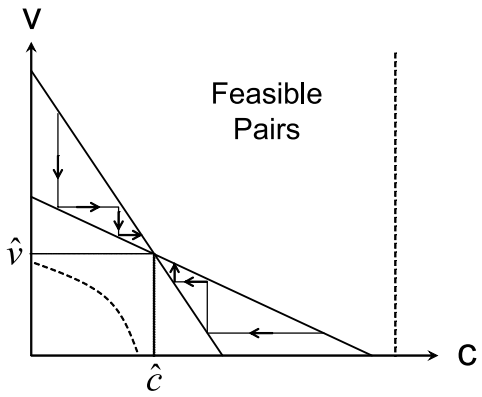

Fig. 6. The dynamics of negotiation using linear response rules (solid lines) in c,v-space. One party (host or parasite) makes an offer that is countered by the other party. The counter-offer is determined by following an arrow from the less steep solid line to the steep solid line or vice versa. Negotiation eventually settles at $(\hat{c},\hat{v})$, the point at which the two solid lines intersect. Dashed lines delineate feasible negotiated outcomes.

$$\hat{c} = \frac{\rho_{host} - \lambda_{host}\rho_{path}}{1 - \lambda_{path}\lambda_{host}} \tag{6a}$$

$$\hat{v} = \frac{\rho_{path} - \lambda_{path}\rho_{host}}{1 - \lambda_{path}\lambda_{host}} \tag{6b}$$

whenever $|\lambda_{path}\lambda_{host}| < 1$ (Taylor and Day, 2004).

We are primarily interested in the co-evolution of negotiated outcomes $(\hat{c},\hat{v})$, but this requires us to model the co-evolution of response-rule parameters $(\rho_{host}, \lambda_{host})$ and $(\rho_{path}, \lambda_{path})$. A natural degeneracy is found in the evolutionary dynamics used to describe the evolution of response rule parameters (Taylor and Day, 2004). Put simply, the degeneracy in this case is due to the fact that there are only two dynamic equations required to describe the evolution of four traits (response-rule parameters). Rather than the standard evolutionary dynamic approach, we explored the evolution of response-rule parameters using a simple computer simulation. The simulation was written in C, and the source code is available from the corresponding author upon request.

Our simulation considered the evolution of response rules used by members of N negotiating partnerships (with each partnership consisting of one host and one pathogen) undergoing discrete, non-overlapping generations.

Response-rule parameters were initially assigned to individuals (host and pathogen) at random, and evolutionary changes in these rules were tracked over 2000 time steps. Preliminary simulation results suggested that population average negotiated outcomes – call them $\hat{c}_{av}$ and $\hat{v}_{av}$ – stabilized much earlier than time = 2000. To ensure that negotiation dynamics always converged to (6), we assumed that both $|\lambda_{host}| < 1$ and $|\lambda_{path}| < 1$.

At the beginning of a time step, negotiated outcomes, $\hat{c}$ and $\hat{v}$, are established and these outcomes are then used to determine pay-offs to host and pathogen. When the negotiated outcome is feasible, pay-offs to host and pathogen are calculated as $H(\hat{v},\hat{c})$ and $P(\hat{v},\hat{c})$, respectively. When the negotiated outcome is not feasible, both partners are given a pay-off

of zero. This provides strong selection for *feasible* outcomes, and ensures that our analysis in this section is subject to the same constraints imposed above.

Reproduction by hosts and pathogens occurs next. We assume a parent (host or pathogen) with a non-zero pay-off produces a large number of asexual offspring, but in proportion to the pay-off that the parent, itself, received. The offspring produced are equipped with mutated versions of the response rule used by their parent. These offspring compete with conspecifics, at random, for the N positions vacated by the parental generation. After competition a new time step begins.

We simulated 30 replicate populations of 10,000 negotiating pairs for a limited set of parameters and we calculated values of sample mean values of $\hat{c}_{av}$ and $\hat{v}_{av}$. Parameter sets were limited to those that admit Nash equilibria and both kinds of Stackelberg equilibria.

Simulated mean values of $\hat{c}_{av}$ and $\hat{v}_{av}$ were always less than corresponding c and v under the no plasticity and pathogen plasticity scenarios (Table 1). Nevertheless, the difference between values was not always significant at the 5% level. Host–pathogen negotiation also led to case mortality levels that were consistently lower than those found under no plasticity and under pathogen plasticity. Moreover, the difference between negotiated and non-negotiated levels was significant (Table 1). No other consistent patterns were evident, but examination of raw data revealed a number of 'extreme' replicates. (The frequency of such replicates depended on the parameter values chosen.)

So-called 'extreme replicates' were characterized by host clearance and pathogen virulence levels much lower than those predicted to evolve in the absence of negotiation (Fig. 7). Case mortality in extreme replicates was always markedly lower than non-negotiated levels, while incidence rate was always markedly greater than its non-negotiated level (Table 1). Given the *post hoc* identification of extreme cases, we carried out no formal analysis on these replicates.

DISCUSSION

A tremendous amount of work has considered the evolution of pathogen virulence (reviewed in Bull, 1994; Frank, 1996; Day and Proulx, 2004), and recent studies have coupled this with the co-evolution of host immune responses (Anderson and May, 1982; van Baalen, 1998; Day and Burns, 2003). However, most of this work has neglected the possibility that infected hosts adjust their immune response, taking into account pathogen virulence, and vice versa. This paper is part of a continued effort to develop theoretical predictions for the effect of information exchange on the co-evolution of host and pathogen. Previous investigations relied on very restrictive epidemiological assumptions (Taylor *et al.*, 2006), and so our objective in this paper was to understand the consequences of host and/or pathogen plasticity using a standard set of epidemiological assumptions.

Given our epidemiological framework, what can we conclude about the influence plasticity has on the co-evolution of host and pathogen? First, we note that building host and pathogen pay-off functions from an explicit epidemiological dynamic as we have done here does not change the basic result reported in Taylor *et al.* (2006). Like Taylor and his colleagues, we find that plasticity tends to encourage the co-evolution of reduced levels of pathogen virulence, and host clearance (a more 'cooperative' outcome). In the absence of plasticity, a population of host and pathogen remains at the Nash equilibrium levels of c^* and v^* and neither host nor pathogen can increase its pay-off by *unilaterally* changing its phenotype. When there is plasticity in one party, however, mutant genotypes of the other

Table 1. Results from 30 replicates of 10,000 negotiating pairs after 2000 simulated generations

	(a)					(b)				
Replicate	No. of negotiating pairs in population	Population average c	Population average v	Population average case mortality	Population average incidence rate	No. of negotiating pairs in population	Population average c	Population average v	Population average case mortality	Population average incidence rate
0	10000	1.8075	9.4433	0.4550	1.0813	9999	0.6281	14.2849	0.5117	2.0814
1	10000	1.2168	9.6350	0.4733	1.0794	10000	0.8789	13.6269	0.4953	2.1387
2	10000	1.2794	10.0696	0.4827	1.0542	4986	0.0032	1.0031	0.0716	28662.7837
3	10000	0.8291	9.6677	0.4834	1.0743	9998	0.4183	13.6433	0.5040	2.1315
4	10000	1.0194	9.7361	0.4805	1.0729	10000	0.7372	13.9828	0.5044	2.1070
5	10000	1.4028	10.1573	0.4820	1.0485	9997	0.3930	13.8598	0.5085	2.1112
6	10000	1.2151	9.2909	0.4643	1.1009	9975	0.0515	3.8777	0.2290	5.8828
7	10000	1.2859	9.7772	0.4753	1.0706	10000	0.5116	13.7769	0.5048	2.1221
8	10000	1.0255	9.8552	0.4834	1.0657	10000	0.9711	13.7669	0.4962	2.1257
9	10000	0.9480	9.5948	0.4785	1.0812	9947	0.0247	1.8669	0.1254	17.1986
10	10000	1.0467	9.6866	0.4787	1.0757	9975	0.0486	4.1579	0.2416	5.4507
11	10000	0.8624	9.9166	0.4888	1.0605	10000	0.7096	14.3009	0.5105	2.0816
12	10000	0.7204	9.7498	0.4881	1.0677	10000	0.7955	14.1118	0.5055	2.0974
13	10000	1.0230	9.9930	0.4868	1.0582	10000	0.9667	14.0522	0.5014	2.1008
14	10000	1.0022	9.4564	0.4737	1.0901	10000	0.5579	14.2269	0.5120	2.0855

15	10000	1.2036	9.7751	0.4771	1.0715	10000	0.8341	14.3365	0.5089	2.0788
16	10000	0.7334	9.7790	0.4886	1.0661	9997	0.3212	13.5575	0.5043	2.1351
17	10000	1.5049	9.4547	0.4620	1.0877	10000	0.6553	14.0501	0.5070	2.1020
18	10000	0.6201	9.5846	0.4863	1.0754	10000	1.0663	13.7624	0.4943	2.1247
19	10000	1.0527	9.6465	0.4775	1.0782	9999	0.3696	13.6088	0.5043	2.1328
20	10000	1.0387	9.6494	0.4779	1.0779	10000	0.9433	14.1637	0.5038	2.0915
21	10000	1.2305	9.5523	0.4708	1.0842	9962	0.0401	2.4816	0.1599	10.4765
22	10000	0.5391	9.8940	0.4963	1.0541	10000	0.7922	14.4326	0.5112	2.0724
23	10000	1.2723	9.7864	0.4759	1.0698	10000	0.5516	14.0580	0.5091	2.0993
24	10000	1.0204	9.6743	0.4790	1.0763	10000	0.7464	14.4645	0.5127	2.0686
25	10000	1.4293	9.8904	0.4749	1.0625	10000	0.9296	14.2043	0.5047	2.0894
26	10000	1.3013	9.5364	0.4688	1.0849	10000	0.9354	13.9624	0.5003	2.1102
27	10000	1.3721	9.5962	0.4685	1.0818	10000	0.7149	13.8933	0.5032	2.1153
28	10000	1.4087	10.0561	0.4795	1.0534	10000	0.7945	14.2986	0.5087	2.0843
29	10000	1.0528	10.0691	0.4882	1.0530	10000	1.2699	14.4818	0.5033	2.0609
Mean		**1.1155**	**9.7325**	**0.4782**	**1.0719**		**0.6220**	**12.1432**	**0.4486**	**958.4780**
S.E.		0.0499	0.0378	0.0016	0.0023		0.0615	0.7794	0.0236	939.2641
No plasticity		**1.2038**	**10.3459**	**0.4915**	**1.0384**		**0.8030**	**14.3890**	**0.5104**	**2.0756**
Host plasticity		**1.1627**	**9.6994**	**0.4763**	**1.0751**		**0.7887**	**13.9307**	**0.5026**	**2.1132**
Pathogen plasticity		**0.5419**	**10.0209**	**0.4995**	**1.0472**		**0.3393**	**14.1453**	**0.5147**	**2.0854**

Note: Parameters are: (a) $\beta_{max} = 1$, $\alpha = b_S = 10$, $\gamma = 0.2$, and $\mu = 9.5$; (b) $\beta_{max} = 4$, $\alpha = 15$, $b_S = 14$, $\gamma = 0.3$, and $\mu = 13$. Raw data are included, together with a data summary, to highlight the occurrence of 'extreme' replicates described in the text (highlighted in grey). Values highlighted by a dark border differ significantly from the corresponding simulated mean at the 5% level.

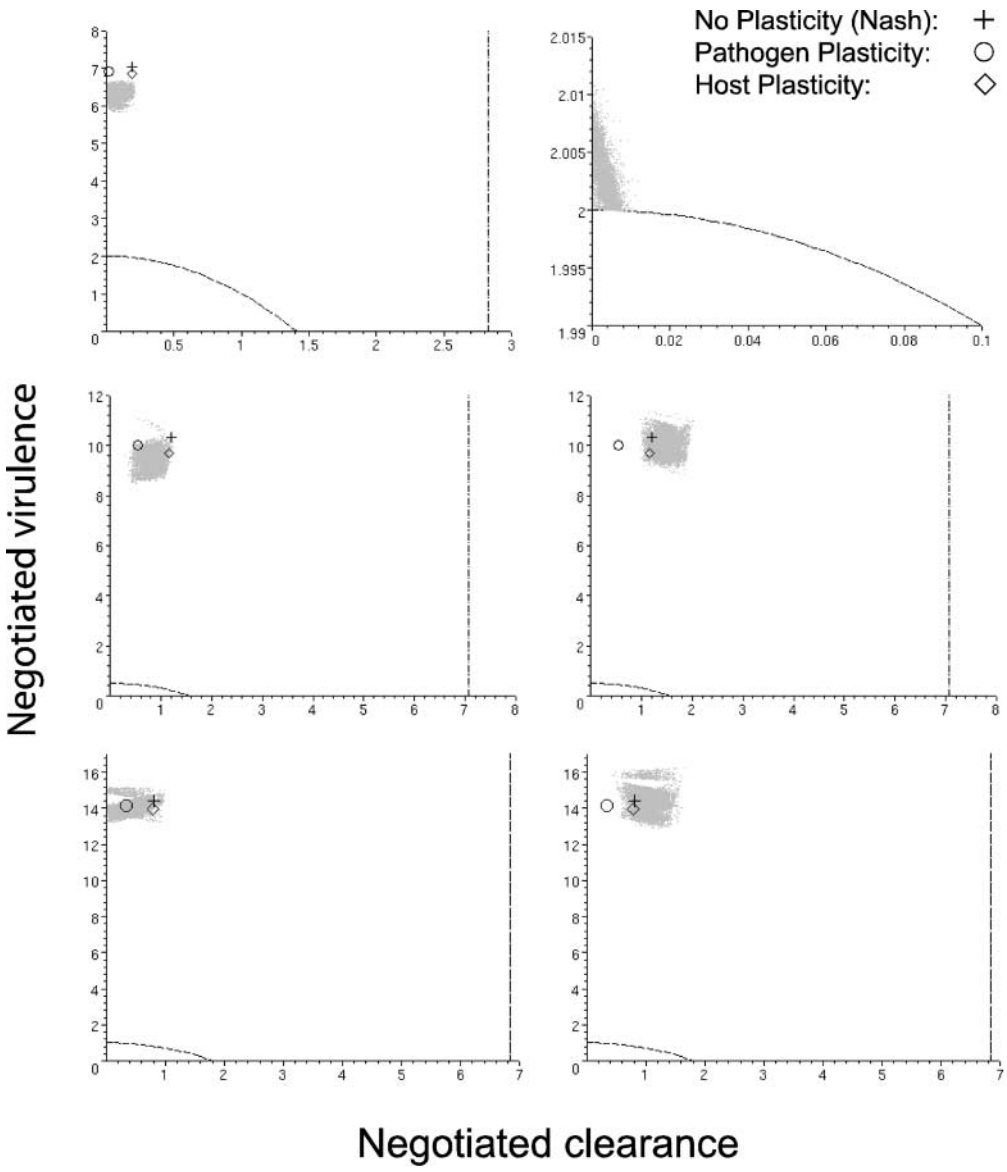

Fig. 7. Sample results for the case of joint host–pathogen plasticity. Results are for 10,000 negotiating pairs over 2000 simulated generations. Parameter values are: $\beta_{max} = 2$, $\alpha = b_S = 8$, $\gamma = 1$, and $\mu = 6$ (top); $\beta_{max} = 1$, $\alpha = b_S = 10$, $\gamma = 0.2$, and $\mu = 9.5$ (middle); $\beta_{max} = 4$, $\alpha = 15$, $b_S = 14$, $\gamma = 0.3$, and $\mu = 13$. Small grey dots correspond to the outcome negotiated by a given pair (these form a 'cloud' of dots). For comparison, we have indicated the Nash equilibrium (cross), the Stackelberg equilibrium for the case of host plasticity (diamond), and the Stackelberg equilibrium for the case of pathogen plasticity (circle). Dashed lines delineate the set of feasible negotiated outcomes. Panel on the top right illustrates an 'extreme' replicate described in the text.

party will induce a plastic change in the strategy of their opponent. In other words, changes are no longer unilateral. Due to the antagonistic nature of host–parasite interactions, this plastic response will typically impose an additional cost on the mutant (i.e. an additional cost of increased virulence in the case of a parasite, or an additional cost of increased clearance in the case of a host). This results in the ESS being reached at lower levels of both virulence and clearance.

Interestingly, a by-product of the reduction in both virulence and clearance is a longer average duration of infection. Unlike other games, where extended periods of interaction promote the success of cooperative strategies (see, for example, Axelrod and Hamilton, 1981), 'cooperative' strategies naturally lead to longer encounters between players. This also suggests that the notion of an effective immune response as being one that reduces the duration of infection and the reproductive success of the pathogen may be too limited. Recovery from infection by the host might not give appreciable fitness benefits to the host if the parasite has instead co-evolved with the host immune response to result in a relatively benign infection.

In terms of the epidemiological consequences of host–pathogen co-evolution, we find that all forms of plasticity promote incidence rates that are higher than those observed in the absence of plasticity. Moreover, both numerical and simulation results suggest that host plasticity can sometimes result in disease incidence rates that are considerably higher than those under pathogen plasticity (Fig. 5B). An intuition for these predictions can be found by noting that plasticity in either host or parasite results in the evolution of reduced clearance and virulence as described above. This increases the duration of an infection, and as a result, tends to produce an increased incidence as well, simply because incidence is proportional to the density of infected hosts.

Our numerical results demonstrate that plasticity also has the potential to alter the relationship between incidence and other model parameters. For example, host plasticity can result in incidence decreasing as the cost of recovery, γ, increases as opposed to the positive relationship that occurs in the absence of plasticity (Fig. 5B). This is more difficult to intuit, but can be understood by again noting that host plasticity tends to impose an additional cost on mutant parasite strains that have an increased virulence. This additional cost always results in the ESS clearance and virulence being attained at lower values than in the absence of plasticity as mentioned above. But the cost itself is a function of γ, and this cost decreases as γ increases. In particular, when γ increases, mounting an immune response becomes more expensive. As a result, the additional cost of virulence imposed on the parasite by the plastic host response is reduced because the host will exhibit a very small plastic increase in clearance when clearance is very expensive. This means that, even though the ESS clearance rate will decrease as immune responses become more expensive, the ESS virulence will nevertheless increase. These two changes have opposing effects on the duration of an infection, and they therefore have opposing effects on disease incidence as well. Depending on the relative magnitudes of these effects, the relationship between incidence and γ can then be reversed from that which occurs in the absence of plasticity.

In very broad terms, we see that the influence of plasticity on case mortality depends critically on the mechanism of plasticity. Under both host plasticity and (possibly) joint plasticity, numerical and simulation results indicate that the co-evolution of clearance and virulence lead to case mortality rates that are lower than those predicted to evolve in the absence of plasticity. Under pathogen-only plasticity, case mortality rates are higher than those predicted in the absence of plasticity. Again we note that the relationship between

fitness (of both host and pathogen) and case mortality is not a simple one, and so the result is certainly not clear *a priori*.

Plasticity in host–pathogen (or host–parasite) co-evolution is probably widespread (Thomas *et al.*, 2005). Wellnitz (2005) has noted that many viruses show latency between the time of initial infection and the time at which the infection itself can be effectively transmitted to a new host. During this period of latency, it is conceivable that a newly infected host is gathering information about (or providing information to) the invader. Alternatively, the period of latency itself may be open to negotiation, since it is during this time that an asymptomatic host *may* continue to carry out normal reproductive functions and/or somatic maintenance.

Despite our expectations about the ubiquity of host–pathogen plasticity, it is unclear which natural system would serve as an adequate testing ground for the predictions made above. One important feature of such a system is the existence of variation (probably geographic variation). In particular, our simulations suggest that geographic 'replicates' of negotiating host and pathogen populations selection will, on occasion, establish cooperative negotiated settlements. We anticipate that future work involving negotiation of specific pathogen life-history traits (including duration of periods of pathogen latency) and the explicit incorporation of negotiation costs will focus empirical efforts on key natural systems.

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APPENDIX

Consider the case where only the pathogen has the ability to facultatively alter virulence (pathogen plasticity). We begin by assuming the existence of at least one feasible Stackelberg equilibrium, i.e. we assume that there exists a feasible solution $(\tilde{v},\tilde{c})$ to system (3).

Recall that equation (3a) states

$$P_v(\tilde{v},\tilde{c}) = 0 \tag{A1}$$

From (A1) we see that $(\tilde{v},\tilde{c})$ must lie on the concave-down curve illustrated in Fig. 2. Equation (A1) defines pathogen virulence as a function of host clearance (in fact, the graph of this function is precisely the concave-down curve in Fig. 2). For clarity, we will call this function $v^{\#}(c)$.

Now, we can write the equation in (3b) as

$$\frac{d}{dc}[H(v^{\#}(c),c)]_{(\tilde{v},\tilde{c})} = H_v(\tilde{v},\tilde{c})\left(\frac{dv^{\#}}{dc}\right)_{(\tilde{v},\tilde{c})} + H_c(\tilde{v},\tilde{c}) = 0$$

or simply,

$$\left.\frac{dv^{\#}}{dc}\right|_{(\tilde{v},\tilde{c})} = -\frac{H_c(\tilde{v},\tilde{c})}{H_v(\tilde{v},\tilde{c})} \tag{A2}$$

It is clear from Fig. 2 that the left-hand side of (A2) is positive. It follows that $(\tilde{v},\tilde{c})$ must lie in a region of v,c-space in which the right-hand side is positive. It is easy to check that H_v is always greater than zero, and so $(\tilde{v},\tilde{c})$ must lie in a region where $H_c > 0$. Again, using Fig. 2 we see that H_c is only greater than zero above the curve that is concave-up. Therefore, we conclude that, under pathogen plasticity, $(\tilde{v},\tilde{c})$ lies on the concave-down curve in Fig. 2, somewhere above the concave-up curve in the same figure. This implies that

the corresponding values of v and c will be smaller than those corresponding to the Nash equilibrium.

Note that the existence of $(\tilde{v},\tilde{c})$ requires that the curves in Fig. 2 intersect, and implies that the case in Fig. 1D need not be considered. Since Fig. 2C illustrates a marginal case, we assert that the existence of a Stackelberg equilibrium $(\tilde{v},\tilde{c})$ necessitates the existence of an internal Nash equilibrium, (v^*,c^*).

The argument above can be used also for the case with host plasticity, *mutatis mutandis*.