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The impact of non-lethal synergists on the population and  
evolutionary dynamics of host-pathogen interactions

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## Abstract

2 Multiple pathogenic infections can influence disease transmission and virulence, and have impor-  
tant consequences for understanding the community ecology and epidemiology of host-pathogen  
4 interactions. Here the population and evolutionary dynamics of a host-pathogen interaction  
with free-living stages are explored in the presence of a non-lethal synergist that hosts must  
6 tolerate. Through the coupled effects on pathogen transmission, host mass gain and allometry  
it is shown how investing in tolerance of a non-lethal synergist can lead to a broad range of  
8 different population dynamics. The effects of the synergist on pathogen fitness are explored  
through a series of life-history trait trade-offs. Coupling trade-offs between pathogen yield and  
10 pathogen speed of kill and the presence of a synergist favour parasites that have faster speeds  
of kill. This evolutionary change in pathogen characteristics is predicted to lead to stable pop-  
12 ulation dynamics. Evolutionary analysis of tolerance of the synergist (strength of synergy) and  
lethal pathogen yield show that decreasing tolerance allows alternative pathogen strategies to  
14 invade and replace extant strategies. This evolutionary change is likely to destabilize the host-  
pathogen interaction leading to population cycles. Correlated trait effects between speed of kill  
16 and tolerance (strength of synergy) show how these traits can interact to affect the potential  
for the coexistence of multiple pathogen strategies. Understanding the consequences of these  
18 evolutionary relationships has important for the both the evolutionary and population dynamics  
of host-pathogen interactions.

20

**Keywords:** allometric scaling; host-pathogen epidemiology; limit cycles; time lags; popula-  
22 tion dynamics

## Introduction

24 Disease has a major impact on the shape and structure of species assemblages (Lafferty et al.  
2006) and on the dynamics of populations (Anderson and May 1991; Hudson et al. 2002).  
26 For instance, it is now well-established that pathogens have the potential to generate sustained  
population fluctuations in the absence of other limiting factors (Anderson and May 1981). The  
28 combination of high levels of parasite-induced mortality, large pathogen yields, long-lived resting  
stages and relative low rates of host population growth can give rise to population instabilities  
30 (Anderson and May 1981; Myers 1988). These effects can be mitigated or enhanced by addi-  
tional ecological factors such as the effects of refuges (Hochberg 1989), the role of intraspecific  
32 competition (Bowers, et al. 1993; Bonsall et al. 1999) or competitive interactions between  
strains (Hochberg and Holt 1990; Bonsall 2004). Studies have also highlighted how pathogens  
34 may exist as covert or latent infections (Burden et al. 2003), that multiple pathogen genotypes  
can coexist within a single host (Hodgson et al. 2003) and that multiple strain infections can  
36 affect the virulence, transmission and competitive interaction amongst pathogens (Raymond et  
al. 2007, 2008, 2009).

38 As such, parasites do not exist in isolation from other natural enemies but within a network  
of interactions within and between hosts. Studies on the role of multiple natural enemies,  
40 such as predators and parasites, on host populations have highlighted that exclusion or control  
of additional natural enemies can affect levels of disease incidence (Packer et al. 2003) with  
42 detrimental consequences for both the population dynamics (especially if parasites are highly  
virulent) and the dynamical patterns of coexistence and exclusion (Hudson et al. 1992; Ives  
44 and Murray 1997). Multiple pathogenic infections can also affect the evolutionary dynamics of  
disease (Levin and Pimentel 1981; Hochberg and Holt 1990). For instance, motivated by the  
46 earlier studies, Hochberg and Holt (1990) illustrated that the dynamics between pathogens can  
be affected by transmission efficiencies, virulence and interactions within the individual host.  
48 Furthermore, within hosts, patterns of multiple infections can affect the maintenance of mixed

infections and consequently pathogen virulence through interactions with competitors and the  
50 host immune system. For instance, Hodgson et al. (2003) argued that the maintenance of  
multiple infections of different baculovirus strains in Pine Beauty moth (*Panolis flammea*) is  
52 mediated through differential co-infection patterns and potential life-history trade-offs leading  
to mixed infections being more pathogenic (killing more insects) and yielding higher levels of  
54 virus. More recently, studies have shown that multiple infections of different entomopathogenic  
and non-pathogenic bacteria can lead to lower levels of pathogen-induced host mortality and  
56 pathogen yield (Raymond et al. 2007). Multiple pathogenic infections can also lead to complex  
interactions with the host immune system (Schweitzer and Anderson 1991) that can affect the  
58 dynamics of immune memory and pathogen virulence (Fenton et al. 2006) and influence the  
spatial distribution of disease (Ellner et al. 2007). Interactions with non-pathogenic commensals  
60 can also cause inflammatory responses that affect virulence evolution (Brown et al. 2008) or the  
evolution of host resistance to infection (Bonsall and Raymond 2008). There is accumulating  
62 evidence that the role of alternative pathogenic and/or non-pathogenic organisms is highly likely  
to affect host-pathogen interactions.

64 Synergistic effects can be broadly defined as any interaction between two species that leads to  
non-additive effects. In host-pathogen systems, the role of alternative and synergistic organisms  
66 has been implicated in affecting the interaction between alternative entomopathogenic bacteria,  
virus-fungal interactions, plant pathogens and human infections. For instance *B. thuringiensis*  
68 *israelensis* and its toxins are more pathogenic to mosquitoes in the presence of *B. sphaericus*  
(Wirth et al. 2004). Multiple infections of *Serratia entomophila* and *Metarhizium anisopliae*  
70 increase mortality in the New Zealand grass grub (*Costelytra zealandica*) (Glare 1994). In  
plants, mixed infections can lead to synergism with an increase in pathogen virulence and a  
72 breakdown of resistance to alternative viral infections (Martin et al. 2004). Similarly, the  
commensal anaerobe, *Bacteroides fragilis*, found in the human intestine is thought to synergise  
74 polymicrobial infections in wounds and abdominal abscesses by disrupting the immune response

(Mazmanian and Kasper 2006).

76 Although multiple parasitic infections can affect host performance (by increasing morbidity  
and/or mortality) (Moore 2002), it is not necessarily a foregone conclusion that these effects  
78 translate into dynamical effects that influence the epidemiological patterns of the host-pathogen  
interactions. Understanding the effects of multiple natural enemies necessitates a broader com-  
80 munity ecology approach to enemy-victim dynamics and this has recently been advocated as  
most appropriate for host-pathogen dynamics and interactions (Pedersen and Fenton 2007).  
82 Representing the dynamics of host-pathogen interactions in terms of a set of direct and indirect  
interactions within hosts provides a novel way in which to focus the role of multiple parasite  
84 effects on host dynamics. Interactions of co-infecting lethal and/or non-lethal parasites are pre-  
dicted to influence host fitness, pathogen transmission and have broad implications for disease  
86 control.

The aim of this study then is to explore how the action of a non-lethal synergist affects the  
88 dynamics of a host-pathogen interaction. A novel host-pathogen-synergist model is developed  
that allows for important life history trade-offs in yield and the effects of host size on the  
90 population and evolutionary dynamics to be explored. It is shown that synergists are capable  
of driving host-pathogen cycles. Furthermore, synergism is shown to influence pathogen fitness  
92 and consequently affect the interplay between evolutionary and population dynamics.

## Mathematical Model

### 94 Model Structure

The biological motivation behind the model is to explore how a host - pathogen interaction with  
96 free-living pathogens is affected by the presence of a non-lethal synergist that the host must  
also tolerate (Bonsall and Raymond 2008). The model is structured into two broad components:  
98 average host mass gain ( $m$ ) and the population dynamics of the host ( $N$ ), pathogen ( $V$ ) and  
synergist ( $S$ ). The key components are the link between individual mass and the population

100 dynamics of the host, pathogen yield and the population growth of the synergist:

*Mass Gain* - Individuals are expected to gain mass through the acquisition and metabolism  
102 of resources. As metabolic rate relationships are underpinned by allometric scaling (Smith 1984),  
these relationships have important consequences for the dynamics of resource gain and loss. For  
104 instance, the allometric relationship between metabolic rate and body size is well established and  
has been the subject of recent studies (West et al. 1997, 2001, 2002). In particular, the evidence  
106 for a  $3/4$  power law underpinning biological activity from mitochondria through to ecological  
communities has been thoroughly explored (West et al. 1997, 2001, 2002; Lane 2005). Although  
108 power-law scalings are a compelling concept recent evidence suggests that this universal scaling  
may not be constant (Lane 2005). As organisms grow to larger size this leads to differential  
110 energy demands that act as a major constraint on the efficient utilisation of energy. This has  
implications for the constancy of any allometric scaling exponent and, in the context of the  
112 current study, implications for the population dynamics of the host-pathogen interaction (De  
Leo and Dobson 1996; Cable et al. 2007; Bolzoni et al. 2008).

114 *Pathogen Yield* - Pathogen yield is known to be affected by insect development and mass.  
Developmental processes alter the rate at which insects moult and have an important influence  
116 on pathogen yield (Cory and Myers 2003). For instance, *egt*, an auxiliary gene involved in  
baculovirus infections of invertebrates, restricts larval moulting and significantly increases virus  
118 yields (O'Reilly et al. 1998). This is now known to have important dynamical implications  
for the persistence of modified viruses (where the *egt* gene is deleted) (Bonsall et al. 2005a).  
120 Furthermore, pathogen yield is also likely to be dependent on both the initial size of a host (at  
the point of infection) and the mass gained during the pathogen incubation period (Hedlund and  
122 Yendol 1974; Shapiro et al. 1986; Li and Skinner 2005). The shape of the relationship between  
pathogen yield and individual mass gain may have important implications for the population  
124 dynamics of the host-pathogen interaction.

*Synergist Population Growth* - Synergistic interactions between pathogens are known to

126 enhance pathogen-induced mortality rates and replication rates in a range of invertebrate hosts  
 (Broderick et al. 2000; Wraight and Ramos 2005; Raymond et al. 2008). For example, Wraight  
 128 and Ramos (2005) illustrate a synergistic interaction between *B. thuringiensis* (Bt) and *B.*  
*bassiana* with the activity of Bt prolonging the time interval between larval moults and providing  
 130 the fungus with increased opportunity to invade the host cuticle. The impact of the synergist  
 is expected to be greatest in later stage (larger hosts) (Wraight and Ramos 2005) and the  
 132 growth of the synergist is therefore expected to be dependent on the size of the host. However,  
 competition with other non-lethal microbes will limit the total density of a synergist within a  
 134 host. Synergistic interactions with non-pathogenic microbes are expected to decrease the cost of  
 investment in virulence factors associated with pathogenic and should influence the population  
 136 and evolutionary stability of a host-pathogen interaction (Raymond et al. 2008).

To explore these different aspects of the interaction between a host, a pathogen and a syn-  
 138 ergist, the population dynamics are described by the following set of differential equations:

$$\frac{dm}{dt} = \frac{a \cdot m^\phi(t)}{N(t)} - b \cdot m(t) - \eta \cdot S(t) \cdot m(t) \quad (1)$$

$$\frac{dN}{dt} = \frac{\rho \cdot N(t) \cdot m(t)}{1 + \kappa \cdot N(t)} - (\beta_0 + \theta \cdot S(t)) \cdot N(t) \cdot V(t) - d_n \cdot N(t) \quad (2)$$

$$\frac{dV}{dt} = \gamma(m(t - \tau)) \cdot (\beta_0 + \theta \cdot S(t - \tau)) \cdot N(t - \tau) \cdot V(t - \tau) \cdot \sigma - d_v \cdot V(t) \quad (3)$$

$$\frac{dS}{dt} = r_s \cdot m(t) \cdot S(t) \cdot \left[1 - \frac{S(t)}{K_s}\right] \quad (4)$$

where  $a$  is the rate of resource acquisition,  $\phi$  is allometric scaling of resource uptake by mass,  
 140  $b$  is the catabolic rate of resource use and  $\eta$  is the effect of the synergist on host mass gain  
 (the cost associated with the host tolerating the synergist). Individual host mass gain ( $m$ )  
 142 increases through the acquisition of resources (at rate  $a$ ) which is scaled by the effects of the  
 host population ( $N$ ) and an allometric constant (e.g.  $m^{3/4}$ ). Finally, mass is lost through the  
 144 catabolism of resources (at rate  $b$ ) and through the costs of tolerating the non-lethal synergist  
 (at rate  $\eta \cdot S(t)$ ).

146 In the absence of pathogens, hosts follow density-dependent growth.  $\rho$  is the birth rate of the  
 host population,  $\kappa$  is the strength of density dependence and hosts die from density-independent  
 148 (non-pathogen related) processes at rate  $d_n$ . In the presence of pathogens, hosts are infected  
 at rate  $\beta_0 \cdot V(t)$  and this transmission can be enhanced by the effects of the synergist ( $\theta$ ) -  
 150  $\beta_0 + \theta \cdot S(t)$ .

Infected hosts die from disease after  $\tau$  time units (a measure of pathogen speed of kill).  
 152 Pathogen yield ( $\gamma$ ) is a function of host mass ( $m$ ) such that  $\gamma(m) = 1 + \psi \cdot m(t)$  (where  $\psi$  is a  
 constant describing the effect of host mass on pathogen yield). Pathogens replicate in infected  
 154 hosts and survive (at rate  $\sigma = \exp(-\mu_j \cdot \tau)$  where  $\mu_j$  is a mortality rate). After cadaver lysis,  
 free-living lethal pathogens are released into the environment and decay at rate  $d_p$ .

156 The dynamics of the non-lethal synergist follow simple logistic population growth that is  
 coupled to the mass ( $m(t)$ ) of the host where  $r_s$  is the growth rate of the synergist (independent  
 158 of the host or pathogen) and  $K_s$  is the carrying capacity of this non-lethal synergist.

## Model Analysis

160 The analysis of the model proceeds in two ways. First, the population dynamics of the effects  
 of synergy under different ecological scenarios is explored. In the absence of time-delays, the  
 162 dynamics of this interaction can be evaluated using standard local stability analysis techniques  
 (Kot 2001). The inclusion of time-delays makes the analysis more complex (Kot 2001; Murdoch  
 164 et al. 2003) as the solution of characteristic equation is now transcendental (not a solution of  
 a polynomial equation with rational coefficients). Solutions of the characteristic equation and  
 166 stability conditions of these differential-difference equations are evaluated using a root solving  
 algorithm and numerical simulations. Second, the evolutionary dynamics are explored using  
 168 techniques from adaptive dynamics and evolutionary invasion analysis (Maynard-Smith 1982;  
 Metz et al. 1992; Vincent and Brown 2005). The conditions under which an alternative rare  
 170 pathogen strategy can invade a persistent host-pathogen-synergist interactions are evaluated.

These invasion conditions are explored under both differences in pathogen life-histories and the  
 172 effects of the synergist.

## Results

174 The results section is divided into two parts. Initially, the population dynamics of the host-  
 pathogen interaction (eqns 1-3) in the absence of the synergist ( $S(t) = 0$ ) are briefly explored  
 176 before the dynamics of the full three species interaction are presented. Following this, the  
 invasion dynamics of the pathogen in the presence of the synergist is explored and the likely  
 178 evolutionary effects together with the consequences for the host-pathogen dynamics are then  
 illustrated.

### 180 Population Dynamics

#### Absence of the synergist

182 The host-pathogen interaction (in the absence of the synergist) has the following equilibria (when  
 $\phi = 3/4$ ):

$$m^* = \frac{a^4}{b^4 \cdot N^{*4}} \quad (5)$$

$$V^* = \frac{\rho \cdot m^* \cdot (1 + \kappa \cdot N^*)^{-1} - d_n}{\beta_0} \quad (6)$$

$$(7)$$

184 with the solution to  $N^*$  found from:

$$\gamma(m^*) \cdot \beta_0 \cdot \sigma \cdot N^* - d_v = 0. \quad (8)$$

The dynamics of the host-pathogen interaction are stable when the pathogen transmission rate  
 186 ( $\beta_0$ ) and the effects of host mass on pathogen yield ( $\psi$ ) are below critical values. High rates of

pathogen yield and/or high levels of pathogen transmission lead to unstable (cyclic) dynamics  
 188 **(Figure 1)**. Aspects of allometric scaling also influence the boundaries separating stable and  
 unstable dynamics. In particular, levels of pathogen transmission and yield coupled with resource  
 190 acquisition that scales to the 3/4 of mass are expected to lead to a broader region of unstable  
 dynamics than conditions where resource acquisition rate scales to the 2/3 of mass **(Figure 1)**.  
 192 Interestingly, other key parameters such as the time taken by the pathogen ( $\tau$ ) or the precise  
 yield function ( $\gamma(m)$ ) have little qualitative effect on the host-pathogen dynamics. These aspects  
 194 of the host-pathogen interaction are explored in the presence of the synergist in the next section.

### Presence of the synergist

196 In the presence of the synergist (eqns 1-4), the interaction has the following equilibria:

$$m^* = \frac{a^4}{(\eta \cdot K_s + b)^4 \cdot N^{*4}} \quad (9)$$

$$V^* = \frac{\rho \cdot m^* \cdot (1 + \kappa \cdot N^*)^{-1} - d_n}{\beta_0 + \theta \cdot K_s} \quad (10)$$

$$S^* = K_s \quad (11)$$

with the solution to  $N^*$  found from:

$$\gamma(m^*) \cdot (\beta_0 + \theta \cdot K_s) \cdot \sigma \cdot N^* - d_v = 0. \quad (12)$$

198 Again, the dynamics and persistence of this full three species interaction are evaluated by ex-  
 ploring the dynamics around these equilibria. Stability analysis reveals that the strength of host  
 200 mass on pathogen yield ( $\psi$ ) **(Figure 2a)** and the strength of the synergist on pathogen trans-  
 mission ( $\theta$ ) **(Figure 2b)** affect the population dynamics. High pathogen yields **(Figure 2a)** and  
 202 strong effects of the synergist **(Figure 2b)** in conjunction with high levels of pathogen transmis-  
 sion ( $\beta_0$ ) are expected to lead to unstable dynamics. Furthermore, the effects of the synergist  
 204 on average host mass gain ( $\eta$ ) can also influence the population dynamics. Across all levels of

pathogen transmission, increasing the effects of the synergist on mass gain is likely to stabilize  
 206 the host-pathogen interaction (**Figure 2c**). Changes in the speed of kill ( $\tau$ ) can also affect the  
 stability of interaction. Interestingly changes in the time taken for the pathogen to kill its host  
 208 in the presence of the synergist can lead to switches in stability from stable through unstable to  
 stable dynamics (Figure 3). Reduced  $\tau$  (faster speed of kill) shortens the period and decreases  
 210 the amplitude of the host-pathogen cycles leading to stable dynamics. Intermediate speed of kill  
 leads to host-pathogen cycles and long speed of kill again favour stable host-pathogen dynamics  
 212 (Figure 3). Other factors also affect the observed population dynamics. For instance, increases  
 in the allometric scaling ( $\phi$ ) also alter the population dynamics. Increasing the exponent from  
 214 ( $2/3$  through  $3/4$  to  $7/8$ ) changes the population interaction between the host and the lethal  
 pathogen from fixed stable dynamics through to higher-order limit cycles and chaos (**Figure 4**).

## 216 Pathogen Evolutionary Dynamics

In this section, evolutionary invasion analyses are used to explore how different pathogen strate-  
 218 gies may evolve under different life-history trait trade-offs and in the presence of the synergist.  
 Two principal trade-offs are considered: first, a trade-off between pathogen yield and speed of  
 220 kill and second a trade-off between the strength of the synergist (or the ability of the host to  
 tolerate this non-lethal strategy) and lethal pathogen yield. Previous studies have illustrated  
 222 that these trade-offs are most appropriate in host-pathogen interactions (Bonsall et al., 2005a;  
 Bonsall and Raymond 2008). The effect of the single traits (speed of kill, strength of syner-  
 224 gist) on pathogen fitness is initially explored before investigating how correlated trait trade-offs  
 (of both speed of kill and synergist strength) affect patterns of evolutionary change in parasite  
 226 fitness and, consequently alterations to the underlying population dynamics.

### Single Trait Trade-offs

228 *Yield-Speed of kill trade-off.* To explore the evolutionary dynamics of the speed of kill ( $\tau_i$ ) on  
 yield, the fitness ( $R_i$ ) of an alternative pathogen strategy ( $V_i$ ) is defined as:

$$R_i = \frac{1}{V_i} \frac{dV_i}{dt} = (1 - \exp(-\alpha_i \cdot \tau_i)) \cdot m^* \cdot (\beta_{0i} + \theta_i \cdot S^*) \cdot \exp(-\mu_{ji} \cdot \tau_i) \cdot N^* - d_{vi} \quad (13)$$

230 where  $(1 - \exp(-\alpha_i \cdot \tau_i))$  is the yield-speed of kill trade-off ( $\alpha_i$  is the strength of the trade-off  
 between yield and speed of kill),  $\beta_{0i}$  is the transmission parameter of the alternative pathogen  
 232 strategy,  $\mu_{ji}$  is the mortality rate of developing pathogen and  $d_{vi}$  is the mortality rate of alter-  
 native free-living pathogen strategy. The equilibril densities of mass, the host population and  
 234 the synergist population are denoted by  $m^*$ ,  $N^*$  and  $S^*$ , respectively. The evolutionary stable  
 (ES) speed of kill strategy  $\left[\frac{dR_i}{d\tau_i} = 0\right]$  is determined from:

$$\frac{dR_i}{d\tau_i} = m^* \cdot (\beta_{0i} + \theta_i \cdot S^*) \cdot N^* \cdot [\alpha_i \cdot \exp(-(\alpha_i + \mu_{ji}) \cdot \tau_i) - \mu_{ji} \cdot \exp(-\mu_{ji} \cdot \tau_i) \cdot (1 - \exp(-\alpha_i \cdot \tau_i))] \quad (14)$$

236 and has an evolutionary optima when:

$$\bar{\tau}_i = \frac{1}{\alpha_i} \log \left( \frac{\alpha_i + \mu_{ji}}{\mu_{ji}} \right) \quad (15)$$

$\bar{\tau}_i$  is an evolutionary stable strategy (ESS) ( $\frac{d^2 R_i}{d\tau_i^2} |_{\tau_i = \bar{\tau}_i} < 0$ ) if:

$$-\exp(-(\alpha_i + \mu_{ji}) \cdot \bar{\tau}_i) \cdot (\alpha_i^2 + 2 \cdot \alpha_i \cdot \mu_{ji} - \mu_{ji}^2 \cdot (\exp(\alpha_i \cdot \bar{\tau}_i) - 1)) \cdot m^* \cdot (\beta_{0i} + \theta_i \cdot S^*) \cdot N^* < 0. \quad (16)$$

238 Taken together with the ES solution (equation 15), the optimal speed of kill is always an  
 ESS since:

$$\alpha_i^2 + 2 \cdot \alpha_i \cdot \mu_{ji} - \mu_{ji}^2 \cdot (\exp(\alpha_i \cdot \bar{\tau}_i) - 1) > 0. \quad (17)$$

240 It then follows that equation 16 is negative for all positive values of  $\alpha_i$  and  $\mu_{ji}$ . Evolutionary  
 invasion and replacement of the pathogen phenotype occurs if the fitness of the alternative  
 242 pathogen strategy ( $R_i$ ) is greater than the fitness of the resident strategy. **Figure 5a** illustrates

boundaries separating regions of invasion and replacement ( $R_i > 0$ ) from regions of exclusion  
 244 ( $R_i < 0$ ) in the presence ( $S^* = K_s$ ) and absence ( $S^* = 0$ ) of the synergist. The presence of  
 the synergist makes the invasion and replacement of alternative pathogen strategies more likely  
 246 and parasites that have faster speeds of kill can invade (favouring parasites that exploit smaller  
 hosts). Other things being equal, this change in pathogen characteristics (faster speed of kill -  
 248 lower values of  $\tau_i$ ) is more likely to lead to stable host-pathogen dynamics (cf. **Figure 3**).

*Strength of synergy - yield trade-off.* The underlying predictions from this trade-off is that as  
 250 the strength of the synergist increases (and consequently the ability of the host to tolerate this  
 non-lethal synergist), mortality will occur faster and yields will be low (as host mass gain is  
 252 lower). The fitness ( $R_i$ ) of an alternative pathogen strategy ( $V_i$ ) under this trade-off scenario is:

$$R_i = \frac{1}{V_i} \frac{dV_i}{dt} = \exp(-\zeta_i \cdot \theta_i) \cdot m^* \cdot (\beta_{0i} + \theta_i \cdot S^*) \cdot \exp(-\mu_{ji} \cdot \tau_i) \cdot N^* - d_{vi} \quad (18)$$

where the parameters are as previously defined and  $\exp(-\zeta_i \cdot \theta_i)$  now describes the negative  
 254 trade-off between the strength of synergist ( $\theta_i$ ) and pathogen yield. The effects of the strength  
 of the synergist on pathogen fitness and the evolutionary fitness optima can be determined from:

$$\frac{dR_i}{d\theta_i} = \exp(-\zeta_i \cdot \theta_i - \mu_{ji} \cdot \tau_i) \cdot m^* \cdot N^* [S^* - \zeta_i \cdot (\beta_{0i} + S^* \cdot \theta_i)] \quad (19)$$

256 which has solution ( $\frac{dR_i}{d\theta_i} = 0$ ):

$$\theta_i = \frac{S^* - \zeta_i \cdot \beta_{0i}}{\zeta_i \cdot S^*} \quad (20)$$

and this is an ESS ( $\frac{d^2 R_i}{d\theta_i^2} < 0$ ) if:

$$\zeta_i \cdot \exp(-\zeta_i \cdot \theta_i - \mu_{ji} \cdot \tau_i) \cdot m^* \cdot N^* [\zeta_i \cdot (\beta_{0i} + S^* \cdot \theta_i) - 2 \cdot S^*] < 0. \quad (21)$$

258 This is always negative (equation 21) and hence the strategy is always an ESS. Evolutionary  
 invasion analysis shows that increases in the strength of the synergist ( $\theta_i$ ) are likely to increase  
 260 the invasion success by alternative pathogen strategies and promoted coexistence (**Figure 5b**).

However, changes in the strength of the synergist are known to affect the population dynamics  
 262 (cf. **Figure 2b**). Other things being equal evolutionary increases in  $\theta$  are likely to destabilise  
 the dynamics and lead to host-pathogen cycles.

### 264 **Correlated Trait Effects**

In this final section we explore how correlations between speed of kill ( $\tau_i$ ) and the strength of  
 266 the synergist ( $\theta_i$ ) can affect pathogen fitness. To begin with if the total variation in fitness ( $R_i$ )  
 depends on both traits independently (no correlation), then the ESS conditions are determined  
 268 from the following total differential:

$$dR_i = \frac{\delta R_i}{\delta \tau_i} d\tau_i + \frac{\delta R_i}{\delta \theta_i} d\theta_i. \quad (22)$$

This is simply the combined derivatives of equations (14) and (19). If, however, there is corre-  
 270 lation between the traits then this association can be described by:

$$\tilde{\tau}_i = \tau_i \cdot (1 - \epsilon \cdot \theta_i). \quad (23)$$

Clearly, this expression allows positive, negative and independent associations between traits as  
 272  $\epsilon$  is a measure of the degree of correlation between traits ( $-1 < \epsilon < 1$ ). The total differential  
 (eqn 22) is now obviously more complex and takes the form:

$$\begin{aligned} dR_i &= \alpha_i \cdot v \cdot (1 - \epsilon \cdot \theta_i) + \exp(-\theta_i - \mu_{ij} \cdot \tau_i \cdot (1 - \epsilon \cdot \theta_i)) \\ &\cdot (1 - \exp(-\alpha_i \cdot \tau_i \cdot (1 - \epsilon \cdot \theta_i))) \left[ \frac{1}{\beta_i + \theta_i \cdot S^*} + [(\mu_{ij} \cdot \epsilon \cdot \tau_i) - 1] \right] \\ &- \mu_{ij} \cdot (1 - \epsilon \cdot \theta_i) \cdot (1 - \exp(-\alpha_i \cdot \tau_i (1 - \epsilon \cdot \theta_i))) \end{aligned} \quad (24)$$

274 where  $v = \exp(-(\alpha_i + \mu_{ij}) \cdot \tau_i \cdot (1 - \epsilon \cdot \theta_i) - \theta_i)$ .

Under weak synergistic effects ( $\theta_i \rightarrow 0$ ) there is an evolutionary optimal intermediate speed  
 276 of kill. This arises as hosts are able to achieve greater mass and hence have a positive effect

on pathogen yield. Higher synergistic effects tend to favour rapid speed of kill so pathogens  
278 maintain yield before the synergist has a marked detrimental effect on host mass gain and  
size. Pathogen fitness is affected by the degree of correlation between traits. Under negative  
280 correlation, evolution favours strong effects of the synergist (high  $\theta_i$ ) and rapid speed of kill (low  
 $\tau_i$ ) (**Figure 6a**). Under no correlation, fitness is maximised when the effect of the synergist is  
282 weak and at intermediate speed of kill (**Figure 6b**). Under positive correlation, multiple fitness  
optima are expected particularly when the strength of the synergist is high (**Figure 6c**).

## 284 Discussion

Here, both the population and evolutionary dynamics of a host-pathogen interaction have been  
286 shown to be influenced by the presence of a synergist. In the absence of this synergist, the  
population dynamics of the interaction between host mass gain, host abundance and pathogen  
288 density follow cyclic dynamics similar to those observed in standard host-pathogen interactions  
(e.g. Anderson and May 1981). Increases in pathogen transmission and/or yield are more  
290 likely to lead to cyclic population dynamics. Changes in the allometric relationship between  
resource metabolism and mass are also expected to influence the dynamics of host-pathogen  
292 interactions (De Leo and Dobson 1996; Cable et al. 2007; Bolzoni et al. 2008). The presence of  
a synergist induces a range of dynamics from stable equilibria through to cyclic dynamics. The  
294 stability of this interaction is also affected by time delays whereby the system switches from  
stable through unstable to stable dynamics as the speed of kill lengthens (Cooke and Grossman  
296 1982; Gopalsamy 1992; Fenton et al. 2006). Time delays can reduce the rate a population  
diverges from unstable points (Beddington and May 1975) and coupled with non-regulatory  
298 effects this can lead to an increase in overall stability (Nunney 1985a,b). As pathogen speed  
of kill is a density-independent process (and influenced by interactions at other trophic levels)  
300 lengthening this process extends the time over which host and pathogen interact and reduces  
the destabilizing effects inherent in these resource-consumer systems. Furthermore, increases in

302 the allometric scaling ( $\phi$ ) and the way in which resources are converted into mass also affect the  
likelihood of cycles or higher dimensional dynamics in this host-pathogen-synergist interaction.

304 The role of allometric relationships have been extensively studied (Huxley 1932) and many  
observed relationships between size, shape and function have been explored through allometry  
306 (Smith 1984). More recently, the dynamical consequences of allometric relationships have been  
considered fundamental to the dynamics of life (West et al. 1997). In particular, West et al.  
308 (2001) derived a theoretical framework based the allocation of energy between maintenance of  
existing tissue and the production of new biomass to explore patterns of ontogenetic growth in  
310 which the anabolism of resources scales to the  $3/4$  power of biomass. Arguing for a universal  
scaling relationship has received increased attention from elucidating the relationships between  
312 organelles in cells (Dingli and Pacheco 2006) through to patterns at higher-levels of organisation  
and scale (West et al. 2002). Although recent work has demonstrated a link between individual  
314 metabolic rate and the key parameters of population growth (e.g., intrinsic rate of increase,  
carrying capacity) (Savage et al. 2004), the population dynamical consequences of such scaling  
316 relationships remains relatively unclear. Here, in the context of a host-pathogen interaction,  
alterations in these allometric scalings can influence the underlying population or evolutionary  
318 dynamics by altering host size. From a pathogen perspective, hosts that achieve larger mass are  
more likely to lead to higher pathogen yields. However, changes in size are also known to affect  
320 the allometric exponents (larger size constrains efficient energy use) and this will obviously have  
consequences for the dynamics of host-pathogen interactions (De Leo and Dobson 1996; Cable  
322 et al.2007; Bolzoni et al. 2008).

While it is well-established that pathogens can have important effects on the demography of  
324 host populations (Moore 2002) and that this effect translates to affect the population dynamics,  
theoretical and empirical work has highlighted how alternative modes of action through sub-  
326 lethal infection or tolerance of non-lethal microbes can also impact on host demography and  
dynamics. Infection strategies in which there is a class of hosts resistant to (or able to tolerate)

328 the pathogen have been shown to have important dynamical implications (Sait et al. 1994;  
Boots et al. 2003; Bonsall et al. 2005b; Bonsall and Raymond 2008). In particular, covert  
330 infection strategies can lead to a range of dynamical outcomes including a persistent stable state  
between only the covertly infected hosts (all hosts are infected) and the pathogen (Bonsall et  
332 al. 2005b). Here, it has been demonstrated that the role of a non-lethal synergist can also alter  
the population dynamics. In the presence of a synergist and the coupled effects on host mass  
334 gain, a wide range of dynamics is much more likely in these higher dimensional systems . Given  
the extent of synergistic interactions, the analysis presented suggests that non-linear dynamics  
336 are likely to be much more prevalent in host-pathogen interactions than necessarily predicted  
by simpler models of enemy-victim interactions (Beddington et al. 1975). The incorporation  
338 of additional dimensions (individual mass gain, synergism) to the host-pathogen interaction  
introduces the potential for different degrees of coupling between each of the variables in the  
340 system. Non-linear coupling of the synergist with the host and pathogen through direct (via  
effects on transmission) and indirect (via effects on host mass gain) processes leads to sets of  
342 dynamics with incommensurate (unequal) frequencies. Clearly, as with any resource-consumer  
system, host-pathogen interactions have the potential to show cyclic dynamics (Anderson and  
344 May 1981) but when coupled with alternative dynamically-interacting systems this can affect  
the type and the way in which these non-linear oscillations occur.

346 Host-pathogen interactions can shape trade-offs in pathogen (and host) life history traits  
and it has recently been established that trade-offs can exist between pathogen virulence and  
348 pathogen transmission (Boots and Meador 2007). Highly virulent pathogens such as those that  
kill hosts quickly may do so at the cost of lower transmission. Competition between parasites  
350 within hosts can affect both pathogen yield and transmission (McKenzie and Bossert 2005).  
Additional mechanisms acting within hosts can also influence the evolution of pathogenicity  
352 (e.g. Brown et al. 2008; Bonsall and Raymond 2008). Invading parasite strategies which raise  
novel immune challenges within hosts may be at an advantage as competitors may be eliminated

354 (Brown et al. 2008). Similarly, the ability of hosts to deal with non-lethal microbes can affect the  
evolution of polymorphic host strategies such that hosts resist or tolerate infections (Miller et al.  
356 2005; Bonsall and Raymond 2008). Here, in the current study, pathogen fitness is shown to be  
influenced by the presence of a synergist. The presence of the synergist makes the invasion and  
358 replacement of alternative pathogen strategies (with faster speeds of kill) more likely. Trade-offs  
between the effect of the synergist and pathogen yield (as smaller hosts yield fewer infectious  
360 pathogen particles) affect both the likelihood of invasion/replacement by alternative parasites  
and the population dynamics.

362 Understanding the dynamical effects of synergy requires appropriate theoretical models and  
analyses. The effect of the synergist on host-pathogen interactions has both population and  
364 evolutionary dynamical implications. The results presented here suggest that a fuller under-  
standing of host-pathogen community ecology will require theoretical and empirical studies that  
366 partition out the relative importance of different mechanisms and the effects of trade-offs on  
parasite dynamics and evolution. As recently highlighted (Pedersen and Fenton 2007), the fo-  
368 cus on host-level patterns for inferring mechanisms about multiple parasitic infections cannot  
provide information on the within-host processes and mechanisms. Understanding these is es-  
370 sential: not only for the population biology of host-pathogen interactions but also in an applied  
context in which we may wish to understand how to manage pathogen virulence or transmission.  
372 The effects of non-lethal infections that synergise pathogenic infections require the same sorts  
of approaches as are been advocated for co-infecting parasitic infections.

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of Colorado potato beetle larvae. J. Invert. Path. 90, 139-150.

524 **Figure Legends**

526 Figure 1 - Stability boundaries for the host-pathogen dynamics with mass gain (in the  
 absence of the synergist) for different combinations of transmission ( $\beta_0$ ) and the effects  
 of host mass on pathogen yield ( $\psi$ ) under different allometric scalings ((a)  $\phi = 3/4$ ,  
 528 (b)  $\phi = 2/3$ ). Boundaries separate regions of stable and unstable (cyclic) dynamics.  
 (Parameters:  $d_n = 1.0$ ,  $d_v = 1.0$ ,  $\rho = 3.0$ ,  $a = 2.0$ ,  $b = 1.0$ ,  $\kappa = 0.1$ ,  $\sigma = 1.0$ ,  $\tau = 2.0$ ).

530 Figure 2 - Dynamics for the host-pathogen-synergist interaction separating regions of stable  
 and unstable (cyclic) population dynamics. (a) Effects of host mass on pathogen yield ( $\psi$ )  
 532 - transmission ( $\beta_0$ ) combinations ( $\tau = 0$ ). High yield - high transmission levels are more  
 likely to give host-pathogen cycles (Key parameters:  $a = 1.5$ ,  $b = 1.0$ ,  $\eta = 0.002$ ,  $\theta = 0.2$ ).  
 534 (b) The effects of the synergist ( $\theta$ ) and transmission ( $\beta_0$ ) (Key parameters:  $a = 2.0$ ,  $b = 3.0$ ,  
 $\psi = 0.001$ ,  $\eta = 0.002$ ). Increasing the effects of the synergist is more likely to destabilise  
 536 the dynamics. (c) The impact of the synergist on host mass gain ( $\eta$ ). Increasing this effect  
 leads to unstable population dynamics. (Key parameters:  $a = 2.0$ ,  $b = 3.0$ ,  $\psi = 0.002$ ,  
 538  $\theta = 0.2$ ). (Other parameters:  $d_n = 1.0$ ,  $d_v = 1.0$ ,  $\rho = 3.0$ ,  $\kappa = 0.1$ ,  $\tau = 1.0$ ,  $\sigma = 1.0$ ,  
 $r_s = 1.1$ ,  $K_s = 10$ ).

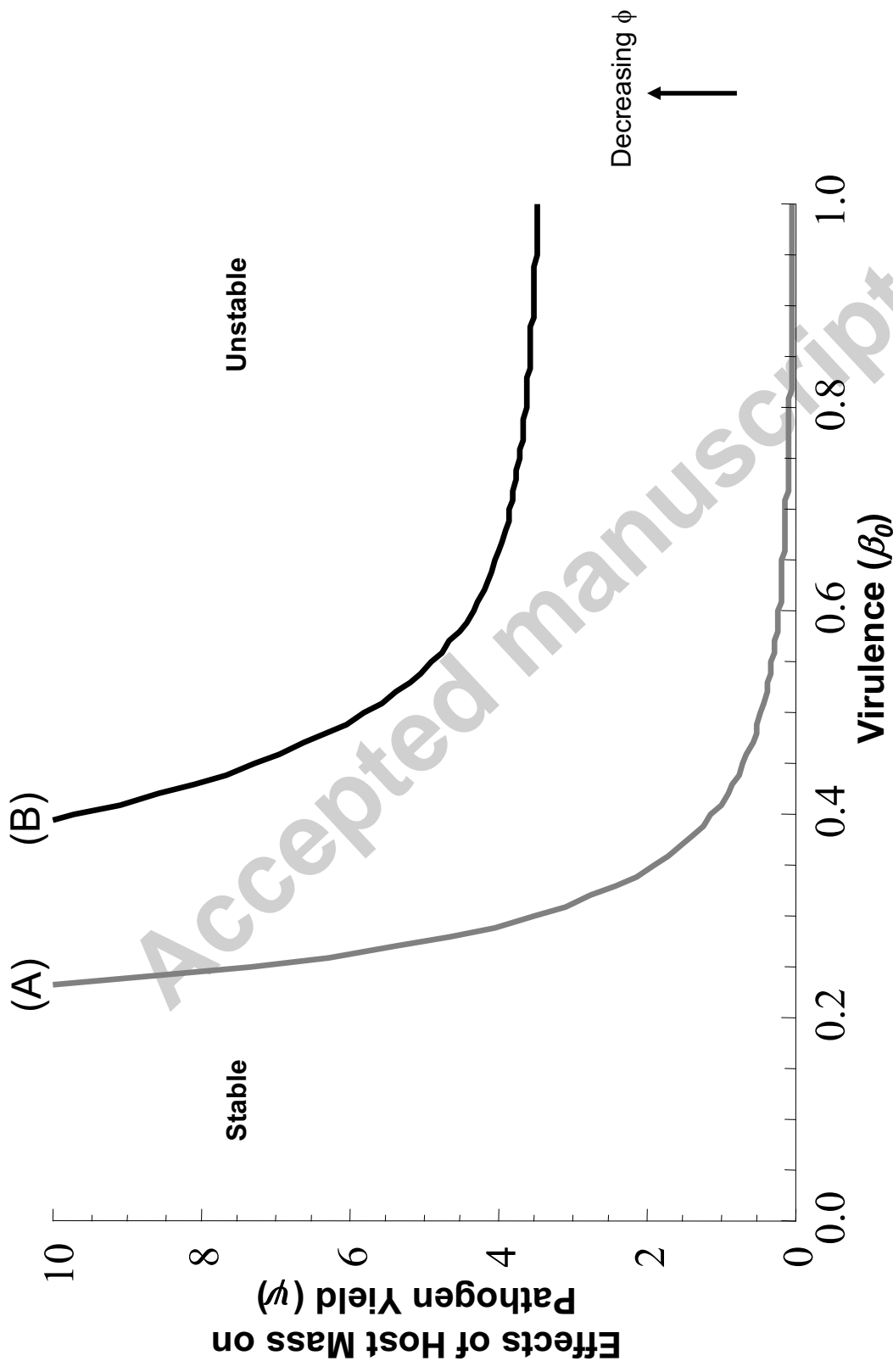
540 Figure 3 - The effects of pathogen speed of kill (time delay -  $\tau$ ) on the dynamics of the  
 host-pathogen interaction in the presence of the synergist (a)  $\tau = 0.01$ , (b)  $\tau = 1.0$ , (c)  
 542  $\tau = 5.0$ . Increasing the time delay switches the dynamics of the interaction from stable  
 ( $\tau = 0.1$ ) through unstable ( $\tau = 1.0$ ) to stable ( $\tau = 5.0$ ). (Parameters:  $d_n = 1.0$ ,  $d_v = 1.0$ ,  
 544  $\rho = 5.0$ ,  $a = 2.0$ ,  $b = 3.0$ ,  $\eta = 0.002$ ,  $\beta_0 = 0.1$ ,  $\theta = 0.2$ ,  $\psi = 0.002$ ,  $\kappa = 0.1$ ,  $\sigma = 1.0$ ,  
 $\phi = 3/4$ ,  $r_s = 1.1$ ,  $K_s = 10$ ).

546 Figure 4 - Host-pathogen dynamics (in the presence of the synergist) for increasing levels  
 of allometric scaling  $\phi$  illustrate the propensity for different scaling exponents to affect the  
 548 host-pathogen population dynamics. (a)  $\phi = 2/3$ , (b)  $\phi = 3/4$ , (c)  $\phi = 7/8$ . (Parameters:

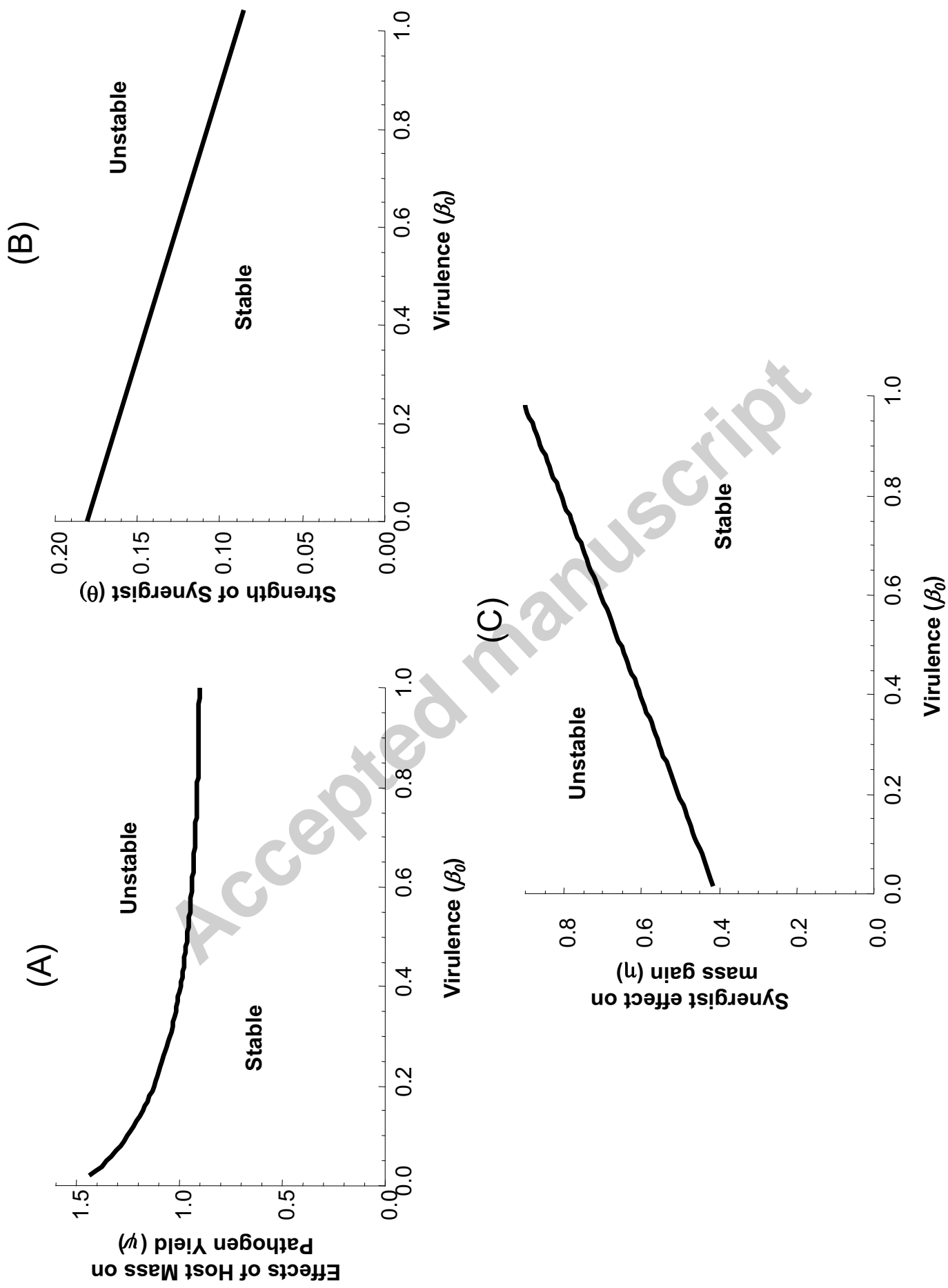
$d_n = 1.0$ ,  $d_v = 1.0$ ,  $\rho = 5.0$ ,  $a = 2.0$ ,  $b = 3.0$ ,  $\eta = 0.002$ ,  $\beta_0 = 0.1$ ,  $\theta = 0.2$ ,  $\psi = 0.002$ ,  
550  $\kappa = 0.1$ ,  $\sigma = 1.0$ ,  $\tau = 3.0$ ,  $r_s = 1.1$ ,  $K_s = 10$ ).

Figure 5 - Evolutionary invasion boundaries. (a) Invasion dynamics in the absence (dashed  
552 line) and presence (solid line) of the synergist for yield (*alpha*) - speed of kill ( $\tau$ ) trade-off.  
Regions of exclusion and co-occurrence of alternative virus strategies are marked in respec-  
554 tive regions. (b) Invasion dynamics under the synergist strength (tolerance) ( $\theta$ ) - yield ( $\beta$ )  
trade-off. Regions of exclusion and co-occurrence of alternative pathogen strategies are  
556 marked in respective regions.

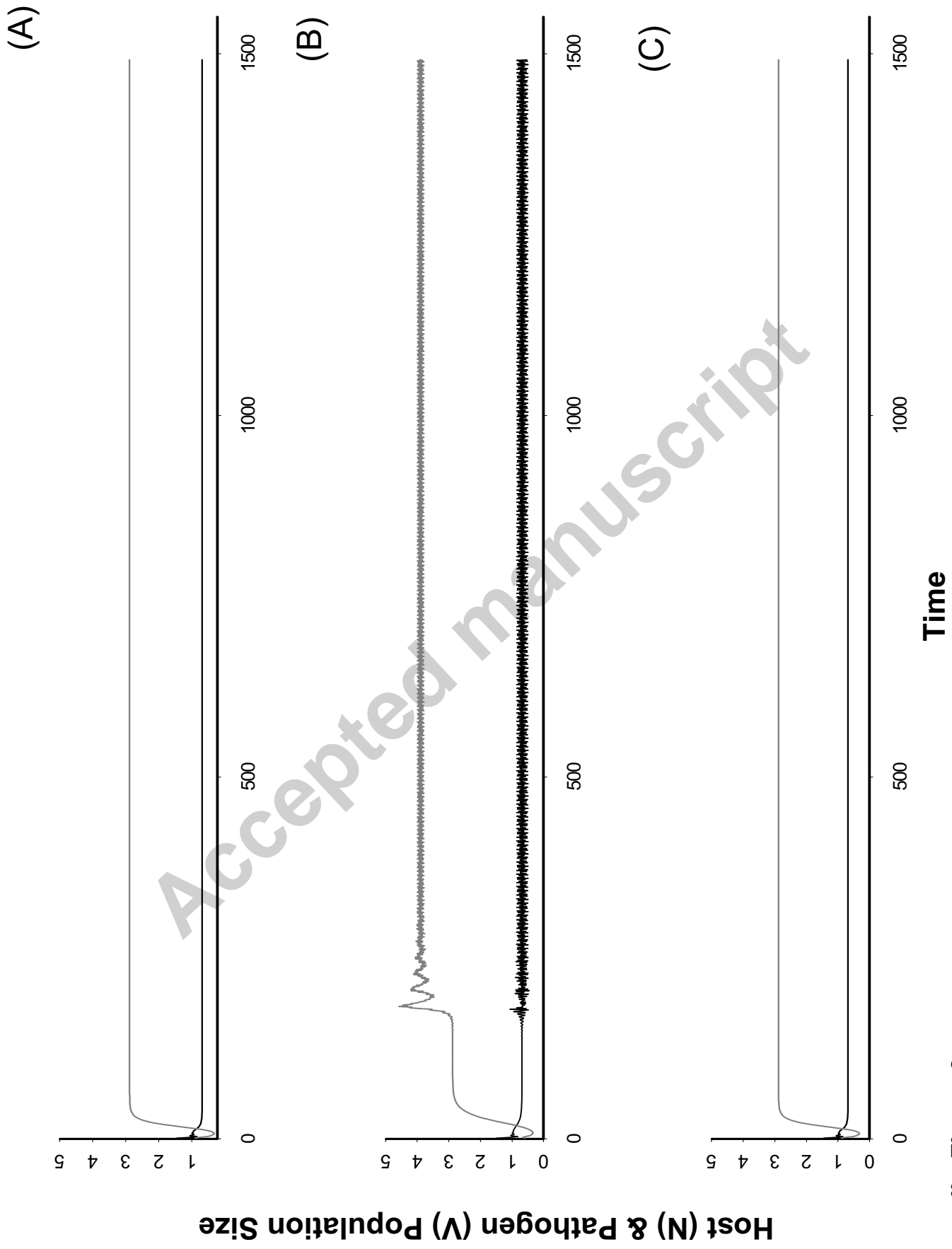
Figure 6 - Fitness surfaces for how correlations between speed of kill ( $\tau$ ) and the strength  
558 of the synergist ( $\theta$ ) affect pathogen fitness under (a) negative ( $\epsilon = -1$ ), (b) no ( $\epsilon = 0$ ), (c)  
positive ( $\epsilon = 1$ ) correlations. Differences in the correlation between traits affect the shape  
560 and magnitude of the fitness surface.



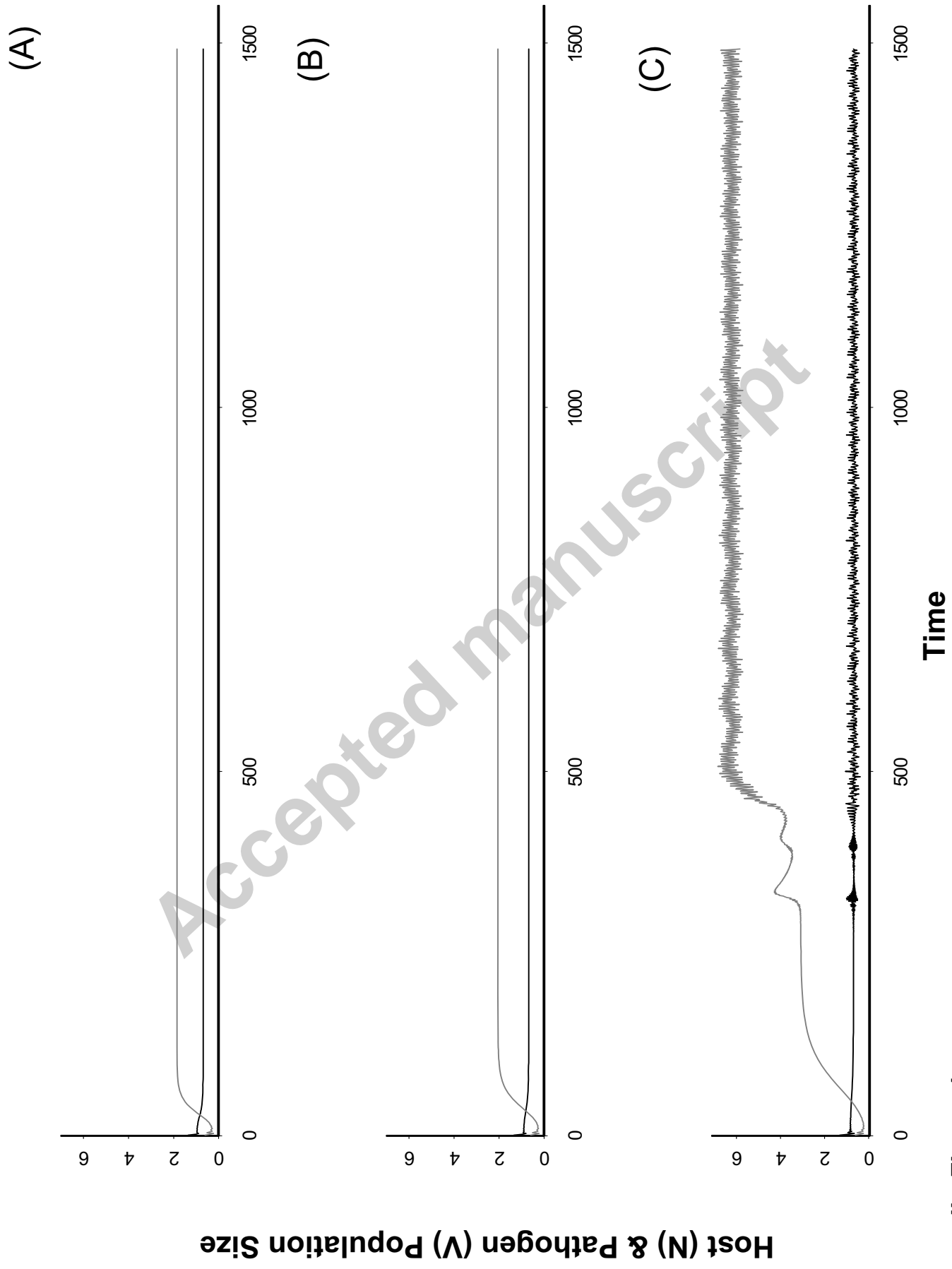
Bonsall - Figure 1



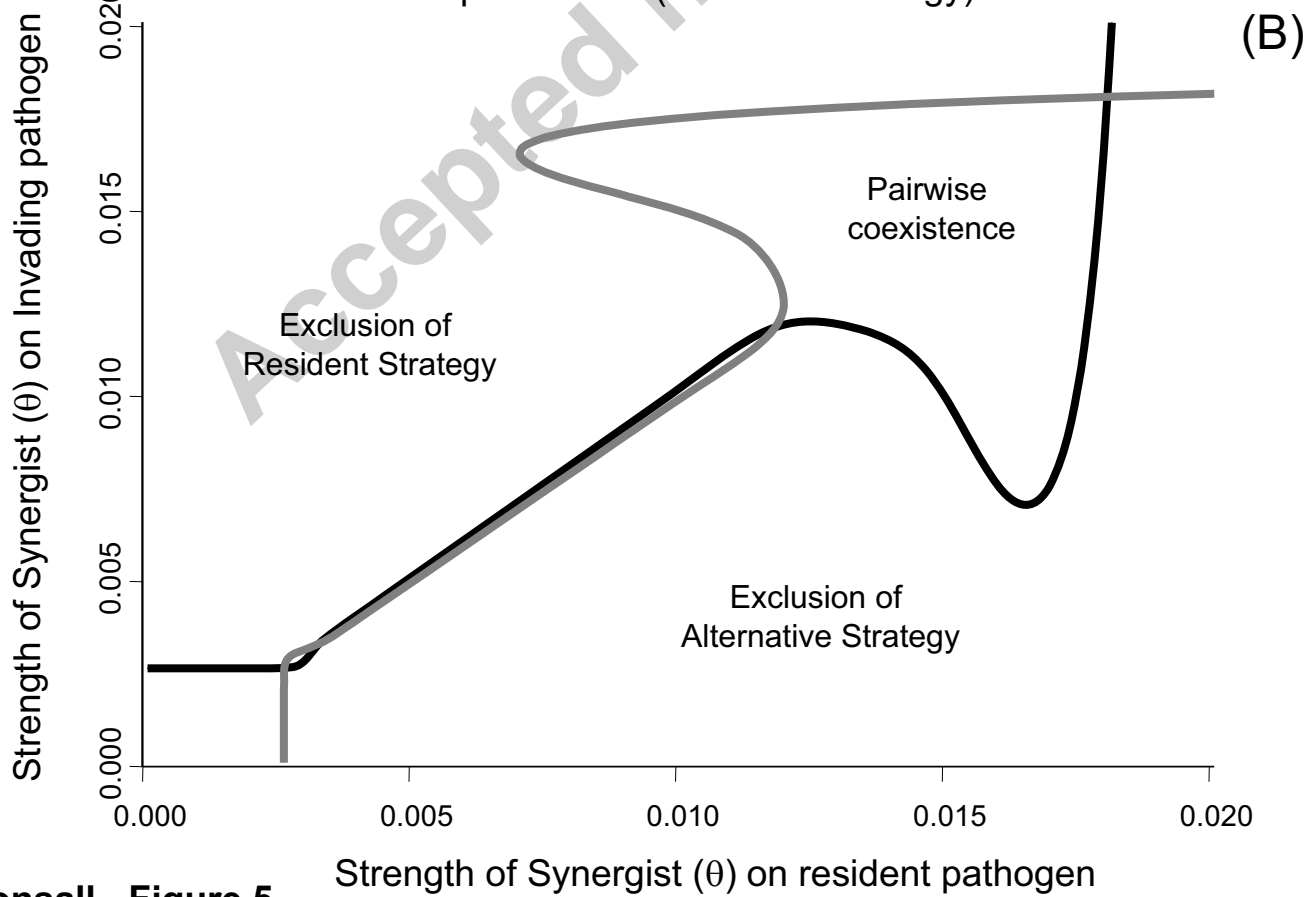
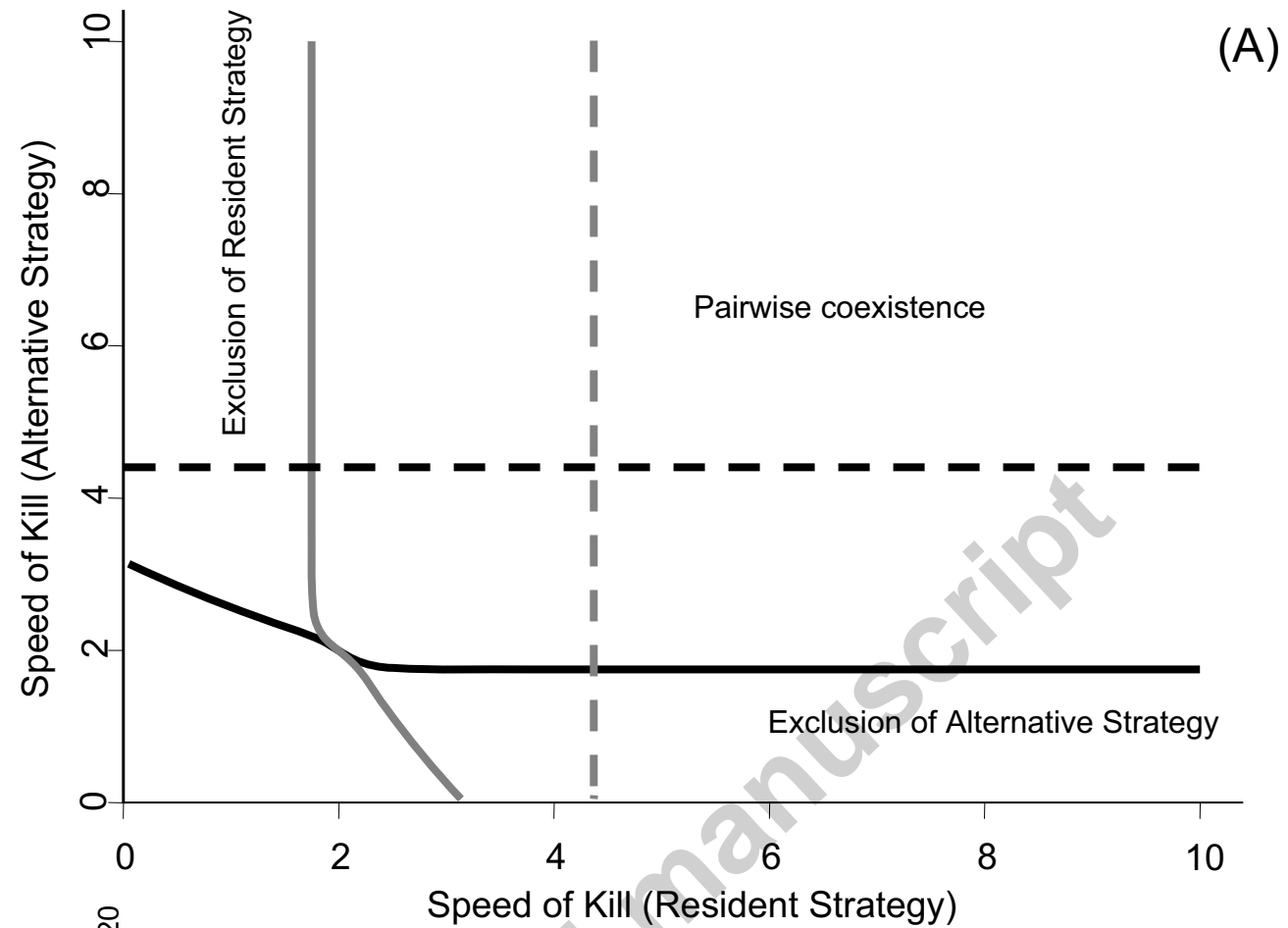
Bonsall - Figure 2



Bonsall - Figure 3

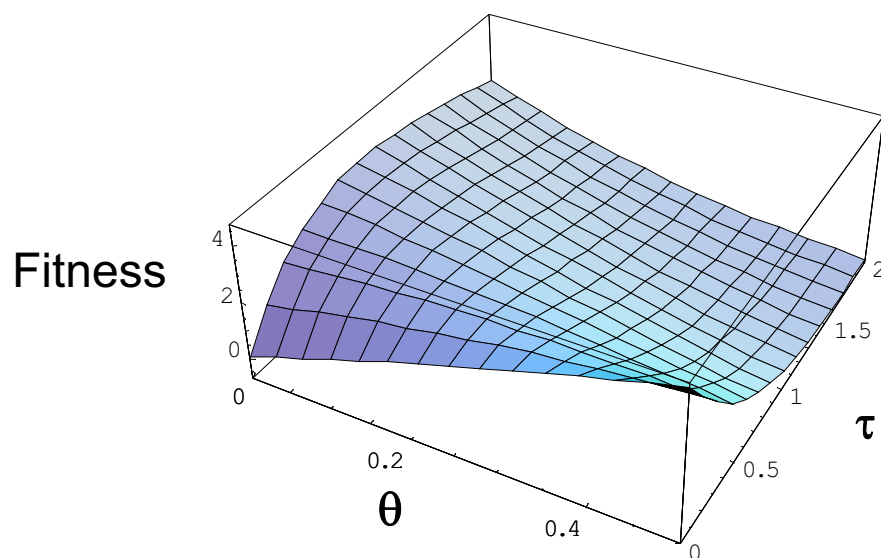


Bonsall - Figure 4

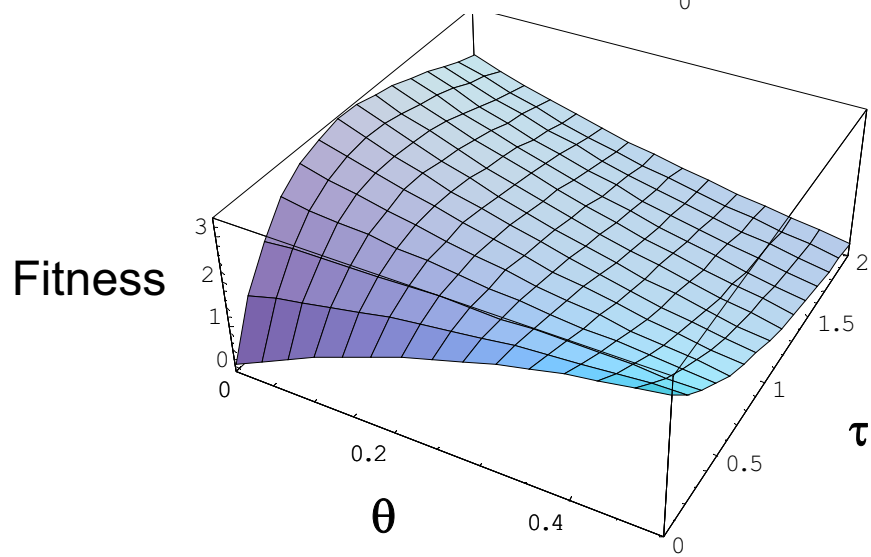


Bonsall - Figure 5

(A)



(B)



(C)

