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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

Multiple pathogenic infections can influence disease transmission and virulence, and have important consequences for understanding the community ecology and epidemiology of host-pathogen 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 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 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 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 population dynamics. Evolutionary analysis of tolerance of the synergist (strength of synergy) and lethal pathogen yield show that decreasing tolerance allows alternative pathogen strategies to 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 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 evolutionary relationships has important for the both the evolutionary and population dynamics of host-pathogen interactions.

Keywords: allometric scaling; host-pathogen epidemiology; limit cycles; time lags; population dynamics

Introduction

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). 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 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 (Anderson and May 1981; Myers 1988). These effects can be mitigated or enhanced by additional ecological factors such as the effects of refuges (Hochberg 1989), the role of intraspecific 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 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 affect the virulence, transmission and competitive interaction amongst pathogens (Raymond et al. 2007, 2008, 2009).

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, 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 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 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 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. Furthermore, within hosts, patterns of multiple infections can affect the maintenance of mixed

infections and consequently pathogen virulence through interactions with competitors and the 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 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 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 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 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 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 evidence that the role of alternative pathogenic and/or non-pathogenic organisms is highly likely to affect host-pathogen interactions.

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 has been implicated in affecting the interaction between alternative entomopathogenic bacteria, virus-fungal interactions, plant pathogens and human infections. For instance *B. thuringiensis 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* 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 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 polymicrobial infections in wounds and abdominal abscesses by disrupting the immune response

(Mazmanian and Kasper 2006).

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 translate into dynamical effects that influence the epidemiological patterns of the host-pathogen interactions. Understanding the effects of multiple natural enemies necessitates a broader community 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). 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 effects on host dynamics. Interactions of co-infecting lethal and/or non-lethal parasites are predicted to influence host fitness, pathogen transmission and have broad implications for disease control.

The aim of this study then is to explore how the action of a non-lethal synergist affects the 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 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 and consequently affect the interplay between evolutionary and population dynamics.

Mathematical Model

Model Structure

The biological motivation behind the model is to explore how a host - pathogen interaction with 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: 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

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 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 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 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 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 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 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).

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 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 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). 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 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 dynamics of the host-pathogen interaction.

Synergist Population Growth - Synergistic interactions between pathogens are known to

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 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 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 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 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 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 synergist, 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, ϕ is allometric scaling of resource uptake by mass, b is the catabolic rate of resource use and η is the effect of the synergist on host mass gain (the cost associated with the host tolerating the synergist). Individual host mass gain (m) 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 catabolism of resources (at rate b) and through the costs of tolerating the non-lethal synergist (at rate $\eta \cdot S(t)$).

In the absence of pathogens, hosts follow density-dependent growth. ρ is the birth rate of the host population, κ is the strength of density dependence and hosts die from density-independent (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 (θ) - $\beta_0 + \theta \cdot S(t)$.

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

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 of the host or pathogen) and K_s is the carrying capacity of this non-lethal synergist.

Model Analysis

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 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 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 stability conditions of these differential-difference equations are evaluated using a root solving algorithm and numerical simulations. Second, the evolutionary dynamics are explored using 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 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 effects of the synergist.

Results

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 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 evolutionary effects together with the consequences for the host-pathogen dynamics are then illustrated.

Population Dynamics

Absence of the synergist

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

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

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

$$(7)$$

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 (β_0) and the effects of host mass on pathogen yield (ψ) are below critical values. High rates of

pathogen yield and/or high levels of pathogen transmission lead to unstable (cyclic) dynamics (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 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). Interestingly, other key parameters such as the time taken by the pathogen (τ) or the precise yield function ($\gamma(m)$) have little qualitative effect on the host-pathogen dynamics. These aspects of the host-pathogen interaction are explored in the presence of the synergist in the next section.

Presence of the synergist

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:

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

Again, the dynamics and persistence of this full three species interaction are evaluated by exploring the dynamics around these equilibria. Stability analysis reveals that the strength of host mass on pathogen yield (ψ) (Figure 2a) and the strength of the synergist on pathogen transmission (θ) (Figure 2b) affect the population dynamics. High pathogen yields (Figure 2a) and strong effects of the synergist (Figure 2b) in conjunction with high levels of pathogen transmission (β_0) are expected to lead to unstable dynamics. Furthermore, the effects of the synergist on average host mass gain (η) 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 the host-pathogen interaction (**Figure 2c**). Changes in the speed of kill (τ) can also affect the stability of interaction. Interestingly changes in the time taken for the pathogen to kill its host in the presence of the synergist can lead to switches in stability from stable through unstable to stable dynamics (Figure 3). Reduced τ (faster speed of kill) shortens the period and decreases 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 (Figure 3). Other factors also affect the observed population dynamics. For instance, increases in the allometric scaling (ϕ) also alter the population dynamics. Increasing the exponent from (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**).

Pathogen Evolutionary Dynamics

In this section, evolutionary invasion analyses are used to explore how different pathogen strategies 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 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 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 synergist) 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 fitness and, consequently alterations to the underlying population dynamics.

Single Trait Trade-offs

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

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

where $(1 - \exp(-\alpha_i \cdot \tau_i))$ is the yield-speed of kill trade-off (α_i is the strength of the trade-off between yield and speed of kill), β_{0i} is the transmission parameter of the alternative pathogen strategy, μ_{ji} is the mortality rate of developing pathogen and d_{vi} is the mortality rate of alternative free-living pathogen strategy. The equilibrium densities of mass, the host population and 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:

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

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) ($\frac{d^2 R_i}{d\tau_i^2} \big|_{\tau_i = \bar{\tau}_i} < 0$) if:

$$-\exp(-(\alpha_i + \mu_{ji}) \cdot \bar{\tau}_i) \cdot (\alpha_i^2 + 2 \cdot \alpha_i \cdot \mu_{ji} - \mu_{ji}^2 \cdot (\exp(\alpha_i \cdot \bar{\tau}_i) - 1)) \cdot m^* \cdot (\beta_0 + \theta_i \cdot S^*) \cdot N^* < 0. \quad (16)$$

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

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

It then follows that equation 16 is negative for all positive values of α_i and μ_{ji} . Evolutionary invasion and replacement of the pathogen phenotype occurs if the fitness of the alternative 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 τ_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 (θ_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 (θ_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
(cf. **Figure 2b**). Other things being equal evolutionary increases in θ are likely to destabilise
the dynamics and lead to host-pathogen cycles.

Correlated Trait Effects

In this final section we explore how correlations between speed of kill (τ_i) and the strength of
the synergist (θ_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
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-
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
 ϵ 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:

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

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
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 θ_i) and rapid speed of kill (low
 τ_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

the allometric scaling (ϕ) 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.

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 (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. (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 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 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 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 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 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 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 et al. 2007; Bolzoni et al. 2008).

While it is well-established that pathogens can have important effects on the demography of 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-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)

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 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 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 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 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 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 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 dynamics with incommensurate (unequal) frequencies. Clearly, as with any resource-consumer system, host-pathogen interactions have the potential to show cyclic dynamics (Anderson and 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.

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 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 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 (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

(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. 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 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 pathogen particles) affect both the likelihood of invasion/replacement by alternative parasites and the population dynamics.

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 evolutionary dynamical implications. The results presented here suggest that a fuller understanding of host-pathogen community ecology will require theoretical and empirical studies that 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 focus on host-level patterns for inferring mechanisms about multiple parasitic infections cannot provide information on the within-host processes and mechanisms. Understanding these is essential: 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. 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.

Figure Legends

Figure 1 - Stability boundaries for the host-pathogen dynamics with mass gain (in the absence of the synergist) for different combinations of transmission (β_0) and the effects of host mass on pathogen yield (ψ) under different allometric scalings ((a) $\phi = 3/4$, (b) $\phi = 2/3$). Boundaries separate regions of stable and unstable (cyclic) dynamics. (Parameters: $d_n = 1.0$, $d_v = 1.0$, $\rho = 3.0$, $a = 2.0$, $b = 1.0$, $\kappa = 0.1$, $\sigma = 1.0$, $\tau = 2.0$).

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 (ψ) - transmission (β_0) combinations ($\tau = 0$). High yield - high transmission levels are more likely to give host-pathogen cycles (Key parameters: $a = 1.5$, $b = 1.0$, $\eta = 0.002$, $\theta = 0.2$). (b) The effects of the synergist (θ) and transmission (β_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 the dynamics. (c) The impact of the synergist on host mass gain (η). Increasing this effect leads to unstable population dynamics. (Key parameters: $a = 2.0$, $b = 3.0$, $\psi = 0.002$, $\theta = 0.2$). (Other parameters: $d_n = 1.0$, $d_v = 1.0$, $\rho = 3.0$, $\kappa = 0.1$, $\tau = 1.0$, $\sigma = 1.0$, $r_s = 1.1$, $K_s = 10$).

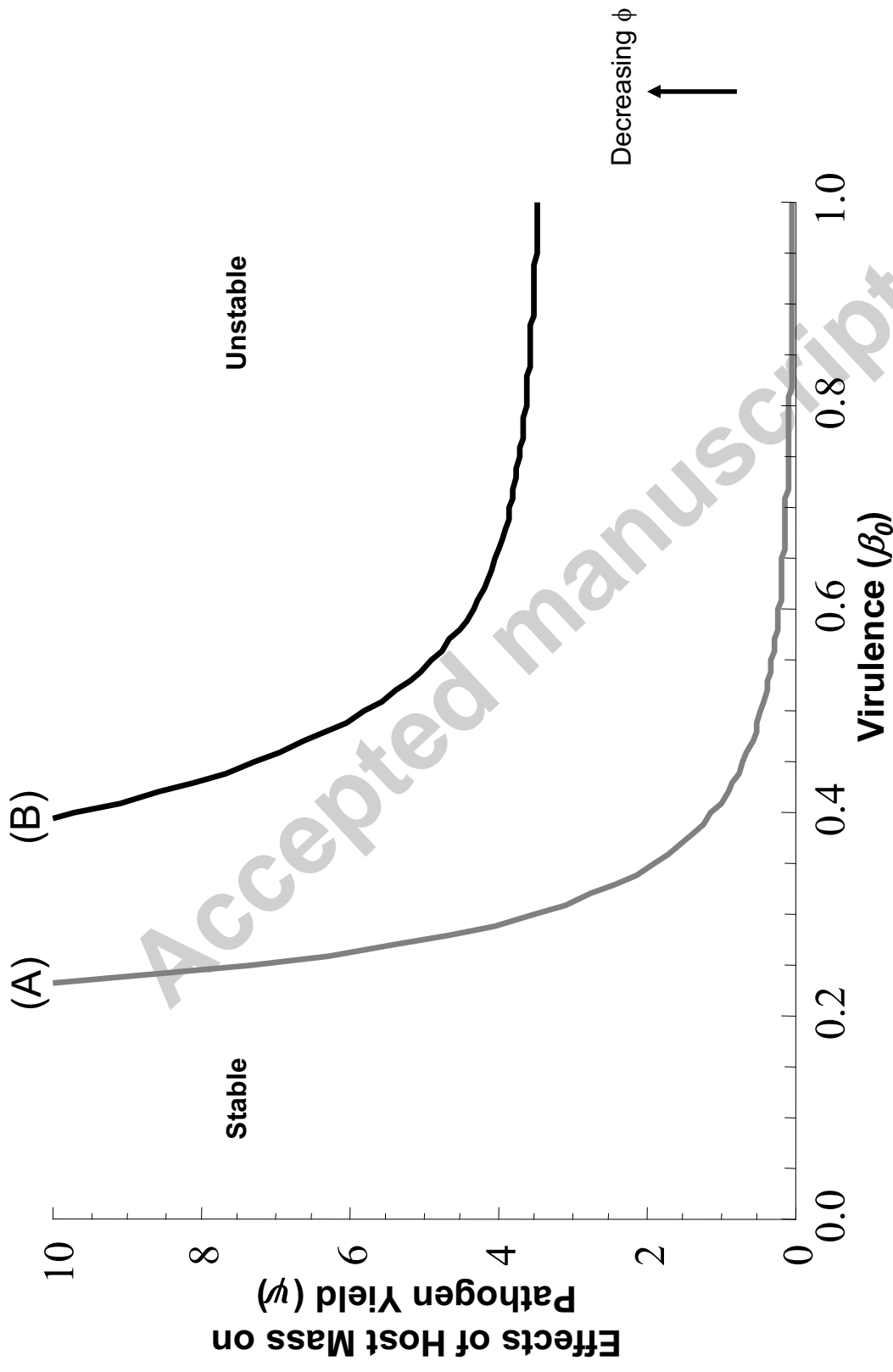
Figure 3 - The effects of pathogen speed of kill (time delay - τ) on the dynamics of the host-pathogen interaction in the presence of the synergist (a) $\tau = 0.01$, (b) $\tau = 1.0$, (c) $\tau = 5.0$. Increasing the time delay switches the dynamics of the interaction from stable ($\tau = 0.1$) through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

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

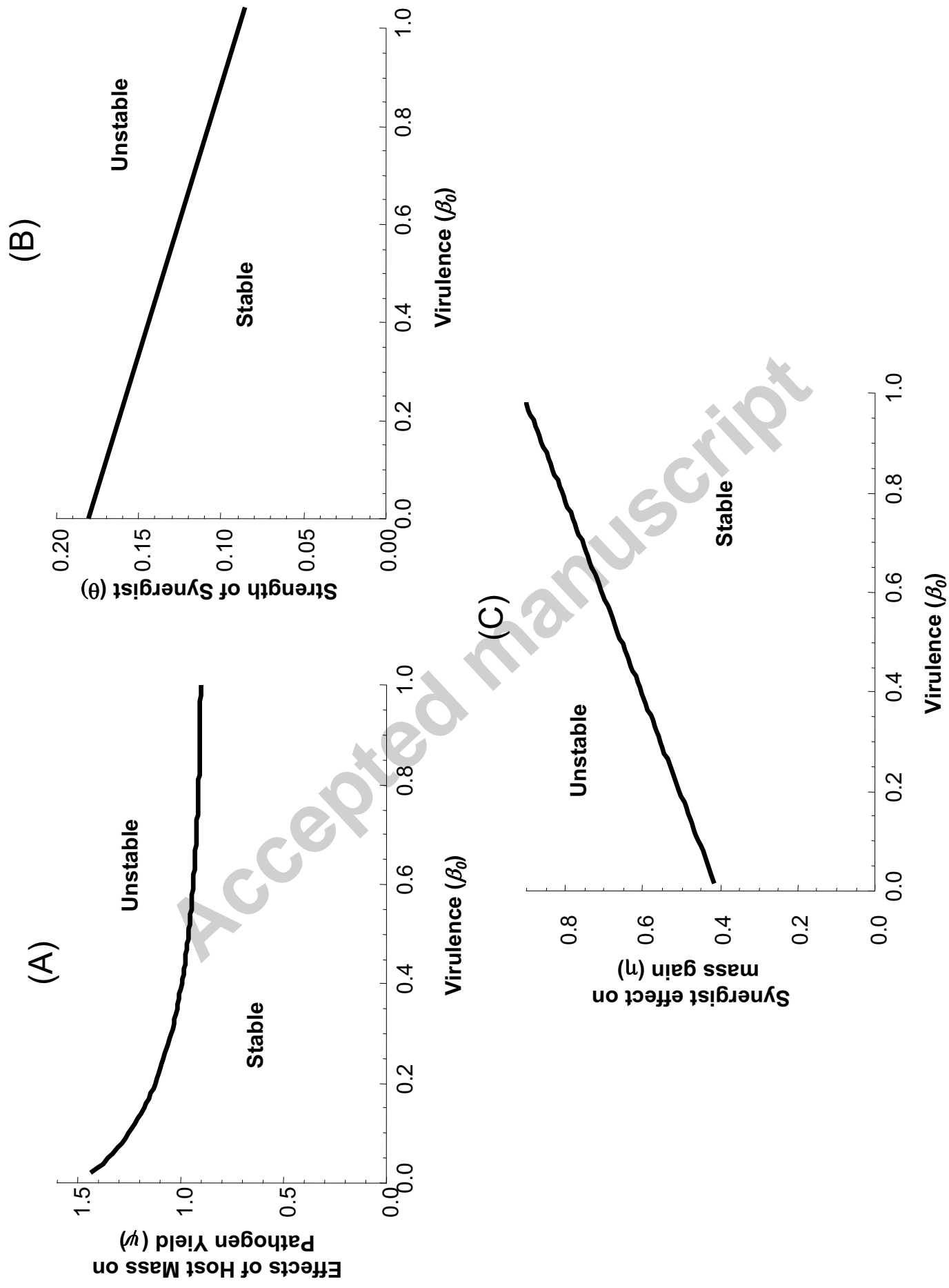
$d_n = 1.0$, $d_v = 1.0$, $\rho = 5.0$, $a = 2.0$, $b = 3.0$, $\eta = 0.002$, $\beta_0 = 0.1$, $\theta = 0.2$, $\psi = 0.002$,
 $\kappa = 0.1$, $\sigma = 1.0$, $\tau = 3.0$, $r_s = 1.1$, $K_s = 10$).

Figure 5 - Evolutionary invasion boundaries. (a) Invasion dynamics in the absence (dashed line) and presence (solid line) of the synergist for yield (α) - speed of kill (τ) trade-off. Regions of exclusion and co-occurrence of alternative virus strategies are marked in respective regions. (b) Invasion dynamics under the synergist strength (tolerance) (θ) - yield (β) trade-off. Regions of exclusion and co-occurrence of alternative pathogen strategies are marked in respective regions.

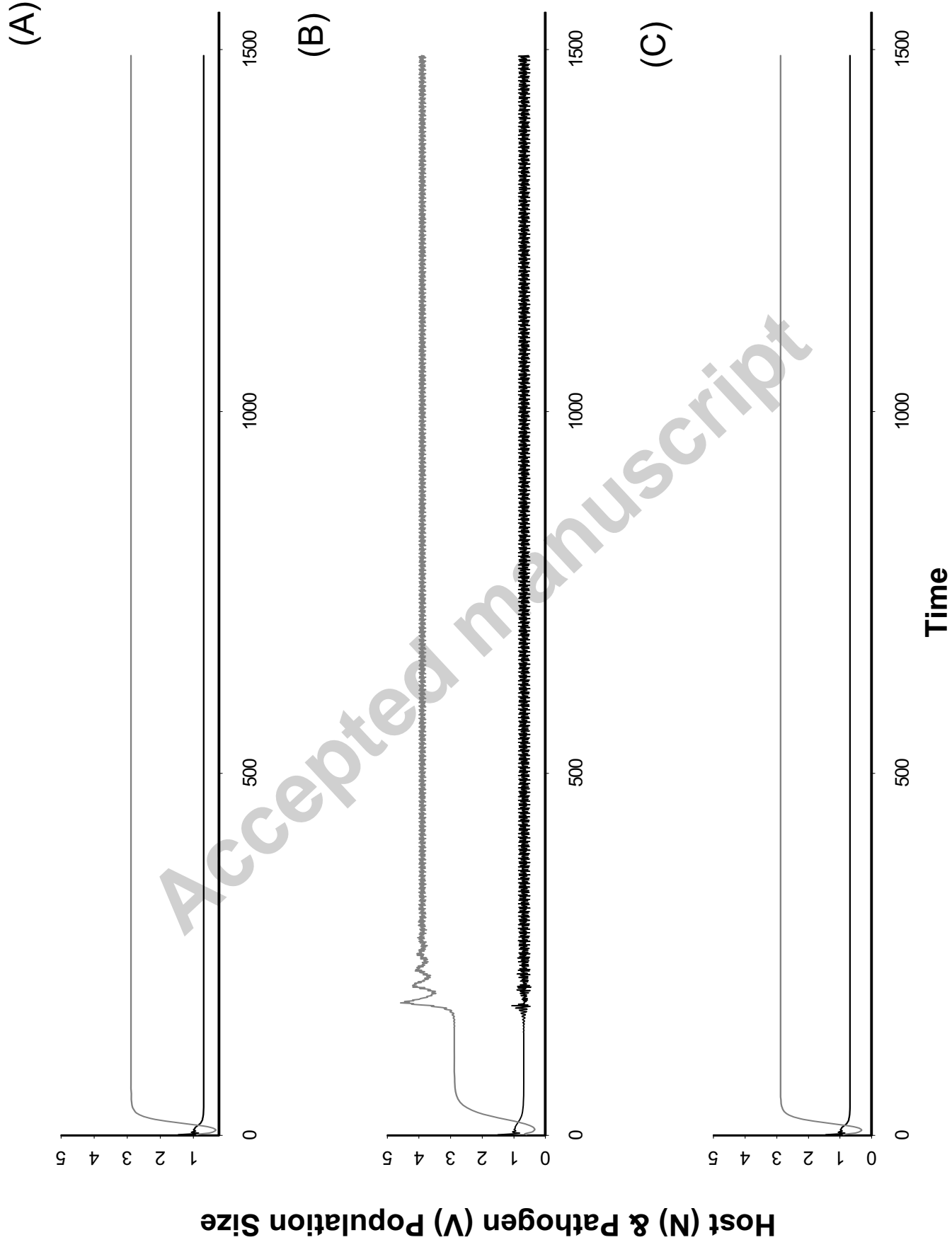
Figure 6 - Fitness surfaces for how correlations between speed of kill (τ) and the strength of the synergist (θ) affect pathogen fitness under (a) negative ($\epsilon = -1$), (b) no ($\epsilon = 0$), (c) positive ($\epsilon = 1$) correlations. Differences in the correlation between traits affect the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



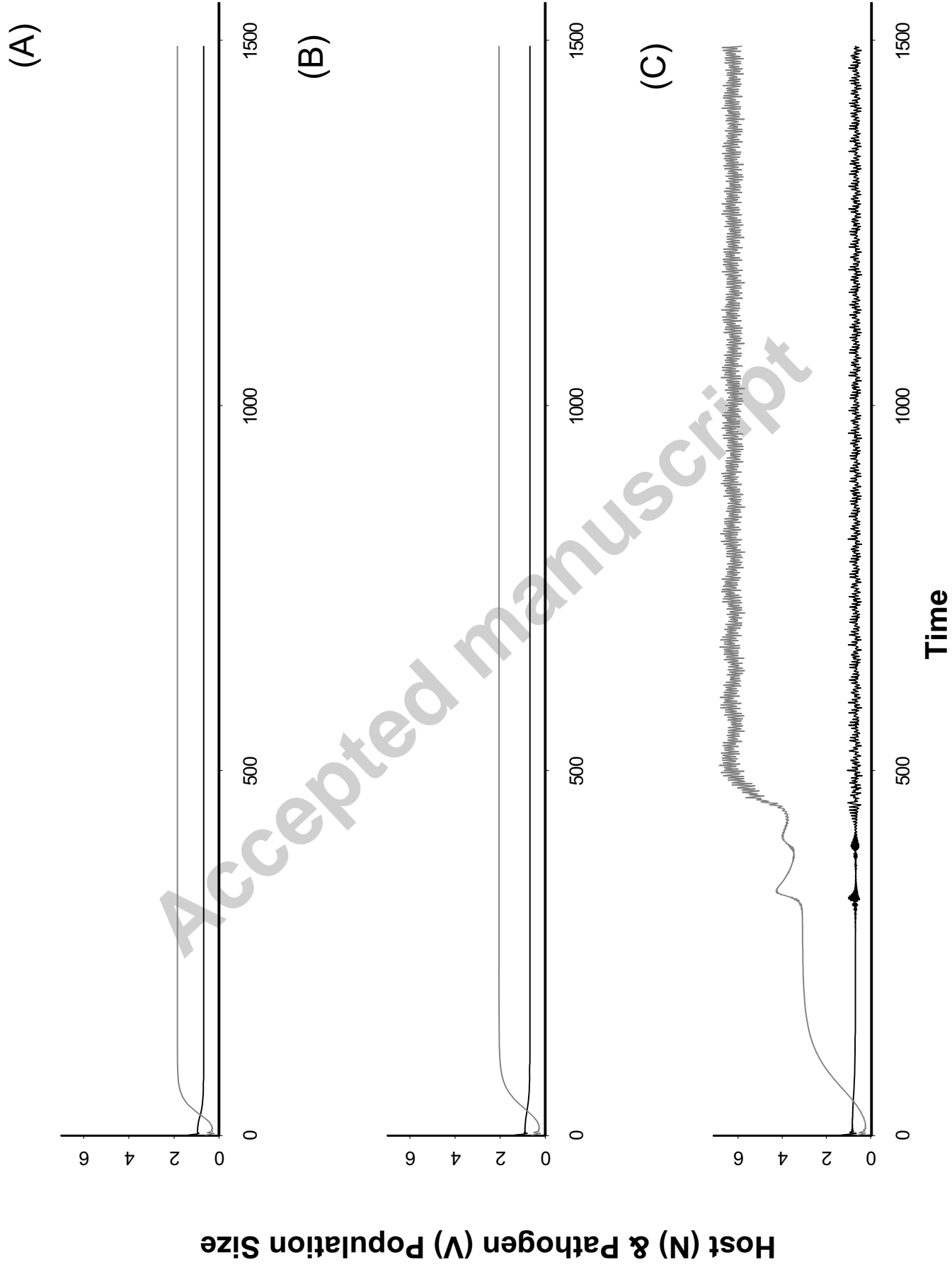
Bonsall - Figure 1



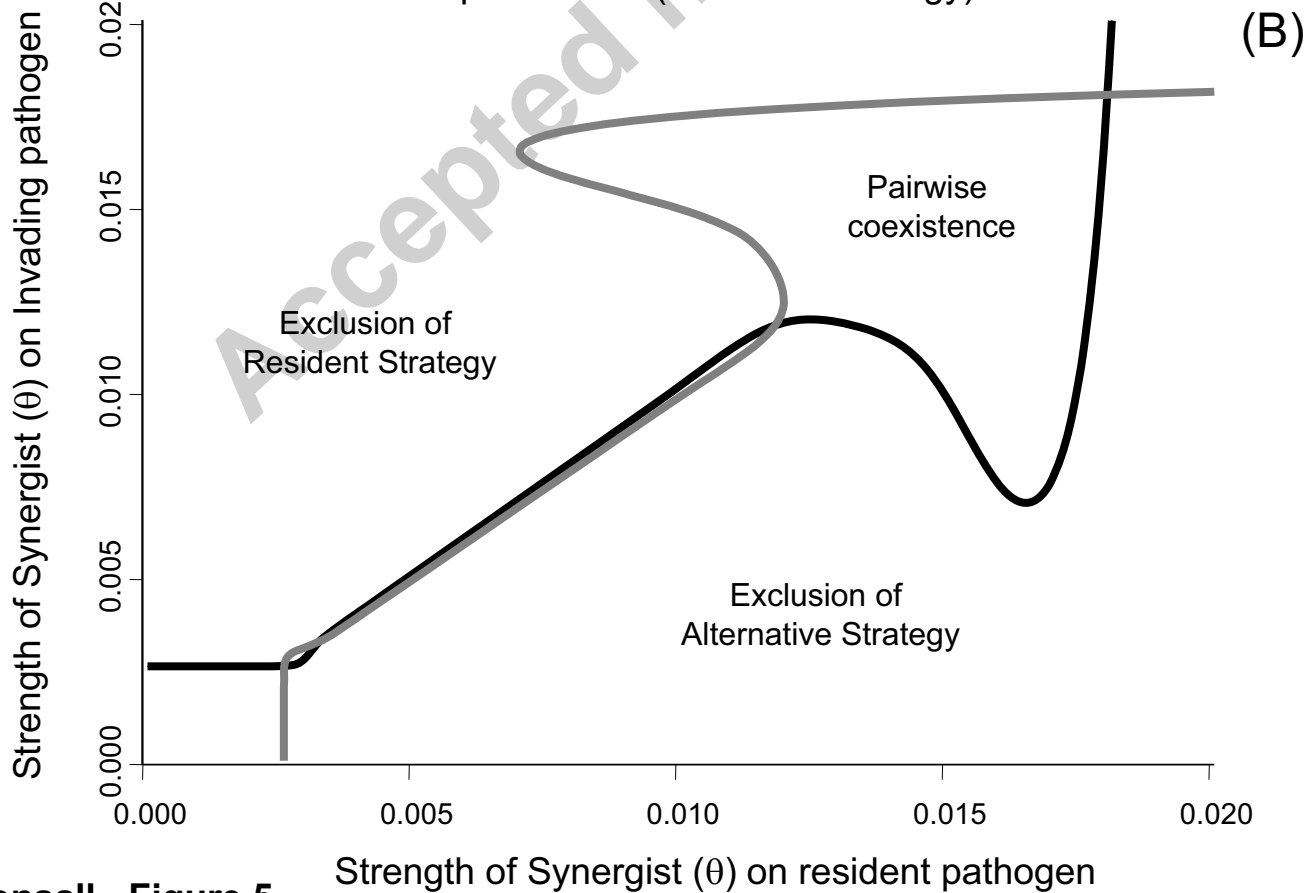
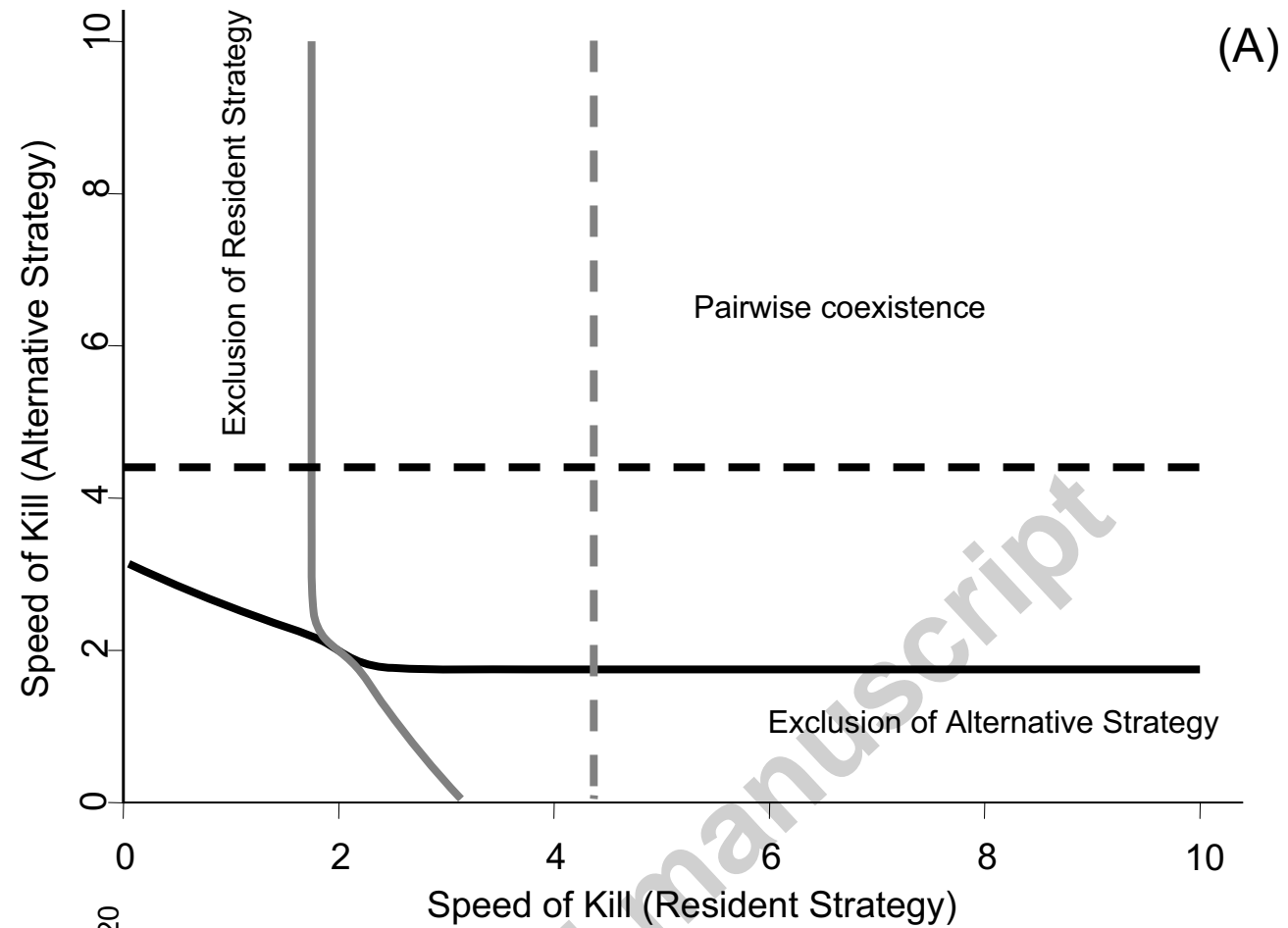
Bonsall - Figure 2



Bonsall - Figure 3



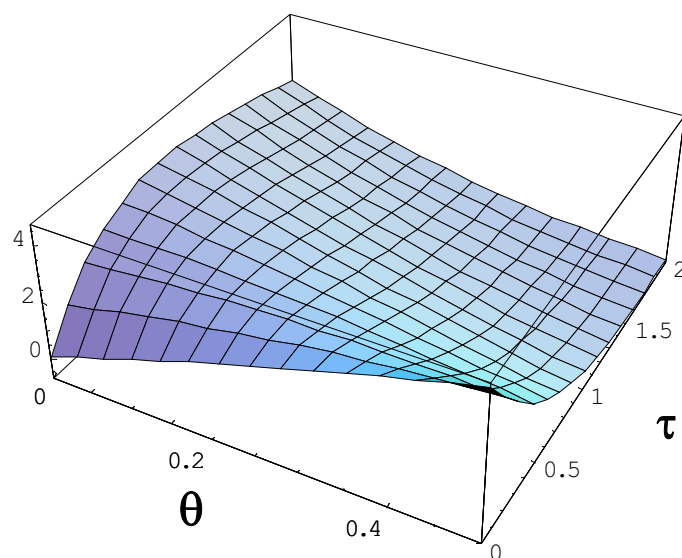
Bonsall - Figure 4



Bonsall - Figure 5

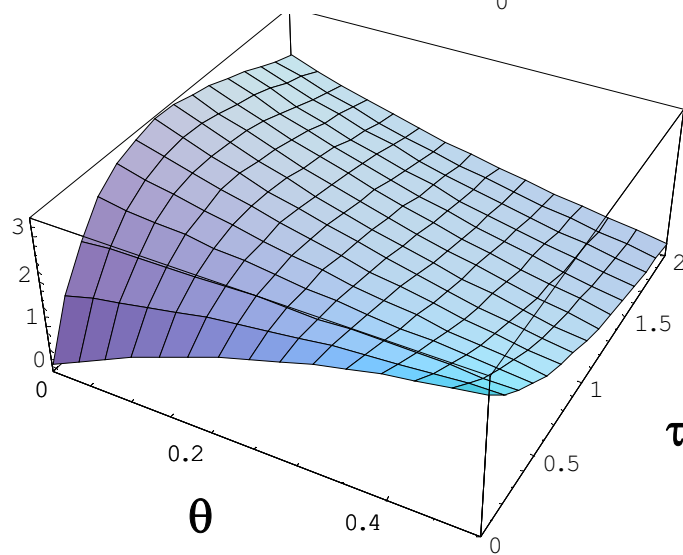
(A)

Fitness



(B)

Fitness



(C)

Fitness

