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Title: The Evolution of Host Defence To Parasitism in Fluctuating Environments.

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Abstract:

Given rapidly changing environments, it is important for us to understand how the evolution of host defence responds to fluctuating environments. Here we present the first theoretical study of evolution of host resistance to parasitism in a classic epidemiological model where the host birth rate varies seasonally. We show that this form of seasonality has clear qualitative and quantitative impacts on the evolution of resistance. When the host can recover from infection, it evolves a lower level of defence when the amplitude is high. However, when recovery is absent, the host increases its defence for higher amplitudes. Between these different behaviours we find a region of parameter space that allows evolutionary bistability. When this occurs, the level of defence the host evolves depends on initial conditions, and in some cases a switch between attractors can lead to different periods in the population dynamics at each of the evolutionary stable strategies. Crucially, we find that evolutionary behaviour found in a constant environment for this model doesn't always hold for hosts with highly variable birth rates. Hence we argue that seasonality must be taken into account if we want to make predictions about evolutionary trends in real-world host-parasite systems.

1. Introduction

Given the ubiquity of infectious diseases in natural systems there is strong selection pressure on host organisms to evolve costly defence mechanisms. A wide range of theoretical work has been developed to understand the evolution of host defence against parasitism, with much of this work focused on the ecological/epidemiological feedbacks that drive selection of quantitative host defence (van Baalen, 1998; Boots & Haraguchi, 1999; Boots & Bowers, 1999, 2004; Restif & Koella, 2003; Miller et al., 2005, 2007; Bonds, 2006; Best et al., 2008, 2009; Carval & Ferriere, 2010). These studies have explored how long-term, stable investment in host defence varies with ecological/epidemiological parameters, as well as determining the conditions that can lead to coexistence of strains through evolutionary branching. However, the vast majority of these studies assume that the populations live in a temporally static environment. In reality, almost all natural systems are subject to some degree of temporal environmental heterogeneity, in particular fluctuations caused by seasonality. For example, many natural species exhibit seasonal reproductive strategies driven by regular environmental fluctuations (Rowan, 1938; Stawski et al., 2014; Ketterson et al., 2015; Furness, 2016). It is therefore essential that we consider the impact of fluctuating environmental conditions on the evolution of host defences.

It is well established that variable climates affect ecological systems (Ewing et al., 2016), including the spread and impact of diseases (Fine & Clarkson, 1982; Finkenstädt & Grenfell, 2000; Altizer et al., 2006). Many theoretical studies have considered the effects of seasonality in purely epidemiological models (i.e., non-evolutionary), often through a periodic transmission rate (Schwartz & Smith, 1983; Aron & Schwartz, 1984; Olsen & Schaffer, 1990). Increasing the amplitude of the transmission rate can generate sub-harmonic oscillations or cause the population dynamics to move through a series of period-doubling bifurcations, eventually leading to chaotic dynamics (Grossman, 1980; Schwartz & Smith, 1983; Greenman et al., 2004; Grassly & Fraser, 2006; Childs & Boots, 2010). Small perturbations in these seasonal models can also trigger the system to switch between distinct attractors, often due to resonance, potentially leading to significant changes in the population dynamics and different patterns of outbreaks (Smith, 1983; Schwartz, 1985; Keeling et al., 2001; Kamo & Sasaki, 2002; Greenman et al., 2004). These complex dynamics have been found to exist less frequently when seasonality is assumed to occur in the host birth rate rather than transmission (White et al., 1996; Begon et al., 2009; Duke-Sylvester et al., 2011; Dorélien et al., 2013; Peel et al., 2014). Predictions about

the impact of a disease are likely to be more accurate when either of these types of seasonality are included in the model (White et al., 1996; Kamo & Sasaki, 2002).

There is an increasing appreciation of the importance of temporal heterogeneity in host-enemy interactions within the experimental evolution literature (Blanford et al., 2003; Friman & Laakso, 2011; Hiltunen et al., 2012; Harrison et al., 2013), for example showing that rapidly fluctuating environments constrain co-evolutionary arms races in a bacteria-phage system (Harrison et al., 2013). Theoretically, however, evolution and seasonality have rarely been studied together in a host-parasite context. The few studies that do exist have either investigated evolution of only the parasite (Koelle et al., 2005; Sorrell et al., 2009; Donnelly et al., 2013), or used a genetic-based, rather than ecology-driven, model for evolution of the host (Nuismer et al., 2003; Mostowy & Engelstädter, 2011; but see Poisot et al., 2012). Seasonality in the host's birth rate does not affect the evolution of the parasite's transmission/virulence strategy unless a density-dependence is applied to virulence (parasite-induced mortality) (Donnelly et al., 2013). This occurs because the average susceptible density, and therefore the parasite fitness, doesn't depend on the seasonal parameters unless this density-dependence is included. Elsewhere, step-wise environmental variation implemented through a dynamic resource was found to change the coevolutionary outcomes in a gene-for-gene based host-parasite system (Poisot et al., 2012). In particular, they found that both the host and parasite invest more in resistance and infectivity respectively for higher amplitudes in the seasonality. However, we currently have no theory specifically addressing the impact that seasonality has on the evolution of host defence to parasitism.

Here we investigate the impact of a continuous seasonal birth rate on the evolution of quantitative host avoidance through small mutation steps using an evolutionary invasion (adaptive dynamics) method. We use a classic SIS (Susceptible-Infected-Susceptible) model, and focus on how the amplitude and period of the implemented seasonality impacts the ecological/epidemiological dynamics, and therefore the evolution of the host.

2. Methods

The population is modelled using an SIS (susceptible-infected-susceptible) framework with the following set of ordinary differential equations:

$$\frac{dS}{dt} = a(1 - qN)S - bS - \beta SI + \gamma I, \tag{1}$$

$$\frac{dI}{dt} = \beta SI - (b + \alpha + \gamma)I, \tag{2}$$

where S and I are the susceptible and infected population sizes respectively, and $N = S + I$ is the total population size (Anderson & May, 1981). All offspring are born susceptible at rate a, and only susceptible hosts are able to reproduce, i.e. the parasite renders the host (temporarily) sterile. The births are limited by density with crowding coefficient q, so that birth rate is low when competition is high. All hosts die at baseline mortality rate b, with an additional infected death rate α. The parasite is transmitted to susceptible hosts at rate βI due to contact with infected individuals. Hosts recover from the parasite at rate γ and return to the susceptible class with no acquired immunity. Default parameter values are given in table 1.

We assume that seasonality occurs on the ecological timescale, so to incorporate this we let the birth rate depend periodically on time t:

$$a = a(t) = a_0(1 + \delta \sin(2\pi t/\epsilon)), \tag{3}$$

where a_0 is the average birth rate, $\delta \in [0, 1]$ is the amplitude and $\epsilon > 0$ is the period of the forcing. Periodic birth rates have been observed in a large number of species (Rowan, 1938; Ketterson et al., 2015), and this type of function has been used many times to model a time-varying birth rate (He & Earn, 2007; Donnelly et al., 2013; Dorélien et al., 2013) or transmission rate (Schwartz & Smith, 1983; Grassly & Fraser, 2006; Childs & Boots, 2010). For our default

Parameter	Definition	Default Value
$\hat{a_0}$	Trade-off coefficient in the average birth rate	108
p	Trade-off coefficient in the average birth rate	103.75
c	Trade-off coefficient in the average birth rate	1.5
β	Transmission coefficient	Varies
$\beta_{\min}$	Minimum transmission coefficient	0.5
$\beta_{\max}$	Maximum transmission coefficient	10
δ	Amplitude of the birth rate forcing	Varies
ϵ	Period of the birth rate forcing	1
q	Crowding coefficient acting on births	0.1
b	Baseline mortality rate	1
γ	Recovery Rate	Varies
α	Virulence/additional death rate due to parasite	1

Table 1: Parameter definitions and default values.

parameter values, the period ϵ is the same as the average lifespan b (1 year), but see section 3.4 for varying ϵ or Appendix F for alternative b.

We assume that the host evolves defence through the transmission coefficient (avoidance) β. We let the average birth rate depend on this as a trade-off so that there is a cost to resisting the parasite, as there is experimental support for such a relation to exist (Boots & Begon, 1993). We use the following trade-off function based on that used by White et al. (2006):

$$a_0 = a_0(\beta) = \hat{a_0} - p\frac{(1 + \frac{\beta-\beta_{\min}}{\beta_{\max}-\beta_{\min}})}{(1 + c\frac{\beta-\beta_{\min}}{\beta_{\max}-\beta_{\min}})}, \tag{4}$$

where $\hat{a_0} > 0$, $0 < p < \hat{a_0}$, $c > 1$ and $\beta \in [\beta_{\min}, \beta_{\max}]$. $a_0(\beta)$ has minimum $\hat{a_0} - p$, and parameters p, c determine the gradient and curvature of the trade-off, which needs to have positive gradient: as the host invests in defence against the parasite (β decreases), less can be invested in reproduction ($a_0(\beta)$ decreases) (Boots & Haraguchi, 1999; Geritz et al., 2007). The constraints on the trade-off parameters give accelerating costs of defence, so that it is more costly to invest in resistance when defence is already high $\left(\frac{d^2a_0(\beta)}{d\beta^2} < 0\right)$, see figure A.1 in Appendix A. Accelerating trade-offs generally lead to evolutionary attractors (Hoyle et al., 2008), which will be our focus here.

We use the adaptive dynamics method to study evolution of the host in the transmission coefficient β. The method involves adding a rare mutant with susceptible and infected population sizes S_{m}, I_{m} and transmission coefficient β_{m} very close to the resident transmission coefficient β. We assume that mutants occur infrequently so that the resident population reaches the dynamic attractor of the population dynamics (generally a limit cycle here) before the next mutant is introduced (Geritz et al., 1998). When a new mutant arises, it is rare compared to the current population, so we assume that the resident remains at its limit cycle as long as the mutant population is small (Geritz et al., 1998). To analyse how the host evolves, we consider the mutant's fitness, defined to be the long-term exponential growth rate of the mutant in the current environment (Metz et al., 1992).

In the case where $\gamma = 0$, the fitness is relatively simple to find. We no longer have infected mutants (they are absorbed into I), and we can read off the time-varying growth rate $r(t)$ of the mutant host from the linearisation of the equation for the susceptible mutant ($dS_{\mathrm{m}}/dt = r(t)S_{\mathrm{m}}$, see Appendix B). Following the method from Donnelly et al. (2013), we can then take the average

of this over one period to find the mutant fitness:

$$r = \frac{1}{T}\int_{P_0}^{P_1} r(t)dt = \frac{a_0(\beta_{\mathrm{m}})}{T}\int_{P_0}^{P_1}\left\{\left[1+\delta\sin\left(\frac{2\pi t}{\epsilon}\right)\right][1-qN(t)]\right\}dt - b - \frac{\beta_{\mathrm{m}}}{T}\int_{P_0}^{P_1} I(t)dt\,, \quad (5)$$

where T is the period of the system, P_0 is an arbitrary time after the resident dynamics have reached a limit cycle, and $P_1 = P_0 + T$.

Unfortunately we cannot use this averaging method when $\gamma > 0$. Instead, we have to find the Lyapunov exponents or Floquet multipliers numerically (Metz et al., 1992; Klausmeier, 2008). We do this by letting the linearly independent solutions of the linearised mutant equations be of the form $\mathbf{X}_i(t) = e^{\mu_i t}\mathbf{p}_i(t)$ for $i \in 1, 2$ (Grimshaw, 1990), and then take the largest μ_i as the mutant fitness. A full discussion of the method is given in Appendix B. We also ran stochastic simulations which relax the separation of timescales assumption, and these confirm our key results, for examples see figure 2 and Appendix D.

3. Results

3.1. Population dynamics

To explore how the population dynamics shape selection, we first consider the nature of the attractors of equations (1) - (2). For most parameter sets, the period of the population dynamics is equal to that of the forcing in the birth rate, i.e. $T = \epsilon$. However, there are parameter regions where the population undergoes a period-doubling bifurcation with resulting cycles of period $T = \lambda\epsilon$ for some positive integer λ. We can also find cases of multiple attractors, often with different periods. After finding this period, we can write down the average size of each class as follows (method in Appendix C):

$$\hat{S} = \frac{1}{T}\int_{P_0}^{P_1} S(t)dt = \frac{\alpha + b + \gamma}{\beta} \quad (6)$$

$$\hat{I} = \frac{1}{T}\int_{P_0}^{P_1} I(t)dt = \frac{\beta}{(\alpha + b + \gamma)T}\int_{P_0}^{P_1} SIdt\,. \quad (7)$$

Immediately we can see that the average susceptible population $\hat{S}$ does not depend on either of the seasonal parameters. However, this is not the case for the average infected population $\hat{I}$,

which we have to evaluate numerically for $\delta > 0$. For the default parameter values in table 1, we find that $\hat{I}$ increases with the amplitude of seasonality δ, and hence the average prevalence $\left(\frac{1}{T}\int_{P_0}^{P_1} \frac{I(t)}{N(t)}dt\right)$ of the parasite also increases. When we vary the period ϵ, $\hat{I}$ increases to a peak at $\epsilon \approx 1.5$ due to resonance with the unforced system, then decreases as ϵ continues to increase. This is discussed further in section 3.4. Considering the fitness expression in (5), it is clear that the effect of seasonality on these population averages will have crucial impacts on host evolution for all recovery values, unlike with parasite evolution (Donnelly et al., 2013). We can therefore use these averages to explain how the host evolves in response to changes in parameters.

3.2. Evolution for $\gamma = 0$

When we set $\gamma = 0$, we revert back to the simpler SI model. As stated in section 2, we can write down the fitness of the host in this case for all $\delta \in [0, 1]$ in equation (5). Here we only consider continuously stable strategies (CSSs) unless stated otherwise, i.e. singular points that are both evolutionarily stable (ES) and convergence stable (CS) as defined by Geritz et al. (1998) which lead to long-term evolutionary attractors. This behaviour was confirmed using pairwise-invasion plots (PIPs) and simulations over a range of parameters, for an example see Appendix D.

When δ is increased from 0, we find that the average infected population increases and so does the investment in defence (i.e. β^* decreases & higher defence), see figure 1(a),(b). This is what we would naively expect: as the average infected population increases, the host has to invest more in resistance against the parasite to reduce the proportion of infected individuals (Boots & Haraguchi, 1999; Boots et al., 2009).

In section 3.1 we mentioned that for particular parameter sets, period-doubling bifurcations and bistability between different attractors in the population dynamics can occur. Figure 1(c),(d) shows an example of this phenomenon together with host selection. As we increase δ, there is a point at which the 1-year solution undergoes a period-doubling bifurcation. The resulting 2-year solution then goes through two folds, after which a stable solution exists, see Appendix E. Bistability between different solutions for $\delta \in (0.57, 0.63)$ causes overlap of the singular points given by each cycle, giving a discrete change in the CSS resistance β^* and average infected population, figure 1(c),(d). Note that due to the basins of attraction for each CSS within the bistability region, the host can only evolve towards the $T = 2$ singular point for initial transmission coefficient β_0 greater than the lower bound of the bistablility region, see Appendix

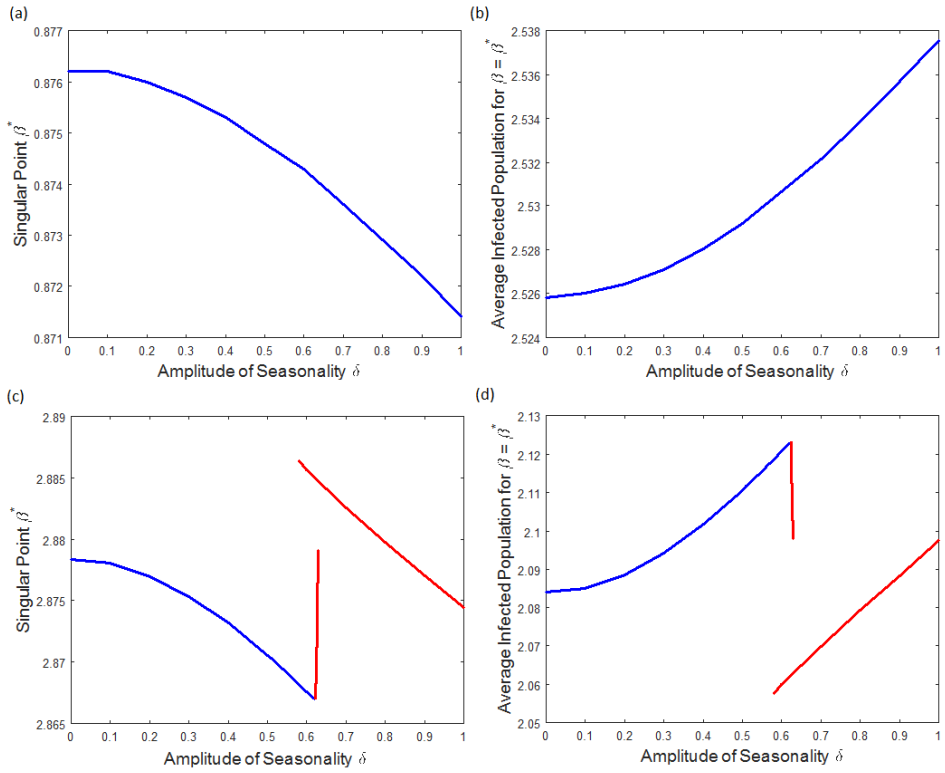

Figure 1: Change in (a),(c) the singular point β^* and (b),(d) the average infected population for $\beta = \beta^*$ as the amplitude of seasonality δ varies for $\gamma = 0$. Default parameters were used in (a),(b), with $\hat{a_0} = 104$ in (c),(d). In (c),(d), on the left only the 1-year solution is stable, and on the right only the 2-year solution. In the centre there is bistability between the 1 and 2-year cycles or between the two different 2-year cycles. Blue - period $T = 1$; Red - period $T = 2$.

E. This jump in the average infected population and singular point occurs whenever a period-doubling bifurcation and bistability between attractors exists for $\gamma = 0$.

Overall the impact of the amplitude of seasonality δ on the singular point for $\gamma = 0$ is weak for a wide range of parameters as seen in figure 1. Seasonality has a much stronger effect for higher recovery rates, as discussed below.

3.3. Evolution for $\gamma > 0$

Unlike in the SI model above, when $\gamma > 0$ we use a numerical approximation to find the host fitness. When γ is relatively close to zero, we find one singular point which decreases as δ increases, as seen in section 3.2. However for positive but small values of γ, this behaviour changes direction. We start to see both the singular point β^* and the average infected population increasing, in contrast to $\gamma = 0$ where the trends go in opposite directions. As recovery increases, selection for defence is weakened, and so at this small recovery maintaining a large population size through births becomes more important than resistance to the parasite, causing the change

in evolutionary direction.

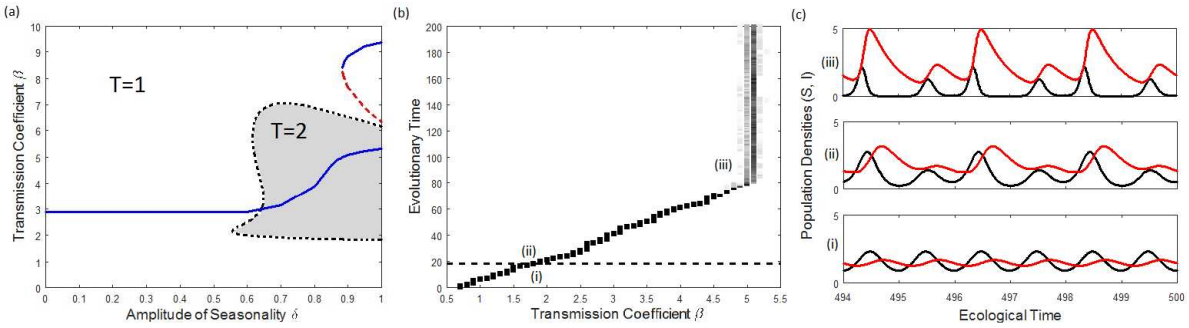

Figure 2: (a) Change in the singular points as δ varies for $\hat{a_0} = 104$, $\gamma = 0.005$. Blue lines indicate the CSS points, red dashed lines the repeller point and black dotted lines the switch between attractors. The period of the population dynamics is 2 in the shaded region and 1 (ϵ) elsewhere. (b) Simulation example corresponding to (a) with initial transmission coefficient $\beta_0 = 0.7$ and $\delta = 0.9$, which evolves towards the lowest CSS $\beta^*_{\mathrm{L}} = 5.067$. Darker squares indicate a higher proportion of the population with the corresponding transmission coefficient β, and the dashed line marks the point where evolution drives the population to switch to an attractor with period $T = 2$. (i)-(iii) correspond to sample population dynamics of the resident strain shown in (c), with black for S and red for I at evolutionary times (i) 10, (ii) 20 and (iii) 100.

As we continue to increase the recovery rate, we reach a region of γ values where three singular points exist, two CSSs with a repeller between them, for an example see figure 2(a). Here we have evolutionary bistability between two CSSs, and for certain parameter sets the CSSs have different cycle lengths due to the stability of the attractors in the population dynamics, as in the example shown. In this case the host could start in a 1-year cycle, but evolution would drive it into a 2-year regime, i.e. evolution can drive changes in the population dynamics, see figure 2(b),(c). We can also have the situation where all three singular points give period two population dynamics (not shown). Figure 3 shows two-dimensional contour plots for two CSS points in the parameter regions where they occur. Both CSS points increase with δ, as argued above, but they go in opposite directions as γ increases. This occurs because at high levels of defence (low β^*, figure 3(a)), selection for even higher defence weakens as recovery increases, and so the host decreases its resistance. However, when the host has a low level of defence (high β^*, figure 3(b)), the susceptible hosts become infected more quickly and an increase in recovery raises the infected population further, hence there is strong selection for defence and the host invests more in resistance. Recovery therefore has a much more complicated effect on evolution when seasonality is included in the model, since most of these bistability regions occur for large amplitudes.

If we increase γ further, the size of the interval of δ values where bistability occurs decreases to zero. For all γ values above this point, we find only one singular point β^* that increases with δ,

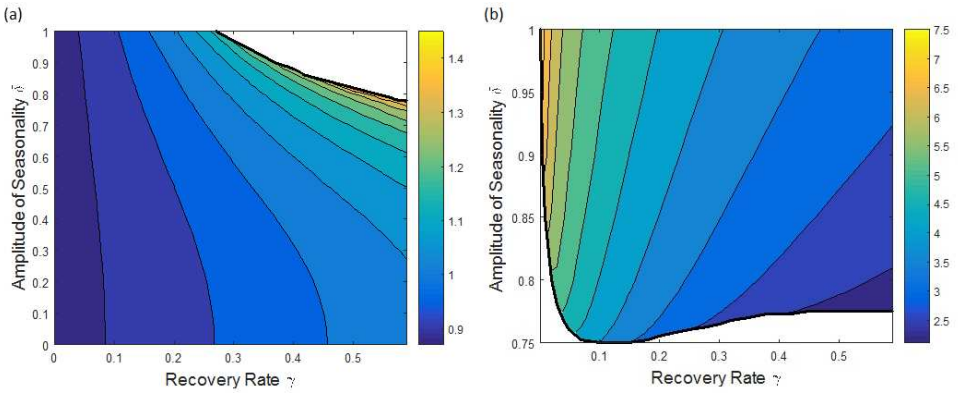

Figure 3: Two-dimensional contour plots showing the change in the two CSS points that occur as γ and δ vary for default parameters. (a) β_L^*, the smallest CSS point; (b) β_H^*, the highest CSS point. White areas indicate where each singular point does not exist.

figure 4(a), for the same reasons as explained above.

Figure 4(a) shows a two-dimensional contour plot for the singular point β^* as δ and γ vary in the region where one singular point exists. For the majority of amplitudes, the average infected population decreases with increasing recovery, and hence the host invests less in defence. However, we have slightly more complicated behaviour for high δ. Initially we find that the host increases defence (decreases β^*), then at an intermediate recovery the trend turns and the host decreases its defence (increases β^*). This behaviour is due to changes in the average infected population, which peaks for intermediate γ since initially the increase in susceptible individuals available to be infected outweighs the loss from recovery.

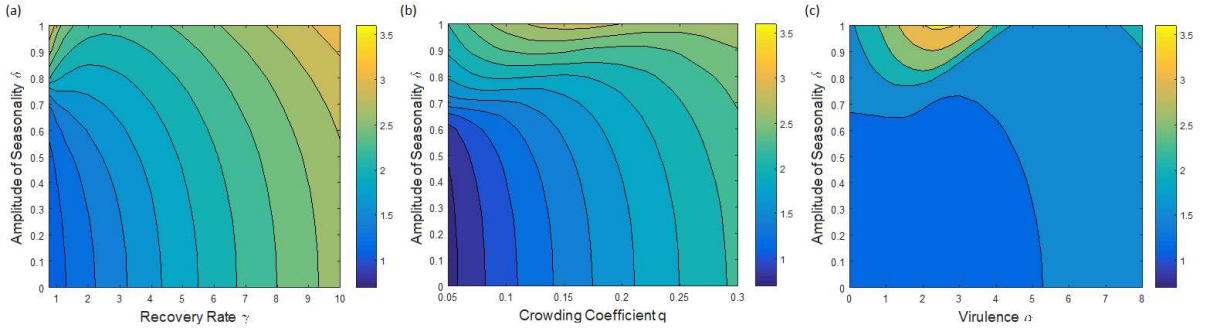

Figure 4: Two-dimensional contour plots showing the value of the singular point β^* as amplitude of seasonality δ and (a) recovery rate γ, (b) crowding factor q and (c) virulence α vary. Other parameters were fixed at default values from table 1 with $\gamma = 1$.

Alterations to other model parameters also causes variation in the host's evolution. Figure 4(b) shows the change in the singular point β^* as δ and the crowding coefficient q are varied. As above, we see that β^* increases with δ for all values of q. As we increase q for fixed δ, the infected population size decreases. We therefore expect the host to invest less in defence as q increases,

i.e. β^* to increase, which is exactly what we find for most values of δ. However, for very high amplitudes we find that the level of defence has a more complicated relationship with q, and in particular that defence is minimal (β^* maximum) for intermediate and very high values of q. For low q, the average infected population decreases as q increases, hence the host invests less in defence as for lower δ. However, there comes a point where the susceptible population is relatively low due to the decreased resistance, and so the host invests more in defence rather than births to increase the average susceptible population. As q continues to increase, the average infected population becomes small enough that selection for defence is weakened, and so the host returns to its previous behaviour and invests less in defence (β^* increases) for very high q.

We find similar results when the virulence α varies, figure 4(c). As α increases, the average infected population decreases and the host can afford to invest less in defence, which is exactly what we find for δ up to intermediate values. However, as for varying q, the trend becomes more complicated for highly seasonal birth rates. In this region, we now have a large peak in β^* for an intermediate value of α, followed by a trough and a small increase in β^* for high α. For small and very large α, this behaviour is due to the average infected population decreasing and therefore the host can afford to invest less in defence. However, the initial behaviour causes the total population to decrease, and there is a region of α values where the host needs to evolve in such a way that the population size increases. Therefore the host has to balance changes in the infected and total population sizes, giving the more complicated evolutionary behaviour for high amplitudes.

The results discussed above are for a parameter set where the host lifespan is equal to the period of forcing (one year). The effects seen are dampened for longer lived hosts (smaller b), and there can be no difference in the evolutionary behaviour with γ, q or α for different amplitudes (see Appendix F). Hence the effect of the amplitude on the host's evolutionary behaviour with other parameters depends on context, and in particular we cannot rely on the behaviour remaining the same as the amplitude of the birth rate increases for short-lived hosts.

3.4. Varying the Period of the Forcing ϵ

The population dynamics have period determined by that of the forcing ϵ, as discussed in section 3.1. We can investigate how changing this period over a wide range of values affects the evolution of the host, figure 5(a) (although in many systems a 1-year cycle ($\epsilon = 1$) may be the

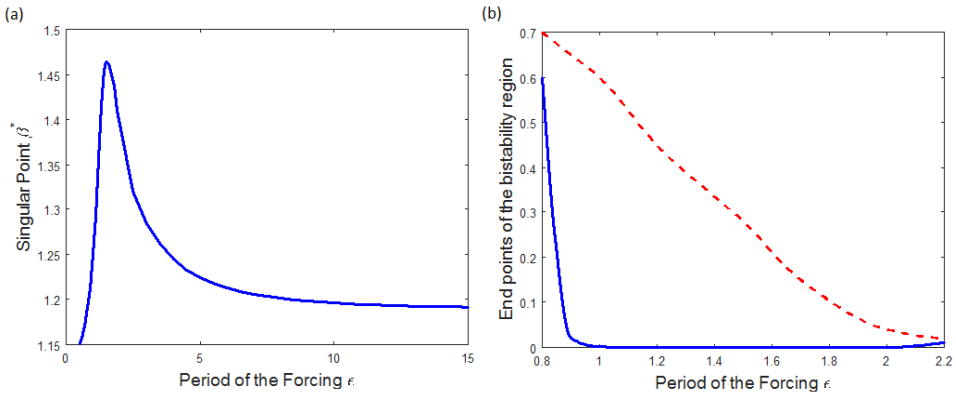

Figure 5: (a) Change in the CSS singular point β^* as ϵ varies for default parameters with $\delta = 0.5$ & $\gamma = 1$. (b) Change in the size of the bistability region in recovery rate γ as ϵ varies. Blue: γ value where bistability starts; Red dashed: γ value where bistability ends.

most appropriate). We found that there is a large peak in both the average infected population and the singular point β^* caused by resonance with the natural timescale of the model, after which they decrease slowly as ϵ is increased further. Hence for rapidly changing environments (ϵ low), any alteration to the period would have a significant impact on the host's evolution. In comparison, for slowly varying environments any change in the period barely alters the host's evolution. This behaviour with ϵ stays roughly the same for all parameters tested. Similarly, when both the period and other parameters are varied simultaneously, the period doesn't affect the evolutionary behaviour we find as other parameters change and vice versa.

The bistability region studied in section 3.3 changes in size for varying period ϵ. Figure 5(b) shows this, indicating that the bistability region is largest (in γ) for $\epsilon \approx 1$, slightly lower than the peak seen in figure 5(a). Above and below this value the bistability region decreases in size and quickly disappears. The period of the seasonality therefore has a large impact on whether or not these bistability regions occur.

4. Discussion

We have shown that seasonality in the ecological dynamics, specifically the birth rate, has a clear quantitative and qualitative effect on the evolution of host resistance against a parasite in our model. The relative size and nature of the impact depends crucially on the underlying epidemiological model, and particularly on the potential for recovery from infection. We found regions of parameter space where there is bistability between two distinct evolutionary strategies (CSS points), which can occur alongside a switch between attractors in the population dynamics.

In these regions, evolution could drive the population to a different attractor, fundamentally altering the population dynamics the host experiences. Crucially, we also found that well known patterns for the host's evolutionary strategy in a constant environment don't necessarily hold for variable birth rates, particularly when the amplitude of fluctuations is high.

We found that the amplitude of the seasonality and the recovery rate are key processes affecting the evolution of the host's defence for a seasonal birth rate in our model. When recovery is absent, the host invests more in defence as the amplitude of seasonality increases as this leads to an increase in the average infected population and thus selection for increased defence. The trends observed were weak, but are consistent with existing theory on the evolution of avoidance in the absence of recovery (Boots & Haraguchi, 1999; Donnelly et al., 2015). When the host can recover from the parasite, the evolutionary dynamics become more complicated. The trend of host investment with the amplitude of seasonality switches direction at a low recovery rate, above which the host decreases its defence as the amplitude increases, since the host is now balancing reduced transmission against the increased contribution to fitness made by infected hosts through recovery. These results emphasise the importance of recovery in host-parasite infections as they prevent the parasite from being a 'functional predator' (Boots, 2004; Donnelly et al., 2015; Best et al., 2017). We also note that our results with recovery for host evolution are similar to the findings of Donnelly et al. (2013) for parasite evolution, where the parasite invests more in infectivity as the amplitude of seasonality increases. This suggests a robust result that in many systems increased seasonal amplitude will lead to higher transmission, though a full coevolutionary study that includes recovery would be needed to confirm this.

There has been a lack of attention to how seasonality might affect host evolution in theoretical studies, even though it has been shown that epidemiological dynamics can be greatly impacted by a variable environment (Altizer et al., 2006; Grassly & Fraser, 2006). In addition, it is well known that a wide range of species reproduce seasonally due to environmental fluctuations, for example in bats (Stawski et al., 2014), killifish (Furness, 2016) and birds (Ketterson et al., 2015). The theorectical studies that do consider seasonality are generally co-evolutionary with a gene-for-gene based infection interaction (Nuismer et al., 2003; Mostowy & Engelstädter, 2011; Poisot et al., 2012). Of particular relevance to our study, Poisot et al. (2012) include explicit ecological dynamics in their model, using an additional resource variable with discrete fluctuations to implement seasonality, as well as a partial gene-for-gene infection mechanism. Despite these

different underlying assumptions, they too find that the host invests more in defence when the amplitude of the seasonality is high and there is no recovery. Moreover, in an experimental study, Blanford et al. (2003) showed that pea aphids, *Acyrthosiphon pisum*, evolved higher resistance against a fungal pathogen, *Erynia neoaphidis*, when periodically exposed to higher temperatures. Since the fecundity of aphids varies with temperature (Ramalho et al., 2015) and aphids lack many of the genes associated with immune response to microbes (Gerardo et al., 2010), these results agree with the theoretical results found here and by Poisot et al. (2012), that increased seasonality leads to increased resistance in the absence of recovery.

Interestingly, we found that evolutionary bistability can exist between two convergence stable strategies for small recovery rates. When the amplitude of the birth rate is high, the host may evolve towards either of two levels of defence depending on initial conditions. This bistability only occurs for a finite range of amplitudes, meaning that a small change in the amplitude could lead to a large change in the level of defence the host evolves. Furthermore, the bistability can occur in conjunction with a switch between attractors with different cycle lengths, with the higher level of defence (lower transmission) giving a regime of two-year cycles in the population dynamics, whereas the lower defence (higher transmission) is in a one-year regime, meaning that evolution can in fact drive the population dynamics into a cycle with a different period. This effect of evolution moving host-parasite systems into regions of qualitatively different population dynamics has also been shown in systems which assume a constant environment but population cycles occur naturally (Hoyle et al., 2011; Best et al., 2013). These results emphasize that ecology/epidemiology and evolution are involved in a two-way feedback, as not only does ecology drive selection, but evolution can determine the nature of the population dynamics.

There have been many studies considering the evolution of host defence against parasites that did not include seasonality (van Baalen, 1998; Boots & Bowers, 1999; Boots & Haraguchi, 1999). We have shown here that many classic results are likely to be true in a weakly seasonal system, but may not hold for an increasingly variable birth rate. For example, as virulence varies, investment in resistance decreases as found previously (Boots & Haraguchi, 1999; Best et al. 2017) for low amplitudes of seasonality, but at high amplitudes is maximized at either minimum or relatively high virulence. We see similar behaviour for varying crowding factor, in that our results agree with those found by Boots & Haraguchi (1999) for low amplitudes, but disagree for high amplitudes. These differences are a result of complicated feedbacks between seasonality,

population sizes and selection which alter the costs/benefits of resistance and births. However, we have shown that this effect is dampened for hosts with longer lifespans, returning to the behaviours seen in previous work for all amplitudes of the seasonality (see Appendix F). It is clear that while many results found for constant environments remain true when the birth rate is variable in time, this may not be the case when the amplitude is particularly high, especially for short-lived hosts.

We also investigated the impact of changing the period of the forcing on the evolution of the host's defence. We found that changing the period induces a peak in the infected density, caused by resonance in the population dynamics with the unforced system. Naively we would expect this to lead to a maximum level of investment in defence, however, as with varying amplitude in the presence of recovery, the host evolves towards a minimum level of defence in order to maintain a large overall population size through increased birth rate. Near the peak, small alterations in the period will lead to relatively large changes in the evolutionary investment in defence. Away from the peak, the curve is almost flat and so the host's evolution is barely affected by changes in the period when it is already large. In an experimental study, Harrison et al. (2013) found that resistance of *P. fluorescens* SBW25 to a phage was constrained most strongly in rapidly fluctuating environments, while Duncan et al. (2017) showed that resistance of the same bacteria evolved more quickly in rapidly fluctuating environments. It is unclear to what extent our results agree with these experimental studies, in part due to these systems being co-evolutionary with genetic specificity, and in part because it is difficult to ascertain which side of the resonance peak these studies may be focusing on. It is clear, though, that the time-frame of the fluctuations has important consequence to the evolutionary outcome.

Temporal heterogeneity, including seasonal fluctuations, are a fundamental aspect of all natural ecological systems. However, both experimental and theoretical studies have rarely investigated the impact of fluctuating environments on evolutionary patterns. Here we have shown that a seasonal birth rate has a significant qualitative impact on the evolution of host defence in an SIS model, which is highly dependent on the presence and size of recovery. It is clear that key features of evolutionary dynamics may be missed by assuming a constant environment, and therefore important for us to consider how seasonality may impact host-parasite evolution more widely. There is clearly scope for further theoretical and experimental work to explore the impacts of seasonality on host-parasite evolution.

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