THE EFFECT OF SEASONAL HOST BIRTH RATES ON DISEASE PERSISTENCE.

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ABSTRACT

In this paper, we add seasonality to the birth rate of an SIR model with density dependence in the death rate.

We find that disease persistence can be explained by considering the average value of the seasonal term. If the basic reproductive ratio $R_0 > 1$ with this average value then the disease will persist and if $R_0 < 1$ with this average value then the disease will die out.

However, if the underlying non-seasonal model displays oscillations towards the equilibrium then the dynamics of the seasonal model can become more complex. In this case the seasonality can interact with the underlying oscillations, resonate and the population can display a range of complex behaviours including chaos. We discuss these results in terms of two examples, Cowpox in bank voles and Rabbit Haemorrhagic Disease in rabbits.

1. INTRODUCTION

It is important to understand how pathogens interact with their host - how they influence host dynamics, how they persist and, conversely, how they can be controlled. This is vital for both public health and economic reasons. In recent years mathematical models have been used very successfully to give insights into important disease systems such as BSE and HIV/AIDS. However, many of the simple mathematical models currently in use fail to capture important biological factors.

In this paper, we are interested in the effects of seasonality in the birth rate of the host on host pathogen dynamics. Seasonality in other parameters has already been incorporated into some models of disease systems. For example, Williams and Dye (1997) investigated the case when the disease transmission rate varies seasonally and they illustrate (to a very good approximation) that for a general class of infected functions the arithmetic mean transmission rate gives an accurate value of the threshold parameter, R_0 - often referred to as the basic reproductive ratio (when $R_0 > 1$, a disease can invade and establish itself within a population). In other words, they show that the average transmission rate can be used to calculate the appropriate threshold parameters.

Roberts and Kao (1998) do look at seasonality in the birth rate, but they consider a pulsed birth rate, where wild animals give birth during a single short period of the year, and apply this to an example of tuberculosis in possums. One drawback of this model is that the analysis requires complex numerical evaluation. We therefore believe that further

research incorporating other forms of seasonality into these models would be beneficial, particularly as a pulsed birth rate is unrealistic for many host populations which have a breeding season which lasts for several weeks or months.

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White et al (1996) considered the effect that seasonal host reproduction has on host-macroparasite interactions and concluded that if seasonal effects are disregarded, regulation of the hosts by the parasite population are overestimated.

In this paper we will illustrate that the effect of seasonality in the birth rate on the persistence of the pathogen can be understood easily, using simple max/min theory and arithmetic averaging as found in Williams and Dye (1997). This is then verified by two specific examples, Cowpox in bank voles and Rabbit Haemorrhagic disease (RHD) in rabbits. However, the population dynamics are not so simple to predict, since complexities in the dynamics may arise when there are underlying oscillations towards a stable equilibrium in the non-seasonal model - this is the case for Rabbit Haemorrhagic Disease. When we add seasonal forcing in this case, it combines with these oscillations and resonates, allowing complex host dynamics and the possibility, within realistic parameter ranges, of chaos.

2. THE SIR MODEL WITH SELF-REGULATION AND NO SEASONALITY

Anderson & May (1979) and Gao &Hethcote (1992) give details of the standard SIR model with self-regulation, and they are summarized here for completeness. The host population is split into three distinct classes: Susceptibles (X), Infecteds (Y) and Immunes (Z); therefore, our total population density H = X + Y + Z. The following set of coupled, non-linear differential equations describes the system:

$$\frac{dX}{dt} = aH - (b + sH)X - \beta XY \qquad (1)$$

$$\frac{dY}{dt} = \beta XY - (\Gamma + sH)Y \qquad (2)$$

$$\frac{dZ}{dt} = \gamma Y - (b + sH)Z \qquad (3)$$

$$\frac{dH}{dt} = (r - sH)H - \alpha Y \qquad (4)$$

Only three of these equations are needed, equation (4) is derived by adding Equations (1) to (3). The parameters are defined in Table 1. We have incorporated density dependence into the death rate, rather than the birth rate, partly for biological realism but also to avoid direct interaction between the seasonality and non-linearities in the density dependence term.

We can find all of the possible equilibria of this system by setting the derivatives in equations (1) to (4) equal to zero. This results in three possible equilibria. There is the origin (H = 0, Y = 0, Z = 0), in which case nothing is present, and (H = K, Y = 0, Z = 0),

in which case there is no disease and the host is at the carrying capacity, K (= r / s). Finally, there is the co-existence equilibrium, given by

$$Y^* = \frac{r}{\alpha} H^* - \frac{s}{\alpha} H^{*2}$$
$$Z^* = \frac{\gamma\left(rH^* - sH^{*2}\right)}{\alpha\left(b + sH^*\right)}$$

where H^* is a solution of the cubic equation

$$H^{*3} + H^{*2}\left(\frac{\Gamma K}{r} - K - \frac{\alpha}{\beta}\right) + H^*\left(\frac{\alpha b K^2}{r^2} - \frac{\alpha(b+\Gamma)K}{r\beta} - \frac{(b+\gamma)K^2}{r}\right) - \frac{\Gamma \alpha b K^2}{r^2 \beta} = 0$$

It can be shown that when $R_0 > 1$ (where R_0 is the basic reproduction number, given by $R_0 = \frac{\beta K}{\Gamma + r}$) then this cubic can be shown to have one root between 0 and K (Appendix 1).

2.1 Stability Analysis

Having found all of the biologically relevant equilibria, we are concerned with when they are locally (and we assume globally) stable. This can be determined by considering the eigenvalues of the Jacobian of the system evaluated at the equilibrium of interest. If the eigenvalues have negative real parts then the equilibrium is stable. It can therefore be shown that the origin, (0,0,0), is only stable if b > a i.e. if the natural death rate exceeds the birth rate and the (K,0,0) equilibrium is only stable if a > b and $R_0 < 1$. Due to the algebraic complexities involved in these analyses, we assume that the disease can be

maintained, only if a > b and $R_0 > 1$. This assumption is backed up by numerical simulations, and also is a consequence of the Theorem in section 3 below.

For this model, we have not been able to prove that the population does not exhibit stable limit cycles but extensive numerical simulations have not shown them. However, there have been seen to be oscillations towards the equilibrium for certain parameter values. This is because under these circumstances, the eigenvalues have negative real parts but are complex, indicating that we have a spiral point in state space.

The model discussed above makes the assumption that the host birth rate takes a constant value over the whole year. However, in reality, many animal species have seasonal birth rates, and this may affect the dynamics and persistence of the disease.

3. SIR MODEL WITH SELF REGULATION AND SEASONALITY

We now wish to represent the birth rate, *a*, by a function which varies over time, $a(t)$. In particular we expect that in most systems the birth rate is higher in the summer than in the winter, this is the case in the voles and rabbit systems which will be discussed later. Many models of childhood diseases have assumed that seasonal forcing could be modelled by a periodic function (Keeling et.al, 2001; Finkenstadt & Grenfell, 2000). Therefore, in accordance with these papers, and to keep the mathematics simple, the following sine function has been chosen, $a(t) = a_0(1 + a_1 \sin(2\pi t))$. We will discuss the relevance of the results to other functional forms for seasonality later in the paper. It

should be noted that if $a_1 = 0$ we recover the previous case, outlined in Section 2. In addition, the average value, $\hat{a}$, of this birth rate comes when the sine function equals zero and hence $\hat{a} = a_0$.

We cannot analyze the equations in the same way as for the non-seasonal model, because equation (1) is now a non-autonomous equation where the right hand side depends explicitly upon time. We want to see if there is a simple way to predict disease persistence in this system. It turns out that a simple criterion may be formulated in terms of the average value $\hat{a}$ of $a(t)$, provided certain conditions given below are satisfied. t

Let us denote $\hat{R}_0 = \dfrac{\beta\hat{K}}{\Gamma + \hat{r}} = \dfrac{\beta\hat{r}}{s(\Gamma + \hat{r})} = \dfrac{\beta(\hat{a} - b)}{s(\Gamma + \hat{a} - b)}$. Then we have the following result.

Theorem:

The disease will persist, in the sense that $\overline{\lim_{T\to\infty}} \dfrac{1}{T}\int_0^T Y(t)dt > 0$ when $\hat{a} > b$ and $\hat{R}_0 > 1$, and the disease will die out, i.e. $Y(t) \to 0$ as $t \to \infty$, when $\hat{R}_0 < 1$.

In fact this result holds for any seasonal birth rate a(t) which satisfies the following assumptions:

i) a(t) is continuous for all t≥0.

ii) There exist constants a_{min} and a_{max} such that $0 \le a_{min} \le a(t) \le a_{max}$ for all t≥0.

iii) For all t ≥ 0 , the average $\frac{1}{T}\int_t^{t+T} a(s)ds \to \hat{a} > 0$ as $T \to \infty$ uniformly in t, i.e. for all $\delta > 0$ there exists $T_0 > 0$ such that $\left|\frac{1}{T}\int_t^{t+T} a(s)ds - \hat{a}\right| < \delta$ for all $T > T_0$ and all $t \geq 0$.

iv) $\hat{r} = \hat{a} - b > 0$

v) All parameters α, b, s, β, $\gamma \geq 0$.

vi) $\Gamma > 0$, $s > 0$, $\gamma > 0$.

Proof:

The proof of this theorem comes in two stages. The first result is a lemma, which is of interest in its own right, for it asserts that for each initial condition in the positive orthant the population is bounded above and below. Thus the lemma shows that for this model the disease cannot drive the population to extinction.

Lemma 1: For each initial condition $X_0, Y_0, Z_0 > 0$, there exist positive constants H_{min} and H_{max} such that for all $t \geq 0$ $H_{\min} \leq H(t) \leq H_{\max}$.

The proof of this lemma is given in Appendix 2.

In order to state and prove the second lemma, we introduce the following notation. For a positive quantity W(t), t≥0, let

$$\left.\begin{matrix}\overline{W} \\ \underline{W} \\ \hat{W}\end{matrix}\right\} = \left\{\begin{matrix}\overline{\lim}_{T\to\infty} \\ \underline{\lim}_{T\to\infty} \\ \lim_{T\to\infty}\end{matrix}\right\} \frac{1}{T}\int_0^T W(t)dt$$

$$\left.\begin{matrix}\overline{\lambda(W)} \\ \underline{\lambda(W)} \\ \lambda(W)\end{matrix}\right\} = \left\{\begin{matrix}\overline{\lim}_{T\to\infty} \\ \underline{\lim}_{T\to\infty} \\ \lim_{T\to\infty}\end{matrix}\right\} \frac{1}{T}\log\frac{W(T)}{W(0)}$$

Thus, when it exists, $\hat{W}$ gives the limiting average value of W(t) , and, similarly, when it exists, $\lambda(W)$ gives the Lyapunov exponent of W(t).

The second ingredient of the proof of the theorem is the following lemma:

Lemma 2: For each initial condition $X_0, Y_0, Z_0 > 0$ the following holds. If $\hat{R}_0 > 1$ then $\bar{p} > 0$ and if $\hat{R}_0 < 1$ then $\hat{p} = 0$ and furthermore $\lim_{t\to\infty} p(t) = \lim_{t\to\infty} Y(t) = 0$ with exponential decay.

Here p(t) is the prevalence of infection, Y(t)/H(t).

Proof: Let $X_0 > 0, Y_0 > 0, Z_0 > 0,$ and $H_0 > 0$ be the initial conditions at t=0. We also assume that $\hat{R}_0 \neq 1$ as our analysis does not apply in this degenerate case.

We note that the threshold conditions $\hat{R}_0 > 1$ and $\hat{R}_0 < 1$ may be written as $\Gamma < (\beta - s)\frac{\hat{r}}{s}$ and $\Gamma > (\beta - s)\frac{\hat{r}}{s}$ respectively. Therefore lemma 2 can be restated as:

If $\Gamma < (\beta - s)\frac{\hat{r}}{s}$ then $\bar{p} > 0$ and if $\Gamma > (\beta - s)\frac{\hat{r}}{s}$ then $\hat{p} = 0$.

First consider the case $\beta - s \leq 0$, for which $\Gamma > (\beta - s)\frac{\hat{r}}{s}$ must necessarily hold. Then

$$\begin{aligned} \frac{dY}{dt} &= \beta XY - (\Gamma + sH)Y \\ &\leq ((\beta - s)H - \Gamma)Y \leq -\Gamma Y \end{aligned}$$

so that $Y(t) \leq Y_0 e^{-\Gamma t}$ where Y_0 is the initial density of infectious individuals. Now since, from Lemma 1, we have $H(t) \geq H_{min}$, we have $\lim_{t\to\infty} p(t) = \lim_{t\to\infty} \frac{Y(t)}{H(t)} = 0$ so that in particular $\bar{p} = \underline{p} = \hat{p} = 0$.

Henceforth assume that $\beta - s > 0$. From Lemma 1, we know that H(t) is bounded above and below, hence $\hat{\lambda}(H) = \lim_{T\to\infty} \frac{1}{T} \ln \frac{H(T)}{H_0} = 0$.

Now suppose that $\bar{p} = \overline{\lim_{t\to\infty}} \frac{Y(t)}{H(t)} > 0$. We shall show that $\Gamma < (\beta - s)\frac{\hat{r}}{s}$.

Now it follows that $\bar{\lambda} = \overline{\lambda(Y)} = \overline{\lim_{t\to\infty}} \frac{1}{t} \log \frac{Y(t)}{Y_0} = 0$. For clearly $\bar{\lambda} \le 0$ since Y(t) is bounded above. Now if $\bar{\lambda} < 0$ then we must have $Y(t) \to 0$ as $t \to \infty$, so that $\bar{p} = \overline{\lim_{t\to\infty}} \frac{Y(t)}{H(t)} = 0$, since H(t) is bounded below.

Now
$$\frac{\dot{Y}}{Y} = \beta X - (\Gamma + sH)$$
$$\le (\beta - s)H - \Gamma$$
so that, taking averages, we have
$$0 = \overline{\lambda(Y)} \le (\beta - s)\bar{H} - \Gamma .$$
We must now estimate $\bar{H}$. Now
$$\dot{H} = (r(t) - sH)H - \alpha Y$$
$$\le (r(t) - sH)H.$$
Thus $sH \le r(t) - \frac{\dot{H}}{H}$ so that
$$s\frac{1}{T}\int_0^T H(t)dt \le \frac{1}{T}\int_0^T r(t)dt - \frac{1}{T}\log\frac{H(T)}{H_0}.$$
On taking the limsup as $T \to \infty$, we obtain $\bar{H} \le \frac{\hat{r}}{s}$, since $\lim_{t\to\infty} \frac{1}{T} \log \frac{H(T)}{H_0} = 0$. Hence

$$0 = \overline{\lambda(Y)} \le (\beta - s)\bar{H} - \Gamma$$
$$\le (\beta - s)\frac{\hat{r}}{s} - \Gamma$$

so that $\Gamma < (\beta - s)\frac{\hat{r}}{s}$, as $\Gamma \ne (\beta - s)\frac{\hat{r}}{s}$.

On the other hand, let $\bar{p} = 0$. We shall show $\Gamma > (\beta - s)\frac{\hat{r}}{s}$. Now, since $\underline{p} = 0$, we have

$$\bar{p} = \underline{p} = \hat{p} \overset{def}{=} \lim_{t\to\infty} \frac{1}{T}\int_0^T p(t)dt = 0$$

Now $\frac{\dot{H}}{H} = r - sH - \alpha p$ and $\lim_{T\to\infty}\frac{1}{T}\int_0^T \frac{\dot{H}}{H}dt = \lim_{T\to\infty}\frac{1}{T}\log\frac{H(t)}{H_0} = 0$ since H is bounded below. Thus

$\hat{H}$ exists and $0 = \hat{r} - s\hat{H} - \alpha\hat{p} = \hat{r} - s\hat{H}$ so $\hat{H} = \frac{\hat{r}}{s}$. We have therefore shown that the limiting average size of the population is the average carrying capacity in this case.

Now $0 \le Y(t) = p(t)H(t) \le p(t)H_{\max}$ so that $0 \le \underline{Y} \le \overline{Y} \le \overline{p}H_{\max} = 0$ and we have $\hat{Y} = 0$.

The equation for $\dot{Z}$ is $\dot{Z} = \gamma Y - (b + sH)Z$ so that

$$(b + sH_{\min})\frac{1}{T}\int_0^T Zdt + \frac{Z(T) - Z_0}{T} \le \frac{\gamma}{T}\int_0^T Ydt \le (b + sH_{\max})\frac{1}{T}\int_0^T Zdt + \frac{Z(T) - Z_0}{T}$$

from which it easily follows that $\hat{Z} = \hat{Y} = 0$. We deduce the relation $\hat{X} = \hat{H}$.

Now $\frac{\dot{Y}}{Y} = \beta X - sH - \Gamma$, so that $0 \ge \lim_{t\to\infty}\frac{1}{T}\log\frac{Y(T)}{Y_0} = (\beta - s)\hat{H} - \Gamma = (\beta - s)\frac{\hat{r}}{s} - \Gamma$

and we conclude $(\beta - s)\frac{\hat{r}}{s} - \Gamma < 0$, since $(\beta - s)\frac{\hat{r}}{s} - \Gamma \neq 0$.

In summary, we have shown that if $\overline{p} > 0$ then $(\beta - s)\frac{\hat{r}}{s} > \Gamma$ and if $\overline{p} = 0$ then $(\beta - s)\frac{\overline{r}}{s} < \Gamma$.

It follows that if $(\beta - s)\frac{\hat{r}}{s} < \Gamma$ i.e $\hat{R}_0 < 1$ then $\overline{p} = 0$ and if $(\beta - s)\frac{\hat{r}}{s} > \Gamma$ i.e. if $\hat{R}_0 > 1$ then $\overline{p} > 0$.

Finally we note that if $(\beta - s)\frac{\hat{r}}{s} < \Gamma$ then $\overline{p} = 0$ so $\hat{H} = \frac{\hat{r}}{s}$ and $\frac{\dot{Y}}{Y} \le (\beta - s)H - \Gamma$ and

$\overline{\lim_{T\to\infty}}\frac{1}{T}\log\frac{Y(T)}{Y_0} \le (\beta - s)\frac{\hat{r}}{s} - \Gamma < 0$ so that $Y(t) \to 0$ exponentially as claimed.

We now apply this result to two real biological systems, firstly cowpox in bank voles and then Rabbit Haemorrhagic disease.

4. COWPOX IN BANK VOLES

Cowpox virus is a member of the genus orthopoxvirus in the family Poxviridae, found throughout much of western Asia and Europe (Begon et al, 2003). Despite its name, Cowpox appears to be rare in cattle (Sandvik et al, 1998). Small wild rodents such as bank voles are believed to be the natural reservoir of Cowpox virus (Baxby and Bennett, 1999). Cowpox is endemic in bank voles (*Lethrionomys glareolus*). It does not cause obvious signs of disease, nor does it affect the survival rate. However, it does have an adverse reaction on reproductive output (see Feore et al, 1997), a feature not present in the model.

Voles are an important source of food for owls, foxes and other wildlife. Several hypotheses exist to attempt to explain the cyclicity of vole populations, such as predation and varying food levels (Jedrzejewska and Jedrzejewska, 1998). However, there has been no definite solution to this problem. (Yoccoz et al 2001) and (Sauvage et al, 2003).

Using the SIR model with self-regulation described previously, parameter values were chosen which were estimated to correspond to Cowpox in bank voles. These are given in Table 2. In this case, with a constant birth rate, there is a stable equilibrium (which is approached monotonically) where host and pathogen persist together.

If we add seasonality to the model as described in Section 3 above and take $a_1 = 0.3$ which is consistent with the data, then we have $a_{\max} = 26$, $a_{\min} = 14$ and $\hat{a} = 20$ per year, which gives $\hat{R}_0 = 19.15$ clearly all of these values are >1 and we would expect the disease to persist. The dynamics of cowpox in bank voles with $\alpha = 0$ is illustrated in Figure 3. In addition, numerical simulations, in which the parameters are varied appropriately confirm that the threshold in $\hat{R}_0$ is, indeed correct.

Since there is uncertainty in the parameter estimates, we have tested this model prediction by running simulations for various parameter values and the results hold. It should also be noted that the pattern observed in the simulation of Figures 3 (a), (b) and (c) is consistent with the expected annual cycle in vole dynamics (Hazel et al, 2000). Also, on closer inspection of the simulations generated for Cowpox in bank voles, with differing levels of seasonal forcing, it can be seen that the peaks and troughs in the infected section of the population come after those in the susceptible population. This is consistent with the observed findings of Begon et al, 1998. Both of these facts imply that this relatively simple model is nevertheless a reasonable one for cowpox in bank voles.

5. RABBIT HAEMORRHAGIC DISEASE

Rabbit Haemorrhagic Disease (RHD) is a highly virulent disease of rabbits, which originated in China in 1984 (White et al, 2001). Using the SIR model with self-regulation, parameter values were chosen which correspond to RHD levels in UK rabbit

populations (Table 3). Figure 4 illustrates the model output with these parameter values when there is no seasonality.

It can be seen that the system exhibits extremely small oscillations towards the equilibrium value. This periodicity corresponds to a stable spiral point in the X-Y state space. If we then add the seasonality to the birth rate as described previously, the system behaviour becomes much more complex and with $a_1 = 0.5$ (which is consistent with the data), we have $\hat{R}_0 = 180$, we predict that the disease will persist for this system, and this is confirmed by the simulation shown in Figure 5. However, dynamically, we appear to have chaos in the population dynamics (Figure 5). This is because when seasonality is added to the model for these parameter values, it combines with the natural oscillations of the system, resonates, and chaos can emerge. To analyze this, we have to make use of the resonance techniques described by Greenman et al 2004, the details of which are presented in another paper (Ireland, Norman and Greenman, 2004).

Although the theory presented earlier helps us to determine when the disease will persist and when it will die out, it does not allow us to predict dynamical behaviour. In some circumstances (for example the cowpox system) we can predict that the dynamics of the seasonal model will be bounded by the equilibrium values of the maximum and minimum non-seasonal model (we would only expect it to reach these bounds if the season was long or the dynamics changed quickly). However, in other systems (for example RHD) we get more complicated dynamics which are not constrained by these bounds. This is because the underlying non-seasonal model has a stable spiral point in state space and we

have oscillations towards the equilibrium. In this case we get resonance between these oscillations and the seasonality.

We can determine when we would expect this type of resonant behaviour to occur by considering the eigenvalues of the Jacobian in the non-seasonal model. When these eigenvalues are negative and real then we get a monotonic approach to equilibrium and hence no resonance with seasonality. When they are complex, with negative real parts then we get oscillations toward equilibrium and the possibility of resonance. We can determine the equation of the boundary to this region and use this to split parameter space into an area where there are no oscillations and an area where there are oscillations towards a stable equilibrium. This is algebraically complex since the characteristic equation is a cubic, but we can also determine the line numerically and this is illustrated in Figure 6 for Rabbit Haemorrhagic Disease. RHD has extreme parameter values, high α, high β and lies in the area where there are oscillations towards a stable equilibrium.

6. DISCUSSION

Many of the simple mathematical models that are currently in use fail to capture important biological factors. Here we extend the current models of host-pathogen interactions to include a sinusoidal seasonal function in the birth rate (although the results still appear to hold if we use a step function with similar variance (Greenman et al 2003, Ireland 2005). We find that we can apply a simple averaging theory to determine the effects of seasonal birth rates on the system. In this case, as the birth rate oscillates over the year between two values a_{max} and a_{min}, the persistence of the disease in the seasonal

model can be determined from the behaviours of the non seasonal model with birth rate equal to $\hat{a}$, the average birth rate over the season, and this result holds for more general a(t) than discussed here. Indeed for some systems we can also predict that the dynamics of the system will be bounded by equilibria of the non-seasonal model with birth rate, a, taking the maximum and minimum values of the seasonal model. These types of predictions do work for some real biological systems, as was illustrated with the example of Cowpox in bank voles. Indeed, this model describes well, at least qualitatively, the behaviour observed empirically in Cowpox-bank vole populations (Hazel et al, 2000). This is not just dependent on the fact that $\alpha = 0$ in the cowpox system. It applies to many other systems in which the non-seasonal model has a monotonically stable equilibrium.

However, although we can predict disease persistence using the averaging theory, the dynamical predictions are not so robust since adding seasonality to the birth rate of even a simple SIR model can lead to complex dynamics and even chaos. This occurs when the underlying non-seasonal model has oscillations towards the equilibrium which interact with the seasonality and resonate. This turns out to be relevant in a number of interesting disease systems, for example, RHD in rabbits, as discussed here, and rabies in foxes (See Ireland et al, 2004).

The work described here has shown that we can predict disease persistence in a simple way for a seasonal model. However, we have also illustrated that it is important to include seasonality in the birth rate of a host, since otherwise important dynamical behaviour would be missed. It is important to know how the underlying non-seasonal

model behaves in order to predict how complex we would expect the seasonal system's dynamics to be. The behaviour predicted by these seasonal models is very sensitive to initial conditions and small changes in parameter values, in particular the "strength" of seasonality (i.e. the size of a_1) (Ireland et al, 2004; Greenman et al 2003). It is therefore important to look at the data and parameterize models as accurately as possible.

Overall, the study here has illustrated that adding seasonality is not always as simple as one might think and can lead to interesting and biologically important dynamics which are in keeping with empirical data.

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Appendix 1

We wish to prove that there is a unique value of H_0 between 0 and K. We know that H_0 satisfies the cubic equation

$$f(H_0) = H_0^3 + H_0^2\left(\frac{\Gamma K}{r} - K - \frac{\alpha}{\beta}\right) + H_0\left(\frac{\alpha b K^2}{r^2} - \frac{\alpha(b+\Gamma)K}{r\beta} - \frac{(b+\gamma)K^2}{r}\right) - \frac{\Gamma\alpha b K^2}{r^2\beta}. \qquad \text{A1}$$

Now $f(0) = -\frac{\Gamma\alpha b K^2}{r^2\beta}$ which is clearly negative for positive parameters (it is assumed throughout that all parameters are positive).

$$f(K) = K^3 + K^2\left(\frac{\Gamma K}{r} - K - \frac{\alpha}{\beta}\right) + K\left(\frac{\alpha b K^2}{r^2} - \frac{\alpha(b+\Gamma)K}{r\beta} - \frac{(b+\gamma)K^2}{r}\right) - \frac{\Gamma\alpha b K^2}{r^2\beta}$$

$$= \frac{\alpha K^2(r+b)}{r^2\beta}(\beta K - (r+\Gamma))$$

So, $f(K) > 0$ when $\beta K > r + \Gamma$ i.e. when $R_o > 1$. Since the coefficient of H_0^3 is positive, then $f(\infty) > 0$ and $f(-\infty) < 0$. So when $R_o > 1$ there are either one or three roots of this cubic which lie between 0 and K.

We now consider the first derivative of the cubic with respect to H_0 in order to determine where the turning points of the cubic lie. We get

$$\frac{df}{dH_0} = 3H_0^2 + 2H_0\left(\frac{\Gamma K}{r} - K - \frac{\alpha}{\beta}\right) + \left(\frac{\alpha b K^2}{r^2} - \frac{\alpha(b+\Gamma)K}{r\beta} - \frac{(b+\gamma)K^2}{r}\right) \qquad \text{A2}$$

Setting $\frac{df}{dH_0} = 0$, we wish to solve for H_0 in order to determine where the turning points of the cubic are. There are three possibilities:

i) If the constant coefficient of the quadratic equation $\frac{df}{dH_0} = 0$ is negative the one of the turning points occurs when H_0 is positive and one when H_0 is

negative, given that $f(\infty)>0$ and $f(-\infty)<0$, this must mean that the cubic has one root of the cubic between 0 and K.

ii) If the constant coefficient of $\frac{df}{dH_0}=0$ is zero, then, give that $f(-\infty)<0$, this must mean that we have a maximum at $f(0)<0$ and so, since $f(\infty)>0$ there is one root of the cubic between 0 and K.

iii) If the constant coefficient of $\frac{df}{dH_0}=0$ is positive then the positions of the two turning points must have the same sign, and we have

$$\left(\frac{\alpha bK^2}{r^2}-\frac{\alpha(b+\Gamma)K}{r\beta}-\frac{(b+\gamma)K^2}{r}\right)>0 \qquad \text{A3}$$
$$\Rightarrow \beta K\alpha b > \beta Krb+\beta Kr\gamma+rb\alpha+r\Gamma\alpha$$

If we now consider the coefficient of H_0 in A2 (since the coefficient of H_o^2 is positive) then if this coefficient is positive then $\frac{df}{dH_0}=0$ has two negative roots, in which case one root of cubic A1 lies between 0 and K. If this coefficient is negative then $\frac{df}{dH_0}=0$ has two positive roots and cubic A1 has three roots which lie between 0 and K.

The coefficient of H_0 can be rewritten in the form

$\frac{2b}{r\beta}\left(\beta K\alpha b+\beta Kb^2+\beta K\gamma b-\beta Krb-rb\alpha\right)$ which, from A3 is positive.

Appendix 2:

In this appendix we give a proof of Lemma 1, which states that for each positive intitial condition, the total population $H(t)$ is bounded above and below. As before, we introduce the following notation. For a positive quantity W(t), t≥0 let

$$\left.\begin{matrix}\overline{W}\\ \underline{W}\\ \hat{W}\end{matrix}\right\} = \left\{\begin{matrix}\overline{\lim_{T\to\infty}}\\ \underline{\lim_{T\to\infty}}\\ \lim_{T\to\infty}\end{matrix}\right\} \frac{1}{T}\int_0^T W(t)dt$$

$$\left.\begin{matrix}\overline{\lambda(W)}\\ \lambda(W)\\ \underline{\lambda(W)}\end{matrix}\right\} = \left\{\begin{matrix}\overline{\lim_{T\to\infty}}\\ \underline{\lim_{T\to\infty}}\\ \lim_{T\to\infty}\end{matrix}\right\} \frac{1}{T}\log\frac{W(T)}{W(0)}$$

Now Let X_0, Y_0, Z_0 and H_0 be positive initial conditions at t=0.

Proof of Lemma 1:

The total population H(t) satisfies the differential equation

$$\dot{H} = (r(t) - sH)H - \alpha Y \quad \text{where r(t) = a(t) - b.}$$

Writing $r_{\max} = a_{\max} - b$, we have $\dot{H} \le 0$ for $H(t) \ge \frac{r_{\max}}{s}$. It follows that

$H(t) \le \max\left(H_0, \frac{r_{\max}}{s}\right)$ for all t≥0. We may therefore take $H_{\max} = \max\left(H_0, \frac{r_{\max}}{s}\right)$ and thus H is bounded above. To prove that H(t) is bounded below, we consider the prevalence of infection $p = Y/H$. The prevalence p satisfies the differential equation

$$\dot{p} = \left(\beta X - \Gamma - r(t) + \alpha p\right)p$$

Note that $0 \le p \le 1$ and $X \le H$, so that for $H \le \delta$

$$\begin{aligned}\dot{p} &\le \left(\beta\delta - \Gamma - r(t) + \alpha\right)p\\ &\le \left(\beta\delta - \Gamma - a_{\min} + b + \alpha\right)p\\ &\le \left(\beta\delta - a_{\min} - \gamma\right)p\end{aligned}$$

Let $\delta > 0$ be chosen sufficiently small so that the following conditions hold:

1) $H_0 \ge \delta$

2) $\beta\delta - \gamma - a_{\min} = -\rho < 0$

3) $\hat{r} - \delta - s\delta = \hat{a} - b - \delta - s\delta > 0$

Such a choice of δ is always possible since $H_0 > 0, \gamma > 0$ and $\hat{r} > 0$. Now suppose H(t) is not bounded below. Then for all $0 < \varepsilon < \delta$ there exists $0 \le t_1 < t_2$ such that $H(t_1) = \delta$ and $H(t_2) = \varepsilon$ and $H(t) \le \delta$ for $t_1 \le t \le t_2$. We show that $H(t)$ is bounded below, by showing that for $\varepsilon > 0$ chosen sufficiently small the time $t_2 - t_1$ is large enough for the average $\hat{r}$ to dominate the dynamics of the differential equation.

Now for $t_1 \le t \le t_2$ we have

$$\dot{p} \le -\rho p \text{ so that } p(t) \le p(t_1)e^{-\rho(t-t_1)} \text{ for } t_1 \le t \le t_2$$

and the prevalence decays exponentially. Now $\dot{H} = (r(t) - sH - \alpha p)H \ge (r_{\min} - s\delta - \alpha)H$ for $t_1 \le t \le t_2$. If $r_{\min} - s\delta - \alpha \ge 0$ we have $H(t) \ge H(t_1) = \delta$ for $t_1 \le t \le t_2$, so that $H(t_2) \ge \delta$ which is a contradiction. Thus we have $r_{\min} - s\delta - \alpha = -\sigma < 0$. Then $H(t) \ge H(t_1)e^{-\sigma(t-t_1)}$ for $t_1 \le t \le t_2$ so $\varepsilon = H(t_2) \ge \delta e^{-\sigma(t_2 - t_1)}$. We deduce that $t_2 - t_1 \ge \dfrac{\log(\delta/\varepsilon)}{\sigma}$.

Now let us choose $T_0 > 0$ such that for $T \ge T_0$ we have the inequality

$\left| \dfrac{1}{T} \int_{t_1}^{t_1+T} (a(t) - b)\ dt - (\hat{a} - b) \right| < \delta$. This is by the uniform convergence hypothesis. Now let $\varepsilon < \delta$ be chosen so that $t_2 - t_1 \ge T_0$ and $(t_2 - t_1)(\hat{a} - b - \delta - s\delta) - \dfrac{\alpha}{\rho} > 0$. (This is possible since $\hat{a} - b - \delta - s\delta > 0$.)

Then $\dot{H} \ge (r(t) - sH - \alpha p)H \ge (r(t) - s\delta - \alpha p)H$ for $t_1 \le t \le t_2$ so that

$$
\begin{aligned}
\varepsilon = H(t_2) &\geq \delta e^{\int_{t_1}^{t_2} r(t) - s\delta - \alpha p dt} \\
&\geq \delta e^{(t_2 - t_1)(\hat{a} - b - \delta - s\delta) - \alpha \int_{t_1}^{t_2} p(t) dt} \\
&\geq \delta e^{(t_2 - t_1)(\hat{a} - b - \delta - s\delta) - \alpha \int_{t_1}^{t_2} p(t_1) e^{-\rho(t - t_2)} dt} \\
&\geq \delta e^{(t_2 - t_1)(\hat{a} - b - \delta - s\delta) - \alpha \frac{p(t_1)}{\rho}\left(1 - e^{-\rho(t_2 - t_1)}\right)} \\
&\geq \delta e^{(t_2 - t_1)(\hat{a} - b - \delta - s\delta) - \frac{\alpha}{\rho 0}} \\
&> \delta
\end{aligned}
$$

which is a contradiction. Thus $H(t) \geq \varepsilon$ and H is bounded below as claimed.

7. REFERENCES

Anderson, R.M. and May, R.M., *Parasite pathogenicity and the depression of host population equilibria*, Nature, **279**, 150-152 (1979)

Anderson, R.M. and May, R.M. (F.R.S.), *The Population Dynamics of Microparasites and their Invertebrate Hosts*, Philosophical Transactions of The Royal Society of London (1981)

Baxby, D.; Bennett, M and Getty, B., *Human cowpox: a review based on 54 cases, 1969-93*, British Journal of Dermatology, **131**, 598-607 (1994)

Begon, M.; Hazel, S.M.; Telfer, S; Bown, K.; Carslake, D.; Cavanagh, R.; Chantrey, J.; Jones, T.; and Bennett, M., *Rodents, cowpox virus and islands: densities, numbers and thresholds*, Journal of Animal Ecology, **72**, issue **2**, 343-355, (2003)

Feore, S.M.; Bennett, M.; Chantrey, J.; Jones, T.; Baxby, D.; and Begon, M., *The Effect of Cowpox Virus Infection on Fecundity in Bank Voles and Woodmice*, Proc. R Soc Lond B Biol Sci, **264**, Part 1387, 1457-61, (1997)

Finkenstadt, B.F. and Grenfell, B.T., *Time Series Modelling of Childhood Diseases: A Dynamical Systems Approach* Appl. Statist. **49**, Part 2, 187-205, (2000)

Gao, L.Q. and Hethcote, H.W., *Disease transmission models with density dependent demographics*, J. Math. Biology, **30**: 717-731 (1992)

Greenman, J.V.; Kamo, M. and Boots, M, *External Forcing of Ecological and Epidemiological Systems: A Resonance Approach*, Physica D, **190,** 136-151, (2004)

Hazel, S.M.; Baxby, D.; Bennett, M.; Bown, K.; Cavanagh, R.; Chantrey, J.; Jones, T.R. and Begon, M., *A longitudinal study of endemic disease in its wildlife reservoir: cowpox and wild rodents*, Epidemiology and Infection, **124**, 551-562, (2000)

Ireland, J.M.; Norman, R.A. and Greenman, J.V., *The effect of seasonal birth rates on population dynamics: A resonance approach*, Journal of Theoretical Biology, **231,** 229-238 (2004)

Ireland, J.M., *Using mathematical models to determine the effect of seasonal host birth rates on population dynamics of infectious disease systems,* PhD thesis, Stirling University, 2004.

Jedrzejewska, B. and Jedrzejewski, W., *Predation in Vertebrate Communities: the Bialowieza primeval forest as a case study*, Ecological Studies **135**, 450 Springer Verlag (1998)

Keeling, M.J.; Rohani, P. and Grenfell, B.T., *Seasonally Forced Disease Dynamics Explored As Switching Between Attractors,* Physica D, 148, 317-335, (2001)

Norman, R.A.; Begon, M.; and Bowers, R.G., *The population dynamics of microparasites and vertebrate hosts: the importance of recovery and immunity*, Theoretical Population Biology, **46**, 96-119, (1994).

Norman, R.A., *Ecological Models of Microparasitic Diseases Shared by Vertebrate Hosts*, PhD. Thesis, University of Liverpool, (1995)

Roberts, M.G. and Kao, R.R., *The dynamics of an infectious disease in a population with birth pulses*, Mathematical Biosciences **149**: 23-36 (1998)

Sandvik, T.; Tryland, M.; Hansen, H.; Mehl, R.; Moens, U.; Olsvik, O.; and Traavik, T., *Natuarally occurring Orthopoxviruses: Potential for recombination with vaccine vectors*, Journal of Clinical Microbiology, **36**, No **9**, 2542-2547, (1998)

Sauvage, F.; Langlais, M.; Yoccoz, N.G., Pontier, D., *Modelling hantavirus in fluctuating populations of bank voles: the role of indirect transmission on virus persistence*, Journal of Animal Ecology, **72**, No **1**, 1 (2003)

White, K.A.J.; Grenfell, B.T.; Hendry, R.J.; Lejeune, O. and Murray, J.D., *Effect of Seasonal Host Reproduction on Host-Macroparasite*, Mathematical Biosciences, **137**:

79-99 (1996)

White, P.J.; Norman, R.A.; Trout, C.R.; Gould, E.A. and Hudson, P.J., *The Emergence of Rabbit Haemorrhagic Disease Virus: Will a Non-Pathogenic Strain Protect the UK?*, Phil. Trans. R. Soc. Lond. B **356**: 1087-1095 (2001)

Williams, B.G. and Dye, C., *Infectious Disease Persistence When Transmission Varies Seasonally*, Mathematical Biosciences **145**:77-88 (1997)

Yoccoz, N.G., Stenseth, N.C., Henttonen, H., Effects of food addition on the seasonal density dependent structure of bank vole Clethrionomys Glareolus populations, Journal of Animal Ecology., **70 (5),** 713-720 (2001)

Zhou, J. and Hethcote, H.W., *Population size dependent incidence in models for diseases without immunity*, J. Math. Biology, **32**: 809-834 (1994)

WWW1: http://212.187.155.84/wnv/Subdirectories_for_Search/SpeciesKingdoms/0Families_ACrM_Rodentia/muridae/Clethrionomys/Clethrionomys_glareolus/Clethrionomys_glareolus.html#Newly_hatched

WWW2: http://pnwsteep.wsu.edu/DirectSeed/conf2k1/dsclprocwitmer.htm

8. LIST OF FIGURE CAPTIONS AND TABLES

Figure 1: Diagram illustrating $(s\,\Gamma + b\,(\beta - s)) / (a(t)\,(\beta - s))$ versus time for $\alpha = 1$. $a_0 = 0.5$, $a_1 = 0.5$, $b = 0.1$, $\gamma = 0.4$, $\beta = 0.05$, $s = 0.01$, $X_0 = 200$, and $Y_0 = 20$

Figure 2: Diagram of infected hosts against time with $\alpha = 1$, $a_0 = 0.5$, $a_1 = 0.5$, $b = 0.1$, $\gamma = 0.4$, $\beta = 0.05$, $s = 0.01$, $X(0) = 200$, $Y(0) = 20$ and $Z(0) = 0$, where $X(0)$, $Y(0)$ and $Z(0)$ are the initial values of X, Y and Z.

Figure 3: Graph of (a) susceptibles vs time for model of Cowpox in bank voles with Parameter values as in Table 2 and $a_1 = 0.3$

(b) infecteds vs time for model of Cowpox in bank voles with parameter values as in Table 2 and $a_1 = 0.3$

(c) total population vs time

Figure 4: Diagram of (a) infecteds vs time for model of Rabbit Haemorrhagic Disease with parameter values $a_0 = 0.02$; $b = 0.01$; $\alpha = 0.475$; $\gamma = 0.025$; $\beta = 0.936$; $s = 0.0001$ and $a_1 = 0$ per day

(b) host population when $a_1=0$

Figure 5: Graph of (a) infecteds vs time for model of Rabbit Haemorrhagic Disease with parameter values taken from Figure 4 and $a_1 = 0.5$

(b) host population when $a_1= 0.5$

Figure 6: Graph of α - β parameter space for the SIR model with self-regulation, with other parameters as for RHD (see legend for Fig 4), showing rates of parameters of which the eigenvalues of the Jacobian are real and we have monotonic approach to equilibrium and rates of parameters for which we have complex eigenvalues and decaying oscillations towards equilibrium.

Table 1: Definition of parameters

Table 2: Parameter values for cowpox in bank vole populations

Table 3: Parameter values for rabbit haemorrhagic disease

Figure 1:

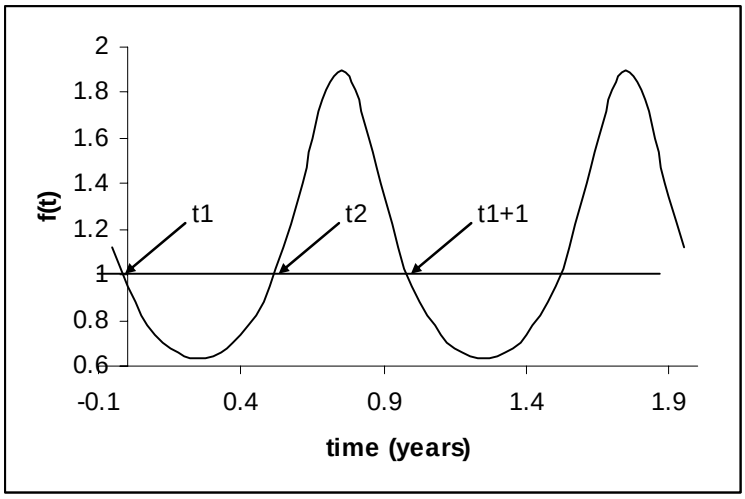


Figure 2:

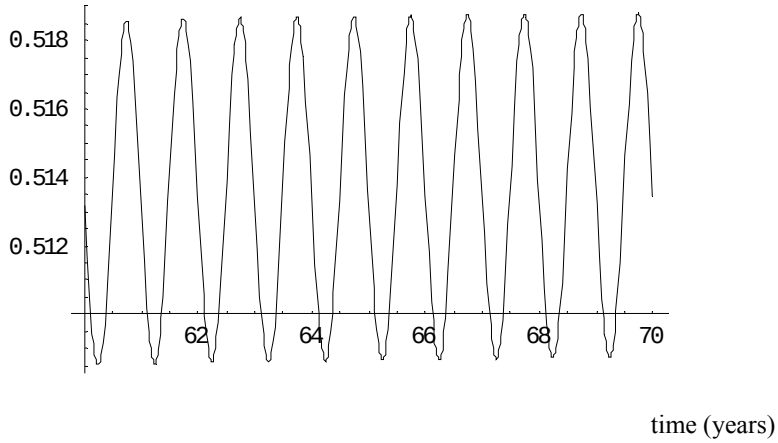


Figure 3:

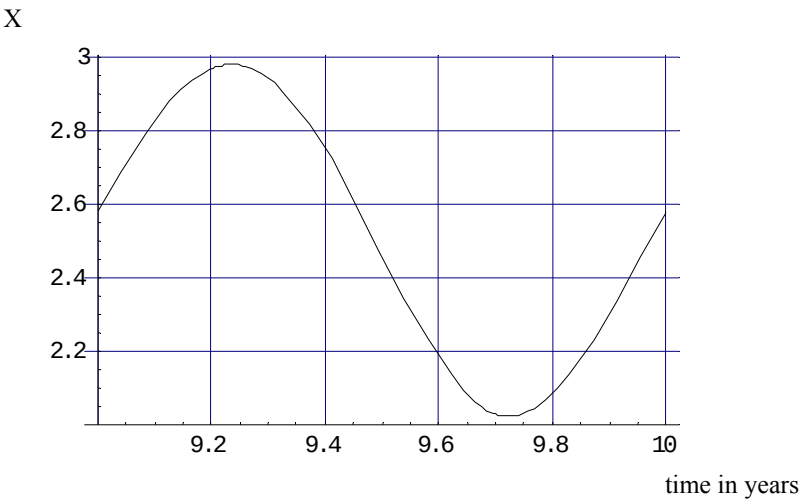


Figure a:

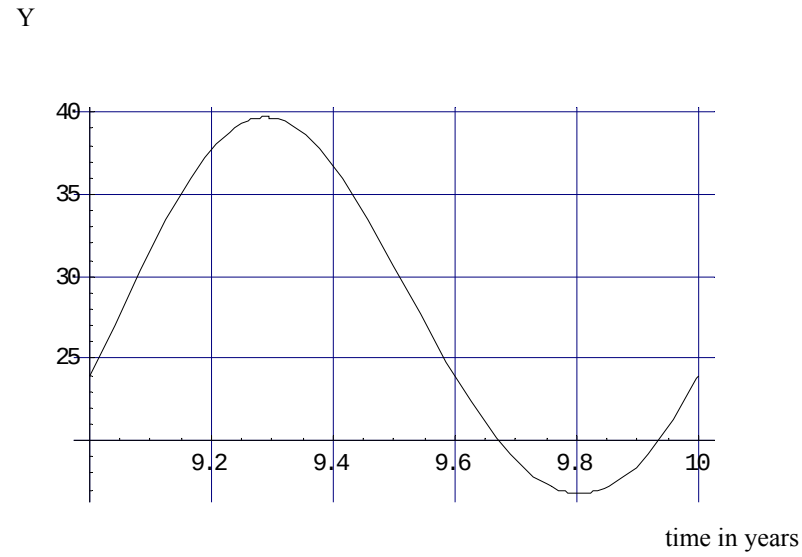


Figure b:

H

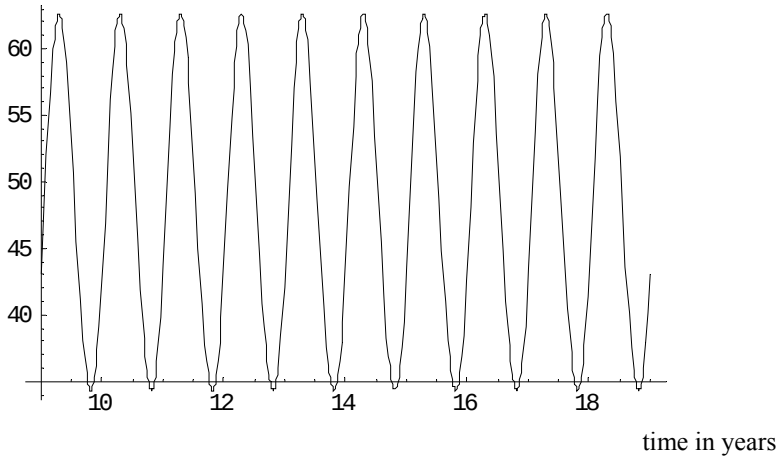
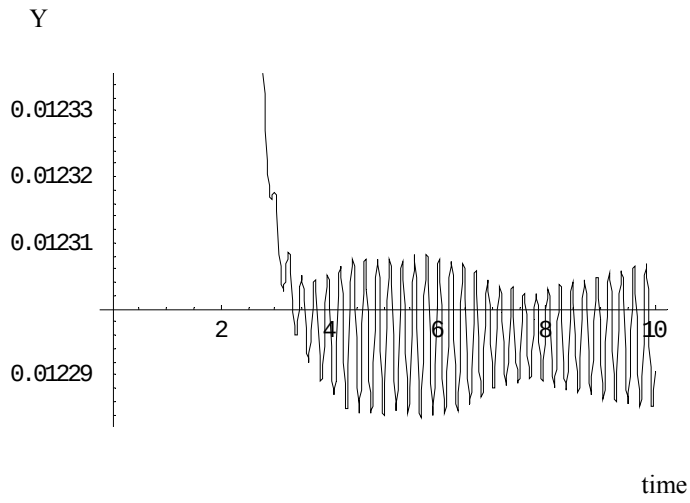


Figure c:

Figure 4:



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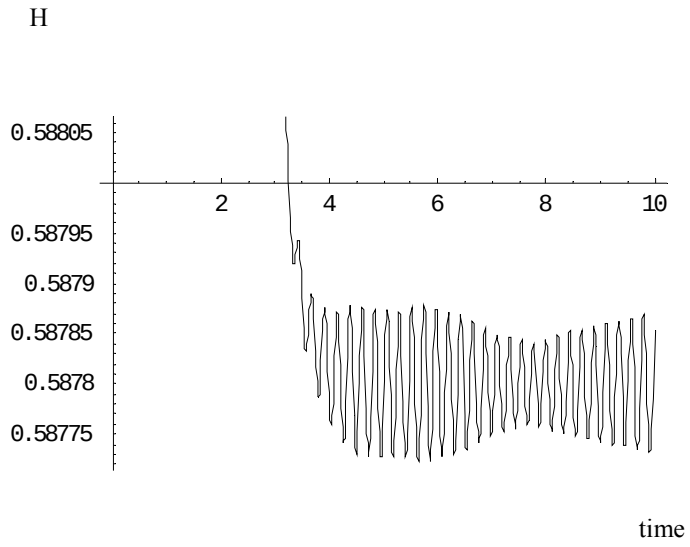
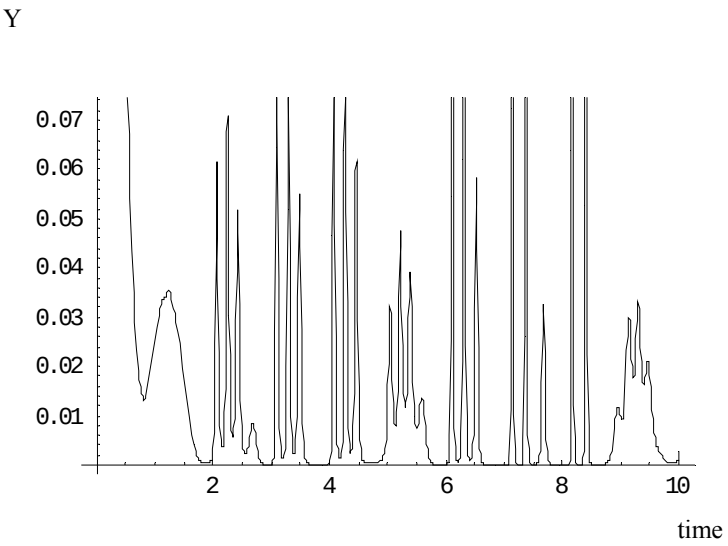


Figure b:

Figure 5:



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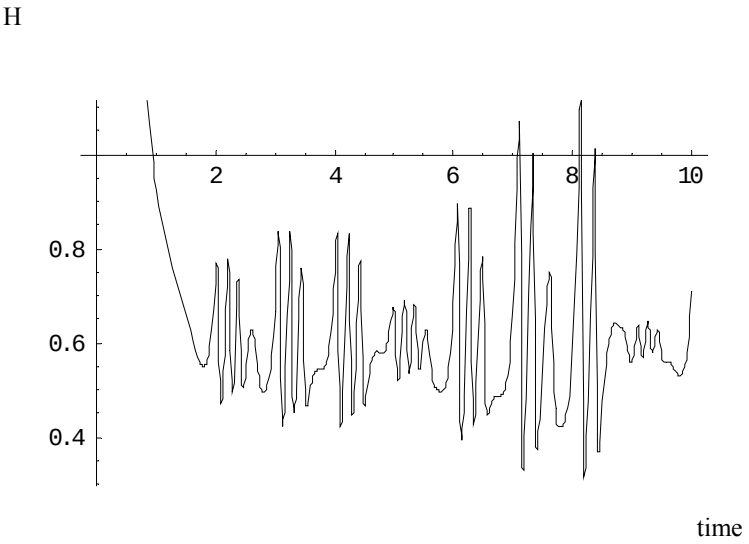

Figure b:

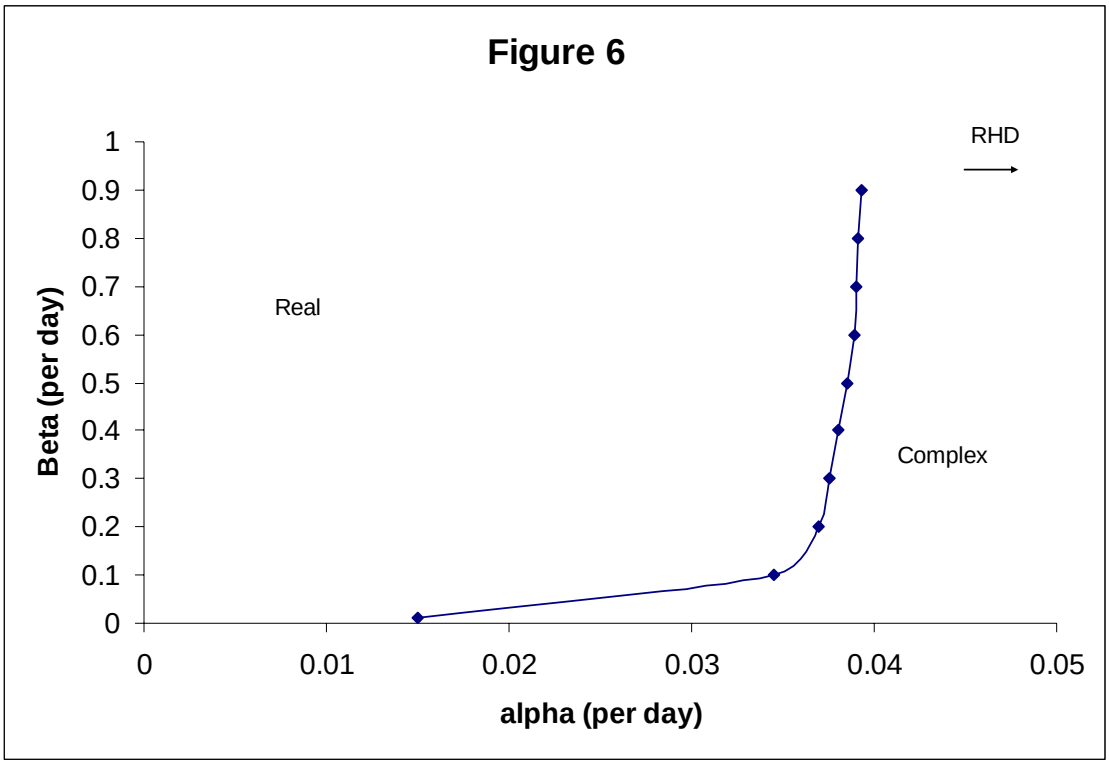
Figure 6
RHD
Real
Complex
Beta (per day)
alpha (per day)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.01
0.02
0.03
0.04
0.05

Table 1:

Symbol	*Meaning*	*Units*
a	per capita seasonal birth rate	time $^{-1}$
b	per capita natural death rate	time $^{-1}$
α	per capita death rate due to the disease	time $^{-1}$
β	transmission parameter	density $^{-1}$ time $^{-1}$
s	density dependent parameter	density $^{-1}$
γ	per capita rate of recovery from the disease	time $^{-1}$
r	per capita population growth rate, a-b	time $^{-1}$
Γ	$\alpha + b + \gamma$	

Table 2:

Parameter	*Value(daily)*	*Value (yearly)*	*Source*
a_0	20/365	20	Feore, 1997
b	1/548	0.666	WWW 1
α	0	0	Approx - from Feore, 1997
β	0.036	13.14	Begon, 1998
s	0.0011	0.4015	Approx since K varies from 10-100 per ha, WWW 2
γ	1/28	13.0357	Begon, 1998

Table 3:

Parameter	*Value(daily)*	*Value (yearly)*	*Source*
a_0	0.02	7.3	White et al, 2001
b	0.01	3.65	White et al, 2001
α	0.475	173.375	White et al, 2001
β	0.936	341.64	White et al, 2001
s	0.0001	0.0365	White et al, 2001
γ	0.025	9.125	White et al, 2001