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Steady state analysis of a continuum model for super-infection.

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Abstract A large system of N strains of parasite and a single host is analyzed as a function of the degree of virulence in the strains when there is super-infection (more virulent strains can infect hosts that are already infected). When a small amount of local mutation is allowed, steady state solutions converge to a continuous distribution as the number of strains increases. The resulting nonlinear-nonautonomous integro-differential equatoon is reduced to a fourth order boundary value problem and the existence of positive solutions is proven.

Keywords Superinfection · virulence · boundary value problem

1 Introduction.

In a series of papers Nowak and his collaborators [6, 7, 1, 4, 9] explored the question of how it is possible for virulent parasites to evolve. Intuitively, if a parasite is to become successful, it should attenuate the severity of the infection in order to maximize the time in which others can be infected. The key idea that these theorists develop is *superinfection* through which it is meant that a more virulent strain can take over a host infected by a less virulent strain. Two factors are important in determining the success of a parasite: the rate at which it can infect the host and the rate at which the host is removed from the general population (called the virulence). The former helps the spread of the infection while the latter impedes it. One of the key observations made by Nowak et al is that the rate of infection and the virulence covary. Nowak et al develop a large system of coupled ordinary differential equations (ODEs) (summarized and reviewed in [8]) and by making some simplifying assumptions on the dependence of the rate of infection on the virulence they simplify their general model and from this reduce the study of equilibria to a Lotka-Volterra equation. In this paper, we take a different approach. We first explore simulations as the number of strains increases. From observations of these simulations, we develop a continuum model for superinfection based on the discrete models. Simulation of the continuum equations shows the convergence to a steady state which satisfies a nonlinear integral equation. We convert the integral equation to a system of nonlinear differential equations and arrive at a four-dimensional non-autonomous boundary value problem (BVP). We numerically solve this, showing how solutions change with the parameters. The main part of the paper consists of an existence proof for solutions to the BVP. In section 2, we discuss the Nowak et al model for superinfection and show some simulations for large numbers of strains and use this to develop the continnum model. We reduce the steady states to

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a boundary value problem for which we show some different numerical solutions. In section 3, we prove the existence result.

2 Superinfection.

Here, we briefly review the ideas behind superinfection. Consider the standard model for infection [3]:

$$\frac{dx}{dt} = k - ux - \beta xy$$
$$\frac{dy}{dt} = y(\beta x - u - v).$$

Here x is the host and y is the parasite. The host (or susceptible) population has a constant death rate u and a constant immigration rate k. The parasite (or infected) population has an additional death rate v which characterizes the virulence of the infection. β determines how easily the parasite infects the host. Starting from an uninfected population, $(x, y) = (k/u, 0)$, the parasite can take hold in the population if dy/dt is positive for small values of y, that is, $(\beta k/u - u - v) > 0$. This last expression is often written as

$$R := \frac{\beta}{u+v}\frac{k}{u} > 1.$$

The parameter R is called the basic reproductive ratio. If there are two strains of parasite, say, y_1, y_2 with respective reproductive ratios, R_1, R_2, then no coexistence is possible and the strain with the highest R wins.

In order to allow for coexistence, which is seen in nature, Nowak and May [6] introduce a parameter s which allows for the more virulent strain to invade a less virulent one. Let v_i denote the virulence of strain i with $v_1 < v_2 \ldots < v_n$ and let β_i be the infectivity of strain i. Then Nowak and May propose:

$$\frac{dx}{dt} = k - ux - x\sum_{j=1}^{n}\beta_j y_j$$
$$\frac{dy_i}{dt} = y_i(\beta_i x - u - v_i + s\beta_i\sum_{j=1}^{i-1} y_j - s\sum_{j=i+1}^{n}\beta_j y_j). \tag{1}$$

The parameter s determines the degree of superinfection possible. Nowak and May suggest that $\beta_i = b(v_i)$ where $b(v)$ is a monotonically increasing function of v. The virulence values, v_i are taken from a distribution, in their model, the distribution is uniform on the interval, $v_{min} < v < v_{max}$. Unless otherwise noted, we take $v_{min} = 0$ and $v_{max} = A = 5$ in our simulations. In their simulations, they take $b(v) = cv/(d + v)$ with $c = 8, d = 1$. To analyze the discrete equations, they replace the equation for x with one in which the immigration of uninfected hosts exactly balances the infection. This means that the sum $x + \sum_i y_i$ is constant. Additionally, they consider the limit as $d \to 0$ in $b(v)$ so that all the parasites have the same degree of infectivity. Under these conditions, the equations reduce to a large set of Lotka-Volterra equations for which there are a number of methods of analysis. They show that the steady states for this tend to a particular form and then find them. In a later paper we will relax these assumptions and prove a result about convergence of the initial value problem to steady states (Chen et al, in preparation).

Figure 1A shows a simulation of the discrete model (1) after a very long transient for three values of N, the number of strains of the parasite. In order that the steady state of x (the remaining hosts) tend to the same value as N changes, we multiply the sums in the equations by a constant, $\Delta := (v_{max} - v_{min})/N$. (This is equivalent to rescaling y_i. Indeed, let $y_i = \Delta Y_i$ and Y_i satisfies (1) with the sums multiplied by Δ.) This figure indicates that the steady state does not seem to approach a smooth limiting distribution for the infected hosts; instead there seem to be "numerical instabilities" with the steady state flipping between two curves. The general shape of the distribution shows something resembling a smooth envelope,

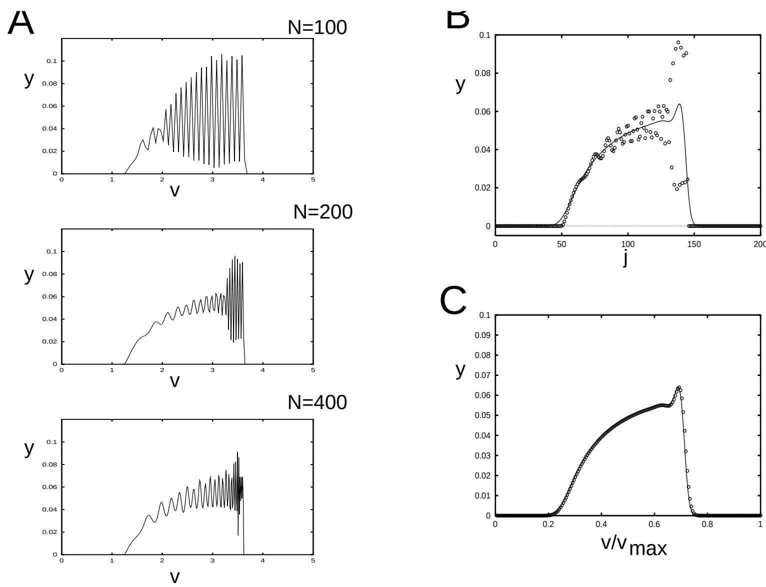

Fig. 1 (A) Steady states, y_i for the scaled model with $s = 1$, $0 < v < 5$ and $b(v) = 8v/(v + 1)$ for three values of N. The solutions do not appear to be tending to a smooth solution. (B) Addition of a small "mutation" in the form of diffusion with $\mu = 0.0001$ leads to convergence to a smooth steady state, shown here for $N = 200$. The smooth solution is close to the diffusion-free steady state. (C) Comparison of the solution to the discrete problem for $N = 200$ and the solution to the boundary value problem.

with no infected hosts below a critical value and then a gradual rise with a sharp fall off. Nowak and May find similar behavior for a fixed $N = 50$ and varying values of s.

In order to regularize the steady state shape, we introduce a small change in their model. We allow for the parasites to spontaneous mutate to their nearest neighbors while infecting the host. That is, we allow for spontaneous transitions from y_j to y_{j+1}, y_{j-1}. While it is unknown to us whether such mutations occur in reality, this small change does not affect the qualitative picture and regularizes the stationary state. Figure 1B shows an example with $N = 200$ and a mutation rate of μ/Δ^2 with $\mu = 0.0001$. We note that even smaller values still regularize the steady state solutions, as do larger values. The figure shows that the steady state distribution still has the same essential features: a gradual increase and an abrupt decline in the density of parasitized hosts plotted against the virulence.

With this scaling, the steady state equations are

$$0 = k - ux - \sum_{i=1}^{n} b(v_i) y_i \Delta$$

$$0 = \mu \frac{y_{i+1} - 2y_i + y_{i-1}}{\Delta^2} + y_i(b(v_i)x - u - v_i + sb(v_i)i \sum_{j=1}^{i-1} y_j \Delta - s \sum_{j=i+1}^{n} b(v_j) y_j \Delta).$$

We let $y_i = y(v_i)$ and proceed to the continuum limit as $N \to \infty$ to obtain the following nonlinear integro-differential equation:

$$0 = k - ux - x \int_0^A b(v) y(v)\ dv \quad (2)$$

$$0 = \mu \frac{d^2 y(v)}{dv^2} + y(v)(b(v)x - u - v + sb(v) \int_0^v y(v')\ dv' - s \int_v^A b(v') y(v')\ dv'). \quad (3)$$

In addition, we have the boundary conditions

$$dy(v)/dv = 0$$

at $v = 0, A$. Here, we have assumed that the virulence is uniformly distributed in the interval $[0, A]$. This is not necessary, but simplifies the resulting analysis. This integro-differential equation can be converted to a pure differential equation by making the following definitions:

$$\begin{aligned} z(v) &:= \int_v^A b(v')y(v')\ dv' \\ w(v) &:= \int_0^v y(v')\ dv'. \end{aligned}$$

With this change of variables, we obtain the boundary value problem:

$$\begin{aligned} \mu^2 y''(v) &= y(v)(u + v - xb(v) + sz(v) - sw(v)b(v)) \\ z'(v) &= -b(v)y(v) \\ w'(v) &= y(v) \end{aligned}$$

subject to the following boundary conditions

$$\begin{aligned} y'(0) &= 0 \\ y'(A) &= 0 \\ z(A) &= 0 \\ w(0) &= 0 \\ x &= \frac{k}{u + z(0)}. \end{aligned}$$

With this boundary value problem (BVP), we are in a position to study steady states as various parameters vary such as the maximum virulence or the amount of superinfectivity, s. Figure 1C shows the solution to the BVP for $s = 1, v_{max} = A = 5, \mu = 0.0001$ along with the steady state for the discrete model with $N = 200$. The agreement is almost exact. Let us first suppose there is no superinfection. The maximum value of $vb(v)$ (recall this is related to the basic reproductive rate) occurs at $v = c$ which for this paper is $c = 1$. Thus in absence of mutation ($\mu = 0$) and superinfection, the steady state solution to the discrete model has $y_j = 0$ except for the j corresponding to $v = 1$. With diffusion, this maximum is smoothed out. Figure 2B shows that for $v_{max} := A = 1$ and small mutation (in this and all remaining figures, $\mu = 0.0001$), the steady-state density $y(v)$ is monotonic. However, if v_{max} increases, then there is an interior maximum centered around $v = 1$ as can be seen in the rest of the curves in figure 2B. (Note the horizontal axis is scaled to 1 for the BVP.) The fraction of the population remaining uninfected remains essentially constant independent of the maximum virulence as seen in figure 2A.

Figure 3A, in contrast, shows that the uninfected population actually increases with superinfection, s. Furthermore, as s increases, the nice Gaussian peak around $v = 1$ becomes skewed toward greater virulence with a maximum moving toward the right. The small "bump" on the density for $s = 0.5, 1$ disappears with larger μ and the density has just a single maximum.

The remainder of this paper is devoted to the analysis of the BVP. We prove that there exists a solution for any reasonable values of the parameters.

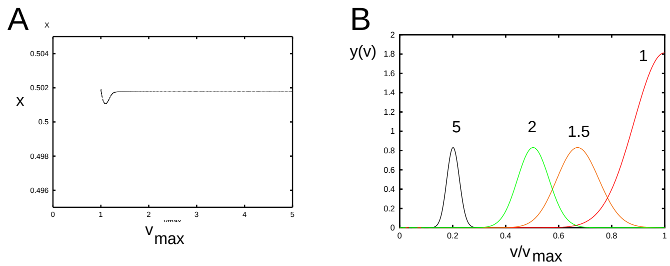

Fig. 2 Solutions to the BVP as v_{max} varies. (A) X, the fraction of uninfected population, remains essentially constant independent of the maximum virulence with no superinfection ($s = 0$) (B) Steady state densities for $s = 0$ at several values of v_{max} with $\mu = 0.0001$.

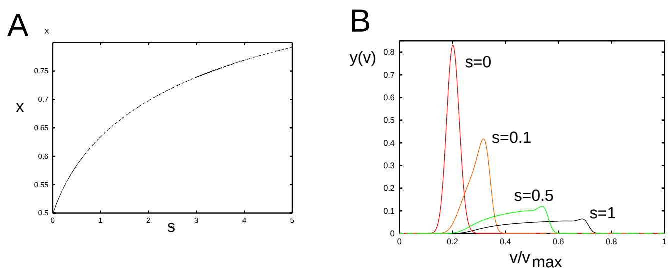

Fig. 3 Solutions to the BVP as s varies for $v_{max} = 5$. (A) Uninfected population increases with superinfection. (B) Infected distribution for several values of s.

3 Existence proof.

We consider the boundary value problem

$$\mu^2 y'' = (1 + v + sz - xb(v) - swb(v))\, y \tag{4}$$

$$z' = -b(v)\, y \tag{5}$$

$$w' = y \tag{6}$$

$$y'(0) = 0, w(0) = 0 \tag{7}$$

$$y'(A) = 0, z(A) = 0, x = \frac{1}{1 + z(0)} \tag{8}$$

where y, z, w are functions of v on $0 \le v \le A$ and

$$b(v) = \frac{cv}{1 + v}$$

for some $c > 0$. We look for a solution (x, y, z, w) with $y > 0$ on $[0, A]$.

First we consider the case $s = 0$:

$$\mu^2 y'' = (1 + v - xb(v))\, y \tag{9}$$

$$z' = -b(v)\, y \tag{10}$$

$$x = \frac{1}{1 + z(0)} \tag{11}$$

$$y'(0) = y'(A) = 0 \tag{12}$$

$$z(A) = 0. \tag{13}$$

We prove:

Theorem 1 *Choose c so large that the unique solution to*

$$\mu^2 y'' = (1 + v - b(v))\, y$$
$$y(0) = 1, y'(0) = 0$$

satisfies $y(v) < 0$ for some $v \in (0, A)$. Then the problem $(9) - (13)$ has a solution with $y > 0$ on $[0, A]$.

Remark 1 The existence of such an c can be shown by a polar coordinate transformation $y = r\cos\theta, y' = r\sin\theta$, as in [Coddington and Levinson, chapter 8]. There is a $c_0 > 0$ such that the hypotheses of the Theorem are satisfied by any $c > c_0$. Alternatively, we can fix c and A so that $b(v) > 1 + v$ for some $v \in [0, A]$ and then choose μ sufficiently small.

Proof Suppose that $x \in (0, 1)$, and y is positive on $[0, A]$ and satisfies (9) and (12). Let $z_0 = \frac{1-x}{x}$ and choose $k > 0$ so that

$$\int_0^A b(v)\, ky(v)\, dv = z_0.$$

Setting $z(v) = z_0 - \int_0^v b(s)\, ky(s)\, ds$ gives a solution (x, ky, z) to $(9) - (13)$.

To solve (9) and (12) for some $x \in (0, 1)$, consider for each x the initial value problem consisting of (9) and initial conditions

$$y(0) = 1, y'(0) = 0. \tag{14}$$

The hypothesis on c insures that if $x = 1$ then $y > 0$ on some maximal interval $[0, v_1)$, with $v_1 < A$ and $y(v_1) = 0, y'(v_1) < 0$. On the other hand, if x is sufficiently small, then $xb(v) < 1 + v$ for all $v \in [0, A]$, insuring that $y' > 0$ on $(0, A]$. In particular, $y'(A) > 0, y(A) > 0$.

Since, for $x = 1$, $y'(v_1) < 0$, the implicit function theorem insures that v_1 (defined by $y(v_1) = 0$) is a continuous function of x on some interval $1 - \varepsilon < x \leq 1$. Further, since a nontrivial solution of (9) cannot satisfy $y(v) = y'(v) = 0$ for any v, we must have $y > 0$ on $[0, v_1)$ and $y'(v_1) < 0$. Define $v_1(x)$ for all $x \in [0, 1]$ as follows: $v_1(x) = \inf\{v > 0 \mid y(v) = 0 \text{ or } v = A\}$. Then $v_1(x)$ is a continuous function of x, and $y'(v_1(0)) > 0, y'(v_1(1)) < 0$. Hence there is an $x_0 \in (0, 1)$ such that $y'(v_1(x_0)) = 0, y(v) > 0$ on $[0, v_1(x_0)]$. Therefore $v_1(x_0) = A$ and this proves the Theorem.

Remark 2 The value of x is easily seen to be unique. The theorem, while easy to prove, does not follow immediately from a standard result, in Coddington and Levinson, for instance, because $b(0) = 0$. However the main reason for presenting this proof is to give a simple example of the method we will use when $s > 0$.

We now consider $s > 0$. In this case, it is convenient to reverse direction in the independent variable of the problem, letting $t = A - v$, $y(v) = Y(t), z(v) = Z(t), w(v) = -P(t)$.

We then look for a solution (x, Y, Z, P), with $Y > 0$, for the following problem:

$$\mu^2 Y'' = (1 + A - t - xb(A - t) + s(Z + b(A - t)P))\, Y \tag{15}$$
$$Z' = b(A - t)\, Y \tag{16}$$
$$P' = Y \tag{17}$$
$$Y'(0) = 0, Z(0) = 0, \tag{18}$$
$$Y'(A) = 0, P(A) = 0 \tag{19}$$
$$x = \frac{1}{1 + Z(A)} \tag{20}$$

Consider also the linear initial value problem

$$\begin{aligned} \mu^2 Y'' &= (1 + A - t - b(A - t))\, Y \\ Y(0) &= 1, Y'(0) = 0. \end{aligned} \tag{21}$$

Theorem 2 *Choose c so large that the unique solution to (21) satisfies $Y(t) = 0$ for some $t \in (0, A)$. Then the problem $(15) - (20)$ has a solution with $Y > 0$ on $[0, A]$.*

Remark 3 The choice of c in Theorem 2 differs, in general, from the c chosen in Theorem 1, even when s is very small. This is because of the reverse in direction. This may give the impression that the solution found does not tend to that of Theorem 1 as $s \to 0$. However this neglects the possibility that for small s, xc may be close to its value when $s = 0$.

More generally, this also raises the question of whether the solutions to $(4) - (8)$ vary continuously with s. While this seems likely from numerical results, we have not proved it, mainly because we cannot prove the uniqueness of the solution for a given s.

Proof The reason for reversing direction in the problem is that $(15) - (18)$ has an important monotonicity property.

Lemma 1 *For given $x \in [0, 1]$, consider the solution (Y, Z, P) of $(15) - (18)$ with further initial conditions $Y(0) = Y_0 > 0, P(0) = P_0$. Then Y, Z and P are each monotone increasing functions of Y_0 and of P_0 as long as $Y > 0$. That is, if $Y_0^1 \geq Y_0^2$ and $P_0^1 \geq P_0^2$, with $\left(Y_0^1, P_0^1\right) \neq \left(Y_0^1, P_0^2\right)$, and $Y^2 > 0$ on some interval $[0, T]$, then $Y^1 > Y^2, Z^1 > Z^2$, and $P^1 > P^2$ on $(0, T]$. Further, as long as $Y > 0$, Y' is an increasing function of Y_0 and of P_0 at any point where $Y' \geq 0$, in the following sense: If $Y_0^1 \geq Y_0^2$ and $P_0^1 \geq P_0^2$, with $\left(Y_0^1, P_0^1\right) \neq \left(Y_0^1, P_0^2\right)$, and if for some $t_1 \in (0, A)$, $Y^2 > 0$ on $[0, t_1]$ and $Y^{1\prime}(t_1) \geq 0$, then $Y^{1\prime}(t_1) > Y^{2\prime}(t_1)$. (It is not required that $Y^{1\prime} \geq 0$ on $[0, t_1]$.)*

Proof Let $\rho = \frac{Y'}{Y}$ and

$$r(t) = 1 + A - t - xb(A - t) + s(Z + b(A - t)\, P)$$

Then $r(t)$ is an increasing function of Z and P for $0 \leq t < A$, and

$$\begin{aligned} \rho' &= \frac{r(t)}{\mu^2} - \rho^2 \\ \rho(0) &= 0. \end{aligned} \tag{22}$$

Suppose that $\left(Y^1, Z^1, P^1\right)$ and $\left(Y^2, Z^2, P^2\right)$ satisfy $(15) - (18)$ with $Y^1(0) = Y_0^1 > Y^2(0) = Y_0^2 > 0$, $P^1(0) = P^2(0)$.

Then $\rho_1'(0) = \rho_2'(0)$ and

$$\mu^2 \rho_1''(0) = -1 + xb'(A) + 2sb(A)\, Y^1(0) - sb'(A)\, P^1(0) > \mu^2 \rho_2''(0).$$

Hence, $\rho_1 > \rho_2$ on some interval $(0, T)$. Since

$$Y(t) = Y_0 e^{\int_0^t \rho},$$

it is also clear that $Y^1 > Y^2$ on $(0, T]$. Also, $Z^1 > Z^2$ and $P^1 > P^2$ on $(0, T]$. If there is a first T in $(0, A)$ such that ρ_2 is bounded on $[0, T]$ and $\rho_1(T) = \rho_2(T)$, then $\rho_1'(T) \leq \rho_2'(T)$, but this contradicts (22). This proves monotonicity of Y, Z, and P. For the statement about monotonicity of Y' we use the monotonicity of ρ and Y and the relation $Y' = \rho Y$. A similar argument holds if $P_0^1 > P_0^2$, completing the proof.

We will also need to consider a family of linear initial value problems. For each $x \in [0,1]$ and $P_0 \leq 0$, consider the problem

$$\begin{gathered} \mu^2 U'' = (1 + A - t - xb(A-t) + sb(A-t)P_0)U \\ U(0) = 1, U'(0) = 0 \end{gathered} \tag{23}$$

Lemma 2 *As long as $U > 0$, U is a monotone decreasing functions of x, for each given P_0, in the same sense as in the statement of Lemma 1 . In addition, as long as $U > 0$, U' is also monotone decreasing in x at each point where $U' \geq 0$, again in the same sense as in lemma 1 . Finally, in a similar way, U is monotone increasing in P_0 for each $x \in [0,1]$, as long as $U > 0$.*

Proof We see that if $x_1 > x_2$, then $U_1''(0) < U_2''(0)$, so $U_1' < U_2'$ and $U_1 < U_2$ on some interval $(0,T)$. Letting $\sigma_i = \frac{U_i'}{U_i}$, we also see that $\sigma_1'(0) < \sigma_2'(0)$ and therefore we can choose T so that $\sigma_1 < \sigma_2$ on $(0,T)$. From here the proof is almost the same as the proof of Lemma 1.

We now define, for each $P_0 \leq 0$, a minimum value of x to be considered, setting

$$\bar{x}(P_0) = \sup \left\{ x \in [0,1] \mid x = 0, \text{ or } U > 0 \text{ on } [0,A] \text{ and } U'(A) \geq 0 \right\}.$$

Note that if c is chosen as in the statement of Theorem 2, then $\bar{x}(0) \in (0,1)$. It is also easy to see that there is a $P_0^* < 0$ such that $0 < \bar{x}(P_0) < 1$ if $P_0^* < P_0 \leq 0$ but $\bar{x}(P_0) = 0$ if $P_0 \leq P_0^*$. Further, $\bar{x}(P_0)$ is continuous, and Lemma 2 implies that it is strictly increasing in P_0 in the interval $[P_0^*, 0]$.

Lemma 3 *If $P_0^* \leq P_0 \leq 0$ and $x = \bar{x}(P_0)$, then for the solution of (23), $U > 0$ on $[0,A]$ and $U'(A) = 0$.*

Proof If U becomes negative in $(0,A)$, or $U'(A) > 0$, then x can be increased by a small amount and still gives the same behavior. (Note that if $U(A) = 0$, and $U'(A) \geq 0$, then necessarily $U'(A) > 0$, and $U = 0$ somewhere in $(0,A)$.) This contradicts the definition of $\bar{x}(P_0)$ in the given range of P_0. Hence, $U'(A) = 0$ and $U > 0$ on $[0,A)$, implying that $U(A) > 0$.

From the definition of $\bar{x}(P_0)$ it is obvious that for $P_0 \leq 0$, if $\bar{x}(P_0) < x \leq 1$, then either U becomes negative or $U'(A) < 0$.

Our method from this point has three main steps:

1. Show that for each $P_0 \leq 0$ and each $x \in (\bar{x}(P_0), 1]$, there is a unique Y_0 such that if $Y(0) = Y_0$, $P(0) = P_0$, and (Y,Z,P) satisfies $(15)-(18)$, then $Y > 0$ on $[0,A]$ and $Y'(A) = 0$.

2. Show that for each $P_0 \leq 0$ there is an $x \in (\bar{x}(P_0), 1)$ such that the solution of $(15)-(18)$ with $Y(0)$ chosen as in step 1, satisfies

$$x = \frac{1}{1 + Z(A)}.$$

3. Show that there is a P_0 and a value of x chosen as in step 2 such that the corresponding solution also satisfies $P(A) = 0$.

The following result carries out step 1.

Lemma 4 *For each $P(0) = P_0 \leq 0$ and $x \in (\bar{x}(P_0), 1]$, there is a unique $Y_0 = Y_0(x, P_0)$ such that the solution to $(15)-(18)$ with $P(0) = P_0$ and $Y(0) = Y_0(x, P_0)$ satisfies $Y > 0$ on $[0,A]$ and $Y'(A) = 0$.*

Proof From the definition of $\bar{x}(P_0)$ it is seen that for the solution of (23), either U becomes negative or $U'(A) < 0$. Let $r_0(t) = 1 + A - t - xb(A - t) + sP_0$ and set

$$M = \max_{0 \le t \le A} r_0(t).$$

As before, set

$$\sigma = \frac{U'}{U}.$$

If $x \in (\bar{x}(P_0), 1]$, then either $\sigma()$ is continuous on $[0, A]$ and $\sigma(A) < 0$, or there is a $t \in (0, A)$ with $\sigma^2(t) > \frac{M}{\mu^2}$. We observe that for $(15) - (18)$, $\lim_{Y(0)\to 0} Y(t) = 0$ uniformly in $[0, A]$. It follows that $\lim_{Y(0)\to 0} Z(t) = \lim_{Y(0)\to 0} (P(t) - P_0) = 0$. With $\rho = \frac{Y'}{Y}$, it follows that for sufficiently small $Y(0)$, ρ must have the same behavior as σ, showing that either $Y = 0$ somewhere in $(0, A)$, or else $Y'(A) < 0$.

On the other hand, suppose that $Y(0) = Y_0$ is large. Then there is an interval $[0, T]$ in which $Y \ge \frac{1}{2} Y_0$. We can assume that $0 < T \le \frac{1}{2}$. Also,

$$\mu^2 Y''' = r'(t) Y + r(t) Y'$$

where

$$\begin{aligned} r(t) &= 1 + A - t - xb(A - t) + sZ + sb(A - t) P) \\ r'(t) &= -1 + xb'(A - t) + s\left(2b(A - t) Y - b'(A - t) P\right). \end{aligned}$$

Then

$$r(t) \ge -xb(A - t) + sb(A) P_0 \ge -2K$$

where K depends on $P_0, x,$ and b, but not on Y_0. We are taking $P_0, x,$ and b as fixed in this proof. Also, we can choose Y_0 so large that, for some $K_1 > 0$ independent of Y_0,

$$r'(t) \ge K_1 Y_0$$

on $[0, T]$. It follows that there is are numbers $L > 0$ and $\delta > 0$ such that if $Y_0 > L$, and $Y \ge \frac{1}{2} Y_0$ on $[0, T]$, then

$$Y''' \ge \delta Y_0^2 - 2K\left|Y'\right| \tag{24}$$

on $[0, T]$. Also,

$$\begin{gathered} Y'(0) = 0 \\ Y''(0) \ge -2KY_0 \end{gathered} \tag{25}$$

From these inequalities, taking note of the Y_0^2 term in (24), it is easy to show that for sufficiently large Y_0, $Y \ge \frac{1}{2} Y_0$ as long on $[0, A]$ as the solution exists, and if Y exists on $[0, A]$, then $Y'(A) > 0$. Further, if Y fails to exist on $[0, A]$, then this is because Y and Y' tend to infinity at some $t_1 \in (0, A]$.

We now define two subsets of the interval $0 < Y_0 < \infty$ as follows:

$$\Lambda_1 = \left\{Y_0 > 0 |\ Y(t) = 0 \text{ for some } t \in (0, A) \text{ or } Y > 0 \text{ on } (0, A) \text{ and } Y'(A) < 0\right\}$$

$$\Lambda_2 = \left\{\begin{array}{c} Y_0 > 0 |\ Y > 0 \text{ on } [0, A] \text{ and } Y'(A) > 0, \text{ or there is a } t_1 \in (0, A] \text{ such that} \\ Y > 0 \text{ on } [0, t_1) \text{ and } \lim_{t \to t_1^-} Y(t) = \infty \end{array}\right\}.$$

We have shown that each of these sets is nonempty. It is clear from their definitions that they are disjoint. Since we cannot have $Y(t) = Y'(t) = 0$ for some $t \in (0, A]$, Λ_1 is open.

To see that Λ_2 is open, we observe that if $Y > 0$ on $[0, A]$ and $Y'(A) > 0$, then these inequalities also hold for nearby Y_0. If, on the other hand, $\lim_{t \to t_1^+} Y(t) = \infty$, then $Z + bP$ must be unbounded. Because

$$Z(t) = \int_0^t b(A - s) Y(s)\, ds > b(A - t)(P(t) - P_0)$$

Z must be unbounded. Also, Z is increasing. Hence $Y'' > 0$ near t_1, and this also holds for nearby Y_0, from which the openness of Λ_2 follows.

Since the half line $Y_0 > 0$ is connected, it cannot be the union of Λ_1 and Λ_2. Hence there is a $Y_0(x, P_0)$ such that Y solves $(15) - (18)$ and $Y'(A) = 0$. The uniqueness of $Y_0(x, P_0)$ follows from Lemma 1.

From now on we will assume in $(15) - (18)$ that $Y(0)$ is chosen as in Lemma 4. The uniqueness of $Y_0(x, P_0)$ insures that it depends continuously on these variables.

Lemma 5 *If* $P_0^* \leq P_0 \leq 0$, *then* $\lim_{x \to \bar{x}(P_0)^+} Y_0(x, P_0) = 0$.

Proof Suppose instead that

$$\limsup_{x \to \bar{x}(P_0)^+} Y_0(x, P_0) = \eta > 0.$$

Consider the solution U_0 of

$$\begin{aligned} &\mu^2 U'' = (1 + A - t - \bar{x}(P_0) b(A - t) + sb(A - t) P_0) U \\ &U(0) = \eta, U'(0) = 0. \end{aligned}$$

By 3, $U_0'(A) = 0$. Consider the solution of $(15) - (18)$ with $x = \bar{x}(P_0), P(0) = P_0$, and $Y(0) = \eta$. We find that

$$Y'''(0) > U_0'''(0)$$

and it follows as in the proof of Lemma 1 that $Y'(A) > 0$. This contradicts the definition of $Y_0(x, P_0)$.

Corollary 1

$$\limsup_{x \to \bar{x}(P_0)^+} z(A) = 0.$$

Corollary 2 *For* $x - \bar{x}(P_0)$ *positive and sufficiently small,*

$$x < \frac{1}{1 + z(A)}.$$

On the other hand, if $x = 1$, then $x > \frac{1}{1+z(A)}$.

We now apply a topological result of McLeod and Serrin [5] This result implies that for any $\bar{P} < 0$ there is a continuum $\Gamma = \Gamma_{\bar{P}}$ contained in the (x, P_0) plane, in the region $\bar{P} \leq P_0 \leq 0, \bar{x}(P_0) < x < 1$ and connecting the horizontal lines $P_0 = 0$ and $P_0 = \bar{P}$, such that if $(x, P_0) \in \Gamma$, then $x = \frac{1}{1+z(A)}$.

Remark 4 It is easy to prove that such an x exists for each P_0. If we could prove for each P_0 that x is unique, we would not have to resort to the McLeod Serrin result. We have not been able to do so because we have not been able to prove a monotonicity of solutions of $(15) - (18)$ with respect to x, for fixed P_0 and choosing Y_0 as in Lemma 4.

From now on we assume that $\left|\bar{P}\right|$ is large and (x, P_0) is chosen in $\Gamma_{\bar{P}}$. Clearly if $P_0 = 0$ then $P(A) > 0$.

On the other hand, consider $P(A) = \bar{P}$. We can integrate the equations in $(15) - (18)$ to obtain

$$\mu^2 Y'(A) = P(A) - P_0 - AP_0 + \int_0^A P(s)\,ds - xZ(A) + sZ(A)P(A).$$

Since

$$xZ(A) = \frac{Z(A)}{1 + Z(A)} < 1,$$

and

$$\int_0^A P(s)\,ds > AP_0$$

we see that for sufficiently large $-P_0$, if $P(A) \geq 0$ then $Y'(A) > 0$, a contradiction. Hence for $\bar{P}$ sufficiently large (and negative), and $P_0 = \bar{P}$, $P(A) < 0$. It follows that for some $P_0 \in \left(0, \bar{P}\right)$ the solution of $(15)-(18)$ with $P(0) = P_0$ and with x and Y_0 chosen as above, all of the conditions $(15)-(20)$ are satisfied. This proves Theorem 2.

We end with a result about the qualitative behavior of the solutions found in Theorems 1 and 2.

Theorem 3 *For given c and μ, and sufficiently large A, the solutions found in the theorems above are non-monotonic.*

Proof The proof uses the Sturm oscillation theorem. We first note that the c in the statement of Theorem 2 (where $b(v) = \frac{cv}{1+v}$) can be chosen independently of A for large A. This is because in equation (21), for large A , in the interval $A - 2 \leq t \leq A - 1$,

$$b(A - t) = \frac{c(A - t)}{1 + A - t} \geq \frac{c}{3}.$$

Hence, in this interval,

$$1 + A - t - b(A - t) \leq 3 - \frac{c}{3}$$
$$\mu^2 Y'' + \left(\frac{c}{3} - 3 + f(t)\right) Y = 0$$

for some $f(t) \geq 0$. Hence for sufficiently large c, depending on μ but not A, and $A > 2$, the solution Y of (21) must have a zero in $[A - 2, A - 1]$. Thus we can fix c and let A increase and still satisfy the hypotheses of Theorem 2.

Now consider a solution (x, Y, Z, P) of $(15) - (20)$, with $Y > 0$ on $[0, A]$. Then

$$\mu^2 Y''(A) = (1 + sZ(A))\,Y(A) > 0.$$

Since $Y'(A) = 0$, it follows that $Y' < 0$ in some interval $(A - \varepsilon, A)$. Also,

$$Y'(0) = 0,$$
$$\mu^2 Y''(0) = (1 + A - xb(A) + sb(A)P(0))\,Y(0).$$

We show that Y is non-monotonic by showing that for large enough A, $Y''(0) > 0$, and hence $Y' > 0$ on some interval $(0, \varepsilon)$. We do this by showing that $P(0)$, while negative, is bounded independent of large A. We see from the proof of Theorem 2 that $P(0) \geq P_0^*$, where P_0^* is defined just before Lemma

2, in terms of the solution U of (23). P_0^* has the property that if $x = 0$ and $P(0) > P_0^*$, then $U > 0$ on $[0, A]$ and $U'(A) > 0$. Write the ode of (23) in the form

$$U'' + q(t)\,U = 0,$$

where

$$q(t) = \frac{1}{\mu^2}\left(t - A - 1 + xb(A-t) - sb(A-t)\,P_0\right)$$

With $x = 0$, in the interval $[A-1, A]$, $q(t) \geq \frac{1}{\mu^2}\left(-2 - sb(1)\,P_0\right)$, so if

$$-sb(1)\,P_0 \geq 2 + \pi^2\mu^2,$$

then the Sturm theorem says that U must vanish on $[A-1, A]$. This gives the required lower bound on P_0^*, independent of A, and so for sufficiently large A, $Y''(0) > 0$.

4 Discussion and conclusions.

We have studied a continuously varying virulence model for superinfection, motivated by work of Nowak and May. By adding a small amount of "mutation", we find that steady state solutions to the superinfection model converge, with suitable scaling, to a continuous integro-differential equations. We converted this to a boundary value problem and for a specific choice of the contact rate, $b(v)$, we are able to prove existence of the solutions. Furthermore Theorem 3 shows that if $v_{max} = A$ is large enough, there is an interior maximum in the steady state density of the infected population as seen in the numerics. It is clear from the proof that the particular choice of $b(v)$ is not that crucial. All we require is that it can be chosen sufficiently large so that certain inequalities hold (see theorem 1). The small mutation rate is necessary in order to get smooth steady states. In a related paper, (in preparation, with X. Chen), we study the $\mu = 0$ case as an initial value problem and characterize the approach to steady states.

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