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MODELLING THE ROLE OF OPPORTUNISTIC DISEASES IN COINFECTION

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Abstract. In this paper, we formulate a model for evaluating the effects of an opportunistic disease affecting only those individuals already infected by a primary disease. The opportunistic disease act on a faster time scale and it is represented by an SIS epidemic model with frequency-dependent transmission. The primary disease is governed by an SIS epidemic model with density-dependent transmission, and we consider two different recovery cases. The first one assumes a constant recovery rate whereas the second one takes into account limited treatment resources by means of a saturating treatment rate. No demographics is included in these models.

Our results indicate that misunderstanding the role of the opportunistic disease may lead to wrong estimates of the overall potential amount of infected individuals. In the case of constant recovery rate, an expression measuring this discrepancy is derived, as well as conditions on the opportunistic disease imposing a coinfection endemic state on a primary disease otherwise tending to disappear. The case of saturating treatment rate adds the phenomenon of backward bifurcation, which fosters the presence of endemic coinfection and greater levels of infected individuals. Nevertheless, there are specific situations where increasing the opportunistic disease basic reproduction number helps to eradicate both diseases.

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1. Introduction

The importance of mathematical models in analyzing the spread and control of infectious diseases is now broadly recognized. The use of models should favor the clarification of the assumptions on variables and parameters, as well as provide conceptual results expressed in terms of thresholds such as the basic reproduction number.

In this work, we focus on a particular case of coinfection. In general, coinfection is understood to be the simultaneous infection of a host by multiple pathogen species. The incidence of coinfection among humans is huge [8] and supposed to be more common than single infection. It is important to know the effects, positive or negative, of pathogen species interactions within their host. From the point of view of human health the net effect of coinfection is found to be negative [13]. A broadly extended coinfection involves tuberculosis (TB) and HIV [20]. The World Health Organization [12, 29] reports that people living with HIV are around 30 times more likely to develop TB than persons without HIV and also that TB is the leading cause of death among

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people infected with HIV. A mathematical modelling analysis of TB-HIV coinfection can be found in [25]. Other diseases that act synergetically with HIV are malaria [1, 24], helminthic infections [18] and sexually transmitted diseases [11]. Another example of extended coinfection is the association of pertussis, influenza and tuberculosis [16].

The coinfection case that we are treating in this work is provoked by two diseases, respectively called primary and opportunistic. An opportunistic disease is a disease that will most often make one sick given the opportunity of a damaged or weakened immune system by a primary disease like, for instance, AIDS. Only relatively few pathogen species cause disease in otherwise healthy individuals [4]. Those few are called primary pathogens and the diseases that they cause primary diseases. An opportunistic disease, on the other hand, would be almost irrelevant for an organism with a fully-functioning immune system. A healthy immune system is able to successfully fight off an opportunistic disease. Nevertheless, as a result of the predisposing effect of a primary disease, an opportunistic disease has the capacity of causing a serious damage. Some diseases, like tuberculosis, can occur in anyone, regardless of their immune status, but are much more likely to cause illness and complications in persons with a damaged/weakened immune systems.

The authors already treated the topic of coinfection by opportunistic diseases in [23]. In that work, the host population is affected by a primary disease, described by an SIS model with demographics; only individuals infected by the primary disease are susceptible of acquiring an opportunistic disease, represented by an SIS model with no demographics. Here, we simplify this framework, eliminating demographics, in order to focus on the diseases interactions.

The primary disease dynamics is represented by an SIS epidemic model with density-dependent transmission. Regarding recovery, we consider two different cases: constant recovery rate and saturated treatment/recovery rate. We assume that the primary disease has a long illness period so that an opportunistic disease could act on the primary infected individuals. In its turn, the opportunistic disease rapidly takes advantage of the compromised immune system. As a simplified approximation of a general case of coinfection, we suppose that the primary disease is a long-term infection that evolves slowly compared to the opportunistic disease, which has a rapid evolution and, thus, can be considered a short-term infection. The density-dependent transmission is generally based upon the assumption that the rate of contact increases directly with the density of the population, whereas a constant rate of contact irrespective of the density of the population is associated to the frequency-dependent transmission [5]. Therefore, the rapid evolution of the opportunistic disease seems to be more appropriately described by an SIS epidemic model with frequency-dependent transmission, considering that in the short-term the number of contacts must be bounded.

The basic model (constant recovery rate) presented as a simplification of the one studied in [23] puts together the main actors in the epidemic process. Its extension (saturated treatment/recovery rate) introduces the important issue of the limited capacity for the treatment of a disease. This issue has been treated in different forms in the literature [9, 17, 21, 27, 28, 30–33]. We propose here a recovery term of the form of a saturated treatment rate. We include in it both the natural recovery rate and the treatment rate as proposed in [22] where it is called treatment/recovery rate. To be precise, we assume that the per capita recovery rate α of the SIS epidemic model associated to the primary disease is not constant, but decreasing with the number of infected individuals I: $\alpha(I) = \alpha/(1+\gamma I)$.

The proposed models have the form of a three dimensional system of ordinary differential equation. Its state variables correspond to the susceptible individuals, those affected by no disease, the infected individuals, affected by the primary disease and susceptible to the opportunistic disease, and coinfected individuals, affected by both diseases. Apart from distinguishing between transmissions, we reflect the different nature of both diseases by assuming that they act at different time scales. The fact that the system of differential equations includes two time scales has the advantage of allowing its complete qualitative analysis with the help of the appropriate reduction method [2, 3].

The analysis of the basic model reveals the net effect of the opportunistic disease on the overall epidemic process. In particular, the effect of the opportunistic disease on the number of infected

individuals by the primary disease can be explicitly and easily calculated. Also, an explicit expression of how the opportunistic disease reinforces the primary disease is obtained. A final insight is that any improvement in primary disease treatment can be ruled out by a strong enough opportunistic disease.

The common feature of epidemic models with saturated treatment rate is what it is known mathematically as backward bifurcation [14, 15]. It entails that even if the disease is being controlled in ways that reduce R_0 below 1 still it might become endemic if there exists a large enough number of infected individuals [6, 10]. The basic reproduction number does not give information on disease elimination; rather disease elimination is determined by the values of critical parameters at the turning points of the bifurcation curve. The study of backward bifurcation in epidemic models is important in order to find conditions for disease control [7, 19, 26].

The analysis of the model with saturated treatment rate shows that the influence of the opportunistic disease mostly enhances the endemic coinfection, though there are specific situations where increasing the basic reproduction number of the opportunistic disease yields diseases eradication. The possibility of the population to be invaded by both diseases is prevented exacerbating the effects of the opportunistic disease. A further increase of this reproduction number indefectibly leads to coinfection endemicity and at greater levels of coinfected individuals than in the constant recovery case.

This paper is organized as follows. In Section 3, we introduce the model that allows for the incorporation of both infections at different time scales, firstly assuming a constant recovery rate and secondly using a more general saturating treatment rate. Section 4 focuses on the asymptotic analysis of the models presented in Section 3, which always corresponds to an equilibrium point: disease-free state, opportunistic disease-free state or endemic coinfection state. Section 4 discusses the consequences of the results obtained in Section 4. The analysis of the basic SIS model with saturating treatment rate is included in Appendix A.

2. Model formulation

We consider a population affected by a primary disease whose individuals are then classified into susceptible and infected. A second opportunistic disease can be contracted only by those individuals already infected by the primary disease. This reflects the fact that the secondary opportunistic disease can only be successful on individuals whose immune system has been weakened by another infection. Thus, we need to distinguish a third class of coinfected individuals, those infected by both diseases. To formulate our model let $S(t)$, $I(t)$ and $C(t)$ be the number of susceptible, infected only by the primary disease, henceforth called infected, and coinfected individuals at time t, respectively. The basic assumptions are as follows:

i. The system of differential equations possesses two time scales: the slow one encompassing the primary disease evolution and the fast one associated with the opportunistic disease evolution. The parameter ε represents the ratio between the time scales.
ii. We consider no demographics.
iii. The opportunistic disease evolution is described by means of an SIS epidemic model with frequency-dependent transmission and constant recovery rate. Let β^{op} and α^{op} be, respectively, the constant transmission and recovery rates.
iv. The primary disease dynamics follows an SIS epidemic model with density-dependent transmission. Susceptible individuals can be infected, at different rates, by infected and coinfected individuals. Let β_I and β_C be the respective transmission coefficients.
We consider two different cases of recovery of the primary disease. The first one assumes a constant recovery rate α, and the second one takes into account limited treatment resources by means of a saturating treatment rate.

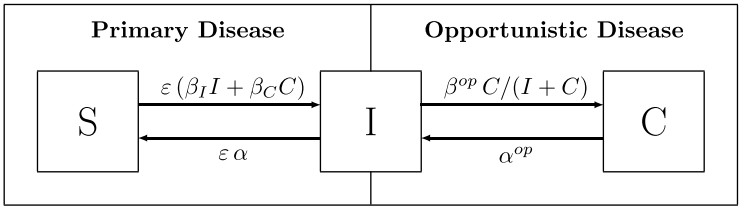


FIGURE 1. Flowchart of the coinfection model with constant recovery rate for the primary disease.

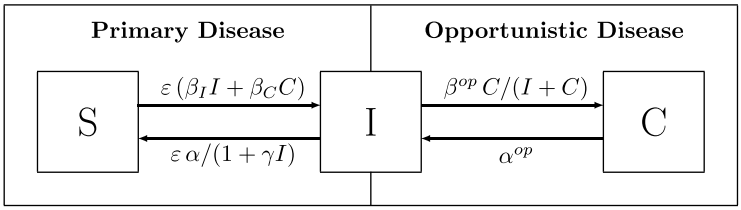


FIGURE 2. Flowchart of the coinfection model with saturating treatment rate for the primary disease.

2.1. Constant recovery rate

Under the above assumptions, summarized in Figure 1, the coinfection model with constant recovery rate takes the following form:

$$\begin{cases} S' = \varepsilon\,(-\beta_I SI - \beta_C SC + \alpha I) \\ I' = -\beta^{op}\dfrac{IC}{I+C} + \alpha^{op} C + \varepsilon\,(\beta_I SI + \beta_C SC - \alpha I) \\ C' = \beta^{op}\dfrac{IC}{I+C} - \alpha^{op} C \end{cases} \tag{2.1}$$

2.2. Saturating treatment rate

In this case, we assume that the per capita recovery rate α depends on treatment and thus it is not constant but a decreasing function, $\alpha(I)$, of the number of infected individuals [22]. We take the following simple form that we call saturating treatment rate:

$$\alpha(I) = \frac{\alpha}{1+\gamma I}, \tag{2.2}$$

where γ is a non-negative parameter that weights the dependence of the recovery rate on the infected individuals density. If $\gamma = 0$, we have again the constant recovery rate. The second coinfection model, which flowchart is in Figure 2, reads as follows:

$$\begin{cases} S' = \varepsilon\left(-\beta_I SI - \beta_C SC + \dfrac{\alpha I}{1+\gamma I}\right) \\ I' = -\beta^{op}\dfrac{IC}{I+C} + \alpha^{op} C + \varepsilon\left(\beta_I SI + \beta_C SC - \dfrac{\alpha I}{1+\gamma I}\right) \\ C' = \beta^{op}\dfrac{IC}{I+C} - \alpha^{op} C \end{cases} \tag{2.3}$$

3. Analysis of the model

We analyze systems (2.1) and (2.3) using the fact that diseases are evolving at different time scales, i.e., $\varepsilon \ll 1$, though, we eventually show that the asymptotic behaviour of solutions does not depend on it. We exploit of the existence of time scales to apply the reduction method developed in [2, 3], that facilitates the analysis.

It consists in a sort of decoupling the fast and the slow parts of the system. The key point of the reduction is in the fast part of the system, i.e., in the SIS model representing the opportunistic disease dynamics:

$$\begin{cases} I' = -\dfrac{\beta^{op} IC}{I+C} + \alpha^{op} C \\ C' = \dfrac{\beta^{op} IC}{I+C} - \alpha^{op} C \end{cases} \tag{3.1}$$

On the one hand, it keeps invariant the total number of individuals infected by the primary disease, infected plus coinfected, that we call $\bar{I}$,

$$I(t) + C(t) = \bar{I}, \tag{3.2}$$

and, on the other hand, the proportions of infected and coinfected individuals rapidly tend to an equilibrium. As it is a classical SIS model with frequency-dependent transmission, it is well known [22] that its basic reproduction number is

$$R_0^{op} = \frac{\beta^{op}}{\alpha^{op}}, \tag{3.3}$$

and the long term behaviour of its solutions with $I(0) \geq 0$ and $C(0) > 0$ is

$$\lim_{t\to\infty} (I(t), C(t)) = (I^*, C^*) = (\nu^*, 1-\nu^*)\bar{I}, \tag{3.4}$$

with $\nu^* = 1$ if $R_0^{op} \leq 1$ and $\nu^* = 1/R_0^{op}$ if $R_0^{op} > 1$. Infected individuals tend to disappear whenever $R_0^{op} \leq 1$ whereas if $R_0^{op} > 1$ the proportions of infected and coinfected individuals tend to $\nu^* = 1/R_0^{op}$ and $1-\nu^* = 1 - 1/R_0^{op}$, respectively.

The second step in the reduction procedure consist in building up a reduced system for variables S and $\bar{I}$ by assuming that the fast part of the system has already attained its equilibria. This new system takes into account the slow part of the initial systems and so we treat separately the cases for systems (2.1) and (2.3).

3.1. Constant recovery rate

The reduced system for the variables S and $\bar{I}$ is obtained from system (2.1). Variables I and C are substituted by $\nu^*\bar{I}$ and $(1-\nu^*)\bar{I}$, respectively. The equation for $\bar{I}$ is the sum of the equations for I and C. The time scale is changed so that the parameter ε disappears, although we maintain the notation for the derivative with respect to the new time variable. Finally, we obtain

$$\begin{cases} S' = -\left(\nu^*\beta_I + (1-\nu^*)\beta_C\right) S\bar{I} + \nu^*\alpha\bar{I}, \\ \bar{I}' = \left(\nu^*\beta_I + (1-\nu^*)\beta_C\right) S\bar{I} - \nu^*\alpha\bar{I}. \end{cases} \tag{3.5}$$

This turns out to be a classical SIS model with density-dependent transmission, where $\bar{\beta} = \nu^*\beta_I + (1-\nu^*)\beta_C$ is its transmission coefficient and $\bar{\alpha} = \nu^*\alpha$ its recovery rate. The total population $N = S(t) + \bar{I}(t)$ remains

constant. Its basic reproduction number

$$\bar{R}_0 = \frac{\bar{\beta}}{\bar{\alpha}} N \tag{3.6}$$

depends on ν^*, so that there are two different cases.

In the first case, when the opportunistic disease is rapidly eradicated, $R_0^{op} \leq 1$, $\nu^* = 1$, system (3.5) becomes the SIS model associated to the primary disease in the absence of the opportunistic disease:

$$\begin{cases} S' = -\beta_I S\bar{I} + \alpha\bar{I}, \\ \bar{I}' = \beta_I S\bar{I} - \alpha\bar{I}, \end{cases}$$

whose basic reproduction number (3.6), that we call R_0^{pr}, becomes

$$R_0^{pr} = \frac{\beta_I}{\alpha} N. \tag{3.7}$$

For $R_0^{op} \leq 1$ the asymptotic behaviour of the solutions of system (3.5) with $S(0) \geq 0$ and $\bar{I}(0) > 0$ is then:

1. If $R_0^{pr} \leq 1$ then

$$\lim_{t\to\infty} (S(t), \bar{I}(t)) = (N, 0). \tag{3.8}$$

2. If $R_0^{pr} > 1$ then

$$\lim_{t\to\infty} (S(t), \bar{I}(t)) = \left(\frac{N}{R_0^{pr}}, N - \frac{N}{R_0^{pr}} \right). \tag{3.9}$$

In the second case, when the opportunistic disease rapidly attains a positive equilibrium, $R_0^{op} > 1$ and $\nu^* = 1/R_0^{op}$. We have $\bar{\beta} = \beta_I/R_0^{op} + (1 - 1/R_0^{op})\beta_C$ and $\bar{\alpha} = \alpha/R_0^{op}$, and hence the basic reproduction number (3.6) of system (3.5), that we call R_0^{coi}, becomes

$$R_0^{coi} = \left(\frac{\beta_I}{\alpha} + \left(\frac{\beta^{op}}{\alpha^{op}} - 1 \right) \frac{\beta_C}{\alpha} \right) N = R_0^{pr} \left(1 + (R_0^{op} - 1) \frac{\beta_C}{\beta_I} \right). \tag{3.10}$$

The corresponding asymptotic behaviour of the solutions of system (3.5) with $S(0) \geq 0$ and $\bar{I}(0) > 0$ becomes:

1. If $R_0^{coi} \leq 1$ then

$$\lim_{t\to\infty} (S(t), \bar{I}(t)) = (N, 0). \tag{3.11}$$

2. If $R_0^{coi} > 1$ then

$$\lim_{t\to\infty} (S(t), \bar{I}(t)) = \left(\frac{N}{R_0^{coi}}, N - \frac{N}{R_0^{coi}} \right). \tag{3.12}$$

Note that R_0^{pr} and R_0^{coi} exchange their role as drivers of the system as R_0^{op} crosses the threshold value 1. If $R_0^{op} < 1$ the opportunistic disease is eradicated and the outcome of the model depends solely on R_0^{pr}. Conversely, if $R_0^{op} > 1$ the opportunistic disease can invade the population and R_0^{coi}, independently of R_0^{pr}, decides on the simultaneous endemicity or eradication of both diseases.

The asymptotic behaviour of the solutions of system (2.1) is closely described by one of the following steady state situations:

1. $\mathbf{E}_0 = (N, 0, 0)$; both diseases are eradicated.
2. $\mathbf{E}_{pr} = (S^*_{pr}, I^*_{pr}, 0) = (N/R_0^{pr}, N(1 - 1/R_0^{pr}), 0)$; the primary disease is endemic and the opportunistic disease disappears.
3. $\mathbf{E}_{coi} = (S^*_{coi}, I^*_{coi}, C^*_{coi}) = (N/R_0^{coi}, N(1 - 1/R_0^{coi})/R_0^{op}, N(1 - 1/R_0^{coi})(1 - 1/R_0^{op}))$; the coinfection is endemic.

Combining the asymptotic results obtained for systems (3.1) and (3.5) in (3.4), (3.8), (3.9), (3.11) and (3.12), we can summarize the long-term behaviour of the solutions of system (2.1) as follows. Consider any solution $\mathbf{X}(t) = (S(t), I(t), C(t))$ of system (2.1) with initial conditions verifying $S(0) \geq 0$, $I(0) > 0$, $C(0) > 0$ and $S(0) + I(0) + C(0) = N$. Then

1. In the case $R_0^{op} < 1$, $R_0^{pr} < 1$ implies that $\mathbf{X}(t)$ approaches $\mathbf{E}_0$ while $R_0^{pr} > 1$ implies that it approaches $\mathbf{E}_{pr}$.
2. In the case $R_0^{op} > 1$, $R_0^{coi} < 1$ implies that $\mathbf{X}(t)$ approaches $\mathbf{E}_0$ while $R_0^{coi} > 1$ implies that it approaches $\mathbf{E}_{coi}$.

The obtained results can be extended to any positive ε due to two convenient properties of the system (2.1). The first one is that for any value of ε, if the quantities $\varepsilon\beta_I$, $\varepsilon\beta_C$ and $\varepsilon\alpha$ are renamed β_I, β_C and α, we reobtain system (2.1) with the choice $\varepsilon = 1$. At the same time the occurrence of these three parameters in the asymptotic behaviour of system (2.1) is in the form of their ratios, R_0^{pr} and R_0^{coi}. It follows thus that the parameter ε plays no role in it.

3.2. Saturating treatment rate

Repeating the process of the previous section, we obtain the reduced system for variables S and $\bar{I}$ associated to system (2.3).

$$\begin{cases} S' = -\left(\nu^*\beta_I + (1-\nu^*)\beta_C\right) S\bar{I} + \dfrac{\nu^*\alpha\bar{I}}{1+\nu^*\gamma\bar{I}}, \\ \bar{I}' = \left(\nu^*\beta_I + (1-\nu^*)\beta_C\right) S\bar{I} - \dfrac{\nu^*\alpha\bar{I}}{1+\nu^*\gamma\bar{I}}. \end{cases} \tag{3.13}$$

This SIS model with density-dependent transmission and saturating recovery rate of the form of (A.1) is analyzed in Appendix A. We still need to distinguish two different cases depending on ν^* being equal to 1 or to $1/R_0^{op}$.

In the first case, $R_0^{op} \leq 1$ and $\nu^* = 1$, system (3.13) becomes the SIS model with saturating recovery rate associated to the primary disease in the absence of the opportunistic disease:

$$\begin{cases} S' = -\beta_I S\bar{I} + \dfrac{\alpha\bar{I}}{1+\gamma\bar{I}}, \\ \bar{I}' = \beta_I S\bar{I} - \dfrac{\alpha\bar{I}}{1+\gamma\bar{I}}. \end{cases}$$

The basic reproduction number of the system is R_0^{pr}, as defined in (3.7). The asymptotic behaviour of its solutions is stated in the appendix Theorem A.1. Contrary to the constant recovery rate case, it presents the phenomenon of backward bifurcation, i.e., for $R_0^{pr} \leq 1$ there are some conditions yielding bi-stability: the disease is either eradicated or endemically established depending on the initial conditions. We postpone the analysis of the details to the next case.

In the second case, when the opportunistic disease rapidly attains a positive equilibrium, $R_0^{op} > 1$ and $\nu^* = 1/R_0^{op}$, the system (3.13) can be written as

$$\begin{cases} S' = -\bar{\beta} S\bar{I} + \dfrac{\bar{\alpha}\bar{I}}{1+\bar{\gamma}\bar{I}} \\ \bar{I}' = \bar{\beta} S\bar{I} - \dfrac{\bar{\alpha}\bar{I}}{1+\bar{\gamma}\bar{I}} \end{cases} \tag{3.14}$$

with $\bar{\beta} = \beta_I/R_0^{op} + (1-1/R_0^{op})\beta_C$, $\bar{\alpha} = \alpha/R_0^{op}$ and $\bar{\gamma} = \gamma/R_0^{op}$. Its basic reproduction number is R_0^{coi} as defined in (3.10).

Calling $\bar{m} = \bar{\gamma}N$, with N being the constant population size, and

$$\begin{aligned} i_1^* &= \left(\bar{m} - 1 - \sqrt{(\bar{m}-1)^2 + 4\bar{m}(1-1/R_0^{coi})}\right)/(2\bar{m}), \\ i_2^* &= \left(\bar{m} - 1 + \sqrt{(\bar{m}-1)^2 + 4\bar{m}(1-1/R_0^{coi})}\right)/(2\bar{m}), \end{aligned} \tag{3.15}$$

the corresponding asymptotic behaviour of the solutions of system (3.14) is detailed in the next theorem.

Theorem 3.1. *Let $(S(t), \bar{I}(t))$ be a solution of system (3.14) with $S(0) \geq 0$ and $\bar{I}(0) > 0$, and $N = S(0) + \bar{I}(0)$. For $R_0^{op} > 1$*

1. *If $R_0^{coi} > 1$ then $\lim_{t\to\infty}(S(t), \bar{I}(t)) = \mathcal{E}_2 := (N(1-i_2^*), Ni_2^*)$.*
2. *If $R_0^{coi} \leq 1$ and $\bar{m} \leq 1$ then $\lim_{t\to\infty}(S(t), \bar{I}(t)) = \mathcal{E}_0 := (N, 0)$.*
3. *If $R_0^{coi} < 4\bar{m}/(\bar{m}+1)^2$ and $\bar{m} > 1$ then $\lim_{t\to\infty}(S(t), \bar{I}(t)) = \mathcal{E}_0$.*
4. *If $4\bar{m}/(\bar{m}+1)^2 \leq R_0^{coi} \leq 1$ and $\bar{m} > 1$ then*
   (a) *If $\bar{I}(0) < Ni_1^*$ then $\lim_{t\to\infty}(S(t), \bar{I}(t)) = \mathcal{E}_0$.*
   (b) *If $\bar{I}(0) > Ni_1^*$ then $\lim_{t\to\infty}(S(t), \bar{I}(t)) = \mathcal{E}_2$.*

Proof. Follows straightforwardly from Theorem A.1 in Appendix A. □

As done in the previous section, assuming $R_0^{op} > 1$, the conditions established in th. (3.1) apply to obtain the approximate asymptotic behaviour of the positive solutions of system (2.3). Thus $\mathcal{E}_0$ and $\mathcal{E}_2$ represent the asymptotic behaviour of the solutions of system (3.14) while for (2.3) the equilibria correspondingly are either $\mathbf{E}_0 = (N, 0, 0)$, the situation where both diseases are eradicated, or

$$\mathbf{E}_{coi}^{\bar{m}} = \left(N(1-i_2^*), Ni_2^*\frac{1}{R_0^{op}}, Ni_2^*\left(1 - \frac{1}{R_0^{op}}\right)\right), \tag{3.16}$$

the situation of endemic coinfection. When γ, and thus $\bar{m}$, tends to 0 only the two first items hold in theorem (3.1) and $\mathbf{E}_{coi}^{\bar{m}}$ tends to $\mathbf{E}_{coi}$. System (2.1) can be considered as the limiting case of system (2.3) when γ tends to 0, i.e., when the saturating recovery becomes linear.

Similar arguments to those developed in the previous section imply that the parameter ε still plays no significant role in the asymptotic behaviour of the solutions of system (2.3).

4. Discussion

We propose models of a population affected by a primary disease whose infected individuals can contract an opportunistic disease acting at a faster time scale than the primary one. A first result of the analysis is that, in the absence of other demographic processes, the asymptotic outcomes of both models do not depend on whether the opportunistic disease evolves at a faster time scale or not.

In the constant recovery rate model (2.1), it is easy to compare S^*_{pr} and S^*_{coi}, the number of susceptible individuals at steady state when the outcome of the model is the primary disease endemic state without coinfection and when instead it settles at the coinfection endemic state. We have

$$\frac{S^*_{pr}}{S^*_{coi}} = 1 + (R_0^{op} - 1)\,\frac{\beta_C}{\beta_I}, \tag{4.1}$$

where the term on the right hand side added to 1 stands for the underestimated proportion of infected individuals that follows from ignoring the effect of coinfective processes.

Focusing on the potential impact of the opportunistic disease, we discuss the case $R_0^{op} > 1$, where in isolation it becomes endemic. It is crucial to determine whether the opportunistic disease, together with the primary disease, will establish or not.

$R_0^{op} > 1$ is a necessary condition but it is not sufficient.

In model (2.1), for any $R_0^{op} > 1$ if the recovery rate α of the primary disease is large enough the population in the long-term attains a disease-free state. To be precise, we need $R_0^{coi} < 1$ that yields

$$(\beta_I + (R_0^{op} - 1)\beta_C)\, N < \alpha.$$

A large enough reduction of the average infectious period of the primary disease, $1/\alpha$, thus eliminates both diseases. In the opposite sense, a low R_0^{pr} can always be compensated by a high R_0^{op} resulting in an endemic coinfection situation, $R_0^{coi} > 1$. For any $R_0^{pr} < 1$, that would entail the primary disease eradication in the absence of the opportunistic one, if the reproduction number of this latter is large enough, more precisely

$$R_0^{op} > 1 + \left(\frac{1}{R_0^{pr}} - 1\right)\frac{\beta_I}{\beta_C},$$

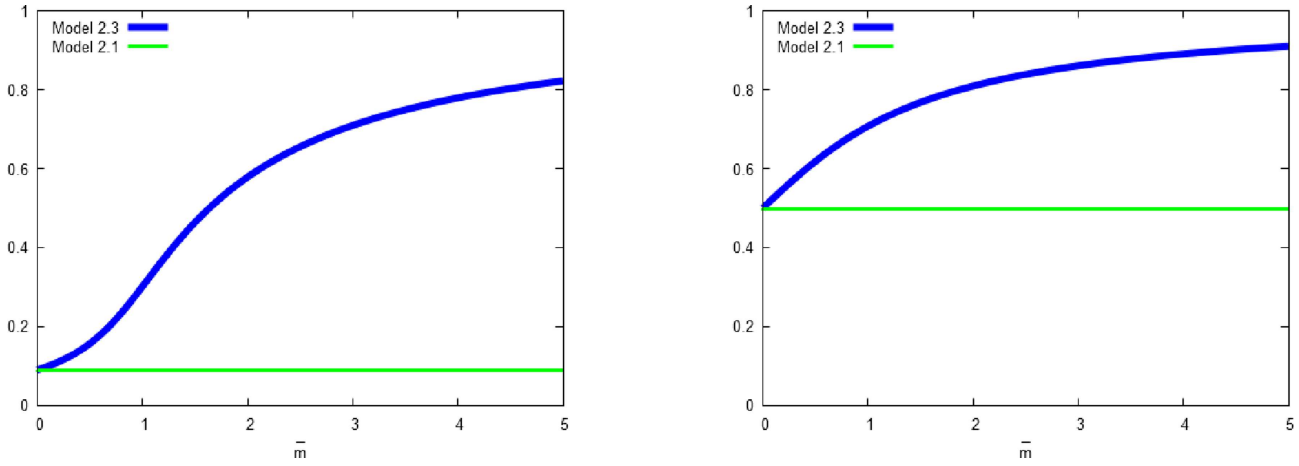
then it is attained the situation where both diseases become endemic. A strong enough secondary disease makes endemic both diseases. The opportunistic disease can be seen acting as a reservoir for the primary disease that strengthens it. Moreover, the size of this strengthening can be measured. As we can see in (3.10), its value turns out to be

$$(R_0^{op} - 1)\,\frac{\beta_C}{\beta_I}.$$

The lack of treatment resources for the primary disease is reflected in model (2.3) by means of a saturating treatment/recovery rate. The parameter γ measures the influence of the number of infected individuals on the time of recovery. For the same number of infected individuals the time of recovery grows linearly with γ. The important difference from the constant recovery rate case, $\gamma = 0$, is that even in the case $R_0^{coi} < 1$ the coinfection may become endemic. The case $R_0^{coi} > 1$ entails the coinfection endemicity in both models, (2.1) and (2.3), with the difference that the total number of infected plus coinfected individuals in the endemic equilibrium, Ni_2^* (3.16), grows with $\bar{m}$. Since $\bar{m} = \gamma N/R_0^{op}$, this total number of disease affected individuals also grows with γ. For $\gamma = 0$ this number is $N(1 - 1/R_0^{coi})$. In Figure 3, we see, for two different values of R_0^{coi}, the fraction of infected plus coinfected individuals i_2^* in model (2.3) as function of $\bar{m}$, in contrast with $1 - 1/R_0^{coi}$ the corresponding fraction in model (2.1).

For $R_0^{coi} = 1.1$, we have $1 - 1/R_0^{coi} = 0.1$ and i_2^* rapidly grows with $\bar{m}$, equivalently with γ. Taking a larger $R_0^{coi} = 2$, the result is $1 - 1/R_0^{coi} = 0.5$ and the growing of i_2^* with $\bar{m}$ is less steep.

The conditions for the coinfection to become endemic in the case $R_0^{coi} < 1$ are expressed in terms of the values of the model parameters, $\bar{m} > 1$ and $4\bar{m}/(\bar{m}+1)^2 \le R_0^{coi} \le 1$, and the total initial number of infected plus coinfected individuals $I(0) + C(0)$ that must be larger than Ni_1^* (3.15).



(A) $R_0^{coi} = 1.1$ (B) $R_0^{coi} = 2$

FIGURE 3. Fraction of infected plus coinfected individuals of the endemic equilibrium: i_2^* (model (2.3)), as function of $\bar{m}$, and $1 - 1/R_0^{coi}$ (model (2.1)). Left frame: $R_0^{coi} = 1.1$; Right frame: $R_0^{coi} = 2$.

These conditions are easily met as the parameter $\bar{m}$ gets larger. On the one hand, we have that $4\bar{m}/(\bar{m}+1)^2$ is a decreasing function of $\bar{m}$ that tends to 0 for $\bar{m}$ tending to infinity and, on the other hand, that the minimum number of infected plus coinfected individuals necessary for the coinfection to become endemic,

$$Ni_1^* = \frac{N}{2}\left(1 - \frac{1}{\bar{m}} - \sqrt{\left(1 - \frac{1}{\bar{m}}\right)^2 + 4\left(\frac{1}{\bar{m}} - \frac{1}{\bar{m}R_0^{coi}}\right)}\right),$$

also tends to 0 with $\bar{m}$ tending to infinity. Recalling that $\bar{m} = \gamma N/R_0^{op}$, we obtain that increasing the population size, or the parameter γ, favours the existence of coinfection endemicity in spite of having $R_0^{coi} < 1$. A larger population together with insufficient treatment resources for the primary disease yields a coinfection endemicity preventable in a constant recovery rate case.

The other factor operating in $\bar{m}$ is R_0^{op}, the opportunistic disease basic reproduction number. The fact that R_0^{op} appears in the denominator of $\bar{m}$ seems to imply that a stronger opportunistic disease helps in eradicating both diseases. This is not true because R_0^{coi} is a linear expression of R_0^{op} and it is larger than 1 whenever

$$R_0^{op} > 1 + \frac{\beta_I}{\beta_C}\left(\frac{1}{R_0^{pr}} - 1\right).$$

Hence, this condition is sufficient to guarantee the achievement of a coinfection endemic state. As in model (2.1), a large enough value of R_0^{op} makes also endemic the primary disease though it would tend to eradication in the absence of the opportunistic disease.

In certain cases it is possible to find the counterintuitive fact that an increase of the value of R_0^{op} helps in eradicating both diseases. To look for this situation, we first need to assume that $R_0^{coi} < 1$ and $R_0^{op} > 1$. In addition, as R_0^{op} grows, the conditions of point 4 in Theorem 3.1, for an asymptotically stable endemic equilibrium, should change into those of point 3, for a globally asymptotically stable disease-free equilibrium.

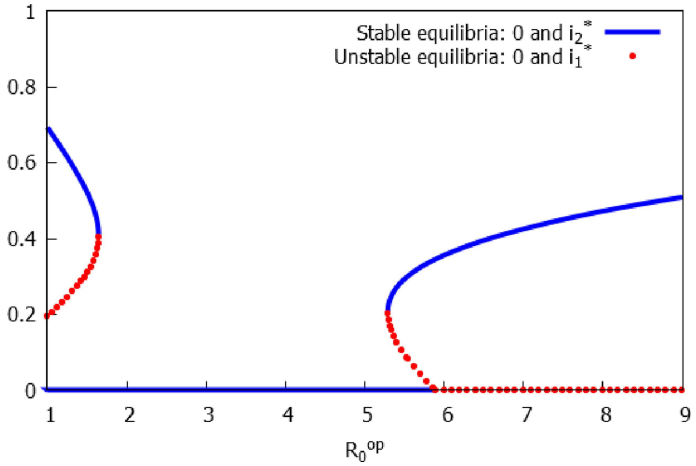


FIGURE 4. Bifurcation diagram of system (3.14) with fraction of infected plus coinfected individuals at equilibria in terms of parameter R_0^{op}, for $\gamma N = 9$, $R_0^{pr} = 9/20$ and $\beta_I/\beta_C = 4$.

We write R_0^{coi} and $4\bar{m}/(\bar{m}+1)^2$ in terms of R_0^{op}:

$$R_0^{coi} = R_0^{pr}\frac{\beta_C}{\beta_I}R_0^{op} - R_0^{pr}\left(1 - \frac{\beta_C}{\beta_I}\right) \tag{4.2}$$

and

$$\frac{4\bar{m}}{(\bar{m}+1)^2} = \frac{4N\gamma R_0^{op}}{(N\gamma + R_0^{op})^2}. \tag{4.3}$$

We need, apart from $\bar{m} = N\gamma/R_0^{op} > 1$, to find α and β, $1 < \alpha < \beta$ such that expression (4.2) be greater than expression (4.3) if $R_0^{op} \in (1, \alpha)$ and (4.3) greater than (4.2) if $R_0^{op} \in (\alpha, \beta)$.

A characterization of the proposed situation does not seem to be straightforward. Thus, we just carry on an illustration of what happens by means of a particular example. As can be seen in (4.2) and (4.3), apart from our variable R_0^{op}, the rest of the parameters appears in three independent expressions: R_0^{pr}, β_C/β_I and $N\gamma$. Once fixed the values for these three expressions, any set of model (2.3) parameter values fitting on them share the same qualitative behaviour of the corresponding system.

Let $R_0^{pr} = 9/20$, $\beta_C/\beta_I = 1/4$ and $N\gamma = 9$. The particular forms of expressions (4.2) and (4.3) are

$$R_0^{coi} = \frac{9}{80}R_0^{op} - \frac{27}{80} \text{ and } \frac{4\bar{m}}{(\bar{m}+1)^2} = \frac{36R_0^{op}}{(9+R_0^{op})^2},$$

and we also have $\bar{m} = 9/R_0^{op}$. It is immediate to verify that there exist $\alpha \approx 1.64456$ and $\beta \approx 5.28957$ for which the above established conditions hold. In addition, $R_0^{coi} > 1$ if $R_0^{op} > 53/9$. Concerning the condition $\bar{m} = 9/R_0^{op} > 1$, it holds, as required, if $R_0^{op} < 53/9$.

The qualitative behaviour of the epidemic model (2.3) for the particular chosen values of the parameters is described in the bifurcation diagram of Figure 4.

If $R_0^{op} \in$(1,1.64456) enough individuals affected by one or both diseases make the system approach the asymptotically stable endemic equilibrium, i.e., the coinfection is established. If R_0^{op} gets through the threshold $\alpha \approx 1.64456$, allowing, for instance, a stronger transmission or reducing the recovery rate of the opportunistic disease, both diseases are eradicated. The situation of the system tending to the stable endemic equilibrium if

the fraction of infected plus coinfected individuals is greater than this same fraction for the unstable endemic equilibrium is again found if $R_0^{op} \in (5.28957, 53/9)$. For $R_0^{op} > 53/9$ the value of R_0^{coi} is larger than 1 and from Theorem 3.1, we obtain that for any positive initial number of coinfected individuals the system tends to the endemic coinfection equilibrium.

The bifurcation at $R_0^{op} = 53/9$ is a typical example of backward bifurcation as presented in the introduction and found in the basic SIS model with saturating treatment analysed in Appendix A.

To summarize our results, we focus on the case of the opportunistic disease not being controlled: $R_0^{op} > 1$. This fact can happen even due to disease overlooking. In the case of constant recovery rate, the options of both diseases eradication go through increasing this recovery rate, equivalently, reducing the average time an individual keeps transmitting the primary disease. Nevertheless, this might not be completely effective since a large enough value of R_0^{op} can cancel its effect out. Therefore, acting on the opportunistic disease, by avoiding transmission or improving recovery, might sometimes be unavoidable. Obviously, the situation gets worse in the case of saturating treatment/recovery rate. This can only be alleviated by reducing the effects of population size on the treatment/recovery rate represented by parameter γ.

Appendix A. SIS model with saturating treatment

$$\begin{cases} S' = -\beta SI + \dfrac{\alpha I}{1+\gamma I} \\ I' = \beta SI - \dfrac{\alpha I}{1+\gamma I} \end{cases} \tag{A.1}$$

The population size does not change: $S(t) + I(t) = N$. The asymptotic behaviour of the solutions of system (A.1) can so be studied by means of the scalar equation for the fraction of infected individuals $i = I/N$ where S is substituted by $N(1-i)$:

$$i' = \beta N(1-i)i - \frac{\alpha i}{1+\gamma N i} \tag{A.2}$$

The basic reproduction number of the system can be defined as $R_0 = \dfrac{\beta}{\alpha} N$. Changing the variable time, $\tau = \alpha t$, equation (A.2) can be written in terms of just two parameters, R_0 and $m = \gamma N$, in the following form:

$$i' = R_0(1-i)i - \frac{i}{1+mi} \tag{A.3}$$

where i' now represents the derivative respect to τ.

A straightforward analysis of equation (A.3) gives the following results.

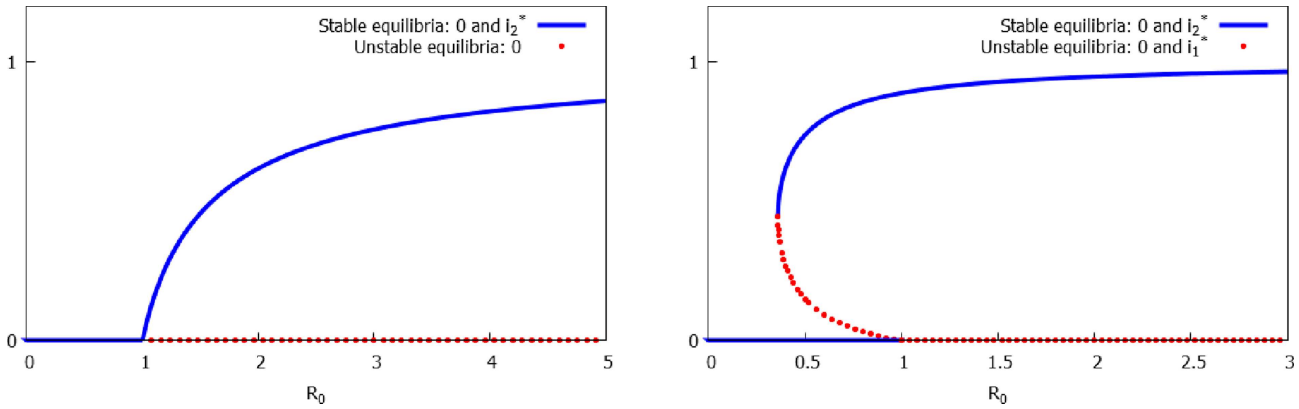
The equilibrium $i_0^* = 0$ is asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Equation (A.3) can still have two other equilibrium points, the solutions of the equation $R_0(1-i)(1+mi) - 1 = 0$:

$$\begin{aligned} i_1^* &= \left(m - 1 - \sqrt{(m-1)^2 + 4m(1-1/R_0)}\right) / (2m) \\ i_2^* &= \left(m - 1 + \sqrt{(m-1)^2 + 4m(1-1/R_0)}\right) / (2m) \end{aligned} \tag{A.4}$$

If $R_0 > 1$ then $i_1^* < 0$ and $i_2^* > 0$. Moreover, i_2^* is asymptotically stable being $(0, \infty)$ its domain of attraction.

If $R_0 < 1$ and $m < 1$ there is no positive equilibrium point and $(0, \infty)$ is in the domain of attraction of $i_0^* = 0$. On the other hand, if $R_0 < 1$ and $m > 1$ then i_1^* and i_2^* are both positive provided that they exist, i.e.,



(A) $m = \gamma N < 1$: Forward bifurcation

(B) $m = \gamma N > 1$: Backward bifurcation

FIGURE A.1. Bifurcation diagram of equation (A.3) in terms of parameter R_0 for $m = 0.5$ in the left frame and for $m = 9$ in the right frame.

if $(m-1)^2 + 4m(1 - 1/R_0) > 0$ holds. This condition can be expressed in the following simpler form:

$$R_0 > \frac{4m}{(m+1)^2}. \tag{A.5}$$

In this case there is bi-stability. To be precise, if $\frac{4m}{(m+1)^2} < R_0 < 1$ and $m > 1$ then $(0, i_1^*)$ is in the domain of attraction of $i_0^* = 0$ and the domain of attraction of i_2^* is (i_1^*, ∞). If inequality (A.5) is reversed then there is no positive equilibrium point and $(0, \infty)$ is again in the domain of attraction of $i_0^* = 0$.

From the previous analysis, we obtain the asymptotic behaviour of the solutions of system (A.1).

Theorem A.1. *Let $(S(t), I(t))$ be a solution of system (A.1) with $S(0) \geq 0$ and $I(0) > 0$, $N = S(0) + I(0)$, $R_0 = \beta N/\alpha$ and $m = \gamma N$.*

1. *If $R_0 > 1$ then $\lim_{t\to\infty} (S(t), I(t)) = \mathcal{E}_2 := (N(1 - i_2^*), Ni_2^*)$.*
2. *If $R_0 \leq 1$ and $m \leq 1$ then $\lim_{t\to\infty} (S(t), I(t)) = \mathcal{E}_0 := (N, 0)$.*
3. *If $R_0 < 4m/(m+1)^2$ and $m > 1$ then $\lim_{t\to\infty} (S(t), I(t)) = \mathcal{E}_0$.*
4. *If $4m/(m+1)^2 \leq R_0 \leq 1$ and $m > 1$ then*
   (a) *If $I(0) < Ni_1^*$ then $\lim_{t\to\infty} (S(t), I(t)) = \mathcal{E}_0$.*
   (b) *If $I(0) > Ni_1^*$ then $\lim_{t\to\infty} (S(t), I(t)) = \mathcal{E}_2$.*

If $m < 1$ the disease cannot invade the population for $R_0 < 1$, there is forward bifurcation at $R_0 = 1$ (Fig. A.1). On the other hand, if $m > 1$ there is a backward bifurcation at $R_0 = 1$ (Fig. A.1), for certain values of $R_0 < 1$ an endemic equilibrium is attained provided that enough infectives are introduced into the population.

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