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Heroin epidemics, treatment and ODE modelling

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Abstract

The UN [United Nations Office on Drugs and Crime (UNODC): World Drug Report, 2005, vol. 1: Analysis. UNODC, 2005.], EU [European Monitoring Centre for Drugs and Drug Addiction (EMCDDA): Annual Report, 2005. http://annualreport.emcdda.eu.int/en/home-en.html.] and WHO [World Health Organisation (WHO): Biregional Strategy for Harm Reduction, 2005–2009. HIV and Injecting Drug Use. WHO, 2005.] have consistently highlighted in recent years the ongoing and persistent nature of opiate and particularly heroin use on a global scale. While this is a global phenomenon, authors have emphasised the significant impact such an epidemic has on individual lives and on society. National prevalence studies have indicated the scale of the problem, but the drug-using career, typically consisting of initiation, habitual use, a treatment-relapse cycle and eventual recovery, is not well understood. This paper presents one of the first ODE models of opiate addiction, based on the principles of mathematical epidemiology. The aim of this model is to identify parameters of interest for further study, with a view to informing and assisting policy-makers in targeting prevention and treatment resources for maximum effectiveness. An epidemic threshold value, R_0, is proposed for the drug-using career. Sensitivity analysis is performed on R_0 and it is then used to examine the stability of the system. A condition under which a backward bifurcation may exist is found, as are conditions that permit the existence of one or more endemic equilibria. A key result arising from this model is that prevention is indeed better than cure.

Keywords: ODE models; Mathematical epidemiology; Heroin use; Reproduction ratio R_0; Drug-using career; Treatment

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1. Background to heroin use in Ireland

The use of heroin and other drugs in Europe and more specifically Ireland and the resulting prevalence are well documented [2,4,5]. However, in spite of the extensive developments in the mathematical and statistical techniques applied to modelling infectious diseases, little has been done to apply this work to the emerging heroin epidemics. In this paper, attempts to extend dynamic disease modelling to the drug-using career are introduced and applied in a general model. A drug user is defined here as an individual whose habitual usage of opiate drugs harms the physical, mental or social well-being of the individual, their family or peer group, or society [6]. Opiate use in Ireland appears to have been minimal until 1979 [7]. Police reports, hospital records and an increase in the numbers presenting for treatment from 5 people in 1979 to 239 people in 1983, made the increase in heroin use very clear [8]. In fact, the period 1981–1983 is seen as defining the first heroin epidemic in Ireland. Subsequent epidemic periods have been noted, alternated with periods of relative stability in the numbers using the drug. Illicit drug-use, by its nature, is a hidden activity. That said, independent prevalence estimates obtained in 1996 and 2000–2001 produced broadly similar results for the total size of the drug-using population. These prevalence estimates of drug-users in Ireland are shown in Table 1. While prevalence has remained approximately constant (although the individuals who comprise the drug-using population may have changed), the total number of individuals seeking treatment has been growing [9]. At the same time, the percentage of individuals seeking treatment for the first time, as a proportion of the total seeking treatment, is dropping [9]. Eighty-seven percent of the respondents in the ROSIE study [10] reported prior treatment episodes. This return to treatment accounts for some increase in treatment demand and also suggests that rather than being a once-off event, a treatment-relapse cycle of some kind exists. Naturally this has important implications for the provision of treatment services and for the perception of 'successful' treatment episodes. The Irish government has committed itself to the National Drugs Strategy ''Building on Experience, 2001–2008''. Agencies with primary responsibility include the National Advisory Committee for Drugs (NACD) and the Drug Misuse Research Division (DMRD) of the Health Research Board (HRB). With the aims of these bodies in mind, this paper provides an initial framework, in the mathematical epidemiology context, within which certain characteristics of the opiate-using career can be identified.

Table 1
Estimated prevalence of opiate use

Year	Age group	Est. No.	Rate per 1000 population	Source
1996	15–54	13,460	2.1	Comiskey[a]
2001	15–64	14,452	0.56	Kelly et al.[b]

[a] Ref. [4].
[b] Ref. [5].

2. Methods

2.1. Mathematical epidemiology

The literature and development of mathematical epidemiology is well documented and can be found in the works of Bailey [11], Anderson and May [12], Murray [13] and Brauer and Castillo-Chavez [14]. Yet, while social problems such as alcohol and drug use have been referred to in terms of epidemics, little has been published on the application of mathematical modelling methods to such problems.

2.2. Approach

On the premise that drug use follows a process that can be modelled in a similar way to the modelling of disease, a mathematical epidemiological treatment of drug use may yield insights on the progression through the drug-using career, from initiation to habitual use, treatment, relapse and eventual recovery. It is of course critical to understand, insofar as it is possible, the process being modelled. Information from the ROSIE study [10] and feedback from professionals in addiction-related areas were fundamental in developing the model shown in Fig. 1. The approach used was to fit the characteristics of the drug-using career to a susceptible-infectious disease model. Each compartment in Fig. 1 represents a stage in the drug-using career. The arrows show the paths that can be taken between compartments. Following standard methods [11,12], once this simple compartment model and its corresponding dynamics were identified, ordinary differential equations were derived to mathematically represent the system. A value for R_0, the basic reproduction number, is then proposed for this system. This number tells us how many secondary infections will result from the introduction of one infected individual into a susceptible population. $R_0 = 1$ means that each infected person will infect one susceptible person. Usually, $R_0 < 1$ implies that an epidemic will not result from the introduction of one infected individual, whereas $R_0 > 1$ implies that an epidemic will occur and $R_0 = 1$ requires further investigation. In the drug-using context, $R_0 > 1$ implies that, on average, during the drug-using career, each single drug user will "infect", that is, introduce to drug use, at least one other individual. However, as will be seen, the model (1)–(3) may imply something further, namely that the threshold value of R_0 must be brought far below one in order to avoid an epidemic and if this does not happen, an endemic equilibrium of drug-users may be established in the population and eradication of drug-use could become more difficult. R_0 is also useful for establishing the existence of equilibrium points and in performing stability analysis for the system.

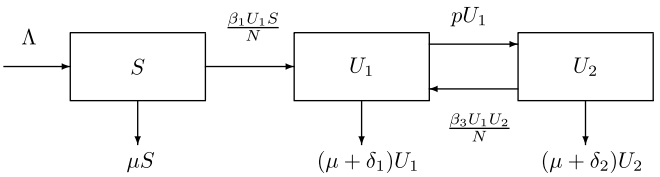

Fig. 1. A model of the opiate-using career.

2.3. A model of the opiate-using career and its parameters

The model presented in Fig. 1 may be represented by the set of Eqs. (1)–(3) below:

$$\frac{dS}{dt} = \Lambda - \frac{\beta_1 U_1 S}{N} - \mu S, \tag{1}$$

$$\frac{dU_1}{dt} = \frac{\beta_1 U_1 S}{N} - pU_1 + \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_1)U_1, \tag{2}$$

$$\frac{dU_2}{dt} = pU_1 - \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_2)U_2. \tag{3}$$

The parameters in (1)–(3) are as follows:

- N: Size of the total population.
- S: The number of susceptible individuals in the population. Here, all individuals range from age 15–64 [17].
- U_1: The number of drug users not in treatment; initial and relapsed drug users.
- U_2: The number of drug users in treatment.
- Λ: The number of individuals in the general population entering the susceptible population, i.e. the demographic process of individuals reaching age 15 in the modelling time period.
- μ: The natural death rate of the general population.
- δ_1: A removal rate that includes drug-related deaths of users not in treatment and a spontaneous recovery rate; individuals not in treatment who stop using drugs but are no longer susceptible.
- δ_2: A removal rate that includes the drug-related deaths of users in treatment and a rate of successful "cure" that corresponds to recovery to a drug free life and immunity to drug addiction for the duration of the modelling time period.
- β_1: The probability of becoming a drug user.
- p: The proportion of drug users who enter treatment.
- β_3: The probability of a drug user in treatment relapsing to untreated use.

Clearly the model involves certain assumptions. These consist of the following:

- $N = S + U_1 + U_2$; the population is assumed to be of constant size within the modelling time period, that is, $\Lambda = \mu S + (\mu + \delta_1)U_1 + (\mu + \delta_2)U_2$.
- A proportion of drug users enter treatment in each modelling time period.
- Per field research, individuals in treatment are using drugs [10].
- A proportion of users who are not in treatment stop using in each modelling time period; this again corresponds to what is observed in practice.
- Drug users not in treatment are infectious to susceptibles and to users in treatment.
- Users in treatment most commonly relapse due to contact with users who are not in treatment [10].
- Drug users in treatment are not infectious to susceptibles.
- Homogeneous mixing is assumed; every individual in the population has an equal chance of encountering any other individual.

- All members of the population are assumed to be equally susceptible to drug addiction. In practice, some sub-populations are more highly susceptible due to environmental, behavioural and genetic factors. Here an average value for β_1 over the general population is used.

3. Results

Presented here are detailed analysis and interpretation of R_0 for the model. R_0 is then itself used to investigate the existence of equilibria for the dynamical system (1)–(3).

3.1. The basic reproduction number, R_0

3.1.1. Explanation of R_0

The basic reproduction number; a threshold value representing how many secondary infections result from the introduction of one infected individual into a population of susceptibles [16]. The value that R_0 takes can indicate the circumstances in which an epidemic is possible. In the drug-using context, R_0 tells us, on average, the total number of people that each single drug user will initiate to drug use during the drug-using career.

3.1.2. R_0 for this model

R_0 here is defined as the probability of becoming addicted to drugs multiplied by the mean amount of time spent using drugs without treatment. In terms of the model parameters,

$$R_0 = \frac{\beta_1}{p + \mu + \delta_1}. \tag{4}$$

3.1.3. Interpretation of R_0 for this model

In this case, the basic reproduction number is the probability of an individual becoming a drug user divided by the sum of the proportion of individuals who enter treatment, the natural death rate of the population and the death rate of drug-using individuals who are not in treatment. The interpretation is very straightforward: when the probability of becoming a drug user (the numerator in R_0) is greater than the sum of the cessation probabilities in the R_0 denominator, prevalence will rise.

3.1.4. R_0 sensitivity analysis

To examine the sensitivity of R_0 to each of its parameters, following Arriola and Hyman [18], the normalised forward sensitivity index with respect to each of the parameters is calculated:

$$A_{\beta_1} = \frac{\frac{\partial R_0}{R_0}}{\frac{\partial \beta_1}{\beta_1}} = \frac{\beta_1}{R_0}\frac{\partial R_0}{\partial \beta_1} = \beta_1\left(\frac{p + \mu + \delta_1}{\beta_1}\right)\left(\frac{1}{p + \mu + \delta_1}\right) = 1. \tag{5}$$

Thus, for example, an increase in β_1 of 2% will result in an increase in R_0 of 2%.

$$
\begin{aligned}
A_p &= \frac{\frac{\partial R_0}{R_0}}{\frac{\partial p}{p}} \\
&= \frac{p}{R_0}\frac{\partial R_0}{\partial p} \\
&= \left|\frac{-p}{p+\mu+\delta_1}\right| < 1. \\
A_\mu &= \frac{\frac{\partial R_0}{R_0}}{\frac{\partial \mu}{\mu}} \\
&= \frac{\mu}{R_0}\frac{\partial R_0}{\partial \mu} \\
&= \left|\frac{-\mu}{p+\mu+\delta_1}\right| < 1. \\
A_{\delta_1} &= \frac{\frac{\partial R_0}{R_0}}{\frac{\partial \delta_1}{\delta_1}} \\
&= \frac{\delta_1}{R_0}\frac{\partial R_0}{\partial \delta_1} \\
&= \left|\frac{-\delta_1}{p+\mu+\delta_1}\right| < 1.
\end{aligned}
$$

It is concluded that R_0 is most sensitive to changes in β_1. An increase in β_1 will bring about an increase of the same proportion in R_0 (equally, a decrease in β_1 will bring about an equivalent decrease in R_0; they are directly proportional). p, μ and δ_1 have an inversely proportional relationship with R_0; an increase in any of them will bring about a decrease in R_0, however, the size of the decrease will be proportionally smaller. Recall that μ is the natural death rate of the population and δ_1 is a removal rate that includes drug-related deaths of users not in treatment and a spontaneous recovery rate; individuals not in treatment who stop using drugs but are no longer susceptible. It is clear that increases in either of these rates is neither ethical nor practical (although spontaneous recovery is welcome, of course!). Thus we choose to focus on one of two parameters: either p, the proportion of users who enter treatment or β_1, the probability of an individual becoming a drug user. Given R_0's sensitivity to β_1 and in the knowledge that a treatment cycle exists (individuals who enter treatment are likely to relapse and re-enter treatment), it seems sensible to focus efforts on the reduction of β_1. In other words, this sensitivity analysis tells us that prevention is better than cure; efforts to increase prevention are more effective in controlling the spread of habitual drug use than efforts to increase the numbers of individuals accessing treatment.

3.2. Stability of drug free equilibrium, $R_0 < 1$

Having derived R_0 for the model, it is now used to determine the existence of equilibria for the system. In particular, it is known that the drug free equilibrium (DFE) of epidemiological models

is locally asymptotically stable at $R_0 < 1$ [16]. For this to hold, the eigenvalues of the Jacobian matrix of the model (1)–(3) with substitutions

$$(S^*, U_1^*, U_2^*) = \left(\frac{\Lambda}{\mu}, 0, 0\right) \tag{6}$$

should have negative real parts. The Jacobian of the system (1)–(3) is

$$J(S, U_1, U_2) = \begin{pmatrix} -\frac{\beta_1 U_1}{N} - \mu & -\frac{\beta_1 S}{N} & 0 \\ \frac{\beta_1 U_1}{N} & \frac{\beta_1 S}{N} - p + \frac{\beta_3 U_2}{N} - (\mu + \delta_1) & \frac{\beta_3 U_1}{N} \\ 0 & p - \frac{\beta_3 U_2}{N} & -\frac{\beta_3 U_1}{N} - (\mu + \delta_2) \end{pmatrix}.$$

Substituting (6) and recalling that at the DFE, $S^* = N$, the matrix becomes

$$J\left(\frac{\Lambda}{\mu}, 0, 0\right) = \begin{pmatrix} -\mu & -\beta_1 & 0 \\ 0 & \beta_1 - (p + \mu + \delta_1) & 0 \\ 0 & p & -(\mu + \delta_2) \end{pmatrix}. \tag{7}$$

The eigenvalues of this matrix are:

$$\lambda_1 = -\mu$$
$$\lambda_2 = -(\mu + \delta_2)$$
$$\lambda_3 = \beta_1 - (p + \mu + \delta_1).$$

λ_1 and λ_2 are clearly real and negative. Also as $R_0 < 1$, then

$$\beta_1 < p + \mu + \delta_1$$

and λ_3 meets the necessary criteria. The system (1)–(3) shows local asymptotic stability at the DFE.

3.3. Analysis at $R_0 = 1$

Castillo-Chavez and Song [19] and Song [20] describe the following method to examine the direction of the bifurcation at $R_0 = 1$:

$$A = D_w f(0, 0) = \left(\frac{\partial f_i}{\partial w_j}(0, 0)\right)$$

is the linearisation matrix of a general system of ordinary differential equations around the equilibrium 0 with bifurcation parameter ϕ evaluated at 0. Zero is a simple eigenvalue of matrix A and all the other eigenvalues of A have negative real parts. A has a right eigenvector $\mathbf{x}$ and a left eigenvector $\mathbf{y}$ that correspond to the zero eigenvalue. Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1} y_k x_i x_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0), \tag{8}$$

$$b = \sum_{k,i=1} y_k x_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0), \tag{9}$$

If $a > 0$ and $b > 0$, the bifurcation at $\phi = 0$ is backward. The existence of a backward bifurcation means that multiple endemic equilibria exist; in particular, an endemic equilibrium exists when $R_0 < 1$ and substantial effort is required to reduce R_0 to a level small enough to eradicate the disease from the population (recall that the DFE has been shown to be locally asymptotically stable only). β_1 is the obvious choice of bifurcation parameter (recall that it represents the rate at which individuals are initiated to drug use), particularly as it has been shown in Eq. (5) that R_0 is more sensitive to changes in β_1 than in its other parameters. At $R_0 = 1$,

$$\frac{\beta_1}{p + \mu + \delta_1} = 1$$

so we define

$$\beta_1^* = p + \mu + \delta_1. \tag{10}$$

The Jacobian matrix is obtained as before in Eq. (7) and the identity (10) is used, leading to:

$$\left(\frac{\Lambda}{\mu}, 0, 0\right) = \begin{pmatrix} -\mu & -\beta_1^* & 0 \\ 0 & 0 & 0 \\ 0 & p & -(\mu + \delta_2) \end{pmatrix}. \tag{11}$$

The matrix (11) has eigenvalues $(0, -\mu, -(\mu + \delta_1))^{\mathrm{T}}$, which meets the requirement of a simple zero eigenvalue and the others having negative real part. The right eigenvector $\mathbf{x}$ corresponding to the zero eigenvalue is

$$\left(\frac{-(p + \mu + \delta_1)(\mu + \delta_2)}{\mu p}, \frac{\mu + \delta_2}{p}, 1\right) x_3^{\mathrm{T}}$$

with x_3 free and the left eigenvector $\mathbf{y}$ corresponding to the zero eigenvalue is $(0, 1, 0)y_2$, with y_2 free. The second derivatives are calculated, evaluated at the DFE $(S^*, U_1^*, U_2^*) = (\frac{\Lambda}{\mu}, 0, 0)$ and with $\beta_1 = \beta_1^*$. The formulas for a and b are then used. It is found that b is positive and a is positive if the following inequality holds:

$$\frac{(p + \mu + \delta_1)^2(\mu + \delta_2)}{\mu p} < \beta_3 \tag{12}$$

(see Appendix A for details of the calculations). Note that if $\beta_3 = 0$, there is no treatment cycle as individuals do not relapse to untreated use, and no backward bifurcation exists. It is the lapse from treatment due to contact with other drug users that drives the possibility of an endemic equilibrium when $R_0 < 1$. This reflects what is usually concluded about backward bifurcations – they are driven by exogenous re-infection, that is, re-infection from an external source [19,15].

3.4. Existence of endemic equilibrium: $R_0 > 1$

It has been shown that the DFE, corresponding to $R_0 < 1$ is locally asymptotically stable and that there is a condition under which an endemic equilibrium may exist when $R_0 < 1$. The existence of one or more non-trivial equilibria is now investigated. At an endemic equilibrium, disease (or in this case, drug addiction) is present in the population and the following hold:

$$S \geqslant 0,$$
$$U_1 > 0,$$
$$U_2 \geqslant 0,$$
$$\frac{dS}{dt} = \frac{dU_1}{dt} = \frac{dU_2}{dt} = 0.$$

To begin, non-trivial equilibrium values for each of the variables S, U_1, U_2 must be found. First solve Eq. (1) equal to zero for equilibrium value, S^*:

$$S^* = \Lambda\left(\frac{N}{\beta_1 U_1} + \frac{1}{\mu}\right).$$

Now, substituting S^* into Eq. (2), setting equal to zero and solving for U_2^* gives

$$\frac{\beta_1 U_1}{N}\left(\Lambda\left(\frac{N}{\beta_1 U_1} + \frac{1}{\mu}\right)\right) - pU_1 + \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_1)U_1 = 0.$$

Hence

$$\Lambda + \frac{\beta_1 U_1 \Lambda}{N\mu} - pU_1 + \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_1)U_1 = 0$$

and re-arranging yields

$$U_2^* = -\frac{N\Lambda}{\beta_3 U_1} + \frac{N}{\beta_3}\left(-\frac{\beta_1 \Lambda}{N\mu} + p + \mu + \delta_1\right).$$

Putting U_2^* into Eq. (3), setting the equation equal to zero and solving for U_1^* gives

$$pU_1 + \left(\frac{N\Lambda}{\beta_3 U_1} + \frac{\beta_1 \Lambda}{\beta_3 \mu} - \frac{N}{\beta_3}(p + \mu + \delta_1)\right)\left(\frac{\beta_3 U_1}{N} + \mu + \delta_2\right) = 0.$$

Further algebraic manipulation produces the following quadratic in U_1:

$$U_1^2\left(\frac{\beta_1 \Lambda}{N\mu} - (\mu + \delta_1)\right) + U_1\left(\Lambda + \frac{1}{\beta_3}\left(-\mu N(p + \mu + \delta_1) + \beta_1 \Lambda - \delta_2 N(p + \mu + \delta_1) + \frac{\delta_2 \beta_1 \Lambda}{\mu}\right)\right) + \frac{N\Lambda}{\beta_3}(\mu + \delta_2) = 0.$$

A real positive value for U_1^* is required for an endemic equilibrium to exist. Obviously the constant term is positive. However, the signs of the co-efficients of U_1^2 and U_1 are not obvious although it is known that

$$\beta_1 > p + \mu + \delta_1$$

as $R_0 > 1$. Thus four quadratic cases arise:

$$aU_1^2 + bU_1 + c = 0$$

in which case, using Descartes' Rule of Signs [21], no sign changes mean that there are no real roots and there is no endemic equilibrium. Using the same rule,

$$aU_1^2 - bU_1 + c = 0$$

has two sign changes and two real positive values for U_1^* would be expected.

$$-aU_1^2 + bU_1 + c = 0$$

has one sign change and therefore one real positive root as does the final case:

$$-aU_1^2 - bU_1 + c = 0.$$

The following inequalities must be investigated to determine the existence of the endemic equilibrium. The co-efficient of U_1^2 will be negative if

$$\left|\frac{\beta_1 \Lambda}{N\mu}\right| < |\mu + \delta_1|.$$

The co-efficient of U_1 can be negative only if

$$\Lambda < \frac{1}{\beta_3}\left|\beta_1 \Lambda\left(1 + \frac{\delta_2}{\mu}\right) - N(p + \mu + \delta_1)(\mu + \delta_2)\right|,$$

where

$$\left|\beta_1 \Lambda\left(1 + \frac{\delta_2}{\mu}\right)\right| < |N(p + \mu + \delta_1)(\mu + \delta_2)|.$$

Either the co-efficient of U_1^2 or U_1 or both must be negative to guarantee the existence of at least one endemic equilibrium.

4. Conclusions

It is found that

$$\frac{\beta_1}{p + \mu + \delta_1}$$

is the basic reproduction ratio, R_0, for the model (1)–(3). This is interpreted as follows: when the probability of becoming a drug user is greater than the sum of the cessation probabilities, prevalence will rise. Sensitivity analysis identifies β_1, the probability of becoming a drug user, as the most useful parameter to target for the reduction of R_0. For practical purposes, this corresponds to prevention being better than cure; efforts to increase prevention are more effective in controlling the spread of habitual drug use than efforts to increase the numbers of individuals accessing treatment. The model (1)–(3) is locally asymptotically stable when $R_0 < 1$ (this is known as the drug free equilibrium). It is found that analysis at $R_0 = 1$ yields the following result: if the inequality

$$\frac{(p + \mu + \delta_1)^2(\mu + \delta_2)}{\mu p} < \beta_3$$

holds, then a backward bifurcation can occur and although R_0 may be less than 1, an endemic equilibrium exists. If this equilibrium is stable, substantial effort may be required to reduce prevalence and avoid an epidemic. When $R_0 > 1$, analysis produces a quadratic equation in U_1. The existence of an endemic equilibrium (or endemic equilibria) depends on the existence of at least one real, positive value for U_1; thus, either the co-efficient of U_1^2 or U_1 or both must be negative to guarantee the existence of at least one endemic equilibrium. This paper introduces a universal model that identifies parameters of interest in the drug-using career. Clearly the collection of data relevant to the key parameters by epidemiologists and treatment providers at a global level, would be of significant use from an implementation and policy perspective.

5. Future work

Using this model within the Irish setting, it is intended to estimate parameters with a view to ascertaining from current available data if a backward bifurcation exists and if an endemic equilibrium exists for $R_0 > 1$. Stability analysis will be performed on any equilibria shown to exist. Further models will incorporate heterogeneous mixing and address the assumption that all individuals have the same level of susceptibility.

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Appendix A. Calculation of a and b for determination of backward bifurcation condition

$$a = \sum_{k,i,j=1} y_k x_i x_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \tag{13}$$

$$b = \sum_{k,i=1} y_k x_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{14}$$

If $a > 0$ and $b > 0$, the bifurcation at $\phi = 0$ is backward. The second derivatives are calculated, evaluated at the DFE $(S^*, U_1^*, U_2^*) = (\frac{A}{\mu}, 0, 0)$ and with $\beta_1 = \beta_1^*$. The formulas for a and b are then used. The non-zero derivatives are as follows:

$$\frac{\partial^2 f_1}{\partial x_2 \partial x_1} = \frac{\partial^2 f_1}{\partial x_1 \partial x_2} = -\frac{\mu(p+\mu+\delta_1)}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \frac{\partial^2 f_2}{\partial x_1 \partial x_2} = \frac{\mu(p+\mu+\delta_1)}{\Lambda},$$
$$\frac{\partial^2 f_2}{\partial x_3 \partial x_2} = \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\beta_3 \mu}{\Lambda},$$
$$\frac{\partial^2 f_3}{\partial x_3 \partial x_2} = \frac{\partial^2 f_3}{\partial x_2 \partial x_3} = -\frac{\beta_3 \mu}{\Lambda},$$
$$\frac{\partial^2 f_1}{\partial x_3 \partial \beta_1} = -1,$$
$$\frac{\partial^2 f_2}{\partial x_2 \partial \beta_1} = 1,$$
$$b = \frac{\partial^2 f_1}{\partial x_3 \partial \beta_1} y_1 x_3 + \frac{\partial^2 f_2}{\partial x_2 \partial \beta_1} y_2 x_2 = (-1)(0)(1) + (1)(1)\left(\frac{\mu+\delta_2}{p}\right) = \frac{\mu+\delta_2}{p} > 0,$$
$$a = \frac{\partial^2 f_1}{\partial x_2 \partial x_1} y_1 x_2 x_1 + \frac{\partial^2 f_1}{\partial x_1 \partial x_2} y_1 x_1 x_2 + \frac{\partial^2 f_2}{\partial x_2 \partial x_1} y_2 x_2 x_1 + \frac{\partial^2 f_2}{\partial x_1 \partial x_2} y_2 x_1 x_2 + \frac{\partial^2 f_2}{\partial x_3 \partial x_2} y_2 x_3 x_2 + \frac{\partial^2 f_2}{\partial x_2 \partial x_3} y_2 x_2 x_3$$
$$+ \frac{\partial^2 f_3}{\partial x_3 \partial x_2} y_3 x_3 x_2 + \frac{\partial^2 f_3}{\partial x_2 \partial x_3} y_3 x_2 x_3 = 2\mu\left(\frac{\mu+\delta_2}{\Lambda p}\right)\left(\frac{-(p+\mu+\delta_1)^2(\mu+\delta_2)}{\mu p} + \beta_3\right).$$

As

$$2\mu\left(\frac{\mu+\delta_2}{\Lambda p}\right) > 0,$$

the backward bifurcation (a, $b > 0$) will occur only if

$$\left|\frac{(p+\mu+\delta_1)^2(\mu+\delta_2)}{\mu p}\right| < \beta_3.$$

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