



Epidemic dynamics on a delayed multi-group heroin epidemic model with nonlinear incidence rate

Xianning Liu^a, Jinliang Wang^{b,*}

^aKey Laboratory of Eco-environments in Three Gorges Reservoir Region (Ministry of Education), School of Mathematics and Statistics, Southwest University, Chongqing 400715, China.

^bSchool of Mathematical Science, Heilongjiang University, Harbin 150080, China.

Communicated by Y. Je Cho

Abstract

For a multi-group Heroin epidemic model with nonlinear incidence rate and distributed delays, we study some aspects of its global dynamics. By a rigorous analysis of the model, we establish that the model demonstrates a sharp threshold property, completely determined by the values of \mathcal{R}_0 : if $\mathcal{R}_0 \leq 1$, then the drug-free equilibrium is globally asymptotically stable; if $\mathcal{R}_0 > 1$, then there exists a unique endemic equilibrium and it is globally asymptotically stable. A matrix-theoretic method based on the Perron eigenvector is used to prove the global asymptotic stability of the drug-free equilibrium and a graph-theoretic method based on Kirchhoff's matrix tree theorem was used to guide the construction of Lyapunov functionals for the global asymptotic stability of the endemic equilibrium. ©2016 All rights reserved.

Keywords: Heroin epidemic model, multi-group, global stability, Lyapunov functionals.

2010 MSC: 34D30, 92D30.

1. Introduction

In recent years, based on the fact that the spread of heroin habituation and addiction shows many phenomena of epidemics, many researchers have paid attentions to investigate epidemic dynamics of heroin users from the mathematical and epidemiological point of view (see e.g. [18, 26, 28] and the references cited therein). For decades, it was believed that the host population is often typically divided into several disjoint classes depending on disease status such as susceptibles, heroin users and heroin users undergoing

*Corresponding author

Email addresses: liuxn@swu.edu.cn (Xianning Liu), jinliangwang@hlju.edu.cn (Jinliang Wang)

treatment, whose numbers are denoted by $S(t)$, $U_1(t)$ and $U_2(t)$, respectively (see e.g. [18, 28] and references cited therein).

However, recent studies have revealed that recovered individuals may revert back to the infective class through the reactivation of the latent infection or incomplete treatment [3]. This is a feature of many infectious disease, for example, human and bovine tuberculosis [15], and herpes [23]. On the other hand, whether having a drug-using partner or having no partner were also significantly associated with a higher risk of relapse situation [14]. Thus it is realistic to consider the relapse phenomenon of frequent heroin using, which may relate to many psychological and behavioral factors, such as perceived stress, negative affects, positive outcome expectancies about substance use [14].

Considering the relapse time is not a constant, distributed parameter over the interval $[0, \tau]$, where τ is the limit superior of the delay, is incorporated into the ODE heroin epidemic model. Liu and Zhang [14] studied the following model:

$$\begin{cases} \frac{dS(t)}{dt} = \Lambda - \beta S(t)U_1(t) - \mu S(t), \\ \frac{dU_1(t)}{dt} = \beta S(t)U_1(t) - pU_1(t) + \int_0^\tau f(s)pU_1(t-s)e^{-(\mu+\delta_2)s} ds - (\mu + \delta_1)U_1(t), \\ \frac{dU_2(t)}{dt} = pU_1(t) - \int_0^\tau f(s)pU_1(t-s)e^{-(\mu+\delta_2)s} ds - (\mu + \delta_2)U_2(t), \end{cases} \quad (1.1)$$

where the epidemic meanings of all parameters in (1.1) are as follows:

Λ : the recruitment rate of entering the susceptible individuals.

μ : the natural death rate of host individuals.

β : the rate of becoming infectious heroin user through contact between susceptible individual and drug user.

p : the rate of drug users who enter treatment.

δ_1 : the sum of rates of drug-related deaths of heroin users and recovery.

δ_2 : the sum of rates of drug-related deaths of heroin users undergoing treatment and immunity to drug addition.

All parameters are assumed to be non-negative for more realistic consideration. It is also assumed that heroin users who quit using drugs but are not longer susceptible individuals. The term

$$\int_0^\tau f(s)pU_1(t-s)e^{-(\mu+\delta_2)s} ds$$

in the equations of (1.1) represents the rate at which the drug users undergoing treatment relapsing to drug users, where $e^{-(\mu+\delta_2)s}$ accounts for the survival probability. f is non-negative and continuous and satisfies $\int_0^\tau f(s)ds = 1$.

Considering the reduced model of (1.1), without the equation of $U_2(t)$, Liu and Zhang [14] studied the dynamics of (1.1). It was concluded that the drug-free equilibrium $E_0 = (\Lambda/\mu, 0)$ is globally asymptotically stable (GAS) if $R_0 = \frac{\beta\Lambda}{p+\mu+\delta_1-p\hat{f}} < 1$, see Theorem 3.1 of [14], where $\hat{f} = \int_0^\tau f(s)e^{-(\mu+\delta_2)s} ds$. Further, if R_0 is more than one, there exists an endemic equilibrium $E^* = (\frac{\Lambda}{\mu R_0}, \frac{\mu(R_0-1)}{\beta})$, which is locally asymptotically stable. The uniform persistence of (1.1) was also established in [14], but no analytic proofs are given to obtain the global stability of endemic equilibrium. By using the direct Lyapunov method and constructing appropriate Lyapunov functional, Huang and Liu in [8] have proved that the endemic equilibrium E^* of (1.1) is globally asymptotically stable whenever it exists.

In this paper, we aim at providing an alternative perspective by focusing on the epidemic dynamics of heroin users. More specifically, we propose a multi-group model described by ordinary differential equations with distributed delays accounting for relapse phenomenon from heroin users undergoing treatment to heroin users. We obtained a similar scenario as that in Huang and Liu in [8] and other multi-group epidemic models.

Since multi-group models can play important roles in considering the heterogeneity (e.g., sex, age, space and so on) of host population, the study of the multi-group heroin model can contribute to aid specialist

teams in devising treatment strategies. It should be pointed here that for a class of multi-group SEIR models described by ordinary differential equations, a graph-theoretic approach to the method of global Lyapunov functions was proposed and used to obtain the global stability of a unique endemic equilibrium in [6]. During the past decades, the multi-group epidemic models have been extensively studied by many authors (see, for example, [5, 6, 9, 12, 13, 21, 24, 25, 27] and the references therein). These studies have enriched our knowledge of epidemic models with heterogeneity.

To the best of our knowledge, the model studied in this paper is new and this is the first result on epidemic dynamics of heroin user in a multi-group model with relapse distribution and nonlinear incidence rate, which provides us with one motivation to conduct our work.

The rest of this paper is organized as follows. In Section 2, we present a multi-group model and its simplified form with distributed delays. Section 3 is devoted to proving that the solutions of our model are positive and bounded. In Section 4, some preliminary results are presented for our model. Sections 5 and 6 provide the proofs of global stability of equilibria. This paper ends with a brief summary.

2. Model formulation

Multi-group models have been developed to study the dynamics of heterogeneity (e.g., sex, age, space and so on) of host population in the literature. We refer the reader to the papers by Guo, Li and Shuai [5, 6, 12], for nice papers on multi-group modeling method and its justification.

The host population is divided into n homogeneous groups. Within i -th group, denote S_i , U_{1i} and U_{2i} the numbers of susceptibles, drug users and drug users undergoing treatment at time t , respectively. Since nonlinear incidence of infection has been observed in disease transmission dynamics, it has been suggested that the standard bilinear incidence rate shall be modified into a nonlinear incidence rate in many researches (see e.g. [10, 16, 17] and references cited therein). Assuming that infection incidence in the i -th group can be calculated as

$$\sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t).$$

The sum in above equation takes into account cross-infections from all groups, and β_{ij} represents the transmission coefficient between compartments S_i and U_{1j} . The nonlinear function $G(S(t))$ is assumed to satisfy

(A₁) $G : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ is continuously differentiable with $G(0) = 0$; $G'(S) > 0$ for $S > 0$.

In this paper, we study some aspects of the global dynamics for the following system of differential equations, n -group heroin epidemic model related to (1.1), to describe the epidemic dynamics of heroin users:

$$\begin{cases} \frac{dS(t)}{dt} = \Lambda_i - \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) - \mu_i S_i(t), \\ \frac{dU_{1i}(t)}{dt} = \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) - p_i U_{1i}(t) + \int_0^\tau f_i(s) p_i U_{1i}(t-s) e^{-(\mu_i + \delta_{2i})s} ds - (\mu_i + \delta_{1i}) U_{1i}, \\ \frac{dU_{2i}(t)}{dt} = p_i U_{1i}(t) - (\mu_i + \delta_{2i}) U_{2i} - \int_0^\tau f_i(s) p_i U_{1i}(t-s) e^{-(\mu_i + \delta_{2i})s} ds, \quad i = 1, 2, \dots, n. \end{cases} \quad (2.1)$$

The parameters are described in Table (1). The initial conditions for model (2.1) are:

$$(S_i(\theta), U_{1i}(\theta), U_{2i}(\theta)) = \phi_i, \quad i = 1, 2, \dots, n, \quad (2.2)$$

where $\phi_i = (\phi_{si}(\theta), \phi_{1i}(\theta), \phi_{2i}(\theta)) \in C([-\tau, 0], \mathbb{R}_+^3)$. $C([-\tau, 0], \mathbb{R}_+^3)$ stands for the space of continuous functions mapping $[-\tau, 0]$ into \mathbb{R}_+^3 , equipped with the supremum norm, $\|\phi_i\| = \max_{\theta \in [-\tau, 0]} |\phi_i(\theta)|$. For the continuity of the solutions of (2.1), we set

$$\phi_{2i}(0) = \int_0^\tau \int_{-s}^0 f_i(s) p_i U_{1i}(\eta) e^{(\mu_i + \delta_{2i})\eta} d\eta ds. \quad (2.3)$$

Table 1: The descriptions of the parameters in the model (2.1).

Parameter	Description
Λ_i	constant recruitment rate in group i ;
μ_i	death rate of individuals in group i ;
p_i	the rate of drug users who enter treatment in group i ;
δ_{1i}	the sum of rates of drug-related deaths of heroin users and recovery in group i ;
δ_{2i}	the sum of rates of drug-related deaths of heroin users undergoing treatment and immunity to drug addition in group i ;
β_{ij}	the rate of becoming infectious heroin user into group i through contact between susceptible individual in group i and drug user in group j .

It follows from the third equation of (2.1) and initial condition (2.3) that

$$U_{2i}(t) = \int_0^\tau \int_{t-s}^t f_i(s)p_i U_{1i}(\eta) e^{-(\mu_i + \delta_{2i})(t-\eta)} d\eta ds.$$

In order to make the mathematics tractable, we make the following assumptions:

Assumption 2.1. Consider system (2.1), we make the following assumptions on parameters:

- (i) $\Lambda_i, \mu_i, p_i, \delta_{1i}, \delta_{2i}$ and β_{ij} are positive for all $i = 1, 2, \dots, n$.
- (ii) β_{ij} is nonnegative, and n -square matrix $(\beta_{ij})_{1 \leq i, j \leq n}$ is irreducible [1].

Denote by $B = (\beta_{ij})_{1 \leq i, j \leq n}$ the contact matrix, which encodes the patterns of contact and transmission among groups that are built into the model.

Based on the fact that U_{2i} does not appear in other equations of (2.1), it suffices only to work on two out of the three variables and therefore, the dynamics are governed by the reduced system

$$\begin{cases} \frac{dS_i(t)}{dt} = \Lambda_i - \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) - \mu_i S_i(t), & i = 1, 2, \dots, n, \\ \frac{dU_{1i}(t)}{dt} = \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) - p_i U_{1i}(t) + \int_0^\tau f_i(s)p_i U_{1i}(t-s) e^{-(\mu_i + \delta_{2i})s} ds - (\mu_i + \delta_{1i}) U_{1i}. \end{cases} \tag{2.4}$$

The initial conditions for model (2.4) are:

$$S_i(\theta) = \phi_{si}(\theta), \quad U_{1i}(\theta) = \phi_{1i}(\theta), \quad i = 1, 2, \dots, n, \tag{2.5}$$

where $\phi_i = (\phi_{si}(\theta), \phi_{1i}(\theta)) \in C([- \tau, 0], \mathbb{R}_+^2)$, the space of continuous functions mapping $[- \tau, 0]$ into \mathbb{R}_+^2 . In the rest of this paper, we shall investigate the dynamics of system (2.4) with initial conditions (2.5).

3. Positivity and boundedness of solutions

The standard fundamental theory of FDEs [7] implies that there is a unique solution

$$(S_i(t), U_{1i}(t)), \quad i = 1, 2, \dots, n$$

to the system with given initial conditions $(\phi_{si}(\theta), \phi_{1i}(\theta), \phi_{2i}(\theta)), i = 1, 2, \dots, n$.

The following results address the well-posedness of system (2.1) with (2.2).

Theorem 3.1. Let $(S_i(t), U_{1i}(t), U_{2i}(t)), i = 1, 2, \dots, n$ be a solution of system (2.1) satisfying (2.2). Then it remains non-negative and bounded for all $t \geq 0$.

Proof. First, for $i = 1, 2, \dots, n$, we prove that $S_i(t) > 0$ for all $t \geq 0$. If there exists a $t_0 > 0$, such that $\min S_i(t_0) = 0$, and $S_i(t) > 0$ for all $t \in (0, t_0)$. Without the loss of generality, we may assume that $S_i(t_0) = 0$. Thus, we obtain $S'_i(t_0) = \Lambda_i > 0$, which leads to a contradiction. Hence, for $i = 1, 2, \dots, n$, $S_i(t) > 0$, for all $t \geq 0$.

Using the variation of constants formula to the second equation of system (2.1), we obtain

$$U_{1i}(t) = e^{-(\mu_i+p_i+\delta_{1i})t}\phi_{1i}(\theta) + \int_0^t e^{-(\mu_i+p_i+\delta_{1i})(t-\xi)} \left[\sum_{j=1}^n \beta_{ij}G(S_i(\xi))U_{1j}(\xi) + \int_0^\tau f_i(s)p_iU_{1i}(\xi-s)e^{-(\mu_i+\delta_{2i})s}ds \right] d\xi.$$

Hence, $U_{1i}(t) \geq 0$ if $\phi_{1i}(\theta) > 0$. Recall that

$$U_{2i}(t) = \int_0^\tau \int_{t-s}^t f_i(s)p_iU_{1i}(\eta)e^{-(\mu_i+\delta_{2i})(t-\eta)}d\eta ds \geq 0.$$

Next, we prove the boundedness of the solutions. From the first equation of (2.1), we have

$$\frac{dS_i(t)}{dt} \leq \Lambda_i - \mu_i S_i(t),$$

it follows that for $i = 1, 2, \dots, n$, we have $\limsup_{t \rightarrow \infty} S_i(t) \leq S_i^0 = \Lambda_i/\mu_i$.

Furthermore, adding all equations of (2.1), we have

$$\begin{aligned} \frac{dS_i(t)}{dt} + \frac{dU_{1i}(t)}{dt} + \frac{dU_{2i}(t)}{dt} &= \Lambda_i - \mu_i(S_i + U_{1i}(t) + U_{2i}(t)) - \delta_{1i}U_{1i}(t) - \delta_{2i}U_{2i}(t) \\ &\leq \Lambda_i - \mu_i(S_i(t) + U_{1i} + U_{2i}(t)), \quad i = 1, 2, \dots, n. \end{aligned}$$

Hence we have $\limsup_{t \rightarrow \infty} (S_i(t) + U_{1i}(t) + U_{2i}(t)) \leq \Lambda_i/\mu_i$. Thus, the compact feasible region

$$\Gamma := \left\{ (S_i, U_{1i}, U_{2i}) \in \mathbb{R}^{3n} : 0 \leq S_i(t) \leq S_i^0, 0 \leq S_i(t) + U_{1i}(t) + U_{2i}(t) \leq \Lambda_i/\mu_i, i = 1, 2, \dots, n \right\}$$

is positively invariant for system (2.1). From the biological significance, we only need to consider (2.4) in the following region

$$\Gamma_0 := \left\{ (S_i, U_{1i},) \in \mathbb{R}^{2n} : 0 \leq S_i(t) \leq S_i^0, 0 \leq S_i(t) + U_{1i}(t) \leq \Lambda_i/\mu_i, i = 1, 2, \dots, n \right\}.$$

That is, the well-posedness of the system (2.4) directly follows. This completes the proof. □

4. Basic reproduction number and equilibria

It is easy to see system (2.4) always admits an equilibrium which is labeled as $P_0 = (S_1^0, 0, \dots, S_n^0, 0)$, where $S_i^0 = \frac{\Lambda_i}{\mu_i}$, $i = 1, 2, \dots, n$, and it is called the drug-free equilibrium (DFE). It can be verified that solutions of (2.4) with initial condition

$$(S_1(0), U_{11}(0), \dots, S_n(0), U_{1n}(0)) \in \mathbb{R}_+^{2n}$$

remain non-negative. Therefore, in what follows, we consider model (2.4) in \mathbb{R}_+^{2n} . Let

$$Q_i := \int_0^\tau f_i(s)e^{-(\mu_i+\delta_{2i})s}ds. \tag{4.1}$$

It can be verified that $Q_i \in (0, 1)$ for all i .

For system (2.4), let

$$\mathcal{F} = \begin{pmatrix} \beta_{11}G(S_1^0) & \beta_{12}G(S_1^0) & \cdots & \beta_{1n}G(S_1^0) \\ \vdots & \vdots & \ddots & \vdots \\ \beta_{n1}G(S_n^0) & \beta_{n2}G(S_n^0) & \cdots & \beta_{nn}G(S_n^0) \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \text{diag}(\mu_i + \delta_{1i} + p_i - p_i Q_i),$$

then the next generation matrix is

$$\mathcal{F}\mathcal{V}^{-1} = \begin{pmatrix} \frac{\beta_{11}G(S_1^0)}{\mu_1 + \delta_{11} + p_1 - p_1 Q_1} & \frac{\beta_{12}G(S_1^0)}{\mu_2 + \delta_{12} + p_2 - p_2 Q_2} & \cdots & \frac{\beta_{1n}G(S_1^0)}{\mu_n + \delta_{1n} + p_n - p_n Q_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\beta_{n1}G(S_n^0)}{\mu_1 + \delta_{11} + p_1 - p_1 Q_1} & \frac{\beta_{n2}G(S_n^0)}{\mu_2 + \delta_{12} + p_2 - p_2 Q_2} & \cdots & \frac{\beta_{nn}G(S_n^0)}{\mu_n + \delta_{1n} + p_n - p_n Q_n} \end{pmatrix}.$$

Thus the basic reproduction number of model (2.4) is defined by the spectral radius of the next generation matrix (see e.g. [4, 22]):

$$\mathfrak{R}_0 = \rho(\mathcal{F}\mathcal{V}^{-1}),$$

where $\rho(\cdot)$ denotes the spectral radius of matrix. It follows from the fact that $\rho(\mathcal{F}\mathcal{V}^{-1}) = \rho(\mathcal{V}^{-1}\mathcal{F})$, we have

$$\mathfrak{R}_0 = \rho(M^0), \tag{4.2}$$

where

$$M^0 = \mathcal{V}^{-1}\mathcal{F} = \begin{pmatrix} \frac{\beta_{11}G(S_1^0)}{\mu_1 + \delta_{11} + p_1 - p_1 Q_1} & \frac{\beta_{12}G(S_1^0)}{\mu_1 + \delta_{11} + p_1 - p_1 Q_1} & \cdots & \frac{\beta_{1n}G(S_1^0)}{\mu_1 + \delta_{11} + p_1 - p_1 Q_1} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\beta_{n1}G(S_n^0)}{\mu_n + \delta_{1n} + p_n - p_n Q_n} & \frac{\beta_{n2}G(S_n^0)}{\mu_n + \delta_{1n} + p_n - p_n Q_n} & \cdots & \frac{\beta_{nn}G(S_n^0)}{\mu_n + \delta_{1n} + p_n - p_n Q_n} \end{pmatrix}.$$

Since it can be verified that system (2.4) satisfies conditions $(A_1) - (A_5)$ of [22, Theorem 2], we have the following lemma.

Lemma 4.1. *For system (2.4), the DFE P_0 is locally asymptotically stable if $\mathfrak{R}_0 < 1$ while it is unstable if $\mathfrak{R}_0 > 1$.*

Equilibrium solution of system (2.4) given by solution $P^* = (S_1^*, U_{1i}^*, \dots, S_n^*, U_{1n}^*) \in \mathbb{R}^{2n}$ in the interior of Γ is called an endemic equilibrium (EE), where $S_i^*, U_{1i}^* > 0$ satisfy the equilibrium equations:

$$\Lambda_i - \sum_{j=1}^n \beta_{ij}G(S_i^*)U_{1j}^* - \mu_i S_i^* = 0, \tag{4.3}$$

and

$$(\mu_i + \delta_{1i} + p_i - p_i Q_i)U_{1i}^* = \sum_{j=1}^n \beta_{ij}G(S_i^*)U_{1j}^*. \tag{4.4}$$

5. Global stability of the DFE

The global dynamical behaviors of the DFE of system (2.4) is completely established in the following theorem. Let

$$H(z) = z - \ln z - 1, \quad \forall z > 0. \tag{5.1}$$

Obviously, $H : \mathbb{R}^+ \rightarrow \mathbb{R}^+$ attains its strict global minimum at $z = 1$ and $H(1) = 0$.

Then we have the following theorem:

Theorem 5.1. *Consider system (2.4) and suppose that (A_1) holds. Then, the DFE of system (2.4) is globally asymptotically stable if $\mathfrak{R}_0 \leq 1$ and it is unstable if $\mathfrak{R}_0 > 1$.*

Proof. Since $B = (\beta_{ij})_{1 \leq i, j \leq n}$ is irreducible, the nonnegative matrix $M^0 = \left(\frac{\beta_{ij} G(S_i^0)}{\mu_i + \delta_{1i} + p_i - p_i Q_i} \right)_{n \times n}$ is also irreducible, and M^0 has a positive left eigenvector $(\omega_1, \omega_2, \dots, \omega_n)$ corresponding to the spectral radius $\Re_0 = \rho(M^0) \leq 1$. Let

$$c_i = \frac{\omega_i}{\mu_i + \delta_{1i} + p_i - p_i Q_i} > 0.$$

Consider a Lyapunov functional

$$L_{DFE} = \sum_{i=1}^n c_i \left[G(S_i^0) H \left(\frac{G(S_i(t))}{G(S_i^0)} \right) + U_{1i}(t) + U_{i+} \right],$$

where U_{i+} is given as $\int_0^\tau \int_0^s f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} U_{1i}(t - \sigma) d\sigma ds$.

By (5.1) and assumption (A_1) , we know that $L_{DFE} \geq 0$ with equality if and only if $S_i(t) = S_i^0, U_{1i}(t) = 0$ and $U_{1i}(t - s) = 0$ for almost all $s \geq 0$.

Using integration by parts, we can compute the derivative of U_{i+} along the solution of (2.4) as follows

$$\begin{aligned} \frac{dU_{i+}}{dt} &= \int_0^\tau f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} \left[\frac{d}{dt} \int_0^s U_{1i}(t - \sigma) d\sigma \right] ds \\ &= - \int_0^\tau f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} \int_0^s \left[\frac{d}{d\sigma} U_{1i}(t - \sigma) \right] d\sigma ds \\ &= \int_0^\tau f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} \left[U_{1i}(t) - U_{1i}(t - s) \right] ds \\ &= Q_i p_i U_{1i}(t) - \int_0^\tau f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} U_{1i}(t - s) ds. \end{aligned}$$

Thus the derivative of L_{DFE} is given as

$$\begin{aligned} \left. \frac{dL_{DFE}}{dt} \right|_{(2.4)} &= \sum_{i=1}^n c_i \left\{ \left[\frac{G(S_i(t)) - G(S_i^0)}{G(S_i(t))} \right] \left[\Lambda_i - \mu_i S_i(t) - \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) \right] \right. \\ &\quad + \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) - p_i U_{1i}(t) + \int_0^\tau f_i(s) p_i U_{1i}(t - s) e^{-(\mu_i + \delta_{2i})s} ds - (\mu_i + \delta_{1i}) U_{1i} \\ &\quad \left. + Q_i p_i U_{1i}(t) - \int_0^\tau f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} U_{1i}(t - s) ds \right\} \\ &= \sum_{i=1}^n c_i \left[\frac{G(S_i(t)) - G(S_i^0)}{G(S_i(t))} \right] \left[\mu_i S_i^0 - \mu_i S_i(t) \right] \\ &\quad + \sum_{i=1}^n \frac{\omega_i}{\mu_i + \delta_{1i} + p_i - p_i Q_i} \left[\sum_{j=1}^n \beta_{ij} G(S_i^0) U_{1j} - (\mu_i + \delta_{1i} + p_i - p_i Q_i) U_{1i}(t) \right] \\ &= \sum_{i=1}^n c_i \left[\frac{G(S_i(t)) - G(S_i^0)}{G(S_i(t))} \right] \left[\mu_i S_i^0 - \mu_i S_i(t) \right] + (\omega_1, \omega_2, \dots, \omega_n) (M^0 U_1 - U_1) \\ &\leq \left(\rho(M^0) - 1 \right) (\omega_1, \omega_2, \dots, \omega_n) U_1 \leq 0, \quad \text{if } \Re_0 \leq 1. \end{aligned} \tag{5.2}$$

Here $U_1 = (U_{11}(t), U_{12}(t), \dots, U_{1n}(t))^T$. Let

$$Y = \left\{ (S_1, U_{11}, \dots, S_n, U_{1n}) \mid L'_{DFE} |_{(2.4)} = 0 \right\},$$

and Z be the largest compact invariant set in Y . We will show $Z = \{(S_1^0, 0, \dots, S_n^0, 0)\}$. From inequality (2.4) and $c_i > 0$, $\frac{dL_{DFE}}{dt}|_{(2.4)} = 0$ implies that $\left[\frac{G(S_i(t))-G(S_i^0)}{G(S_i(t))}\right] \left[\mu_i - \mu_i S_i(t)\right] = 0$, and thus $S_i(t) = S_i^0 = \frac{\Lambda_i}{\mu_i}$. Hence, from the first equation of (2.4), we obtain

$$\sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) = 0,$$

and thus

$$\beta_{ij} G(S_i(t)) U_{1j}(t) = 0$$

for all $t \geq 0$ and $1 \leq i, j \leq n$. Then, by irreducibility of B , for each j , there exists $i \neq j$ such that $\beta_{ij} \neq 0$, thus $U_{1j}(t) = 0$, $j = 1, 2, \dots, n$. Therefore $Z = (S_1^0, 0, \dots, S_n^0, 0)$. Thus, from the LaSalle’s invariance principle [11], it follows that the DFE P_0 is globally asymptotically stable in Γ .

If $\mathfrak{R}_0 > 1$ and $U_1 \neq 0$, it follows that $(\rho(M^0) - 1)(\omega_1, \omega_2, \dots, \omega_n)U_1 > 0$, which implies that, in a sufficiently small enough neighborhood of $(S_1^0, 0, \dots, S_n^0, 0)$, $\frac{dL_{DFE}}{dt}|_{(2.4)} > 0$. Therefore, $(S_1^0, 0, \dots, S_n^0, 0)$ is unstable if $\mathfrak{R}_0 > 1$. □

6. Global stability of the EE

In this section, question such as the global stability of the EE will be analyzed. Before going into details, we need one lemma to ensure that EE exists when $\mathfrak{R}_0 > 1$. In fact, an argument similar to that in the proof of [27, Theorem 3.2] can be used to show that system (2.4) is uniformly persistent. Together with the uniform boundedness of solutions in Γ_0 , we arrive at the following lemma, illustrating that EE of system (2.4) exists in Γ_0 (see e.g. [2, Theorem 2.8.6] or [20, Theorem D.3]).

Lemma 6.1. *If $\mathfrak{R}_0 > 1$, then system (2.4) is uniformly persistent. Furthermore, there exists an P^* in the interior Γ_0 of Γ .*

Using Lemma 6.1, we prove the following theorem, which is one of the main results of this paper.

Theorem 6.2. *Consider system (2.4) and suppose that (A_1) holds. If $\mathfrak{R}_0 > 1$ and $(S_i(t), U_{1i}(t))$ is a solution to (2.4) that lies in Γ , then*

$$\lim_{t \rightarrow \infty} (S_i(t), U_{1i}(t)) = P^* = (S_1^*, U_{11}^*, \dots, S_n^*, U_{1n}^*)$$

in the interior of Γ_0 .

Proof. Define a Lyapunov functional as

$$L_{EE} = L_S + L_I + L_{i-},$$

where

$$\begin{cases} L_S = \int_{S_i^*}^{S_i(t)} \frac{G(\lambda) - G(S_i^*)}{G(\lambda)} d\lambda; \\ L_I = U_{1i}^* H\left(\frac{U_{1i}}{U_{1i}^*}\right); \\ L_{i-} = \int_0^\tau \int_0^s f_i(s) p_i e^{-(\mu_2 + \delta_{2i})s} U_{1i}^* H\left(\frac{U_{1i}(t-\sigma)}{U_{1i}^*}\right) d\sigma ds. \end{cases} \tag{6.1}$$

It follows from (A_1) that $L_{EE} \geq 0$ with equality if and only if $S_i(t) = S_i^*$, $U_{1i}(t) = U_{1i}^*$ and $U_{1i}(t-\sigma) = U_{1i}^*$ for almost all $\sigma \geq 0$. In fact, the non-negativity of L_I and L_{i-} are obvious. $L_S \geq 0$ based on the facts that $\left(1 - \frac{G(S_i^*)}{G(S_i)}\right)(S_i - S_1^*) \geq 0$ when $S_i \geq S_i^*$ and $\left(1 - \frac{G(S_i^*)}{G(S_i)}\right)(S_1^* - S_i) \geq 0$ when $S_i \leq S_i^*$.

Differentiating L_S along the solution of system (2.4) and using equilibrium equations (4.3)-(4.4), we obtain

$$\begin{aligned} \frac{dL_S}{dt} \Big|_{(2.4)} &= \frac{G(S_i) - G(S_i^*)}{G(S_i)} \left[\mu_i S_i^* + \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}^* - \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) - \mu_i S_i(t) \right] \\ &= \frac{G(S_i) - G(S_i^*)}{G(S_i)} \left[\mu_i S_i^* - \mu_i S_i(t) \right] + \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}^* - \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) \\ &\quad - \sum_{j=1}^n \beta_{ij} \frac{[G(S_i^*)]^2 U_{1j}^*}{G(S_i)} + \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}(t). \end{aligned} \tag{6.2}$$

Differentiating L_I along the solution of system (2.4), we obtain

$$\begin{aligned} \frac{dL_I}{dt} \Big|_{(2.4)} &= \frac{U_{1i} - U_{1i}^*}{U_{1i}} \left\{ - \left[\sum_{j=1}^n \beta_{ij} G(S_i^*) \frac{U_{1j}^*}{U_{1i}^*} + p_i Q_i \right] U_{1i}(t) + \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) \right. \\ &\quad \left. + \int_0^\tau f_i(s) p_i U_{1i}(t-s) e^{-(\mu_i + \delta_{2i})s} ds \right\} \\ &= - \sum_{j=1}^n \beta_{ij} G(S_i^*) \frac{U_{1j}^* U_{1i}(t)}{U_{1i}^*} - p_i Q_i U_{1i}(t) + \sum_{j=1}^n \beta_{ij} G(S_i(t)) U_{1j}(t) \\ &\quad + \int_0^\tau f_i(s) p_i U_{1i}(t-s) e^{-(\mu_i + \delta_{2i})s} ds + \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}^* + p_i Q_i U_{1i}^* \\ &\quad - \sum_{j=1}^n \beta_{ij} \frac{G(S_i(t)) U_{1j}(t) U_{1i}^*}{U_{1i}(t)} - \int_0^\tau f_i(s) p_i \frac{U_{1i}(t-s) U_{1i}^*}{U_{1i}(t)} e^{-(\mu_i + \delta_{2i})s} ds. \end{aligned} \tag{6.3}$$

Taking derivative to L_{i-} with respect to t and using integration by parts, we obtain

$$\begin{aligned} \frac{dL_{i-}}{dt} \Big|_{(2.4)} &= \int_0^\tau U_{1i}^* f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} \frac{d}{dt} \left[\int_0^s H \left(\frac{U_{1i}(t-\sigma)}{U_{1i}^*} \right) d\sigma \right] ds \\ &= - \int_0^\tau U_{1i}^* f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} \int_0^s \frac{d}{d\sigma} \left[H \left(\frac{U_{1i}(t-\sigma)}{U_{1i}^*} \right) \right] d\sigma ds \\ &= - \int_0^\tau U_{1i}^* f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} H \left(\frac{U_{1i}(t-\sigma)}{U_{1i}^*} \right) \Big|_0^{\sigma=s} ds \\ &= \int_0^\tau f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} \left[U_{1i}(t) - U_{1i}(t-s) + U_{1i}^* \ln \frac{U_{1i}(t-s)}{U_{1i}(t)} \right] ds. \end{aligned} \tag{6.4}$$

Combining equations (6.2)-(6.4) yields

$$\begin{aligned} \frac{dL_{EE}}{dt} \Big|_{(2.4)} &= \frac{G(S_i) - G(S_i^*)}{G(S_i)} \left[\mu_i S_i^* - \mu_i S_i(t) \right] \\ &\quad + \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}^* \left[2 - \frac{G(S_i(t)) U_{1j}(t) U_{1i}^*}{G(S_i^*) U_{1j}^* U_{1i}(t)} - \frac{G(S_i^*)}{G(S_i)} + \frac{U_{1j}(t)}{U_{1j}^*} - \frac{U_{1i}(t)}{U_{1i}^*} \right] \\ &\quad - U_{1i}^* \int_0^\tau f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} H \left(\frac{U_{1i}(t-s)}{U_{1i}(t)} \right) ds \\ &= \frac{G(S_i) - G(S_i^*)}{G(S_i)} \left[\mu_i S_i^* - \mu_i S_i(t) \right] - \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}^* H \left(\frac{G(S_i^*)}{G(S_i(t))} \right) \end{aligned}$$

$$\begin{aligned}
 & - \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}^* H \left(\frac{G(S_i(t)) U_{1j}(t) U_{1i}^*}{G(S_i^*) U_{1j}^* U_{1i}(t)} \right) \\
 & - U_{1i}^* \int_0^\tau f_i(s) p_i e^{-(\mu_i + \delta_{2i})s} H \left(\frac{U_{1i}(t-s)}{U_{1i}(t)} \right) ds \\
 & + \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}^* \left[\frac{U_{1j}(t)}{U_{1j}^*} - \frac{U_{1i}(t)}{U_{1i}^*} - \ln \frac{U_{1i}^* U_{1j}(t)}{U_{1i}(t) U_{1j}^*} \right] \\
 & \leq \sum_{j=1}^n \beta_{ij} G(S_i^*) U_{1j}^* \left[\frac{U_{1j}(t)}{U_{1j}^*} - \frac{U_{1i}(t)}{U_{1i}^*} - \ln \frac{U_{1i}^* U_{1j}(t)}{U_{1i}(t) U_{1j}^*} \right].
 \end{aligned}$$

Here we have used the following inequalities:

$$\left\{ \begin{aligned}
 & \frac{G(S_i) - G(S_i^*)}{G(S_i)} \left[\mu_i S_i^* - \mu_i S_i(t) \right] \leq 0; \\
 & H \left(\frac{G(S_i(t))}{G(S_i^*)} \right) \geq 0; \\
 & H \left(\frac{G(S_i(t)) U_{1j}(t) U_{1i}^*}{G(S_i^*) U_{1j}^* U_{1i}(t)} \right) \geq 0; \\
 & H \left(\frac{U_{1i}(t-s)}{U_{1i}(t)} \right) \geq 0.
 \end{aligned} \right. \tag{6.5}$$

Further, we set

$$\bar{\beta}_{ij} = \beta_{ij} G(S_i^*) U_{1j}^*, \quad 1 \leq i, j \leq n,$$

and

$$\bar{B} = \begin{bmatrix} \sum_{l \neq 1} \bar{\beta}_{1l} & -\bar{\beta}_{21} & \cdots & -\bar{\beta}_{n1} \\ -\bar{\beta}_{12} & \sum_{l \neq 2} \bar{\beta}_{2l} & \cdots & -\bar{\beta}_{n2} \\ \vdots & \vdots & \ddots & \vdots \\ -\bar{\beta}_{1n} & -\bar{\beta}_{2n} & \cdots & \sum_{l \neq n} \bar{\beta}_{nl} \end{bmatrix}.$$

Note that \bar{B} is the Laplacian matrix of the matrix $(\bar{\beta}_{ij})_{1 \leq i, j \leq n}$. Since $(\beta_{ij})_{1 \leq i, j \leq n}$ is irreducible, it follows that matrices $(\bar{\beta}_{ij})_{1 \leq i, j \leq n}$ and \bar{B} are also irreducible. Let C_{ij} denote the cofactor of the (i, j) entry of \bar{B} . We know that system $\bar{B}v = 0$ has a positive solution $v = (v_1, v_2, \dots, v_n)$, where $v_i = C_{ii} > 0$ for $i = 1, 2, \dots, n$.

Set

$$L = \sum_{i=1}^n v_i L_{EE},$$

then

$$\begin{aligned}
 \sum_{i=1}^n v_i \frac{dL_{EE}}{dt} \Big|_{(2.4)} & \leq \sum_{i,j=1}^n v_i \bar{\beta}_{ij} \left[\frac{U_{1j}(t)}{U_{1j}^*} - \frac{U_{1i}(t)}{U_{1i}^*} - \ln \frac{U_{1i}^* U_{1j}(t)}{U_{1i}(t) U_{1j}^*} \right] \\
 & = \sum_{i,j=1}^n v_i \bar{\beta}_{ij} \left[\frac{U_{1j}(t)}{U_{1j}^*} - \frac{U_{1i}(t)}{U_{1i}^*} \right] - \sum_{i,j=1}^n v_i \bar{\beta}_{ij} \left[\ln \frac{U_{1i}^* U_{1j}(t)}{U_{1i}(t) U_{1j}^*} \right] \\
 & =: H_1 - H_2,
 \end{aligned}$$

where

$$\left\{ \begin{aligned}
 & H_1 = \sum_{i,j=1}^n v_i \bar{\beta}_{ij} \left[\frac{U_{1j}(t)}{U_{1j}^*} - \frac{U_{1i}(t)}{U_{1i}^*} \right]; \\
 & H_2 = \sum_{i,j=1}^n v_i \bar{\beta}_{ij} \left[\ln \frac{U_{1i}^* U_{1j}(t)}{U_{1i}(t) U_{1j}^*} \right].
 \end{aligned} \right.$$

Next, we prove that $H_1 \equiv 0$ for all $U_{11}, U_{12}, \dots, U_{1n} > 0$. From $\bar{B}v = 0$, we have

$$\sum_{j=1}^n \bar{\beta}_{ji} v_j = \sum_{k=1}^n \bar{\beta}_{ik} v_i.$$

Putting $\bar{\beta}_{ji} = \beta_{ji} G(S_j^*) U_{1i}^*$ into above yields

$$\sum_{j=1}^n \beta_{ji} G(S_j^*) U_{1i}^* v_j = \sum_{k=1}^n \beta_{ik} G(S_i^*) U_{1k}^* v_i, \quad i = 1, 2, \dots, n.$$

This implies that

$$\sum_{i,j=1}^n v_i \beta_{ij} G(S_i^*) U_{1j}(t) = \sum_{i=1}^n U_{1i} \sum_{j=1}^n \beta_{ji} G(S_j^*) v_j = \sum_{i=1}^n \frac{U_{1i}}{U_{1i}^*} \sum_{k=1}^n \beta_{ik} G(S_i^*) U_{1k}^* v_i = \sum_{i,j=1}^n v_i \beta_{ij} G(S_i^*) U_{1j}^* \frac{U_{1i}}{U_{1i}^*},$$

and thus $H_1 \equiv 0$ for all $U_{11}, U_{12}, \dots, U_{1n} > 0$. Similar to the arguments in Section 5 of [19], just replacing $k = 1$, $E_k = U_{1i}$ and $E_j = U_{1j}$ in the equations (5.9) and (5.10) of [19], we can easily obtain $H_2 \equiv 0$ for all $U_{11}, U_{12}, \dots, U_{1n} > 0$, from the classic graph-theoretic method based on Kirchoff's matrix tree theorem.

Therefore, the function $L = \sum_{i=1}^n v_i L_{EE}$ as defined in the Theorem 3.1 of [12] is a Lyapunov function for system (2.4), namely, $\frac{dL}{dt} \leq 0$ for all $(S_1, U_{11}, S_2, U_{12}, \dots, S_n, U_{1n}) \in \Gamma$. One can only show that the largest invariant subset where $\{\frac{dL}{dt} = 0\}$ is the singleton $\{P^*\}$ using the same argument as that in [6, 12, 19]. By LaSalle's invariance principle, P^* is globally asymptotically stable in Γ . That is, $\lim_{t \rightarrow \infty} (S_i(t), U_{1i}(t)) = P^* = (S_1^*, U_{11}^*, \dots, S_n^*, U_{1n}^*)$. This completes the proof of Theorem 6.2. \square

7. Conclusion

In this paper, we considered a delayed multi-group heroin epidemic model with relapse phenomenon and nonlinear incidence rate. The main contributions of the paper are the proofs of global stability of equilibria. The distributed delays are introduced by the time needed to return to an untreated drug user, which are not constants but vary according to drug users' different temporal, social, and physical contexts. Although including the nonlinear incidence rate combined with the relapse distributed delays into the multi-group model leads to the analysis of the resulting system becoming very complex, we are able to make a rigorous analysis of the model and establish a sharp threshold property. By using the method of constructing Lyapunov functionals based on graph-theoretical approach for coupled systems, sufficient conditions for the global stability of equilibria are given.

Acknowledgements

The authors would like to thank the editors and the referees for their helpful comments. J. Wang was supported by National Natural Science Foundation of China (Nos. 11401182, 11471089), Science and Technology Innovation Team in Higher Education Institutions of Heilongjiang Province (No. 2014TD005), X. Liu was supported by the National Natural Science Foundation of China (No. 11271303).

References

- [1] A. Berman, R. J. Plemmons, *Nonnegative matrices in the mathematical sciences*, Academic Press, New York, (1979).2.1
- [2] N. P. Bhatia, G. P. Szegő, *Dynamical Systems: Stability Theory and Applications*, in: *Lecture Notes in Mathematics*, vol. 35, Springer, Berlin, (1967).6
- [3] C. Chin, *Control of Communicable Diseases Manual*, American Public Health Association, Washington, (1999).1
- [4] O. Diekmann, J. A. P. Heesterbeek, J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*, J. Math. Biol., **28** (1990), 365–382.4

- [5] H. Guo, M. Y. Li, Z. Shuai, *Global stability of the endemic equilibrium of multigroup SIR epidemic models*, Can. Appl. Math. Q., **14** (2006), 259–284.1, 2
- [6] H. Guo, M. Y. Li, Z. Shuai, *A graph-theoretic approach to the method of global Lyapunov functions*, Proc. Amer. Math. Soc., **136** (2008), 2793–2802.1, 2, 6
- [7] J. K. Hale, *Theory of Functional Differential Equations*, Springer, New York, (1997).3
- [8] G. Huang, A. Liu, *A note on global stability for heroin epidemic model with distributed delay*, Appl. Math. Lett., **26** (2013), 687–691.1
- [9] G. Huang, J. Wang, J. Zu, *Global dynamics of multi-group dengue disease model with latency distributions*, Math. Meth. Appl. Sci., **38** (2015), 2703–2718.1
- [10] A. Korobeinikov, *Global properties of infectious disease models with nonlinear incidence*, Bull. Math. Biol., **69** (2007), 1871–1886.2
- [11] J. P. Lasalle, *The Stability of Dynamical Systems*, in: *Regional Conference Series in Applied Mathematics*, Philadelphia, SIAM, (1976). 5
- [12] M. Y. Li, Z. Shuai, *Global-stability problem for coupled systems of differential equations on networks*, J. Differential Equations, **248** (2010), 1–20.1, 2, 6
- [13] M. Y. Li, Z. Shuai, C. Wang, *Global stability of multi-group epidemic models with distributed delays*, J. Math. Anal. Appl., **361** (2010), 38–47.1
- [14] J. Liu, T. Zhang, *Global behaviour of a heroin epidemic model with distributed delay*, Appl. Math. Lett., **24** (2011), 1685–1692.1, 1
- [15] S. W. Martin, *Livestock Disease Eradication: Evaluation of the Cooperative State Federal Bovine Tuberculosis Eradication Program*, National Academy Press, Washington, (1994).1
- [16] C. C. McCluskey, *Global stability for an SIR epidemic model with delay and nonlinear incidence*, Nonlinear Anal. Real World Appl., **11** (2010), 3106–3109.2
- [17] C. C. McCluskey, *Global stability of an SIR epidemic model with delay and general nonlinear incidence*, Math. Biosci. Eng., **7** (2010), 837–850.2
- [18] G. Mulone, B. Straughan, *A note on heroin epidemics*, Math. Biosci., **218** (2009), 138–141.1
- [19] H. Shu, D. Fan, J. Wei, *Global stability of multi-group SEIR epidemic models with distributed delays and nonlinear transmission*, Nonlinear Anal. Real World Appl., **13** (2012), 1581–1592.6
- [20] H. Smith, P. Waltman, *The Theory of the Chemostat: Dynamics of Microbial Competition*, Cambridge University Press, Cambridge, (1995).6
- [21] R. Sun, *Global stability of the endemic equilibrium of multigroup SIR models with nonlinear incidence*, Comput. Math. Appl., **60** (2010), 2286–2291.1
- [22] P. van den Driessche, J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci., **180** (2002), 29–48.4, 4
- [23] K. E. VanLandingham, H. B. Marsteller, G. W. Ross, F. G. Hayden, *Relapse of herpes simplex encephalitis after conventional acyclovir therapy*, JAMA, **259** (1988), 1051–1053.1
- [24] J. Wang, X. Liu, J. Pang, D. Hou, *Global dynamics of a multi-group epidemic model with general exposed distribution and relapse*, Osaka. J. Math., **52** (2015), 117–138.1
- [25] J. Wang, J. Pang, X. Liu, *Modeling diseases with relapse and nonlinear incidence of infection: a multi-group epidemic model*, J. Biol. Dynam., **8** (2014), 99–116.1
- [26] X. Wang, J. Yang, X. Li, *Dynamics of a heroin epidemic model with very population*. Appl. Math., **2** (2011), 732–738.1
- [27] J. Wang, J. Zu, X. Liu, G. Huang, J. Zhang, *Global dynamics of a multi-group epidemic model with general relapse distribution and nonlinear incidence rate*, J. Biol. Sys., **20** (2012), 235–258.1, 6
- [28] E. White, C. Comiskey, *Heroin epidemics, treatment and ODE modelling*, Math. Biosci., **208** (2007), 312–324.1