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Disease emergence in multi-host epidemic models

Robert K. McCormack,

Linda J. S. Allen

Department of Mathematics and Statistics, Texas Tech University, Lubbock, Texas 79409-1042

Abstract

Most pathogens are capable of infecting multiple hosts. These multiple hosts provide many avenues for the disease to emerge. In this investigation, we formulate and analyze multi-host epidemic models and determine conditions under which the disease can emerge. In particular, SIS and SIR epidemic models are formulated for a pathogen that can infect n different hosts. The basic reproduction number is computed and shown to increase with n, the number of hosts that can be infected. Therefore, the possibility of disease emergence increases with the number of hosts infected. The SIS model for two hosts is studied in detail. Necessary and sufficient conditions are derived for the global stability of an endemic equilibrium. Numerical examples illustrate the dynamics of the two- and three-host epidemic models. The models have applications to hantavirus in rodents and other zoonotic diseases with multiple hosts.

Keywords

multi-host epidemic model; basic reproduction number; hantavirus

1. Introduction

Most pathogens are capable of infecting multiple hosts, and in addition, many of these pathogens can also be transmitted by multiple hosts (Woolhouse *et al*., 2001). According to Woolhouse *et al*. (2001), approximately sixty percent of human pathogens are zoonotic causing diseases such as Lyme disease, influenza, sleeping sickness, rabies, and hantavirus pulmonary syndrome. To prevent human infection from these zoonoses, it is necessary to identify the animal reservoirs (Haydon *et al*., 2002). One or more animal reservoirs may exist depending on the disease and the location. For example, domestic dogs and jackals (*Canis adustus*) in Africa may both serve as reservoirs for the rabies virus (Haydon *et al*., 2002; Rhodes *et al*., 1998). In Britain, red foxes (*Vulpes vulpes*) are a reservoir population for rabies in wildlife and European badgers (Meles meles) may be a secondary host (Smith, 2002). Eliminating rabies in only one of these populations may be insufficient to prevent the disease from spreading to humans.

Hantaviruses are rodent-borne zoonotic agents that cause hemorrhagic fever with renal syndrome (HFRS) in humans throughout Europe and Asia (Schmaljohn & Hjelle, 1997). In the Americas, the infection in humans is known as hantavirus pulmonary syndrome (HPS) (Schmaljohn & Hjelle, 1997). Thirty different hantaviruses are recognized throughout the world (Mills *et al*., 1999; Schmaljohn & Hjelle, 1997). But each virus is primarily associated

with one reservoir species that is indigenous to a particular geographic region (Chu *et al.*, 2003; Mills *et al.*, 1999; Schmaljohn & Hjelle, 1997; Yahnke *et al.*, 2001). Hantaviruses are transmitted to humans primarily through inhalation of aerosolized saliva and/or excreta from infected rodents (Mills *et al.*, 1999; Schmaljohn & Hjelle, 1997). Spillover infection to other rodents has been reported (Chu *et al.*, 2003), but it is generally thought that these other rodents cannot maintain the disease. The role played by these other species in disease emergence or persistence is not clear.

In the present study, we are interested in the role that multiple hosts play in the emergence and persistence of disease. Our models were developed with hantavirus infection in mind, where there is a primary reservoir host and other rodents are referred to as spillover species. Rodents generally prefer certain habitats (e.g., cropland, pasture, forest) and those species carrying hantavirus strains transmissible to humans are often associated with human habitations or agriculture (Mills *et al.*, 1999; Yahnke *et al.*, 2001). As anthropogenic influences continually change landscape patterns (e.g., clearcutting of forests for cropland and pastures), there is greater overlap in species habitats resulting in increased contacts between rodent reservoir hosts, other rodents, and humans.

In our multi-host epidemic models, we assume that each individual in a host population is classified according to their disease status, either susceptible (S), infected (I), or recovered and immune to reinfection (R). Rodents infected with hantavirus do not shed virus for their entire life. Therefore, we study two different types of models. In the first model, infected rodents recover but do not develop immunity (SIS), and in the second model, infected rodents recover and develop immunity (SIR).

Allen and Cormier (1996) studied SIS epidemic models, similar to ours, but they considered only two hosts with no disease-related deaths. Holt and Pickering (1985) studied a two-host SIS epidemic model with exponential growth. Begon *et al.* (1992) included self regulation in the two-host model and free-living infective stages (Begon and Bowers, 1994). Equilibria and local stability analyses were performed for these latter models. Gandon (2004) applied multi-host SIS models to the study of parasite evolutionary dynamics. An SIS epidemic model with multiple groups within a single population was applied to gonorrhea by Lajmanovich and Yorke (1976). In this latter model, the total population size was constant and there were no births nor deaths. This model and others with multiple groups were studied by Capasso (1993) using quasimonotone methods. Other two-species models with disease affecting at least one of the two species such as predator and prey or two competing species have been analyzed (e.g., Chattopadhyay & Arino, 1999; Hadeler & Freedman, 1999; Han & Hethcote, 2001; Hethcote *et al.*, 2004; Venturino, 1994; Venturino, 1995; 2001; 2002). In our multi-host epidemic models, species do not have a predator-prey or competitive relationship. They are related only through infection by a common pathogen. Previous models developed for hantavirus infection in rodents have been restricted to one host (Abramson & Kenkre, 2002; Abramson *et al.*, 2003; Allen *et al.*, 2003; 2006; Sauvage *et al.* 2003). In this investigation, we extend these models to n hosts. We assume that multiple hosts can be infected with the disease but one species is the primary reservoir host. The multi-host epidemic models are described in Sect. 2. The basic reproduction number, an important threshold parameter in epidemiology, is computed in Sect. 3. It is shown that

the basic reproduction number can increase with n, the number of hosts. A special case of a two-host model is analyzed in Sect. 4. Necessary and sufficient conditions are derived for global stability of the endemic equilibrium. In the last section, some numerical examples for two and three-host models are presented.

2. Description of Models

First, we formulate a multi-host SIS epidemic model for n different hosts that can be infected by a common pathogen. Second, we formulate a multi-host SIR epidemic model. We assume that there is one reservoir species and $n - 1$ spillover species.

2.1 SIS Model

Let S_1 and I_1 denote the susceptible and infected reservoir species and S_j and I_j the susceptible and infected spillover species, $j = 2, \ldots, n$. Each species may recover from the disease but immunity does not occur. Therefore, the model is known as an SIS epidemic model. We assume that the only interaction between species is via the disease. In particular, there are no competitor or predator-prey relationships among the populations. This is a reasonable assumption among rats and mice, carriers of hantavirus. Although rodents have many predators, we are not modeling the predator populations here, only the rodent populations. In our models, the maximal population size is limited by the availability of environmental resources, the size of the carrying capacity. Growth is regulated by a density-dependent death rate.

The SIS multi-host epidemic model is given by the following system of differential equations:

$$\frac{dS_j}{dt} = N_j b_j - S_j d_j(N_j) - S_j \sum_{k=1}^{n} \left(\beta_{jk}(N_k) \frac{I_k}{N_k} \right) + \gamma_j I_j, \tag{2.1}$$

$$\frac{dI_j}{dt} = -I_j d_j(N_j) + S_j \sum_{k=1}^{n} (\beta_{jk}(N_k) \frac{I_k}{N_k}) - (\gamma_j + \alpha_j) I_j, \tag{2.2}$$

where the total population size for species j is $N_j = S_j + I_j$, $j = 1,2, \ldots, n$. The initial conditions satisfy $S_j(0) > 0$ and $I_j(0) \geq 0$ for $j = 1,2, \ldots, n$. The birth rate for each host population j is given by b_j, $b_j > 0$. The parameter $\gamma_j \geq 0$ is the recovery rate and $\alpha_j \geq 0$ is the disease-related death rate for species j. In the case where $\gamma_j = 0$, i.e. there is no recovery from the disease, the SIS model becomes an SI model. The density-dependent death rate, $d_j(N_j)$, for species j depends on the total population size N_j. The transmission rate between an infected individual of species k and a susceptible individual of species j is $\beta_{jk}(N_k)$, $\beta_{jk}(N_k) \geq 0$.

To distinguish the dynamics of the reservoir species from the spillover species we assume a higher transmission rate from the reservoir species than from the spillover species or between members of the spillover species. That is,

$$\beta_{11}(N_1) > \beta_{j1}(N_1) \geq \begin{cases} \beta_{jk}(N_k), & j,k = 2,\ldots,n, \\ \beta_{1j}(N_j), & j = 2,\ldots,n\,. \end{cases} \tag{2.3}$$

In addition, we assume that the reservoir species has a longer period of infectivity than the spillover species. In particular, the recovery and disease-related death rates are smaller for the reservoir species than for the spillover species,

$$0 \leq \gamma_1 + \alpha_1 \leq \gamma_j + \alpha_j,\ j = 2,\ldots,n\,. \tag{2.4}$$

The transmission rate β_{jk} may depend on the total population size N_k (of the infected species). We consider two well-known forms for β_{jk}. In our models, the incidence rate $\beta_{jk}(N_k)S_jI_k/N_k$ can be either standard incidence or mass action incidence, where $\beta_{jk}(N_k)$ is either constant, $\beta_{jk}(N_k) \equiv \lambda_{jk}$, or proportional to N_k, $\beta_{jk}(N_k) \equiv \lambda_{jk}N_k$, respectively. For animal populations, it is reasonable to assume a mass action incidence rate because as the population size increases so do the contacts, i.e., $\beta_{jk}(N_k) \equiv \lambda_{jk}N_k$ (also referred to as density-dependent transmission). Mass action incidence has been assumed in some hantavirus models (Abramson & Kenkre, 2002; Abramson *et al.*, 2003; Allen *et al.*, 2006; Sauvage *et al.*, 2003) and standard incidence in others (Allen *et al.*, 2003).

The following assumptions are made concerning the density-dependent natural death rate $d_j(N_j)$.

- **i.** $d_j \in C^1[0,\infty)$.
- **ii.** $0 < d_j(0) < b_j - \alpha_j$.
- **iii.** d_j is increasing for $N_j \geq 0$.
- **iv.** There exists $K_j > 0$ such that $d_j(K_j) = b_j$.

Assumptions (i)-(iv) imply that the total population has a logistic growth curve, a reasonable assumption for wildlife populations. Logistic growth has been assumed in models for hantavirus infection in rodents (Abramson & Kenkre, 2002; Abramson *et al.*, 2003; Allen *et al.*, 2003, 2006; Begon & Bowers, 1994; Begon *et al.*, 1992; Sauvage *et al.*, 2003) and in many other epidemic models where population growth is limited (e.g., Ackleh & Allen, 2003; 2005; Allen & Cormier, 1996; Gao & Hethcote, 1992; Mena-Lorca & Hethcote, 1992). The total population size for each host satisfies the following differential equation:

$$\frac{dN_j}{dt} = N_j[b_j - \alpha_j i_j - d_j(N_j)], \tag{2.5}$$

where $i_j = I_j/N_j$ is the proportion infected of species j for $j = 1,2,\ldots,n$. In the absence of infection, $\lim_{t\to\infty} N_j(t) = K_j$, where K_j is the carrying capacity for species j. It follows from assumptions (i)-(iv) that the total population size is positive and bounded. In particular,

$$0 < L_j \leq \liminf_{t\to\infty} N_j(t) \leq \limsup_{t\to\infty} N_j(t) \leq K_j, \tag{2.6}$$

where L_j is the unique solution satisfying $d(L_j) = b_j - \alpha_j$. The disease-free equilibrium (DFE) for (2.1) and (2.2) is the unique solution satisfying $\bar{S}_j = K_j$ and $\bar{I}_j = 0$, $j = 1,2, \ldots, n$, where the equilibrium point is denoted as $E_0 = (\bar{S}_1, \bar{I}_1, \ldots, \bar{S}_n, \bar{I}_n) = (K_1, 0, \ldots, K_n, 0)$. The existence of a nonnegative endemic equilibrium E_1 with $\bar{I}_k > 0$ requires that $\bar{I}_j > 0$ when $\beta_{jk}(N_k) > 0$. In other words, persistence of the disease in one host population results in disease persistence in another host if there is transmission between the two.

2.2 SIR Model

In the SIR epidemic model, individuals develop immunity to the disease; an immune class, R_j, is added to the SIS multi-host epidemic model (2.1) and (2.2) for each host j. The SIR multi-host epidemic model is given by the following system of differential equations:

$$\frac{dS_j}{dt} = N_j b_j - S_j d_j(N_j) - S_j \sum_{k=1}^{n} \left(\beta_{jk}(N_k) \frac{I_k}{N_k} \right), \tag{2.7}$$

$$\frac{dI_j}{dt} = -I_j d_j(N_j) + S_j \sum_{k=1}^{n} \left(\beta_{jk}(N_k) \frac{I_k}{N_k} \right) - (\gamma_j + \alpha_j) I_j, \tag{2.8}$$

$$\frac{dR_j}{dt} = -R_j d_j(N_j) + \gamma_j I_j, \tag{2.9}$$

where $N_j = S_j + I_j + R_j$ and $S_j(0) > 0$, $I_j(0) \geq 0$ and $R_j(0) \geq 0$ for $j = 1,2, \ldots, n$. All parameters are interpreted as in the SIS model except for the parameter γ_j which represents the rate at which infected individuals recover and enter the immune class R_j. The total population size N_j satisfies the differential equation (2.5). Assumptions (i)-(iv) hold. Therefore, the total population size is bounded as in (2.6) and the unique DFE is given by $\bar{S}_j = K_j$ and $\bar{I}_j = 0 = \bar{R}_j$ for $j = 1,2, \ldots, n$.

3. Basic Reproduction Number

The basic reproduction number $\mathcal{R}_0$ is one of the most important parameters in epidemiology. The basic reproduction number is defined as the average number of secondary infections that occur when an infected individual is introduced into a completely susceptible population (Dietz, 1975; Hethcote, 2000). If $\mathcal{R}_0 > 1$, then the disease may emerge in one of the populations. However, if $\mathcal{R}_0 < 1$, then the DFE is locally asymptotically stable (van den Driessche & Watmough, 2002). We compute the basic reproduction number for the SIS and SIR multi-host epidemic models based on the next generation approach (Diekmann *et al.*, 1990; van den Driessche & Watmough, 2002). It is shown that the basic reproduction number is the same for both models.

Theorem 3.1

The basic reproduction number for the SIS multi-host epidemic model, (2.1) *and* (2.2), *and the SIR multi-host epidemic model*, (2.7), (2.8) *and* (2.9), *is given by the spectral radius of the* $n \times n$ *matrix* $M_n = (\mathcal{R}_{jk})_{j,k=1}^{n}$,

$$\mathscr{R}_0 = \rho(M_n),$$

where

$$\mathscr{R}_{jk} = \frac{K_j \beta_{jk}(K_k)}{K_k(\gamma_k + \alpha_k + b_k)},$$

is the jk entry in the matrix M_n, $j, k = 1,2, ..,n$. *In the special case of* $n = 2$ *hosts, the basic reproduction number is*

$$\mathscr{R}_0 = \frac{\mathscr{R}_{11} + \mathscr{R}_{22} + \sqrt{(\mathscr{R}_{11} - \mathscr{R}_{22})^2 + 4\mathscr{R}_{12}\mathscr{R}_{21}}}{2}. \tag{3.1}$$

Proof—We apply the method developed by Diekmann *et al.* (1990) and van den Driessche & Watmough (2002) to calculate the next generation matrix for the SIS model, equations (2.1) and (2.2), and the SIR model, equations (2.7), (2.8), and (2.9). Since these models have the same differential equations for the infectious state and the same DFE (where $\bar{S}_j = K_j$, $j = 1,2, \ldots, n$ and the other equilibrium values are zero), they have the same basic reproduction number.

The terms in the differential equations for the infected states, $I = (I_1, I_2, \ldots, I_n)^T$, are separated according to new infections and recovery or death. Then the system of differential equations for the vector I satisfies $dI/dt = \mathcal{F}(I) - V(I)$, where $\mathcal{F}(I)$ and $V(I)$ are vector functions for the new infections and recovery or death, respectively. Computing the Jacobian matrix of these two functions, $F = D\mathcal{F}$ and $V = DV$, and evaluating at the DFE, we obtain the following $n \times n$ matrices:

$$F = \begin{pmatrix} \beta_{11}(K_1) & \frac{K_1}{K_2}\beta_{12}(K_2) & \cdots & \frac{K_1}{K_n}\beta_{1n}(K_n) \\ \frac{K_2}{K_1}\beta_{21}(K_1) & \beta_{22}(K_2) & \cdots & \frac{K_2}{K_n}\beta_{2n}(K_n) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{K_n}{K_1}\beta_{n1}(K_1) & \frac{K_n}{K_2}\beta_{n2}(K_2) & \cdots & \beta_{nn}(K_n) \end{pmatrix} \tag{3.2}$$

and $V = \mathrm{diag}(\gamma_j + \alpha_j + b_j)$. The basic reproduction number is the spectral radius of the matrix $M_n = FV^{-1} = (\mathscr{R}_{jk})_{j,k=1}^n$.

In the special case where there are $n = 2$ species,

$$M_2 = \begin{pmatrix} \dfrac{\beta_{11}(K_1)}{\gamma_1+\alpha_1+b_1} & \dfrac{K_1\beta_{12}(K_2)}{K_2(\gamma_2+\alpha_2+b_2)} \\ \dfrac{K_2\beta_{21}(K_1)}{K_1(\gamma_1+\alpha_1+b_1)} & \dfrac{\beta_{22}(K_2)}{(\gamma_2+\alpha_2+b_2)} \end{pmatrix} = \begin{pmatrix} \mathcal{R}_{11} & \mathcal{R}_{12} \\ \mathcal{R}_{21} & \mathcal{R}_{22} \end{pmatrix}. \tag{3.3}$$

It can be easily shown that the spectral radius of M_2 satisfies (3.1).

In the case where there is no recovery, $\gamma_k = 0$ in equations (2.1) and (2.2), the SIS model becomes an SI model; Theorem 3.1 still holds true. That is, the basic reproduction number for the SI model is given by the formula in Theorem 3.1 with $\gamma_k = 0$.

The basic reproduction number for each species j, when there is no contact with other species, is defined by $\mathcal{R}_{jj}$, $j = 1,2, \ldots, n$. It follows from assumptions (2.3) and (2.4) that the basic reproduction number for the reservoir species is greater than the basic reproduction number for the spillover species,

$$\mathcal{R}_{11} > \mathcal{R}_{jj}, j = 2, \ldots, n.$$

The expressions $\mathcal{R}_{jj}$ simplify when either mass action or standard incidence are assumed. For mass action incidence, $\beta_{jk}(K_k) = \lambda_{jk}K_k$. The value of $\mathcal{R}_{jj}$ simplifies to

$$\mathcal{R}_{jj} = \frac{K_j\lambda_{jj}}{\gamma_j+\alpha_j+b_j}.$$

Notice for mass action incidence that the species basic reproduction numbers increase at a rate proportional to their carrying capacity K_j. For standard incidence, $\beta_{jk}(K_k) = \lambda_{jk}$ so that

$$\mathcal{R}_{jj} = \frac{\lambda_{jj}}{\gamma_j+\alpha_j+b_j}.$$

Favorable environmental conditions can lead to increased rodent densities (resulting in increased contacts λ_{jk} or increased carrying capacities K_j) which, in turn, can lead to hantavirus outbreaks. Increased densities of deer mice (*Peromyscus maniculatus*), the reservoir host for the hantavirus known as Sin Nombre virus, was one of the driving factors in the hantavirus outbreak in New Mexico in 1993 (Mills *et al.*, 1999).

The next theorem shows that the presence of multiple species capable of transmitting the disease can result in an increase in the basic reproduction number for the system. The form of the next generation matrix is very important to verification of this next result.

Theorem 3.2

Assume that the SIS multi-host epidemic model, (2.1) and (2.2), *and the SIR multi-host epidemic model*, (2.7), (2.8) *and* (2.9), *with n hosts have a basic reproduction number given by the spectral radius of the n × n matrix* M_n, $\rho(M_n)$, *where* M_n *is defined in Theorem*

3.1. If one spillover species is added to each of the model equations and all parameters of the original system with n hosts remain unchanged, then the new SIS and SIR multi-host epidemic models with n + 1 hosts has a spectral radius $\rho(M_{n+1})$ that satisfies

$$\rho(M_{n+1}) \geq \rho(M_n) \geq \mathcal{R}_{11}. \tag{3.4}$$

If, in addition, the transmission rate for host n satisfies

$$\beta_{n1}(K_1)\beta_{1n}(K_n) \neq 0, n \neq 1, \tag{3.5}$$

then

$$\rho(M_n) > \mathcal{R}_{11} \tag{3.6}$$

Proof—Augment the $n \times n$ matrix M_n with one row and one column of zeros, so that the augmented matrix M_n^0 is of size $n + 1 \times n + 1$,

$$M_n^0 = \begin{pmatrix} M_n & \mathbf{0}^T \\ \mathbf{0} & 0 \end{pmatrix},$$

where $\mathbf{0}$ is a zero row vector of size n. Notice that the $n \times n$ submatrix of M_n^0 equals M_n and equals the $n + 1 \times n + 1$ submatrix of M_{n+1},

$$M_{n+1} = \begin{pmatrix} M_n & A \\ B & \mathcal{R}_{n+1,n+1} \end{pmatrix},$$

where $\rho(M_{n+1})$ is the basic reproduction number of the SIS and SIR epidemic models with $n + 1$ hosts. From the assumptions in the SIS and SIR multi-host epidemic models and the next generation approach, it follows that the column and row vectors A and B of matrix M_{n+1} have nonnegative entries. Hence, it follows from the theory of nonnegative matrices (6.1.12, page 225, Ortega, 1987) that

$$\rho(M_n) = \rho(M_n^0) \leq \rho(M_{n+1}).$$

If $n = 1$, $\rho(M_1) = \mathcal{R}_{11}$.

Assumption (3.5) and the assumptions regarding the nonnegativity (or positivity) of the basic parameters imply $\mathcal{R}_{n1} > 0$ and $\mathcal{R}_{1n} > 0$ for $n \neq 1$. Consider the 2 ×2 matrix,

$$M = \begin{pmatrix} \mathcal{R}_{11} & \mathcal{R}_{1n} \\ \mathcal{R}_{n1} & 0 \end{pmatrix}.$$

It is straightforward to verify that $\rho(M) > \mathcal{R}_{11}$, where the inequality is strict. Applying the preceding argument shows that $\rho(M_n) \geq \rho(M)$. Hence, the strict inequality (3.6) holds.

Assumption (3.5) implies that there is transmission of the disease back and forth between the reservoir species and species $n + 1$. The system with an additional species has a basic reproduction number that is greater than the basic reproduction number of the reservoir host. The inequality (3.4) regarding the spectral radii can be applied to more general SEIR epidemic models with multiple hosts, where the state E represents individuals in a latent or exposed class.

For SIS and SIR models, it is not always the case that the basic reproduction number increases with multiple species. If either $\mathcal{R}_{n+1,\,j} = 0$ or $\mathcal{R}_{j,\,n+1} = 0$ for all $j = 1, \ldots, n$, then the basic reproduction number does not increase, but $\rho(M_{n+1}) = \rho(M_n)$. For the basic reproduction number to strictly increase with the addition of a spillover species into the system, the disease must be able to infect the spillover species and also be transmitted back to the reservoir host from this spillover species (inequality (3.5) must hold).

Because hantavirus infection in rodents is primarily associated with one reservoir species, intraspecies transmission in spillover species, $\beta_{jj}(K_j)$, $j = 2, \ldots, n$, may be very low or negligible. Interspecies transmission between spillover species, $\beta_{kj}(K_j)$, $j,\ k = 2, \ldots, n$, is probably very low also. Therefore, the only positive entries in the next generation matrix may be the entries in the first column or first row, indicating there is transmission from the reservoir species to a spillover species or from a spillover to the reservoir species, respectively. There is evidence of transmission from the reservoir species to spillover species (positive antibody titers in the spillover species). Then $\beta_{j1}(K_1) > 0$ for $j = 1,2, \ldots, n$; the first column of the next generation matrix M_n has positive entries. If, in addition, for some $j \neq 1$, $\beta_{1j}(K_j) > 0$, then, according to Theorem 3.2, our model predicts that the basic reproduction number in the system with the reservoir and spillover species is greater than with the reservoir host alone. For example, if $\mathcal{R}_{11} = \rho(M_1) < 1$, then the presence of spillover species in the system can increase the reproduction number to a value greater than one, $\mathcal{R}_0 = \rho(M_n) > 1$ for $n > 1$.

4. Two-Host SIS Epidemic Model with Standard Incidence

Consider a special case of the general n host model, where there is only the reservoir species and one spillover species. Assume that the incidence rate is standard incidence so that $\beta_{jk}(N_k) = \lambda_{jk}$ is constant. An explicit expression for the basic reproduction number is given in (3.1).

The SIS multi-host epidemic model (2.1) and (2.2) for $n = 2$ hosts can be expressed in terms of proportions. Let the proportion of infected individuals for the two hosts be denoted as $i_1 = I_1/N_1$ and $i_2 = I_2/N_2$. Then the differential equations for the two-host SIS epidemic model can be expressed in terms of the proportions as follows:

$$\frac{di_1}{dt} = \lambda_{12} i_2 - i_1[b_1 + \gamma_1 + (1 - i_1)(\alpha_1 - \lambda_{11}) + \lambda_{12} i_2], \tag{4.1}$$

$$\frac{di_2}{dt} = \lambda_{21} i_1 - i_2[b_2 + \gamma_2 + (1 - i_2)(\alpha_2 - \lambda_{22}) + \lambda_{21} i_1]\,. \tag{4.2}$$

Based on the assumptions (i)-(iv), $N_j(t) > L_j > 0$ for $j = 1,2$. An endemic equilibrium of (2.1) and (2.2) requires that $\bar{I}_j > 0$ and $\bar{S}_j > 0$, $j = 1,2$. Hence, there exists an endemic equilibrium of (2.1) and (2.2) if and only if there exists an endemic equilibrium of (4.1) and (4.2) with $\bar{\imath}_j = \bar{I}_j/(\bar{I}_j + \bar{S}_j) < 1$, $j = 1,2$. The next result states that a unique endemic equilibrium exists to the two-host SIS epidemic model if and only if $\mathcal{R}_0 > 1$. In addition, two conditions, equivalent to $\mathcal{R}_0 > 1$, are given that express this inequality in terms of the species basic reproduction numbers $\mathcal{R}_{jj}$, $j = 1,2$ and that relate to condition (3.5) in Theorem 3.2.

Theorem 4.1

A unique endemic equilibrium exists for the two-host SIS epidemic model (2.1) *and* (2.2) *with standard incidence if and only if*

- **i.** $\mathcal{R}_{jj} > 1$ *for some* $j = 1,2$ *or*
- **ii.** $\mathcal{R}_{jj} \le 1$ *for* $j = 1,2$ *and* $(1 - \mathcal{R}_{11})(1 - \mathcal{R}_{22}) < \mathcal{R}_{12}\mathcal{R}_{21}$.

Conditions (i) and (ii) are equivalent to $\mathcal{R}_0 > 1$, *where* $\mathcal{R}_0$ *is defined in* (3.1) *and*

$$\mathcal{R}_{jk} = \frac{K_j \lambda_{jk}}{K_k(\gamma_k + \alpha_k + b_k)},\ j,k = 1,2.$$

The second inequality in part (ii) of Theorem 4.1 relates to condition (3.5) in Theorem 3.2. If the species basic reproduction numbers are less than one, $\mathcal{R}_{jj} \le 1$, $j = 1,2$, and if $\mathcal{R}_0 > 1$, then there must be transmission between the reservoir and the spillover species (inequality (3.5)) because condition (ii) implies $\mathcal{R}_{12}\mathcal{R}_{21} > 0$ which implies $\lambda_{12}\lambda_{21} > 0$. The presence of the spillover species increases the basic reproduction number of the system to a value greater than one, $\mathcal{R}_{11} \le 1 < \mathcal{R}_0$.

Proof—The nullclines for system (4.1) and (4.2) can be expressed as

$$i_2 = f_1(i_1) = \frac{i_1[\gamma_1 + \alpha_1 + b_1 - \lambda_{11} + i_1(\lambda_{11} - \alpha_1)]}{\lambda_{12}(1 - i_1)},$$
$$i_1 = f_2(i_2) = \frac{i_2[\gamma_2 + \alpha_2 + b_2 - \lambda_{22} + i_2(\lambda_{22} - \alpha_2)]}{\lambda_{21}(1 - i_2)}.$$

Notice that the region $D = [0,1] \times [0,1]$ is invariant for this system, that is, if $i_j = 0$ then $di_j/dt > 0$, and if $i_j = 1$, then $di_j/dt < 0$ for $j = 1,2$. The nullclines always intersect at the origin. Additionally, f_1 has an asymptote at $i_1 = 1$, and f_2 has an asymptote at $i_2 = 1$. The denominators of both functions are positive in the interior of region D.

First, we show conditions (i) and (ii) imply there exists a unique endemic equilibrium. We examine three different cases for the nullclines by considering the signs of the coefficients of the functions f_1 and f_2.

Case (i): Suppose $\lambda_{11} > \gamma_1 + a_1 + b_1$ and $\lambda_{22} > \gamma_2 + a_2 + b_2$. These two inequalities are equivalent to $\mathcal{R}_{11} > 1$ and $\mathcal{R}_{22} > 1$, respectively. In addition,

$$\frac{df_1}{di_1} \mid_{i_1 = 0} < 0 \text{ and } \frac{df_2}{di_2} \mid_{i_2 = 0} < 0.$$

The nullclines are graphed in Figure 1. There exists a unique point of intersection in the interior of D.

Case (ii): Suppose $\lambda_{11} > \gamma_1 + a_1 + b_1$ and $\lambda_{22} < \gamma_2 + a_2 + b_2$. Then $\mathcal{R}_{11} > 1$, $\mathcal{R}_{22} < 1$,

$$\frac{df_1}{di_1} \mid_{i_1 = 0} < 0, \text{ and } \frac{df_2}{di_2} \mid_{i_2 = 0} > 0.$$

Again there exists a unique point of intersection of the nullclines in D (see Figure 2). A similar result holds if the two inequalities are reversed, when $\mathcal{R}_{11} < 1$ and $\mathcal{R}_{22} > 1$.

Case (iii): Suppose $\lambda_{11} < \gamma_1 + a_1 + b_1$ and $\lambda_{22} < \gamma_2 + a_2 + b_2$. Then $\mathcal{R}_{11} < 1$ and $\mathcal{R}_{22} < 1$. Both nullclines have positive slope at the origin. For the nullclines to intersect in D it must be the case that the slopes at the origin satisfy

$$\frac{df_1}{di_1} \mid_{i_1 = 0} < \frac{1}{[df_2/di_2] \mid_{i_2 = 0}}.$$

This condition can be expressed as

$$\frac{(b_1 + \gamma_1 + \alpha_1 - \lambda_{11})(b_2 + \gamma_2 + \alpha_2 - \lambda_{22})}{\lambda_{12}\lambda_{21}} < 1$$

or equivalently $(1 - \mathcal{R}_{11})(1 - \mathcal{R}_{22}) < \mathcal{R}_{12}\mathcal{R}_{21}$. Under these conditions, the nullclines cross at a unique point in the interior of the region D (see Figure 3).

Suppose there exists a unique endemic equilibrium but conditions (i) and (ii) are not satisfied, that is, $\mathcal{R}_{11} < 1$, $\mathcal{R}_{22} < 1$ and $(1 - \mathcal{R}_{11})(1 - \mathcal{R}_{22}) \geq \mathcal{R}_{12}\mathcal{R}_{21}$. This case cannot occur because the nullclines do not cross in the interior of the region D (see Figure 4).

Next we show that $\mathcal{R}_0 > 1$ if and only if conditions (i) or (ii) hold. Suppose (i) holds. Without loss of generality, assume $\mathcal{R}_{11} > 1$ and $\mathcal{R}_{11} > \mathcal{R}_{22}$. Then

$$\mathcal{R}_0 \geq \frac{\mathcal{R}_{11} + \mathcal{R}_{22} + \sqrt{(\mathcal{R}_{11} - \mathcal{R}_{22})^2}}{2} = \mathcal{R}_{11} > 1.$$

Suppose (ii) holds. Then

$$\mathcal{R}_0 > \frac{\mathcal{R}_{11} + \mathcal{R}_{22} + \sqrt{(\mathcal{R}_{11} - \mathcal{R}_{22})^2 + 4(1 - \mathcal{R}_{11})(1 - \mathcal{R}_{22})}}{2}$$

$$= \frac{\mathcal{R}_{11} + \mathcal{R}_{22} + \sqrt{(2 - \mathcal{R}_{11} - \mathcal{R}_{22})^2}}{2} = 1.$$

Next assume $\mathcal{R}_0 > 1$. Then

$$2 - \mathcal{R}_{11} - \mathcal{R}_{22} < \sqrt{(\mathcal{R}_{11} - \mathcal{R}_{22})^2 + 4\mathcal{R}_{12}\mathcal{R}_{21}}\,. \tag{4.3}$$

If $2 - \mathcal{R}_{11} - \mathcal{R}_{22} < 0$, then either $\mathcal{R}_{11} > 1$ or $\mathcal{R}_{22} > 1$ so that condition (i) holds. If $2 - \mathcal{R}_{11} - \mathcal{R}_{22} \geq 0$, then squaring both sides of (4.3) and simplifying leads to

$$(1 - \mathcal{R}_{11})(1 - \mathcal{R}_{22}) < \mathcal{R}_{12}\mathcal{R}_{21}\,. \tag{4.4}$$

Thus, $\mathcal{R}_{jj} \leq 1$ for $j = 1,2$ and inequality (4.4) implies condition (ii) holds.

Conditions similar to (i) and (ii) in Theorem 4.1 were derived by Allen and Cormier (1996). In their SIS models there was no disease-related deaths, $a_j = 0$. Figures 1-4 illustrate the four possibilities of the nullclines and are helpful in verifying global stability of the endemic equilibrium when $\mathcal{R}_0 > 1$.

Theorem 4.2

For the two-host SIS epidemic model (2.1) *and* (2.2) *with* $n = 2$ *and standard incidence the basic reproduction number determines the global dynamics. In particular*,

- **i.** *If* $\mathcal{R}_0 \leq 1$, *then the DFE is globally asymptotically stable*.
- **ii.** *If* $\mathcal{R}_0 > 1$, *then the endemic equilibrium is globally asymptotically stable*.

Proof—Suppose $\mathcal{R}_0 \leq 1$. According to Theorem 4.1, there is no endemic equilibrium. The only equilibrium is the DFE and it is locally asymptotically stable (van den Driessche & Watmough, 2002). Because solutions are bounded, Poincare-Bendixson theory can be applied. The origin is globally asymptotically stable; part (i) has been proved.

Suppose $\mathcal{R}_0 > 1$. Then by Theorem 4.1 a unique endemic equilibrium exists. The proportions model (4.1) and (4.2) is analyzed. The endemic equilibrium for model (4.1) and (4.2) is globally asymptotically stable if and only if the endemic equilibrium for the two-host model (2.1) and (2.2) is globally asymptotically stable. The region $D = [0,1] \times [0,1]$ is invariant for the proportions model.

First, we show that no solution can approach the DFE (the origin in the case of the proportions model). The Jacobian matrix for the proportions model evaluated at the origin is given by

$$J = \begin{pmatrix} \lambda_{11} - (\gamma_1 + \alpha_1 + b_1) & \lambda_{12} \\ \lambda_{21} & \lambda_{22} - (\gamma_2 + \alpha_2 + b_2) \end{pmatrix}$$

The eigenvalues of J are real and are given by

$$\lambda^{\pm} = \frac{r_1 + r_2 \pm \sqrt{(r_1 - r_2)^2 + 4\lambda_{12}\lambda_{21}}}{2},$$

where $r_1 = \lambda_{11} - (\gamma_1 + \alpha_1 + b_1)$ and $r_2 = \lambda_{22} - (\gamma_2 + \alpha_2 + b_2)$. Since $\mathcal{R}_0 > 1$, clearly $\lambda^+ > 0$. If $\lambda^- > 0$, then the DFE is a repellor. If $\lambda^- < 0$, the eigenvector corresponding to λ^- is given by

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} 1 \\ \frac{\lambda^- - r_1}{\lambda_{12}} \end{pmatrix}$$

Since $\lambda^- < 0$, x_2 is negative. Thus, the stable manifold of the origin lies outside the region D. No solutions approach the DFE.

Consider the i_1 and i_2 nullclines for system (4.1) and (4.2), $i_2 = f_1(i_1)$ and $i_1 = f_2(i_2)$, respectively (see Figures 1-4). We show that the regions enclosed by the nullclines are invariant. Along the i_1-nullcline, inside the region D, but below the endemic equilibrium, $di_2/dt > 0$ (see Figure 5). In addition, along the i_2-nullcline, inside D, but to the left of the endemic equilibrium, $di_1/dt > 0$. Thus, region A in Figure 5 is invariant. The direction of flow changes as the endemic equilibrium is crossed, so that region B is also invariant.

As a result, there can be no periodic solutions inside region D. Poincare-Bendixson theory can be applied. Thus, the endemic equilibrium is globally asymptotically stable.

5. Numerical Examples

Two numerical examples are presented to illustrate the dynamics of the SIS epidemic model with standard and mass action incidence. In the first example, standard incidence is assumed, where $\beta_{jk}(N_k) = \lambda_{jk}$. With only two hosts the DFE is locally asymptotically stable, $\mathcal{R}_0 < 1$, but addition of a third host results in $\mathcal{R}_0 > 1$. In the second example, mass action incidence is assumed, where $\beta_{jk}(N_k) = \lambda_{jk}N_k$. In this example, we show that increasing the carrying capacity increases the basic reproduction number and the level of prevalence.

Hantavirus in rodents results in very few, if any, disease-related deaths. Therefore, we let $\alpha_j = 0.01$, $j = 1, \ldots, n$. We assume that conditions (2.3) and (2.4) hold. That is, $\lambda_{11} > \lambda_{j1} \geq \lambda_{jk}$, $j, k = 2, \ldots, n$, $\lambda_{j1} \geq \lambda_{1j}$, and $\gamma_1 < \gamma_j$, $j = 2, \ldots, n$.

In the first numerical example, for the two-host SIS epidemic model, let $\lambda_{11} = 3.5$, $\lambda_{12} = 0.3 = \lambda_{22}$, $\lambda_{21} = 2\lambda_{22}$, $\gamma_1 = 0.55$, and $\gamma_2 = 1$. For example, if the time period is two months, then the average length of the infectious period for the reservoir host is $1/\gamma_1 = 3.6$

months and for the spillover species it is $1/\gamma_2 = 2$ months. For the per capita birth rates, let $b_i = 3$ for $i = 1,2$, where the average litter size is 6 (males and females). These are reasonable estimates based on the rice rat *Oryzomys palustris* which is the reservoir host for the hantavirus known as Bayou virus (Davis & Schmidley, 1994; McIntyre *et al.*, 2005). We assume a simple form for the density-dependent death rates, $d_1(N_1) = 0.5 + 0.005N_1$ and $d_2(N_2) = 0.5 + 0.01N_2$. These forms result in carrying capacities of $K_1 = 500$ and $K_2 = 250$. The basic reproduction number for the two-host SIS epidemic model, based on these parameter values, is $\mathcal{R}_0 = 0.9968 < 1$. Thus, the disease dies out and the DFE is globally asymptotically stable (Theorem 4.2). The dynamics over time are graphed in Figure 6 for the susceptible S_j, infected I_j, and proportion infected i_j, $j = 1,2$. It can be seen that $\lim_{t\to\infty} I_j(t) = 0 = \lim_{t\to\infty} i_j(t)$ for $j = 1,2$.

Suppose a third host is added to the two-host model. The third host is a spillover species similar to the second host with the same parameter values as the second host. In particular, $a_3 = a_2$, $\gamma_3 = \gamma_2$, $b_3 = b_2$, $\lambda_{13} = \lambda_{33} = \lambda_{22}$, $\lambda_{31} = \lambda_{21}$, $d_3(N_3) = 0.5 + 0.01N_3$, and $\lambda_{32} = 0 = \lambda_{23}$. The latter assumption implies there is no disease transmission between the two spillover species. The carrying capacity of the third species is $K_3 = 250$. With the introduction of the third host, the basic reproduction number for the three-host SIS epidemic model increases to $\mathcal{R}_0 = 1.0101 > 1$; the disease persists. There exists a unique endemic equilibrium which is locally asymptotically stable, $(\bar{S}_1, \bar{I}_1, \bar{S}_2, \bar{I}_2, \bar{S}_3, \bar{I}_3) \approx (495,5,249.6,0.4,249.6,0.4)$ (see Figure 7).

The prevalence of infection within the spillover species and the reservoir host is very low at the endemic equilibrium, 0.16% and 1%, respectively, but it is much greater in the reservoir host. In this example, it is the presence of the spillover species that allows the disease to persist in the system.

In the second numerical example, mass action incidence with $\beta_{jk}(N_k) = \lambda_{jk}N_k$ is assumed. We assume the transmission rates have the same values at the carrying capacity as in the previous example, i.e., $\beta_{jk}(K_k) = \lambda_{jk}$. For example, $\beta_{11}(K_1) = 3.5$ so that $\beta_{11}(N_1) = 0.007N_1$. In addition, we assume $\beta_{1j}(N_j) = 0.0012N_j = \beta_{jj}(N_j)$, $\beta_{j1}(N_1) = 0.0012N_1$ for $j = 2,3$, and $\beta_{23}(N_3) = 0 = \beta_{32}(N_2)$. With these transmission rates and the same parameter values as in the preceding three-host example, the basic reproduction number is the same, $\mathcal{R}_0 = 1.0101$. To illustrate the impact of the carrying capacity on the dynamics, we double the carrying capacities. The same parameter values are assumed as in the preceding example, except for the density-dependent death rates and the assumptions we made regarding the transmission rates. The density-dependent death rates are $d_1(N_1) = 0.5 + 0.0025N_1$, $d_2(N_2) = 0.5 + 0.005\mathrm{N}_2$, and $d_3(N_3) = 0.5 + 0.005N_3$. In this second example, the carrying capacities for the three-host SIS model are $K_1 = 1000$ and $K_2 = 500 = K_3$. When all of the carrying capacities double so does the basic reproduction number, $\mathcal{R}_0 = 2.0202$. This can be easily seen from the next generation matrix M_2 given in (3.3). The jk entry in matrix M_2 is $\mathcal{R}_{jk} = K_j\lambda_{jk}/(\gamma_k + a_k + b_k)$. An increase in K_j to $2K_j$ increases all of the matrix entries of M_2 by a factor of 2 and as a result the spectral radius of the new matrix increases by a factor of 2.

There exists a locally stable endemic equilibrium for this three-host epidemic model given by $(\bar{S}_1, \bar{I}_1, \bar{S}_2, \bar{I}_2, \bar{S}_3, \bar{I}_3) \approx (483.7,514.3,424.8,74.9,424.8,74.9)$ (see Figure 8). The level of

prevalence has increased substantially in this second example. At the endemic equilibrium, the total percentage of the rodent population infected is 33% (51.5% in the reservoir host and 15% in the spillover species).

In a three-host SIR epidemic model with mass action incidence having the same parameter values and carrying capacities as in the second example, the basic reproduction is the same, $\mathcal{R}_0 = 2.0202$. There is a unique locally stable endemic equilibrium in the SIR model but the prevalence of infection is less than for the SIS model (43.5% in the reservoir host and 12.4% in the spillover species).

6. Concluding Remarks

We formulated and analyzed SIS and SIR epidemic models with multiple hosts with a goal of applying our results to the study of hantavirus in rodent populations. Our analyses and simulations show that the presence of spillover species can be an important factor in the emergence and persistence of hantavirus in wild rodent populations. The important question to address for hantavirus is whether the spillover species can transmit the disease back to the reservoir host. Our theoretical results can be applied to any diseases that involve multiple hosts. The results in Theorem 3.2 imply as the number of hosts increases so does the basic reproduction number. Multiple hosts can play an important role in disease outbreaks and in disease persistence.

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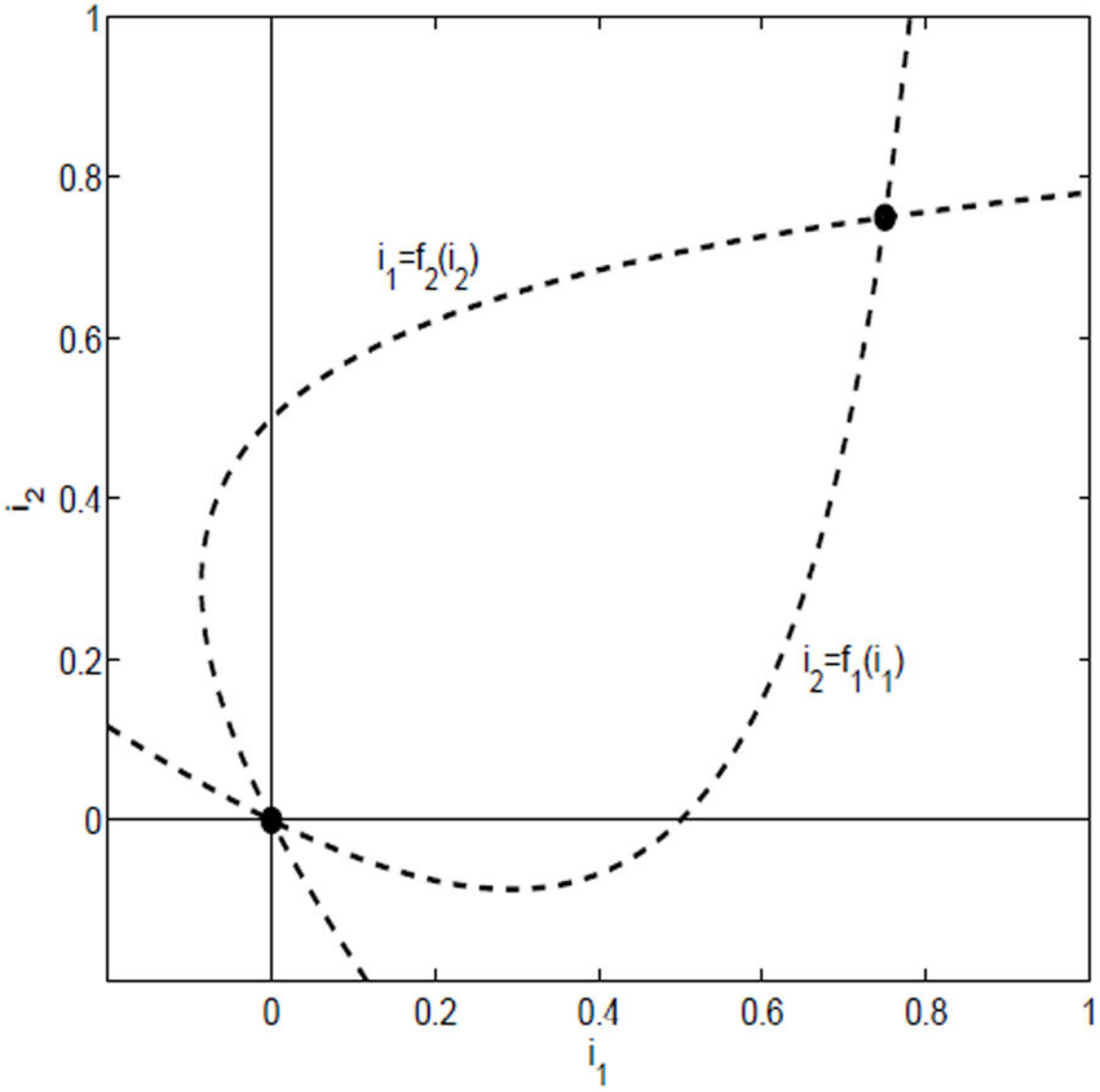

Fig. 1.
The nullclines for case (i), $\mathcal{R}_{11} > 1$ and $\mathcal{R}_{22} > 1$

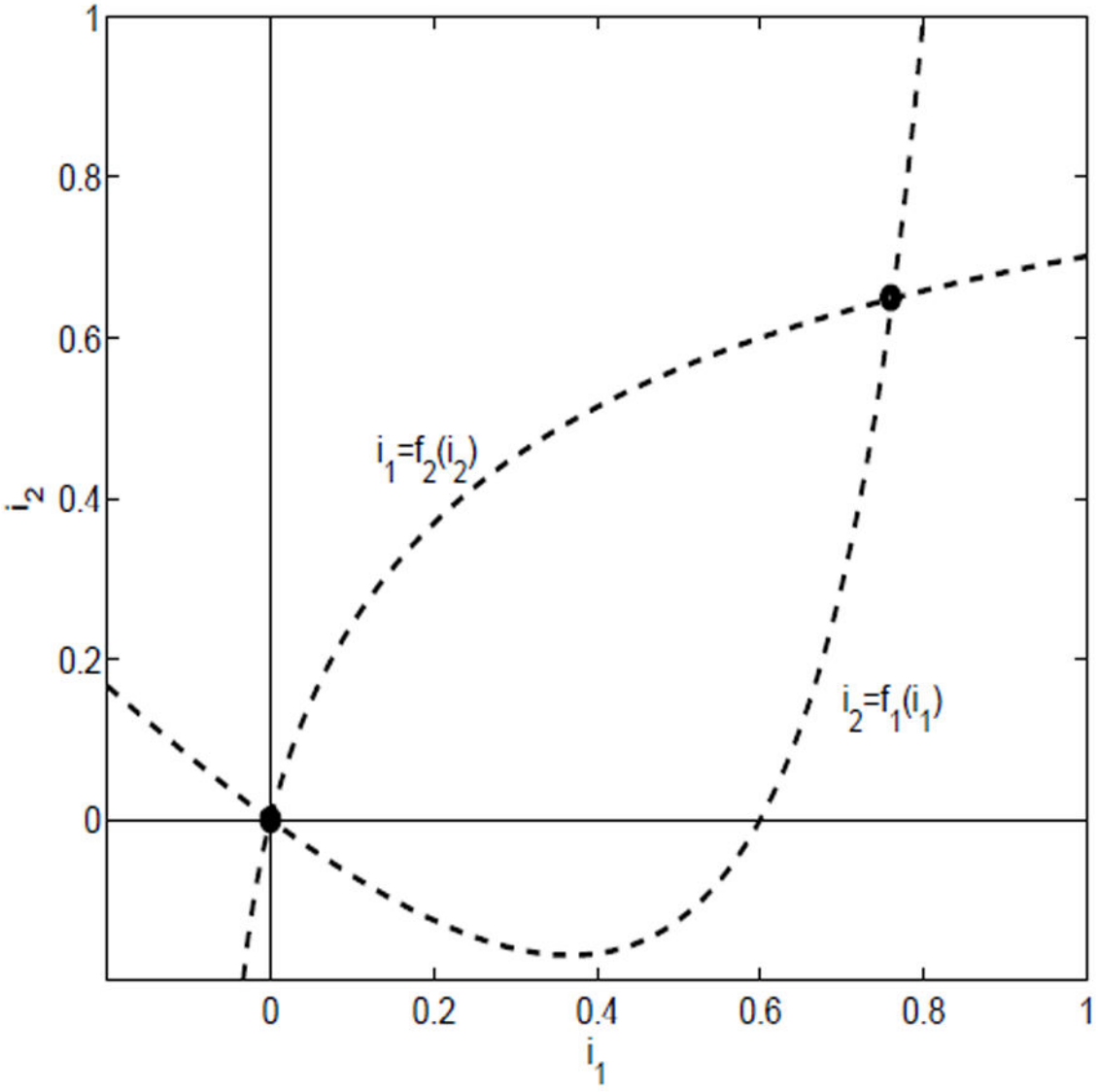

Fig. 2.
The nullclines for case (ii), $\mathcal{R}_{11} > 1$ and $\mathcal{R}_{22} < 1$

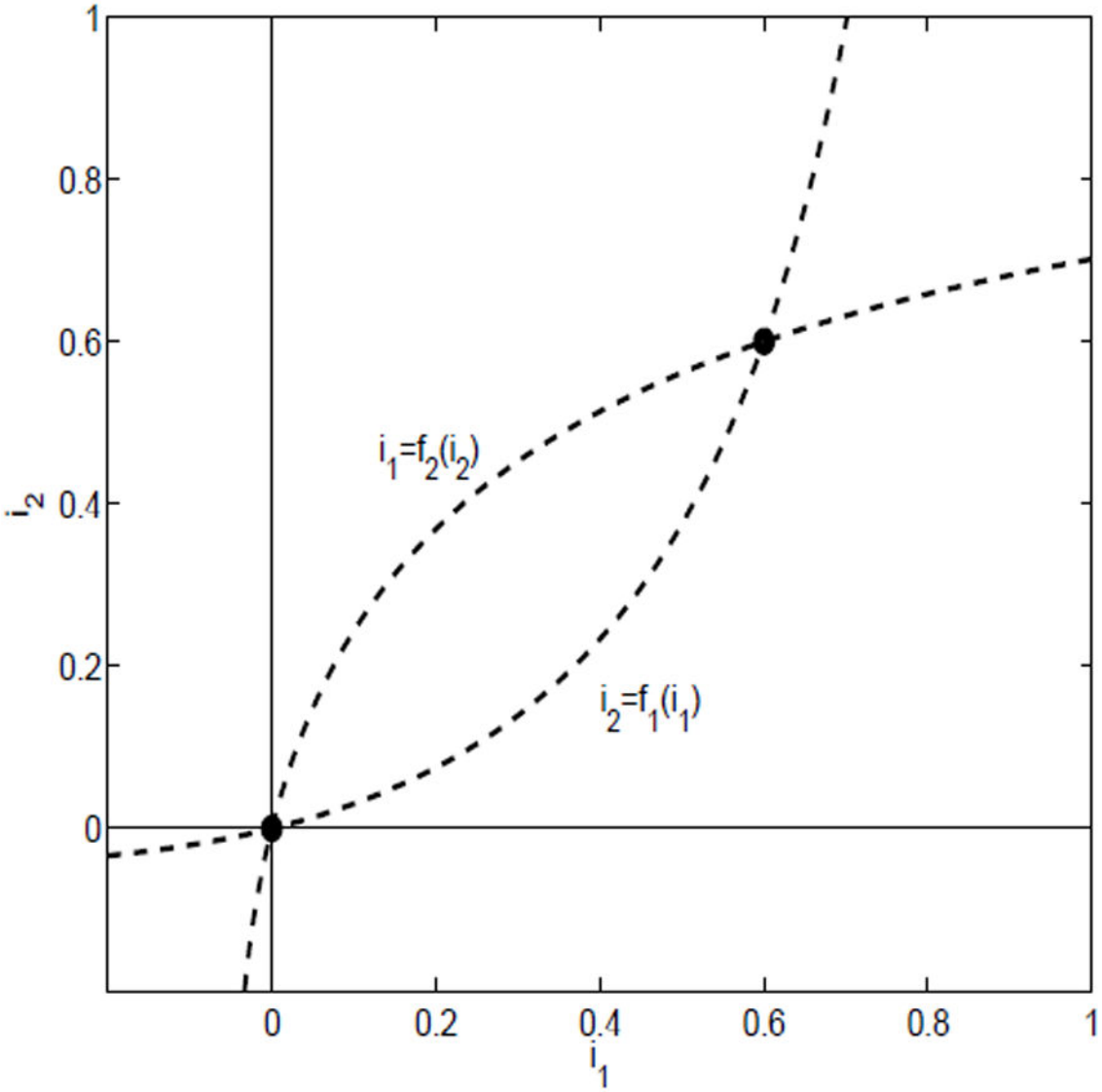

Fig. 3.
The nullclines for case (iii), $\mathcal{R}_{11} < 1$ and $\mathcal{R}_{22} < 1$ and $(1 - \mathcal{R}_{11})(1 - \mathcal{R}_{22}) < \mathcal{R}_{12}\mathcal{R}_{21}$

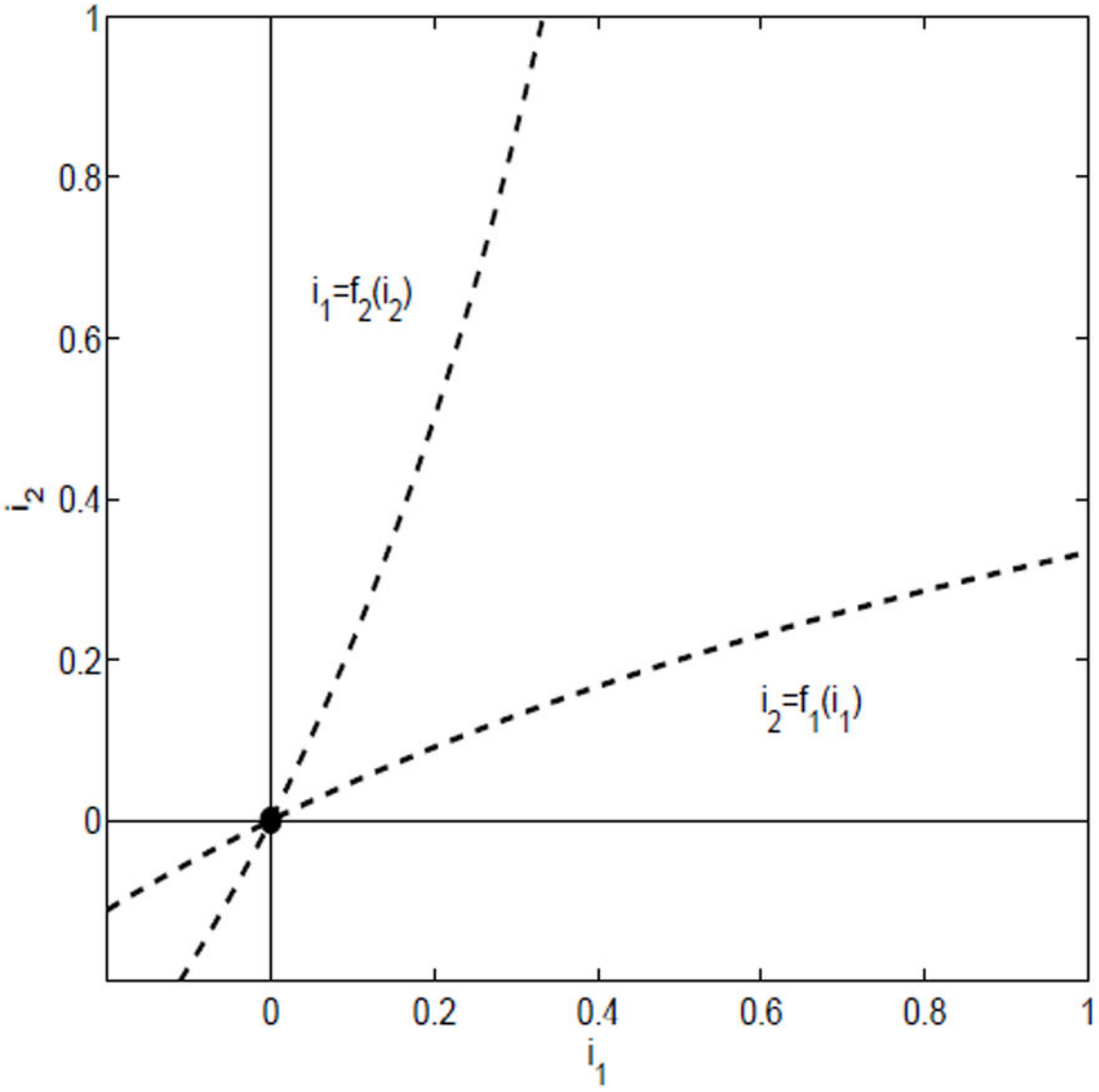

Fig. 4.

$\mathcal{R}_{11} < 1$ and $\mathcal{R}_{22} < 1$ and $(1 - \mathcal{R}_{11})(1 - \mathcal{R}_{22}) \geq \mathcal{R}_{12}\mathcal{R}_{21}$

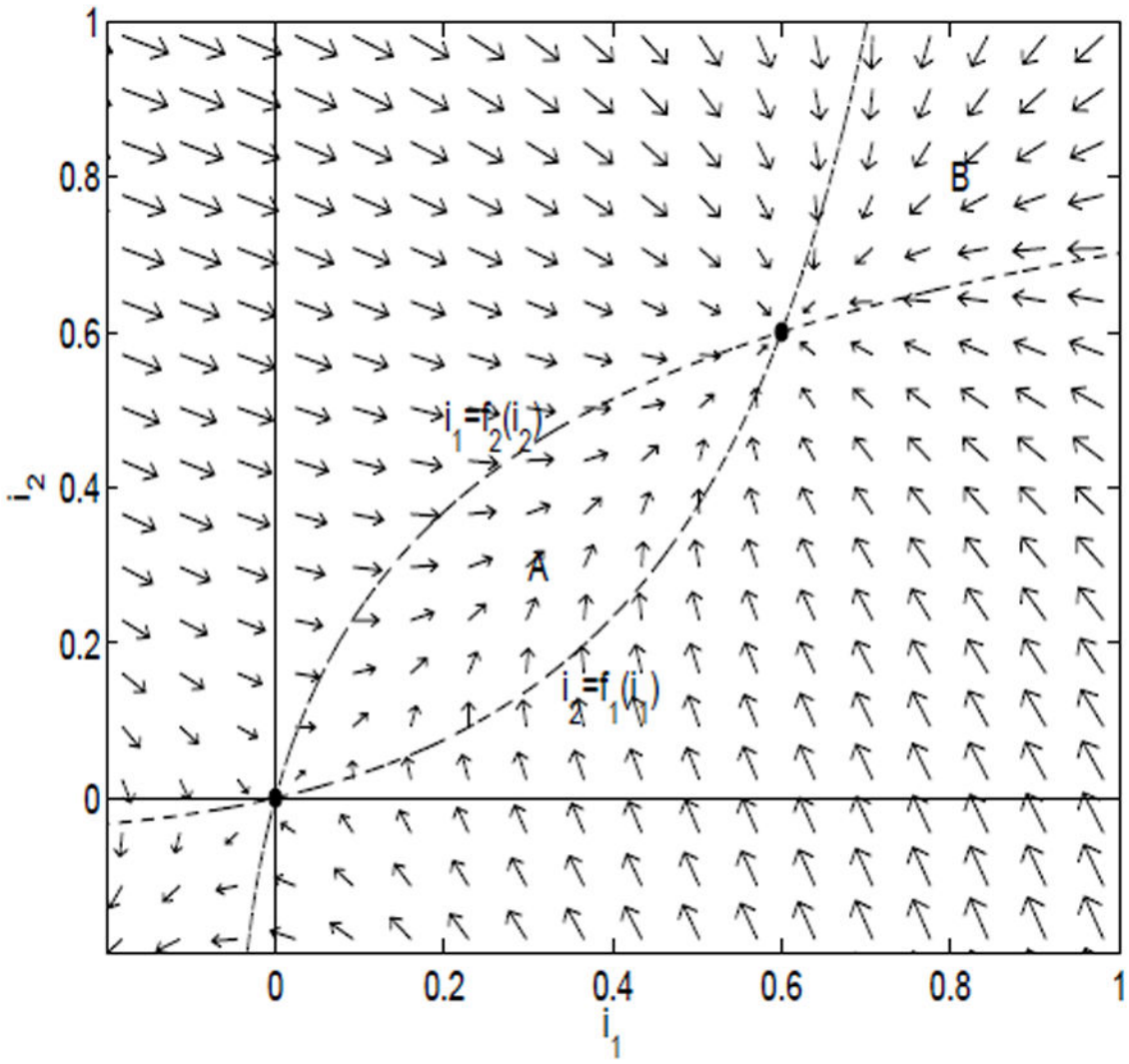

Fig. 5.
Direction field for the case $\mathcal{R}_{11} < 1$ and $\mathcal{R}_{22} < 1$ and $(1 - \mathcal{R}_{11})(1 - \mathcal{R}_{22}) < \mathcal{R}_{12}\mathcal{R}_{21}$

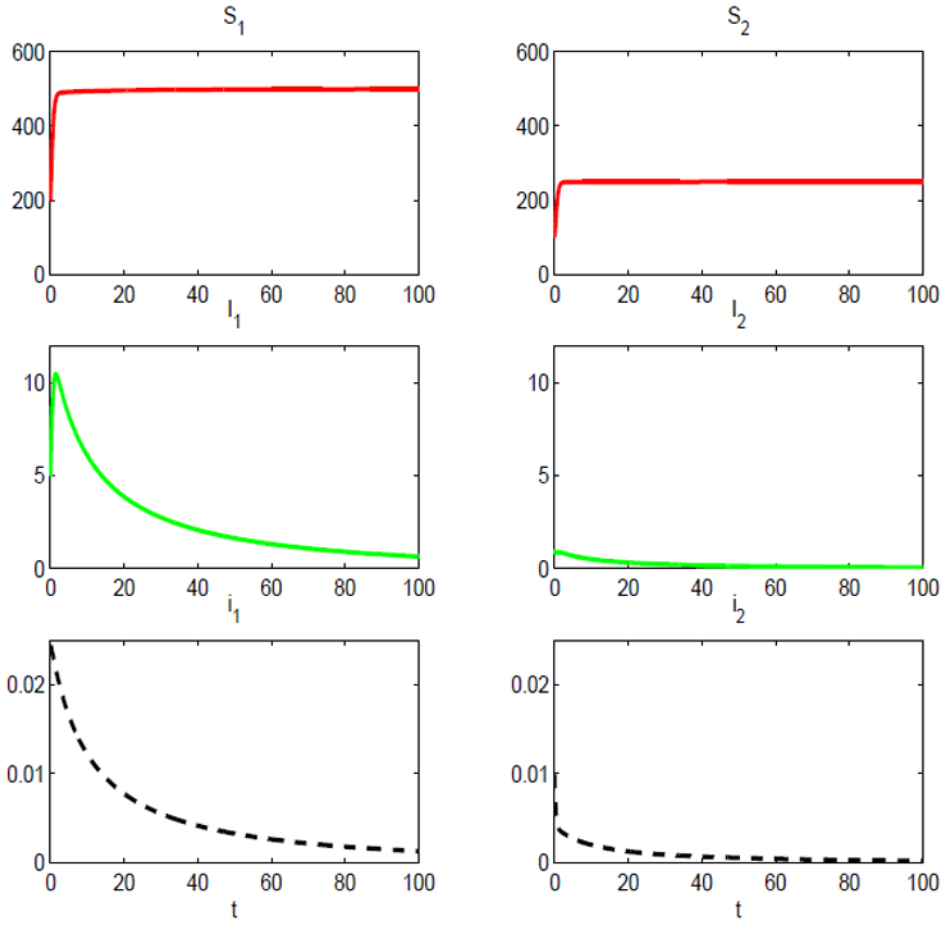

Fig. 6.

Solution of the two-host SIS epidemic model with standard incidence for initial conditions: $S_1(0) = 200$, $S_2(0) = 100$, $I_1(0) = 5$, and $I_2(0) = 1$; $\mathcal{R}_0 = 0.9968 < 1$.

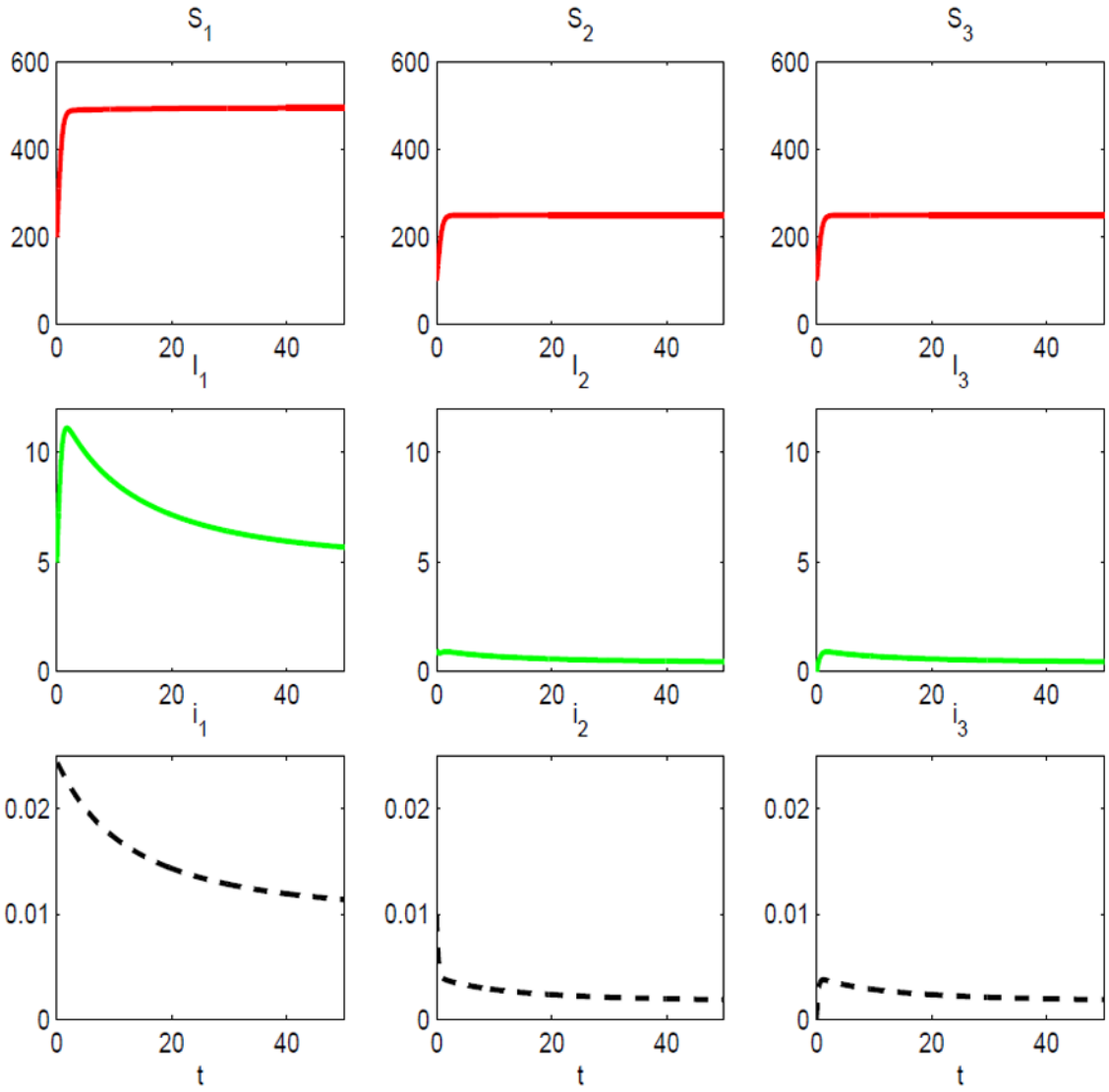

Fig. 7.

Solution of the three-host SIS epidemic model with standard incidence for initial conditions: $S_1(0) = 200$, $S_2(0) = 100 = S_3(0)$, $I_1(0) = 5$, $I_2(0) = 1$ and $I_3(0) = 0$; $\mathcal{R}_0 = 1.0101 > 1$.

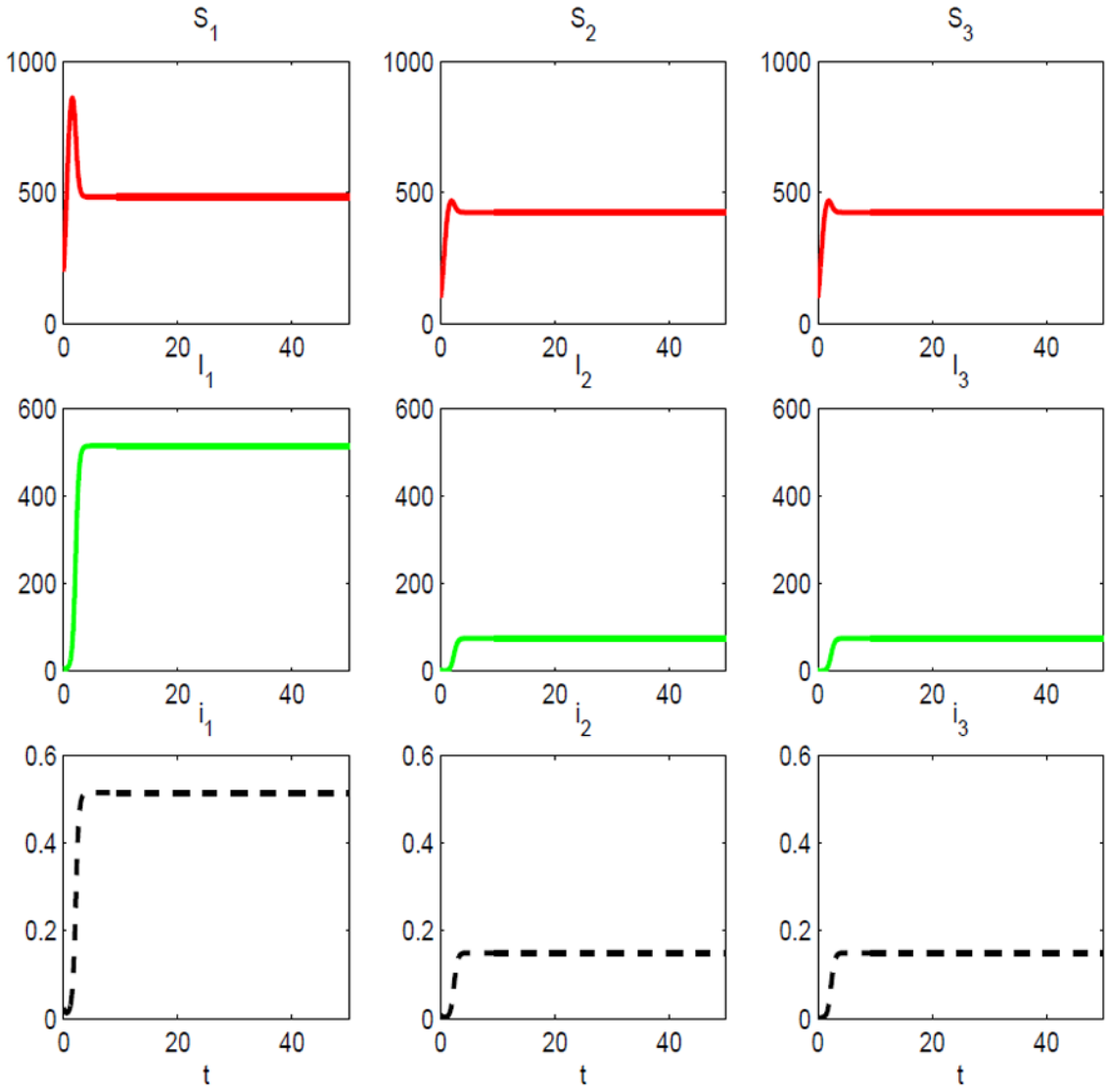

Fig. 8.

Solution of the three-host SIS epidemic model with mass action incidence for the initial conditions: $S_1(0) = 400$, $S_2(0) = 200 = S_3(0)$, $I_1(0) = 5$, $I_2(0) = 1$ and $I_3(0) = 0$; $\mathcal{R}_0 = 2.0202 > 1$.