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Differential Susceptible and Staged Progression Model for HIV

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Abstract

In this paper we first review the mathematical formulation of the original differential infectivity DI and staged-progression SP models, then we formulate a HIV new model with differential susceptibility and staged-progression DSSP to account for variations in viral loads and in the rate of disease progression in infected individuals. Then we derive an explicit formula for the reproductive number of infection for this model, then we provide numerical example for it.

Mathematics Subject Classification: 92BXX

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1 Introduction

Mathematical models based on the underlying transmission mechanisms of the disease can help the medical/scientific community understand and anticipate the spread of an epidemic and evaluate the potential effectiveness of different approaches for bringing an epidemic under control. Models can be used to improve our understanding of the essential relationships between the social and biological mechanisms that influence the spread of a disease. The relative influence of various factors on the spread of an epidemic, as well as the sensitivity to parameter variation, can be ascertained. Because the transmission dynamics from a complex nonlinear dynamical system, the behavior of the epidemic is a highly nonlinear function of the parameter values and levels of

intervention strategies. This at times may even lead to changes in infection spread that are counter to both intuition and simple extrapolated predictions. We can use the knowledge gained from studying models to help set priorities in research, saving time, resources, and lives.

In the studies of the transmission dynamics of **HIV**, two fundamental hypotheses for variations in infectiousness have been employed. In the staged-progression (**SP**) hypothesis, the infected individuals sequentially pass through a series of stages, being highly infectious in the first few weeks after their own infection, then having low infectivity for many years, and finally becoming gradually more infectious as their immune system breaks down and progress to AIDS [1, 6]. Based deterministic and statistic **SP** models have been formulated and studied to understand the impact of the disease progression on the spread of **HIV** [1, 12, 13, 19]. Based on other clinic findings and blood serum level studies [3], another hypothesis is the differential infectivity (**DI**) hypothesis, where infected individuals enter one of several groups, depending on their infectivity, and stay in that group until they develop AIDS.

The sensitivity of the epidemic in the **DI** and **SP** models to factors such as infectiousness and migration, and the impact of partner notification and screening programs on the spread of infection were studied further in [7, 8]. However, these studies left a number of questions unanswered about how best to control the spread of infection, which can only be addressed by a full model that incorporates aspects of both temporal (**SP**) and individual (**DI**) variations in infectiousness.

In this article we formulate a **HIV** model with differential susceptibility and staged-progression (**DSSP**) to account for variations in viral loads and in the rate of disease progression in infected individuals. Then we derive an explicit formula for the reproductive number (R_0) of infection for this model, then we provide numerical example for it.

2 The DI and SP Models

2.1 The DI Model

During the chronic stage of infection, viral levels differ by many orders of magnitude between individuals. Those with high viral loads in the chronic phase tend to progress rapidly to AIDS, while those with low loads tend to progress slowly to AIDS [3, 4, 15,21]. The **DI** model (Fig.1) accounts for the distribution of times from infection to AIDS by assuming variations between individuals in their duration of infection, dividing the infected population into n groups.

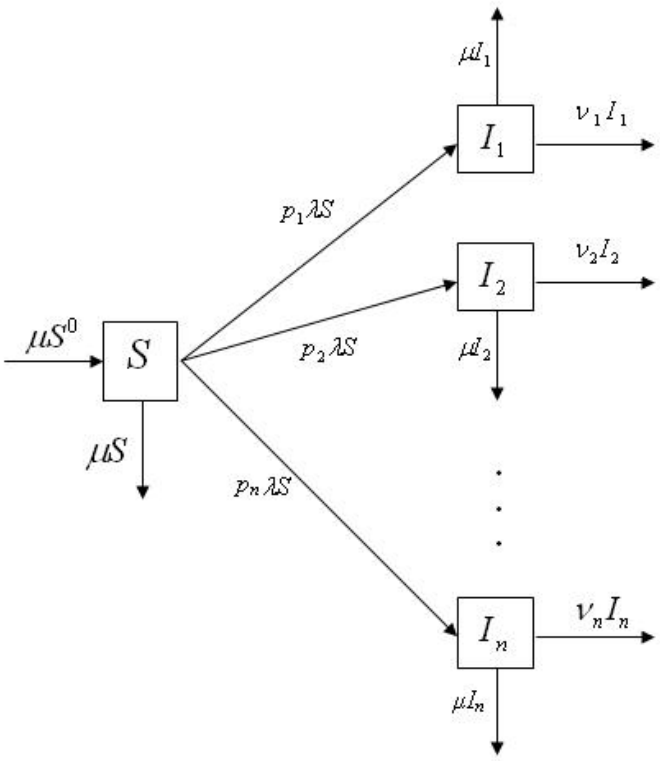

Figure 1: *The DI model divides the infected population into groups according to their infectiousness or differences in rates of developing AIDS. In this model HIV is primarily spread by a small, highly infectious, group of superspreaders.Since the transmission caused by individuals in group A is neglected, group A is not shown in this schematic diagram.*

The equations for the model illustrated in Fig.1 are,

$$\begin{cases} dS/dt = \mu(S^0 - S) - \lambda S, \\ dI_i/dt = p_i\lambda S - (\mu + \nu_i)I_i, \quad i = 1, ..., n, \\ dA/dt = \sum\limits_{j=1}^{n} \nu_i I_i - \delta A, \end{cases} \tag{1}$$

$\lambda(t) = \sum\limits_{i=1}^{n} \lambda_i(t)$ and $\lambda_i(t) = r\beta_i(I_i(t)/N(t))$,

where $N(t) = S(t) + \sum\limits_{j=1}^{n} I_i(t)$. Here S denotes the susceptibles, I_i denotes the number of infected individuals in group i, and A denotes the number of infected individuals no longer transmitting the disease. S^0 is the constant steady state population maintained by inflow when no virus is present in the population. The total removal rate μ accounts for both natural death in the

absence of **HIV** infection and people moving in and out of the sexually active susceptible population due to behavior changes or physical migration. $\lambda(t)$ is the rate of infection per susceptible, r is the partner acquisition rate, and β_i is the probability of transmission per partner from infected individuals in group i. Upon infection, an individual enters subgroup i with probability p_i, where $\sum_{i=1}^{n} p_i = 1$, and stays in this group until becoming inactive in transmission. Finally, ν_i is the rate at which infected individuals in group i enter group A, and δ is the death rate of people in group A. All infected individuals are assumed to eventually enter group A prior to death due to their infection.

2.2 The SP Model

The viral burden during **HIV** infection varies as a function of time within an individual. Initially, the **HIV-1 RNA** levels in plasma and serum can become extremely high during the first weeks of acute primary infection, even before there is a detectable immune response [16, 17]. These levels are higher than at any other time during infection. Acute primary infection is followed by a chronic phase during which the **HIV RNA** levels drop several orders of magnitude and remain at a nearly constant level for years [5, 15, 21]. In the late chronic stages of an infection the **HIV-1 RNA** levels may increase as much as ten fold [5] over what they have been during the rest of the chronic stage. The **SP** model (Fig.2) accounts for the temporal changes in the infectiousness of an individual by a staged Markov process of n infected stages progressing from the initial infection to AIDS.

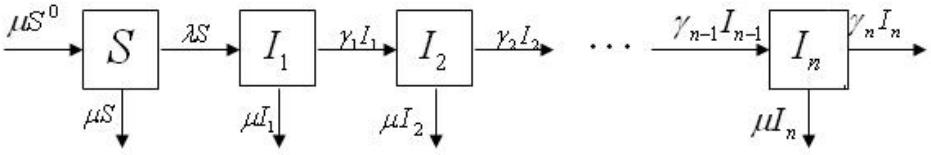

Figure 2: *In the SP model every infected individual goes through the same series of stages. This model can account for a short early highly infectious stage equivalent to the acute phase of infection, a middle period of low infectiousness, and a late chronic stage with higher infectiousness. Since the transmission caused by individuals in group A is neglected, group A is not shown in this schematic diagram.*

The equations for the **SP** model illustrated in Fig.2 are,

$$\begin{cases} dS/dt = \mu(S^0 - S) - \lambda S, \\ dI_1/dt = \lambda S - (\gamma_1 + \mu)I_1, \\ dI_i/dt = \gamma_{i-1}I_{i-1} - (\gamma_i + \mu), \\ dA/dt = \gamma_n I_n - \delta A, \end{cases} \quad 2 \le i \le n, \tag{2}$$

$\lambda(t) = \sum_{i=1}^{n} \lambda_i(t)$ and $\lambda_i(t) = r\beta_i(I_i(t)/N(t))$,
where now I_i is the number of infected individuals in each group infected stage. Note that all individuals go into group 1 upon infection. γ_i is the rate at which individuals move from stage i of infection to stage $i+1$. The meaning of S^0, μ, r, and δ are the same as in the **DI** model, and β is the probability of transmission per partner from infected individuals in stage i. Previous studies of **SP** models can be found in [2, 9, 10, 11, 12, 13].

3 The DSSP Model Formulation

We assume in the **DSSP** model, shown in Fig.3, that the population is homogeneous except in its response to **HIV** infection. In the absence of infection, the population of susceptible individuals, S, has a constant steady state, S^0, via a constant inflow and outflow, where each individual remains in the population an average of μ^{-1} years; thus μ is the removal rate due to natural death in the absence of **HIV** infection, migration, and changes in sexual behavior. Individuals are infected by **HIV** at a per capita rate λ.

First the susceptible S, divide to n susceptibles group S_i, then, the infected population of per group S_i to inter to group I_i such that individuals in each group have the same infectivity, but those from different groups have differential infectivities. The group that an individual belongs to upon infection is determined by the individuals physiology and/or the **HIV** virus infecting him/her. We assume that this infection group is not a transmissible property of the **HIV** virus, since there is no solid evidence that the individuals infected by an individual who is more infectious than others in the same population are themselves more infectious (or vice versa). The stay in this group until they leave the high-risk population because of behavior changes that are induced by either **HIV**-related illnesses or a positive **HIV** test and the subsequent desire not to transmit infection. We denote this subgroup of removed individuals by A. We further assume that each group i of the infected population is subdivided into m subgroups, $I_{i,1}, I_{i,2}, ..., I_{i,m}$, with different infection stages such that infected susceptible individuals enter the first subgroup $I_{i,1}$ and then gradually progress from subgroup $I_{i,m}$. Let $\gamma_{i,k}$ be the average rate of progression from subgroup $I_{i,k}$ to subgroup $I_{i,k+1}$, for $k = 1, ..., m-1$, and $\gamma_{i,m}$ be the rate at which infectives in subgroup $I_{i,m}$ enter the remove population, A. The

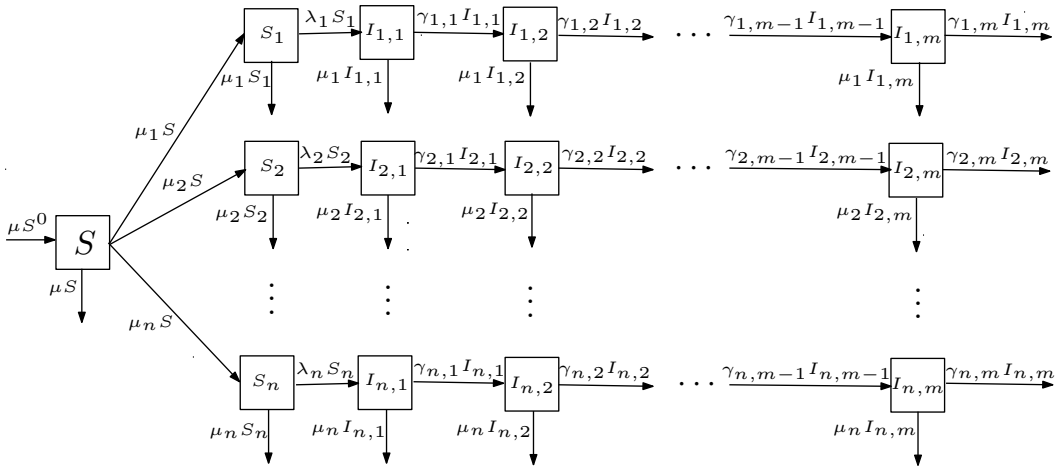

Figure 3: *In this DSSP model,first susceptible S invite to n susceptibles group S_i with rate $\mu_i S$, then when a susceptible of S_i is infected, this individual enters to $I_{i,1}$. Each infection group progresses through a series of stages where the progression rates $\gamma_{i,j}$ and infectivity $\beta_{i,j}$ vary. Since the transmission caused by individuals in group A is neglected, group A is not shown in this schematic diagram.*

rate of leaving the high risk population and entering the removed population may depend on the index i because there may be a link between the amount of viral shedding and how quickly an individual becomes sick. people in A are assumed to have a higher removal rate $\delta \geq \mu$, where μ accounts for both natural death in the absence of **HIV** infection and migration in and out of the susceptible population.

We neglect transmission by the A group, under the assumption that individuals in this group have significantly reduced their sexual activity or infectivity such that the transmission caused by them is negligible compared to the rest of the infected population. Then the dynamics of the **DSSP** model are governed

by the following equations,

$$\begin{cases} dS/dt = \mu S^0 - \mu S - \sum\limits_{i=1}^{n} \mu_i S, \\ dS_i/dt = \mu_i(S - S_i) - \lambda_i S_i, \\ dI_{i,1}/dt = \lambda_i S_i - (\mu_i + \gamma_{i1}) I_{i1}, \qquad i = 1, ..., n, j = 2, ..., m, \\ dI_{i,j}/dt = \gamma_{i,j-1} I_{i,j-1} - (\mu + \gamma_{i,j}) I_{ij}, \\ dA/dt = \sum\limits_{i=1}^{n} \gamma_{i,m} I_{i,m} - \delta A, \end{cases} \tag{3}$$

$\mu = \sum\limits_{i=1}^{n} \mu_i$, $\lambda_i = r \sum\limits_{j=1}^{m} \beta_{i,j}(I_{i,j}/N_i)$,

where $N_i = S_i + \sum\limits_{j=1}^{m} I_{i,j}$.

Therefore, the rate of infection, λ_i, depends on the product of the infectivity or the transmission probability per contact, β_{ij}, of individuals in group i during jth infection stage, the proportion of the population in the subgroup, $I_{i,j}/N_i$, and the number of contacts of an individual per unit of time, r. We assume that the r contacts are randomly distributed over the whole population.

4 The Reproductive Number of Infection

We note that since the transmission by **AIDS** cases has been neglected under our assumptions, the transmission dynamics of (3) are determined by the transmission dynamics of the susceptibles and infectives. We ignore the equation for group A hereafter, and derive an explicit formula for reproductive number of the system.

We derive an explicit formula for the reproductive of infection by determining the spectral radius of the next generation operator of system (3) with $\lambda_i = r \sum\limits_{j=1}^{m} \beta_{i,j}(I_{i,j}/N_i)$, as follows.

System (3) has an infection-free equilibrium, given by ($S_i = S = S^0/2, I_{i,j} = 0, i = 1, ..., n, j = 1, ..., m$). Linearizing system (3) around the infection-free equilibrium, we have the following Jacobian matrix:

$$J_{n,m} := \begin{pmatrix} -\mu - \sum\limits_{i=1}^{n} \mu_i & 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ -\mu_i & \cdot & \cdot & \cdot & \cdot & \cdots & \cdot & \cdot \\ 0 & A_{1,1} + B_{1,1} & A_{1,2} & A_{1,3} & A_{1,4} & \cdots & A_{1,m-1} & A_{1,m} \\ 0 & B_{2,1} & B_{2,2} & 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & B_{3,2} & B_{3,3} & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & \cdots & B_{m,m-1} & B_{m,m} \end{pmatrix} \tag{4}$$

where

$$A_{1,j} := \begin{pmatrix} r\beta_{1,j} & 0 & \cdots & 0 \\ 0 & r\beta_{2,j} & \cdots & 0 \\ \vdots & \vdots & \ddots & 0 \\ 0 & 0 & 0 & r\beta_{n,j} \end{pmatrix}, \quad j = 1, ..., m, \tag{5}$$

$$B_{j,j} := \begin{pmatrix} -\sigma_{1,j} & 0 & \cdots & 0 \\ 0 & -\sigma_{2,j} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & -\sigma_{n,j} \end{pmatrix}, \quad j = 1, ..., m, \tag{6}$$

and

$$B_{j,j-1} := \begin{pmatrix} \gamma_{1,j-1} & 0 & \cdots & 0 \\ 0 & \gamma_{2,j-1} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \gamma_{n,j-1} \end{pmatrix}, \quad j = 2, ..., m, \tag{7}$$

with $\sigma_{i,1} = \mu_i + \gamma_{i,1}$ for $i = 1, ..., n$, and $\sigma_{i,j} = \mu + \gamma_{i,j}$ for $i = 1, ..., n$, $j = 2, ..., m$. Employing the technique developed in [5, 6, 21], we only consider the entries in $J_{n,m}$ that are from infective equations $dI_{i,j}/dt$ and use the same notations as in [21].

Define matrices F and V as

$$F := \begin{pmatrix} A_{1,1} & A_{1,2} & A_{1,3} & \cdots & A_{1,m} \\ 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 0 \end{pmatrix}, \tag{8}$$

$$V := \begin{pmatrix} -B_{1,1} & 0 & 0 & \cdots & 0 & 0 \\ -B_{2,1} & -B_{2,2} & 0 & \cdots & 0 & 0 \\ 0 & -B_{3,2} & -B_{3,3} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & -B_{m-1,m-1} & 0 \\ 0 & 0 & 0 & \cdots & -B_{m,m-1} & -B_{m,m} \end{pmatrix}. \tag{9}$$

Then F is a nonnegative matrix and V is a nonsingular $M-$matrix. Hence the reproductive number, R_0, is equal to the spectral radius of the next generation operator FV^{-1} [19]:

$$R_0 = \rho(FV^{-1}).$$

To determine the spectral radius of FV^{-1}, we first represent the inverse of V by the following lower triangular matrix:

$$V^{-1} = \begin{pmatrix} V_{1,1} & 0 & \cdots & 0 \\ V_{2,1} & V_{2,2} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ V_{m,1} & V_{m,2} & \cdots & V_{m,m} \end{pmatrix}, \tag{10}$$

where

$$V_{i,i} = -B_{i,i}^{-1},\ i = 2, ..., m,$$

and $V_{i,j}$ are defined recursively by

$$V_{i,j} = -B_{i,i-1}V_{i-1,j}B_{i,i}^{-1}, \quad i = 2, ..., m, \quad j < i. \tag{11}$$

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In fact, because every diagonal submatrix of VV^{-1} is an identity matrix, we only consider an arbitrary $(i, j)-$submatrix of VV^{-1} for $j < i$. Notice that $B_{i,j}$ are all $n \times n$ diagonal matrices. Matrices $B_{i,j}$ and $B_{i,j}^{-1}$ are all commutative. Hence

$$\begin{aligned} -B_{i,i-1}V_{i-1,j} - B_{i,i}V_{i,j} &= -B_{i,i-1}V_{i-1,j} + B_{i,i}B_{i,i-1}V_{i-1,j}B_{i,i}^{-1} \\ &= -B_{i,i-1}V_{i-1,j} + B_{i,i-1}V_{i-1,j} = 0. \end{aligned}$$

Since $-B_{i,i-1}$ and $-B_{i,i}$ are the only nonzero submatrices on row i, for $i = 2, ..., m$, in V, every $(i, j)-$submatrix of VV^{-1} for $j < i$ is a zero matrix.
Now we are ready to derive an explicit formula for the reproductive number R_0. Since matrix F has rank 1, the spectral radius $\rho(FV^{-1})$ is equal to the trace of matrix FV^{-1}. Note that the only nonzero submatrices of F are $A_{1,i}$. Then

$$trace(FV^{-1}) = trace(\sum_{i=1}^{m} A_{1,i}V_{i,1}).$$

Using the recursive formula (11), we have

$$V_{i,1} = (-1)^i \prod_{k=2}^{i} B_{k,k-1} \prod_{k=1}^{i} B_{k,k}^{-1}, \tag{13}$$

which can be shown by induction as follows.
Given that

$$V_{1,1} = -B_{1,1}^{-1} = (-1)^1 \prod_{k=2}^{1} B_{k,k-1} \prod_{k=1}^{1} B_{k,k}^{-1},$$

(13) holds for $i = 1$. Suppose (13) holds for i. It follows from (12) and (13) that

$$\begin{aligned} V_{i+1,1} &= -B_{i+1,i}V_{i,1}B^{-1}_{i+1,i+1} = (-1)^{i+1}B_{i+1,i}\prod_{k=2}^{i}B_{k,k-1}\prod_{k=1}^{i}B^{-1}_{k,k}B^{-1}_{i+1,i+1} \\ &= (-1)^{i+1}\prod_{k=2}^{i+1}B_{k,k-1}\prod_{k=1}^{i+1}B^{-1}_{k,k}. \end{aligned}$$

Hence (14) holds for $i+1$, and therefore holds for all $i = 1, ..., m$. Substituting $B_{k,k-1}$ and $B_{k,k}$ given in (6) and (7) into (13), we have

$$\begin{aligned} V_{i,1} &= (-1)^i diag\left(\prod_{k=2}^{i}\gamma_{1,k-1}, \prod_{k=2}^{i}\gamma_{2,k-1}, ..., \prod_{k=2}^{i}\gamma_{n,k-1}\right) \\ &\quad \times(-1)^i diag\left(\prod_{k=1}^{i}\sigma^{-1}_{1,k}, \prod_{k=1}^{i}\sigma^{-1}_{2,k}, ..., \prod_{k=1}^{i}\sigma^{-1}_{n,k}\right) \\ &= diag\left((1/\sigma_{1,i})\prod_{k=1}^{i-1}(\gamma_{1,k}/\sigma_{1,k}), (1/\sigma_{2,i})\prod_{k=1}^{i-1}(\gamma_{2,k}/\sigma_{2,k}), ...\right. \\ &\quad \left., (1/\sigma_{n,i})\prod_{k=1}^{i-1}(\gamma_{n,k}/\sigma_{n,k})\right). \end{aligned}$$

The diagonal entries of $A_{1,i}V_{i,1}$ are

$$r(\beta_{j,i}/\sigma_{j,i})\prod_{k=1}^{i-1}(\gamma_{j,k}/\sigma_{j,k}), \qquad j = 1, ..., n.$$

Therefore

$$traceFV^{-1} = trace\sum_{i=1}^{m}A_{1,i}V_{i,1} = r\sum_{j=1}^{n}\sum_{i=1}^{m}(\beta_{j,i}/\sigma_{j.i})\prod_{k=1}^{i-1}(\gamma_{j,k}/\sigma_{j,k}).$$

4.1 Theorem

Define the reproductive number R_0 as

$$\begin{aligned} R_0 &= r\sum_{j=1}^{n}\sum_{i=1}^{m}(\beta_{j,i}/\sigma_{j,i})\prod_{k=1}^{i-1}(\gamma_{j,k}/\sigma_{j,k}) \\ &= r\sum_{i=1}^{m}(\beta_{1,i}/(\mu_i+\gamma_{1,i}))\prod_{k=1}^{i-1}(\gamma_{1,k}/(\mu_k+\gamma_{1,k})) \\ &\quad +r\sum_{j=2}^{n}\sum_{i=1}^{m}(\beta_{j,i}/(\mu+\gamma_{j,i}))\prod_{k=1}^{i-1}(\gamma_{j,k}/(\mu+\gamma_{j,k})). \end{aligned} \tag{14}$$

If $R_0 < 1$ the infection-free equilibrium is locally asymptotically stable, and if $R_0 > 1$ the infection-free equilibrium is unstable.

4.2 Example

Consider a two group model with $n = 2$ and $m = 2$ governed by

$$\begin{cases} dS/dt = \mu S^0 - \mu S - \sum\limits_{i=1}^{n} \mu_i S, \\ dS_i/dt = \mu_i(S - S_i) - \lambda_i S_i, \\ dI_{i,1}/dt = \lambda_i S_i - (\mu_i + \gamma_{i1}) I_{i1}, \qquad i = 1, 2, j = 2, \\ dI_{i,j}/dt = \gamma_{i,j-1} I_{i,j-1} - (\mu + \gamma_{i,j}) I_{ij}, \\ dA/dt = \sum\limits_{i=1}^{2} \gamma_{i,2} I_{i,2} - \delta A, \end{cases} \tag{15}$$

$\mu = \sum\limits_{i=1}^{2} \mu_i$, $\lambda_i = r \sum\limits_{j=1}^{2} \beta_{i,j}(I_{i,j}/N_i)$,
We use the following model parameters:
$S^0 = 500, S_1(0) = 300, S_2(0) = 200, I_{11}(0) = 50, I_{21}(0) = 100, I_{12}(0) = 5$, $I_{22}(0) = 0, \mu_1 = 0.025, \mu_2 = 0.015, \gamma_{11} = 0.025, \gamma_{12} = 0.02$, $\gamma_{21} = 0.02, \gamma_{22} = 0.035, r = 10$,
Depending on the probability transmission, the dynamics of the infecteds ($I_{i,j}^{,}$s) for different $\beta_{i,j}^{,}$s are shown for group 1 in Fig.4 and for group 2 in Fig.5.

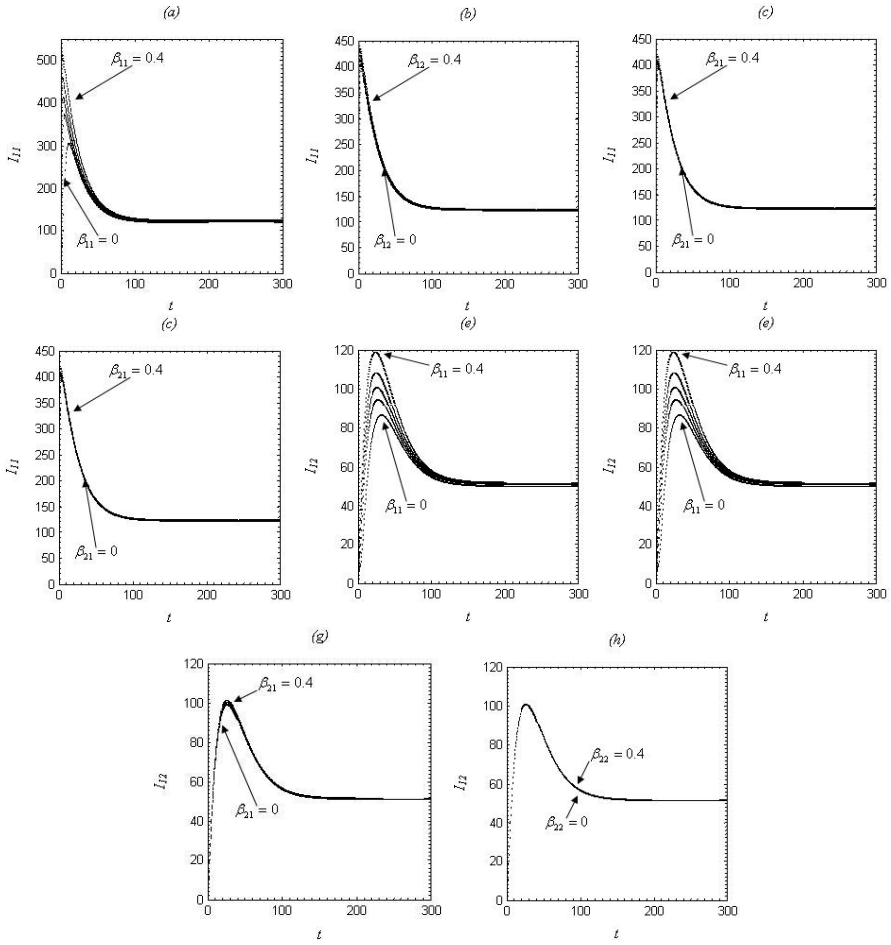

Figure 4: $(a) : 0 \leq \beta_{11} \leq 0.4, \beta_{12} = 0.1, \beta_{21} = 0.05, \beta_{22} = 0.1$, $(b) : \beta_{11} = 0.2, 0 \leq \beta_{12} \leq 0.4, \beta_{21} = 0.05, \beta_{22} = 0.1$, $(c) : \beta_{11} = 0.2, \beta_{12} = 0.1, 0 \leq \beta_{12} \leq 0.4, \beta_{22} = 0.1$, $(d) : \beta_{11} = 0.2, \beta_{12} = 0.1, \beta_{21} = 0.05, 0 \leq \beta_{22} = 0.1 \leq 0.4, (e) : 0 \leq \beta_{11} \leq 0.4, \beta_{12} = 0.1, \beta_{21} = 0.05, \beta_{22} = 0.1$, $(f) : \beta_{11} = 0.2, 0 \leq \beta_{12} \leq 0.4, \beta_{21} = 0.05, \beta_{22} = 0.1$, $(g) : \beta_{11} = 0.2, \beta_{12} = 0.1, 0 \leq \beta_{12} \leq 0.4, \beta_{22} = 0.1$, $(h) : \beta_{11} = 0.2, \beta_{12} = 0.1, \beta_{21} = 0.05, 0 \leq \beta_{22} = 0.1 \leq 0.4$.

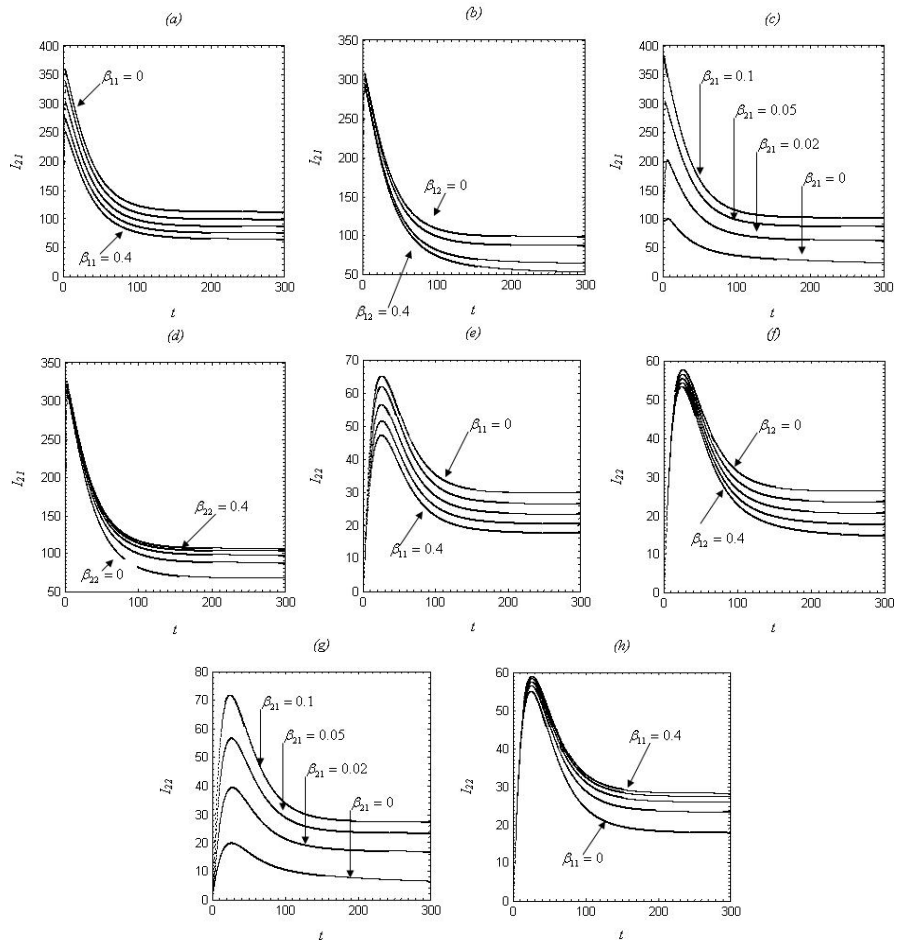

Figure 5: $(a) : 0 \leq \beta_{11} \leq 0.4, \beta_{12} = 0.1, \beta_{21} = 0.05, \beta_{22} = 0.1$, $(b) : \beta_{11} = 0.2, 0 \leq \beta_{12} \leq 0.4, \beta_{21} = 0.05, \beta_{22} = 0.1$, $(c) : \beta_{11} = 0.2, \beta_{12} = 0.1, 0 \leq \beta_{12} \leq 0.1, \beta_{22} = 0.1$, $(d) : \beta_{11} = 0.2, \beta_{12} = 0.1, \beta_{21} = 0.05, 0 \leq \beta_{22} = 0.1 \leq 0.4, (e) : 0 \leq \beta_{11} \leq 0.4, \beta_{12} = 0.1, \beta_{21} = 0.05, \beta_{22} = 0.1$, $(f) : \beta_{11} = 0.2, 0 \leq \beta_{12} \leq 0.4, \beta_{21} = 0.05, \beta_{22} = 0.1$, $(g) : \beta_{11} = 0.2, \beta_{12} = 0.1, 0 \leq \beta_{12} \leq 0.1, \beta_{22} = 0.1$, $(h) : \beta_{11} = 0.2, \beta_{12} = 0.1, \beta_{21} = 0.05, 0 \leq \beta_{22} = 0.1 \leq 0.4$.

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