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Stability of Differential Susceptibility and Infectivity Epidemic Models

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Abstract

We introduce classes of differential susceptibility and infectivity epidemic models. These models address the problem of flows between the different susceptible, infectious and infected compartments and differential death rates as well. We prove the global stability of the disease free equilibrium when the basic reproduction ratio $\mathcal{R}_0 \leq 1$ and the existence and uniqueness of an endemic equilibrium when $\mathcal{R}_0 > 1$. We also prove the global asymptotic stability of the endemic equilibrium for a differential susceptibility and staged progression infectivity model, when $\mathcal{R}_0 > 1$. Our results encompass and generalize those of [18, 22].

Keywords : Nonlinear dynamical systems, global stability, Lyapunov methods, differential susceptibility models, reproductive number, HBV.

AMS subject classification : 34A34, 34D23, 34D40, 92D30

1 Introduction

The primary objective of this paper is to give results on global stability for epidemiological models with differentiation in susceptibility for infection and differentiation in infectivity. The first models with differential infectivity has been introduced for studying HIV infection [29, 28, 37] by Jacquez et al. circa 1990s. The term differential infectivity has been coined by Hyman et al. in [23, 18, 21, 19]. Models with differential susceptibility has been introduced in the references [18, 22].

The rationale to introduce differential infectivity and susceptibility is motivated by the heterogeneity, concerning the mode of infection, for the individuals.

For many reasons difference in susceptibility to infection can occur : genetic variations, different social behaviors, different states of immunization, different vaccines ...

The infection by HBV, hepatitis B, is typically a disease where simultaneously differential susceptibility and infectivity appear :

Hepatitis B virus (HBV) is a bloodborne and sexually transmitted virus. The liver is the primary site of HBV replication. After a susceptible person is exposed, the virus enters the liver via the bloodstream. Hepatitis B is one of the major diseases of mankind and is a serious global public health problem. Of the 2 billion people who have been infected with the hepatitis B virus

(HBV), more than 350 million have chronic (lifelong) infections. Rates of new infection and acute disease are highest among adults, but chronic infection is more likely to occur in persons infected as infants or young children. These chronically infected persons are at high risk of death from cirrhosis of the liver and liver cancer, diseases that kill about one million persons each year. According to CDC and WHO, risk for chronic infection is inversely related to age at infection: approximately 90% of infected infants and 30% of infected children aged under 5 years become chronically infected, compared with 5% of adults. This difference in the evolution of infection introduces naturally differential susceptibility.

Indeed hepatitis B is a major public health problem in developing countries of Africa and Asia (where prevalence is greater than 8%). In much of the developing world, (sub-Saharan Africa, most of Asia, and the Pacific), most people become infected with HBV during childhood, and 8% to 10% of people in the general population become chronically infected. In these regions liver cancer caused by HBV figures among the first three causes death by cancer in men.

Asymptomatic carriers play an important role in the transmission of HBV. Usually asymptomatic carriers are considered as less infectious than acute carriers, which is a reason for incorporating differential susceptibility. Vaccination is recognized as the most efficient way of preventing hepatitis B. But the problem of imperfect vaccine introduce naturally differential susceptibility. Even if HBV vaccine is very efficient it does not offer 100% protection against infection. According WHO, Hepatitis B vaccine is 95% effective in preventing HBV infection and its chronic consequences, Then vaccinated individuals form a class of individual with different susceptibility.

In [2], May and Anderson consider a model of HBV infection. They distinguishes, in this model the susceptible individuals according to their response. They assume that a proportion of births to infected carriers are themselves infected carriers, while the remaining fraction of these births give susceptibles in the carrier carrier group. This model is clearly a differential susceptibility and infectivity model.

In [11], a SVEICR model is considered for modeling HBV infection.

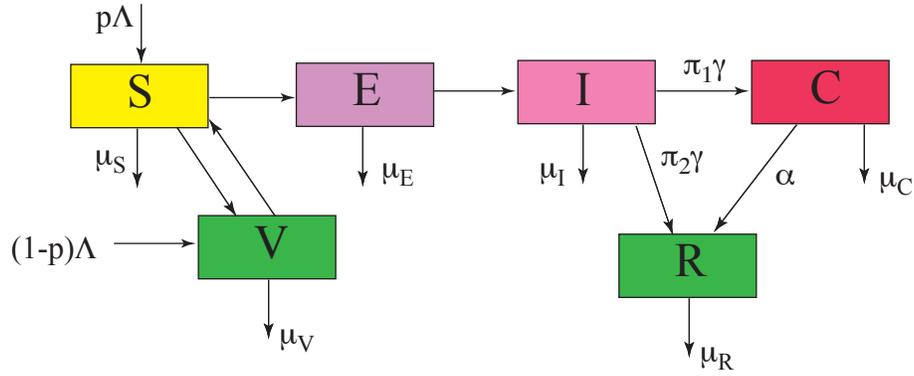


Figure 1: a Differential susceptibility and infectivity model

When different strains are taken into account differential susceptibility and infectivity models are given in [41, 42].

More generally the stage-progression HIV model with imperfect vaccine of [15] is also a differential susceptibility systems and infectivity model.

We consider a general class of differential susceptibility systems and infectivity models with bilinear mass action as in [18] and give stability results. We could have use a standard incidence mass action $c(N) \beta \frac{I}{N}$ [7, 36]. The stability results of the disease free equilibrium remain true by an easy adaptation. However the proof of existence and uniqueness of the endemic equilibrium, as well as the stability of this endemic equilibrium, work only with the bilinear mass action. This mass action becomes natural when N is constant or $c(N) = c_0 N$ or else when the model is dealing with proportions. For homogeneity of exposition, we will use bilinear mass action throughout the paper.

The models considered in this paper address the issue of flows between the different compartments of infected and infectious individuals as well as flows between the different compartment of susceptible individuals. Moreover the differences of death-rates between classes are also taken into account. These models encompass the models with bilinear mass action of [13, 14, 15, 22, 18].

We give a brief outline of the paper. In section 2 we introduce the class of system considered. Our models are differential susceptibility and infectivity epidemic models. These models take into account flows between the different classes of susceptible, infected and infectious compartments. The death rate

can be different for each compartment. Since our model is presented in a general setting we add hypotheses for biological soundness. These hypotheses are satisfied in the models in [15, 22, 18]. In this section we give, for natural subclasses of our general systems, a simple analytical expression for the basic reproduction ratio \mathcal{R}_0 . We prove the global stability of the disease free equilibrium (DFE) when $\mathcal{R}_0 \leq 1$ and the existence and uniqueness of a strongly endemic equilibrium when $\mathcal{R}_0 > 1$. The proof of the global stability of the endemic equilibrium is always a challenge. We give the global stability of the endemic equilibrium for a differential susceptibility and infectivity epidemic model which generalizes the results in [22, 18].

2 A general class of systems

Throughout this paper we will use the following notations. If x is a vector of \mathbb{R}^n then $\text{diag}(x)$ will be the $n \times n$ diagonal matrix, whose diagonal elements are the components of x . We will denote by $\langle | \rangle$ the usual inner product on \mathbb{R}^n . In \mathbb{R}^n Let $\{e_1, \dots, e_n\}$ be the canonical basis of \mathbb{R}^n . We will denote by $\mathbf{1}$ the vector given by $\mathbf{1} = (1, \dots, 1)^T = e_1 + \dots, e_n$, where the superscript T denotes transpose.

We use the ordering in \mathbb{R}^n generated by the cone \mathbb{R}_+^n . We write $x \leq y$, if $y - x \in \mathbb{R}_+^n$ and $x < y$ if $x \leq y$ and $x \neq y$. Finally $x \ll y$ will mean $x_i < y_i$ for any index i .

We consider the following general model

$$\begin{cases} \dot{S} = \Lambda - \text{diag}(\mu_S) S + A_S S - \text{diag}(B I) S, \\ \dot{I} = P \text{diag}(B I) S - \text{diag}(\mu_I + \gamma_I) I + A_I I, \\ \dot{R} = L I - \text{diag}(\mu_R) R + A_R R, \end{cases} \quad (1)$$

where $S \in \mathbb{R}_+^n$ is the state of susceptible individuals, $I \in \mathbb{R}_+^m$ is the state of infectious and infected individuals and $R \in \mathbb{R}_+^p$ the state of recovered and immune individuals. The recruitment, in each susceptible compartment, is described by a nonnegative vector $\Lambda > 0$. The positive vector $\mu_S \gg 0$ represents the death rate of the different classes of susceptible individuals. The matrix A_S represents the flows between the susceptible compartments. In the words of Jacquez the coefficients of A_I are the *fractional transfer coefficients* [27]. Since A_S represents only the movement between the S

compartments, A_S is a compartmental Metzler matrix, whose column sums are zero, i.e., the sum of the elements of each column is zero.

The matrix $B > 0$ represents the coefficients of infectivity, actually $B(i, j) = \beta_{ij}$ is the contact and infectivity of I_j in the group S_i . The matrix B is also known as the WAIFW matrix (Who Acquire Infection From Whom [2]). The matrix P is a column-stochastic $m \times n$ matrix:

$$P = \begin{pmatrix} p_{11} & p_{12} & \cdots & p_{1n} \\ p_{21} & p_{22} & \cdots & p_{2n} \\ \vdots & \cdots & \ddots & \cdots \\ p_{m1} & p_{m2} & \cdots & p_{mn} \end{pmatrix}$$

This matrix represents the distribution of susceptible individual after infection. A susceptible individual in group S_i enters group I_j with probability

$$p_{ji}, \text{ hence } \sum_{j=1}^m p_{ji} = 1.$$

Analogously as before, the matrix A_I represents the movements between the I compartments. The vector $\mu_I \gg 0$ and $\gamma_I > 0$ represent respectively, the death rate and the recovery rate of the infectious-infected compartments I_i . The vector γ_I is supposed only nonnegative, since an infected individual does not necessarily recover and usually move in an infected compartment.

Finally, the matrix L represents the distribution of the I compartment toward the R compartments. The vector μ_R and the matrix A_R are defined as their corresponding analogue in the S and I compartments.

We remark that in this setting, since B is a non zero nonnegative matrix, the model (1) can contain compartments of infected individuals that are not infectious or latent individuals. They are simply the I_j compartments, with no transmission, i.e., for which $B_{i,j} = 0$, for any i . However the matrix B cannot contain a row whose elements are all zero. In other words, for all $i \in \{1, \dots, n\}$ there exist $k \in \{1, \dots, m\}$ such that $B_{i,k} \neq 0$, otherwise if there is an index i_0 such that $B_{i_0,k} = 0$ for all $k \in \{1, \dots, m\}$ this would mean that the individuals of compartment S_{i_0} can never be infected and hence the individuals of S_{i_0} would not be susceptible.

Using Gershgorin theorem it is clear that the matrices

$$-\text{diag}(\mu_S) + A_S, \quad -\text{diag}(\mu_I) + A_I, \quad \text{and} \quad -\text{diag}(\mu_R) + A_R$$

are stable Metzler matrices and are in particular non singular. This implies,

that when there is no transmission, the infected, infectious and the removed individuals disappear.

We will use the following properties repeatedly in the sequel : a Metzler matrix (off-diagonal entries are nonnegative) M is stable if and only if $-M^{-1} > 0$ [5, 38]. This also has for consequence that if $x \gg 0$ then $-M^{-1}x \gg 0$. There are two schools for matrices like these matrices. The first one, uses Metzler matrices (called also quasipositive matrices) and it is represented by J.A. Jacquez, D. Luenberger, H.L. Smith or H. Thieme [26, 27, 34, 39, 38]. The second one uses M -matrices : the negative of a stable Metzler matrix is a nonsingular M -matrix. This school is represented, for example, by Berman and Plemmons[5] or van den Driessche and Watmough ([40]). We choose to stick to the Jacquez formalism, natural for compartmental models, since our matrices A represent the exchanges between compartments.

For the stability analysis we can discard the last equation

$$\dot{R} = LI - \text{diag}(\mu_R)R + A_R R.$$

Since the variables R do not play a part in the preceding equations, the stability analysis can be reduced to the system (1) without the last equation. Therefore we will consider, from now on, the following system

$$\begin{cases} \dot{S} = \Lambda - \text{diag}(\mu_S)S + A_S S - \text{diag}(BI)S \\ \dot{I} = P \text{diag}(BI)S - \text{diag}(\mu_I + \gamma_I)I + A_I I, \end{cases} \quad (2)$$

Throughout the paper, we shall use the matrix \tilde{A}_I defined by

$$\tilde{A}_I = -\text{diag}(\mu_I + \gamma_I) + A_I$$

Supplementary assumptions: Our systems are general, we will add some hypotheses for to be biologically consistent. For formulating these hypothesis we will use some definitions from graph theory [5]. To our system we associate a directed graph as usual. We have $m+n$ vertices, n vertices corresponding to susceptible compartments, m vertices for infected or infectious compartments. Our system (2) can be rewritten under a canonical form for compartmental systems [27]:

$$\begin{bmatrix} \dot{S} \\ \dot{I} \end{bmatrix} = \begin{bmatrix} \Lambda \\ 0 \end{bmatrix} + \begin{bmatrix} -\text{diag}(\mu_S) + A_S - \text{diag}(BI) & 0 \\ 0 & \text{diag}(S)B - \text{diag}(\mu_I + \gamma_I) + A_I \end{bmatrix} \begin{bmatrix} S \\ I \end{bmatrix} \quad (3)$$

The matrix appearing in this equation is a compartmental Metzler matrix [27]. We denote by $M(S, I)$ this matrix.

$$M(S, I) = \begin{bmatrix} -\text{diag}(\mu_S) + A_S - \text{diag}(BI) & 0 \\ 0 & \text{diag}(S)B - \text{diag}(\mu_I + \gamma_I) + A_I \end{bmatrix}$$

In our associated graph an edge leads from a vertex j to a different vertex $i \neq j$ if $M(S, I)_{i,j} > 0$ for some (S, I) . We say that j has an access to i , if in the graph there is a path from j to i . This is equivalent to say that, for some $p > 0$, $M^p(S, I)_{i,j} > 0$ [5]. We thus shall assume that the following hypothesis is fulfilled:

H1 *We will assume in the sequel that any “susceptible” compartment is accessible from a “susceptible” compartment with recruitment.*

This property depends only of the matrix A_S and the location of recruitment. For any $x \geq 0$, the matrix $-\text{diag}(\mu_S) + A_S - \text{diag}(x)$ is a Hurwitz Metzler matrix. Hypothesis **H1** implies the following

Lemma 2.1 *For any $x \geq 0$, we have*

$$-[-\text{diag}(\mu_S) + A_S - \text{diag}(x)]^{-1} \Lambda \gg 0.$$

This implies, in particular, that the disease free equilibrium (DFE) of system (2) given by $(S^, 0) = (-[A_S - \text{diag}(\mu_S)]^{-1} \Lambda, 0)$ satisfies $S^* \gg 0$.*

Proof.

We have only to consider the connected components from the recruitment. If we denote by e_1 , the vector of the canonical basis, corresponding to a recruitment compartment, by $M(x)$ the matrix $[-\text{diag}(\mu_S) + A_S - \text{diag}(x)]$, we have to prove that for any e_i accessible from e_1 we have

$$\langle -M(x)^{-1} e_1 | e_i \rangle > 0.$$

Since the matrix $M(x)$ is Hurwitz, it satisfies $\int_0^\infty e^{tM(x)} dt = -M(x)^{-1}$. Thus we can write

$$\langle -M(x)^{-1} e_1 | e_i \rangle = \int_0^\infty \langle e^{tM(x)} e_1 | e_i \rangle dt.$$

The expression under the integral, in the right hand side, is nonnegative and analytic in t . Hence, it suffices to prove that $\left. \frac{d^k}{dt^k} \langle e^{tM(x)} e_1 | e_i \rangle \right|_{t=0} > 0$

for some $k > 0$. We choose for k the integer satisfying $\langle A_S^k e_1 | e_i \rangle > 0$ and $\langle A_S^p e_1 | e_i \rangle = 0$ for $0 \leq p < k$. This integer exists thanks to Assumption **H1**. We then have

$$\frac{d^k}{dt^k} \langle e^{tM(x)} e_1 | e_i \rangle \Big|_{t=0} = \langle M(x)^k e_1 | e_i \rangle$$

$\langle M(x)^k e_1 | e_i \rangle = \sum_{p=0}^k C_k^p (-1)^{k-p} (\mu_{S_1} + x_1)^{k-p} \langle A_S^p e_1 | e_i \rangle = \langle A_S^k e_1 | e_i \rangle > 0$. This completes the proof of the lemma. ■

An entry-point compartment for infection is an infected-infectious compartment with an edge coming from the susceptible compartments. Equivalently this is the compartment with index for which the components of $P \mathbf{1}$ are positive.

Since this model can deal with infected people that are not infectious, i.e., we allow the possibility of having some compartments I_j for which $B_{i,j} = 0$, we must add some hypotheses. The infectious individuals must appear from transmission. If we have, a typical set of different susceptible, $c \gg 0$, becoming infected, then distributed in the infected-infectious compartments as $P c$ we assume that all these individuals will evolve through all the infected-infectious compartments. This hypothesis is the analogous of the preceding hypothesis. This can also be formulated in the following manner:

H2 *Any infected-infectious compartment is accessible from at least one compartment which is an “entry-point” for infection.*

A consequence of hypothesis **H2** is $-\tilde{A}_I^{-1} P c \gg 0$ for any $c \gg 0$. The proof is similar to the proof of the preceding lemma.

Remark 2.1 *With these two hypotheses, when there are some infection, then the trajectories of our system are in the positive orthant. However our hypothesis are weaker than an irreducibility hypothesis on the flow graph of our system.*

This model encompasses known models of DI (differential infectivity), SP (staged progression), or differential susceptibility models, with bilinear mass action. We will generalize the results obtained in [22, 18, 4, 12]. In particular, we shall prove the global asymptotic stability of the endemic equilibrium when $\mathcal{R}_0 > 1$. This has been conjectured in [22] according to numerical simulations.

2.1 Basic reproduction ratio

It is not difficult using the results on \mathcal{R}_0 [10, 17, 9, 40, 16] to obtain a formula for the basic reproduction ratio. Since this formula expresses \mathcal{R}_0 as the spectral radius $\rho(\mathcal{G})$ of the next generation matrix \mathcal{G} , we cannot expect, in general, to obtain an analytical expression.

Using the techniques developed in [40], we claim that the basic reproduction ratio \mathcal{R}_0 for the general system (2) is

$$\mathcal{R}_0 = \rho\left(-P \operatorname{diag}(S^*) B \tilde{A}_I^{-1}\right) = \rho\left(-\tilde{A}_I^{-1} P \operatorname{diag}(S^*) B\right). \quad (4)$$

Where

$$\tilde{A}_I = -\operatorname{diag}(\mu_I + \gamma_I) + A_I.$$

We use the expression $(-\tilde{A}_I^{-1})$ to put the emphasis on the fact that the matrix $(-\tilde{A}_I^{-1}) > 0$ because the matrix A is Metzler stable. Using the framework of [40], we denote by $\mathcal{F}_i(S, I)$ the rate of appearance of new infections in compartment i , and by $\mathcal{V}_i(S, I)$ the rate of transfer of individuals in and out the compartment i by all other means. The matrix \mathcal{V} is the ‘‘mass’’ balance of the compartments. Note that our \mathcal{V} is the opposite of the one used in [40]. Then

$$\mathcal{F}(S, I) = \begin{bmatrix} 0 \\ P \operatorname{diag}(B I) S \end{bmatrix},$$

and

$$\mathcal{V}(S, I) = \begin{bmatrix} \Lambda - \operatorname{diag}(\mu_S) S + A_S S - \operatorname{diag}(B I) S \\ \tilde{A}_I I \end{bmatrix}.$$

The Jacobian matrices are

$$D\mathcal{F}(S, I) = \begin{bmatrix} 0 & 0 \\ P \operatorname{diag}(B I) & P \operatorname{diag}(S) B \end{bmatrix},$$

and

$$D\mathcal{V}(S, I) = \begin{bmatrix} -\operatorname{diag}(\mu_S) + A_S - \operatorname{diag}(B I) & -\operatorname{diag}(S) B \\ 0 & \tilde{A}_I \end{bmatrix}.$$

Noting that we have sorted the variables in the reverse order in comparison with [40], we set $F = P \operatorname{diag}(S^*) B$ and $V = \tilde{A}_I$. It is proved in [40] that the basic reproduction number is the spectral radius of the next generation

matrix for the model, namely $-FV^{-1}$, computed at the DFE (the minus sign comes from Metzler matrices used in place of M -matrices). This proves our claim.

However there are two cases where we can get explicit formulas. These cases are when the distribution stochastic matrix P or when the WAIFW matrix B are rank one matrices. We will now specialize to these two subcategories. In these two cases we can give a simple elegant formula for the basic reproduction ratio \mathcal{R}_0 (compare with [22, 18]).

2.1.1 Model with rank one stochastic distribution matrix P

We claim that in this case, the stochastic distribution matrix P we can always be written $P = p \mathbf{1}^T$, where $p \in \mathbb{R}^m$ is a nonnegative stochastic vector, i.e., $\sum_{i=1}^m p_i = 1$ and $\mathbf{1} \in \mathbb{R}^n$. This is quite evident since we can write, by Perron-Frobenius, $P = u v^T$ for two nonnegative vector $u \in \mathbb{R}^n$, $v \in \mathbb{R}^m$. Since upon infection a susceptible individual moves in the I compartments, we have $v \gg 0$. Using the stochasticity of P , the result follows. With this expression for P and the fact that

$$p \mathbf{1}^T \text{diag}(B I) S = \langle \mathbf{1} \mid \text{diag}(B I) S \rangle p = \langle B I \mid S \rangle p,$$

we obtain the following system

$$\begin{cases} \dot{S} = \Lambda - \text{diag}(\mu_S) S + A_S S - \text{diag}(B I) S \\ \dot{I} = \langle B I \mid S \rangle p - \text{diag}(\mu_I + \gamma_I) I + A_I I, \end{cases} \quad (5)$$

This model does not take into account the origin of the susceptible individuals upon infection. Once infected the individuals are distributed and enter the I compartment according to the stochastic vector p .

In this peculiar case, the hypothesis **H2** has for consequence $-\tilde{A}_I^{-1} p \gg 0$, which in turn implies $-B \tilde{A}_I^{-1} p \gg 0$.

We claim that for system (5), the basic reproduction number \mathcal{R}_0 is given by

$$\mathcal{R}_0 = \langle B (-\tilde{A}_I^{-1}) p \mid S^* \rangle = S^{*T} B (-\tilde{A}_I^{-1}) p. \quad (6)$$

Applying the preceding general formula (4) to system (5), we have

$$\mathcal{R}_0 = \rho \left(-p \mathbf{1}^T \text{diag}(S^*) B \tilde{A}_I^{-1} \right) = \rho \left(p S^{*T} B (-\tilde{A}_I^{-1}) \right)$$

It is clear that $p S^{*T} B (-\tilde{A}_I^{-1})$ is a rank one matrix. The only nonzero eigenvalue is given by $S^{*T} B (-\tilde{A}_I^{-1}) p$, which is exactly our claim.

2.1.2 Model with rank one WAIFW matrix B

In this case we can write $B = \alpha \beta^T$, where $\alpha \gg 0$ is a positive vector of \mathbb{R}^n and $\beta > 0$ is a nonzero nonnegative vector of \mathbb{R}_+^m . From the modeling point of view, this means that for a given class of susceptible S_i , the infectivity factor of the different classes of infected is multiplied by a same coefficient α_i .

For this model $\mathcal{R}_0 = \rho \left((-\tilde{A}_I^{-1}) P \text{diag}(S^*) \alpha \beta^T \right)$

We again have a rank one matrix, then the spectral radius is given by

$$\mathcal{R}_0 = \left\langle \beta \mid -(\tilde{A}_I^{-1}) P \text{diag}(\alpha) S^* \right\rangle$$

2.2 A compact positively invariant absorbing set

We will show that there exists a compact positively invariant absorbing set K for (2). An absorbing set K for a dynamical system is a set K such that, for any initial condition, the forward trajectory starting from the initial condition enters for a positive time the set K .

We denote by $N(t)$ the total population at time t . We have $N = \langle S \mid \mathbf{1} \rangle + \langle I \mid \mathbf{1} \rangle$.

Using the fact that A_S, A_I are zero column sum matrices and P is a one column sum matrix we have the relations

$$\langle A_S S \mid \mathbf{1} \rangle = \langle S \mid A_S^T \mathbf{1} \rangle = 0, \quad \langle A_I I \mid \mathbf{1} \rangle = \langle I \mid A_I^T \mathbf{1} \rangle = 0,$$

and

$$\langle P \text{diag}(B I) S \mid \mathbf{1} \rangle = \langle \text{diag}(B I) S \mid P^T \mathbf{1} \rangle = \langle \text{diag}(B I) S \mid \mathbf{1} \rangle = \langle B I \mid S \rangle.$$

We get

$$\dot{N} = \langle \Lambda \mid \mathbf{1} \rangle - \langle \mu_S \mid S \rangle - \langle \mu_I + \gamma_I \mid I \rangle.$$

Let μ_0 be defined by $\mu_0 = \min(\mu_S, \mu_I + \gamma_I) > 0$, then we have

$$\dot{N} \leq \langle \Lambda \mid \mathbf{1} \rangle - \mu_0 N$$

Lemma 2.2 *Let $\mu_0 = \min(\mu_S, \mu_I + \gamma_I) > 0$. For any $\varepsilon > 0$, The subset K_ε of the nonnegative orthant $\mathbb{R}_+^n \times \mathbb{R}_+^m$, defined by*

$$K_\varepsilon = \left\{ (S, I) \mid S \geq 0 ; I \geq 0 ; N \leq (\langle \Lambda | \mathbf{1} \rangle + \varepsilon) / \mu_0 \right\},$$

is a positively invariant compact absorbing set for (2)

It is straightforward to check that the nonnegative orthant is positively invariant by the system (2). If we use the relation $\dot{N} \leq \langle \Lambda | \mathbf{1} \rangle - \mu_0 N$, then the lemma follows.

We also remark that $(S^*, 0) \in K_0$. Indeed we have $\langle \Lambda | \mathbf{1} \rangle = \langle \mu_S | S^* \rangle$, the conclusion follows from $\mu_0 \mathbf{1} \leq \mu_S$.

We have also a positively invariant set contained in K_ε .

Lemma 2.3 *The set Ω defined by*

$$\Omega = \left\{ (S, I) \in K_\varepsilon \mid S \leq S^* \right\},$$

is a positively invariant compact set for system (2).

On the boundary $S = S^*$ we have $\dot{S} = -\text{diag}(B I) S^* \leq 0$. This proves the positive invariance of Ω .

2.3 Global stability of the DFE

We will prove the global stability of the DFE for each category of models.

2.3.1 Model with rank one stochastic distribution matrix $P = p \mathbf{1}^T$

Theorem 2.1 *If $\mathcal{R}_0 \leq 1$ then the DFE of system (5) is globally asymptotically stable on the nonnegative orthant. If $\mathcal{R}_0 > 1$ the DFE is unstable.*

Proof.

If $\mathcal{R}_0 > 1$ the instability of the DFE is classical and is a consequence of the results of [10].

We suppose now that $\mathcal{R}_0 \leq 1$, and we consider the following candidate Lyapunov function

$$V_{DFE}(S, I) = \langle B(-\tilde{A}_I^{-1}) I \mid S^* \rangle.$$

This function is nonnegative on the positive orthant and is zero at the DFE. The derivative of V along the trajectories is given by

$$\dot{V}_{DFE} = \langle BI | S \rangle \langle B(-\tilde{A}_I^{-1})p | S^* \rangle - \langle BI | S^* \rangle = \langle BI | \mathcal{R}_0 S - S^* \rangle.$$

Taking into account the formula (6) for \mathcal{R}_0 , it is clear that on the compact set Ω we have $\dot{V}_{DFE} \leq 0$.

We consider the largest invariant set \mathcal{L} , contained in the set

$$\{(S, I) \in \Omega \mid \dot{V}_{DFE}(S, I) = 0\}.$$

- For $\mathcal{R}_0 < 1$, using $S^* \gg 0$ (by hypothesis **H1**) we have if $S < S^*$ the relation $\mathcal{R}_0 S - S^* \ll 0$. This implies $BI = 0$, which gives $\dot{I} = \tilde{A}_I I$. Since \tilde{A}_I is Metzler stable, the largest invariant set contained in Ω satisfies $I = 0$, which in turn implies $S = S^*$. By Lasalle's invariance principle [32] (one can also see [6], Theorem 3.7.11, page 346) since we are in a positively invariant compact set, the DFE is globally asymptotically stable in Ω when $\mathcal{R}_0 < 1$.
- When $\mathcal{R}_0 = 1$, we have

$$\dot{V}_{DFE} = \langle BI | S - S^* \rangle \leq 0, \text{ for all } (S, I) \in \Omega.$$

Once again, it is sufficient to show that $\mathcal{L} = \{(S^*, 0)\}$. Let $(S, I) \in \mathcal{L}$, the trajectory of (5) corresponding to this initial point satisfy $\langle BI(t) | S(t) - S^* \rangle = 0$, for all $t \geq 0$. Suppose $I(0) > 0$, then by hypothesis **H2**, $BI(t) \gg 0$ for all $t > 0$ and hence, $S(t) - S^* = 0$ for all $t > 0$. This, together with the first equation of (5), would imply $BI(t) \equiv 0$ which contradict $I > 0$. Hence, if $(S, I) \in \mathcal{L}$ then necessarily $I = 0$ and so $S = S^*$ thanks to the first equation of (5). Therefore, the DFE is globally asymptotically stable in Ω when $\mathcal{R}_0 = 1$.

Since K_ε is absorbing, it remains to examine the trajectories starting in the set $K_\varepsilon \setminus \Omega$.

The set defined by $I = 0$ is invariant by the system. Therefore, any trajectory starting from a point in $K_\varepsilon \setminus \Omega$, with $I = 0$, will converge to $(S^*, 0)$.

Now if a starting point in $K_\varepsilon \setminus \Omega$ satisfies $I > 0$, then by hypothesis **H2**, $BI(t) \gg 0$, for all $t > 0$. Hence from the first equation the trajectory will enter Ω and then converge to the DFE. This proves the global asymptotic stability of the DFE $(S^*, 0)$ in the nonnegative orthant. ■

2.3.2 Model with rank one WAIFW matrix $B = \alpha \beta^T$

With rank one WAIFW matrix $B = \alpha \beta^T$ the system is

$$\begin{cases} \dot{S} = \Lambda - \text{diag}(\mu_S) S + A_S S - \langle \beta | I \rangle \text{diag}(\alpha) S, \\ \dot{I} = \langle \beta | I \rangle P \text{diag}(\alpha) S - \text{diag}(\mu_I + \gamma_I) I + A_I I. \end{cases} \quad (7)$$

Theorem 2.2 *Consider system (7). If $\mathcal{R}_0 \leq 1$, then the DFE is globally asymptotically stable on the nonnegative orthant. If $\mathcal{R}_0 > 1$, the DFE is unstable.*

We consider the following function

$$V(S, I) = \langle \beta | -\tilde{A}_I^{-1} I \rangle$$

We compute the derivative along the trajectories in Ω

$$\begin{aligned} \dot{V} &= \langle \beta | I \rangle \left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) S \right\rangle - \langle \beta | I \rangle \\ &= \langle \beta | I \rangle \left(\left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) S \right\rangle - 1 \right) \\ &\leq \langle \beta | I \rangle (\mathcal{R}_0 - 1) \leq 0 \end{aligned}$$

- For $\mathcal{R}_0 < 1$, the largest invariant set contained in the set $\dot{V} = 0$ contained in the compact set Ω , satisfies $\langle \beta | I \rangle = 0$. Since \tilde{A}_I is Metzler stable, this set is reduced to $I = 0$, which in turn, by invariance, implies $S = S^*$. By LaSalle invariance's principle, since we are in a positively invariant compact set [32, 6], the DFE is globally asymptotically stable in Ω . A similar argument, as in the proof of Theorem 2.1, permits to conclude to the global stability in the nonnegative orthant.

- For $\mathcal{R}_0 = 1$, we can write

$$\begin{aligned} \dot{V} &= \langle \beta | I \rangle \left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) S \right\rangle - \langle \beta | I \rangle \\ &= \langle \beta | I \rangle \left(\left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) S^* - \tilde{A}_I^{-1} P \text{diag}(\alpha) (S - S^*) \right\rangle - 1 \right) \\ &= \langle \beta | I \rangle \left(\left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) S^* \right\rangle + \left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) (S - S^*) \right\rangle - 1 \right) \\ &= \langle \beta | I \rangle \left(\mathcal{R}_0 - 1 + \left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) (S - S^*) \right\rangle \right) \\ &= \langle \beta | I \rangle \left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) (S - S^*) \right\rangle. \end{aligned}$$

Therefore $\dot{V}(S, I) = 0$ if and only if

$$\langle \beta | I \rangle = 0 \text{ or } \left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) (S - S^*) \right\rangle = 0.$$

Let $(S, I) \in \mathcal{L}$ the largest invariant set contained in $\{(S, I) \in \Omega : \dot{V}(S, I) = 0\}$. If $\langle \beta | I \rangle = 0$ then we conclude as in the case $\mathcal{R}_0 < 1$. Otherwise, we define $f(S) = \left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) S \right\rangle = \left\langle \text{diag}(\alpha) P^T (-\tilde{A}_I^{-1})^T \beta | S \right\rangle$

The map $f(S)$ is not identically null since $f(S^*) = \mathcal{R}_0$. Hence the vector $\text{diag}(\alpha) P^T (-\tilde{A}_I^{-1})^T \beta > 0$, i.e., it has at least one nonzero component, say, $(\text{diag}(\alpha) P^T (-\tilde{A}_I^{-1})^T \beta)_i \neq 0$ for some $i \in \{1, \dots, n\}$.

Thus $\left\langle \beta | -\tilde{A}_I^{-1} P \text{diag}(\alpha) (S - S^*) \right\rangle = 0$ implies at least that $S_i(t) \equiv S_i^*$. The equation governing the evolution of $S_i(t)$ is (e_i being the i th vector of the canonical basis of \mathbb{R}^n):

$$\dot{S}_i = -\mu_{S_i}(S_i(t) - S_i^*) + e_i^T A_S (S(t) - S^*) - \langle \beta | I(t) \rangle \alpha_i S_i(t)$$

Since $S_i(t) \equiv S_i^*$, the matrix A_S is a Metzler matrix and $S \leq S^*$ in Ω , we obtain $e_i^T A_S (S(t) - S^*) = \langle \beta | I(t) \rangle \alpha_i S_i^* = 0$. In particular we have $\langle \beta | I(t) \rangle = 0$ and so we can conclude as in the case $\mathcal{R}_0 < 1$.

2.4 Endemic equilibrium

The proofs for the two systems are similar and use the same principle. However the computations are different so we distinguishes the two proofs.

2.4.1 Model with rank one stochastic distribution matrix $P = p \mathbf{1}^T$

Theorem 2.3 *There exists a unique endemic equilibrium in the nonnegative orthant for system (5) if and only if $\mathcal{R}_0 > 1$.*

Proof. We look for an equilibrium (\bar{S}, \bar{I}) with $\bar{I} > 0$. From the relations

$$\begin{cases} 0 = \Lambda - \text{diag}(\mu_S) \bar{S} + A_S \bar{S} - \text{diag}(\bar{B} \bar{I}) \bar{S}, \\ 0 = \langle \bar{B} \bar{I} | \bar{S} \rangle p + \tilde{A}_I \bar{I} \end{cases} \quad (8)$$

we deduce, since \tilde{A}_I is Metzler stable, that $\bar{I} = \langle \bar{B} \bar{I} | \bar{S} \rangle (-\tilde{A}_I^{-1}) p$. From the second relation of (8) and taking the inner product with p we obtain, setting $\|p\|_2^2 = \langle p | p \rangle$

$$\|p\|_2^2 \langle \bar{B} \bar{I} | \bar{S} \rangle = -\langle \tilde{A}_I \bar{I} | p \rangle.$$

Finally

$$\bar{I} = -\frac{1}{\|p\|_2^2} \langle \tilde{A}_I \bar{I} | p \rangle (-\tilde{A}_I^{-1}) p. \quad (9)$$

Then to compute \bar{I} it is sufficient to find $-\langle \tilde{A}_I \bar{I} | p \rangle$.

Again with the expression $\bar{I} = \langle \bar{B} \bar{I} | \bar{S} \rangle (-\tilde{A}_I^{-1}) p$, we get

$$\langle \bar{B} \bar{I} | \bar{S} \rangle = \langle \bar{B} \bar{I} | \bar{S} \rangle \langle B(-\tilde{A}_I^{-1}) p | \bar{S} \rangle.$$

The condition $\langle \bar{B} \bar{I} | \bar{S} \rangle = 0$ implies, since \tilde{A}_I is Metzler stable, $\bar{I} = 0$, hence $\bar{S} = S^*$. We obtain the DFE and not an endemic equilibrium.

Then if $\langle \bar{B} \bar{I} | \bar{S} \rangle \neq 0$, by simplifying the preceding relation, we get

$$\langle B(-\tilde{A}_I^{-1}) p | \bar{S} \rangle = 1. \quad (10)$$

From the first equation in (8) we have

$$\bar{S} = -[-\text{diag}(\mu_S + B\bar{I}) + A_S]^{-1} \Lambda \quad (11)$$

Using the value of $B\bar{I}$ from relation (9) gives

$$\begin{aligned} \bar{S} &= -\left[-\text{diag}\left(\mu_S + \frac{(-\langle \tilde{A}_I \bar{I} | p \rangle)}{\|p\|_2^2} B(-\tilde{A}_I^{-1}) p\right) + A_S \right]^{-1} \Lambda \\ &= -M(-\langle \tilde{A}_I \bar{I} | p \rangle)^{-1} \Lambda. \end{aligned} \quad (12)$$

Where we have set, for $x \geq 0$

$$M(x) = -\text{diag}\left(\mu_S + \frac{x}{\|p\|_2^2} B(-\tilde{A}_I^{-1}) p\right) + A_S$$

The matrix $M(x)$ is a stable Metzler matrix depending linearly on the positive value x .

Replacing in relation (10), \bar{S} by the expression given by (12) gives

$$\left\langle B(-\tilde{A}_I^{-1})p \mid -M(-\langle \tilde{A}_I \bar{I} \mid p \rangle)^{-1} \Lambda \right\rangle = 1.$$

In other words the scalar $-\langle \tilde{A}_I \bar{I} \mid p \rangle$ is a solution of $H(x) = 1$ with

$$H(x) = \left\langle B(-\tilde{A}_I^{-1})p \mid -M(x)^{-1} \Lambda \right\rangle.$$

We claim that that $H(x)$ is a strictly decreasing function. The derivative of H is given by

$$H'(x) = \left\langle B(-\tilde{A}_I^{-1})p \mid -M(x)^{-1} \text{diag} \left(\frac{B(-\tilde{A}_I^{-1})p}{\|p\|_2^2} \right) M(x)^{-1} \Lambda \right\rangle.$$

On the one hand, we have $B(-\tilde{A}_I^{-1})p \gg 0$ thanks to hypothesis **H2**. On the other hand hypothesis **H1** implies $-M(x)^{-1}\Lambda \gg 0$. Therefore $H'(x) < 0$. This proves that $H(x)$ is strictly decreasing.

The function $H(x)$ satisfies $\lim_{x \rightarrow +\infty} H(x) = 0$. Then a unique positive solution exists if and only if $H(0) > 1$. So we have a unique positive solution since $H(0) = \mathcal{R}_0 > 1$

From (11) we have $S^* > \bar{S} > 0$ and from (9), with $-\langle \tilde{A}_I \bar{I} \mid p \rangle > 0$ and hypothesis **H2** we deduce $\bar{I} \gg 0$, and then the equilibrium is endemic. An endemic equilibrium such that $\bar{I} \gg 0$ is also called a strongly endemic equilibrium [39].

From the preceding analysis we see that if $\mathcal{R}_0 = 1$ then the unique equilibrium is the DFE. In the case $\mathcal{R}_0 < 1$ we have $\bar{I} < 0$, which means that the equilibrium is not biologically feasible. ■

2.4.2 Model with rank one WAIFW matrix $B = \alpha \beta^T$

Theorem 2.4 *There exists a unique endemic equilibrium in the nonnegative orthant, for system (7) if and only if $\mathcal{R}_0 > 1$.*

Proof.

The proof is in the same spirit as the proof for the case of rank one stochastic distribution matrix. We have the relations for an equilibrium (\bar{S}, \bar{I})

$$\begin{cases} 0 = \Lambda + \tilde{A}_S \bar{S} - \langle \beta | \bar{I} \rangle \text{diag}(\alpha) \bar{S}, \\ 0 = \langle \beta | \bar{I} \rangle P \text{diag}(\alpha) \bar{S} + \tilde{A}_I \bar{I}. \end{cases} \quad (13)$$

Where as usual we set $\tilde{A}_S = -\text{diag}(\mu_S) + A_S$ and the analogous setting for \tilde{A}_I .

From the first equation we deduce, since the matrix $-\text{diag}(\mu_S) - \langle \beta | \bar{I} \rangle \text{diag}(\alpha) + A_S$ is Metzler stable for any \bar{I} ,

$$\begin{aligned} \bar{S} &= -[-\text{diag}(\mu_S) - \langle \beta | \bar{I} \rangle \text{diag}(\alpha) + A_S]^{-1} \Lambda \\ &= -M(\langle \beta | \bar{I} \rangle)^{-1} \Lambda. \end{aligned} \quad (14)$$

Where have set

$$M(x) = -\text{diag}(\mu_S + x\alpha) + A_S,$$

as a stable Metzler matrix, depending linearly on $x > 0$.

From the second equation, since \tilde{A}_I is Metzler stable, we get

$$\bar{I} = \langle \beta | \bar{I} \rangle (-\tilde{A}_I^{-1}) P \text{diag}(\alpha) \bar{S}. \quad (15)$$

Then it is sufficient to determine $\langle \beta | \bar{I} \rangle$ in order to compute (\bar{S}, \bar{I}) .

Using relation (15) we have

$$\langle \beta | \bar{I} \rangle = \langle \beta | \bar{I} \rangle \left\langle \beta \left| (-\tilde{A}_I^{-1}) P \text{diag}(\alpha) \bar{S} \right. \right\rangle.$$

If $\langle \beta | \bar{I} \rangle = 0$, then the relations (13) imply $\bar{I} = 0$ and $\bar{S} = S^*$, i.e., the DFE. Otherwise we can simplify and obtain

$$\left\langle \beta \left| (-\tilde{A}_I^{-1}) P \text{diag}(\alpha) \bar{S} \right. \right\rangle = 1.$$

Replacing \bar{S} by its value in (14)

$$\left\langle \beta \left| (-\tilde{A}_I^{-1}) P \text{diag}(\alpha) [-M(\langle \beta | \bar{I} \rangle)^{-1}] \Lambda \right. \right\rangle = 1.$$

In other words the scalar $\langle \beta | \bar{I} \rangle$ is a solution of $H(x) = 1$ with

$$H(x) = \left\langle \beta \left| (-\tilde{A}_I^{-1}) P \text{diag}(\alpha) [-M(x)^{-1}] \Lambda \right. \right\rangle.$$

We claim that $H(x)$ is a strictly decreasing function. The proof is identical to preceding proof of Theorem 2.3, we have just to check carefully that the derivative $H'(x)$ is negative.

$$H'(x) = \left\langle \beta \mid (-\tilde{A}_I^{-1}) P \text{diag}(\alpha) M(x)^{-1} (-\text{diag}(\alpha)) M(x)^{-1} \Lambda \right\rangle$$

By hypothesis **H1**, we have $-M(x)^{-1}\Lambda \gg 0$, and since $\alpha \gg 0$, we have $\text{diag}(\alpha) M(x)^{-1} (-\text{diag}(\alpha)) M(x)^{-1}\Lambda \gg 0$. Therefore, by hypothesis **H2**, we conclude $(-\tilde{A}_I^{-1}) P \text{diag}(\alpha) M(x)^{-1} (-\text{diag}(\alpha)) M(x)^{-1}\Lambda \ll 0$. This, with $\beta > 0$, implies $H'(x) < 0$.

Since $H(x)$ satisfies $\lim_{x \rightarrow +\infty} H(x) = 0$, a unique positive solution exists if and only if $H(0) > 1$. Since $H(0) = \mathcal{R}_0 > 1$, we then have a unique positive solution. Since, from (14) we have $S^* > \bar{S} \gg 0$ and from (15), with $\langle \beta \mid \bar{I} \rangle > 0$, we get $\bar{I} \gg 0$. Hence the equilibrium is strongly endemic.

From the preceding analysis we see that if $\mathcal{R}_0 = 1$ then the unique equilibrium is the DFE. In the case $\mathcal{R}_0 < 1$ we have $\bar{I} < 0$, which means that this equilibrium is not biologically feasible.

3 Global stability of the endemic equilibrium for differential susceptibility and staged progression infectivity models

To prove the global stability of the endemic equilibrium we need to use in more details the structure of A_I and A_S . We will treat in this section a differential susceptibility with staged progression infectivity model. This system has the same form as system (5) with $A_S = 0$.

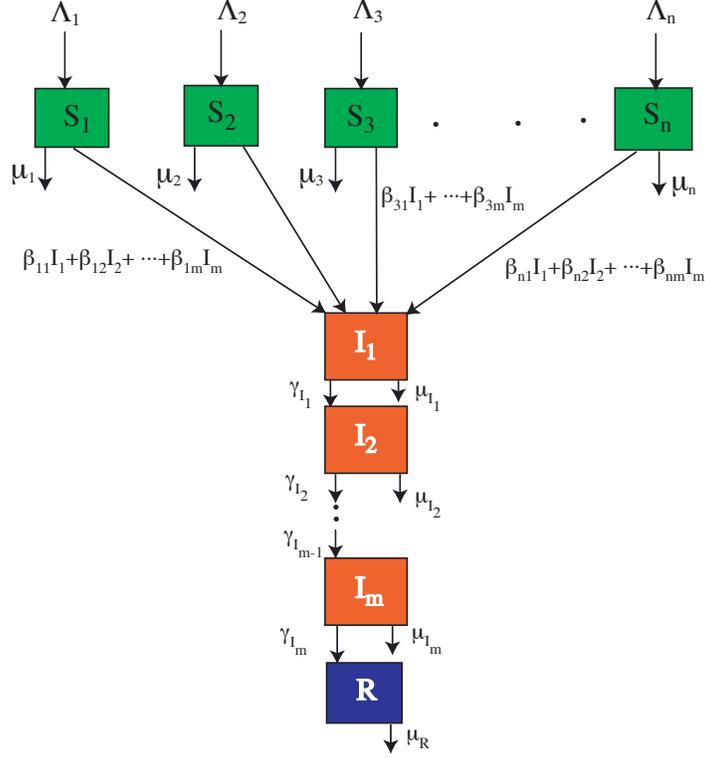


Figure 2: The n susceptible classes and m infected classes model

As before some I_i can be infected and non infectious compartments. For the stability analysis, we discard the removed compartments, by the argument given in the introduction.

The model is given by the following system of ordinary differential equations. We write for simplicity A in lieu of A_I .

$$\begin{cases} \dot{S} = \Lambda - \text{diag}(\mu_S) S - \text{diag}(B I) S \\ \dot{I} = \langle B I | S \rangle e_1 + A I. \end{cases} \quad (16)$$

With e_1 the first vector of the canonical basis of \mathbb{R}^m and A the matrix given by

$$A = \begin{bmatrix} -\alpha_1 & 0 & 0 & \cdots & 0 \\ \gamma_1 & -\alpha_2 & 0 & \cdots & 0 \\ 0 & \gamma_2 & -\alpha_3 & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & \gamma_{m-1} & -\alpha_m \end{bmatrix}.$$

Where we have set $\alpha_i = \gamma_{I_i} + \mu_{I_i}$ and $\gamma_i = \gamma_{I_i}$.

Using coordinates, system (16) can be written as follows

$$\begin{cases} \dot{S}_i = \Lambda_i - \mu_{S_i} S_i - \sum_{j=1}^{j=m} \beta_{ij} S_i I_j & \text{for } i = 1 \dots n \\ \dot{I}_1 = \sum_{i=1}^{i=n} \sum_{j=1}^{j=m} \beta_{ij} S_i I_j - \alpha_1 I_1 \\ \dot{I}_j = \gamma_{j-1} I_{j-1} - \alpha_j I_j & \text{for } j = 2 \dots m \end{cases}$$

For system (16), the stability of the DFE is addressed by Theorem 2.1.

Theorem 3.1 *If $\mathcal{R}_0 > 1$ then the unique endemic equilibrium of system (16) is globally asymptotically stable on $\mathbb{R}_+^{n+m} \setminus \{(S, I) : I = 0\}$ the nonnegative orthant minus the stable manifold of the disease free equilibrium.*

The stable manifold of the DFE is the set $\{(S, I) \in \mathbb{R}_+^{n+m} : I = 0\}$.

Proof

We use the following Lyapunov function on the positive orthant. This kind of Lyapunov function has been used, in a different way, in [33, 31, 30, 24, 1, 25, 4, 8]. The challenge is actually to prove that its derivative is nonpositive.

$$V_{EE}(S, I) = \left\langle S - \text{diag}(\bar{S}) \ln S \mid \mathbf{1} \right\rangle + \left\langle B(-A^{-1}) (I - \text{diag}(\bar{I}) \ln I) \mid \bar{S} \right\rangle - \Pi.$$

Where Π is given by $\Pi = \langle \bar{S} - \text{diag}(\bar{S}) \ln \bar{S} \mid \mathbf{1} \rangle + \langle B(-A^{-1}) (\bar{I} - \text{diag}(\bar{I}) \ln \bar{I}) \mid \bar{S} \rangle$.

With the matrix A in this section, we have $(-A^{-1})e_1 \gg 0$, hence from subsection 2.4 we have $\bar{I} \gg 0$. An equilibrium such that $\bar{I} \gg 0$ is called a strongly endemic equilibrium.

We know that $\bar{S} \gg 0$. Then the assumption $B > 0$ implies $B^T \bar{S} > 0$. Since A is Metzler stable $-A^{-1} > 0$ we conclude that $-(A^{-1})^T B^T \bar{S} > 0$. Therefore $V(S, I)$ is nonnegative and that the endemic equilibrium satisfies $V(\bar{S}, \bar{I}) = 0$.

The derivative \dot{V}_{EE} along the trajectories of (16) is given by

$$\begin{aligned}\dot{V}_{EE} = & \langle \Lambda | \mathbf{1} \rangle - \langle \text{diag}(\mu_S) S | \mathbf{1} \rangle - \langle \text{diag}(BI) S | \mathbf{1} \rangle \\ & - \langle \bar{S} | \text{diag}(S)^{-1} \Lambda \rangle + \langle \bar{S} | \mu_S \rangle + \langle \bar{S} | \text{diag}(S)^{-1} \text{diag}(BI) S \rangle \\ & + \langle BI | S \rangle \langle B(-A^{-1}) e_1 | \bar{S} \rangle + \langle B(-A^{-1}) AI | \bar{S} \rangle \\ & - \langle BI | S \rangle \langle B(-A^{-1}) \frac{\bar{I}_1}{I_1} e_1 | \bar{S} \rangle - \langle B(-A^{-1}) \text{diag}(\bar{I}) \text{diag}(I)^{-1} AI | \bar{S} \rangle.\end{aligned}$$

This can be written

$$\begin{aligned}\dot{V}_{EE} = & \langle \Lambda | \mathbf{1} \rangle - \langle S | \mu_S \rangle - \langle BI | S \rangle - \langle \text{diag}(S)^{-1} \bar{S} | \Lambda \rangle + \langle \bar{S} | \mu_S \rangle + \langle \bar{S} | BI \rangle \\ & + \langle BI | S \rangle \langle B(-A^{-1}) e_1 | \bar{S} \rangle - \langle BI | \bar{S} \rangle \\ & - \langle BI | S \rangle \langle B(-A^{-1}) \frac{\bar{I}_1}{I_1} e_1 | \bar{S} \rangle - \langle B(-A^{-1}) \text{diag}(\bar{I}) \text{diag}(I)^{-1} AI | \bar{S} \rangle.\end{aligned}$$

Using the relation (10), $\langle B(-A^{-1}) e_1 | \bar{S} \rangle = 1$, we have

$$\begin{aligned}\dot{V}_{EE} = & \langle \Lambda | \mathbf{1} \rangle - \langle S | \mu_S \rangle - \langle \text{diag}(S)^{-1} \bar{S} | \Lambda \rangle + \langle \bar{S} | \mu_S \rangle \\ & - \frac{\bar{I}_1}{I_1} \langle BI | S \rangle - \left\langle B(-A^{-1}) \text{diag}(\bar{I}) \text{diag}(I)^{-1} AI | \bar{S} \right\rangle.\end{aligned}$$

Using the relation $\Lambda = \text{diag}(\mu_S) \bar{S} + \text{diag}(B \bar{I}) \bar{S}$ we obtain

$$\begin{aligned}\dot{V}_{EE} = & \langle \bar{S} | \mu_S \rangle + \langle B \bar{I} | \bar{S} \rangle - \langle S | \mu_S \rangle \\ & - \langle \text{diag}(S)^{-1} \bar{S} | \text{diag}(\mu_S) \bar{S} \rangle - \langle \text{diag}(S)^{-1} \bar{S} | \text{diag}(B \bar{I}) \bar{S} \rangle + \langle \bar{S} | \mu_S \rangle \\ & - \frac{\bar{I}_1}{I_1} \langle BI | S \rangle - \left\langle B(-A^{-1}) \text{diag}(\bar{I}) \text{diag}(I)^{-1} AI | \bar{S} \right\rangle.\end{aligned}$$

$$\begin{aligned}\dot{V}_{EE} = & \left\langle \text{diag}(\mu_S) \bar{S} | \mathbf{2} - \text{diag}(S)^{-1} \bar{S} - \text{diag}(\bar{S})^{-1} S \right\rangle \\ & + \langle B \bar{I} | \bar{S} \rangle - \langle \text{diag}(S)^{-1} \bar{S} | \text{diag}(B \bar{I}) \bar{S} \rangle \\ & - \frac{\bar{I}_1}{I_1} \langle BI | S \rangle - \left\langle B(-A^{-1}) \text{diag}(\bar{I}) \text{diag}(I)^{-1} AI | \bar{S} \right\rangle.\end{aligned}$$

The first line of the previous equation is non positive. We will prove that the sum of the 4 remaining expressions is also non positive. We will express the different expressions.

$$\Omega_1 = \langle B \bar{I} | \bar{S} \rangle = \sum_{i=1}^n \sum_{j=1}^m \beta_{ij} \bar{S}_i \bar{I}_j.$$

$$\Omega_2 = -\langle \text{diag}(S)^{-1} \bar{S} | \text{diag}(B \bar{I}) \bar{S} \rangle = -\sum_{i=1}^n \sum_{j=1}^m \beta_{ij} \bar{S}_i \bar{I}_j \frac{\bar{S}_i}{S_i}.$$

$$\Omega_3 = -\frac{\bar{I}_1}{I_1} \langle B I | S \rangle = -\sum_{i=1}^n \beta_{i1} \bar{S}_i \bar{I}_1 \frac{S_i}{\bar{S}_i} - \sum_{i=1}^n \sum_{j=2}^m \beta_{ij} \bar{S}_i \bar{I}_j \frac{S_i}{\bar{S}_i} \frac{\bar{I}_1}{I_1} \frac{I_j}{\bar{I}_j}$$

We will rewrite the last expression

$$\Omega_4 = -\left\langle B(-A^{-1}) \text{diag}(\bar{I}) \text{diag}(I)^{-1} A I | \bar{S} \right\rangle.$$

We have, for $k = 1, \dots, m-1$, the relations $A e_k = -\alpha_k e_k + \gamma_k e_{k+1}$ and for the last index $A e_m = -\alpha_m e_m$. Then

$$\begin{aligned} \Omega_4 &= -\sum_{k=1}^m I_k \left\langle B(-A^{-1}) \text{diag}(\bar{I}) \text{diag}(I)^{-1} A e_k | \bar{S} \right\rangle \\ &= \sum_{k=1}^m \alpha_k \bar{I}_k \left\langle B(-A^{-1}) e_k | \bar{S} \right\rangle - \sum_{k=1}^{m-1} I_k \gamma_k \frac{\bar{I}_{k+1}}{I_{k+1}} \left\langle B(-A^{-1}) e_{k+1} | \bar{S} \right\rangle. \end{aligned}$$

Let u_k be defined by $u_k = \langle B(-A^{-1}) e_k | \bar{S} \rangle$. We claim that the following relation holds for $k = 2, \dots, m$

$$\gamma_{k-1} u_k \bar{I}_{k-1} = \sum_{j=k}^m \bar{I}_j \langle B e_j | \bar{S} \rangle. \quad (17)$$

We will prove this expression later. For the moment we assume this relation. If we take into account $\alpha_k \bar{I}_k = \gamma_{k-1} \bar{I}_{k-1}$ for $k = 2, \dots, m$ and $\alpha_1 \bar{I}_1 = \langle B \bar{I} | \bar{S} \rangle$, we obtain

$$\begin{aligned} \Omega_4 &= \sum_{k=1}^m \left(\sum_{j=k}^m \bar{I}_j \langle B e_j | \bar{S} \rangle \right) - \sum_{k=1}^{m-1} \frac{I_k}{\bar{I}_k} \frac{\bar{I}_{k+1}}{I_{k+1}} \left(\sum_{j=k+1}^m \bar{I}_j \langle B e_j | \bar{S} \rangle \right), \\ &= \sum_{i=1}^n \sum_{j=1}^m j \beta_{ij} \bar{S}_i \bar{I}_j - \sum_{i=1}^n \sum_{j=2}^m \beta_{ij} \bar{S}_i \bar{I}_j \left(\sum_{k=1}^{j-1} \frac{I_k}{\bar{I}_k} \frac{\bar{I}_{k+1}}{I_{k+1}} \right). \end{aligned}$$

Then we get for the sum of these four expressions

$$\begin{aligned} \sum_{i=1}^4 \Omega_i &= \sum_{i=1}^n \beta_{i1} \bar{S}_i \bar{I}_1 \left[2 - \frac{\bar{S}_i}{S_i} - \frac{S_i}{\bar{S}_i} \right] \\ &\quad + \sum_{i=1}^n \sum_{j=2}^m \beta_{ij} \bar{S}_i \bar{I}_j \left[j + 1 - \frac{\bar{S}_i}{S_i} - \frac{S_i}{\bar{S}_i} \frac{\bar{I}_1}{I_1} \frac{I_j}{\bar{I}_j} - \sum_{k=1}^{j-1} \frac{I_k}{\bar{I}_k} \frac{\bar{I}_{k+1}}{I_{k+1}} \right]. \end{aligned}$$

Using the comparison between the arithmetical and the geometrical means we see that $\dot{V}_{EE} \leq 0$. It must be noticed however that \dot{V}_{EE} is not negative definite since some β_{ij} can be zero.

The endemic equilibrium satisfies

$$\langle \Lambda | \mathbf{1} \rangle - \langle \mu_S \bar{S} | \mathbf{1} \rangle + \langle A \bar{I} | \mathbf{1} \rangle = 0$$

Since $\langle A \bar{I} | \mathbf{1} \rangle = -\gamma_m \bar{I}_m - \langle \mu_I \bar{I} | \mathbf{1} \rangle$, and using the definition of μ_0 (Lemma 2.2), we get $\langle \bar{S} | \mathbf{1} \rangle + \langle \bar{I} | \mathbf{1} \rangle \leq \frac{\langle \Lambda | \mathbf{1} \rangle}{\mu_0}$ which proves that the endemic equilibrium (\bar{S}, \bar{I}) belongs to K_ε for all $\varepsilon \geq 0$.

Let \mathcal{L} be the largest invariant subset of K_ε , contained in $\dot{V}_{EE} = 0$. Each element (S, I) of \mathcal{L} must satisfy

$$\left\langle \text{diag}(\mu_S) | \mathbf{2} - \text{diag}(S)^{-1} \bar{S} - \text{diag}(\bar{S})^{-1} S \right\rangle = 0.$$

Since $\mu_S \gg 0$ this implies $S = \bar{S}$, and so in \mathcal{L} , we must have $\text{diag}(BI) \bar{S} = \Lambda - \text{diag}(\mu_S) \bar{S}$. On the other hand we have $\text{diag}(B \bar{I}) \bar{S} = \Lambda - \text{diag}(\mu_S) \bar{S}$. Thus in \mathcal{L} , the dynamics of I are governed by

$$\dot{I} = \langle B \bar{I} | \bar{S} \rangle - A I$$

Since A is stable the largest invariant set \mathcal{L} is then reduced to $\{(\bar{S}, \bar{I})\}$. This proves the global asymptotic stability of the endemic equilibrium (\bar{S}, \bar{I}) in the interior of K_ε by Lasalle's invariance principle [32, 6]. The global asymptotic stability of the endemic equilibrium on $\mathbb{R}_+^n \times \mathbb{R}_+^m \setminus \{(S, 0)\}$ follows from the fact that the set K_ε is an absorbing set and that the boundary of the positive orthant minus the stable manifold of the DFE is not invariant by (16).

To end the proof we have to prove our claim 17. The proof of the validity of our claim is made by induction on k .

We prove the claim for $k = 2$. We have, using $\langle B(-A^{-1})e_i | \bar{S} \rangle = 1$, the following equalities

$$\begin{aligned}
A e_1 &= -\alpha_1 e_1 + \gamma_1 e_2 \\
-e_1 &= -\alpha_1 (-A^{-1}) e_1 + \gamma_1 (-A^{-1}) e_2 \\
\gamma_1 \bar{I}_1 \langle B(-A^{-1})e_2 | \bar{S} \rangle &= \alpha_1 \bar{I}_1 \langle B(-A^{-1})e_1 | \bar{S} \rangle - \bar{I}_1 \langle B(-A^{-1})e_1 | \bar{S} \rangle \\
\gamma_1 u_2 \bar{I}_1 &= \alpha_1 \bar{I}_1 - \bar{I}_1 \\
\gamma_1 u_2 \bar{I}_1 &= \langle B(-A^{-1})e_1 | \bar{S} \rangle \bar{I}_1 - \bar{I}_1 + \sum_{i=2}^m \langle B(-A^{-1})e_i | \bar{S} \rangle \\
\gamma_1 u_2 \bar{I}_1 &= \sum_{i=2}^m \langle B(-A^{-1})e_i | \bar{S} \rangle
\end{aligned}$$

We now suppose that

$$\gamma_{k-2} u_{k-1} \bar{I}_{k-2} = \sum_{j=k-1}^m \langle B(-A^{-1})e_j | \bar{S} \rangle$$

Then

$$\begin{aligned}
A e_{k-1} &= -\alpha_{k-1} e_{k-1} + \gamma_{k-1} e_k \\
-e_{k-1} &= -\alpha_{k-1} (-A^{-1}) e_{k-1} + \gamma_{k-1} (-A^{-1}) e_k \\
\gamma_{k-1} \bar{I}_{k-1} \langle B(-A^{-1})e_k | \bar{S} \rangle &= \alpha_{k-1} \bar{I}_{k-1} \langle B(-A^{-1})e_{k-1} | \bar{S} \rangle \\
&\quad - \bar{I}_{k-1} \langle B(-A^{-1})e_{k-1} | \bar{S} \rangle \\
\gamma_{k-1} u_k \bar{I}_{k-1} &= \alpha_{k-1} \bar{I}_{k-1} u_{k-1} - \bar{I}_{k-1} \langle B(-A^{-1})e_{k-1} | \bar{S} \rangle \\
\gamma_{k-1} u_k \bar{I}_{k-1} &= \gamma_{k-2} \bar{I}_{k-2} u_{k-1} - \bar{I}_{k-1} \langle B(-A^{-1})e_{k-1} | \bar{S} \rangle \\
\gamma_{k-1} u_k \bar{I}_{k-1} &= \sum_{j=k-1}^m \langle B(-A^{-1})e_j | \bar{S} \rangle - \bar{I}_{k-1} \langle B(-A^{-1})e_{k-1} | \bar{S} \rangle \\
\gamma_{k-1} u_k \bar{I}_{k-1} &= \sum_{j=k}^m \langle B(-A^{-1})e_j | \bar{S} \rangle
\end{aligned}$$

This ends the proof of the theorem. ■

4 Summary and discussion

We have formulated a general differential susceptibility and infectivity model. Genetic variation of susceptible individuals may lead to differentiation of susceptibility on infection. For example it has been observed a resistance to Dengue hemorrhagic fever (DHF) in Cubans of African descent. Different behaviors, susceptibility varying with age ... are also sources of heterogeneity, and give rationale for introducing different classes of susceptible individuals.

There have been studies on variable infectivity [29, 20, 23, 19, 35, 21, 25], but few models are incorporating variable susceptibility [18, 22, 12].

In reference [18] differential susceptibility is introduced with one class of infective. The authors derived an explicit formula for the basic reproduction ratio \mathcal{R}_0 . They prove, in the bilinear case, that the DFE is globally asymptotically stable when $\mathcal{R}_0 < 1$. They prove the existence and uniqueness of an endemic equilibrium when $\mathcal{R}_0 > 1$, and prove the global asymptotic stability when there is no disease-induced mortality.

The studies in [23, 21, 18] give insight into the transmission dynamics of diseases with differential susceptibility or differential infectivity but not both. For many disease transmissions, the susceptibility and infectivity factors are coupled and cannot be completely separated. In [22] the authors propose a combined differential susceptibility and infectivity model. The susceptible individuals are divided into n susceptible groups. The infective individuals are divided into m groups, a susceptible S_i , upon infection, enters groups I_j with probability q_{ij} until becoming recovered or immune. There is no flows between the different susceptible compartments nor between the different infective compartments. The authors give an explicit formula for \mathcal{R}_0 and show that the DFE is globally asymptotically stable if $\mathcal{R}_0 < 1$, for the bilinear incidence or for constant total population.

In [18, 22] there are no flows between the different compartments of susceptibles, and no flows between the different compartments of infected individuals. But in many diseases the infectivity or the susceptibility can evolve. This is, for example, the case of diseases where stage progression are considered [23, 21]. The case of hepatitis B virus (HBV) infection is an illuminating example. Infection with HBV can lead to long-term carriage of the virus, often resulting in chronic liver damage or hepatocellular carcinoma. The risk for chronic infection varies according to the age at infection and is greatest

among young children. According to CDC approximately 90% of infants will remain chronically infected with HBV. By contrast, approximately 95% of adults recover completely from HBV infection and do not become chronically infected. Then there is a need for other models. For example, a model for HBV transmission can be derived from the flow graph of Figure 3. When a susceptible is infected, he moves either in a latent compartment evolving to chronicity or to a latent compartment evolving to acute infection, according to the probability indicated in the flow graph. The given figures are taken from CDC data.

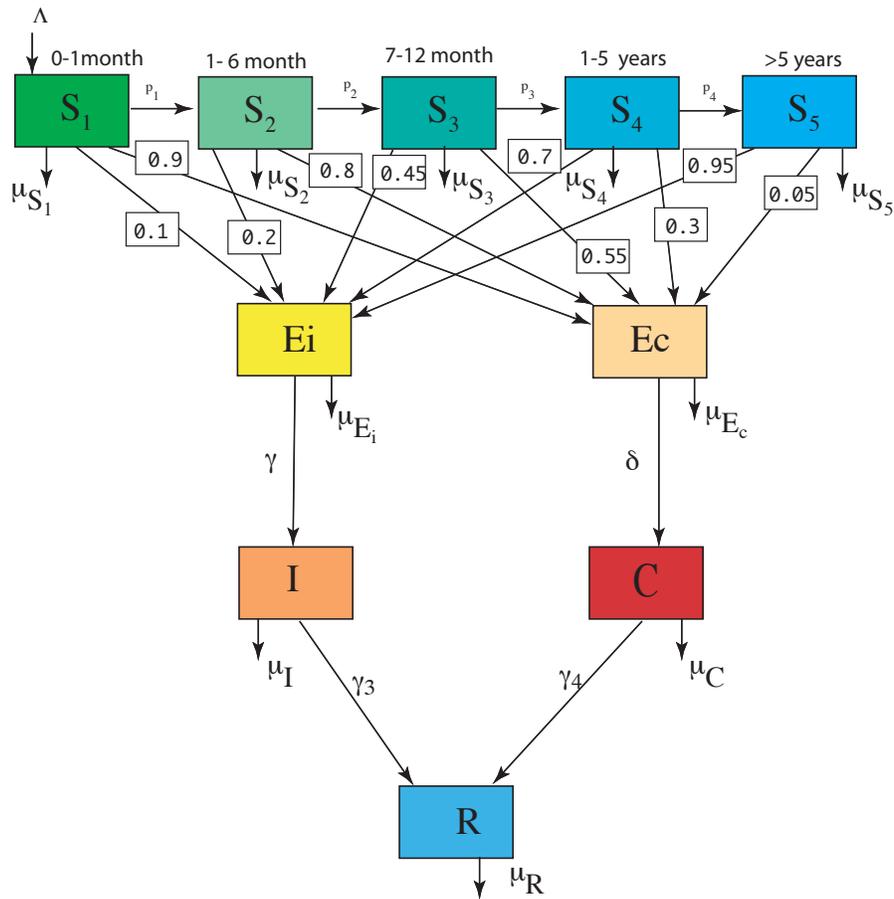


Figure 3: A model for transmission of HBV

This model has five classes of susceptible individuals and four classes of

infected/infectious individuals. There are flows between different classes of susceptible individuals and between different classes of infected individuals. This model can be written under the form of the general model (1) and satisfies hypotheses **H1** and **H2**. If we assume, as it is generally considered [11, 41, 42], that chronic are relatively less infectious, independently of the susceptible class, the rank one hypothesis is satisfied. It must be noticed that this HBV model does not fit the form of the models introduced in [23, 21], whereas models introduced in [23, 21] can be put under the form of model (1), with hypotheses **H1** and **H2** and rank one assumption satisfied for the WAIFW matrix.

We give an explicit formula for \mathcal{R}_0 , we prove that if $\mathcal{R}_0 \leq 1$ then the DFE is globally asymptotically stable, and if $\mathcal{R}_0 > 1$ there exists a unique endemic equilibrium. This contains the analogous results of [23, 21], for the bilinear case or for the constant population models. We prove the global stability of the endemic equilibrium when the infective compartments evolve according to a staged progression model, hence generalizing analogous result of [18]. It would be interesting, but a difficult challenge, to prove the global asymptotic stability of the endemic equilibrium of the model considered in [22], where the infective compartments are represented in a differential infectivity setting.

Finally we would like to notice that our model does not take into account diseases with no immunity or non permanent immunity, then cannot deal, for example, with the models considered in [3].

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