Parameter estimation of a tuberculosis model in a patchy environment: case of Cameroon

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Abstract

1 Introduction

2 Model formulation

In this section, we proceed to the formulation of a mathematical patch model of the spread of tuberculosis disease in Cameroon. The model is based on the interaction between the populations of the different cities of the country. To do so, we use the compartmental modelling approach with a meta population. We consider the following compartments.

2.1 Meta population model

Our model is strongly based on the patches model formulates and studied by D.P. Moualeu and al (2013)[2] , and notations and indices are all preserved. therefore, D.P. Moualeu and al[2] in his study, had not taken into account the reinfection that accurs during the contact between a latent and an infectious person. Thus, taking into account this reinfection is the reason of being of our current study.

Consider a population divided into several subgroups called patches, which the total human population present in each patch i at time t is denoted by N_i, for $i = 1, ..., n$: we use an n-patches of TB disease dynamics.

In this model, we do not take into account the place of residence of an individual. But, we just considers where he is at time t. The transfer rate from a patch i to a patch j, for $i \neq j$, is denoted by $m_{ji} \geqslant 0$. We assume that infection and death due to disease do not occur during the move. Thus, the dynamics of the total population in the patch i at time t is given by:

$$\dot{N}_i = \Psi_i - \mu_i N_i + \sum_{j=1;j\neq i}^{n} m_{ij} N_j - N_i \sum_{j=1;j\neq i}^{n} m_{ji} \quad for \quad i = (1, \cdots, n), \tag{1}$$

where μ_i denotes the natural mortality rate of individuals in patch i, and ψ_i the recruitment rate inside the population of patch i.

Then, the model system (1) can be written in the following compact form:

$$\dot{N} = \psi - diag(\mu)N + \mathcal{M}N, \tag{2}$$

where, $N = (N_1, N_1, \cdots, N_n)^T$, $\psi = (\psi_1, \cdots, \psi_n)^T$, $\mu = (\mu_1, \cdots, \mu_n)^T$. The matrix $\mathcal{M}$ is defined by: $\mathcal{M}_{i,j} = m_{ij}$ for $i \neq j$, and $\mathcal{M}(i,i) = -\sum_{j=1;j\neq i}^{n} m_{ji}$. $diag(\mu)$ defined the diagonal matrix with μ_i as its $(i;i)$ entry.

2.2 Multigroup model

In the epidemiological literature, the term "multigroup" usually refers to the division of a heterogeneous population into several homogeneous groups based on individual behaviour. Each group is then subdivided into epidemiological compartments[2].

The population of each patch is subdivided into several classes:

1. The class of susceptible (S)
   This class is made up of people who are healthy but at risk of contracting the disease. We denote by $S(t)$, the number of persons at risk at time t and S_i the susceptible in the patch i.

2. The class of latently infected (E)
   This class is composed by persons exposed to TB, but not infectious. Then, $E(t)$ represent the number of latently infected at time t and E_i the latently in the patch i.

3. The class of diagnosed infectious (I)
   It's the class of persons who have an active TB confirmed after a sputum examination at the hospital. $I(t)$ is therefore the number of diagnosed infectious at time t and I_i the diagnosed infectious in the patch i.

4. The class of undiagnosed infectious (J)
   It's the class of persons who have an active TB not confirmed by a sputum

examination at the hospital. $J(t)$ is the number of undiagnosed infectious at time t and J_i the undiagnosed in the patch i.

5. The class of recovered individuals (R)
   This class is composed by the persons cured after a therapy of treatment in the hospital. $R(t)$ represent the number of persons who have recovered individuals at time t and R_i, the recovered individuals in the patch i.

Thus, the total population in the i at time t is defined by:

$$N_i(t) = S_i(t) + E_i(t) + I_i(t) + J_i(t) + R_i(t) \tag{3}$$

In addition to these classes the following assumptions have been made:

- Since diagnosed infectious have been detected in the health centers, we assume that the transmission of the infection from diagnosed infectious to susceptible individuals is assumed to be frequency-dependent (limited). Indeed, diagnosed infectious are educated from TB disease so that they can avoid contacts with susceptible individuals.

- While the TB transmission from undiagnosed infectious to susceptible individuals is assumed to be density-dependent (non-limited). Since some undiagnosed infectious do not know their TB-status, people around them are not aware of their TB-status, and thus interact with them naturally.

Figure 1 presents the compartmental diagram of the model.

Recruitment in each patch is into the susceptible classes and is at the constant rate ψ_i. The constant rate for non-disease related death is μ_i. Diagnosed and undiagnosed infectious have addition death rates due to disease with rates d_i and δ_i, respectively. Transmission of TB bacteria occurs after adequate contacts between susceptible individuals, diagnosed and undiagnosed infectious. Then, susceptible individuals of patch i acquire TB infection from individuals with active TB at rate λ_i, given by:

$$\lambda_i = \beta_i^I \frac{I_i}{N_i} + \beta_i^J J_i, \tag{4}$$

where, β_i^I and β_i^J are effective contact rates of diagnosed and undiagnosed infectious that are sufficient to transmit the infection to a susceptible individual in patch i. P_i is the Proportions of new infected among susceptible individuals assumed to undergo a fast progression of the disease and will transfer directly to the classes of infectious I_i and J_i, while the remainder $(1 - P_i)$ develops a latent TB and enter the latent class E_i. Latently infected individuals are assumed to acquire some immunity as a result of the infection, which reduces the risk of subsequent infection but does not fully prevent it.

Once latently infected, an individual can follow a *chemoprophylaxis* which reduces their risk of reactivation. We denote by α_i the *chemoprophylaxis* rate of latently-infected

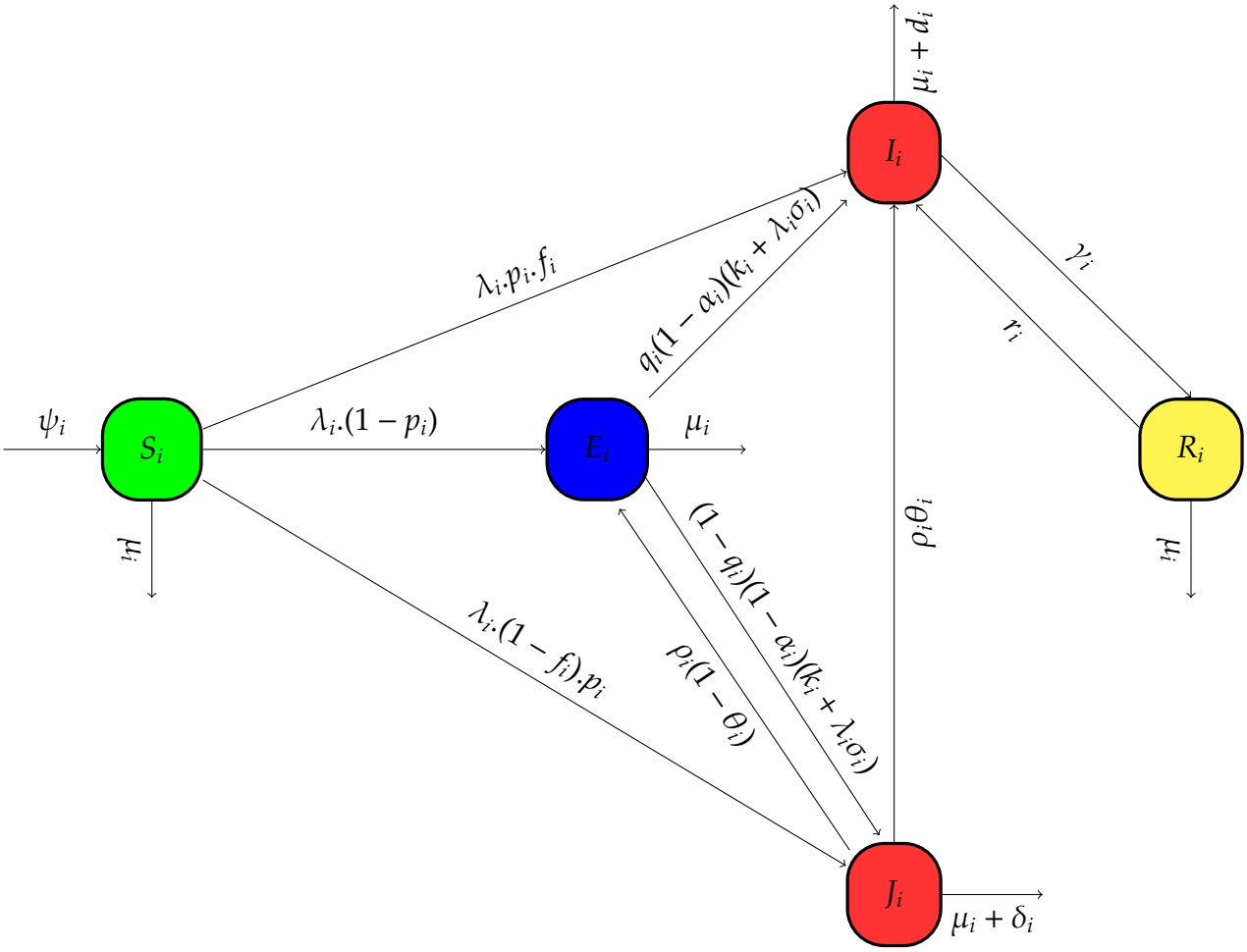

Figure 1: Structure of the model

individuals in patch i; In this case, the individual do not become recovered but just stay latently infected.

While due to endogenous reactivation, a proportion $(1-\alpha_i)$ of latently infected individuals who did not received effective *chemoprophylaxis* becomes infectious at rate k_i.

We assume that a latently infected, in contact with an infectious can be reinfected and then becomes an infectious person at the rate σ_i, a proportion q_i of them are diagnosed and enter in the class of diagnosed infectious, while the remainder $(1-q_i)$ enter the class of undiagnosed infectious.

We assume that after many attempts to treat the disease, a proportion θ_i of undiagnosed infectious can decide to go to the hospital at the constant rate ρ. Due to their own immunity, traditional medicine and self-medication trough street-drugs, a proportion $(1-\theta_i)$ of undiagnosed infectious can spontaneously recover from the disease at rate ρ_i and enters the latent class E_i.

After a therapy of treatment, diagnosed infectious will be declared cured of the

disease and will enter the recovered class R_i at rate r_i, but can only have a partial immunity. Hence, they can undergo a reactivation of the disease and will move to the class I_i at rate γ_i.

According to the steps given above, we have the following system defining the dynamic of TB disease in each patch $i = 1, \cdots, n$:

$$\begin{cases} \dot{S}_i = \psi_i - \lambda_i S_i - \mu_i S_i + \sum_{j=1;j\neq i}^{n} m_{ij} S_j - \sum_{j=1;j\neq i}^{n} m_{ji} S_i, \\ \dot{E}_i = ((1-P_i)\lambda_i)\, S_i + \rho_i(1-\theta_i) J_i - ((1-\alpha_i)\sigma_i\lambda_i)\, E_i - A_{E_i} E_i \\ + \sum_{j=1;j\neq i}^{n} m_{ij} E_j - \sum_{j=1;j\neq i}^{n} m_{ji} E_i, \\ \dot{I}_i = (P_i f_i \lambda_i)\, S_i + \rho_i \theta_i J_i + \gamma_i R_i + (q_i(1-\alpha_i)\sigma_i\lambda_i)\, E_i + q_i(1-\alpha_i) k_i E_i - A_{I_i} I_i \\ + \eta\left(\sum_{j=1;j\neq i}^{n} m_{ij} I_j - \sum_{j=1;j\neq i}^{n} m_{ji} I_i\right), \\ \dot{J}_i = (P_i(1-f_i)\lambda_i)\, S_i + ((1-\alpha_i)(1-q_i)\sigma_i\lambda_i)\, E_i \\ + (1-\alpha_i)(1-q_i) k_i E_i - A_{J_i} J_i + \eta\left(\sum_{j=1;j\neq i}^{n} m_{ij} J_j - \sum_{j=1;j\neq i}^{n} m_{ji} J_i\right), \\ \dot{R}_i = r_i I_i - A_{R_i} R_i + \sum_{j=1;j\neq i}^{n} m_{ij} R_j - \sum_{j=1;j\neq i}^{n} m_{ji} R_i, \end{cases} \tag{5}$$

where m_{ij} and m_{ji} are the migrations rates from patch j to patch i and for patch i to patch j (with $i \neq j$) respectively,
η is a modification parameter which captures the reduced movements of diagnosed and undiagnosed infectious because of the disease,and:

$$\begin{cases} A_{E_i} = k_i(1-\alpha_i) + \mu_i \\ A_{I_i} = r_i + \mu_i + d_i \\ A_{J_i} = \mu_i + \delta_i + \rho_i\theta_i + \rho_i(1-\theta_i) \\ A_{R_i} = \gamma_i + \mu_i \end{cases} \tag{6}$$

For the bellow model system (5), the dynamic of the total population of each patch is given by:

$$\dot{N}_i = \psi_i - \mu_i N_i - d_i I_i - \delta_i J_i + \sum_{j=1;j\neq i}^{n} m_{ij}\left(S_j + E_j + \eta(I_j + J_j) + R_j\right) - (S_i + E_i + \eta(I_i + J_i) + R_i) \sum_{j=1;j\neq i}^{n} m_{ji}, \tag{7}$$

and the total population dynamics for all the n patches at time t is given by:

$$\dot{H} = \sum_{i=1}^{n} \psi_i - \sum_{i=1}^{n} \mu_i N_i - \sum_{i=1}^{n} (I_i d_i + J_i \delta_i) \tag{8}$$

Table 1 and 2 recapitulate variables and parameters of model system (5).

Setting $S = (S_1; \cdots; S_n)^T, E = (E_1; \cdots; E_n)^T, I = (I_1; \cdots; I_n)^T, J = (J_1; \cdots; J_n)^T$ and $R = (R_1; \cdots; R_n)^T$, model system (4) becomes:

Table 1: Variable of model system (5)

Symbols	Biological meanings	Unit
S_i	Susceptible population	Numbers
E_i	Latently infected population	Numbers
I_i	Diagnosed infectious population	Numbers
J_i	Undiagnosed infectious population	Numbers
R_i	Recovered population	Numbers
N_i	Total human population in patch i	Numbers
H	Total human population of n patches	Numbers

Table 2: Parameters of model system (5)

Parameters	Symbol
Recruitment rate of susceptible	ψ_i
Contact rate of diagnosed and undiagnosed infectious	$\beta_i^I; \beta_i^J$
Fast route to infectious class	P_i
Proportion of person with the fast root to diagnosed infectious	f_i
Natural mortality	μ_i
TB mortality of diagnosed infectious	d_i
TB mortality of undiagnosed infectious	δ_i
Chemoprophylaxis of latently infected individuals	α_i
Diagnosis rate of active TB	h_i
The reinfection rate	σ_i
Proportion of person with the root to diagnosed infectious after a reinfection	q_i
Recovery rate of diagnosed infectious	r_i
Natural recovery rate of undiagnosed infectious	ρ_i
Relapse of recovered individuals	γ_i
Diagnosis rate of undiagnosed infectious	θ_i
Migration rate from patch i to patch j	m_{ji}
Migration rate from patch j to patch i	m_{ij}
Enhancement factor of migration	η

$$
\begin{cases}
\dot{S} = \psi - diag(\mu)S - diag(\lambda)S + \mathcal{M}S, \\
\dot{E} = diag\left((1-P).\lambda\right)S + diag\left(\rho.(1-\theta)J - diag((1-\alpha).\sigma.\lambda\right)E \\
-diag(A_E)E + \mathcal{M}E, \\
\dot{I} = diag\left[P.f.\lambda\right]S) + diag(\rho\theta)J + diag(\gamma)R + diag\left(q.(1-\alpha)\sigma.\lambda\right)E \\
+diag\left(q(1-\alpha).k\right)E - diag(A_I)I + \eta\mathcal{M}I, \\
\dot{J} = diag\left[P.(1-f).\lambda\right]S + diag\left((1-q)(1-\alpha).\sigma.\lambda\right)E \\
+diag\left((1-q)(1-\alpha).k\right)E - diag(A_J)J + \eta\mathcal{M}J, \\
\dot{R} = diag(r)I - diag(A_R)R + \mathcal{M}R,
\end{cases}
\tag{9}
$$

where, $\psi = (\psi_1; \cdots; \psi_n)^T, \lambda = (\lambda_1; \cdots; \lambda_n)^T, \mu = (\mu_1; \cdots; \mu_n)^T, P = (P_1; \cdots; P_n)^T, \rho = (\rho_1; \cdots; \rho_n)^T, f = (f_1, \cdots, f_n)^T, q = (q_1; \cdots; q_n)^T, \theta = (\theta_1; \cdots; \theta_n)^T, \alpha = (\alpha_1; \cdots; \alpha_n)^T, A_E = (A_{E_1}; \cdots; A_{E_n})^T, A_I = (A_{I_1}; \cdots; A_{I_n})^T, A_J = (A_{J_1}; \cdots; A_{J_n})^T, A_R = (A_{R_1}; \cdots; A_{R_n})^T, h = (h_1; \cdots; h_n)^T, r = (r_1; \cdots; r_n)^T$, and $1 = (1; \cdots; 1)^T$.

$\mathcal{M} \in \mathbb{M}_{n\times n}$ is the matrix defined as in Eq(2) and $N \in \mathbb{R}_+^n$ is the vector size of population for $i \in \{1, \cdots, n\}$, such that $N = S + E + I + J + R$.

Then, using the system model (9), the dynamic of the population for the vector size of population is given by:

$$\dot{N} = \psi - diag(\mu)N + \mathcal{M}[S + E + \eta(I + J) + R] - [diag(\delta)J + diag(d)I] \tag{10}$$

3 Mathematical analysis of the metapopulation model

In this chapter, we present the mathematical analysis of model system (11) or the model (9).

3.1 Basic properties

* Positivity of the solution.

  Let's $X(t) = (S(t), E(t), I(t), J(t), R(t))$ be a solution of the model (9). We have the following result.

  Lemma 1. *The system (9) is positively invariant in* $\mathbb{R}_+^{5n}$

  Proof. By posing $S = x \in \mathbb{R}_+^n$ and $y = (E, I, J, R)^T \in \mathbb{R}_+^{4n}$, the system model (9) can be written in the following compact system:

$$\begin{cases} \dot{x} = \psi - diag(\lambda)x + (\mathcal{M} - diag(\mu))\, x \\ \dot{y} = Bdiag(\lambda)x + V_y y, \end{cases} \tag{11}$$

  where, $B \in \mathbb{M}_{4nxn}$ is a block matrix defined by:

$$B = (diag(1 - p); diag(p.f); diag(p.(1 - f)); 0)^T \tag{12}$$

  and $V_y \in \mathbb{M}_{4nx4n}$ is a block matrix defined by:

$$V_y = \begin{pmatrix} V_{11} & 0 & diag(\rho.(1-\theta)) & 0 \\ V_{21} & \eta\mathcal{M} - diag(A_I) & diag(\theta) & diag(\gamma) \\ V_{31} & 0 & \eta\mathcal{M} - diag(A_J) & 0 \\ 0 & diag(r) & 0 & \mathcal{M} - diag(A_R) \end{pmatrix} \tag{13}$$

  Where,

  $V_{11} = \mathcal{M} - diag(A_E) - diag(1 - \alpha)diag(\sigma)diag(N^{-1})\left[diag(\beta^I I) + diag(\beta^J J)\right]$

$V_{21} = diag(q.(1-\alpha))\left[diag(k) + diag(\sigma)diag(N^{-1})\left[diag(\beta^I I) + diag(\beta^J J)\right]\right]$

$V_{31} = diag((1-q)(1-\alpha))\left[diag(k) + diag(\sigma)diag(N^{-1})\left[diag(\beta^I I) + diag(\beta^J J)\right]\right]$

For the system (11), we observed that V_y and $[\mathcal{M} - diag(\mu)]$ are Metzler matrix for all $X \in \mathbb{R}^{5n}_+$, since their off-diagonal entries are non-negative [3].

The system model (11) can be written in the following compact forme:

$$\dot{X} = AX + \bar{\psi}, \tag{14}$$

with,

$$A = \begin{pmatrix} -diag(\lambda) + (\mathcal{M} - diag(\mu)) & 0 \\ Bdiag(\lambda) & V_y \end{pmatrix}, \bar{\psi} = \begin{pmatrix} \psi \\ 0 \end{pmatrix}. \tag{15}$$

Since A is a Metzler matrix and $\bar{\psi} \geq 0$, system (9) is positively invariant in $\mathbb{R}^{5n}_+$, which means that any trajectory of the system starting from an initial state in the positive orthant $\mathbb{R}^{5n}_+$ remains forever in $\mathbb{R}^{5n}_+$. □

* Boundedness of the solution

Lemma 2. *Each non-negative solution of model system (9) is bounded.*

Proof. For the equation(8) of the total population dynamics of all n patches, we have:

$$\begin{aligned} \dot{H}(t) &= \sum_{i=1}^{n} \dot{N}_i(t) && (16) \\ &\leq \sum_{i=1}^{n} \psi_i - \mu_{min} \sum_{i=1}^{n} N_i(t) && (17) \\ &\leq \chi - \mu_{min} H(t), && (18) \end{aligned}$$

where, $\chi = \sum_{i=1}^{n} \psi_i$ and $\mu_{min} = \min_{i \in \{1,\cdots,n\}} \{\mu_i\}$.

Using the Gronwall Lemma, one has that:

$$H(t) \leq \frac{\chi}{\mu_{min}} + \left(H(o) - \frac{\chi}{\mu_{min}}\right) e^{(-\mu_{min} t)}, \quad \forall t \geq 0, \tag{19}$$

- if $H(0) \leq \frac{\chi}{\mu_{min}}$, then $H(t) < \frac{\chi}{\mu_{min}}, \forall t > 0$.
- if $H(0) \geq \frac{\chi}{\mu_{min}}$,

then, by the comparison theorem [5],

$$\lim_{t \to +\infty} \sup_t H(t) \leq \frac{\chi}{\mu_{min}} \leq H(0). \tag{20}$$

(*) and (**) implied that $0 \leq H(t) \leq \max(\frac{\chi}{\mu_{min}}, H(0)) \ \ \forall t > 0$.

then $N_i(t)$, the total population in a given patch i, is also bounded by $\max(\frac{\chi}{\mu_{min}}, H(0))$.

Then

$$\forall t \geq 0, N(t)_i \leq \max(\frac{\chi}{\mu_{min}}, H(0)), \quad \forall i = 1, 2, \cdots, n \tag{21}$$

.

This completes the proof. □

Corollary 1. *Let,*

$$\Omega = \left\{ X(t) = (S(t), E(t), I(t), J(t), R(t)) \in \mathbb{R}_+^{5n}, 0 \leq H(t) \leq \max\left(\frac{\chi}{\mu_{min}}, H(0)\right)\right\} \tag{22}$$

for any initial condition $X(0) \geq 0$, every solution of the system Ω is bounded, so Ω is compact and absorbing.

* existence and uniqueness of the solution

Theorem 1. *For every non-zero, non-negative initial value, the solution of the model system (9) exists for all $t \geq 0$*

Proof. By posing the (9) in the form $\dot{X}(t) = f(t, X)$, and considering the following Cauchy problem,

$$\begin{cases} \dot{X}(t) = f(t, X) \\ X(0) \in \mathbb{R}_+^{5n} \end{cases} \tag{23}$$

f is a $C^1(\Omega)$ function as component of function of class $C^1(\Omega)$. By using the inequality of the finite increment, one can conclude that f is locally Lipschitzian. Then, Cauchy Lipschitz Theorem ensures the existence of a unique maximal solution of the model system (9), that is unique for any initial condition $(t_0; X(0)) \in \mathbb{N} \times \mathbb{R}_+^{5n}$ fixed. Moreover, these solutions are bounded, this implies they are global. This concludes the proof. □

The system admits a unique maximum solution; the domain Ω is compact, absorbing, positively invariant; therefore the model is well posed and it is sufficient to consider the dynamics generated by the system

3.2 The disease-free equilibrium (DFE)

Here, we calculate the disease free equilibrium of model system (9) and study its stability.

* Local stability of the disease-free equilibrium

The disease-free equilibrium of model system denoted by $Q_0 = (S^0; E^0; I^0; J^0; R^0)$ obtained by setting the right-hand sides of equations in the model to zero. It's a steady state where the infection is absent the population; that is:$I^0 = J^0 = 0$, thus $\lambda = 0$.

these values lead to: $Q_0 = (S^0, 0, 0, 0, 0) \in \mathbb{R}_+^{5n}$,
where

$$S^0 = -\left[\mathcal{M} - diag(\mu)\right]^{-1} \psi \in \mathbb{R}_+^n \tag{24}$$

Lemma 3. *The disease-free equilibrium of model system (9) is $Q_0 = (S^0, 0, 0, 0, 0)$ where S^0 is defined as in Eq(24),*

3.3 The basic reproduction number

The basic reproduction number R_0 is computed using the next generation approach developed in van den Driessche and Watmough[6].

Then, From the equation of (11), the jacobian at the point Q_0 using the equation of E,I,J and R is given by:

$$J = F + V, \tag{25}$$

where,

$$F = \begin{pmatrix} 0 & diag(1-p)diag(\beta^I) & diag(1-p)diag(\beta^J)diag(S^0) & 0 \\ 0 & diag(f.p)diag(\beta^I) & diag(f.p)diag(\beta^J)diag(S^0) & 0 \\ 0 & diag((1-f).p)diag(\beta^I) & diag((1-f).p)diag(\beta^J)diag(S^0) & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{26}$$

and,

$$V = \begin{pmatrix} \mathcal{M} - diag(A_E) & 0 & diag(\rho.(1-\theta)) & 0 \\ diag(k.(1-\alpha).q) & \eta\mathcal{M} - diag(A_I) & diag(\theta) & diag(\gamma) \\ diag\left(k.(1-q).(1-\alpha)\right) & 0 & \eta\mathcal{M} - diag(A_J) & 0 \\ 0 & diag(r) & 0 & \mathcal{M} - diag(A_R) \end{pmatrix} \tag{27}$$

The matrix F can be writing as follow:

$$F = B\left[F_1 + diag(S^0)F_2\right], \tag{28}$$

with:

$$F_1 = [0; diag(\beta^I); 0; 0], \quad F_2 = [0; 0; diag(\beta^J); 0] \quad B = [diag(1-p); diag(f.p); diag\left((1-f).p\right); 0] \tag{29}$$

Lemma 4. *The V matrix is a Metzler stable matrix, that is, all its eigenvalues have negative real parts.*

Proof.

- Let's $V(i,i)$ the elements of the diagonal of the Metzler V matrix. One has that, V is a diagonal column dominant matrix.

  Indeed,

  - for $i = 1, \cdots, n$, one has that:

$$A_{E_i} = k_i(1-\alpha_i) + \mu_i \implies A_{E_i} > k_i(1-\alpha_i) \quad (30)$$

$$\implies \sum_{j=1,j\neq i}^{n} m_{ji} + A_{E_i} > \sum_{j=1,j\neq i}^{n} m_{ji} + k_i(1-\alpha_i) \quad (31)$$

$$\implies |-\sum_{j=1,j\neq i}^{n} m_{ji} - A_{E_i}| > \sum_{j=1,j\neq i}^{n} |m_{ji}| + k_i(1-\alpha_i), \quad (32)$$

then

$$\sum_{j\neq i}^{4n} |V(i,j)| = k_i(1-\alpha_i) + \sum_{j=1;j\neq i}^{n} |m_{ji}| < A_{E_i} + \sum_{j\neq i}^{n} m_{ji} = |-A_{E_i} - \sum_{j=1;j\neq i}^{n} m_{ji}| = |V(i,i)| \quad (33)$$

- from the same way, for $i = n+1; \cdots ; 2n$, one has:

$$\sum_{j\neq i}^{4n} |V(i,j)| = r_i + \sum_{j\neq i}^{n} \eta m_{ji} < A_{I_i} + \sum_{j=1;j\neq i}^{n} \eta m_{ji} = |-A_{I_i} - \sum_{j=1;j\neq i}^{n} \eta m_{ji}| = |V(i,i)| \quad (34)$$

- For $i = 2n+1; \cdots ; 3n$, one has:

$$\sum_{j\neq i}^{4n} |V(i,j)| = \theta_i + \rho_i(1-\theta_i) + \sum_{j=1;j\neq i}^{n} \eta m_{ji} < A_{J_i} + \sum_{j=1;j\neq i}^{n} \eta m_{ji} = |-A_{J_i} - \sum_{j=1;j\neq i}^{n} \eta m_{ji}| = |V(i,i)| \quad (35)$$

For $i = 3n+1; \cdots ; 4n$, one has:

$$\sum_{j\neq i}^{4n} |V(i,j)| = \gamma_i + \sum_{j=1;j\neq i}^{n} m_{ji} < A_{R_i} + \sum_{j\neq i}^{n} m_{ji} = |-A_{R_i} - \sum_{j=1;j\neq i}^{n} m_{ji}| = |V(i,i)| \quad (36)$$

- Due to the Gershgorin theorem [4], we know that the set of eigenvalues is included in the union of the Gerschgorin disks of the V matrix. Then, for all z be a eigenvalue of the V matrix, $z \in \bigcup_{i\in\{1,\cdots,4n\}} C_i$, with:

$$C_i = \{z \in \mathbb{C} / |z - V_y(i,i)| < \sum_{j\neq i}^{4n} |V_y(i,j)|\}. \quad (37)$$

According to the above, one has that $\sum_{j\neq i}^{4n} |V_y(i,j)| < |V_y(i,i)|$ for all $i = \{1, \cdots, 4n\}$, then for all $z \in C_i$, $\mathcal{R}(z) < 0$.

This concluded the proof.

□

V is a Meztler asymptotically stable matrix: then, it's invertible and we have $-V^{-1}$ is nonnegative[3].

The same proof can be used to show that the Metzler matrix $[diag(\mu) - \mathcal{M}]$ is stable and invertible and that

$$-[diag(\mu) - \mathcal{M}]^{-1} \tag{38}$$

is non negative.

Thus, the basic reproduction number is by:

$$\mathcal{R}_0 = \rho[(-FV^{-1})] = \rho\left(-B[F_1 + diag(S^0)F_2]V^{-1}\right) \tag{39}$$

where ρ is the spectral radius of the matrix FV^{-1}.

The basic reproduction number $\mathcal{R}_0$, is the average number of secondary cases produced by a single infective individual which is introduced into an entirely susceptible population.

The disease-free equilibrium Q_0 of the model system (11) is locally asymptotically stable when $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

3.4 Global stability of the disease-free equilibrium

Indeed, from the first equation of model system (9), one has:

$$\dot{S} \leq \psi + [\mathcal{M} - diag(\mu)]S \tag{40}$$

Let the linear comparison system,

$$\dot{Y}_i = \psi - [\mathcal{M} - diag(\mu)]S \tag{41}$$

The linear comparison system (41) has a unique positive equilibrium $S^0 = -[\mathcal{M} - diag(\mu)]^{-1}\psi$ which is non negative Since,$[\mathcal{M} - diag(\mu)]$ is invertible and Mertzler matrix stable.

Then, by the comparison theorem for cooperative systems one has that,

$$\lim_{t\to+\infty} \sup_t S(t) \leq S^0 \tag{42}$$

Moreover, Let us consider Eqs(9). Using the fact that, $S(t) \leq S^0$, $\frac{S_i(t)}{N_i(t)} \leq 1 \ \forall \ i \in \{1, \cdots, n\}$, and $\lambda_i = \beta^I \frac{I}{N} + \beta^J J$, we obtain the following comparison linear system in E, I, J and R:

$$\begin{cases} \dot{E} = diag(1-P)diag(\beta^I)I + \left[diag(1-P)diag(\beta^J)diag(S^0) + diag\left(\rho(1-\theta)\right)\right]J \\ -\left(diag(A_E) - \mathcal{M}\right)E, \\ \dot{I} = diag(f.p)diag(\beta^I)I + \left[diag(f.p)diag(\beta^J)diag(S^0) + diag(\theta)\right]J + diag(\gamma)R - diag(A_I)I \\ +\eta\mathcal{M}I + diag\left(k(1-\alpha)q\right)E + diag\left(q(1-\alpha)\sigma\right)\left[diag(\beta^I) + diag(\beta^J)diag(J^0)\right]E, \\ \dot{J} = diag((1-f)p)diag(\beta^I)I + \left[diag((1-f)p)diag(\beta^J)diag(S^0) - diag(A_J) + \eta\mathcal{M}\right]J \\ +diag\left(k(1-q)(1-\alpha)\right)E + diag((1-q)(1-\alpha)\sigma)\left[diag(\beta^I) + diag(\beta^J)diag(J^0)\right]E, \\ \dot{R} = diag(r)I - diag(A_R) + \mathcal{M}R \end{cases} \tag{43}$$

The system bellow (43) can be written in the following compact form:

$$\dot{Y} = GY, \tag{44}$$

with $G = U - V'$,

where $Y = (0,0,0,0)$ is the unique equilibrium of this linear comparison system, with,

$$U = \begin{pmatrix} U_{11} & diag(1-p)diag(\beta^I) & diag(1-p)diag(\beta^J)diag(S^0) & 0 \\ U_{21} & diag(f.p)diag(\beta^I) & diag(f.p)diag(\beta^J)diag(S^0) & 0 \\ U_{31} & diag((1-f).p)diag(\beta^I) & diag((1-f).p)diag(\beta^J)diag(S^0) & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{45}$$

$$= \begin{pmatrix} 0 & diag(1-p)diag(\beta^I) & diag(1-p)diag(\beta^J)diag(S^0) & 0 \\ 0 & diag(f.p)diag(\beta^I) & diag(f.p)diag(\beta^J)diag(S^0) & 0 \\ 0 & diag((1-f).p)diag(\beta^I) & diag((1-f).p)diag(\beta^J)diag(S^0) & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} + \begin{pmatrix} U_{11} & 0 & 0 & 0 \\ U_{21} & 0 & 0 & 0 \\ U_{31} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{46}$$

$$= F + A \tag{47}$$

where, $U_{11} = -diag\left((1-\alpha)\sigma\right)\left[diag(\beta^I) + diag(\beta^J)diag(J^0)\right]$
$U_{21} = diag\left(q(1-\alpha)\sigma\right)\left[diag(\beta^I) + diag(\beta^J)diag(J^0)\right]$
$U_{32} = diag((1-q)(1-\alpha)\sigma)\left[diag(\beta^I) + diag(\beta^J)diag(J^0)\right]$
and,

$$V' = -\begin{pmatrix} \mathcal{M} - diag(A_E) & 0 & diag(\rho.(1-\theta)) & 0 \\ diag(k.(1-\alpha).h) & \eta\mathcal{M} - diag(A_I) & diag(\eta) & diag(\gamma) \\ diag\left(k.(1-h).(1-\alpha)\right) & 0 & \eta\mathcal{M} - diag(A_J) & 0 \\ 0 & diag(r) & 0 & \mathcal{M} - diag(A_R) \end{pmatrix} \tag{48}$$

G is Metzler stable if

$$s(U - V') < 0 \Leftrightarrow R_c = \rho(-UV^{-1}) < 1, \tag{49}$$

$$R_c = \rho(-FV^{-1} - AV^{-1}) \tag{50}$$

The jacobian matrix of the major system (43) is stable if and only if

$$\rho(-FV^{-1} - AV^{-1}) < 1 \quad \Rightarrow \quad \lim_{k \to +\infty} (-FV^{-1} - AV^{-1})^k = 0$$

then,

$$\forall \xi > 0, \exists k_\xi \in \mathbb{N}, k > k_\xi \Rightarrow \| (-FV^{-1} - AV^{-1})^k \| \leqslant \xi$$

since

$$\begin{aligned} \| (-FV^{-1} - AV^{-1})^k \| &= \| \sum_{p=0}^{k} C_k^p (-FV^{-1})^p (-AV^{-1})^{k-p} \| \\ &\leq \sum_{p=0}^{k} C_k^p \| (-FV^{-1})^p \| . \| (-AV^{-1})^{k-p} \| \end{aligned}$$

then,

$$\begin{aligned} \forall \xi > 0, \exists k_\xi \in \mathbb{N}, k > k_\xi \quad &\Longrightarrow \quad \sum_{p=0}^{k} C_k^p \| (-FV^{-1})^p \| . \| (-AV^{-1})^{k-p} \| \leq \xi \\ &\Longrightarrow \quad C_k^p \| (-FV^{-1})^p \| . \| (-AV^{-1})^{k-p} \| \leq \xi \\ &\Longrightarrow \quad \| (-FV^{-1})^p \| \leq \frac{\xi}{C_k^p \| (-AV^{-1})^{k-p} \|} \\ &\Longrightarrow \quad \| (-FV^{-1})^p \|^{\frac{1}{p}} \leq \frac{\xi^{\frac{1}{p}}}{\rho((-AV^{-1})^{k-p})^{\frac{1}{p}}} \\ &\Longrightarrow \quad \lim_{p \to +\infty} \| (-FV^{-1})^p \|^{\frac{1}{p}} \leq \lim_{p \to +\infty} \frac{\xi^{\frac{1}{p}}}{\rho((-AV^{-1}))^{k/p-1}} \\ &\Longrightarrow \quad \rho(-FV^{-1}) \leq \frac{1}{\rho((-AV^{-1}))^{-1}} = \rho((-AV^{-1})) < 1 \end{aligned}$$

indeed, since the matrix $A + V$ is Metzler stable,

$$s(A + V) < 0 \Longrightarrow \rho(-AV^{-1}) < 1$$

Then, the disease-free equilibrium of model system (9), $Q_0 = (S^0, 0, 0, 0, 0)$ with, $S^0 = -[\mathcal{M} - diag(\mu)]^{-1} \psi \in \mathbb{R}_+^n$ is globally asymptotically stable if $R_0 \leq \xi < 1$ (with $\xi = \rho(-AV^{-1})$, and unstable if $R_0 > 1$ in Ω (22). On the other hand, if $\xi \leq R_0 < 1$,the backward bifurcation phenomenon appears; i.e, the disease-free equilibrium can coexist with two equilibria: one asymptotically stable and the other unstable.

4 Sensitivity analysis

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