Definition
Theorem

ANÁLISIS DE UN MODELO EPIDÉMICO PARA EL ESTUDIO DE LA PROPAGACIÓN DEL COVID-19

AUTHOR: CARMEN LEGARRETA
ADVISOR: SANTIAGO ALONSO QUESADA
ADVISOR: MANUEL DE LA SEN PARTE

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The system can be defined as deterministic or stochastic depending on how the population of one block transforms into the other, that is; deterministic models consider that the ratios (e.g chance to be infected) maintain constant with respect to time, and therefore there is a unique solution for each initial condition. In contrast, stochastic models add random or probabilistic variables into the ratios, and the model will give a set of probable solutions. Even if human behaviour and infections have stochastic components, when the real system (stochastic) is composed by a large group of people, a deterministic models could be used to represent the system [7]. Then, the ratios are constant and could be determined by statistical results.

The graphical representation of the system is made by a group of blocks (or compartments), each one represents certain part of the population, and the arrows make the connection between two blocks (e.g $A \rightarrow B$) and define the way in which part of the population from A, transforms into the inhabitants of the block B. To build up the model flow chart it is important to know the features of the tackling disease; which are the stages of the disease, incubation period, immunity period,...

Regarding CoVid-19, the Word Health Organization reported that there are three main ways in which the disease is transmitted; pre-symptomatic, symptomatic and asymptomatic transmissions [9]. Pre-symptomatic transmission, possible during the incubation period (time between the exposure and the symptoms onset) which is 5-6 days [9, 8], is more likely to happen 1-3 days before symptoms appear [13]. The preliminary way of transmission is via symptomatic cases, but even if the percentage of asymptomatic cases is 16%-17% [4, 2] they show similar viral loads [17, 4, 10]. Some research have spotlight the importance of pre-symptomatic and asymptomatic cases since contribute to the virus high spread [16], therefore many countries were force to include quarantine periods to reduce the spreading. The flow chart depicted in Figure 1 shows a deterministic model of CoVid-19 which includes the characteristics mentioned before.

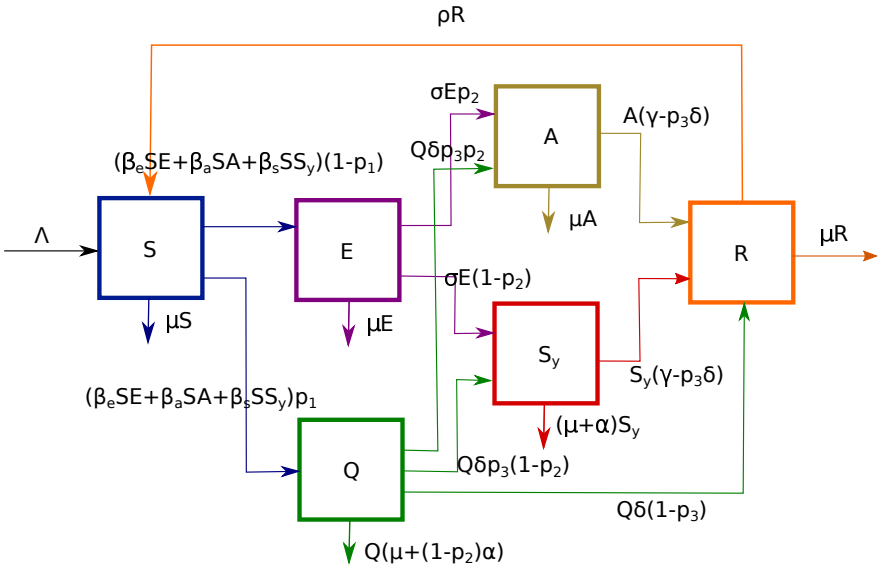

Figure 1: System flow chart.

Figure 1 shows 5 different compartments,

- **Susceptible** (S): this class is constructed by the group of individuals that can get the disease and are not yet infected.
- **Exposed** (E): those individuals of the group S that have been in contact with infected people and therefore are infected too, but they do not present symptoms because they are still incubating the virus. They move freely, thus they will maintain an average number k_{free} of close contacts per day.

- **Quarantined** (Q): this group is made by a group of S that has been in contact with infected people and therefore are infected, but they have been traced and put in quarantine. Since their close contacts, medical staff, and themselves are aware of their infection, they are cautious and their probability to infect others is low, which in this case study it will be assumed that the probability is low enough to consider it as null.
- **Symptomatic** (S_y): the group of infected people that present symptoms. If the symptoms are poor the host will still moving freely, so the average number of close contacts per day will be equal to k_{free}. In contrast, the host could visit the doctor due to grave symptoms, so he or she will be put in quarantine and the average number of close contacts per day will drop. Consequently, members of this group will keep an average number of close contacts k_s which values is between k_{free} and 0. Depending on the assumptions and approximations that are applied to calculate k_s different values will be obtained.
- **Asymptomatic** (A): the group of infected people that don't present symptoms. They move freely with an average number of close contacts equal to k_{free}.
- **Recovered** (R): when infected people recover from the diseases and have some immunity against it during a period of time.

This system population size (N) is assumed to be large and constant; the natural deaths and births have the same rate. The newborns are introduced in the class S with Λ, and from all the classes it is removed a size which is proportional to each population and μ (daily death rate).

It is considered that the population is homogeneously mixed, so it is possible to determine the rates β_e, β_a and β_s, which indicate the probability to infect susceptible people when they are in contact with exposed, asymptomatic and symptomatic people, respectively. The mathematical expression is,

$$\beta_e = k_e p_e, \quad \beta_a = k_a p_a, \quad \beta_s = k_s p_s$$

where k_i is the average number of close contacts per day in i, and p_i the probability to infect others when there is a close contact in i, where $i \in \{E, S_y, A\}$. As it was mentioned before, it will be assumed that $k_e = k_a = k_{free}$, $k_e > k_s > 0$, and $p_a \approx p_s > p_e$. These are necessary parameters to define the transformation from S to the groups E and Q. p_1 will determine the probability to detect infected people by tracing techniques.

Exposed people after the incubation time ($1/\sigma$ days) will transform into asymptomatic people with a probability p_2. The regarding ones will transform into symptomatic, and they will have a risk to die from the disease, which will be characterized by the disease daily rate α. After $1/\gamma$ days asymptomatic and symptomatic people will test negative and the will be part of recovered population during the immunity period ($1/\rho$ days).

People in Q will remain there during the quarantine period ($1/\delta$ days), which is assumed to be less than or equal to $1/\gamma$. There is a chance p_3 that after $1/\delta$ days the host could still be infected, and therefore it will be reinserted in A or S_y. The rest population of Q will be already recovered and they will go to R. Those that have been reinserted in A or S_y will remain there an average of $1/(\gamma - \delta)$ days. Those members from Q that present symptoms ($p_2 Q$), they will die as a consequence of the disease with a daily rate α.

6 block are presented in the scheme presented in Figure 1, so 6 differential equation are needed to represent the system. Manage with 6 equations might be difficult, therefore a new compartment is defined to reduce the number of equations from 6 to 5, that is;

$$I = A + S_y, \quad A = p_2 I, \quad \text{and} \quad S_y = (1 - p_2) I \tag{1}$$

and in Figure 2 substitutes the blocks A and S_y with the block I (infectious) by following the rule 1.

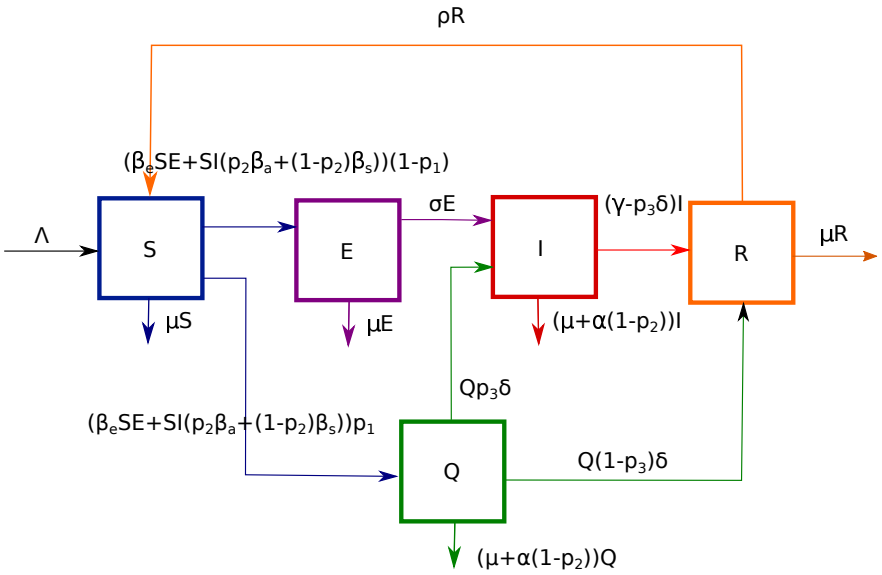

Figure 2: Reduced flow chart.

The differential equation representing the model is given by the following set of equations,

$$\begin{aligned}
\dot{S} &= \Lambda + R\rho - \beta_e SE - SI(p_2\beta_a + (1-p_2)\beta_s) - \mu S \\
\dot{Q} &= (\beta_e SE + SI(p_2\beta_a + (1-p_2)\beta_s))p_1 - Q(\mu + (1-p_2)\alpha + p_3\delta) \\
\dot{E} &= (\beta_e SE + SI(p_2\beta_a + (1-p_2)\beta_s))(1-p_1) - E(\sigma + \mu) \\
\dot{I} &= \sigma E + Q\delta p_3 - I(\mu + (1-p_2)\alpha + \gamma - p_3\delta) \\
\dot{R} &= I(\gamma - p_3\delta) + Q\delta(1-p_3) - (\rho + \mu)R
\end{aligned} \tag{2}$$

and regarding the total population,

$$\begin{aligned}
N &= S + Q + E + I + R \\
\dot{N} &= \Lambda - \mu N - \alpha(1-p_2)(I+Q)
\end{aligned} \tag{3}$$

and the variables are conditioned by,

$$0 \leqslant \mu, \alpha, \beta_s, \beta_e, \beta_a, \sigma, \gamma, \delta, \rho, \quad \text{and} \quad 0 \leqslant p_1, p_2, p_3 \leqslant 1.$$

To demonstrate the consistency of the equation, the sizes of the population S, Q, E, I, R and N must not be negative, it can be shown that all the solutions will maintain positive for a initial conditions $(S_0, Q_0, E_0, I_0, R_0) \in \mathbb{R}_5^+$ if the differential equations are semi-positive when $(S, Q, E, I, R) \in \mathbb{R}_5^+$ [11],

$$\begin{aligned}
\dot{S}\big|_{S=0} &= \Lambda + R\rho \geqslant 0 \\
\dot{Q}\big|_{Q=0} &= (\beta_e SE + SI(p_2\beta_a + (1-p_2)\beta_s))p_1 \geqslant 0 \\
\dot{E}\big|_{E=0} &= (SI(p_2\beta_a + (1-p_2)\beta_s))(1-p_1) \geqslant 0 \\
\dot{I}\big|_{I=0} &= \sigma E + Q\delta p_3 \geqslant 0 \\
\dot{R}\big|_{R=0} &= Q(1-p_3)\delta + I(\gamma - p_3\delta) \geqslant 0
\end{aligned}$$

Moreover, it is possible to prove that the entire population will be bounded: considering that nobody is dying because of the disease ($\alpha = 0$), the solution of the differential equation 3 is given by,

$$N = N_0 e^{-t\mu} + \frac{\Lambda}{\mu}$$

and the limit,

$$\lim_{t\to\infty}\left[N_0 e^{-t\mu}+\frac{\Lambda}{\mu}\right]=\frac{\Lambda}{\mu}$$

So, all the solutions of the systems 2 will be bounded and the region **D** will hold all the possible solutions,

$$\mathbf{D}=\left\{(S,Q,E,I,R)\in\mathbb{R}^5_+ : N\leqslant\frac{\Lambda}{\mu}\right\}$$

3.1 The Equilibrium State

To know how the system 2 will converge, its solution (S^*,Q^*,E^*,I^*,R^*) must be obtained when it is at equilibrium ($\dot{S}=\dot{Q}=\dot{E}=\dot{I}=\dot{R}=0$). Depending if the disease persist or not two equilibrium cases can be distinguish; *disease-free equilibrium* and *endemic equilibrium*.

Disease-free equilibrium occurs when the disease is vanished ($E^*_{dfe}=I^*_{dfe}=0$). If there is no infectious person Q and R will decay to zero since their states are non-stationary, and therefore S will hold all the population ($S=N=\Lambda/\mu$). This can be easily seen by substituting the mentioned conditions into the system 2,

$$\begin{aligned}
0 &= \Lambda+R^*_{dfe}\rho+\epsilon\delta Q^*_{dfe}-\mu S^*_{dfe}\\
0 &= \delta\epsilon Q^*_{dfe}-(1-\delta)\sigma Q^*_{dfe}-\mu Q^*_{dfe}\\
0 &= (Q^*_{dfe}(1-\delta))\sigma\\
0 &= \rho R^*_{dfe}-\mu R^*_{dfe}
\end{aligned}\tag{4}$$

from 3th and 4th equations $Q=0$ and $R=0$ is obtained, respectively. So, the solution in *disease-free equilibrium* is

$$P_{dfe}=(S^*_{dfe},Q^*_{dfe},E^*_{dfe},I^*_{dfe},R^*_{dfe})=(\Lambda/\mu,0,0,0,0)$$

Regarding *endemic equilibrium* point

$$P_{eq}=(S^*_{eq},Q^*_{eq},E^*_{eq},I^*_{eq},R^*_{eq}),$$

it occurs when the disease continue affecting the population ($E^*_{eq}\neq 0$, $I^*_{eq}\neq 0$). The system to be solved is the following one,

$$\begin{aligned}
0 &= \Lambda+R^*_{eq}\rho-\beta_e S^*_{eq}E^*_{eq}-S^*_{eq}I^*_{eq}(p_2\beta_a+(1-p_2)\beta_s)-\mu S^*_{eq}\\
0 &= (\beta_e S^*_{eq}E^*_{eq}+S^*_{eq}I^*_{eq}(p_2\beta_a+(1-p_2)\beta_s))p_1-Q^*_{eq}(\mu+\sigma+\gamma p_2)\\
0 &= (\beta_e S^*_{eq}E^*_{eq}+S^*_{eq}I^*_{eq}(p_2\beta_a+(1-p_2)\beta_s))(1-p_1)-E^*_{eq}(\sigma+\mu)\\
0 &= (E^*_{eq}+Q^*_{eq}(1-p_2))\sigma-I^*_{eq}(\mu+\alpha(1-p_2)+\gamma)\\
0 &= \gamma I^*_{eq}+Q^*_{eq}(\sigma+\gamma)p_2-R^*_{eq}(\rho+\mu)
\end{aligned}\tag{5}$$

and its solution,

$$\begin{aligned}
S^*_{eq} &= \frac{1}{\mu}\left[\frac{\rho(\gamma-p_3\delta)}{(\mu+\rho)(\mu+(1-p_2)\alpha+\gamma-p_3\delta)}\left[\sigma+\frac{p_1p_3\delta(\sigma+mu)}{(1-p_1)(\mu+(1-p_2)\alpha+p_3\delta)}+\frac{p_1(\sigma+\mu)\delta(1-p_3)}{\gamma-p_3\delta}\right]-\frac{\sigma+\mu}{1-p_1}\right]E^*_{eq}+\frac{\Lambda}{\mu},\\
Q^*_{eq} &= \frac{(\sigma+\mu)p_1}{(\mu+(1-p_2)\alpha+p_3\delta)(1-p_1)}E^*_{eq},\\
I^*_{eq} &= \frac{1}{(\mu+(1-p_2)\alpha+\gamma-p_3\delta)}\left(\sigma+\frac{p_1p_3\delta(\sigma+\mu)}{(\mu+(1-p_2)\alpha+p_3\delta)(1-p_1)}\right)E^*_{eq},\\
R^*_{eq} &= \frac{1}{(\rho+\mu)(\mu+(1-p_2)\alpha+\gamma-p_3\delta)}\left[(\gamma-p_3\delta)\left[\sigma+\frac{p_1p_3\delta(\sigma+\mu)}{(\mu+(1-p_2)\alpha+p_3\delta)(1-p_1)}\right]+p_1(\sigma+\mu)\delta(1-p_3)\right]E^*_{eq},
\end{aligned}$$

for $\forall\ E^*_{eq} \in \mathbb{R}_+$. To prove whether the obtained solution is correct or not, the set of equations in 5 have been manipulated to obtain the following linear system,

$$\begin{aligned} 0 &= \sigma E^*_{eq} + Q^*_{eq}\delta p_3 - I^*_{eq}(\mu + (1-p_2)\alpha + \gamma - p_3\delta) \\ 0 &= I^*_{eq}(\gamma - p_3\delta) + Q^*_{eq}\delta(1-p_3) - R^*_{eq}(\mu+\rho) \\ 0 &= E^*_{eq}p_1(\mu+\sigma) - (1-p_1)(\mu + (1-p_2)\alpha + p_3\delta)Q^*_{eq} \\ 0 &= \Lambda + \rho R^*_{eq} - \mu S^*_{eq} - E^*_{eq}(\mu+\sigma) - Q^*_{eq}(\mu + (1-p_2)\alpha + p_3\delta) \\ E^*_{eq} &= 100 \end{aligned} \tag{6}$$

where $\Lambda = 1000$. It has been solved numerically, by giving to the unknown variables random values, and checked if it matches with the manual results, got to appendix A.1 to see the Matlab code.

3.2 Basic Reproduction Number

The basic reproduction number $\mathcal{R}_0$ is a threshold which value determines whether the disease free equilibrium (DFE) is locally asymptotically stable or not. More precisely, when $\mathcal{R}_0 > 1$ is it said that DFE is unstable and the disease could invade the population, on the other hand if $\mathcal{R}_0 < 1$ DFE is locally asymptotically stable . In [12] it is explained how the basic reproduction number is defined, and it shows its mathematical proof and examples of how to apply it in different cases. To obtain the mathematical definition of $\mathcal{R}_0$, the demonstration from [12] has been studied, see appendix C, and applied.

To obtain V and F firstly the vectors $\mathcal{F}$ and $\mathcal{V}$ which indicate the rate of appearance of new infections and the transfer (in and out) of individuals, respectively, in the compartments E, Q, and I must be defined[1],

$$\mathcal{F} = \begin{pmatrix} (\beta_e SE + SI(p_2\beta_a + (1-p_2)\beta_s))(1-p_1) \\ (\beta_e SE + SI(p_2\beta_a + (1-p_2)\beta_s))p_1 \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (\mu+\sigma)E \\ (\mu+\sigma+\gamma p_2)Q \\ I(\mu + \alpha(1-p_2) + \gamma) - \sigma(E + Q(1-p_2)) \end{pmatrix}.$$

Note that $\mathcal{F}_3 = 0$ because in the compartment I there is no new infections, that is; E and Q present the new infections, and the infected individuals from I are a consequence (they were already infected) of people from E and Q. The matrix F and V are the derivative of $\mathcal{F}$ and $\mathcal{V}$, respectively, around P_{dfe},

$$F = \begin{pmatrix} \beta_e S(1-p_1) & 0 & S(p_2\beta_a + (1-p_2)\beta_s)(1-p_1) \\ \beta_e S p_1 & 0 & S(p_2\beta_a + (1-p_2)\beta_s)p_1 \\ 0 & 0 & 0 \end{pmatrix}\Bigg|_{P_{dfe}},$$

$$V = \begin{pmatrix} \mu+\sigma & 0 & 0 \\ 0 & (\mu+\sigma+\gamma p_2) & 0 \\ -\sigma & -\sigma(1-p_2) & \mu + \alpha(1-p_2) + \gamma \end{pmatrix}\Bigg|_{P_{dfe}}$$

In the appendix D the steps to calculate the spectral radius of $V^{-}F$ are presented, and the result is,

$$\rho(V^{-}F) = \frac{\beta_e S(1-p_1)}{\mu+\sigma} + \frac{S\sigma(p_2\beta_a + (1-p_2)\beta_s)}{\mu + \alpha(1-p_2) + \gamma}\left[\frac{1-p_1}{\mu+\sigma} + \frac{p_1(1-p_2)}{\mu+\sigma+p_2\gamma}\right]\Bigg|_{S=\Lambda/\mu} \tag{7}$$

and it has been proved that it matches with the numerical results, see appendix A.2.

1 As far as F and V only hold the infected compartments, the expression of $\mathcal{F}$ and $\mathcal{V}$ will be reduced to the those compartments too.

3.3 Stability Analysis

The stability of a system can be characterized by an bounded output, or a tend to a equilibrium point. However, its mathematical definition depends on the system characteristics (algebraic/dynamical, linear/nonlinear,...), and the type of stability. There are 3 common stability definitions for the case of nonlinear dynamical systems; the Lyapunov stability with respect the equilibrium point, the structural stability, and the orbital stability. Specially in this work, it is important to calculate the stability of the system 12 around its equilibrium points P_{dfe} and P_{eq}, because, by analysing the conditions for stability, it will be possible to obtain an indicator and therefore apply rules, in real cases which are similar to the case study of this work, which could prevent from a disease growth.

Let's consider the system

$$\dot{\mathbf{x}} = f(t, \mathbf{x}) \tag{8}$$

with the equilibrium point $\mathbf{x}^*$, such that $f(t, \mathbf{x}^*) = 0$.

Given $\delta > 0$ and $\epsilon > 0$, it is said that $\mathbf{x}*$ is stable if for a the next condition is satisfied [6, 3],

$$|\mathbf{x} - \mathbf{x}^*| < \delta \quad \text{at } t_0 \Rightarrow |\mathbf{x} - \mathbf{x}^*| < \epsilon \quad \forall t > t_0. \tag{9}$$

The system it is said to be asymptotically stable around $\mathbf{x}^*$ if

$$|\mathbf{x} - \mathbf{x}^*| < \delta \quad \text{at } t_0 \Rightarrow |\mathbf{x}| \to |\mathbf{x}^*| \quad \text{when } t \to \infty. \tag{10}$$

There are two Lyapunov theorems which determine the asymptotic stability of a nonlinear system [3]. The first case needs from the system jacobian and its eigenvalues, and the second one uses the Lyapunov function $V(t, \mathbf{x})$, which can be interpreted as the system's energy representation. Even if in some cases it is not straightforward obtaining a representation for the system's energy, in [5, 15] approaches for Lyapunov functions are presented.

Theorem 3.1. *If the eigenvalues of the Jacobian matrix,*

$$J = \frac{d\mathbf{f}}{d\mathbf{x}}\Big|_{x^*},$$

have negative real part, the system is asymptotically stable in x^*.

Theorem 3.2. *If* $V(t, \mathbf{x})$ *is locally positive definite* ($V(t, \mathbf{x}) > 0 \ \forall \ x \neq 0, \ t > t_0$) *and the derivative is negative definite* ($\dot{V(t, \mathbf{x})} < 0 \ \forall \ t > t_0$), *then* x^* *is asymptotically stable.*

The stability of the system 12 will be analyzed by using Theorems 3.1 and 3.2, so firstly the Jacobian will be calculated for a generic equilibrium point $P = (S^*, Q^*, E^*, I^*, R^*)$,

$$J = \begin{pmatrix} -(\beta_e E^* + I^*(p_2\beta_a + (1-p_2)\beta_s)) - \mu & -\beta_e S^* & 0 & -S^*(p_2\beta_a + (1-p_2)\beta_s) & \rho \\ (\beta_e E^* + I^*(p_2\beta_a + (1-p_2)\beta_s))p_1 & \beta_e S^* p_1 & -(\mu + \sigma + \gamma p_2) & S^*(p_2\beta_a + (1-p_2)\beta_s)p_1 & 0 \\ (\beta_e E^* + I^*(p_2\beta_a + (1-p_2)\beta_s))(1-p_1) & \beta_e S^*(1-p_1) & 0 & S^*(p_2\beta_a + (1-p_2)\beta_s)(1-p_1) & 0 \\ 0 & \sigma & \sigma(1-p_2) & -(\mu + \alpha(1-p_2) + \gamma) & 0 \\ 0 & 0 & (\sigma+\gamma)p_2 & \gamma & -(\rho+\gamma) \end{pmatrix}$$

In the following two subsections the generic equilibrium point will be substituted by the P_dfe and Pee, respectively.

3.3.1 *Disease Free Equilibrium Case*

The disease free equilibrium point has all the population sizes equal to zero except S, so the resulting Jacobian matrix is the following one,

$$J = \begin{pmatrix} -\mu & -\beta_e S^* & 0 & -S^*(p_2\beta_a + (1-p_2)\beta_s) & \rho \\ 0 & \beta_e S^* p_1 & -(\mu+\sigma+\gamma p_2) & S^*(p_2\beta_a + (1-p_2)\beta_s)p_1 & 0 \\ 0 & \beta_e S^*(1-p_1) - (\mu+\sigma) & 0 & S^*(p_2\beta_a + (1-p_2)\beta_s)(1-p_1) & 0 \\ 0 & \sigma & \sigma(1-p_2) & -(\mu+\alpha(1-p_2)+\gamma) & 0 \\ 0 & 0 & (\sigma+\gamma)p_2 & \gamma & -(\rho+\gamma) \end{pmatrix}$$

It is difficult to obtain its eigenvalues since the matrix size and the number of nonzero terms is high, therefore two different cases will be evaluated; everybody goes into the quarantine ($p_1 = 1$) or nobody goes into the quarantine ($p_1 = 0$). Two stability criteria will be obtained, and they will inform if the system's stability is asymptotically stable, unstable, or unknown. Moreover, it will verified if these criteria agree with $\mathcal{R}_0$.

Everybody goes into the quarantine ($p_1 = 1$)
The Jacobian matrix is deffined as follows,

$$J = \begin{pmatrix} -\mu & -\beta_e S^* & 0 & -S^*(p_2\beta_a + (1-p_2)\beta_s) & \rho \\ 0 & \beta_e S^* & -(\mu+\sigma+\gamma p_2) & S^*(p_2\beta_a + (1-p_2)\beta_s) & 0 \\ 0 & -(\mu+\sigma) & 0 & 0 & 0 \\ 0 & \sigma & \sigma(1-p_2) & -(\mu+\alpha(1-p_2)+\gamma) & 0 \\ 0 & 0 & (\sigma+\gamma)p_2 & \gamma & -(\rho+\gamma) \end{pmatrix}$$

and its eigenvalues,

$$\lambda_{1,2,3} = -\mu, -(\mu+\sigma), -(\mu+\rho) \leqslant 0$$

$$\lambda_{4,5} = \frac{-(a+b) \pm \sqrt{(a+b)^2 + 4(ab-cd)}}{2}$$

where $a = (\mu + \gamma p_2 + \sigma)$, $b = (\mu + \alpha(1-p_2))$, $c = S(\beta_a p_2 + (1-p_2)\beta_s)$, and $d = \sigma(1-p_2)$. The positivity of λ_4 depends on the term $ab - cd$, that is;

$$\text{if } ab - cd > 0 \Rightarrow \lambda_4 > 0 \Rightarrow \text{unstable.}$$

Let's define $\mathcal{R}_Q$ as the basic reproduction number for this specific case,

$$\mathcal{R}_Q = \frac{S^*(\beta_a p_2 + (1-p_2)\beta_s)\sigma(1-p_2))}{(\mu+\gamma p_2+\sigma)(\mu+\alpha(1-p_2)+\gamma)} \tag{11}$$

which value is equal to $\mathcal{R}_0$ when $p_1 = 1$.

Nobody goes into quarantine ($p_1 = 0$)

The Jacobian matrix is deffined as follows,

$$J = \begin{pmatrix} -\mu & -\beta_e S^* & 0 & -S^*(p_2\beta_a + (1-p_2)\beta_s) & \rho \\ 0 & 0 & -(\mu+\sigma+\gamma p_2) & 0 & 0 \\ 0 & \beta_e S^* - (\mu+\sigma) & 0 & S^*(p_2\beta_a + (1-p_2)\beta_s) & 0 \\ 0 & \sigma & \sigma(1-p_2) & -(\mu+\alpha(1-p_2)+\gamma) & 0 \\ 0 & 0 & (\sigma+\gamma)p_2 & \gamma & -(\rho+\gamma) \end{pmatrix}$$

and its eigenvalues,

$$\lambda_{1,2,3} = -\mu, -(\rho+\mu), -(\mu+\sigma+\gamma p_2)$$

$$\lambda_{4,5} = \frac{-(b-a) \pm \sqrt{(b-a)^2 + 4(\sigma c - ab)}}{2}$$

where $a = \beta_e S^* - (\sigma+\mu)$, $b = (\mu + \alpha(1-p_2))$, and $c = S(\beta_a p_2 + (1-p_2)\beta_s)$. As it was seen before, λ_4 positivity depends on $\sigma c - ab$, that is;

$$\text{if } \sigma c - ab > 0 \Rightarrow \lambda_4 > 0 \Rightarrow \text{unstable.}$$

Let's define $\mathcal{R}_{NQ}$ as the basic reproduction number for this case,

$$\mathcal{R}_{NQ} = \frac{\beta_s S^*}{\sigma + \mu} + \frac{S^* \sigma(\beta_a p_2 + (1 - p_2)\beta_s)}{(\sigma + \mu)(\mu + \alpha(1 - p_2))}$$

which also matches with $\mathcal{R}_0$ when $p_1 = 0$.

Based on the first Lyapunov theorem for asymptotic stability, a criteria for stability in the case of disease free equilibrium has been created;

- if $\mathcal{R}_Q > 1$ and $\mathcal{R}_{NQ} > 1$, then the system is unstable.
- if $\mathcal{R}_Q < 1$ and $\mathcal{R}_{NQ} < 1$, then the system is asymptotically stable.
- if ($\mathcal{R}_Q < 1$ and $\mathcal{R}_{NQ} > 1$) or ($\mathcal{R}_Q > 1$ and $\mathcal{R}_{NQ} < 1$), the stability is unknown.

3.3.2 *Endemic Equilibrium Case*

4 MODEL SIMULATION

A CODES

A.1 Endemic Equilibrium

- Constants definition
- Manual solution
- Numerical solution
- Verification

```
% Date: 13/10/2020
% Author: Carmen Legarreta
%
% Create an script to prove that the obtained results from the system in
% the endemic equilibium case are the same as the obtained manually. The
% system equations depende of variables which values are unknown, for the
% simulation random values will be asigned to these variables.
```

Constants definition

```
la = 1000; rho = rand(); be = rand(); bs = rand(); ba = rand();
p2 = rand();  p1 = rand(); p3 = rand();  mu = rand(); sigma = rand();
gamma = rand(); alpha = rand(); delta = rand();
```

Manual solution

```
e = 100;

s = 1.0 / mu * (rho* (gamma - p3 * delta) / (rho + mu) / ...
    (mu + (1 - p2) * alpha + gamma - p3*delta) * ((sigma + p1 * p3 * ...
    delta * (sigma + mu) / (1 - p1) / (mu + (1 - p2) * alpha + p3 * ...
    delta)) + p1 * (sigma + mu) * delta * (1 - p3) / (gamma - p3 * delta))- ...
    (sigma + mu)/(1 - p1)) * e + la/mu ;

q = (sigma + mu)*p1*e/(mu + (1-p2) * alpha + p3 * delta)/(1-p1);

i = (sigma + p1 * p3 * delta * (sigma + mu) / (1 - p1) / ...
    (mu + (1 - p2) * alpha + p3 *delta)) * e / (mu + (1 - p2) * alpha + ...
    gamma - p3 * delta);

r = ((gamma - p3 * delta)*(sigma + p1 * p3 * delta * (sigma + mu) / (1 - p1) / ...
    (mu + (1 - p2) * alpha + p3 *delta)) + p1 * (sigma + mu) * delta * ...
    (1 - p3)) * e / (rho + mu) / (mu + (1 - p2) * alpha + gamma - p3 * delta);
```

Numerical solution

```
system_a = zeros (5, 5);

% first array
system_a(1, 3) = (mu + (1 - p2) * alpha + p3 * delta)*(1-p1);
system_a(1, 2) = -(sigma + mu)*p1;
```

```
% second array
system_a(2, 1) = -mu;
system_a(2, 2) = -(sigma + mu);
system_a(2, 3) = -(mu + (1 - p2) * alpha + p3 * delta);
system_a(2, 5) =  rho;

% third array
system_a(3, 2) = sigma;
system_a(3, 3) = delta * p3;
system_a(3, 4) = -(mu + alpha*(1 - p2) + gamma - p3 * delta);

% fourth array
system_a(4, 3) = delta * (1 - p3);
system_a(4, 4) = (gamma - p3 * delta);
system_a(4, 5) = -(mu + rho);

% fifth array
system_a(5, 2) = 1;

% system
system_b = [0, -la, 0, 0, e]';

% solution
solution = linsolve(system_a, system_b);
```

Verification

```
eps = 1.0e-3;
solution2 = [s, e, q, i, r];
v = 1;

for i = 1:length(solution)
    v = v * solution(i) - eps < solution2(i) < solution(i) +eps;
end
```

A.2 Spectral Radius

Contents

- Constants definition
- Manual solutions
- Numerical solution
- Check

```
% Date: 20/10/2020
% Author: Carmen Legarreta
%
% Script to prove that the obtained results of the spectral radius are the
% same as the obtained manually. The obtained results depends on variables
% which values are unknown, therefore for the simulation random values will
% be asigned to these variables.
```

Constants definition

```
la = 1000; rho = rand(); be = rand(); bs = rand(); ba = rand();
p2 = rand();  p1 = rand(); mu = rand(); sigma = rand(); gamma = rand();
alpha = rand();
```

Manual solutions

```
% the inverse of V
manual_inv_V = zeros(3, 3);
manual_inv_V(1, 1) = 1/(mu + sigma);
manual_inv_V(2, 2) = 1/(mu + sigma + p2*gamma);
manual_inv_V(3, 1) = sigma / (sigma + mu) / (mu + alpha * (1 - p2) + gamma);
manual_inv_V(3, 2) = sigma*(1 - p2)/ (mu + sigma + gamma * p2) / ...
    (mu + alpha * (1 - p2) + gamma);
manual_inv_V(3, 3) = 1 / (mu + alpha * (1 - p2) + gamma);

% the product of V^{-1} and F
manual_M = zeros(3, 3);
manual_M(1, 1) = be * la * (1 - p1) / (mu + sigma) / mu;
manual_M(1, 3) = la * (p2 * ba + (1 - p2) * bs) * (1 - p1) / mu / (mu + sigma);
manual_M(2, 1) = be * la * p1 / (mu + sigma + p2 * gamma) / mu;
manual_M(2, 3) = la * (ba * p2 + (1 - p2) * bs) * p1 / mu / ...
    (mu + sigma + p2 * gamma);
manual_M(3, 1) = be * sigma * la * ((1 - p1) / (sigma + mu) + ...
    p1 * (1 - p2) / (mu + sigma + p2 * gamma)) / ...
    (mu + alpha * (1- p2) + gamma) / mu;
manual_M(3, 3) = la * (p2 * ba + (1 - p2) * bs) * sigma * ((1 - p1) / ...
    (sigma + mu) + p1 * (1 - p2) / (mu + sigma + p2 * gamma)) / ...
    (mu + alpha * (1 - p2) + gamma) / mu;

% the spectral radius
spectral = be * la * (1 - p1) / mu / (mu + sigma) +...
    la * sigma * (p2 * ba + (1 - p2) * bs) *...
    ((1 - p1) / (mu + sigma) + p1 * (1 - p2) / ...
    ( mu + sigma + p2 * gamma))/ mu / (mu+alpha*(1-p2)+gamma);
```

Numerical solution

```
F = zeros(3,3);
V = zeros(3,3);

% matrices terms definition
F(1, 1) = be * la *(1-p1)/mu; F(1,3) = la * (p2 * ba + (1 - p2) * bs) *...
    (1 - p1) / mu;
F(2, 1) = be * p1 * la / mu; F(2, 3) = la * (p2 * ba + (1 - p2) * bs) *...
    p1 / mu;

V(1, 1) = mu + sigma; V(2, 2) = mu + sigma + gamma * p2;
V(3, 1) = -sigma; V(3, 2) = -sigma * (1 - p2); V(3, 3) = mu + alpha * ...
    (1 - p2) + gamma;
```

```
% calculate V^{-1}F
inv_V = inv(V);
M = inv_V*F;

% calculate the eigenvalues
e = eig(M);
```

Check

```
eps = ones(3, 3);
eps = 1e-2 * eps;

% check if the manual and numerical V^{-1} is the shame
if inv_V - eps < manual_inv_V
    if manual_inv_V < inv_V + eps
        check1 = 1;
    end
end

% check if the manual and numerical V^{-1}F is the shame
if M - eps < manual_M
    if manual_M < M + eps
        check2 = 1;
    end
end

% check if the manual and numerical nonzero eigenvalues match
for li = 1:length(e)
    if e(li) ~= 0 && e(li) - 1e-3 < spectral < e(li) + 1e-3
        check3 = 1;
    end
end

% display the results
display(check1 * check2 * check3)
```

```
     1
```

B SINGULAR AND NON-SINGULAR M MATRIX

In cases in which a system is defined by a set of differential equations, it is often seen that its matrix representation has the following form,

$$A = \begin{bmatrix} a_{11} & -a_{12} & \dots \\ -a_{21} & a_{22} & \dots \\ \vdots & \vdots & \ddots \end{bmatrix} \quad : \; a_{ij} \geqslant 0, \; \forall\, i \neq j \in m$$

in these cases the matrix has Z sign pattern ($A \in Z^{m\,x\,m}$).

Definition B.1. [12, 1, 14] If $A \in Z^{m\,x\,m}$ and it can be represented as $A = sI - P$, where $P \geqslant 0$ and $s \geqslant \rho(P)$, then A is called M matrix ($\rho(\cdot)$ represents the spectral radius).

Depending on s two different M matrix can be distinguish; *non-singular* and *singular*.

Theorem B.1. *[1, 14] A matrix A is a non-singular M matrix if s is greater than P's spectral radius ($s > \rho(P)$). The implications are the following ones*[2]*,*

- *The real part of A's eigenvalues is positive ($Re(\lambda(A)) > 0$).*
- *The principal minors of A are positive.*
- *The inverse of A (A^-) exists, and it is positive ($A^- \geqslant 0$).*
- *Exist a vector $X > 0$ such that $AX > 0$.*
- *A is monotone on V_A,*

$$Ax > 0 \Rightarrow x > 0 \quad \textit{and},$$
$$Ax = 0 \Rightarrow x = 0 \quad \forall\, x \in V_A$$

- *A has a convergent regular splitting,*

$$A = M - N, \quad M^- \geqslant 0, \quad N \geqslant 0$$

where MN^- is convergent ($\rho(M^-N) < 1$).

Theorem B.2. *[1, 14] A matrix A is a singular M matrix if s is equal to P's spectral radius ($s = \rho(P)$). The implications are the following ones,*

- *Exists and eigenvalue of A which real part is equal to zero.*
- *There exists a vector $X > 0$ such that $AX = 0$.*
- *all principal minors are nonnegative.*
- *A is monotone in V_A,*

$$Ax \geqslant 0 \Rightarrow x \geqslant 0 \quad \forall x \in V_A.$$

Theorem B.3. *[1] A M matrix A has a regular splitting,*

$$A = M - N, \quad M^- \geqslant 0, \quad N \geqslant 0,$$

where $V_{M^-A} = V_A$ and $\rho(M^-N) \leqslant 1$.

2 when it is about non-singular M matrices many implication can bee seen (e.g in [1] 50 implications are defined), however in this case I limit the number to that ones that will be used in the future.

Corollary B.1. *Considering that a M matrix A has a regular splitting such that* $A = M - N$, *see Theorem B.3, then* $M^{-}A$ *is nonsingular if and only if* A *is nonsingular, and* $M^{-}A$ *is singular if and only if* A *is singular.*

Proof: singular M matrix $A \implies M^{-}A$ singular M matrix.

- There exists $X_1 > 0$ such that $AX_1 = 0$. Then, $(M^{-}A)X_1 = M^{-}\mathbf{o} = 0$
- Considering $M^{-}A$ as nonsingular M matrix, then $(M^{-}A)X_1 > 0$ (against the first implication). Considering $M^{-}A$ as a singular M matrix, there exist $X_2 > 0$ such that $(M^{-}A)X_2 = 0$. Since $V_{M^{-}N} = V_A$, then $X_2 = X_1$.

The same procedure can be followed to prove the backward implication (singular M matrix $A \Leftarrow M^{-}A$ singular M matrix), and also in the case of nonsingular M matrices.

Corollary B.2. *If* A *is a singular M matrix, it has a regular splitting, see B.3, and* $\rho(M^{-}N) = 1$.

Proof: if A is a singular M matrix $\iff M^{-}A$ is a singular M matrix. So, $M^{-}A = I - M^{-}N$ must fulfill with $M^{-}A = \rho(M^{-}A)I - M^{-}N$. Thus, $\rho(M^{-}N) = 1$.

C THE BASIC REPRODUCTION NUMBER

The disease transmission model is written as follows,

$$\dot{x}_i = \mathcal{F}_i(x) - \mathcal{V}_i(x) = \mathcal{F}_i(x) - (\mathcal{V}_i^{-}(x) - \mathcal{V}_i^{+}(x)) \quad i = 1, \dots n \tag{12}$$

where $x = (x_1, \dots, x_n)^t : x_i \geqslant 0$ represents the population size in the block i (the first m blocks will represent the population that firstly suffer from the disease). $\mathcal{F}_i(x)$ is the new infection appearance rate in the block i, and $\mathcal{V}_i^{-}(x)$ ($\mathcal{V}_i^{+}(x)$) express how the population is going out (in) into the block i. Let's define $\mathbf{X}_s$ as the set of free disease states,

$$\mathbf{X}_s = \{x \geqslant 0 | \, x_i = 0, \, i = 1, \dots, m\},$$

so if the system remains in a free disease state, it is not possible a infected population growth because the first m compartments are empty.

The vectors $\mathcal{F}(x)$, $\mathcal{V}_i^{+}(x)$, $\mathcal{V}_i^{-}(x)$ must accomplish the next conditions:

- $x \geqslant 0 \Rightarrow \mathcal{F}(x), \mathcal{V}_i^{+}(x), \mathcal{V}_i^{-}(x) \geqslant 0$.
- If the block i is empty, there is no leaving population, that is: $x_i = 0 \Rightarrow V_i^{-}(x) = 0$.
- $\mathcal{F}_i(x) = 0$ if $i > m$
- $x \in \mathbf{X}_s \Rightarrow \mathcal{F}_i(x), V_i^{+}(x), V_i^{-}(0) = 0 : i = 1, \dots, m$
- if $\mathcal{F} = 0$, then the system's eigenvalues will have negative real parts.

Considering that the system stands in the DFE x_0, the system 12 can be linearized around x_0 by using the Taylor approximation method,

$$\dot{x}_i \approx \left(\frac{d\mathcal{F}_i(x)}{dx_j} - \frac{d\mathcal{V}_i(x)}{dx_j} \right) \Big|_{x_0} (x - x_0) \tag{13}$$

and the equation 13 can be rewritten as,

$$\dot{x} \approx \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix} - \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix} \tag{14}$$

where F and V are matrices with $m \times m$ dimension and they represent the derivatives, evaluated in x_0, of $\mathcal{F}_i$ and $\mathcal{V}_i$, respectively, when $1 \leqslant i, j \leqslant m$.

It can be easily proven that F is non-negative by applying Euler approximation,

$$F = \frac{d\mathcal{F}_i}{dx_j}\Big|_{x_0} \approx \lim_{h\to 0^+} \frac{\mathcal{F}_i(x_0 + he_j) - \mathcal{F}_i(x_0)}{h} = \lim_{h\to 0^+} \frac{\mathcal{F}_i(x_0 + he_j)}{h} \geqslant 0$$

where $e_j = \{e_i | 1 \leqslant i \leqslant m\}$ is a vector with a dimension m which value is equal to 1 when $i = j$, otherwise it is equal to 0. Regarding the V matrix it is a non-singular M matrix (see appendix B to know more about this type of matrices), that is,

$$V = \frac{d\mathcal{V}_i}{dx_j}\Big|_{x_0} \approx \lim_{h\to 0^+} \frac{\mathcal{V}_i(x_0 + he_j) - \mathcal{V}_i(x_0)}{h} = \lim_{h\to 0^+} \frac{\mathcal{V}_i^-(x_0 + he_j) - \mathcal{V}_i^+(x_0 + he_j)}{h}$$

Considering the first m compartment and the second condition that matrices from 12 must fulfill ($x_i = 0 \Rightarrow V_i^-(x) = 0$),

$$V = \lim_{h\to 0^+} \frac{1}{h} \begin{pmatrix} \mathcal{V}_1(h, 0, \dots) & -\mathcal{V}_1^+(0, h, \dots) & \dots \\ -\mathcal{V}_2^+(h, 0, \dots) & \mathcal{V}_2(0, h, \dots) & \dots \\ \vdots & \vdots & \ddots \end{pmatrix}$$

so V has the Z sign pattern. As consequence of the 5th condition, V's eigenvalues will have a positive real part, and therefore V is a non-singular M matrix.

The DFE x_0 is asymptotically stable if the real part of the eigenvalues of the system, given by 14, are negative. In contrast, if the eigenvalues have a positive real part x_0 will be unstable. The subsystem defined by $-J_3 - J_4$ has eigenvalues with negative real part (see the 5th condition that systems like 12 must fulfill), so the system's stability depends on the subsystem defined by $V - F$. The following theorem defines the basic reproduction number $\mathcal{R}_0$ which is a threshold for the system stability, and it is consequence of $V - F$ stability analysis.

Theorem C.1. *[12] The basic reproduction number $\mathcal{R}_0$ is equal to the spectral radius of V^-F ($\mathcal{R}_0 = \rho(V^-F)$). The system will be locally asymptotically stable around x_0 if $\mathcal{R}_0 < 1$, otherwise if $\mathcal{R}_0 > 1$ unstable.*

Proof: to create the nexus between $\mathcal{R}_0$ and $F - V$ stability, the subsystem will be rewritten as $J = V - F$, which has a Z sing pattern, and definitions and theorems from appendix B will be used. Moreover, the proof will be divided in two steps; they will prove why $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 0$ implies stability and unstability, respectively.

- Let's consider that $F - V$ is asymptotically stable, so J has eigenvalues with positive real parts. Since J has Z sing pattern and eigenvalues with positive real part, it is a nonsingular M matrix, see Theorem B.1; J can be rewritten as $J = sI - P$ where $s > \rho(P)$.
  By multiplying J with V^- (the inverse of V exists and $V^-1 \geqslant 0$ because it is a nonsingular M matrix), $V^-J = I - V^-F$ is obtained. Since J is nonsingular, V^-J is nonsingular, see Corollary B.1, and $\rho(V^-F) > 1$.

- Let's consider that $F - V$ has an eigenvalue which real part is equal to zero. Since J has a Z sing pattern and eigenvalues with zero real part, it is a singular M matrix, see Theorem B.2; J can be rewritten as $J = \rho(P)I - P$.
  By multiplying J with V^-, $V^-J = I - V^-F$ is obtained. Since J is singular, V^-J is singular, see Corollary B.1, and $\rho(V^-F) = 1$. Therefore, when $\rho(V^-F) = 1$ the system might be unstable (it depends of the multiplicity of eigenvalues with zero real part), and unstable when $\rho(V^-F) < 1$.

D $V^{-}F$'S SPECTRAL RADIUS

This section will focus on explaining the steps followed to obtain the spectral radius of $V^{-}F$, since V and F matrices dimensions are 3x3 and they contain considerable variables and the procedure might be tricky. Firstly, the inverse matrix V^{-} of V and the product $V^{-}F$ will be calculated. Then, $V^{-}F$ eigenvalues will be obtained and determined which of them will have the maximum absolute value.

The matrix F and V are the following ones,

$$F = \left(\begin{array}{ccc} \beta_e S(1-p_1) & 0 & S(p_2\beta_a + (1-p_2)\beta_s)(1-p_1) \\ \beta_e S p_1 & 0 & S(p_2\beta_a + (1-p_2)\beta_s)p_1 \\ 0 & 0 & 0 \end{array} \right)\Bigg|_{P_{dfe}},$$

$$V = \left(\begin{array}{ccc} \mu+\sigma & 0 & 0 \\ 0 & (\mu+\sigma+\gamma p_2) & 0 \\ -\sigma & -\sigma(1-p_2) & \mu+\alpha(1-p_2)+\gamma \end{array} \right)\Bigg|_{P_{dfe}}$$

Considering that the inverse matrix is defined as

$$V = \frac{V^T}{\det(V)},$$

let's calculate the determinant of V;

$$\det(V) = (\mu+\sigma)(\mu+\sigma+p_2\gamma)(\mu+\alpha(1-p_2)+\gamma)$$

and the adjugate of the matrix V,

$$V^T = \left(\begin{array}{ccc} (\mu+\sigma+p_2\gamma)(\mu+\alpha(1-p_2)+\gamma) & 0 & 0 \\ 0 & (\mu+\sigma)(\mu+\alpha(1-p_2)+\gamma) & 0 \\ \sigma(\mu+\sigma+p_2\gamma) & \sigma(\mu+\sigma)(1-p_2) & (\mu+\sigma)(\mu+\sigma+p_2\gamma) \end{array} \right)$$

so the inverse matrix is the following one,

$$V^{-} = \left(\begin{array}{ccc} (\mu+\sigma)^{-1} & 0 & 0 \\ 0 & (\mu+\sigma+p_2\gamma)^{-1} & 0 \\ \sigma\left[(\sigma+\mu)(\mu+\alpha(1-p_2)+\gamma)\right]^{-1} & \sigma(1-p_2)\left[(\mu+\sigma+\gamma p_2)(\mu+\alpha(1-p_2)+\gamma)\right]^{-1} & (\mu+\alpha(1-p_2)+\gamma)^{-1} \end{array} \right)$$

Now, let's calculate the product $M = V^{-}F$,

$$M_{11} = \beta_e S(1-p_1)(\mu+\sigma)^{-1}, \quad M_{12} = 0, \quad M_{13} = S(p_2\beta_a + (1-p_2)\beta_s)(1-p_1)(\mu+\sigma)^{-1},$$

$$M_{21} = \beta_e S p_1(\mu+\sigma+p_2\gamma)^{-1}, \quad M_{22} = 0, \quad M_{23} = S(\beta_a p_2 + (1-p_2)\beta_s)p_1(\mu+\sigma+p_2\gamma)^{-1},$$

$$M_{31} = \beta_e S\sigma(\mu+\alpha(1-p_2)+\gamma)^{-1}\left[(1-p_1)(\sigma+\mu)^{-1} + p_1(1-p_2)(\mu+\sigma+p_2\gamma)^{-1}\right], \quad M_{32} = 0,$$

$$M_{32} = S(p_2\beta_a + (1-p_2)\beta_s)\sigma(\mu+\alpha(1-p_2)+\gamma)^{-1}\left[(1-p_1)(\sigma+\mu)^{-1} + p_1(1-p_2)(\mu+\sigma+p_2\gamma)^{-1}\right].$$

To make easier the calculation of the eigenvalues, the next change of variables are proposed,

$$a = (\mu+\sigma)^{-1}, \quad b = (\mu+\alpha(1-p_2)+\gamma)^{-1}, \quad c = (\mu+\sigma+p_2\gamma)^{-1}, \quad d = S(p_2\beta_a + (1-p_2)\beta_s), \quad e = \beta_e S$$

so the eigenvalues are obtained by solving the next equation,

$$-\lambda \begin{vmatrix} ae(1-p_1)-\lambda & ad(1-p_1) \\ ebc\sigma\,[a(1-p_1)+cp_1(1-p_2)] & bd\sigma\,[a(1-p_1)+cp_1(1-p_2)]-\lambda \end{vmatrix} = 0$$

$$\Rightarrow -\lambda^2(\lambda-(ae(1-p_1)+bd\sigma\,[a(1-p_1)+cp_1(1-p_2))])) = 0$$

$$\Rightarrow \lambda = 0,\ ae(1-p_1)+bd\sigma(a(1-p_1)+cp_1(1-p_2))$$

and the spectral radius,

$$\rho(V^{-}F) = \frac{\beta_e S(1-p_1)}{\mu+\sigma} + \frac{S\sigma(p_2\beta_a+(1-p_2)\beta_s)}{\mu+\alpha(1-p_2)+\gamma}\left[\frac{1-p_1}{\mu+\sigma}+\frac{p_1(1-p_2)}{\mu+\sigma+p_2\gamma}\right]\Bigg|_{S=\Lambda/\mu}$$

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