Basic reproduction number in mathematical epidemiology

Gladstone Thabo Madito (gladstone@aims.ac.za)
African Institute for Mathematical Sciences (AIMS)

Supervised by: Prof. Jacek Banasiak
University of Pretoria, South Africa

22 September 2020

Submitted in partial fulfillment of a structured masters degree at AIMS South Africa

African Institute for Mathematical Sciences
SOUTH AFRICA

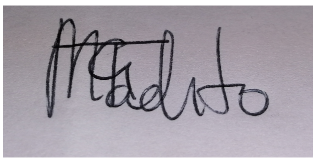
Abstract

Mathematical and computational techniques used to study the transmission of infectious diseases are effective tools in epidemiological modelling. Theoretical results that are obtained from the investigation of mathematical models are often beneficial to our understanding of the dynamics of a disease. The concept of the basic reproduction number, $\mathcal{R}_0$, serves as a powerful tool in determining whether a disease will spread in the population or not. We apply two methods to an epidemiological model and obtain two equivalent threshold conditions, for which a disease will not spread into the population.

Keywords: Metzler matrix, reproduction number, Lyapunov function, stability, next generation matrix, spectral radius

Declaration

I, the undersigned, hereby declare that the work contained in this research project is my original work, and that any work done by others or by myself previously has been acknowledged and referenced accordingly.



Gladstone Thabo Madito, 22 September 2020

Contents

1. Introduction

The prevalence of disease outbreaks has led to a considerable interest in the study and control of infectious diseases. An epidemiological understanding of the main features of the transmission of infectious diseases in communities, regions and countries can assist in designing practical approaches to control the spread of these diseases. Mathematical models and computer simulations analysing the dynamics of certain diseases (Malaria, Measles, HIV/AIDS, etc. see (Hethcote, 2000)) have been developed and have become important theoretical and empirical tools in epidemiological modelling.

Formulation of models describing the spread of infectious diseases involves assumptions specific to the disease, such as age, spatial location or behaviour. Individuals within the population are grouped into sub-populations or compartments/classes based on whether they are susceptible to the disease, have had sufficient contact with an infected individual and have become exposed to the disease or whether they are infected and capable of infecting others or they have recovered from the disease. Mathematical models that group individuals in terms of susceptible, exposed, infectious and recovered compartments are called S-E-I-R models and are usually expressed by systems of differential equations describing the evolution of the number of individuals in these compartments. Parameters such as the transmission/infection rates, death rates and transition rates are assumed to be the same for individuals within a compartment but may be different from compartment to compartment, that is, individual in the same compartment transmit, die and transition to other compartments at the same rate, but these rates may not be the same between compartments (Watmough and Van den Driessche, P., 2002).

Analysis of these models yields conceptual results which contribute to identifying key parameters that can be determined or estimated from collected data relating to the disease. We restrict our attention to one of the conceptual results that can be obtained from the investigation of dynamical systems that arise from epidemiological modelling, called the basic reproduction number, $\mathcal{R}_0$, which is defined as the expected number of secondary infections that are produced in a completely susceptible population by an infected individual during their entire period of infectiousness (variations of this definition are given in these papers (Dietz, 1993), (Watmough and Van den Driessche, P., 2002) and (Perasso, 2018)). A brief history of the reproduction number is given in (Heesterbeek, 2002), for interested readers.

The reproduction number is related to the stability of a steady, or equilibrium state of an epidemiological dynamical system called the Disease Free Equilibrium (DFE), which is defined as an equilibrium in the absence of the disease. According to the definition of $\mathcal{R}_0$, it is expected that if $\mathcal{R}_0 < 1$, the disease cannot spread in the population and for $\mathcal{R}_0 > 1$, the disease is able to spread, leading to an epidemic. Given the usefulness of the reproduction number in controlling the spread of infection, developing methods or approaches to obtain it is important, hence we consider two of these approaches. The first is discussed in (Kamgang and Sallet, 2008), which exploits the properties of Metzler matrices, i.e matrices whose off diagonal entries are non-negative, and the second approach, discussed in (Watmough and Van den Driessche, P., 2002), uses the concept of the next generation matrix to define $\mathcal{R}_0$ and hence determine the stability of the DFE. The DFE is asymptotically stable if the introduction of a "small" number of infectives in a completely susceptible population will, without any special intervention, not result in the spread of the disease.

We provide a survey of basic concepts of differentiability, non-negative matrices and spectral radius, used throughout the essay and we give a formal definition of stability, along with the stability of Metzler matrices and their relation to dynamical systems in Chapter 2. In Chapter 3, we consider the block decomposition and regular splitting of a Metzler matrix together with related theorems. A general system of ordinary differential equations (ODEs) that arises in epidemiological modelling is considered in Chapter 4, where we encounter the concept of the next generation matrix and an application of the two approaches mentioned above to compute the reproduction number.

2. Preliminaries

This section provides some definitions for the total differential, differentiability class and also for non-negative and Metzler matrices. The spectral bound and spectral radius of a matrix are also defined. Furthermore, a list of equivalent statements relating to Metzler stability and a definition of a regular splitting of a matrix is given.

Total differential and differentiability class

The following definitions are given in (Stewart, 2012) and (Warner, 1983).

2.0.1 Definition. Let f be a function $f : U \to \mathbb{R}^m$ such that $U \subseteq \mathbb{R}^n$ then

(a) The total differential df of f is given by

$$df = \sum_{i=1}^{n} \frac{\partial f}{\partial x_i} dx_i$$

for $x = (x_1, x_2, ..., x_n) \in U$

(b) If $x_i = g_i(s)$ then

$$df = \left(\sum_{i=1}^{n} \frac{\partial f}{\partial x_i} \frac{dg_i}{ds} \right) ds$$

for $x = (x_1, x_2, ..., x_n) \in U$ and $s \in \mathbb{R}$

(c) f is of differentiability class C^k (f is C^k) if and only if the function f and the partial (ordinary for $U \subset \mathbb{R}$) derivatives $\frac{\partial^r f}{\partial x_i^r}$ exist and are all continuous, where k is a non-negative integer, $r = 1, 2, 3, ..., k-1, k$ and $x_i \in (x_1, x_2, ..., x_n)$. (A function f which is C^1 is said to be continuously differentiable)

We review some definitions and properties of the transpose, inverse, determinant, eigenvalue and eigenvector of a matrix, which are used throughout this work. All these definitions and properties are adopted from (Strang, 2011).

Basic concepts

2.0.2 Definition. Consider any real matrices (in $\mathbb{R}^{n\times n}$) $\boldsymbol{A} = (a_{ij})$, $\boldsymbol{B} = (b_{ij})$ and $\boldsymbol{M} = (m_{ij})$. Then

(a) The transpose of $\boldsymbol{A}$ is $\boldsymbol{A}^T = (a_{ji})$,

(b) $\boldsymbol{A}^{-1}$ is the inverse of $\boldsymbol{A}$ if and only if $\boldsymbol{A}\boldsymbol{A}^{-1} = \boldsymbol{A}^{-1}\boldsymbol{A} = \boldsymbol{I}$, where $\boldsymbol{I}$ is the identity matrix. We say that $\boldsymbol{A}$ is non-singular if and only if its inverse $\boldsymbol{A}^{-1}$ exists,

(c) A number λ (complex or real) is an eigenvalue of $\boldsymbol{M}$ if and only if $\det(\boldsymbol{M} - \lambda \boldsymbol{I}) = 0$,

(d) λ is an eigenvalue of $\boldsymbol{M}$ and a vector $\boldsymbol{x}$ is an associated eigenvector if and only if they satisfy the eigenvalue equation $\boldsymbol{M}\boldsymbol{x} = \lambda \boldsymbol{x}$.

Properties of matrices

(a) The transpose of $\boldsymbol{A}+\boldsymbol{B}$ is given by $(\boldsymbol{A}+\boldsymbol{B})^T = \boldsymbol{A}^T + \boldsymbol{B}^T$,

(b) The inverse of $\boldsymbol{AB}$ is given by $(\boldsymbol{AB})^{-1} = \boldsymbol{B}^{-1}\boldsymbol{A}^{-1}$,

(c) The determinant of the transpose of $\boldsymbol{M}^T$ is equal to the determinant of $\boldsymbol{M}$, that is, $\det(\boldsymbol{M}^T) = \det(\boldsymbol{M})$.

2.0.3 Example. Consider the following matrices

$$\boldsymbol{A} = \begin{pmatrix} 3 & 1 \\ 0 & -8 \end{pmatrix},\ \boldsymbol{B} = \begin{pmatrix} 3 & 2 \\ 5 & 0 \end{pmatrix},\ \boldsymbol{C} = \begin{pmatrix} 7 & 4 \\ 5 & 6 \end{pmatrix} \text{ and } \boldsymbol{M} = \begin{pmatrix} -1 & 0 & 0 \\ 0 & -2 & 1 \\ 7 & 0 & -9 \end{pmatrix}.$$

Then

(i) The transpose of $\boldsymbol{A}$ is given by $\boldsymbol{A}^T = \begin{pmatrix} 3 & 0 \\ 1 & -8 \end{pmatrix}$ and that of $\boldsymbol{B}$ is $\boldsymbol{B}^T = \begin{pmatrix} 3 & 5 \\ 2 & 0 \end{pmatrix}$. Also, the transpose of $\boldsymbol{C}$ is $\boldsymbol{C}^T = \begin{pmatrix} 7 & 5 \\ 4 & 6 \end{pmatrix}$ and $\boldsymbol{M}^T = \begin{pmatrix} -1 & 0 & 7 \\ 0 & -2 & 0 \\ 0 & 1 & -9 \end{pmatrix}$.

(ii) The sum $\boldsymbol{B}+\boldsymbol{C}$ is given by

$$\boldsymbol{B}+\boldsymbol{C} = \begin{pmatrix} 3 & 2 \\ 5 & 0 \end{pmatrix} + \begin{pmatrix} 7 & 4 \\ 5 & 6 \end{pmatrix} = \begin{pmatrix} 10 & 8 \\ 10 & 6 \end{pmatrix},$$

which yields

$$(\boldsymbol{B}+\boldsymbol{C})^T = \begin{pmatrix} 10 & 10 \\ 8 & 6 \end{pmatrix}.$$

However,

$$\boldsymbol{B}^T + \boldsymbol{C}^T = \begin{pmatrix} 3 & 5 \\ 2 & 0 \end{pmatrix} + \begin{pmatrix} 7 & 5 \\ 4 & 6 \end{pmatrix} = \begin{pmatrix} 10 & 10 \\ 8 & 6 \end{pmatrix},$$

therefore we obtain $(\boldsymbol{B}+\boldsymbol{C})^T = \boldsymbol{B}^T + \boldsymbol{C}^T$.

(iii) Consider $\boldsymbol{A}^{-1} = \begin{pmatrix} \frac{1}{3} & \frac{1}{24} \\ 0 & -\frac{1}{8} \end{pmatrix}$ and $\boldsymbol{B}^{-1} = \begin{pmatrix} 0 & \frac{1}{5} \\ \frac{1}{2} & -\frac{3}{10} \end{pmatrix}$. It follows from

$$\boldsymbol{AA}^{-1} = \begin{pmatrix} 3 & 1 \\ 0 & -8 \end{pmatrix}\begin{pmatrix} \frac{1}{3} & \frac{1}{24} \\ 0 & -\frac{1}{8} \end{pmatrix} = \boldsymbol{I} \quad \text{and} \quad \boldsymbol{A}^{-1}\boldsymbol{A} = \begin{pmatrix} \frac{1}{3} & \frac{1}{24} \\ 0 & -\frac{1}{8} \end{pmatrix}\begin{pmatrix} 3 & 1 \\ 0 & -8 \end{pmatrix} = \boldsymbol{I},$$

that $\boldsymbol{A}^{-1}$ is the inverse $\boldsymbol{A}$. Also, $\boldsymbol{B}^{-1}$ is the inverse of $\boldsymbol{B}$ since

$$\boldsymbol{BB}^{-1} = \begin{pmatrix} 3 & 2 \\ 5 & 0 \end{pmatrix}\begin{pmatrix} 0 & \frac{1}{5} \\ \frac{1}{2} & -\frac{3}{10} \end{pmatrix} = \boldsymbol{I} \quad \text{and} \quad \boldsymbol{B}^{-1}\boldsymbol{B} = \begin{pmatrix} 0 & \frac{1}{5} \\ \frac{1}{2} & -\frac{3}{10} \end{pmatrix}\begin{pmatrix} 3 & 2 \\ 5 & 0 \end{pmatrix} = \boldsymbol{I}.$$

(iv) The product $\boldsymbol{AB}$ is given by

$$\boldsymbol{AB} = \begin{pmatrix} 3 & 1 \\ 0 & -8 \end{pmatrix}\begin{pmatrix} 3 & 2 \\ 5 & 0 \end{pmatrix} = \begin{pmatrix} 14 & 6 \\ -40 & 0 \end{pmatrix}.$$

Consider

$$(\boldsymbol{AB})^{-1} = \begin{pmatrix} 0 & -\frac{1}{40} \\ \frac{1}{6} & \frac{7}{120} \end{pmatrix}.$$

If follows from

$$(\boldsymbol{AB})(\boldsymbol{AB})^{-1} = \begin{pmatrix} 14 & 6 \\ -40 & 0 \end{pmatrix} \begin{pmatrix} 0 & -\frac{1}{40} \\ \frac{1}{6} & \frac{7}{120} \end{pmatrix} = \boldsymbol{I},$$

and

$$(\boldsymbol{AB})^{-1}(\boldsymbol{AB}) = \begin{pmatrix} 0 & -\frac{1}{40} \\ \frac{1}{6} & \frac{7}{120} \end{pmatrix} \begin{pmatrix} 14 & 6 \\ -40 & 0 \end{pmatrix} = \boldsymbol{I},$$

that $(\boldsymbol{AB})^{-1}$ is the inverse of $\boldsymbol{AB}$. The product $\boldsymbol{B}^{-1}\boldsymbol{A}^{-1}$ is given by

$$\boldsymbol{B}^{-1}\boldsymbol{A}^{-1} = \begin{pmatrix} 0 & \frac{1}{5} \\ \frac{1}{2} & -\frac{3}{10} \end{pmatrix} \begin{pmatrix} \frac{1}{3} & \frac{1}{24} \\ 0 & -\frac{1}{8} \end{pmatrix} = \begin{pmatrix} 0 & -\frac{1}{40} \\ \frac{1}{6} & \frac{7}{120} \end{pmatrix},$$

that is,

$$(\boldsymbol{AB})^{-1} = \boldsymbol{B}^{-1}\boldsymbol{A}^{-1}.$$

(v) The determinant of $\boldsymbol{M}$ is given as

$$\det(\boldsymbol{M}) = \det \begin{pmatrix} -1 & 0 & 0 \\ 0 & -2 & 1 \\ 7 & 0 & -9 \end{pmatrix} = (-1)(-2)(-9) = -18,$$

and that of the transpose $\boldsymbol{M}^T$ is

$$\det(\boldsymbol{M}^T) = \det \begin{pmatrix} -1 & 0 & 7 \\ 0 & -2 & 0 \\ 0 & 1 & -9 \end{pmatrix} = (-1)(-2)(-9) = -18,$$

therefore we have $\det(\boldsymbol{M}^T) = \det(\boldsymbol{M})$.

(vi) Setting $\det(\boldsymbol{M} - \lambda\boldsymbol{I}) = 0$ leads to

$$\det(\boldsymbol{M} - \lambda\boldsymbol{I}) = \det \begin{pmatrix} -1-\lambda & 0 & 0 \\ 0 & -2-\lambda & 1 \\ 7 & 0 & -9-\lambda \end{pmatrix} = (-1-\lambda)(-2-\lambda)(-9-\lambda) = 0,$$

then the eigenvalues of $\boldsymbol{M}$ are $\lambda_1 = -1$, $\lambda_2 = -2$ and $\lambda_3 = -9$.

2.1 Non-negative and Metzler matrices

The definitions of non-negative and Metzler matrices along with those of the spectral bound and radius can be found in (Kamgang and Sallet, 2008).

2.1.1 Definition. Consider any real matrices (in $\mathbb{R}^{n\times n}$) $\boldsymbol{A} = (a_{ij})$, $\boldsymbol{B} = (b_{ij})$ and $\boldsymbol{M} = (m_{ij})$. Then

(a) $\boldsymbol{A} \leq \boldsymbol{B}$ if and only if $a_{ij} \leq b_{ij}$ for all pairs (i, j),

(b) $\boldsymbol{A} < \boldsymbol{B}$ if and only if $\boldsymbol{A} \leq \boldsymbol{B}$ and there exists at-least one pair (i, j), such that $a_{ij} \neq b_{ij}$,

(c) $\boldsymbol{A} << \boldsymbol{B}$ if and only if $a_{ij} < b_{ij}$ for all pairs (i, j),

(d) $\boldsymbol{A}$ is non-negative if and only if $\boldsymbol{A} \geq \boldsymbol{0}$, that is $a_{ij} \geq 0$ for all pairs (i, j),

(e) $\boldsymbol{A}$ is positive if and only if $\boldsymbol{A} >> \boldsymbol{0}$, that is $a_{ij} > 0$ for all pairs (i, j),

(f) $\boldsymbol{M}$ is Metzler if and only if its off-diagonal elements are non-negative, that is $m_{ij} \geq 0$ for all $i, j = 1, 2, ..., n$ such that $i \neq j$,

(g) $\boldsymbol{M}$ is asymptotically or Metzler stable if all of its eigenvalues have negative real parts.

2.1.2 Example. Consider the following matrices

$$\boldsymbol{A} = \begin{pmatrix} 3 & 1 \\ 0 & -8 \end{pmatrix}, \ \boldsymbol{B} = \begin{pmatrix} 3 & 2 \\ 5 & 0 \end{pmatrix}, \ \boldsymbol{C} = \begin{pmatrix} 7 & 4 \\ 5 & 6 \end{pmatrix} \text{ and } \boldsymbol{M} = \begin{pmatrix} -1 & 3 & 0 \\ 0 & 2 & 1 \\ 7 & 0 & -9 \end{pmatrix}.$$

Then

(i) It is clear that $\boldsymbol{B} \geq \boldsymbol{0}$, since the entries of $\boldsymbol{B}$ are non-negative. Also, all the entries of $\boldsymbol{C}$ are strictly positive, thus $\boldsymbol{C} >> \boldsymbol{0}$.

(ii) Comparing the entries of $\boldsymbol{A}$, $\boldsymbol{B}$ and $\boldsymbol{C}$, then we deduce that $\boldsymbol{A} < \boldsymbol{B}$, $\boldsymbol{B} < \boldsymbol{C}$ and $\boldsymbol{A} << \boldsymbol{C}$.

(iii) The matrix $\boldsymbol{M}$ is Metzler since all of its off-diagonal entries are non-negative.

(iv) $\boldsymbol{M}$ has eigenvalues $\lambda_1 = -1$, $\lambda_2 = -2$ and $\lambda_3 = -9$, the matrix $\boldsymbol{M}$ is Metzler stable since its eigenvalues are real and negative.

Spectral bound and radius

2.1.3 Definition. Let $\lambda_1, \lambda_2, ..., \lambda_{n-1}, \lambda_n$ (complex or real) be the eigenvalues of a matrix $\boldsymbol{M}$.

(a) Let $\Re(\lambda)$ denote the real part of a complex eigenvalue λ. The spectral bound (stability modulus) $\alpha(\boldsymbol{M})$ of $\boldsymbol{M}$ is defined as

$$\alpha(\boldsymbol{M}) = \max\{\Re(\lambda_1), \Re(\lambda_2), ..., \Re(\lambda_{n-1}), \Re(\lambda_n)\},$$

that is, it is the greatest real part of the eigenvalues of $\boldsymbol{M}$.

(b) The spectral radius $\rho(\boldsymbol{M})$ of $\boldsymbol{M}$ is defined as

$$\rho(\boldsymbol{M}) = \max\{|\lambda_1|, |\lambda_2|, ..., |\lambda_{n-1}|, |\lambda_n|\},$$

that is, it is the largest absolute value of the eigenvalues of $\boldsymbol{M}$.

2.1.4 Example. Consider the matrices $\boldsymbol{M_1}$ and $\boldsymbol{M_2}$ given by

$$\boldsymbol{M_1} = \begin{pmatrix} -2 & 3 & 0 \\ 1 & -6 & 0 \\ 7 & 0 & -1 \end{pmatrix} \text{ and } \boldsymbol{M_2} = \begin{pmatrix} 3 & 0 & 9 \\ 0 & -1 & -4 \\ 0 & 1 & -1 \end{pmatrix}.$$

Then from the equation $\det(\boldsymbol{M_1} - \lambda \boldsymbol{I}) = 0$, we obtain the eigenvalues of $\boldsymbol{M_1}$ as $\lambda_1 = -4 + \sqrt{7}i$, $\lambda_2 = -4 - \sqrt{7}i$ and $\lambda_3 = -1$. Hence, the spectral bound is given as

$$\alpha(\boldsymbol{M_1}) = \max\{\Re(-4 + \sqrt{7}i), \Re(-4 - \sqrt{7}i), \Re(-1)\} = \max\{-4, -4, -1\} = -1,$$

and the spectral radius

$$\rho(\boldsymbol{M_1}) = \max\{|-4 + \sqrt{7}i|, |-4 - \sqrt{7}i|, |-1|\} = \max\{\sqrt{65}, \sqrt{65}, 1\} = \sqrt{65}.$$

Similarly from the equation $\det(\boldsymbol{M_2} - \lambda \boldsymbol{I}) = 0$, the eigenvalues of $\boldsymbol{M_2}$ are $\lambda_1 = 3$, $\lambda_2 = -1 + 2i$ and $\lambda_3 = -1 - 2i$. Therefore, the spectral bound is given as

$$\alpha(\boldsymbol{M_2}) = \max\{\Re(3), \Re(-1 + 2i), \Re(-1 - 2i)\} = \max\{3, -1, -1\} = 3,$$

and the spectral radius

$$\rho(\boldsymbol{M_2}) = \max\{|3|, |-1 + 2i|, |-1 - 2i|\} = \max\{3, \sqrt{5}, \sqrt{5}\} = 3.$$

2.2 Stability

We provide several definitions related to the stability of an equilibrium point and state the Lyapunov stability theorem then consider the concept of Metzler stability.

2.2.1 Theorem. *(Glendinning, 1994) (Local existence and uniqueness) Suppose*

$$\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x}), \quad \boldsymbol{x} \in U \subset \mathbb{R}^n, \tag{2.2.1}$$

and $\boldsymbol{f} : U \to \mathbb{R}^n$ is continuously differentiable. Then there exists $t_1, t_2 > 0$ such that a solution $\boldsymbol{x}(t)$ with an initial value of $\boldsymbol{x}(t_0) = \boldsymbol{x}_0$ exists and is unique for all $t \in (t_0 - t_1, t_0 + t_2)$.

From now on we consider solutions $\boldsymbol{x}(t)$ of Equation (2.2.1) which are defined on U for all $t \geq 0$. Here we define $\mathbb{R}^n_+$ as $\mathbb{R}^n_+ = \{\boldsymbol{x} \in \mathbb{R}^n | \boldsymbol{x} \geq 0\}$.

2.2.2 Definition. (Glendinning, 1994) The solutions $\boldsymbol{x}(t)$ of Equation (2.2.1) define a continuous function $\boldsymbol{\psi} : U \times \mathbb{R}_+ \to \mathbb{R}^n$ such that $\boldsymbol{\psi}(\boldsymbol{x}, t)$ is a solution of $\dot{\boldsymbol{\psi}}(\boldsymbol{x}, t) = \boldsymbol{f}(\boldsymbol{\psi}(\boldsymbol{x}, t))$, with $\boldsymbol{\psi}(\boldsymbol{x}(t), 0) = \boldsymbol{x}(t)$, for all $t \geq 0$. That is, the solution $\boldsymbol{x}(t)$, with the initial condition $\boldsymbol{x}(0) = \boldsymbol{x}_0$ is $\boldsymbol{\psi}(\boldsymbol{x}_0, t)$. The function $\boldsymbol{\psi}(\boldsymbol{x}, t)$ is called the flow of Equation (2.2.1) on U.

2.2.3 Definition. (Glendinning, 1994) A point $\boldsymbol{x}_e$ is an equilibrium point of Equation (2.2.1) if $\boldsymbol{f}(\boldsymbol{x}_e) = \boldsymbol{0}$. It follows that $\boldsymbol{x}_e$ is a fixed point of the flow, that is, $\boldsymbol{\psi}(\boldsymbol{x}_e, t) = \boldsymbol{x}_e$ for all $t \geq 0$.

2.2.4 Definition. (Glendinning, 1994) A set U is forward (positive) invariant if and only if for any $\boldsymbol{x} \in U$, $\boldsymbol{\psi}(\boldsymbol{x}, t) \in U$ for every $t > 0$.

The following defines three types of stability of an equilibrium point.

2.2.5 Definition. (Glendinning, 1994) Let $\boldsymbol{x}_e$ be an equilibrium point of Equation (2.2.1) in a forward invariant set U.

(i) $\boldsymbol{x}_e$ is Lyapunov stable if and only if for all $\epsilon > 0$, there exists $\delta > 0$ such that $|\boldsymbol{x}_e - \boldsymbol{\psi}(\boldsymbol{x}, t)| < \epsilon$ whenever $|\boldsymbol{x}_e - \boldsymbol{x}| < \delta$ for every $t \geq 0$.

(ii) $\boldsymbol{x}_e$ is quasi-asymptotically stable if and only if there exists $\delta > 0$ such that if $|\boldsymbol{x}_e - \boldsymbol{x}| < \delta$ then $|\boldsymbol{x}_e - \boldsymbol{\psi}(\boldsymbol{x}, t)| \to 0$ as $t \to \infty$.

(iii) $\boldsymbol{x}_e$ is asymptotically stable if and only if it is both Lyapunov and quasi-asymptotically stable.

2.2.6 Remark. A description of Lyapunov stability is that flows that start at points near an equilibrium point remain nearby. If the flows that start near an equilibrium point eventually tend to the point, then the point is quasi-asymptotically stable. Therefore, an equilibrium point is asymptotically stable if flows that start nearby remain nearby and eventually tend to the point.

Suppose $\boldsymbol{x}_e$ is an equilibrium point of $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$. Let $\boldsymbol{z} = \boldsymbol{x} - \boldsymbol{x}_e$ such that $\dot{\boldsymbol{z}} = \boldsymbol{f}(\boldsymbol{z} + \boldsymbol{x}_e) =: \boldsymbol{f}(\boldsymbol{z})$ and $\boldsymbol{z} = \boldsymbol{0}$ is an equilibrium point of $\dot{\boldsymbol{z}} = \boldsymbol{f}(\boldsymbol{z})$. It follows that $\boldsymbol{z} = \boldsymbol{0}$ is asymptotically stable if and only if $\boldsymbol{x} = \boldsymbol{x}_e$ is asymptotically stable (Braun, 1993). Therefore we can consider the asymptotic stability of the origin $\boldsymbol{z} = \boldsymbol{0}$ without loss of generality. Taylor expanding the system $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$ at $\boldsymbol{x} = \boldsymbol{x}_e$ yields

$$\boldsymbol{f}(\boldsymbol{x}) = \boldsymbol{f}(\boldsymbol{x_e}) + \frac{\partial \boldsymbol{f}_i}{\partial x_j}(\boldsymbol{x_e})(\boldsymbol{x} - \boldsymbol{x_e}) + O(|\boldsymbol{x} - \boldsymbol{x}_e|).$$

By definition $\boldsymbol{f}(\boldsymbol{x_e}) = \boldsymbol{0}$, so with $\boldsymbol{z} = \boldsymbol{x} - \boldsymbol{x}_e$, each component of $\dot{\boldsymbol{z}}$ is given by

$$\dot{\boldsymbol{z}}_i = \boldsymbol{f}_i(\boldsymbol{z}) = \frac{\partial \boldsymbol{f}_i}{\partial x_j}(\boldsymbol{x}_e)\boldsymbol{z}_i + O(|\boldsymbol{z}|).$$

Neglecting $O(|\boldsymbol{z}|)$ yields the linear system,

$$\dot{\boldsymbol{z}} = \boldsymbol{J}\boldsymbol{z} \quad \text{with} \quad \boldsymbol{J}_{ij} = \frac{\partial \boldsymbol{f}_i}{\partial x_j}(\boldsymbol{x}_e),$$

where the matrix $\boldsymbol{J}$ is called the Jacobian. The transformation of Equation $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$ to the linear system $\dot{\boldsymbol{z}} = \boldsymbol{J}\boldsymbol{z}$ is called linearization.

2.2.7 Definition. (Glendinning, 1994) Suppose that the origin $\boldsymbol{x} = \boldsymbol{0}$, is an equilibrium point of Equation (2.2.1). Let U be an open neighbourhood of the origin and $\boldsymbol{V} : cl(U) \to \mathbb{R}^n$ be a continuously differentiable function. Then the evolution of $\boldsymbol{V}$ is defined as

$$\dot{\boldsymbol{V}} = \frac{d\boldsymbol{V}}{dt} = \dot{\boldsymbol{x}}^T \nabla \boldsymbol{V} = \boldsymbol{f}(\boldsymbol{x})^T \nabla \boldsymbol{V} = \sum_{i=1}^{n} \boldsymbol{f}_i(\boldsymbol{x}) \frac{\partial \boldsymbol{V}}{\partial x_i}, \tag{2.2.2}$$

where $cl(U)$ is the closure of the set U and the subscripts i denote the components of $\boldsymbol{f}(\boldsymbol{x})$ and $\boldsymbol{x}$. We say that $\boldsymbol{V}$ is Lyapunov function on U if and only if $\boldsymbol{V}$ is a continuously differentiable function on $cl(U)$ and

(i) $\boldsymbol{V}(\boldsymbol{x}) \geq \boldsymbol{0}$ for all $\boldsymbol{x} \in cl(U)$ and $\boldsymbol{V}(\boldsymbol{x}) = \boldsymbol{0}$ if and only if $\boldsymbol{x} = \boldsymbol{0}$,

(ii) $\dot{\boldsymbol{V}} \leq \boldsymbol{0}$ for all $\boldsymbol{x} \in U$.

2.2.8 Theorem. *(a proof of this theorem is given in (Glendinning, 1994)) Suppose $\boldsymbol{x}_e = \boldsymbol{0}$, is an equilibrium point of Equation (2.2.1) and a Lyapunov function $\boldsymbol{V}$ can be defined on U. If $\dot{\boldsymbol{V}}(\boldsymbol{x}) < \boldsymbol{0}$ for every $\boldsymbol{x} \in U \backslash \{\boldsymbol{0}\}$, then $\boldsymbol{x}_e = \boldsymbol{0}$ is asymptotically stable.*

2.3 Metzler stability

The following is a list of equivalent statements related to the stability of a Metzler matrix from a wide range of statements given in (Berman and Plemmons, 1994), (Varga, 2000) and (Horn and Johnson, 1991). Those that are stated here play an important role in the derivation of the next generation matrix, which is related to the reproduction number $\mathcal{R}_0$.

2.3.1 Proposition. (see Theorem 1.1 in (Berman and Plemmons, 1994)) If $\boldsymbol{G}$ is a non-negative matrix, then there is a non-negative vector $\boldsymbol{x}$ associated to $\rho(\boldsymbol{G})$.

2.3.2 Proposition. (see Theorem 3.15 in (Varga, 2000) for proof) Let $\boldsymbol{G} \geq \boldsymbol{0}$, then $1 > \rho(\boldsymbol{G})$ if and only if $\boldsymbol{I} + \boldsymbol{G} + \boldsymbol{G}^2 + \ldots$ converges to $(\alpha \boldsymbol{I} - \boldsymbol{G})^{-1}$.

2.3.3 Proposition. (Theorem 3.16 in (Varga, 2000)), If $\boldsymbol{G} \in \mathbb{R}^{n \times n}$ such that $\boldsymbol{G} \geq \boldsymbol{0}$ and α is any positive real number, then the following statements are equivalent.

(a) $\alpha > \rho(\boldsymbol{G})$,

(b) $\alpha \boldsymbol{I} - \boldsymbol{G}$ is non-singular and $(\alpha \boldsymbol{I} - \boldsymbol{G})^{-1} \geq \boldsymbol{0}$.

Proof.
$(a) \to (b)$ Suppose $\alpha > \rho(\boldsymbol{G})$ and let $\boldsymbol{A} = \alpha \boldsymbol{I} - \boldsymbol{G}$. For λ such that $\boldsymbol{G}\boldsymbol{x} = \lambda \boldsymbol{x}$, we have $(\frac{\boldsymbol{G}}{\alpha})\boldsymbol{x} = (\frac{\lambda}{\alpha})\boldsymbol{x}$, since $|\frac{\boldsymbol{\lambda}}{\boldsymbol{\alpha}}| = \frac{|\lambda|}{\alpha}$, then this leads to $\rho(\frac{\boldsymbol{G}}{\alpha}) = \frac{\rho(\boldsymbol{G})}{\alpha}$. Hence, from $\alpha > \rho(\boldsymbol{G})$, we get $1 > \frac{\rho(\boldsymbol{G})}{\alpha}$, that is, $1 > \rho(\frac{\boldsymbol{G}}{\alpha})$.

Since $\frac{\boldsymbol{G}}{\alpha} \geq \boldsymbol{0}$, then by Proposition 2.3.2, the series $\boldsymbol{I} + \frac{\boldsymbol{G}}{\alpha} + \frac{\boldsymbol{G}^2}{\alpha^2} + \ldots$ converges to $(\boldsymbol{I} - \frac{\boldsymbol{G}}{\alpha})^{-1} \geq \boldsymbol{0}$. However, $\boldsymbol{A}$ can be rewritten as $\boldsymbol{A} = \alpha(\boldsymbol{I} - \frac{\boldsymbol{G}}{\alpha})$, therefore $\boldsymbol{A}^{-1} = \frac{1}{\alpha}(\boldsymbol{I} - \frac{\boldsymbol{G}}{\alpha})^{-1} \geq \boldsymbol{0}$, that is, $(\alpha \boldsymbol{I} - \boldsymbol{G})^{-1} \geq \boldsymbol{0}$.

$(b) \to (a)$ To prove the converse, assume $(\alpha \boldsymbol{I} - \boldsymbol{G})^{-1} \geq \boldsymbol{0}$ and let $\boldsymbol{x} \geq 0$ be an eigenvector of $\boldsymbol{G} \geq \boldsymbol{0}$, then by Proposition 2.3.1, we obtain $\boldsymbol{G}\boldsymbol{x} = \rho(\boldsymbol{G})\boldsymbol{x}$. This leads to $(\alpha \boldsymbol{I} - \boldsymbol{G})\boldsymbol{x} = (\alpha - \rho(\boldsymbol{G}))\boldsymbol{x}$, that is $(\alpha \boldsymbol{I} - \boldsymbol{G})^{-1}\boldsymbol{x} = \frac{\boldsymbol{x}}{\alpha - \rho(\boldsymbol{G})}$.

However, $(\alpha \boldsymbol{I} - \boldsymbol{G})^{-1} \geq \boldsymbol{0}$, therefore, $\frac{\boldsymbol{x}}{\alpha - \rho(\boldsymbol{G})} \geq \boldsymbol{0}$, which yields $\alpha - \rho(\boldsymbol{G}) > 0$, that is $\alpha > \rho(\boldsymbol{G})$. □

The following remark is a list of important results which are vital to the proof of Proposition 2.3.5 (see Proposition 2.5 and 2.6 of (Haddad et al., 2010), these results are stated in the book for essentially non-negative which are the same as the Metzler matrices in this work).

2.3.4 Remark. Consider a linear dynamical system

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{M}\boldsymbol{x}(t), \quad \text{such that} \quad \boldsymbol{x}(0) = \boldsymbol{x_0}, \quad t \geq 0, \tag{2.3.1}$$

where $\boldsymbol{x} \in \mathbb{R}^n_+$ and $\boldsymbol{M} \in \mathbb{R}^{n \times n}$, then Equation (2.3.1) has the solution $\boldsymbol{x}(t) = e^{t\boldsymbol{M}}\boldsymbol{x_0}$ for $t \geq 0$. Proposition 2.5 of (Haddad et al., 2010), proves that $\boldsymbol{M}$ is Metzler if and only if $e^{t\boldsymbol{M}}$ is non-negative for $t \geq 0$.

Let $\boldsymbol{M}$ be Metzler. The following statements are equivalent

(i) The equilibrium point $\boldsymbol{x}_e = \boldsymbol{0}$ of Equation (2.3.1) is asymptotically stable,

(ii) $\boldsymbol{M}$ is Metzler stable,

(iii) $\lim_{t\to\infty} e^{t\boldsymbol{M}} = \mathbf{0}$.

The equivalent statements above illustrate that the Metzler stability of $\boldsymbol{M}$ is equivalent to the asymptotic stability of the origin, the equilibrium point $\boldsymbol{x}_e = \mathbf{0}$ of the linearized system.

2.3.5 Proposition. Let $\boldsymbol{M} \in \mathbb{R}^{n\times n}$ be Metzler. The following are equivalent

(a) $\boldsymbol{M}$ is Metzler stable,

(b) There exists some vector $\boldsymbol{v} >> \mathbf{0}$ such that $\mathbf{0} >> \boldsymbol{M}\boldsymbol{v}$,

(c) $\boldsymbol{M}$ is non-singular such that $-\boldsymbol{M}^{-1} \geq \mathbf{0}$.

Proof.
$(a) \to (c)$ Assuming that $\boldsymbol{M}$ is Metzler stable, it follows from Remark 2.3.4 that $e^{t\boldsymbol{M}}$ is non-negative for $t \geq 0$, therefore $\int_0^t e^{s\boldsymbol{M}} ds \geq \mathbf{0}$.

Consider the exponential series

$$e^{t\boldsymbol{M}} = \sum_{n=0}^{\infty} \frac{(t\boldsymbol{M})^n}{n!} = \boldsymbol{I} + t\boldsymbol{M} + \frac{t^2\boldsymbol{M}^2}{2!} + \cdots .$$

We obtain

$$\int_0^t e^{s\boldsymbol{M}} ds = \int_0^t \Big(\sum_{n=0}^{\infty} \frac{(s\boldsymbol{M})^n}{n!} \Big) ds,$$

and integrating term-wise leads to

$$\int_0^t e^{s\boldsymbol{M}} ds = \sum_{n=0}^{\infty} \Big(\int_0^t \frac{s^n\boldsymbol{M}^n}{n!} ds \Big),$$

which is

$$\int_0^t e^{s\boldsymbol{M}} ds = \sum_{n=0}^{\infty} \left[\frac{s^{n+1}\boldsymbol{M}^n}{(n+1)n!} \right]_0^t \quad \text{or} \quad \int_0^t e^{s\boldsymbol{M}} ds = \sum_{n=0}^{\infty} \frac{t^{n+1}\boldsymbol{M}^n}{(n+1)!}.$$

Since $\boldsymbol{M}$ is non-singular, $\boldsymbol{M}^{-1}$ exists, so

$$\int_0^t e^{s\boldsymbol{M}} ds = \sum_{n=0}^{\infty} \frac{t^{n+1}\boldsymbol{M}^{-1}\boldsymbol{M}\boldsymbol{M}^n}{(n+1)!},$$

which leads to the equality

$$\int_0^t e^{s\boldsymbol{M}} ds = \boldsymbol{M}^{-1} \sum_{n=0}^{\infty} \frac{t^{n+1}\boldsymbol{M}^{n+1}}{(n+1)!}.$$

It follows that

$$\int_0^t e^{s\boldsymbol{M}} ds = \boldsymbol{M}^{-1} \Big(t\boldsymbol{M} + \frac{t^2\boldsymbol{M}^2}{2!} + \cdots \Big),$$

therefore, from

$$\int_0^t e^{s\boldsymbol{M}} ds = \boldsymbol{M}^{-1} \Big(-\boldsymbol{I} + \boldsymbol{I} + t\boldsymbol{M} + \frac{t^2\boldsymbol{M}^2}{2!} + \cdots \Big),$$

we obtain

$$\int_0^t e^{s\boldsymbol{M}} ds = \boldsymbol{M}^{-1} \Big(-\boldsymbol{I} + \sum_{n=0}^{\infty} \frac{t^n\boldsymbol{M}^n}{n!} \Big).$$

Consequently we obtain

$$\lim_{t\to\infty}\int_0^t e^{s\boldsymbol{M}}ds = \lim_{t\to\infty}\boldsymbol{M}^{-1}(e^{t\boldsymbol{M}}-\boldsymbol{I}),$$

that is,

$$\lim_{t\to\infty}\int_0^t e^{s\boldsymbol{M}}ds = \boldsymbol{M}^{-1}\lim_{t\to\infty}(e^{t\boldsymbol{M}}-\boldsymbol{I}).$$

Therefore Remark 2.3.4 (iii) leads to

$$\int_0^\infty e^{s\boldsymbol{M}}ds = \boldsymbol{M}^{-1}(\boldsymbol{0}-\boldsymbol{I}) \geq \boldsymbol{0},$$

hence $-\boldsymbol{M}^{-1} \geq \boldsymbol{0}$.

$(c) \to (b)$ Let $-\boldsymbol{M}^{-1} \geq \boldsymbol{0}$ and $\boldsymbol{u}$ be a positive vector such that $\boldsymbol{v} = -\boldsymbol{M}^{-1}\boldsymbol{u} >> \boldsymbol{0}$. Then, $\boldsymbol{Mv} = -\boldsymbol{u}$, which leads to $\boldsymbol{0} >> \boldsymbol{Mv}$, since $\boldsymbol{u} >> \boldsymbol{0}$.

$(b) \to (a)$ It should be clear that since $\boldsymbol{M}$ is Metzler then $\boldsymbol{M}^T$ is also Metzler. Now, consider the ODE

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{M}^T\boldsymbol{x}(t), \quad \text{such that} \quad \boldsymbol{x}(0) = \boldsymbol{x_0}, \quad t \geq 0, \tag{2.3.2}$$

where $\boldsymbol{x} \in \mathbb{R}^n_+$, $\boldsymbol{M} \in \mathbb{R}^{n\times n}$ and Equation (2.3.2) has the solution $\boldsymbol{x}(t) = e^{t\boldsymbol{M}^T}\boldsymbol{x_0}$ for $t \geq 0$. Assume $\boldsymbol{0} >> \boldsymbol{Mv}$ with $\boldsymbol{u} >> \boldsymbol{0}$ such that $\boldsymbol{v} = -\boldsymbol{M}^{-1}\boldsymbol{u} >> \boldsymbol{0}$.

Consider an open set $U \subset \mathbb{R}^n_+\backslash\{\boldsymbol{0}\}$ such that the function $V(\boldsymbol{x}) = \boldsymbol{v}^T\boldsymbol{x}$ is defined on $\boldsymbol{x} \in cl(U) \subset \mathbb{R}^n_+$. Since $\boldsymbol{v} >> \boldsymbol{0}$ and $\boldsymbol{x} \geq \boldsymbol{0}$, we obtain $V(\boldsymbol{x}) \geq \boldsymbol{0}$ on $\mathbb{R}^n_+$ and $V(\boldsymbol{x}) = \boldsymbol{0}$ if and only if $\boldsymbol{x} = \boldsymbol{0}$.

Furthermore, the evolution of $V(\boldsymbol{x})$ is given by $\dot{V}(\boldsymbol{x}) = \boldsymbol{v}^T\dot{\boldsymbol{x}}$, therefore $\dot{V}(\boldsymbol{x}) = \boldsymbol{v}^T\boldsymbol{M}^T\boldsymbol{x}$. This leads to $\dot{V}(\boldsymbol{x}) = (\boldsymbol{Mv})^T\boldsymbol{x}$, however, $\boldsymbol{0} >> \boldsymbol{Mv}$ and $\boldsymbol{x} >> \boldsymbol{0}$ for $\boldsymbol{x} \in U$, therefore $\dot{V}(\boldsymbol{x}) < \boldsymbol{0}$ on $\mathbb{R}^n_+\backslash\{\boldsymbol{0}\}$.

Therefore, by Theorem 2.2.8, $\boldsymbol{x_e} = \boldsymbol{0}$ is asymptotically stable and it follows from Remark 2.3.4 that $\boldsymbol{M}^T$ is Metzler stable. However, $\det(\boldsymbol{M}^T - \lambda\boldsymbol{I}) = \det(\boldsymbol{M}^T - \lambda\boldsymbol{I}^T)$, hence this leads to

$$\det(\boldsymbol{M}^T - \lambda\boldsymbol{I}) = \det\left((\boldsymbol{M} - \lambda\boldsymbol{I})^T\right).$$

From $\det(\boldsymbol{M} - \lambda\boldsymbol{I}) = \det\left((\boldsymbol{M} - \lambda\boldsymbol{I})^T\right)$, then we obtain

$$\det(\boldsymbol{M}^T - \lambda\boldsymbol{I}) = \det(\boldsymbol{M} - \lambda\boldsymbol{I}),$$

thus for $\det(\boldsymbol{M} - \lambda\boldsymbol{I}) = 0$, then $\boldsymbol{M}^T$ and $\boldsymbol{M}$ have the same eigenvalues, that is $\boldsymbol{M}$ is also Metzler stable. □

2.3.6 Proposition. Let $\boldsymbol{M} = (m_{ij})$ be a Metzler matrix. If $\boldsymbol{M}$ is Metzler stable then $\boldsymbol{M}$ has strictly negative diagonal entries, that is ($m_{ij} < 0$ for all $i = j$).

Proof. Let $\boldsymbol{v} >> \boldsymbol{0}$ such that $\boldsymbol{Mv} << \boldsymbol{0}$. which is possible by Proposition 2.3.5 (b), then each entry

$$(\boldsymbol{Mv})_i = \sum_{j=1}^n m_{ij}v_j < 0 \quad \text{for all} \quad i = 1, 2, 3, \ldots, n.$$

It follows that

$$0 > m_{11}v_1 + \sum_{j=2}^{n} m_{1j}v_j \quad \text{for} \quad i = 1,$$

however, every $m_{1j} \geq 0$ and $v_j > 0$, therefore

$$\sum_{j=2}^{n} m_{ij}v_j \geq 0 \quad \text{or} \quad m_{11}v_1 + \sum_{j=2}^{n} m_{1j}v_j \geq m_{11}v_1.$$

Thus $0 > m_{11}v_1$, which leads to $0 > m_{11}$. A similar argument for $i = 2, 3, \ldots, n$ is used to deduce $m_{ij} < 0$ for $i = j$, thus we obtain $m_{ij} < 0$ for all $i = j$. □

Regular splitting

2.3.7 Definition. (see Definition 3.2 in (Kamgang and Sallet, 2008)) We say that $\boldsymbol{M} = \boldsymbol{A} + \boldsymbol{N}$ is a regular splitting of a real Metzler matrix $\boldsymbol{M}$ if $\boldsymbol{A}$ is Metzler stable and $\boldsymbol{N}$ is a non-negative matrix ($\boldsymbol{N} \geq \boldsymbol{0}$).

2.3.8 Example. Consider a Metzler matrix $\boldsymbol{M}$ given by

$$\boldsymbol{M} = \begin{pmatrix} -1 & 3 & 4 \\ 10 & 0 & 1 \\ 7 & 3 & 1 \end{pmatrix}.$$

Then the splitting

$$\boldsymbol{M} = \begin{pmatrix} -2 & 3 & 0 \\ 1 & -6 & 0 \\ 7 & 0 & -1 \end{pmatrix} + \begin{pmatrix} 1 & 0 & 4 \\ 9 & 6 & 1 \\ 0 & 3 & 2 \end{pmatrix}$$

is a regular splitting, since $\boldsymbol{N} = \begin{pmatrix} 1 & 0 & 4 \\ 9 & 6 & 1 \\ 0 & 3 & 2 \end{pmatrix} \geq \boldsymbol{0}$ and $\boldsymbol{A} = \begin{pmatrix} -2 & 3 & 0 \\ 1 & -6 & 0 \\ 7 & 0 & -1 \end{pmatrix}$ has the eigenvalues $\lambda_1 = -4 + \sqrt{7}i$, $\lambda_2 = -4 - \sqrt{7}i$ and $\lambda_3 = -1$, which have negative real parts, therefore $\boldsymbol{A}$ is Metzler stable.

3. Metzler matrices

The Metzler stability of a block decomposed matrix and a regular splitting are considered. Also, some theorems and proofs which provide conditions for stability these matrices are given in this section.

3.1 Block decomposition

3.1.1 Lemma. The main-diagonal sub-matrices of a Metzler matrix $\boldsymbol{M}$ are Metzler.

Proof. Without loss of generality, consider a block decomposed Metzler matrix $\boldsymbol{M} \in \mathbb{R}^{n\times n}$ where $\boldsymbol{A} \in \mathbb{R}^{r\times r}$, $\boldsymbol{B} \in \mathbb{R}^{r\times n-r}$, $\boldsymbol{C} \in \mathbb{R}^{n-r\times r}$ and $\boldsymbol{D} \in \mathbb{R}^{n-r\times n-r}$ for $r \leq n$ such that $\boldsymbol{M}$ is given by:

$$\boldsymbol{M} = \begin{pmatrix} \boldsymbol{A} & \boldsymbol{B} \\ \boldsymbol{C} & \boldsymbol{D} \end{pmatrix}.$$

Let $M = \{m_{ij} \geq 0 \quad \text{for all} \quad i,j = 1,2,...,n \quad \text{such that} \quad i \neq j\}$ be the set of off-diagonal elements of $\boldsymbol{M}$. Consider the diagonal sub-matrix $\boldsymbol{A} = (a_{ij})$ then it is clear that $a_{ij} \in M$ for all $i,j = 1,2,...,r$ where $i \neq j$ then $a_{ij} \geq 0$ and similarly for $\boldsymbol{D} = (d_{ij})$ then $d_{ij} \in M$ for all $i,j = n-r, n-r+1, ..., n$ where $i \neq j$ then $d_{ij} \geq 0$. That is, the off-diagonal elements of $\boldsymbol{A}$ and $\boldsymbol{D}$ are non-negative, thus $\boldsymbol{A}$ and $\boldsymbol{D}$ are Metzler. □

3.1.2 Remark. We observe that $\boldsymbol{B}$ and $\boldsymbol{C}$ are off-diagonal sub-matrices of the Metzler matrix $\boldsymbol{M}$, therefore they only contain non-negative entries, that is $\boldsymbol{B} \geq \boldsymbol{0}$ and $\boldsymbol{C} \geq \boldsymbol{0}$.

3.1.3 Lemma. The main-diagonal sub-matrices of a Metzler stable matrix $\boldsymbol{M}$ are Metzler stable.

Proof. Consider a block decomposed Metzler matrix $\boldsymbol{M} \in \mathbb{R}^{n\times n}$ where $\boldsymbol{A} \in \mathbb{R}^{r\times r}$, $\boldsymbol{B} \in \mathbb{R}^{r\times n-r}$, $\boldsymbol{C} \in \mathbb{R}^{n-r\times r}$ and $\boldsymbol{D} \in \mathbb{R}^{n-r\times n-r}$ for $r \leq n$ such that $\boldsymbol{M}$ is given by:

$$\boldsymbol{M} = \begin{pmatrix} \boldsymbol{A} & \boldsymbol{B} \\ \boldsymbol{C} & \boldsymbol{D} \end{pmatrix}.$$

If $\boldsymbol{M}$ is Metzler stable then by Proposition 2.3.5 (b), there exists $\boldsymbol{v} >> \boldsymbol{0}$ in $\mathbb{R}^n_+$ where $\boldsymbol{v} = \begin{pmatrix} \boldsymbol{v_1} \\ \boldsymbol{v_2} \end{pmatrix}$ with $\boldsymbol{v_1} \in \mathbb{R}^r_+$ and $\boldsymbol{v_2} \in \mathbb{R}^{n-r}_+$ such that $\boldsymbol{0} >> \boldsymbol{M}\boldsymbol{v}$, this yields $\boldsymbol{0} >> \boldsymbol{A}\boldsymbol{v_1} + \boldsymbol{B}\boldsymbol{v_2}$ and $\boldsymbol{0} >> \boldsymbol{C}\boldsymbol{v_1} + \boldsymbol{D}\boldsymbol{v_2}$. However $\boldsymbol{B} \geq \boldsymbol{0}$ and $\boldsymbol{C} \geq \boldsymbol{0}$, thus $\boldsymbol{B}\boldsymbol{v_2} \geq \boldsymbol{0}$ or $\boldsymbol{A}\boldsymbol{v_1} + \boldsymbol{B}\boldsymbol{v_2} \geq \boldsymbol{A}\boldsymbol{v_1}$ which yields $\boldsymbol{0} >> \boldsymbol{A}\boldsymbol{v_1}$, similarly from $\boldsymbol{C}\boldsymbol{v_1} \geq \boldsymbol{0}$ we obtain $\boldsymbol{C}\boldsymbol{v_1} + \boldsymbol{D}\boldsymbol{v_2} \geq \boldsymbol{D}\boldsymbol{v_2}$ which is $\boldsymbol{0} >> \boldsymbol{D}\boldsymbol{v_2}$. Hence it follows from Proposition 2.3.5 (b), that the Metzler matrices $\boldsymbol{A}$ and $\boldsymbol{D}$ are Metzler stable. □

3.1.4 Theorem. *(This theorem is presented as Proposition 3.3 in (Kamgang and Sallet, 2008)) Consider a block decomposed Metzler matrix $\boldsymbol{M} \in \mathbb{R}^{n\times n}$ where $\boldsymbol{A} \in \mathbb{R}^{r\times r}$, $\boldsymbol{B} \in \mathbb{R}^{r\times n-r}$, $\boldsymbol{C} \in \mathbb{R}^{n-r\times r}$ and $\boldsymbol{D} \in \mathbb{R}^{n-r\times n-r}$ for $r \leq n$ such that $\boldsymbol{M}$ is given by:*

$$\boldsymbol{M} = \begin{pmatrix} \boldsymbol{A} & \boldsymbol{B} \\ \boldsymbol{C} & \boldsymbol{D} \end{pmatrix}.$$

then $\boldsymbol{M}$ is Metzler stable if and only if $\boldsymbol{A}$ and $\boldsymbol{D} - \boldsymbol{C}\boldsymbol{A}^{-1}\boldsymbol{B}$ are Metzler stable.

Proof. Let $\boldsymbol{M}$ be Metzler stable, Then there exists $\boldsymbol{v} >> \mathbf{0}$ in $\mathbb{R}^n_+$ where $\boldsymbol{v} = \begin{pmatrix} \boldsymbol{v_1} \\ \boldsymbol{v_2} \end{pmatrix}$ with $\boldsymbol{v_1} \in \mathbb{R}^r_+$ and $\boldsymbol{v_2} \in \mathbb{R}^{n-r}_+$ such that $\mathbf{0} >> \boldsymbol{Mv}$, this yields $\mathbf{0} >> \boldsymbol{Av_1} + \boldsymbol{Bv_2}$ and $\mathbf{0} >> \boldsymbol{Cv_1} + \boldsymbol{Dv_2}$.

We have shown that if $\boldsymbol{M}$ is Metzler stable then $\boldsymbol{A}$ and $\boldsymbol{D}$ are also Metzler stable, see Lemma 3.1.3, hence by Proposition 2.3.5 (c), there exists an inverse $\boldsymbol{A}^{-1}$ such that $-\boldsymbol{A}^{-1} \geq \mathbf{0}$ or $-\boldsymbol{CA}^{-1} \geq \mathbf{0}$ since $\boldsymbol{C} \geq \mathbf{0}$.

From $\mathbf{0} >> \boldsymbol{Av_1} + \boldsymbol{Bv_2}$ and $-\boldsymbol{CA}^{-1} \geq \mathbf{0}$ then $\mathbf{0} \geq -\boldsymbol{Cv_1} - \boldsymbol{CA}^{-1}\boldsymbol{Bv_2}$ therefore adding this to $\mathbf{0} >> \boldsymbol{Cv_1} + \boldsymbol{Dv_2}$ we obtain $\mathbf{0} >> \boldsymbol{Dv_2} - \boldsymbol{CA}^{-1}\boldsymbol{Bv_2}$ or $\mathbf{0} >> (\boldsymbol{D} - \boldsymbol{CA}^{-1}\boldsymbol{B})\boldsymbol{v_2}$, that is, $\boldsymbol{D} - \boldsymbol{CA}^{-1}\boldsymbol{B}$ is Metzler stable.

Conversely, suppose $\boldsymbol{A}$ and $\boldsymbol{D} - \boldsymbol{CA}^{-1}\boldsymbol{B}$ be Metzler stable, then there exists $\boldsymbol{v} >> \mathbf{0}$ in $\mathbb{R}^n_+$ where $\boldsymbol{v} = \begin{pmatrix} \boldsymbol{v_1} \\ \boldsymbol{v_2} \end{pmatrix}$ with $\boldsymbol{v_1} \in \mathbb{R}^r_+$ and $\boldsymbol{v_2} \in \mathbb{R}^{n-r}_+$ such that $\mathbf{0} >> (\boldsymbol{D} - \boldsymbol{CA}^{-1}\boldsymbol{B})\boldsymbol{v_2}$ or $\mathbf{0} >> \boldsymbol{Dv_2} - \boldsymbol{CA}^{-1}\boldsymbol{Bv_2}$.

Let $\boldsymbol{v_3} = -\boldsymbol{A}^{-1}\boldsymbol{Bv_2} \geq \mathbf{0}$ since $-\boldsymbol{A}^{-1} \geq \mathbf{0}$, $\boldsymbol{B} \geq \mathbf{0}$ and $\boldsymbol{v_2} >> \mathbf{0}$, then $\boldsymbol{Av_3} + \boldsymbol{Bv_2} = \mathbf{0}$ and $\mathbf{0} >> \boldsymbol{Dv_2} + \boldsymbol{Cv_3}$. Consider $\boldsymbol{v_4} >> \mathbf{0}$ in $\mathbb{R}^r_+$ such that $\boldsymbol{Av_4} << \mathbf{0}$ since $\boldsymbol{A}$ is Metzler stable. Hence with $\boldsymbol{v_1} = \boldsymbol{v_3} + \epsilon\boldsymbol{v_4}$ for $\epsilon > 0$ we obtain $\boldsymbol{Av_1} + \boldsymbol{Bv_2} = \boldsymbol{Av_3} + \boldsymbol{Bv_2} + \epsilon\boldsymbol{Av_4} = \epsilon\boldsymbol{Av_4} << \mathbf{0}$.

Similarly $\boldsymbol{Dv_2} + \boldsymbol{Cv_1} = \boldsymbol{Dv_2} + \boldsymbol{Cv_3} + \epsilon\boldsymbol{Cv_4} << \epsilon\boldsymbol{Cv_4}$, thus $\boldsymbol{Dv_2} + \boldsymbol{Cv_1} << \mathbf{0}$ which leads to $\mathbf{0} >> \boldsymbol{Av_1} + \boldsymbol{Bv_2}$ and $\mathbf{0} >> \boldsymbol{Cv_1} + \boldsymbol{Dv_2}$, that is, $\mathbf{0} >> \boldsymbol{Mv}$, therefore $\boldsymbol{M}$ is Metzler stable. □

3.2 Regular splitting

3.2.1 Lemma. (see remark in (Varga, 2000), page 95) Let $\boldsymbol{M}$ be a real Metzler stable matrix and $\boldsymbol{M} = \boldsymbol{A} + \boldsymbol{N}$ be its regular splitting, then the eigenvalue of $-\boldsymbol{NA}^{-1}$ (μ) is related to the eigenvalue of $-\boldsymbol{NM}^{-1}$ (λ) by the relationship $\mu = \frac{\lambda}{1+\lambda}$ where $1 + \lambda \neq 0$.

Proof. Given that $\boldsymbol{M} = \boldsymbol{A} + \boldsymbol{N}$ is a regular splitting, $\boldsymbol{A}$ is Metzler stable, thus the inverse $\boldsymbol{A}^{-1}$ exists, therefore $-\boldsymbol{NA}^{-1} = -\boldsymbol{N}(\boldsymbol{M} - \boldsymbol{N})^{-1}$.

Since $\boldsymbol{M}^{-1}\boldsymbol{M} = \boldsymbol{I}$, then

$$\begin{aligned} -\boldsymbol{NA}^{-1} &= -\boldsymbol{NM}^{-1}\boldsymbol{M}(\boldsymbol{M} - \boldsymbol{N})^{-1} \\ &= -\boldsymbol{NM}^{-1}((\boldsymbol{M} - \boldsymbol{N})\boldsymbol{M}^{-1})^{-1} - \boldsymbol{NM}^{-1}(\boldsymbol{I} - \boldsymbol{NM}^{-1})^{-1} \\ &= \boldsymbol{G}(\boldsymbol{I} + \boldsymbol{G})^{-1} \quad \text{with} \quad \boldsymbol{G} = -\boldsymbol{NM}^{-1}. \end{aligned}$$

Given an eigenvector $\boldsymbol{x}$ of $\boldsymbol{G} = -\boldsymbol{NM}^{-1}$ then from $\boldsymbol{Gx} = \lambda\boldsymbol{x}$ and $\boldsymbol{Ix} = \boldsymbol{x}$ we obtain $(\boldsymbol{I} + \boldsymbol{G})\boldsymbol{x} = (1 + \lambda)\boldsymbol{x}$. It follows from Proposition 2.3.3, that $\boldsymbol{I} + \boldsymbol{G} = \boldsymbol{I} - \boldsymbol{NM}^{-1}$ is invertible and $1 + \lambda$ is an eigenvalue of $\boldsymbol{I} + \boldsymbol{G}$, then $1 + \lambda \neq 0$. Therefore, $(\boldsymbol{I} + \boldsymbol{G})^{-1}\boldsymbol{x} = \frac{\boldsymbol{x}}{1+\lambda}$ with $1 + \lambda \neq 0$.

This yields $\boldsymbol{G}(\boldsymbol{I} + \boldsymbol{G})^{-1}\boldsymbol{x} = \frac{\lambda\boldsymbol{x}}{1+\lambda}$, that is $-\boldsymbol{NA}^{-1}\boldsymbol{x} = \mu\boldsymbol{x}$ with $\mu = \frac{\lambda}{1+\lambda}$ where $1 + \lambda \neq 0$. □

3.2.2 Theorem. *(Theorem 3.29 in (Varga, 2000) proves a similar result) Let $\boldsymbol{M} = \boldsymbol{A} + \boldsymbol{N}$ be a regular splitting of a real Metzler matrix $\boldsymbol{M}$, then $\boldsymbol{M}$ is Metzler stable if and only if $\rho(-\boldsymbol{NA}^{-1}) < 1$.*

Proof. Suppose $\boldsymbol{M}$ is Metzler stable, then by Lemma 3.2.1, $-\boldsymbol{NA}^{-1} = \boldsymbol{G}(\boldsymbol{I} + \boldsymbol{G})^{-1}$ with $\boldsymbol{G} = -\boldsymbol{NM}^{-1} \geq \mathbf{0}$, since $-\boldsymbol{M}^{-1} \geq \mathbf{0}$. That is, the eigenvalue of $-\boldsymbol{NA}^{-1}$ is related to the eigenvalue of $\boldsymbol{G}$ by the relationship $\mu = \frac{\lambda}{1+\lambda}$, where $1 + \lambda \neq 0$.

Since $\boldsymbol{G} \geq \boldsymbol{0}$, then by Proposition 2.3.1, there exists a non-negative eigenvector $\boldsymbol{x}$ of $\boldsymbol{G}$ such that $\boldsymbol{G}\boldsymbol{x} = \rho(\boldsymbol{G})\boldsymbol{x} \geq \boldsymbol{0}$.

Therefore considering non-negative eigenvalues $\lambda \geq 0$, we get $1 + \lambda > \lambda \geq 0$, hence we obtain $1 > \frac{\lambda}{1+\lambda} \geq 0$. However, the function $\mu = \frac{\lambda}{1+\lambda}$ is strictly increasing for increasing values of λ, thus maximizing the non-negative eigenvalue λ maximizes μ, therefore choosing $\lambda = \rho(\boldsymbol{G})$ leads to $\mu = \rho(-\boldsymbol{N}\boldsymbol{A}^{-1}) = \frac{\rho(\boldsymbol{G})}{1+\rho(\boldsymbol{G})} < 1$, which proves the necessary condition.

Conversely, let $\boldsymbol{M} = \boldsymbol{A}+\boldsymbol{N}$ be a regular splitting of a real Metzler matrix $\boldsymbol{M}$ such that $\rho(-\boldsymbol{N}\boldsymbol{A}^{-1}) < 1$. We have $-\boldsymbol{N}\boldsymbol{A}^{-1} \geq \boldsymbol{0}$, since $\boldsymbol{N} \geq \boldsymbol{0}$ and $-\boldsymbol{A}^{-1} \geq \boldsymbol{0}$.

We obtain

$$-\boldsymbol{M}\boldsymbol{A}^{-1} = -(\boldsymbol{A} + \boldsymbol{N})\boldsymbol{A}^{-1} = -(\boldsymbol{I} - (-\boldsymbol{N}\boldsymbol{A}^{-1})),$$

therefore the inverse of $-\boldsymbol{M}\boldsymbol{A}^{-1}$ is given by

$$-\boldsymbol{A}\boldsymbol{M}^{-1} = -(\boldsymbol{I} - (-\boldsymbol{N}\boldsymbol{A}^{-1}))^{-1},$$

hence $-\boldsymbol{M}^{-1} = -\boldsymbol{A}^{-1}(\boldsymbol{I} - (-\boldsymbol{N}\boldsymbol{A}^{-1}))^{-1}$.

From $\rho(-\boldsymbol{N}\boldsymbol{A}^{-1}) < 1$, then by Proposition 2.3.3 (with $\alpha = 1$) $(\boldsymbol{I} - (-\boldsymbol{N}\boldsymbol{A}^{-1}))^{-1} \geq \boldsymbol{0}$ exists, that is, $-\boldsymbol{M}^{-1} \geq \boldsymbol{0}$. Therefore by Proposition 2.3.5 (c), $\boldsymbol{M}$ is Metzler stable thus proving the sufficient condition. □

3.2.3 Remark. Since all the eigenvalues of the Metzler stable matrix $\boldsymbol{M}$ have negative real parts (see Definition 2.1.1 (g)), then by Definition 2.1.3 (a), we get $\alpha(\boldsymbol{M}) < 0$. It follows from Theorem 3.2.2 that any regular splitting $\boldsymbol{M} = \boldsymbol{A} + \boldsymbol{N}$ of a Metzler stable matrix $\boldsymbol{M}$, yields the condition $\rho(-\boldsymbol{N}\boldsymbol{A}^{-1}) < 1$ if and only if $\alpha(\boldsymbol{M}) < 0$.

4. Modelling

We consider a system of ODEs that arise from epidemiological modelling and the Jacobian matrix at the Disease Free Equilibrium of the system is derived. Consequently, a special case of a Susceptible-Exposed-Infectious-Recovered (S-E-I-R) model is investigated to compute the next generation matrix and give a definition of the reproduction number. The model considered in this chapter is discussed extensively by (Kamgang and Sallet, 2008).

4.1 System of ODEs

Consider a system of ODEs which results from epidemiological modelling that has the form

$$\begin{aligned} \dot{\boldsymbol{x}}_{\mathbf{1}} &= \boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}, \boldsymbol{x}_{\mathbf{2}}), \\ \dot{\boldsymbol{x}}_{\mathbf{2}} &= \boldsymbol{f}_{\mathbf{2}}(\boldsymbol{x}_{\mathbf{1}}, \boldsymbol{x}_{\mathbf{2}}), \end{aligned} \tag{4.1.1}$$

where $\boldsymbol{x}_{\mathbf{1}} \in \mathbb{R}_+^m$ and $\boldsymbol{x}_{\mathbf{2}} \in \mathbb{R}_+^n$. The functions $\boldsymbol{f}_{\mathbf{1}}, \boldsymbol{f}_{\mathbf{2}}$ are C^1 in $\mathbb{R}_+^{m+n}$. The pair that represents the state of the system is denoted by $\boldsymbol{x} = (\boldsymbol{x}_{\mathbf{1}}, \boldsymbol{x}_{\mathbf{2}}) \in \Omega \subset \mathbb{R}_+^m \times \mathbb{R}_+^n$. The population densities of susceptible, immune, recovered individuals are represented by the variable $\boldsymbol{x}_{\mathbf{1}}$, that is, the variable denotes the populations (number of individuals) in different compartments of individuals who are not infected or transmitting the disease under investigation. The variable $\boldsymbol{x}_{\mathbf{2}}$ denotes the population densities of infected individuals, which are the number of individuals in different compartments who are infected by the disease, these can be infectious, latent, disease carrying individuals, etc. The S-E-I-R model considered in the next section are of the form (4.1.1), with

$$\boldsymbol{x}_{\mathbf{1}} = \begin{pmatrix} \boldsymbol{S} \\ \boldsymbol{R} \end{pmatrix} \quad \text{and} \quad \boldsymbol{x}_{\mathbf{2}} = \begin{pmatrix} \boldsymbol{E} \\ \boldsymbol{I}_i \end{pmatrix}.$$

The variable $\boldsymbol{x}_{\mathbf{1}}$ is identified with the state $(\boldsymbol{x}_{\mathbf{1}}, \mathbf{0}) \in \Omega$ and $\boldsymbol{x}_{\mathbf{2}}$ is identified with $(\mathbf{0}, \boldsymbol{x}_{\mathbf{2}}) \in \Omega$ and it is supposed that the system is well-posed in the biological sense, that is the system is defined on a positive invariant Ω.

Suppose there exists a state $\boldsymbol{x}^* = (\boldsymbol{x}_{\mathbf{1}}^*, \mathbf{0}) \in \Omega$ such that $\boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}^*, \mathbf{0}) = \mathbf{0}$ and $\boldsymbol{f}_{\mathbf{2}}(\boldsymbol{x}_{\mathbf{1}}^*, \mathbf{0}) = \mathbf{0}$. This state corresponds to the DFE of the system, which is a steady state without the disease (without the presence of infected individuals). Given the DFE $\boldsymbol{x}^*$, $\boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}, \boldsymbol{x}_{\mathbf{2}})$ can be written as

$$\boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}, \boldsymbol{x}_{\mathbf{2}}) = \boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}, \boldsymbol{x}_{\mathbf{2}}) - \boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}^*, \mathbf{0})$$

Now consider a function ϕ which is C^1 from $[0,1]$ to $\mathbb{R}^m$ given as

$$\phi(s) = \boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}^* + s(\boldsymbol{x}_{\mathbf{1}} - \boldsymbol{x}_{\mathbf{1}}^*), s\boldsymbol{x}_{\mathbf{2}})$$

such that $\phi(1) = \boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}, \boldsymbol{x}_{\mathbf{2}})$ and $\phi(0) = \boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}^*, \mathbf{0})$. It follows that

$$\begin{aligned} \boldsymbol{f}_{\mathbf{1}}(\boldsymbol{x}_{\mathbf{1}}, \boldsymbol{x}_{\mathbf{2}}) &= \phi(1) - \phi(0) \\ &= \int_0^1 \phi'(s) ds \\ &= \int_0^1 d\phi. \end{aligned}$$

Therefore the total differential $d\phi = d\boldsymbol{f_1}$ at $(\boldsymbol{x_1^*} + s(\boldsymbol{x_1} - \boldsymbol{x_1^*}), s\boldsymbol{x_2}) \in \Omega$ is given by

$$d\boldsymbol{f_1} = \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_1}}(\boldsymbol{x_1^*} + s(\boldsymbol{x_1} - \boldsymbol{x_1^*}), s\boldsymbol{x_2})(\boldsymbol{x_1} - \boldsymbol{x_1^*})ds + \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_2}}(\boldsymbol{x_1^*} + s(\boldsymbol{x_1} - \boldsymbol{x_1^*}), s\boldsymbol{x_2})\boldsymbol{x_2}ds,$$

which leads to

$$\boldsymbol{f_1}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \int_0^1 \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_1}}(\boldsymbol{x_1^*} + s(\boldsymbol{x_1} - \boldsymbol{x_1^*}), s\boldsymbol{x_2})(\boldsymbol{x_1} - \boldsymbol{x_1^*})ds + \int_0^1 \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_2}}(\boldsymbol{x_1^*} + s(\boldsymbol{x_1} - \boldsymbol{x_1^*}), s\boldsymbol{x_2})\boldsymbol{x_2}ds,$$

however, $\boldsymbol{x_1^*}$, $\boldsymbol{x_1}$ and $\boldsymbol{x_2}$ are independent of s so they can be removed from the integral, thus

$$\boldsymbol{f_1}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \left\{\int_0^1 \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_1}}(\boldsymbol{x_1^*} + s(\boldsymbol{x_1} - \boldsymbol{x_1^*}), s\boldsymbol{x_2})ds\right\}(\boldsymbol{x_1} - \boldsymbol{x_1^*}) + \left\{\int_0^1 \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_2}}(\boldsymbol{x_1^*} + s(\boldsymbol{x_1} - \boldsymbol{x_1^*}), s\boldsymbol{x_2})ds\right\}\boldsymbol{x_2}.$$

Since $\boldsymbol{f_1}$ is assumed to be C^1, there exists continuous matrices $\boldsymbol{A}_{11} \in \mathbb{R}^{m\times m}$ and $\boldsymbol{A}_{12} \in \mathbb{R}^{m\times n}$ such that

$$\boldsymbol{f_1}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \boldsymbol{A}_{11}(\boldsymbol{x_1}, \boldsymbol{x_2})(\boldsymbol{x_1} - \boldsymbol{x_1^*}) + \boldsymbol{A}_{12}(\boldsymbol{x_1}, \boldsymbol{x_2})\boldsymbol{x_2},$$

where

$$\boldsymbol{A}_{11}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \int_0^1 \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_1}}(\boldsymbol{x_0})ds \quad \text{and} \quad \boldsymbol{A}_{12}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \int_0^1 \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_2}}(\boldsymbol{x_0})ds.$$

The effects of immigration are ignored by assuming that there is no inflow of infected individuals into the different infected compartments $\boldsymbol{x_2}$ from outside the total population. Then the newly infected individuals are from the non-infected compartments $\boldsymbol{x_1}$ (such as the susceptible population), as a result of sufficient contact with members of the infected populations, that is, $\boldsymbol{f_2}(\boldsymbol{x_1}, \boldsymbol{0}) = \boldsymbol{0}$ since there are no infected individuals to transmit the disease. Provided $\boldsymbol{f_2}$ is C^1 and $\boldsymbol{f_2}(\boldsymbol{x_1}, \boldsymbol{0}) = \boldsymbol{0}$ then similarly to $\boldsymbol{f_1}$ there exists a continuous matrix $\boldsymbol{A}_{22} \in \mathbb{R}^{n\times n}$ such that

$$\boldsymbol{f_2}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \boldsymbol{A}_{22}(\boldsymbol{x_1}, \boldsymbol{x_2})\boldsymbol{x_2}.$$

The matrix $\boldsymbol{A}_{22}$ can be determined using

$$\boldsymbol{f_2}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \psi(1) - \psi(0) = \int_0^1 d\psi,$$

where $\psi(s) = \boldsymbol{f_2}(\boldsymbol{x_1}, s\boldsymbol{x_2})$ is C^1, therefore the total differential at $(\boldsymbol{x_1}, s\boldsymbol{x_2}) \in \Omega$ is given as

$$d\psi = d\boldsymbol{f_2} = \frac{\partial \boldsymbol{f_2}}{\partial \boldsymbol{x_2}}(\boldsymbol{x_1}, s\boldsymbol{x_2})\boldsymbol{x_2}ds,$$

which leads to

$$\boldsymbol{f_2}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \left\{ \int_0^1 \frac{\partial \boldsymbol{f_2}}{\partial \boldsymbol{x_2}}(\boldsymbol{x_1}, s\boldsymbol{x_2}) ds \right\} \boldsymbol{x_2},$$

hence we obtain

$$\boldsymbol{A}_{22}(\boldsymbol{x_1}, \boldsymbol{x_2}) = \int_0^1 \frac{\partial \boldsymbol{f_1}}{\partial \boldsymbol{x_2}}(\boldsymbol{x_1}, s\boldsymbol{x_2}) ds.$$

Finally the well-posed system of ODEs resulting from compartmental modelling can be written on Ω, in a pseudo-triangular form

$$\begin{aligned} \dot{\boldsymbol{x}}_{\boldsymbol{1}} &= \boldsymbol{A}_{11}(\boldsymbol{x_1}, \boldsymbol{x_2})(\boldsymbol{x_1} - \boldsymbol{x_1^*}) + \boldsymbol{A}_{12}(\boldsymbol{x_1}, \boldsymbol{x_2})\boldsymbol{x_2}, \\ \dot{\boldsymbol{x}}_{\boldsymbol{2}} &= \boldsymbol{A}_{22}(\boldsymbol{x_1}, \boldsymbol{x_2})\boldsymbol{x_2}, \end{aligned}$$

that is,

$$\begin{pmatrix} \dot{\boldsymbol{x}}_{\boldsymbol{1}} \\ \dot{\boldsymbol{x}}_{\boldsymbol{2}} \end{pmatrix} = \begin{pmatrix} \boldsymbol{A}_{11}(\boldsymbol{x_1}, \boldsymbol{x_2}) & \boldsymbol{A}_{12}(\boldsymbol{x_1}, \boldsymbol{x_2}) \\ \boldsymbol{0} & \boldsymbol{A}_{22}(\boldsymbol{x_1}, \boldsymbol{x_2}) \end{pmatrix} \begin{pmatrix} \boldsymbol{x_1} - \boldsymbol{x_1^*} \\ \boldsymbol{x_2} \end{pmatrix}.$$

The matrix $\boldsymbol{J}$ given by

$$\boldsymbol{J} = \begin{pmatrix} \boldsymbol{A}_{11}(\boldsymbol{x_1^*}, \boldsymbol{0}) & \boldsymbol{A}_{12}(\boldsymbol{x_1^*}, \boldsymbol{0}) \\ \boldsymbol{0} & \boldsymbol{A}_{22}(\boldsymbol{x_1^*}, \boldsymbol{0}) \end{pmatrix},$$

is the Jacobian of the system at the DFE.

4.2 SEIR models

Most epidemiological models involve dividing the population into sub-populations called classes/compartments. Various types of epidemiological models are discussed in great detail in (Bauer et al., 2008), among them are S-E-I-R models, which are central to our discussion in this section. For S-E-I-R models, the population is divided into susceptible, exposed, infectious, and recovered classes.

- Susceptibles are members of the population which do not have immunity to the disease and might become infected if exposed to the disease,
- The exposed class contains individuals who have come into contact with infected individuals and have been infected but cannot transmit the disease to others. Exposed individuals spend the entirety of the incubation period of the disease in this compartment,
- Members of the infectious class are infected individuals who can transmit the disease to others,
- Recovered individuals are either immune or have recovered from the disease and cannot be infected if they come into contact with infectious individuals. This class is often called "removed" class since members of this sub-population do not affect the transmission of the disease by interacting or coming into contact with other individuals.

For diseases with temporary immunity or without immunity, infected individuals who recover from the disease can be reinfected, so once an individual recovers from a disease and/or losses immunity, the individual become part of the susceptible class. In these cases, the recovered class affects transmission dynamics of the disease. We consider a models where the movement of individuals from compartment to compartment follows a directed path, that is, individuals move from the susceptible to the exposed class, and from the exposed to the infectious class, then move to the recovered class. We also neglect the effects of immigration, however, individuals are removed from the population by death due to the disease or some other causes. Given a population at a DFE, the reproduction number is a good measure of whether a disease will spread or not, when an infective is introduced to the population. A heuristic definition of the $\mathcal{R}_0$ for models with a single infectious class is the product of the infection rate and the mean duration of the infection (Watmough and Van den Driessche, P., 2002). Infections like Tuberculosis, malaria, etc., which can be transmitted by several strains or to different susceptible populations, multiple susceptible, exposed, infectious, and recovered classes have to be considered in our models. In multi-compartmental models like these, the heuristic definition of $\mathcal{R}_0$ will not suffice, which is the reason methods discussed in the next section are critical to the analysis of epidemiological models.

4.3 Computation of the reproduction number $\mathcal{R}_0$

To illustrate how the discussion so far relates to the reproduction number, we compute the next generation matrix $\boldsymbol{K'}$ in a special case of a multi-compartmental S-E-I-R model. We consider two approaches in this section, the Metzler matrix approach, which employs the tools we have discussed so far and the next generation matrix approach adopted from (Watmough and Van den Driessche, P., 2002).

Metzler matrix approach

Consider a multi-compartmental S-E-I-R model considered in (Diekmann et al., 1990) and also discussed by (Kamgang and Sallet, 2008). The model describes the movement of susceptible ($\boldsymbol{S}$) individuals from being exposed ($\boldsymbol{E}$) to the disease to being infectious ($\boldsymbol{I_i}$, the subscript $\boldsymbol{i}$ is used to differentiate the infectious compartments from the identity matrix) and later the recovered ($\boldsymbol{R}$) classes.

Let $\boldsymbol{T(S)}$ be the transmission matrix which contains the rates of transmission (the entries of $\boldsymbol{T(S)}$ may be given by $\boldsymbol{T(S)}_{ij} = \beta_{ij}\boldsymbol{S}_j$, where $\beta_{ij} \geq 0$ are the contact rates, see (Sharomi and Malik, 2015)) of the disease from infectious to susceptible individuals. Let $\boldsymbol{M_1}$ and $\boldsymbol{M_2}$ be diagonal matrices of the death rates (per capita) in the exposed and infectious classes, respectively. Let the diagonal matrix $\boldsymbol{\Sigma}$ describe the transition of individuals from the exposed to the infectious classes and $\boldsymbol{D}$ be a diagonal matrix of the transition rates of individuals from the infectious to the recovered classes such that the evolution of the various classes are given by

$$\begin{aligned}
\dot{\boldsymbol{S}} &= -\boldsymbol{T(S)I_i}, \\
\dot{\boldsymbol{E}} &= \boldsymbol{T(S)I_i} - \boldsymbol{M_1E} - \boldsymbol{\Sigma E}, \\
\dot{\boldsymbol{I}}_i &= -\boldsymbol{DI_i} - \boldsymbol{M_2I_i} + \boldsymbol{\Sigma E}, \\
\dot{\boldsymbol{R}} &= \boldsymbol{DI_i}.
\end{aligned}$$

The transition and death rates are assumed to be positive constants, thus the matrices $\boldsymbol{M_1}$, $\boldsymbol{M_2}$, $\boldsymbol{D}$ and $\boldsymbol{\Sigma}$ are non-negative matrices with constant entries. $\boldsymbol{T(S)}$ is non-negative but its entries are not constant since its dependant on $\boldsymbol{S}$. New infections are represented by the movement of individuals from the susceptible classes into the exposed classes. A fraction of these individuals that transition to the infectious classes can then cause secondary infections or transition into the recovered classes. Therefore, to track the number of secondary infections, it is sufficient to investigate the evolution of exposed and infectious classes since population changes in these compartments is mainly responsible for secondary infections. Hence, consider the reduced system

$$\begin{aligned} \dot{\boldsymbol{E}} &= \boldsymbol{T}(\boldsymbol{S})\boldsymbol{I}_i - \boldsymbol{M_1}\boldsymbol{E} - \boldsymbol{\Sigma}\boldsymbol{E}, \\ \dot{\boldsymbol{I}}_i &= -\boldsymbol{D}\boldsymbol{I}_i - \boldsymbol{M_2}\boldsymbol{I}_i + \boldsymbol{\Sigma}\boldsymbol{E}, \end{aligned} \tag{4.3.1}$$

which can be rewritten as

$$\begin{pmatrix} \dot{\boldsymbol{E}} \\ \dot{\boldsymbol{I}}_i \end{pmatrix} = \begin{pmatrix} -(\boldsymbol{\Sigma} + \boldsymbol{M_1}) & \boldsymbol{T}(\boldsymbol{S}) \\ \boldsymbol{\Sigma} & -(\boldsymbol{D} + \boldsymbol{M_2}) \end{pmatrix} \begin{pmatrix} \boldsymbol{E} \\ \boldsymbol{I}_i \end{pmatrix}.$$

Therefore the Jacobian of the system (4.3.1) at the DFE is given by

$$\boldsymbol{J} = \begin{pmatrix} -(\boldsymbol{\Sigma} + \boldsymbol{M_1}) & \boldsymbol{T}(\boldsymbol{S}^*) \\ \boldsymbol{\Sigma} & -(\boldsymbol{D} + \boldsymbol{M_2}) \end{pmatrix}.$$

The matrices $\boldsymbol{T}(\boldsymbol{S})$ and $\boldsymbol{\Sigma}$ are non-negative. Furthermore, since $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$ and $-(\boldsymbol{D} + \boldsymbol{M_2})$ are diagonal matrices, $\boldsymbol{J}$ is Metzler and, from Lemma 3.1.3, $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$ and $-(\boldsymbol{D} + \boldsymbol{M_2})$ are also Metzler. Since $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$ and $-(\boldsymbol{D} + \boldsymbol{M_2})$ are diagonal, for every diagonal entry λ of $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$, $\det\big(-(\boldsymbol{\Sigma} + \boldsymbol{M_1}) - \lambda \boldsymbol{I}\big) = 0$. That is, λ is also an eigenvalue of $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$. Since $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$ has negative diagonal entries, $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$ is Metzler stable. A similar argument to deduce that $-(\boldsymbol{D} + \boldsymbol{M_2})$ is Metzler stable, holds.

The Jacobian $\boldsymbol{J}$ is block decomposed, so by Theorem 3.1.4, $\boldsymbol{J}$ is Metzler stable if and only if the matrices $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$ and $\boldsymbol{J_1} = -(\boldsymbol{D} + \boldsymbol{M_2}) + \boldsymbol{\Sigma}(\boldsymbol{\Sigma} + \boldsymbol{M_1})^{-1}\boldsymbol{T}(\boldsymbol{S}^*)$ are Metzler stable.

We have deduced that $-(\boldsymbol{\Sigma} + \boldsymbol{M_1})$ is Metzler stable, therefore we investigate the Metzler stability of $\boldsymbol{J_1}$.

Let $\boldsymbol{J_1} = \boldsymbol{A} + \boldsymbol{N}$ be a splitting defined by $\boldsymbol{A} = -(\boldsymbol{D} + \boldsymbol{M_2})$ and $\boldsymbol{N} = \boldsymbol{\Sigma}(\boldsymbol{\Sigma} + \boldsymbol{M_1})^{-1}\boldsymbol{T}(\boldsymbol{S}^*)$. Since $\boldsymbol{A} = -(\boldsymbol{D} + \boldsymbol{M_2})$ is Metzler stable, then $-\boldsymbol{A}^{-1} \geq \boldsymbol{0}$ (see Proposition 2.3.5 (c)) and $\boldsymbol{N} \geq \boldsymbol{0}$, therefore $\boldsymbol{J_1} = \boldsymbol{A} + \boldsymbol{N}$ is a regular splitting. It follows from Theorem 3.2.2 that $\boldsymbol{J_1}$ is Metzler stable if and only if $\rho(-\boldsymbol{N}\boldsymbol{A}^{-1}) = \rho(\boldsymbol{\Sigma}(\boldsymbol{\Sigma} + \boldsymbol{M_1})^{-1}\boldsymbol{T}(\boldsymbol{S}^*)(\boldsymbol{D} + \boldsymbol{M_2})^{-1}) < 1$. Hence, $\boldsymbol{J}$ is Metzler stable if and only if $\rho(\boldsymbol{K}) < 1$, with $\boldsymbol{K} = \boldsymbol{\Sigma}(\boldsymbol{\Sigma} + \boldsymbol{M_1})^{-1}\boldsymbol{T}(\boldsymbol{S}^*)(\boldsymbol{D} + \boldsymbol{M_2})^{-1}$.

Therefore the DFE of the system is asymptotically stable (see Remark 2.3.4 (i) and (ii)) if and only if the Jacobian $\boldsymbol{J}$ is Metzler stable ($\rho(\boldsymbol{K}) < 1$).

We shall show that the condition $\rho(\boldsymbol{K}) < 1$ is corresponds to the condition $\mathcal{R}_0 < 1$, where $\mathcal{R}_0$ is the basic reproduction number defined by the next generation matrix discussed in the next section.

Next generation matrix approach

This section focuses on implementing the approach on the S-E-I-R model discussed above to define the next generation matrix and consequently compute the reproduction number. As discussed above, the time evolution of exposed and infectious classes is sufficient to track secondary infections, therefore we consider

$$\dot{\boldsymbol{E}} = \boldsymbol{T}(\boldsymbol{S})\boldsymbol{I}_i - \boldsymbol{M}_1\boldsymbol{E} - \boldsymbol{\Sigma}\boldsymbol{E},$$
$$\dot{\boldsymbol{I}}_i = -\boldsymbol{D}\boldsymbol{I}_i - \boldsymbol{M}_2\boldsymbol{I}_i + \boldsymbol{\Sigma}\boldsymbol{E},$$

which can be written in the following form

$$\begin{pmatrix} \dot{\boldsymbol{E}} \\ \dot{\boldsymbol{I}}_i \end{pmatrix} = \begin{pmatrix} \boldsymbol{T}(\boldsymbol{S})\boldsymbol{I}_i \\ \boldsymbol{\Sigma}\boldsymbol{E} \end{pmatrix} - \begin{pmatrix} (\boldsymbol{\Sigma} + \boldsymbol{M}_1)\boldsymbol{E} \\ (\boldsymbol{D} + \boldsymbol{M}_2)\boldsymbol{I}_i \end{pmatrix},$$

from which we differentiate between new infections and other changes in the population then obtain the matrices containing the rates of transfer of individuals into the exposed and infectious compartments due to new infection $\boldsymbol{\mathcal{F}}$, the rates of transfer of individuals into the exposed and infectious compartments by other means $\boldsymbol{\mathcal{V}}^+$ and the rates of transfer of individuals out of the exposed and infectious compartments $\boldsymbol{\mathcal{V}}^-$. It follows that

$$\boldsymbol{\mathcal{F}} = \begin{pmatrix} \boldsymbol{T}(\boldsymbol{S})\boldsymbol{I}_i \\ \boldsymbol{\Sigma}\boldsymbol{E} \end{pmatrix} \quad \text{and} \quad \boldsymbol{\mathcal{V}} = \begin{pmatrix} (\boldsymbol{\Sigma} + \boldsymbol{M}_1)\boldsymbol{E} \\ (\boldsymbol{D} + \boldsymbol{M}_2)\boldsymbol{I}_i \end{pmatrix}.$$

Where

$$\boldsymbol{\mathcal{V}} = \boldsymbol{\mathcal{V}}^- - \boldsymbol{\mathcal{V}}^+,$$

such that

$$\boldsymbol{\mathcal{V}}^+ = \begin{pmatrix} \boldsymbol{0} \\ \boldsymbol{0} \end{pmatrix} \quad \text{and} \quad \boldsymbol{\mathcal{V}}^- = \begin{pmatrix} (\boldsymbol{\Sigma} + \boldsymbol{M}_1)\boldsymbol{E} \\ (\boldsymbol{D} + \boldsymbol{M}_2)\boldsymbol{I}_i \end{pmatrix}.$$

We define $\boldsymbol{X} = \begin{pmatrix} \boldsymbol{E} \\ \boldsymbol{I}_i \end{pmatrix}$, which contains the infective populations (exposed and infectious) then show that the matrices $\boldsymbol{\mathcal{F}}$, $\boldsymbol{\mathcal{V}}^+$ and $\boldsymbol{\mathcal{V}}^-$ satisfy the following assumptions (these assumption are discussed in (Watmough and Van den Driessche, P., 2002))

1. (A1) Each matrix represents a directed transfer of individuals, hence they are all non-negative. That is, if $\boldsymbol{X} \geq \boldsymbol{0}$, then the matrices $\boldsymbol{\mathcal{F}}$, $\boldsymbol{\mathcal{V}}^+$ and $\boldsymbol{\mathcal{V}}^-$ are non-negative,
2. (A2) There cannot be a transfer of individuals out of a compartment by infection, death nor other means, if the compartment is empty. This means, $\boldsymbol{\mathcal{V}}^- = \boldsymbol{0}$ whenever $\boldsymbol{X} = \boldsymbol{0}$,
3. (A4) The effects of immigration are neglected, that is, there cannot be an inflow of infective from outside the population. Hence the inflow of individuals into the exposed and infectious compartments is due to new infection only. Therefore, if $\boldsymbol{X} = \boldsymbol{0}$, then $\boldsymbol{\mathcal{F}} = \boldsymbol{0}$ and $\boldsymbol{\mathcal{V}}^+ = \boldsymbol{0}$. This means that new infections cannot arise without the presence of an infective in the population.

We do not need to assumption (A3) since we are considering a reduced system without the susceptible and recovered populations. Assumption (A5) is considered below, but first we need to compute the matrices $\boldsymbol{F}$ and $\boldsymbol{V}$ which are defined as

$$\boldsymbol{F} = \left[\frac{\partial \boldsymbol{\mathcal{F}}_j}{\partial x_j}(\boldsymbol{S}^*)\right] \quad \text{and} \quad \boldsymbol{V} = \left[\frac{\partial \boldsymbol{\mathcal{V}}_j}{\partial x_j}(\boldsymbol{S}^*)\right],$$

where x_j is an entry of $\boldsymbol{X}$, and the entries of $\boldsymbol{\mathcal{F}}$ and $\boldsymbol{\mathcal{V}}$ are denoted by $\boldsymbol{\mathcal{F}}_j$ and $\boldsymbol{\mathcal{V}}_j$, respectively. Therefore, taking the derivatives with respect to each entry x_j and evaluating the results at the DFE given by

$$(\boldsymbol{S}, \boldsymbol{E}, \boldsymbol{I}_i, \boldsymbol{R}) = (\boldsymbol{S}^*, \boldsymbol{0}, \boldsymbol{0}, \boldsymbol{0}),$$

we obtain

$$\boldsymbol{F} = \begin{pmatrix} \boldsymbol{0} & \boldsymbol{T}(\boldsymbol{S}^*) \\ \boldsymbol{\Sigma} & \boldsymbol{0} \end{pmatrix} \quad \text{and} \quad \boldsymbol{V} = \begin{pmatrix} \boldsymbol{\Sigma} + \boldsymbol{M_1} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{D} + \boldsymbol{M_2} \end{pmatrix}.$$

This yields $\boldsymbol{F} \geq \boldsymbol{0}$ and it clear that $\boldsymbol{V}$ has non-negative entries and is a non-singular Metzler matrix since the its inverse is given by

$$\boldsymbol{V}^{-1} = \begin{pmatrix} (\boldsymbol{\Sigma} + \boldsymbol{M_1})^{-1} & \boldsymbol{0} \\ \boldsymbol{0} & (\boldsymbol{D} + \boldsymbol{M_2})^{-1} \end{pmatrix}.$$

Since $-(-\boldsymbol{V})^{-1} >> \boldsymbol{0}$, it follows from Proposition 2.3.5 (b) that $-\boldsymbol{V}$ is Metzler stable. We observe that $\boldsymbol{J} = (-\boldsymbol{V}) + \boldsymbol{F}$ is a regular splitting and $\boldsymbol{F}\boldsymbol{V}^{-1} \geq \boldsymbol{0}$. We showed in the Metzler approach that the Jacobian $\boldsymbol{J}$ is Metzler stable ($\rho(\boldsymbol{F}\boldsymbol{V}^{-1}) < 1$) if and only if the DFE is asymptotically stable, i.e this means that assumption (A5) is satisfied. Finally the next generation matrix is defined as $\boldsymbol{K'} = \boldsymbol{F}\boldsymbol{V}^{-1}$, that is

$$\begin{aligned} \boldsymbol{K'} &= \begin{pmatrix} \boldsymbol{0} & \boldsymbol{T}(\boldsymbol{S}^*) \\ \boldsymbol{\Sigma} & \boldsymbol{0} \end{pmatrix} \begin{pmatrix} (\boldsymbol{\Sigma} + \boldsymbol{M_1})^{-1} & \boldsymbol{0} \\ \boldsymbol{0} & (\boldsymbol{D} + \boldsymbol{M_2})^{-1} \end{pmatrix} \\ &= \begin{pmatrix} \boldsymbol{0} & \boldsymbol{T}(\boldsymbol{S}^*)(\boldsymbol{D} + \boldsymbol{M_2})^{-1} \\ \boldsymbol{\Sigma}(\boldsymbol{\Sigma} + \boldsymbol{M_1})^{-1} & \boldsymbol{0} \end{pmatrix}. \end{aligned}$$

The reproduction number, $\mathcal{R}_0 = \rho(\boldsymbol{K'})$, is defined as the spectral radius of the next generation matrix $\boldsymbol{K'}$. That is, the DFE is asymptotically stable if and only if $\mathcal{R}_0 = \rho(\boldsymbol{K'}) < 1$.

4.3.1 Remark. We conclude that the condition $\rho(\boldsymbol{K}) < 1$ for the asymptotic stability of the DFE calculated by the approach of (Kamgang and Sallet, 2008) using Metzler matrices coincides with the condition $\mathcal{R}_0 < 1$ obtained by the next generation matrix approach. Although the conditions coincide, only $\mathcal{R}_0$ has a biological meaning. The only common feature between $\rho(\boldsymbol{K})$ and $\mathcal{R}_0$ is their predictive behaviour about the asymptotic stability of the DFE (see discussions in Kamgang and Sallet (2008) and Heesterbeek (2002)).

We return to the definition of $\mathcal{R}_0$, which is defined as the expected number of secondary infection produce by an infective in a completely susceptible population during its entire period of infectiousness. A completely susceptible population corresponds to the DFE, here we have shown that the DFE is asymptotically stable if and only if $\rho(\boldsymbol{K}) < 1$ or $\mathcal{R}_0 < 1$. We use $\mathcal{R}_0$ determine whether an infection will spread into the population due to the introduction of an infective into a completely susceptible initial population, one might argue that once the spread has begun, conditions (parameters such as infection, transition, death rates, etc.) favourable to the spread of the disease might change and $\mathcal{R}_0$ may not be a good measure of the transmission (Bauer et al., 2008). However, $\mathcal{R}_0$ is dependant on the parameters of the disease, so re-computing the next generation matrix ($\boldsymbol{K'}$) for the initial population with the changed parameters then computing the spectral radius $\rho(\boldsymbol{K'})$, which gives $\mathcal{R}_0$, we can still determine whether the infection will spread or not, independent of the initial population (Heesterbeek, 2002).

5. Concluding remarks

We have considered a system of ODEs of the form $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$, whose solution $\boldsymbol{x}(t)$ with initial value $\boldsymbol{x}(t_0) = \boldsymbol{x}_0$, exists and is unique for $t \geq 0$. We defined a flow $\boldsymbol{\psi}(\boldsymbol{x}, t)$, which is dependant on the solution $\boldsymbol{x}(t)$. A point $\boldsymbol{x_e}$ is a fixed point of the flow if and only if $\boldsymbol{x_e}$ is an equilibrium point of $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$. Furthermore, different kinds of stability of $\boldsymbol{x}_e$ were discussed and, in particular, the asymptotic stability. The asymptotic stability of $\boldsymbol{x}_e$ is equivalent to the asymptotic stability of the origin for a linearized system only if there are no eigenvalues λ, with $\Re(\lambda) = 0$.

Properties of non-negative matrices proved to be foundational in deducing important results related to Metzler matrices, such as Metzler stability and regular splitting. Given a linear system $\dot{\boldsymbol{x}} = \boldsymbol{M}\boldsymbol{x}$, the Metzler stability of $\boldsymbol{M}$ is equivalent to the asymptotic stability of $\boldsymbol{x}_e$. A significant result which is discussed in Theorem 3.2.2, associates the Metzler stability of a regular splitting $\boldsymbol{M} = \boldsymbol{A} + \boldsymbol{N}$, to a threshold condition $\rho(-\boldsymbol{N}\boldsymbol{A}^{-1}) < 1$ on the spectral radius.

We obtained the Jacobian matrix $\boldsymbol{J}$, associated to the DFE, from analysis of a system of ODEs $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$ arising from epidemiological modelling. An example of such a model is the S-E-I-R model considered Chapter 4.

The application of both the Metzler and next generation matrix approaches to a multi-compartmental S-E-I-R model yielded the matrix $\boldsymbol{K} = \boldsymbol{\Sigma}(\boldsymbol{\Sigma} + \boldsymbol{M_1})^{-1}\boldsymbol{T}(\boldsymbol{S}^*)(\boldsymbol{D} + \boldsymbol{M_2})^{-1}$ using properties of Metzler matrices and the next generation matrix $\boldsymbol{K'}$ using the next generation matrix approach. Moreover, we obtained threshold conditions, $\rho(\boldsymbol{K}) < 1$ on the spectral radius of the matrix $\boldsymbol{K}$ and $\mathcal{R}_0 < 1$ on the reproduction number, for the asymptotic stability of the DFE. That is, the DFE is asymptotically stable if and only if the spectral radius of the matrix $\boldsymbol{K}$ or the reproduction number is less than 1.

5.1 Possible future work

The S-E-I-R model considered in this work is for a general case, and not for a particular disease. For future work, we can study the application of these approaches to models of diseases such as Tuberculosis, HIV/AIDS and other infectious diseases which continue to plague various parts of Africa. This will serve as tool for decision makers in the needed domains. Disease control strategies that may be implemented require data that are specific to a disease, such as infection rates, recovery rates and transition rates, which are incorporated into $\mathcal{R}_0$. Hence the application of methods discussed here to disease specific models will considerably enhance the use of $\mathcal{R}_0$ in the implementation and design of infectious disease control strategies, which will be of great benefit to the health sector.

Acknowledgements

I want to acknowledge AIMS and it's funders for supporting this work, as well as my supervisor, Prof. Jacek Banasiak from University of Pretoria and my tutor, Ms. Rahinatou Yuh NJAH for their contributions in the writing of this essay.

References

Bauer, F., Van den Driessche, P., and Wu, J. *Mathematical Epidemiology*. Springer-Verlag Berlin Heidelberg, 2008.

Berman, A. and Plemmons, R. J. *Nonnegative Matrices in the Mathematical Sciences*. New York: Academic Press, 1994.

Braun, M. *Differential Equations and Their Applications*, volume 11. Springer-Verlag New York, 1993.

Diekmann, O., Heesterbeek, J., and Metz, J. On the definition and the computation of the basic reproduction ratio $\mathcal{R}_0$ in models for infectious-diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28:365–82, 02 1990.

Dietz, K. The estimation of the basic reproduction number for infectious diseases. *Statistical Methods in Medical Research*, 2:23–41, 1993.

Glendinning, P. *Stability, Instability and Chaos: An Introduction to the Theory of Nonlinear Differential Equations*. Cambridge Texts in Applied Mathematics. Cambridge University Press, 1994.

Haddad, W., Chellaboina, V., and Hui, Q. *Nonnegative and Compartmental Dynamical Systems*, volume 41. Princeton University Press, 2010.

Heesterbeek, J. A brief history of $\mathcal{R}_0$ and a recipe for its calculation. *Acta Biotheoretica*, 50:189–204, 2002.

Hethcote, H. W. The mathematics of infectious diseases. *SIAM Review*, 42(4):599–653, 2000. ISSN 00361445.

Horn, R. A. and Johnson, C. R. *Stable matrices and inertia*. Topics in Matrix Analysis. Cambridge University Press, 1991.

Kamgang, J. C. and Sallet, G. Computation of threshold conditions for epidemiological models and global stability of the disease-free equilibrium (DFE). *Mathematical Biosciences*, 213(1):1–12, 2008.

Perasso, A. An introduction to the basic reproduction number in mathematical epidemiology. *ESAIM: Proceedings and Surveys*, 62:123–138, 2018.

Sharomi, O. and Malik, T. Optimal control in epidemiology. *Annals of Operations Research*, 251:55–71, 2015.

Stewart, J. *Multivariable calculus*. Australia: Brooks/Cole, 2012.

Strang, G. *Linear Algebra and its Applications (Fourth Edition)*. Academic Press, 2011.

Varga, R. S. *Matrix Iterative Analysis*. Springer, Berlin, Heidelberg, 2000.

Warner, F. W. *Foundations of Differentiable Manifolds and Lie Groups*. Springer-Verlag New York, 1983.

Watmough, J. and Van den Driessche, P. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180:29–48, 2002.