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Stability analysis of the SEIR model

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Abstract

The SEIR (Susceptible-Exposed-Infected-Removed) model is a compartmental epidemiological model used to investigate and predict the spread of disease. In this thesis a modification is presented in which the transferals between compartments is modified.

The main purpose of this thesis is to study the stability of equilibrium points of both the conventional SEIR model as well as the modified version. The stability characteristics of equilibria is significant epidemiologically as it determines whether a given disease will die out or persist in the population.

Local stability is determined through linearization utilizing the Hartman-Grobman theorem, and asymptotic stability is determined through the use of Lyapunov functions and LaSalle's invariance theorem.

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Introduction

The aim of this thesis is to describe the SEIR (Susceptible-Exposed-Infected-Removed) model and to determine the stability of its equilibria. In addition a modified version of the SEIR model is described and the local stability of the equilibria determined. The tools used to do this are linearization, utilizing the Hartman-Grobman Theorem [12], LaSalle's invariance theorem [16] and Lyapunov functions [18]. The stability analysis is not only interesting from a mathematical standpoint, but are also significant epidemiologically. The stability of the equilibria is a determining factor in whether the disease persists in the population or not. Establishing under what conditions a given equilibrium is stable is therefore important, as the insights can be used to inform mitigation or eradication efforts.

1.1 Background

Pestilence and parasites have been constant and destructive companions of mankind. As technology has progressed we have unlocked new tools to combat disease, but we have also become more connected through transportation and trade. Pathogens can be accidentally transported across the globe, turning a local outbreak into a pandemic. Global outbreaks are of course particularly troublesome, by virtue of spreading in a large portion of the total population and because of that potentially causing large scale casualties, and large scale disruptions to the economy. Pandemics occured several times throughout the previous century. The epidemics varied in severity, as one would expect, with the 1918 influenza estimated to have caused the death of >50 million people, while the 1957-1958 influenza and the 1968 influenza pandemics are estimated to have caused around 1 million deaths each [8, 9, 10]. These examples are not even a comprehensive list of influenza pandemics that occurred in the 1900's.

At the time of this thesis being written there are two major ongoing pandemics.

HIV/AIDS had caused an estimated 32.7 million deaths as of the end of 2019, and COVID-19 had caused an estimated 3.1 million deaths as of 27-04-2021 [1, 2]. It is clear that fairly damaging pandemics are not black swan events, but should rather be expected to occur. Consider then that in addition to the risk of epidemics and pandemics, diseases like tuberculosis are endemic to parts of the world and cause great harm year after year.

Disease does not only cause direct harm to human beings. Economic damage can be done by disrupting trade networks. By affecting plants or animals a pathogen can decrease biodiversity, or cause food insecurity.

By understanding a disease and by accurate modelling we may be able to formulate better strategies to mitigate and overcome it. Overcoming or mitigating a disease may mean protecting livelihoods and the availability of vital supplies, it may mean protecting our environment, and most importantly it may mean preventing deaths.

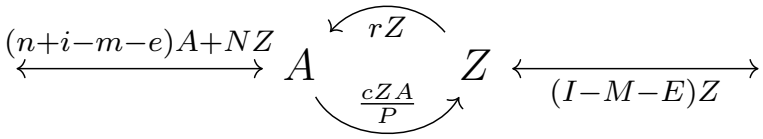
1.2 A brief history

In this section we will give a cursory account of the development of compartmental models in epidemiology, particularly the SIR (Susceptible-Infected-Removed) model. We will focus on the models themselves, and results directly relevant to the focus of this thesis.

We will begin with a paper by Sir Ronald Ross published in 1916 [21]. The paper is concerned with "a priori pathometry", which may require some explanation. Pathometry is a now largely obsolete term that means measurement of disease, and a priori pathometry is then simply epidemiological modelling (we construct the model based on a priori knowledge). Ross had been doing research in this area since 1899, then in the context of malaria. Worth noting is that he was awarded the 1902 Nobel prize in physiology or medicine for his work on malaria, but not for his work in epidemiological modelling.

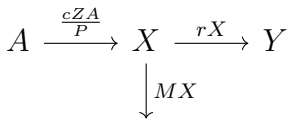
The model presented in the paper divides a population P into two compartments, Z for affected and A for not affected, which to me seem like somewhat confusing names. The parameters n, m, i and e represent nativity, mortality, immigration and emigration for the unaffected compartment A, while N, M, I and E represent the same for the affected compartment Z. This means that the model allows for different birthrates, different immigration rates and so on for the two compartments, which is pretty interesting in my opinion. Finally there are two parameters governing

the transition between compartments, h governing the transition from A to Z and r governing Z to A. The model is not framed as specifically an epidemiological model. The parameters h and r are named as such as a "happening" causes an unaffected individual to become affected, and they later "revert" to being unaffected. The different applications of the model mentioned in the paper are interesting, but sadly not relevant to this thesis. In the case of infectious diseases, the case which we are interested in, h will be a function of Z. Specifically $h(Z) = \frac{cZ}{P}$ [21]. The following diagram is a visualization of the model for such a scenario.



This is what we would call a SIS model today, simply replacing the terms not affected with susceptible, and affected with infected (as well as using some simpler vital dynamics typically). This type of model is used to this day for modelling diseases that do not confer immunity, or diseases where you are infectious in perpetuity (setting $r = 0$).

The second paper that we will look at is written by Sir Ronald Ross again, this time joined by Dr Hilda Phoebe Hudson. The paper was published in 1917 [22], and we are presented with another model. The model is intended for situations in which individuals may not become affected again after having been previously affected. The model parameters are named in the same way as for the previous model, but now with an additional compartment. The compartments are now unaffected A, infectious X and immune Y. Most of the parameters such as immigration are discarded for the sake of simplicity in the paper, only keeping M as mortality caused by the disease. To include the others, one would simply add them to the model in a manner analogous to the previous model.



This is for all intents and purposes what we today would call a SIR model, with compartments Susceptible, Infected and Removed. The model as presented is functionally what we could call a SIRD model, only lacking a compartment for the dead, because of the mortality associated with the disease [22].

In the final paper of this brief history, the authors William Ogilvy Kermack and Anderson Gray McKendrick are dealing with a much more general model. The SIR model is a special case of this much more complex model, and is described in section B of the paper.

The fact that many epidemics eventually end had been hypothesized to be caused by either a reduction in the infectiousness of the pathogen over time, or by there simply being no susceptible individuals left in the population. These ideas clearly have some problems. There does not seem to be any good reason why a pathogen itself would become less infectious as an epidemic progresses, and outbreaks of disease seem to end without the entire population having become ill. This paper demonstrates that in a SIR model an epidemic can end before the exhaustion of susceptible individuals, without decreasing the infectiousness of the pathogen. This demonstrated that neither hypothesis is necessarily true, given that the model is an accurate approximation of reality. Most importantly for the understanding of the model itself, it is shown that given the infection-, death- and recovery rates, there exists a critical population density. If this population density is exceeded an epidemic will occur, and if this population density is increased the extent of the outbreak will as well. If it is below the critical density, no epidemic will occur. In section B of the paper the following model is examined:

$$\begin{cases} \frac{dx}{dt} & = -\kappa xy \\ \frac{dy}{dt} & = \kappa xy - ly \\ \frac{dz}{dt} & = ly \\ N & = x + y + z \end{cases}$$

The N represents the population density in this paper. This model is completely recognizable as a SIR model without vital dynamics. The magnitude of the pandemic (z at the end of the epidemic) is found to be $2\frac{l}{\kappa}\frac{N-\frac{l}{\kappa}}{N}$, and it follows that $N_0 = \frac{l}{\kappa}$ is the threshold density required for there to be an epidemic [15]. If we want to deal with N as the population rather then the density, we simply replace κ with $\frac{\kappa}{N}$. It then follows that the magnitude will be $2N\frac{l}{\kappa}\left(1 - \frac{l}{\kappa}\right)$ and we get that $\frac{l}{\kappa} < 1$ is required for an epidemic. This is more commonly expressed as $R_0 = \frac{\kappa}{l} > 1$, where R_0 is called the basic reproduction number.

The basic reproductive number had been developed previously in demographics modelling, or modelling of vector borne diseases (such as malaria), but Ogilvy

Kermack and McKendrick were (to the best of my knowledge) the first to develop it for a model where the disease is transmitted by interaction between infected and susceptible individuals [19].

2

The models

The models in this paper are non-linear ordinary differential equations that both split the population into four compartments, Susceptible, Exposed, Infected and Removed. To avoid confusion I will refer to the conventional version as the SEIR-model, and I will refer to the modified version as "the modification" or variants thereof.

The models are not directly time dependent, but depend only on the state itself. This means that a given state will always evolve in the same way. There are versions of SEIR where this is not the case, such as when the parameter governing the spread of disease is a function of time rather then a constant. This is commonly used to model diseases that have seasonality such as influenza, where infectivity is higher in the winter giving rise to influenza seasons [17].

2.1 SEIR

The SEIR model aims to incorporate the fact that an individual does not immediately become infectious once exposed. For some diseases the period between exposure and infectivity can be significant. Lets imagine a scenario where a disease has a 10 day latency period between an individual being exposed and becoming infectious. If we fit a SIR model based on how many people are currently ill, we will not be able to capture the fact that there is a ten day backlog of exposed individuals. In the SIR model individuals essentially run into each other and instantly turn each other infectious. In SEIR we could have a situation where the disease is very infectious, and also has a long latency period. In such a situation lots of people would be exposed very quickly, to then slowly but surely trickle into the Infected compartment.

Remark 2.1. In this thesis all parameters and variables of the models will be elements of $\mathbb{R}$ or $\mathbb{R}^n$ unless explicitly stated.

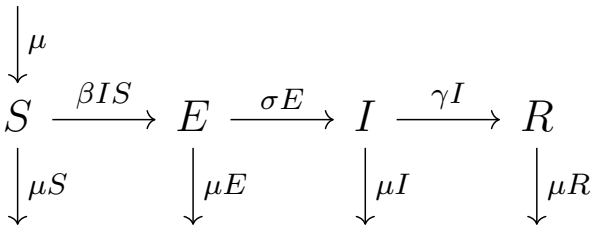
$$\begin{cases} \dot{S} = & \mu - \mu S - \beta IS \\ \dot{E} = & \beta IS - (\mu + \sigma)E \\ \dot{I} = & \sigma E - (\gamma + \mu)I \\ \dot{R} = & \gamma I - \mu R \end{cases} \quad \text{where } \beta, \sigma, \gamma, \mu > 0$$

The basic reproduction number of the SEIR model is:

$$R_0 = \frac{\sigma}{\gamma + \mu} \frac{\beta}{\mu + \sigma}$$

This is interesting because if $\mu = 0$ we get $\frac{\beta}{\gamma}$. So R_0 only depends on σ if people can die. If there is no other way to leave exposed than becoming infected, the speed at which exposed become infected is irrelevant to the long term outcome of the outbreak. If people can die, however, the fact that some exposed individuals will die before becoming infectious is very relevant to the long term outcome of the outbreak.

The following diagram is intended to illustrate the transitions between compartments, as well as the vital dynamics.



2.2 SEIR: Modification

This modification is intended to correspond to a scenario where some exposed people act as spreaders of the disease without ever getting ill themselves. These individuals will be called asymptomatic, while those who do not spread the disease while exposed

and get ill will be called symptomatic.

$$\begin{cases} \dot{S} = & \mu - \mu S - \beta\left(\frac{\sigma_2}{\sigma_1+\sigma_2}E + I\right)S \\ \dot{E} = & \beta\left(\frac{\sigma_2}{\sigma_1+\sigma_2}E + I\right)S - (\mu+\sigma_1+\sigma_2)E \\ \dot{I} = & \sigma_1 E - (\gamma+\mu)I \\ \dot{R} = & \sigma_2 E + \gamma I - \mu R \end{cases} \quad \text{where } \beta, \sigma_1, \sigma_2, \gamma, \mu > 0$$

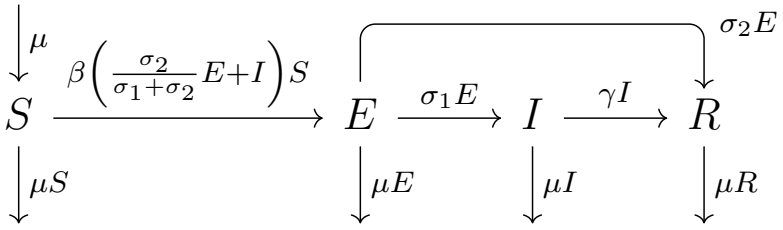
This modification is an attempt to model asymptomatic transmission without increasing the dimensionality of the state space. The basic reproduction number of the model is

$$R_0 = R_0^I + R_0^E$$

Where

$$R_0^I = \frac{\beta\sigma_1}{(\mu+\sigma_1+\sigma_2)(\mu+\gamma)}, \quad R_0^E = \frac{\beta\sigma_2}{(\mu+\sigma_1+\sigma_2)(\sigma_1+\sigma_2)}$$

The reasoning for the notation is then that R_0^I describes the spread in a completely susceptible population caused by infected individuals. In the same way R_0^E describes the spread caused by exposed individuals. The following diagram illustrates the transitions between compartments as well as the vital dynamics.



2.3 The parameters

For the SEIR model with vital dynamics and constant population there are four parameters to consider, μ, β, γ and σ. In this thesis the birth rate is assumed to be equal to the (natural) mortality μ, and as such the population is of constant size. This assumption is not always appropriate, but when considering a population where the change in population is steady and small on the time scales we are interested in, it is a fair approximation. The importance of the μ is mainly that without vital dynamics it is not possible to have an equilibrium with $E, I > 0$. This is intuitively clear, as the total number susceptible individuals is finite if $\mu = 0$. When $\mu > 0$ there

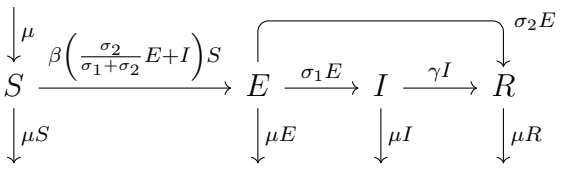
is a continuous replenishment of susceptible individuals. It is therefore possible for the disease to persist indefinitely, given the right conditions. The parameters σ and γ are fairly straightforward. They govern the rate at which people go from exposed to infected, and infected to removed respectively. Additionally $\frac{1}{\sigma+\mu}$ and $\frac{1}{\gamma+\mu}$ give us the average time spent as Exposed or Infected.

The parameter β is a bit more complicated, and as such requires a bit more explanation. It is clear that exposure to a pathogen requires an interaction between susceptible and infected individuals. Consider a physical system of two ideal gases A and B. Then the collision frequency Z is

$$Z = N_A N_B \sigma_{AB} c_{AB}$$

where $N_A,\ N_B$ are the number of particles in each gas, σ_{AB} is the collisional crossection and c_{AB} is the average velocity of particles in the system [4]. As we are not overly interested in the specific physical properties of a gas we can consider the cross section and the velocity to be simply a constant that affects the number of collisions. Consider a collision between a particle of type A and a particle of type B analogous to an interaction where an infected individual exposes a susceptible individual. With β being a constant governing the frequency of collisions analogous to the physical constants we then have βIS collisions, and thus exposures, per unit time.
One issue with this approach is that every particle in an ideal gas is equally likely to collide with any other. In reality we tend to see behaviours such as clustering of cases, rather then a uniform spread throughout the entire population. Consider a human being living in some particular city as an example. It seems likely that this individual will interact with other denizens of their city more frequently then denizens of other cities. We should be aware that the uniform probability of interaction in the entirety of the population is a simplification that may or may not be appropriate.

The modification is very similar to the ordinary SEIR-model in terms of parameters.



The first difference is that the transition rate out of the exposed compartment is

governed by two parameters (disregarding μ). The first, σ_1 acts in an identical manner to σ in the SEIR-model. The second parameter, σ_2, acts as a bypass of the infected compartment. Disregarding deaths (we assume that those who die while exposed are asymptomatic and symptomatic in the same proportion as those who live), per time unit $(\sigma_1+\sigma_2)E$ leave the exposed compartment, and are either symptomatic or asymptomatic. Of these $\sigma_2 E$ enter the removed compartment, and are thus asymptomatic. If we consider that the asymptomatic are precisely those who enter the removed compartment from the exposed compartment, then the fraction $\frac{\sigma_2}{\sigma_1+\sigma_2}$ is simply the proportion of asymptomatic individuals in E. The second difference compared to the SEIR model is the term $\beta\frac{\sigma_2}{\sigma_1+\sigma_2}ES$. This acts in the same manner as βIS, except only the asymptomatic portion, $\frac{\sigma_2}{\sigma_1+\sigma_2}E$, can expose others while exposed. This portion are assumed to be precisely as infectious as those in the Infected compartment.[1]

The basic reproduction number R_0 is often described as the number of infections an infected individual is expected to cause. This is essentially true, but there is a nuance to keep in mind. It is more precisely the number of expected infections in a completely susceptible population. Intuitively we can think of it as the number of infections per infected when there are no limiting factors such as immunity or others already being infected.

2.4 CWD as a SEIR candidate

In the interest of further motivating the importance of analysing these models, we will consider Chronic Wasting Disease.

Reading the paper by Osterholm et. al. published in 2019 [20], as well as the center of disease control website [6, 7], we can learn the following about the disease. Chronic wasting disease is a transmissible spongiform encephalopathy (TSE) affecting cervids, such as moose, deer and reindeer. The disease affects the nervous system and brain, and is like all TSE's always fatal. Once infected there is a significant incubation period, perhaps over a year. The pathogen is a prion, a misfolded protein with the unfortunate property that it causes normal variants of the protein to become misfolded too. The prions cause neurons to die, which in turn gives the brain a sponge-like appearance under a microscope. The prions are present in bodily fluids

[1] The choice of $\beta\frac{\sigma_2}{\sigma_1+\sigma_2}$ as the constant governing spread caused by exposed individuals is discussed in the Closing Remarks

such as saliva, feces and urine, and can persist in the environment for years. The most likely main mechanism of spread is direct contact between cervids, although it is possible for animals to become infected by contact with excreted prions in the environment. Human activity, such as the movement and feeding of cervids, is contributing by transporting infected animals to unaffected areas and by concentrating animals at locations where they are fed. Currently the evidence of zoonotic potential is not strong, but the CDC recommends taking steps to minimize exposure. Even so, it is estimated that 7000-15000 infected animals are consumed each year by humans. If there is zoonotic transmission of CWD, the long incubation period of similar prion diseases in humans likely means that once cases are detected transmission has been ongoing for some time. This is exacerbated by the difficulty in diagnosis, which may further delay discovery of animal to human transmission [20, 6, 7]. Shedding of CWD prions have been detected "as early as" 3 months post exposure in white-tailed deer [14]. Coupled with the long incubation this means that animals are likely infectious for an extended period before symptoms manifest.

CWD is a strong candidate to be modelled by an autonomous SEIR-model for a number of reasons. As a consequence of the lethality of the pathogen reinfections are not a factor that needs to be considered. The long time between exposure and shedding motivates the inclusion of an Exposed compartment. There is no evidence of seasonality as far as the sources of this thesis are concerned, which lends credence to constant parameters being sufficient for modelling. It is also a concerning pathogen, even if one disregards the zoonotic potential.

3

Theory

The aim of this section is to provide a sufficiently thorough account of dynamical systems and the theory underpinning the analysis performed in this thesis in particular. The overview of dynamical systems is intended to be very general, while the section on autonomous continuous-time ODE is intended to be more specific .

3.1 An overview of dynamical systems

Dynamical systems are, as one might suspect, dynamic. They evolve and change, and this is their defining feature. The fact that we live in a universe that evolves in a manner described by mathematical laws, means that these systems are very useful for those with a bent toward application. Many phenomena are prime candidates for modelling as dynamical systems, such as simulations of physical systems and modelling populations of animals. Dynamical systems are of course not limited to practical applications, a personal favourite of mine is the Mandelbrot set which arises out of a dynamical system. The unifying principle is dealing with a state that evolves over time, where time is more or less literal depending on the system at hand.

To have a dynamical system, we need a set of states which the system can be in, and a mechanism for the states to change.

Definition 3.1 (Dynamical system)**.** A dynamical system is a triple (M, T, φ) satisfying:

1. $M \neq \varnothing$ is a set
2. T is a monoid.
3. $D \subseteq M \times T$ s.t. $proj_1(D) = M$ where $proj_1 : (x, t) \mapsto x$
4. $\varphi : D \to M$ with $\varphi(x,\ 0) = x$ and $\varphi(\varphi(x,\ t_2),\ t_1) = \varphi(x,\ t_1 + t_2)$ for $t_2, t_1 + t_2 \in I(x) = \{t \in T \mid (x, t) \in D\},\ t_1 \in I(\varphi(x, t_2))$

The set M is called the state space of the system, T is called the time set of the system and φ is called the state transition of the system [11].

The condition requiring that $M \neq \varnothing$ is fairly self explanatory, a dynamical system without states isn't very dynamic at all.
As for T, consider four common choices: $\mathbb{Z}$, $\mathbb{Z}^+$, $\mathbb{R}$ and $\mathbb{R}^+$. The differences between the four structures are very significant to the system. With $\mathbb{Z}$ and $\mathbb{Z}^+$ we have a discrete time system, whilst with $\mathbb{R}$ and $\mathbb{R}^+$ we will have a continuous time system. The fact that $\mathbb{Z}^+$ and $\mathbb{R}^+$ are monoids under addition (they lack additive inverses) on the other hand will yield time irreversible systems. For $\mathbb{Z}$ and $\mathbb{R}$ we have time reversible systems (perhaps for a very limited interval of time), where we can apply the state transition φ on a state with negative time to 'wind back the clock' of the system. In practice however it is common to say that $t \in \mathbb{R}$ even when the system is irreversible.

Invariant Sets

In this thesis we are mainly interested in the limiting behaviour of the system that we are modelling, and more precisely we are interested in the limiting behaviour as time increases. We wonder if, given the state of the system today, whether the disease will persist or die out as time passes.

Definition 3.2 (Trajectory)**.** Given a dynamical system (D, T, φ), $x \in D$ the set

$$\gamma_x = \{\varphi(x, t) | t \in I(x)\}$$

is called the **trajectory** of x.

The trajectory is in other words the states that x evolves into. The term **orbit** is also used for this concept in the literature, but we elect for the term trajectory for clarity, as orbit can imply a periodic or closed nature (such as the orbits of celestial bodies).

Definition 3.3 (Invariant set)**.** Consider the dynamical system (D, T, φ), and the subset $\Omega \subseteq D$ of the state space. The set Ω is said to be **invariant**, if the image of $\Omega \times T$ under the state transition φ is Ω:

$$\varphi(\Omega,\ T) = \{\varphi(x,t) \mid x \in \Omega,\ t \in T\} = \Omega$$

This means that for all $x \in \Omega$ we have that $I(x) = T$. It also means that $\forall x \in \Omega,\ \gamma_x \subseteq \Omega$. This is a good start to understanding the dynamics of the system. If we have an invariant set, we know that all states therein remain there for all time. If the system is time reversible, e.g. $T = \mathbb{R}$, that means that not only do no states leave the set, no states that are outside the set can enter. There is a special kind of invariant set that we are especially interested in in this thesis.

Definition 3.4 (Equilibrium point)**.** The point $\overline{x}$ is said to be an **equilibrium point** of the dynamical system (D, T, φ) if $\varphi(\overline{x}) = \overline{x}$ for all $t \in T$.

The final type of set we will define in this section is a limit set.

Definition 3.5 (ω-limit set)**.** The ω-limit set of a trajectory γ_x is the set:

$$\lim_{\omega} \gamma_x = \bigcap_{s \in T} \overline{\{\varphi(x,t) \mid t > s\}}$$

If we consider $t < s$ above we arrive at the α-limit set.

3.2 Autonomous Continuous-time ODE

There are some specific terms used for the particular type of dynamical systems that this thesis deals with, autonomous continuous time ODE.

Definition 3.6. A system of ODE

$$\dot{x}(t) = f(x(t)),\ f : \mathbb{R}^n \to \mathbb{R}^n$$

is called **autonomous** if f does not depend explicitly on t.

This means that the evolution of the system depends only on the state of the system. The systems that are considered in this thesis are autonomous, however there are many cases in epidemiology alone where non-autonomous systems may be a better choice. A good example is influenza, as we are more than likely to be aware of the "influenza season". This is caused by seasonal changes that affect the infectiousness of the pathogen. In the case of the models in this thesis this would be modelled by having parameters be time-dependent, thus losing the autonomy of the system. More generally there are other approaches, and for anyone interested in particulars about the seasonality and modelling of influenza I recommend [17].

There are a few types of invariant sets that we did not include in the previous section that will be important going forward. The reason why they are relegated to this section is that they are a bit difficult to put in such general terms. So in the interest of clarity I will define them in a context where the time set is $\mathbb{R}$. Definition 3.3 is certainly a useful definition, but what if we are only interested in one direction of time? If one is concerned with forecasting, or perhaps understanding the origins of some current state, then the behaviour of the model is only of interest as it progresses in a certain direction in time. This is exactly the case in the epidemiological models in this thesis. In fact, we can begin in a state that is valid in the context of the model, and by moving the clock backwards we can enter invalid states. But this is of no concern to us, as long as the set of valid states is positively invariant, any valid initial state will remain so as it evolves forward in time.

Definition 3.7 (Positively- and Negatively invariant sets)**.** Consider the dynamical system $(D, \mathbb{R}, \varphi)$ and the subset $\Omega \subseteq D$ of the state space. Furthermore define the following sets:

$$\mathbb{R}^+ = \{t \in \mathbb{R} \mid t \geq 0\}, \quad \mathbb{R}^- = \{t \in \mathbb{R} \mid t \leq 0\}$$

Then Ω is said to be **positively invariant** and/or **negatively invariant** if

$$\varphi(\Omega, \mathbb{R}^+) = \Omega, \quad \varphi(\Omega, \mathbb{R}^-) = \Omega$$

respectively.

This means that if Ω is positively invariant, then all $x \in \Omega$ have $R^+ \subseteq I(x)$. I will give a proof of this fact for $\dot{x} = f(x)$ when f is locally Lipschitz in proposition 3.15. The definition of sets that tend toward some equilibrium point is also relegated to this less general section.

Definition 3.8 (Stable and unstable sets)**.** For a dynamical system $(D, \mathbb{R}, \varphi)$, with an equilibrium point $\overline{x} \in D$ and $t \in \mathbb{R}$, the stable set of $\overline{x}$ is defined as

$$\{x \in D \mid \varphi(x,t) \to \overline{x},\ t \to \infty\}$$

and the unstable set of $\overline{x}$ is defined as

$$\{x \in D \mid \varphi(x,t) \to \overline{x},\ t \to -\infty\}$$

The commonly used term for a state transition is different when dealing with continuous time systems:

Remark 3.9 (Flow). A state transition $\varphi : M \times \mathbb{R} \to M$ is called a **flow**.

As the models in this thesis are continuous time models, the state transition function will be referred to as the flow. At times $x(t)$ may be referred to as the flow, as $x(t) = \varphi(x(0), t)$. Continuous time systems have an added benefit of equilibrium points being easy to identify:

Remark 3.10 (Equilibrium point). The point $\overline{x}$ is an equilibrium point of the system $\dot{x} = f(x)$, where $f : \mathbb{R}^n \to \mathbb{R}^n$, if $f(\overline{x}) = 0$.

This fact will be of use when identifying equilibrium points of the models.

Existence and Uniqueness

The existence and uniqueness of solutions to a particular problem is a theme that runs through much of mathematics. Can a certain problem be solved, is a potential solution unique? These questions are often the ones that we seek to answer. When considering systems that are supposed to model some kind of physical reality, however, we may have to make assumptions to ensure the existence of a unique solution, at least locally.
Let's consider a simple pendulum, as an example. It would be problematic if the same initial state could lead to different evolutions of the system, as we expect it to evolve deterministically. As the models in this thesis aim to model the spread of disease in a deterministic fashion we are interested in what assumptions are required to ensure it. There are stochastic models of disease spread, but they are beyond the scope of this thesis.

Definition 3.11. For metric spaces (X, d_X) and (Y, d_Y) function $f : X \to Y$ is said to be **locally Lipschitz continuous** if for all $x \in X$ there exists a neighborhood $x \in N \subseteq X$ and $k \in \mathbb{R}^+$ such that

$$\forall x_1, x_2 \in N,\ d_Y\left(f(x_1), f(x_2)\right) \leq k \cdot d_X(x_1, x_2)$$

If $k < 1$, then f is a contraction, and the Banach fixed point theorem can be used. This can in turn be used to prove the upcoming uniqueness and existence theorem. However we will utilize the following inequality as it will be of help when we consider a compact positively invariant set.

Proposition 3.12 (Grönwall's Inequality)**.** *Let I be an interval $[t_0, T]$, $[t_0, T)$ or $[t_0, \infty)$ and $\mathcal{C}(I)$ be the class of continuous functions on I. Furthermore let $a,\ f,\ g : I \to \mathbb{R}$ where $g, f \in \mathcal{C}(I)$ and the negative part of a is integrable on every compact sub-interval of I. Then if $g \geq 0$, a is not decreasing and f satisfies*

$$f(t) \leq a(t) + \int_{t_0}^{t} f(s)g(s)ds$$

then f satisfies

$$f(t) \leq a(t)e^{\int_{t_0}^{t} f(s)g(s)ds}$$

Proof: See Bellman, 1943 [5].

The above is the integral version of Grönwall's inequality.

Theorem 3.13 (Picard-Lindelöf)**.** *Let $f : \mathbb{R}^n \to \mathbb{R}^n$ and consider the system*

$$\begin{cases} \dot{x}(t) = f(x(t)) \\ x(t_0) = x_0 \end{cases}$$

If f is locally Lipschitz continuous in x, then there exists a unique solution $x^*(t) \in \mathcal{C}^1\left((t_0 - \varepsilon, t_0 + \varepsilon)\right)$

Proof: Assume there exists two different solutions y, x satisfying the initial value problem. If there is in fact a unique solution on some interval, then the metric $d(x(t), y(t))$ must be zero on that interval. Let us write the metric in terms of the norm, $||x(t) - y(t)||$. A solution must furthermore satisfy $x(t) = x(t_0) + \int_{t_0}^{t} \dot{x}(s)ds$.

$$||x(t) - y(t)|| = ||\int_{t_0}^{t} \dot{x}(s) - \dot{y}(s)ds|| \leq \int_{t_0}^{t} ||\dot{x}(s) - \dot{y}(s)||ds$$

By the continuity of $x(t)$ and $y(t)$, as well as the fact that $x(t_0) = y(t_0)$, we can find t such that $x(t), y(t) \in N$, where N is the neighborhood of $x(t_0)$ where f is Lipschitz continuous. In this neighborhood we have:

$$\int_{t_0}^{t} ||f(x(s)) - f(y(s))|| \leq \int_{t_0}^{t} K||x(s) - y(s)||ds$$

Using Grönwalls Inequality with $f(t) = ||x(t) - y(t)||,\ a(t) = 0,\ g(t) = K$, we get

$$||x(t) - y(t)|| \leq 0 \iff x(t) = y(t) \text{ for } x(t), y(t) \in N$$

By continuity there exists a $\varepsilon > 0$ such that

$$x(t), y(t) \in N,\ \forall t \in (t_0 - \varepsilon, t_0 + \varepsilon)$$

So there is a unique solution locally. □
In the context of the models in this thesis, and the assumption that birth and death rates are the same, we are really only interested in a positively invariant subset of $\mathbb{R}^3$.

Proposition 3.14. *If $f : \mathbb{R}^n \to \mathbb{R}^n$ is a locally Lipschitz continuous function in x, and Ω is a positively invariant compact set of the system*

$$\begin{cases} \dot{x} = f(x) \\ x(t_0) = x_0 \in \Omega \end{cases}$$

then there exists a unique solution for $t \in [t_0, \infty)$.

Proof: As f is locally Lipschitz continuous, there exists a neighborhood around every point in Ω where f is Lipschitz continuous. The union of all these open sets form an open cover of Ω, and by the compactness of Ω there is a finite subcover. It follows that there is a Lipschitz constant K such that f is Lipschitz continuous in x in the entirety of Ω.
Let $x(t), y(t)$ be solutions to the system. Following the procedure of the previous theorem, but with Ω instead of an neighborhood, we arrive at

$$x(t) = y(t),\ x(t), y(t) \in \Omega$$

which by positive invariance of Ω is true for $t \in [t_0, \infty)$. □

So we have arrived at the conclusion that any initial state in the compact invariant set has a unique solution forward in time. This is welcome as the models are intended to evolve in a deterministic manner.
Note: As solutions are unique this means that no trajectory can reach an equilibrium point in finite time, as this would violate the uniqueness of solutions.

3.3 Stability

The main focus of this thesis is the stability of the equilibrium points of the models in question. As such it is important to have a notion of what exactly it means for an equilibrium point to be stable. There are two notions of stability that are adressed in this text. The first is the idea that states close to the equilibrium should stay close:

Definition 3.15. An equilibrium point x^* is called **Lyapunov stable** if

$$\forall \varepsilon > 0,\ \exists \delta > 0,\ \text{s.t. } ||x(t_0) - x^*|| < \delta \implies ||x(t) - x^*|| < \varepsilon,\ \forall t \geq t_0$$

This stability is limited in some ways. It does not really tell us much of the larger scale behaviour of the system, as it is mainly focused on states in the neighborhood of the equilibrium. As we are interested in a more global notion of stability we introduce the second type of stability:

Definition 3.16. An equilibrium point x^* is called **asymptotically stable** if, in addition to being stable, it satisfies

$$\exists \delta_0,\ ||x(t_0) - x^*|| < \delta_0 \implies \lim_{x \to \infty} x(t) = x^*$$

This is much more stringent, as it requires states to approach the equilibrium as $t \to \infty$. The main focus of this thesis is the asymptotic stability of equilibrium points. A point that satisfies this condition is called 'attractive' or an 'attractor'. An equilibrium is called **locally asymptotically stable** if there is a neighborhood where it is asymptotically stable. If an equilibrium is asymptotically stable on some invariant set, we will say that it is **globally stable**.

3.4 Local Stability

Linear ODE are nice to deal with, especially in terms of stability. A linear system $\dot{x} = Ax$ is asymptotically stable at 0 if all eigenvalues λ_i of A satisfy $\mathrm{Re}(\lambda_i) < 0$. Under what circumstances are the behaviours of a non linear system and its linearization the same in terms of stability?

Definition 3.17. An equilibrium x^* of a system $\dot{x} = f(x)$ is said to be hyperbolic, if all eigenvalues λ_i of the Jacobian $\mathcal{J}_f(x^*)$ satisfy

$$\mathrm{Re}(\lambda_i) \neq 0$$

Definition 3.18. A system $\dot{x} = f(x)$ with a flow φ is said to be **topologically flow conjugate** with another system $\dot{y} = g(y)$ with flow ψ if there is a homeomorphism h such that

$$\begin{array}{ccc} x_0 & \xrightarrow{\varphi} & x_t \\ \downarrow h & & \downarrow h \\ y_0 & \xrightarrow{\psi} & y_t \end{array}$$

commutes.

That h is a homeomorphism means that it is bijective, continuous and that its inverse h^{-1} is continuous.

Theorem 3.19 (Hartman-Grobman)**.** *A system $\dot{x} = f(x)$ with smooth f and a hyperbolic equilibrium point x^* is topologically flow conjugate to its' linearization $\dot{X} = \mathcal{J}_f(x^*)X$ in some neighborhood of x^*.*

Proof: See Hartman 1964 [13].

The Hartman-Grobman Theorem tells us that when a system has a hyperbolic fixpoint it will behave locally as its linearization does. This is powerful because there is an algorithmic method to determine when the eigenvalues all have negative real part, the Routh-Hurwitz Criterion.

Proposition 3.20 (Routh-Hurwitz stability Criterion)**.** *For second and third degree polynomials in particular:*

$$x^2 + ax + b \text{ has all roots in the open left half plane} \iff a, b > 0$$

$$x^3 + ax^2 + bx + c \text{ has all roots in the open left half plane} \iff a, c > 0,\ ab > c$$

For higher degree polynomials the Routh-Hurwitz stability criterion gets rather complicated, but since we will have to deal with 3rd degree polynomials at most we will leave it at that.

3.5 Global stability

Local asymptotic stability is good, but what about asymptotic stability on arbitrary sets?

Theorem 3.21 (LaSalle theorems)**.** *Let M be some set. We say that $x(t) \to M$ if for all $\varepsilon > 0$ there exists a $T > 0$ such that for all $t > T$ there exists $p \in M$ such that $||x(t) - p|| < \varepsilon$.*

1. *Let Ω be a compact positively invariant set, and suppose $V(x) \in \mathcal{C}^1(\Omega)$ and $\dot{V}(x) \leq 0$ in Ω. Let M be the maximal invariant subset of $\{x \in \Omega \mid \dot{V}(x) = 0\}$, then*
$$x \in \Omega,\ t \to \infty \implies x \to M$$

2. *Let $\Omega := \{x \mid V(x) \leq c\}$ for some c. Suppose $V(x) \in \mathcal{C}^1(\Omega)$ and that $\forall x \in \Omega,\ \dot{V}(x) \leq 0$. Let M be the maximal invariant subset of $\{x \in \Omega \mid \dot{V}(x) = 0\}$. Then*
$$x \in \Omega,\ t \to \infty \implies x \to M$$

Proof: See Lasalle, 1960 [16].
The fact that $x \to M$ means that the limiting set $\lim_\omega \gamma_x$ is contained in M. This theorem will be very useful, because functions that satisfy the conditions in it are easier to find than Lyapunov functions (because the conditions are more lenient).

Definition 3.22 (Lyapunov function)**.** Consider a system $\dot{x} = f(x)$, and WLOG let 0 be an equilibrium point. We say that a function $V : \mathbb{R}^n \to \mathbb{R}$, $V \in \mathcal{C}^1$, is a **Lyapunov function** if

1. $V(x) > 0 \iff x \neq 0$

2. $V(x) = 0 \iff x = 0$

3. $\dot{V}(x) = \nabla V(x) \cdot f(x) \leq 0$

Definition 3.23 (Lyapunov function)**.** Given a system $\dot{x} = f(x)$ We say that a function $V : \mathbb{R}^n \to \mathbb{R}$ is a **Strict Lyapunov function**, if, in addition to being a Lyapunov function it satisfies

$$\dot{V}(x) = \nabla V(x) \cdot f(x) < 0, \ \forall x \neq 0$$

A common way to explain these functions is as similar to the energy of a physical system. A physical system tends toward its lowest energy state, and in an analogous manner we want to find the 'energy' of our system. By this line of thinking the goal is to demonstrate that the 'energy' of our system will decrease until it reaches the equilibrium. I personally, however, found that it was more intuitive to think of it in a different manner. For the sake of our intuition we will consider a vector field in two dimensions. Our goal then is to find a surface such that all vectors in the vector field point "downhill", and where the lowest point is the equilibrium point. A initial point then I think of as something like a marble placed on the surface, and then rolling down toward the equilibrium. This is not a very rigorous way of thinking about Lyapunov functions, but it did help me to get an intuitive idea of how stability follows from the existence of such a function.
In the case where the set of interest is the entirety of $\mathbb{R}^n$, the following is true:

Remark 3.24. Let $V(x)$ be a strict Lyapunov function for a system. If it is **radially unbounded**, that is $V(x) \to \infty$ as $||x|| \to \infty$, then the system is globally stable on $\mathbb{R}^n$.

We want to determine sufficient conditions on a Lyapunov function for global stability on arbitrary sets however.

Definition 3.25 (sublevel set)**.** Given a real valued function, a set of the form

$$\{x \mid f(x) \leq C\}$$

is called a **sublevel set**.

In the case of Lyapunov functions, which have a minimum of 0, the preimage $V^{-1}([0, C])$ is the sublevel set $\{x \mid V(x) \leq C\}$.

Proposition 3.26. *The requirement of radial unboundedness for global stability is equivalent to requiring compact sublevel sets.*

Proof: The condition is that $V(x)$ is a **proper** map, that is for all compact sets $S \subseteq \mathbb{R}$ the preimage $V^{-1}(S)$ is a compact set in $\mathbb{R}^n$. By the definition of radial unboundedness we know that the preimage of a compact interval is bounded, and by continuity we know that it is closed. It follows from Heine-Borel that the preimage is compact, and therefore the sublevel set is compact. □

Theorem 3.27 (Lyapunov direct method)**.** *If $V(x)$ is a strict Lyapunov function with compact sublevel sets on $\Omega \subseteq \mathbb{R}^n$, then the equilibrium x^* is asymptotically stable and attractive for all points in Ω.*

Proof: As V is a strict Lyapunov function it certainly satisfies the conditions on V in theorem 3.21 *ii*. Ω may not be compact, but $\forall y \in \Omega$ the sublevel set $V^{-1}([0, V(y)])$ is compact by assumption, and positively invariant since $0 \leq V(t) \leq V(s)$ when $t > s$. All elements in Ω is part of such a sublevel set. As there is only one x such that $\dot{V}(x) = 0$, and since this point x^* is invariant it follows by theorem 3.21 that

$$\forall x(t_0) \in \Omega, \ \lim_{t \to \infty} x(t) = x^*$$

And x^* is therefore asymptotically stable and attractive in Ω. □

This concludes the theory section, and we are now ready to begin the analysis of the models.

4

Analysis of the models

In this section the analysis of the models is presented. Initially the basic reproduction number will found using the next generation method, and then the existence of equilibria will be established. After that the set of viable states will be shown to be positively invariant. Finally the local and global stability of the equilibria will be analyzed using linearization, Lyapunov functions and LaSalle's invariance theorem.

4.1 The Basic reproduction number

There are surprisingly many ways to calculate the basic reproduction number R_0 for a model. The method we will use is the next generation method.

Definition 4.1 (Next generation matrix)**.** Consider a compartmental model with m infected compartments x_i (such as exposed and infected). Let $\dot{x_0} = f_i(x) - v_i(x)$ where f_i is the rate of transition into compartment i, excluding incoming transitions from other infected compartments. v_i is the rate of transition out of compartment i, minus the influx to compartment i from other infected compartments. Let F and V be matrices with entries:

$$F_{i,j} = \frac{\partial f_i(x_0)}{\partial x_j}, V_{i,j} = \frac{\partial g_i(x_0)}{\partial x_j}$$

Then the next generation matrix is:

$$FV^{-1}$$

The idea is that R_0 is the spectral radius (maximum magnitude eigenvalue) of the next generation matrix [19].

Let us begin with the SEIR-model.

$$\begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\mu+\sigma} & 0 \\ \frac{1}{(\mu+\gamma)(\mu+\sigma)} & \frac{1}{\mu+\gamma} \end{pmatrix} = \begin{pmatrix} \frac{\beta\sigma}{(\mu+\sigma)(\mu+\gamma)} & \frac{\beta}{\mu+\gamma} \\ 0 & 0 \end{pmatrix}$$

The spectral radius is clearly $\frac{\beta\sigma}{(\mu+\sigma)(\mu+\gamma)} = R_0$. Let's do the same for the modification.

$$\begin{pmatrix} \beta\frac{\sigma_2}{\sigma_1+\sigma_2} & \beta \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\mu+\sigma_1+\sigma_2} & 0 \\ \frac{\sigma_1}{(\mu+\gamma)(\mu+\sigma_1+\sigma_2)} & \frac{1}{\mu+\gamma} \end{pmatrix} = \begin{pmatrix} \frac{\beta\sigma_2}{(\mu+\sigma_1+\sigma_2)(\sigma_1+\sigma_2)} + \frac{\beta\sigma_1}{(\mu+\sigma_1+\sigma_2)(\mu+\gamma)} & \frac{\beta}{\mu+\gamma} \\ 0 & 0 \end{pmatrix}$$

The spectral radius is then $\frac{\beta\sigma_2}{(\mu+\sigma_1+\sigma_2)(\sigma_1+\sigma_2)} + \frac{\beta\sigma_1}{(\mu+\sigma_1+\sigma_2)(\mu+\gamma)} = R_0$.

4.2 Equilibria

The existence and stability of equilibria is of great interest in these epidemiological models, as we can determine the behaviour of an outbreak. A globally stable Disease Free Equilibrium, for an example, will as the name implies mean that the disease will die out on its own.

The first order of business is to determine the equilibria of the models in question. A fundamental requirement for an equilibrium is that the time derivatives at that point are zero.

$$\begin{cases} 0 = & \mu - \mu S - \beta IS \\ 0 = & \beta IS - (\mu+\sigma)E \\ 0 = & \sigma E - (\gamma+\mu)I \\ 0 = & \gamma I - \mu R \end{cases}$$

That a Disease Free Equilibrium exists can easily be intuited, if there is no one who can transmit the disease, then no one will move from Susceptible to Exposed. This equilibrium, $(1, 0, 0, 0)$, follows from assuming there is an equilibrium that is without infected. With strictly positive parameters it follows that there can be no Exposed nor Recovered, and that $S = 1$. This Equilibrium will exist for all models presented in this text, and will often be referred to as the 'DFE'.

If we instead posit that there is an Endemic Equilibrium ("EE") with $I > 0$ we arrive

at the following through the derivation in the section 7.1 of the appendix:

$$\begin{cases} S = & \frac{1}{R_0} \\ E = (R_0 - 1)\frac{\mu(\gamma+\mu)}{\sigma\beta} \\ I = & (R_0 - 1)\frac{\mu}{\beta} \\ R = & (R_0 - 1)\frac{\gamma}{\beta} \end{cases}$$

We can see that it is necessary for R_0 to be greater that 1 for this equilibrium to exist, and that as R_0 approaches one this equilibrium will get arbitrarily close to the DFE.
We proceed in the exact same manner for the modification

$$\begin{cases} 0 = & \mu - \mu S - \beta\left(\frac{\sigma_2}{\sigma_1+\sigma_2}E + I\right)S \\ 0 = \beta\left(\frac{\sigma_2}{\sigma_1+\sigma_2}E + I\right)S - (\mu + \sigma_1 + \sigma_2)E \\ 0 = & \sigma_1 E - (\gamma + \mu)I \\ 0 = & \sigma_2 E + \gamma I - \mu R \end{cases}$$

Appendix 7.2 details the derivation of the Endemic Equilibrium in the modification. We arrive at:

$$\begin{cases} S = & \frac{1}{R_0} \\ E = & \left(1 - \frac{1}{R_0}\right)\frac{\mu}{\mu+\sigma_1+\sigma_2} \\ I = & \left(1 - \frac{1}{R_0}\right)R_0^I\frac{\mu}{\beta} \\ R = \left(1 - \frac{1}{R_0}\right)\frac{\gamma R_0^I + (\sigma_1+\sigma_2)R_0^E}{\beta} \end{cases}$$

4.3 Invariant set

As we are modelling a population it is of importance that $S, E, I \geq 0$. There is no such thing as a negative number of infected individuals, and it is important that our models reflect this. As we have made an assumption that the population remains constant, it is also important that $S + E + I \leq 1$. It is therefore necessary that as any "valid" initial state (a state that satisfies the two conditions above) of the system evolves, it remains valid. The set defined by these constraint needs to be a positively invariant set to ensure that this remains true for any initial state that is valid.

Proposition 4.2. *The compact set*

$$\Omega := \{(S, E, I) |\ S, E, I \geq 0,\ S + E + I \leq 1\}$$

is a positively invariant set for the SEIR model and the modification.

Proof: The boundary $\partial\Omega$ consists of four planes in $\mathbb{R}^3$, $S = 0$, $E = 0$, $I = 0$ and $S + E + I = 1$.

$$S = 0 \implies \dot{S} = \mu > 0,$$

$$E = 0 \implies \dot{E} = \beta IS \geq 0$$

$$I = 0 \implies \dot{I} = \sigma E \geq 0$$

So (S, E, I) will not leave the positive octant of $\mathbb{R}^3$

$$S + E + I = 1 \implies \dot{S} + \dot{E} + \dot{I} = -\gamma I \leq 0$$

$S + E + I$ will not be greater than 1. For the modification we have:

$$S = 0 \implies \dot{S} = \mu > 0$$

$$E = 0 \implies \dot{E} = \beta IS \geq 0$$

$$I = 0 \implies \dot{I} = \sigma_1 E \geq 0$$

$$S + E + I = 1 \implies \dot{S} + \dot{E} + \dot{I} = -\sigma_2 E - \gamma I \leq 0$$

It follows that the set is invariant for both models □

This conforms with the expectation we have based on the underlying reality that we are modelling. This set is, in addition to positively invariant, compact. It follows that solutions exist and are unique for $t \in [t_0, \infty)$ for both models.

4.4 Local stability

Initially we will assess the stability of the equilibria locally. This is not only interesting in its own right, but a locally unstable equilibrium is clearly unstable in general. In some sense the most important thing to establish using this method is under what circumstances the DFE is stable. To have even a sliver of hope of eradicating the disease, the disease free equilibrium must be locally stable.

Using the fact that $E + I + R = 1 - S$ it is sufficient to consider the system

$$\begin{cases} \dot{E} = \beta I(1 - E - I - R) - (\mu + \sigma)E \\ \dot{I} = \sigma E - (\gamma + \mu)I \\ \dot{R} = \gamma I - \mu R \end{cases}$$

Evaluating the Jacobian at the Disease Free Equilibrium $(E, I, R) = (0, 0, 0)$ we find:

$$\mathcal{J}(\overline{x}_{DFE}) = \begin{pmatrix} -\mu - \sigma & \beta & 0 \\ \sigma & -\gamma - \mu & 0 \\ 0 & \gamma & -\mu \end{pmatrix}$$

We want to find the characteristic polynomial of this matrix.

$$\det\left(\mathcal{J}(\overline{x}_{DFE}) - \lambda I\right) = (-\mu - \lambda)((-\mu - \sigma - \lambda)(-\gamma - \mu - \lambda) - \sigma\beta)$$

We disregard the factor $(-\mu - \lambda)$, since this eigenvalue will always be negative. Using the Routh-Hurwitz Criterion for second degree polynomials on the expanded expression

$$\lambda^2 + (\gamma + 2\mu + \sigma)\lambda - \sigma\beta + (\mu + \sigma)(\mu + \gamma)$$

we conclude that all eigenvalues will lie in the negative half plane when

$$\sigma\beta < (\mu + \sigma)(\mu + \gamma) \iff R_0 < 1$$

For the Endemic Equilibrium we follow the same procedure.

$$\mathcal{J}(\overline{x}_{EE}) = \begin{pmatrix} -\mu(R_0 - 1) - \mu - \sigma & \frac{\beta}{R_0} & 0 \\ \sigma & -\gamma - \mu & 0 \\ 0 & \gamma & -\mu \end{pmatrix}$$

$$\det\left(\mathcal{J}(\overline{x}_{EE}) - \lambda I\right) = (-\mu - \lambda)\begin{vmatrix} -\mu R_0 - \sigma - \lambda & \frac{\beta}{R_0} \\ \sigma & -\gamma - \mu - \lambda \end{vmatrix}$$

Again, disregard the factor $(-\mu - \lambda)$.

$$\lambda^2 + (\mu R_0 + \sigma + \gamma + \mu)\lambda + (\mu R_0 + \sigma)(\gamma + \mu) - (\gamma + \mu)(\sigma + \mu)$$

Simplifying we get the following expression:

$$\lambda^2 + (\mu R_0 + \sigma + \gamma + \mu)\lambda + (R_0 - 1)\mu(\gamma + \mu)$$

By the Routh-Hurwitz stability criterion for second degree polynomials, the eigenvalues have negative real part if and only if $R_0 > 1$.

In conclusion we find that when $R_0 < 1$ the Disease Free Equilibrium is locally stable, and that when $R_0 > 1$ we have a locally stable Endemic Equilibrium and an unstable Disease Free Equilibrium. When $R_0 = 1$ linearization can not be used to evaluate the stability as the equilibria are not hyperbolic.

The Modification

Because the modification is a little bit more complex than SEIR, the characteristic polynomials end up being pretty cluttered in comparison. The Jacobian for the DFE is:

$$\mathcal{J}(x_{DFE}) = \begin{pmatrix} -\mu & -\frac{\beta\sigma_2}{\sigma_1+\sigma_2} & -\beta \\ 0 & \frac{\beta\sigma_2}{\sigma_1+\sigma_2} - \mu - \sigma_1 - \sigma_2 & \beta \\ 0 & \sigma_1 & -\gamma - \mu \end{pmatrix}$$

We want to find the characteristic polynomial of this matrix. Using Laplace expansion we get:

$$\det\left(\mathcal{J}(\overline{x}_{DFE}) - \lambda I\right) = (-\mu - \lambda)\begin{vmatrix} \frac{\beta\sigma_2}{\sigma_1+\sigma_2} - \mu - \sigma_1 - \sigma_2 - \lambda & \beta \\ \sigma_1 & -\gamma - \mu - \lambda \end{vmatrix}$$

Disregarding the term $(-\mu - \lambda)$, as this eigenvalue is always negative, we get:

$$\left(\frac{\beta\sigma_2}{\sigma_1 + \sigma_2} - \mu - \sigma_1 - \sigma_2 - \lambda\right)(-\gamma - \mu - \lambda) - \sigma_1\beta$$

Expanding this expression we get:

$$\lambda^2 + \left((\gamma + 2\mu + \sigma_1 + \sigma_2 - \frac{\beta\sigma_2}{\sigma_1 + \sigma_2}\right)\lambda + (\gamma + \mu)(\mu + \sigma_1 + \sigma_2) - \frac{\beta\sigma_2(\gamma + \mu)}{\sigma_1 + \sigma_2} - \sigma_1\beta$$

We can rewrite the constant term as follows using the definition of R_0:

$$(\gamma+\mu)(\mu+\sigma_1+\sigma_2)-\frac{\beta\sigma_2(\gamma+\mu)}{\sigma_1+\sigma_2}-\sigma_1\beta=-(\gamma+\mu)(\mu+\sigma_1+\sigma_2)(1-R_0)$$

By the Routh-Hurwitz criterion for second degree polynomials we need

$$(\gamma+\mu)(\mu+\sigma_1+\sigma_2)\,(1-R_0)>0$$

and

$$\gamma+\mu+(\mu+\sigma_1+\sigma_2)(1-R_0^E)>0$$

for all eigenvalues to lie in the open half left plane. Thus we require that:

$$R_0=R_0^I+R_0^E<1 \text{ and } R_0^E<\frac{\mu+\gamma}{\mu+\sigma_1+\sigma_2}+1$$

Since $R_0^I, R_0^E>0$ only the first constraint is needed. It follows that the DFE is locally stable when $=R_0<1$.
Recall the Endemic equilibrium of the modification:

$$\begin{cases} S= & \frac{1}{R_0} \\ E=\left(1-\frac{1}{R_0}\right)\frac{\mu}{\mu+\sigma_1+\sigma_2} \\ I= & \left(1-\frac{1}{R_0}\right)R_0^I\frac{\mu}{\beta} \end{cases}$$

The Jacobian at the endemic equilibrium is then:

$$\mathcal{J}(x_{EE})=\begin{pmatrix} -\mu R_0 & -\frac{R_0^E}{R_0}(\mu+\sigma_1+\sigma_2) & -\frac{\beta}{R_0} \\ \mu(R_0-1) & (\mu+\sigma_1+\sigma_2)\left(\frac{R_0^E}{R_0}-1\right) & \frac{\beta}{R_0} \\ 0 & \sigma_1 & -\mu-\gamma \end{pmatrix}$$

We want to find the characteristic polynomial of this matrix.

$$\det(\mathcal{J}(x_{EE})-\lambda I)=\begin{vmatrix} -\mu R_0-\lambda & -\frac{R_0^E}{R_0}(\mu+\sigma_1+\sigma_2) & -\frac{\beta}{R_0} \\ \mu(R_0-1) & (\mu+\sigma_1+\sigma_2)\left(\frac{R_0^E}{R_0}-1\right)-\lambda & \frac{\beta}{R_0} \\ 0 & \sigma_1 & -\mu-\gamma-\lambda \end{vmatrix}$$

Using Laplace expansion we get

$$-\sigma_1 \begin{vmatrix} -\mu R_0 - \lambda & -\frac{\beta}{R_0} \\ \mu(R_0 - 1) & \frac{\beta}{R_0} \end{vmatrix} - (\mu + \gamma + \lambda) \begin{vmatrix} -\mu R_0 - \lambda & -\frac{R_0^E}{R_0}(\mu + \sigma_1 + \sigma_2) \\ \mu(R_0 - 1) & (\mu + \sigma_1 + \sigma_2)\left(\frac{R_0^E}{R_0} - 1\right) - \lambda \end{vmatrix}$$

which finally results in the following characteristic polynomial

$$-\lambda^3 - \lambda^2 \left(\mu + \gamma + \mu R_0 + \frac{R_0^I}{R_0}(\mu + \sigma_1 + \sigma_2)\right)$$

$$-\lambda \left(\mu R_0(\mu + \gamma) + \frac{R_0^I}{R_0}(\mu + \sigma_1 + \sigma_2)(\mu + \gamma) + \left(R_0^I + R_0^E\left(1 - \frac{1}{R_0}\right)\right)\mu(\mu + \sigma_1 + \sigma_2) + \frac{\sigma_1 \beta}{R_0}\right)$$

$$-\left(R_0^I + R_0^E\left(1 - \frac{1}{R_0}\right)\right)\mu(\mu + \sigma_1 + \sigma_2)(\mu + \gamma) + \frac{\sigma_1 \beta \mu}{R_0}$$

This polynomial is unwieldy to say the least. Luckily we have the Routh-Hurwitz criterion for 3rd degree polynomials: the polynomial $x^3 + ax^2 + bx + c$ has all roots in the open left half plane if and only if $a, c > 0$ and $ab > c$. Using this criterion we first get

$$\mu + \gamma + \mu R_0 + \frac{R_0^I}{R_0}(\mu + \sigma_1 + \sigma_2) > 0$$

which is always true given the restrictions on our parameters. Let $\left(R_0^I + R_0^E\left(1 - \frac{1}{R_0}\right)\right) = \overline{r}$, then the next inequality is:

$$\overline{r}\mu(\mu + \sigma_1 + \sigma_2)(\mu + \gamma) - \frac{\sigma_1 \beta \mu}{R_0} > 0$$

Multiplying by R_0 and using the definition of R_0^E we get

$$R_0 \overline{r}(\mu + \sigma_1 + \sigma_2)(\mu + \gamma) > R_0^I(\mu + \sigma_1 + \sigma_2)(\mu + \gamma)$$

By the fact that parameters are positive and non-zero it follows that

$$R_0 \overline{r} > R_0^I \iff R_0(R_0^I + R_0^E) - R_0^E > R_0^I \iff R_0^2 > R_0 \implies R_0 > 1$$

For the final inequality it is sufficient to consider:

$$(\mu + \gamma + \mu R_0)\overline{r}\mu(\mu + \sigma_1 + \sigma_2) - \overline{r}\mu(\mu + \sigma_1 + \sigma_2)(\mu + \gamma) + \frac{\sigma_1 \beta \mu}{R_0} > 0$$

As the full product of the coefficients for λ^2 and λ is greater than this and

$$\overline{r}(\mu R_0)\mu(\mu+\sigma_1+\sigma_2)+\frac{\sigma_1\beta\mu}{R_0}>0,\ \text{for}\ R_0>1$$

It follows that we have local asymptotic stability when $R_0 > 1$.

So, in a similar way to the conventional SEIR model, the DFE of the modification is locally stable when $R_0 < 1$. When $R_0 > 1$ there is a locally stable EE, and the DFE is unstable. When $R_0 = 1$ the equilibrium is again not hyperbolic, and linearization is not usable.

4.5 Lyapunov functions for SEIR

Lyapunov functions are tricky to find, and there are no general methods that allows you to produce them for arbitrary systems. There are known Lyapunov functions for certain types of system, and for sufficiently smooth systems one can find an approximate Lyapunov function by finding one for the polynomial approximation of the system.

The Lyapunov functions in this section are not of my making. See Korobeinikov, 2004 [3] for the more general versions of the functions which I have simplified here. The functions as written do not necessarily equal zero at the equilibrium as written, but this is only a matter of adding a constant and as such it is omitted for parsimony. Recall that $(S_0, E_0, I_0) = (1, 0, 0)$ is the disease free equilibrium.

Proposition 4.3. *The function*

$$V_{DFE}(S,E,I)=S-\ln(S)+E+\frac{\sigma+\mu}{\sigma}I$$

Is a Lyapunov function for the SEIR model in $\{(S,E,I)|S>0,\ E,I\geq 0\}$ *when* $R_0 \leq 1$

Since $S > \ln(S)$ and $\sigma, \mu, S, E, I \geq 0$ it is clear that $V_{DFE} \geq 0$. $V_{DFE}(1, 0, 0)$ is the minimum, and we simply add a constant such that $V_{DFE}(1, 0, 0) = 0$.

$$\dot{V}_{DFE}=-\mu(1-S)\left(\frac{1}{S}-1\right)-\frac{(\gamma+\mu)(\sigma+\mu)}{\sigma}(1-R_0)I$$

Since $\gamma,\ \mu,\ \sigma,\ R_0,\ S,\ I, \geq 0$

$$-\frac{(\gamma+\mu)(\sigma+\mu)}{\sigma}(1-R_0)\leq 0,\ \text{for}\ R_0\leq 1$$

$$-\mu(1-S)\left(\frac{1}{S}-1\right)\leq 0$$

For a more detailed version see Appendix 7.3.
As such $\dot{V}_{DFE}(S,E,I)<0$ for $(S,E,I)\neq(1,0,0)$, and $\dot{V}_{DFE}(1,0,0)=0$. It follows that V_{DFE} is a strict Lyapunov function for $\{(S,E,I)|S>0,\ E,I\geq 0\}$ [3]. It follows that the Disease free equilibrium is globally stable in this set when $R_0\leq 1$.

Let S^*,E^*,I^* be the endemic equilibrium.

Proposition 4.4. *The function*

$$V_{EE}(S,E,I)=S-S^*\ln(S)+E-E^*\ln(E)+\frac{\sigma+\mu}{\sigma}(I-I^*\ln(I))$$

Is a Lyapunov function for the SEIR-model in $\{(S,E,I)|S,E,I>0\}$ *when* $R_0>1$.

The gradient of this function is

$$\nabla V_{EE}(S,E,I)=\left(1-\frac{S^*}{S},\ 1-\frac{E^*}{E},\ \frac{\sigma+\mu}{\sigma}\left(1-\frac{I^*}{I}\right)\right)$$

Which has a minimum at (S^*,E^*,I^*).

$$\dot{V}_{EE}(S,E,I)=\left(1-\frac{S^*}{S}\right)\dot{S}+\left(1-\frac{E^*}{E}\right)\dot{E}+\frac{\sigma+\mu}{\sigma}\left(1-\frac{I^*}{I}\right)\dot{I}$$

The fact that this function is a strict Lyapunov in the positively invariant set for $R_0>1$ is shown in the paper by Korobeinikov [3]. However, as this paper deals with a variation of the model there are extra variables and a variable substitution that is superfluous in the case of the ordinary SEIR-model. Furthermore there are some 'non-obvious' steps taken. As such I am including a somewhat more comprehensive version that is specific to this model in the Appendix 7.4. Hopefully this will be helpful to elucidate how exactly we arrive at the conclusion that this is in fact a strict Lyapunov function.

4.6 LaSalle invariance theorem for the DFE of both models

While Lyapunov functions, especially strict Lyapunov functions, are incredibly powerful they are also difficult to find. In this section two functions will be presented, one for SEIR and one for the modification, that utilize theorem 3.21 by LaSalle [16].

Both functions are of the form $V = AE+BI$, where we will have $\dot{V} = 0$ on the S-axis, and $\dot{V} < 0$ elsewhere in the invariant set $\{(S, E, I) \mid S, E, I \geq 0,\ S + E + I \leq 1\}$. It follows from theorem 3.21, and the fact that the only possible limit set on the S-axis is the singleton set $\{(1, 0, 0)\}$, that the DFE is asymptotically stable for all initial states in the invariant set. These functions only really tell us this when $R_0 < 1$, which is a drawback. The advantage is that in the case of the SEIR model the Lyapunov function is not defined when $S = 0$, and in the case of the modification we do not have a Lyapunov function.

Proposition 4.5. *The function*

$$V = E + \frac{\sigma\beta + (\sigma + \mu)(\gamma + \mu)}{2\sigma(\gamma + \mu)} I$$

Proves asymptotic stability in $\{(S, E, I) \mid S, E, I \geq 0,\ S+E+I \leq 1\}$ *for the disease free equilibrium* $(1, 0, 0)$ *of the SEIR model when* $R_0 < 1$.

Proof: See appendix 7.5.

Proposition 4.6. *The function*

$$V(x) = E + \frac{(1 - R_0^E + R_0^I)(\sigma_1 + \sigma_2 + \mu)}{2\sigma_1} I$$

Proves asymptotic stability in $\{(S, E, I) \mid S, E, I \geq 0,\ S+E+I \leq 1\}$ *for the disease free equilibrium* $(1, 0, 0)$ *of the modification when* $R_0 < 1$.

Proof: See appendix 7.5.

The method of finding these functions is very straightforward. We know that we have a compact invariant set, and as such theorem 3.21 $i)$ is applicable. We also know that the S-axis is a stable set of the DFE (when $E, I = 0$ then $\left(\dot{S}, \dot{E}, \dot{I}\right) = (\mu - \mu S,\ 0,\ 0)$. As such the only requirements are that the function is continuously differentiable, and that the time derivative is negative except on the S-axis where it should be zero. To find a suitable function of the form $AE+BI$ is therefore merely a matter of finding A, B such that the time derivative is negative wherever $A, B > 0$. The process to determine the particular values of A and B used here can be found in Appendix 7.5.

5

Closing remarks

When I first encountered the literature on compartmental epidemiological models I found it to be a much more sizeable body of work then I had expected. I found the variety of models, and variants of models overwhelming. As such I am fairly certain that the modification in this thesis is not truly novel. But I came up with it on my own, and I felt strongly about any results that I produced regarding it. As such there are two main things I would want to do if I were to continue working on this: I would like to show asymptotic stability for the modifications endemic equilibrium on (almost) the entire invariant set (for $R_0 > 1$), and I would like to generalize the modification.

The choice of $\beta\frac{\sigma_2}{\sigma_1+\sigma_2}$ as the constant governing the spread caused by exposed individuals was, in hindsight, a bit misguided. It was made to allow for asymptomatic transmission of the disease. There where two main motivations for doing it this way. The first was to preserve the dimensionality of the SEIR model, as it is essentially 3 dimensional and as such it is possible to visualize to a greater extent then a higher dimensional model. Therefore I opted for not adding a compartment for asymptomatic individuals like in a SEIAR (Susceptible-Exposed-Infected-Aymptomatic-Removed) model. The second motivation was a desire to add as few new parameters to estimate as possible. In the modification there is only one additional parameter as compared to the SEIR model. As I have become more familiar with epidemiology I see that this minimalist urge has led to a pretty constrained model. For one it does not allow for asymptomatic individuals to be more or less infectious then symptomatic individuals. In addition increasing the proportion of asymptomatic individuals essentially means increasing the speed at which asymptomatic individuals leave the exposed compartment. This means that this model is not particularly well suited for the purpose I intended for it. If I were to continue working on this, I would certainly consider a model such as the following:

$$\begin{cases} \dot{S} = & \mu - \mu S - \alpha ES + \beta IS \\ \dot{E} = \alpha ES + \beta IS & - (\mu + \sigma_1 + \sigma_2)E \\ \dot{I} = & \sigma_1 E - (\gamma + \mu)I \\ \dot{R} = & \sigma_2 E + \gamma I - \mu R \end{cases}$$

The modification in this thesis is, after all, only a special case of this more general model. It allows for interesting things, like exposed individuals being infectious without there being any asymptomatic individuals, essentially modelling two stages of infectivity. It could also be used in scenarios like the previous one, except some individuals do not become infected. This relatively simple change to the model makes it more flexible, and more applicable to real disease.

In terms of expanding on the subject, there are a number of fairly obvious directions to go in. Analyzing non-autonomous versions of the models is a clear next step to take. Time varying population is particularly interesting to me, as in the case of CWD it may be an important factor to consider. Animal populations can fluctuate a great deal and it may be important to capture this in order to model the disease accurately. Models with more compartments are also an option to analyze, particularly the previously mentioned SEIAR model.

6

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7

Appendix

7.1 Derivation of EE in SEIR

$$\begin{cases} 0 = & \mu - \mu S - \beta IS \\ 0 = & \beta IS - (\mu + \sigma)E \\ 0 = & \sigma E - (\gamma + \mu)I \\ 0 = & \gamma I - \mu R \end{cases}$$

Rearranging (recall that parameters are positive and non-zero) we get

$$\begin{cases} S = 1 - \frac{\beta IS}{\mu} \\ E = \frac{\beta IS}{(\mu+\sigma)} \\ I = \frac{\sigma}{(\gamma+\mu)}E \\ R = \frac{\gamma}{\mu}I \end{cases}$$

Using the fact that $I = \frac{\sigma}{(\gamma+\mu)}E$ and $E = \frac{\beta IS}{(\mu+\sigma)}$ we get

$$\frac{\gamma+\mu}{\sigma}I = \frac{\beta}{\mu+\sigma}IS \iff \frac{\gamma+\mu}{\sigma}\frac{\mu+\sigma}{\beta} = S \iff \frac{1}{R_0} = S$$

Using this we can express both E and R in terms of I

$$1 = S + E + I + R = \frac{1}{R_0} + \frac{\gamma+\mu}{\sigma}I + I + \frac{\gamma}{\mu}I \iff \left(1 - \frac{1}{R_0}\right) = I\left(\frac{\gamma+\mu}{\sigma} + 1 + \frac{\gamma}{\mu}\right)$$

Dividing by the coefficient of I we get

$$\left(1 - \frac{1}{R_0}\right)\frac{\sigma\mu}{\gamma\mu + \mu^2 + \sigma\mu + \gamma\sigma} = \left(1 - \frac{1}{R_0}\right)\frac{\sigma\mu}{(\mu+\gamma)(\mu+\sigma)} = \left(1 - \frac{1}{R_0}\right)\frac{\sigma\mu}{(\mu+\gamma)(\mu+\sigma)} = I$$

Where

$$\frac{\sigma\mu}{(\mu+\gamma)(\mu+\sigma)} = \frac{\sigma\mu}{\frac{\sigma\beta}{R_0}} = \frac{\mu R_0}{\beta}$$

Thus we have an expression of the endemic equilibrium in terms of the parameters:

$$\begin{cases} S = & \frac{1}{R_0} \\ E = & \left(1-\frac{1}{R_0}\right)\frac{\mu R_0}{\beta}\frac{\gamma+\mu}{\sigma} \\ I = & \left(1-\frac{1}{R_0}\right)\frac{\mu R_0}{\beta} \\ R = & \left(1-\frac{1}{R_0}\right)\frac{\mu R_0}{\beta}\frac{\gamma}{\mu} \end{cases}$$

7.2 Derivation of EE in modification

$$\begin{cases} 0 = & \mu - \mu S - \beta\left(\frac{\sigma_2}{\sigma_1+\sigma_2}E + I\right)S \\ 0 = & \beta\left(\frac{\sigma_2}{\sigma_1+\sigma_2}E + I\right)S - (\mu+\sigma_1+\sigma_2)E \\ 0 = & \sigma_1 E - (\gamma+\mu)I \\ 0 = & \sigma_2 E + \gamma I - \mu R \end{cases}$$

Rearranging, and using that $E = \frac{\gamma+\mu}{\sigma_1}I$ we get

$$\begin{cases} \mu = & \left(\mu + \beta(\frac{\sigma_2}{\sigma_1+\sigma_2}\frac{(\gamma+\mu)}{\sigma_1}I + I)\right)S \\ (\mu+\sigma_1+\sigma_2)\frac{(\gamma+\mu)}{\sigma_1}I = & \beta(\frac{\sigma_2}{\sigma_1+\sigma_2}\frac{(\gamma+\mu)}{\sigma_1}I + I)S \\ E = & \frac{(\gamma+\mu)}{\sigma_1}I \\ \mu R = & \left(\sigma_2\frac{(\gamma+\mu)}{\sigma_1} + \gamma\right)I \end{cases}$$

Let $I > 0$ (if $I = 0$ this is the Disease free equilibrium). Then we can divide by I in the second equation.

$$(\mu+\sigma_1+\sigma_2)\frac{(\gamma+\mu)}{\sigma_1} = \beta(\frac{\sigma_2}{\sigma_1+\sigma_2}\frac{(\gamma+\mu)}{\sigma_1} + 1)S$$

Rearranging we get

$$\frac{(\mu+\sigma_1+\sigma_2)(\gamma+\mu)}{\sigma_1} = \frac{\beta\sigma_2(\gamma+\mu) + \beta\sigma_1(\sigma_1+\sigma_2)}{\sigma_1(\sigma_1+\sigma_2)}S$$

Dividing by the coefficient of S (recall that coefficients are non-zero and positive).

$$\frac{(\mu+\sigma_1+\sigma_2)(\gamma+\mu)}{\sigma_1}\frac{\sigma_1(\sigma_1+\sigma_2)}{\beta\sigma_2(\gamma+\mu)+\beta\sigma_1(\sigma_1+\sigma_2)}=S$$

$$\frac{(\mu+\sigma_1+\sigma_2)(\gamma+\mu)(\sigma_1+\sigma_2)}{\beta\sigma_2(\gamma+\mu)+\beta\sigma_1(\sigma_1+\sigma_2)}=S$$

Recall that

$$R_0=R_0^I+R_0^E=\frac{\beta\sigma_1}{(\mu+\sigma_1+\sigma_2)(\mu+\gamma)}+\frac{\beta\sigma_2}{(\mu+\sigma_1+\sigma_2)(\sigma_1+\sigma_2)}$$

We therefore arrive at

$$\frac{1}{R_0}=S$$

Using that $S+E+I+R=1$ and the fact that E and R can be expressed in terms of I

$$1-\frac{1}{R_0}=E+I+R=\left(\frac{\mu+\gamma}{\sigma_1}+1+\frac{\sigma_2(\mu+\gamma)+\sigma_1\gamma}{\sigma_1\mu}\right)I$$

Simplify

$$1-\frac{1}{R_0}=\frac{(\mu+\sigma_1+\sigma_2)(\gamma+\mu)}{\sigma_1\mu}I$$

We can now express I in terms of the parameters

$$I=\left(1-\frac{1}{R_0}\right)\frac{\sigma_1\mu}{(\mu+\sigma_1+\sigma_2)(\mu+\gamma)}$$

As a result we can also express E and R the same manner:

$$E=\left(1-\frac{1}{\tilde{R}_0}\right)\frac{\mu}{\mu+\sigma_1+\sigma_2},\quad R=\left(1-\frac{1}{R_0}\right)\frac{\sigma_2(\mu+\gamma)+\sigma_1\gamma}{(\mu+\sigma_1+\sigma_2)(\mu+\gamma)}$$

We arrive at an expression of the EE in terms of the parameters.

$$\begin{cases} S= & \frac{1}{R_0} \\ E= & \left(1-\frac{1}{R_0}\right)\frac{\mu}{\mu+\sigma_1+\sigma_2} \\ I= & \left(1-\frac{1}{R_0}\right)R_0^I\frac{\mu}{\beta} \\ R= & \left(1-\frac{1}{R_0}\right)\frac{\gamma R_0^I+(\sigma_1+\sigma_2)R_0^E}{\beta} \end{cases}$$

7.3 SEIR Lyapunov DFE

This section aims to clarify that the function

$$V_{DFE}(S, E, I) = S - \ln(S) + E + \frac{\sigma + \mu}{\sigma} I$$

is a Lyapunov function for the specific SEIR model in this thesis. The gradient of V_{DFE} is:

$$\nabla V_{DFE} = \left(1 - \frac{1}{S},\ 1,\ \frac{\sigma + \mu}{\sigma}\right)$$

The time derivative is then

$$\dot{V}_{DFE} = \left(1 - \frac{1}{S}\right)(\mu - \mu S - \beta IS) + \beta IS - (\sigma + \mu)E + \frac{\sigma + \mu}{\sigma}(\sigma E - (\gamma + \mu)I)$$

By simplifying we get

$$\dot{V}_{DFE} = -\mu S + 2\mu - \frac{\mu}{S} + \left(\beta - \frac{(\sigma + \mu)(\gamma + \mu)}{\sigma}\right) I$$

and by using the following

$$-\mu S + 2\mu - \frac{\mu}{S} = -\mu(1 - S)\left(\frac{1}{S} - 1\right)$$

$$\beta = R_0 \frac{(\sigma + \mu)(\gamma + \mu)}{\sigma}$$

We have arrived at

$$\dot{V}_{DFE} = -\mu(1 - S)\left(\frac{1}{S} - 1\right) - (1 - R_0)\frac{(\sigma + \mu)(\gamma + \mu)}{\sigma} I$$

Which is negative when $R_0 \leq 1$ for $E, I \geq 0$ and $S > 0$.

7.4 SEIR Lyapunov EE

The following is intended to give a clearer account on why the function

$$V_{EE}(S, E, I) = S - S^* \ln(S) + E - E^* \ln(E) + \frac{\sigma + \mu}{\sigma}(I - I^* \ln(I))$$

is a Lyapunov function for the specific SEIR model in this thesis. The gradient of this function is

$$\nabla V_{EE}(S,E,I) = \left(1 - \frac{S^*}{S},\ 1 - \frac{E^*}{E},\ \frac{\sigma+\mu}{\sigma}\left(1 - \frac{I^*}{I}\right)\right)$$

which has a minimum at (S^*, E^*, I^*). The time derivative is then:

$$\dot{V}_{EE}(S,E,I) = \left(1 - \frac{S^*}{S}\right)\dot{S} + \left(1 - \frac{E^*}{E}\right)\dot{E} + \frac{\sigma+\mu}{\sigma}\left(1 - \frac{I^*}{I}\right)\dot{I}$$

Recall that

$$\begin{cases} \dot{S} = & \mu - \mu S - \beta IS \\ \dot{E} = & \beta IS - (\mu+\sigma)E \\ \dot{I} = & \sigma E - (\gamma+\mu)I \end{cases}$$

With endemic equilibrium and R_0

$$\begin{cases} S^* = & \frac{1}{R_0} \\ E^* = & (R_0 - 1)\,\frac{\mu(\gamma+\mu)}{\sigma\beta} \\ I^* = & (R_0 - 1)\,\frac{\mu}{\beta} \end{cases}$$

$$R_0 = \frac{\sigma\beta}{(\mu+\gamma)(\mu+\sigma)}$$

Let's first expand the terms of $\dot{V}_{EE}$ individually.

$$\left(1 - \frac{S^*}{S}\right)\dot{S} = \mu - \mu S - \beta IS - \mu\frac{S^*}{S} + \mu S^* + \beta IS^*$$

$$\left(1 - \frac{E^*}{E}\right)\dot{E} = \beta IS - (\mu+\sigma)E - \frac{\beta E^* IS}{E} + (\mu+\sigma)E^*$$

$$\frac{\sigma+\mu}{\sigma}\left(1 - \frac{I^*}{I}\right)\dot{I} = \left(\frac{\sigma+\mu}{\sigma}\right)\left(\sigma E - (\gamma+\mu)I - \frac{\sigma E I^*}{I} + (\gamma+\mu)I^*\right)$$

Adding these together we arrive at

$$\dot{V}_{EE}(S,E,I) = \mu - \mu S - \mu\frac{S^*}{S} + \mu S^* + \beta IS^* - \frac{\beta S E^* I}{E} + (\mu+\sigma)E^*$$

$$+ \left(\frac{\mu+\sigma}{\sigma}\right)(\gamma+\mu)I^* - \left(\frac{\mu+\sigma}{\sigma}\right)(\gamma+\mu)I - (\sigma+\mu)\frac{EI^*}{I}$$

We begin by simplifying the terms that are constants

$$\left(\frac{\mu+\sigma}{\sigma}\right)(\gamma+\mu)I^* = \left(\frac{\mu+\sigma}{\sigma}\right)(\gamma+\mu)(R_0-1)\frac{\mu}{\beta} = \mu\left(1-\frac{1}{R_0}\right) = \mu - \mu S^*$$

$$(\mu+\sigma)E^* = (\mu+\sigma)(R_0-1)\frac{\mu(\gamma+\mu)}{\sigma\beta} = \mu\left(1-\frac{1}{R_0}\right) = \mu - \mu S^*$$

We proceed with the goal of getting $(\mu - \mu S^*)$ as a factor.

$$-(\sigma+\mu)\frac{EI^*}{I} = -(\sigma+\mu)E^*\frac{EI^*}{E^*I} = -\frac{\mu}{R_0}(R_0-1)\frac{EI^*}{E^*I} = -(\mu-\mu S^*)\frac{EI^*}{E^*I}$$

$$-\frac{\beta SE^*I}{E} = -\beta S^*I^*\frac{SE^*I}{S^*EI^*} = -(\mu-\mu S^*)\frac{SE^*I}{S^*EI^*}$$

Knowing the expression for R_0 we find that

$$\beta IS^* - \left(\frac{\mu+\sigma}{\sigma}\right)(\gamma+\mu)I = \frac{\beta}{R_0}I - \frac{\beta}{R_0}I = 0$$

We arrive at

$$\dot{V}_{EE}(S,E,I) = (\mu-\mu S^*)\left(2 - \frac{EI^*}{E^*I} - \frac{SE^*I}{S^*EI^*}\right) + \mu - \mu S + \mu S^* - \mu\frac{S^*}{S}$$

$$\dot{V}_{EE}(S,E,I) = (\mu-\mu S^*)\left(3 - \frac{S^*}{S} - \frac{EI^*}{E^*I} - \frac{SE^*I}{S^*EI^*}\right) - \mu S - \mu\frac{(S^*)^2}{S} + 2\mu S^*$$

Which neatly leads us to

$$\dot{V}_{EE}(S,E,I) = (\mu-\mu S^*)\left(3 - \frac{S^*}{S} - \frac{EI^*}{E^*I} - \frac{SE^*I}{S^*EI^*}\right) - \mu S^*\left(\frac{S}{S^*} + \frac{S^*}{S} - 2\right)$$

let $\frac{S}{S^*} = x$, $\frac{E^*I}{EI^*} = y, a = (\mu - \mu S^*), b = \mu S^*$

$$a\left(3 - \frac{1}{x} - \frac{1}{y} - xy\right) + b\left(2 - x - \frac{1}{x}\right)$$

Since $a, b > 0$ given that $R_0 > 1$, the following must be true for $\dot{V}_{EE}$ to satisfy the conditions on a strict Lyapunov function

$$\frac{\frac{1}{x} - \frac{1}{y} - xy}{3} > 1 \text{ and } \frac{x + \frac{1}{x}}{2} > 1$$

Using the inequality between arithmetic- and geometric mean we have

$$\frac{\frac{1}{x}-\frac{1}{y}-xy}{3} \geq \sqrt[3]{\frac{xy}{xy}} = 1 \text{ and } \frac{x+\frac{1}{x}}{2} > \sqrt{\frac{x}{x}} = 1$$

With equality only when $\frac{1}{x} = \frac{1}{y} = xy$ and $x = \frac{1}{x}$ respectively (when $S = S^*, E = E^*, I = I^*$). The function therefore satisfies the conditions on a strict Lyapunov function.

7.5 LaSalle invariance theorem for DFE (both models)

Finding Lyapunov functions can be difficult. We will instead find a simpler function satisfying the conditions in theorem 3.21 *i*). To do this we will leverage the fact that any point on the S-axis ($E = I = 0$) goes to the DFE as $t \to \infty$.
Let us begin with the modification. Consider a function of the form $V(x) = AE+BI$. Then its time derivative will be

$$\dot{V}(x) = A\left(\frac{\beta\sigma_2}{\sigma_1+\sigma_2}ES + \beta IS - (\mu+\sigma_1+\sigma_2)E\right) + B(\sigma_1 E - (\gamma+\mu)I)$$

which we can rearrange as

$$E\left(A\frac{\beta\sigma_2}{\sigma_1+\sigma_2}S + B\sigma_1 - A(\mu+\sigma_1+\sigma_2)\right) + I(A\beta S - B(\gamma+\mu))$$

We want $\dot{V}(x) = 0$ for $x = (S, 0, 0)$ and $\dot{V}(x) < 0$ otherwise in the invariant set. As $E, I \geq 0$ this is achieved if

$$A\beta S - B(\gamma+\mu) < 0 \text{ and } A\frac{\beta\sigma_2}{\sigma_1+\sigma_2}S + B\sigma_1 - A(\mu+\sigma_1+\sigma_2) < 0$$

Let $S = 1$ and rearrange the inequalities.

$$A\beta < B(\gamma+\mu)$$

By the positivity of the parameters and the definition of R_0^I

$$A(\sigma_1+\sigma_2+\mu)R_0^I < B\sigma_1$$

Continuing with the second inequality in a similar manner

$$A\frac{\beta\sigma_2}{\sigma_1+\sigma_2}+B\sigma_1<A(\sigma_1+\sigma_2+\mu)$$

Rearranging and applying the definition of R_0^E

$$B\sigma_1<A(1-R_0^E)(\sigma_1+\sigma_2+\mu)$$

We have therefore bounded $B\sigma_1$, and therefore B, from below as well as above.

$$A(\sigma_1+\sigma_2+\mu)R_0^I<B\sigma_1<A(1-R_0^E)(\sigma_1+\sigma_2+\mu)$$

Such a $B\sigma_1$ can only exist if

$$A(1-R_0^E)(\sigma_1+\sigma_2+\mu)-A(\sigma_1+\sigma_2+\mu)R_0^I>0$$

which is neatly rewritten as

$$A(\sigma_1+\sigma_2+\mu)(1-R_0^E-R_0^I)>0$$

It follows that $A,B\geq 0$ since $R_0^E,R_0^I\geq 0$. More importantly we see that $R_0^E+R_0^I=R_0<1$ is a requirement. So let $A=1$ and B be the arithmetic mean of the bounds divided by σ_1

$$A=1,B=\frac{(1-R_0^E+R_0^I)(\sigma_1+\sigma_2+\mu)}{2\sigma_1}$$

Then we arrive finally at the following function

$$V(x)=E+\frac{(1-R_0^E+R_0^I)(\sigma_1+\sigma_2+\mu)}{2\sigma_1}I$$

By theorem 3.21 i)

$$\forall x_0\in\{(S,E,I)\mid 0\leq S,E,I,\ S+E+I\leq 1\},\ \lim_{t\to\infty}x(t)\to\{(S,0,0)\mid 0\leq S\leq 1\}$$

Which means that $E(t),I(t)\to 0$ as $t\to\infty$. In fact $x(t)\to(1,0,0)$, as $\dot{x}(t)$ does not go to zero anywhere else on the S-axis.
The same can be done for the SEIR model with little trouble. Following the same

steps as for the modification (presented in an ebbreviated manner)

$$(A\beta S - B(\gamma + \mu))I + (B\sigma - A(\sigma + \mu))E$$

$$A\frac{\beta}{(\gamma + \mu)} < B < A\frac{(\sigma + \mu}{\sigma}$$

let $A = 1$, then the following is required for B to exist

$$\frac{\sigma + \mu}{\sigma} - \frac{\beta}{\gamma + \mu} = \frac{(\sigma + \mu)(\gamma + \mu) - \sigma\beta}{\sigma(\gamma + \mu)} > 0$$

From the definition of R_0 and the positivity of parameters we have

$$(\sigma + \mu)(\gamma + \mu) - \sigma\beta > 0 \text{ when } R_0 < 1$$

So the function

$$V = E + \frac{\sigma\beta + (\sigma + \mu)(\gamma + \mu)}{2\sigma(\gamma + \mu)}I$$

Satisfies theorem 3.21 i), and thus the DFE of the SEIR model is asymptotically stable in the invariant set when $R_0 < 1$

7.6 Illustration

In the two dimensional case phase portraits can be analysed to great effect. In higher dimensions this approach is significantly less useful as a tool to determine asymptotic behaviour of the system. However it is still help to gain some intuitive understanding and insight into the system. Where ever the boundary of the invariant set intersects the plane shown (other than the axes) will be illustrated with a dashed red line in the images. When there is only one equilibrium, that is when $R_0 \leq 1$, four images will be presented. The area to the left and below the red dotted lines are the areas of these planes contained in the invariant set.

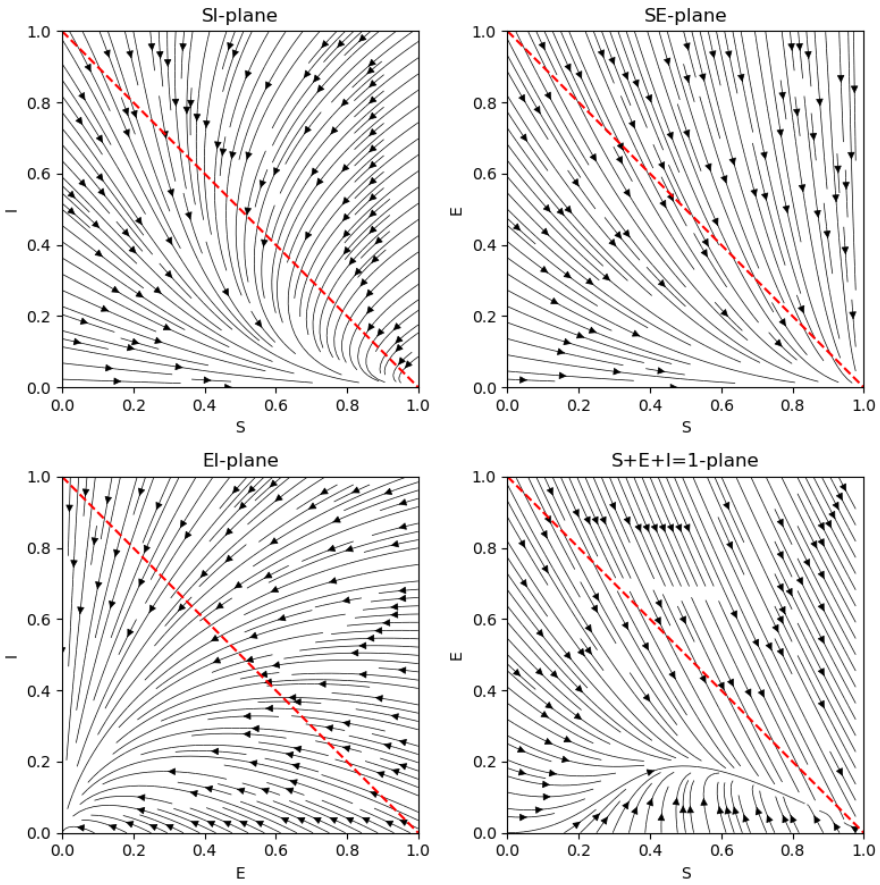

Figure 1: Phase portraits, SEIR, at the boundary, $R_0 = 0.72$

We get the sense of how the trajectories go to $(S, E, I) = (1, 0, 0)$, as well as a sense of the fact that the subset is positively invariant, but clearly not negatively invariant. We must keep in mind that we are only seeing a few slices of the three dimensional system however, and that this illustration does not give us a complete picture.

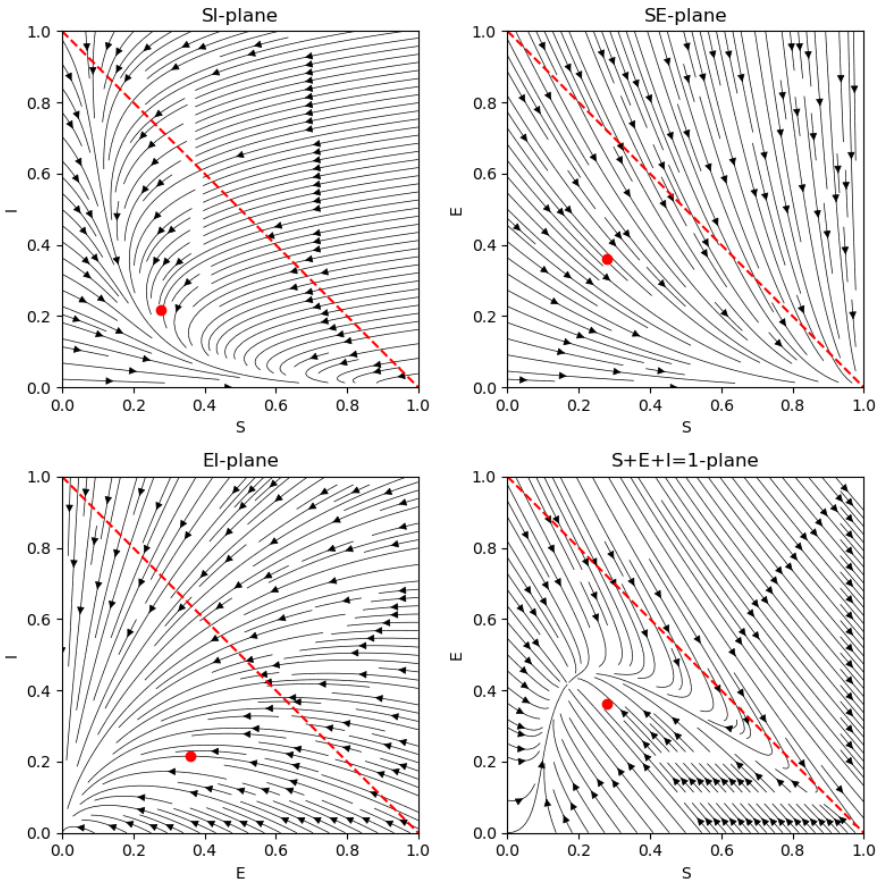

Figure 2: Phase portraits, SEIR, at the boundary, $R_0 = 3.6$

When $R_0 > 1$ the behavior along the boundary may not seem to fit our expectations. Take as an example the SE-plane. It looks like the system is approaching the disease free equilibrium. However a trajectory will not travel in the SE-plane in the manner that it appears, because exposed individuals will transition to infected individuals and the trajectory will move into the interior of the set. To show the behavior around the endemic equilibrium somewhat more accurately, we will show three planes intersecting the equilibrium point, each being paralell to one of the axes.

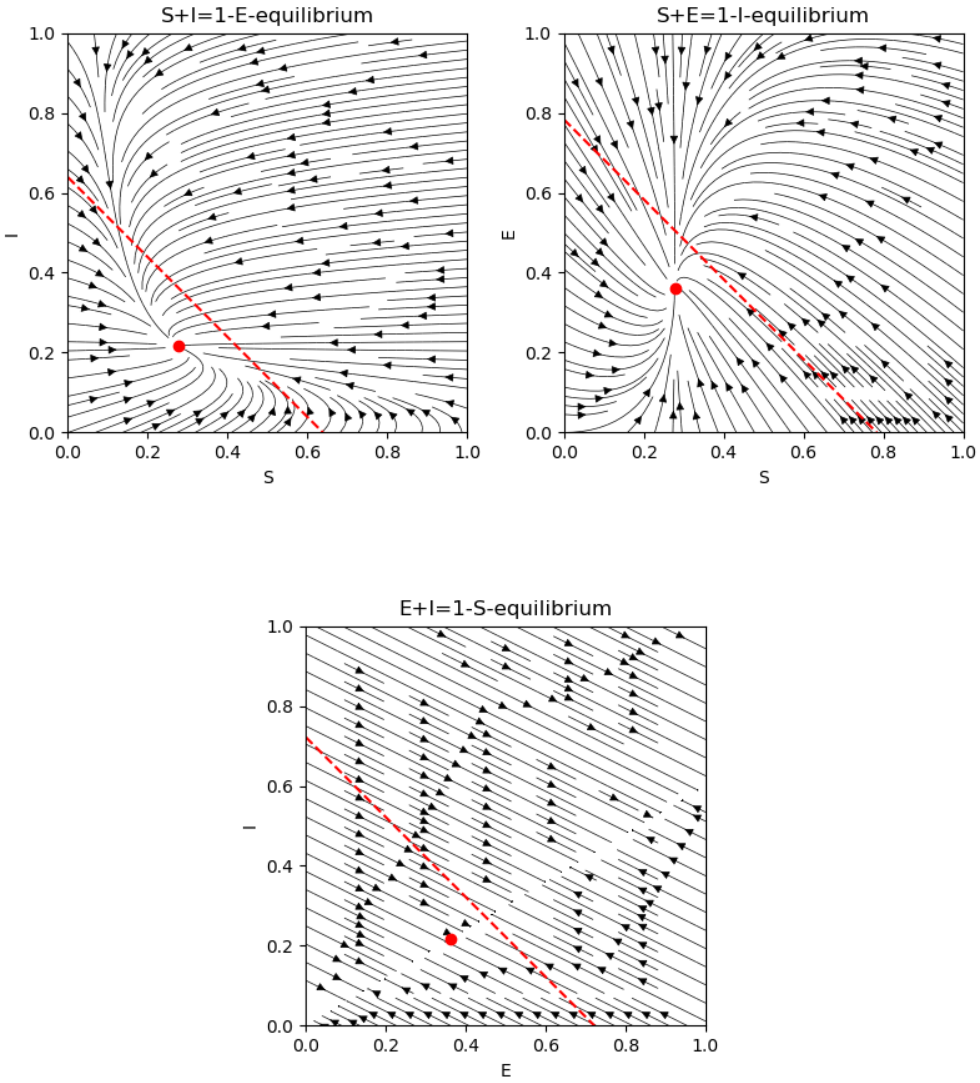

Figure 3: Phase portraits, SEIR, planes intersecting at equilibrium, $R_0 = 3.6$

Here we get a fairly clear sense of the fact that the endemic equilibrium is indeed asymptotically stable, at least for most of the invariant set. We should still keep in mind that these images do not prove anything in and of themselves.