KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY

A Comparative Analysis on the Mathematical Models of Pertussis and Measles

By

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Declaration

I hereby declare that this submission is my own work towards the award of the MSc degree and that, to the best of my knowledge, it contains no material previously published by another person nor material which had been accepted for the award of any other degree of the university, except where due acknowledgement had been made in the text.

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Dedication

To my Son Nesta Opoku Ankomah Bentil

Abstract

The motivation of the study is based on the problems that arise from the mathematical model of Pertussis and Measles. The purpose is to depict the differences that occur in variations of mathematical systems. This is done by analyzing and interpreting this model, as well as a simpler model, and then comparing the solutions for the two. From the analysis, an insight to the theoretical and mathematical description of spread and contamination patterns has been obtained. The two models are then compared to each other. The intention is to reveal the consequence of expanding upon a compartment model, and thus the system of differential equations. The two models display a different level of detail which is reflected in the associated analysis. The simple model is a Measles model, and the pertussis model has the higher degree of detail. The analytic methods applied when describing the systems of differential equations appear to have a limited use in the expanded system. This leads to mathematical complications.

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Chapter 1

Introduction

1.1 Background of the study

Mathematical modelling is a rapidly growing field reflecting interdisciplinary co-operation of mathematics and biology in solving complex life-science problems. The involvement of mathematical perspectives has shown to be essential in many fields concerning population biology (Murray, 2001). The application of mathematics has successfully explained complex epidemiological patterns of various childhood diseases (Moghadas, 2003; Nguyen, 2007). A classical example of such models is the SIR- model explaining outbreaks. This model has been very successful and subject to many variations among them, the modeling of the measles epidemic (Hethcode, 1976) (in implementing current vaccination programs and strategies responsible for minimizing measles infection).

Another disease that mathematicians have tried to depict with the use of mathematics is Pertussis, also called "whooping cough,". Pertussis is a very contagious disease caused by bacteria called *Bordetella pertussis*. It is estimated by WHO that, about 300 000 deaths and 50 million cases of pertussis occur every year (WHO 2003). Pertussis is usually mild in older children and adults, but it often

causes serious problems in very young children (that is, infants less than one year of age). Nevertheless, existing mathematical models have struggled to explain the observed resurgence of pertussis which has been reported (Fishman et. al, 2011).

Disease phenomena are often displayed by a variety of models analyzing specific disease-related factors. These are a product of the mathematician's goals, assumptions and previous work. The various types of models reflect the attempts to describe interactions in populations, and their role in the distribution of these diseases. Since countless variables and interrelations could characterize this interaction, the dynamics are often stripped to the simplest conceivable forms. The process of modeling includes unification of results and comparisons of previously formulated models.

Understanding the variations of the mathematical models gives clues to the underlying biological mechanisms driving such occurrences is the focus of this thesis. The two mathematical models treated in the following represent the standard epidemiological model and an extension. Measles is a fairly well-understood disease described by a classical SIR (susceptible, infected, removed) model, serving as the basic example of an epidemical model. In contrast the underlying mechanisms of pertussis remain uncertain (Hethcode, 1976: Lavine, 2011). The uncertainty is reflected by a continuous discussion in the academic community (Aguasa , 2006). This has led to a variety of models that attempt to explain the resurgence.

A severe decrease in pertussis was observed in the mid-20th century. The disease was thought to be driven towards extinction in the developed countries (United States Center for Disease Control). However it was observed that the immunity was of a limited duration. This meant that vaccinated individuals would eventually lose their immunity and could once again be infected with the disease

(Lavine, 2011). The resurgence has been motivated by loss of immunity, because of an unexpected temporal change in transmission pattern. This pronounces a shift in the age distribution of infection from, a dominant infantile prevalence toward high infection prevalence of older groups (Lavine, 2011). Consequently, the occurrence of pertussis cases have been sustained in developed countries. For the interpretation of these observations we have looked at the $SIRW$ model of pertussis proposed by Lavine et al 2011. The comparison of the two models is based on a mathematical analysis followed by a discussion of the biological interpretation.

Epidemiology is the study of disease incidence, prevalence, and control of disease in large populations, which are caused by various factors (http://dictionary.reference.com/, epidemiology). Incidence and prevalence factors of communicable disease involve both disease-related factors such as transmission, incubation periods (the period from where an individual is infected to the disease symptoms appear), susceptibility and immunization and societal factors such as economy, geography. We distinguish between the disease incidence, which is the number of new disease cases at a given time, and disease prevalence, which is the total number of disease cases in a population.

Communicable diseases are generally classified according to an epidemic or an endemic disease occurrence. The occurrence of epidemic diseases is described by seasonal fluctuations of outbreaks, whereas endemic diseases are habitually present (Jensen, 2005). It is assumed that the population behaves more or less like homogenous particles in a gas. That is, their contact rate is based on basic statistical view that each individual will experience the same number of contacts (on average). Infectious diseases are usually modeled by classifying individuals into different classes which size change with time t. This categorization of the

population is defined according to individuals' health status with respect to the disease progression. The models discussed in this thesis are SI, SIS, and SIR - models (S, I, R models), where the letters S, I and R indicate different classes in an infected population. These definitions are key notations that are used throughout the study. The susceptible class, S, comprises healthy individuals, that can incur the infection. The infective class, I, comprises individuals that are both infected and infectious. Finally, the removed class R comprises individuals that are removed from the classes of S and I either by being or achieving permanent immunization or through isolation until recovery.

The simplest epidemic model is the SI model, describes a disease course with no recovery. If the individuals recover with no immunity, then recovered individuals will once again become susceptible. This is described by a so called SIS model. Conversely, if individuals that recover gain immunity, then the model is called an SIR model. In general, the SIR models are used to model viral epidemics whereas bacterial epidemics are modeled by SIS models. The difference is based on immunological differences between the two types of infection. Viral infection usually induces long lasting immunity as oppose to bacterial infection which induces either no immunity or a short duration of immunity (Hethcote 1976; Lavine, 2011). The S, I, R, Measles and Pertussis models are introduced here in their original form. This process will be thoroughly reviewed in a subsequent chapter.

1.2 Statement Of Problem

Children with pertussis have decreased ability to cough up respiratory secretions and develop thick, glue-like mucus in the windpipe. This causes severe coughing spells that make it difficult for them to eat, drink, or breathe. The child may suffer from coughing spells for two to three weeks or longer. Sometimes the child

coughs several times before breathing in. When the child finally does breathe in there is often a loud gasp or a whooping sound. The disease is most severe when it occurs early in life and it often requires hospitalization. Despite numerous management and control strategies of pertussis currently in place, pertussis continue to cause great health effect worldwide.

Measles is respiratory infection caused by single-stranded virus of the Morbilli paramyxovirus family. Measles is mainly spread through airborne droplets expelled by the coughing and sneezing of infected. As measles access the respiratory tract it further extent to destroy lymph nodes. Subsequent the virus spreads to involve the skin, the viscera, kidney and bladder. The virus mainly infects children, so vaccination is used routinely where available. As opposed to most bacterial diseases, a person that recovers from the measles virus gains permanent immunity. Vaccination has caused a decrease in mortality in many developed countries; however it still remains one of the deadliest child diseases in developing countries (Jansen and Stollenwerk 2005, Vries et al, 2012).

Many mathematical researchers have done a lot of work on the modelling and controlling the effects of these diseases on human.

However, no comparative study have been done on the dynamics of models of these two diseases. Therefore, this study intends to fill this gap.

1.3 Research Objectives

1.3.1 General Objective

The main objective of this study is to perform a comparative analysis on the pertussis and measles models.

1.3.2 Specific Objectives

The specific objectives of this study are as follows:

1. To study the dynamics of the pertussis and measles models.
2. To determine the stability of the equilibrium points of the pertussis and measles models.
3. To compare the dynamics of whooping cough mathematical model to that of Measles epidemics.

1.4 Significance of the Study

The significance of the study will include the following;

1. The model will help health personnel to understand the dynamics of pertussis and measles and set strategies on how to increase vaccination among pertussis infected individuals.
2. The study will create awareness and inform people of the effect of pertussis and measles.
3. The study will also act as a base for further research on the effect of pertussis and measles and other related diseases.
4. The study intends to contribute to strategies of addressing Pertussis and Measles on how to increase vaccination among infected individuals

1.5 Outline of the study

The thesis consists of five main chapters. Chapter 1 talks about the background of the study, problem statement, objectives as well as significance of the study. In Chapter 2 we will review some literatures relevant to the study. Chapter 3 consists of methodology used in carrying out this study. In Chapter 4 we will come up with the mathematical analysis of the models. In Chapter 5, we will discuss the research findings and make the necessary conclusions and recommendations.

Chapter 2

Review of Literature

2.1 The Biology of Pertussis

Pertussis, also known as whooping cough, is an acute infectious disease of the human respiratory tract caused by the Gram-negative bacterium Bordetella pertussis (Tozzi, Celentano, degli Atti ML, & Salmaso, 2005). Estimated by WHO, 300 000 deaths and 50 million cases of pertussis occur every year (WHO 2003).

2.1.1 Pertussis infection and symptoms

Pertussis is mainly transmitted by B. pertussis containing airborne droplets from cough or sneeze during the first three weeks of infection (N. Crowcroft & Pebody, 2006; Heininger, 2001; Kerr & Matthews, 2000; Loeffelholz, 2003). The household members are the source of infection in 7382% of infants with pertussis (Wendelboe, Njamkepo, & Bourillon, 2007). The disease is highly contagious evidenced by the secondary attack rate among family members being over 80% (Long, Welkon, & Clark, 1990; Mertsola, Ruuskanen, Eerola, & Viljanen, 1983). However, as much as 46% of the secondary cases are asymptomatic and not ex-

pected to be diseased (Mertsola et al., 1983; Schellekens, von Konig, & Gardner, 2005). It has been estimated that every primary case of symptomatic pertussis leads to approximately five secondary cases of asymptomatic or clinically insignificant infection (Ward, Cherry, & Chang, 2006). The clinical symptoms are mainly caused by virulence factors such as bacterial toxins that B.pertussis secretes (Kerr & Matthews, 2000).

The disease typically lasts 6 to 12 weeks or longer with three stages: catarrhal, paroxysmal and convalescent (Loeffelholz, 2003). First, after exposure to the bacteria, the incubation period of 710 days precedes the development of symptoms. During the catarrhal stage, non-specific symptoms appear with rhinitis and mild cough lasting approximately 7 to 14 days. At this stage, the disease is highly communicable but rarely suspected. The cough gradually becomes paroxysmal with severe coughing spells followed by whooping and possibly post-tussive vomiting. The patients may also become cyanotic and require airway support. This paroxysmal cough is the typical symptom of pertussis, but the whoop may be absent in the infants younger than 6 months, who may only present apnoea or even sudden death (Heininger, Kleemann, Cherry, & Group, 2004). Other characteristic signs during the paroxysmal stage in infants include leucocytosis, lymphocytosis, and weight loss due to the post-tussive vomiting. After 2 to 8 weeks, the frequency and severity of the paroxysms decrease referring to the transition of the illness to the convalescent or recovery stage. The paroxysms are gradually improved but may, however, recur during other respiratory infections leading to a misdiagnosis of prolonged cough or asthma (Greenberg et al., 2007). Co-infections such as respiratory syncytial virus infection may modify the symptoms and thus complicate the diagnosis at all stages of the disease (N. S. Crowcroft, Booy, & Harrison, 2003; Korppi & Hiltunen, 2007).

Severe pertussis and complications such as cyanosis and pneumonia primarily occur among infants too young to be vaccinated, and over 80% of the fatal cases are among infants younger than 4 months (Crowcroft, Andrews, Rooney, Brisson, & Miller, 2002; N. S. Crowcroft et al., 2003; Greenberg, von Konig, & Heininger, 2005; Vitek, Pascual, Baughman, & Murphy, 2003). Older patients often have less severe or asymptomatic infections that are more difficult to be diagnosed (Gregory, 2006; Hewlett & Edwards, 2005). The individuals with partial immunity - such as infants with some maternal antibodies, incompletely vaccinated children, or adolescents and adults with waning immunity - may show atypical symptoms with less severe paroxysms and shorter course of illness causing misdiagnosis during the early stages of pertussis (Tozzi et al., 2005). As these patients are not diagnosed and treated during the most contagious stage of the illness, they frequently serve as sources of infection and expose the susceptible infants to the disease (Hewlett & Edwards, 2005).

According to R. Parton, Bordetella pertussis produces a complex array of adhesins, aggressins and toxins that are presumed to be important in the colonisation of its human host and in ensuring its survival and propagation. The organism also has highly sophisticated mechanisms for regulating virulence factor expression, in response to environmental signals or by reversible mutations. Despite the rapidly increasing knowledge of these aspects of the biology of B. pertussis, our understanding of the pathogenesis of whooping cough is still far from clear. In defining the role of individual factors, reliance has to be placed on in vitro assays or animal models of the human infection, particularly in the mouse, where different conditions may prevail. Some clues to pathogenic mechanisms may be provided by considering other bordetellae, especially B. parapertussis, B. bronchiseptica and B. avium, their similar, but not identical, range of virulence factors

and the common features of the diseases caused by these species in their respective hosts. The bordetellae are usually defined as obligate, non-invasive parasites of the respiratory tracts of warmblooded animals, including birds, with a predilection for the respiratory ciliated epithelium. This definition has been challenged by a number of recent observations. For example, the ability of Bordetella spp. to regulate virulence factor expression in response to external signals strongly suggests that they have alternative habitats where such regulation would be an advantage. These habitats may be intracellular, since it has been shown that B. pertussis, B. parapertussis and B. bronchiseptica can invade and survive within host cells, or they may be in other sites within the same or different hosts. Recent DNA fingerprinting studies of B. pertussis have revealed hitherto unsuspected heterogeneity amongst isolates which could be reflected in antigenic differences between strains. Some of these new perspectives on Bordetella pathogenicity may have implications for pertussis vaccine development.(Parton, 1999)

2.2 The Biology of Measles

Measles is an acute viral infectious disease. References to measles can be found from as early as the 7th century. The disease was described by the Persian physician Rhazes in the 10th century as "more dreaded than smallpox." In 1846, Peter Panum described the incubation period of measles and lifelong immunity after recovery from the disease. Enders and Peebles isolated the virus in human and monkey kidney tissue culture in 1954. Before a vaccine was available, infection with measles virus was nearly universal during childhood, and more than 90% of persons were immune by age 15 years. Measles is still a common and often fatal disease in developing countries. The World Health Organization estimates there were 164,000 deaths globally from measles in 2008.

The measles virus is a paramyxovirus, genus *Morbillivirus*. It is 100-200nm in diameter, with a core of single-stranded Ribonucleic acid (RNA), and is closely related to the rinderpest and canine distemper viruses. Two membrane envelope proteins are important in pathogenesis. They are the F (fusion) protein, which is responsible for fusion of virus and host cell membranes, viral penetration, and hemolysis, and the H (hemagglutinin) protein, which is responsible for adsorption of virus to cells.

There is only one antigenic type of measles virus. Although studies have documented changes in the H glycoprotein, these changes do not appear to be epidemiologically important (that is to say, no change in vaccine efficacy has been observed). Measles virus is rapidly inactivated by heat, light, acidic pH, ether, and trypsin. It has a short survival time (less than 2 hours) in the air or on objects and surfaces.

2.2.1 Measles infection and symptoms

The first symptoms of infection with measles are fever, tiredness, runny nose, cough and sore red eyes. These symptoms usually last for several days before a red blotchy rash appears. The rash starts on the face over 1 to 2 days and spreads down the body. Sometimes the rash peels. The rash will last for 4 to 7 days. Up to a third of people infected with measles will experience a complication. Complications are more common in young children and in adults. Complications include ear infections, diarrhoea and pneumonia, and may require hospitalisation. About one in every 1000 people with measles develops encephalitis (swelling of the brain).

Measles can be difficult to diagnose because there are many other viruses that

cause similar illnesses with a fever and a rash. Sometimes the presence of white spots inside the mouth, called Koplik's spots, the timing of the fever and the rash, and the characteristics of the rash, can help a doctor to make the diagnosis. Whenever measles is suspected, a blood test and/or swabs from the throat should be collected to confirm the diagnosis. Confirming the diagnosis is important so that other people who may be at risk of measles can be identified. By law, cases of measles are notified to public health units so that measures can be taken to help control further spread. The treatment for the symptoms of measles are rest, plenty of fluids and paracetamol for fever. Where measles causes complications, other treatments may be needed. While a person is infectious with measles it is important that they remain at home to reduce the possibility of spread to other people.

2.3 Modelling epidemics

Subjects that have the direct relationship to human's life had been paid a lot of attention from the scientist. They provided tools and principles to represent better understanding and perspective to such issues. Epidemics are one of the most related subjects to humans life. They considered being an attractive field of research since long time ago. Epidemiological scientist did their best to model this phenomenon and help the policy makers by providing them with accurate predictions and tools to make decisions that keep human life safe. The better understood the diffusion of diseases the more efficiency the reaction can be (*Considerations for a Social and Geographical Framework for Agent-Based Epidemics*, 2009). Epidemics have been modelled with different type of models: mathematical-stochastic, network-based and computational approaches(both cellular automata and agent-based modelling) since past century.

The mathematical models assumed homogeneity in the population and it divided the population into groups of sub-population based on their infection status. SI models which refers to the two groups of the population (Susceptible and Infected). They assumed that every individual in the population has contact with every individual (Anderson & May, 1979; Bonten & Austin, 2001). These models followed by some others all depended and referred to the classification of the total population such as SIR, $SEIR$, SIS, and $SIRS$. The "E" means the exposure, "R" recovered or removed based on the type of disease. However,in reality, these assumptions cannot be achieved. The human population is heterogeneous and individuals in the population are not in contact with each other. Furthermore, it is impossible to discriminate on who infected and on individual response(Perez & Dragicevic, 2009).

The second approach, which is the network-based approach, is widely used in simulating the disease spread. This approach depends on the social interaction between individuals. It represent the population's social networks. The approach assumed that the disease is spread along the edge which connects two nodes(Eames & Keeling, 2002; Read, 2008). The nodes represent the individuals and the relationship/contact between them is the edge. For simulating diseases, which required social contacts to spread such as HIV/AIDS the network-based models, are very useful(*Considerations for a Social and Geographical Framework for Agent-Based Epidemics*, 2009). However, Claude, Perrin et al(2009) argued that for several layers of social interaction or casual contact between strangers in the crowded area network-based approach cannot count.

Agent-based modelling(ABM) is one of these models that have been used to simulate the spread of the disease within people. ABMs are differing than traditional models not only in leading to better understanding the process of disease propa-

gation but with their efficiency to simulate the heterogeneity of the population. It takes in account the temporal and spatial aspects of the diffusion of a disease. In additions, ABMs provide the individual contact and behaviour level of data. Furthermore, it provides tools to build and test theories related to diffusion process, test control measurement such as vaccination, design and analysis surveys of the epidemiological(Yang & Atkinson, 2007).

It is important to understand the process of disease transfer at the level of individuals(Yang & Atkinson, 2007). This understanding is crucial for building the simulation model for the disease. ABMs were being used to simulate different types of epidemics such as influenza or avian flu (Ferguson & Cummings, 2006; Brown & Riolo, 2004), smallpox(Barrett & Eubakn, 2005) and HIV/AIDS(Teweldemedhin & Marwala, 2004). Usually, these models are based on the interaction and the contacts between agents(individuals). The contact might be face-to-face or skin-to-skin or both to make the disease spread from infectious agent to a susceptible agents. It could be transmitted via vector such as blood-borne diseases(Gu & Novak, 2009).

The disease ABMs are variance than each other in the way of simulating even if they are dealing with the same phenomenon(the same disease) and believe on the same principles. For instance, for both the above smallpox ABMs, they were dealing with spread of smallpox from different perspective and presented their model different from each other. Epstein and Cummings et al. (2004) used the grid cell to represent the population living in two cities, while Barret and Eubank et al. (2005) used the virtual city model (EpiSims) to represent the Chicago city environment. These differences in simulating such phenomenon is a very healthy result and proof the flexibility and efficiency of ABMs in such fields of studying. It is good to state that the models above be termed as individual-based models

(IBMIs) as well as they are known as ABMs(Bian, 2004).

IBM have the ability to explicitly describe the differences between individuals based on their attributes, which have direct effect on the process of disease diffusion such as physical (e.g. immunity level), social (e.g. friends), economic (e.g. workers or non-workers), and environmental characteristics (Yang & Atkinson, 2007).

Among all of these agent-based modelling and of course there were more we did not mentioned here, Individual Space-Time Activity-based Model(ISTAM) model which is presented by Yang, Atkinson et al. (2007;2008) was the most attractive and interesting to start from in building this research's disease model. It provides a new way of building a dynamic contact network based on the individuals' activity patterns. The dynamics of the contact network means the individuals contact change over time the order of these contacts affect on the disease diffusion. The following section would provide a brief overview about this model and the principles presented.

The ISTAM model (Individual Space-Time Activity-based Model) is a disease IBM model developed by Yang and Atkinson (2007) integrating "the contact pattern of individuals' an infectious disease process model, and a stochastic infection model by simulating ABs". It is time discrete stochastic model. Its implementation is based on Repast and java. Individual Space-Time Activity-based Model consists of three objects: the infectious diseases, individuals and activity bundles. For the infectious disease, they defined thee parameters to describe the applied infectious disease: effective contact, disease severity and evolution of the disease within the host. The disease diffusion in ISTAM depends on the distance between infectious and susceptible individuals if there are no obstacles between them as well as directly related to the duration of contact. For an individual in ISTAM's

model, s/he has three groups of attributes: static, dynamic and intelligent attributes. The attributes including demographic information, health level activity pattern that are not changed during the simulation and the reaction attributes to the current situation. In Individual Space-Time Activity-based Model the individual space-time model is described at two levels: between activity bundle and within activity bundle.

Activity bundles or as in Individual Space-Time Activity-based Model known as AB are unites of space. In Individual Space-Time Activity-based Model space where most of individuals' interactions occur is divided into number of activity bundles. AB could be a room, a whole building or a building complex. They can be classified into different groups according to the human activity type and the function of the space. The parameters used to express an AB are the space-time dynamics of individual within the AB and the geometry of the space such as it is size and spatial layout. Movement within AB has been considered in Individual Space-Time Activity-based Model; in some AB, individuals remain static during the simulation time while in some other AB movement is required.

The contact network in Individual Space-Time Activity-based Model is generated from individuals space-time dynamics constrained both by the physical condition of the space and the individuals' activities. At the level of between ABs and within ABs the activity pattern, spatial effects and contact network are considered. At the level of between ABs the individuals are visiting locations near their current location more likely. their activity patterns can reflect this expectation. On the other hand, at the within ABs level, the effective contact concept is applied.

Individual Space-Time Activity-based Model was performed to simulate a hypothetical influenza epidemic at the University of Southampton. The first year of

undergraduate students was the ISTAM population whom their data had been collected via a questionnaire survey. The questionnaire was consists of three parts: personal information, time point and activity preferences and durations. The information of this survey was used to build activity patterns per individual.

2.3.1 SI Epidemic Model

The following system represents a simple no-recovery model without vital dynamics. The relationship between the two states S and I, is illustrated in the system.

where S are the class of susceptible and I the class of infected. The parameter b is the contact rate. The compartment diagram provides us with the following SI model for the population:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI \end{aligned} \tag{2.1}$$

where the parameter β is a positive contact rate. The initial conditions satisfy $N = S(0) + I(0)$ for $S(0) > 0$ and $I(0) > 0$. This type of model describes disease up till the stage of infection and is especially applicable when modeling high large infection proportions of populations such as influenza. Communicable diseases with similar epidemiological dynamics are characterized by a high infection force. Here the disease is transmitted through whole populations in a short amount of time, and then eventually die out (Allen, 20o7).

2.3.2 SIS Epidemic Model

The following SIS model is an expansion of the previous SI model with the addition of recovery and vital dynamics:

where S are the class of susceptible and I the class of infected. The parameter b is the contact rate, g is the recovery rate and m is rate of birth and death.

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI + \gamma I + \mu - \mu S \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I \end{aligned} \tag{2.2}$$

where β and γ denote the contact and recovery rate, receptively. The parameter μ denotes birth and death rate, such that birth rate is equal to the death rate. The dynamics described by an SIS models are applicable to commutable diseases with behavior of sexually transmitted diseases such as syphilis and gonorrhea (Allen, 2007).

2.3.3 SIR Epidemic Model

In an SIR model with vital dynamics immunity is obtained by recovery rate. The S are the class of susceptible, I the class of infected and R the class of removed. The parameter b is the contact rate, g is the recovery rate and m is rate of birth and death.

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI + \mu - \mu S \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I \\ \frac{dR}{dt} &= \gamma I - \mu R \end{aligned} \tag{2.3}$$

where β, γ, μ are contact rate, recovery rate and vital rate, respectively. The initial conditions satisfy $N = S(0) + I(0)$ for $S(0) > 0$ and $I(0) > 0$. However since $N(t) = S(t) + I(t) + R(t)$, $R(t)$ can be obtained from $S(t)$ and $I(t)$. This means that R can be defined as $R(t) = 1 - S(t) + I(t)$. This type of model is applicable when modeling viral disease that describes outbreaks over longer periods of time. The model used for Measles, is later discussed in great detail. This SIR model can exhibit the traits of periodic outbreaks in small communities, but also endemic behavior of Measles in large populations (Allen, 2007).

2.4 The models

In this section we will introduce the two models of pertussis and measles in their original form, as proposed by their authors. This is followed by a non-dimensionalization, which will be the subsequent notation throughout.
Measles and Pertussis have been the subject of thorough investigation for many years. Various models have been proposed, to understand the underlying dynamical forces and approximate data of observation. The models that have been subject to this study are:

Measles model

This model is described by (Hethcode, 1976):

$$
\begin{aligned}
S'(t) &= -\lambda IS + \mu - \mu S \\
I'(t) &= \lambda IS - \gamma I - \mu I \\
R'(t) &= \gamma I - \mu R \\
&\textit{and} \\
R(t) &= 1 - S(t) - I(t)
\end{aligned}
\tag{2.4}
$$

Pertussis model

This model is described by (Lavine, 2011):

$$
\begin{aligned}
\frac{dS}{dt} &= \mu(1-\nu) - (\mu + \beta I)S + \sigma^* W \\
\frac{dI}{dt} &= \beta IS - (\mu + \gamma)I \\
\frac{dW}{dt} &= 2\sigma R - (\mu + \sigma^* + \kappa\beta I)W \\
\frac{dR}{dt} &= \kappa\lambda W + \gamma I + \mu\nu - (\mu + \sigma^*)R
\end{aligned}
\tag{2.5}
$$

2.5 Non-dimensionalization of pertussis and Measles Models

Before the commencement of an analysis, it is useful to simplify a model. This can cause a decrease in computation time, arithmetic and errors and possibly increase transparency in interpretation. In some situations, an effective tool is non-dimensionalization of systems (a particularly common trait among physicists). By substituting appropriate units, equations appear without any specific unit attachment. This allows parameterization, collection of terms and secures

dimensional agreement throughout. This can enable isolation of parameters and thus minimize the number of coefficients - preferably to the order of one. The number of parameters or variables are therefore reduced at least one dimension. It should be noted that this operation only changes units.

Obviously, ratios must be conserved such, that a system retains its dynamics. A dimensionless system can thus yield fewer parameters, which in some cases cause a decrease in computation time and arithmetic, during analysis. Ultimately it is possible to perform a reverse calculation into terms of original units.

2.6 Dynamics of the Measles Model

The biological understanding of the measles model, the different parameters and their interpretations, flow diagram and threshold will be explained well in details. Measles is respiratory infection caused by single-stranded RNA - virus of the Morbilli paramyxovirus family. Measles is mainly spread through airborne droplets expelled by the coughing and sneezing of infected. However it is also spread through close personal contact or direct contact with infected nasal or throat secretion from infected individuals. As measles access the respiratory tract it further extent to destroy lymph nodes. Subsequently the virus spreads to involve the skin, the viscera, kidney and bladder.

The virus mainly infects children, so vaccination is used routinely where available. As opposed to most bacterial diseases, a person that recovers from the measles virus gains permanent immunity. Vaccination has caused a decrease in mortality in many developed countries; however it still remains one of the deadliest child diseases in developing countries (Jansen and Stollenwerk 2005, Vries 2012)

Derivation of model from the flow diagram (Measles)

The Measles model presented in the following is an SIR model with vital dynamics. The model has been redefined such that both models use analogous parameters. The model is constructed using different compartments that denote the division applied to the given population groups. A time dependent flow connects the population groups in the compartments, and is defined by rates, denoted by Greek letters.

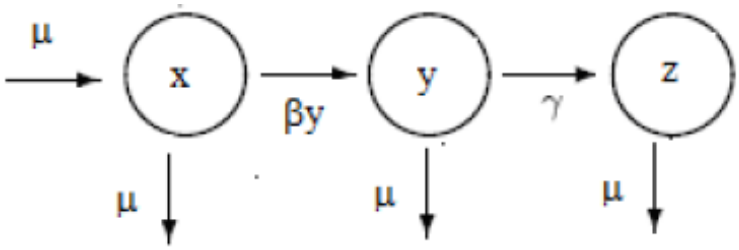

Figure 2.1: A Compartmental model for Measles

Table 2.1: Symbols and Description of Model Variables.

Symbol	Description
x	the class of susceptible
y	class of infected
z	class of removed
βy	contact rate dependent on the size of the y class
γ	recovery rate
μ	rate of birth and death

The three compartments are the three basic compartment types of the SIR-model:

1. the susceptible (x), which represents the fraction of the population which is able to conceive Measles,

2. the infected (y), which is the part of the population which has become infected with Measles and

3. the recovered (z), which is the share of the population that has obtained immunity.

The flow diagram includes one source and three sinks. The source represents births, which is considered only to be into the susceptible compartment. Hence you can not be born infected nor immune (in this model). The sinks show that the individuals can die in either compartment, since people obviously can die whether they are susceptible, infected or recovered. The rates that characterize the flow are given as follows:

$[x'] = \frac{1}{time}$, $[y'] = \frac{1}{time}$,, $[z'] = \frac{1}{time}$,

$[x'] = \frac{1}{time(individualsflow)}$, $[x'] = \frac{1}{time(contactrate)}$ $[x'] = \frac{1}{time(recoveryrate)}$

$\frac{1}{\mu}$ then interprets average lifetime of an individual in population and $\frac{1}{\mu}$ the average infection period (Hethcode, 1976).

The compartment dynamics of this flow diagram is characterized by a one-directional, irreversible flow from left to right. This means, that once you have been infected you can't become susceptible and once you have recovered you can't get infected again (thus nor susceptible). The internal compartment-by-compartment dynamics have the following properties:

1. The x-compartment transfers individuals from x into y at a rate proportional to both x and y. This makes sense since: the larger the group of x, the more susceptible individuals will be to measles. Also, the larger the group of infected, the more carriers. The contact rate is applied, since infection is caused by direct interaction. The underlying assumption here is that each person in the compartment has an average number of interactions. Of these interactions, a certain fraction is with susceptible individuals and a

fraction of these interactions will then result in infection (Hethcode, 1976). Combining this observation with the sink and source contributions the following equation for x' is obtained:

$$x' = \mu - \mu x - \beta y x$$

2. The y-compartment has its positive contribution from the negative contribution of x, due to the source and flow direction considerations. The output in y is considered proportional to y itself only, since no other compartment affects the rate of recovery. Thus the differential equation of this compartment is given by:

$$y' = \beta y x - (\gamma + \mu) y$$

3. The z-compartment only has input from the feed of y, and the sink of deaths. This tells that once you have recovered from infection, the only way you leave the recovered group is by passing away. Hence gaining immunity is permanent - you can't get susceptible (or infected) again. From this you get the expression:

$$z' = \gamma y - \mu z$$

The total population is expressed by $N = x + y + z = 1$. The population is restricted, such that $\frac{dN}{dt} = 0$ and thus: $\frac{dx}{dt} + \frac{dy}{dt} + \frac{dz}{dt} = 0$. This means, that the 3-dimensional system,

$$x' = \mu - \mu x - \beta y x$$
$$y' = \beta y x - (\gamma + \mu) y$$
$$z' = \gamma y - \mu z$$

is reduce it to a two dimensional system, by factoring out z, since x' and y' are only mutually coupled. This gives:

$$x' = \mu - \mu - \beta y x$$
$$y' = \beta y x - (\gamma + \mu) y$$

2.6.1 Threshold for an epidemic outbreak of Measles

The threshold parameter R_0 is the value that determines whether or not an epidemic can happen. This parameter is defined as:

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

This parameter is based on the assumption that epidemics are based exclusively on the infective proportion of a population. Thus only the inputs and outputs of y determine the epidemic outcome. The threshold parameter for the measles model has the value one. The dynamics for the Measles model are therefore divided into either, $R_0 \leq 1$ or $R_0 > 1$.

If $R_0 \leq 1$, the fraction of infected will approach zero, as there won't be enough infected to start an epidemic. This can be interpreted as, if each infected individual infects one or less (on average), the compartment of y will decrease exponentially.

This relates to fact that the y compartment has an output that contributes to the recovered population. Conversely, if $R_0 > 1$, an epidemic will break out, as the number of infected individuals exceeds the threshold (Hethcode, 1976).

2.7 Dynamics of the Pertussis Model

Pertussis, or whooping cough, has since its first discovery in the middle Ages, appeared in all populations with unimmunized children. Pertussis is a respiratory infection arising from the colonization of the lung epithelial cells by the aerobic bacillus Bordetella Pertussis. The pathogenesis of a pertussis infection is initiated by transmission of the infection agents through the respiration system. As these infectious agents reach the lungs organelles the bacteria's surfaceprotein attach to the hair, otherwise known as cilia. This prevents the removal of mucus from the lungs. The accumulation of mucus in the lungs forces the host into a coughing fit, of which some bacteria airdrops are expelled, free to contaminate other individuals. Disease manifestations are well documented for first case infections as they span a variety of symptoms - the most prominent of these is the whooping sound produced as the infected inhales after coughing(Cherry, 1996).

The incubation period is usually between 6 to 20 days (WHO, 2011). Historical records of the pre-vaccine era of pertussis reveal a peak in the infection cycle every 2-5 year. The isolation of Pertussis in 1906, promoted the discovery of the whole cell vaccine This led to a convention of mass immunization in developed countries from the 1950's (Cherry, 1996). At first sight, the vaccination program seemed to have a rather significant effect; however it was soon observed that the vaccine and the immunization produced was of limited duration.

Pertussis remains endemic, affecting nearly 16 million people a year (WHO, 2011). Infected persons are treated with antibiotica, and infection is prevented by age -

distributed vaccine programs (Statens Serum Institute, 2012).

2.7.1 Derivation of model from the flow diagram (Pertussis)

The following compartmental model explains the pertussis model. explains the compartments and the derivation of equations based on this compartment.

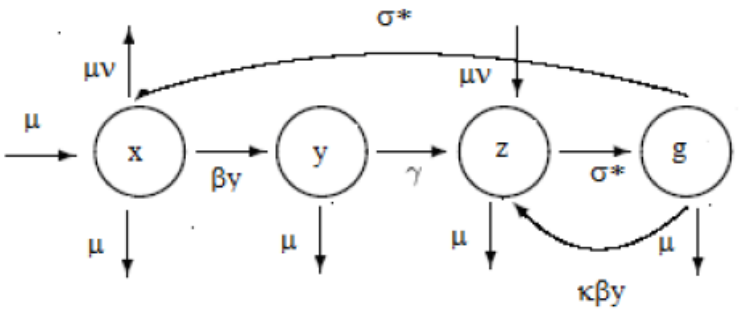

Figure 2.2: A Compartmental model for Whooping cough

Table 2.2: Symbols and Description of Model Variables.

Symbol	Description
x	the class of susceptible
y	class of infected
z	class of recovered
g	the class of immune individuals that loose there immunity
σ^*	rate with which g looses immunity
βy	contact rate dependent on the size of the y class
κ	the boosting coefficient
$\kappa\beta y$	the boosting rate multiplies with the contact rate dependent on the size of the y class
γ	recovery rate
μ	rate of birth and death
$\mu\nu$	vaccination rate

The model described in Lavine et al., 2010, is based on a "$SIRS - model$". However it incorporates an extension that embodies the observed characteristic of Pertussis. That is the reemergence of infection, after achievement of immunity. The model represents the three basic SIR classes, where the class of immune is divided into two "sub"-compartments; the standard recovered compartment (z)

and the new compartment: waning (g). This sub-compartment structure is the model-equivalent of the re-emergence of Pertussis, interpreted in terms of decreasing effect of a vaccine given.

There is only one source in this compartment, and this is the birth rate, μ. However, since we assume that we have a constant population, the source must be the same size as the combined output of the sinks, hence $\mu = \mu(x + y + z)$(otherwise our population would grow with time). Thus the sink, which in this case is the mortality rate, is denoted by the same symbol as the source. The source contributes positively to the x compartment. The sink contributes negatively to all compartments since individuals can die in any given compartent. The interrelating dynamics between the compartments has been visualized in the flow diagram. The susceptible compartment, x, consists of the individuals born into the population and the people transferred from g, who lost their immunity due to lack of exposure to infection. Two negative contributions are present in the dynamics of this group. A part is moved directly into the immune group, z. The underlying, simplified assumption is that infants are vaccinated at the moment they are born. Another part is infected and thus transferred into y. Two positive contributions are also present. One is individuals born into x, who remain in x. The other is individuals whose immunity has vanished due to lack of exposure. These get transferred from g into x.

Deriving x', it's first noted that the positive contribution of births is not dependent on any compartment, thus it is constant in x. We express it as $\mu(1 - \nu)$ where the negative contribution of ν denotes the births into immunity due to vaccine. It is obvious that the input of the waning is proportional to g, that is we write $\sigma^* g$. The mortality and infection rate must be proportional to the size of x, thus we write -$(\mu + \beta y)x$- negative since it is an output. Putting this together,

we get:

$$x' = \mu(1-\nu) - (\mu + \beta y)x + \sigma^* g$$

The infected compartment only has one input and one output in the flow indication. The input from x being infection, and the output to z being recovered. That is individuals always pass straight through the y compartment (unless they die). In the differential equation, the positive contribution is from x and proportional to x and itself. Thus we write βyx. The negative contribution is into W and proportional to y itself, that is written $(-\mu + \gamma)y$. Putting them together gives

$$y' = (\beta x - (\mu + \gamma))y$$

The recovered compartment has 3 inputs and one output. The possibilities for individuals entering this compartment in this situation are that they either recover from illness (γ), get vaccinated ν or get immune boosted from $g(\kappa\lambda = \kappa\beta I)$. The only output from z is to g, when individuals loose parts of their immunity. This is also the only input in g. g, nonetheless, has two outputs. One returning to z (boosting) and the other one to x (complete immunity loss).

Biologically, the interpretation of the dynamics of these is that individuals in z are highly resistant to the infection and therefore not in need of immune boosting. As individuals in z transfer to the waning class, their immune weakens permitting two possibilities. First possibility is that they lose their immunity due to absence of exposure, returning them to susceptible class. The other possibility is that, the infection rate is high, and their immunity is boosted such that they once again are to return to the recovered class.

The derivation for z' and g' is, based on the above:

$$
\begin{aligned}
z' &= \kappa\beta yg + \gamma\nu - (\mu\sigma^*)z \\
g' &= \sigma^*(N - y - x - g) - g(\mu + \sigma^* + \kappa\beta y)
\end{aligned}
\tag{2.6}
$$

The second expression is derived by using the assumption that $N = 1$.

2.7.2 Threshold for an epidemic outbreak of Pertussis

The threshold for Pertussis is slightly different from the one for Measles. That is; In a SIR epidemic model the threshold for a Measles epidemic is as follows:

$$For R_0 \leq 1$$

no endemic will occur.

$$For R_0 > 1$$

an endemic will occur.

In the whooping cough there are different values for when an epidemic will start. In the model for whooping cough the parameter $P_{vaccinated}$ is used to describe, when there will be an epidemic. This describes how large a percentage of the population, $N(for N = 1)$, that is vaccinated. The parameter $P_{vaccinated}$ is defined as $1 - \nu$, where ν is the vaccine probabilities (Lavine, 2011). The link between the two thresholds is defined by:

$$R_e = R_0(1 - P_{vaccinated}) < 1$$

$$\frac{\beta(1 - P_{vaccinated})}{\gamma + \mu} < 1 \Leftrightarrow$$

$$\frac{\gamma + \mu}{\beta} > 1 - P_{vaccinated} \Leftrightarrow$$

$$P_{vaccinated} > 1 - \frac{1}{R_0}$$

Chapter 3

Methodology

3.1 Introduction

This chapter provide an overall understanding of the structure and the method used to analize the mathematical models.

3.1.1 Dynamics

In analysis of dynamical systems, the characterization is often expressed in terms of differential equations. That is, equations describe the behavior of the system, or more specifically: the rate of a variable with respect to its state variable. In terms of a variable x, evaluated in time(t), this could have the basic form

$$\frac{dx}{dt} = f(x, t)$$

. The models for pertussis and Measles, in our analysis are categorized as a system of ordinary differential equation (ODE). Ordinary means our equations only have one independent variable, and we only take derivatives with respect to this one variable, as opposed to partial differential equations. The system is

also autonomous, which simply explains that the equations in question, do not explicitly depend on time. Hence no t-terms enter our equations - only variables implicitly depending on time $(x(t), y(t))$, etc.

Furthermore we see that these autonomous systems of ordinary differential equations are coupled and hence non-linear. At a first glance, the pertussis model seems like it only consists of linear terms on the right-hand side of the differential equations. However, the term λ implies the rate βI, which means we have composition of variables. This means we have non-linear terms that model the interaction between our compartments, such that, for example, the rate of growth of the infected compartment, I, is proportional to the size of the susceptibles, S. They are coupled, because the variable terms appear in combination in the rates of each term. Thus we see that $\frac{ds}{dt}$ is determined by the variables S and W, $\frac{ds}{dt}$ by S and I, and so forth. Since the dynamical system is described in terms of differential equations, we also call the system a continuous system (Strogatz, 2001). That is to say we have a 3-dimensional continuous coupled non-linear autonomous system of ordinary differential equations(Edwards, 2010).

3.2 Existence and uniqueness

Theorem: Consider the initial value problem

$$\dot{x} = f(x), x(0) = x0$$

Suppose that f is continuous and that all its partial derivatives $\frac{\partial f_i}{\partial x_j}, i, j = 1, 2, 3, ..., n$ are continuous for x in some open connected set $D \subseteq R^n$. Then for $x_0 \in D$, the initial value problem has a solution $x(t)$ on some interval $(-t, t)$ about $t = 0$, and the solution is unique. - Nonlinear dynamics and chaos by Steven H. Strogatz.

The Theorem of existence and uniqueness is a very powerful theorem when solving differential equations. It's especially powerful when dealing with scalar or 2-dimensional cases, which makes it valuable to the Measles model. The reason this is important is because the theorem states that there exists a solution for a given initial value (existence), and solutions cannot intersect each other (uniqueness). If solution curves did intersect then there would be two solutions starting at some initial value and thus it violates the uniqueness term in the aforementioned theorem (Strogatz, 2001).

When dealing with three dimensions, which in this case refer to the whooping cough model, the solutions can move in the 3rd direction. This means that a 2-D plot of the behaviour usually is not adequate when describing solutions. An example that illustrates this is, if there is a limit cycle in the plane in 2 dimensions then the solution to an initial value inside the limit cycle cannot escape.

However if it's in 3-dimensions the solutions would be able to escape the limit cycle because of the 3rd direction (Strogatz, 2001).

3.3 Model Linearization

An autonomous homogenous linear differential equation system can be written as the following:

$$\frac{dX}{dt} = BX$$

In this study we are dealing with nonlinear autonomous homogenous differential equation system which can be written as:

$$\frac{dX}{dt} = F(X), where F(X) = (f_1X, f_2X, f_3X, ..., f_nX)^T$$

Systems of nonlinear differential equations are much trickier to evaluate, than linear differential equations. However, by using Taylor's expansion we are able to transform a nonlinear system to its linear equivalent system near each of its equilibrium point. That is, if we consider the higher order terms of the Taylor expansion as very small, then we can neglect these as λ is different from zero (Allen, 2007).

Let us consider a 2-dimensional nonlinear system first:

$$\frac{dX}{dt} = F(X) = \begin{bmatrix} \frac{dx_1}{dt} \\ \frac{dX_2}{dt} \end{bmatrix} = \begin{bmatrix} f_1(x_1, x_2) \\ f_2(x_1, x_2) \end{bmatrix}$$

This system is then expanded around its equilibrium point (x_0, y_0). First we will define two new functions, $u = x_1 - x_{1,0}$ and $v = x_2 - x_{2,0}$ and assume that f have continuous second-order partial derivatives. Then the expansion yields:

$$\frac{du}{dt} = f(x_{1,0}, x_{2,0}) + f_{x_1}(x_{1,0}, x_{2,0})u + f_{x_2}(x_{1,0}, x_{2,0})u + f_{x_1x_2}(x_{1,0}, x_{2,0})\frac{u^2}{2} + ...$$
$$\frac{dv}{dt} = f(x_{1,0}, x_{2,0}) + f_{x_1}(x_{1,0}, x_{2,0})v + f_{x_2}(x_{1,0}, x_{2,0})v + f_{x_1x_2}(x_{1,0}, x_{2,0})\frac{v^2}{2} + ...$$

Now since $f(x_0, y_0) = 0$ and neglect the higher order terms, this may be written as:

$$\frac{dZ}{dt} = JZ$$

where $J = \begin{pmatrix} f_{1x_1}(x_1, x_2) & f_{1x_2}(x_1, x_2) \\ f_{2x_1}(x_1, x_2) & f_{2x_2}(x_1, x_2) \end{pmatrix}$ evaluated at $x_1 = x_{1,0}$ and $x_2 = x_{2,0}$ and $Z = \begin{pmatrix} u \\ v \end{pmatrix}$

Hence we have written our nonlinear system as an approximately linear sys-

tem.

It should be noted that if the eigenvalues $\lambda = 0$, then the small terms of the Taylor expansion does not hold enough information to linearize the system. When this is the case it is not sufficient to use the Jacobian matrix to linearization (Allen, 2007). In an n-dimensional system, J is called the Jacobian matrix and is written as

$$J = \begin{pmatrix} f_{1x_1}(x_1, x_2, ..., x_n) & \cdots & f_{1x_n}(x_1, x_2, ..., x_n) \\ \vdots & \ddots & \vdots \\ f_{nx_1}(x_1, x_2, ..., x_n) & \cdots & f_{nx_n}(x_1, x_2, ..., x_n) \end{pmatrix}$$

Evaluated at $x_1 = x_{1,0}$, $x_2 = x_{2,0}, x_{2,1}..., x_{n,0}$

3.4 Stability Analysis

3.4.1 Classification of fixed point

A system can be defined by a set of interacting elements, to the extent that there are cause and effect relations in the phenomena that occur to the elements of this set. Some characteristics of the interacting elements change over time in dynamical system. From the Calculus invented by Newton and Leibniz it is apprehended with certainty that the variation of an object (characteristic) $x(t)$ in a continuous time is measured by the derivative $\frac{dx(t)}{dt}$. In this sense the system evolution in time can be described mathematically by:

$$x' = \frac{dx(t)}{dt} \tag{3.1}$$

$$x' = f(x, \beta) \tag{3.2}$$

Where f is the variation rate, x is the state variable, and β is a parameter of the system. When f does not depend on time explicitly the system is called autonomous. Certain values, $\lim_{t\to\infty} x(t) = x^*$ with $f(x^*) = 0$ do not change over time, depicting a stationary solution or the equilibrium solution of equation 3.1.

The classification of these equilibrium fixed point are well explained by the stability and the topological property of a phase portrait. A phase portrait (phase space or phase diagram) is a plot of the system's trajectories in the state space in which the axes are the state variables. Figures 3.2 , 3.3 and 3.4 are the phase portrait for stable and unstable focus, stable and unstable node, a center and a saddle.

Lyapunov Stability

In dynamical systems the most important type of stability regarding the solution of differential equations (DE) is the solutions near the point of equilibrium. This was discussed by Lyapunov his book "The General Problem of Stability of Motion" in 1892. According to Lyapunov, stability is a property of system behaviour in neighbourhoods of equilibria, Lyapunov(1892). Lyapunov stability considers changes in the initial conditions for a fixed system whiles a perturbations of the system itself is called structural stability. When the initial conditions, $x(0)$, fit in with an equilibrium point the system remains indefinitely in this point. However, when the initial conditions are inside a sphere of radius δ whose centre is a specific equilibrium, x^*, it can be defined as *asymptotically stable* when all the trajectories, $x(t)$, converge to x^*. It is *locally stable* if this sphere has a finite radius this point is, otherwise when the radius approaches infinity the point is *globally stable*. We can conclude on this that :

$\rightarrow$ If we choose $\epsilon > 0$, there exist a $\delta = \delta(\epsilon) > 0$ such that, if $\| x(0) - x^* \| < \delta$,

then $\| x(0) - x^* \| < \epsilon$ for all $t \geq 0$, the equilibrium of 3.1 is *Lyapunov stable.*

→ If the system is Lyapunov stable, and if there exist $\delta > 0$, such that, if $\| x(0) - x^* \| < \delta$, then $\lim_{t \to \infty} \| x(0) - x^* \| = 0$, then the equilibrium of 3.1 is *asymptotically stable.*

→ If the system is asymptotically stable, and if there exist $\wp, \ell, \delta > 0$, such that, if $\| x(0) - x^* \| < \delta$, then $\| x(0) - x^* \| \leq \wp \| x(0) - x^* \| e^{-\ell t}$, for $t \geq 0$, then the equilibrium of 3.1 is *exponential stable.*

All these classification is based on the temporal evolution of the distance between a trajectory $x(t)$ and x^*, for the complicated systems. (Lyapunov, 1892) developed a another method for assessing the conditions of stability indirectly. This method involves linearizing f at x^*, with a set of jacobian matrix of f denoted by $\mathbf{J}$, evaluating at x^* gives as:

$$J = \frac{\partial f(x, \beta)}{\partial x}|_{x=x^*} \tag{3.3}$$

The eigenvalues of J determine whether x^* is stable. These are scaler values λ_i such that $det(J - \lambda_i I) = 0$, that is the roots of the characteristic polynomial of J, where I is the identity matrix. In this way, if the eigenvalues are all distinct, it is possible to write an exponential approximation for general solution of the linearized system by:

$$x(t) = k_1 v_{01} e^{\lambda_1 t} + k_2 v_{02} e^{\lambda_2 t} + ... + k_n v_{0n} e^{\lambda_n t} \tag{3.4}$$

where k_i are the arbitrary constants that are given by the initial conditions, n is the dimension of the system and the vectors v_{oj} are the eigenvectors corresponding

with each eigenvalue and determined by:

$$Jv_{0i} = \lambda_i v_{0i} \qquad (i = 1, 2, ..., n) \tag{3.5}$$

Sometimes the Jacobian matrix presents equal real eigenvalues, in this case the multiplicity of the eigenvalues has to be considered in order to generate linearly independent solutions. Where the multiplicity is the number of equal eigenvalues. If the multiplicity of an eigenvalue is two, there are two eigenvalues of this same value, an example of a two-dimensional system that has two equal eigenvalues ($\lambda_1 = \lambda_2 = \lambda$) has a general solution for the degenerate case as:

$$x(t) = k_1 v_{01} e^{\lambda_1 t} + k_2 v_{02} t e^{\lambda_2 t} \tag{3.6}$$

In n-dimensional case for eigenvalues with multiplicity m the associated functions are $e^{\lambda_i t}$, $te^{\lambda_i t}$, $t^2 e^{\lambda_i t}$, . . . ,$t^{m-1} e^{\lambda_i t}$, thus, in the same way as for distinct eigenvalues, the general solution is the linear combination of these functions and then uses the initial conditions to calculate the arbitrary constants.

It is important to note that the equilibrium behaviour of the non-linear system in the is the same the approximated linear system except when the equilibrium point of the approximated linear system is a centre. A further analysis is needed to determine the nature of the original non linear system, which could be stable centre, a stable spiral sink, or an unstable spiral source.

Poincaré Approach

Poincaré also classified fixed points in a two dimensional plane by the trace T and the determinant D of the J matrix:

$\rightarrow$ if $D < 0, \lambda_{1,2}$ are real and of opposite signs, the fixed point is called a an

unstable saddle.

→ if $D > 0$ and $T^2 - 4D > 0, \lambda_{1,2}$ are real and with the same sign. If $T > 0$ the point is called a nodal source, and a nodal sink for if $T < 0$.

→ if $D > 0$ and $T^2 - 4D < 0, \lambda_{1,2}$ are complex conjugated. If $T > 0$ the fixed point is a spiral source, if $T < 0$ it is a spiral sink and if $T = 0$ the point is a stable center.

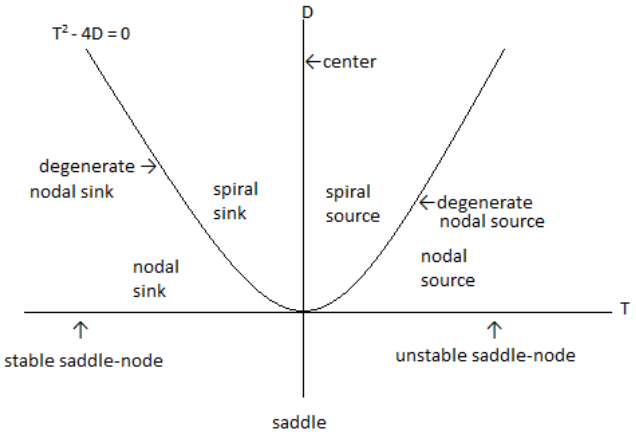

Figure 3.1: Trace Determinant Plane

On the line $T^2 - 4D = 0$ are lying the degenerate nodes and star points, with this cases the system has two equal eigenvalues. In the case of star points, only the main diagonal of J is different of zero with equal elements, thus the solutions being straight lines passing through x^* in the phase plane, the star is unstable if the elements of the diagonal are positive, if the elements of the diagonal are negative the star is asymptotically stable. When $T^2 = 4D$ there is a degenerate node that is stable when $T < 0$ and unstable when $T > 0$. If $D = 0$ at least one of the eigenvalues is zero and in this case there is a whole line or a plane of fixed

points. Figure 2.4 shows some of the different mentioned types of fixed points and the degenerate cases.

Observing the form of the solution of equation (2.3) it can be seen that it converges to stable solution when $Re\lambda_i < 0$ and diverges when at least one eigenvalue λ_i is positive. But in the degenerate cases such as center, star, degenerate node and non-isolated fixed points, the linear system does not guaranty a correct picture of the phase portrait near the fixed point, degenerate points can be altered by small nonlinear terms. In such cases stability must be determined considering non-linear terms of the Taylor series of $f(x, \beta)$

Routh-Hurwitz Approach

Edward John Routh and Adolf Hurwitz found independently the solution to find out whether all the roots of a polynomial have it real part being negative. As mentioned earlier the stability of an equilibrium point is established by the sign of the real part of its eigenvalues. Therefore to determine the stability of this solution, taking into account that a fixed point is stable when $Re(\lambda_i < 0)$ for all i, is therefore necessary to know if the signs of the real parts of λ_i are negative or not. This approach of stability known as Routh-Hurwitz theorem is very helpful specially when the eigenvalues of the Jacobian J is of order higher than five and it is in general impossible to calculate analytically its roots. The theorem explains that the real part of all roots of the polynomial:

$$\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_{n-1}\lambda + a_n = 0 \tag{3.7}$$

are negative if all the coefficients a_i are positive and if all upper-left determinants $D_i(i = 1, ..., n)$ of the Hurwitz matrix H are positive. If the jacobian matrix J is $n \times n$ so is H. The H matrix are made in the following way:

→ The coefficients a_i with odd indices and increasing j are written in the first row. In the second line are written the coefficients with even indices and increasing j. Notice that the coefficient of λ^n, a_0, is 1. the other positions are filled up with zeros.

→ The two preceding lines are obtained moving the first two lines one column to the right, filling-in the empty positions with zeros.

→ The other rows are built repeating the procedure above until a_n occupies the lower right edge of the matrix.

In this way, for example, for $n = 6$ the Hurwitz matrix is

$$H = \begin{pmatrix} a_1 & a_3 & a_5 & 0 & 0 & 0 \\ 1 & a_2 & a_4 & a_6 & 0 & 0 \\ 0 & a_1 & a_3 & a_5 & 0 & 0 \\ 0 & 1 & a_2 & a_4 & a_6 & 0 \\ 0 & 0 & a_1 & a_3 & a_5 & 0 \\ 0 & 0 & 1 & a_2 & a_4 & a_6 \end{pmatrix}$$

and the upper-left determinants $D_i (i = 1, ..., n)$ are:

$$D_1 = \left| a_1 \right|, D_2 = \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix}, D_3 = \begin{vmatrix} a_1 & a_3 & a_5 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{vmatrix}, ..., D_6 = \left| H \right|$$

The behaviours of this differential equation in the neighbourhood of the steady state is summarized below

1. If the eigenvalues are real and distinct then:

→ If the eigenvalues are positive, then the equilibrium point is an unstable source.

→ If the eigenvalues are negative, then the equilibrium point is stable sink.

→ If at least one of them is positive, then the equilibrium point is an unstable saddle.

2. If the eigenvalues are real and equal, and the eigenvectors are independent.

→ If the eigenvalues are positive, then the equilibrium point is an unstable star source.

→ If the eigenvalues are negative, then the equilibrium point is stable star sink.

3. If the eigenvalues are real and equal, and at least one of the eigenvectors are dependent.

→ If the eigenvalues are positive, then the equilibrium point is an unstable improper source (degenerate nodal source).

→ If the eigenvalues are negative, then the equilibrium point is stable improper sink (degenerate nodal sink).

4. If the eigenvalues are complex:

→ If the eigenvalues are purely imaginary, then the equilibrium point is a stable centre.

→ If the eigenvalues have positive real component, then the equilibrium point is an unstable spiral source.

→ If the eigenvalues have negative real component, then the equilibrium point is a stable spiral sink.

5. If one of the eigenvalues is zero, with the other given as φ.

   $\rightarrow$ If $\varphi > 0$, then the equilibrium is an unstable saddle-node.

   $\rightarrow$ If $\varphi < 0$, then the equilibrium is a stable saddle-node.

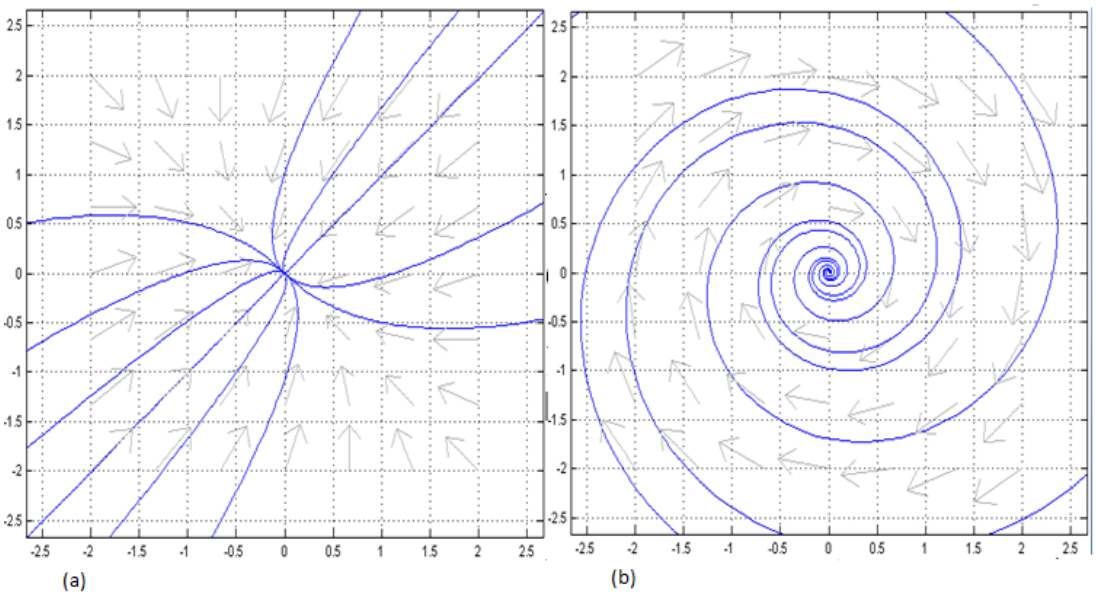

Figure 3.2: Phase diagram indicating stable node and stable spiral
(a) is a stable node and the equations used are $x' = -3x - y, y' = -x - 3y$,
(b) is a stable spiral, drawn with equations $x' = -0.2x + y, y' = -x - 0.2y$

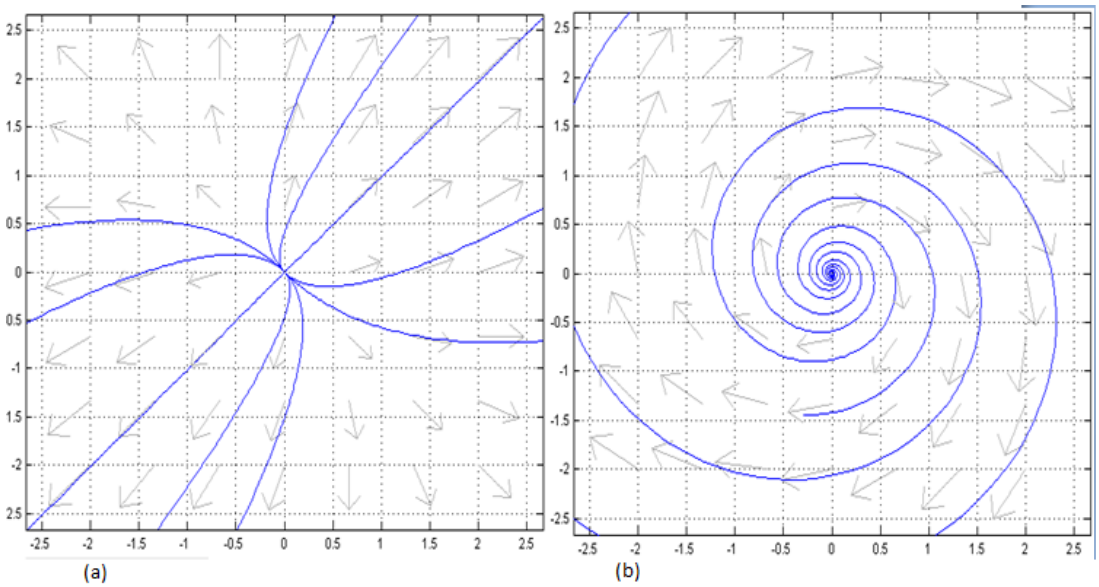

Figure 3.3: Phase diagram indicating unstable node and unstable spiral
(a) is an unstable node and the equations used are $x' = -3x - y, y' = -x - 3y$,
(b) is a unstable spiral, drawn with equations $x' = 0.2x + y, y' = -x + 0.2y$

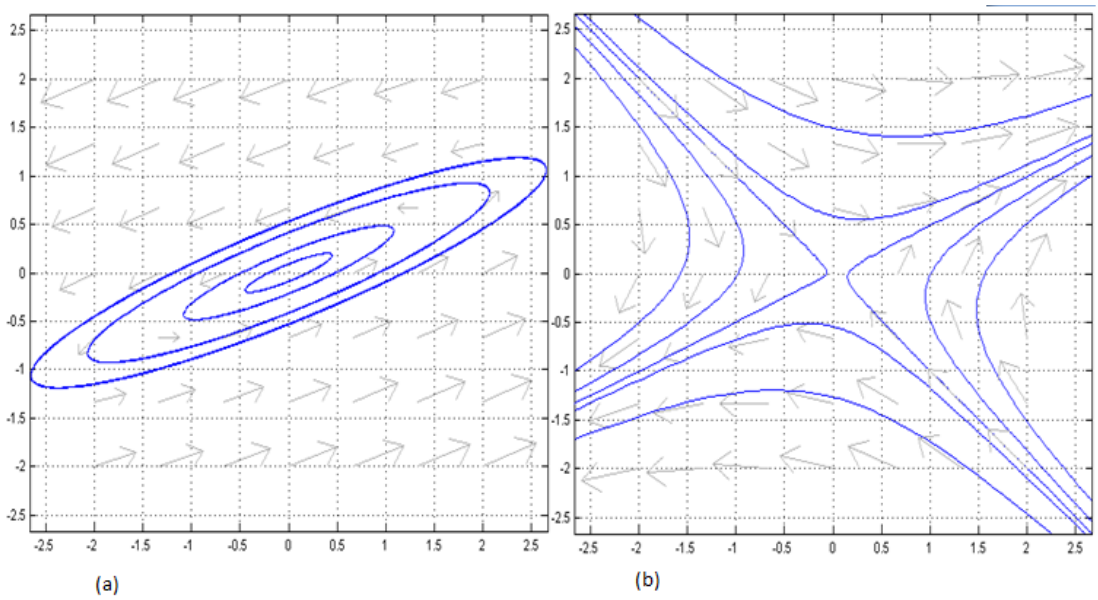

Figure 3.4: Phase diagram indicating a centre and a saddle
(a) is a centre and the equations used are $x' = 4x - 10y, y' = 2x - 4y$,
(b) is a saddle, and equations used are $x' = x + 4y, y' = 2x - y$

Chapter 4

Analysis of the Mathematical Models

This chapter contains the stability analysis of the measles and pertussis models. This includes the stability analysis and the finding of equilibrium point of the models.

4.1 Stability analysis of the Measles Model

The parameter values of the differential equation system are the following

$\beta = 0.4$, $\mu = 0.0001$ and $\gamma = 0.2$

The system of equations for the model is the following

$$x' = \mu - \mu x - \beta y x$$

$$y' = \beta y x - (\gamma + \mu) y$$

$$z' = \gamma y - \mu z$$

At equilibrium, we have;

$$0 = \mu - \mu x - \beta y x$$

$$0 = \beta y x - (\gamma + \mu) y$$

$$0 = \gamma y - \mu z$$

Finding the equilibrium points in the initial step, we have; $y = 0 = y(\beta x - \gamma - \mu) \Rightarrow y_1^* = 0$ and $x_2^* = \frac{\mu+\gamma}{\beta}$.

Using $y_1^* = 0$ yields the first equilibrium point: $x' = \mu - \mu x = 0 \Rightarrow x_1^* = 1$ Next, the value of $x_2^* = \frac{\mu+\gamma}{\beta}$ yields the equilibrium point;

$$x' = \mu - \mu\frac{\mu+\gamma}{\beta} - \beta y\frac{\mu+\gamma}{\beta} = 0 \Rightarrow y_2^* = (\mu - \mu\frac{\mu+\gamma}{\beta})\frac{1}{\mu+\gamma}$$

Hence, the following equilibrium points of the system: $(x_1^* = 1, y_1^* = 0)$

$$x_2^* = \frac{\gamma+\mu}{\beta}, y_2^* = (\mu - \mu\frac{\mu+\gamma}{\beta})\frac{1}{\mu+\gamma}$$

To linearize the differential equation system, the theory of calculating the Jacobian matrix is used. The Jacobian, J, is computed by the following matrix of partial derivatives;

$$J(x,y) = \begin{pmatrix} \frac{\partial x'}{\partial x} & \frac{\partial y'}{\partial x} \\ \frac{\partial x'}{\partial y} & \frac{\partial y'}{\partial y} \end{pmatrix} = \begin{pmatrix} -\mu - \beta y & -\beta x \\ \beta y & \beta x - (\gamma + \mu) \end{pmatrix}$$

Determining the eigenvalues of this Jacobian matrix implies

$$A - \lambda I = \begin{pmatrix} -\mu - \beta y - \lambda & -\beta x \\ \beta y & \beta x - (\gamma + \mu) - \lambda \end{pmatrix}$$

$$J(x_1^*, y_1^*) = \begin{pmatrix} -\mu & -\beta \\ 0 & \beta - (\gamma + \mu) \end{pmatrix}$$

$$Det(J(x_1^*, y_1^*) - \lambda I) = 0 = \begin{pmatrix} -\mu - \lambda & -\beta \\ 0 & \beta - (\gamma + \mu) - \lambda \end{pmatrix} = (-\mu - \lambda)(\beta - \gamma - \mu - \lambda) = 0$$

The eigenvalues are therefore given by; $\lambda_1 = -\mu$ and $\lambda_2 = -\gamma - \mu + \beta$.
The trace $Tr(A) = \lambda_1 + \lambda_2 = -2\mu - \gamma + \beta$ and $Det(A) = (-\mu)(\beta - \gamma - \mu)$.
$Tr(A) < 0$ if and only if $2\mu + \gamma > \beta$, $Tr(A) > 0$ if and only if $\gamma + \mu < \beta$ and the determinant of A is positive if and only if $\gamma + \mu > \beta$ and negative if and only if $\gamma + \mu < \beta$ In order to determine the behavior of the solutions in the phase plane we then need to calculate these values using the parameter values; $\beta = 0.4, \mu = 0.0001, \gamma = 0.2$. $2\mu + \gamma \approx 0.2002 < \beta$ and $\mu + \gamma \approx 0.2002 < \beta$. Hence, we have a *saddle point.*

Determining the stability of the second equilibrium point using the above approach gives;

$$(J(x_2^*, y_2^*) - \lambda I) = 0 = \begin{pmatrix} -\mu - \beta\left(\mu - \mu\frac{\mu+\gamma}{\beta}\right)\frac{1}{\mu+\gamma} - \lambda & -(\gamma + \mu) \\ \beta\left(\mu - \mu\frac{\mu+\gamma}{\beta}\right)\frac{1}{\mu+\gamma} & -\lambda \end{pmatrix}$$

Let $a = -\beta\left(\mu - \mu\frac{\mu+\gamma}{\beta}\right)\frac{1}{\mu+\gamma}$ and $b = \beta\left(\mu - \mu\frac{\mu+\gamma}{\beta}\right)\frac{1}{\mu+\gamma}$. The Characteristics polynomial is

$$\lambda^2 - (a - \mu)\lambda + b(\gamma + \mu) = 0$$

$$\lambda = \frac{a - \mu \pm \sqrt{(a - \mu)^2 - 4b(\gamma + \mu)}}{2}$$

This gives the following eigenvalues;

$$\lambda_1 = \frac{a - \mu + \sqrt{(a-\mu)^2 - 4b(\gamma+\mu)}}{2} = 4.338 \times 10^{-3}$$

and

$$\lambda_2 = \frac{a - \mu - \sqrt{(a-\mu)^2 - 4b(\gamma+\mu)}}{2} = -4.338 \times 10^{-3}$$

The values of the trace and determinant are $a-\mu = -9.995\times10^{-8}$ and $b(\gamma+\mu) = -9.995 \times 10^{-5}$. Hence it is a saddle point.

4.2 Stability analysis of the Pertussis Model

Analyzing the pertussis system stability, is based on the Routh-Hurwitz criteria. This criterion ensures that we do not have to actually solve the characteristic equation in order to say something about the stability of the equilibrium points. This is due to the fact that if the eigenvalues at some equilibrium point lie in the left half of the complex plane, then the point is stable as the solution will decay exponentially towards the point. Let?s consider the differential equation system giving, where the variable R has been replaced by $N - y - x - g$, $\alpha = \beta y$ and $2\sigma = \sigma^*$

$$\begin{aligned} x' &= \mu(1-\nu) - (\mu + \beta y)x + \sigma^* g \\ y' &= (\beta x - (\mu + \gamma))y \\ g' &= \sigma^*(N - y - x - g) - g(\mu + \sigma^* + \kappa\beta y) \end{aligned} \tag{4.1}$$

The Jacobian matrix A is then computed as:

$$J = \begin{pmatrix} \frac{\partial x'}{\partial x} & \frac{\partial y'}{\partial x} & \frac{\partial g'}{\partial x} \\ \frac{\partial x'}{\partial y} & \frac{\partial y'}{\partial y} & \frac{\partial g'}{\partial y} \\ \frac{\partial x'}{\partial g} & \frac{\partial y'}{\partial g} & \frac{\partial g'}{\partial g} \end{pmatrix} = \begin{pmatrix} -(\mu\beta y) & -\beta & \sigma^* \\ \beta y & \beta x - (\mu + \gamma) & 0 \\ \sigma^* & -\sigma^* - \kappa\beta g & -2\sigma^* - \mu - \kappa\beta y \end{pmatrix}$$

Then the eigenvalues are calculated as

$$A - \lambda I = \begin{pmatrix} -(\mu\beta y) - \lambda & -\beta & \sigma^* \\ \beta y & \beta x - (\mu + \gamma) - \lambda & 0 \\ \sigma^* & -\sigma^* - \kappa\beta g & -2\sigma^* - \mu - \kappa\beta y - \lambda \end{pmatrix}$$

The characteristic polynomial is determined by calculating the determinant, $det(A - \lambda I) = 0$. That is

$$-\lambda^* + \lambda^2 Tr(A) - \lambda M + Det(A) = 0$$

The determinant and trace are then computed as;

$Det(A) =$

$$-\beta x \begin{vmatrix} -\beta x & \sigma^* \\ -\sigma^* - \kappa\beta g & -2\sigma^* - \mu - \kappa\beta y \end{vmatrix} + (\beta x - (\mu + \gamma)) \begin{vmatrix} -(\mu + \beta y) & \sigma^* \\ -\sigma^* & -2\sigma^* - \mu - \kappa\beta y \end{vmatrix}$$

$$Tr(A) = x\beta - 3\mu - 4\sigma - y\beta - \gamma - y\beta\kappa$$

From the characteristic equation, we can conclude that there is at least one coefficient in the characteristic equation which is negative, by using the Routh-Hurwitz theorem. Thus, there will be at least one eigenvalue with a positive real part. The next step is to actually calculate the eigenvalues, in order to do this the

equilibrium points must be calculated. That is

$$0 = \mu(1-\nu) - (\mu+\beta y)x + \sigma^* g$$
$$0 = (\beta x - (\mu+\gamma))y$$
$$0 = \sigma^*(N-y-x-g) - g(\mu+\sigma^*+\kappa\beta y)$$

The equilibrium points (y^*, x^*, g^*) are "simultaneously" calculated such that solutions satisfy $x', y', g'(y^*, x^*, g^*) = 0$. The approach is to find solutions for a single differential equation and then substitute into the next. From $y' = (\beta x - (\mu+\nu))y = 0$, $y = 0$, $x = \frac{(\mu+\gamma)}{\beta}$

$$x' = \mu(1-\nu) - (\mu+\beta y)\left(\frac{(\mu+\gamma)}{\beta}\right) + 2\sigma g = 0$$

$\Rightarrow$

$$g = \frac{(\mu+\beta I)(\mu+\gamma)}{(2\sigma\beta)} - \frac{\mu(1-\nu)}{2\sigma}$$

and

$$y = \frac{\mu(1-\nu) - \frac{(\mu+\gamma)}{\beta} + 2\sigma g}{\mu-\nu}$$

The derived expression for x and g are our preliminary equilibrium points, from y', x'. The next step is to substitute x and g into g', leaving solutions in terms of y. This yields a second order polynomial equation for y:

$$2\sigma\left[1 - \frac{\mu+\gamma}{\beta} - y - \left(\frac{(\mu+\beta y)(\mu+\gamma)}{2\sigma}\right)\right] - \left(\frac{\mu+\beta y}{2\beta\sigma} - \frac{\mu(1-\nu)}{2\sigma}\right)(\mu+2\sigma+\beta y\kappa) = 0$$

Solving for y symbolically, leaves a lengthy and unmanageable expression, so it

is solved numerically, with the rates specified in [Lavine et al., 2011], yielding:

$$y_{n,0} = \begin{pmatrix} y_{1,0} \\ y_{2,0} \end{pmatrix} = \begin{pmatrix} 0.001386 \\ 0.0003688 \end{pmatrix}$$

This value can then be utilized to enter into the g solution for x' above, such that:

$$g_{solve} = \left(\frac{(\mu + \beta y_{n,0})(\mu + \gamma)}{2\sigma\beta} - \left(\frac{\mu(1-\nu)}{2\sigma} \right) \right)$$

$$g_{solve} = \begin{pmatrix} g_{s1} \\ g_{s2} \end{pmatrix} = \begin{pmatrix} 0.024 \\ -0.125 \end{pmatrix}$$

where g_{s1} corresponds to the solution $y_{1,0}$ and g_{s2} corresponds to the solution $y_{2,0}$. This leads to two equilibrium points;

$E_1^* = (y_{1,0}, g_{s1}, x^*)$ and $E_2^* = (y_{2,0}, g_{s2}, x^*)$

To find other equilibrium points, the next step goes back to the second equilibrium solution for y', where $y^* = 0$. Substituting y^* into $x' = 0$, leads to:

$$g = -\left(\frac{\mu(1-\nu) - \mu S}{2\sigma} \right)$$

If g then is substituted into the expression for $g' = 0$, this directly gives the equilibrium point $x_{1,0} = x$ such that:

$$g' = 2\sigma \left[1 - x - \left(\frac{\mu(1-\nu) - \mu x}{2\sigma} \right) \right] + \left(\frac{\mu(1-\nu) - \mu x}{2\sigma} \right) (\mu + 2\sigma) = 0$$

$$x = \frac{4\sigma^2 + \mu^2(1-\nu)}{(\mu^2 + 4\sigma^2)}$$

Substituting $x^*_{1,0} = s$ into g, we get:

$$g^* = \frac{\mu(1-\nu) - \mu x}{2\sigma} = 0$$

This concludes the equilibrium point's analysis and yields three equilibrium solutions:

$$E^*_1 = (x^*, y_{1,0}, g_{s1})$$
$$E^*_2 = (x^*, y_{2,0}, g_{s2})$$
$$E^*_3 = (x, y^*, g^*)$$

These equilibrium points are then evaluated in the Jacobian matrix previously calculated, and given by:

$$\mathbf{J} = \begin{bmatrix} -(\mu+\beta y) & -\beta x & \sigma^* \\ \beta y & \beta x - (\mu+\gamma) & 0 \\ -\sigma^* & -2\sigma - \kappa g \beta & -(2\sigma^* + \mu + \kappa\beta y) \end{bmatrix}$$

The Jacobian evaluated in equilibrium point 1 is assigned the letter λ_A, and gives: Solving for eigenvalues numerically yields three solutions:

$$\mathbf{J}(x^*, y_{1,0}, g_{s1}) = \begin{bmatrix} -(\mu+\beta y) & -\beta x^* & \sigma^* \\ \beta y_{1,0} & \beta x^* - (\mu+\gamma) & 0 \\ -\sigma^* & -2\sigma - \kappa g_{s1}\beta & -(2\sigma^* + \mu + \kappa\beta y_{1,0}) \end{bmatrix}$$

$$\text{Eigenvalues } \mathbf{J}(x^*, y_{1,0}, g_{s1}) = \lambda_A = \begin{pmatrix} -0.12 + 2.681i \\ -0.12 + 2.681i \\ -7.766 \end{pmatrix}$$

The Jacobian of equilibrium point 2 is denoted λ_B and given by:

$$\mathbf{J}(x^*, y_{1,0}, g_{s1}) = \begin{bmatrix} -(\mu + \beta y) & -\beta x^* & \sigma^* \\ \beta y_{2,0} & \beta x^* - (\mu + \gamma) & 0 \\ -\sigma^* & -2\sigma - \kappa g_{s2}\beta & -(2\sigma^* + \mu + \kappa\beta y_{2,0}) \end{bmatrix}$$

This yields the eigenvalues:

$$\text{Eigenvalues } \mathbf{J}(x^*, y_{2,0}, g_{s2}) = \lambda_B = \begin{pmatrix} -2.194 \\ 1.884 + 1.8i \\ 1.884 - 1.8i \end{pmatrix}$$

The Jacobian for equilibrium 3, given by λ_C: λ_C and given by:

$$\mathbf{J}(x^*, y^*, g^*) = \begin{bmatrix} -\mu & -\beta & \sigma^* \\ 0 & \beta - (\mu + \gamma) & 0 \\ -\sigma^* & -2\sigma & -(2\sigma^* + \mu) \end{bmatrix}$$

By using the actual parameter values, this also gives the following eigenvalues:

$$\text{Eigenvalues } \mathbf{J}(E_3^*) = \lambda_C = \begin{pmatrix} -0.22 \\ -0.22 \\ 242.98 \end{pmatrix}$$

All the eigenvalues calculated from matrix A, B and C confirms our earlier prediction namely; there will be at least one eigenvalue that lies in the right half of the complex plane (we actually got three). Looking at the equilibrium points, it is obvious that the biologically most relevant part is that of the equilibrium point A and C. Since equilibrium point B has a negative population g, it is clearly non-biological.

4.2.1 Interpretation of the Analysis of the Measles Model

The analysis of the measles model shows that the behaviour of the equilibrium solutions produces saddle points. It is obvious that for our disease free equilibrium, no disease will occur, since no healthy individuals can infect others. That is x will remain constant. For the infected equilibrium the trajectory of the phase plane will tend infinity in the x-direction and consequently y will tend to zero. This means that even if the disease exists in the population, it will eventually die out, due to immunity. This is clearly not always the case, but relies solely on the rates in and out of infection. This relation is the previously mentioned factor R_0, which is the threshold that translates to number of successful infective interactions per time.

4.2.2 Interpretation of the Analysis of the Measles Model

The analytic results in our analysis of the pertussis model indicate that the dynamics around the infected equilibrium point have cyclical behaviour due to the imaginary parts of the eigenvalues. This indicates that the flow between the compartments has time-dependent (likely seasonal) variations. This is consistent with the traits of an epidemic. If the spiral is attracting it might tend to the equilibrium point where the seasonal variations cease to exist. It might also tend towards a limit cycle near the equilibrium point where the seasonal variations are constant.

The disease free equilibrium yields a slightly different and less trivial solution than the solution for the measles model. This seems a somewhat artificial result since the dynamics between the waning susceptible and immune might be of little interest if the infection is non-present. However, it could hold some information on what the susceptible population would be in a society that has no pertussis,

still get vaccinated, but is subject to the waning effect of vaccination.

Chapter 5

Conclusion

5.1 Conclusion

Comparing the two different models of the analysis, it is clear that two different types of solution dynamics are present. The measles model predicts an unstable dynamical picture which in time leads to either an infection of either the whole population or none at all. The whooping cough model shows cyclical behaviour which means it predicts seasonal variations of the disease. Over time, this variation exhibits a decreasing oscillation around a mean ratio of infected in the population (given by the equilibrium point). Each model has the underlying assumption that people, with respect to interacting with other people, behaves more or less like particles in a gas. That is, their contact rate is based on basic statistical view that each individual will experience the same number of contacts (on average). This is obviously a simplification of human interaction patterns, but since these models do not include behavioural patterns, cultural or social differences in lifestyles, population density, seasonality etc., this seems like the best conceivable approximation.

Furthermore the models assume a uniform ability of individual's immune re-

sponse to infection. This might somehow be inferred in the age-group structure of the whooping model. This is also reflected in the lack of congenital immunity, which is a real biological factor in the measles model. A variety of other factors could be conceived according to the problem at hand. However, this level of detail in a given system comes at a cost. It is clear that the measles model is less involved than the pertussis model. This is mainly due to two configurations, namely the feedback mechanism and the extra compartment of the pertussis model. These are not present in the measles model. The reason behind the diversity between the models is partly due to simplification of the system and partly due to biological differences. The effect of the difference is evident in the mathematical treatment of the two problems. The measles model has a straight forward solution strategy that both analytically and numerically yields biologically intuitive results. Some information must lack and only few parameters can be adjusted in the model. In contrast, the whooping cough model entails greater attention to detail, which subsequently means that the mathematical structure and computations will contain increased degrees of difficulty. The consequence of this is that, aside from having included more consideration, parameters will be adjustable such that they have values that cause the system to mimic real life observations. These parameters can then be interpreted for biological meaning.

However, there is also a cost involved. Unfolding the analytic solution for the pertussis model does not yield a straight forward approach, and thus the degree of difficulty is elevated. What is more critical is that, both numerical and analytic results lack transparency in terms of biological interpretation. Due to the uniform direction of flow in the measles model, it is quite clear how to interpret the implicit role of z. In the whooping cough model, however, the interpretation of z is well hidden within the confines of the transformed system. The solution

strategy is clearer, but the biological interpretation of the hidden variables gets even more clouded.

The possible loss of qualities, leads us to one of the main difficulties when dealing with high order systems: that the existence and uniqueness theorem loses its significance. This leaves very few tools for analysis, such as the sign of the eigenvalues given by the Jacobian matrix evaluated at the respective equilibrium points. The absence of thorough all-purpose solution tools is unquestionably a major contribution to what makes the discipline of analyzing high dimensional non-linear differential equation systems so problematic. Apart from increasing the difficulty level of analytical solution strategies, uncertainties may grow, error estimation and management becomes increasingly difficult and round-off errors might expand.

The investigation on variations on the basic SIR-model has illustrated the consequences of additional compartments in well-known models as well as the computational complexity that arises. The presentation might show more in terms of expanding compartment models, than actual disease dynamics, since some key-elements such as age distribution and population variations is left out of our mathematical considerations. However, limiting variations and omitting some influences are of utmost importance when constructing models. In fact, this is a main point of the comparison, namely that every addition to one's system comes at a computational cost. This is evident from the two analyses in chapter 4. Apart from increasing the difficulty level of solution strategies, uncertainties may grow in numerical computation. Also, the transparency of the biological implications of the solutions becomes cluttered.

5.2 Recommendation

This study only relates to a part of the model proposed by Lavine et al. (2011). The age specific resurgence, which has been one of the main foci of pertussis epidemiology, has not been taken into account because it was considered to be a distortion of the focus of this study. That is the pertussis model we have investigated is only describing the dynamics of the age indifferent disease. This represents a lack in the total picture of the spread pattern of the disease. However, a number of other population dynamics could be proposed as possible influences, such as population density, are not included either. There are various ways to improve the model. One could be to differentiate the rates of the sinks in the different compartments. That is, if one considers infection to be fatal, it could be implied that a group of infected would have a slightly increased rate of death.

Another way to change the dynamics of the system is to reconsider the population mixing pattern, such that it gets more realistic. This can be done by letting the contact rate vary with the age groups, such that the mixing pattern varies over a life time. Moreover demographic dynamics could be included. There could also exist a correlation between age and population density, if you consider younger people to live in more densely populated areas than older. This might also affect the contact rate. Living conditions might also be an important factor, which would have to be introduced by a new parameter. The possible interrelations are practically endless, and just a few added parameters have been shown to make a significant expansion in computational efforts. Furthermore, added parameters do not necessarily increase the precision in which the model reflects on real life dynamics.

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