Department of Mathematics

Mathematical study of competition between Staphylococcus strains within the host and at the host population level

MATH554: Main Dissertation

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Statement of Originality

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Summary

Human bodies are constantly under attack from bacteria which cause diseases. Yet, these bodies are also considered to be a shelter to a large number of harmless bacterial species that would not cause any illnesses or infections. These types of bacteria can be used against another member of the same family with a different effect. In other words, the harmless bacteria can be an effective cure against the harmful cousins [2, 3, 6]. To understand the idea, Staphylococcus genus will be defined and considered. Staphylococcus genus includes more than thirty species, several species identified as commensals of humans, which means that these species are advantageous while the host is unaffected. In this genus, most diseases are caused by two well-known species, S. aureus and S. epidermidis, extending from negligible infections to life-threatening conditions. S. epidermidis strain is rarely pathogenic, by contrast, S. aureus infections are more aggressive, associating with both chronic and acute diseases [2, 3].

A significant number of studies have been conducted to discover a potential treatment against Staphylococcus aureus, which colonizes the nose. Usually, these colonies are not serious. However, if a full infection occurs, the result can include life- threatening diseases. With the continued progress of S. aureus and other staph strains through developing a mutation against antibiotics, the threats of these strains have never been greater [3]. S. epidermidis shares the same environment with S. aureus (the nose). It is the most common commensal in our bodies. Furthermore, S. epidermidis is considered harmless, unless the immune system of a body has been compromised. Moreover, recent studies have shown that S. epidermidis has the ability to prevent and inhibit S. aureus invasion and lower the rate of infections [2].

In this dissertation, two types of competition will be considered. The first competition between these strains will take place among population classes while the second within the host. In the first and the second papers [1, 2], the competition between these strains will be for them to coexist together in a balanced environment. Otherwise, the full colonisation of one strain will drive the other strain to extinction and in another scenario, the dominant strain might also become extinct due to the lack of carriers.

By way of explanation, in the mathematical model presented in [1], two strains distinguished by their level of virulence compete, assuming that, the whole population is colonised by the avirulent strain. Thus the other virulent strain will be driven to extinction. Conversely, if the entire population is colonised by the virulent strain, this means not only the avirulent strain will vanish, but also the virulent strain, which has a high propensity to develop an infection, will eventually become extinct due to the fact that the population will die, and this will be the dead end of this strain as well. Likewise, in the other mathematical model presented in [2], where two strains distinguished by their level of toxicity compete, total domination by one of them will lead to the exclusion of the other strain, and vice versa. While the competition in the last paper [4], will be between Staphylococcus strains within the host.

Hence, in this dissertation we will review these three papers [1, 2, 4]. Furthermore, throughout the second chapter, we will analyze the presented mathematical model in the first paper [1]. The third chapter will comprise mathematical analysis of the model presented in the paper [2]. Finally, in the fourth chapter, we will produce a simple mathematical model to illustrate the presented data in the third paper [4]. This dissertation will be concluded by the discussion chapter.

Chapter 1

Introduction

1.1 Overview of the model developed in the paper "The evolution and maintenance of virulence in Staphylococcus aureus: a role for host-to-host transmission?" (*Nature*, 2006)

Although the advanced and the rapid growth of infectious disease biology, such as the emergence of genomic sequencing, has enhanced our ability to understand a significant number of phenomena that occur in this area, the creation and maintenance of microbial virulence and the reasons and the criteria that control it remain in the process of expectations and speculations. Diverse factors were identified to be responsible for increased virulence and host damage; this identification was through comparative genomic analysis between virulent and avirulent strains. However, for solid understanding of how infectious diseases arise, the forces that underlie the multifaceted virulence are needed to be known and determined. That are the reasons that made one microbial species to be virulent, while another species maintains less virulent. Two strains of the Staphylococcus genus, Staphylococcus aureus and Staphylococcus epidermidis, were highlighted and taken into consideration, in order to fully understand this aspect of pathogen biology, and ask why S. epidermidis strain is considered to be less virulent than S. aureus, and vice versa. Several hypotheses have built a strong argument based on the fact that, unlike the situation in S. epidermidis, where skin contact affords easier transmission between hosts, the complex transmission pathway of S. aureus is the primary factor and the rationale behind the evolution and maintenance of virulence in this specific strain. Furthermore, a mathematical model was used to support this argument. Although, many questions about the level of virulence have been answered by identifying the components that contribute to making one strain more virulent than another. Some questions remained unanswered, such as the reason that makes the

acquisition of these mobile genetic elements beneficial for S. aureus? Alternative hypotheses were discussed in this paper to explain the evolution of virulence. Moreover, a mathematical model, that identified the transmission rate as the primary reason that assist S. aureus to be more virulent than S. epidermidis, was presented in this paper.
In general, the experimental evidence and the mathematical model reveal that the level of virulence in a pathogen can be determined by the ease of transmission. Thus the differences in virulence between S. aureus and S. epidermidis is associated with the ease of transmission. According to the results obtained in this paper, S. epidermidis strain has a higher rate of transmission among individuals. Through an analysis of the transmission properties of these strains, three reasons were given explaining the reason of S. aureus strain to be more challenging to transfers between hosts than S. epidermidis. First, there is a common belief that every human is colonised by S. aureus strain given the fact that it is known as being commensal bacteria, and so far there are no known host barriers preventing colonisation by such strain, on the contrary, only a limited population of humans are colonised by S. aureus. Second, the dynamic of transmission in S. epidermidis considered being easier than the transmission in S. aureus. Given the fact that a direct contact is more efficient regarding transmission of the bacteria between two hosts. Moreover, S. epidermidis located on the skin, and that means, transfer between two hosts is possible to occur daily and considered as a relatively simple process, unlike the situation in the other strain S. aureus, which required a complex process to transfer from one host to another. Third, in S. aureus there are four different Agr which have been identified. Also, recent studies have revealed that when one type of these Agr of S. aureus colonises a host the invasion by a different Agr type will be inhibited by the competitive nature of Agr interference.
A simple mathematical model was used to determine the relationship between transmission and virulence in a single species consist of two competing strains; one strain described by having a low level of virulence, while the other strain had a high level of virulence. According to this model, virulence can be defined as the propensity to develop infections, which means that the disease symptoms have started to appear on the colonized individuals. In this model, a higher rate of transmission between the susceptible and infected individuals was assumed based on the fact that in the case of infection a certain level of attention is required so that the contact between the healthy individuals, for instance in a hospital and the patients occurred in regular basses. Nevertheless, this contact may also result in individual patients being treated and moved back into the susceptible class. As mentioned before, this model was applied to two different species, each of which contains two different strains with different level of virulence. The only considered distinction between them in this model is the fact that

one of them (S. epidermidis) has a higher transmission rate than the other species (S. aureus).

The findings of this paper indicated that, in both scenarios, S. epidermidis and S. aureus species, the competition between the two strains have led to exclude one strain against the other. In the case where the transmission rate was relatively high (S. epidermidis), the avirulent strain becomes dominant, and that drives the other virulent strain to extinction. While the situation is completely different in the other case (S. aureus), where the transmission rate was relatively low the virulent strain out-competed the avirulent strain and exclude it. Thus, the findings of this model showed the negative correlation between the level of virulence and the transmission rate.

1.2 Overview of the model developed in the paper "Evolutionary Trade-Offs Underlie the Multifaceted Virulence of Staphylococcus aureus" (*PLOS Biology*, (2015)

Full awareness of the factors that control the virulence in microbial pathogens would enable us to produce long-term and efficient methods to prevent such pathogens. One of the most important factors that played a leading role in disease pathology is the secretion of the toxins. Which promote the image that in bacterial infections, the toxicity level is positively associated with the virulence and the severity of the disease. This belief also was enhanced through the results of several tests which were conducted on animals, it showed that highly toxin isolates cause more severe disease symptoms. However, through recent medical analysis on humans isolated with invasive diseases, such as bacteraemia, it revealed that the S. aureus strains that caused these diseases often have a low level of toxicity. Differing bacterial virulence depends on the interaction between the host and the pathogen, which determine the severity and the level of infections. The aim of this paper is to justify and understand the complex relationship between the level of toxicity and the disease severity through considering S. aureus strain. This particular strain was chosen in this study given the fact that it is considered as a global health-care issue. For that, several experiments have been conducted on S. aureus species, where two strains were examined in the research. These two strains were distinguished by their level of toxicity. The first strain has a low level of toxicity while the other strain has relatively high level of toxicity. The diversity of the level of toxicity is caused by the mutations which we were able to determine.

Furthermore, many toxicity-affecting genes were identified. A mathematical model was constructed to determine the implications of each level of toxicity, in other words, the role of the toxicity level of the severity of the disease.

Unexpectedly, our findings indicated a negative correlation between the level of toxicity and the disease severity. It turns out that, the least toxic strains caused the most severe disease. A significant number of studies was performed to explain the high propensity of the low toxic strain to cause a bacteraemia, these studies pointed the implication of the differences in the fitness between high- and low-toxicity strains within the host, and described it as an important factor. Being infected by high-level toxic strain is usually the end of the road for these bacteria, due to the fact that these types are highly challenging to transmit between individuals. To be able to explain the reasons behind the high propensity of low toxin strain to cause a bacteraemia, although the health of the patient is considered as a privilege in their vulnerability to bacteraemia. There is no solid evidence which supports the fact that their propensity to cause a bacteraemia is higher than the high toxin strain. However, we were able to identify the negative relationship between the toxicity and the relative fitness of the strain. Due to that, the high toxin strain is less likely to develop a bacteraemia from the infection class. Thus, this explains the results indication. A mathematical model was also used to support this argument. The outcome of this model indicates the negative correlation between the toxicity level and the virulence of the diseases. The results validate that, a distinction between toxicity can affect the nature of bacterial virulence.

1.3 Overview of the paper "The effects of spatial structure, frequency dependence and resistance evolution on the dynamics of toxin-mediated microbial invasions" (*Evolutionary Applications*, 2015)

A continuous carriage by S. aureus is frequently asymptomatic, Yet, it might develop an infection in particular patients. The response to treatment can be low in these frequent infections. Moreover, the risk of increased disease severity and mortality rates is significantly higher for immunocompromised carriers. Recent studies and experiments indicate that the interference competition between the bacteria types which colonise the nasal airway of humans could contribute to the distribution of these types, either by preventing the colonisation or, in extreme cases, by displacing each other. This inter-

ference competition is considered as an addition to the factors affecting the colonisation.

The aim of this paper is to inspect the role of the toxic interference competition within the nasal microbial community. In order to achieve that, several experiments have been conducted on two well-known strains, S. aureus and S. epidermidis, in both structured and unstructured environments to investigate the role of the toxin interference competitions. The selection of these particular types of strains resulted from the fact that the nasal microbial community mainly includes the species S. aureus and S. epidermidis. The process of investigation is involved S. aureus strain to be cultured with toxin and non-toxin producing S. epidermidis and vice versa.

Simple communities of S. epidermidis and S. aureus were constructed in this paper to investigate the hypothesis that the interference competition could contribute negatively to the distributions of these species in nasal communities. Predictions of the theory propose that interference competition has a critical role in both restricting and encouraging the invasion of resident communities. The promotion of the invasion is indicated when the invader strain produces toxins which might lead to the resident population extinction. However, the advantages gained from producing toxins must be higher than the disadvantages of producing them. Also, the invader and resident populations must not divide the benefits between them. If these conditions were not obtained, then the chance of invasion will be reduced by the interference competition. Two scenarios were discovered in which S. aureus could be excluded through toxins production by S. epidermidis. The first scenario: when invasion by susceptible S. aureus is inhibited by resident toxin-producing S. epidermidis, while the second scenario is when the resident susceptible S. aureus population is displaced by the invasion of the toxin-producing S. epidermidis. Furthermore, a manipulation of two environmental parameters (the spatial structure, (structured or mix), of the environment and the starting frequency of invaders), could affect the process of toxin-mediated interference competition. The interference competition between bacteria occurs via toxin secretion within the environment of the community. Thus the structure of the environment affects the process. Several experiments revealed that in structured environments, the invasion could occur with low frequency (concentration) of the invasive strain, whereas, in a mixed environment in order to achieve an invasion it required a relatively high frequency. By performing an experiment on the yeast Saccharomyces cerevisiae to investigate the impact of the environment structure on the success of the invasion. The outcome demonstrated that structured environments promoted the invasion more than the mixed environment. Hence, we predict that S. epidermidis strain will have a better

chance to invade in a structured environment.

To inspect these predictions, competition experiments were performed. In one hand, whereby S. epidermidis strain was invaded into resident populations of S. aureus. On the other hand, a mutual invasion of S. aureus was performed into resident populations of S. epidermidis to test whether S. aureus invasion could be restricted by S. epidermidis.

The outcome of the first experiment, as illustrated in Fig (1.1), when a population of S. aureus was invaded by toxin-producing and non-producing strains of S. epidermidis in both structured and mix environment by three different frequencies. In mix environment, non-toxin producers were more successful in invading than the toxin produces which were never able to invade. However, in a structured environment, the population of S. aureus were more successfully invaded by the toxin-producing S. epidermidis than non-producers. Thus, the structured environment promotes the invasion. In addition, during the invasion, the resident strain has developed a toxic resistance which prevents the total displacement by the invasive strain, in other words, beneficial mutations that are pre-adapted to survive the conditions of an invasion were developed by the resident strain.

Whereas the second experiment findings, as illustrated in Fig (1.1), when populations of toxin and non-toxin producing S. epidermidis were invaded by S. aureus strain from three different frequencies, in both types of environments. S. aureus successfully invaded into the population of toxin and non-toxin producers of S. epidermidis in mix environments. However, the toxin-producing S. epidermidis inhibit the invasion of the S. aureus in a structured environment. In a reciprocal experiment, S. aureus strain has successfully invaded the resident population of toxin-producing S. epidermidis via the evolution of toxin resistance. Moreover, the invasion was more efficient under certain conditions, high initial frequency and low spatial structure. In many invading populations of S. epidermidis, the toxin production has been enhanced. Therefore, toxin production has played a significant role in both promoting the invasion by and inhibiting the invasion into, the population of producers. Furthermore, both of these invasions were enhanced by a structured environment.

The success of the invasions was determined and quantified through a calculation of the selection rate constant for each invader which required the use of relative bacterial frequencies throughout the period. In other words, the use of the following equation

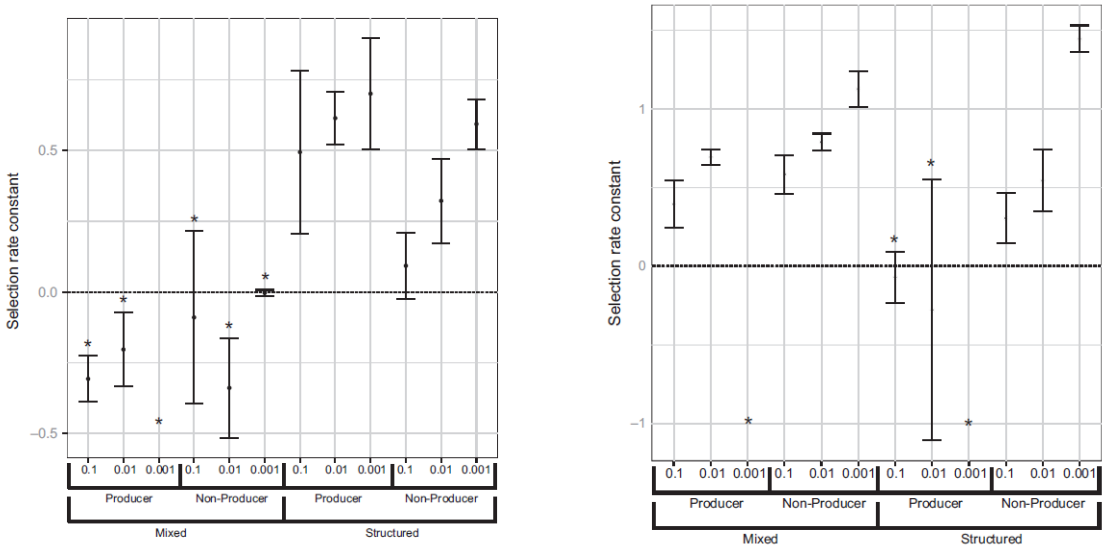

Figure 1.1: **Selection rate coefficients for interference competition between S. aureus and S epidermidis strains**: determining the outcome of the invasion required the use of relative bacterial frequencies throughout the period to calculate a selection rate constant for each invader. On other words, the use of (1.1) equation, enabled us to define the results of each invasion. (Left): the outcome of the invasion by toxin and non toxin producing S. epidermidis into a population of S. aureus, at relative frequencies of 10, 100 and 1000, in both structured and mix environment. the negative selection rate coefficients indicate that the invasion has not occurred. (Right): illustration of the outcome of the mutual experiment, where a populations of toxin and non toxin producing S. epidermidis were invaded by S. aureus, the negative values indicated that invasion was not possible, whereas positive values indicated invasion was possible.

enabled us to define the results of each invasion:

$$C_{ir} = \frac{\ln\left[N_i(7)/N_i(0)\right] - \ln\left[N_r(7)/N_r(0)\right]}{7days} \tag{1.1}$$

where (i) represents the invader strain while (r) represents the resident.$N(0)$ represents the initial density of the population, $N(7)$ reprents the density of the population after 7 days.

The failure of the invasions was indicated by the negative values, whereas the possibility of invasions was indicated by the positive values.

In conclusion, the findings of this study strongly argue that colonisation by S. aureus can be limited and restrained by manipulating some factors of the nasal microbial community. Also, that could lead to lower the infection transmission rates.

Chapter 2

Analysis of the model developed in "The evolution and maintenance of virulence in Staphylococcus aureus: a role for host-to-host transmission?"

The main principle of this model is to indicate the role of virulence and the relationship between the level of virulence and the transmission rate in two different bacterial strains.

2.1 Description of the mathematical model.

The population in this model is divided into four different classes or stages. The first stage is the susceptible class (S), which can be transformed into two different colonial stages either a virulent strain (C_v), or avirulent strain (C_a), by the rate (β_c). Those individuals that are colonised by a virulent strain might turn into an infection stage (I), with a higher rate of transmission(β_i), based on the assumption that infected people transmit at a much higher rate through increased contact. However, recovery from this class can return individuals back into the susceptible class by rate (σ).

This model can be represented by a set of nonlinear differential equations as follow:

$$\frac{dS}{dt} = \mu - \beta_c C_a S - \beta_c C_v S - \beta_i I S - \mu S \tag{2.1}$$

$$\frac{dC_a}{dt} = \beta_c C_a S - \mu C_a \tag{2.2}$$

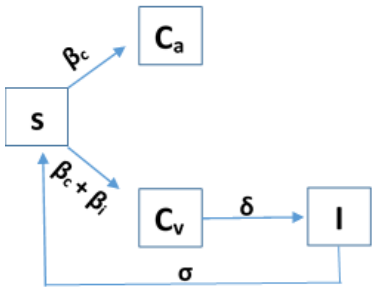

Figure 2.1: Diagram illustrating the mathematical model.

$$\frac{dC_v}{dt} = \beta_c C_v S + \beta_i I S - (\delta + \mu) C_v \tag{2.3}$$

$$\frac{dI}{dt} = \delta C_v - (\sigma + \mu) I \tag{2.4}$$

Remark 1 *According to the equations that were taken from [1], it can be noticed that, there was one term missing from equation (2.1), that is the recovery back into the susceptible class term and in order to fix this error this term* (σI) *was added to that equation. Therefore, the modified equation takes this form:*

$$\frac{dS}{dt} = \mu - \beta_c C_a S - \beta_c C_v S - \beta_i I S - \mu S + \sigma I$$

So that,

$$\frac{d}{dt}(S + C_a + C_v + I) = \mu - \mu S - \mu C_a - \mu C_v - \mu I$$

$$\frac{d}{dt}(S + C_a + C_v + I) = \mu(1 - (S + C_a + C_v + I))$$

Let

$$u = (S + C_a + C_v + I)$$

Thus;

$$\frac{du}{dt} = \mu(1 - u)$$

$$\int \frac{du}{1 - u} = \int \mu dt$$

$$\ln(1-u) = \mu(t+k)$$

k is a constant

$$(1-u) = Ke^{\mu t}$$

where $K = e^{\mu k}$

$$u = 1 - Ke^{\mu t}$$

2.2 Identifying the equilibrium points of non-linear system of ODEs

An equilibrium point is a constant solution or solution of a system [7]. Therefore, in order to find the equilibrium points of this model, the previous differential equations must be set to equal zero as follow:

$$\frac{dS}{dt} = \frac{dC_a}{dt} = \frac{dC_v}{dt} = \frac{dI}{dt} = 0$$

According to equation (2.2), $\frac{dC_a}{dt} = 0$ if:

$$C_a = 0, \ or \ S = \frac{\mu}{\beta_c}$$

In addition, from (2.4), $\frac{dI}{dt} = 0$ if:

$$C_v = I = 0 \ \ or \ \ C_v = \frac{(\sigma+\mu)I}{\delta}$$

First, Substituting this $C_a = 0, \ and \ C_v = I = 0$ back into the system:

$$\frac{dS}{dt} = \mu - \beta_c C_a S - \beta_c C_v S - \beta_i I S - \mu S + \sigma I = 0$$

$$\frac{dC_a}{dt} = \beta_c C_a S - \mu C_v = 0$$

$$\frac{dC_v}{dt} = \beta_c C_v S + \beta_i I S - (\delta+\mu)C_v = 0$$

$$\frac{dI}{dt} = \delta C_v - (\sigma+\mu)I = 0$$

yields;

$$\frac{dS}{dt} = \mu - \mu S = 0, \;\; \frac{dC_a}{dt} = 0, \;\; \frac{dC_v}{dt} = 0, \;\; \frac{dI}{dt} = 0$$

Thus, the first equilibrium point is at $(S,\, C_a,\, C_a,\, I) = (1,\, 0,\, 0, 0)$

Secondly, substituting another condition, when $(C_a = 0, \; and \; C_v = \frac{(\sigma+\mu)I}{\delta})$ into the system, yields:

$$\frac{dS}{dt} = \mu - \frac{\beta_c \; S\,(\sigma+\mu)\,I}{\delta} - \beta_i \, S \, I - \mu \, S + \sigma \, I = 0$$

$$\frac{dC_a}{dt} = 0$$

$$\frac{dC_v}{dt} = \frac{\beta_c \, S\,(\sigma+\mu)\,I}{\delta} + \beta_i \, S \, I - (\sigma+\mu)\,I - \frac{\mu\,(\sigma+\mu)\,I}{\delta} = 0$$

$$\frac{dI}{dt} = 0$$

By solving these two non-zero equations leads to two solutions, either $(S = 1 \, and \, I = 0)$, which is the same as the first equilibrium point, where $(S,\, C_a,\, C_a,\, I) = (1, 0, 0, 0)$ or

$$S = \frac{\delta\,\mu + \delta\,\sigma + \mu^2 + \mu\,\sigma}{\beta_c\,\mu + \beta_c\,\sigma + \beta_i\,\delta}$$

$$C_a = \; 0$$

$$C_v = \frac{(\sigma+\mu)\,(\beta_c\,\mu + \beta_c\,\sigma + \beta_i\,\delta - \delta\,\mu - \delta\,\sigma - \mu^2 - \mu\,\sigma)}{\beta_c\,\delta\,\mu + \beta_c\,\delta\,\sigma + \beta_c\,\mu^2 + 2\,\beta_c\,\mu\,\sigma + \beta_c\,\sigma^2 + \beta_i\,\delta^2 + \beta_i\,\delta\,\mu + \beta_i\,\delta\,\sigma}$$

$$I = \frac{\delta\;(\beta_c\,\mu + \beta_c\,\sigma + \beta_i\delta - \delta\,\mu - \delta\,\sigma - \mu^2 - \mu\,\sigma)}{\beta_c\,\delta\,\mu + \beta_c\,\delta\,\sigma + \beta_c\,\mu^2 + 2\,\beta_c\,\mu\,\sigma + \beta_c\,\sigma^2 + \beta_i\,\delta^2 + \beta_i\,\delta\,\mu + \beta_i\,\delta\,\sigma}$$

Thirdly, substituting another condition, when $(S = \frac{\mu}{\beta_c}, \; and \; C_v = I = 0)$ into the system, yields:

$$\frac{dS}{dt} = \mu - \mu\,C_a - \frac{\mu^2}{\beta_c} = 0, \; \frac{dC_a}{dt} = \frac{dC_v}{dt} = \frac{dI}{dt} = 0$$

Thus, the third equilibrium point is at $(S,\, C_a,\, C_v,\, I) = (\frac{\mu}{\beta_c},\, 1 - \frac{\mu}{\beta_c},\, 0,\, 0)$

Fourthly, substituting the last condition, when $(S = \frac{\mu}{\beta_c}, \; and \; C_v = \frac{(\sigma+\mu)I}{\delta})$ into the system, yields:

$$\frac{dS}{dt} = \mu - \mu\,C_a - \frac{\mu\;(\sigma+\mu)\,I}{\delta} - \frac{\beta_i\,I\,\mu}{\beta_c} - \frac{\mu^2}{\beta_c} + \sigma\,I$$

$$\frac{dC_a}{dt} = 0$$

$$\frac{dC_v}{dt} = \frac{\beta_i\, I\, \mu}{\beta_c} - (\sigma + \mu)\, I$$

$$\frac{dI}{dt} = 0$$

Solving these non-zero equations leads to the forth equilibrium point, which is at $(S,\, C_a,\, C_v,\, I) = (\frac{\mu}{\beta_c},\, 1 - \frac{\mu}{\beta_c},\, 0,\, 0)$, similar to the third equilibrium point.

Summary: Solving this system of nonlinear ODEs has led to three equilibrium points:

1. $(S,\, C_a,\, C_v,\, I) = (1,\, 0,\, 0, 0)$.
2. $(S,\, C_a,\, C_v,\, I) = (\frac{\mu}{\beta_c},\, 1 - \frac{\mu}{\beta_c},\, 0,\, 0)$.
3. $(S,\, C_a,\, C_v,\, I) = \Big(\frac{\delta\,\mu+\delta\,\sigma+\mu^2+\mu\,\sigma}{\beta_c\,\mu+\beta_c\,\sigma+\beta_i\,\delta}, 0, \frac{(\sigma+\mu)\left(\beta_c\,\mu+\beta_c\,\sigma+\beta_i\,\delta-\delta\,\mu-\delta\,\sigma-\mu^2-\mu\,\sigma\right)}{\beta_c\,\delta\,\mu+\beta_c\,\delta\,\sigma+\beta_c\,\mu^2+2\,\beta_c\,\mu\,\sigma+\beta_c\,\sigma^2+\beta_i\,\delta^2+\beta_i\,\delta\,\mu+\beta_i\,\delta\,\sigma}, \frac{\delta\left(\beta_c\,\mu+\beta_c\,\sigma+\beta_i\delta-\delta\,\mu-\delta\,\sigma-\mu^2-\mu\,\sigma\right)}{\beta_c\,\delta\,\mu+\beta_c\,\delta\,\sigma+\beta_c\,\mu^2+2\,\beta_c\,\mu\,\sigma+\beta_c\,\sigma^2+\beta_i\,\delta^2+\beta_i\,\delta\,\mu+\beta_i\,\delta\,\sigma}\Big)$

2.3 Stability analysis

To determine the stability of each equilibrium point, there is a necessary procedure in order to find out whether the equilibrium at this certain point is stable or unstable. This procedure is known as linearization technique.

2.3.1 Introduction to the linearization technique

Consider the independent system:

$$\begin{cases} \frac{dx}{dt} = f(x, y) \\ \frac{dy}{dt} = g(x, y). \end{cases}$$

Let $(x_0,\, y_0)$ be the equilibrium point, then we choose (x, y) to be

$$x = x_0 + \Sigma, \quad y = y_0 + \Psi$$

And Σ, Ψ are small terms, so that we can find the closest linear system when (x,y) is close to $(x_0,\, y_0)$. Then approximating the functions $f(x, y)$ and $g(x, y)$ yields:

$$\begin{cases} \frac{dx}{dt} = f(x_0,\, y_0) + \frac{\partial f}{\partial x}(x_0,\, y_0)\,\Sigma + \frac{\partial f}{\partial y}(x_0,\, y_0)\,\Psi \\ \frac{dy}{dt} = g(x_0,\, y_0) + \frac{\partial g}{\partial x}(x_0,\, y_0)\,\Sigma + \frac{\partial g}{\partial y}(x_0,\, y_0)\,\Psi. \end{cases}$$

Since $(x_0,\, y_0)$ is an equilibrium point, then we have $f(x_0,\, y_0) = g(x_0,\, y_0) = 0$. Hence,

$$\begin{cases} \frac{dx}{dt} = \frac{\partial f}{\partial x}(x_0,\, y_0)\,\Sigma + \frac{\partial f}{\partial y}(x_0,\, y_0)\,\Psi \\ \frac{dy}{dt} = \frac{\partial g}{\partial x}(x_0,\, y_0)\,\Sigma + \frac{\partial g}{\partial y}(x_0,\, y_0)\,\Psi. \end{cases}$$

The Jacobian matrix of the system at the point $(\mathrm{x_0}, \mathrm{y_0})$ is:

$$J = \begin{pmatrix} \frac{\partial f}{\partial x}\,(x_0,\, y_0) & \frac{\partial f}{\partial y}\,(x_0,\, y_0) \\ \frac{\partial g}{\partial x}\,(x_0,\, y_0) & \frac{\partial g}{\partial y}\,(x_0,\, y_0) \end{pmatrix}.$$

Next step is to,
Find the eigenvalues of the Jacobian matrix.
Determine the state of the solutions around the equilibrium point from the eigenvalues: If the eigenvalues are all negative, then the equilibrium at this certain point is considered to be stable, (sink). If the eigenvalues are complex, with a negative real part, then the solutions will spiral into the equilibrium point, (Sink). If the eigenvalues are all or at least one positive, then the equilibrium at this certain point is considered to be unstable, (Source). If the eigenvalues are complex, with a positive real part, then the solutions will spiral out of the equilibrium point, (Source), [10].

2.3.2 Determining the stability of the equilibrium points

There are two sets of parameters $\{S,\, C_a,\, C_v,\, I\}$ and $\{\mu, \beta_c, \beta_i, \delta, \sigma\}$. The second set of parameters represents the average life expectancy is given by $\{\frac{1}{\mu}\}$, the rate of transmission through contacting susceptible individuals with colonised individuals, the rate of added transmission through infections, the propensity of the pathogen to develop an infection and the recovery rate for infected individuals, respectively. This set of parameters does not change except the $\{\beta_c\}$ parameter, which represents the rate of transmission. Through experimental studies and analysis of the transmission, properties detect three reasons are indicating that S.epidermidis transferring between hosts is less challenging than it is in the other strain S.aureus. First, there is a common belief that every human is colonised by this type of bacteria, in other words there are no barriers in the host that could prevent the transmission of such a kind, or at least it is not known yet. The second factor, the dynamic of transmission is much easier in this particular strain given the fact that a direct contact is more efficient at transferring between hosts. As S. epidermidis located in the skin, a direct contact could occur daily. On the contrary, then the situation in S.aureus strain that exists in the internal

tissue of the nose, which requires more complex procedures to transfer from one host to another. The third factor, four different Agr groups of S.aureus have been identified, moreover, once the host is colonised by one type, the competition between these types will inhibit the colonisation of any transmitted different kind.
The general form of the Jacobian matrix of the system is:

$$J_(S,\ C_a,\ C_v,\ I) = \begin{bmatrix} -\beta_c\, C_a - \beta_c\, C_v - \beta_i\, I - \mu & -\beta_c\, S & -\beta_c\, S & -\beta_i\, S + \sigma \\ \beta_c\, C_a & \beta_c\, S - \mu & 0 & 0 \\ \beta_c\, C_v + \beta_i\, I & 0 & \beta_c\, S - \delta - \mu & \beta_i\, S \\ 0 & 0 & \delta & -\mu - \sigma \end{bmatrix}$$

Example 2.3.1 The S. Epidermidis strain will be considered first, with the defined parameters as follow:

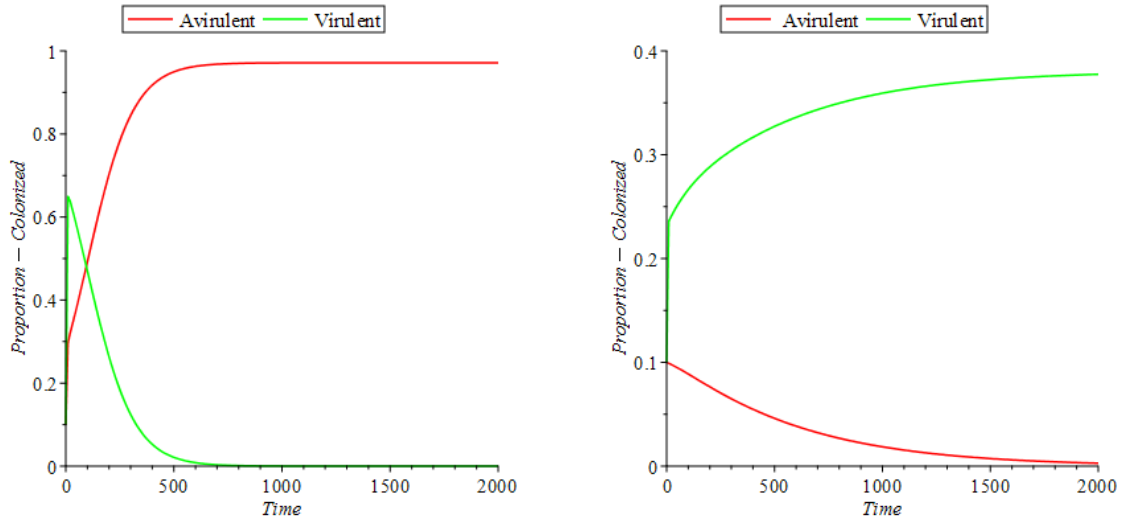

Figure 2.2: **The effect of the transmission rate on the role of virulence:** this figure shows the predicted population; a host population colonised with an avirulent C_a (red) and a virulent C_v (green) strain in two different strain of bacteria. (1). When the rate of transmission is relatively high as in the S. epidermidis scenario ($\beta_c = 0.5$), the avirulent strain $[C_a]$ becomes dominant and the other strain with increased virulent $[C_v]$ is driven to extinction. (2). When the rate of transmission is lower as the situation in S.aureus, ($\beta_c = 0.02$), the strain with increased virulent $[C_v]$ surpass the avirulent strain $[C_a]$ and push it to extinction.

$$\boxed{\mu = 1/70, \beta_c = 0.5, \beta_i = 100, \delta = 1/100, \sigma = 52}$$

By substituting these parameters into the Jacobian matrix to determine the stability

of the first equilibrium point.

$$J(1,0,0,0) = \begin{bmatrix} -0.01428571429 & -0.5 & -0.5 & -48 \\ 0.0 & 0.4857142857 & 0 & 0 \\ 0 & 0 & 0.4757142857 & 100 \\ 0 & 0 & 0.01 & -52.0143 \end{bmatrix}$$

Eigenvalues for this matrix are:

$$\boxed{\lambda_1 = -0.014286,\ \lambda_2 = -52.033,\ \lambda_3 = 0.49475,\ \lambda_4 = 0.48571}$$

Since there are two positive eigenvalues. That means this equilibrium is unstable. Moreover, to determine whether it remains unstable the eigenvalues will be expressed in terms of the variables rather than numbers.

$$J(1,0,0,0) = \begin{bmatrix} -\mu & -\beta_c & -\beta_c & -\beta_i + \sigma \\ 0 & \beta_c - \mu & 0 & 0 \\ 0 & 0 & \beta_c - \delta - \mu & \beta_i \\ 0 & 0 & \delta & -\mu - \sigma \end{bmatrix}$$

Eigenvalues:

$$\lambda_1 = -\mu$$

$$\lambda_2 = -\frac{\delta}{2} - \mu - \frac{\sigma}{2} + \frac{\beta_c}{2} - \frac{1}{2}\sqrt{{\beta_c}^2 - 2\beta_c\,\delta + 2\beta_c\,\sigma + 4\beta_i\,\delta + \delta^2 - 2\delta\,\sigma + \sigma^2}$$

$$\lambda_3 = -\frac{\delta}{2} - \mu - \frac{\sigma}{2} + \frac{\beta_c}{2} + \frac{1}{2}\sqrt{{\beta_c}^2 - 2\beta_c\,\delta + 2\beta_c\,\sigma + 4\beta_i\,\delta + \delta^2 - 2\delta\,\sigma + \sigma^2}$$

$$\lambda_4 = \beta_c - \mu$$

To verify that any equilibrium is unstable we must prove that there is at least one positive eigenvalue. Hence, according to the given parameters λ_4 is always positive; $\beta_c > \mu \ \rightarrow\ \beta_c - \mu > 0$.

Substituting the second equilibrium point ($\frac{\mu}{\beta_c}$, $1-\frac{\mu}{\beta_c}$, 0, 0) and the set of the defined parameters into the Jacobian matrix yields:

$$J = \begin{bmatrix} -0.5 & -0.01428571429 & -0.01428571429 & 49.14285714 \\ 0.4857142857 & 0 & 0 & 0 \\ 0 & 0 & -0.01 & 2.857142858 \\ 0 & 0 & 0.01 & -52.01429 \end{bmatrix}$$

Eigenvalues for this matrix are:

$$\boxed{\lambda_1 = -0.014286,\ \lambda_2 = -0.48571,\ \lambda_3 = -52.015,\ \lambda_4 = -0.0094506}$$

Eigenvalues regarding variables:

$$\lambda_1 = -\mu$$

$$\lambda_2 = -\beta_c + \mu$$

$$\lambda_3 = -\frac{\delta}{2} - \frac{\mu}{2} - \frac{\sigma}{2} - \frac{1}{2\beta_c}\sqrt{{\beta_c}^2\delta^2 - 2\,{\beta_c}^2\delta\,\mu - 2{\beta_c}^2\delta\,\sigma + {\beta_c}^2\mu^2 + 2{\beta_c}^2\mu\,\sigma + {\beta_c}^2\sigma^2 + 4\,\beta_c\,\beta_i\,\delta\,\mu}$$

$$\lambda_4 = -\frac{\delta}{2} - \frac{\mu}{2} - \frac{\sigma}{2} + \frac{1}{2\beta_c}\sqrt{{\beta_c}^2\delta^2 - 2\,{\beta_c}^2\delta\,\mu - 2{\beta_c}^2\delta\,\sigma + {\beta_c}^2\mu^2 + 2{\beta_c}^2\mu\,\sigma + {\beta_c}^2\sigma^2 + 4\,\beta_c\,\beta_i\,\delta\,\mu}$$

Given these eigenvalues, which all have negative values, this equilibrium is stable.

Finally, Substituting the third equilibrium point $\left(\frac{\delta\,\mu+\delta\,\sigma+\mu^2+\mu\,\sigma}{\beta_c\,\mu+\beta_c\,\sigma+\beta_i\,\delta}, 0,\right.$
$\left.\frac{(\sigma+\mu)\left(\beta_c\,\mu+\beta_c\,\sigma+\beta_i\,\delta-\delta\,\mu-\delta\,\sigma-\mu^2-\mu\,\sigma\right)}{\beta_c\,\delta\,\mu+\beta_c\,\delta\,\sigma+\beta_c\,\mu^2+2\,\beta_c\,\mu\,\sigma+\beta_c\,\sigma^2+\beta_i\,\delta^2+\beta_i\,\delta\,\mu+\beta_i\,\delta\,\sigma}, \frac{\delta\left(\beta_c\,\mu+\beta_c\,\sigma+\beta_i\delta-\delta\,\mu-\delta\,\sigma-\mu^2-\mu\,\sigma\right)}{\beta_c\,\delta\,\mu+\beta_c\,\delta\,\sigma+\beta_c\,\mu^2+2\,\beta_c\,\mu\,\sigma+\beta_c\,\sigma^2+\beta_i\,\delta^2+\beta_i\,\delta\,\mu+\beta_i\,\delta\,\sigma}\right)$,
and the set of the defined parameters into the Jacobian matrix yields:

$$J = \begin{bmatrix} -0.5091303511 & -0.02338648128 & -0.02338648128 & 47.32270374 \\ 0 & 0.00910076699 & 0 & 0 \\ 0.4948446368 & 0 & -0.00089923301 & 4.677296257 \\ 0 & 0 & 0.01 & -52.0143 \end{bmatrix}$$

Eigenvalues for this matrix are:

$$\boxed{\lambda_1 = -0.014285,\ \lambda_2 = -0.49493,\ \lambda_3 = -52.015,\ \lambda_4 = 0.0091008}$$

Eigenvalues regarding variables:

$$\lambda_1 = -\mu$$

$$\lambda 2 = \text{Obtained in the appendix}$$

$$\lambda_3 = \text{Obtained in the appendix}$$

$$\lambda_4 = \frac{\delta\ (\beta_c\,\mu + \beta_c\,\sigma - \ \beta_i\,\mu)}{\beta_c\,\mu + \beta_c\,\sigma + \beta_i\,\delta}$$

These eigenvalues indicate instability of this equilibrium point. Furthermore, this occurred because of the fourth eigenvalue.

Summary: In the case of S.epidermidis given parameters there is only one stable equilibrium which occurs at the particular point $(\frac{\mu}{\beta_c},\ 1-\frac{\mu}{\beta_c},\ 0,\ 0)$, while the other two equilibrium points are unstable.

Example 2.3.2 The S.aureus strain will be considered in this example, with the defined parameters as follow:

$$\boxed{\mu = 1/70, \beta_c = 0.02, \beta_i = 100, \delta = 1/100, \sigma = 52}$$

Testing the stability of the first equilibrium point yields:

$$J(1,0,0,0) = \begin{bmatrix} -0.01428571429 & -0.02 & -0.02 & -48 \\ 0 & 0.00571428571 & 0 & 0 \\ 0 & 0 & -0.00428571429 & 100 \\ 0 & 0 & 0.01 & -52.0143 \end{bmatrix}$$

Eigenvalues for this matrix are:

$$\boxed{\lambda_1 = -0.014286,\ \ \lambda_2 = -52.033,\ \ \lambda_3 = 0.014934,\ \ \lambda_4 = 0.0057143}$$

Again, proving instability of an equilibrium point required to have at least one positive eigenvalue; $\lambda_4 = 0.0057143 = \beta_c - \mu > 0$, as $\beta_c > \mu$.

Substituting the second equilibrium point $(\frac{\mu}{\beta_c},\ 1-\frac{\mu}{\beta_c},\ 0,\ 0)$ yields:

$$J = \begin{bmatrix} -0.02 & -0.01428571429 & -0.01428571429 & -19.42857145 \\ 0.005714285710 & 0 & 0 & 0 \\ 0 & 0 & -0.01 & 71.42857145 \\ 0 & 0 & 0.01 & -52.0143 \end{bmatrix}$$

Eigenvalues for this matrix are:

$$\boxed{\lambda_1 = -0.014285,\ \lambda_2 = -0.0057145,\ \lambda_3 = -52.028,\ \lambda_4 = 0.0037317}$$

This equilibrium is unstable, due to the value of λ_4, which can be represented in term of variables as follow:

$$\lambda_4 = -\frac{\delta}{2} - \frac{\mu}{2} - \frac{\sigma}{2} + \frac{1}{2\beta_c}\sqrt{{\beta_c}^2\delta^2 - 2\,{\beta_c}^2\delta\,\mu - 2{\beta_c}^2\delta\,\sigma + {\beta_c}^2\mu^2 + 2{\beta_c}^2\mu\,\sigma + {\beta_c}^2\sigma^2 + 4\,\beta_c\,\beta_i\,\delta\,\mu} \tag{2.5}$$

Finally, inserting the third equilibrium point $\left(\frac{\delta\,\mu+\delta\,\sigma+\mu^2+\mu\,\sigma}{\beta_c\,\mu+\beta_c\,\sigma+\beta_i\,\delta}, 0,\right.$
$\left.\frac{(\sigma+\mu)\left(\beta_c\,\mu+\beta_c\,\sigma+\beta_i\,\delta-\delta\,\mu-\delta\,\sigma-\mu^2-\mu\,\sigma\right)}{\beta_c\,\delta\,\mu+\beta_c\,\delta\,\sigma+\beta_c\,\mu^2+2\,\beta_c\,\mu\,\sigma+\beta_c\,\sigma^2+\beta_i\,\delta^2+\beta_i\,\delta\,\mu+\beta_i\,\delta\,\sigma}, \frac{\delta\left(\beta_c\,\mu+\beta c\,\sigma+\beta_i\delta-\delta\,\mu-\delta\,\sigma-\mu^2-\mu\,\sigma\right)}{\beta_c\,\delta\,\mu+\beta_c\,\delta\,\sigma+\beta_c\,\mu^2+2\,\beta_c\,\mu\,\sigma+\beta_c\,\sigma^2+\beta_i\,\delta^2+\beta_i\,\delta\,\mu+\beta_i\,\delta\,\sigma}\right)$,
into the Jacobian yields:

$$J = \begin{bmatrix} -0.02922261581 & -0.01238261949 & -0.01238261949 & -9.91309743 \\ 0 & -0.00190309480 & 0 & 0 \\ 0.01493690152 & 0 & -0.01190309480 & 61.91309743 \\ 0 & 0 & 0.01 & -52.0143 \end{bmatrix}$$

Eigenvalues for this matrix are:

$$\boxed{\lambda_1 = -0.014937,\ \lambda_2 = -0.014285,\ \lambda_3 = -52.026,\ \lambda_4 = -0.0019031}$$

These eigenvalues indicate that with this value of β_c, this equilibrium point becomes stable, in contrast to what it was before with the other value of β_c. In general, changing the value of this parameter has changed the stability of the second and third equilibrium points.

2.4 Bifurcation analysis for the model.

In order to understand this part of the analysis, a couple of concepts are needed to be defined.

Definition 2.4.1 *Bifurcation:* Studying the changes in the qualitative or topological structure of a given family, such the family of differential equations, from a mathematical point of view is known as the "Bifurcation theory", [12, 13, 14]. When a minor and smooth change occurs to the parameter values of the system, which in our case [β_c], leads to an unexpected 'qualitative' or topological change in its behaviour, this shows

that a bifurcation has happened. Bifurcations occur in both continuous and discrete systems.

There are two types of bifurcations; Local bifurcation: this type occurs when a parameter change causes the stability of equilibrium to change. Global bifurcation: which often occurs to larger invariant sets of the system 'collide' with each other, or with equilibria of the system. They are quite challenging to be detected by a stability analysis of the equilibria, [12, 13, 14].

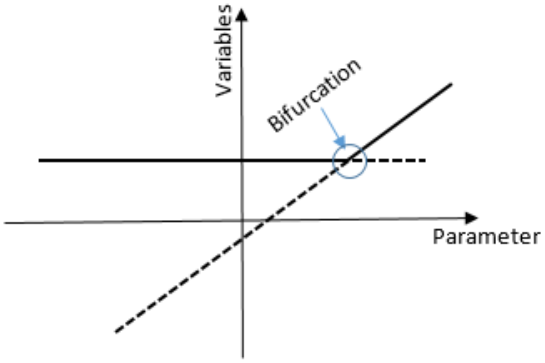

Figure 2.3: **The bifurcation diagram for transcritical bifurcation:** The solid line shows the stable equilibrium point and the dashed line shows the unstable equilibrium.

Definition 2.4.2 *Transcritical bifurcation:* This particular type of Local bifurcation occurs as one or more of the parameters are varied, an equilibrium point interchanges its stability with another equilibrium point. Meaning that, an equilibrium having an eigenvalue whose real part passes through zero. In other words, assume having two equilibrium points, first point is stable and the other is not. As the parameter changes, they collide and interchange their stability state and vice versa, [12, 13, 14].

Manipulating the value of (β_c) has led to interchange the stability of two equilibrium points.

When $\beta_c = 0.5$, this equilibrium where,

$$(S,\, C_a,\, C_v,\, I) = (\frac{\mu}{\beta_c},\, 1 - \frac{\mu}{\beta_c},\, 0,\, 0) \tag{2.6}$$

was stable,

while the other equilibrium where,

$$(S,\, C_a,\, C_v,\, I) = \Big(\frac{\delta\,\mu + \delta\,\sigma + \mu^2 + \mu\,\sigma}{\beta_c\,\mu + \beta_c\,\sigma + \beta_i\,\delta}, 0,$$
$$\frac{(\sigma+\mu)\,(\beta_c\,\mu + \beta_c\,\sigma + \beta_i\,\delta - \delta\,\mu - \delta\,\sigma - \mu^2 - \mu\,\sigma)}{\beta_c\,\delta\,\mu + \beta_c\,\delta\,\sigma + \beta_c\,\mu^2 + 2\,\beta_c\,\mu\,\sigma + \beta_c\,\sigma^2 + \beta_i\,\delta^2 + \beta_i\,\delta\,\mu + \beta_i\,\delta\,\sigma},$$
$$\frac{\delta\,(\beta_c\,\mu + \beta_c\,\sigma + \beta_i\delta - \delta\,\mu - \delta\,\sigma - \mu^2 - \mu\,\sigma)}{\beta_c\,\delta\,\mu + \beta_c\,\delta\,\sigma + \beta_c\,\mu^2 + 2\,\beta_c\,\mu\,\sigma + \beta_c\,\sigma^2 + \beta_i\,\delta^2 + \beta_i\,\delta\,\mu + \beta_i\,\delta\,\sigma}\Big) \tag{2.7}$$

was unstable. The exact opposite occurs when changing the value of β_c to become (0.02).

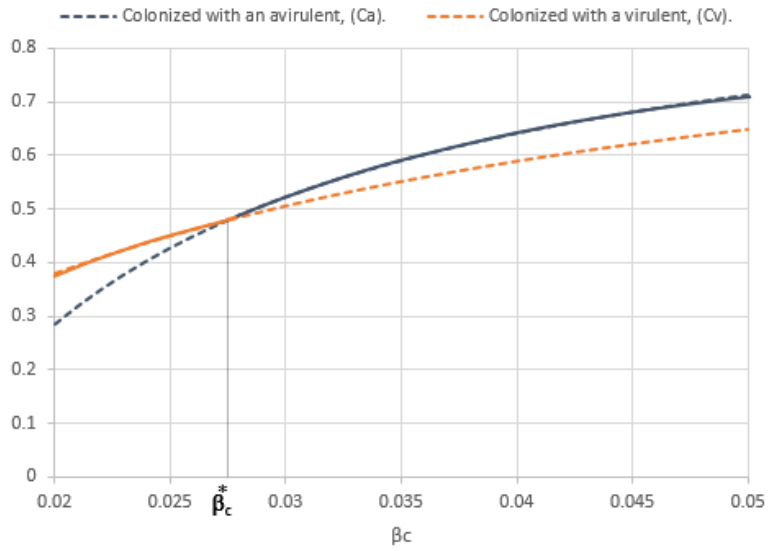

Figure 2.4: **Illustration of the bifurcation point in the system (2.1-2.4).** Shows that: the equilibrium point (2.7), represented by (orange), is stable when ($\beta_c < \beta_c{}^\star$), otherwise unstable. Moreover, the equilibrium point (2.6), represented by (blue), is stable when($\beta_c > \beta_c{}^\star$), otherwise unstable. Hence, the value of $\beta_c{}^\star = 0.027465$, as mentioned in (2.11)

As mentioned before, in each equilibrium there is only one eigenvalue that changes its sign when changing the value of the parameter. In order to identify the bifurcation point ($\beta_c{}^\star$), the eigenvalue that changes its sign in each equilibrium point needed to be detected and the expression of $\beta_c{}^\star$ can be obtained by make them equal to zero.
From the equilibrium (2.6), the eigenvalue that changed its sign is:

$$\lambda_4 = -\frac{\delta}{2} - \frac{\mu}{2} - \frac{\sigma}{2} + \frac{1}{2\beta_c}\sqrt{\beta_c{}^2\delta^2 - 2\,\beta_c{}^2\delta\,\mu - 2\beta_c{}^2\delta\,\sigma + \beta_c{}^2\mu^2 + 2\beta_c{}^2\mu\,\sigma + \beta_c{}^2\sigma^2 + 4\,\beta_c\,\beta_i\delta\,\mu} \tag{2.8}$$

In addition, from the equilibrium (2.7), the eigenvalue that changed its sign is:

$$\lambda_4 = \frac{\delta\ (\beta_c\,\mu + \beta_c\,\sigma -\ \beta_i\,\mu)}{\beta_c\,\mu + \beta_c\,\sigma + \beta_i\,\delta} \tag{2.9}$$

Obtaining the value of $(\beta_c{}^\star),$ from equation (2.8), or similarly from (2.9) yields:

$$\beta_c{}^\star = \frac{\beta_i\,\mu}{\sigma + \mu} \tag{2.10}$$

Substituting the value of the given parameters into equation (2.10), gives,

$$\beta_c{}^\star = \frac{(100)(1/70)}{52 + 1/70} = \frac{100}{3641} = 0.027465 \tag{2.11}$$

2.5 Conclusion

In this chapter, we were able to amend the given model by adding the missing recovery term, (σI), to the first equation, which represents the changes that occur in the susceptible class over time. Furthermore, we solve the system numerically to obtain the equilibrium points. Through the use of linearization technique we were able to examine the equilibrium points to determine their stability, by substituting the equilibrium points into the Jacobian matrix and then analyse the eigenvalues to each fixed point. Changing one particular parameter has led to interchange the stability of two equilibrium points. By investigating these two equilibrium points on the scale of that particular parameter and determining the eigenvalue that changes its sign at each point, a bifurcation point was found. Through the definition and the types of bifurcation we were capable of identifying the occurrence of the transcritical bifurcation.

Chapter 3

Analysis of the model developed in "Evolutionary Trade-Offs Underlie the Multifaceted Virulence of Staphylococcus aureus"

The idea of this model is to demonstrate the role of toxicity level on the nature of bacterial virulence. By studying two different strains of S. aureus, which have a different degree of toxicity.

3.1 Description of the mathematical model

Unlike the previous model, this model is dividing the population into seven different stages. Starting with the susceptible individuals class S, which can be either colonised,

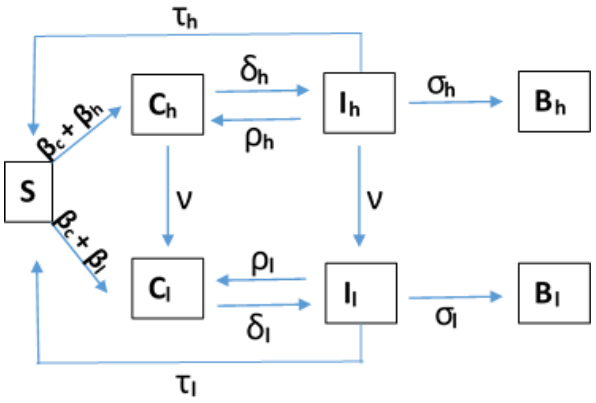

Figure 3.1: Diagram illustrating the mathematical model.

(by high toxicity C_h, or low toxicity C_l strain of S. aureus at rate β_c), or infected

(by high toxicity I_h, or low toxicity I_l strain of S. aureus with transmission rates β_h and β_l , respectively). The colonised individuals by either high or low toxicity strain might develop an infection at rate $\delta_i, (i = h, l)$. From the infection stage, individuals either recover, (back to the susceptible class by treatment at rate τ_i, or back to the colonised class by developing immunity to the disease at rate ρ_i), or go on to bacteraemia stage B_i with rate σ_i. Colonised and infected individuals with high toxicity strain can mutate at a rate ν towards lower levels of toxicity.
This model can be represented by a set of nonlinear differential equations as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \mu - \big(\beta_c\, C_l + \beta_l\, I_l\big) S - \big(\beta_c\, C_h + \beta_h\, I_h\big) S + \tau_l\, I_l + \tau_h\, I_h - \mu\, S \\
\frac{dC_l}{dt} &= \big(\beta_c\, C_l + \beta_l\, I_l\big) S + \upsilon\, C_h + \rho_l\, I_l - \mu\, C_l - \delta_l\, C_l \\
\frac{dC_h}{dt} &= \big(\beta_c\, C_h + \beta_h\, I_h\big) S + \rho_h\, I_h - \upsilon\, C_h - \mu\, C_h\ -\ \delta_h\, C_h \\
\frac{dC_h}{dt} &= \big(\beta_c\, C_h + \beta_h\, I_h\big) S + \rho_h\, I_h - \upsilon\, C_h - \mu\, C_h - \delta_h\, C_h \\
\frac{dI_l}{dt} &= \delta_l\, C_l + \upsilon\, I_h - \rho_l\, I_l - \sigma_l\, I_l - \mu\, I_l - \tau_l\, I_l \\
\frac{dI_h}{dt} &= \delta_h\, C_h - \upsilon\, I_h - \rho_h\, I_h - \sigma_h\, I_h - \mu\, I_h - \tau_h\, I_h \\
\frac{dB_l}{dt} &= \sigma_l\, I_l\ - (\mu + \chi)\, B_l \\
\frac{dB_h}{dt} &= \sigma_h\, I_h\ - (\mu + \chi)\, B_h
\end{aligned} \tag{3.1}$$

Where, μ represents birth and natural death rate, χ stands for death caused by disease rate, υ represents the rate of high toxic strains mutates towards a lower level of toxicity, β_c the rate of transmission through contacting susceptible individuals with colonised individuals, β_i , $(i = h, l)$ the rate of added transmission through infections, δ_i , $(i = h, l)$ the rate of a pathogen to develop an infection, τ_i , $(i = h, l)$, the rate of recovery through treatment, ρ_i , $(i = h, l)$ the rate of recovery through developing immunity, σ_i , $(i = h, l)$ the rate of infection to develop invasive disease.
Within this system, a positive correlation was assumed between the level of toxicity and the propensity of the pathogen to develop an infection. Furthermore, the transmission and recovery rates of infected individuals also agreed to the degree of toxicity.

3.2 Identifying the equilibrium points of non-linear system of ODEs

Finding the explicit or implicit solutions of a nonlinear system considered to be challenging. The qualitative and numerical approximation are significant given the fact that it could provide us with conclusions whether the solutions were known or not. This system of nonlinear differential equations were solved regarding variables. However, the expressions of the equilibrium points were too complicated and long to be obtained within the text given the fact that this system considered having seven dimensions. [It can be seen in the appendix]

Therefore, the equilibrium point in this model were obtained numerically as follows: By substituting the values of the given parameters: $\mu = 0.017, \chi = 5, \upsilon = 0.002, \beta_c = 0.05, \beta_l = 4, \beta_h = 4.4, \delta_l = 2, \delta_h = 2.2, \tau_l = 3, \tau_h = 3.3, \rho_l = \rho_h = 10,$ into the system of nonlinear ODEs (3.1) , the system takes this form;

$$\begin{aligned}
\frac{dS}{dt} &= 0.017 - \big(0.05\,C_l + 4\,I_l\big)S - \big(0.05\,C_h + 4.4\,I_h\big)S + 3\,I_l + 3.3\,I_h - 0.017\,S \\
\frac{dC_l}{dt} &= \big(0.05\,C_l + 4\,I_l\big)S + 0.002\,C_h + 10\,I_l - 2.017\,C_l \\
\frac{dC_h}{dt} &= \big(0.05\,C_h + 4.4\,I_h\big)S + 10\,I_h - 2.219\,C_h \\
\frac{dI_l}{dt} &= 2\,C_l + 0.002\,I_h - 14.017\,I_l \\
\frac{dI_h}{dt} &= 2.2\,C_h - 14.319\,I_h \\
\frac{dB_l}{dt} &= 0.01\,I_l - 5.017\,B_l \\
\frac{dB_h}{dt} &= 0.01\,I_h - 5.017\,B_h
\end{aligned} \tag{3.2}$$

Finding the equilibrium or fixed points $(S, C_l, C_h, I_l, I_h, B_l, B_h)$ of the system, which can be defined as the intersection point of all the nullclines, where the nullcline is the set of points which satisfy:

$$S' = {C_l}' = {C_h}' = {I_l}' = {I_h}' = {B_l}' = {B_h}' = 0 \tag{3.3}$$

Solving this system of nonlinear ODEs numerically has led to three equilibrium points:

$$(S, C_l, C_h, I_l, I_h, B_l, B_h) = (1,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0). \tag{3.4}$$

$$(S, C_l, C_h, I_l, I_h, B_l, B_h) = (0.9507,\ 0.0052,\ 0,\ 0.0007,\ 0,\ 0.0001,\ 0). \tag{3.5}$$

$$(S, C_l, C_h, I_l, I_h, B_l, B_h) = (0.9402,\ 0.0015,\ 0.0044,\ 0.0002,\ 0.0007,\ 0.0001,\ 0.0002). \tag{3.6}$$

Remark 2 *: The expression of the second equilibrium points regarding variables will be obtained in the appendix.*
In addition, each of these three fixed points was validated to satisfy (3.3) by substituting them into the original system (3.2).

3.3 The linearized form of the system

As the equilibria of the system (3.2) are obtained at the hand, the next step is to linearize the equations about these three points. Linearizing requires computation of the Jacobian matrix $J_{(S,C_l,C_h,I_l,I_h,B_l,B_h)}$ of the vector field $(S', C_l', C_h', I_l', I_h', B_l', B_h')^T$, we have;

$$J_{(S,C_l,C_h,I_l,I_h,B_l,B_h)} = \begin{bmatrix} \frac{\partial S'}{\partial S} & \frac{\partial S'}{\partial C_l} & \frac{\partial S'}{\partial C_h} & \frac{\partial S'}{\partial I_l} & \frac{\partial S'}{\partial I_h} & \frac{\partial S'}{\partial B_l} & \frac{\partial S'}{\partial B_h} \\ \frac{\partial C_l'}{\partial S} & \frac{\partial C_l'}{\partial C_l} & \frac{\partial C_l'}{\partial C_h} & \frac{\partial C_l'}{\partial I_l} & \frac{\partial C_l'}{\partial I_h} & \frac{\partial C_l'}{\partial B_l} & \frac{\partial C_l'}{\partial B_h} \\ \frac{\partial C_h'}{\partial S} & \frac{\partial C_h'}{\partial C_l} & \frac{\partial C_h'}{\partial C_h} & \frac{\partial C_h'}{\partial I_l} & \frac{\partial C_h'}{\partial I_h} & \frac{\partial C_h'}{\partial B_l} & \frac{\partial C_h'}{\partial B_h} \\ \frac{\partial I_l'}{\partial S} & \frac{\partial I_l'}{\partial C_l} & \frac{\partial I_l'}{\partial C_h} & \frac{\partial I_l'}{\partial I_l} & \frac{\partial I_l'}{\partial I_h} & \frac{\partial I_l'}{\partial B_l} & \frac{\partial I_l'}{\partial B_h} \\ \frac{\partial I_h'}{\partial S} & \frac{\partial I_h'}{\partial C_l} & \frac{\partial I_h'}{\partial C_h} & \frac{\partial I_h'}{\partial I_l} & \frac{\partial I_h'}{\partial I_h} & \frac{\partial I_h'}{\partial B_l} & \frac{\partial I_h'}{\partial B_h} \\ \frac{\partial B_l'}{\partial S} & \frac{\partial B_l'}{\partial C_l} & \frac{\partial B_l'}{\partial C_h} & \frac{\partial B_l'}{\partial I_l} & \frac{\partial B_l'}{\partial I_h} & \frac{\partial B_l'}{\partial B_l} & \frac{\partial B_l'}{\partial B_h} \\ \frac{\partial B_h'}{\partial S} & \frac{\partial B_h'}{\partial C_l} & \frac{\partial B_h'}{\partial C_h} & \frac{\partial B_h'}{\partial I_l} & \frac{\partial B_h'}{\partial I_h} & \frac{\partial B_h'}{\partial B_l} & \frac{\partial B_h'}{\partial B_h} \end{bmatrix} \tag{3.7}$$

Remark 3 *The original form of the Jacobian matrix regarding the variables will be added to the appendix.*

3.4 Determining the stability of the equilibria.

In this section, we will analyse each equilibrium points separately, for each point alone. Starting with first equilibrium point which was obtained in (3.4). Then testing the

stability of the second point as illustrated in (3.5). Finally, we will end this section with the last equilibrium point (3.6).

3.4.1 Determining the stability of the first equilibrium point

By substituting the equilibrium point (S, C_l, C_h, I_l, I_h, B_l, B_h) = (1, 0, 0, 0, 0, 0, 0), into the Jacobian matrix (3.7) to determine the stability of the first equilibrium point.

$$\begin{bmatrix} -\mu & -\beta_c & -\beta_c & -\beta_c+\tau_l & -\beta_h+\tau_h & 0 & 0 \\ 0 & \beta_c-\mu-\delta_l & \upsilon & \beta_l+\rho_l & 0 & 0 & 0 \\ 0 & 0 & \beta_c-\upsilon-\mu-\delta_h & 0 & \beta_h+\rho_h & 0 & 0 \\ 0 & \delta_l & 0 & -\rho_l-\sigma_l-\mu-\tau_l & \upsilon & 0 & 0 \\ 0 & 0 & \delta_h & 0 & -\upsilon-\rho_h-\sigma_h-\mu-\tau_h & 0 & 0 \\ 0 & 0 & 0 & \sigma_l & 0 & -\mu-\chi & 0 \\ 0 & 0 & 0 & 0 & \sigma_h & 0 & -\mu-\chi \end{bmatrix}$$

The eigenvalues of this matrix are:

$$\lambda_1 = -\mu \tag{3.8}$$

$$\lambda_2 = -\mu-\chi \tag{3.9}$$

$$\lambda_3 = -\mu-\chi \tag{3.10}$$

$$\lambda_4 = -2\mu+\beta_c-\delta_l-\rho_l+\sigma_l+\tau_l+\big[(\beta_c)^2-2\beta_c\sigma_l+2\beta_c\rho_l+2\beta\sigma_l+2\beta\tau_l+4\beta_l\sigma_l +(\delta_l)^2+2\delta_l\rho_l-2\delta_l\tau_l+(\rho_l)^2+2\rho_l\sigma_l+2\rho_l\tau_l+(\sigma_l)^2+2\sigma_l\tau_l+(\tau_l)^2\big]^{\frac{1}{2}} \tag{3.11}$$

$$\lambda_5 = -2\mu+\beta_c-\delta_l-\rho_l+\sigma_l+\tau_l-\big[(\beta_c)^2-2\beta_c\sigma_l+2\beta_c\rho_l+2\beta\sigma_l+2\beta\tau_l+4\beta_l\sigma_l +(\delta_l)^2+2\delta_l\rho_l-2\delta_l\tau_l+(\rho_l)^2+2\rho_l\sigma_l+2\rho_l\tau_l+(\sigma_l)^2+2\sigma_l\tau_l+(\tau_l)^2\big]^{\frac{1}{2}} \tag{3.12}$$

$$\lambda_6 = -2\mu-2\upsilon+\beta_c-\delta_h-\rho_h-\sigma_h-\tau_h+\big[4\beta_h\delta_h+(\beta_c)^2-2\beta_c\delta_h+2\beta_c\rho_h+2\beta_c\sigma_h +2\beta_c\tau_h+(\delta_h)^2+2\delta_h\rho_h-2\delta_h\sigma_h-2\delta_h\tau_h+(\rho_h)^2+2\rho_h\sigma_h+2\rho_h\tau_h+(\sigma_h)^2+2\sigma_h\tau_h+(\tau_h)^2\big]^{\frac{1}{2}} \tag{3.13}$$

$$\lambda_7 = -2\mu-2\upsilon+\beta_c-\delta_h-\rho_h-\sigma_h-\tau_h-\big[4\beta_h\delta_h+(\beta_c)^2-2\beta_c\delta_h+2\beta_c\rho_h+2\beta_c\sigma_h +2\beta_c\tau_h+(\delta_h)^2+2\delta_h\rho_h-2\delta_h\sigma_h-2\delta_h\tau_h+(\rho_h)^2+2\rho_h\sigma_h+2\rho_h\tau_h+(\sigma_h)^2+2\sigma_h\tau_h+(\tau_h)^2\big]^{\frac{1}{2}} \tag{3.14}$$

Through the stability analysis, it turns out that, $\big(\lambda_1, \lambda_2, \lambda_3, \lambda_5, \lambda_7\big)$, are always negative. However the sign of λ_4 depends on the value of σ_l, if

$$\begin{cases} \sigma_l \geqslant 1.2179, & \text{then} \quad \lambda_4 \text{ is negative,} \\ \sigma_l < 1.2179, & \text{then} \quad \lambda_4 \text{ is positive.} \end{cases}$$

Whereas the sign of λ_6 depends on the value of σ_h, if:

$$\begin{cases} \sigma_h \geqslant 1.286809126, & \text{then} \quad \lambda_6 \text{ is negative,} \\ \sigma_h < 1.286809126, & \text{then} \quad \lambda_6 \text{ is positive.} \end{cases}$$

Knowing that, these exact values of σ_l and σ_h, were obtained by following these steps:

1. Setting the value of these eigenvalues to zero. $\lambda_4\,,\ \lambda_6 = 0$
2. Isolating the expression for σ_l and σ_h from the equations (3.11) and (3.13) respectively, yields:

$$\begin{aligned} \sigma_l =& -(\beta_c\rho_l + \beta_c\tau_l + \mu\,\beta_c - \delta_l\tau_l + \beta_l\delta_l - \mu\,\delta_l - \mu\,\rho_l - \mu\,\tau_l - \mu^2)/(\beta_c - \delta_l - \mu) \\ \sigma_h =& -(\beta_c\rho_h + \beta_c\tau_h + \mu\,\beta_c + \upsilon\,\beta_c + \beta_h\delta_h - \delta_h\tau_h - \mu\,\delta_h \\ & - \upsilon\,\delta_h - \mu\,\rho_h - \upsilon\,\rho_h - \mu\,\tau_h - \upsilon\,\tau_h - \mu^2 - 2\,\mu\,\upsilon - \upsilon^2)/(\beta_c - \delta_h - \mu - \upsilon) \end{aligned}$$

3. Substituting the parameters into the resulted equation yields:

$$\boxed{\sigma_l = 1.2179}\ ,\ \boxed{\sigma_h = 1.286809126}$$

Hence, the first equilibrium point (3.4) is;

$$\begin{cases} \text{stable}\,, & \text{if } \sigma_l \geqslant 1.2179,\ \sigma_h \geqslant 1.286809126, \\ \text{unstable}, & \text{otherwise.} \end{cases}$$

3.4.2 Determining the stability of the second equilibrium point

Following a similar procedure as in the previous section to examine the stability of the second equilibrium point (3.5).

$$\begin{bmatrix} -0.02020625458 & -0.04753724636 & -0.04753724636 & -0.802979709 & -0.883277680 & 0 & 0 \\ 0.003206254574 & -1.969462754 & 0.002 & 13.80297971 & 0 & 0 & 0 \\ 0.0 & 0 & -2.171462754 & 0 & 14.18327768 & 0 & 0 \\ 0 & 2 & 0 & -13.02700000 & 0.002 & 0 & 0 \\ 0 & 0 & 2.2 & 0 & -13.32900000 & 0 & 0 \\ 0 & 0 & 0 & 0.01 & 0 & -5.017 & 0 \\ 0 & 0 & 0 & 0 & 0.01 & 0 & -5.017 \end{bmatrix}$$

The eigenvalues:

$$\boxed{\lambda_1 = -0.016969, \lambda_2 = -5.0170, \lambda_3 = -5.0170, \lambda_4 = 0.12707, \lambda_5 = -15.125, \lambda_6 = .14437, \lambda_7 = -15.645}$$

It showed that, $\big(\lambda_1, \lambda_2, \lambda_3, \lambda_5, \lambda_7\big)$, are always negative. However, the sign of λ_4 depends on the value of σ_l, if:

$$\begin{cases} \sigma_l \geqslant 0.838, & \text{then} \quad \lambda_4 \text{ is negative,} \\ \sigma_l < 0.838, & \text{then} \quad \lambda_4 \text{ is positive.} \end{cases}$$

While the sign of λ_6 depends on the value of σ_h, if:

$$\begin{cases} \sigma_h \geqslant 1.0505, & \text{then} \quad \lambda_6 \text{ is negative,} \\ \sigma_h < 1.0505, & \text{then} \quad \lambda_6 \text{ is positive.} \end{cases}$$

Thus, the second equilibrium point (3.5) is:

$$\begin{cases} \text{stable}\,, & \text{if } \sigma_l \geqslant 0.838,\ \sigma_h \geqslant 1.0505, \\ \text{unstable}, & \text{otherwise.} \end{cases}$$

3.4.3 Determining the stability of the third equilibrium point

By substituting the value of the third equilibrium point (3.6) into the Jacobian matrix (3.7), then obtaining the eigenvalues of the resulting matrix.

$$\begin{bmatrix} -0.02117212672 & -0.04700802236 & -0.04700802236 & -0.760641788 & -0.836705967 & 0 & 0 \\ 0.0009619030498 & -1.969991978 & 0.002 & 13.76064179 & 0 & 0 & 0 \\ 0.003210223669 & 0 & -2.171991978 & 0 & 14.13670597 & 0 & 0 \\ 0 & 2 & 0 & -13.02700000 & 0.002 & 0 & 0 \\ 0 & 0 & 2.2 & 0 & -13.32900000 & 0 & 0 \\ 0 & 0 & 0 & 0.01 & 0 & -5.017 & 0 \\ 0 & 0 & 0 & 0 & 0.01 & 0 & -5.017 \end{bmatrix}$$

The eigenvalues:

$$\boxed{\lambda_1 = -0.016969, \lambda_2 = -5.0170, \lambda_3 = -5.0170, \lambda_4 = 0.12707, \lambda_5 = -15.125, \lambda_6 = .14437, \lambda_7 = -15.645}$$

We conclude that, $\big(\lambda_1, \lambda_2, \lambda_3, \lambda_5, \lambda_7\big)$, are always negative. However the value of σ_l determines the sign of λ_4, if:

$$\begin{cases} \sigma_l \geqslant 0.94, & \text{then} \quad \lambda_4 \text{ is negative,} \\ \sigma_l < 0.94, & \text{then} \quad \lambda_4 \text{ is positive.} \end{cases}$$

In addition, the sign of λ_6 is determined by the value of σ_h, if:

$$\begin{cases} \sigma_h \geqslant 0.9956, & \text{then} \quad \lambda_6 \text{ is negative,} \\ \sigma_h < 0.9956, & \text{then} \quad \lambda_6 \text{ is positive.} \end{cases}$$

Therefore, the third equilibrium point (3.6) is:

$$\begin{cases} \text{stable}\,, & \text{if } \sigma_l \geqslant 0.94,\ \sigma_h \geqslant 0.9956, \\ \text{unstable}, & \text{otherwise.} \end{cases}$$

3.5 Comparing our results with the results presented in the paper [2]

As the results of the second model indicate the negative correlation between the level of toxicity and the probability of bacteraemia occurrences, i.e., the low toxic strain is most likely to cause a bacteraemia than the high toxic strain. Due to the fact that, the high propensity of the high toxic strain to develop an infection is positively correlated with the rate of recovery either by the treatment or the mutation. To validate and prove this theory, two hypothesises were conducted on two different strains of S. aureus which diverse in their level of toxicity. The first scenario was based on, the assumption that, both the high and the low strain have an equal propensity to cause a bacteraemia, i.e., $(\sigma_l = \sigma_h)$.

The outcome of this hypothesis was illustrated in the Figure (3.2), which shows that the low toxic strain becomes a dominant in both the carriage and the bacteraemia stages. Which means that the higher toxic strain was defeated by, the lower toxic strain and the reasons behind this are the fast virulence-induced clearance rates of the high toxic strain.

Whereas, the second scenario was based on the assumption that there is a negative relationship between the level of toxicity and the rate of transmission to the bacteraemia stage, i.e., $(\sigma_l > \sigma_h)$.

The consequences of the second hypothesis as illustrated in the Figure (3.3), are: at the carriage stage, the high toxic strain has gained an advantage of the leadership. However the desire of the low toxic strain to remain in the population promotes it to develop mutations which support its dominant position in the bacteraemia stage.

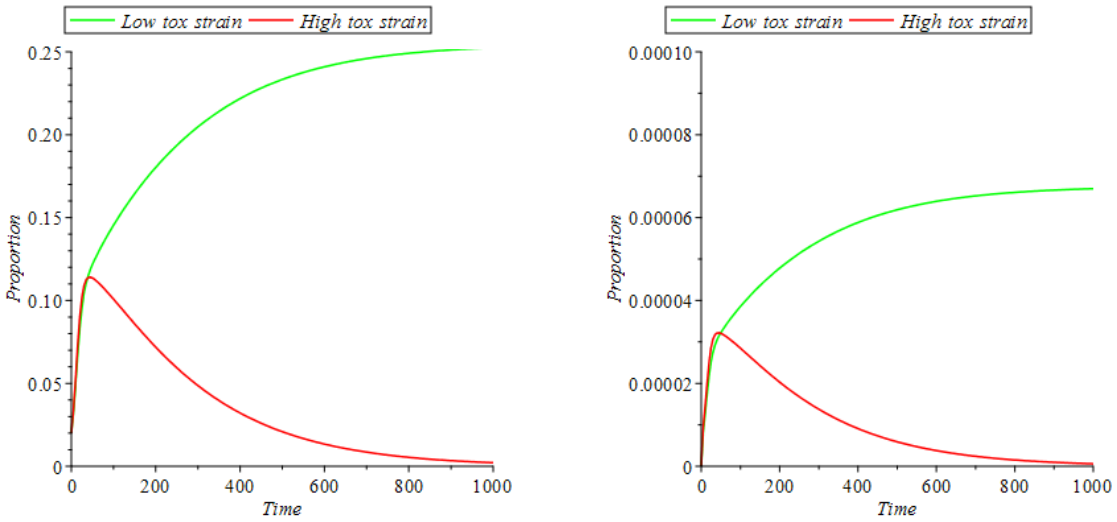

Figure 3.2: **Evolution towards increased levels of virulence, when** ($\sigma_l = \sigma_h = 0.01$)**.** This figure illustrates the results of the first hypothesis. The high toxic strain (red) out-competed by the low toxic strain (green) in both stages the carriage (left), and the bacteraemia (right). This defeat occurs because of the high rate of the recovery in the high toxic strain which promotes and encourages the lower toxic strain to become the prevailing in both carriage and bacteraemia stages.

3.6 Conclusion

Throughout this chapter, we were able to describe the mathematical model, which divided the population into seven different classes and defined a set of parameters that controls the transmission from one class to another. However, two of the parameters (σ_l) and (σ_h), were undefined in the given set of parameters, which we discovered them later on to produce the figures. We found that, ($\sigma_l = \sigma_h = 0.01$) in the assumption that, both the high and the low strains have an equal propensity to cause a bacteraemia, while ($\sigma_l = 0.1 > \sigma_h = 0.01$) in the second assumption that, low toxic strains have more ability to cause a bacteraemia. Through the translation of the mathematical model into differential equations we were able to solve this system of nonlinear differential equation numerically, given the fact that this system has seven dimensions. Three equilibrium points were obtained from the solution. Linearized form of the system was required to examine the stability of the equilibria. Applying the stability analysis on the equilibrium points determined and identified the boundary of the stability for each point. Finally, the results of the model were reviewed and discussed.

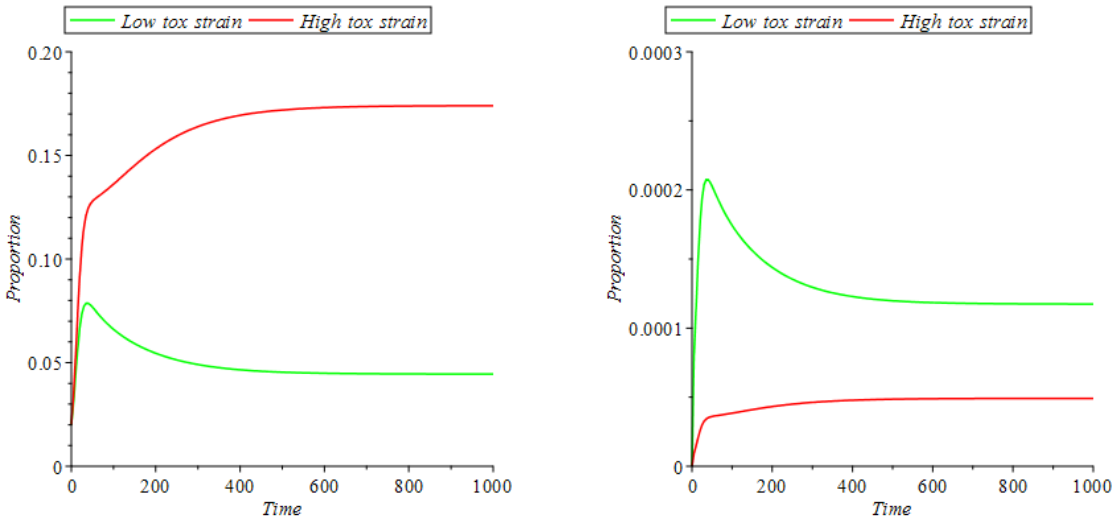

Figure 3.3: **Evolution towards increased levels of virulence, when ($\sigma_l = 0.1 > \sigma_h = 0.01$).** Creates the change in the transmission rate σ_i, in favour to the low toxic strain (green), has led to gained the high toxic strain (red), the leadership in the carriage stage (left). Yet, the low toxic strain remained occupied the high frequency at the bacteraemia stage (right), because of its relentless seeking to maintain in the population through the development of mutations.

Summary: Solving this system of nonlinear ODEs has led to three equilibrium points:

1. $(S,\, C_l,\, C_h,\, I_l,\, I_h,\, B_l,\, B_h) = (1,\, 0,\, 0,\, 0,\, 0,\, 0,\, 0)$.

$$\begin{cases} \text{stable}\,, & \text{if } \sigma_l \geqslant 1.2179,\ \sigma_h \geqslant 1.286809126, \\ \text{unstable}, & \text{otherwise.} \end{cases}$$

2. $(S,\, C_l,\, C_h,\, I_l,\, I_h,\, B_l,\, B_h) = (0.9507,\, 0.0052,\, 0,\, 0.0007,\, 0,\, 0.0001,\, 0)$.

$$\begin{cases} \text{stable}\,, & \text{if } \sigma_l \geqslant 0.838,\ \sigma_h \geqslant 1.0505, \\ \text{unstable}, & \text{otherwise.} \end{cases}$$

3. $(S,\, C_l,\, C_h,\, I_l,\, I_h,\, B_l,\, B_h) = (0.9402,\, 0.0015,\, 0.0044,\, 0.0002,\, 0.0007,\, 0.0001,\, 0.0002)$.

$$\begin{cases} \text{stable}\,, & \text{if } \sigma_l \geqslant 0.94,\ \sigma_h, \geqslant 0.9956, \\ \text{unstable}, & \text{otherwise.} \end{cases}$$

Chapter 4

Modelling the data presented in "The effects of spatial structure, frequency dependence and resistance evolution on the dynamics of toxin-mediated microbial invasions"

4.1 Introducing the mathematical model

While the previous models indicated and discussed the negative correlation between the role of (the transmission rate and the level of toxicity) and the level of disease severity, on the population classes. This model has a different story. In this model, we indicate the competition within the nasal microbial community. By introducing two different strains of the Staphylococcus microbe to each other. This occurs by culturing S.aureus with toxin and non-toxin producing S.epidermis. we manged to create the interference competition and observe the role of the toxin in both structured and unstructured environments. Manipulating some factors in the microbial community could take the role of the antibiotic by limiting colonisation by S. aureus and lower the transmission and infection rates, [4].

A simple illustration of the competition within the nasal microbial community presented in the "The effects of spatial structure, frequency dependence and resistance evolution on the dynamics of toxin-mediated microbial invasions" can be shown by this system of "Logistic Equation" as follow:

$$\frac{du}{dt} = r_u\, u\,(1-u) \tag{4.1}$$

$$\frac{dv}{dt} = r_v\, v\,(1 - v) \tag{4.2}$$

Where r_u and r_v are positive constants.

Definition 4.1.1 *: Logistic Equation* (sometimes known as the Verhulst model or logistic growth curve) represents the increase of the population, first published by Pierre Verhulst (1845, 1847). The model is continuous in time. However, the logistic map which is commonly used, can be defined as a discrete quadratic recurrence equation by adjusting the continuous equation [5, 6]. The continuous form of the logistic model is can be defined by the differential equation:

$$\frac{dN}{dt} = \frac{r\,N\,(K - N)}{K}. \tag{4.3}$$

Where, N represents the population size, r represents the rate of the maximum increase in population, i.e.,(birth rate minus death rate) and K represents the maximum possible and potential population, also known as the carrying capacity, [11].
By dividing both sides by K and defining $u = N/K$ then we obtained:

$$\frac{d}{dt}(\frac{N}{K}) = \frac{r\,N\,(K - N)}{K^2} \;\rightarrow\; \frac{du}{dt} = r\,u\,(1 - u). \tag{4.4}$$

In this simple model noted by the logistic equations, we assumed that (u) represents one strain, while (v) represented the other. Moreover, to guarantee and ensure the occurrence of interaction and interference between those strains, we modified the logistic equation (4.2), by adding the inhibition term $(b\,u\,v)$. So the system takes this form:

$$\frac{du}{dt} = r_u\,u\,(1 - u) \tag{4.5}$$

$$\frac{dv}{dt} = r_v\,v\,(1 - v - b\,u). \tag{4.6}$$

Where $0 \leqslant b < 1$.

4.2 Identifying the equilibrium points of non-linear system of ODEs

To identify the equilibrium points of the system (4.5 – 4.6), we start by setting,

$$\frac{du}{dt} = \frac{dv}{dt} = 0. \tag{4.7}$$

$$\frac{du}{dt} = 0, \quad \text{If} \quad u = 0 \text{ or } u = 1. \tag{4.8}$$

$$\frac{dv}{dt} = 0, \quad \text{If} \quad v = 0 \text{ or } v = 1 - bu. \tag{4.9}$$

This results in four equilibrium points,

$$\boxed{(u, v) = (0, 0),\ (0, 1),\ (1, 0) \text{ and } (1, 1 - b)}$$

4.3 The linearized form of the system.

Applying the linearization technique on the system (4.5 – 4.6), yields:

$$\begin{aligned} J_{(u,v)} &= \begin{bmatrix} \frac{\partial u'}{\partial u} & \frac{\partial u'}{\partial v} \\ \frac{\partial v'}{\partial u} & \frac{\partial v'}{\partial v} \end{bmatrix} \\ &= \begin{bmatrix} r_u\,(1 - 2u) & 0 \\ -r_v v b & r_v\,(1 - 2v - bu) \end{bmatrix} \end{aligned} \tag{4.10}$$

4.4 Determining the stability of the equilibria.

By inserting the first equilibrium point (0,0) into the Jacobian matrix (4.10), to determine its stability.

$$J_{(0,0)} = \begin{bmatrix} r_u & 0 \\ 0 & r_v \end{bmatrix}$$

A linear transformation or a matrix is non-invertible if and only if its determinant is zero. So $det(J - \lambda\, I) = 0$, for non-trivial solutions.

$$det(J - \lambda\, I) = \begin{bmatrix} r_u - \lambda & 0 \\ 0 & r_v - \lambda \end{bmatrix} = (r_u - \lambda)\,(r_v - \lambda) = 0$$

As $\lambda = r_u,\ r_v > 0,$ Thus, this equilibrium point is unstable. Inserting the second equilibrium point (0,1) into the Jacobian matrix (4.10), to determine its stability.

$$J_{(0,1)} = \begin{bmatrix} r_U & 0 \\ -r_V b & -r_V \end{bmatrix}$$

Obtaining the determinant, yields:

$$det(J - \lambda I) = \begin{bmatrix} r_u - \lambda & 0 \\ -r_v b & -r_v - \lambda \end{bmatrix} = (r_u - \lambda)(-r_v - \lambda) = 0$$

As $\lambda = -r_v < 0,\ r_u > 0,$ Thus, this equilibrium point is unstable. Applying the same

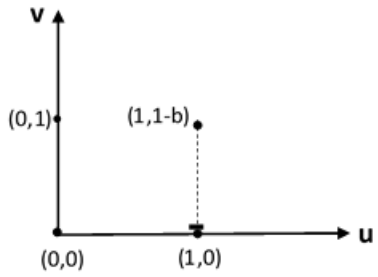

Figure 4.1: **Illustration of the equilibrium points of the model.** As shown through the stability analysis, there is only one stable equilibrium point in this mathematical model, that is $(u, v) = (1, 1-b)$ where, $(0 \leqslant b < 1)$.

procedure to the third equilibrium $(1, 0)$ point yields;

$$J_{(1,0)} = \begin{bmatrix} -r_u & 0 \\ 0 & r_v (1 - b) \end{bmatrix}$$

So that, the determinant of this Jacobian matrix is;

$$det(J - \lambda I) = \begin{bmatrix} -r_u - \lambda & 0 \\ 0 & r_v (1 - b) - \lambda \end{bmatrix} = (-r_u - \lambda)(r_v (1 - b) - \lambda) = 0$$

Given the fact that , $(0 \leqslant b < 1)$ so $\lambda = -r_u < 0\,,\ r_v (1 - b) \not< 0.$ Thus, this equilibrium point is unstable. Determining the stability of the last equilibrium point $(1, 1 - b)$, through the insertion of the point into the Jacobian matrix (4.10);

$$J_{(1,1-b)} = \begin{bmatrix} -r_u & 0 \\ -r_v (1 - b) b & -r_v (1 - b) \end{bmatrix}$$

So that,

$$det(J - \lambda\, I) = \begin{bmatrix} -r_u - \lambda & 0 \\ -r_v\,(1-b)\,b & -r_v\,(1-b) - \lambda \end{bmatrix} = (-r_u - \lambda)\,(-r_v\,(1-b) - \lambda) = 0$$

According to the value of (b), this equilibrium point is stable, which ensure the occurrence of interaction between these two strains.
Where, $\lambda = -r_u < 0\,,\ -r_v\,(1-b) < 0$. The illustration of the equilibrium points is obtained in Fig(4.1)

4.5 Competition experiments

Simple communities of S. epidermidis and S. aureus were constructed to examine the hypothesis that interference competition could contribute negatively to the distributions of these species in nasal communities. Predictions of the theory suggest that interference competition has a critical role in both restrict and encourage the invasion of resident communities. The promotion of the invasion is indicated when the invader strain produces toxins which might lead to killing the resident population. However, the advantages gained from producing toxins must be higher than the disadvantages of producing them. Also, the invader and resident populations must not divide the benefits between them. If these conditions were not obtained, then the chance of invasion will be reduced by the interference competition. Two scenarios were discovered in which S. aureus could be excluded through toxins production by S. epidermidis. The first scenario: when invasion by susceptible S. aureus is inhibited by resident toxin-producing S. epidermidis, while the second scenario is when the resident susceptible S. aureus population is displaced by the invasion of the toxin-producing S. epidermidis. Furthermore, a manipulation of two environmental parameters (the spatial structure of the environment and the starting frequency of invaders), could effect the process of toxin mediated interference competition.

As mentioned before, the model that we presented in this dissertation is a simple illustration of the invader - inhibitor process where the spatial structure of the environment and the starting frequency of invaders were neglected. Also, developing mutations during the invasion which might change the outcome of the process were not taking into consideration. To examine these predictions, competition experiments were performed whereby S. epidermidis strain was invaded into resident populations of S. aureus. On the other hand, a mutual invasion of S. aureus was performed into resident populations of S. epidermidis to test whether S. aureus invasion could be re-

stricted by S. epidermidis . Applying our system of nonlinear differential equation with appropriate initial conditions as follow:

$$\boxed{u(0) = 1, \quad u(0) = \xi, \; v(0) = 1, \quad v(0) = \xi}$$

And,

$$\boxed{b = \xi, \quad b = 0.99}$$

Where, $(0 < \xi \ll 1)$.

According to these initial conditions and the value of b, we will end up with four cases of interaction.

1. $b = \xi, \quad u(0) = 1, \quad v(0) = \xi.$
2. $b = \xi, \quad u(0) = \xi, \quad v(0) = 1.$
3. $b = 0.99, \quad u(0) = 1, \quad v(0) = \xi.$
4. $b = 0.99, \quad u(0) = \xi, \quad v(0) = 1.$

The first case represents the strain $u(t)$ as the resident (cultured) strain, (S. aureus), with high concentration, where $u(0) = 1$, and $v(t)$ as the invasive strain, (S. epidermidis), with low concentration, where $v(0) = \xi$, and $(b = \xi)$.

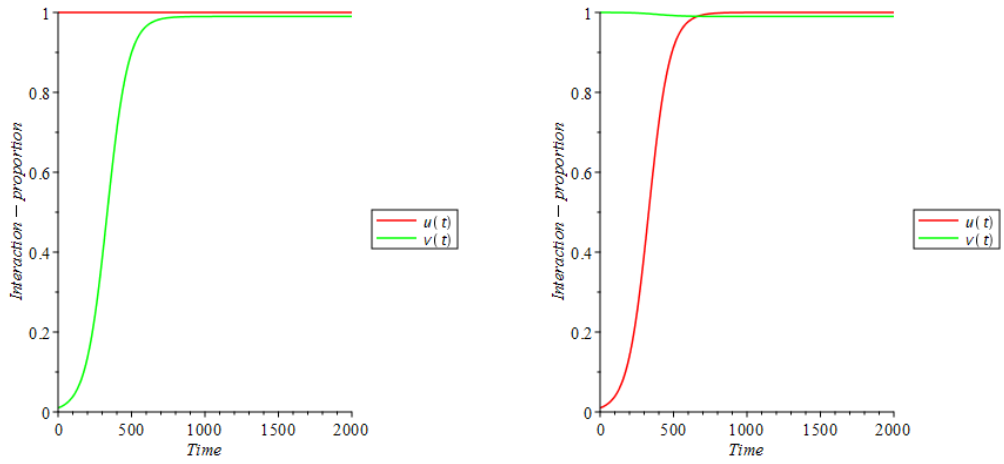

Figure 4.2: **Illustration of the first and the second cases of interaction.** (Left): this figure represents the strain $u(t)$ as the resident (cultured) strain, (S. aureus), with high concentration, where $u(0) = 1$, and $v(t)$ as the invasive strain, (S. epidermidis), with low concentration, where $v(0) = 0.01$. (Right): this figure represents the strain $v(t)$ as the resident (cultured) strain, (S. epidermidis), with high concentration, where $v(0) = 1$ and $u(t)$ as the invasive strain, (S. aureus), with low concentration, where $u(0) = 0.01$ and the inhibition parameter $b = 0.01$ for both cases. As shown, no inhibition occurred in both cases due to the elimination of the inhibition term $(b\,u\,v)$, which equal to zero when $(b \approx 0)$.

As Fig (4.2) demonstrates the evolution of the first condition, no inhibition occurred

when the resident population of S. aureus with high concentration was invaded by the invasive strain of S. epidermidis, when $(b = \xi)$. In another word, no change over time has happened to the resident strain. However, the invasive strain has increased over time.

Considering the second case, represented in Fig (4.2), where a population of S. epidermidis with high concentration, $v(0) = 1$, was invaded by the strain of S. aureus with a relatively low concentration, $u(0) = \xi$, and the inhibition parameter $b = \xi$.
Regarding the results of the first and the second cases, one may argue that, when $(b \approx 0)$, no inhibition occurred and that caused by the elimination of the inhibition term in the system (4.5–4.6). By proceeding to examine the results of the interaction between different strains of the Staphylococcus microbe. The third case of interaction is considered, which can be described as follow; a resident strain of S. aureus with high concentration $u(t) = 1$, is invaded by an invasive strain of S. epidermidis with low concentration $v(t) = \xi$, and $(b = 0.99)$.

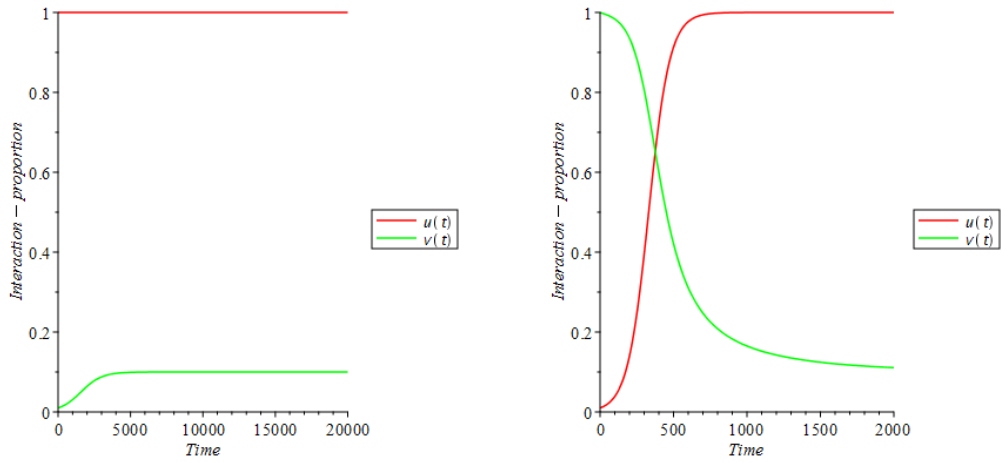

Figure 4.3: **Illustration of the third and the fourth cases of interaction.** (Left): this figure represents the strain $u(t)$ as the resident (cultured) strain, (S. aureus), with high concentration, where $u(0) = 1$, and $v(t)$ as the invasive strain, (S. epidermidis), with low concentration, where $v(0) = 0.01$. (Right): this figure represents the strain $v(t)$ as the resident (cultured) strain, (S. epidermidis), with high concentration, where $v(0) = 1$ and $u(t)$ as the invasive strain, (S. aureus), with low concentration, where $u(0) = 0.01$, and $b = 0.99$ for both cases.

According to Fig (4.3), the resident strain (S. aureus), $u(t)$, has inhibited and restricted the invasion of the invasive strain (S. epidermidis), $v(t)$. Conversely, when applied the fourth case conditions the invasive strain (S. aureus), $u(t)$, had successfully invaded the resident strain (S. epidermidis), $v(t)$, when $(b = 0.99)$.

4.6 Conclusion

In this chapter, we were able to analyse the data presented in the paper "The effects of spatial structure, frequency dependence and resistance evolution on the dynamics of toxin-mediated microbial invasions". The findings suggest that the interference competition within the microbial communities can be used as a potential cure to eliminate the colonisation by S. aureus, furthermore, lower the rate of infection, as it could be an alternative to the antibiotics.

The represented data considered the crucial role of the interference competition between S. aureus and S. epidermidis in two types of environments, structured and mix environment, with different frequencies.

To illustrate the idea, two experiments were performed, the first experiment, when a population of S. aureus (resident), was invaded by toxin and non-toxin producing S. epidermidis, (invasive strains), in both structured and mix environments. Each of the invasions was carried out at relative frequencies of 10, 100 and 1000. The outcomes of these invasions were illustrated in Fig (1.1), as mentioned before, both invasive strains of S. epidermidis (toxin-producing and non-producing), successfully invaded the resident population of S. aureus in a structured environment. Whereas the negative values indicate that no invasions were possible in the mixed environment. To test whether the populations of toxin and non-toxin producers strains of S. epidermidis would inhibit and restrict the invasion by S. aureus, a reciprocal invasion were performed. So that, the second experiment, when populations of toxin and non-toxin producing S. epidermidis, (resident strains), invaded by S. aureus in both structured and mix environments. Each of the invasions was carried out at relative frequencies of 10, 100 and 1000. The findings of this experiment indicate that only a population of toxin-producing S. epidermidis was able to inhibit the invasion. However, we were able to construct a simple mathematical model which only considered the particular case of these interference competitions, (invasive - inhibitor) model in mix environment. Where the structured type of the environments was neglected along with mutations issue, which might change the outcome of the invasion.

First, through the use of the logistic equations a mathematical model was built. Furthermore, we modified one of the equations by adding a nonlinear term, to ensure the interference between these strains during the invasion. Second, we analyse the stability of this model by finding the equilibrium points and linearized the system to obtain the eigenvalues so that we can determine the stability of these points. Finally, we performed the interference competition between these two strains by considering S. aureus and S. epidermidis, which represented in our model by $u(t)$, $v(t)$ respectively.

We obtain four different scenarios, where the S. epidermidis invaded into a population of S. aureus and conversely when a population of S. epidermidis was invaded by S. aureus, at two different concentration. The outcomes of this model can be concluded as follow: No successful invasions occurred when the value of ($b \approx 0$). However, when the value of b was relatively high, S. aureus resident strain was able to inhibit in restrict the invasion of S. epidermidis, and successfully invaded into the population of S. epidermidis in the mutual experiment.

Chapter 5

Discussion

Through the use of different mathematical concepts, we were able to analyse the data, and the mathematical models are given in the first two papers [1, 2]. The main idea that underlies the first model is to determine the relationship between the transmission rate and the level of virulence and severity of the disease. By considering two species of Staphylococcus microbe each of this species contains two different strains distinguished by their level of virulence. S. aureus and S. epidermidis were chosen in this study based on many criteria, First, due to the fact that these two strains are the most famous species of the genus Staphylococcus. Second, they have a different rate of transmission, S. epidermidis is well-known as the commensal in our bodies, and thus it has a high transmission rate while S. aureus has a lower rate of transmission. To explain this phenomenon, the experimental studies and analysis of the transmission, properties identify three reasons are indicating that S. epidermidis transferring between hosts is less challenging than it is in the other strain S. aureus. First, there is a common belief that every human is colonised by this type of bacteria, in other words there are no barriers in the host that could prevent the transmission of such a kind, or at least it is not known yet. The second factor, the dynamic of transmission is easier in this particular strain given the fact that a direct contact is more efficient at transferring between hosts. As S. epidermidis located on the skin, a direct contact could occur daily. On the contrary, then the situation in S. aureus strain that exists in the internal tissue of the nose, which requires more complex procedures to transfer from one host to another. The third factor, there are four different agr groups of S. aureus have been identified, moreover, once the host is colonised by one type, the competition between these types will inhibit the colonisation of any transmitted different kind. The findings of this paper indicate a negative correlation between the rate of transmission and the level of virulence. A mathematical model was presented to support this argument. The dynamics of this model was presented as a system of nonlinear differential equations. However, a missing term in the model was detected and added to achieve the balance

of the system. By solving this system at equilibrium, we were able to obtain three equilibrium points. The stability analysis enabled us to determine the stability of the equilibrium points. By defining the bifurcations and applying the bifurcation analysis the type of the local bifurcation which justifies the interchange of the two equilibrium points in the system was determined as the transcritical bifurcation.

Moving into the second mathematical model represented in [2], where the main idea of this model is to indicate the relationship between the toxicity and the severity of the disease. In this model two of S. aureus strains were considered and they were distinguished by their level of toxicity. The population in this model were divided into seven classes, and the set of transmissions parameters between these stages were defined except two parameters σ_l and σ_h. We discovered them later on to produce the figures. We found that, $(\sigma_l = \sigma_h = 0.01)$ in the assumption that, both the high and the low strains have an equal propensity to cause a bacteraemia, while $(\sigma_l = 0.1 > \sigma_h = 0.01)$ in the second assumption that, low toxic strains have more ability to cause a bacteraemia. Through the translation of the mathematical model into differential equations, we were able to solve this system of nonlinear differential equations numerically, given the fact that this system has seven dimensions. Three equilibrium points were obtained from the solution. Linearized form of the system was required to examine the stability of the equilibria. Applying the stability analysis on the equilibrium points determined and identified the boundary of the stability for each point. Finally, the findings of this paper indicate a negative relationship between the toxicity and the disease severity. Furthermore, by comparing our results with that obtained in the paper [2], we found out that, the results of the mathematical model approved this negative correlation.

While the first two papers [1, 2], represented mathematical models to illustrate the relationship between two important factors and the level of disease severity on population, the third paper [4], discussed another hypothesis . that is the benefits of the interference competitions between the commensals and the harmful bacteria within the host, which might lead to eliminating the colonisation of the bacteria with a high propensity to develop infections. Hence, lower the rate of the infections eventually.

Simple communities of toxin producing and non-toxin producing S. epidermidis and S. aureus were constructed to assay this hypothesis. Predictions of the theory suggest that interference competition has a critical role in both restrict and encourage the invasion of resident communities. Likewise, toxins production by S. epidermidis enhances and inhibits the invasion. Two scenarios were discovered in which S. aureus

could be excluded through toxins production by S. epidermidis. The first scenario: when a resident strain of toxin-producing S. epidermidis inhibits the invasion by the invasive strain S. aureus, whereas the second scenario is when a resident strain of S. aureus is displaced by the invasive strain of toxin-producing S. epidermidis. Moreover, the process of toxin-mediated interference competition could be affected by two environmental parameters, the shape of the environment, structured or unstructured, and the starting concentration of invaders.

As mentioned previously, the model that we presented in this dissertation is a simple illustration of the invader - inhibitor process where the spatial structure of the environment and the starting concentrations of invaders were neglected. Also, developing mutations during the invasions, which might change the results of the process, were not taken into consideration. However, a couple of modifications can be added to this model to consider these neglected factors. For instance, to consider the structured and unstructured environments, we need to add the diffusion term (space variables). Furthermore, to consider the mutations issues, we need for example, to change the value of b to be a function of time instead of constant. As the results obtained in the fourth chapter indicated that when ($b \approx 0$), no invasions were possible, likewise with the mutation case, if a strain has mutated against the other, then no invasion could be possible.

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Chapter 6

Maple Appendix

6.1 Eigenvalues for the third equilibrium point in the section 2.3.2, (Example 2.3.1).

$$\lambda_1 = -\mu$$

$$\lambda_2 = -0.5\,\delta^3\beta_i - \delta^2\mu\,\beta_i - 0.5\,\delta^2\sigma\,\beta_i - 0.5\,\delta^2{\beta_i}^2 - 0.5\,\delta\,\mu^2\beta_i - \delta\,\mu\,\sigma\,\beta_i - \delta\,\mu\,\beta_c\beta_i - 0.5\,\delta\,\sigma^2\beta_i - \delta\,\sigma\,\beta_c\beta_i - 0.5\,\mu^2\sigma\,\beta_c - 0.5\,{\beta_c}^2\mu^2 - \mu\,\sigma^2\beta_c - \mu\,\sigma\,{\beta_c}^2 - 0.5\,\sigma^3\beta_c - 0.5\,\sigma^2{\beta_c}^2 + 0.5\,\Big(\delta^6{\beta_i}^2 - 2\,\delta^5{\beta_i}^3 + \delta^4{\beta_i}^4 + \mu^4{\beta_c}^4 + \sigma^6{\beta_c}^2 - 2\,\sigma^5{\beta_c}^3 + \sigma^4{\beta_c}^4 + 28\,\delta^4\mu\,\sigma\,{\beta_i}^2 + 38\,\delta^3\mu^2\sigma\,{\beta_i}^2 + 28\,\delta^3\mu\,\sigma^2{\beta_i}^2 + 16\,\delta^2\mu^3\sigma\,{\beta_i}^2 + 18\,\delta^2\mu^2\sigma^2{\beta_i}^2 + 18\,\delta^4\mu^2{\beta_i}^2 + 11\,\delta^4\sigma^2{\beta_i}^2 + 16\,\delta^3\mu^3{\beta_i}^2 + 5\,\delta^2\mu^4{\beta_i}^2 + 6\,\delta^2\mu^2{\beta_c}^2{\beta_i}^2 + 8\,\delta^2\mu\,\sigma^3{\beta_i}^2 - 12\,\delta^2\mu\,\sigma^2{\beta_c}^3 + 10\,\delta^2\sigma^4\beta_c\beta_i - 22\,\delta^2\sigma^3{\beta_c}^2\beta_i - 6\,\delta^2\sigma^3\beta_c{\beta_i}^2 + 6\,\delta^2\sigma^2{\beta_c}^2{\beta_i}^2 + 4\,\delta\,\mu^3{\beta_c}^3\beta_i + 2\,\delta\,\sigma^5\beta_c\beta_i - 6\,\delta\,\sigma^4{\beta_c}^2\beta_i + 4\,\delta\,\sigma^3{\beta_c}^3\beta_i - 8\,\delta^4\mu\,\beta_c{\beta_i}^2 - 8\,\delta^4\sigma\,\beta_c{\beta_i}^2 - 10\,\delta^3\mu^2{\beta_c}^2\beta_i + 4\,\delta^3\mu\,\beta_c{\beta_i}^3 - 10\,\delta^3\sigma^2{\beta_c}^2\beta_i - 20\,\delta^3\sigma^2\beta_c{\beta_i}^2 + 4\,\delta^3\sigma\,\beta_c{\beta_i}^3 - 12\,\delta^2\mu^2\sigma\,{\beta_c}^3 - 62\,\delta^2\mu^2\sigma\,{\beta_c}^2\beta_i - 22\,\delta^2\mu^2\sigma\,\beta_c{\beta_i}^2 - 64\,\delta^2\mu\,\sigma^2{\beta_c}^2\beta_i - 20\,\delta^2\mu\,\sigma^2\beta_c{\beta_i}^2 - 36\,\delta\,\mu^3\sigma\,{\beta_c}^2\beta_i - 48\,\delta\,\mu^2\sigma^2{\beta_c}^2\beta_i - 28\,\delta\,\mu\,\sigma^3{\beta_c}^2\beta_i - 36\,\delta^3\mu\,\sigma\,\beta_c{\beta_i}^2 + 8\,\delta^4\mu^2\beta_c\beta_i + 8\,\delta^4\sigma^2\beta_c\beta_i + 24\,\delta^3\mu^3\beta_c\beta_i + 12\,\delta^3\mu^2\sigma\,{\beta_c}^2 + 12\,\delta^3\mu\,\sigma^2{\beta_c}^2 + 18\,\delta^3\sigma^3\beta_c\beta_i + 24\,\delta^2\mu^4\beta_c\beta_i + 44\,\delta^2\mu^3\sigma\,{\beta_c}^2 + 60\,\delta^2\mu^2\sigma^2{\beta_c}^2 + 36\,\delta^2\mu\,\sigma^3{\beta_c}^2 + 8\,\delta\,\mu^5\beta_c\beta_i + 52\,\delta\,\mu^4\sigma\,{\beta_c}^2 + 88\,\delta\,\mu^3\sigma^2{\beta_c}^2 + 72\,\delta\,\mu^2\sigma^3{\beta_c}^2 + 28\,\delta\,\mu\,\sigma^4{\beta_c}^2 + 4\,\delta^3\mu^3{\beta_c}^2 + 4\,\delta^3\sigma^3{\beta_c}^2 + 12\,\delta^2\mu^4{\beta_c}^2 + 8\,\delta^2\sigma^4{\beta_c}^2 + 12\,\delta\,\mu^5{\beta_c}^2 + 20\,\mu^5\sigma\,{\beta_c}^2 + 41\,\mu^4\sigma^2{\beta_c}^2 + 44\,\mu^3\sigma^3{\beta_c}^2 + 26\,\mu^2\sigma^4{\beta_c}^2 + 16\,\delta^4\mu\,\sigma\,\beta_c\beta_i + 66\,\delta^3\mu^2\sigma\,\beta_c\beta_i + 60\,\delta^3\mu\,\sigma^2\beta_c\beta_i + 84\,\delta^2\mu^3\sigma\,\beta_c\beta_i + 106\,\delta^2\mu^2\sigma^2\beta_c\beta_i + 56\,\delta^2\mu\,\sigma^3\beta_c\beta_i + 34.\,\delta\,\mu^4\sigma\,\beta_c\beta_i + 56\,\delta\,\mu^3\sigma^2\beta_c\beta_i + 44\,\delta\,\mu^2\sigma^3\beta_c\beta_i + 4\,\mu^6{\beta_c}^2 - 4\,\delta^2\mu^3{\beta_c}^3 + \delta^2\sigma^4{\beta_i}^2 - 4\,\delta^2\sigma^3{\beta_c}^3 + 4\,\delta\,\sigma^5{\beta_c}^2 - 8\,\delta\,\sigma^4{\beta_c}^3 + 4\,\mu^3\sigma\,{\beta_c}^4 + 6\,\mu^2\sigma^2{\beta_c}^4 + 8\,\mu\,\sigma^5{\beta_c}^2 + 4\,\mu\,\sigma^3{\beta_c}^4 - 6\,\delta^4\sigma\,{\beta_i}^3 + 6\,\delta^3\sigma^3{\beta_i}^2 - 2\,\delta^3\sigma^2{\beta_i}^3 - 20\,\delta^2\mu^3{\beta_c}^2\beta_i - 8\,\delta^2\mu^3\beta_c{\beta_i}^2 - 10\,\delta\,\mu^4{\beta_c}^2\beta_i - 32\,\delta\,\mu^3\sigma\,{\beta_c}^3 - 48\,\delta\,\mu^2\sigma^2{\beta_c}^3 - 32\,\delta\,\mu\,\sigma^3{\beta_c}^3 - 16\,\delta^3\mu^2\beta_c{\beta_i}^2 - 4\,\delta^3\mu\,\sigma\,{\beta_i}^3 - 20\,\delta^3\mu\,\sigma\,{\beta_c}^2\beta_i + 12\,\delta^2\mu\,\sigma\,{\beta_c}^2{\beta_i}^2 + 12\,\delta\,\mu^2\sigma\,{\beta_c}^3\beta_i + 16\,\delta\,\mu\,\sigma^4\beta_c\beta_i + 12\,\delta\,\mu\,\sigma^2{\beta_c}^3\beta_i + 8\,{\beta_i}^2\delta^5\mu + 6\,{\beta_i}^2\delta^5\sigma - 4\,\delta^4\mu\,{\beta_i}^3 - 2\,\delta^3\mu^2{\beta_i}^3 - 8\,\delta\,\mu^4{\beta_c}^3 - 18\,\mu^4\sigma\,{\beta_c}^3 - 32\,\mu^3\sigma^2{\beta_c}^3 - 28\,\mu^2\sigma^3{\beta_c}^3 - 12\,\mu\,\sigma^4{\beta_c}^3 -$$

$$4\,\mu^5{\beta_c}^3\Big)^{1/2}/\Big(\beta_i\delta^2+\delta\,\mu\,\beta_c+\mu\,\beta_i\delta+\delta\,\sigma\,\beta_c+\beta_i\delta\,\sigma+\mu^2\beta_c+2\,\mu\,\sigma\,\beta_c+\sigma^2\beta_c\Big)$$

$$\lambda_3=-0.5\,\delta^3\beta_i-\delta^2\mu\,\beta_i-0.5\,\delta^2\sigma\,\beta_i-0.5\,\delta^2{\beta_i}^2-0.5\,\delta\,\mu^2\beta_i-\delta\,\mu\,\sigma\,\beta_i-\delta\,\mu\,\beta_c\beta_i-0.5\,\delta\,\sigma^2\beta_i-$$

$$\delta\,\sigma\,\beta_c\beta_i-0.5\,\mu^2\sigma\,\beta_c-0.5\,{\beta_c}^2\mu^2-\mu\,\sigma^2\beta_c-\mu\,\sigma\,{\beta_c}^2-0.5\,\sigma^3\beta_c-0.5\,\sigma^2{\beta_c}^2-0.5\,\Big(\delta^6{\beta_i}^2-$$

$$2\,\delta^5{\beta_i}^3+\delta^4{\beta_i}^4+\mu^4{\beta_c}^4+\sigma^6{\beta_c}^2-2\,\sigma^5{\beta_c}^3+\sigma^4{\beta_c}^4+28\,\delta^4\mu\,\sigma\,{\beta_i}^2+38\,\delta^3\mu^2\sigma\,{\beta_i}^2+28\,\delta^3\mu\,\sigma^2{\beta_i}^2+$$

$$16\,\delta^2\mu^3\sigma\,{\beta_i}^2+18\,\delta^2\mu^2\sigma^2{\beta_i}^2+18\,\delta^4\mu^2{\beta_i}^2+11\,\delta^4\sigma^2{\beta_i}^2+16\,\delta^3\mu^3{\beta_i}^2+5\,\delta^2\mu^4{\beta_i}^2+6\,\delta^2\mu^2{\beta_c}^2{\beta_i}^2+$$

$$8\,\delta^2\mu\,\sigma^3{\beta_i}^2-12\,\delta^2\mu\,\sigma^2{\beta_c}^3+10\,\delta^2\sigma^4\beta_c\beta_i-22\,\delta^2\sigma^3{\beta_c}^2\beta_i-6\,\delta^2\sigma^3\beta_c{\beta_i}^2+6\,\delta^2\sigma^2{\beta_c}^2{\beta_i}^2+$$

$$4\,\delta\,\mu^3{\beta_c}^3\beta_i+2\,\delta\,\sigma^5\beta_c\beta_i-6\,\delta\,\sigma^4{\beta_c}^2\beta_i+4\,\delta\,\sigma^3{\beta_c}^3\beta_i-8\,\delta^4\mu\,\beta_c{\beta_i}^2-8\,\delta^4\sigma\,\beta_c{\beta_i}^2-10\,\delta^3\mu^2{\beta_c}^2\beta_i+$$

$$4\,\delta^3\mu\,\beta_c{\beta_i}^3-10\,\delta^3\sigma^2{\beta_c}^2\beta_i-20\,\delta^3\sigma^2\beta_c{\beta_i}^2+4\,\delta^3\sigma\,\beta_c{\beta_i}^3-12\,\delta^2\mu^2\sigma\,{\beta_c}^3-62\,\delta^2\mu^2\sigma\,{\beta_c}^2\beta_i-$$

$$22\,\delta^2\mu^2\sigma\,\beta_c{\beta_i}^2-64\,\delta^2\mu\,\sigma^2{\beta_c}^2\beta_i-20\,\delta^2\mu\,\sigma^2\beta_c{\beta_i}^2-36\,\delta\,\mu^3\sigma\,{\beta_c}^2\beta_i-$$

$$48\,\delta\,\mu^2\sigma^2{\beta_c}^2\beta_i-28\,\delta\,\mu\,\sigma^3{\beta_c}^2\beta_i-36\,\delta^3\mu\,\sigma\,\beta_c{\beta_i}^2+8\,\delta^4\mu^2\beta_c\beta_i+8\,\delta^4\sigma^2\beta_c\beta_i+24\,\delta^3\mu^3\beta_c\beta_i+$$

$$12\,\delta^3\mu^2\sigma\,{\beta_c}^2+12\,\delta^3\mu\,\sigma^2{\beta_c}^2+18\,\delta^3\sigma^3\beta_c\beta_i+24\,\delta^2\mu^4\beta_c\beta_i+44\,\delta^2\mu^3\sigma\,{\beta_c}^2+60\,\delta^2\mu^2\sigma^2{\beta_c}^2+$$

$$36\,\delta^2\mu\,\sigma^3{\beta_c}^2+8\,\delta\,\mu^5\beta_c\beta_i+52\,\delta\,\mu^4\sigma\,{\beta_c}^2+88\,\delta\,\mu^3\sigma^2{\beta_c}^2+72\,\delta\,\mu^2\sigma^3{\beta_c}^2+28\,\delta\,\mu\,\sigma^4{\beta_c}^2+$$

$$4\,\delta^3\mu^3{\beta_c}^2+4\,\delta^3\sigma^3{\beta_c}^2+12\,\delta^2\mu^4{\beta_c}^2+8\,\delta^2\sigma^4{\beta_c}^2+12\,\delta\,\mu^5{\beta_c}^2+20\,\mu^5\sigma\,{\beta_c}^2+41\,\mu^4\sigma^2{\beta_c}^2+$$

$$44\,\mu^3\sigma^3{\beta_c}^2+26\,\mu^2\sigma^4{\beta_c}^2+16\,\delta^4\mu\,\sigma\,\beta_c\beta_i+66\,\delta^3\mu^2\sigma\,\beta_c\beta_i+60\,\delta^3\mu\,\sigma^2\beta_c\beta_i+84\,\delta^2\mu^3\sigma\,\beta_c\beta_i+$$

$$106\,\delta^2\mu^2\sigma^2\beta_c\beta_i+56\,\delta^2\mu\,\sigma^3\beta_c\beta_i+34.\,\delta\,\mu^4\sigma\,\beta_c\beta_i+56\,\delta\,\mu^3\sigma^2\beta_c\beta_i+44\,\delta\,\mu^2\sigma^3\beta_c\beta_i+4\,\mu^6{\beta_c}^2-$$

$$4\,\delta^2\mu^3{\beta_c}^3+\delta^2\sigma^4{\beta_i}^2-4\,\delta^2\sigma^3{\beta_c}^3+4\,\delta\,\sigma^5{\beta_c}^2-8\,\delta\,\sigma^4{\beta_c}^3+4\,\mu^3\sigma\,{\beta_c}^4+6\,\mu^2\sigma^2{\beta_c}^4+8\,\mu\,\sigma^5{\beta_c}^2+$$

$$4\,\mu\,\sigma^3{\beta_c}^4-6\,\delta^4\sigma\,{\beta_i}^3+6\,\delta^3\sigma^3{\beta_i}^2-2\,\delta^3\sigma^2{\beta_i}^3-20\,\delta^2\mu^3{\beta_c}^2\beta_i-8\,\delta^2\mu^3\beta_c{\beta_i}^2-10\,\delta\,\mu^4{\beta_c}^2\beta_i-$$

$$32\,\delta\,\mu^3\sigma\,{\beta_c}^3-48\,\delta\,\mu^2\sigma^2{\beta_c}^3-32\,\delta\,\mu\,\sigma^3{\beta_c}^3-16\,\delta^3\mu^2\beta_c{\beta_i}^2-4\,\delta^3\mu\,\sigma\,{\beta_i}^3-20\,\delta^3\mu\,\sigma\,{\beta_c}^2\beta_i+$$

$$12\,\delta^2\mu\,\sigma\,{\beta_c}^2{\beta_i}^2+12\,\delta\,\mu^2\sigma\,{\beta_c}^3\beta_i+16\,\delta\,\mu\,\sigma^4\beta_c\beta_i+12\,\delta\,\mu\,\sigma^2{\beta_c}^3\beta_i+8\,{\beta_i}^2\delta^5\mu+6\,{\beta_i}^2\delta^5\sigma-$$

$$4\,\delta^4\mu\,{\beta_i}^3-2\,\delta^3\mu^2{\beta_i}^3-8\,\delta\,\mu^4{\beta_c}^3-18\,\mu^4\sigma\,{\beta_c}^3-32\,\mu^3\sigma^2{\beta_c}^3-28\,\mu^2\sigma^3{\beta_c}^3-12\,\mu\,\sigma^4{\beta_c}^3-$$

$$4\,\mu^5{\beta_c}^3\Big)^{1/2}/\Big(\beta_i\delta^2+\delta\,\mu\,\beta_c+\mu\,\beta_i\delta+\delta\,\sigma\,\beta_c+\beta_i\delta\,\sigma+\mu^2\beta_c+2\,\mu\,\sigma\,\beta_c+\sigma^2\beta_c\Big)$$

$$\lambda_4=\frac{\delta\,(\beta_c\,\mu+\beta_c\,\sigma-\beta_i\,\mu)}{\beta_c\,\mu+\beta_c\,\sigma+\beta_i\,\delta}$$

6.2 Identifying the equilibrium points of non-linear system of ODEs regarding varibles in section (3.2).

The second equilibrium point (3.5), can be represented regarding variables as follow:

$$(S,\,C_l,\,C_h,\,I_l,\,I_h,\,B_l,\,B_h)=(\,\tfrac{\mu^2+\mu\,\delta_l+\mu\,\rho_l+\mu\,\sigma_l+\mu\,\tau_l+\delta_l\sigma_l+\delta_l\tau_l}{\mu\,\beta_c+\beta_c\rho_l+\beta_c\sigma_l+\beta_c\tau_l+\beta_l\delta_l}\,,$$

$$-\big(\mu\,(\mu^2-\mu\,\beta_c+\mu\,\delta_l+\mu\,\rho_l+\mu\,\sigma_l+\mu\,\tau_l-\beta_c\rho_l-\beta_c\sigma_l-\beta_c\tau_l-\beta_l\delta_l+\delta_l\sigma_l+\delta_l\tau_l)$$

$$(\mu+\rho_l+\sigma_l+\tau_l)\big)/\big(\mu^3\beta_c+\mu^2\beta_c\delta_l+2\,\mu^2\beta_c\rho_l+2\,\mu^2\beta_c\sigma_l+2\,\mu^2\beta_c\tau_l+\mu^2\beta_l\delta_l+\mu\,\beta_c\delta_l\rho_l+$$

$2\,\mu\,\beta_c\delta_l\sigma_l + \mu\,\beta_c\delta_l\tau_l + \mu\,\beta_c{\rho_l}^2 + 2\,\mu\,\beta_c\rho_l\sigma_l + 2\,\mu\,\beta_c\rho_l\tau_l + \mu\,\beta_c{\sigma_l}^2 + 2\,\mu\,\beta_c\sigma_l\tau_l + \mu\,\beta_c{\tau_l}^2 + \mu\,\beta_l{\delta_l}^2 + \mu\,\beta_l\delta_l\rho_l + \mu\,\beta_l\delta_l\sigma_l + \mu\,\beta_l\delta_l\tau_l + \beta_c\delta_l\rho_l\sigma_l + \beta_c\delta_l{\sigma_l}^2 + \beta_c\delta_l\sigma_l\tau_l + \beta_l{\delta_l}^2\sigma_l\big)\,,\ 0\,,$
$-\big(\mu\,\delta_l\,(\mu^2 - \mu\,\beta_c + \mu\,\delta_l + \mu\,\rho_l + \mu\,\sigma_l + \mu\,\tau_l - \beta_c\rho_l - \beta_c\sigma_l - \beta_c\tau_l - \beta_l\delta_l + \delta_l\sigma_l + \delta_l\tau_l)\big)/$
$\big(\mu^3\beta_c + \mu^2\beta_c\delta_l + 2\,\mu^2\beta_c\rho_l + 2\,\mu^2\beta_c\sigma_l + 2\,\mu^2\beta_c\tau_l + \mu^2\beta_l\delta_l + \mu\,\beta_c\delta_l\rho_l + 2\,\mu\,\beta_c\delta_l\sigma_l + \mu\,\beta_c\delta_l\tau_l + \mu\,\beta_c{\rho_l}^2 + 2\,\mu\,\beta_c\rho_l\sigma_l + 2\,\mu\,\beta_c\rho_l\tau_l + \mu\,\beta_c{\sigma_l}^2 + 2\,\mu\,\beta_c\sigma_l\tau_l + \mu\,\beta_c{\tau_l}^2 + \mu\,\beta_l{\delta_l}^2 + \mu\,\beta_l\delta_l\rho_l + \mu\,\beta_l\delta_l\sigma_l + \mu\,\beta_l\delta_l\tau_l + \beta_c\delta_l\rho_l\sigma_l + \beta_c\delta_l{\sigma_l}^2 + \beta_c\delta_l\sigma_l\tau_l + \beta_l{\delta_l}^2\sigma_l\big)\,,\ 0$
$,\ -\big(\sigma_l\mu\,\delta_l\,(\mu^2 - \mu\,\beta_c + \mu\,\delta_l + \mu\,\rho_l + \mu\,\sigma_l + \mu\,\tau_l - \beta_c\rho_l - \beta_c\sigma_l - \beta_c\tau_l - \beta_l\delta_l + \delta_l\sigma_l + \delta_l\tau_l)\big)/$
$\big((\mu^3\beta_c + \mu^2\beta_c\delta_l + 2\,\mu^2\beta_c\rho_l + 2\,\mu^2\beta_c\sigma_l + 2\,\mu^2\beta_c\tau_l + \mu^2\beta_l\delta_l + \mu\,\beta_c\delta_l\rho_l + 2\,\mu\,\beta_c\delta_l\sigma_l + \mu\,\beta_c\delta_l\tau_l + \mu\,\beta_c{\rho_l}^2 + 2\,\mu\,\beta_c\rho_l\sigma_l + 2\,\mu\,\beta_c\rho_l\tau_l + \mu\,\beta_c{\sigma_l}^2 + 2\,\mu\,\beta_c\sigma_l\tau_l + \mu\,\beta_c{\tau_l}^2 + \mu\,\beta_l{\delta_l}^2 + \mu\,\beta_l\delta_l\rho_l + \mu\,\beta_l\delta_l\sigma_l + \mu\,\beta_l\delta_l\tau_l + \beta_c\delta_l\rho_l\sigma_l + \beta_c\delta_l{\sigma_l}^2 + \beta_c\delta_l\sigma_l\tau_l + \beta_l{\delta_l}^2\sigma_l)$
$(\mu + \chi)\big)\ ,\ 0)$

6.3 The original form of the Jacobian matrix in section (3.3).

$$\begin{bmatrix} -\beta_c C_l - \beta_l I_l - \mu & -\beta_c S & -\beta_c S & -\beta_l S + \tau_l & -S\beta_h + \tau_h & 0 & 0 \\ \beta_c C_l + I_l\,\beta_l & \beta_c S - \mu - \delta_l & \upsilon & S\,\beta_l + \rho_l & 0 & 0 & 0 \\ C_h\,\beta_c + I_h\,\beta_h & 0 & \beta_c S - \mu - \upsilon - \delta_h & 0 & S\,\beta_h + \rho_h & 0 & 0 \\ 0 & \delta_l & 0 & -\mu - \rho_l - \sigma_l - \tau_l & \upsilon & 0 & 0 \\ 0 & 0 & \delta_h & 0 & -\mu - \upsilon - \rho_h - \sigma_h - \tau_h & 0 & 0 \\ 0 & 0 & 0 & \sigma_l & 0 & -\mu - \chi & 0 \\ 0 & 0 & 0 & 0 & \sigma_h & 0 & -\mu - \chi \end{bmatrix}$$