Compartmental Modelling of Diseases and the Basic Reproduction Number

An Analysis of Cellular Disease Dynamics of a Hepatitis B Infection

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Abstract

The insight we gain from epidemiology provides an outlet to numerous possibilities of control measures in this seemingly perennial struggle we endure against the effects of disease. This report outlines the theory of compartmental disease modelling, and it's use in intervention measures against disease. Specifically, the focus is on the Basic Reproduction Number, $\mathcal{R}_0$, which simply put is a threshold of the initial severity of a disease. Several qualitative aspects of the basic reproduction number are discussed, and a summary of the Next Generation Matrix Method to obtain $\mathcal{R}_0$ is given.

We then propose an original compartmental model for the viral dynamics among the hepatocyte population under a Hepatitis B virus (HBV) infection. Generalizations of the model are made, with further development of the model with explicit time delay. Expressions for $\mathcal{R}_0$ are sought for each model, which incorporates the study of systems of differential equations, delay differential equations, the Next Generation Matrix method, and the stability analysis of steady states.

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Chapter 1

Introduction

Infectious diseases have invariably accompanied human history, and have frequently dominated the main stage of its course. Within the last hundred years, five major flu pandemics have affected the world, including the infamous Spanish influenza which took between an estimated 50-100 million lives suggested by a 2002 note on the global mortality of the influenza [5]. Furthermore, despite research and development of vaccines and cures, numerous infectious diseases nevertheless affect our lives without discrimination. Hence the importance of the study of such capable entities naturally arise to the 'potentially affected'.

There are in general three things that we, as the 'potentially affected', do upon the strike of a disease. Those are to treat the diseased, record the cost such as human lives lost, and to predict and prevent future cases. The process of formulating a mathematical model of disease transmission arises from the phenomenological results of the first two courses of action. Then the model can be analysed both numerically and analytically to develop rational strategies against future encounters with an epidemic.

We start by observing that the 'potentially affected' population can be categorised into the discrete state of *affected* and *not affected* by the disease. Undeniably, this is a subjective and ambiguous process, thus it is imperative that we acknowledge the differences between different model definitions and assumptions.

1.1 Analysis of Compartmental Disease Dynamics

As introduced above, we consider a population composed of individuals, each of whom are considered to be a single variable assuming one of many discrete states. Therefore, we can classify the population into sub-populations or *compartments* defined by the discrete states that the individuals take.

1.1.1 Setting the Scene

The discrete states are given by the progression of a disease on an individual. The simplest classification, and what becomes the basis of all the other models is a dichotomy of the population into the compartments: *Susceptible*(S) and *Infected*(I). Some other prominently featuring compartments include, *Exposed*(E), and *Recovered/Removed*(R). The 'Exposed' compartment appears with diseases that have incubation periods or latency periods (Average incubation periods of some well-known diseases are : Common Cold - 24 to 72 hours, Measles - 10 to 12 days, Creutzfeldt-Jakob disease - 11 to 12 years, etc.), and the 'Recovered/Removed' compartment is associated with acquired immunity to the disease or death by the disease. Depending on the model formulation, the population can be divided into numerous compartments, which may include additional compartments such as quarantined, or those undergoing treatment.

In the partitioned system, let us distinguish between the 'disease' class and the 'non-disease' class. As an example, consider a population consisting of 4 compartments: S, E, I, R. Then, we can say that the E and I compartments are in the disease class, and S and R in the 'non-disease' class. For a general population with $k = n + m$ compartments, where n denotes the number of compartments in the disease class and m the number of compartments in the non-disease class, let us denote the ith compartment of each class as follows:

$$\begin{aligned} x_i &= i\text{th disease compartment, where } i \in \{1, 2, \dots, n\} \\ y_i &= i\text{th non-disease compartment, where } i \in \{1, 2, \dots, m\} \end{aligned}$$

It is intuitive that in a given population, there are interactions between each compartment in x_i and y_i, governing their respective inflow and outflow. Embedded in the mechanism of an individual transiting through the discrete states, by those interactions, is the dynamics of disease transmission and progression. Therefore, the mathematical modelling of the *rate* of increase and decrease of the compartments gives an overarching view of the governing dynamics between the sub-populations.

Naturally, a system of differential equations can arise from the concept above, formulating the mathematical model for disease transmission. The rate of change of compartment size is dependent on several factors such as the rate of infection and rate of recovery. Hence the system of differential equations are formed with these factors which affect the rate of change of compartment size. The ith differential equation has the form:

$$\frac{d}{dt}(i\text{th Compartment size}) = \text{Inflow rates} - \text{Outflow rates}$$

Generally, the system of differential equations can be expressed with the following 4 components.

$\mathcal{I}_i(x,y)$: Rate of natural influx into the ith compartment independent of the disease progression. e.g. Birth rate, Immigration rate

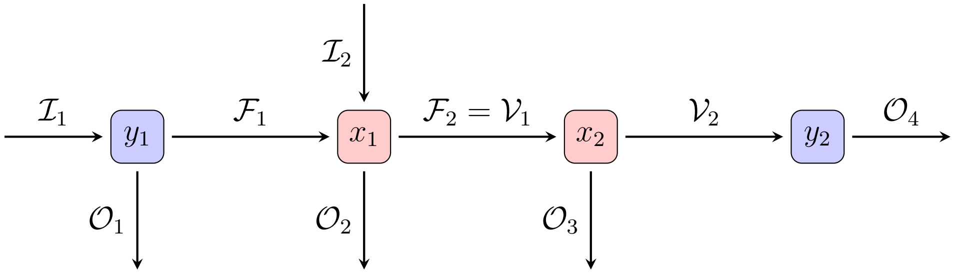
$\mathcal{F}_i(x,y)$: Rate of increase of the ith disease compartment due to infection, and disease progression.

$\mathcal{V}_i(x,y)$: Rate of decrease of the ith disease compartment due to disease progression, death by disease, and recovery from disease.

$\mathcal{O}_i(x,y)$: Rate of natural outflux to the ith compartment independent of the disease progression e.g. Death rate, Immigration rate

Such notation can be seen clearly with the following examples,

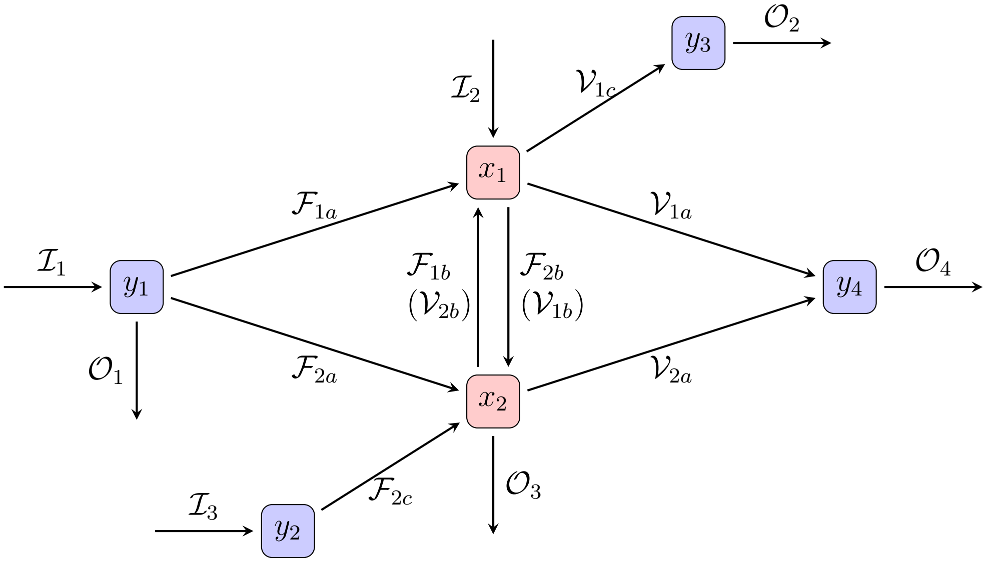
1. A Simple Linearly Progressing Disease:



The above diagram of a disease system is formalized as the following:

$$\begin{aligned}
\frac{dy_1}{dt} &= \mathcal{I}_1 - \mathcal{F}_1 - \mathcal{O}_1 \\
\frac{dx_1}{dt} &= \mathcal{I}_2 + \mathcal{F}_1 - \mathcal{V}_1 - \mathcal{O}_2 \\
\frac{dx_2}{dt} &= \mathcal{F}_2 - \mathcal{V}_2 - \mathcal{O}_3 \\
\frac{dy_2}{dt} &= \mathcal{V}_2 + \mathcal{O}_4
\end{aligned}$$

2. A Complicated Example :



The above diagram of a disease system is formalised as the following:

$$\frac{dy_1}{dt} = \mathcal{I}_1 - \mathcal{F}_{1a} - \mathcal{F}_{2a} - \mathcal{O}_1$$
$$\frac{dy_2}{dt} = \mathcal{I}_3 - \mathcal{F}_{2c}$$
$$\frac{dx_1}{dt} = \mathcal{I}_2 + \mathcal{F}_1 - \mathcal{V}_1, \quad \text{Where } \mathcal{F}_1 = \mathcal{F}_{1a} + \mathcal{F}_{1b} \text{ and } \mathcal{V}_1 = \mathcal{V}_{1a} + \mathcal{V}_{1b} + \mathcal{V}_{1c}$$
$$\frac{dx_2}{dt} = \mathcal{F}_2 - \mathcal{V}_2 - \mathcal{O}_3, \quad \text{Where } \mathcal{F}_2 = \mathcal{F}_{2a} + \mathcal{F}_{2b} + \mathcal{F}_{2c} \text{ and } \mathcal{V}_2 = \mathcal{V}_{2a} + \mathcal{V}_{2b}$$
$$\frac{dy_3}{dt} = \mathcal{V}_{1c} + \mathcal{O}_2$$
$$\frac{dy_4}{dt} = \mathcal{V}_{1a} + \mathcal{V}_{2a} - \mathcal{O}_4$$

As you can see from the examples above, $\mathcal{F}$ and $\mathcal{V}$ are closed within the proposed systems, as they cancel out as a whole. The eventual net rate of increase/decrease of the system is only dependent on $\mathcal{I}$ and $\mathcal{O}$ which suggests that the system reduces to the standard population dynamics, meaning, for example, the dynamics of birth, death and migration, when the disease is not considered. Therefore, arguably the disease dynamics of the whole system can be encapsulated in the following set of differential equations, which is a simplification of the decoupling of these types of systems (at a steady state).

$$x_i' = \mathcal{F}_i(x, y) - \mathcal{V}_i(x, y) \quad i = 1, \ldots, n$$

1.1.2 Key Concepts

Before moving on to analysing the differential equations, let us first outline the key objectives of such analysis in current studies of mathematical epidemiology.

- To understand the factors involved in the transmission of a disease
- To find a threshold that can present us with an idea of the severity of an epidemic
- To solve the models of epidemiology both qualitatively and quantitatively to seek steady states, and to predict long-term behaviour
- To deduce possible intervention strategies based on the above results to reduce disease spread

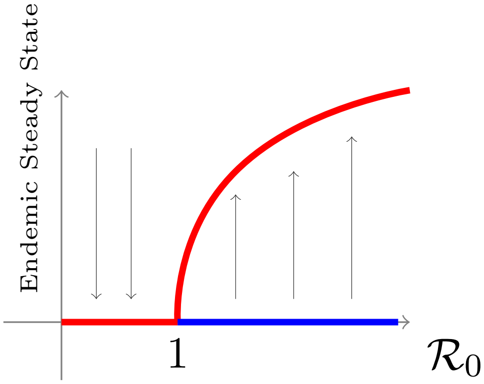
These aims give rise to the need for certain important mathematical concepts, and one of the most important of all is known as the **Basic Reproduction Number**, $\mathcal{R}_0$. Simply put, it is a threshold with the property that if $\mathcal{R}_0 < 1$ then the disease dies out, and if $\mathcal{R}_0 > 1$ then it becomes an epidemic. $\mathcal{R}_0$ is acquired through the study of the stability of steady states of the disease dynamics. There are in general two important types of steady states that arise from the systems of differential equations.

The first is the 'Disease-Free Equilibrium', which is the steady state where all 'disease variables' are zero. For example, the disease free equilibrium of a SEIR model can be represented as $(S, 0, 0, R)$. This can be considered in two scenarios, the first being the initial starting point where the disease is about to spread, and the latter is when the epidemic has passed through, and there are no more infected individuals.

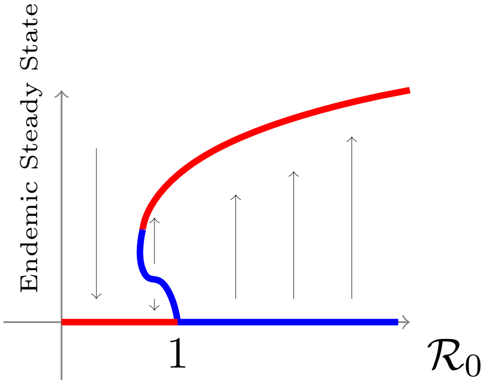
The second steady state is the 'Endemic Steady State', where all compartmental values are non-zero. For example, an endemic equilibrium of a SEIR model will look like (S^*, E^*, I^*, R^*) where $S^*, E^*, I^*, R^* > 0$.

The value of the basic reproduction number can indicate the potential for a newly introduced disease to spread in the given population, and can thus be related to the stability of the disease-free equilibrium. If the disease-free equilibrium is stable then a small introduction of disease will die out and the system will go back to the disease-free equilibrium. We only expect the system to evolve to the endemic equilibrium in situations where the disease-free equilibrium is unstable. The stability of the disease-free equilibrium is usually given by a condition imposed on an expression made of the model parameters, and therefore it suits our definition as a basic reproduction number. It can be thought of as a critical point up to where the system will return to the initial stable disease-free equilibrium when a small perturbation has been applied (whereby small perturbation we usually mean the introduction of a small number of infectious individuals).

Already from the attempt of defining the basic reproduction number, we can see that it cannot have a rigorous definition among all models and all diseases. The 'critical point' is given by the analysis of the model at the initial disease-free equilibrium, and does not completely guarantee the global stability of the steady state. Furthermore, there are cases where a disease-free equilibrium does not exist, or is unstable. At most the basic reproduction number signifies that if $\mathcal{R}_0 < 1$, the disease free equilibrium is *locally* stable. In some cases, such as when an endemic equilibrium coexists with a disease free equilibrium, bifurcation can happen in the backward direction, and thus another condition for global stability might be required (see diagram below).



Forward Bifurcation



Backward Bifurcation

The above are the bifurcation curves at $\mathcal{R}_0 = 1$ for the forward and backward bifurcation cases. The plotted curves represent the asymptotic steady state, with the blue denoting an unstable equilibrium, and red denoting a stable equilibrium, as also shown by the arrows. As seen from the graphs, for the forward bifurcation case, $\mathcal{R}_0 < 1$ implies that the disease free state (when endemic steady state $= 0$), is globally stable, but in the backward bifurcation case, a value for $\mathcal{R}_0$ smaller than one, doesn't necessarily imply global stability of the disease-free equilibrium. In backward bifurcation cases, an endemic steady state can exist even with $\mathcal{R}_0 < 1$. A more detailed discussion on $\mathcal{R}_0$ and the local and global stability of the disease-free equilibrium is given in [3].

With these caveats in understanding the basic reproduction number $\mathcal{R}_0$, the use of $\mathcal{R}_0$ is highlighted more so in the analysis of the model itself rather than as a comparative metric between diseases. In fact, most of the key objectives outlined previously are satisfied in the attempt to obtain such a number, and in the examination of it. Many of the factors that are involved in the transmission of the disease are embedded in the model parameters used to form $\mathcal{R}_0$, and thus we can deduce real strategies about those parameters to reduce disease spread (i.e. make $\mathcal{R}_0$ smaller). Furthermore, we have found a strong candidate for a threshold which defines the severity of an epidemic and the method to obtain that threshold is the steady state analysis of the system and stability analysis of the steady states. Thus, it is clear to see that despite its limits, $\mathcal{R}_0$ by its nature provides compelling information to the epidemiologist.

Chapter 2

Computing the Basic Reproduction Number, $\mathcal{R}_0$

As seen in the previous chapter, the calculation of the basic reproduction number is subjective to the model and the disease characteristics. Presented here is the general principle of acquiring the expression for the basic reproduction number, $\mathcal{R}_0$.

2.1 The Kermack-McKendrick Model

Let us now consider a simple model presented by Kermack and McKendrick [6], discussing a SIR (Susceptible (S), Infectious (I), Removed (R)) model in a closed population. The system of differential equations is as follows:

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI\\ \frac{dI}{dt} &= \beta SI - \gamma I\\ \frac{dR}{dt} &= \gamma I\end{aligned}$$

As reviewed earlier, the disease dynamics can be simplified to the set of differential equations of the variables in the diseased class for the study of initial disease dynamics about the disease-free equilibrium. If one is interested in the initial dynamics of a small introduction of infectious individuals to a susceptible population, then, for this particularly simple system, one can determine the initial growth or decay of $I(t)$ from

$$\frac{dI}{dt} = \beta S(0)I - \gamma I.$$

Usually the right hand sides of the differential equations for the disease compartments are linearised close to a disease-free equilibrium. The Kermack-McKendrick model does not have a single disease-free equilibrium, it has a whole line of equilibria with $I = 0$, and so we simply evaluate S at $S(0)$, rather than at a steady state value.

The philosophy behind the basic reproduction number is to seek a quantity which describes the initial 'invasive severity' of a disease to a population. Thus suppose a small number of infected individuals $I(0)$ are introduced to the completely susceptible population. Then the differential equation near the beginning of the dynamics as noted above approximates to:

$$\frac{dI}{dt} = (\beta S(0) - \gamma)I$$

This can be solved easily for I with respect to t and given the initial introduction of the infected individuals $I(0)$, the solution is as follows:

$$I(t) = I(0)\ e^{(\beta S(0) - \gamma)t}$$

As we have an explicit formula describing the initial behaviour of the infected class, the 'invasive severity' of the disease can be said to be analogous to whether the I compartment will grow or not. From the exponential function, it is clear to see that $I(t)$ will grow if $\beta S(0) > \gamma$ and $I(t)$ will decay if $\beta S(0) < \gamma$. Here it is already clear to see that we can attain a form of $\mathcal{R}_0$ based on the definition that $\mathcal{R}_0 < 1$ means the disease will die out and otherwise continue to spread. Rearranging the ineqaulities above, we find that the following quantity satisfies the conditions stated above.

$$\mathcal{R}_0 = \frac{\beta S(0)}{\gamma}$$

We see that in the above case, the basic reproduction number depends on the initial value $S(0)$ for the variable S. This simple example illustrates the philosophy behind computing the basic reproduction number. To elaborate, the process is to, if possible, approximate or linearize about the disease free equilibrium (or the initial state), then to study the resulting linearized system to find the condition for the disease free equilibrium to be stable (or any notion that can be used to suggest the 'invasive severity').

The interpretation of such a process is subjective, and so there are numerous methods to calculate the basic reproduction number. It is also important to note that sometimes attaining a quantity that can embody the concept of a basic reproduction number might be impossible to find. Nonetheless, in the next subsection a method that attempts to standardize the process first introduced by Diekmann, Heesterbeek, and Metz [1] is summarized.

2.2 The Next Generation Matrix Method

The mathematical background for the next generation matrix method for calculating the basic reproduction number can be found in the books [2] and [3]. The method itself captures the changes in states of individuals in compartments per generation given by a 'next generation' matrix. It is from this matrix that one seeks a threshold that resembles the basic reproduction number. We investigate parameters involved in the matrix such that successive iterations of applying the 'next generation matrix' to the original distribution of individuals will result in a convergence to a stable distribution, in our case the disease free equilibrium.

2.2.1 The Idea

This notion can be condensed into a difference equation.

$$\phi_{t+1} = K\phi_t$$

where ϕ_t is a vector representing the distribution of states at generation t, and K represents the so called next generation matrix. The solution of this difference equation is simply:

$$\phi_t = K^t\phi_0$$

K^t represents t successive matrix multiplication of K and, ϕ_0 is an initial distribution. Here we can represent the initial distribution as a linear combination of the independent eigenvectors of K, assuming they are linearly independent, which will form a basis. Thus ϕ_0 can be written as:

$$\phi_0 = c_1\vec{x_1} + c_2\vec{x_2} + \cdots + c_n\vec{x_n}$$

where the c_i are constants and the $\vec{x_i}$ are the eigenvectors of K. Multiplying ϕ_0 by K would imply :

$$K\phi_0 = c_1\lambda_1\vec{x_1} + c_2\lambda_2\vec{x_2} + \cdots + c_n\lambda_n\vec{x_n}$$

by the definition of eigenvectors and eigenvalues, $K\vec{x_i} = \lambda_i K$. Therefore, it is possible to 'explicitly' write the solution to the difference equation as:

$$\phi_t = K^t\phi_0 = c_1\lambda_1^t\vec{x_1} + c_2\lambda_2^t\vec{x_2} + \cdots + c_n\lambda_n^t\vec{x_n}$$

Assuming that K is an irreducible non-negative real matrix, then by the Perron-Frobenius theorem, K has a unique strictly dominant real eigenvalue which we will denote λ_d. Then, it is clear that we can form a threshold which determines whether successive generations will mean an increase of size of the diseased compartments or not. If $\lambda_d = 1$, then the solution becomes:

$$\phi_t = K^t\phi_0 = c_d\vec{x_d} + \text{terms that tend to 0 as } t \to \infty$$

The implication is that an endemic steady state is found when $\lambda_d = 1$, and when $\lambda < 1$ the solution converges to 0 (disease-free steady state), and diverges (epidemic) otherwise. Thus, if we can formulate our next generation matrix K such that it reflects the linearisation of the disease compartments at the disease-free equilibrium, then we are able to define the spectral radius of K, $\rho(K)$ as the basic reproduction number $\mathcal{R}_0$, for the system.

2.2.2 Formulating the Next Generation Matrix

As mentioned before, the basic reproduction number is a measure of the severity of the initial disease progression, thus the evaluation is performed at the linearised disease-free steady state representing the moment the disease enters a population. The elements of the next generation matrix are generational changes that a compartment causes in another compartment. Considering only the reduced system of disease class compartments, this 'generational change' for the given initialisation above can be identified with the expected number of infections produced per newly introduced infected individuals to the system. Successive applications of the generational changes to the initial distribution of the disease compartments shows the progression of the increase in disease compartments. Additionally, as shown before, the dominant eigenvalue of the next generation matrix governs the long term growth of the disease compartment.

First recall that the initial disease dynamics of a system are encapsulated in the set of differential equations of disease compartments as they are decoupled from the remaining equations when linearised at the disease-free equilibrium:

$$x_i' = \mathcal{F}_i(x, y) - \mathcal{V}_i(x, y) \quad i = 1, \dots, n, \text{ with}$$

$\mathcal{F}_i(x, y)$: Rate of increase of the ith disease compartment due to infection only.
$\mathcal{V}_i(x, y)$: Rate of decrease of the ith disease compartment due to disease progression, death by disease, and recovery from disease.

Linearising these equations about the disease free equilibrium $(0, y_0)$ and writing in matrix form (per individual in compartment) results in:

$$x' = (F - V)x, \quad \text{where} \quad F_{ij} = \frac{\partial \mathcal{F}_i}{\partial x_j}(0, y_0) \quad and \quad V_{ij} = \frac{\partial \mathcal{V}_i}{\partial x_j}(0, y_0)$$

As the differential equations are composed of rates of transmission/ transition, one can naturally think to calculate the expected number of infections using the rates. With simple dimensional analysis, it is trivial to see that the expected number of infections can be given by the product of the rate of infection and the expected duration for which the infection can occur. From the matrix representation of the system, the infection rate is already given by F, where it's elements F_{ij}, are defined to be the rate of increase in the ith disease compartment due to an infection by an individual in compartment j. On the other hand, retrieving the expected duration of infectiousness is not as easy. We can think of the expected duration in compartment i as :

$$\sum_{\tau=0}^{\infty} (\tau \cdot Pr(\tau, i))$$

Where τ stands for a unit duration of time, and Pr denotes the probability that the individual is in the compartment for τ amounts of time. A key note would be that the expected time that an infected individual stays in a compartment is independent of new infections but only dependent on state transitions and death.

Here Pr can be evaluated by noticing

$$\frac{dPr}{d\tau} = \text{rate of change of probability over unit time interval}$$

where given the note above, the rate of change of probability over unit time interval can be given as $(C - D)Pr$, the matrix C representing compartmental progresssion and D means deaths. Notice that the matrix $-V$ from the linearized matrix equation above is exactly the quantity being described, where the elements of $-V_{ij}$ are the rate of change in the compartment i by an individual's non-infective action (death, progression) in compartment j. Thus with initial condition (disease-free equilibrium, all disease variables are 0) $x(0) = x_0$,

$$\frac{dPr}{d\tau} = -V \; Pr$$

This results in the solution :

$$Pr(\tau, i) = e^{-V\tau} x_0$$

Connecting back to retreiving the expected duration, the continuous form of the summation defined above would be

$$\int_0^\infty e^{-V\tau} x_0 \; d\tau = V^{-1} x_0$$

Consequently, the next generation matrix can now be formulated using the given system as follows:

$$K = (\text{expected rate of infection})(\text{expected duration}) \; = \; FV^{-1}$$

2.2.3 A Clarifying Example, the SEIR Model

A demonstration of the method described above can be seen though this example of the SEIR model.

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \beta SI - \mu S \\
\frac{dE}{dt} &= \beta SI - (\mu + \kappa)E \\
\frac{dI}{dt} &= \kappa E - (\mu + \alpha)I \\
\frac{dR}{dt} &= \alpha I - \mu R
\end{aligned}$$

From the system of differential equations, the equations describing the disease dynamics are extracted.

$$\begin{aligned}\frac{dE}{dt} &= \beta SI - (\mu+\kappa)E \\ \frac{dI}{dt} &= \kappa E - (\mu+\alpha)I\end{aligned}$$

With this extracted system, we can define the $\mathcal{F}$ and $\mathcal{V}$ for the SEIR model, where

$$\mathcal{F} = \begin{pmatrix} \beta SI \\ 0 \end{pmatrix}, \qquad \mathcal{V} = \begin{pmatrix} (\mu+\kappa)E \\ (\mu+\alpha)I - \kappa E \end{pmatrix}$$

Thus, the Jacobian matrix equivalent F and V at the linearized disease free equilibrium are

$$F = \begin{pmatrix} 0 & \beta S_0 \\ 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \mu+\kappa & 0 \\ -\kappa & \mu+\alpha \end{pmatrix}$$

where $S_0 = \frac{\Pi}{\mu}$.

The next step would be to find K, the next generation matrix. By definition it is given by $K = FV^{-1}$ as shown above, thus

$$K = FV^{-1} = \begin{pmatrix} 0 & \beta S_0 \\ 0 & 0 \end{pmatrix} \frac{1}{(\mu+\kappa)(\mu+\alpha)} \begin{pmatrix} \mu+\alpha & 0 \\ \kappa & \mu+\kappa \end{pmatrix}$$

Therefore, the next generation matrix for the SEIR system is

$$K = \frac{1}{(\mu+\kappa)(\mu+\alpha)} \begin{pmatrix} \beta\kappa S_0 & \beta S_0(\mu+\kappa) \\ 0 & 0 \end{pmatrix}$$

Following the idea developed from the previous subsection that the dominant real eigenvalue determines the threshold which can be defined as the basic reproduction number, we find the spectral radius $\rho(K)$ of K.

$$\mathcal{R}_0 = \rho(K) = \max_{i=1,\ldots,n} |\lambda_i|$$

where λ_i denotes the eigenvalues of the matrix K.

The eigenvalues of the above matrix K are 0 and $\frac{\beta\kappa S_0}{(\mu+\kappa)(\mu+\alpha)}$. Hence the basic reproduction number for the given SEIR system can be given as:

$$\mathcal{R}_0 = \frac{\beta\kappa S_0}{(\mu+\kappa)(\mu+\alpha)}$$

This is a realistic basic reproduction number, as it makes epidemiological sense. $\mathcal{R}_0$ increases with β and Π (recall that $S_0 = \frac{\Pi}{\mu}$), which is natural as the more susceptible beings (Π) there are, the more likely an infection will happen, and the more frequent the contact (β) between susceptibles and infected, the more likely an epidemic will occur. On the other hand, the natural mortality rate (μ), and recovery rate (α) are inversely proportional to the basic reproduction number, as expected. It is through this type of analysis of the basic reproduction number that we can make relevant strategies to prevent and prepare for an epidemic. For simple models like this, there may not be many parameters to consider and there might not be a realistic parameter that we can control, but for more complicated and 'realistic' models, we can attempt to find intervention strategies to control the initial severity/progression of a disease. Sometimes $\mathcal{R}_0$ is highly sensitive to a parameter that cannot in practice be controlled by intervention measures such as μ which models natural death.

2.3 Delay Differential Equations

Delay differential equations capture the notion of an 'aftereffect' or a time-delay in a process. The derivative of a function is given in terms of $(t-\tau)$, indicating the delay with τ, in this report, always a constant. This is a useful tool for epidemiological modelling, as many involve time delays which can model latent periods, dormant stages, etc.

2.3.1 SEIR example

We can modify the SEIR example from before, to make it into a system of delay differential equations.

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \beta SI - \mu S \\
\frac{dE}{dt} &= \beta SI - \beta S(t-\tau)I(t-\tau)e^{-\mu\tau} - \mu E \\
\frac{dI}{dt} &= \beta S(t-\tau)I(t-\tau)e^{-\mu\tau} - (\mu+\alpha)I \\
\frac{dR}{dt} &= \alpha I - \mu R
\end{aligned}$$

As seen from the equations, this describes a definite time of τ spent in the 'Exposed' compartment before moving into the 'Infected' compartment. The exponential term indicates the natural death of individuals in the E compartment during the time delay period.

To deduce a basic reproduction number for this system, the convential next generation matrix method is ill-suited due to presence of the time delay. Instead, as introduced in the formulation of the basic reproduction number, a more direct approach of finding a stability threshold is required.

Linearising about the disease-free equilibrium $(S, E, I, R) = (\frac{\Pi}{\mu}, 0, 0, 0)$, by setting

$$\begin{aligned}
S(t) &= \frac{\Pi}{\mu} + \widetilde{S}(t) \\
E(t) &= 0 + \widetilde{E}(t) \\
I(t) &= 0 + \widetilde{I}(t) \\
R(t) &= 0 + \widetilde{R}(t)
\end{aligned}$$

where $\widetilde{S}, \widetilde{E}, \widetilde{I}, \widetilde{R}$ are small, we have the linearised system (ignoring products of small quantities):

$$\begin{aligned}
\frac{d\widetilde{S}}{dt} &= -\beta\frac{\Pi}{\mu}\widetilde{I}(t) - \mu\widetilde{S}(t) \\
\frac{d\widetilde{E}}{dt} &= \beta\frac{\Pi}{\mu}\widetilde{I}(t) - \beta\frac{\Pi}{\mu}\widetilde{I}(t-\tau)e^{-\mu\tau} - \mu\widetilde{E}(t) \\
\frac{d\widetilde{I}}{dt} &= \beta\frac{\Pi}{\mu}\widetilde{I}(t-\tau)e^{-\mu\tau} - (\mu+\alpha)\widetilde{I} \\
\frac{d\widetilde{R}}{dt} &= \alpha\widetilde{I} - \mu\widetilde{R}
\end{aligned}$$

The linearized $\widetilde{E}$ and $\widetilde{I}$ equations can be studied independently because, as a system of two equations, they only involve $\widetilde{E}$ and $\widetilde{I}$ (they form a decoupled subsystem).

The decoupled subsystem determining $\widetilde{E}$ and $\widetilde{I}$ is linear, thus trying a solution of the form

$$(\widetilde{E}(t), \widetilde{I}(t)) = (c_1, c_2)e^{\lambda t}$$

gives

$$\begin{aligned}
\lambda c_1 e^{\lambda t} &= \beta\frac{\Pi}{\mu}c_2 e^{\lambda t} - \beta\frac{\Pi}{\mu}c_2 e^{-\mu\tau}e^{\lambda(t-\tau)} - \mu c_1 e^{\lambda t} \\
\lambda c_2 e^{\lambda t} &= \beta\frac{\Pi}{\mu}c_2 e^{-\mu\tau}e^{\lambda(t-\tau)} - (\mu+\alpha)c_2 e^{\lambda t}
\end{aligned}$$

Cancelling the $e^{\lambda t}$ we arrive at

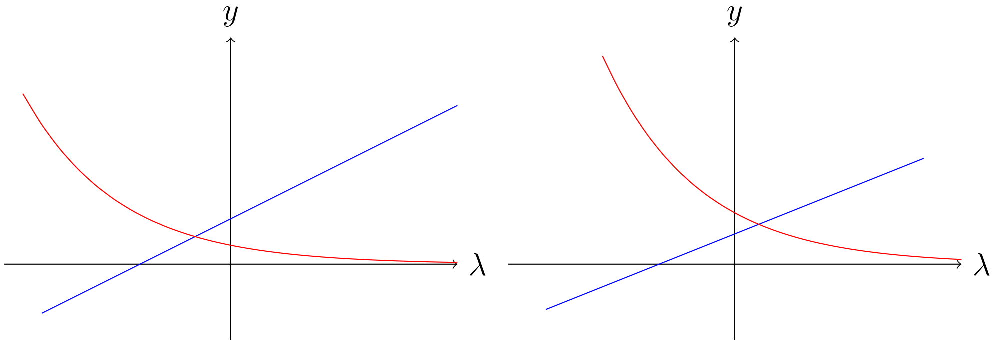
$$\begin{aligned}
\lambda c_1 e^{\lambda t} &= \left(\beta\frac{\Pi}{\mu} - \beta\frac{\Pi}{\mu}e^{-\mu\tau}e^{-\lambda\tau} - \mu\right)c_2 \\
\left(\lambda + \mu + \alpha - \beta\frac{\Pi}{\mu}e^{-\mu\tau}e^{-\lambda\tau}\right)c_2 &= 0
\end{aligned}$$

From the second equation we find a condition for a non-trivial solution. It requires that

$$\lambda + \mu + \alpha = \beta \frac{\Pi}{\mu} e^{-(\mu+\lambda)\tau}$$

This is the characteristic equation (to be solved for λ), but it cannot be solved for λ exactly, because it is a transcendental equation; not a polynomial. The stability of the disease-free steady state is guaranteed if the compartments E and I are converging to 0 as $t \to \infty$. Thus we require λ to be negative or complex with negative real part. We need to know under what conditions its roots all satisfy $Re(\lambda) < 0$. The trancendental equation will have infinitely many complex roots and finitely many real roots. In this case, there is actually only one real root. We determine graphically whether the real root is negative or positive. Plotting the graph of

$$y = \lambda + \mu + \alpha \text{ (blue)} \quad \text{and} \quad y = \beta \frac{\Pi}{\mu} e^{-(\lambda+\mu)\tau} \text{ (red)}$$



we have 2 cases, the left depicting the case where the real root is negative, and the right showing the real root to be positive. The graph shows that the only real root is negative if

$$\Big[\lambda + \mu + \alpha\Big]_{\lambda=0} \quad > \quad \Big[\beta \frac{\Pi}{\mu} e^{-(\lambda+\mu)\tau}\Big]_{\lambda=0}$$

$$\iff \mu + \alpha \quad > \quad \beta \frac{\Pi}{\mu} e^{-\mu\tau}$$

This implies that $\mathcal{R}_0 < 1$ where

$$\mathcal{R}_0 = \frac{\beta \Pi e^{-\mu\tau}}{\mu(\mu+\alpha)} = \frac{\beta S_0 e^{-\mu\tau}}{\mu + \alpha}$$

Therefore, we have a basic reproduction number involving the explicit time delay τ. Notice how the SEIR model with and without the delay are two approaches to model latency. The comparison between the basic reproduction number of the two models gives insight into how latency is modelled differently.

Recall the SEIR model without the delay

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \beta SI - \mu S \\
\frac{dE}{dt} &= \beta SI - (\mu + \kappa)E \\
\frac{dI}{dt} &= \kappa E - (\mu + \alpha)I \\
\frac{dR}{dt} &= \alpha I - \mu R
\end{aligned}$$

The basic reproduction number for this model is derived in the previous subsection as

$$\mathcal{R}_0 = \frac{\beta S_0}{\mu + \alpha}\frac{\kappa}{\mu + \kappa}$$

The difference between the two basic reproduction numbers is that $e^{-\mu\tau}$ gets replaced by $\frac{\kappa}{\mu+\kappa}$. In one model, τ is the latency (the same for every individual), and the other model we only take the mean latency time $\frac{1}{\kappa}$.

Obviously $e^{-\tau\mu}$ is not equal to $\frac{\kappa}{\mu+\kappa}$, but note that

$$e^{-\mu\tau} = \frac{1}{e^{\mu\tau}} = \frac{1}{1 + \mu\tau + \frac{\mu^2\tau^2}{2!} + \cdots} \simeq \frac{1}{1 + \mu\tau}$$

if the latency time τ is small.

Then we can say that

$$\frac{1}{1 + \mu\tau} = \frac{\kappa}{\mu + \kappa}$$

provied $\tau = \frac{1}{\kappa}$. This makes sense because we have already noted that in one model the latency time is τ while in the other the mean latency time is $\frac{1}{\kappa}$.

Chapter 3

Dynamics of Hepatitis B

In this chapter we apply the knowledge and methodologies of previous chapters to a real life example, Hepatitis B. We propose and study systems with and without time delays, analysing their differences, and deriving a basic reproduction number for each model.

The models proposed in this chapter are my own original work and do not come from published literature.

3.1 Hepatitis B

Hepatitis B is a general liver infection of the hepatitis B DNA virus, affecting the hepatocytes. The infection can either result in a self-limiting acute infection or a persisting chronic infection, and it is easily distinguishable via the different serology (a presence of the IgM anti-HBc antibody indicates an acute infection) of the two. The World Health Organisation estimates that 257 million people live with a hepatitis B infection. This is about 8 times more than the estimated number of people living with HIV, asserting the fact that hepatitis B creates a huge burden on society and the medical field. Its prevalence and its serious yet overlooked impact on the world community gives rise to the urgency and necessity to study and research its properties with the ultimate goal of eradication.

Transmitted through the contact of bodily fluids, most infections of hepatitis are asymptomatic except for a mild flu-like symptom during acute infections. The real concern lies with the chronic infection, which is associated with many secondary complications such as cirrhosis and hepatocellular carcinoma (HCC) after a long period of liver damage. These are serious complications which often decrease the quality of life and the expected life span of the patients. The chronic infection affects the majority (90%) of people with a prenatal infection, and the risk of the infection going chronic decreases with age (less than 5% when infectd as an adult).

The clinical progression of an acute hepatitis B infection is as follows:
Once infected, there are three pathways.

- Recovery
- Evolution into Chronic Hepatitis - spread of virus through the entire hepatocyte population, without effective immune response.
- Fulminant Hepatitis - an unlikely event where a large portion of the hepatocyte population is destroyed, resulting in liver failure and death.

In the event that the infection persists, i.e a chronic infection, the course of the disease is hypothesised to follow a certain stage structure, not completely mutually exclusive to each other.

1. Immunotolerant phase : Unresponsive immune system to the viral infection, high viral titre, low inflammation.
2. Immune clearance phase : Cytotoxic T cells (CTLs) target and destroy infected cells resulting in a drop in viral titre, at the expense of increased inflammation.
3. Inactive phase : Virtually non-existent replication of virus.
4. Reactivation phase : Increase in viral activity and inflammation.
5. Cirrhosis and HCC : Mutation of the hepatocyte into a fibrous cell and/or a cancer cell. Incidence is higher with age and viral titre.

The summary of the molecular biology of a hepatitis B virus infection is covered in a concise manner by Seeger and Mason [8]. Addtionally, the World Health Organisation and the Center for Disease Control has professional summaries which aided in the foundation of certain assumptions made during the formulation of the following model.

3.2 A Cellular Model of the Disease Progression of a Hepatitis B infection

In accordance to the knowledge of the disease progression on the cell population level, a model with 6 cell population compartments is proposed below, which aims to describe the dynamics in the previous section. A brief introduction of the six compartments are below:

1. **Healthy Hepatocytes** (H) : This is the compartment equivalent to the Susceptible class.

2. **Exposed (E)** : Cells that are exposed to the Hepatitis B virus, yet due to the time required to start replication, are currently not replicating yet
3. **Infectious but under Immune Tolerance (I_{tol})** : These are cells that are infected with the virus, replicating, yet do not receive immune pressure from the CTLs in a natural phenomenon called Immune Tolerance. The ‘tol’ stands for ‘tolerant’, to describe the immune tolerant cells.
4. **Infectious and inducing Immune Response (I_{vul})** : These are cells that are infected with the virus and replicating the virus, which are receiving immune pressure and being killed by CTLs. The ‘vul’ stands for ‘vulnerable’, as to say that the cells are vulnerable to immune attacks.
5. **HBV resistant and Normal looking cells (H_r)** : After a few generations of HBV infection, cells will evolve into HBV resistant cells from the Immune pressure received by CTLs which keeps killing them. Once HBV resistant, it will not replicate the virus, yet it has a chance to either undergo fibrosis or carcinoma.
6. **Free Virions/Virus Population in Plasma (V)** : Free virions are produced by infected cells which replicate the virus, and the virions will only be ‘naturally’ removed (through lymphatic actions etc) if no treatment is given.

3.3 Model without Delay

The first model presented here is without time delay, and a system of five differential equations is presented here, with a description of the parameters:

$$\frac{dH}{dt} = \Pi - (\beta_1 + \beta_2)VH + c_1 I_{\text{tol}} + c_2 I_{\text{vul}} - \mu H$$

$$\frac{dI_{\text{tol}}}{dt} = \beta_1 VH - (\sigma + c_1 + \mu + f(d))I_{\text{tol}}$$

$$\frac{dI_{\text{vul}}}{dt} = \beta_2 VH + \sigma I_{\text{tol}} - (c_2 + d + \mu)I_{\text{vul}}$$

$$\frac{dH_r}{dt} = f(d)I_{\text{tol}} - \mu H_r - \delta V H_r$$

$$\frac{dV}{dt} = k(I_{\text{tol}} + I_{\text{vul}}) - \mu_v V$$

Π	The cell regeneration/birth rate, here the assumption is that the cell always regenerates into a healthy cell
$(\beta_1 + \beta_2)$	Incidence ratio of infection. We are under the assumption of a constant liver size/constant starting size.
$c_1,\ c_2$	The cure rate from the I_{tol}, and I_{vul} compartment respectively, simply assumed to be a mass action incidence.
$\mu,\ \mu_v$	Cell natural death rate, and the natural death rate of viruses. This is assumed to be equal for all cells regardless of their compartment.
$\beta_1,\ \beta_2$	The transmission ratio to the infected compartments, I_{tol}, and I_{vul} respectively.
σ	Transfer rate from the I_{tol} to the I_{vul} compartment.
d	Death rate of cells in the I_{vul} compartment, due to cytotoxic activity (by immune response) etc.
$f(d)$	Evolution rate into a HBV resistant cell which are susceptible to fibrosis/carcinoma
δ	Rate of fibrosis/carcinoma of HBV resistant cells
k	Rate of virion replication

Note that this model is not exclusive to Hepatitis B, but can be applicable to any infections that undergo a similar progression.

3.3.1 Explanation of the model

As noted from the molecular biology of a Hepatitis B infection, the compartments were chosen in accordance to the stages that a cell undergoes during a viral attack. The non-disease states are the healthy cell compartment, and the HBV resistant compartment. All of the other compartments take part in forming the picture of a HBV infection.nThe inclusion of the pathway from the exposed to the immune vulnerable stage describes the contended subject [8] of whether there are any cytotoxic activities during the immune tolerant stage. This hypothesis can be controlled by the parameters β_1 and β_2.

As the immune tolerant stage does not involve death due to cytotoxic activity, the only 'death' terms are it's natural death parameter μ and its 'evolution' parameter $f(d)$. Eventually, the cells in the immune tolerant stage will be targeted by the immune response, controlled by the paramter σ. $\frac{1}{\sigma}$ can also be thought of as the mean time that a cell in the I_{tol} compartment spends before progressing into the I_{vul} compartment. The 'evolution' parameter $f(d)$ describes the notion of cells mutating to HBV resistant cells in accordance with the immune pressure that they are subjected to. This evolution is hypothesised to be governed by a strictly increasing function $f(d)$, a function dependent on the death rate of immune vulnerable cells due to immune activity.

The 'evolved' cells are termed 'HBV resistant and healthy looking cells' H_r, and this compartment is similar to the standard 'Removed' class in the sense that it is a final compartment which outfluxes the diseased cells. The parameter δ describes the 'mutation' rate into a fibrous cell (fibrosis) or a cancerous cell (carcinoma). There are indications in the literature [8] that this mutation is more prominent with higher viral titres which is the reason behind the mass action incidence with both the viral population and the HBV resistant population.

The parameters c_1 and c_2 indicate random curing of cells from the infected compartments suggested by [8], which gave rise to the idea that the entire liver population isn't just destroyed by the cytotoxic activities of the T-cells but still maintains a structure, and persists in a chronic state without organ failure (in the case of a chronic infection).

Finally, one can conjecture the various pathways of a HBV infection through this model:

1. **Acute Infection**:	High β_2, c_2, σ, μ_v	Low β_e, k, $f(d)$
2. **Chronic Hepatitis**:	High β_e, β_1,	Low σ, c_1, c_2
3. **Fulminant Hepatitis**:	High β_2, d, σ	Low c_1, c_2

3.3.2 Verification of the Model

Here I present further details regarding the validity of the model by studying the non-negativity and boundedness of the solutions for the system.

Non-negativity of Solutions

Claim : Suppose that $H(0), I_{\text{tol}}(0), I_{\text{vul}}(0), H_r(0), V(0) \geq 0$.
Then $H(t), I_{\text{tol}}(t), I_{\text{vul}}(t), H_r(t), V(t) \geq 0$ for all $t > 0$.

Proof Consider the modified system (with $\epsilon > 0$)

$$\frac{dH}{dt} = \Pi - (\beta_1 + \beta_2)VH + c_1 I_{\text{tol}} + c_2 I_{\text{vul}} - \mu H + \epsilon$$

$$\frac{dI_{\text{tol}}}{dt} = \beta_1 VH - (\sigma + c_1 + \mu + f(d))I_{\text{tol}} + \epsilon$$

$$\frac{dI_{\text{vul}}}{dt} = \beta_2 VH + \sigma I_{\text{tol}} - (c_2 + d + \mu)I_{\text{vul}} + \epsilon$$

$$\frac{dH_r}{dt} = f(d)I_{\text{tol}} - \mu H_r - \delta V H_r + \epsilon$$

$$\frac{dV}{dt} = k(I_{\text{tol}} + I_{\text{vul}}) - \mu_v V + \epsilon$$

and call its solution $H^\epsilon(t),\ I^\epsilon_{\text{tol}}(t),\ I^\epsilon_{\text{vul}}(t),\ H^\epsilon_r(t),\ V^\epsilon(t)$ which is assumed to satisfy

$$\begin{aligned} H^\epsilon(0) &= H(0) + \epsilon \\ I^\epsilon_{\text{tol}}(0) &= I_{\text{tol}}(0) + \epsilon \\ I^\epsilon_{\text{vul}}(0) &= I_{\text{vul}}(0) + \epsilon \\ H^\epsilon_r(0) &= H_r(0) + \epsilon \\ V^\epsilon(0) &= V(0) + \epsilon \end{aligned}$$

Note that $H^\epsilon(0),\ I^\epsilon_{\text{tol}}(0),\ I^\epsilon_{\text{vul}}(0),\ H^\epsilon_r(0),\ V^\epsilon(0) > 0$, since $\epsilon >\ 0$.

Suppose that a variable goes negative, and that the first to do so is $H^\epsilon(t)$. Then there exists a t^*such that

$$H^\epsilon(t^*) = 0, \qquad \frac{dH^\epsilon}{dt} \leq 0$$

and the other variables satisfy

$$I^\epsilon_{\text{tol}}(t^*) \geq 0,\ I^\epsilon_{\text{vul}}(t^*) \geq 0,\ H^\epsilon_r(t^*) \geq 0,\ V^\epsilon(t^*) \geq 0$$

Then at time t^*,

$$\frac{dH^\epsilon}{dt}(t^*) = \Pi - (\beta_1+\beta_2)\underbrace{V^\epsilon(t^*)}_{\geq 0}\underbrace{H^\epsilon(t^*)}_{= 0} + c1\underbrace{I^\epsilon_{\text{tol}}(t^*)}_{\geq 0} + c2\underbrace{I^\epsilon_{\text{vul}}(t^*)}_{\geq 0} - \mu\underbrace{H^\epsilon(t^*)}_{= 0} + \underbrace{\epsilon}_{> 0} > 0$$

which contradicts $\frac{dH^\epsilon}{dt}(t^*) \leq 0$. Without loss of generality we can say the same thing about the other variables by letting the variable to be the first variable that goes negative. This contradiction shows that $H^\epsilon(t),\ I^\epsilon_{\text{tol}}(t),\ I^\epsilon_{\text{vul}}(t),\ H^\epsilon_r(t),\ V^\epsilon(t) \geq 0$

Finally, let $\epsilon \to 0$, then $H^\epsilon(t) \to H(t)$, etc. Hence, $H(t) \geq 0, I_{\text{tol}}(t) \geq 0, I_{\text{vul}}(t) \geq 0, H_r(t) \geq 0, V(t) \geq 0$ for all $t > 0$.

Boundedness of Solutions

Now that the non-negativity of the solutions is guaranteed, the boundedness of the solutions can be discussed as well.

Recall the system as

$$\frac{dH}{dt} = \Pi - (\beta_1+\beta_2)VH + c_1 I_{\text{tol}} + c_2 I_{\text{vul}} - \mu H$$

$$\frac{dI_{\text{tol}}}{dt} = \beta_1 VH - (\sigma + c_1 + \mu + f(d))I_{\text{tol}}$$

$$\frac{dI_{\text{vul}}}{dt} = \beta_2 VH + \sigma I_{\text{tol}} - (c_2 + d + \mu)I_{\text{vul}}$$

$$\frac{dH_r}{dt} = f(d)I_{\text{tol}} - \mu H_r - \delta V H_r$$

$$\frac{dV}{dt} = k(I_{\text{tol}} + I_{\text{vul}}) - \mu_v V$$

Adding the first 4 equations gives,

$$\begin{aligned}\frac{d}{dt}(H + I_{\text{tol}} + I_{\text{vul}} + H_r) &= \Pi - \mu H - \mu I_{\text{tol}} - dI_{\text{vul}} - \mu I_{\text{vul}} - \delta V H_r - \mu H_r \\ &\leq \Pi - \mu(H + I_{\text{tol}} + I_{\text{vul}} + H_r)\end{aligned}$$

Thus,

$$\frac{dy}{dt} \leq \Pi - \mu y \qquad \text{where } y = H + I_{\text{tol}} + I_{\text{vul}} + H_r$$

and thus we can say that,

$$y \leq \bar{y} \qquad \text{where } \frac{d\bar{y}}{dt} = \Pi - \mu\bar{y}(t)$$

The limit of $\bar{y}$ as $t \to \infty$ is then

$$\lim_{t\to\infty} \bar{y}(t) = \frac{\Pi}{\mu}.$$

But $y(t) \leq \bar{y}(t)$. Therefore,

$$\limsup_{t\to\infty} y(t) \leq \lim_{t\to\infty} \bar{y}(t) = \frac{\Pi}{\mu}$$

which implies that $y(t)$ is bounded.

Since $y(t) = H + I_{\text{tol}} + I_{\text{vul}} + H_r$, and each of these four functions is greater than or equal to 0 as shown from the section before, it follows that $H(t),\ I_{\text{tol}}(t),\ I_{\text{vul}}(t),\ H_r(t)$ are bounded.

To prove the boundedness of $V(t)$, let K_1 and K_2 be bounds for I_{tol} and I_{vul} respectively that hold for all t. Then,

$$V'(t) \leq k(K_1 + K_2) - \mu_v V(t)$$

Therefore, $V(t) \leq \bar{V}(t)$ where $\bar{V}'(t) = k(K_1 + K_2) - \mu_v\bar{V}(t)$. Following a similar argument as above, we have that

$$\lim_{t\to\infty} \bar{V}(t) = \frac{k(K_1 + K_2)}{\mu_v}$$

and that

$$\limsup_{t\to\infty} V(t) \leq \lim_{t\to\infty} \bar{V}(t) = \frac{k(K_1 + K_2)}{\mu_v}$$

implying that $V(t)$ is bounded.

Thus we have shown that the model proposed behaves accordingly and suitably for a model regarding cell population dynamics, being non-negative and bounded. We can now proceed to analyse the model with confidence that it is valid.

3.3.3 Next Generation Matrix Method Analysis of the Model

Linearisation about the disease-free steady state produces a decoupled system :

$$\begin{aligned}
\frac{dI_{\text{tol}}}{dt} &= \beta_1 V\frac{\Pi}{\mu} - (\sigma + c_1 + \mu + f(d))I_{\text{tol}} \\
\frac{dI_{\text{vul}}}{dt} &= \beta_2 V\frac{\Pi}{\mu} + \sigma I_{\text{tol}} - (c_2 + d + \mu)I_{\text{tol}} \\
\frac{dV}{dt} &= k(I_{\text{tol}} + I_{\text{vul}}) - \mu_v V
\end{aligned}$$

which is sufficient to determine $I_{\text{tol}}, I_{\text{vul}}$ and V.

In which case we can separate the infection influx and progression outflux as below,

$$\mathcal{F} = \begin{pmatrix} \beta_1 V \frac{\Pi}{\mu} \\ \beta_2 V \frac{\Pi}{\mu} \\ k(I_{\text{tol}} + I_{\text{vul}}) \end{pmatrix} \qquad \mathcal{V} = \begin{pmatrix} (\sigma + c_1 + \mu + f(d)) I_{\text{tol}} \\ -\sigma I_{\text{tol}} + (c_2 + d + \mu) I_{\text{vul}} \\ \mu_v V \end{pmatrix}$$

Then, writing the system in matrix form, $x' = (F - V)x$, we can deduce the matrix F, and V, from the vectors above.

$$F = \begin{pmatrix} 0 & 0 & \beta_1 \frac{\Pi}{\mu} \\ 0 & 0 & \beta_2 \frac{\Pi}{\mu} \\ k & k & 0 \end{pmatrix} \qquad V = \begin{pmatrix} \sigma + c_1 + \mu + f(d) & 0 & 0 \\ -\sigma & c_2 + d + \mu & 0 \\ 0 & 0 & \mu_v \end{pmatrix}$$

According to the Next Generation Matrix method, the Next Generation Matrix K is given by FV^{-1}. Therefore we must find the inverse of V. Using the cofactor matrix (C) method, the inverse of V is given by

$$\begin{aligned} V^{-1} = {} & \frac{1}{det(V)} \, C^T \\ = {} & \frac{1}{(\sigma + c_1 + \mu + f(d))(c_2 + d + \mu)\mu_v} \\ & \cdot \begin{pmatrix} (c_2 + d + \mu)\mu_v & 0 & 0 \\ \sigma \mu_v & (\sigma + c_1 + \mu + f(d))\mu_v & 0 \\ 0 & 0 & \begin{array}{r} (\sigma + c_1 + \mu + f(d)) \\ \cdot (c_2 + d + \mu) \end{array} \end{pmatrix} \end{aligned}$$

where C^T denotes the transpose of the matrix of cofactors.

Multiplying F to V^{-1}, we arrive at the next generation matrix, K :

$$\begin{aligned} K = {} & FV^{-1} = \frac{1}{(\sigma + c_1 + \mu + f(d))(c_2 + d + \mu)\mu_v} \\ & \cdot \begin{pmatrix} 0 & 0 & \begin{array}{r} \beta_1 \dfrac{\Pi}{\mu}(\sigma + c_1 + \mu + f(d)) \\ \cdot (c_2 + d + \mu) \end{array} \\ 0 & 0 & \begin{array}{r} \beta_2 \dfrac{\Pi}{\mu}(\sigma + c_1 + \mu + f(d)) \\ \cdot (c_2 + d + \mu) \end{array} \\ k((c_2 + d + \mu) + \sigma \mu_v) & k(\sigma + c_1 + \mu + f(d))\mu_v) & 0 \end{pmatrix} \end{aligned}$$

A search for the eigenvalues(λ) of the above matrix (without the factor in front) gives rise to the characteristic equation :

$$\begin{aligned}0 = &-\lambda(\lambda^2 - \beta_2\frac{\Pi}{\mu}(\sigma + c_1 + \mu + f(d))^2(c_2 + d + \mu)k\mu_v)\\ &+ \beta_1\frac{\Pi}{\mu}(\sigma + c_1 + \mu + f(d))(c_2 + d + \mu)\lambda k((c_2 + d + \mu)\mu_v + \sigma\mu_v)\end{aligned}$$

Hence, the eigenvalues of the matrix are either $\lambda = 0$, or satisfy

$$\begin{aligned}0 = &\lambda^2 - \beta_2\frac{\Pi}{\mu}(\sigma + c_1 + \mu + f(d))^2(c_2 + d + \mu)k\mu_v\\ &- \beta_1\frac{\Pi}{\mu}(\sigma + c_1 + \mu + f(d))(c_2 + d + \mu)k((c_2 + d + \mu)\mu_v + \sigma\mu_v)\end{aligned}$$

This is a simple quadratic equation, and thus the spectral radius of the matrix is

$$\rho(FV^{-1}) =$$

$$\sqrt{\frac{\Pi}{\mu}(\sigma + c_1 + \mu + f(d))(c_2 + d + \mu)k\mu_v}\sqrt{\beta_2(\sigma + c_1 + \mu + f(d)) + \beta_1(c_2 + d + \mu + \sigma)}$$

After we restore the factor in front of the above matrix, this gives:

$$\mathcal{R}_0^{NGM} = \sqrt{\frac{\Pi k(\beta_2(\sigma + c_1 + \mu + f(d)) + \beta_1(c_2 + d + \mu + \sigma))}{\mu\mu_v(\sigma + c_1 + \mu + f(d))(c_2 + d + \mu)}}$$

The expression of $\mathcal{R}_0^{NGM}$ suggests there are particularly sensitive parameters which affect its numerical value. The terms Π, k, β_2, and β_1 only appear on the numerator, suggesting these parameters can affect the value of the basic reproduction number significantly. An increase in any of those parameters would indicate an increase in $\mathcal{R}_0$. This makes epidemiological sense as,

- Π, This is the rate in which the susceptible population is replenished, so the greater the size of the susceptible population, the higher the chance of infection.

- k, This is the viral replication rate. Increased number of the HBV virus suggests a higher chance of infection.

- β, The terms β_1 and β_2 are incidence ratios which describe a contact between a healthy cell and a virus resulting in the transfer to two different infected compartments. The higher this ratio is, the greater the ability of the infection to thrive.

On the other hand, an increase in μ and μ_v is related to the decrease of $\mathcal{R}_0$. This is also sensible as the less cells and virus there are, the less likely it is that an infection will spread.

The rest of the parameters have a precarious balance on the value for $\mathcal{R}_0$. A rise in the cure rates c_1 and c_2 indicates an increase in $\mathcal{R}_0$, probably due to the increase in susceptible cell population which relates to more potential infections. Yet a dominant c_1 and c_2 will mean that the hepatocytes can endure more severe infections. Likewise many of the other parameters require further study to gain more insight into their nature in the governing of the value of the basic reproduction number.

With these qualitative analyses of the parameter values, we can create practical intervention strategies to decrease the invasive severity of the disease, that is, to reduce the value of $\mathcal{R}_0$. It is hard to provide practical comments about realistic intervention methods to control those parameters due to the lack of my biological and medical knowledge.

3.3.4 Numerical Results

For Fig. 3.1, and Fig. 3.2 below, the initial condition $(H, I_{\text{tol}}, I_{\text{vul}}, H_r, V) = (\frac{\Pi}{\mu}, 0, 0, 0, 10)$ is used, and for Fig. 3.3 $(H, I_{\text{tol}}, I_{\text{vul}}, H_r, V) = (\frac{\Pi}{\mu}, 0, 0, 0, 100)$ is used.

As expected for a system with a basic reproduction number bigger than 1, the system shown in Fig. 3.1 diverges from the disease-free equilibrium and eventually reaches an endemic equilibrium. As hypothesised for this model, the I_{vul} compartment rises later than the I_{tol} compartment, describing the delay in the body's immune tolerance to immune active stage. Eventually the cells of the liver are dominated by these types of cells, yet the total population is not destroyed, it persists. The graph seems to portray a case where the patient develops a chronic infection, with the virus population persisting, and most of the hepatocyte population converted into diseased cells.

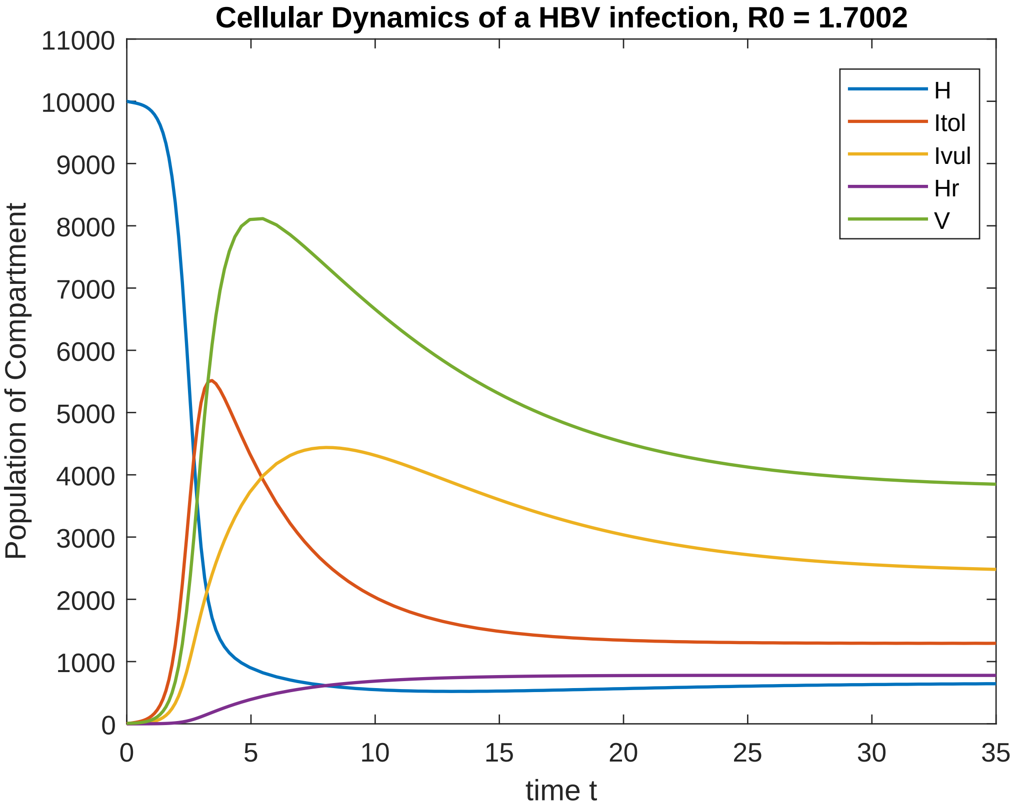


Figure 3.1: The graph above shows a case where $\mathcal{R}_0$ is 1.7002. The parameter values chosen were $\Pi = 500,\ \mu = 0.05,\ \beta_1 = 0.00085,\ \beta_2 = 0.00013,\ d = 0.1,\ k = 1.7,\ \mu_v = 1.67,\ f(d) = 3d^2,\ \sigma = 0.05,\ c_1 = 1.5,\ c_2 = 0.01,\ \delta = 10^{-9}$. These values do not reflect realistic values found in medical data; they have been chosen arbitrarily to depict general results for the model.

It was hard to find parameter values which describe a return to the disease-free equilibrium after an introduction of disease, i.e $\mathcal{R}_0 < 1$. In fact, an endemic steady state was shown for many of the cases with $\mathcal{R}_0 < 1$ as shown from the graph in Fig. 3.2 which is for a system with $\mathcal{R}_0 = 0.7142$.

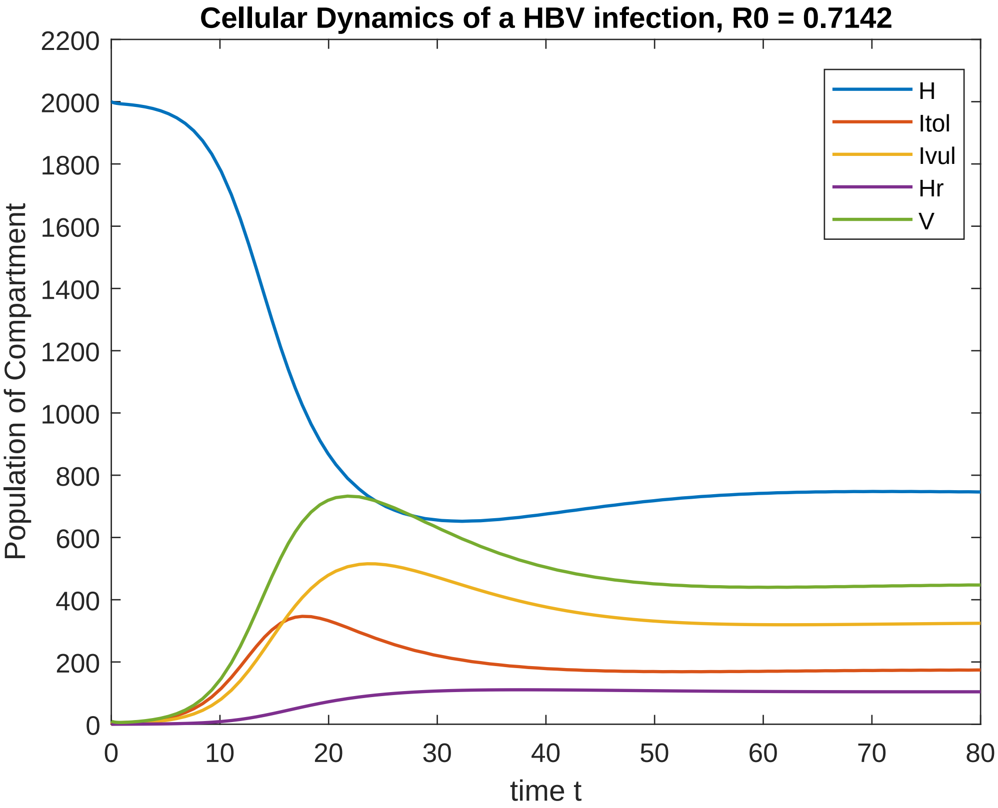


Figure 3.2: The parameter values chosen were $\Pi = 100$, $\mu = 0.05$, $\beta_1 = 0.00085$, $\beta_2 = 0.00013$, $d = 0.1$, $k = 1.5$, $\mu_v = 1.67$, $f(d) = 3d^2$, $\sigma = 0.05$, $c_1 = 1.5$, $c_2 = 0.01$, $\delta = 10^{-9}$. This gives $\mathcal{R}_0 = 0.7142 < 1$, and the graph highly suggests a backward bifurcation occuring, where despite $\mathcal{R}_0 < 1$, the disease-free equilibrium is not the only stable equilibrium. Depending on the parameters, the endemic steady state may be stable as shown from the figure above. This notion will be further discussed in the section 'Further Analysis of the Model without Delay' below, where we attempt to find an expression for the endemic steady state.

This presents a possible area for further research, to find the global condition for the stability of the disease-free equilibrium.

For certain parameters where $\mathcal{R}_0 < 1$, the graph displayed behaviours like below, where the system evolves over a very short period, and returns to the disease-free equilibrium.

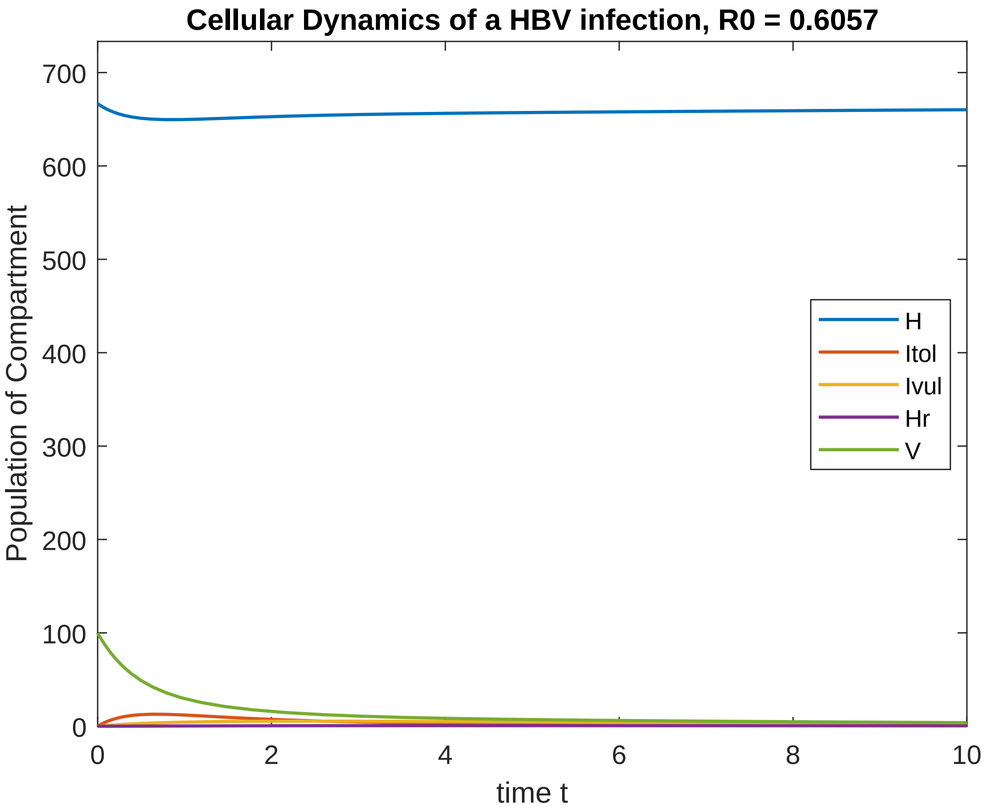


Figure 3.3: Parameter Values : $\Pi = 100,\ \mu = 0.15,\ \beta_1 = 0.00085,\ \beta_2 = 0.00013,\ d = 0.1,\ k = 1.5,\ \mu_v = 1.67,\ f(d) = 3d^2,\ \sigma = 0.05,\ c_1 = 1.5,\ c_2 = 0.01,\ \delta = 10^{-9}$. This is the usual behaviour we would expect when the basic reproduction number $\mathcal{R}_0$ is less than 1, yet as seen with the 2^{nd} case above, it is not definite for the case $\mathcal{R}_0 < 1$

This can be an example that demonstrates the caution that comes with the analysis of the basic reproduction number mentioned before. The basic reproduction number is not an objective quantity that can be compared between diseases, and it is not defined uniquely for each model. It requires thorough analysis about its nature and significance in order to be utilised in other practical fields.

Generalisations of the model I proposed earlier include the following.

3.4 Model with Exposed Class

$$\frac{dH}{dt} = \Pi - \beta VH + c_1 I_{\text{tol}} + c_2 I_{\text{vul}} - \mu H$$

$$\frac{dE}{dt} = \beta VH - (\kappa_1 + \kappa_2)VH - \mu E$$

$$\frac{dI_{\text{tol}}}{dt} = \kappa_1 VH - (\sigma + c_1 + \mu + f(d))I_{\text{tol}}$$

$$\frac{dI_{\text{vul}}}{dt} = \kappa_2 VH + \sigma I_{\text{tol}} - (c_2 + d + \mu)I_{\text{vul}}$$

$$\frac{dH_r}{dt} = f(d)I_{\text{tol}} - \mu H_r - \delta VH_r$$

$$\frac{dV}{dt} = k(I_{\text{tol}} + I_{\text{vul}}) - \mu_v V$$

This model incorporates an 'Exposed' compartment E, where the exposed compartment represents the temporary transition of the healthy hepatocytes into a state where it isn't yet infective due to the time required for viral transcription, production, etc. β_1 and β_2 is removed, and a single β is in the first equation as a standardized mass incidence ratio at which the contact between a healthy cell and a virus creates an exposed cell. Two new paramters κ_1, κ_2 are added which represents the rate at which the exposed cells progress on to the I_{tol} and I_{vul} compartment respectively. Recall the SEIR model example from the previous chapter. By comparing the basic reproduction number between a model with and without delay, it is noted that the parameter κ is comparable to the delay τ. Hence the parameters κ_1, κ_2 also relates to the mean latency time $\frac{1}{\kappa}$ that the cells are in the exposed class before becoming a fully infected cell.

The basic reproduction number for this model can be simply obtained using the same next generation matrix method used for the standard model in the previous section. I have not included the calculation nor the basic reproduction number for this model. Our main focus will be on the model with an explicit time delay as given below.

3.5 Model with Explicit time Delay

$$\frac{dH}{dt} = \Pi - (\beta_1 + \beta_2)VH + c_1 I_{\text{tol}} + c_2 I_{\text{vul}} - \mu H$$

$$\frac{dE}{dt} = (\beta_1 + \beta_2)VH - (\beta_1 + \beta_2)V(t-\tau)H(t-\tau)e^{-\mu\tau} - \mu E$$

$$\frac{dI_{\text{tol}}}{dt} = \beta_1 V(t-\tau)H(t-\tau)e^{-\mu\tau} - (\sigma + c_1 + \mu + f(d))I_{\text{tol}}$$

$$\frac{dI_{\text{vul}}}{dt} = \beta_2 V(t-\tau)H(t-\tau)e^{-\mu\tau} + \sigma I_{\text{tol}} - (c_2 + d + \mu)I_{\text{vul}}$$

$$\frac{dH_r}{dt} = f(d)I_{\text{tol}} - \mu H_r - \delta V H_r$$

$$\frac{dV}{dt} = k(I_{\text{tol}} + I_{\text{vul}}) - \mu_v V$$

As noted from the previous model, this model simply re-iterates the point of the time delay occuring between a healthy cell becoming 'fully' infectious due to viral mechanisms. The difference is that here an explicit time delay τ is given, instead of parameters κ_1 and κ_2.

The time delay term in the second equation can be derived using an age-structured modelling approach. It is the term that corresponds to the rate in which exposed cells mature into infected cells. Let $i(t, a)$ be the population density at time t that were infected a time units before t. That is, cells with 'disease age' a. Consider a small increment of time dt, then the change in the population density is given by the simple conservation law, 'birth - death'. In our case, birth rate references rate of new infections. This 'birth' rate only contributes to $i(t, 0)$, i.e cells of age 0. Thus in general $di(t, a)$ the small change in population density during the small increment of time dt is only governed by the death of cells, simply given by $\mu \cdot i(t, a)dt$. Which then gives rise to the following equation.

$$di(t, a) = \frac{\partial i}{\partial t}dt + \frac{\partial i}{\partial a}da = -\mu i(t, a)dt$$

This equation can be divided by dt with the note that $\frac{da}{dt} = 1$ as the unit change in age and time is the same. Thus we arrive at the following equation,

$$\frac{\partial i}{\partial t} + \frac{\partial i}{\partial a} = -\mu i(t, a)$$

This linear partial differential equation is the McKendrick-von Foerster equation, and a summary of the theory is outlined in [7] by Murray.

Our equation is subject to the condition

$$i(t,0) = (\beta_1 + \beta_2)V(t)H(t)$$

where $i(t,0)$ denotes the rate at whcih new infections arise. The term of interest to us is $i(t,\tau)$ which is the population density at time t with cells of disease age τ, that is the population density of cells which have been 'matured' in the exposed compartment. This is the rate at which cells moved from the exposed compartment to the infected compartments. Hence, we need to solve for $i(t,\tau)$.

Defining $i^{\xi}(a) = i(a+\xi, a)$, the McKendrick-von Foerster equation simplifies to $\frac{di^{\xi}(a)}{da} = -\mu i^{\xi}(a)$. This is a simple ODE that can be solved trivially as follows,

$$i^{\xi}(a) = i^{\xi}(0)e^{-\mu a} = i(\xi,0)e^{-\mu a} = (\beta_1+\beta_2)e^{-\mu a}V(\xi)H(\xi)$$

Therefore, we can find the term of our interest $i(t,\tau)$, by setting $a = \tau$, and $\xi = t - \tau$ which yields

$$i(t,\tau) = (\beta_1+\beta_2)e^{-\mu\tau}V(t-\tau)H(t-\tau)$$

This derivation shows that the exposed compartment serves as an intermediate 'age period' in which an infected healthy cell 'ages' until becoming completely infectious. The exponential term corresponds to the death of the cells while 'aging'. With the model derived thoroughly, we can now start to analyse the disease-free steady state of the model.

The linearisation of the system about the disease-free equilibrium $(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0)$ gives rise to the following decoupled subsystem : (where the tilde variables represent the linearised variables, which are small perturbations from the equilibrium)

$$\frac{d\widetilde{I}_{\text{tol}}}{dt} = \frac{\Pi}{\mu}\beta_1\widetilde{V}(t-\tau)e^{-\mu\tau} - (\sigma + c_1 + \mu + f(d))\widetilde{I}_{\text{tol}}$$

$$\frac{d\widetilde{I}_{\text{vul}}}{dt} = \frac{\Pi}{\mu}\beta_2\widetilde{V}(t-\tau)e^{-\mu\tau} + \sigma\widetilde{I}_{\text{tol}} - (c_2 + d + \mu)\widetilde{I}_{\text{vul}}$$

$$\frac{d\widetilde{V}}{dt} = k(\widetilde{I}_{\text{tol}} + \widetilde{I}_{\text{vul}}) - \mu_v\widetilde{V}$$

As this system is linear, we can try the following solution for the system of linear ODEs:

$$(\widetilde{I}_{\text{tol}},\ \widetilde{I}_{\text{vul}},\ \widetilde{V}) = (p_1,\ p_2,\ p_3)e^{\lambda t}$$

where p_1, p_2 and p_3 are constants.

Substituting this ansatz into the linearised system, and expressing the resulting equations in matrix form:

$$\begin{pmatrix} -(A_1+\lambda) & 0 & \frac{\Pi}{\mu}\beta_1 e^{-(\lambda+\mu)\tau} \\ \\ \sigma & -(A_2+\lambda) & \frac{\Pi}{\mu}\beta_2 e^{-(\lambda+\mu)\tau} \\ \\ k & k & -(\mu_v+\lambda) \end{pmatrix} \begin{pmatrix} p_1 \\ \\ p_2 \\ \\ p_3 \end{pmatrix} = \begin{pmatrix} 0 \\ \\ 0 \\ \\ 0 \end{pmatrix}$$

where $A_1 = \ (\sigma + c_1 + \mu + f(d)),\ A_2 = \ (c_2 + d + \mu)$.

For non-trivial solutions $(p_1,\ p_2,\ p_3)$, it is required that the matrix should be non-invertible, hence it's determinant is 0. Thus with this condition, we can obtain a characteristic equation for λ, which is given by:

$$\frac{(A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda)}{\beta_2(A_1+\lambda)+\beta_1(A_2+\lambda+\sigma)} = \frac{\Pi k}{\mu}e^{-(\lambda+\mu)\tau}$$

3.5.1 Deriving an R_0 for the Delayed System

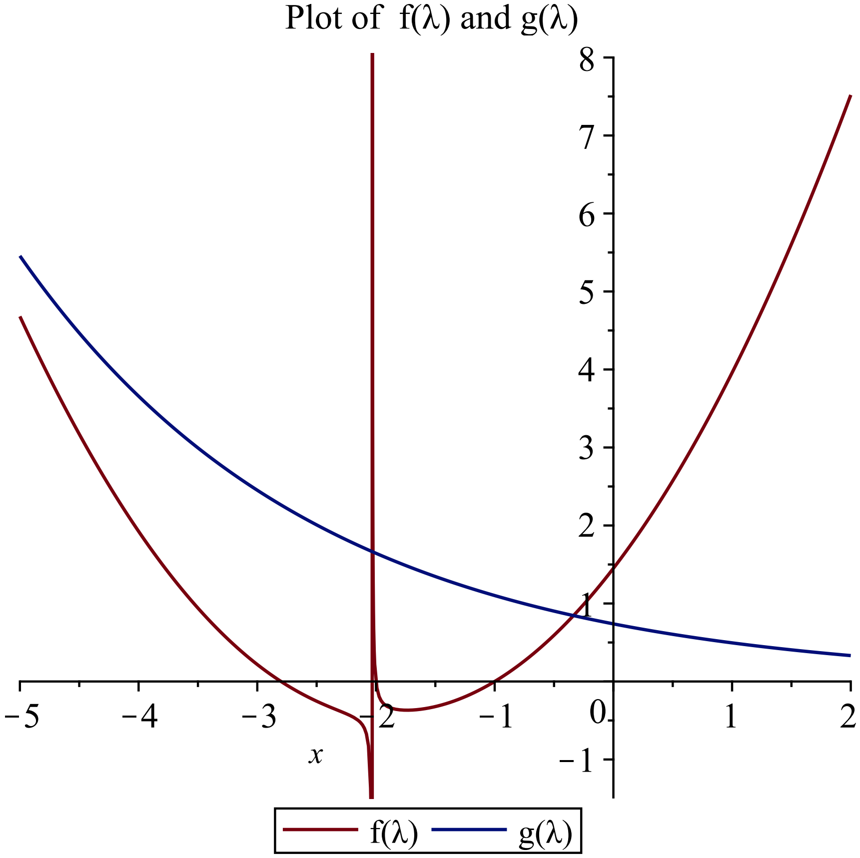
The structure of the system above is of a cooperative system in the sense of Smith [9]. Additionally, by Theorem 5.5.1 on page 92 of Smith [9], it is assured that the dominant root (the root of greatest real part) of the characteristic equation is a real number. Therefore, it is sufficient to restrict attention to the real roots, and graphical arguments can help.

Let us define two functions, $f(\lambda)$ and $g(\lambda)$ as the following

$$f(\lambda) = \frac{(A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda)}{\beta_2(A_1+\lambda)+\beta_1(A_2+\lambda+\sigma)}$$

$$g(\lambda) = \frac{\Pi k}{\mu}e^{-(\lambda+\mu)\tau}$$

Then we can numerically plot the functions with arbitrary parameter values to see the general behaviour of the two functions.



The plots were made with arbitrary parameter values that depicts the general behaviour of the functions. The graph of $f(\lambda)$ as seen above has a single vertical asymptote of a negative value $\lambda =$ (root of denominator $= 0$).

We can see from the graph that any real root of the characteristic equation $f(\lambda) = g(\lambda)$ will be negative if $f(0) > g(0)$. To make this more rigorous, we claim that in fact $f'(\lambda) > 0$ for $\lambda > 0$ and $g'(\lambda) < 0$ when $\lambda > 0$. The second claim is obvious.

Regarding the first, routine differentiation shows that

$$f'(\lambda) = \frac{(\beta_2(A_1+\lambda)+\beta_1(A_2+\lambda+\sigma))\frac{d}{d\lambda}((A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda))}{(\beta_2(A_1+\lambda)+\beta_1(A_2+\lambda+\sigma))^2} - \frac{(A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda)(\beta_1+\beta_2)}{(\beta_2(A_1+\lambda)+\beta_1(A_2+\lambda+\sigma))^2}$$

it is enough to show the numerator is positive.

Extracting the numerator,

$$\begin{aligned}\text{Num.} = {} & (\beta_2(A_1+\lambda)+\beta_1(A_2+\lambda+\sigma))((A_1+\lambda)(2\lambda+A_2+\mu_v)+(A_2+\lambda)(\mu_v+\lambda)) \\ & - (A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda)(\beta_1+\beta_2) \\ \\ = {} & (\beta_2(A_1+\lambda)+\beta_1(A_2+\lambda+\sigma))((A_1+\lambda)(A_2+\lambda)+(A_1+\lambda)(\mu_v+\lambda) \\ & + (A_2+\lambda)(\mu_v+\lambda)) - (A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda)(\beta_1+\beta_2)\end{aligned}$$

As σ is a positive constant, the following is true (by omitting σ)

$$\begin{aligned}& (\beta_2(A_1+\lambda)+\beta_1(A_2+\lambda+\sigma))((A_1+\lambda)(A_2+\lambda)+(A_1+\lambda)(\mu_v+\lambda)+(A_2+\lambda)(\mu_v+\lambda)) \\ & - (A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda)(\beta_1+\beta_2) \\ \\ > {} & \beta_2(A_1+\lambda)(A_1+\lambda)(A_2+\lambda)+\beta_2(A_1+\lambda)(A_1+\lambda)(\mu_v+\lambda){\color{red}+\beta_2(A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda)} \\ & + \beta_1(A_2+\lambda)(A_1+\lambda)(A_2+\lambda){\color{blue}+\beta_1(A_2+\lambda)(A_1+\lambda)(\mu_v+\lambda)}+\beta_1(A_2+\lambda)(A_2+\lambda)(\mu_v+\lambda) \\ & - (A_1+\lambda)(A_2+\lambda)(\mu_v+\lambda)({\color{blue}\beta_1}+{\color{red}\beta_2})\end{aligned}$$

The colour coded terms of the polynomial cancel out, and thus there are only positive terms left in the polynomial, asserting the fact that the numerator of $f'(\lambda)$ is greater than 0 for $\lambda > 0$.

This proves that $f'(\lambda) > 0$ for all $\lambda > 0$. Knowing that $f'(\lambda) > 0$ and $g'(\lambda) < 0$ for all $\lambda > 0$, it follows rigorously that if $f(0) > g(0)$, then all real roots of the characteristic equation must be negative. Thus we have a condition for the characteristic equation to produce a negative root resulting in a condition for stability of the disease-free equilibrium.

The condition $f(0) > g(0)$ becomes

$$\frac{(\sigma+c_1+\mu+f(d))(c_2+d+\mu)\mu_v}{\beta_2(\sigma+c_1+\mu+f(d))+\beta_1(c_2+d+\mu+\sigma)} > \frac{\Pi k}{\mu}e^{-\mu\tau}$$

which is therefore the condition for stability of the disease-free steady state.

Hence, a basic reproduction number for this system can be defined as

$$\mathcal{R}_0(\tau) = \frac{\Pi k e^{-\mu\tau}(\beta_2(\sigma+c_1+\mu+f(d))+\beta_1(c_2+d+\mu+\sigma))}{\mu\mu_v(\sigma+c_1+\mu+f(d))(c_2+d+\mu)}$$

Recall that

$$\mathcal{R}_0^{NGM} = \sqrt{\frac{\Pi k(\beta_2(\sigma+c_1+\mu+f(d))+\beta_1(c_2+d+\mu+\sigma))}{\mu\mu_v(\sigma+c_1+\mu+f(d))(c_2+d+\mu)}}$$

Therefore for $\tau = 0$,

$$\sqrt{\mathcal{R}_0(0)} = \mathcal{R}_0^{NGM}$$

and so $\mathcal{R}_0^{NGM} < 1$ if and only if $\mathcal{R}_0(0) < 1$, verifying the consistency between the model without delay and with explicit delay. The square root for the next generation matrix method arises since it takes a virus to infect a different cell, i.e it takes 2 steps for the infected cells to 'infect' susceptible cells.

3.5.2 Numerical Results

For all of the results below, the initial condition $(H, I_{\text{tol}}, I_{\text{vul}}, H_r, V) = (\frac{\Pi}{mu}, 0, 0, 0, 10)$ is used.

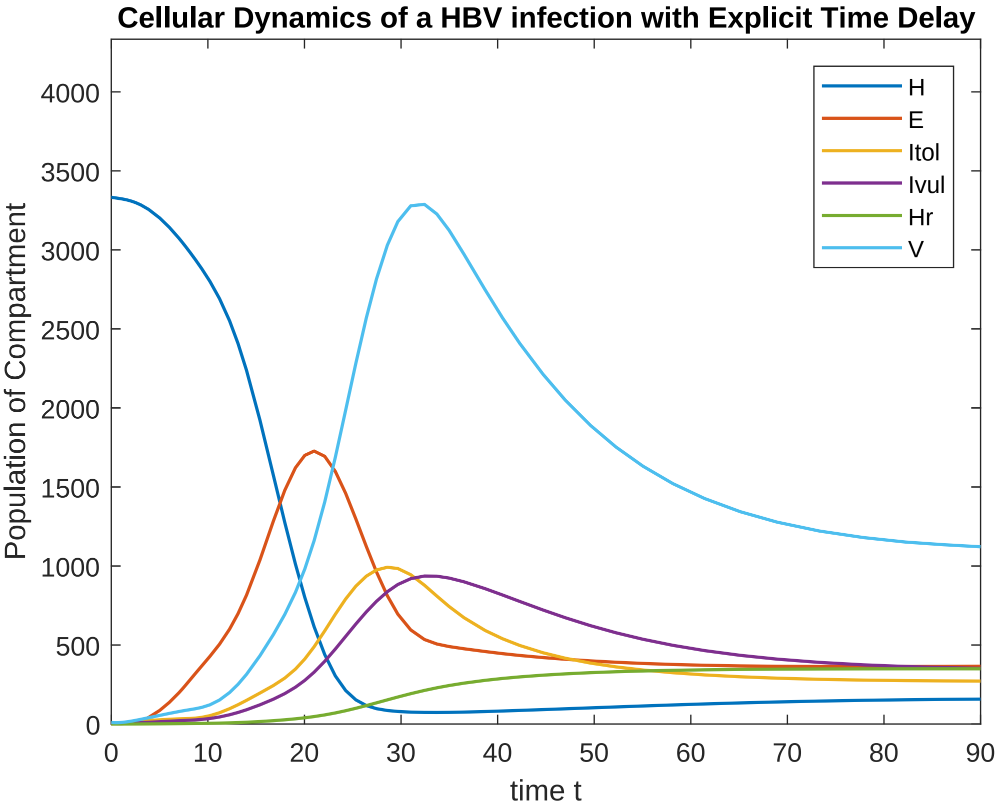


Figure 3.4: Parameter Values : $\Pi = 50$, $\mu = 0.015$, $\beta_1 = 0.00025$, $\beta_2 = 0.000073$, $d = 0.08$, $k = 1.2$, $\mu_v = 0.67$, $f(d) = 3d^2$, $\sigma = 0.1$, $c_1 = 0.013$, $c_2 = 0.018$, $\delta = 10^{-9}$, $\tau = 7$. A graph of the time delayed system which has a basic reproduction number $\mathcal{R}_0$ of 20.6799. As expected, the system evolves away from the disease-free equilibrium and eventually reaches an endemic equilibrium. The time delay is clearly seen by the delay in the peak between the exposed compartment and the $I_{\text{vul}}, I_{\text{tol}}$ compartments. The graph also suggests a signifcant amount of hepatocyte destruction, yet the hepatocyte population is not completely wiped out.

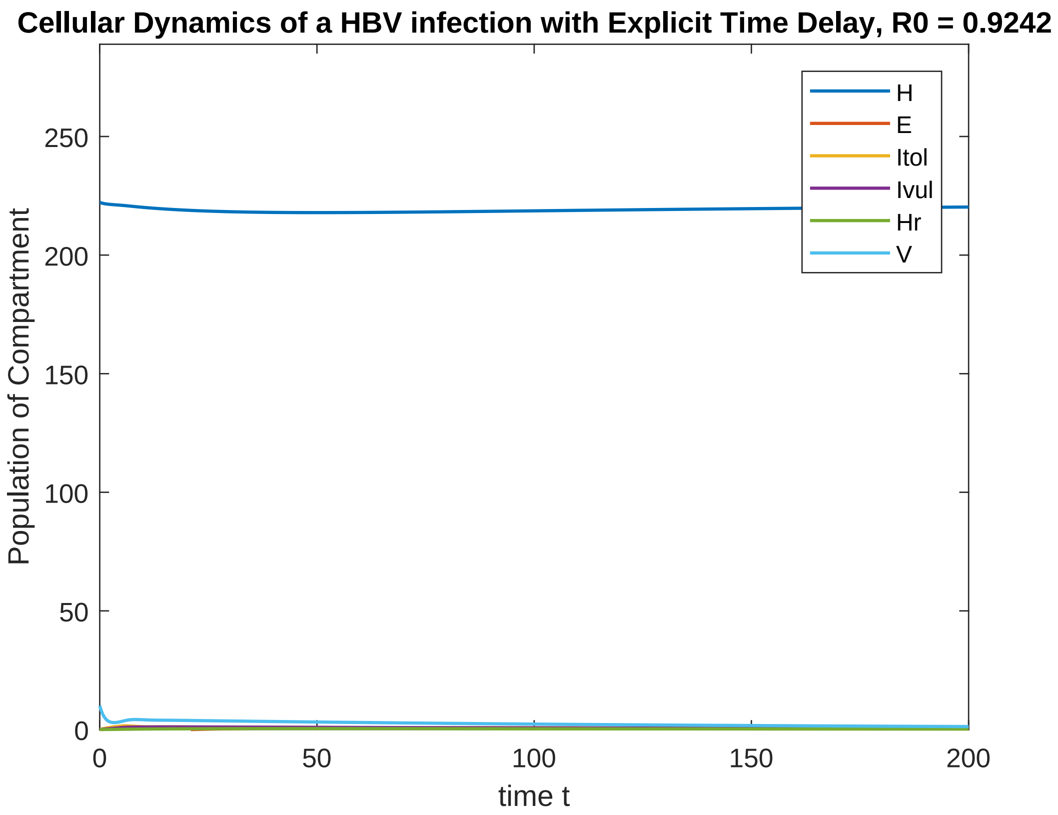


Figure 3.5: Parameter Values : $\Pi = 10$, $\mu = 0.045$, $\beta_1 = 0.00025$, $\beta_2 = 0.000073$, $d = 0.08$, $k = 1.2$, $\mu_v = 0.67$, $f(d) = 3d^2$, $\sigma = 0.1$, $c_1 = 0.013$, $c_2 = 0.018$, $\delta = 10^{-9}$, $\tau = 5$. This graph shows that, for a set of parameter values with $\mathcal{R}_0 < 1$, the system evolves to the disease-free equilibrium after an initial introduction of disease. Various sets of parameter values which give $\mathcal{R}_0 < 1$ do suggest that, for this model, unlike the standard model without time delay, the bifurcation (with $\mathcal{R}_0$ as bifurcation parameter) is a transcritical forward bifurcation from a disease-free steady state to an endemic steady state. Further analytical research into the endemic steady state, and the condition for global stability of the disease-free steady state, would provide rigorous insight into this claim.

3.6 Further Analysis of the Model without Delay

In this section, the model without delay is studied further, to seek the existence of endemic steady states. An endemic steady state is a steady state where the disease compartments are positive values. It occurs when $\mathcal{R}_0 > 1$, representing a sustained state of disease progression.

Recall the model without delay is as follows:

$$\frac{dH}{dt} = \Pi - (\beta_1 + \beta_2)VH + c_1 I_{\text{tol}} + c_2 I_{\text{vul}} - \mu H$$

$$\frac{dI_{\text{tol}}}{dt} = \beta_1 VH - (\sigma + c_1 + \mu + f(d))I_{\text{tol}}$$

$$\frac{dI_{\text{vul}}}{dt} = \beta_2 VH + \sigma I_{\text{tol}} - (c_2 + d + \mu)I_{\text{vul}}$$

$$\frac{dH_r}{dt} = f(d)I_{\text{tol}} - \mu H_r - \delta V H_r$$

$$\frac{dV}{dt} = k(I_{\text{tol}} + I_{\text{vul}}) - \mu_v V$$

Using the 1^{st}, 2^{nd}, 3^{rd}, and 5^{th} equations of the above model, we can start to extract information about possible endemic steady states.

From the 2^{nd} equation, at a steady state ($\frac{dI_{\text{tol}}}{dt} = 0$), we have

$$\beta_1 VH = (\sigma + c_1 + \mu + f(d))I_{\text{tol}} \tag{3.1}$$

Similarly, from the 3^{rd} equation,

$$\beta_2 VH + \sigma I_{\text{tol}} = (c_2 + d + \mu)I_{\text{vul}} \tag{3.2}$$

and therefore substituting VH from equation (1), we have

$$\frac{\beta_2}{\beta_1} I_{\text{tol}}(\sigma + c_1 + \mu + f(d)) \tag{3.3}$$

The fifth equation gives, at a steady state

$$V = \frac{k}{\mu_v}(I_{\text{tol}} + I_{\text{vul}}) \tag{3.4}$$

From the first equation, we have at a steady state,

$$\Pi + c_1 I_{\text{tol}} + c_2 I_{\text{vul}} = (\beta_1 + \beta_2) V H - \mu H \tag{3.5}$$

We can eliminate H in equation 3.5 by substituting $VH = (\sigma + c_1 + \mu + f(d)) \frac{I_{\text{tol}}}{\beta_1}$ (and H) from equation 3.1,

$$\begin{aligned} \Pi + c_1 I_{\text{tol}} + c_2 I_{\text{vul}} = (\beta_1 + \beta_2)(\sigma + c_1 + \mu + f(d)) \frac{I_{\text{tol}}}{\beta_1} \\ -\mu(\sigma + c_1 + \mu + f(d)) \frac{I_{\text{tol}}}{\beta_1 V} \end{aligned} \tag{3.6}$$

Hence we are left with 3 simultaneous equations $(3.3, 3.4, 3.6)$, with 3 variables $(I_{\text{tol}}, I_{\text{vul}}, V)$.

Next, we aim to eliminate I_{vul}. From equation 3.3,

$$I_{\text{vul}} = \frac{I_{\text{tol}}}{c_2 + d + \mu} \left(\frac{\beta_2}{\beta_1} (\sigma + c_1 + \mu + f(d)) + \sigma \right)$$

Then, equation 3.4 becomes,

$$V = \frac{k I_{\text{tol}}}{\mu_v} \left\{ 1 + \frac{1}{c_2 + d + \mu} \left(\frac{\beta_2}{\beta_1} (\sigma + c_1 + \mu + f(d)) + \sigma \right) \right\}$$

Therefore, by substituting these two equations into equation 3.6 yields

$$\Pi + c_1 I_{\text{tol}} + \frac{c_2 I_{\text{tol}}}{c_2 + d + \mu} \left\{ \frac{\beta_2}{\beta_1} (\sigma + c_1 + \mu + f(d)) + \sigma \right\}$$

$$\begin{aligned} &= (\beta_1 + \beta_2)(\sigma + c_1 + \mu + f(d)) \frac{I_{\text{tol}}}{\beta_1} \\ &\quad - \frac{\mu(\sigma + c_1 + \mu + f(d))}{\beta_1} \frac{\mu_v}{k} \left(\frac{1}{1 + \frac{1}{c_2 + d + \mu} \left(\frac{\beta_2}{\beta_1} (\sigma + c_1 + \mu + f(d)) + \sigma \right)} \right) \end{aligned}$$

The last equation involves I_{tol} only, the other unknowns having been eliminated. Simplifying, we get

$$\Pi + \frac{\mu\mu_v}{\beta_1 k}(\sigma + c_1 + \mu + f(d))\left(\frac{1}{1 + \frac{1}{c_2+d+\mu}\left(\frac{\beta_2}{\beta_1}(\sigma + c_1 + \mu + f(d)) + \sigma\right)}\right)$$

$$= I_{\text{tol}}\left[\frac{\beta_1+\beta_2}{\beta_1}(\sigma + c_1 + \mu + f(d)) - c_1 - \frac{c_2}{c_2+d+\mu}\left\{\frac{\beta_2}{\beta_1}(\sigma + c_1 + \mu + f(d)) + \sigma\right\}\right]$$

$$= I_{\text{tol}}\left[\frac{\beta_1+\beta_2}{\beta_1}(\sigma + \mu + f(d)) + \frac{\beta_2}{\beta_1}c_1 - \frac{c_2}{c_2+d+\mu}\left\{\frac{\beta_2}{\beta_1}(\sigma + c_1 + \mu + f(d)) + \sigma\right\}\right]$$

$$\begin{aligned}= \frac{I_{\text{tol}}}{c_2+d+\mu}\Bigg[&\frac{\beta_1+\beta_2}{\beta_1}(\sigma + \mu + f(d))(c_2+d+\mu) + \frac{\beta_2}{\beta_1}c_1(c_2+d+\mu)\\ &- c_2\left\{\frac{\beta_2}{\beta_1}(\sigma + c_1 + \mu + f(d)) + \sigma\right\}\Bigg]\end{aligned}$$

$$\begin{aligned}= \frac{I_{\text{tol}}}{c_2+d+\mu}\Bigg[&(\sigma + \mu + f(d))(c_2+d+\mu) + \frac{\beta_2}{\beta_1}(\sigma + \mu + f(d))(c_2+d+\mu)\\ &+ \frac{\beta_2}{\beta_1}c_1(d+\mu) - c_2\left\{\frac{\beta_2}{\beta_1}(\sigma + \mu + f(d)) + \sigma\right\}\Bigg]\end{aligned}$$

$$= \frac{I_{\text{tol}}}{c_2+d+\mu}\left[(\mu + f(d))(d+\mu) + \frac{\beta_2}{\beta_1}(\sigma + \mu + f(d))(d+\mu) + \frac{\beta_2}{\beta_1}c_1(d+\mu)\right]$$

Therefore, we have that

$$I_{\text{tol}} = \frac{(c_2+d+\mu)\left(\frac{\Pi + \frac{\mu\mu_v}{\beta_1 k}(\sigma+c_1+\mu+f(d))}{1+\frac{1}{c_2+d+\mu}\left(\frac{\beta_2}{\beta_1}(\sigma+c_1+\mu+f(d))+\sigma\right)}\right)}{(\mu + f(d))(d+\mu) + \frac{\beta_2}{\beta_1}(\sigma + \mu + f(d))(d+\mu) + \frac{\beta_2}{\beta_1}c_1(d+\mu)}$$

Hence, the endemic steady state of this system is given by,

$$I^*_{\mathrm{tol}} = \frac{(c_2+d+\mu)\left(\frac{\Pi+\frac{\mu\mu_v}{\beta_1 k}(\sigma+c_1+\mu+f(d))}{1+\frac{1}{c_2+d+\mu}\left(\frac{\beta_2}{\beta_1}(\sigma+c_1+\mu+f(d))+\sigma\right)}\right)}{(\mu+f(d))(d+\mu)+\frac{\beta_2}{\beta_1}(\sigma+\mu+f(d))(d+\mu)+\frac{\beta_2}{\beta_1}c_1(d+\mu)}$$

$$I^*_{\mathrm{vul}} = \frac{I_{\mathrm{tol}}}{c_2+d+\mu}\left(\frac{\beta_2}{\beta_1}(\sigma+c_1+\mu+f(d))+\sigma\right)$$

$$V^* = \frac{kI_{\mathrm{tol}}}{\mu_v}\left\{1+\frac{1}{c_2+d+\mu}\left(\frac{\beta_2}{\beta_1}(\sigma+c_1+\mu+f(d))+\sigma\right)\right\}$$

$$H^* = \frac{(\sigma+c_1+\mu+f(d))I_{\{}\mathrm{tol}}{\beta_1 V}$$

$$H^*_r = \frac{f(d)I_{\mathrm{tol}}}{\mu+\delta V}$$

where I_{tol} is given by the first equation above, and V by the third equation.

The fact that the endemic steady state expressions are made completely of positive values suggests a difficulty in finding a condition for the parameter values which determines the occurence of the endemic steady state. It seems the endemic equilibrium exists without any condition, and this is also shown in our numerical results where an endemic steady state was found even for $\mathcal{R}_0 < 1$.

The stability of the endemic equilibrium is determined by the analysis of the Jacobian matrix of the system evaluated at the endemic steady state. Using the 1^{st}, 2^{nd}, 3^{rd} and 5^{th} equations only, we have the Jacobian matrix, evaluted at the endemic steady state as,

$$J(H^*,\ I^*_{\mathrm{tol}},\ I^*_{\mathrm{vul}},\ V^*) =$$

$$\begin{pmatrix} -(\beta_1+\beta_2)V^*-\mu & c_1 & c_2 & -(\beta_1+\beta_2)H^* \\ \beta_1 V^* & -(\sigma+c_1+\mu+f(d)) & 0 & \beta_1 H^* \\ \beta_2 V^* & \sigma & -(c_2+d+\mu) & \beta_2 H^* \\ 0 & k & k & -\mu_v \end{pmatrix}$$

where $H^*,\ I^*_{\mathrm{tol}},\ I^*_{\mathrm{vul}},\ V^*$ are given by the equations above.

The characteristic equation for this matrix is given by $det(J(H^*,\ I^*_{\text{tol}},\ I^*_{\text{vul}},\ V^*) - \lambda I)$, where I is a 4×4 identity matrix. Thus in matrix form it is,

$det(J(H^*,\ I^*_{\text{tol}},\ I^*_{\text{vul}},\ V^*) - \lambda I) =$

$$\begin{vmatrix} -(\beta_1+\beta_2)V^* - \mu - \lambda & c_1 & c_2 & -(\beta_1+\beta_2)H^* \\ \beta_1 V^* & -(\sigma + c_1 + \mu + f(d)) - \lambda & 0 & \beta_1 H^* \\ \beta_2 V^* & \sigma & -(c_2 + d + \mu) - \lambda & \beta_2 H^* \\ 0 & k & k & -\mu_v - \lambda \end{vmatrix}.$$

This will be a very complicated quartic equation considering the expressions we got for the endemic steady states, and it will be virtually impossible to solve analytically. In theory, the study of the expressions of λ, which are the eigenvalues of the Jacobian matrix evaluated at the endemic steady state, will show insight to the condition for stability of the endemic steady state.

Chapter 4

Limitations and Discussion

4.1 General Discussion

In this report, the idea behind epidemiological modelling was discussed, and an important quantity called the basic reproduction number was derived and studied.

It is noted that the basic reproduction number describes the initial severity of a disease, and it has been mentioned that it is not an objective metric which we can use to compare diseases, rather it is a threshold value used in the study of a disease model, with different interpretations and derivations. It is mainly studied to determine controllable factors in a disease, in order to find intervention strategies decreasing the adverse effects of a disease.

We have also discussed a standardised method which simplifies the derivation of $\mathcal{R}_0$, called the Next Generation Matrix Method. It uses the concept of generational change to a distribution represented by a matrix. It is a novel method which attempts to provide a rigorous and standardised pathway to obtaining a basic reproduction number, making it an attractive method in contrast to the general method of directly finding a threshold condition. The Next Generation Matrix Method is limited in the sense that it can only be used on relatively simple models, for example we cannot use it for models with time delay.

The integral part of epidemiology lies in the aim of finding the factors involved in the transmission and progression of a disease in order to control it. Therefore, the mathematical modelling of diseases need to be a holistic process generalising what is known in medicine, viability of practical measures, and mathematical theory. A good mathematical model of disease is one which is not too complicated to produce limited analysis and limited attractive mathematical features, and not too simple which might overlook the complexity of the dynamics of the disease.

Additionally, on top of adequate model formulation, a rigorous methodology and definition of the model is required. There is already a divide in the definition of the basic reproduction number between epidemiologists (who use the definition 'the average number of infections that one individual generates') and mathematicians, and despite the fact that both defintions can be related, it is this kind of divide which might impede with the comprehensive study of a disease. Hence developments such as the Next Generation Matrix Method, attempting to generalise and provide a uniform definition and method are encouraged for the advancement of this field into a systematic study invloving approaches that include epidemiology, biology, medicine, sociology, and mathematics. Thus good practices, and areas of future research will include the following :

- Forming models with measurable parameters for model validation and functional predictions.
- Attempts to develop methods which give rise to a rigorous definition of the basic reproduction number.
- Defining other critical values in the mathematical model which can have realistic meanings.
- Connecting different models in different scales of space and time (e.g Population dynamics to Cell dynamics) to produce an encompassing model.

4.2 Discussion about the Hepatitis B Viral Dynamics Models

A model for Hepatitis B was devised, with further generalisations of the model including the model with time delay. We have verified that the system is a valid epidemiological model, and its analysis gave interesting insights.

4.2.1 Aims

- To develop a model which can describe the viral and cellular population dynamics of a HBV attack on hepatocytes.
- To find an expression for $\mathcal{R}_0$ for the model
- To find controllable parameters which can have real life significance.
- Analysis of endemic steady states.

4.2.2 Achievements

- Three models were proposed based on my knowledge gained about Hepatitis B.
- The basic reproduction number was found for the ‘standard’ model and the model with explicit time delay.
- The endemic steady state of the ‘standard’ model was analysed.

4.2.3 Limitations and Ideas for Further Research

Although the proposed model is valid in a mathematical sense, and the numerical results are promising, there are many limitations to the formulation and analysis of my work.

The most prominent limitation is to do with the time delay given in the model with the time delay. A time delay is inserted in the exposed compartment to describe the delay in viral replication which delays the exposed cell becoming an infectious cell. The addition of an explicit time delay relieves a parameter that would have been given as a ‘rate of transfer‘ which is then interpreted as the average time it spends in the compartment. Instead, it states a definite time delay of time τ which is spent before moving on to the next compartment. This makes more epidemiological sense for processes that are not due to interactions of the individuals in the compartment, but for processes that are actual delays in the progression of the individual’s state.

Accordingly, instead of the σ term representing the rate of transfer from the I_{tol} to the I_{vul}, this should in fact be given as a time delay as well. Sources such as [8], state that the ‘delay’ of a cell staying in the immune tolerant stage can last up to 30 years or more, and this is hence more likely a time delay rather than a molecular process between individuals in the compartment given by a parameter. Considering the fact that the time delay is very long, it would have been more suitable to model the time that the cell is in the immune tolerant stage as a time delay.

This analysis was omitted from this report as systems with two or more time delays are significantly harder to analyse than systems with only one time delay. Therefore, this is an area of further research which will make the model more aligned with the biological knowledge I have gained.

On a similar note, an idea to make the model more rigorous is to concretely define the parameters used to formulate the model. Only a basic description of what the parameters are meant to represent is given in this report, and to have practical significance, the parameters should be described more thoroughly. There are areas which can be improved by modifying the parameters and the model expression such as:

- The cure rate is given as a mass incidence ratio which is unrealistic. Currently it implies that the cure rate is directly proportional to the infected compartment size, but that is an over-simplification.

- $\mathcal{R}_0$ is dependent on initial size, $\frac{\Pi}{\mu}$ of the susceptible population. This is also unrealistic as it means a bigger liver is more likely to go endemic. Measures such as making the mass incidence rate of infection(β_1, β_2) into a 'standardised' incidence ratio by dividing by the total population $(H(t) + E(t) + I_{\text{tol}}(t) + I_{\text{vul}}(t) + H_r(t))$ can be a solution as demonstrated by [4].

- With further development of the H_r compartment, the model can be used to predict the size of cirrhosis and cancer depending on parameters.

Considering the numerical analysis of the models, the time unit for the proposed model is not concretely defined, and the parameter values used for the numerical analysis are not from medical data. Fine-tuning the model to retrieve realistic numerical results with medical data is an area of further research that can be done.

Finally, some ideas that can further improve the models are

- Finding other thresholds than the basic reproduction number, such as an expression regarding the threshold between an acute infection and a chronic infection. A clearance of disease after a short period of Immune-tolerant/Immune-vulnerable stage is representative of an acute infection, and an endemic steady state is representative of a chronic infection.

- Finding the global stability condition for the basic reproduction number as for the 'standard' model without time delay, we have a backward bifurcation occuring.

- Including a serology compartment, as many of the states of a hepatitis B infection are classified using serology. A 'switch' parameter could be used to change model parameters depending on the serology.

- It is hypothesised from sources, including [8], that the hepatocytes undergo a 'reactivation' phase after the immune-tolerance/immune-vulnerable stage. This is where virus titres and inflammation of the hepatocytes increase again, and the population levels in the different compartments are 'unstable', undulating about a mean value. In a mathematical sense, this is suggestive of a Hopf bifurcation occuring where an endemic steady state becomes a periodic limit cycle solution. Thus finding parameter values which can show this kind of behaviour or modifying the model to depict this phase is an area of further research.

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