MMath Group Project - Mathematical Virology

Harrison O'Neill, Matthew Knowles, Sabrina Duxbury, Yuanbo Liang

Department of Mathematics,
University of York,
United Kingdom

Contents

1 On Differential Equations in Molecular Virology **2**
1.1 Introduction . . . 2
1.1.1 Biological Background of Molecular Virology . . . 2
1.1.2 Overview Differential Equations in Molecular Virology . . . 2
1.2 An ODE model for in-host viral dynamics . . . 3
1.2.1 Deriving the model . . . 3
1.2.2 Model of an Unifected Person . . . 3
1.2.3 Model for an Infected Person . . . 5
1.2.4 Advancing the ODE model - Parameter Estimation . . . 5
1.3 The Stochastic Differential Equation Model . . . 7
1.3.1 Outline of a Stochastic Process . . . 7

Chapter 1

On Differential Equations in Molecular Virology

1.1 Introduction

1.1.1 Biological Background of Molecular Virology

Before diving into the maths of virology, we will briefly look at some of the biological processes involved, as a way of giving context to the maths that is employed later. Viral Pathogenesis is a very complex process with lots of varying factors. It can be somewhat boiled down to a balancing act between the host and the virus. The goal of any virus that wants to survive is to hijack the cells in a host and replicate as much as possible. This is done by a process known as *replication*.[1] [2]

There are three stages involved in replication, **Initiation of Infection**, **Replication and Expression of the viral genome** and **Release of mature virions**. The modelling we will undertake primarily focuses on steps 1 and 3.

1.1.2 Overview Differential Equations in Molecular Virology

Differential Equations are very relevant in applied mathematics. Virology is no exception. In this chapter we will be focusing on a micro scale, looking in depth at the equations used to model in-host viral dynamics. There are two main types of differential equations we will look at: ordinary (ODE) and stochastic (SDE). We assume the reader is familiar with ODEs, but SDE's are slightly more specialised. [3].

Definition 1 *A **Stochastic Differential Equation (SDE)** is a differential equation of the form*

$$dX_t = b(X_t, t)dt + \sigma(X_t, t)dW_t$$

We see two terms here that need further explanation.

- $b(X_t, t)$ is the **drift coefficient** of the equation. It describes the deterministic part of the equation.

- $\sigma(X_t, t)dW_t$ is the **diffusion coefficient**. It describes random motion, which is what seperates SDEs from ODEs. If this term was not here, we would simply have an ODE.

1.2 An ODE model for in-host viral dynamics

1.2.1 Deriving the model

Consider a human being. We can split the molecular constituents of this person into 3 categories: **Uninfected cells**, **Cells already infected cells** and **Free virions**. We denote the amount of these present at a time t as $T(t)$, $I(t)$ and $V(t)$ respecitvely. The body of the person in question will produce

[1] Creative, I know

fresh uninfected cells at a rate λ, however these cells will be removed from this category if they die or become infected. We use k to denote the rate at which uninfected cells become infected per virion. Secondly, these cells die naturally at a rate of μ_T. In the same way, μ_I is the rate at which infected cells are removed, the three options for this are natural cell death, immune response and *lysis*, which is where fresh virions are ejected from the cell, breaking the membrane and killing the cell. Similarly, μ_V is the rate at whcic virions are removed from the host. Finally, N gives the average number of new virions produced during the life of an infected cell.

With all of this in mind, we can derive differential equations for T, I, and V. Starting with T, we have a constant λ feeding new cells, but then we are removing them at a rate k per virion, and a proportion μ_T die of natural cell death. So we have:

$$\frac{dT}{dt} = \lambda - \mu_T T - kTV$$

Then for I, the kTV term from the above becomes positive, because these cells are going from uninfected to infected. These cells also die off at a rate of μ_T which encompasses natural death and the immune system. Putting this together gives:

$$\frac{dI}{dt} = kTV - \mu_I I$$

Finally, for V, we have to include N and μ_I into one term, because N virions can only be ejected from a cell if it dies. THen again we have the term μ_V for the removal of these cells from the host.

$$\frac{dV}{dt} = N\mu_I I - \mu_V V$$

All that is left to do is combine these three into a sytem of ODEs which we call the **Standard Model for In-Host Viral Dynamics** [4].

$$\begin{cases} \frac{dT}{dt} = \lambda - \mu_T T - kTV \\ \frac{dI}{dt} = kTV - \mu_I I \\ \frac{dV}{dt} = N\mu_I I - \mu_V V \end{cases} \tag{1.1}$$

1.2.2 Model of an Unifected Person

Before someone is infected, they have no free virions. With $V = N = I = 0$, we now model the person with two equations.

$$\frac{dT}{dt} = \lambda - \mu_T T \tag{1.2}$$

The solution for this system is given as

$$T(t) = Ae^{-\mu_T t} + \frac{\lambda}{\mu_T} \tag{1.3}$$

Since there are no infected cells, and no free virions, we just have the number of target cells increasing exponentially. Which makes sense because one's body creates more cells than it kills off- or at least, ideally that's what happens.

We can plot a sketch of what this looks like with values $\mu_T = \frac{1}{10} * \lambda$. This can be seen in figure 1. Clearly the values are restircted by my computing power, a human person (hopefully) has more than a total of 20000 cells.

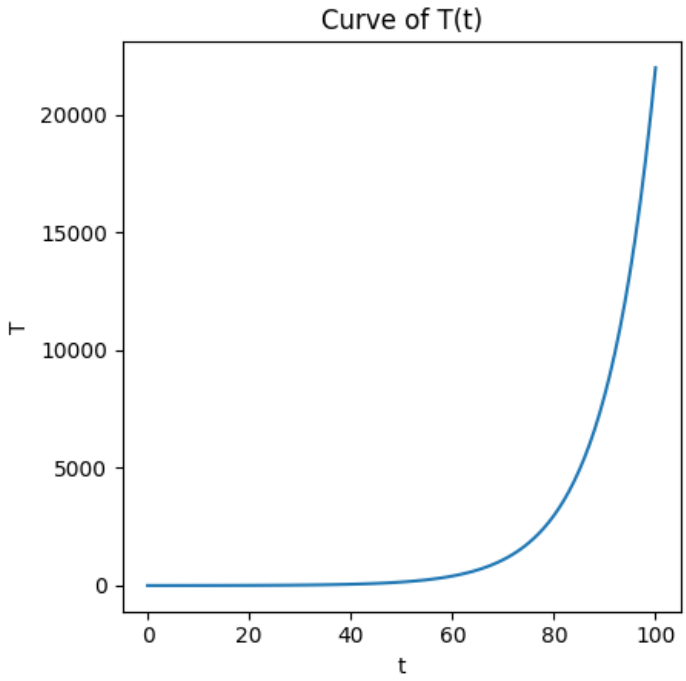

Figure 1.1: Sketch of T(t)

So we see that the exponential shape as mentioned. This is clearly slightly simplified, to make a more realistic model, we wouldn't have $\frac{d\lambda}{dt} = 0$. As a person gets older, their body will produce less cells, which would cause the graph to curve off and eventually stop.

1.2.3 Model for an Infected Person

We now turn to someone who has caught a virus. There are now V free virions present. The important factor is N. To see just how much this factor varies the results, a plot of this system was created in the *Python* programming language.[2]

We first look at positive N. When N is 1, each time an infected cell dies, only 1 new virion is released, analagous for N=10 and 50. The plotted graphs for these models can be seen below:

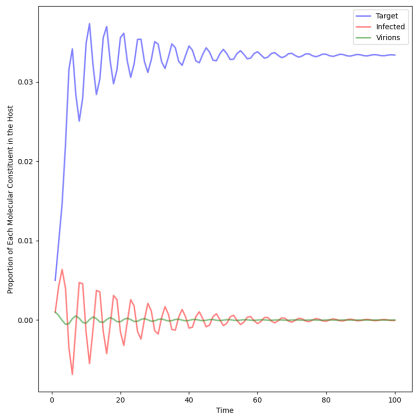

Figure 1.2: ODE Model with N=1

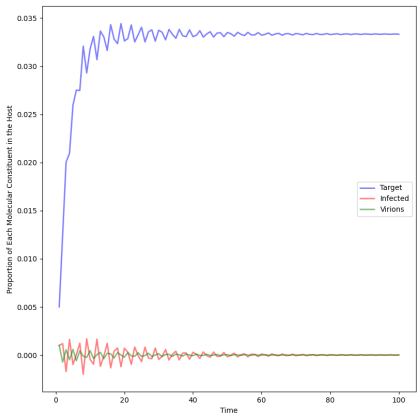

Figure 1.3: ODE Model with N=10

[2]Python was selected due to it's efficiecny and helpful modules which makes solving these equations much easier.

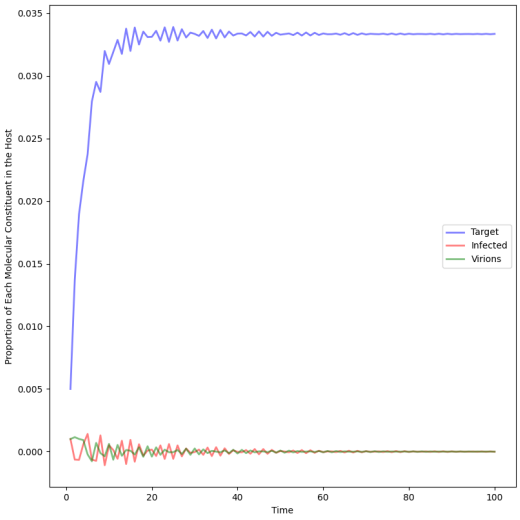

Figure 1.4: ODE Model with N=50

We can see that these equations result in a oscilating graph in each case. These coupled differential equations show how the amount of infected vs target cells changes over a given time period. When N is lower, the initial oscillation is greater. From a biological standpoint, this makes perfect sense as the host's body won't be as agressive in attacking the pathogen.[3] In the scenario where N is lower, we can see from the above models that the infection is sustained for longer, whereas when N is longer, the host will be more aggressive in fighting the pathogen, and so the infection won't last as long. Through genetic variations, the virus aims to find a balancing act between these performances. If a virus kills off its host too quickly, it will not reproduce and spread to others, which goes agains the aim of evolution.

Further, note that here we have not considered medications and treatments, this will be discussed in a later chapter.

1.2.4 Advancing the ODE model - Parameter Estimation

Differential equations are a great tool for this kind of scientific enquiry, and the model we have seen above has demonstrated it's power in acurately describing reality. But how can we improve it? Firstly, it depends on the virus being modelled. There are many viral infections, HIV, Dengue, SARS-CoV2 to name a few. These individual viruses behave differently internally and externally, the way we model this difference is through th parameters given to the equations. This can be seen intuitively by comparing something like HIV and SARS-CoV2. HIV is an immunodeficiency virus, this means that it destroys the hosts immune system, so our parameters like λ and μ_I will actually decrease over time as the virus takes hold. Comparitively, SARS-based viruses are respiritory illnesses, so they dont taget the hosts defense systems in the same way, and so these parameters will remain roughly the same throughout.

These parameters are derived from analysing large amounts of data. But this can be improved as time goes on by using Bayesian Statistics. This is discussed extensively in a 1989 paper by Zeger et. al [5]. This paper was focused on the AIDS epidemic in the US in the 1980s. By using log-linear models, they are able to estimate trends and numbers in the epidemic whilst correcting for new incoming data. It is this correcting aspect which is most relevant to our discussion. By correcting the models we can get a set of more accurate parameters which can then be used to fine tune our differential equations to model an epidemic. This is less to do with our models but it is useful to see how this works. Before this, we recall an incredibly important theorem:

[3] This is analagous to the fable of the boiling frog.

Theorem 2 *Bayes: Let* $\{H_1, \ldots, H_k\}$ *be a partition of an event-space* $\mathbb{H}$ *then for some other event E, Bayes' Theorem gives us:*

$$Pr(H_j|E) = \frac{Pr(E|H_j)Pr(H_j)}{\sum_k Pr(E|H_k)Pr(H_k)} \tag{1.4}$$

Example 3 *Parameter estimation for* μ_I
Suppose there is some disease circulating thorughout a population. We observe some dataset y of infection data. Our parameter of interest is μ_I *then Theorem 2 gives us:*

$$p(\mu_I|y) \propto p(y|\mu_I)p(\mu_I).$$

Since infection data for epidemics follows a normal distribution, the probability density functions can be subsituted in and the necessary calculations made from this, although this is beyond the scope of this chapter.

1.3 The Stochastic Differential Equation Model

We met the definition of a Stochastic Differetnial Equation (SDE) in the overview, definition 1. We will be focussing now on the $\sigma(X_t, t)dW_t$ term. Firstly, we ask "why use SDEs when we have seen that ODES give a good model?". Intuitively, there is an element of randomness to pathology, just because you have a disease, it doesn't mean you have a 100% chance of passing it on if you come into contact with an infected person. Analously, a pathogen might not necessarily make it all the way through the pathogenesis process of infecting a cell. So introducing the randomness term can refine our models nicely.

1.3.1 Outline of a Stochastic Process

The σ term is a *Stochastic Process*. We introduce the following definition for a stochastic process as given in [1]:

Definition 4 *A stochastic process is a family of random variables* $\sigma(t)$ *parametrised by* $t \in T \subset \mathbb{R}$. *When T is a continuous inteval in* $\mathbb{R}$ *(As in our case) then we call* σ *a stochastic process in continuous time.*

Bibliography

[1] Zdzislaw Brzezniak and Tomasz Zastawniak. *Basic stochastic processes: a course through exercises.* Springer Science & Business Media, 2000.

[2] Alan Cann. *Principles of Moclecular Virology.* Elsevier Academic Press, 2015.

[3] Miranda Holmes-Cerfon. Lecture notes on stochastic differential equations.

[4] Stephen Pankavich and Christian Parkinson. Mathematical analysis of an in-hot model of viral dynamics with spatial hetrogeneity. *arXiv preprint arXiv:1508.07617*, 2015.

[5] Scott L Zeger, Lai-Chu See, and Peter J Diggle. Statistical methods for monitoring the aids epidemic. *Statistics in Medicine*, 8(1):3–21, 1989.