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Incorporating Time Delays in the Mathematical Modelling of the Human Immune Response in Viral Infections

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Abstract

Mathematical modelling helps to describe the functional and causal relationships between objects in the physical world. The complexity of these models increases as more components and variables are added to maintain and observe. Differential equations are regularly used in these models, as they are able to display the interactions between several variables and describe non-linear behaviour. Differential equations are commonly used in immune response mathematical models to help describe these complex and dynamic interactions within the immune system of the organism. Time delays in the immune system are common and are often disregarded due to the low-resolution of models, which provide limited description of the specific section of immune system being studied. The few models that incorporate time delays are mostly at the epidemiological level, to track the spread of the virus in the population. In this paper we review the applications of the models based on differential equations and describe their potential utilization for the studies of immune response in SARS-CoV-2.

Keywords: Mathematical Modelling; Time Delay; Viral Infection

1. Introduction

Mathematical and computational modelling turns a conceptual model into a quantitative description of a system. These types of models not only help to understand the systems they are modelling but can provide insights into the

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complexities of the systems by studying the effect of changes made to the model. This is useful to narrow down possible hypotheses before transferring the models to *in vivo* models in the lab. Since computing costs are decreasing it is relatively inexpensive to perform hundreds of simulations, quite the opposite to performing hundreds of *in vivo studies*. Mathematical models have been used to advance a wide array of scientific fields from physics to biology though the role of modelling in biology is a recent development [1].

Before the advancement of computers, modelling of biological systems by hand would have been impossible due to the large number of variables; for instance, due to the constant movement of cells their position would have to be recalculated repeatedly. With computers this modelling becomes instantaneous and allows researchers to observe and simulate the interactions between different cells or system elements [2]. This is tremendously useful as biological functions and systems are quite complex with many moving and variable parts; which is further complicated due to the scale of modelling depending on the population versus the cellular levels.

Systems biology is considered to be the study of the interactions and behaviour of the components of biological entities such as cells, tissues, organs and organisms [3]. One aspect of systems biology is to focus on the immune system mechanisms of the human body. This can be either the innate or the adaptive immune responses or in most cases the interaction of both of these two responses [4]. Computational immunology, also known as immunological bioinformatics or immunoinformatics, uses computational modelling to model and analyse the dynamics of molecular and cellular entities of the immune system including its disorders and various infections [5]. Through many cycles of model building, simulation, and experimentation one can develop complete and informative models of immunological processes [6]. These *in silico* representations of the processes of interest are invaluable in hypothesis testing before moving to further testing *in vivo*.

The immune system is a dynamic and fast changing system to model, and its responses have a large temporal range from milliseconds to decades. Clinically one can only follow the disease progression by slices of time and can then interpolate from these data points what happens in between. Although from these points it is sometimes difficult to determine the true disease rate of progression and the treatment response effects [7]. These missing data points and these interpolations could miss time delays in the immune response, as the rate of pathogen spread could be exponential. Time delays in the immune response to viral infections are often disregarded due to the low-resolution models, which provide a limited description of the specific section of immune system being studied [8, 9]. However, time delays are common in the immune system. For example, the time between becoming infected and T cell activation varies and the time between these events may impact the course of the infection in the host. Therefore, the length of the time delay between infection and immune initiation, rate of effective immune build-up, and the presence of specific immune memory have profound implications for the pathogen's host exploitation strategy [8].

Differential equations (DEs) are regularly used in viral kinetic mathematical models to help describe these complex and dynamic interactions within the immune system of the organism. A DE is an equation that relates one or more functions and their derivatives. The functions usually represent physical quantities and their derivatives represent the rate of change. Their applications are used in fields such as economics, engineering, and biology. Various types of DEs are frequently used for modelling biological systems due to their ability to effectively capture non-linear behaviour and demonstrate the interactions between numerous variables.

Ordinary differential equation (ODE) models are the most common and the basis upon which most complex models are created and adapted from. They are used to create kinetic models describing average interactions between large numbers of cells, molecules, and/or individuals. ODEs typically describe dynamics over a continuous time period and are able to incorporate a time delay by adding in a term to account for various time delays. However, delay differential equations (DDEs) are more suited to incorporating time delays into the interactions between components. These time delays are important in correctly modelling certain viral infections in the human body [10]. DDEs may also result in a better fit for systems without modelling all components of the process causing the delay. Currently most models using DEs are deterministic meaning they do not include random stochastic events in the responses. Therefore, the outputs of the model are determined entirely by the input parameters guaranteeing reproducibility each time. Stochastic differential equations are not reproducible as they incorporate one or more terms to allow inherent randomness into the model. These are commonly not used as they are computationally complex and more difficult to parameterize than deterministic models [10, 11].

This paper is organized as follows. In Section 2, we present a literature review for four acute viral infections to highlight the lack of models for coronaviruses. Section 3 focuses on the aspects of modelling in these viral infections and examines several current models both deterministic and stochastic. In Section 4, we describe

numerical simulation using a delay differential equation to feature the varying infection outcomes. Finally, we summarize our research and discuss future work.

Nomenclature

ODE   Ordinary Differential Equation
DDE   Delay Differential Equation
SDE   Stochastic Differential Equation
CoVs   Coronaviruses
SARS   Severe Acute Respiratory Syndrome
MERS   Middle Eastern Respiratory Syndrome

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2. Review of Viruses & Models Associated in the Literature

In this section, we present a review of the literature on mathematical modelling for acute viral infections, limited to coronaviruses and Influenza A. We intentionally focus on models that use differential equations to represent time delays.

Coronaviruses (CoVs) are enveloped, non-segmented, positive-sense, single-stranded RNA viruses. They can typically be separated into the four genera α, β, γ and δ CoVs, though the human CoVs are caused by α, β genera's [12]. The severity of these human CoVs range from the upper respiratory tract infections resembling the common cold to lower respiratory tract infections such as pneumonia [13]. Both MERS-CoV and SARS-CoV are from the same family as SARS-CoV-2, so we included them in the literature review.

Influenza A was included in this literature review, as several mathematical models of viral infection have shown great success in modelling the infection progression.

For SARS-CoV, MERS and Influenza A searches, the OVID Medline database was utilized with the following indicators: Epub Ahead of Print, In-Process & Other Non-Indexed Citations and the years were limited to 2000-2019 to exclude papers on SARS-CoV-2. Search terms with the phrase ".ti,ab." indicated that the term must appear in either the title or abstract, whereas any terms within quotation indicated that the exact phrase must occur. An asterisk after the term meant that the database search finds all forms of that root, with the term 'exp' indicating that the database will be searched for the specific term as well as more specific terms related to the original. For SARS-CoV-2 the search was identical to SARS-CoV though the years were limited to 2019-to the current date. The final search query was defined as follows. However, for Influenza A the final search query was modified to exclude influenza's pertaining to animals, and so its virus search term was (Influenza, Human/).

([FULL NAME OF VIRUS]/ **OR** [VIRUS ABBREVIATION].ti,ab.) **AND** (("mathematical model" or "mathematical modelling" or "mathematical modelling" or "differential equation*").ti,ab. **OR** exp *models, theoretical/)

2.1. SARS-CoV-2

SARS-CoV-2 is currently the cause of the worldwide pandemic, first emerging in November 2019 in Wuhan, China. Like both SARS and MERS, SARS-CoV-2 attacks the respiratory system and causes symptoms such as fever and shortness of breath. Though SARS-CoV-2 is less deadly it is much more transmissible than either MERS or SARS-CoV which is responsible for causing the virus to spread around the world [14].

After performing the literature review, only 15 papers were included in the final results; most papers were describing epidemiological studies or animal models of the virus. However, the paper by Sohail *et al.* focused on the molecular mechanisms of spreading the SARS-CoV-2 virus infection [15]. Sohail *et al.* developed a delay differential equation model to describe the interactions of the infected, uninfected and the virions; this was done through reverse-engineering of the disease based on the virus characteristics such as its cytokine storm and readmission of patients after previous infection [15].

2.2. MERS

MERS is caused by a coronavirus known as MERS-CoV and its first emergence was in 2012. MERS-CoV attacks the respiratory system and causes severe pneumonia in humans [16]. Its mortality rate has been reported to be greater than 37%, though fortunately MERS' person-to-person transmission is quite ineffective [14, 17, 18]. Some infected persons may exhibit no symptoms or mild cold-like symptoms instead, though the primary symptoms of MERS are cough, fever, and shortness of breath [16]. Many epidemiological models have been created to show the transmissibility of this disease and have overshadowed immunological modelling of the viral infection within the host.

The literature search resulted in 132 papers. After reviewing the abstracts, we have determined that only two papers were related to in-host modelling [16, 19]. Though only one paper by Tang *et al.* utilized DEs to create a novel four-dimensional dynamic model to describe the infection of MERS-CoV and the expression of dipeptidyl peptidase 4 (DPP4). DPP4 is believed to be the receptor for MERS-CoV; it is generally expressed in endothelial and epithelial cells [16, 20]. Although this model does not represent time delays and randomness, it is found to be a good approximation for modelling the MERS-CoV infection and the expression of DPP4.

2.3. SARS-CoV-1

SARS-CoV first emerged in late 2002 in Southern China and caused an outbreak of severe acute respiratory syndrome. It was a highly lethal coronavirus but, due to intense public health mitigation measures, it faded out before becoming a worldwide pandemic. According to Petersen *et al.,* transmissibility, R_0, at the epidemiological level of SARS-CoV-2 and SARS-CoV are 2.5 and 2.4, respectively, whereas the incubation period is 4-12 days for SARS-CoV-2 and 2-7 days for SARS-CoV [14]. This means that the model for time delays should be adjusted accordingly to appropriately represent these differences in time delays. Interestingly, the proportion of mild illness is higher in SARS-CoV-2 than SARS-CoV, whereas the proportion of patients requiring hospitalization is smaller in SARS-CoV-2 (20%) than in SARS-CoV (70%) [14]. Since the SARS-CoV virus is genetically closely related to SARS-CoV-2, the SARS-CoV viral infection was included in our study of models for CoVs.

The literature review lead to the finding of 104 papers, though upon reviewing abstracts for relatedness only two papers were found to be relevant to in-host modelling [21, 22]. Further review found neither were related to modelling with differential equations or focusing on time delays.

2.4. Influenza A

Influenza is highly contagious and is easily transmitted through contact with droplets from the nose and throat of an infected person who is coughing and sneezing [23]. Virus replication is localized to the upper respiratory tract and its standard pattern of infection in adults is characterized by an exponential growth of virus titer peaking after two to three days post infection followed by an exponential decrease [24].

The literature search produced a total of 1,088 papers; however, when the keyword "time delay*".ti,ab. has been included the results were reduced to 5 papers. These all were at the epidemiological level. Although the papers do not focus on time delay, we include the presented models and we discussed them in Sections 3.1 and 3.2 [24, 25].

3. Aspects of Modelling Viral Kinetics

In this section, we discuss two aspects of modelling that are often overlooked such as time and the inherent randomness of viral infections. These aspects can be integrated in various DE models that were created to model and track the viral infection kinetics within the host. Understanding how the host responses control the viral spread and how possible antiviral therapies will work are made easier by use of mathematical modelling. This is evidenced by the development of the Human Immunodeficiency Virus model leading to the understanding of its hidden viral kinetics [19, 26].

3.1. Explicit Modelling of Time in Infected Cell Populations Using Delay Differential Equations

DDEs have built-in time delays in that the derivative of an unknown function at any time depends on the solution at a preceding time, a trait that traditional ODEs lack. With this it makes modelling more like the biological systems they were created for.

Baccam *et al.* utilized delay differential equations in their model on a data set of individual's experimentally infected H1N1 Influenza A virus [16]. This was to be able to separate the production of free virus into two populations of infected epithelial cells. One represents the infected but not yet producing virus (I_1) while the second represents the infected and actively producing virus cells (I_2). They then incorporate another term to address the average transition time between going from the I_1 to I_2 as k [24]. T and V represent the uninfected target cells and the virions, respectively. The rate of infected cell death and the rate of which uninfected cells can be infected by the virus particles are represented by δ and β, respectively. Finally, the infected target cells produce virus particles at a rate of p and these are degraded or cleared by the immune system at a rate of c. This described delay model is shown below in equation 1.1 [24].

$$\frac{dT}{dt} = -\beta TV,$$

$$\frac{dI_1}{dt} = \beta TV - kI_1,$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2, \tag{1.1}$$

$$\frac{dV}{dt} = pI_2 - cV.$$

DDE's are better suited for specifying time delays especially in the sense that infected cells do not immediately start producing virions so it is best to separate these two populations to better account for properties of the disease, such as the incubation period.

3.2. Explicit Modelling of Immune Response Time Delays Using Ordinary Differential Equations

ODEs describe interactions between large numbers of cells, molecules, and/or individuals over a continuous time period but do not implicitly account for time delays. However, one can add a time delay to a set of ODEs instead. This is the route Handel *et al.* took when fitting models based on ODEs to two datasets from previous experimental influenza A studies. Both the innate immune response and the adaptive immune response were included to account for different activation periods of each immune response type. The model is shown in equation 1.2.

$$\dot{U} = \lambda D - bUV \qquad \dot{V} = \frac{pI}{1 + \kappa F} - cV - \gamma BUV - \kappa VX$$

$$\dot{E} = bUV - gE$$

$$\dot{I} = gE - dI \qquad \dot{F} = \omega V - \delta F \tag{1.2}$$

$$\dot{D} = dI - \lambda D \qquad \dot{X} = fV + rX$$

Where *U, E, I, D* and *V* relate to uninfected cells, infected cells not producing virions, infected cells producing virions, dead cells and free virus, respectively. *F* and *X* represent the innate and adaptive immune responses, respectively. Uninfected cells are infected at a rate of b, which leads to infected cells not producing virions, which after a period of $1/g$ hours start to produce virions at a rate p. The virus producing cells die after some time $1/d$ and

the replacement of dead cells with new uninfected cells is at a rate of λ. The conversion between infectious virions and plaque forming units or egg infectious doses is represented as γ.

The innate response, *F*, in this model is assumed to be triggered upon infection and increases proportionally to free virus at a rate of *w*, with a first order clearance rate of δ. While the adaptive response *X*, is activated proportional to free virus load at rate *f*. This activation is then followed by antigen-independent clonal expansion at an effective growth rate *r* and the kill rate of adaptive immune response is *k*. The time delay that is incorporated into this model is $F(1-\tau)$ which is used to represent the time delay between the level of interferon and its action of reducing virus production [25].

3.3. Explicit Modelling of Uncertainty Using Stochastic Differential Equations

MERS, SARS and Influenza are known as acute viral infections unlike chronic viral infections such as HIV, a viral infection that is currently incurable. HIV was one of the first viral infections that benefited from rigorous mathematical modelling to understand the underlying viral kinetics. With stochastic modelling one can allow essential randomness, a characteristic that would benefit a chronic disease like HIV.

Stochastic models have been created for HIV to account for latency and for viral release strategies. Liu *et al.* created a model to account for the latency period of HIV, a period where the infection lies dormant and is a great hindrance to viral elimination in infection processes [27]. HIV transcription is a random process and produces fluctuations in the gene products; these fluctuations could play a part in HIV transactivation and in latency. Their model accounts for latent infections, T-cell logistic growth, antiretroviral therapy and random fluctuations [27]. Yuan *et al.* focused on viral release strategies in early HIV infection, specifically budding and bursting [28]. Budding has virus particles produced throughout the life cycle of the cell, budding from the surface, whereas bursting has the virus particles enveloped within the cell and released on death of the cell. They found that in models with no immune responses the bursting strategy was more successful whereas with an immune response it was vice versa [28].

While HIV is a chronic disease unlike the others studied in Section 2, the HIV models using stochastic differential equations would be a good starting place for modelling of acute infections.

4. Basic Simulation

The DSAIRM modelling tools is an R package created by Handel *et al.* to allow for the exploration of dynamical systems modelling of within-host infection and immune response dynamics [29]. From this R package we adapted

Table 1. Parameters used to simulate viral infection utilizing COVID-19 data.

Parameter	Description	Start Value	Units
T_0	Start number of uninfected cells	4×10^{-8}	cells
I_1	Number of infected non-producing cells	0	cells
I_2	Number of infected producing cells	0	cells
V	Number of Virions	10	copies/ml
δ	Rate of infected cell death	4.71	day^{-1}
c	Rate of degradation of infected cells by immune system	0.7	day^{-1}
β	Rate of which uninfected cells can be infected by the virus particles	3.97×10^{-7}	$(Copies/ml)^{-1} day^{-1}$
p	Rate at which infected cells produce virus particles	8.2	$Copies/ml\ day^{-1}\ cell^{-1}$
k	Average transition time between I_1 and I_2	2	days
tstart	Start time of simulation	0	days
tfinal	Final time of simulation	10	days

the basic viral simulation R source file to allow for the modelling of the eclipse phase with two infected populations. One represents the infected but not yet producing virus (I_1) while the second represents the infected and actively producing virus cells (I_2). This model is described in Section 3.1 for the influenza A model Baccam *et al.* utilized [24]. Data for this model was from the preprint paper by Hernandez *et al.*, which was derived from preliminary virological assessments of patients with COVID-19; the variables are defined in Table 1 [30, 31]. The starting value for uninfected cells was taken from Baccam *et al.*'s calculation of the approximate number of epithelial cells in the upper respiratory tract [24].

From this we further altered the model to show the differences between varying the length eclipse phase using k values between 1 and 10 as shown in Figure 1. This demonstrates how shorter eclipse times lead to a greater build up of a population of infected non-producing cells whereas, when the eclipse time increases, the infected cells that produce virions reach a much greater peak than infected non-producing cells.
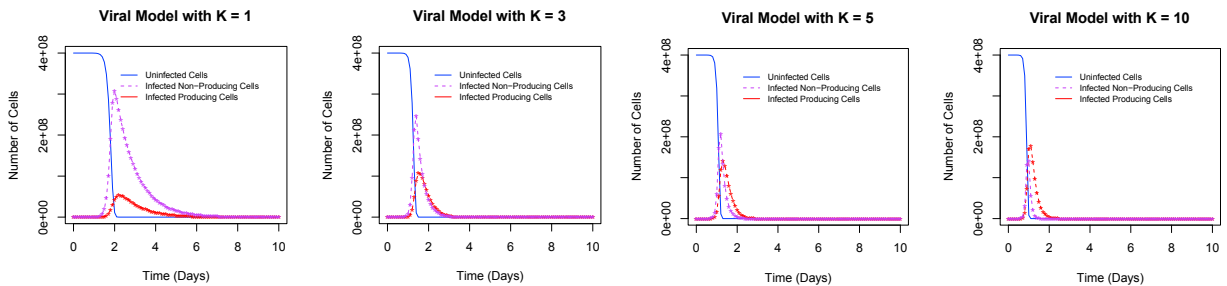

Fig. 1. Simulation modelling of COVID-19 data with varying K values to represent the time between infected non-producing cells and producing infected cells.

This visualization of incorporating the eclipse phase is meant to illustrate how varying the time delay of this phase greatly varies the length of the infection until all infected cells go to zero. As seen when $k = 1$, the number of infected cells does not go to zero until roughly 6 days whereas, when $k = 3$, it is roughly 3 days. Likewise, when $k = 5$ or $k = 10$, the length of time is roughly 2 days which is a much faster resolution of the infection than when the eclipse phase is much shorter.

Viral kinetics can vary widely depending on the types of cells infected, the type of virus, and the host. This has already been seen in the way COVID-19 affects people with some having mild cold symptoms and others requiring intensive care. Thus when creating simulations from models, it is important to note that generalizing accurately to the entire population is challenging before also considering time delays and the speed of viral infection progression.

5. Conclusions

Modelling within-host viral kinetics is a complex issue that is necessary for understanding the progression of infection and for understanding the viral mechanisms of the invading pathogen. The inclusion of time and randomness within these models to accurately simulate the infection further complicates this problem. However, removing or ignoring time delays has profound implications for understanding the pathogen's host exploitation strategy. As such, creating these *in silico* representations of the processes of interest are invaluable in hypothesis testing before moving to further testing *in vivo*.

The human immune system and its response mechanism are extremely complex, and are not yet fully understood. However, the recent developments in AI and Big Data analytics provide new approaches to modelling in immunology, virology and healthcare. In this paper we highlighted the difficult aspects of modelling such as integrating randomness and managing time delays. The review of literature on MERS, SARS-CoV, SARS-CoV-2 and Influenza A, showed the lack of models for CoVs despite the abundance of literature on Influenza A and HIV. This gap in modelling may be due to SARS and MERS infections being not as prevalent as HIV or Influenza A.

In our simulation utilizing SARS-CoV-2 infection data, we were able to demonstrate the effects of time by changing the length of the eclipse phase or time delay between infected non-producing cells and infected cells producing virions. Varying the value of k between 1-10 showed a large effect in the duration of infection. Our results demonstrated the importance of incorporating time delays.

Future work involves adapting the current model to represent stochastic processes and integrating immune response time delays into the model. Incorporating time delays in the mathematical model of immune response is of particular interest because the length of time delay between activation of the innate and adaptive immune systems has a major impact on efficient and effective clearing of the SARS-CoV-2 virus [32]. Furthermore, we plan to build upon current models for the Influenza A and HIV infections to investigate the dynamics of SARS-CoV-2 infection.

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