Influenza Virus Infection Modeling

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Chapter 1

Background and Aims

1.1 Biological Problem and Previous Work

The influenza virus is responsible for a variety of diseases, ranging from the common cold to worldwide pandemics like the Bird flu. For the purpose of treating, and ultimately preventing infections from the virus, it would be desirable to generate a model which simulates the course of viral infection in the human respiratory epithelium. By investigating how viruses interfere with the integrity of the epithelium and the amount of time that is required for the immune response to clear the virus,
Moreover, it would be most ideal if all aspects of human epithelial immunology (*e.g.* interaction of cytokines, effector cells, antibodies, virions, *etc.*) are incorporated into the prospective model. Initially, a model was devised in 2007 which encompasses many of the factors involved in the immune response [1], such as:

a. Antibodies and their affinity toward the circulating virus,

b. Antigen presentation,

c. Production and clearance of the virus, *etc.*

This original model, as shown in is a continuum model based on a series of ordinary differential equations (ODEs); it ultimately predicts changes in the population of healthy and infected cells, and levels of the free virus over the course of infection.

In 2013, the results of the model have been reproduced by members of Group G by using a series of Matlab and C++ code [2]. This computational model has soundly demonstrated the cellular and viral dynamics in a hypothetical infection scenario with considerable accuracy to the data from the original work. This computational model was superb in that, the user has the freedom to customise the duration of simulations and also set the values for 27 parameters, such as viral release rates, antibody maturation and cellular turnover.

However, having said this, we felt that the computational model showed modest clinical relevance. The model is designed so that the parameters can be tailored to each patient's immune capacity and each virus strain's virulence, but the model only reflects the natural biological response (*i.e.* the adaptive and innate immune responses) to the virus. In contrast, our group felt that incorporating the effects of anti-influenza drugs on the cellular and viral dynamics was a more pragmatic interpretation of the problem. Consequently,

this would allow users to see if treatment is a viable option at specific time points, and raise the need for potential changes in treatment regimes (*e.g.* combinatorial therapy of neuraminidase inhibitors).

Furthermore, though our group realised that incorporating more user-dependent parameters could generate outputs for a wide variety of biological scenarios, we equally felt that having absolute control over all 27 parameters may yield biologically-irrelevant results. This would especially be the case if users inadvertently use unreasonable parameter values. For instance, the user may decide to use extremely high rate constants for viral infection (γ_{HV}) which could lead to false negatives of survival against a viral infection. We also felt that the model assumes some level of staticity; for instance, it assumes that the rate constant of virus formation from the infected cell, γ_{HV}, is the same in every infected cell. In theory, this value is likely to vary on a cell-to-cell basis (provide reference). Hence, in order to introduce a component to reflect the inherent randomness of the system, we have decided to randomise the input parameters with a pseudorandom number generator. Effectively, we wanted to introduce a level of stochasticity which is controllable to some extent, yet random enough to reflect the randomness of the process.

Effectively, we propose the following list of changes to the computational model to improve its general biomedical relevance:

1. Considering the effects of anti-influenza drugs such as Tamiflu and Relenza (neuraminidase inhibitors) on the release capacity of the virus

2. Removing the need for submitting an initial value for antigenic compatibility and viral release rates - both parameters will be randomised and solved by stochastic differential equation solvers which accounts for noise in the system

3. Effector cells are said to be removed by "natural death"; considering that healthy cells can inactivate effector cells like natural killer (NK) cells (provide ref), we also propose a healthy cell-dependence on the levels of effector cells

4. Addition of helper T-cell dynamics as they help to form plasma cells and effector cells, but their role has been omitted in the original and computational models.

1.2 Extension of the Model I – Modelling Antiviral therapy

To extend the model, we decided to investigate the effects of adding an antiviral agent to the system. Antivirals are drugs used to control viral infections both theraputically and prophylactically. They operate by interfering with the virus copying sequence at one or more points in its replication cycle. For example, two common antiviral targets are:

1. **Viral M2 proton channels:** Disruption of viral unpackaging in host cytosol *via* the competetive inhibition of the viral M2 proton channel; []

2. **Viral Neuraminidase:** Prevention of viral budding *via* competetive inhibition of the neuraminidases responsible for severing newly-created virus particles from their host cells.[]

Instances of antivirals exploiting the above mechanisms include Amantadine (trade name "Symmetrel') and Oseltamivir phosphate (Tamiflu).

Kinetic models have previously been used to investigate the influence of an antiviral drug on viral dynamics within infected individuals. Here we acknowledge the work of Smith and Perelson, [3] who modelled drug influences in simple kinetic models. The influence of the 2 drug types was accommodated by changing terms in:

- $\gamma_H V \rightarrow$ sometheing else TBD
- $\gamma_V \rightarrow$ sometheing else TBD

However, the change assumed a drug concentration that was constant with respect to time. This would have prevented us from analysing effects such as the dependency of drug impact on the drug administration time. We sought to extend this work by combining a more realistic, temporal drug model with the extended dynamic model of group G. Key questions include:

1. How does the time delay between infection onset and drug administration effect the treatment outcome?
2. Can polytherapy exhibit synergy? *I.e.* could 2 drugs working together ever acheiver more than the sum of their invidudual effects?

Modelling Viral Drug resistance

Viruses such as Influenza A are known to be capable of rapidly developing resisitance both to Tamilfu and Symmetrel. Indeed, innate viral resistance to Symmetrel is now so widespread that it has been withdrawn as a drug. We sought to model the onset of viral drug resistance by splitting the viral populaton V into subpopulations of different mutants, displaying increasing levels of drug resistance[1]. Initially, all viruses were of an unmutated type, but subsequent mutations (modelled by stochastic population transfers) allow occasional transfer to progressively more resistant types which then proliferate faster owing to the selective pressure imposed by the drug.

1.3 Introduction of Stochasticity

To improve the current computational model, we felt that giving the user the freedom to incorporate stochasticity into their analyses was essential. The idea was not to replace the code *per se*, but instead give the user a more realistic account of how cell populations and viral titre can vary over time.
For example, one of the parameters, S (antigenic compatibility of antibodies) is initialised by the user. By using a fixed initial value of antigenic compatibility, *e.g.* $S(0) = x$, we ignore the process of naive B-cell selection (and the possible delay in the immune response due to selection), we also assume that all serum antibodies have affinity x for the virus. In theory, every antibody is constructed from a diverse genetic framework and every antibody has a different affinity for the virus - only the antibody that binds strongest is selected for further expansion in the geminal centres

[1]The drug resistance was modelled as having an associated fitness cost, making mutation favourable in the presence of antivirals but marginally unfavourable in their absence.

In order to achieve our aims listed in the previous section, we:

Chapter 2

Our code in comparison to Group G

Bibliography

[1] David Swigon Baris Hancioglu and Gilles Clermont. A dynamical model of human immune response to influenza a virus infection. *Journal of Theoretical Biology*, 246:70–86, 2007.

[2] N. Pearce L. Bowler F. Wolfreys M. Aldeghi I. Frost and P. Taylor. A dynamical model of human immune response to influenza a virus infection. 2013.

[3] Amber M. Smith and Alan S. Perelson. Influenza a virus infection kinetics: quantitative data and models. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, 3(4):429–445, 2011.