

Modeling the Viral Kinetics of Influenza A During Infection in Humans

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Abstract - This study explores the natural control system in the body for responding to exposure to the Influenza A virus. More specifically, it delves into the development of a model to simulate the responses of target uninfected cell counts, infected cell counts, and viral titers. There are two particular models of interest: a delayed model that incorporates the brief inactive period for newly infected cells, and a non-delayed model reflecting only infected cells without delay after initial infection. Both models are commonly used in the literature and the benefits of each model are studied and explained. We generate Simulink models for both the delayed and non-delayed sets of ordinary differential equations (ODEs) to simulate responses to different viral titer impulses. Additionally, this study aims to extrapolate these models to the case for a vaccinated individual. To do this, we modify the viral clearance rate and infected cell death rate of our initial model to account for the improved immune response generated by vaccines.

I. INTRODUCTION

Influenza A is a leading cause of lower and upper respiratory tract infections and causes a significant amount of morbidity and mortality. This strain alone causes upwards of 15 million respiratory infections and 200,000 hospitalizations on a yearly basis. [1-5] Additionally, the weaker immune responses of the elderly leads to over 36,000 deaths due to the flu virus or its complications, which may include bacterial pneumonia, sinus infections, and worsening of existing medical conditions such as asthma. [3,5] Additionally, the flu can temporarily make someone significantly more susceptible to other infections, usually bacterial or other viruses. These issues all contribute to the flu season's high annual cost of over 10 billion dollars. [6] Currently, vaccinations are the best way to help prevent and fight infection, but with the great number of different strains, the constant emergence of new strains, and the poor efficacy of current antiviral treatments, the virus is always difficult to deal with. [1-4] The impact of constantly changing strains can be seen as recently as 2009 with the Swine Flu Pandemic. Although the general immune response is understood, the rapid kinetics of the virus still is not fully understood. [5,7]

The two most widely used models for flu viral kinetics are a group of four and three ODEs, respectively, that track the populations: target (epithelial) cells (T), infected cells (I), and viral titers (V). [2-8] Target cells are epithelial cells, cells that line surfaces within the body, that are uninfected, which means they are susceptible to viral infection. The infected cells are the epithelial cells that the virus has attached to, and are being used to produce more virus until the cell dies. Viral titer is the

concentration of virions in the bloodstream. The four ODE model (Delay Model) tracks two classes of infected cells (I_1 and I_2) in which I_1 represents the idle infected cell, and I_2 represents the virus producing infected cell. The Delay model is considered more biologically accurate as this accounts for the delay between becoming infected and being able to produce more virions.

$$\frac{dT}{dt} = -\beta TV \quad (1)$$

$$\frac{dI_1}{dt} = \beta TV - kI_1 \quad (2)$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2 \quad (3)$$

$$\frac{dV}{dt} = pI_2 - cV \quad (4)$$

The three ODE model (Non Delay Model) ignores this incubation period between the transition of group 1 infected cells to group 2, and considers only one population of infected cells, in which they are able to spread virus as soon as infection occurs.

$$\frac{dT}{dt} = -\beta TV \quad (5)$$

$$\frac{dI}{dt} = \beta TV - \delta I \quad (6)$$

$$\frac{dV}{dt} = pI - cV \quad (7)$$

These models also have the values p , the rate of viral titer increase, δ , the rate of infected cell death, β , the infection rate constant, and c , the body's viral clearance rate. Target cells become infected at a rate of βV per cell, and undergo an incubation period called the eclipse phase before being able to produce and spread more virus. The average lifetime of the infected cells is estimated to be 11 hours, and the half life of a free infectious cell is roughly 3 hours. [5] It is estimated that a single infected cell can produce over 22 productive infections. [5] The model is effective at predicting the dynamics of influenza infection based on target epithelial cells as this is the infection's limiting factor, but is limited by its ability to properly consider varying host responses to viral infection.

$$R_0 = \frac{p\beta T_0}{c\delta} \quad (8)$$

The R_0 value is the basic reproductive number. Its value represents the average number of second generation infections created by a single infected cell in an environment of healthy, susceptible cells. [5] The value determines whether or not an infection will establish itself or die off quickly. If R_0 is greater than 1, more second generation cells will be created to replace the infected cell as it dies, which keeps spreading the infection and lets it establish itself in the susceptible population. If R_0 is less than 1, not enough second generation cells will be generated to replace the infected cell as it dies, letting the infection die off rapidly. The equation applies to both the delayed and non-delayed models.

II. METHODS

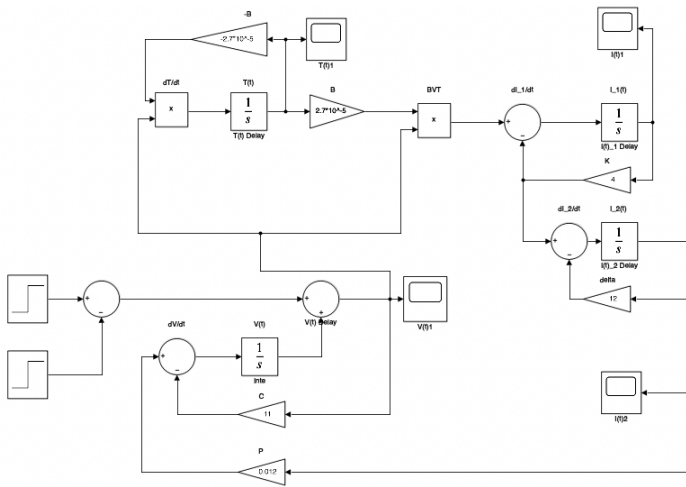


Figure 1: Delay Simulink Model

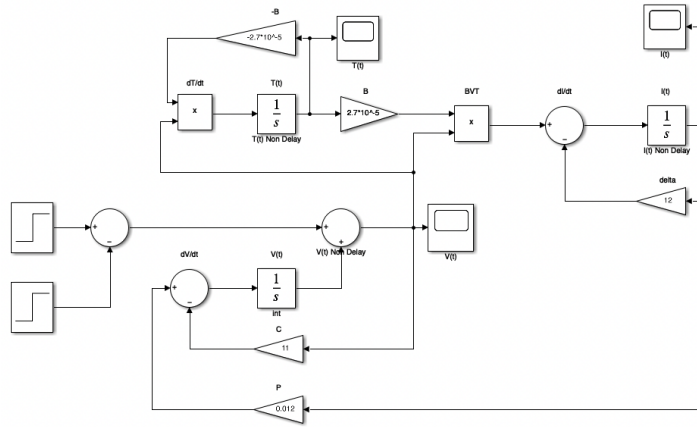


Figure 2: Non Delay Simulink Model

Several assumptions must be made for the current model:

1. The ODEs generated from experimental data in the literature are valid for modeling the influenza A virus infection
2. No regeneration of target uninfected cells
3. Infected cells are active immediately

4. Viral clearance rate, infected cell viral shedding, and infected cell death rate are constant
5. Initial target uninfected cells is consistent between patients and represents number of cells in the lungs
6. Exposure to the virus can be modeled with an impulse in viral titers $V(t)$
7. Receiving a vaccination can be modeled by increasing viral clearance rate and infected cell death rate

These assumptions help simplify our model in order to create a Simulink model of the system. The models are identical except for the differentiation between I_1 and I_2 that adds the delay between infection and the ability to infect others.

The transfer function of the Non Delayed model was also derived in order to better understand the input versus output response. The Non Delayed model was chosen as the equations are slightly simpler while still maintaining the same effective response and because the model more accurately simulates the expected responses to a viral titer impulse.

$$\frac{dT}{dt} = -\beta(V_{ss} T - VT_{ss}) \quad (9)$$

$$\frac{dI}{dt} = -\delta I + \beta(V_{ss} T + VT_{ss}) \quad (10)$$

$$\frac{dV}{dt} = pI - cV \quad (11)$$

These linearized equations were generated using Taylor polynomials of the original ODEs. The SS subscript represents steady state values for the specific variables and the variables themselves represent the linearized version, not the original version.

$$sT = -\beta V_{ss} T - \beta VT_{ss} \quad (12)$$

$$sI = -\delta I + \beta V_{ss} T + \beta VT_{ss} \quad (13)$$

$$sV = pI - cV \quad (14)$$

We took the Laplace transforms of all of the linearized ODEs and used the resulting equations to determine our transfer function.

$$H(s) = \frac{\beta T_{ss}}{(s+\delta)(s+\beta V_{ss})} \quad (15)$$

The transfer function contains steady state values of the variables for target uninfected cells and viral titers. We were unable to find Bode responses in the literature so we could not determine these values. Experimental data is required to

determine steady state values so we were unable to generate our own Bode response within this study.

III. RESULTS

Figures 3-6 show the graphs for $T(t)$, $V(t)$, and $I(t)$. $T(t)$ represents the number of uninfected target cells. $V(t)$ is the amount of infectious viral titer. $I(t)$ represents the amount of infected cells that also have the ability to infect other cells. In the delayed model, $I_1(t)$ is the amount of idle infected cells while $I_2(t)$ is the amount of productively infected cells.

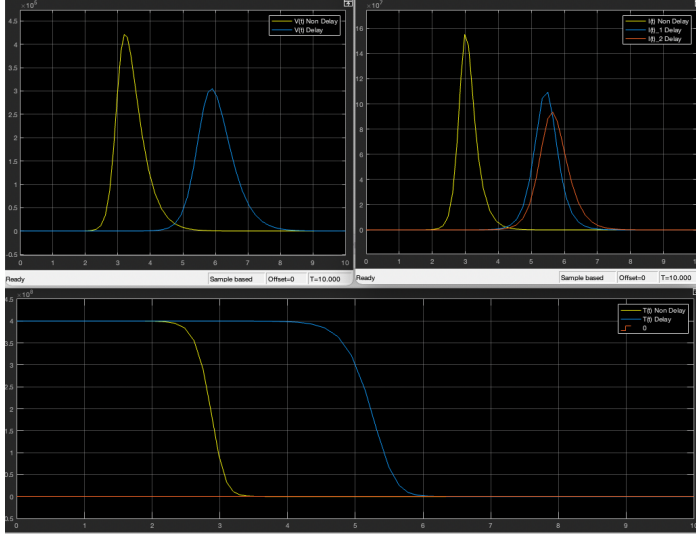


Figure 3: $c = 3$, $\delta = 4$, $R_0 = 10.8$, $V_0 = 9.2E-2$ (Literature Values)

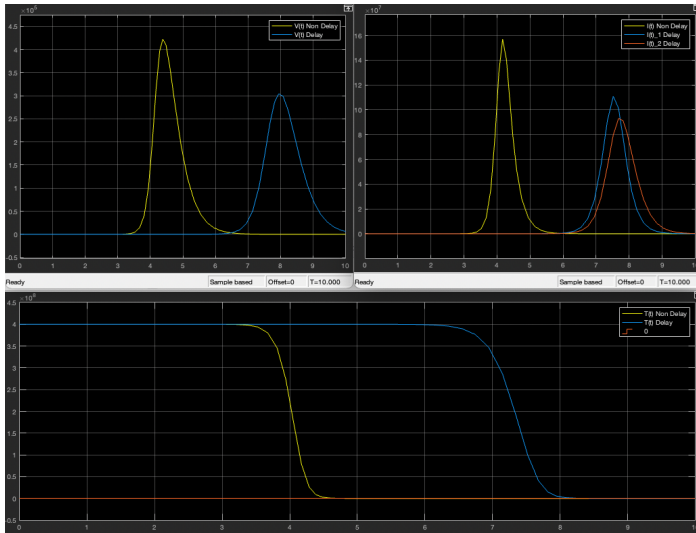


Figure 4: $c = 3$, $\delta = 4$, $R_0 = 10.8$, $V_0 = 9.2E-6$ (Low Exposure Case)

Figures 3 and 4 show two cases where the infection will establish itself in the body because the R_0 value is greater than 1.

The difference is in V_0 , the initial amount of viral titer. In the case of Figure 3, we used average values of several subjects from our literature research as approximations for c and δ . With a lower amount of initial viral titer, Figure 4 shows that the infection takes longer to establish itself, taking 4 days instead of 3 for the infection to peak in the non-delayed model and 7 days instead of 5 days in the delayed model. Both models show $T(t)$ drops to zero as the infection establishes itself and infects all available target cells. $V(t)$ and $I(t)$ both rise as the infection spreads, but then the infected cells die and viral titer is cleared and both values drop to zero. In both figures, the delayed model shows how $I_2(t)$ rises and falls slightly after $I_1(t)$ as the infected cells exit their idle stage and are able to infect other cells.

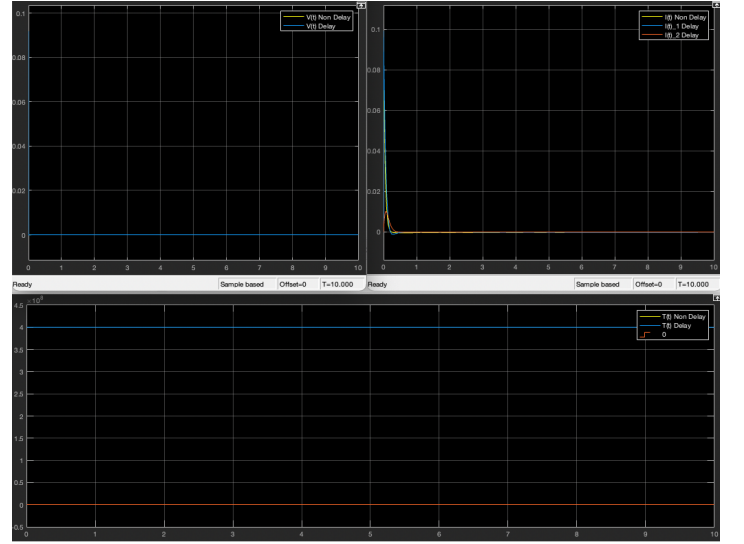


Figure 5: $c = 11$, $\delta = 12$, $R_0 = 0.98$, $V_0 = 9.2E-2$ ("Vaccinated" Case)

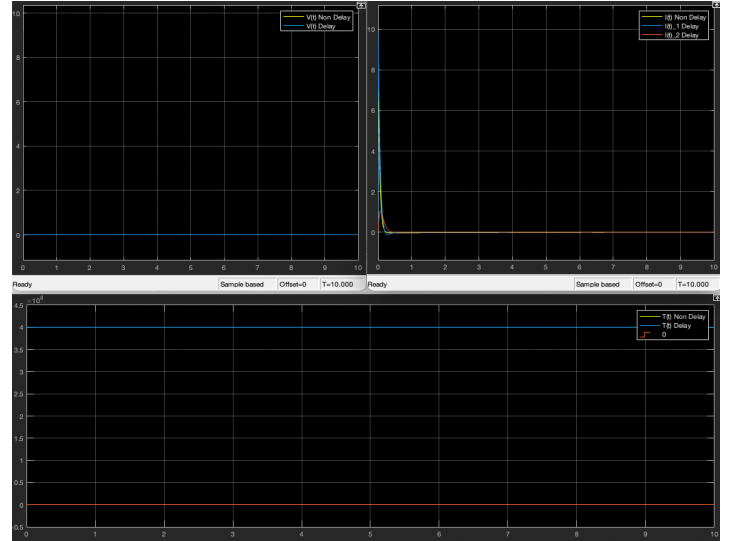


Figure 6: $c = 11$, $\delta = 12$, $R_0 = 0.98$, $V_0 = 9.2$ ("Vaccinated" High Exposure Case)

Figures 5 and 6 show the case where the R_0 value is less than 1, so the infection will rapidly die out as not enough second generation infections are made. Both test cases here are modeling a vaccinated individual, so the c and δ values are both higher because viral clearance and viral death rate are presumed to be higher. Different values for initial viral titer, V_0 , are also used to illustrate how effective a vaccine can be, even in the case of high exposure with a high initial viral titer value. $T(t)$ is relatively untouched in both cases, and when zooming in we can see that there is a very minor decrease in the value of $T(t)$ that is irrelevant with respect to the high magnitude of $T(t)$. $V(t)$ and $I(t)$ see similar patterns as the infection does not have enough reproductive power to establish itself, so there is never a significant peak in either graph. At most, the infections are eliminated in less than a day.

IV. CONCLUSION

Based off of our results, we conclude that both the delayed and non-delayed models can be used to accurately model the spread of an Influenza A viral infection. We determined that the non-delayed model produces peaks for infected cell count and viral titer that more closely resemble the actual experimental peaks determined in the literature. Due to this result, we opt to use the non-delayed model over the delayed model. Additionally, while the delayed model is a more accurate biological model, the use of an extra parameter results in failure to pass statistical validity tests [1].

After determining the preferred model, we aimed to extend the model to simulate the response in a vaccinated individual. Looking at the results in figures 5 and 6, we note that by reducing R_0 to less than 1, the virus fails to spread effectively. We argue that this is a valid model of a vaccinated case since the antibodies produced via vaccinations serve to increase both viral clearance rate and infected cell death rate. Inspection of our models for both the vaccinated and unvaccinated cases reveals the importance of developing fast and strong immune responses to viral infections through the use of vaccines. If R_0 is not less than 1, we see a rapid spread of the virus even at low exposures.

It is important to note that our unvaccinated case represents a healthy immune response to the Influenza A virus. An immunocompromised system would likely react even less efficiently in clearing the virus and eliminating infected cells (reduced value for c and δ). This would result in a much faster response to an impulse exposure in $V(t)$ and a slower decay in both $I(t)$ and $V(t)$.

Given our initial set of ODEs for the non-delayed model, we were able to linearize the equations and determine a transfer function. However, the literature does not go into Bode responses for these models and we are unable to determine steady state values for our linearized equations. For this reason, we were unable to generate our own Bode responses. We are not particularly concerned with the frequency response of our

system since exposure to the Influenza A virus is modeled using an impulse response.

Overall, our model successfully models the case of an Influenza A viral exposure and spread for a healthy but unvaccinated individual. Slight modifications to our constants allow us to extrapolate our model to a vaccinated or immunocompromised case, but we have not determined the accuracy of these models. They respond as expected based on our R_0 values, but the timing of the responses may not accurately reflect the real life viral spread rate. Further study is required to confirm if our model can be used for these more specific cases.

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