MODELING INTERFERON RESPONSE IN PANDEMIC H1N1 INFLUENZA VIRUS INFECTED MICE USING GENE EXPRESSION DATA

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INTRODUCTION

Innate immune response is essential for viral clearance during infection. However, there are drawbacks to this response. Inflammation caused by cytokines, such as interferon, can cause adverse and sometimes deadly effects [1]. Developing an engineering model of the interferon response dynamics can help researchers understand the potential drawbacks of a powerful immune response. The purpose of this project is to model the inflammatory interferon response to pandemic H1N1 (pH1N1) influenza virus infection in mice using gene expression data.

METHODS

Gene expression data and experimental conditions were previously reported [2]. Three mice were humanely sacrificed at each time point to collect lung infection data; in total, 168 mice were sacrificed. Gene expression data was averaged at each time point. Samples from mock-infected, time-matched animals served as controls.

To cluster the genes, weighted correlation network analysis (WGCNA) was performed [3]. After clustering, DAVID Gene Ontology Tool was used to determine which clusters are associated with interferon production. From this analysis, Module (cluster) 4 was found to be the most enriched in interferon production, inflammation, and immune response (p-value = $10^{-3.8}$). The eigengene (first principle component of the gene expression matrix) was used to describe gene expression dynamics.

Matlab was used to generate the model shown in Tables 1 and 2. The model consists of 4 ordinary differential equations (ODEs) and 9 parameters. Each equation adheres to biological principles and mass-action kinetics. The 4 species in the model are target cell fraction (T), infected cell fraction (c), viral load (v), and interferon (i). Target cells decrease as they are infected by the virus and also decrease as they naturally die. Infected cells will increase at the same rate that target cells become infected, but will then decrease as they lyse and release more virus.

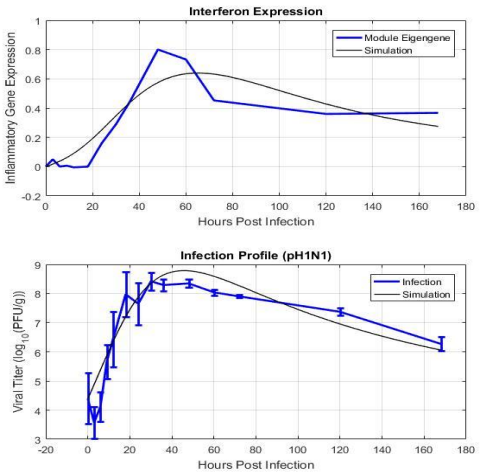


Figure 1: The experimental (blue) and simulated profiles (black). The error for the simulation was 5.0791. (Time Bounds: 0 to 168 hours post infection).

Table 1: Model Equations, Descriptions, and Initial Conditions

Equation	Description	Start
$\frac{dT}{dt} = -k_{infect} * (v) * T - k_{death} * T$	Target Cells	1
$\frac{dc}{dt} = k_{infect} * (v) * T - k_{inf,death} * c$	Infected Cells	0
$\frac{dv}{dt} = k_{v,prod} * (v) * c - k_{v,neg} * i - k_{v,death} * v$	Virus Growth	4.3985
$\frac{di}{dt} = \frac{k_{i,prod} * v^3}{K_A{}^3 + v^3} + (-k_{i,deg}) * i$	Interferon Production	0

Table 2: Model Parameters

Parameter	Value	Units
k_{infect}	0.002379	$h^{-1} * \log(PFU/g)^{-1}$
k_{death}	0.050347	h^{-1}
$k_{inf,death}$	12.05254	h^{-1}
$k_{v,prod}$	42.95610	h^{-1}
$k_{v,neg}$	0.004912	$\log(PFU/g)*h^{-1}$
$k_{v,death}$	0.000276	h^{-1}
$k_{i,prod}$	104.8979	h^{-1}
K_A	55.28594	log(PFU/g)
$k_{i,deg}$	0.058559	h^{-1}

The virus concentration will increase as the infected cells release more viral copies, but will decrease as interferon concentration increases and as the virus naturally dies. Cells will recognize foreign viral RNA and respond by producing interferon at a rate described by Hill kinetics.

The model was parameterized using FMINCON to minimize the simulation error found by comparing the simulation to the WGCNA-generated eigengene as well as the observed viral titers. The fitted model parameters and resulting dynamics are shown in Table 2 and Figure 1, respectively.

RESULTS

As can be seen from Figure 1, the model simulates the experimental results well. Not only does the model follow the experimental results, but the inclusion of target cells and infected cells allows the model to "shut off". Figures 2 and 3 show this behavior. As the virus dies off over a longer period of time, the model stops interferon production, which adheres to biological principles of homeostasis.

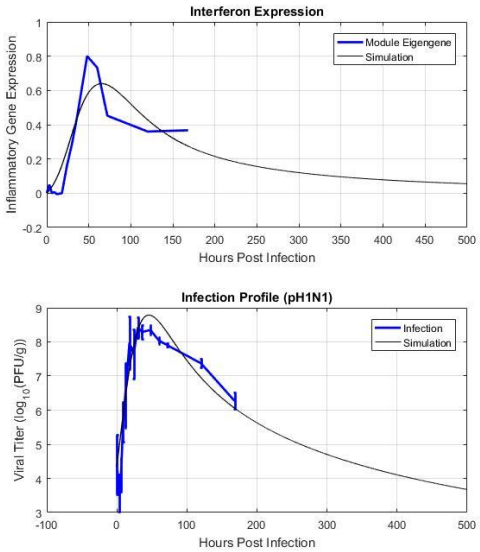


Figure 2: "Shut-off" dynamics of the model against time. (Time Bounds: 0 to 500 hours post infection).

Figure 3 also suggests a nonlinear sensitive interferon response to viral titer as interferon production rate changes, a result that would not have been found without mathematical modeling.

DISCUSSION

Given the nonlinear relationship between inflammation and viral load, it may not be beneficial to regulate interferon production to limit virus

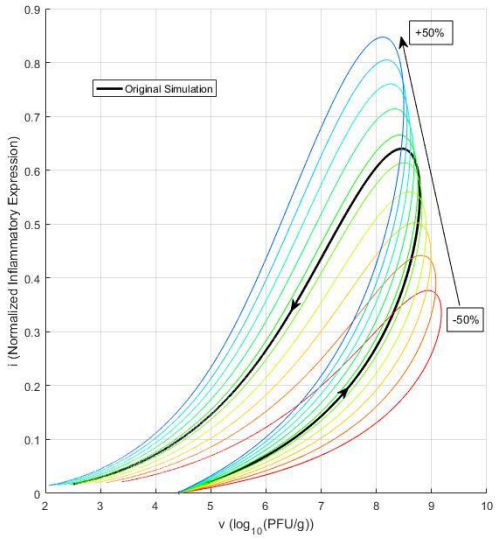


Figure 3: Interferon Expression against Viral Titer for Iterations of Interferon Production ($k_{i,prod}$). The red line represents the original parameter reduced 50%, while the purple line represents the original parameter increased 50%. (Time Bounds: 0 to 1000 hours post infection).

replication. Figure 3 shows that changing the rate at which interferon is produced creates a heightened inflammatory response to viral titer. If the goal is to decrease inflammation, regulating interferon response would not work. As interferon production increases by 50%, maximum viral titer decreases by 3.75%, but maximum inflammation increases by 34.9%. Therefore, the decrease in viral titer is not worth the possibility of a more inflamed response, which could result in host death.

Future works for this model include sensitivity and bifurcation analysis to see what aspects of cellular dynamics effect viral infection the most. More sensitive parameters can be baselines for future drug targets and vaccines to prevent future outbreaks.

REFERENCES

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