Dynamics of Two-Strain Influenza with Isolation and Cross-Immunity

BU-1530-M

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July 29, 2000

Abstract

The evolution of influenza type A virus is linked to a non-fixed evolutionary landscape driven by tight co-evolutionary interactions between hosts and influenza strains. Cross-immunity, host isolation, and age-structure are three factors responsible for the coexistence of multiple strains of influenza. Here we show that cross-immunity and host isolation alone may support multi-strain epidemics. Further, we show it is possible to produce sustained oscillations with realistic periods. We establish these predictions via Hopf-bifurcation theory, and illustrate our results with numerical simulations. Period lengths agree with reported data.

Keywords: Isolation; Cross-immunity; Antigent; Antigent shift

1 Introduction

Early recordings of influenza pandemics indicate that the virus antigent variability is responsable for recurrent epidemics. Surface antigens haemagglutinin, and neuraminidase undergo two types of antigenic variation. Antigenic shift involves major changes that result in new subtypes, that later contribute to major epidemics. The lifespan of a subtype is determined by the time it takes until a new subtype appears(pandemic). For example, a virus having H3 antigents is said to be responsible for the 1918 pandemics. On the other hand, antigenic drift involves relative minor, but frequent changes(variants) that take place every one to three years. There are several theories that contribute to the origin of new viruses. Unfortunately, it is the combination of various factors that determine the complexity of influenza type A virus. Studies show that influenza strains crossbreed stronger than other virus, therefore, we investigate epidemic recurrence via interacting strains. As a matter of fact, interaction of multiple strains for influenza type A virus has been analyzed under distinct frameworks[2][5][6][11]. It has been shown that cross-immunity, age-structure, and quarantine are contributing forces to sustained oscillations[1][3][5]. In particular, due to the long-lasting cross-immunity between related strains, serious consideration of cross-immunity has been presented[3][5]. In this paper we demonstrate that for a two-strain model with quarentine and cross-immunity, sustained oscillations persist. For strongly couple strains($\sigma = 0.2$), the system goes through cycles with a period of 3 years, where each cycle contains multiple outbreaks. As cross-immunity is weaken, the two strains become antigenically unrelated, resulting in damped oscillations.

2 Epidemiology of Influenza type A

Type A virus particles contain at least four antigenic components. Only the surface antigens, haemagglutinin and neuraminidase are responsible for the virus variability. Specifically, haemagglutinin is responsible for the attachment of the virus particle to the receptor sites on the surfaces of the host cells. Even though anti-neuraminidase antibodies fail to neutralize the virus infectivity, it determines the virus subtypes and variants. Type A influenza virus has been isolated and classified into three subtypes: H1N1, N2H2, and N3H3. Interaction among the strains of a subtype give rise to new strains as

the haemagglutinin protein changes its antigenic structure(antigenic drift). Recent studies show that for influenza type A virus, strains belonging to similar subtypes share a level of cross-immunity. Through cross-immunity, the presence of one strain of the virus can reduce the pool of susceptible individuals for co-circulationg strains[3]. Furthermore, it has been shown that cross-immunity among related strains may determine possible survival of related strains. On the other hand, antigenic shifts results in new subtypes that give rise to major pandemics. Factors that contribute to the complexity of influenza virus have been explored in the last years. Age-structure, proportionate mixing, and cross-immunity, are among some of the mechanisms responsible for recurrent epidemics[5][7]. Reports show that during cold months the virus is significally more infective, therefore causing serious illness[15]. During the appearance of Asian and Hong Kong subtypes, it was observed that a change in transmission, as well as seasonal effects, perpetuated the slow development of the pandemic experienced in U.S.A. during 1957 and 1968 [14]. Preparation of influenza vaccine is based on the strains in circulation at the time of production. It is likely that an unpredicted new strain will appear after the vaccine has been manufactured and distributed. As a result of new strains, individuals with antibodies stimulated either by previous infection, or vaccination, may no longer be protected from new strains.

3 The Model

We study the following two-strain influenza model. The population is divided into ten different classes: S is the susceptible class, I_i denotes those infected by strain i, Q_i denotes the isolated individuals from strain i, R_i are individuals recovered from strain i, W_i are individuals recovered from strain i, but still susceptible to strain j. Lastly, W describes individuals who have recovered from strains i, and j.

Figure 1 describes the interactions among the classes of the two-strain model. Λ is the rate at which individuals are born into the population, β_i denotes the per-capita infection rate for strain i, μ is the per-capita mortality rate, δ_i is the quarantine per-capita rate, γ_i denotes the per-capita recovery rate from strain i, α_i is the per-capita rate at which individuals leave the isolated class, and σ denotes the cross-immunity among strains.

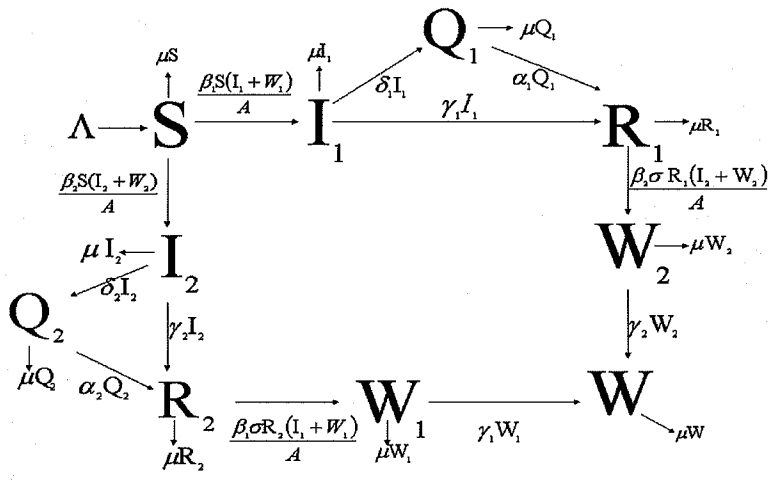

Figure 1: Diagram of the Compartmental Model

We assume that individuals are born into the population at a constant rate. Individuals have a life expectancy of 70 years. For influenza, the infectious period lasts from 2 to 7 days, therefore the per-capita recovery rate is based on a two day recovery period[15]. We assume that individuals in isolation do not infect anybody. Individuals that go to isolation do so after having been infected for a period of 2 to 3 days. Since the incubation period last from 1 to 3 days, and duration of infectiousness last from 3 to 6 days, we assume that individuals stay home until they recover. We refer to total cross-immunity by $\sigma = 0$, whereas, $\sigma = 1$ denotes no cross-immunity. For $0 \leq \sigma \leq 0.3$, cross-immunity is strong, and $0.7 \leq \sigma \leq 0.9$ describes weak cross-immunity.

Our assumptions lead to the following model:

$$\frac{dS}{dt} = \Lambda - \beta_1 S\frac{(I_1+W_1)}{A} - \beta_2 S\frac{(I_2+W_2)}{A} - \mu S, \quad (1)$$

$$\frac{dI_i}{dt} = \beta_1 S\frac{(I_1+W_1)}{A} - (\mu+\gamma_1+\delta_1)I_1, \qquad i=1,2 \quad (2)$$

$$\frac{dQ_i}{dt} = \delta_1 I_1 - (\mu+\alpha_1)Q_1, \qquad i=1,2 \quad (3)$$

$$\frac{dR_i}{dt} = \gamma_1 I_1 + \alpha_1 Q_1 - \mu R_1 - \beta_2\sigma R_1\frac{(I_2+W_2)}{A}, \qquad i=1,2 \quad (4)$$

$$\frac{dW_i}{dt} = \beta_1\sigma R_2\frac{(I_1+W_1)}{A} - (\mu+\gamma_1)W_1, \qquad i=1,2 \quad (5)$$

$$\frac{dW}{dt} = \gamma_1 W_1 + \gamma_2 W_2 - \mu W, \quad (6)$$

4 Stability of Equilibria

Adding the differential equations (1-6) we find for the population size $N = A_i + Q_i = S + I_i + Q_i + R_i + W_i$, where $i = 1, 2$. Further we observe that $A = N - Q_i$. The stability analysis of the system at the disease-free state is simplified by the absence of the infected classes. Note that since no infectives are considered then recovered classes do not exist, were $\Lambda = \mu N^*$.

$$\frac{dS}{dt} = \Lambda - \mu S$$

At disease-free we obtain $S = N^*$. Therefore, disease free-equilibrium is described by the following:

$$E^0 = (N^*, 0, 0, 0, 0, 0, 0, 0, 0, 0,)$$

Since stability at disease-free is determined by the corresponding eigenvalues, we find conditions that depend on $\mathbf{R_0}$ to assure stability. The **BasicReproductiveNumber**, $\mathbf{R_0}$ describes the number of secondary infections caused by infected individuals in a population of susceptibles. For interacting strains we find that

$$\mathbf{R_1} = \frac{\beta_1}{\mu+\gamma_1+\delta_1},$$

and

$$\mathbf{R_2} = \frac{\beta_2}{\mu+\gamma_2+\delta_2}.$$

If

$$\mathbf{R_1 < 1}$$

and

$$\mathbf{R_2 < 1}$$

the disease-free equilibria is locally asymptotically stable. Let

$$\mathbf{R_0 = max(R_1, R_2)}$$

where $\mathbf{R_0 < 1}$. To study our model at the endemic state, we analyze the endemic equilibria for strain 1, $\mathbf{E_1}$. We partitioned the original 10 by 10 state matrix into four submatrices A_{11}, A_{12}, A_{21}, and A_{22}(Appendix). Recall that at the endemic state, $\mathbf{R_1}$ and $\mathbf{R_2}$ are greater than 1.
Hence

$$Trace = \beta_2(\frac{1}{\mathbf{R_1}} - \frac{1}{\mathbf{R_2}}) + \frac{\beta_2 \sigma R_1}{A} - (\mu + \gamma_2) < 0$$

and

$$\mathbf{R_2} < \frac{\mathbf{cR_1}(\Delta + \mu)}{\Delta + \mu - \sigma\Delta(\mathbf{R_1 - 1})} = \mathbf{f(R_1)}$$

where

$$c = \frac{\mu + \gamma_2}{\mu + \gamma_2 + \delta_2} + 1$$

$$Determinant = -(\mu + \gamma_2)\beta_2(\frac{1}{\mathbf{R_1}} - \frac{1}{\mathbf{R_2}}) - \frac{\beta_2^2 \sigma R_1}{\mathbf{R_2 A}} > 0$$

$$\frac{R_1}{A} = \frac{\Delta(1 - \frac{1}{\mathbf{R_0}})}{\Delta + \mu}$$

$$\mathbf{R_2} < \frac{\mathbf{1}}{\mathbf{R_1}} - \frac{(\mu + \gamma_2 + \delta_2)\sigma\Delta(\mathbf{1} - \frac{\mathbf{1}}{\mathbf{R_1}})}{(\mu + \gamma_2)(\Delta + \mu)} = \mathbf{f(R_1)}$$

Therefore, endemic stability is determined by the region where both, trace and determinant conditions are satisfied. To complete the stability analysis for the system, we explore the conditions of stability for the A_{11} matrix.

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 \;=\; 0 \qquad (7)$$

$$
\begin{aligned}
a_1 &= 2\mu + \alpha_1 + \frac{\beta_1 I_1}{A} \\
a_2 &= \frac{\mu\beta_1 I_1}{A} + \frac{\beta_1\alpha_1 I_1}{A} + \frac{\beta_1\delta_1 I_1}{\mathbf{R_0 A}} + \frac{\beta_1^2 I_1}{\mathbf{R_0 A}} + \mu^2 + \mu\alpha_1 \\
a_3 &= \frac{\mu\beta_1\delta_1 I_1}{A\mathbf{R_0}} + \frac{\mu\beta_1^2 I_1}{A\mathbf{R_0}} + \frac{\alpha_1\beta_1^2 I_1}{A\mathbf{R_0}}
\end{aligned}
$$

Using Routh-Hurwitz criteria we show that the necessary inequalities are $a_1 > 0, a_3 > 0$, and $a_2 a_3 > a_1$. Referring back to equation (7), and using a Taylor expansion on ϵ, we obtain.

$$\lambda_1 = \lambda_2 = 0 + b\epsilon + c\epsilon^2 + d\epsilon^3 + ...$$

$$\lambda_3 = -\alpha_1 + \underline{b}\epsilon^2 + \underline{c}\epsilon^4 + ...$$

where

$$\epsilon = \sqrt{\mu}$$

To simplify the leading coefficients of the characteristic polynomial, we let

$$\frac{I_1}{A} = \frac{\Delta(1 - \frac{1}{\mathbf{R_0}})}{\Delta + \mu}.$$

$$\omega^3 + a_1\omega^2 + a_2\omega + a_3 = 0 \tag{8}$$

$$\omega = \omega_1\epsilon + \omega_2\epsilon^2 + \omega_3\epsilon^3$$

Substitute in $\mu = \epsilon^2$ in (8) to obtain.

$$
\begin{aligned}
a_1 &= \alpha_1 + 2\epsilon^2\mathbf{R_0} \\
a_2 &= -\epsilon^4 + 2\epsilon^4\mathbf{R_0} - \epsilon^2\alpha_1 + \mathbf{2}\epsilon^2\mathbf{R_0}(\alpha_1 + \delta_1 + \beta_1) \\
a_3 &= (1 - \frac{1}{\mathbf{R_0}})(2\epsilon^4\delta_1 + 2\beta_1\epsilon^4 + 2\delta_1\epsilon^2\beta_1)
\end{aligned}
$$

Now the leading coefficients of (7) are in terms of $\mathbf{R_0}$. We show that Routh-Hurwitz inequalities are satisfied. First, since $\mu = \epsilon^2$ and $\mathbf{R_0} > \mathbf{1}$, this implies that $a_1 > 0$. For the endemic state, $\mathbf{R_0} > \mathbf{1}$, therefore, condition $a_3 > 0$ is satisfied. Lastly, for parameters that pertain to influenza virus, the conditions $a_1 a_2 > a_3$ are met.

5 Hopf-Bifurcation

The stability our system is determined by the conditions obtained from the submatrices, A_{22}, A_{11}. In particular, for the A_{11} submatrix, we showed that the Routh-Hurwitz criteria is satisfied. Ignoring higher order terms of (8), we find conditions that lead to a Hopf-Bifurcation. For our case, if the σ is varied the trace corresponding to the Taylor expansion changes in sign. Specifically, the trace changes from negative to positive, whereas, the determinant remains positive. A bifurcation may transform a stable equilibrium into a stable or unstable periodic solution. To determine the sign of ω, we look at the corresponding ϵ terms and determine conditions under which a Hopf-bifurcation appears. Analyzing ϵ^3 terms leads to the condition that originates the change in stability.

$$\alpha_1^c = \frac{\delta_1}{\mathbf{R_0}} - \delta_1 - \frac{\beta_1}{\mathbf{R_0}} + \beta_1$$

Furthermore, solving for the condition where the determinant equals to zero, we obtain a function ω_2 that depends on the isolation period.

$$2\alpha_1\omega_2 + 2\alpha_1\mathbf{R_0} + \mathbf{2}\delta_1\mathbf{R_0} - \mathbf{2}\delta_1 + \mathbf{2}\beta_1 - \mathbf{2}\frac{\beta_1}{\mathbf{R_0}} = \mathbf{0}$$

$$\omega_2(\alpha_1) = -\mathbf{R_0} - \frac{\delta_1}{\alpha_1}(\mathbf{R_0} - \mathbf{1}) + \frac{\beta_1}{\alpha_1}(\frac{\mathbf{1} - \mathbf{R_0}}{\mathbf{R_0}})$$

We can conclude that for certain condition that depend on the isolation period, our system loses stability. For $\omega_2(\alpha_1) > 0$, if $\alpha_1 < \alpha_1^c$, endemic equilibrium, $\mathbf{E_1}$ is stable. For $\omega_2(\alpha_1) < 0$, if $\alpha_1 > \alpha_1^c$, then $\mathbf{E_1}$ is unstable. For the case when the determinant is equal to zero, that is, $\omega_2(\alpha_1) = 0$, a Hopf-Bifurcation occurs takes place at α_c.

6 Numerical Solutions

In this section we use Runge-Kutta Method to analyze the model equations numerically. In particular, we study influenza dynamics by considering parameters that are pertinent to the type A virus. We assume that the acute phase ranges from 3 to 5 days, therefore, infectious period lasts 3 days. For influenza, we assume a life expectancy of 70 years. Since influenza virus is

particularly infectious, individuals that stay home, remain there from 5-7 days. We analyze the interaction of both strains with symmetric as well as asymmetric contact rates. We study the change in behavior as we vary cross-immunity and transmission coefficient. For all illustrations, we assume an isolation period of 7 days, and mention that ignoring quarantine always results in damped oscillations. For isolation periods of 60 days, periodic cycles coexist similar to the cases where isolation period is 7 days. By exploring total cross-immunity, we obtain sustained oscillations for the one-strain case[1]. Further, as cross-immunity increases, periodic cycles get shorter, and multiple outbreaks occur. For our two-strain model, we show that for small symmetric contact rates, and quarantine oscillations with multiple outbreaks take place. As the contact rates increase, oscillations become damped for many cross-immunity rates and isolation periods. For asymmetric contact rates, isolation and cross-immunity introduce 9 month periodic cycles with multiple outbreaks. We refer to strong cross-immunity for σ=0.1, medium for σ= 0.4, and large for σ= 0.8.

6.1 Simulations

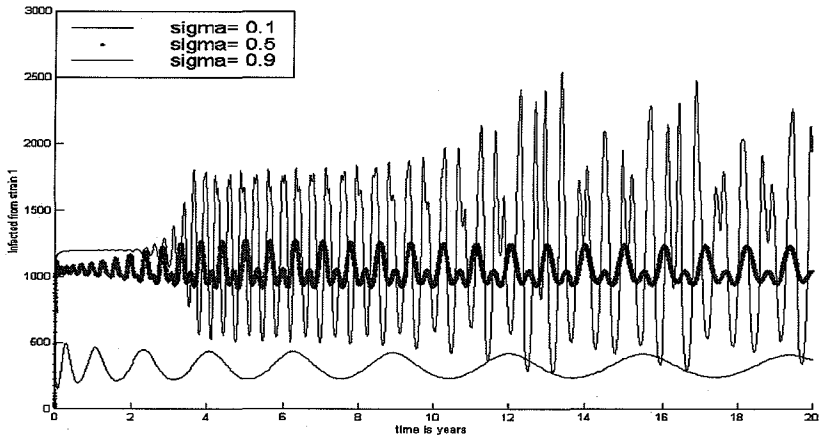

Figure 2: Describes individuals infected from strain 1. For $\sigma = 0.1$, 4 year period cycles appear. As σ increases, periodic cycles shortened to 6 months(weak cross-immunity). Simulations agree with previous results in [1] and [5], where quarantine was responsible for sustained oscillations.

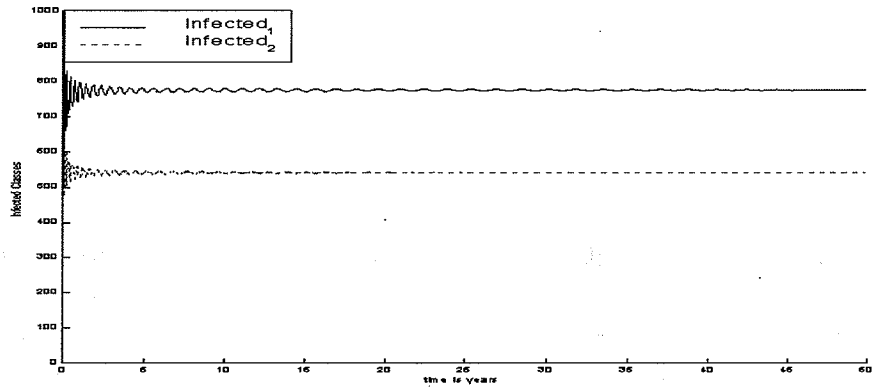

Figure 3: Depicts the behavior of two interacting strains without isolation. As expected, even in the case of co-interacting strains, damped oscillations result. In the following simulations, we will illustrate the impact of isolation under strong and weak cross-immunity.

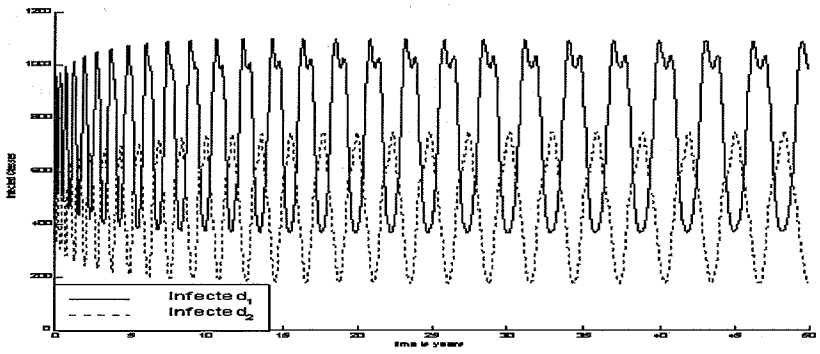

Figure 4: $\sigma = 0.2$ $\beta_1 > \beta_2$ Isolation = 7 days

Oscillations for strain appear with a year frequency, but after 30 years, multiple outbreaks show every 3 years. Strain 2 oscillations, although shorter in amplitude, have similar period, but not recurrent outbreaks.

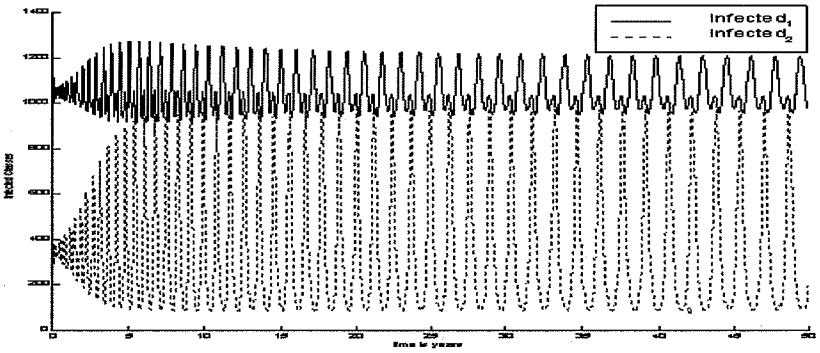

Figure 5: $\sigma = 0.5$ $\beta_1 > \beta_2$ Isolation = 7 days

Note that for strain 1, weaker cross-immunity has shorten the period cycle to a year, and the amplitude of the oscillations has decreased dramatically. On the other hand, strain 2 amplitud of oscillations has increase, eventhough period cycles have shorten to a year. It is worth noting that even weaker cross-immunity, $\sigma = 0.8$, shorter period oscillations persist.

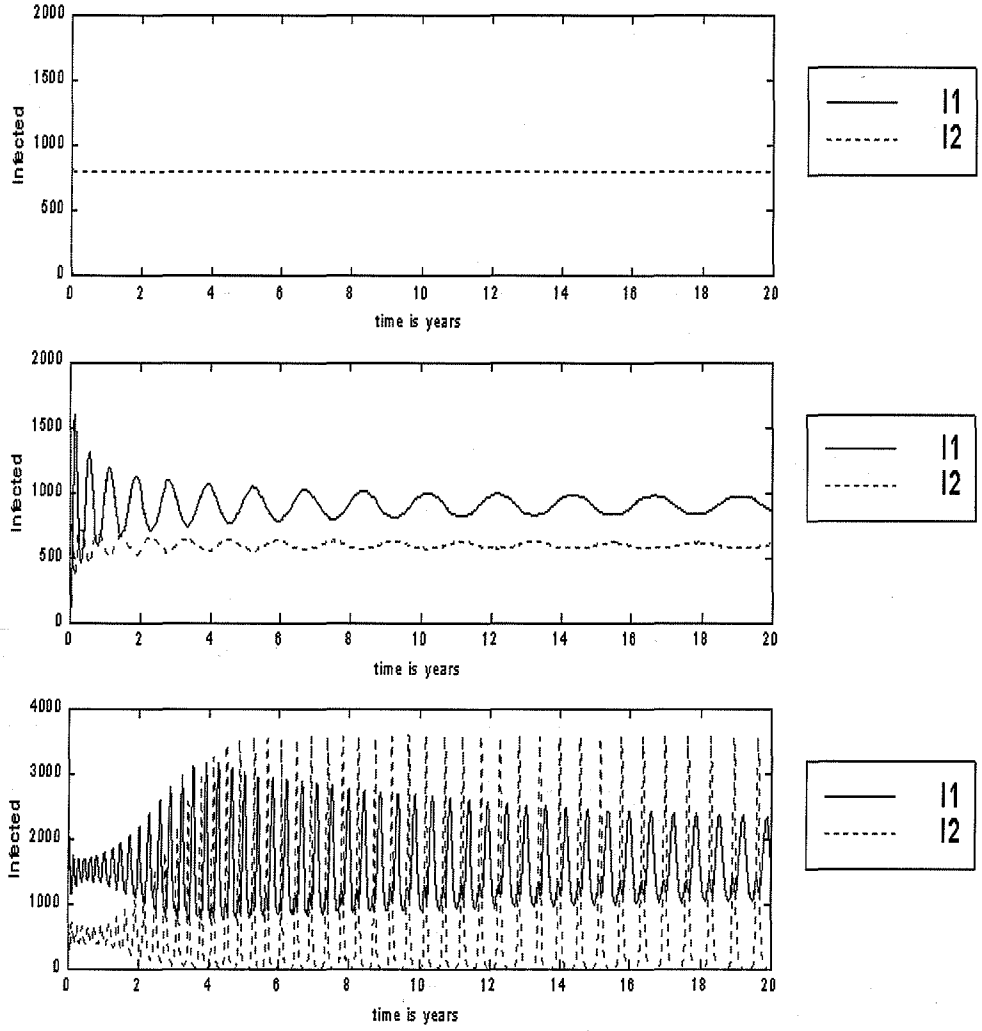

Figure 6: $\sigma = \sigma_1 = \sigma_2$ and $\beta_1 = \beta_2 =$ small.

For the remaining simulations we assume a 7 day quarentine period and observe the effects of infection as we consider strong, medium and weak cross-immunity correspondingly. For strong cross-immunity the disease eventually dampens. For medium cross-immunity, cycles of period two and small amplitude appear. As cross-immunity becomes weak, cycles of multiple outbreaks with period of 6 months to one year persist.

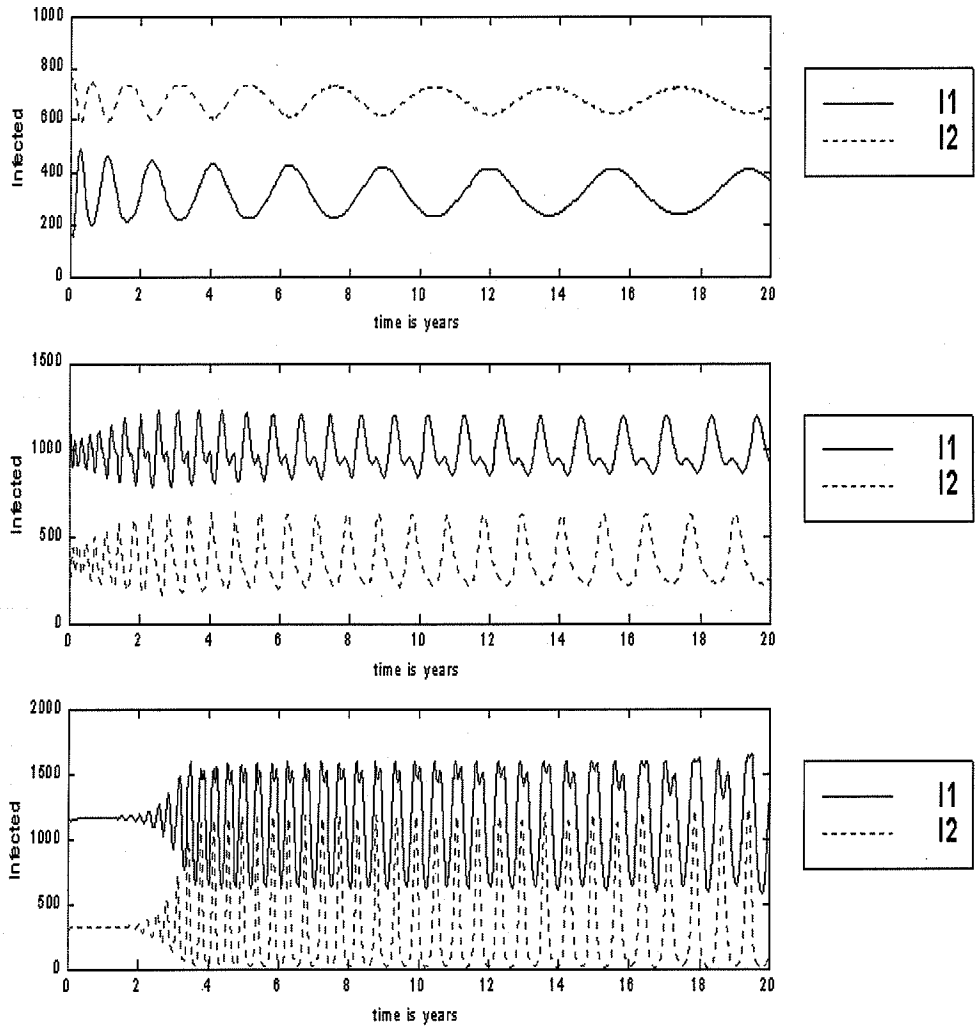

Figure 7: $\sigma = \sigma_1 = \sigma_2$ and $\beta_1 = k\beta_2$
For strong cross-immunity we observe 6 month to 4 year periodic cycle. As immunity weakens, 8 month cycles with multiple outbreaks can be observed for the strain with highest transmission coefficient. For very weak cross-immunity, 7 month periodic cycle occur with multiple outbreaks. The rates of infection for each strain are different, here k = 2.

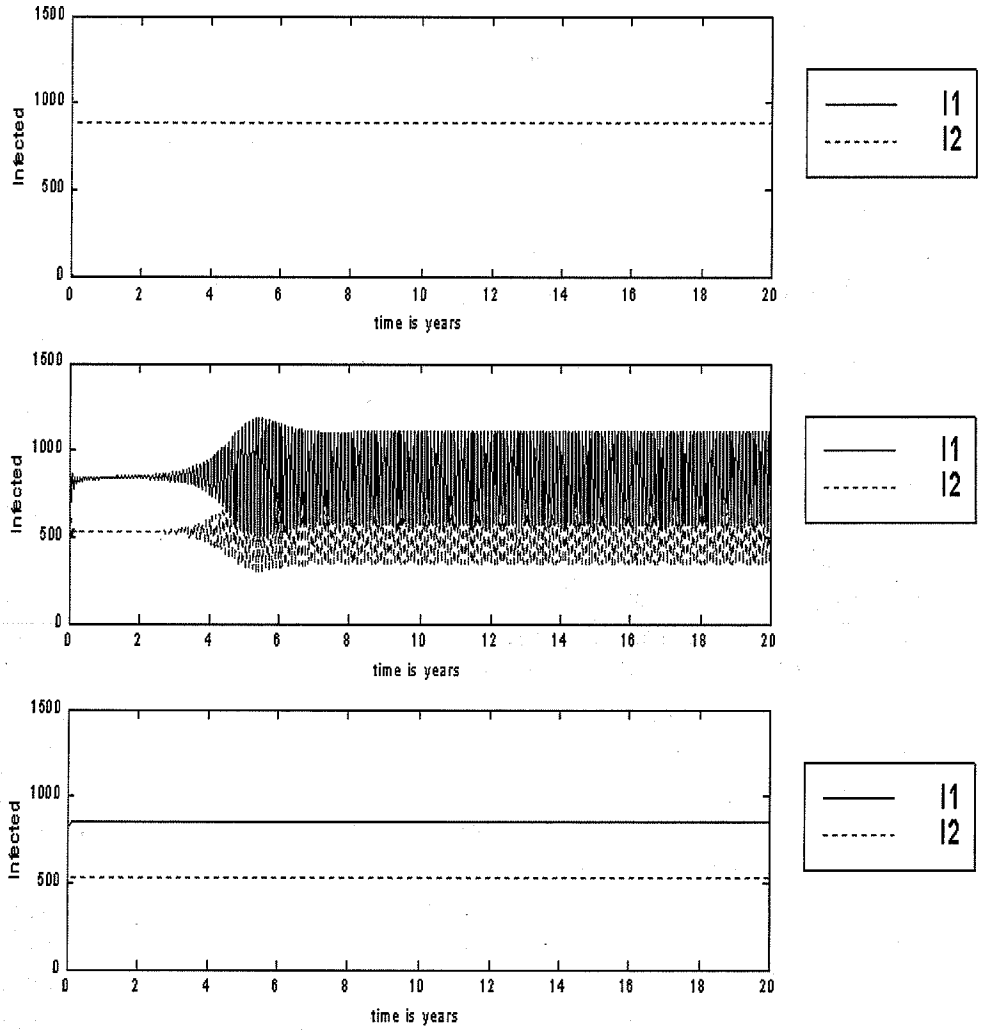

Figure 8: $\sigma = \sigma_1 = \sigma_2$ and $\mid \beta_1 - \beta_2 \mid$ = small
As the difference of β_1 and β_2 becomes small. For strong and weak cross-immunity, sustained oscillations do not appear. For medium values of cross-immunity, as $\mid \beta_1 - \beta_2 \mid$ becomes small, the amplitude of oscillations and period cycles are reduced. Sufficiently small difference, and medium cross-immunity result in damped oscillations. Damped oscillations later become excited as $\beta_1 = \beta_2$.

7 Discussion

Since the isolation of the various strains and subtypes of influenza type A virus began, researches have focused in the factors that contribute to recurrent epidemics. Statistics indicate that newsubtypes responsable for the major pandemics cannot be predicted. On the other hand, new rising strains may be explained by considering factors such as, cross-immunity, age-structure, and isolation, and other enviromental factors[1][3][4][5][6][7][8]. We have analyzed a two-strain model with quarentine and cross-immunity. Our results rehabilitate sustained oscillations previously shown as a quarentine class is considered for a single-strain case. In section 4 we give conditions for which disease-free, as well as the endemic state equilibria eixst. For the disease-free equilibria, we give conditions under which $\mathbf{R_0}$ provides disease eradication. We showed stability of boundary endemic equilibria by using Routh-Hurwitz criteria. We show that conditions for stability are met. Furthermore, we show that for conditions that depend on the period of isolation, sustained oscillations persist. Such oscillations change periodicity, as well as amplitud as we vary cross-immunity. Our numerical explorations seem to indicate that after 30 years, multiple outbreaks occur for strong cross-immunity($\sigma = 0.2$), and 7 days periods of isolation. As cross-immunity becomes weaker, $\sigma = 0.8$, the period of recurrent eidemics lenghtens, and oscillations eventually dampen out. As a result of periodic solutions of our model, we predict the occurrence of a Hopf-bifurcation. We found a bifurcation point that depends on the isolation period, and hope to prove the existence of limit cycles via central manifold theory. As a explanation to the recurrent epidemics caused by antigenic variation of the influenza type A virus, we hope that considering the factors that give rise to the virus unique entity can provide some solutions for the virus eradication. In particular, targeting key periods of isolation, as well as cross-immunity levels that perpetuate the recurrence of multiple outbreaks may allow for diasese control. As previously explored in [5][8], age-structured must also be considered since significant portion of the virus spreading takes place among children.

Appendix

One strain endemic equilibrium analysis:
The following illustration describes the partitioning of the 10 by 10 Jacobian matrix analyzed for single strain endemic equilibria.

Analysis of 10 by 10 matrix

$$\begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix}$$

A_{11} describes the interactions with Strain 1

A_{22} describes the interactions with Strain 2

A_{12} and A_{21} describe the interactions driven by $\sigma = 0$

Note that our initial 10 by 10 matrix can be easily simplified by noting a negative real part eigenvalue along the diagonal. The remaining 9 by 9 matrix is partitioned into the following two matrices. Since we are interested in exploring the cases where strains range from closely related, to distinct subtypes. We ignore matrices A_{12}, and A_{21}.

$$A_{11} = \begin{bmatrix} \frac{\beta_1 I_1}{A} - \mu & \frac{-\beta_1 S}{A} & 0 & \frac{\beta_1 S I_1}{A} \\ \frac{\beta_1 I_1}{A} & \frac{\beta_1 S}{A} - (\mu + \gamma_1 + \delta_1) & 0 & \frac{-\beta_1 S I_1}{A^2} \\ 0 & \gamma_1 & -\mu & \alpha_1 \\ 0 & \delta_1 & 0 & -(\mu + \alpha_1) \end{bmatrix}$$

This 4 by 4 matrix describes strain 1 endemic equilibrium. Conditions needed to establish stability are simplified by the eigenvalues along the diagonal.

Similarly, this 5 by 5 matrix describes strain 2 endemic equilibrium. In section 4 conditions that guarantee stability of endemic equilibria are provided.

$$A_{22}=\begin{bmatrix} \frac{\beta_2 S}{A}-(\mu+\gamma_2+\delta_2) & 0 & 0 & 0 & \frac{\beta_2 S}{A} \\ \gamma_2 & -\mu-\frac{\beta_1\sigma(I_1+W_1)}{A} & \alpha_1 & 0 & 0 \\ \delta_2 & 0 & -(\mu+\alpha_2) & 0 & 0 \\ 0 & \frac{\beta_1\sigma(I_1+W_1)}{A} & 0 & -(\mu+\gamma_1) & 0 \\ \frac{\beta_2\sigma R_1}{A} & 0 & 0 & 0 & \frac{\beta_2\sigma R_1}{A}-(\mu+\gamma_2) \end{bmatrix}$$

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Acknowledgements

The research in this manuscript has been partially supported by grants given by the National Science Foundation (NSF Grant), the National Security Agency (NSA Grant). I thank the INTEL corporation for providing the latest high performance computer and software. I also like to thank the Biometrics Unit for allowing the use of CAL'S facilities and for the moral support. I along with my advisors, are solely responsible for the views and opinions expressed in this report. The research in this report does not necessarily reflect the views and/or opinions of the founding agencies and/or Cornell University. My most sincere appreciation goes to my advisors Carlos Castillo-Chavez, Maia Matcheva, Zhilan Feng. Specially, I would like to thank Carlos Castillo-Chavez for allowing me the opportunity to participate in MTBI.