An Agent-Based Model with Drift and Cross-Immunity for Influenza

Jorge A. Alfaro-Murillo

Abstract

An agent-based model is used to describe the dynamics of influenza drift and cross-immunity in host populations with different characteristics. Each different mutation of the virus is represented as a point in a two-dimensional space, constructed in such a way to represent the genetic distances between the mutations (genetic map). A strain of the virus is represented by a region in that map. Each individual has a history of all his previous infections, represented by a vector consisting of points in the map. At a given time each infected individual will have contact with other individuals of the population. The probability that this contact results in an infection depends on how far the virus is from the closest point in the history of the individual to be infected (cross-immunity). If contact is effective, the individual will be infected in the next time period. However, since the virus may mutate in the host in the next time period, the active mutation generated will differ from the one that caused the initial infection; but will remain genetically close to it (drift). This work was motivated and gives special attention to the infection of influenza in the tropics, since this area has not been well characterized by mathematical models. Patterns similar to the ones observed in the tropics are obtained in the simulations with low values of infection probability or contact rate.

1 Introduction

Influenza viruses are currently a major cause of human morbidity worldwide. They infect 5 to 15% of the global population and kill nearly half a million people annually [22]. Last year's H1N1 pandemic has been detected in more than 214 countries with 18311 deaths, with 8516 in America alone [27]. Influenza has been widely studied and characterized for temperate regions, and it is clear that there are seasonal variations in its occurrence, with marked peaks in the winter of each year [11, 20, 25]. Meanwhile influenza seasonality in the tropics is less defined. The virus remains all year long at a relatively constant intermediate level with some peaks that vary worldwide [1, 5, 14, 19, 24, 26]. It has been suggested that most of the seasonal outbreaks of influenza originated in China and spread to the rest of the world [6], nevertheless more recent studies give evidence supporting the hypothesis that virus strains originated in other regions of the tropics and travel from there to subtropical zones [1]. Mapping of the viral genomes from temperate populations has also led to the hypothesis of a sink-source of viral ecology located in the tropics in which new strains are constantly seeded from a persistent influenza reservoir [16]. This suggests the possibility of studying a host population in the tropics (the sink-source). Mutation of influenza will be intrinsic in the model, hence new outbreaks produced by new strains are a result of the model itself.

Evidence of the differences between influenza spread in the tropics and other regions is given by the fact that transmission of the virus may be more predominant due to contact in the tropics (in contrast with aerosol transmission [12]), due to the fact that high temperatures block aerosol transmission [13]. Therefore more attention should be placed on contact rates of individuals in the tropics.

The current situation of the H1N1 pandemic gives rise to additional questions about the dynamics underlying a flu infection. The peak of the infection last year was much sooner than expected in the United States, around the end of October, and although it was predicted [23], the reason behind this change is not clear. In contrast, during the early part of the winter season in the southern hemisphere, little pandemic or seasonal influenza activity had been reported [27]. Different behavior for the waves of H1N1 as compared with seasonal influenza, has also been reported for tropical countries [7]. This implies that the seasonality associated with influenza might be closely linked with contact rates, cross-immunity of the population and other parameters

while possible having little to do with cold weather.

In some tropical countries there has been recent active co-circulation of H1N1 and seasonal H3N2 viruses [8, 27]. This phenomena has been analyzed, including the cross-immunity within the strains, with discrete and continuous time models, and it has been proven that sustained oscillations are possible in this context [4]. Recent work has tried to describe partially what the dynamics of an SIR-model of n interacting strains would be [2, 15]. These type of models do not include drift from one strain to another. Efforts in that direction have been focused in approximating drift as a diffusion process on a one-dimensional axis of variant types [9, 10, 17, 18]. The complexity of these SIR-models is that there are going to be as many recovered class as all the elements of the power set of all types of strains are included in the model. With a finite number of strains n, 2^n recovered classes are needed, so the analysis usually has to be limited to 2 or 3 strains. In the model with diffusion, since one has an infinitely uncountable number of strains, the cardinality of the recovered classes is so big that no standard theory of partial differential equations can be employed. This imposes the necessity of additional assumptions: for these models, it is assumed that individuals gain total immunity to all previous circulating strains with the infection of a newer one. This enables the division of the recovery classes to have at least the cardinality of the real numbers. The objective of this work is to formulate an agent-based model which extends the idea of cross-immunity and drift to any number of strains without such restrictions.

The main idea of the model, is that the genetic evolution of influenza can be represented in a two-dimensional space (the genetic map), where points on the map represent different mutations of the virus, and the map is divided into regions that represent each different type of strain. For the virus to drift from one strain to another, there must exist enough infections that cause mutations that go in the direction of the new strain. Genetic maps including the different strains each point belongs to, are available for influenza [16, 21]. The one constructed here is only theoretical, to serve as a starting point for the simulations. More about these types of genetic maps will be discussed in Section 4.

2 The Model

The agents in this model are individuals of the host population and the active viruses in a given period of time. The individuals don't have any particular location in the model. The active viruses are points (x, y) in a two-dimensional space (called a genetic map). The x and y-axis for this map, do not have any specific biological meaning. Having two dimensions is most important because this enables for a given mutation (x, y) to possess an infinite number of mutations that have, in the map, the same distance to (x, y). This is not possible in one dimensional space.

The plane is then divided into patches, each one representing a different strain of influeza; any virus located in a given patch is (to the opposing immune systems) the same strain of influenza. Each person has a different infection history, that is, individuals are linked to every different strain previously infected with. For simplicity we assume that the patches are all unit squares. Thus, we can easily identify the strain types with the bottom left point of its patch, that is, with a pair of integers (n, m).

At a given period of time t there is a given number (which may differ from time to time) of active viruses in the population. We can identify them by their location in the plane as a list of points: $(x_1, y_1), ..., (x_n, y_n)$. Individuals having each virus will contact, with random value c (the contact rate), other individuals in the population. Their infection will depend on various factors: if the person already had a virus of the same strain, then he or she remains uninfected. If the person is in the susceptible class, that is if he or she has no history of infection, then the probability of getting infected is β, the infection probability ($0 < \beta < 1$). If the person doesn't have that strain in his or her history, but has at least one point in his history, then the probability of getting infected is going to depend on the distance of the virus to the closest strain in his or her history, the closer it is, the lower the probability of getting infected (this feature models cross-immunity).

If $f((x, y), H)$ represents the probability that the virus located at (x, y) infects a person having a history H, then:

$$f((x, y), H) = \begin{cases} \beta & \text{if } H = \emptyset \\ \beta \frac{d}{d+\theta} & \text{if } H \neq \emptyset \end{cases}$$

Here $d = \min ||([x], [y]) - (n, m)||$, where $[z]$ is the integer part of z, and the minimum is taken over all the points (n, m) representing all the strain types in H. The 1-norm is used to take distances. Since all finite dimensional

norms are equivalent taken, the 1-norm should not make a difference in the model, and since the strains are represented by integers, taking 1-norms has a computational advantage since the distances are also integers.

The parameter θ is referred to as the cross-immunity coefficient. It can be any value greater than or equal to 0 and it measures how fast cross-immunity changes, the higher θ is, the higher the cross protection against other strains. Notice that $f((x,y),H) = 0$ if $([x],[y])$ is in H, and that $f((x,y),H) \to \beta$ as $d \to \infty$. This means that an individual gains total immunity to a strain if he or she was already infected with a virus of that strain, and that a very distant mutation acts in an individual the same way it would act in susceptible individual.

If the person gets infected with a virus (x,y), the corresponding strain $([x],[y])$ is added to his or her history for the next time period, $t+1$. Since the virus will mutate inside this individual, a close virus $(x+\Delta x, y+\Delta y)$ will be active for time $t+1$ (this mimics the drift). The Δx and Δy are going to be random numbers from a uniform distribution $[-\delta, \delta]$, where $\delta \geq 0$ denotes the drift-coefficient in the model.

The time scale is in weeks, hence each period represents one week. This time scale implies that the virus (x,y) will not be active for time $t+1$, because an infected individual is no longer infectious after one week. This assumption is based on the infectivity rates used by Carrat et al. [3], where, based on data from experimental studies, the infectivity lasted a maximum of 10 days but the rate after the 8th day was significantly reduced. In this study it is also shown that the peaks of infectivity are within the second and third day, but the model assumes that the infectivity rate is an average of the values experienced during the whole week.

It is also assumed, for simplicity, that the mortality rate is equal to the birth rate, so that the population remains constant. For the simulations the population size is assumed to be 100000 individuals. Simulations with a population of 1 million individuals or more were also run, but they did not alter the patterns generated using only 100000 individuals and were rather demanding computationally. Also no deaths associated with the influenza infection are taken into account, such deaths should be covered in the mortality rate of the population, since individuals are not being distinguished by age. For all the simulations an average life expectancy of 70 years is assumed. That is, $\frac{100000}{52\times 70} \approx 27$ random individuals are killed each period of time and 27 susceptible individuals are added to the population each period of time. Varying life expectancy of the population was not considered because no

significant changes were observed when running the model with this feature.

The whole population is assumed to be susceptible at the beginning of the simulation, that is, the history of each individual is empty. This assumption is far from reality, however it simplifies the initialization process, otherwise one would have to take into account differences in age (see Section 4). This models an antigenic shift of influenza, *e.g* the H1N1 pandemic of 2009. More about this assumption is discussed in Section 4.

A virus mutation located at $(0.5, 0.5)$ is then introduced to the population. For critical mass this infection is given to 3 individuals of the population. This makes no difference in the model (the first period can be thought of as the second one), it just helps to get infections that do not die out during the first week. Finally the parameters for contact rates, infection probabilities, cross-immunity coefficients and drift coefficients are varied to obtain different results in the simulations.

All the simulations were run in Python Programming Language (`www.python.org`) using modules of SciPy (`www.scipy.org`) for the mathematical computations and graphs.

3 Results

First, control simulations are run in which either drift or cross-immunity are not included. This provides some insight into parameter perturbation effects model outcome. Next, the results for simulations which include drift and cross-immunity are discussed. For this part, the results for high probability of infection and contact rates, high cross-immunity, reemergence of infections and periodicity are discussed separately.

3.1 Control: No Drift

First, some simulations were run with a drift coefficient equal of 0, in order to model a typical infection of influenza in a completely susceptible popualtion. The infections grow to a peak and then decay to 0. Decreasing the contact rate (see Figure 2) or the infection probability (see Figure 3) tends to make the peak of the infection lower and the duration of the infection longer, until a point were they are so small that the infection dies out in a couple of weeks as is seen in Figure 1. Here, the cross-immunity coefficient is not important. Again several changes were made to the average life expectancy to see if a non trivial equilibrium could be obtained, but that was not observed. This shows that the results of several peaks of infection come exclusively by including the drift factor into the model.

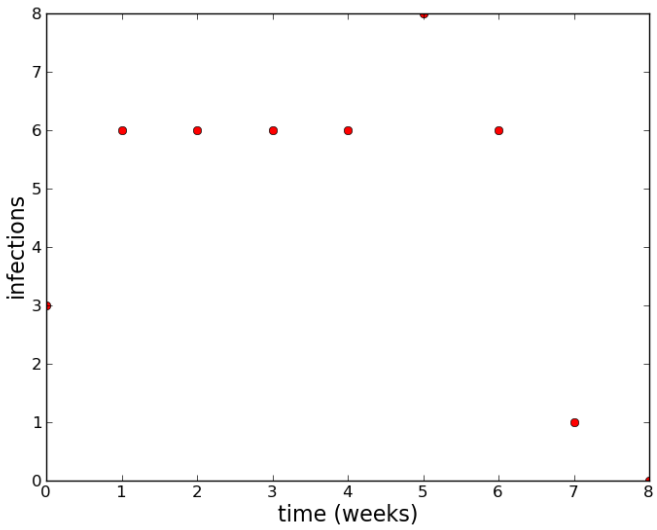

Figure 1: $c = 7$, $\beta = 0.12$, $\theta = 0.15$, $\delta = 0$: Contact and infection rates are so small that the infection is not sustained past 8 weeks and the total infected population negligible.

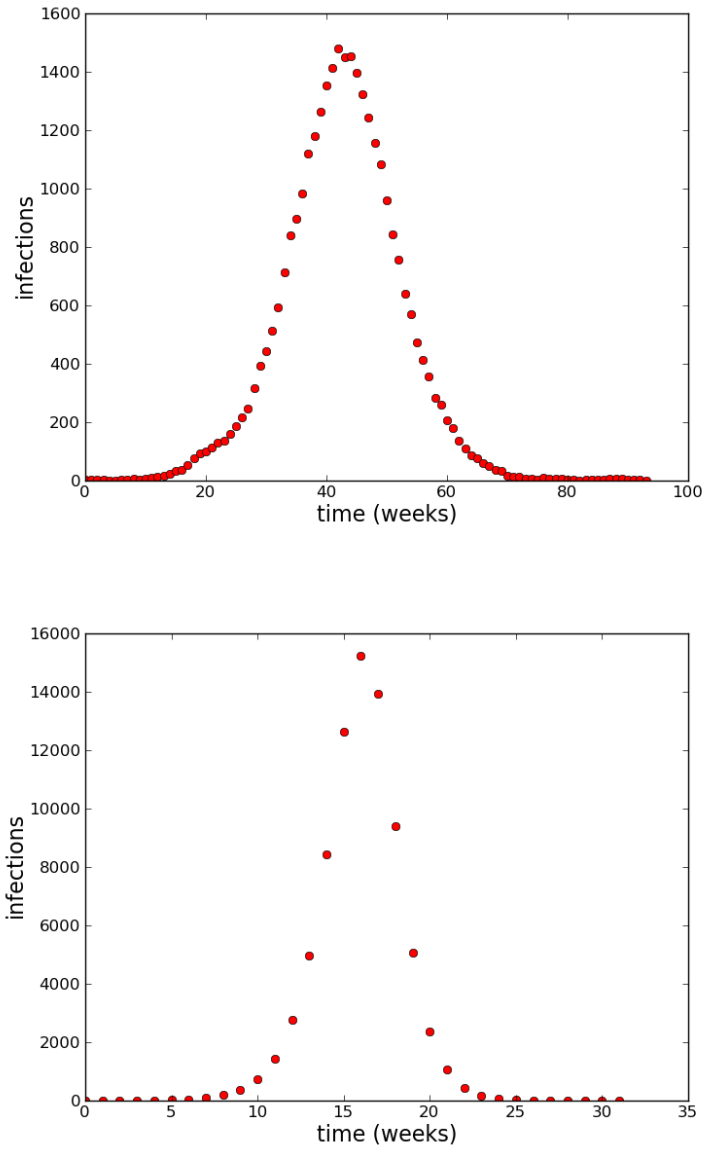

Figure 2: $c = 10$, $\beta = 0.12$ (up) and $\beta = 0.2$ (down), $\theta = 0.15$, $\delta = 0$: A higher contact rate leads to a higher peak and a shorter duration of the infection.

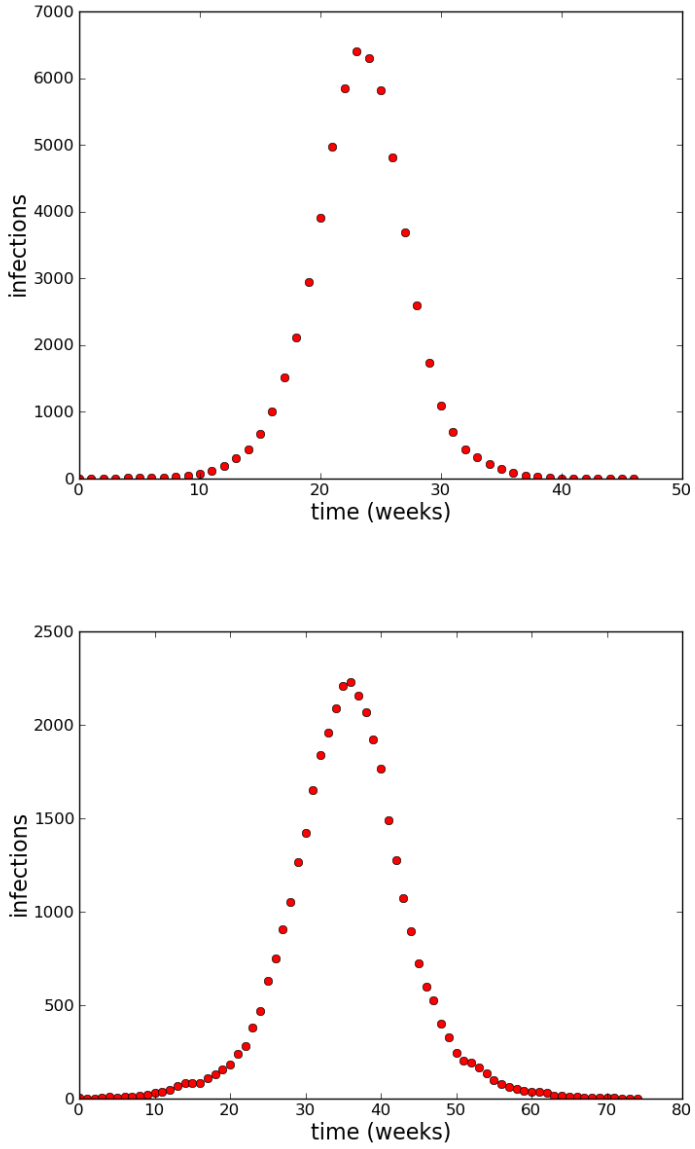

Figure 3: $c = 5$, $\beta = 0.30$ (up) and $\beta = 0.25$ (down), $\theta = 0.15$, $\delta = 0$: A higher contact rate also causes a higher peak and a shorter duration of the infection.

3.2 Control: No Cross-immunity

When the simulation is run for a population where there is no protection against closely related strains ($\theta = 0$), we get different results depending on how high the drift coefficient is. If the drift is too fast another peak of infections, even higher than the initial, is observed (Figure 4); this happens because individuals get infected with two strains simultaneously. Observe that in all the graphs the y-axis represents infections, and not infected individuals, so we can even have more infections than the population size. When the drift causes the new strain to arrive, after the first infection is almost extinct, the second peak is similar to the first one (Figure 5), and even 3 periods can be obtained (Figure 6). As expected, when we compare Figures 4, 5 and 6 we see roughly the same number of infections as in the first peak, if we keep the other parameters constant.

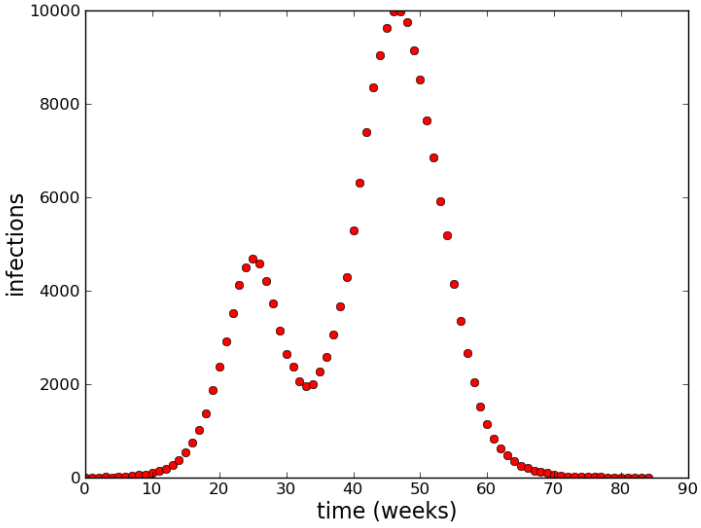

Figure 4: $c = 10$, $\beta = 0.14$, $\theta = 0$, $\delta = 0.07$: The second strain arrives when there is still a multitude of hosts with the first infection; we observe individuals infected with both strains in the same period of time.

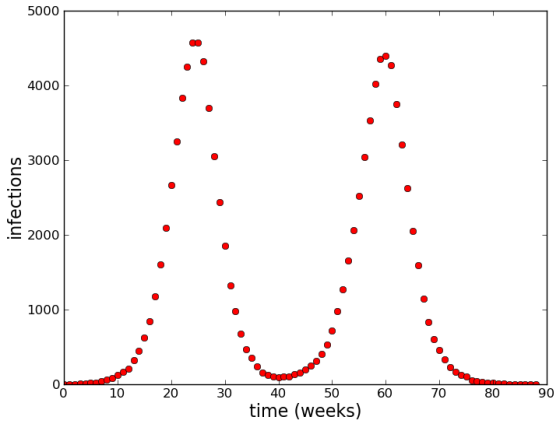

Figure 5: $c = 10$, $\beta = 0.14$, $\theta = 0$, $\delta = 0.04$: The second strain arrives when the infection period of the first strain is at an end, so the second infection is very similar to the first one.

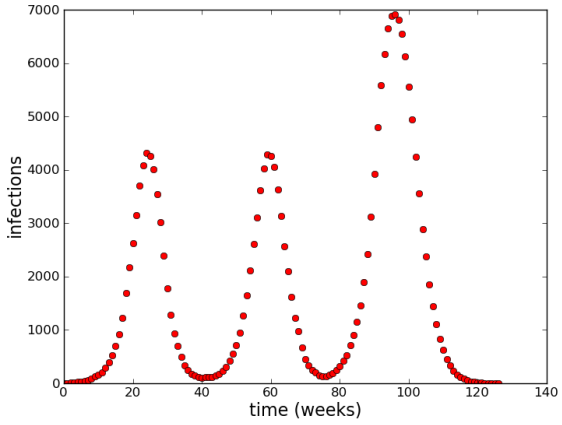

Figure 6: $c = 10$, $\beta = 0.14$, $\theta = 0$, $\delta = 0.05$: More than 2 similar infections can be obtained if the drift coefficient permits the new strains to arrive at the precise moment.

3.3 Drift and Cross-immunity: High Infectivity

As seen in Figures 7, 8 and 9 when drift and cross-immunity are both included in the model, there is a point where if the combination of contact and infection rate is high enough, results similar to the ones in Section 3.1 are obtained: the infection also decreases to 0 after the maximum. This happens because the infection occurs in such a short period that the virus does not have enough time to mutate. A large number of individuals from the population gain immunity against the strain, consequently there are not enough susceptible individuals for the virus to infect.

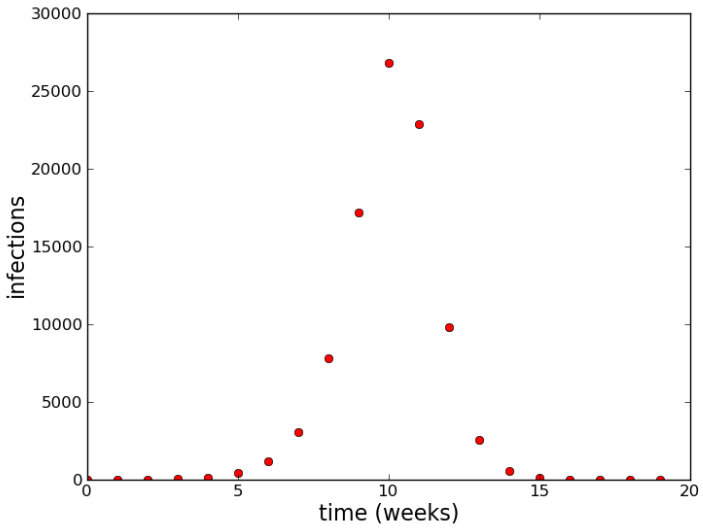

Figure 7: $c = 7$, $\beta = 0.4$, $\theta = 0.11$, $\delta = 0.07$: Effect of a high infection probability.

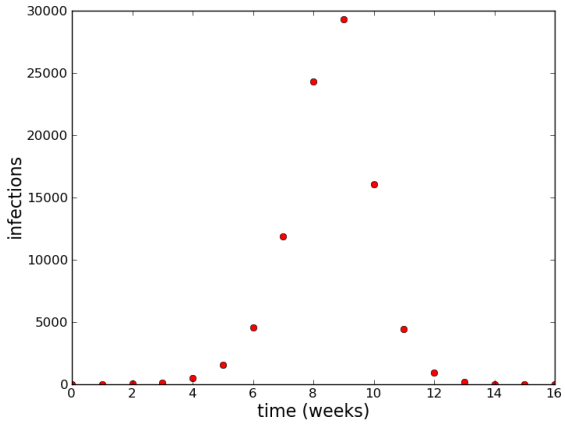

Figure 8: $c = 30$, $\beta = 0.1$, $\theta = 0.11$, $\delta = 0.07$: Effect of a high contact rate.

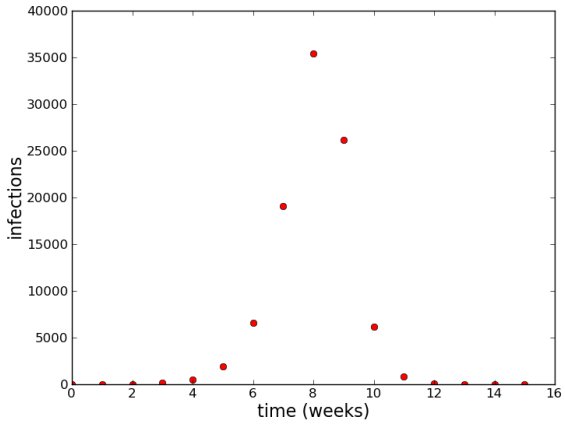

Figure 9: $c = 12$, $\beta = 0.3$, $\theta = 0.11$, $\delta = 0.07$: Intermediate infection probability or contact rate, but the combination of both is high, gives the same result as in the previous two figures.

3.4 Drift and Cross-immunity: High Protection

If the cross-immunity coefficient is high enough with respect to the value of the drift coefficient then the pattern of infection tends to be similar to the one in Sections 3.1 and 3.3: the infection dies after only one high peak. A new strain comes to the population, but most individuals are protected against it. The difference with Sections 3.1 and 3.3 is that the infection dies out after a couple of years as opposed to a couple of weeks. It may remain at very low levels so that it probably will be undetectable in a population (Figure 10), or it can get another peak much lower than the first one, and then die out (Figure 11).

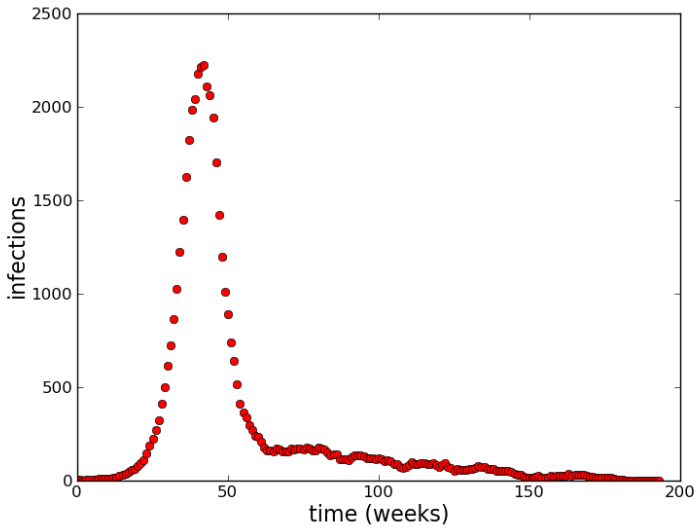

Figure 10: $c = 5$, $\beta = 0.25$, $\theta = 0.11$, $\delta = 0.07$: Second infection is almost unnoticed.

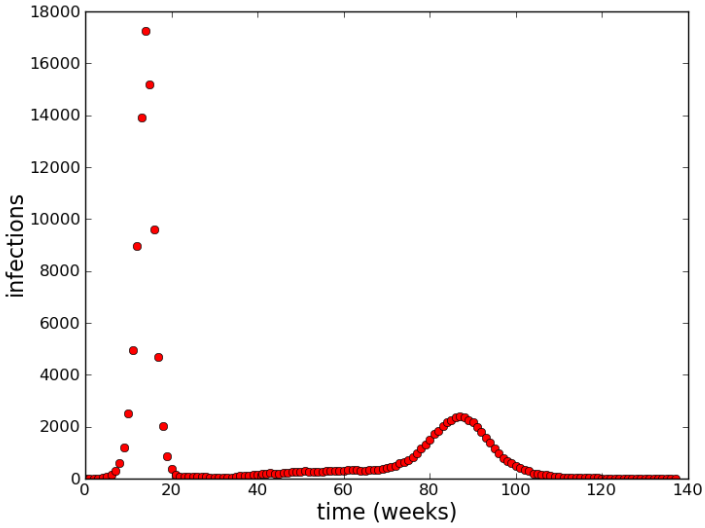

Figure 11: $c = 7$, $\beta = 0.3$, $\theta = 0.15$, $\delta = 0.07$: A peak much lower than the first one is achieved and no third strain reaches the population.

3.5 Drift and Cross-immunity: Reemergence of Infections

When the infection probability or contact rate are low enough, we see the reemergence of another infection peak in the population (see Figures 12 and 13). As expected, the second peak is lower than the first one, this is because members of the population already have cross protection against the new strain. As seen on Figure 12 the drift coefficient is what determines when the new strain attacks the population. Interestingly enough, when the cross-immunity coefficient is varied, the second peak is also shifted. This result is similar to that obtained by Castillo-Chavez et al. [4] using a system of differential equations.

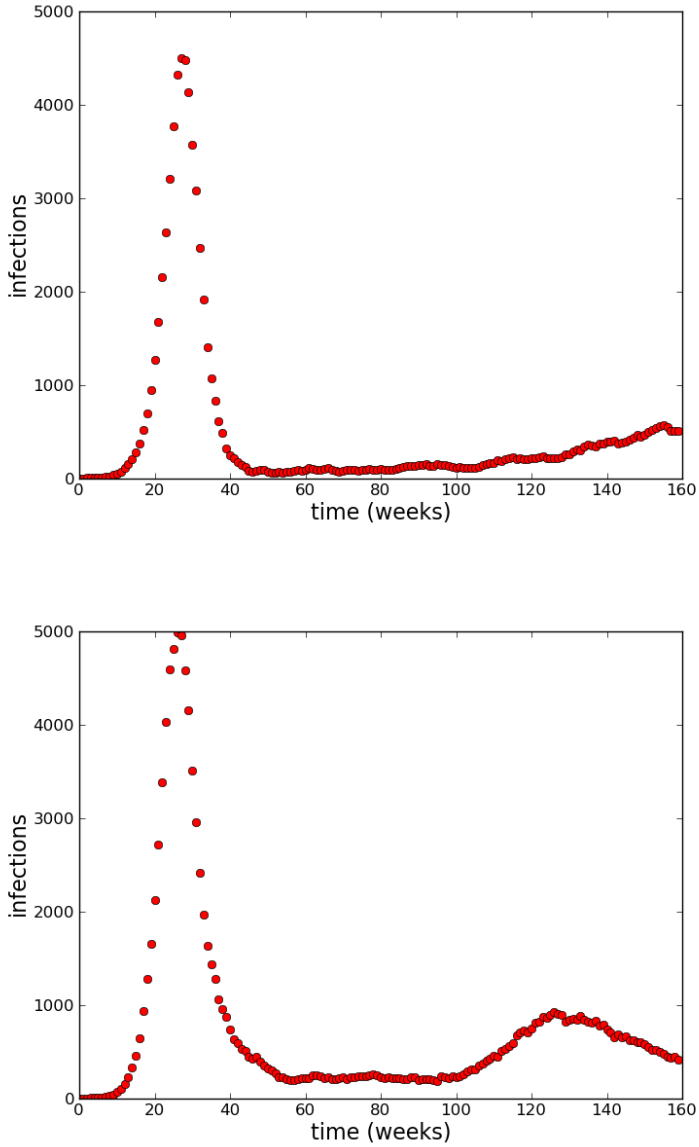

Figure 12: $c = 10$, $\beta = 0.14$, $\theta = 0.11$, $\delta = 0.075$ (up) and $\delta = 0.1$ (down): Making the virus drift quickly allows the second strain to arrive faster; so the second peak occurs earlier.

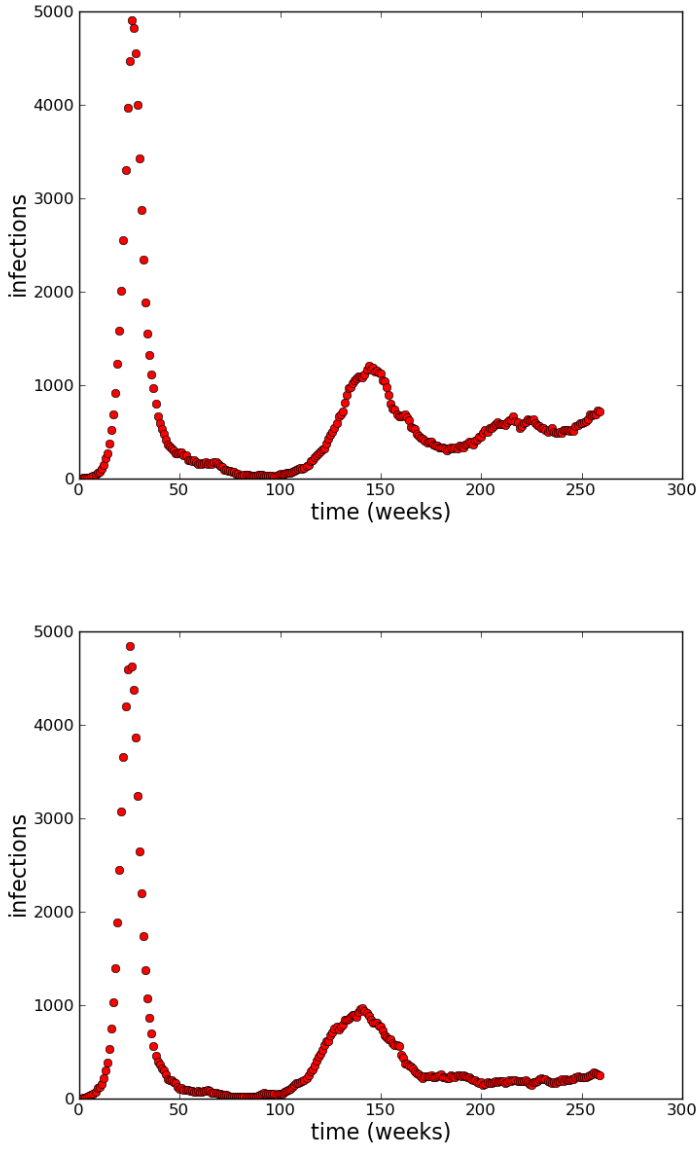

Figure 13: $c = 10$, $\beta = 0.14$, $\theta = 0.12$ (up) and $\theta = 0.13$ (down), $\delta = 0.1$: Small changes in cross-immunity also effects the onset of the second peak (the peak in the second figure occurs about 10 weeks earlier).

3.6 Drift and Cross-immunity: Periodicity

When parameters are chosen so the virus mutates and the simulations are run for long periods of time, low level periodicity emerges (see Figures 14, 15, 16 and 17). The time between peaks, as well as peak altitude, tends to vary. This is the kind of behavior observed in the tropics [5, 14, 19, 24, 26]. Observe that the parameters for infection probabilities in Figures 14 and 17 are relatively small compared to the ones used for other graphs. A low infection probability should be the case in the tropics as it tends to have higher temperatures all year long; a high temperature blocks aerosol transmission of influenza [12, 13]. On the other hand Figures 15 and 16 have relatively small contact rates, this should also be the case for the tropics since without winter, there is less concentration of people in closed spaces where contact rates are higher.

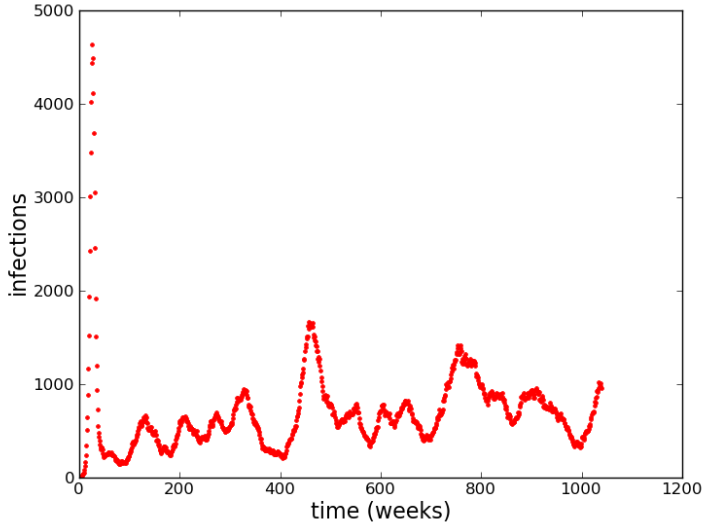

Figure 14: $c = 10$, $\beta = 0.14$, $\theta = 0.13$, $\delta = 0.1$: The peak around week 450 is almost twice as big as the other peaks, and the infection probability is the same. This means that infections with some strains can cause more illness within a population even if the strain is weakly infectious, this is because the population does not have reliable cross-immunity against the strain.

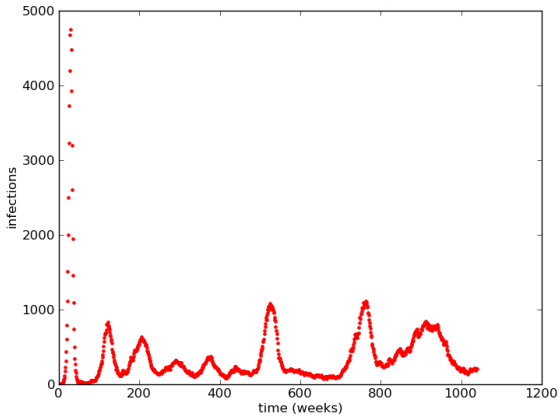

Figure 15: $c = 7$, $\beta = 0.2$, $\theta = 0.11$, $\delta = 0.07$: A period of almost four years with negligible levels of infection is observed between two peaks in weeks 550 and 750.

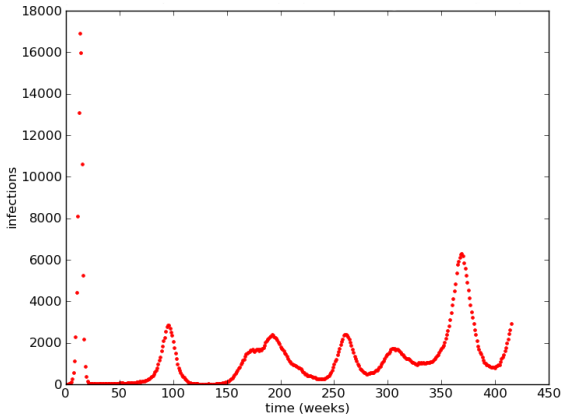

Figure 16: $c = 7$, $\beta = 0.3$, $\theta = 0.16$, $\delta = 0.07$: A very high peak in the infections is noticed around week 375. No change in infection probability or contact rate, not even an antigenic shift, is necessary to produce an unusually high peak in infections.

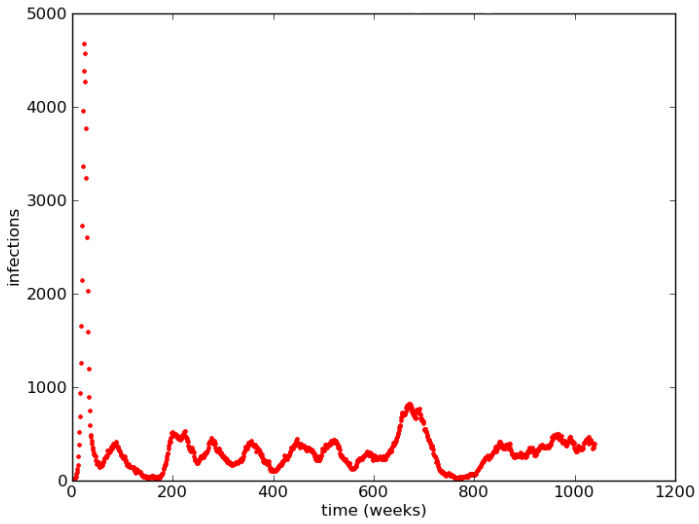

Figure 17: $c = 10$, $\beta = 0.145$, $\theta = 0.11$, $\delta = 0.07$: There are values of the parameters such that the infections may remain at very low levels for all of the relevant time period; just production of new strains that infect very few individuals of the population.

4 Discussion

Since influenza is an RNA virus, it is dependent on an RNA polymerase to replicate, and therefore lacks proof reading and correction ability. This causes mutations to be common during viral replication. This process creates new strains of influenza, the process is referred to as antigenic drift. Since new strains are constantly evolving, a mathematical model that includes several strains should consider drift and the emergence of new strains as well. This was the starting point of this project.

The main result was to show that there exits parameters in the model such that the infection of influenza persists all year long and has small peaks with no constant pattern. This is what is observed for influenza in the tropics [5, 14, 19, 24, 26]. The mechanism employed in this model to reproduce those patterns was antigenic drift, a source to generate new strains. This was obtained by using low parameters of infection probability or contact rate and

was discussed in Section 3.6; this case is similar to the phenomena occurring in the tropics. This supports the hypothesis suggested by Rambaut et al. [16] and Alonso et al. [1] that the tropics can be the source of the influenza types that later travel to the north or south to cause seasonal influenza infections.

Since a population is only seldom subject to a completely different strain, one could argue that the results of this model are only applicable for cases with antigenic shift. Nevertheless, one can think of the first infection as minimally destructive, giving the population some initial cross-immunity against the stronger, second strain. The behavior that usually present in the temperate zones can also be observed, as in, just one peak (two in the simulations) and then the infection goes extinct, see for example Figure 11.

With the results of this model, there is also a lot of discussion that could be started about the evolution of influenza viruses as a family of viruses. The infection probability and drift coefficient for the virus should have been naturally selected to adapt in the best way possible to given variables of the environment, *e.g.* the contact rate of their host species. The best strategy is not necessarily to have a very high infection probability as was shown here, but one that leaves the drift enough time to evolve into another strain. Moreover, low levels of drift coefficient in some types of influenza as in those of type B and C, might be the cause of reemergence of noticeable infections sometimes being very distant from each other, as was presented in Section 3.5.

As was discussed in Section 1, there are genetic maps available for influenza, which serve as the basis for identifying points on the plane as different mutations of influenza. Antigenic maps of the same strains are also available. One can construct binding assays based on the ability of influenza viruses to agglutinate red blood cells and the ability of antisera of animals raised against that particular strain or related ones, to block the agglutination [21]. A twofold dilution of the antiserum in such a hemagglutination inhibition assay corresponds to a unit of distance in the antigenic maps [21]. These distances could be used in this model to measure the cross-immunity from strain to strain in a more realistic way.

One extension of this model includes, considering the age of the individuals (agents) as variables. This would allow a better way to generate initial conditions to start the simulation. Also mortality could play a bigger role in this case, as it could be assumed higher for older individuals (so older individuals would have more points in their history).

Another plausible extension of this model could be the consideration of

three populations with distinct values of infection and contact rates to model the southern and northern hemisphere and the tropics. Varying the contact rates in the winter season for the temperate zones could cause seasonality if random individuals are allowed to travel between the populations (so that they carry the infections that originate in the tropics). That result would serve as further evidence in favor of the hypothesis that the tropics are the source of the influenza viruses plaguing the world.

5 Acknowledgments

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