

Modeling competition between two influenza strains

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Abstract. We use spatial and non spatial models to argue that competition alone may explain why two influenza strains do not usually coexist during a given flu season. The more virulent strain is likely to crowd out the less virulent one. This can be seen as a consequence of the Exclusion Principle of Ecology. We exhibit, however, a spatial model for which coexistence is possible.

1. Introduction. The seasonal flu strain was a lot less prevalent during the 2009/2010 influenza season than during the previous years, see Fluvview (the weekly CDC influenza report) . On the other hand, some time during Spring 2009 the new so called swine strain appeared. There seems to be a relation between these two events. In this paper we propose to explain this phenomenon using competition models. We will use spatial and non spatial models to show that in a given flu season coexistence of two strains is unlikely due to competition alone. We will also show that geometry and space may be critical for coexistence. Our models deal with competition over only one flu season. In the real world, because of mutations the fight between two strains may go on for several flu seasons before one strain outcompetes the other. This picture is consistent with the very skinny shape of the phylogenetic tree for influenza, see for instance Koelle et al. (2006) and van Nimwegen (2006). In this paper the two competing strains are assumed not to undergo mutations and therefore the time scale we focus on is one flu season.

A competing explanation of the non coexistence of the two influenza strains is cross immunity. For instance, immunity may explain why older generations have not been as much affected as the younger ones in the swine flu epidemic. It may be due to some previous exposure to a similar strain, see the Discussion in Greenbaum et al. (2009). However, using a cross immunity argument to explain why the swine strain crowds out the seasonal one may be more difficult. The hypothesis would be that the swine strain must confer some immunity against the seasonal flu. But, clearly the seasonal strain does

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not confer any immunity against the swine strain: after all even young people (the group most severely affected by the swine strain) have usually been exposed to the seasonal strain and do not seem to be protected against the swine strain. Hence, for this argument to work the swine strain must confer some immunity against the seasonal strain but the seasonal strain cannot confer any immunity against the swine strain. In contrast to this cross immunity hypothesis we argue in this paper that even in models for which there is no immunity at all (every individual that recovers is immediately susceptible again!) coexistence of two competing strains is rather unlikely.

2. The ODE Model. Our first model is a system of ordinary differential equations. Let $u_1(t)$ and $u_2(t)$ be the density of individuals infected at time t with strains 1 and 2, respectively. We set

$$\begin{aligned} u_1' &= \lambda_1 u_1 u_0 - \delta_1 u_1 \\ u_2' &= \lambda_2 u_2 u_0 - \delta_2 u_2 \end{aligned}$$

where $u_0(t)$ is the density of susceptible individuals at time t . In words, individuals infected with strain i infect susceptible individuals at rate λ_i and get healthy at rate δ_i , for $i = 1, 2$. We assume that the only possible states are 0, 1 and 2. Hence, at any time $t > 0$ we have $u_0(t) + u_1(t) + u_2(t) = 1$. In particular, as soon as an infected individual gets healthy it is back in the susceptible pool.

Let 1 be the seasonal and 2 be the swine strains. Some reports indicate that the swine strain may be more virulent than the seasonal strain, see Fraser et al. (2009). Under that assumption,

$$\frac{\lambda_1}{\delta_1} < \frac{\lambda_2}{\delta_2}.$$

Assume also that at some point in time the ODE model is at the equilibrium $(0, 1 - \frac{\delta_2}{\lambda_2})$. That is, there is no seasonal strain and the swine strain is in equilibrium. Now introduce a little bit of seasonal strain (small u_1). Will the seasonal strain be able to grow? Using that u_1 is almost 0 and that u_2 is almost $1 - \frac{\delta_2}{\lambda_2}$ we make the approximation

$$u_0 = 1 - u_1 - u_2 \sim 1 - (1 - \frac{\delta_2}{\lambda_2}) = \frac{\delta_2}{\lambda_2}.$$

Hence,

$$u_1' \sim \lambda_1 u_1 \frac{\delta_2}{\lambda_2} - \delta_1 u_1 = u_1 (\lambda_1 \frac{\delta_2}{\lambda_2} - \delta_1).$$

Since we are assuming that $\frac{\lambda_1}{\delta_1} < \frac{\lambda_2}{\delta_2}$ we get $u_1' < 0$. That is, under these assumptions and according to this model the seasonal flu will not take hold.

In fact this system of ODE is a particular case of a well-known competition model. For the general version of this model it is known that one of the strains will vanish, see Exercise 3.3.5 in Hofbauer and Sigmund (1998). The point is that we have two populations (the population of individuals infected with strain 1 and the population of individuals infected with strain 2) that compete for a single resource (the susceptible individuals). It turns out that in such a model one population will drive the other one out. This is a particular case of the so called "Exclusion Principle" of Ecology: if the number of populations is larger than the number of resources all the populations cannot subsist in the long run, see 5.4 in Hofbauer and Sigmund (1998).

2. The spatial stochastic model. In the preceding model there is no space structure and all the individuals in the population can be seen as neighbors of each other. In this section we go to the other extreme where there is a rigid space structure and each individual has a fixed number of neighbors.

We now describe a spatial stochastic model called the multitype contact process, see Neuhauser (1992). Let S be the integer lattice \mathbf{Z}^d (d is the dimension) or the homogeneous tree \mathbf{T}_d for which each site has $d + 1$ neighbors. The system is described by a configuration $\xi \in \{0, 1, 2\}^S$, where $\xi(x) = 0$ means that site x is occupied by a susceptible individual, $\xi(x) = 1$ means that x is occupied by an individual infected by strain 1 and $\xi(x) = 2$ means that x is occupied by an individual infected by strain 2. If S is \mathbf{Z}^d then each site has $2d$ neighbors, if S is \mathbf{T}_d then each site has $d + 1$ neighbors. For $x \in S$ and $\xi \in \{0, 1, 2\}^S$, let $n_1(x, \xi)$ and $n_2(x, \xi)$ denote the number of neighbors of x that are infected by strain 1 and strain 2, respectively.

The multitype contact process ξ_t with birth rates λ_1, λ_2 makes transitions at x when the configuration of the process is ξ

$$\begin{aligned} 1 &\rightarrow 0 \text{ at rate } 1 \\ 2 &\rightarrow 0 \text{ at rate } 1 \\ 0 &\rightarrow 1 \text{ at rate } \lambda_1 n_1(x, \xi), \\ 0 &\rightarrow 2 \text{ at rate } \lambda_2 n_2(x, \xi), \end{aligned}$$

In words, a susceptible individual gets infected by an infected neighbor at rates λ_1 or λ_2 , depending on which strain the neighbor is infected with. An infected individual gets healthy (and is immediately susceptible again) at rate 1. Note that compared to the ODE model we are assuming in this model that $\delta_1 = \delta_2 = 1$. This is so because most of the mathematical results have been proved under the assumption $\delta_1 = \delta_2$. We take this common value to be 1 to minimize the number of parameters.

The multitype contact process is a generalization of the basic contact process which has only one type. The transitions of the basic contact process are given by

$$\begin{aligned} 1 &\rightarrow 0 \text{ at rate } 1 \\ 0 &\rightarrow 1 \text{ at rate } \lambda_1 n_1(x, \xi), \end{aligned}$$

For the basic contact process there exists a critical value λ_c whose exact value is not known and which depends on the graph the model is on. If $\lambda_1 > \lambda_c$ then starting with even a single infected individual there is a positive probability of having infected individuals at all times somewhere in the graph. On the other hand if $\lambda_1 \leq \lambda_c$ then starting from any finite number of infected individuals all the infected individuals will disappear after a finite time. See Liggett (1999) for more on the basic contact process on the square lattice and on trees.

2.1 The space is the square lattice \mathbf{Z}^d . We now go back to the multitype contact process. Assume that $\lambda_2 > \lambda_c$ and $\lambda_2 > \lambda_1$ then there is no coexistence of strains 1 and 2 in the sense that

$$\lim_{t \rightarrow \infty} P(\xi_t(x) = 1, \xi_t(y) = 2) = 0$$

for any sites x and y in \mathbf{Z}^d . In fact, strain 2 always drives out strain 1 in the following sense. Conditioned on strain 2 not disappearing then

$$\lim_{t \rightarrow \infty} P(\xi_t(x) = 1) = 0,$$

for any site x in \mathbf{Z}^d and any initial configuration. See Theorem 2 in Cox and Schinazi (2009) and also Neuhauser (1992). Hence, assuming that $\lambda_2 > \lambda_1$ (that is, strain 2 is more virulent than strain 1) this model too predicts that the seasonal flu will be crowded out by the swine strain. The spatial structure seems to have no influence on the outcome. The next section will show that this is not always so and that a different (more crowded) space structure allows coexistence.

2.2 The space is the tree \mathbf{T}_d . There is a fundamental difference between the basic contact process on the square lattice and the same model on the tree. There are two (instead of one) critical values for the basic contact process on the tree. The definition of λ_c is as before. We also define another critical value λ_{cc} in the following way. Consider the basic (one type) contact process with birth rate λ_1 . Let O be a fixed site on the tree or square lattice. Start the process with a single infected individual at O . The probability that the infection will return to site O infinitely many times is positive

if and only if $\lambda_1 > \lambda_{cc}$. It turns out that $\lambda_c < \lambda_{cc}$ on the tree but $\lambda_c = \lambda_{cc}$ on the square lattice.

The fact that the basic contact process has two distinct critical values on the tree has interesting consequences for the multitype contact process on the tree. Let λ_1 and λ_2 be in $(\lambda_c, \lambda_{cc})$ then strains 1 and 2 may coexist on the tree in the following sense. Under suitable initial configurations we have for any site x

$$\liminf_{t \rightarrow \infty} P(\xi_t(x) = 1) > 0 \text{ and } \liminf_{t \rightarrow \infty} P(\xi_t(x) = 2) > 0.$$

See Theorem 1 in Cox and Schinazi (2009). Note that coexistence occurs even for $\lambda_1 < \lambda_2$ but both parameters need to be in the rather narrow interval $(\lambda_c, \lambda_{cc})$. This result shows that space structure and geometry may be crucial in allowing coexistence.

3. Discussion. Our models show that at least in theory coexistence of two competing strains is unlikely. Coexistence is however possible for the multitype contact process on a tree. The tree can be thought of as a model for high density populations (in a ball of radius r there are $(d+1)d^{r-1}$ individuals on the tree \mathbf{T}_d but only about r^d on the lattice \mathbf{Z}^d). In order to have coexistence both infection rates cannot be too low or too high but may be unequal. In all other cases there will be no coexistence on the tree and there is never coexistence on \mathbf{Z}^d unless λ_1 is exactly equal to λ_2 , a rather unlikely possibility, see Neuhauser (1992). Interestingly the behavior of the mean-field ODE model is the same as the behavior of the model on \mathbf{Z}^d but different from the model on the tree. In general, it is expected that the model on the tree to be closer to the mean-field model than to the model on \mathbf{Z}^d . This is not so in this example.

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