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and

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Abstract:

This text consists of two papers on the epidemiology and natural selection of influenza A.

In the first paper, *The dynamics of cocirculating influenza strains conferring partial cross-immunity,* we formulate a model of a finite number of interacting strains retaining the full information about previous infections. We discuss dynamical aspects of the model and demonstrate how interesting dynamical behavior may arise.

The second paper, *A model of influenza A drift evolution,* focusses on the continuous change of the antigenic properties of influenza virus over time. This is described as a travelling wave through 'immunity space.'

The dynamics of cocirculating influenza strains conferring partial cross-immunity is in press in J. Math. Biol.

A model of influenza A drift evolution is in press in Zeitschr. Angew. Math. Mech. (Proc. International Conference on Industrial and Applied Mathematics, Hamburg, July 1995).

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The dynamics of cocirculating influenza strains conferring partial cross-immunity

Viggo Andreasen, Juan Lin, and Simon Levin

We develop a model that describes the dynamics of a finite number of strains that confer partial cross-protection among strains. The immunity structure of the host population is captured by an index-set notation where the index specifies the set of strains to which the host has been exposed. This notation allows us to derive threshold conditions for invasion of a new strain and to show existence of an endemic multi-strain equilibrium in a special case. The dynamics of systems consisting of more than two strains can exhibit sustained oscillations caused by an overshoot in the immunity to a specific strain if cross-protection is sufficiently strong.

1 Introduction

The hemagglutinin and neuraminidase molecules, the antigenically active parts of the influenza A surface, exhibit considerable polymorphy due to a high mutation rate in the viral genome. Especially the gene coding for the surface protein hemagglutinin mutates so rapidly that this has been interpreted as a sign of positive Darwinian selection (Fitch et al., 1991). The surface proteins of the influenza virus undergo two kinds of change, shift and drift. In shifts, a new virus with an antigenically distinct hemagglutinin (HA) or neuraminidase (NA) region appears, the new virus is referred to as a new *subtype*. The virus drift consists in point mutations continuously changing the composition of the antigenic sites giving rise to new virus *strains* (Palese and Young, 1982; Webster et al., 1982). It is well known that variation in surface molecules contributes to antigenic variation and that this property confers a selective advantage to new viral strains allowing them to escape partially the host immunity acquired from previous infections. The fate of a new mutant strain, however, is affected by the presence of other strains since infection by one strain reduces the susceptibility to related strains. The aim of this paper is to describe the dynamics of interaction among such related strains.

Immunity to influenza A — and hence cross protection — is mainly related to the recognition of the HA surface-structure, although antibodies are formed to many other viral proteins (for reviews see Levine, 1992; Webster et al., 1992). The HA-receptor site responsible for the virus penetration through the cell membrane is protected in such a way that antibodies cannot bind to it. Instead antibodies bind to five so-called epitopes on the HA-structure, effectively neutralizing the virus. Point mutations in the gene

coding for HA may result in minor changes in one or more of the epitopes. Apparently the human immune system varies among individuals in its ability to recognize slight changes in epitope composition. Mutant strains therefore meet a host population that is somewhat but not completely protected. This cross-immunity has been demonstrated in vitro by use of hemagglutination inhibition (Levine, 1992). In vivo the existence of cross immunity has been shown both in artificially challenged volunteers (Larson et al., 1978) and in long term studies of closed populations (Davies et al., 1984; Davies et al., 1986). Finally the pattern of influenza epidemics supports the idea that immunity to previous strains gives some protection. This is corroborated by observations of smaller annual and biannual epidemics following the appearance of the first pandemic of a new subtype. Thus the study of Spicer and Lawrence (1984) on influenza epidemics based on London's mortality records suggests that the infectivity of a subtype as measured by its basic reproduction number (Dietz, 1975) decreases as time passes since its introduction. Cross protection may occur between subtypes but empirical studies show no clear pattern (Frank et al., 1983; Sonoguchi et al., 1985).

The intensity of cross-protection has been linked to the number of amino acid substitutions in the HA-gene (Both et al., 1983; Sleigh et al., 1981; Sleigh and Both, 1981; Levine, 1992) although the evidence is somewhat conflicting (Xu et al., 1993).

Only few theoretical studies have investigated the effects of cross-immunity. The selective forces acting on the strains are mediated through the disease transmission dynamics. Therefore, by keeping track of the number of hosts infected with each strain, one can use an extension of the well known SIR models to describe the outcome of natural selection acting upon a finite number of interacting strains. This approach has been used to model the co-circulation of strains that interfere by prohibiting superinfection (Dietz, 1979) or by conferring partial cross-immunity (Castillo-Chavez et al., 1989). Both investigations focused on two interacting strains and found that stable co-existence is possible when suitable invasion conditions are satisfied. Gupta et al. (1994) modeled the effect of cross-immunity on two co-occurring strains of malaria by including into the Castillo-Chavez et al. (1989) model an explicit account of vector-transmission. In this situation more complicated dynamics could result; and, as we shall see, similar dynamics arise in the case of direct transmission when more than two strains interact. The consequences of cross-immunity for the transmission dynamics of influenza have been studied through stochastic Monte Carlo simulations although the emphasis has been on the detectability of viral interactions through their effects on observed attack rates (Ackerman et al., 1990).

These approaches provide a static view of viral evolution, allowing no place for the "drift" in viral strain that is observed in nature. Pease (1987) improved the description by using an SIR-type model to show how a slow change in the antigenicity of a single influenza variant affects the epidemiology of the disease. While Pease's "evolutionary epidemiology" describes the effect of drift (in the viral strains) on disease epidemiology, his model does not account for the selective forces that give rise to the drift.

Our aim is to combine these two views of influenza epidemiology. Thus we wish to include in our description enough strains to allow for a change in the prevalence of the strains, while at the same time retaining a faithful description of the selection regime induced by cross-reaction.

In the first section we introduce an SIR-model of n interacting strains and a notation that allows us to describe the system compactly. The flow between state variables is extremely complex and only a partial description of the dynamics is possible. We derive in the following section threshold conditions for invasion of new strains, and show how they relate to the well-known basic reproduction rate from epidemic theory. Since our interest is in understanding how host immunity acts as a selective force, we focus on a uniform version of the model, thus removing all other sources of natural selection. The uniform model turns out to have a uniform endemic equilibrium that undergoes a Hopf-bifurcation for high levels of cross-protection.

2 The model

Our starting point is the well-known SIR-model of the transmission-dynamics of a single infectious agent. In this model the population is divided into three compartments: susceptibles S, infected and infectious I, and recovered and immune R. In order to keep track of the immunity structure induced by interacting strains, we now introduce a more detailed subdivision of the population. We will assume that immunity is life-long and independent of the sequence in which infections have been experienced. The immunity profile of a person can now be summarized by stating the set of all previous infections.

If we let

$$\mathcal{K} = \{1, 2, 3, \ldots, n\}$$

denote the set of all possible strains, the uninfected part of the population falls into 2^n classes corresponding to the subsets of$\mathcal{K}$. We denote by $S_{\mathcal{J}}$ the number of individuals that are currently uninfected and who have previously been infected by the strains listed in the set $\mathcal{J} \subseteq \mathcal{K}$. Thus for example $S_{\{1,4\}}$ denotes the number of uninfected individuals who have previously been infected by strains 1 and 4 while $S_{\emptyset}$ denotes the number of individuals who have not encountered any infections (Adler and Brunet, 1991; Christiansen, 1988). The index $\mathcal{J}$ runs over the power set $2^{\mathcal{K}}$ of the set $\mathcal{K}$ and the total number of uninfected individuals is

$$S = \sum_{\mathcal{J} \in 2^{\mathcal{K}}} S_{\mathcal{J}} = \sum_{\mathcal{J} \subseteq \mathcal{K}} S_{\mathcal{J}}.$$

Similarly $I^i_{\mathcal{J}}$ gives the number of individuals currently infected by strain i who have previously recovered from infections with the strains in $\mathcal{J}$, i.e. $i \notin \mathcal{J}$. The number of infectious classes is $n2^{n-1}$. This description excludes the possibility of superinfection

i.e. simultaneous infection with two viral strains. However, for influenza this appears to be a rare phenomenon due to the cell based secondary immune system.

The exact way in which cross-immunity affects infection probability is not known. We will assume that cross-immunity works by reducing the probability of infection when the immune system is challenged with a related strain, because a partial immune response is induced by the virus with slightly different surface structure. Another possibility is that some individuals achieve complete protection against related strains while antibodies of other individuals are more specific and hence don't recognize strains with slightly different surfaces. Finally, it appears that cross-protection in some cases acts by reducing the severity of the second infection; this in turn may reduce infectivity. Since our primary goal is the description and understanding of the immunity structure we allow ourselves to focus on the first type of cross-protection. However, our basic results will hold for the other types of cross-immunity as well; we shall return to the question in the discussion.

In the completely unprotected part of the population, the force of infection of virus type i, Λ^i can now be determined by summing over all infectious individuals of type i. We get

$$\Lambda^i = \beta_i \sum_{\mathcal{J} \subseteq \mathcal{K} \setminus i} I^i_{\mathcal{J}},$$

where the transmission coefficient β_i is a measure of the infectivity of viral type i. Here and in the following we use the symbol $\mathcal{J} \setminus j$ to denote the set consisting of all elements in $\mathcal{J}$ except the element j, i.e. $\mathcal{J} \setminus j = \mathcal{J} \setminus \{j\}$. For individuals with immune history $\mathcal{J}$, cross-immunity reduces susceptibility by a factor $\sigma^i_{\mathcal{J}}$, which will depend on some measure of the distance between i and the set $\mathcal{J}$. In particular we set $\sigma^i_{\emptyset} = 1$ for all i. We will assume that additional immunity can only increase cross-protection and hence that $\sigma^i_{\mathcal{J}} \leq \sigma^i_{\mathcal{L}}$ for $\mathcal{L} \subseteq \mathcal{J}$.

The dynamics of $S_{\mathcal{J}}$ includes two loss terms and one gain term. The loss terms are due to deaths $\mu S_{\mathcal{J}}$ and due to infections with strains not yet experienced, $i \notin \mathcal{J}$

$$\sum_{i \notin \mathcal{J}} \sigma^i_{\mathcal{J}} \Lambda^i S_{\mathcal{J}}.$$

For the $S_{\emptyset}$-class the gain term represents births at a rate b and for other $S_{\mathcal{J}}$-classes the gain term represents recovery from infections for individuals that have the immune profile $\mathcal{J}$ after recovery, i.e.

$$\sum_{j \in \mathcal{J}} \nu I^j_{\mathcal{J} \setminus j},$$

where ν denotes the rate at which infected recover from infection. Thus the equation for $S_{\mathcal{J}}, \mathcal{J} \neq \emptyset$ becomes

$$\dot{S}_{\mathcal{J}} = \sum_{j \in \mathcal{J}} \nu I^j_{\mathcal{J} \setminus j} - \sum_{i \notin \mathcal{J}} \sigma^i_{\mathcal{J}} \Lambda^i S_{\mathcal{J}} - \mu S_{\mathcal{J}}$$

and for the completely susceptible class $S_\emptyset$

$$\dot{S}_\emptyset = b - \mu S_\emptyset - \sum_{j \in \mathcal{K}} \Lambda^j S_\emptyset.$$

Similar considerations lead to the following dynamics for the infectious class $I^i_\mathcal{J}$, $\mathcal{J} \subset \mathcal{K}, i \notin \mathcal{J}$

$$\dot{I}^i_\mathcal{J} = \sigma^i_\mathcal{J} \Lambda^i S_\mathcal{J} - (\mu + \nu) I^i_\mathcal{J}.$$

The total population size N is determined by summing up over all classes, and we find that

$$\dot{N} = b - \mu N.$$

In order to avoid the complications of varying population size, we will assume that the population has reached its equilibrium size N^* so that $b = \mu N^*$ and $N = N^*$.

3 Non-dimensional model

We start by observing that if we measure time in units of the average infectious period $(\nu+\mu)^{-1}$ and S and I as fractions of the total population N, the number of parameters is reduced by two. The new parameters are $e = \mu/(\mu + \nu)$, $r_i = \beta_i N/(\mu + \nu)$, while $\sigma^i_\mathcal{J}$ is not affected by the change.

In these variables, the model reads

$$\dot{S}_\emptyset = e - eS_\emptyset - \sum_{j \in \mathcal{K}} \Lambda^j S_\emptyset \quad (1)$$

$$\dot{I}^i_\emptyset = \Lambda^i S_\emptyset - I^i_\emptyset \quad (2)$$

and for general $\mathcal{J} \subseteq \mathcal{K}$ and $i \notin \mathcal{J}$

$$\dot{S}_\mathcal{J} = (1-e) \sum_{j \in \mathcal{J}} I^j_{\mathcal{J} \setminus j} - eS_\mathcal{J} - \sum_{j \notin \mathcal{J}} \sigma^j_\mathcal{J} \Lambda^j S_\mathcal{J} \quad (3)$$

$$\dot{I}^i_\mathcal{J} = \sigma^i_\mathcal{J} \Lambda^i S_\mathcal{J} - I^i_\mathcal{J} \quad (4)$$

where

$$\Lambda^i = r_i \sum_{\mathcal{M} \subseteq \mathcal{K} \setminus i} I^i_\mathcal{M}$$

gives the force of infection for strain i.

Some quantities of epidemic interest can be found by summation over the dynamic equations. Thus we find that the dynamics of the force of infection for strain i is determined by

$$\dot{\Lambda}^i = \left(r_i \sum_{\mathcal{J} \subseteq \mathcal{K} \setminus i} \sigma^i_\mathcal{J} S_\mathcal{J} - 1 \right) \Lambda^i, \quad (5)$$

and similarly that $R_{\mathcal{M}}$ the fraction of individuals who are immune to all strains in $\mathcal{M}$ (irrespective of whether they are immune to other strains as well) is determined by

$$\dot{R}_{\mathcal{M}} = (1-e)\sum_{i\in\mathcal{M}}\sum_{\mathcal{J}\supseteq\mathcal{M}\setminus i} I^i_{\mathcal{J}} - eR_{\mathcal{M}}.$$

In practice the dynamics of $R_{\mathcal{M}}$ is determined by observing that the only way to leave $R_{\mathcal{M}}$ is through deaths while one enters the class by recovering from one of the strains in $\mathcal{M}$ and already being immune to all the other strains in $\mathcal{M}$. In particular the total proportion of the population that is immune to strain i is

$$\dot{R}_i = (1-e)\sum_{\mathcal{J}\subseteq\mathcal{K}\setminus i} I^i_{\mathcal{J}} - eR_i = \frac{(1-e)}{r_i}\Lambda^i - eR_i.$$

Hence the relation between force of infection and seroprevalence at equilibrium is the same as in the case of a single strain.

In the appendix we shall make use of another auxiliary quantity that can be derived in a similar way, namely $N_{\mathcal{M}}$ the proportion of the population which has not been exposed to any of the strains in $\mathcal{M}$.

4 Linearization and threshold conditions

The equilibria of the model can be characterized by an implicit equation in the forces of infection $\underline{\Lambda} = (\Lambda^1, \ldots, \Lambda^n)$ in a way similar to the characterization of equilibria in subdivided populations, e.g. (Hethcote and Thieme, 1985). For simplicity the equilibrium values will be denoted simply by the name of the corresponding variable.

If $\underline{\Lambda}$ is known, equations (1–2) give

$$S_\emptyset(\underline{\Lambda}) = \frac{e}{e+\sum_{k\in\mathcal{K}}\Lambda^k} \tag{6}$$

$$I^i_\emptyset(\underline{\Lambda}) = \Lambda^i S_\emptyset(\underline{\Lambda}) = \frac{e\Lambda^i}{e+\sum_{k\in\mathcal{K}}\Lambda^k} \tag{7}$$

and equations (3–4) allow us to determine $S_{\mathcal{J}}(\underline{\Lambda})$ and $I^i_{\mathcal{J}}(\underline{\Lambda})$ by induction after the cardinality of the index set $\mathcal{J}$:

$$S_{\mathcal{J}}(\underline{\Lambda}) = \frac{(1-e)\sum_{j\in\mathcal{J}} I^j_{\mathcal{J}\setminus j}(\underline{\Lambda})}{e+\sum_{k\notin\mathcal{J}}\sigma^k_{\mathcal{J}}\Lambda^k} \tag{8}$$

$$I^i_{\mathcal{J}}(\underline{\Lambda}) = \sigma^i_{\mathcal{J}}\Lambda^i S_{\mathcal{J}}(\underline{\Lambda}), \tag{9}$$

If all coordinates of $\underline{\Lambda}$ are non-negative, all values of S and I (including $S_{\mathcal{K}}$) are non-negative and sum to unity, so these values correspond to a feasible equilibrium provided that $\underline{\Lambda}$ satisfies the equations

$$\Lambda^i = r_i\sum_{\mathcal{J}\subseteq\mathcal{K}\setminus i} I^i_{\mathcal{J}}(\underline{\Lambda}) = r_i\sum_{\mathcal{J}\subseteq\mathcal{K}\setminus i}\sigma^i_{\mathcal{J}}\Lambda^i S_{\mathcal{J}}(\underline{\Lambda}) \qquad i\in\mathcal{K}. \tag{10}$$

Thus $\underline{\Lambda}$ is an equilibrium provided that $\underline{\Lambda}$ is such that for all coordinates i,

$$\Lambda^i = 0 \qquad \text{or} \qquad 1 = r_i \sum_{\mathcal{J} \subseteq \mathcal{K} \setminus i} \sigma^i_{\mathcal{J}} S_{\mathcal{J}}(\underline{\Lambda}). \tag{11}$$

Thus the model may have many (boundary) equilibria, and we will not attempt to give a complete characterization of its dynamics and possible equilibria.

In general the linearization around any equilibrium $(S^\dagger_{\mathcal{J}}, I^\dagger_{\mathcal{J}})$ can be determined explicitly as

$$\frac{\partial \dot{S}_{\mathcal{J}}}{\partial S_{\mathcal{M}}} = \begin{cases} -e - \sum_{j \notin \mathcal{J}} \sigma^j_{\mathcal{J}} \Lambda^j, & \text{if} \quad \mathcal{J} = \mathcal{M}; \\ 0, & \text{if} \quad \mathcal{J} \neq \mathcal{M}, \end{cases} \tag{12}$$

$$\frac{\partial \dot{S}_{\mathcal{J}}}{\partial I^i_{\mathcal{M}}} = \begin{cases} 1 - e, & \text{if} \quad \mathcal{J} = \mathcal{M} \cup \{i\} \text{ and } i \notin \mathcal{M}; \\ -r_i \sigma^i_{\mathcal{J}} S_{\mathcal{J}}, & \text{if} \quad i \notin \mathcal{J}; \\ 0, & \text{else}, \end{cases} \tag{13}$$

$$\frac{\partial \dot{I}^i_{\mathcal{J}}}{\partial S_{\mathcal{M}}} = \begin{cases} \sigma^i_{\mathcal{M}} \Lambda^i, & \text{if} \quad \mathcal{J} = \mathcal{M}; \\ 0, & \text{if} \quad \mathcal{J} \neq \mathcal{M}, \end{cases} \tag{14}$$

$$\frac{\partial \dot{I}^i_{\mathcal{J}}}{\partial I^j_{\mathcal{M}}} = \begin{cases} r_i \sigma^i_{\mathcal{J}} S_{\mathcal{J}} - 1, & \text{if} \quad i = j, \mathcal{J} = \mathcal{M}; \\ r_i \sigma^i_{\mathcal{J}} S_{\mathcal{J}}, & \text{if} \quad i = j, \mathcal{J} \neq \mathcal{M}; \\ 0, & \text{if} \quad i \neq j, \end{cases} \tag{15}$$

where all expressions are evaluated at the equilibrium.

In particular, the stability of the disease-free equilibrium may easily be determined since at that equilibrium $\Lambda^i = 0$ for all i and $S_{\mathcal{J}} = 0$ for $\mathcal{J} \neq \emptyset$ while $S_\emptyset = 1$. Dividing the variables into three types $S_{\mathcal{J}}$, $I_\emptyset$ and $I_{\mathcal{M}}$ with $\mathcal{M} \neq \emptyset$ yields a linearization with a block matrix of the form

$$\begin{pmatrix} -e\mathbf{1} & \mathbf{A} & \mathbf{B} \\ \mathbf{0} & \mathbf{r} - \mathbf{1} & \mathbf{C} \\ \mathbf{0} & \mathbf{0} & -\mathbf{1} \end{pmatrix}.$$

Here $\mathbf{A}$, $\mathbf{B}$, and $\mathbf{C}$ are non-zero matrices while $\mathbf{1}$ is the identity matrix and $\mathbf{r}$ is a diagonal matrix with r_i in the diagonal. Obviously the disease-free equilibrium changes stability exactly when $r_i = 1$ for the largest r_i.

The ability of a rare strain to increase in numbers can be determined directly from (5). Hence if the system is at an equilibrium $(S^\dagger_{\mathcal{J}}, I^\dagger_{\mathcal{J}})$ where strain i — and possibly other strains — are absent, strain i can invade exactly if

$$r_i \sum_{\mathcal{J} \subseteq \mathcal{K} \setminus i} \sigma^i_{\mathcal{J}} S^\dagger_{\mathcal{J}} > 1. \tag{16}$$

Condition (16) has the well known form of a threshold condition. In fact, in the absence of all other strains, the basic reproductive rate of strain i would be r_i, and (16)

shows that at $(S^\dagger_{\mathcal{J}}, I^\dagger_{\mathcal{J}})$ the reproduction rate r_i should be multiplied by the proportions of contacts that are made with individuals still susceptible to the disease taking into account their relative susceptibility. The invasion condition can be obtained directly from the linearization of the full model by observing that the entries in the Jacobian corresponding to $S_{\mathcal{J}}$ with $i \in \mathcal{J}$ and $I^i_{\mathcal{M}}$ with $i \notin \mathcal{M}$ form a block triangular matrix where the diagonal element corresponding to $S_{\mathcal{J}}$ is always stable while the diagonal matrix-element of $I^i_{\mathcal{M}}$ changes stability depending on (16).

The bifurcation condition (16) suggests that $(S^\dagger, I^\dagger)$ changes stability by coalescence with an equilibrium determined by (11) with $\Lambda^i \neq 0$.

5 The uniform endemic equilibrium

To simplify the discussion we now focus on a symmetric model with n strains where all strains are similar in the sense that $r_i = r$ for all i. In addition we assume that the viral strains can be ordered along a one-dimensional axis indicating their degree of relatedness. This mimics the pattern observed in nature where the phylogeny of influenza at the molecular level looks like a tree with very short branches. Finally to avoid boundary effects we close the axes by assuming that strain 1 and strain n are neighbors so that the relatedness of strain i and j can be determined by the distance $|i-j| \bmod n$.

We are now able to look for *uniform* endemic equilibria. That is we will focus on equilibria where the force of infection Λ is the same for all types. Equations (6–9) now simplify to implicit relations

$$S_\emptyset(\Lambda) = \frac{e}{e+n\Lambda} \qquad S_{\mathcal{J}}(\Lambda) = \frac{(1-e)\sum_{j\in\mathcal{J}} I^j_{\mathcal{J}\setminus j}(\Lambda)}{e+m_{\mathcal{J}}\Lambda}$$
$$I^i_\emptyset(\Lambda) = \frac{e\Lambda}{e+n\Lambda} \qquad I^i_{\mathcal{J}}(\Lambda) = \sigma^i_{\mathcal{J}}\Lambda S_{\mathcal{J}}(\Lambda),$$

here $m_{\mathcal{J}} = \sum_{j\notin\mathcal{J}} \sigma^j_{\mathcal{J}}$. Thus $m_{\mathcal{J}}$ measures the total susceptibility of individuals in $S_{\mathcal{J}}$ and since $\sigma^i_{\mathcal{J}} \leq \sigma^i_{\mathcal{L}}$ for $\mathcal{L} \subseteq \mathcal{J}$, we have $\mathcal{L} \subset \mathcal{J} \Rightarrow m_{\mathcal{L}} \geq m_{\mathcal{J}}$.

The values given above correspond to an endemic equilibrium provided that $\Lambda > 0$ is a fixed point of the function

$$F(\Lambda) = r \sum_{\mathcal{J}\subseteq\mathcal{K}\setminus i} I^i_{\mathcal{J}}(\Lambda) = \frac{r}{n} \sum_{i\in\mathcal{K}} \sum_{\mathcal{J}\subseteq\mathcal{K}\setminus i} I^i_{\mathcal{J}}(\Lambda) \tag{17}$$

which by assumption is independent of i.

The following properties of $F(\Lambda)$ hold and allow the determination of the number of fixed points

1) $F(0) = 0$ and $F'(0) = r$.
2) $F'(\Lambda) > 0$
3) F is bounded as $\Lambda \to \infty$

4) $F(\Lambda)/\Lambda$ is a strictly decreasing function of Λ.

Conditions 1)–4) give a threshold condition: There exists a unique positive, uniform equilibrium iff $r > 1$. If $r < 1$ the disease-free equilibrium is the only uniform equilibrium.

It is straightforward to determine $F(0)$ and to show that $F(\Lambda)$ is bounded. To find F' we compute $I'_{\mathcal{J}}$ recursively on the number of elements in the index set $\mathcal{J}$:

$$\frac{dI^i_\emptyset}{d\Lambda} = \frac{e^2}{(e+n\Lambda)^2} > 0$$

and

$$\frac{dI^i_{\mathcal{J}}}{d\Lambda} = \frac{\sigma^i_{\mathcal{J}} e}{e+m_{\mathcal{J}}\Lambda} S_{\mathcal{J}} + \frac{(1-e)\sigma^i_{\mathcal{J}}\Lambda}{e+m_{\mathcal{J}}\Lambda} \sum_{j\in\mathcal{J}} \frac{dI^j_{\mathcal{J}\setminus j}}{d\Lambda}$$

which by simple induction gives

$$\frac{dI^i_{\mathcal{J}}}{d\Lambda} > 0$$

and hence $F'(\Lambda) > 0$. Similarly we find

$$\frac{dI^i_{\mathcal{J}}}{d\Lambda}_{|\Lambda=0} = 0 \qquad \text{for} \qquad \mathcal{J} \neq \emptyset$$

which shows that $F'(0) = r$.

The final relation 4) may be written as

$$\begin{aligned} \frac{F(\Lambda)}{\Lambda} &= \frac{r}{n\Lambda} \sum_{\mathcal{J}\subseteq\mathcal{K}} \sum_{j\notin\mathcal{J}} I^j_{\mathcal{J}} \\ &= \frac{r}{n\Lambda} \sum_{\mathcal{J}\subseteq\mathcal{K}} \sum_{j\notin\mathcal{J}} \sigma^j_{\mathcal{J}} \Lambda S_{\mathcal{J}} \\ &= \frac{r}{n} \sum_{\mathcal{J}\subseteq\mathcal{K}} m_{\mathcal{J}} S_{\mathcal{J}}, \end{aligned}$$

so that 4) says that the weighted proportions of susceptibles is a decreasing function of Λ. This claim is proved in Appendix 1.

6 The dynamics of the model

The dynamics of the symmetric model can be quite complicated. We focus on the special case where cross-protection is symmetric as in the previous section and where in addition cross-immunity extends only to nearest neighbors

$$\sigma^i_{\mathcal{J}} = \begin{cases} 0 & \text{if } j \in \mathcal{J}, \\ \sigma & \text{if } j+1 \in \mathcal{J} \text{ or } j-1 \in \mathcal{J} \text{ and } j \notin \mathcal{J}, \\ 1 & \text{else.} \end{cases}$$

For $n = 2$ (Castillo-Chavez et al., 1989) shoved that the two strain equilibrium is always stable when it exists, and we have found by numerical investigations that the same holds for $n = 3$. However, for $n \geq 4$ sustained oscillations can occur. We first discuss in details the bifurcations in the case $n = 4$ and then return to $n > 4$.

The system is highly symmetric and degenerate so we make a partial unfolding in that we assume that strain 1 and 3 have the same reproduction ratio r_1 while strains 2 and 4 have the reproduction ratio r_2. In itself this is a quite complicated model with 16 susceptible classes and 32 infectious classes.

The symmetrically opposite strains interact only through viral interference prohibiting simultaneous infections with both strains so that the available susceptible pool for one strain is reduced by the proportion of individuals that are infected by the other strain. Since the infectious period is short for influenza only a small proportion of the population is infected at any time. We will neglect the effects of viral interference and find that the one-strain equilibria are always unstable to invasion by the symmetrically opposite strain except for a small region in parameter space near $r_i = 1$, for details see (Dietz, 1979). The most interesting boundary equilibria are therefore the two symmetric ones at $(\Lambda, 0, \Lambda, 0)$ and $(0, \Lambda, 0, \Lambda)$. We focus attention on $B_1 = (\Lambda, 0, \Lambda, 0)$.

Since at B_1 immunity to strains 2 and 4 is not present, the force of infection for strain 1 (or 3) at the equilibrium is characterized by

$$r_1 \left(S_\emptyset(\Lambda) + S_1(\Lambda)\right) = 1,$$

where we have used the notation $S_1 = S_{\{1\}}$. It is possible to solve explicitly for Λ but to simplify the discussion we assume that $e \ll 1$ and retain only the leading terms in e:

$$\Lambda = e(r_1 - 1) + O(e^2).$$

Regarded as a model in strain 1 and 3 only, the equilibrium is stable for $r_1 > 1$ and according to our remarks in section 4, strain 2 and 4 cannot invade if

$$r_2 \left(S_\emptyset(\Lambda) + \sigma S_1(\Lambda) + \sigma S_3(\Lambda) + \sigma S_{\{1,3\}}(\Lambda)\right) < 1.$$

To first order in e this gives the condition

$$r_2 < \rho(r_1) = \frac{2r_1 - 1}{1 + 2\sigma(r_1 - 1)}$$

Fig. 1 shows the bifurcation curve in the (r_1, r_2)-parameter space. In particular if at $r_1 = 1$ we have $d\rho/dr_1 > 1$, there will exist a region in parameter space where both boundary equilibria B_1 and B_2 are stable. A simple computation shows that this happens exactly when $\sigma < \frac{1}{2}$. The region with two stable boundary equilibria is symmetric in r_1 and r_2 and starts at $r_1 = r_2 = 1$ while the maximal r-value in the region is $r_1 = r_2 = 1/2\sigma$. From the analysis of the uniform equilibria we know that a uniform equilibrium exists everywhere on the half-line $r_1 = r_2 > 1$ and by an

implicit function argument one sees that this equilibrium exists in a neighborhood of the symmetry line. In the region where both boundary equilibria are stable, numerical simulations show that the internal uniform equilibrium is a saddle separating the basin of attraction for the two stable equilibria, see Fig. 1.

In the parameter region where the boundary equilibria are both unstable, we expect that the system will have at least one internal equilibrium. For $r_1 = r_2$ we have seen that exactly one internal symmetric equilibrium exist and by a continuation argument this equilibrium must exist in a neighborhood of the symmetry line. We can determine the spectrum of the equilibrium for specific parameter values by the following method. First Λ is determined by numerically solving the equation $F(\Lambda) = \Lambda$. Then the linearization is determined by computing the derivatives as indicated in (12–15). Finally the eigenvalues of the linearized system are found by a QR-algorithm as described in Press et al. (1992, p. 486ff).

Numerical determination of the spectrum shows that for $\sigma > 0.453$, the internal equilibrium is always stable when the two strain boundary equilibria are both unstable. For $\sigma < 0.453$, the internal equilibrium undergoes a Hopf bifurcation on a curve in (r_1, r_2)-space. Inside the curve the internal equilibrium is unstable and the system exhibits sustained oscillations. As σ is decreased for fixed (r_1, r_2), the amplitude of the oscillations increase. Numerical simulations suggest that the limit cycle disappears in a global bifurcation involving a homoclinic orbit through a two-strain boundary equilibrium exactly for the same value of σ where the boundary equilibrium becomes stable.

Fig. 2 shows the bifurcation diagram for the symmetric model where $r_1 = r_2 = r$. Since the model is now symmetric, the homoclinic orbit is replaced by a heteroclinic orbit through both boundary equilibria.

For $n > 4$ the qualitative behavior the uniform model appears to be similar. For odd n, however, equilibria with a 2 fold symmetry do not exist and the behavior for small σ is determined by multiple boundary equilibria. Fig. 3 shows the bifurcation curve for the Hopf bifurcation in the symmetric model for various n.

Fig. 4 shows an example of the sustained oscillations. Notice that the total prevalence of all strains as well as the prevalence of a specific strain varies. Due to the n-fold symmetry the total prevalence $I_\bullet$ oscillates with a period than is n times shorter than that of a single strain I_1. The population based cross-immunity structure plays a significant role in these oscillations: While the fraction of the population that is immune to a given strain R_1 varies by a factor of 2 over the oscillation, the total susceptibility to that strain as measured by the threshold quantity $R_\bullet$, cf. (16) varies only about 10%.

7 Discussion

The presence of several cross-reacting strains affects the static as well as the dynamic aspects of the epidemiology. In the static description the threshold condition for the onset of an epidemic with an invading strain is a straightforward generalization of the standard result in that the threshold is proportional to the number of susceptibles weighted by their relative susceptibility to the challenging strain. Similarly, the concept of the 'force of infection' generalizes nicely and turns out to be a powerful tool in the characterization of the system. In particular we find in accordance with the theory for diseases with one strain that at equilibrium the number of individuals that are immune to a specific strain is proportional to the force of infection of that strain.

The effect of the cross-immunity on the dynamics of the epidemics may be more surprising. Castillo-Chavez et al. (1989) showed that in the case where only two strains interact, the two-strain endemic equilibrium is asymptotically stable when it exists. However, cross-immunity destabilizes the system even in the two-strain case in the sense that the introduction of a delay can cause the two-strain system to oscillate. Andreasen (1989) demonstrates this in the case where the host population has a fixed life span and Gupta et al. (1994) report that the introduction of a vector into the two strain situation, also gives rise to oscillations.

Without introducing delays, we found that the co-occurrence of more strains can give rise to oscillations in the prevalence of the individual strain as well as in the total prevalence of the disease. In the paper we focussed on a symmetric situation because this allowed us to obtain at least a partial characterization of the dynamics and explicitly state the linearization around the symmetric endemic equilibrium.

Our numerical simulations suggest that oscillations occur for other cross-immunity structures as well. In particular we have found that the essential ingredient causing the oscillations is the presence of a long range interaction between two strains that are not neighbors e.g. strains 1 and 3 in our cyclic model. Thus similar oscillations can be found in a model with 3 strains where strains 1 and 3 have no cross-reaction while strain 2 cross-immunizes partially with both of the other strains. We are currently investigating this phenomenon as part of our work on simplifying the model (Lin et al., in prep).

Throughout the paper we have assumed that cross-immunity acts by reducing the susceptibility to related strains, however, cross-immunity may act in other ways. Our general representation of the population based immune history allows us to explore such alternatives.

The situation where cross-immunity induces complete protection to related strains for some individuals while others do not acquire additional protection may be represented by a probability distribution $\tau_{\mathcal{M}}^{i\mathcal{J}}$ that gives the probability that an individual with immune history $\mathcal{J}$ who recovers from infection with strain i will acquire complete immunity to the strains in $\mathcal{M}$. In our model this means that the flow out of the infectious class $I_{\mathcal{J}}^{i}$ is distributed among $S_{\mathcal{M}}$ according to $\tau_{\mathcal{M}}^{i\mathcal{J}}$. Thus the flow into $S_{\mathcal{M}}$ is

determined by

$$\sum_{\mathcal{J}\subset\mathcal{K},\ i\notin\mathcal{J}} \tau^{i\mathcal{J}}_{\mathcal{M}} I^i_{\mathcal{J}}$$

while $\sigma^i_{\mathcal{J}} = 1$ for all i and $\mathcal{J}$.

Similarly if cross-immunity reduces infectivity during subsequent infections with related strains, the expression for the force of infection can be determined by

$$\Lambda^i = \sum_{\mathcal{J}\subseteq\mathcal{K}\setminus i} \beta^i_{\mathcal{J}} I^i_{\mathcal{J}}$$

where $\beta^i_{\mathcal{J}}$ describes the infectivity of individuals who are infected with strain i and who have immune history $\mathcal{J}$.

In both these situations our principal analytical results hold, in that equilibria can be determined by a recursion scheme on the cardinality of the index set combined with non-linear equations in the forces of infection. In particular we can derive threshold conditions for the invasion of a new mutant strain showing that a new strain can invade only if the basic reproduction number multiplied by the average susceptibility to the strain in the population exceeds unity. In the symmetric case, we can prove the existence and uniqueness of a uniform endemic equilibrium in both situations provided that cross-immunity reduces infectivity, that is provided respectively that $\tau^{i\mathcal{J}}_{\mathcal{M}} = 0$ for $\mathcal{M} \subseteq \mathcal{J} \cup \{i\}$ and that $\beta^i_{\mathcal{J}} \geq \beta^i_{\mathcal{M}}$ for $\mathcal{M} \supseteq \mathcal{J}$.

By modeling several co-occurring strains of influenza, we have obtained enough flexibility in our description to allow for changes in the genetic composition of the viral population. In this respect the model is a clear improvement over the previous ones; also the model demonstrates how the population based immunity structure plays a central role in influenza epidemiology.

On the other hand, the model misses several central aspects of influenza drift evolution. First, in real influenza, drift evolution is caused by point mutations that would correspond to a small flow between neighboring strains in the model. Such flow seems to have a stabilizing effect on the endemic equilibrium. Second, the dynamics of influenza evolution are intrinsically transient in the sense that new types are introduced while old types die out. In principle this could be described by the present model simply by modeling a linear immunity structure of sufficient length. However, the number of state variables grows so fast with the number of strains that this is impractical. We are currently investigating ways to simplify the description by excluding old strains and introducing new ones. The simplest way to do this is by assuming that infection with a given strain confers complete immunity to all "previous strains", say to all strains with lower index. With this cross-immunity structure we need not keep track of immunity to all types in order to avoid reinfection of the same individuals with the same type. In a model with this cross-immunity structure (and with strains lying on a continuous axis) cross-immunity in combination with diffusion type drift mutation gives rise to a traveling wave type solution (Andreasen et al., 1995). One would like to combine these

two descriptions to obtain a biologically reasonable immunity structure and selection while at the same type letting mutation drift introduce the new types.

Acknowledgements

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Appendix 1 Uniqueness of the uniform equilibrium

Before proving that the function $F(\Lambda)/\Lambda$ is decreasing, we first show that $N_{\mathcal{M}}$, the total fraction of hosts who have been exposed only to (some of) the strains in a specified subset $\mathcal{M}$ is a decreasing function of Λ. This will demonstrate the basic idea in a simple case.

Let

$$N_{\mathcal{M}} = \sum_{\mathcal{J}\subseteq\mathcal{M}} S_{\mathcal{J}} + \sum_{\mathcal{J}\subseteq\mathcal{M}} \sum_{i\notin\mathcal{J}} I^i_{\mathcal{J}}$$

denote the fraction of hosts who are immune only to (some of) the strains in $\mathcal{M}$, i.e. $N_{\mathcal{M}}$ denotes the fraction of the population that have not recovered from infections with any of the strains in $\mathcal{K}\setminus\mathcal{M}$.

By summing over the equations (1–4) we obtain

$$\dot{N}_{\mathcal{M}} = e - eN_{\mathcal{M}} - (1-e)\sum_{\mathcal{J}\subseteq\mathcal{M}}\sum_{i\notin\mathcal{M}} I^i_{\mathcal{J}}.$$

The loss terms reflect the fact that hosts can leave the $N_{\mathcal{M}}$-class only through deaths or by obtaining immunity to strains that are not in $\mathcal{M}$. At a symmetric equilibrium with $\Lambda^i = \Lambda$ for all i, we have that all $I^i_{\mathcal{J}}(\Lambda)$ are increasing. This implies that at equilibrium $N_{\mathcal{M}}$ must be decreasing showing that the total fractions of hosts with immunity only to strains in $\mathcal{M}$ is a decreasing function of the force of infection. The total fraction of susceptible hosts with immunity only to strains in $\mathcal{M}$

$$T_{\mathcal{M}}(\Lambda) = \sum_{\mathcal{J}\subseteq\mathcal{M}} S_{\mathcal{J}},$$

is decreasing as well since the functions $I^i_{\mathcal{J}}(\Lambda)$ are increasing.

We can apply the same argument to

$$P_{\mathcal{M}} = \sum_{\mathcal{J}\subseteq\mathcal{M}} m_{\mathcal{J}} S_{\mathcal{J}} + \sum_{\mathcal{J}\subseteq\mathcal{M}}\sum_{i\notin\mathcal{J}} m_{\mathcal{J}} I^i_{\mathcal{J}}$$

giving the fraction of individuals who are immune only to some of the strains in $\mathcal{M}$ weighted by their remaining susceptibility. Again we include hosts who are currently

infected. Multiplying the dynamic equations for $S_{\mathcal{J}}$ and $I^i_{\mathcal{J}}$ by $m_{\mathcal{J}} = \sum_{j \notin \mathcal{J}} \sigma^j_{\mathcal{J}}$ and summing over $\mathcal{J} \subseteq \mathcal{M}$, we get

$$\dot{P}_{\mathcal{M}} = ne - eP_{\mathcal{M}} - (1-e) \sum_{\mathcal{J} \subseteq \mathcal{M}} \sum_{j \in \mathcal{J}} (m_{\mathcal{J}\setminus j} - m_{\mathcal{J}}) I^j_{\mathcal{J}\setminus j} - (1-e) \sum_{\mathcal{J} \subseteq \mathcal{M}} \sum_{j \notin \mathcal{M}} m_{\mathcal{J}} I^j_{\mathcal{J}}.$$

At equilibrium, we find that since $m_{\mathcal{J}\setminus j} \geq m_{\mathcal{J}}$ and $I^j_{\mathcal{J}}(\Lambda)$ is increasing, $P_{\mathcal{M}}(\Lambda)$ is a decreasing function of Λ. It now follows that

$$F(\Lambda)/\Lambda = \frac{r}{n} \sum_{\mathcal{J} \subseteq \mathcal{K}} m_{\mathcal{J}} S_{\mathcal{J}} = \frac{r}{n} \left(P_{\mathcal{K}}(\Lambda) - \sum m_{\mathcal{J}} I^i_{\mathcal{J}} \right)$$

is decreasing.

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Figure 1. Bifurcation diagram for the 4 strain model with $r_1 = r_3$ and $r_2 = r_4$ and symmetric immunity structure. Fig. 1a shows the diagram for $\sigma = 0.42$ and $e = 0.02$. Between the solid curves the internal equilibrium is unstable and a stable limit cycle exists. At the solid line the internal equilibrium undergoes a Hopf bifurcation and in the region between the solid lines and the broken lines the internal equilibrium is stable. Between the broken line and the axis, the corresponding two strain boundary equilibrium is stable. Near $r_i = 1$ the two broken curves intersect. Hence near $r = 1$, a region exists with two stable equilibria. Fig. 1b shows this phenomenon in detail for $\sigma = 0.368$.

Figure 2. Bifurcation diagram for the symmetric 4 strain model with $r_1 = r_2$ and all other parameters as in Fig. 1. In the schematic phase portraits an open circle indicates an unstable equilibrium while a filled circle indicates a stable equilibrium. The internal symmetric equilibrium undergoes a Hopf bifurcation on the solid line. The two strain boundary equilibria $(\Lambda, 0, \Lambda, 0)$ and $(0, \Lambda, 0, \Lambda)$ are stable below the broken line.

Figure 3. Bifurcation curve for the Hopf bifurcation of the symmetric equilibrium with $n = 4, \ldots, 9$ strains, all other parameters the same as in Fig. 1. Below the line the symmetric equilibrium is unstable and a stable limit cycle exist, for details see text.

Figure 4. Sustained oscillations in the model (1–4). The figure shows the prevalence I_1 of strain 1, the total prevalence $I_\bullet$, the fraction of individuals immune to strain 1, $R_1 = \sum_{\mathcal{J} \ni 1} S_{\mathcal{J}} + \sum_{i \neq 1, \mathcal{J} \ni 1} I^i_{\mathcal{J}}$, and the fraction of individuals susceptible to strain 1 weighted by their relative susceptibility $R_\bullet = \sum_{\mathcal{J} \subseteq \mathcal{K} \setminus 1} \sigma^1_{\mathcal{J}} S_{\mathcal{J}}$. The values of the I-variables are multiplied by a factor of 5. The parameters are $n = 5$, $r_i = 3$, $e = 0.02$, and cross-protection σ^i_j extending only to nearest neighbor where strains 1 and 5 are considered to be neighbors ($\sigma = 0.2$). Notice that the total prevalence $I_\bullet$ oscillates 5 times as fast as I_1 due to the 5-fold symmetry.

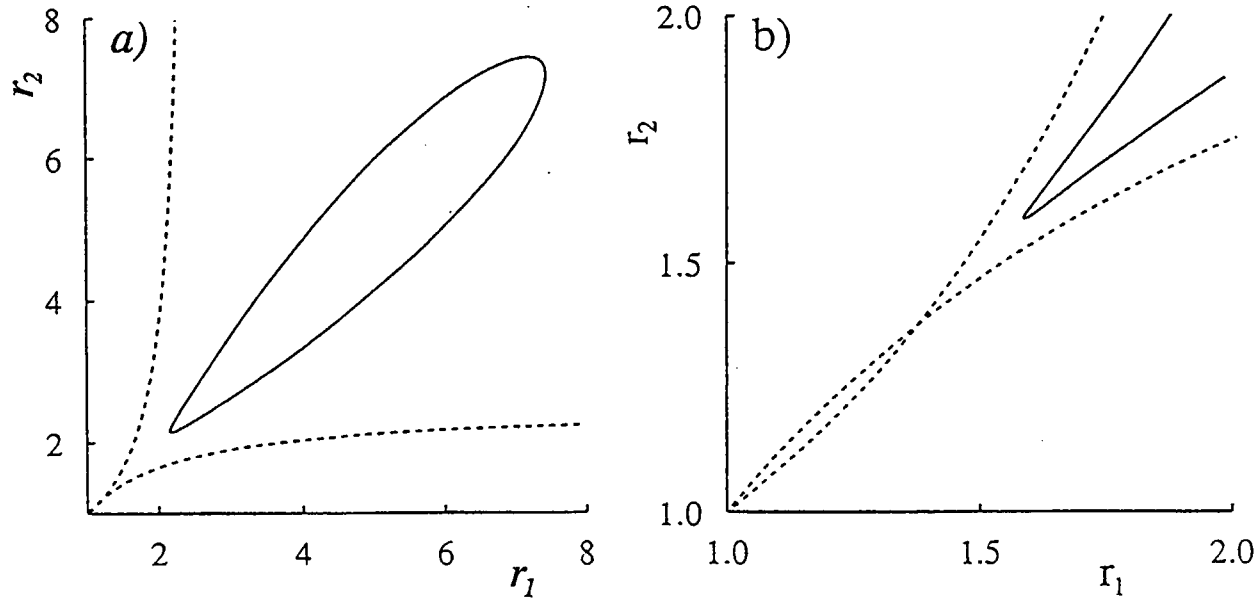

Fig 1

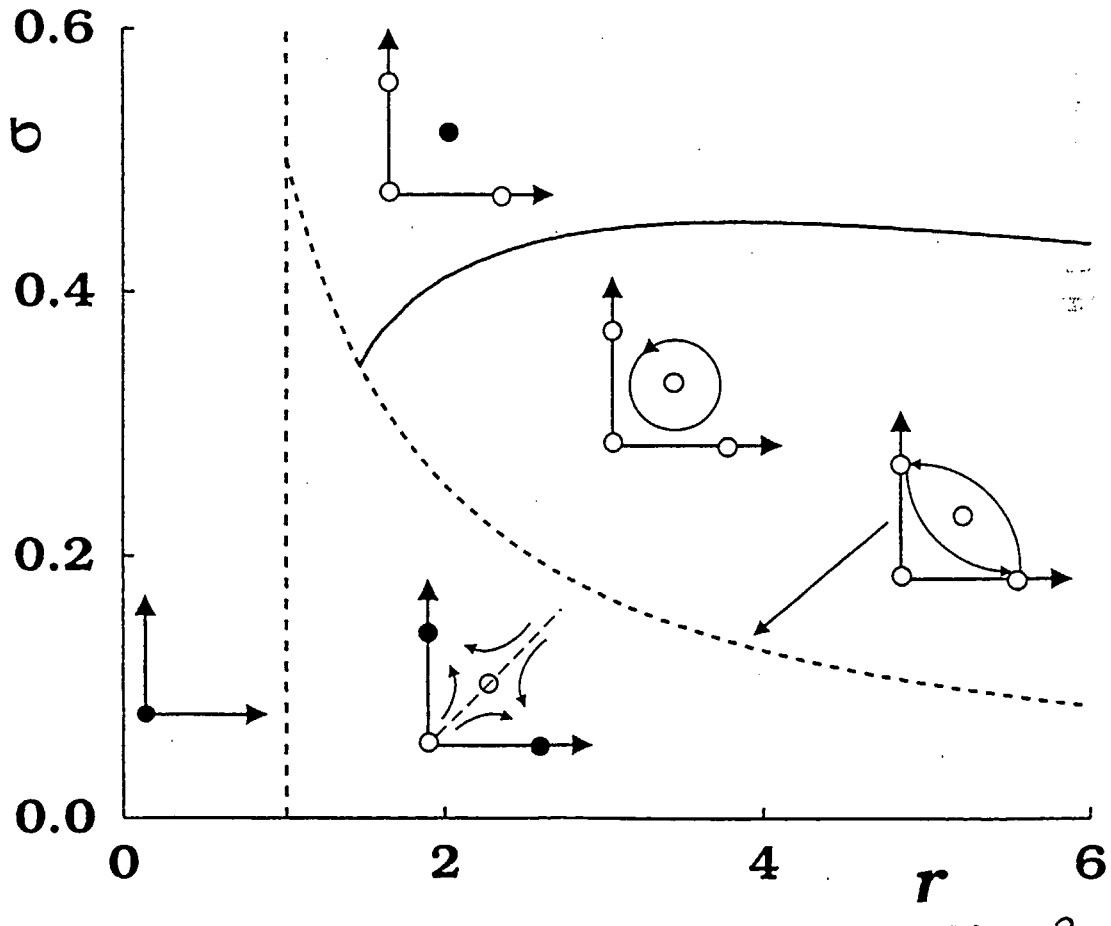

Fig 2

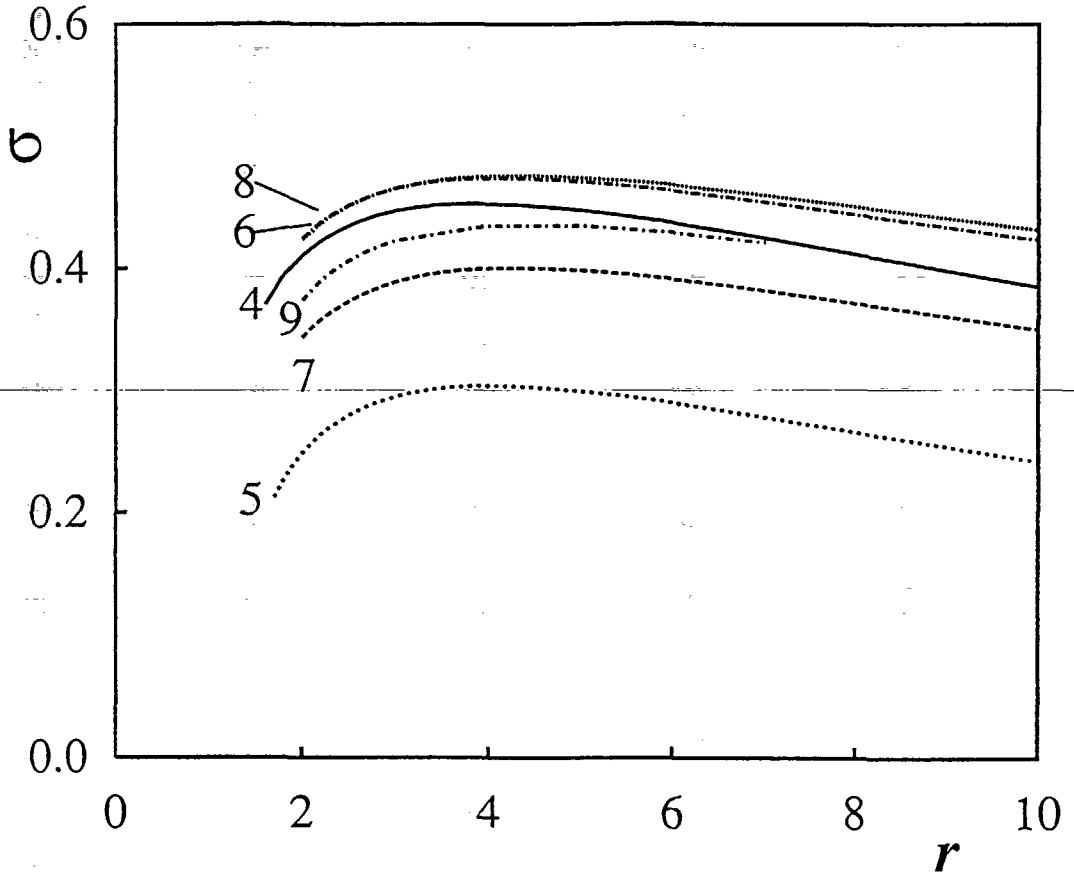

Fig 3

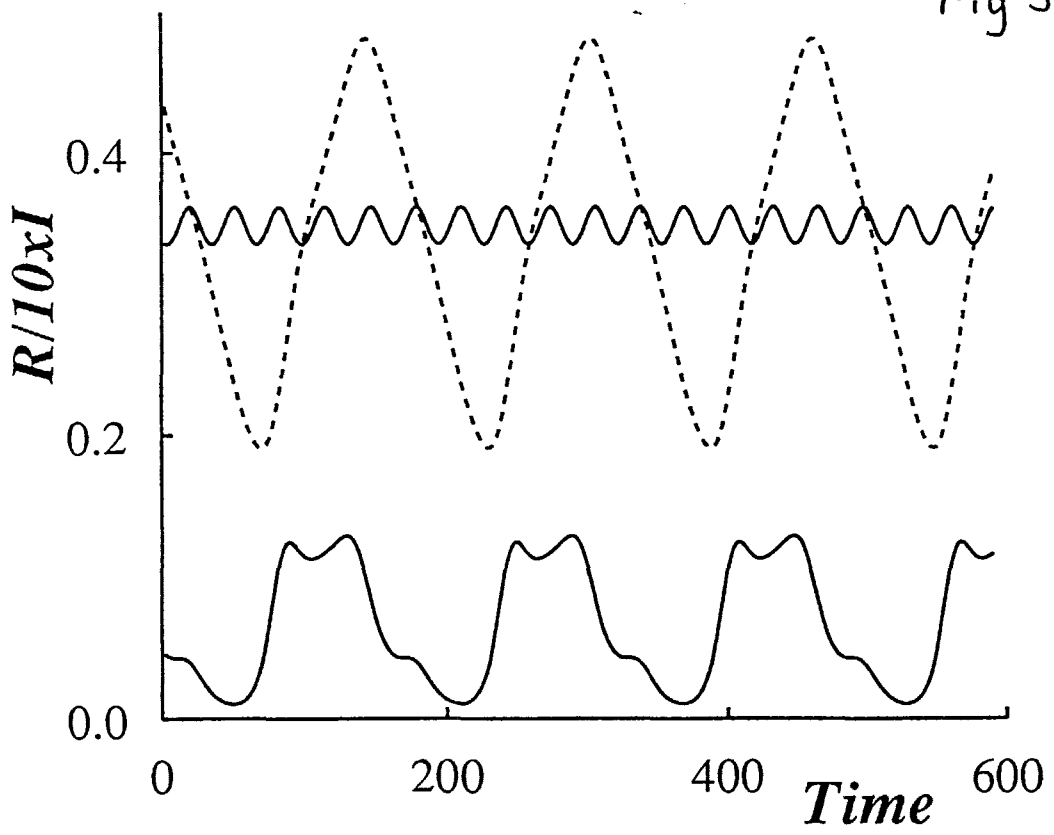

Fig 4

ANDREASEN, VIGGO; LEVIN, SIMON; LIN, JUAN

A model of influenza A drift evolution

The antigenic properties of the influenza A virus drift slowly due to point mutations in the viral genome. The drift is enhanced by the partial immunity of the host population to the new viral strains. Assuming a one dimensional axis of antigenic types we develop a model for the drift and find that a traveling wave of disease prevalence moves along the axis with a speed that depends on the immune surveillance in the population.

1. Influenza genetics

The influenza A virus evades the human immune system by rapid point mutations, allowing for reinfection every two to four years. In addition to the point mutations, known as virus drift, the influenza virus undergoes every few decades shift mutations, where whole segments of the virus are changed giving rise to a new subtype often replacing the previous subtype. The ability to mutate enough to allow for reinfection of individuals makes the influenza virus highly unusual among viruses infecting the human population. In contrast, the viruses that cause childhood diseases infect each person only once in a lifetime and rely on population turn-over to produce new susceptible hosts through births; other viruses induce life-long infections, e. g. herpes. At the other extreme, the causative agent of AIDS, the HIV virus, mutates so rapidly that several distinct strains may co-circulate within the same patient [13]. The influenza mutation rate may thus be seen as intermediate, allowing only one strain per infected person, but permitting several strains to interact at the host population level. In this paper, we propose a model that describes the dynamics of the drift process and in particular focuses on how cross-immunity affects the amino-acid substitution rate.

The human immune system reacts to two antigenic structures, haemagglutinin (HA) and neuraminidase (NA), of which HA seems to be the more important. It appears that these structures function in such a way that their antigenic properties can vary without impairing their ability to facilitate the penetration of host cells. Molecular studies show that amino-acid substitutions in the genes coding for the HA surface arise at a constant rate, and that virus specimens collected at the same time in different areas differ only at few locations [4,12,19]. The amino-acid substitutions correspond to a gradual change in antigenic properties in the sense that the probability of reinfection grows with the number of amino acid locations at which the challenging strain differs from the immunizing strain [6,7,18,20]. A new mutant drift strain therefore will be subject to selective forces induced by the partial protection that is conferred to the hosts by related viral types, and it has been documented that genes coding for the HA surface structure are subject to Darwinian selection [9].

Only a few studies have approached the dynamics of drift evolution. As part of a large-scale effort to simulate local spread of influenza using discrete stochastic simulations [1] and [8] investigated the effects of two closely related co-circulating strains but found no statistically significant effect on disease prevalence, while [5] investigated the long-term dynamics of two interacting strains of influenza. Pease [14] improved the description by showing how a slow change in the antigenic type of a single influenza variant affects the dynamics of influenza. Pease's 'evolutionary epidemiology' thus accounts for the effect of viral drift on the influenza epidemiology, but his model does not explain what causes this drift. In his study of how pathogens evade immune surveillance within an individual host, Sasaki [15] described how pathogens mutate into new antigenic types, thus outrunning the activation of B-lymphocytes. This mechanism is similar to the one we propose for influenza, but the dynamics of the individual host's response differ significantly from the response we introduce at the host population level.

2. The model

Following the ideas of Levin and Pimentel [11], we will keep track only of the number of individuals infected with a given strain, rather than keeping track on the total number of virus particles. Since the infection period for influenza is short compared to the mutation rate, it seems reasonable to assume that all virus within one patient is of the same type; for HIV the assumption would not hold as discussed above. This observation allows us to base our model on standard epidemic methods.

Simple epidemic theory [2] assumes that in a host population of size N, the rate at which susceptible individuals acquire the infection is proportional to the number of infected individuals I. Neglecting the latency period and assuming a constant rate of recovery ν, the rate of change in I becomes

$$\dot{I} = \beta IS - \nu I,$$

where S denotes the number of susceptibles. The constant β is known as the transmission coefficient; it depends on host infectivity and susceptibility as well as on population structure and mixing patterns.

When one is describing the dynamics of an influenza strain, the rate of new infections must be modified to allow for the fact that the susceptibility and hence β will vary among individual hosts depending on the immune status they have acquired through past infections. To describe this multi strain immunity we assume that influenza strains can be ordered along a one-dimensional axis measuring the number of changes in the amino acid composition of the surface genes – or maybe measuring a more general 'shape' aspect, sensu Segel and Perelson [16]. Molecular studies show that immunity to specific strains are long lasting (though maybe not perfect) and ideally one would like to retain a full record of all past infections. To simplify the description of viral drift we will assume that only the most recent infection is important in determining the immune status of an individual but that infection with strain z implies

protection against all strains of type $w < z$. This last assumption of immunity to all 'previous' strains is necessary to ensure that reinfections with the same strain are not possible and thus exclude the possibility of circularities where the same individual gets reinfected with the same few strains repeatly. From in vitro studies we know that this asymmetrical immunity structure is not biologically correct, but in practice the assumption may hold simply because the previous strains have died out. We shall return to this problem in the discussion. Finally we assume that the immunity space is isotropic in the sense that the probability of infection depends only on the distance δ between the immunizing strain and the infecting strain, The partial cross-protection now corresponds to assuming that the transmission coefficient is a function of δ, $\beta(\delta)$.

With these assumptions about the immunty structure, the susceptible population now can be describe by a density function $S(z,t)$ on the z-axis summarizing the population's immune status. Hence $\int_w^z S(\zeta,t)\,d\zeta$ denotes the number of individuals who at time t are susceptible and whose last infection was of a type located in the interval $[w;z]$. Similarly infectious individuals are described by a density function $I(z,t)$ on the immunity axis. With this formulation, we are neglecting the introduction of new completely susceptible hosts through births, but since reinfections in adult hosts occur every few years, births seem to play a minor role.

The rate at which individuals of type z get infected at time t can be determined by integrating over all strains capable of infecting that type

$$S(z,t)\int_z^\infty \beta(\zeta - z)I(\zeta,t)\,d\zeta,$$

while the rate at which new infections of type z are recruited is

$$I(z,t)\int_{-\infty}^z \beta(z-\zeta)S(\zeta)\,d\zeta.$$

Finally the genetic drift induced by the point-mutations is modeled as diffusion in I along the z-axis in order to reflect the fact that reproducing, and hence mutating, vira can exist only in the I.

The full dynamics of the system now become:

$$\begin{aligned}\frac{\partial I}{\partial t} &= I(z,t)\int_{-\infty}^z \beta(z-\zeta)S(\zeta,t)\,d\zeta - \nu I(z,t) + \sigma^2\frac{\partial^2 I}{\partial z^2}\\ \frac{\partial S}{\partial t} &= -S(z,t)\int_z^\infty \beta(\zeta - z)I(\zeta,t)\,d\zeta + \nu I(z,t).\end{aligned}$$

Since the model includes no vital dynamics, the total population size

$$N = \int_{-\infty}^\infty (S(\zeta,t) + I(\zeta,t))\,d\zeta$$

is a constant independent of time. We shall not specify initial conditions as we will be looking for traveling waves.

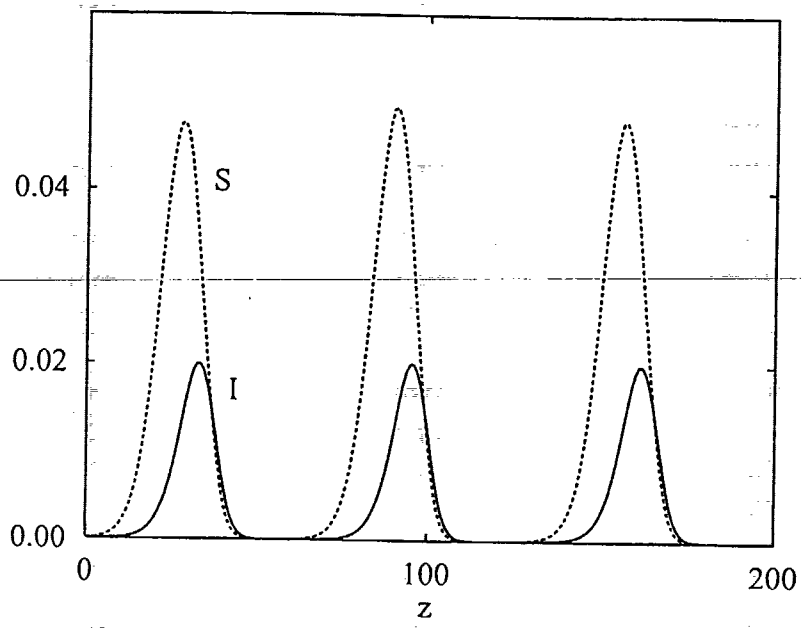

Figure 1: Traveling wave of prevalence I of influenza virus type z and of the susceptibles S whose most recent infection was z. The wave moves from the left to the right along a one-dimensional axis representing the possible antigenic drift-variants and is shown at three times, 30 time units apart. The parameter values are $\nu = 1$, $\sigma^2 = 1$, and $\beta(\delta) = 5\delta^2/(\delta^2 + 10^2), \delta > 0$.

First observe that the system may be expressed in non-dimensional variables by measuring time τ in units of ν^{-1} and aspect space a in units of $\sqrt{\sigma^2/\nu}$ while S and I are replaced by the proportions of the total population, $s = S/N$ and $i = I/N$. The model now becomes

$$\begin{aligned} \frac{\partial i}{\partial \tau} &= i(a)\int_{-\infty}^{a} \rho(a-\alpha)s(\alpha)\,d\alpha - i(a) + \frac{\partial^2 i}{\partial a^2} \\ \frac{\partial s}{\partial \tau} &= -s(a)\int_{a}^{\infty} \rho(\alpha-a)i(\alpha)\,d\alpha + i(a) \end{aligned}$$

with the constraint that $\int_{-\infty}^{\infty}(s+i)\,d\alpha = 1$ and with the one remaining parameter $\rho = \beta N/\nu$. Numerical solutions of the system show traveling waves (fig. 1).

By assuming that only a small proportion of the population is infected at any given time,

$$\int_{-\infty}^{\infty} i\,d\alpha \ll \int_{-\infty}^{\infty} s\,d\alpha,$$

we can obtain the approximate wave speed c by linearization at the wave front yielding,

$$c = 2\sqrt{\rho(\infty) - 1} \sim 2\sqrt{(R_0 - 1)\sigma^2\nu}.$$

Here $R_0 = \beta(\infty)N/\nu$ resembles the threshold quantity 'the basic reproduction number' known from simple epidemic theory. However, numerical investigations suggest that although c is of the right order of magnitude, the agreement is not very good and in addition c should not be independent of the intensity of the cross-immunity as measured by β near $\delta = 0$.

We are currently investigating the structure of the associated traveling wave solutions.

3. Discussion

Although the model gives a simplistic view of influenza drift evolution, it reproduces a central feature of viral drift in that a single pulse moves through the aspect space and we can obtain at least numerical estimates of the speed. Empirical information about the speed is available; Fitch et al [9] noticed that the mutation rate of the gene coding for the HA1 segment of the HA-structure is 3 times faster than that of the NS gene coding for a non-structural part of the influenza virus. However influenza evolution takes place on a global scale and it is unclear if the standard disease model is appropriate at that scale. Furthermore influenza has pronounced seasonal and geographical dynamics which may play a role in the changes of the virus [10,17].

The main shortcoming of the present model is its crude representation of the host immunity structure that is assumed by introducing an asymmetric cross-immunity β among types. However with a symmetric cross-immunity one must keep track of more details of the host population's history of infections in order to avoid the situation that individuals are subject to frequent reinfections with the same viral type. We have developed a model of a finite set of interacting strains where the full immunity history of the host population is included [3]. Although the model's complexity explodes as the number of strains increases, it can be shown that significant cross-correlations among the prevalences of neighboring strains will arise and that the cross-immunity structure under some circumstances will cause sustained oscillations in the prevalence of individual strains as well as in total disease prevalence. The main challenge for developing the theory of drift evolution is thus to obtain a sufficiently detailed, yet manageable, representation of the population based-immunity structure.

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