TEKST NR 192 1990

Age-dependent host mortality in the dynamics of endemic infectious diseases

and

SIR-models of the epidemiology and natural selection of co-circulating influenza virus with partial cross-immunity

by

Viggo Andreasen

TEKSTER fra

IMFUFA ROSKILDE UNIVERSITETSCENTER
INSTITUT FOR STUDIET AF MATEMATIK OG FYSIK SAMT DERES FUNKTIONER I UNDERVISNING, FORSKNING OG ANVENDELSER

IMFUFA, Roskilde Universitetscenter, Postbox 260, 4000 Roskilde

Age-dependent host mortality in the dynamics of endemic infectious diseases

and

SIR-models of the epidemiology and natural selection of co-circulating influenza virus with partial cross-immunity.

by: Viggo Andreasen

IMFUFA tekst nr. 192/90 39 sider ISSN 0106-6242

Abstract.

Age-dependent host mortality in the dynamics of endemic infectious diseases

page 1

For human populations, the age-dependent survival is well described by a fixed duration of life. In such a population the endemic equilibrium of a model for a contagious, immunizing disease with a short infectious period is locally asymptotically stable. The analysis utilizes an asymptotic expansion in the ratio between the time scale associated with the hosts' life span and the period of infectiousness and gives implicit but algebraically simple expressions for the dominant part of the linearization.

SIR-models of the epidemiology and natural selection of co-circulating influenza virus with partial cross-immunity

page 17

Infection with influenza A virus confers only a partial protection against infections by similar viral variants. An extension of the SIR-model allows us to study the epidemiology and genetics of two co-circulating strains with partial cross-immunity. The condition for polymorphy or co-existence takes the form of an invasion criterion where the invading strain can establish only if it can invade when the other strain is already endemic. In the presence of a cross-reacting strain, the incidence of the individual strain as well as the observed basic reproductive number is decreased. For a model with constant host life length, I find that the local stability analysis suggests the existence of oscillations in the prevalence of each strain for certain parameter values. The analysis utilizes an asymptotic expansion in the ratio between the duration of infection and the host life length.

AGE-DEPENDENT HOST MORTALITY IN THE DYNAMICS OF ENDEMIC INFECTIOUS DISEASES

The purpose of this paper is to study the effect of host demographic structure on the dynamics of an endemic disease under the simplest possible assumptions about disease course and transmission. Classical models of epidemiology assume a constant mortality and hence – with a constant population size – an exponentially distributed duration of life. In contrast I here assume that host life has a fixed duration. Disease models with this mortality structure were proposed by Anderson and May (1983) because such a mortality fits well to the observed age-dependent survival in industrialized countries. If exposed individuals acquire permanent immunity, older individuals are more likely to be immune due to previous exposure (Dietz, 1975). Therefore, in a population with fixed duration of life, more deaths will occur among immune individuals than in a population with constant mortality. Thus the vital dynamics of the host population affect disease transmission. Our aim is to understand the effect of the mortality structure on the dynamics near the endemic state.

Recently, age-structured models of epidemics have been studied intensively for both biological and mathematical reasons. Biologically the host age-structure is important for several aspects of infectious disease epidemiology: (i) The rate of contacts between hosts appears to be highly age-dependent with transmission peaking at school age (Anderson and May, 1982, 1985); (ii) the severity of many childhood diseases, e.g., rubella, increases with age (Knox, 1980; Dietz, 1981; Anderson and May, 1983); and (iii) often empirical data are available in an age-stratified form making it desirable to utilize this type of information (Dietz, 1975; Muench, 1959; Griffiths, 1974). Finally age structure has been added to make the models more realistic and their predictions closer to observed disease statistics (Schenzle, 1984).

The numerical simulations that are included in these investigations usually assume some kind of age-dependent host mortality, in part because this adds significantly to the realism of the models, in part because a finite maximum host life span is easier to handle numerically. In this study we isolate the effects of age-dependent host mortality, thus providing a baseline to which one can compare the effects of additional age-dependent factors.

Parallel to the biological interest, age-structured models have received much attention in the mathematical literature starting with the work of Hoppensteadt (1974) and Dietz (1975). By now it is well known that age-dependent SIS- and SIR-models are well posed for reasonable choices of age-dependent parameters. In addition, Dietz and Schenzle (1985) identified a threshold quantity that determines the existence of an endemic equilibrium and the local stability of the disease-free equilibrium (Castillo-Chavez et al., 1989; Busenberg et al., 1988; Greenhalgh, 1987). Busenberg et al. (1988) show that in an SIS model the endemic equilibrium is always stable when it exists. However, the stability of the *endemic* equilibrium in SIR models remains an open question.

Clearly the general question of the local stability of the endemic equilibrium is hard since the Lotka-type characteristic equation is transcendental and quite complicated. To simplify the computations, I focus on realistic parameter values. All studies of the problem report on the background of numerical investigations that for such parameters the endemic equilibrium is stable, and I here give an explanation for these observations. The key property of realistic parameter

Table 1. Duration of infectiousness D and basic reproductive number R_0 for some viral diseases. The basic reproductive number varies with population density and social conditions. The ratio ε of D to average host life span A is computed for $A = 71.6$ years. Data for influenza from Spicer (1982) and Bailey (1986); all other data from Anderson (1982).

	$D = \nu^{-1}$ in days	$\epsilon = D/A$	R_0
Measles	6–7	$2.3–2.7 \times 10^{-4}$	5–16
Chicken pox	10–11	$3.9–4.2 \times 10^{-4}$	7–10
Rubella	11–12	$4.2–4.6 \times 10^{-4}$	6–7
Influenza	2–3	$0.8–1.2 \times 10^{-4}$	2–5

values is demonstrated in Table 1. The table shows that for many viral diseases, the system involves processes at two different time scales, namely the host death and renewal processes and the duration of infection. The ratio between the two time scales can be 3–4 orders of magnitude thus allowing for simplification by the use of asymptotic expansions (Andreasen, 1989a).

The presence of multiple time scales has been recognized in connection with numerical difficulties (Castillo-Chavez et al., 1989). Anderson and May (1983) use first order approximations to give approximate expressions for the age-dependent disease incidence and a discretization in time to asses the period of the oscillations in the model we study here.

In the first section of the paper, I discuss the implications of the two time scales for the stability of the standard SIR-model with constant host mortality. I then formulate the age-structured version of the SIR-model with fixed host life span and demonstrate by rescaling how ε, the ratio between the two time scales, enter. In order to determine the stability properties of the model, we will need second order approximations of the Lotka characteristic equation. As a first step, I analyze the endemic equilibrium and obtain an expansion in ε of the force of infection at equilibrium. The machinery is now set up for the final section which describes the dominant part of the spectrum for the linearization. The computations in the final section get quite involved and are done using a symbol manipulator MACSYMA.

Host population with constant mortality

Our starting point is the classical SIR model of the transmission dynamics of an immunizing contagious disease in a host population where we take into account the host's vital dynamics (Hethcote, 1974; Dietz, 1975). The host population is divided into 3 classes, susceptibles, S, infectious, I, and recovered and immune, R. Assuming that the per capita mortality rate is μ for

all classes, and that births balance deaths, we arrive at the SIR-model:

$$\begin{aligned} \dot{S} &= -\beta SI - \mu S + \mu N \\ \dot{I} &= \beta SI - (\mu + \nu)I \\ \dot{R} &= \nu I - \mu R. \end{aligned} \tag{1}$$

Here ν is the recovery rate, and βSI gives the rate at which the susceptibles get infected. As is common when modeling the spread of a directly transmitted disease, the incidence rate βSI is thus assumed to be proportional to as well the number of infectious as to the number of susceptible (Anderson, 1982). For large populations it is biologically more reasonable to assume that the incidence rate is proportional to the fraction of individuals who are infectious (Schenzle and Dietz 1987; Andreasen, 1989b), but since we are concerned solely with models of fixed population size N this will lead to the same basic model.

It is well known (Hethcote, 1974; Dietz 1975) that (1) has an *endemic* equilibrium, an equilibrium where the disease is present, if and only if $R_0 > 1$, where R_0 is the number of secondary cases per primary case in a totally susceptible population:

$$1 < R_0 = \frac{\beta N}{\mu + \nu}.$$

The quantity R_0, a dimensionless number, is known as the *basic reproductive number*, and it provides a measure of how easily the disease spreads in the population. For many infectious diseases the magnitude of R_0 is on the order of 2–20 (Table 1). After elimination of the redundant R-equation from (1), the stability of the fixed point is determined by the dominant eigenvalue λ of the linearized S, I-equations near equilibrium:

$$\begin{aligned} \lambda &= -\frac{\mu R_0}{2} \pm \mathrm{i}\sqrt{\mu(\mu+\nu)(R_0-1) - (\tfrac{1}{2}\mu R_0)^2} \\ &\approx -\frac{\mu R_0}{2} \pm \mathrm{i}\sqrt{\mu\nu(R_0-1)}. \end{aligned}$$

The eigenvalues are complex with negative real part, therefore the model exhibits damped oscillations. Since the average life span of a host μ^{-1} is about 70 years, the real part of the eigenvalue is about 1/35 year^{-1}, so the half life of the amplitude is about 20 years (May, 1986). The period of the oscillations, the interepidemic period, is determined as $T = 2\pi/\omega$, where ω is the imaginary part of the eigenvalue. Thus $T \approx 2\pi\sqrt{AD/(R_0-1)}$, where $D = \nu^{-1}$ is the duration of infections. In most cases, T is on the order of 2–5 years, and the model (1) predicts weakly damped oscillations. Notice that the damping term, the real part of the eigenvalue, is determined by the time scale associated with the host life span A while the period of the oscillations is determined by the geometric average of A and D.

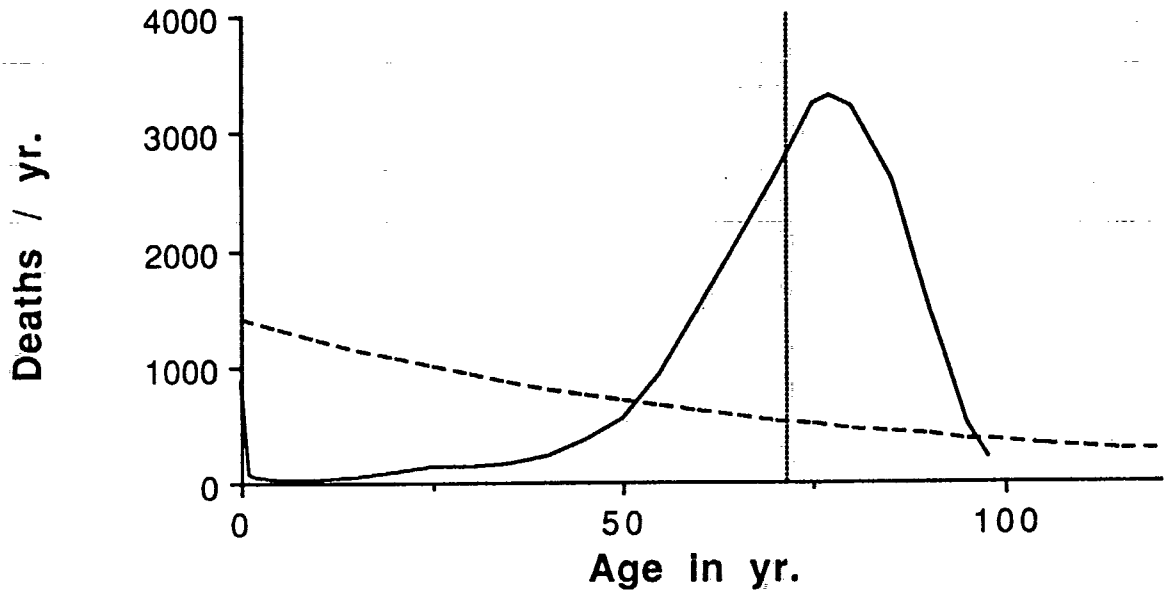

Figure 1. Number of deaths per year for a cohort of 100,000 danish men, based on the vital statistics for 1984–85 (solid line). In 1984–85 the expectation of life for danish men was 71.6 years. The broken line shows the number of deaths that will occur in a population which experiences a constant mortality of 1/71.6 years. The doted line indicates a delta function at 71.6 years corresponding to a fixed host life of 71.6 years. (Data from Danmarks Statistik, 1987).

Age-dependent mortality

In model (1) the host mortality is a constant independent of age, corresponding to an exponentially distributed duration of life. For human populations in industrialized countries, this gives only a crude description of the vital dynamics as the number of deaths in a given cohort is negligible up to age 50–60 years, peaks at age 75 and then falls off (Figure 1). Figure 1 shows two approximations to the age-dependent incidence of death. The broken line shows the number of deaths per year that would occur under the assumptions of model (1), while the dotted line, symbolizing a Dirac delta-function at the average life expectancy, indicates the death incidence that would occur if host life had a fixed length. Clearly the model with fixed duration of life approximates better the observed data.

In terms of mortality the fixed duration of host life A correspond to zero mortality up to age A and an "infinite mortality" at age A.

Since we assume that mortality is age-dependent, we need to reformulate (1) for an age-structured population. This formulation can be found in Hoppensteadt (1974) and in Dietz (1975). The special case of a fixed duration of host life is discussed by Anderson and May (1983) and by

Greenhalgh (1987, 1988). With the notation from above, we have

$$\begin{aligned}
\frac{\partial S}{\partial a} + \frac{\partial S}{\partial t} &= -\Lambda S \\
\frac{\partial I}{\partial a} + \frac{\partial I}{\partial t} &= \Lambda S - \nu I \\
\frac{\partial R}{\partial a} + \frac{\partial R}{\partial t} &= \nu I \qquad (2) \\
\Lambda(t) &= \beta \int_0^A I \, d\alpha \\
S(0,t) = \varrho \qquad & I(0,t) = R(0,t) = 0.
\end{aligned}$$

Here Λ denotes the force of infection and a the age of the host. The variables $S(a,t), I(a,t)$, and $R(a,t)$ give the age distribution of susceptibles, infectious, and recovered respectively, so that $\int_a^b S(\alpha,t)\,d\alpha$ gives the number of susceptibles between age a and age b at time t, etc. New individuals are born susceptible, and the birth rate ϱ is constant, insuring that the total population size is fixed:

$$\int_0^A (S + I + R)\, d\alpha = \varrho A = N.$$

The equation for R is thus redundant. The equations (2) are valid for $0 \leq a \leq A$; at age A all individuals die, and $S(a,t) = I(a,t) = R(a,t) = 0$ for $a > A$. Since we are concerned with the limit behavior, we omit explicit reference to initial conditions.

Explicit construction of solutions along characteristics shows that model (2) is well posed in the sense that solutions exists and are unique and that solutions with positive initial conditions will remain positive and finite (Castillo-Chavez et al., 1989; Busenberg et al., 1988; Greenhalgh, 1987).

Furthermore — as for model (1) — one can identify a basic reproductive number R_0 as the number of secondary cases per primary case in a susceptible population (Diekmann et al., 1989). If R_0 is less than unity the disease-free equilibrium at $S = \varrho$, $I = R = 0$ is the only non-negative equilibrium. If R_0 exceeds unity, an additional endemic equilibrium appears (Dietz and Schenzle, 1985).

Multiple time scales

The analysis of the endemic equilibrium in age-structured SIR-models has proved to be difficult because the Lotka-type characteristic equation is too complex (Castillo-Chavez et al., 1989; Greenhalgh, 1987). I here simplify the analysis by observing that (2) encompasses two different time scales, since the host renewal process is associated with the host life span A while the recovery process is associated with the duration of the disease $D = \nu^{-1}$. In industrialized countries humans live for around 70 years (Figure 1) and for many viral diseases, the infectious period lasts on the order of one week, so the time scales differ by 3–4 orders of magnitude (Table 1).

The effect of the two time scales becomes clear after rescaling time t and age a in units of host life span and measuring S and I in units of ϱ. The new dimensionless variables $s = S/\varrho$ and $i = I/\varrho$ give the fraction of a given cohort which is susceptible and infectious respectively.

The rescaled equations become

$$\begin{aligned} \frac{\partial s}{\partial a} + \frac{\partial s}{\partial t} &= -\lambda s \\ \frac{\partial i}{\partial a} + \frac{\partial i}{\partial t} &= \lambda s - \frac{1}{\varepsilon} i \\ \lambda(t) &= \frac{b}{\varepsilon} \int_0^1 i \, d\alpha \\ s(0,t) = 1 \qquad & i(0,t) = 0, \end{aligned} \tag{3}$$

where the two dimensionless parameters are $b = \beta N D$ and $\varepsilon = D/A$. The ratio between the two time scales $\varepsilon \ll 1$ now appears explicitly in the model. The remaining parameter b is closely related to the reproductive number R_0 since b gives the number of secondary infections per primary infection in a susceptible population if we neglect deaths during the infections period. For many viral diseases including childhood diseases and influenza, R_0 is on the order of 2–20 so we assume that b is on the order of $1 \gg \varepsilon$.

The equilibrium age distribution

Direct application of asymptotic expansions to (3) does not appear to yield new insights and I focus on the analysis of the equilibria. I first derive a second order expansion of λ^*, the force of infection at the endemic equilibrium and show that λ^* is on the order of unity.

Any equilibrium age-distribution (s^*, i^*) for (3) can be found by the use of the method of Dietz (1975). The crucial point in Dietz's method is to observe that at equilibrium, the force of infection $\lambda(t)$ is a constant λ^* independent of age. Therefore we can use a two-step process to find λ^*. In the first step, we solve the steady-state equations assuming that λ^* is an (unknown) constant:

$$\begin{aligned} \frac{ds^*}{da} &= -\lambda^* s^* \\ \frac{di^*}{da} &= \lambda^* s^* - \frac{1}{\varepsilon} i^* \\ s^*(0) = 1 \qquad & i^*(0) = 0. \end{aligned} \tag{4}$$

It is easy to see that the solution to (4) will remain positive for all $a > 0$, and hence that they correspond to biologically meaningful age distributions (Greenhalgh, 1987). In the second step, we determine λ^* implicitly by requiring that

$$\lambda^* = \frac{b}{\varepsilon} \int_0^1 i^* \, d\alpha = \frac{b\lambda^*}{1 - \varepsilon\lambda^*} \left(\frac{1 - e^{-\lambda^*}}{\lambda^*} - \frac{1 - e^{-1/\varepsilon}}{1/\varepsilon} \right). \tag{5}$$

Since $\lim_{\lambda \to 0}(1 - e^{-\lambda})/\lambda = 1$, equation (5) has a root at $\lambda^* = 0$, corresponding to a disease free equilibrium. For fixed b, ε, the equation has at most one positive root and hence at most one endemic equilibrium (Dietz and Schenzle, 1985). Regarded as an equation in b, (5) is linear, and we can get some insight into the behavior of the root λ^* by studying $b(\lambda^*)$. The function $b(\lambda^*)$ is monotonically increasing; further more its range is determined by the limits

$$\lim_{\lambda^* \to 0} b(\lambda^*) = b_0 = \frac{1}{1 - \varepsilon + \varepsilon e^{-1/\varepsilon}}$$

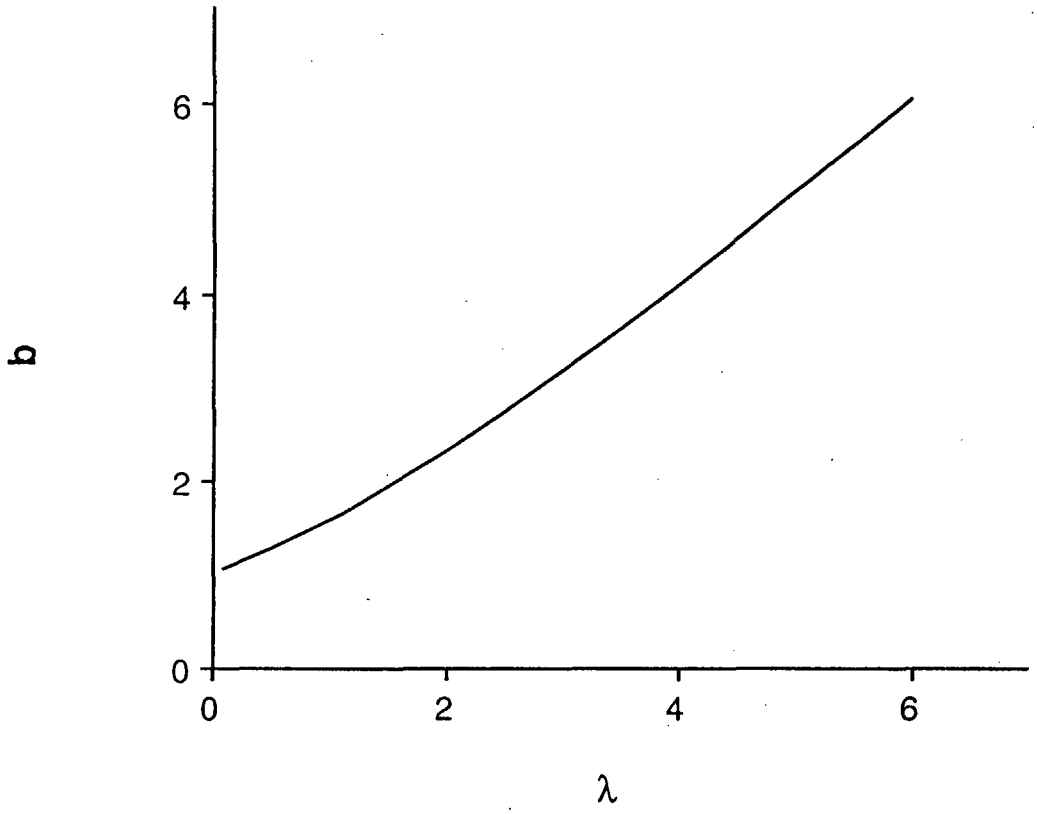

Figure 2. Force of infection λ as a function of the transmission coefficient b at the endemic equilibrium, for model (3) with fixed host life span. Force of infection and transmission coefficient are in dimensionless units, see text.

and

$$b \to \infty \quad \text{as } \lambda^* \to \infty.$$

The graph of $b(\lambda^*)$ is shown on Figure 2.

The lower limit, b_0, is the smallest transmission rate that allows the disease to persist. This gives the following condition for the existence of an endemic equilibrium:

$$1 < b/\frac{1}{1-\varepsilon+\varepsilon e^{-1/\varepsilon}}. \tag{6}$$

The right hand side of (6) gives the basic reproductive number R_0 (Dietz and Schenzle, 1985; Busenberg et al., 1988). That is

$$R_0 = b/\frac{1}{1-\varepsilon+\varepsilon e^{-1/\varepsilon}}. \tag{7}$$

In other words: an endemic equilibrium exists if and only if $R_0 > 1$, just as in the non-age-structured model (1).

For small ε, the equilibrium condition (5) simplifies to

$$\begin{aligned} 1/b =& \frac{1}{1-\varepsilon\lambda}\left(\frac{1-e^{-\lambda}}{\lambda} - \frac{1-e^{-1/\varepsilon}}{1/\varepsilon}\right) \\ =& (1-e^{-\lambda})/\lambda - \varepsilon e^{-\lambda} + O(\varepsilon^2). \end{aligned} \tag{8}$$

Here and in the following section, we have omitted the *. At the equilibrium, the value of λ is on the order $1/R_0 = O(1)$, and near the endemic equilibrium, (3) contains rates that differ by 3–4 orders of magnitude. Hence, near the equilibrium the proportion of infectious $i(a,t)$ will track the proportion of susceptibles $s(a,t)$ closely, $i(a,t) \approx \lambda(t)s(a,t)\varepsilon$ (Anderson and May, 1985). Since the magnitude of $\lambda(t)$ is known only near the endemic equilibrium, we cannot use this approach to solve (3) in general. However, the fact that $\varepsilon \ll 1$ facilitates the local analysis of the endemic equilibrium.

Stability of the endemic equilibrium

The local stability of an equilibrium of (3) can be determined by linearizing the equations near the equilibrium and examining separable perturbations of the form

$$\begin{aligned} \hat{\mathrm{s}}(a,t) &= \mathrm{s}(a)e^{pt} \\ \hat{\mathrm{i}}(a,t) &= \mathrm{i}(a)e^{pt} \\ \hat{\theta}(t) &= \theta e^{pt}, \end{aligned}$$

where $\hat{\mathrm{s}}$ and $\hat{\mathrm{i}}$ denote displacements away from the equilibrium values of s and i respectively, while $\hat{\theta}$ is the displacement of λ. Castillo-Chavez et al. (1989) and Busenberg et al. (1988) show, under more general conditions, that the disease free equilibrium is stable if and only if $R_0 < 1$; i.e., if and only if there is no endemic equilibrium. The age distributions of the perturbations off the endemic equilibrium must to the first order follow the equations

$$\begin{aligned} \frac{d\mathrm{s}}{da} &= -\lambda^*\mathrm{s} - \theta s^* - p\mathrm{s} \\ \frac{d\mathrm{i}}{da} &= \lambda^*\mathrm{s} + \theta s^* - (p+1/\varepsilon)\mathrm{i} \\ \mathrm{s}(0) &= \mathrm{i}(0) = 0. \end{aligned}$$

In order for the perturbation to be consistent with the definition of $\hat{\theta}$, we in addition require (Castillo-Chavez et al., 1989)

$$\theta = \frac{b}{\varepsilon}\int_0^1 \mathrm{i}(\alpha)\, d\alpha.$$

This yields the stability equation in the eigenvalue, p,

$$\begin{aligned} \frac{\varepsilon}{b} = & \frac{p}{\lambda(p+1/\varepsilon)(p+\lambda)} + \frac{\lambda e^{-\lambda-p}}{(\lambda-1/\varepsilon)p(p+\lambda)} \\ & - \frac{(p-\lambda)e^{-\lambda}}{\lambda p(p-\lambda+1/\varepsilon)} - \frac{e^{-p-1/\varepsilon}}{\varepsilon(\lambda-1/\varepsilon)(p+1/\varepsilon)(p-\lambda+1/\varepsilon)} \end{aligned} \tag{9}$$

(Greenhalgh, 1987).

Equation (9) can not be solved analytically, but the fact that $\varepsilon \ll 1$ allows us to find approximate solutions for the roots near the imaginary axis. These roots give the dominant eigenvalues and are hence the ones that determine the stability of the model.

The term involving $e^{-p-1/\varepsilon}$ can be important only when either $e^{-p-1/\varepsilon}$ is large or when $p \approx -1/\varepsilon,\ \lambda - 1/\varepsilon$. In both cases the real part of p is much smaller than -1, so the term is not relevant for determining the stability of (3). Multiplying through in (9) by the common denominator shows that the remaining part of the equation is essentially of the form $w(p) = u(p)e^{-p}$ where $w(p)$ and $u(p)$ are polynomials of degree 4 and 2 respectively. Equations of this form have at most a finite number of roots with positive real part (Bellman and Cooke, 1963).

To simplify (9) first multiply through by $p(p+\lambda)/\varepsilon$ and omit the order $e^{-1/\varepsilon}$ term:

$$0 = -\frac{p(p+\lambda)}{b} + \frac{p^2}{\lambda(1+\varepsilon p)} - \frac{\lambda e^{-\lambda-p}}{1-\varepsilon\lambda} - \frac{(p^2-\lambda^2)e^{-\lambda}}{\lambda(1+\varepsilon p-\varepsilon\lambda)}.$$

Multiplying through by $p(p+\lambda)$ introduces extraneous roots in (10) at $p = 0, -\lambda$, which are not roots for (9). The equation contains terms that are of different magnitude since by (7) and (8), b and λ are of order 1 while $\varepsilon \ll 1$. The order of p is determined by trying roots of the form $|p| \approx c\varepsilon^q$.

One sees that the p^2/b is unbalanced if $q < -1$. For $q = -1$ the terms of order p^2 and $p^2/(\varepsilon p+1)$ must cancel but by (8) this is only possible when $\varepsilon p + 1 = 1 + O(\varepsilon)$. We conclude that $q > -1$ and expand in powers of ε:

$$\begin{aligned} 0 = &-\frac{p(p+\lambda)}{b} + \frac{p^2}{\lambda}(1-\varepsilon p+\varepsilon^2 p^2+\ldots) \\ &- \lambda e^{-\lambda-p}(1+\varepsilon\lambda+\varepsilon^2\lambda^2+\ldots) \\ &- \frac{(p^2-\lambda^2)e^{-\lambda}}{\lambda}(1-\varepsilon(p-\lambda)+\varepsilon^2(p-\lambda)^2+\ldots). \end{aligned}$$

Using (8) to remove the p^2 terms and to simplify the εp^3 term, we get

$$\begin{aligned} 0 = &[-p\lambda/b + \lambda e^{-\lambda}(1-e^{-p})] \\ &+ \varepsilon[-p^3/b - \lambda e^{-\lambda}(\lambda e^{-p} + p - \lambda) \\ &+ \varepsilon^2[p^4/b] + O(\varepsilon^2 p^3) + O(\varepsilon^3). \end{aligned} \tag{10}$$

By trying roots of the form $|p| \approx c\varepsilon^q$, one sees that there are only two possible types of other roots for (10) with real part near the imaginary axis, $|p| \approx c + O(\varepsilon)$ and $|p| \approx c\varepsilon^{-1/2} + O(1)$.

For $|p| \approx c$, the equation becomes

$$-p\lambda/b + \lambda e^{-\lambda}(1-e^{-p}) + O(\varepsilon) = 0 \tag{11}$$

In appendix A we prove that all roots of (11), except the ones at 0 and at $-\lambda$ have real part less than x_1 where x_1 is given implicitly by

$$a^2 e^{-2x_1} = \pi^2/4 + (a - x_1)^2,$$

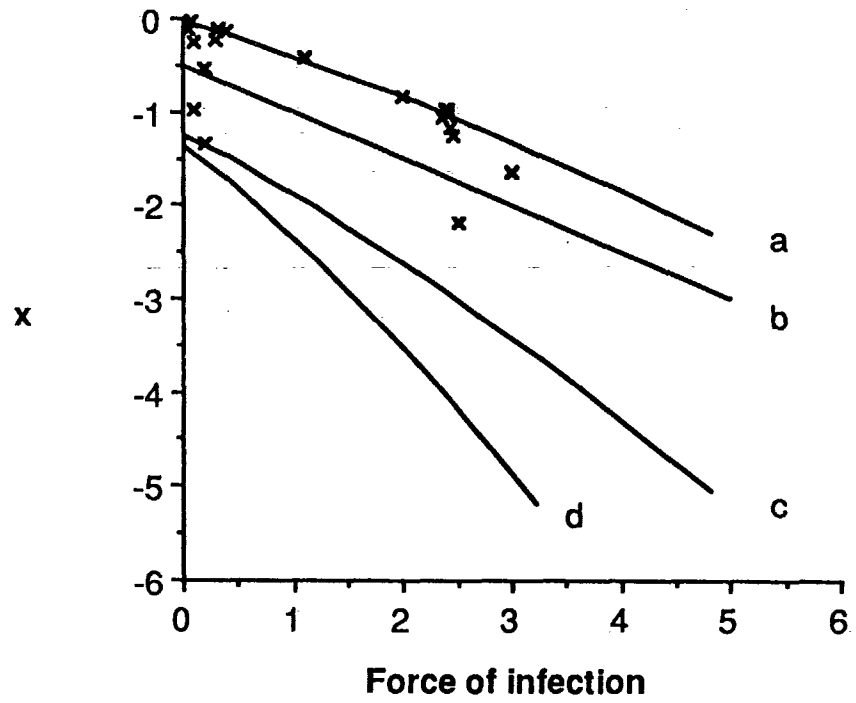

Figure 3. Bounds for the eigenvalues determining the stability of the endemic equilibrium of model (3). The two curves (a) and (d) give upper and lower bound for the real part of the eigenvalues with imaginary part close to $\sqrt{\lambda/\varepsilon}$. The curve (c) is an upper estimate of the real part of roots with imaginary part near 0. The line (b) shows the real part of the eigenvalue in the non-age-structured model (1). The dots represent numerical solutions of (9) at selected values of λ.

and $a = \lambda/(e^{\lambda} - 1) > 0$.

For $|p| \approx c\varepsilon^{-1/2}$, the roots are

$$p = \pm i\sqrt{\lambda/\varepsilon} + O(1). \tag{12}$$

In appendix B, we show by computing the second order term that for roots of type (12), the real part of p is negative. A more careful analysis, which also can be found in appendix B, shows that the real part of p must be less than a critical value x_0 implicitly determined by the largest root to the equation

$$e^{-2x_0} = (\frac{2x_0}{a} + e^{\lambda})^2.$$

A heuristic argument indicates that as b varies the dominant eigenvalue will fluctuate rapidly within an interval $[x_m; x_0]$. Numerical solutions of (9) support this claim (Figure 3).

Numerical solutions of (9) show that the order $\varepsilon^{-1/2}$ roots are the dominant ones, although the heuristically derived lower bound for the real part of the order $\varepsilon^{-1/2}$-roots x_m is always smaller

than x_1, the upper limit for the real part of the order 1 roots. Therefore, the model is stable, and the stability is characterized by the weakly damped, long period oscillations associated with the roots of type (12), see Figure 3.

For $\varepsilon = 10^{-4}$, a typical value for viral diseases (Table 1), roots of the type (12) have an imaginary part that is about 100 times as large as the real part. This explains why several authors (Anderson and May, 1983; Castillo-Chavez et al., 1989) find numerically that age-structured models tend to be weakly damped. The numerical values for real and imaginary parts correspond well with the values reported by Castillo-Chavez et al. (1989) for a closely related discrete time model.

The imaginary part of the eigenvalue $\omega \approx \sqrt{\lambda/\varepsilon}$ determines the period of the oscillation. Therefore, the interepidemic period predicted by the model is $T = 2\pi/\omega \approx 2\pi\sqrt{\varepsilon/\lambda}$ measured in units of A — or in dimensional variables: $T \approx 2\pi\sqrt{D/\Lambda} \approx 2\pi\sqrt{DK}$, where K is the average age at which an individual contracts the disease and D is the duration of the disease (Dietz, 1975). The age-structured model (3) thus predicts the same interepidemic period as does the standard non-age-structured SIR-model (1), since in the non-age-structured model $K = A/(R_0 - 1)$. The damping time in the age-structured model is similar to that of the model (1), but in most cases somewhat larger (Figure 3).

Discussion

The presence of an endemic infectious disease is due to a balance between the introduction of new susceptibles and the loss of susceptibles through infection and subsequent recovery or death. For a disease that confers permanent immunity, new susceptibles appear only through host births, and the time scale of this process is closely linked to the host life span (Yorke et al., 1979). Susceptibles become infected through contact with infectious individuals so the course of the disease within the individual host determines the disease transmission. The maintenance of an endemic disease thus depends on the interaction between two biologically distinct phenomena. The key observation in this paper is that for many infectious diseases, host renewal and individual infection take place on time scales that differ by 3–4 orders of magnitude.

After a rescaling of the variables, the ratio between the two time scales appears explicitly in the age-dependent SIR-model. Asymptotic expansion of the stability equation at the endemic equilibrium yields implicit but manageable expressions for the dominant elements of the spectrum.

With the aid of this analysis, the effect of the human demography on disease transmission dynamics becomes clear. The survival curve for human populations is described well by a fixed duration of life with the life span set to the mean life expectancy. For a population with this mortality structure, the incidence of a contagious, immunizing disease exhibits damped oscillations with a period of approximately $2\pi\sqrt{DK}$, where D denotes the duration of infection and K is the average age at infection. The period of the oscillation is the same as in the model with constant mortality, but for most parameter values the fixed life span model leads to less damped oscillations.

The analysis thus confirms the popular wisdom that age-structured models in epidemiology exhibit slowly damped, long period oscillations (Anderson and May, 1983), but it also shows that the damping time is not well determined. To the first order, the dominant eigenvalues are purely

imaginary, so the stability of the model is determined by the second order equation. The real part of the eigenvalue x is always negative. I give a rigorous upper bound for x and a heuristically derived lower bound. Within those bounds, x appears to be extremely sensitive to variation in the transmission factor β. For many airborne diseases, β varies with the season, probably due to people's tendency to stay inside more in the winter (e.g. influenza and measles, Beveridge, 1977; London and Yorke, 1973; Fine and Clarkson 1982). Due to the sensitivity to β, the dynamics may be altered significantly by temporal variation in the transmission coefficient. Simulations with the discrete time model of Castillo-Chavez et al. (1989) show very complex dynamics even for modest seasonal variations in β (5%–10%); but I hesitate to draw conclusions about the continuous model from these result because the discretization of Castillo-Chavez et al. (1989) may have introduced adventitious oscillations.

Although the age-dependent host mortality itself cannot cause sustained oscillations in SIR-models, it enhances the oscillatory propensity of the models. In a companion paper (Andreasen, 1990) I demonstrate that the mortality structure indeed can induce oscillations in an epidemic model that would otherwise not oscillate. The model in question describes the co-circulation of influenza strains that confer partial cross-immunity (Castillo-Chavez et al., 1988, 1989). Using asymptotic expansions on the ratio between the time scales, I can demonstrate in a special case that there exist parameter values such that the characteristic equation has purely imaginary eigenvalues. The imaginary eigenvalues indicate the possibility of a Hopf-bifurcation in a direction associated with the deviation in incidence of the two strains. Since the corresponding model with constant mortality is always stable in the deviation between the two strains, we conclude that age-dependent mortality can indeed cause sustained oscillations in SIR-models that would otherwise be stable.

Acknowledgement

I thank F. Adler, C. Castillo-Chavez, H. Hethcote, W-m. Liu, S.A. Levin, and R. Waldstätter for their help and encouragement with this project. I am pleased to acknowledge the support from NSF grant BSR DMS 8406472 to S.A. Levin and from Center for Applied Mathematics, Cornell University. The final preparation of this manuscript was supported by grant 11-8296 from the Danish Natural Science Research Council.

Appendix A

First order approximation to roots of order 1

In this appendix we estimate the magnitude of the real part of roots for

$$-p\lambda/b + \lambda e^{-\lambda}(1 - e^{-p}) + O(\varepsilon) = 0. \tag{11}$$

As a first step we observe that by (8), $\lambda/b = (1 - e^{-\lambda}) + O(\varepsilon)$, so that equation (11) may be rewritten as

$$p - a(1 - e^{-p}) = 0, \tag{A1}$$

where $a = \lambda/(e^{\lambda} - 1) > 0$.

Equation (A1) has two real roots at $p = 0, -\lambda$. As observed in the main text, these roots are not roots for the characteristic equation (9), so the roots of interest must be complex. Setting $p = x + iy$, we get

$$a - x = ae^{-x}\cos y \tag{A2}$$

$$y = ae^{-x}\sin y. \tag{A3}$$

Focusing on the roots with positive imaginary part, $y > 0$, we observe that since $\sin y < y$, (A3) shows that $1 < ae^{-x}$ or $x < \log a < a - 1$, so that

$$1 < a - x.$$

Rewriting (A2)–(A3) gives

$$y/(a - x) = \tan y \tag{A4}$$

$$y^2 + (a - x)^2 = a^2 e^{-2x}. \tag{A5}$$

Simple geometry and (A4) now show that $y > \pi/2$, and (A5) yields

$$a^2 e^{-2x} = y^2 + (a - x)^2 > \pi^2/4 + (a - x)^2,$$

giving an upper limit for the value of x.

Appendix B

Second order approximation to roots of order $\varepsilon^{-1/2}$

Since the first order approximation to (9) gave purely imaginary roots of the form $i\omega = i\sqrt{\lambda/\varepsilon}$, the stability of the model is determined by the second order terms. We assume that the terms are of order 1 and set $p = x+i(y+\omega)$. After some algebra, well suited for symbolic computer manipulation, we arrive at the following equation, where we have retained only terms of order 1:

$$e^{-x}\cos(y+\omega) - x2(e^{\lambda}-1)/\lambda - e^{\lambda}$$
$$+ ie^{-\lambda}\left(e^{-x}\sin(y+\omega) - y2(e^{\lambda}-1)/\lambda\right) + O(\varepsilon^{1/2}) = 0.$$

With $a = \lambda/(e^{\lambda}-1) > 0$, as in the previous appendix, we have

$$e^{-x}\cos(y+\omega) = 2x/a + e^{\lambda}$$
$$e^{-x}\sin(y+\omega) = 2y/a.$$

It follows that

$$e^{-2x} = (2x/a + e^{\lambda})^2 + (2y/a)^2. \qquad (A6)$$

Since $e^{\lambda} > 1$, the right hand side of (A6) is greater than 1 for $x > 0$, while the left hand side is less than 1, hence (A6) has no positive roots and model (3) is always stable for small ε.

The real part of the order $\varepsilon^{-1/2}$ eigenvalue x is determined by the intersection of the graph for e^{-2x} and the parabola $(2x/a+e^{\lambda})^2+(2y/a)^2$. The rightmost intersection of e^{-2x} and the parabola $(2x/a + e^{\lambda})^2$ thus determines an upper bound x_0 on the real part of the order $\varepsilon^{-1/2}$ eigenvalue (Figure 3).

We now describe the behavior of the roots as a bifurcation sequence in λ by the following heuristic argument. The imaginary, second order correction term, y, is determined by the equation

$$\tan(y+\omega) = \frac{2}{2x + ae^{\lambda}}y. \qquad (A7)$$

I conjecture that (A7) has a root between $-\pi/2$ and $\pi/2$. (This is not clear, since (A7) depends on x, but I argue that x does not matter in the sense that for any given x, (A7) has at least one solution between $-\pi/2$ and $\pi/2$.) The equation will have additional roots with larger magnitude of y, but by (A6) they cannot give rise to the dominant order $\varepsilon^{-1/2}$ eigenvalue. Since $\omega = \sqrt{\lambda/\varepsilon}$, ω changes rapidly when λ varies, and we expect that the roots of (A7) will vary rapidly between $-\pi/2$ and $\pi/2$. The variation in y will force x to vary between x_0 and x_m, where x_m is the intersection between e^{-2x} and the parabola $(2x/a + e^{\lambda})^2 + (\pi/a)^2$ (Figure 3).

Notice that the bifurcation sequence may just as well be regarded as a sequence in the transmission factor b, since λ is a monotonically increasing function of b.

References

Anderson, R.M. 1982. Directly transmitted viral and bacterial infections in man. In *The Population Biology of Infectious Diseases,* R.M. Anderson (ed.), pp. 1–37. Chapman and Hall, London.

Anderson, R.M., and R.M. May. 1982. Directly Transmitted Infectious Diseases: Control by Vaccination. *Science*, **215**: 1053–1060.

Anderson, R.M., and R.M. May. 1983. Vaccination Against Rubella and Measles: Quantitative Investigations of Different Policies. *J. Hyg., Camb.*, **90**: 259–325.

Anderson, R.M., and R.M. May. 1985. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. *J. Hyg., Camb.*, **94**: 365–436.

Andreasen, V. 1989a. Multiple time scales in the dynamics of infectious diseases. In *Mathematical Approaches to Problems in Resource Management and Epidemiology,* C. Castillo-Chavez, S.A. Levin, and C. Shoemaker (eds.), pp. 142–151. Springer Verlag, Berlin–Heidelberg.

Andreasen, V. 1989b. Disease Regulation of Age-Structured Host P opulations. *Theor. Popul. Biol.*, **36**: 214–239.

Andreasen, V. 1990. SIR-models of the epidemiology and natural selection of co-circulating influenza virus with partial cross-immunity (submitted).

Bailey, N.T.J. 1986. Macro-modelling and prediction of epidemic spread at community level. *Math. Modelling*, **7**: 689–717.

Bellman, R., and K.L. Cooke. 1963. *Differential-Difference Equations.* Academic Press, New York.

Beveridge, W.I.B. 1977. *Influenza: The last Great Plague.* Heineman, London.

Busenberg, S., K. Cooke, and M. Iannelli. 1988. Endemic thresholds and stability in a class of age-structured epidemics. *SIAM J. Appl. Math.*, **48**: 1379–1395.

Castillo-Chavez, C., H.W. Hethcote, V. Andreasen, S.A. Levin, and W-m. Liu. 1988. Cross-immunity in the Dynamics of Homogeneous and Heterogeneous Populations. In *Mathematical Ecology,* T.G. Hallam, L. J. Gross, and S.A. Levin (eds.), pp. 303–316. World Scientific Publ., Singapore.

Castillo-Chavez, C., H.W. Hethcote, V. Andreasen, S.A. Levin, and W-m. Liu. 1989. Epidemiological models with age structure, proportionate mixing, and cross-immunity. *J. Math. Biol.*, **27**: 233–258.

Danmarks Statistik. 1987. *Statistical Yearbook.* Danmarks Statistik, Copenhagen.

Diekmann, O., J.A.P. Heesterbeek, and J.A.J. Metz. 1989. On the definition and the computation of the basic reproductive ratio R_0 in models for infectious diseases in heterogeneous populations (preprint).

Dietz, K. 1975. Transmission and Control of Arbovirus Diseases. In *Epidemiology,* D. Ludwig and K.L. Cooke (eds.), pp. 104–121. Society for Industrial and Applied Mathematics, Philadelphia.

Dietz, K. 1981. The evaluation of rubella vaccination strategies. In *The Mathematical Theory of the Dynamics of Biological Populations, Vol II,* R.W. Hiorns and D. Cooke (eds.), pp. 81–97. Academic Press, London.

Dietz, K., and D. Schenzle. 1985. Proportionate mixing models for age-dependent infection transmission. *J. Math. Biol.*, **22**: 117–120.

Fine, P.E.M., and J.A. Clarkson. 1982. Measles in England and Wales - I: An Analysis of Factors Underlying Seasonal Patterns. *Int. J. Epidemiol.*, **11**: 5–14.

Greenhalgh, D. 1987. Analytical Results on the Stability of Age-Structured Recurrent Epidemic

Models.. *IMA J. Appl. Med. Biol.*, **4**: 109–144.

Greenhalgh, D. 1988. Analytical Threshold and Stability Results on Age-Structured Epidemic Models with Vaccination. *Theor. Popul. Biol.*, **33**: 266–290.

Griffiths, D.A. 1974. A catalytic model of infection of measles. *Appl. Statist.*, **23**: 330–339.

Hethcote, H.W,. 1974. Asymptotic behaviour and stability of epidemic models. In *Mathematical Problems in Biology,* P. van der Driessche (ed.), pp. 83–92. Springer, Berlin.

Hoppensteadt, F. 1974. An Age Dependent Epidemic Model. *J. Franklin Inst.*, **297**: 325–333.

Knox, E.G. 1980. Strategy for Rubella Vaccination. *Int. J. Epidemiol.*, **9**: 13–23.

London, W.P., and J.A. Yorke. 1973. Recurrent outbreaks of measles, chickenpox, and mumps. *Amer. J. Epidemiol.*, **98**: 453–468.

May, R.M. 1986. Population Biology of Microparasitic Infections. In *Mathematical Ecology,* T.G. Hallam and S.A. Levin (eds.), pp. 405–442. Springer, Berlin.

Muench, H. 1959. *Catalytic Models in Epidemiology.* Harvard University Press, Cambrdige, Ma.

Schenzle, D. 1984. An Age-Structured Model of Pre- and Post-Vaccination Measles Transmission. *IMA J. Math. Appl. Med. Biol.*, **1**: 169–191.

Schenzle, D., and K. Dietz. 1987. Critical population sizes for endemic virus transmission. In *Räumliche Persistenz und Diffusion von Krankenheiten,* W. Finche and E. Hinz (eds.), pp. 31–42. Geographisches Institutes der Universität Heidelberg, Heidelberg.

Spicer, C.C. 1982. Models of the temporal spread of epidemics (2). In *Influenza Models,* P. Selby (ed.), pp. 133-137. MTP Press, Lancaster.

Yorke, J.A., N. Nathanson, G. Pianigiani, and J. Martin. 1979. Seasonality and the requirements for perpetuation and eradication of viruses in populations. *Amer. J. Epidemiol.*, **109**: 103–123.

SIR-MODELS OF THE EPIDEMIOLOGY AND NATURAL SELECTION OF CO-CIRCULATING INFLUENZA VIRUS WITH PARTIAL CROSS-IMMUNITY

Unlike most other contagious viral diseases, infection with influenza virus type A gives only a partial immunity (cross-immunity) to other variants of influenza (Thacker, 1986). The virus variants therefore interact indirectly by modifying the susceptibility of their shared host population. In this paper I develope epidemic models to describe the dynamics of this co-circulation of viral strains in order to understand the effect of cross-immunity on the epidemiology of influenza A and on the natural selection experienced by these virus.

On the basis of marked serological differences, the influenza virus family is divided into 3 types A, B, and C. Of these, type A is the most common and the one we will be concerned with in this paper. The influenza virus consists of 8 strands of RNA surrounded by an inner shell of matrix protein and an outer lipid bilayered membrane. The outer membrane is covered densely with spikes of the two glycosylated proteins, hemagglutinin (HA) and neuraminidase (NA). The hemagglutinin is believed to play a role in the initial attachment of the virus to the cell while the neuraminidase facilitates the release of the virus particles from the infected cell (Fraenhel-Conrat et al., 1988).

Immunity to the influenza virus is induced in response to stimulation by the two surface proteins, HA and NA, and the variation in the virus' antigenic properties is due to variation in the composition of these proteins. Both the HA and the NA proteins undergo two kinds of change. The most significant changes are referred to as *shifts*, the less dramatic changes as *drift*. In the process known as virus drift, new variants with minor biochemical differences continuously arise through point mutations changing the amino acid composition of the antigenic sites on the HA and NA structures (Webster et al., 1982; Palese and Young, 1982). A shift is characterized by the appearance of a new *subtype* with antigenically distinct HA and/or NA surface regions. The mechanism that gives rise to virus shift is not known but shift may be due to virus recombination involving wild life subtypes or due to a sudden change in the surface structure caused by the accumulating mutations (Dowdle et al.,1974; Thacker, 1986).

To the human immune-system, different subtypes appear as antigenically unrelated infectious agents if both surface antigens are distinct, while viral strains of the same subtype exhibit considerable variation in the cross-reactive immune response (Couch and Kassel, 1983). Although reinfection with the same influenza drift variant has been observed (Thacker, 1986) such events probably are rare and we will not consider reinfections by the same variant here. Experiments using artificial infection (Larson et al., 1978; Potter et al., 1977) and observations of natural disease patterns (Gill and Murphy, 1976; Couch and Kassel, 1983; Davies et al., 1986) show that the probability of infection often is reduced for individuals which have a history of previous infection with a related strain. Thus virus drift and perhaps shift can be responsible for the existence of viral strains that confer the type of partial cross-immunity we are studying. The observations in this paper do not depend on the way in which the cross-reacting strains were created.

Simultaneous occurrence of different subtypes was not observed until 1977 when the H1N1 and H3N2 subtypes both were found in the United States during the epidemic season (Kendal et al., 1979). Currently both of these subtypes are active in the human population. Also different variants of the same subtype can be active at the same time; usually one variant accounts for

most of the infections while other strains occur sporadically and are detected only by large scale surveillance programs (Kendal et al., 1979; Glezen et al., 1982; Chakraverty et al., 1986).

How can one represent the co-circulation of viral strains ?

Simple SIR-models give good fit to the time series of a single epidemic with a basic reproductive number $\mathcal{R}_0 \approx 2$–5 and an infectious period on the order of 3–5 days depending on the strain and community in question (Spicer and Lawrence, 1984; Bailey, 1986). For other modelling approaches, see Fine (1982a). As observed by Levin and Pimentel (1981) and Dietz (1979), SIR-models with multiple infectious classes can describe the interaction between related strains by keeping track of the number of hosts infected with each strain since superinfection, i.e. simultaneous infection with two different strains rarely is observed. I therefore use a generalized version of the SIR-models to characterize co-circulation.

Only few studies address the transmission dynamics of co-circulating strains. Elveback et al. (1971) and Dietz (1979) describe the two-strain interactions that are manifest as temporary immunity, prohibiting superinfection ("virus interference"). For diseases with short duration, such as influenza, the strains have only weak influence on each other's host population, and virus interference does not alter significantly the stable, endemic equilibria. The situation where interacting strains confer complete cross-immunity has been studied extensively in connection with the myxoma-rabbit system (Fenner and Ratcliffe, 1965; Anderson and May, 1982a; May and Anderson, 1983; Saunders, 1981; Bremermann and Thieme, 1989). Standard SIR-models with full cross-immunity among strains in homogeneous host populations show that all but one strain will be excluded, but the conclusion rely heavily on the assumed linearity in these models (Andreasen, in prep.). The observed co-circulation of different myxoma strains in natural systems probably is due to heterogeneity in such factors as space and rabbit resistance (Dwyer et al., 1990).

The interaction of influenza strains with partial cross-immunity is described first by Castillo-Chavez et al. (1988, 1989) who propose to model partial cross-immunity as a reduction in the transmission rates for previously exposed individuals. In a host population without age-structure, they find — depending on the parameter values — that partial cross-immunity can lead to exclusion of one of the two strains or to co-existence at a stable, endemic equilibrium where the prevalence of either strain is reduced by the presence of the other strain relative to the prevalence it would attain in isolation. Castillo-Chavez et al. (1989) generalize their model to allow for age-dependence in the parameters, and they find numerically that cross-immunity in conjunction with a fixed duration of host life span causes sustained oscillations in the relative abundance of the two strains when the cross-immunity is sufficiently high. Our aim in this paper is to provide a better biological and analytical understanding of these phenomena.

In the first section of the paper, I introduce the model of Castillo-Chavez et al. with age-independent mortality and interpret the model's asymptotic behavior in the context of invasion by a competing organism or polymorphy in a haploid population. I then extend the model allowing for age-dependent mortality thus making the underlying epidemiological assumptions more realistic.

In order to analyze this situation, we need a technical trick which essentially consists in observing that for influenza as for most infectious diseases, the SIR-models contain two different time scales, the duration of infection D and the host life length A. Andreasen (1990) uses asymptotic

expansions in $\varepsilon = D/A \ll 1$, the ratio between the two time scales to analyze the stability of an SIR-model with constant host life span. I here generalize that method to allow for multiple infections and transform the coordinate system in order to display the structure of the endemic equilibrium. The following sections are concerned with obtaining asymptotic expressions for the endemic force of infection and stability equation respectively. This analysis will allow us to determine how the presence of cross-immunity affects the age-dependent attack rates. After the analysis, I discuss the model's implications for the frequency dependent natural selection experienced by related influenza strains and for the epidemiology of influenza.

Two strains with partial cross-immunity

If an SIR-type model is to describe the simultaneous presence of interacting viral strains, it must i) record the serology of the host population, i.e. the hosts' history of previous infections, and ii) specify for each strain the infection rate. For two co-circulating variants, Figure 1 shows how eight epidemic classes can summarize the population's serological status. Since the number of ways to achieve full immunity to n interacting strains is $n!$, this approach quickly becomes unreasonably complex when more strains are involved. In this paper we study only two strain interactions.

The force of strain 1 infection experienced by the fully susceptibles, depends on the number of individuals infectious with strain 1. We will assume that cross-response does not interfere with the production of virus particles in infected hosts and hence that infectious with no previous exposure I_1 and infectious with a previous infection V_1 are equally good at transmitting the disease. Furthermore we will make the usual "mass-action" assumption that the force of infection Λ_1 is proportional to the prevalence of strain 1,

$$\Lambda_1 = \beta_1(I_1 + V_1).$$

Following the idea of Castillo-Chavez et al. (1988) and Pease (1987), we model the reduced probability of infection for the partially immune R_2 by a cross-immunity factor σ_1 $(0 \leq \sigma_1 \leq 1)$ that denote the fraction by which the force of infection is reduced. Hence for the individuals in the R_2 class, the force of infection is $\sigma_1\Lambda_1$. Assuming constant mortality and recovery rates μ and ν respectively, we obtain a model of 8 O.D.E.s

$$\begin{aligned}
\dot{S} &= -\beta_1(I_1 + V_1)S - \beta_2(I_2 + V_2)S - \mu S + \mu N \\
\dot{I}_l &= \beta_l(I_l + V_l)S - (\nu_l + \mu)I_l \\
\dot{R}_l &= \nu_l I_l - \sigma_k\beta_k(I_k + V_k)R_l - \mu R_l \qquad\qquad l{=}1{,}2 \quad k{=}2{,}1 \qquad (4) \\
\dot{V}_l &= \sigma_l\beta_l(I_l + V_l)R_k - (\nu_l + \mu)V_l \\
\dot{Z} &= \nu_1 V_1 + \nu_2 V_2 - \mu Z.
\end{aligned}$$

To avoid the complications of a changing population size, the vital dynamics of the host are kept as crude as possible: All individuals are born susceptible, and the number of births μN equals the number of deaths, making the total population size a constant N. Since N is a constant, the Z-equation is redundant.

Model (4) may be seen as a generalization of Dietz's (1979) model of virus interference, though the biological assumptions are very different. Dietz's model includes only the effect of the temporary

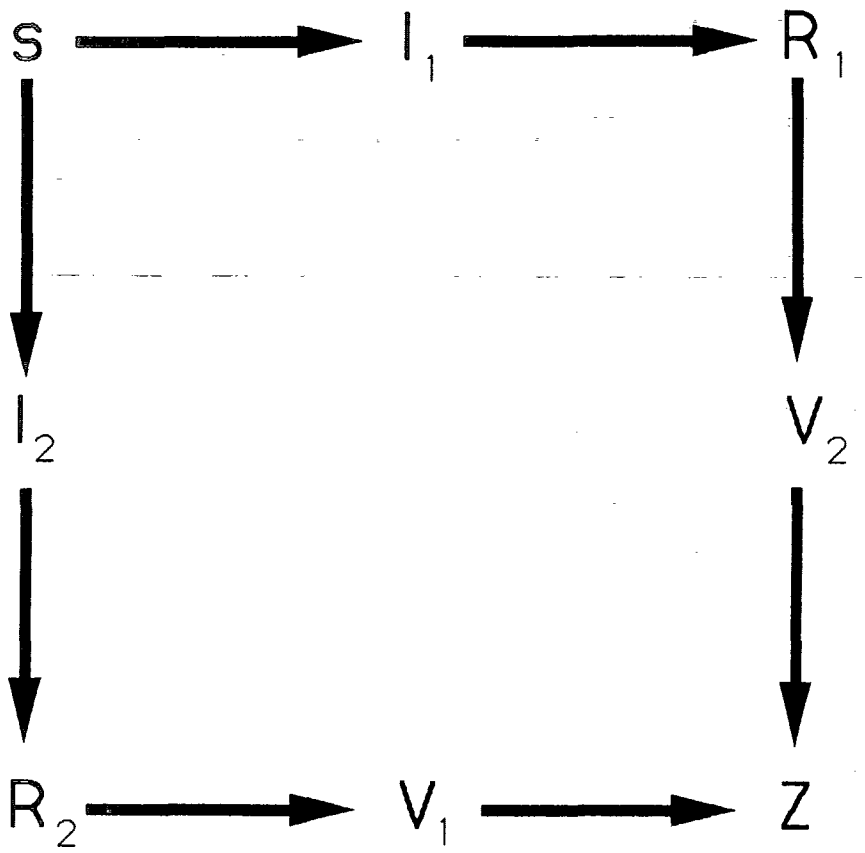

Figure 1. Transfer diagram for the 8 epidemic classes in a model with two strains conferring partial cross-immunity. Individuals are born into the susceptible class S and can get infected with either strain 1 or 2. When recovered from infection with strain 1, the individuals enter R_1, the class of hosts immune to strain 1. Such individuals still can get infected by strain 2. When recovering from the second infection, they enter Z, the class of completely protecteds. Thus there are two ways to achieve full immunity to both strains. For simplicity the diagram does not show the vital dynamics. (After Castillo-Chavez et al., 1989).

immunity that prohibits superinfection, while the present model also includes permanent decreases in susceptibility.

Castillo-Chavez et al. (1989) characterize the stability of the model (4). Rather than repeating their detailed analysis, I here give a biological interpretation of their findings. Figure 2 schematically show the four possible equilibria: The disease-free equilibrium G_o; the two equilibria where only one strain is present, G_1, G_2; and the equilibrium G_* where both strains are present. The stability and non-negativity of the equilibria are determined by the two reproductive numbers

$$\mathcal{R}_l = \frac{\beta_l N}{\mu + \nu_l} \qquad l = 1, 2$$

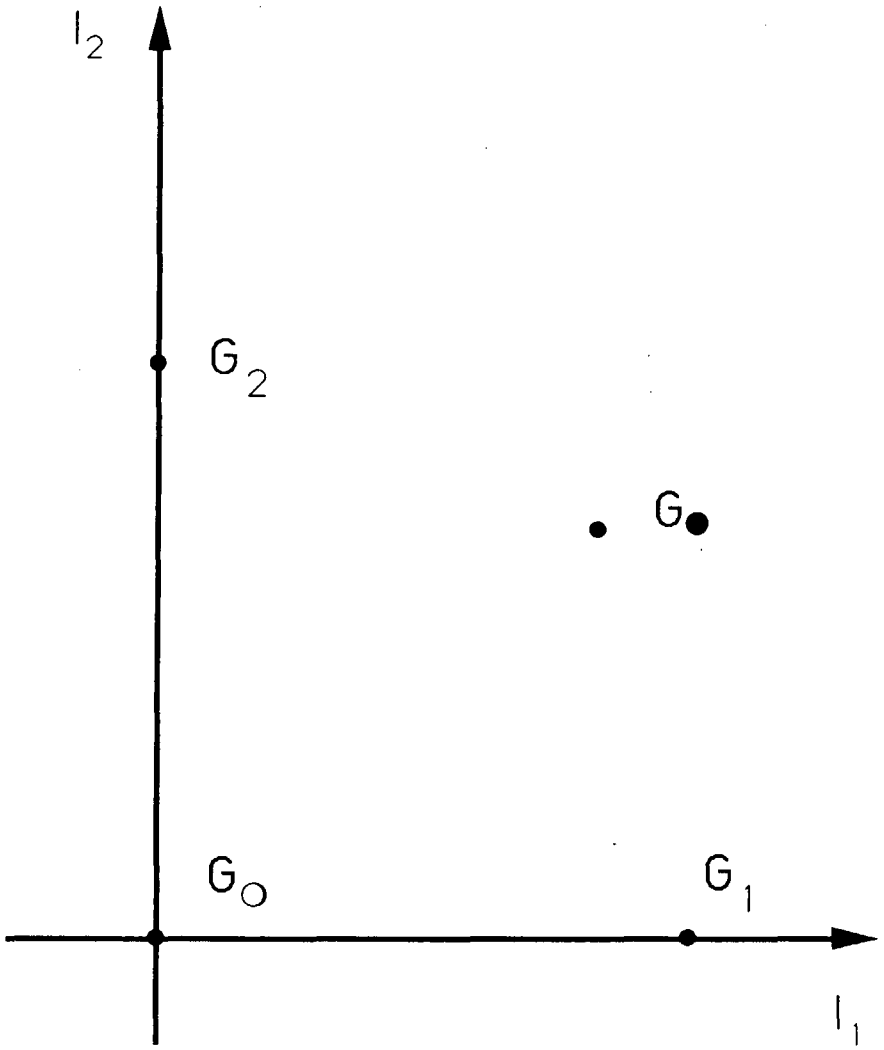

Figure 2. Position of the four possible equilibria in model (4).

and by the two reduced susceptibilities

$$M_l = \frac{1}{N}\left\{\frac{N}{\mathcal{R}_l} + \sigma_k N(1-\frac{1}{\mathcal{R}_l})\frac{\mu}{\mu+\nu_l}\right\} \qquad l=1,2 \quad k=2,1.$$

The reduced susceptibility M_l gives the fraction of the population that is susceptible to strain k at G_l so that $M_l\mathcal{R}_k$ gives the number of secondary infections resulting from one person infected with strain k at the equilibrium G_l where strain l is already established.

Table 1 shows the stability of the equilibria. In any parameter region at most one equilibrium is stable. Strain l can persist if $\mathcal{R}_l > 1$ and it will persist always if it can invade when the other strain is already established.

The situation is analogous to competition between two species where the two strains compete by exploiting the available space in the human immune response. Since the two strains do not utilize exactly the same resource, their co-existence does not contradict the extended competitive exclusion principle Levin (1970). In the special case of full cross-immunity $\sigma = 0$, the two strains share a common resource, and we have $M_l = 1/\mathcal{R}_l$ prohibiting the existence of $G_\bullet$. The competitive exclusion principle of virus thus applies to model (4) (Bremermann and Thieme, 1989). If no cross-immunity is present $\sigma = 1$, $N(1-\frac{1}{\mathcal{R}_l})\frac{\nu_l}{\nu_l+\mu_l}$ individuals are temporarily removed from the susceptible pool for strain k due to an on-going infection by strain l (Dietz, 1979). Since the duration of infection ν^{-1} is short compared to the host life span μ^{-1}, we have $\nu/(\nu+\mu) \ll 1$. Hence the effect of strain l on strain k is negligible when $\sigma = 1$.

When $\mathcal{R}_1 > 1/M_2$ and $\mathcal{R}_2 > 1/M_1$, the two strain fixed point $G_\bullet$ exists and numerical solution of the stability equation shows that $G_\bullet$ is always stable. However even the local analysis for this 7-dimensional model is too complicated and we here focus on the symmetric case $\beta_1 = \beta_2 = \beta \quad \sigma_1 = \sigma_2 = \sigma \quad \nu_1 = \nu_2 = \nu$ and on symmetric equilibria. The situation where two strains have similar parameter values could arise when two viral strains only recently have become antigenically distinct, so it may be the situation of interest for virus evolution. In contrast to Castillo-Chavez et al. (1989), we here assume arbitrary positive initial conditions.

After a change of coordinate system

$$I = i_1 + i_2 \quad i = i_1 - i_2 \qquad \text{etc.}, \tag{5}$$

the model becomes

$$\begin{aligned}
\dot{S} &= -\beta(I+V)S - \mu S + \mu N \\
\dot{I} &= \beta(I+V)S - (\nu+\mu)I \\
\dot{R} &= \nu I - \frac{1}{2}\sigma\beta\left[(I+V)R - (i+v)r\right] - \mu R \\
\dot{V} &= \frac{1}{2}\sigma\beta\left[(I+V)R - (i+v)r\right] - (\nu+\mu)V \\
\dot{i} &= \beta(i+v)S - (\nu+\mu)i \\
\dot{r} &= \nu i - \frac{1}{2}\sigma\beta\left[(I+V)r - (i+v)R\right] - \mu r \\
\dot{v} &= -\frac{1}{2}\sigma\beta\left[(I+V)r - (i+v)R\right] - (\nu+\mu)v.
\end{aligned} \tag{6}$$

In the symmetric case, model (6) has a unique, endemic equilibrium if and only if $\mathcal{R}_1 = \mathcal{R}_2 > 1$. At low disease prevalence, the two strains both experience a population of only susceptibles, so the threshold for their establishment is independent of the presence of the other strain.

At the symmetric equilibrium $i = r = v = 0$, the linearization decouples in a block describing the perturbations of (S, I, R, V) and a block for (i, r, v), indicating that locally near the endemic equilibrium, the host-disease interaction is independent of the interaction between strains.

Assuming that $A/D = \nu/\mu = \varepsilon \ll 1$ and $\beta/\nu \approx \mathcal{R} = O(1)$, the subsystem (i, r, v) has eigenvalues of the form $p = i\sqrt{\nu\Lambda^*\sigma/2} + O(\mu)$. The Routh-Hurwitz-criterion shows that the (i, r, v) subsystem is always locally asymptotically stable so the subsystem will exhibit slowly damped

oscillations with a period of $T \approx 2\pi\sqrt{2D/\sigma\lambda^*} = 2\pi\sqrt{D/\sigma\lambda^*}$, where λ^* is the force of infection for *one* strain at equilibrium. For the (S, I, R, V) block, Castillo-Chavez et al. (1989) use the symbol manipulator MACSYMA to show that the Routh-Hurwitz criteria are always satisfied and hence that this subsystem is stable. We conclude that the symmetric equilibrium of model (6) is stable with slowly damped oscillations in the relative abundance of the strains.

Age-dependent mortality

Host age-structure affects several epidemiological factors such as host mortality and contact rates (Anderson and May, 1982b; Longini et al., 1982). The frequency of immunity grows with host age since older individuals are more likely to previously have contracted the disease (Dietz, 1975). We therefore expect that the partial protection by cross-immunity is most important for older individuals, and we focus on this interaction between cross-protection and host age in order to understand its effects on the previous results. I concentrate on the results of assuming a fixed host life span since this is the simplest model for which Castillo-Chavez et al. (1989) found that age-dependent parameters can induce oscillations. For a more general approach allowing age-dependent contact rates, see Castillo-Chavez et al. (1989).

The SIR-model of one infections agent in an age-structured population by Hoppensteadt (1974) can be modified to include two strains yielding an age-structured version of (4). The techniques developed by Dietz and Schenzle (1985), Busenberg et al. (1988), and Castillo-Chavez et al. (1989) to analyze fixed points and their local stability in the Hoppensteaedt model generalize in a straight forward manner (Castillo-Chavez et al., 1989). For the local analysis of the SIR-model with constant duration of host life, see Greenhalgh (1987). With the same notation as in the previous section, the model becomes

$$
\begin{aligned}
\frac{\partial S}{\partial a} + \frac{\partial S}{\partial t} &= -(\Lambda_1 + \Lambda_2)S \\
\frac{\partial I_1}{\partial a} + \frac{\partial I_1}{\partial t} &= \Lambda_1 S - \nu_1 I_1 \\
\frac{\partial I_2}{\partial a} + \frac{\partial I_2}{\partial t} &= \Lambda_2 S - \nu_2 I_2 \\
\frac{\partial R_1}{\partial a} + \frac{\partial R_1}{\partial t} &= \nu I_1 - \sigma_2 \Lambda_2 R_1 \\
\frac{\partial R_2}{\partial a} + \frac{\partial R_2}{\partial t} &= \nu I_2 - \sigma_1 \Lambda_1 R_2 \qquad 0 \le a \le A \\
\frac{\partial V_1}{\partial a} + \frac{\partial V_1}{\partial t} &= \sigma_1 \Lambda_1 R_2 - \nu_1 V_1 \\
\frac{\partial V_2}{\partial a} + \frac{\partial V_2}{\partial t} &= \sigma_2 \Lambda_2 R_1 - \nu_2 V_2 \\
\frac{\partial Z}{\partial a} + \frac{\partial Z}{\partial t} &= \nu(V_1 + V_2)
\end{aligned}
\tag{7}
$$

$$
\Lambda_1(t) = \beta_1 \int_0^A (I_1 + V_1)\, d\alpha \qquad \Lambda_2(t) = \beta_2 \int_0^A (I_2 + V_2)\, d\alpha
$$

$$
S(0,t) = \varrho \qquad I_1 = I_2 = R_1 = R_2 = V_1 = V_2(0,t) = 0.
$$

Table 1. Stability of the two strain model (4). For the 8 possible parameter regions, the table shows the stable equilibrium. Unstable, non-negative equilibria are indicated in parenthesis. Strain l can persist in isolation if $\mathcal{R}_l > 1$ and it can invade the other strain when $\mathcal{R}_l > 1/M_k$. Here $\mathcal{R}_l$ is the basic reproductive number for strain l and M_l gives the fraction of the population which is susceptible to strain k at G_l. For the location of the fixed points, see Figure 2. The stability and uniqueness of G_* has been established only in special cases, see text.

	$\mathcal{R}_1 < 1$	$1 < \mathcal{R}_1 < 1/M_2$	$1/M_2 < \mathcal{R}_1$
$\mathcal{R}_2 < 1$	G_0	G_1 (o)	G_1 (o)
$1 < \mathcal{R}_2 < 1/M_1$	G_2 (o)	impossible	G_1 (o 2)
$1/M_1 < \mathcal{R}_2$	G_2 (o)	G_2 (o 1)	G_* (o 1 2)

Here Λ_l denotes the force of infection of strain l and a the age of the host. The number of susceptibles between age a and b is $\int_a^b S(\alpha)\,d\alpha$ and the definition of the other variables is similar. The equation (7) is valid for ages up to the host life span $0 \le a \le A$; at $a = A$, individuals die, and $S(a,t) = I_1(a,t) = \ldots = 0$ for $a > A$.

Since the number of births per time is a constant ϱ, the population size N is constant

$$N = \int_0^A (S(\alpha,t) + I_1(\alpha,t) + \ldots)\,d\alpha = A\varrho.$$

Furthermore, the total population P of any age a is a constant ϱ as $\frac{\partial P}{\partial a} + \frac{\partial P}{\partial t} = 0$. The equation for Z is therefore redundant. For simplicity we have assumed that no vertical transmission of infection or immunity takes place so that all individuals are born susceptible.

In situations where at most one strain is endemic, the introduction of age-structured mortality does not alter the stability property of the model: the disease-free equilibrium is stable iff $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$ where $\mathcal{R}_l$ is the basic reproductive number for strain l.

The steady state with strain l present and the other strain not occurring is stable iff i) strain l is stable in isolation, and ii)

$$b_k \int_0^1 \int_0^a [S_l^*(\alpha) + \sigma R_l^*(\alpha)] e^{\nu(\alpha - a)} d\alpha\, da < 1. \qquad k \neq l \tag{8}$$

Here $S_l^*(\alpha)$ and $R_l^*(\alpha)$ denote the equilibrium age-distribution of susceptibles and individuals immune to infection by strain l respectively. The expression (8) gives the number of secondary infections per primary infection of strain k in a population which is partially immunized by strain l. For influenza with its short infectious period the results of Andreasen (1990) show that condition i) is satisfied — i.e. strain l is stable in isolation — iff $\mathcal{R}_l > 1$. Finally we note that condition (8) cannot be satisfied for both strains simultaneously. Excepting the case where both strains are endemic, the local asymptotic stability of model (7) is therefore characterized by Table 1.

The symmetric equilibrium

For the remainder of this paper, I concentrate on the analysis of the equilibrium where the two strains circulate simultaneously. I first transform the model to display the structure of the multiple time scales and of the decomposition from last section. As in the study of the model with constant mortality, we assume that the two strains are similar so that their parameters are identical and focus on the properties of the symmetric equilibria.

The transformation of model (7) consists of two steps. In the first step we change into non-dimensional variables $\tilde{S} = S/\varrho, \tilde{I}_l = I_l/\varrho \ldots$ and measure time and age in units of A, the host life length (Andreasen, 1990). In the second step, the coordinate system is turned using the transformation (5).

$$
\begin{aligned}
\frac{\partial S}{\partial a} + \frac{\partial S}{\partial t} &= -\Lambda S \\
\frac{\partial I}{\partial a} + \frac{\partial I}{\partial t} &= \Lambda S - \frac{1}{\varepsilon} I \\
\frac{\partial R}{\partial a} + \frac{\partial R}{\partial t} &= \frac{1}{\varepsilon} I - \frac{\sigma}{2}(\Lambda R - \lambda r) \\
\frac{\partial V}{\partial a} + \frac{\partial V}{\partial t} &= \frac{\sigma}{2}(\Lambda R - \lambda r) - \frac{1}{\varepsilon} V \\
\frac{\partial i}{\partial a} + \frac{\partial i}{\partial t} &= \lambda S - \frac{1}{\varepsilon} i \qquad\qquad 0 \le a \le 1 \\
\frac{\partial r}{\partial a} + \frac{\partial r}{\partial t} &= \frac{1}{\varepsilon} i - \frac{\sigma}{2}(\Lambda r - \lambda R) \\
\frac{\partial v}{\partial a} + \frac{\partial v}{\partial t} &= -\frac{\sigma}{2}(\Lambda r - \lambda R) - \frac{1}{\varepsilon} v \\
\Lambda(t) = \frac{b}{\varepsilon}\int_0^1 (I+V)\,d\alpha \qquad & \lambda(t) = \frac{b}{\varepsilon}\int_0^1 (i+v)\,d\alpha \\
S(0,t) = 1 \qquad & I = R = V = i = r = v(0,t) = 0.
\end{aligned}
\tag{9}
$$

The non-dimensional parameter $b = \beta N D$ gives the number of secondary infections per primary infection if the entire population is susceptible and we neglect death during the infection. Hence $b \approx \mathcal{R} = O(1)$. The ratio between the time scales $\varepsilon = D/A \ll 1$ now appears explicitly.

In order to determine the equilibrium age-distribution and infection rate, we use a modification of the method of Dietz (1975) to obtain an implicit expression for Λ^*, the total force of infection experienced by the population at the endemic equilibrium. Knowing the value of Λ^*, one can easily obtain the steady state age distribution. Possible symmetric steady state age distributions, $(S^*, I^*, R^*, V^*, i^*, r^*, v^*)$, are determined by the steady state for the first 4 variables in (9) since $i^* = r^* = v^* = \lambda^* = 0$ at any symmetric equilibrium. By our assumptions, the force of infection Λ^* is proportional to the total prevalence of the two strains:

$$\Lambda^* = \frac{b}{\varepsilon}\int_0^1 (I^* + V^*)\,d\alpha.$$

After some tedious but uneventful algebra and omitting the $*$, we obtain an implicit expression for Λ:

$$\begin{aligned}\Lambda = &-\frac{b}{\varepsilon}\frac{\frac{\sigma}{2}}{1-\frac{\sigma}{2}}\frac{L(\Lambda)}{1-\varepsilon\Lambda}+\frac{b}{\varepsilon}\frac{1}{1-\frac{\sigma}{2}}\frac{L(\Lambda\frac{\sigma}{2})}{1-\varepsilon\Lambda\frac{\sigma}{2}}+\frac{b}{\varepsilon}L(\Lambda)\\ &+\frac{b}{\varepsilon}\frac{\varepsilon^2\Lambda^2\frac{\sigma}{2}}{(1-\varepsilon\Lambda)(1-\varepsilon\Lambda\frac{\sigma}{2})}\left(\varepsilon-(1+\varepsilon)e^{-1/\varepsilon}\right),\end{aligned} \tag{10}$$

where

$$L(\Lambda)=\frac{\varepsilon\Lambda}{1-\varepsilon\Lambda}\left(\frac{1-e^{-\Lambda}}{\Lambda}-\frac{1-e^{-1/\varepsilon}}{1/\varepsilon}\right).$$

The function $L(\Lambda)$ gives the fraction of the population that is infected at equilibrium if only one strain is present. Equation (10) has a root at $\Lambda = 0$ corresponding to a disease free equilibrium.

Since (10) is linear in b, $b(\Lambda)$ is uniquely determined for each $\Lambda > 0$ and we can use the methods of Andreasen (1990) to study $b(\Lambda)$. The threshold transmission coefficient b_0 is determined by

$$\begin{aligned}1 &= \frac{b_0}{\varepsilon}\lim_{\Lambda\to 0}\left(\frac{\frac{\sigma}{2}}{1-\frac{\sigma}{2}}\frac{L(\Lambda)}{\Lambda(\varepsilon\Lambda-1)}-\frac{\frac{\sigma}{2}}{1-\frac{\sigma}{2}}\frac{L(\Lambda\frac{\sigma}{2})}{\Lambda\frac{\sigma}{2}(\varepsilon\Lambda\frac{\sigma}{2}-1)}+\frac{L(\Lambda)}{\Lambda}\right)\\ &\quad+\frac{b_0}{\varepsilon}\lim_{\Lambda\to 0}\frac{\varepsilon\Lambda\frac{\sigma}{2}}{(\varepsilon\Lambda-1)(\varepsilon\Lambda\frac{\sigma}{2}-1)}\left(1-\varepsilon e^{-1/\varepsilon}(1+\varepsilon)\right)\\ &= \frac{b_0}{\varepsilon}\lim_{\Lambda\to 0}L(\Lambda)/\Lambda.\end{aligned}$$

Thus,

$$b_0=\frac{1}{1-\varepsilon+\varepsilon e^{-1/\varepsilon}},$$

is identical to the threshold for the one strain model obtained by Andreasen (1990).

For $\varepsilon \ll 1$, (10) yields the approximate formula

$$\begin{aligned}\frac{1}{b} =&\frac{1-\sigma}{1-\frac{\sigma}{2}}\frac{1-e^{-\Lambda}}{\Lambda}+\frac{\frac{\sigma}{2}}{1-\frac{\sigma}{2}}\frac{1-e^{-\sigma\Lambda/2}}{\Lambda\frac{\sigma}{2}}\\ &+\frac{(3\frac{\sigma}{2}-1)e^{-\Lambda}-\sigma e^{-\sigma\Lambda/2}}{1-\frac{\sigma}{2}}\varepsilon+O(\varepsilon^2).\end{aligned} \tag{11}$$

It is easy to show that $b(\Lambda)$ in the approximation (11) is a monotonically increasing function, and therefore that for small ε, the model has exactly one symmetric, endemic equilibrium for $b > b_0$.

Since Λ gives the total force of infection, the force of infection for each strain is $\Lambda/2$. Figure 3 shows $b(\Lambda/2)$, giving the relationship between b and the force of infection for *one* of the strains for various values of the cross-immunity coefficient σ. As expected, the force of infection for each strain decreases in the presence of a second strain. Equation (11) and Figure 3 give a one-to-one correspondence between b and Λ; for practical reasons we will regard in the remainder of this paper the model as parameterized by σ, Λ, and ε.

In the special case $\sigma = 1$, model (7) is an age-structured version of Dietz's (1979) model of virus interference, and equation (10) gives the effect of virus interference on infection rate. For

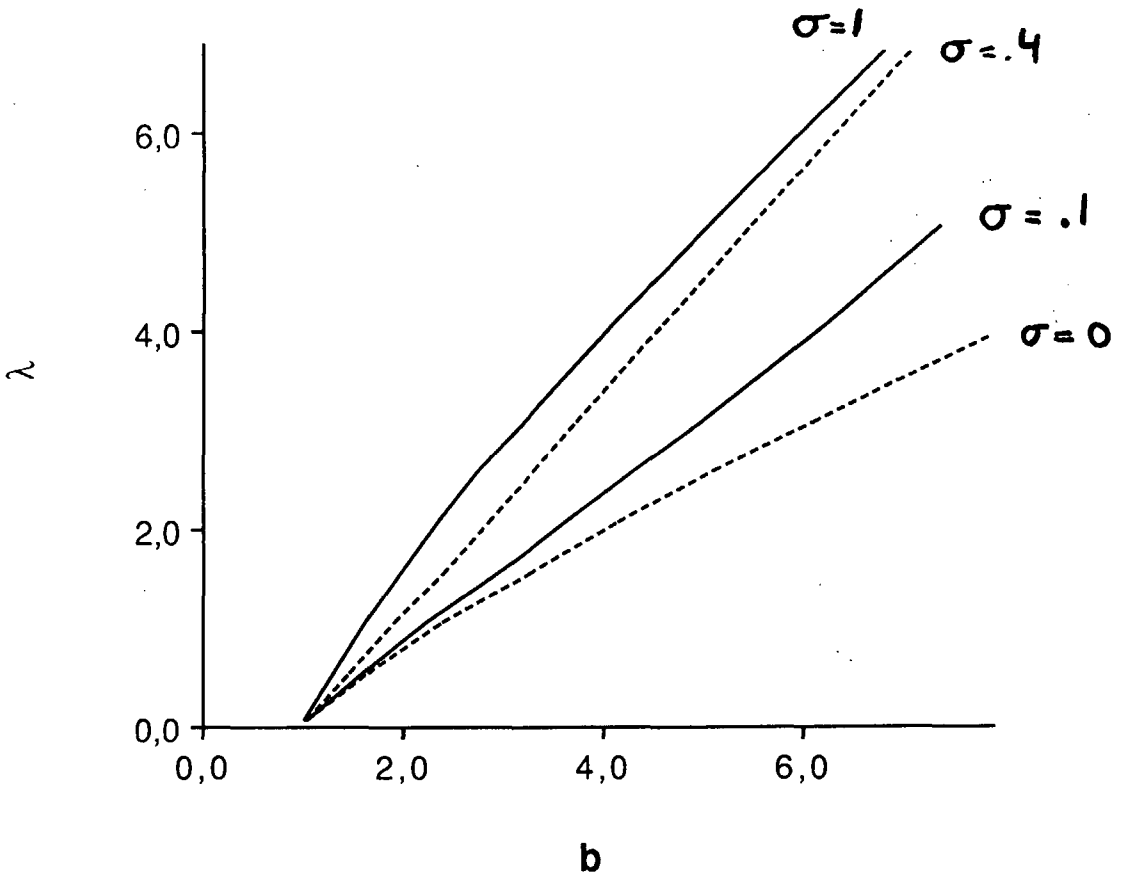

Figure 3. Force of infection λ for one strain as a function of the transmission coefficient b at the endemic equilibrium for various values of the cross-immunity factor σ. Small values of σ correspond to strong cross-reactivity and reduces λ the most. The parameters b and λ are in non-dimensional units, see text.

$\sigma = 1$,the approximation (11) gives the same value of $\Lambda/2$ as the one strain approximation of Andreasen (1990) indicating that virus interference to order $O(\varepsilon)$ has no effect significant on the force of infection. Since virus interference takes place only during infection, we would not expect to see any effect of virus interference under such circumstances.

For $0 < \sigma < 1$, the value of Λ facilitates the computation of the age-dependent attack rates for one strain at the endemic state:

$$\frac{1}{2}(I^* + V^*)(a) = \frac{1}{2}\frac{\varepsilon\Lambda}{1-\varepsilon\Lambda}e^{-a\Lambda} + \frac{1}{2}\frac{\varepsilon\frac{\sigma}{2}\Lambda}{1-\frac{\sigma}{2}}\left[\frac{1}{(1-\varepsilon\frac{\sigma}{2}\Lambda)^2}e^{-a\sigma\Lambda/2} - \frac{1}{(1-\varepsilon\Lambda)^2}e^{-a\Lambda}\right] + ke^{-a/\varepsilon}.$$

In Figure 4, the attack rates are compared to those of one strain in isolation with the same transmission coefficient b and $\varepsilon \ll 1$. The presence of a cross-reacting strain has two effects: first it reduces the force of infection Λ as indicated on Figure 3; second individuals previously recovered from infection with the cross-reacting strain introduce a second cohort of infectious with a longer tail. Therefore a subtype which has circulated for some years — and hence has conferred partial immunity to a portion of the hosts — will tend to be more common among older individuals than is a newly introduced influenza subtype or other viral disease. The shift towards older individuals is most pronounced for intermediate values of the cross-immunity factor σ.

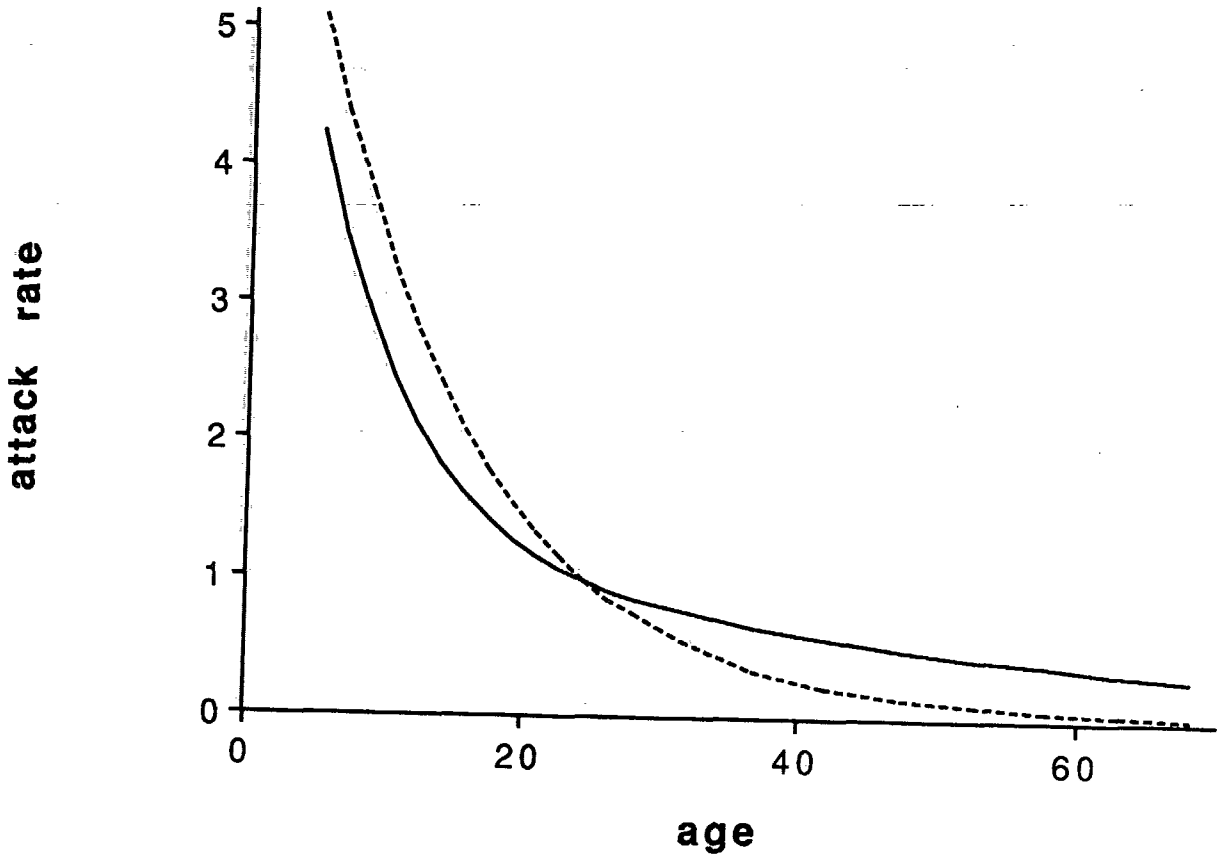

Figure 4. The effect of an antigenically cross-reacting strain on the age-dependent attack rates. The figure shows the percentage of the incidence that occurs in a year-class. The transmission factor b is 6 in non-dimensional units corresponding to a basic reproductive number $\mathcal{R}$ of approximately 6, the cross-immunity factor is $\sigma = 0$ (broken line) and $\sigma = 0.3$ (solid line).

Stability of the two strain model

The stability of the symmetric, endemic equilibrium can be studied by means of separable perturbations of the form $\hat{\mathbf{S}}(a,t) = \mathbf{S}(a)e^{pt}$ etc. where bold face indicates perturbations off the endemic equilibrium age-distributions $(S^*, I^*, R^*, V^*, 0, 0, 0)$ while the perturbations of Λ and λ take the form $\hat{\Theta}(t) = \Theta e^{pt}$ and $\hat{\vartheta}(t) = \vartheta e^{pt}$ respectively.

Since $\lambda^* = r^* = 0$, the system decouples in the same manner as (9) into an $(\mathbf{S}, \mathbf{I}, \mathbf{R}, \mathbf{V}, \Theta)$-block and an $(\mathbf{i}, \mathbf{r}, \mathbf{v}, \vartheta)$-block. Here I focus on the latter block since the simulations of Castillo-Chavez et al. (1989) indicate that I is a constant during the observed oscillations, so that instability in the i-direction is most likely to explain their results.

The $(\mathbf{i}, \mathbf{r}, \mathbf{v}, \vartheta)$-system simplifies to

$$\begin{aligned}
\frac{d\mathbf{i}}{da} &= \vartheta S^* - (\frac{1}{\varepsilon} + p)\mathbf{i} \\
\frac{d\mathbf{r}}{da} &= \frac{1}{\varepsilon}\mathbf{i} + \frac{\sigma}{2}\vartheta R^* - (\frac{\sigma}{2}\Lambda^* + p)\mathbf{r} \\
\frac{d\mathbf{v}}{da} &= -\frac{\sigma}{2}(\Lambda^*\mathbf{r} - \vartheta R^*) - (\frac{1}{\varepsilon} + p)\mathbf{v} \\
\vartheta &= \frac{b}{\varepsilon}\int_0^1 (\mathbf{i} + \mathbf{v})\, d\alpha \\
\mathbf{i}(0) &= \mathbf{r}(0) = \mathbf{v}(0) = 0,
\end{aligned} \tag{12}$$

where Λ^*, S^*, and R^* are solutions to the steady state equations.

Equation (12) can be solved in a two step process since ϑ may be regarded as an (unknown) constant when one is solving the linear differential equations (12). In order that the exponential perturbation be consistent with the linearized equations, the value of ϑ must satisfy $\vartheta = b\int_0^1(\mathbf{i} + \mathbf{v})\, d\alpha$. Since $\mathbf{i}$ and $\mathbf{v}$ are proportional to ϑ, ϑ is a scaling factor and I obtain the stability equation in p:

$$\begin{aligned}
\frac{1}{b} = {} & \frac{p(2 + \varepsilon\frac{\sigma}{2}\Lambda + \varepsilon 2p)}{(1+\varepsilon p)^2(\frac{\sigma}{2}\Lambda + p)\Lambda} - \frac{e^{-\Lambda}}{(1 + \varepsilon p - \varepsilon\Lambda)\Lambda} \\
& + \frac{\frac{\sigma}{2}\Lambda[\frac{\sigma}{2}\Lambda - p + \varepsilon\frac{\sigma}{2}\Lambda(p - \frac{\sigma}{2}\Lambda) + \varepsilon p^2]e^{-\sigma\Lambda/2 - p}}{(1 - \varepsilon\frac{\sigma}{2}\Lambda)^2(\frac{\sigma}{2}\Lambda + p)[p - (1 - \frac{\sigma}{2})\Lambda](1 - \varepsilon\frac{\sigma}{2}\Lambda - \varepsilon p)p} \\
& + \frac{(\frac{\sigma}{2}\Lambda - p)e^{-\sigma\Lambda/2}}{(1 - \frac{\sigma}{2})(1 - \varepsilon\frac{\sigma}{2}\Lambda)(1 + \varepsilon p - \varepsilon\frac{\sigma}{2}\Lambda)\Lambda p} \\
& - \frac{\frac{\sigma}{2}[(\frac{\sigma}{2}\Lambda - p) + \varepsilon(1 - \frac{\sigma}{2})\Lambda^2 - \varepsilon(p - \Lambda)^2]e^{-\Lambda}}{(1 - \varepsilon\Lambda)(1 + \varepsilon p - \varepsilon\Lambda)^2(1 - \frac{\sigma}{2})[p - (1 - \frac{\sigma}{2})\Lambda]\Lambda} \\
& + f_\varepsilon(p)e^{-1/\varepsilon}.
\end{aligned} \tag{13}$$

The function $f_\varepsilon(p)$ has a singularity near $p = -1/\varepsilon$ but when $\varepsilon \ll 1$, this last term will have no influence on the dominant eigenvalues. For the exact form of $f_\varepsilon(p)$, see Andreasen (1988).

To facilitate the analysis, multiply through by the common denominator $p(p + \frac{\sigma}{2}\Lambda)[p - (1\frac{\sigma}{2})\Lambda]$

$$\begin{aligned}
\frac{1}{b}p(p + \frac{\sigma}{2}\Lambda)[p - (1 - \frac{\sigma}{2})\Lambda] = {} & \frac{p^2[p - (1 - \frac{\sigma}{2})\Lambda](2 + \varepsilon\frac{\sigma}{2}\Lambda + \varepsilon 2p)}{(1 + \varepsilon p)^2\Lambda} \\
& - \frac{e^{-\Lambda}p(p + \frac{\sigma}{2}\Lambda)[p - (1 - \frac{\sigma}{2})\Lambda]}{(1 + \varepsilon p - \varepsilon\Lambda)\Lambda} \\
& + \frac{\frac{\sigma}{2}\Lambda[\frac{\sigma}{2}\Lambda - p + \varepsilon\frac{\sigma}{2}\Lambda(p - \frac{\sigma}{2}\Lambda) + \varepsilon p^2]e^{-\sigma\Lambda/2 - p}}{(1 - \varepsilon\frac{\sigma}{2}\Lambda)^2(1 - \varepsilon\frac{\sigma}{2}\Lambda - \varepsilon p)} \\
& + \frac{(\frac{\sigma}{2}\Lambda - p)(p + \frac{\sigma}{2}\Lambda)[p - (1 - \frac{\sigma}{2})\Lambda]e^{-\sigma\Lambda/2}}{(1 - \frac{\sigma}{2})(1 - \varepsilon\frac{\sigma}{2}\Lambda)(1 + \varepsilon p - \varepsilon\frac{\sigma}{2}\Lambda)\Lambda} \\
& - \frac{\frac{\sigma}{2}p(p + \frac{\sigma}{2}\Lambda)[(\frac{\sigma}{2}\Lambda - p) + \varepsilon(1 - \frac{\sigma}{2})\Lambda^2 - \varepsilon(p - \Lambda)^2]e^{-\Lambda}}{(1 - \varepsilon\Lambda)(1 + \varepsilon p - \varepsilon\Lambda)^2(1 - \frac{\sigma}{2})\Lambda} \\
& + \tilde{f}_\varepsilon(p)e^{-1/\varepsilon}.
\end{aligned} \tag{14}$$

The multiplication introduces roots at $p = 0, -\frac{\sigma}{2}\Lambda$, and $(1-\frac{\sigma}{2})\Lambda$ which do not correspond to roots in (13). The order of the roots p are determined by trying roots of the form $|p| \approx c\varepsilon^q$. For $q < -1$, the term p^3/b is unbalanced and for $q = -1$, the p^3-terms are only balanced if $1 + \varepsilon p = 1 + O(\varepsilon)$, so we conclude that $q > -1$ and hence that $|\varepsilon p| \ll 1$.

To simplify the equations further, I expand in powers of ε and replace $1/b$ by the approximation (11). After some involved but trivial algebra, (14) reduces to

$$\begin{aligned} 0 = &\left\{ \frac{\sigma}{2}\psi p^2 + \left[-2(1-\frac{\sigma}{2}) - \frac{1-\sigma}{1-\frac{\sigma}{2}}\frac{\sigma}{2}e^{-\Lambda} + \frac{1-\sigma}{1-\frac{\sigma}{2}}e^{-\sigma\Lambda/2} + e^{-\sigma\Lambda/2-p} \right] \frac{\sigma}{2}\Lambda p \right. \\ &\left. + (\frac{\sigma}{2}\Lambda)^2 e^{-\sigma\Lambda/2}(1-e^{-p}) \right\} \\ &+ \varepsilon \left\{ \frac{\psi}{\Lambda}p^4 + \left[-2 + \frac{\sigma}{2} + (1-\frac{\sigma}{2})e^{-\Lambda} + e^{-\sigma\Lambda/2} \right] p^3 \right\} \\ &+ \varepsilon^2 \{ -\frac{\psi}{\Lambda}p^5 \} + O(\varepsilon p^2) + O(\varepsilon^2 p^4), \end{aligned} \tag{15}$$

where

$$\psi = 2 - \frac{1-\sigma}{1-\frac{\sigma}{2}}e^{-\Lambda} - \frac{1}{1-\frac{\sigma}{2}}e^{-\sigma\Lambda/2}. \tag{16}$$

In the case $\sigma = 0$, the highest order term vanishes, and one expects a degeneracy at this point. Biologically, this is not surprising, since $\sigma = 0$ corresponds to a situation where the virus population is divided into two identical strains with full cross immunity. In this situation co-existence is not possible (Levin and Pimentel, 1981; Anderson and May, 1982a; Bremermann and Thieme, 1989), and the degeneracy is a consequence of the assumption that the two strains be exactly identical.

For $\sigma > 0$, there are two possible types of roots for the stability equation, $|p| \approx 1$, and $p \approx \pm i\sqrt{\sigma\Lambda/(2\varepsilon)}$. In the appendix, I argue that roots with positive real part and large imaginary part can exist only in the region indicated on Figure 5, and I conjecture that such roots occur near the boundary of the region. This indicates the possibility of limit cycles appearing through Hopf bifurcations in the region.

For small values of σ, the two strains are antigenically similar, and the model predicts that the relative abundance of the strains will oscillate with a period of $T = 2\pi\sqrt{D/(\sigma\lambda A)}$ in units of A, where A and D denote the host life span and the duration of the disease respectively, and λ is the force of infection for *one* strain (in non-dimensional units). In dimensional quantities this gives $T \approx 2\pi\sqrt{D/(\sigma\lambda)}$. As the strains become antigenically more dissimilar, the period decreases, and the system eventually becomes stable. When $\sigma = 1$, the model reduces to an age-dependent version of Dietz's (1979) model of virus interference, the dynamics of the two strains are essentially decoupled, and the stability property of the system is the same as for a one strain model, i.e., the system is stable, with an the interepidemic period of $T \approx 2\pi\sqrt{D/\lambda}$.

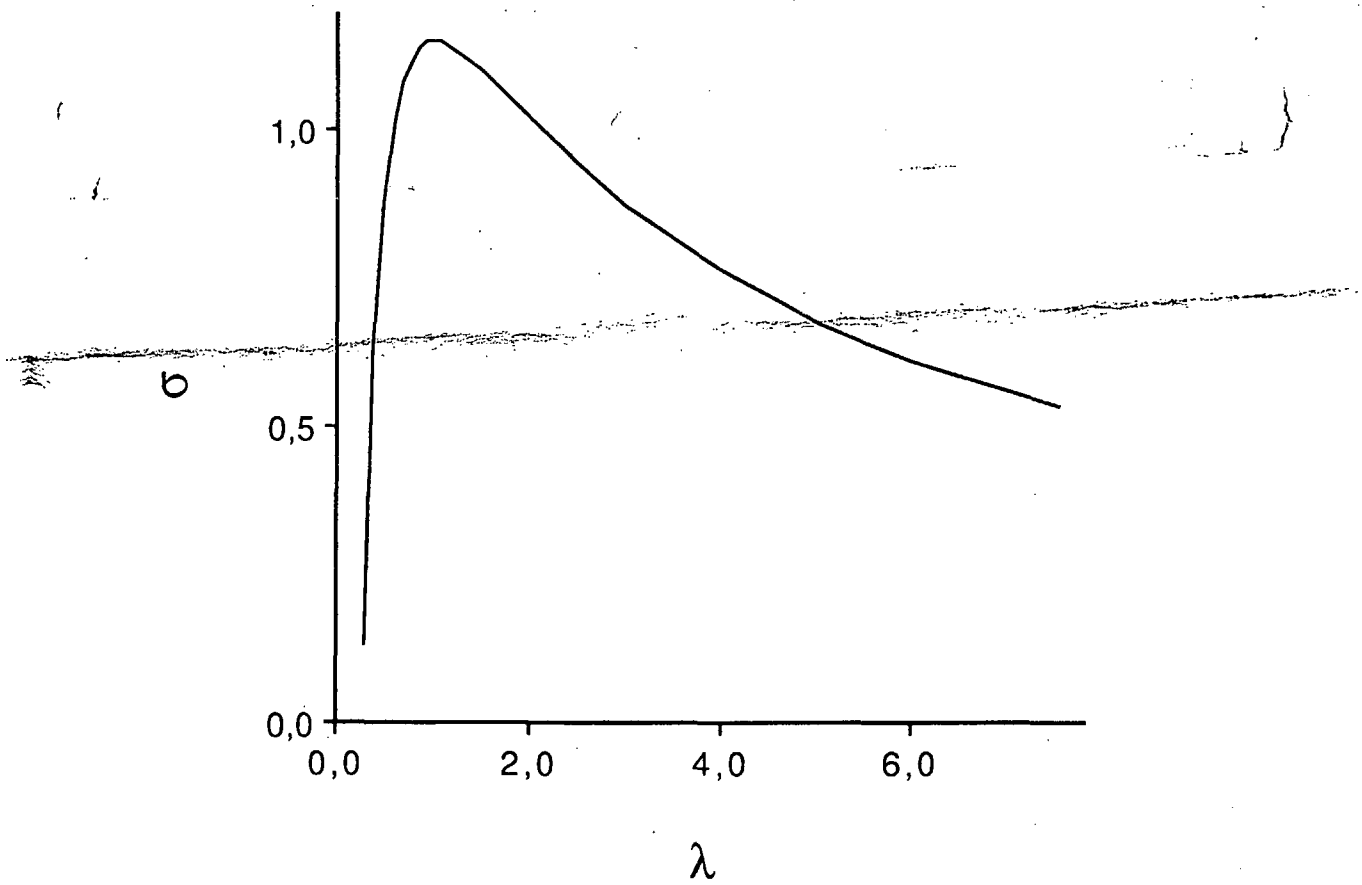

Figure 5. Approximate bifurcation diagram for the two-strain model (7). Purely imaginary roots can occur only below the curve. Numerical solution of the stability equation indicates that there are several curves of purely imaginary eigenvalues in the region. The force of infection λ for one strain at equilibrium is in non-dimensional units, see text.

Conclusion and discussion

The co-circulation of viral strains with antigenic cross-reaction can be described by modified SIR-epidemic models since the number of infected hosts measures the amount of each virus variant present in the population. I model the viral interaction mediated by the immunologic memory of the hosts by assuming that previous infection with a related strain decreases the probability that an individual gets infected when challenged with the new virus. Thus in the model, a few epidemic classes captures the entire immune history of the host population. The simplicity of the approach quickly disappears with the introduction of more interacting strains.

The analysis shows that partial cross-immunity has implications for both the epidemiology and the genetics of the influenza A virus. In the presence of a related strain, the force of infection — i.e. the rate at which individuals get infected — is reduced. A decrease in the force of infection increases the average age at infection (Dietz, 1975). For older individuals who are more likely to have experienced a previous infection with a related strain, the apparent force of infection

Table 2. Dynamical behavior of one-strain and two-strain, symmetric SIR-models under different assumptions about host mortality in the case where both strains can invade. Here D denotes the duration of infections, while λ is the force of infection at for one strain equilibrium. T is the interepidemic period, and $\hat{T}$ is the period between epidemics of a given strain.

	Constant host mortality	Fixed duration of host life span
One strain	Stable, endemic equilibrium Damped oscillations, $T \approx 2\pi\sqrt{D/\lambda}$	Stable, endemic equilibrium. Damped oscillations, $T \approx 2\pi\sqrt{D/\lambda}$
Two strains, partial cross-immunity, σ	Stable, endemic equilibrium with both strains present. $\hat{T} \approx 2\pi\sqrt{D/\sigma\lambda}$	Symmetric, endemic equilibrium. Limit cycles for high levels of cross-immunity. $\hat{T} \approx 2\pi\sqrt{D/\sigma\lambda}$

is further reduced. Thus, the age-dependent attack rate will be more uniform than for other contagious diseases. Chin et al., (1960) observed this trend during two consecutive epidemics of Asian (H2N2) influenza, but a detailed comparison with data would not be meaningful since the effect is confounded by age-dependent contact rates (Longini et al., 1982) and by the significant deviation from the endemic state during epidemics.

Since a new strain usually enters a population in which some individuals are only partially susceptible, the basic reproductive number $\mathcal{R}$, obtained by fitting to a time series will tend to underestimate the true number of "secondary cases per primary case in a fully susceptible population." This fits well with Spicer's (1979) tentative observation that $\mathcal{R}$ for the resident H2N2 subtype gradually declined from 1958 to 1965 while $\mathcal{R}$ for the new H3N2 subtype in 1969–1970 was high. For our understanding of the influenza transmission dynamics during the period between subtype shifts, it may be more useful to introduce a quantity which accounts for the communicability of the disease within a population with a history of previous infections by related strains (Elveback, 1982; Fine 1982b). However, it is not clear that the invasion criterion captures the true complexity of the host population's past exposure to similar variants of influenza A.

Host age-structure interacts with the cross-immunity in an unexpected way. For a model with constant host life-span, analysis of the Lotka-type characteristic equation suggests that for virus with high transmissibility and strong cross-reaction, the incidence of both strains — but not their combined incidence — will oscillate. As shown in Table 2, the oscillations are produced by the synergistic effects of age-dependent mortality and cross-immunity. The oscillations may explain the "herald wave" phenomenon in influenza epidemiology which refers to the observation that next season's viral strain often appear in low prevalence towards the end of the previous epidemic season (Six et al., 1981; Fox et al., 1982; Glezen et al., 1982). The herald wave fits well with the slow build up associated with the model's oscillations. However, the oscillations are predicted solely from a partial mathematical analysis and their possible biological explanation is not clear.

The use of SIR-models provides an epidemiologically justified characterization of the frequency dependent natural selection experienced by the influenza A virus and it allows for a discussion of the haploid genetics of the virus. The persistence of the virus variants is determined by an invasion criterion similar to the one known from competition models and diploid genetics: If one person infected with a new strain can produce more than one secondary infection in a population where the existing strain has already (partially) immunized the hosts, then the new strain will persist. For some parameter values, the two strains will co-exist. Influenza surveillance programs have shown that only one variant circulate in the population with high prevalence at any time and that the emergence of a new strain implies the disappearance of the previous one (Kendal et al., 1979; Thacker, 1986). The invasion criterion shows that the selective advantage of the new strain is not enough to explain the fade out of the old one.

Although the model assumes that both strains continuously circulate in the population, the simultaneous presence need not apply to any given area in any given epidemic season. The virus interact indirectly through the hosts' immune memory, and the "simultaneous presence" therefore applies to the time scale of the host life span. In practice the persistence of a viral strain is affected by the heterogeneity in human contact patterns and by the seasonal variation in disease transmission. While the latter factor decreases the chances for persistence of a rare type, especially for influenza with its short infectious period, heterogeneity may facilitate virus perpetuation (Yorke et al., 1979; Fine, 1982b; Travis and Lenhart, 1987).

In addition to the decrease in susceptibility, a previous infection can reduce the severity of the disease and maybe the transmission potential of the infected person. Where as antibodies to HA help prevent infection of the cell, NA-antibodies reduces the amount of virus synthesized in the cell (Couch and Kassel, 1983). Davies et al. (1984) found that subclinical infections were more common among boys which had previously been infected with a related strain. It is unknown how a cross-reaction which gives rise to as a reduction in transmission potential will affect the co-circulation.

The two-strain interaction model of this paper presents a static picture of influenza virus evolution focusing on the frequency dependent selection mediated by the host population. In the model there is no room for the introduction of new strains through virus drift or shift. Pease (1987) presents the dual picture of influenza evolution where only one strain circulates at any time but where this strain slowly drifts in antigenic type with the new variant instantaneously replacing the previously dominant one in the entire population. Pease' model of "evolutionary epidemics" thus describes the continuous change of the influenza virus but it cannot capture the selective mechanisms responsible for this drift.

One of the unsolved puzzles of influenza genetics concerns this mechanism. Although several strains occur in low numbers in the population, only one strain dominates during an epidemic (Kendal et al., 1979). Why do the other strains not increase in numbers in spite of their selective advantage of having a larger susceptible pool? The interaction between influenza genetics and disease transmission dynamics with partial cross-immunity may provide an answer, but in order to describe the interaction one must in the same model include the virus drift with its creation of multiple strains, the complex serology of a host population exposed to multiple strains, and the disease epidemiology. The combination of Pease' evolutionary epidemiology and the present model of interacting strains will be the topic of a future publication.

Acknowledgements

I gratefuly acknowledge the support of the National Science Foundation through grant BSR-DMS 8406472 and of a MacIntire-Stennis grant NYC-183568 both to S.A. Levin. The final preparation was supported by a grant 11-8296 from the Danish Natural Science Research Council. I thank F. Adler, C. Castillo-Chaves, H. Hethcote, S.A. Levin, and W.-m. Liu for many helpful comments and discussions.

Appendix

Bifurcation condition for the order $\varepsilon^{-1/2}$ eigenvalues

The real part of the root $p = \mathrm{i}\varepsilon^{-1/2}\sqrt{\sigma\Lambda/2} + O(1)$ is determined by the second order terms in (15). We will not give explicit expressions for the real part of p, but show that purely imaginary roots occur on curves lying in a certain region of the (Λ, σ) parameter space.

The approximate location of the purely imaginary roots are determined by by setting $p = \mathrm{i}(y + \omega)$, where $\omega = \varepsilon^{-1/2}\sqrt{\sigma\Lambda/2}$. Retaining only terms of order $\varepsilon^{-1/2}$ (15) reduces to

$$\begin{aligned} 0 =& 2\frac{\sigma}{2}\psi\omega y + \frac{\sigma}{2}\Lambda e^{-\sigma\Lambda/2}\omega\sin(\omega + y) \\ &+ \mathrm{i}\omega\left(-\frac{\sigma}{2}\Lambda - \Lambda(1 - \frac{\sigma}{2})e^{-\Lambda} + \Lambda e^{-\sigma\Lambda/2}\cos(y + \omega)\right), \end{aligned} \tag{17}$$

where ψ is given by (16).

A necessary condition for the existence of roots of (17) is that there exist real solutions to

$$4\psi^2 y^2 = \Lambda^2 e^{-\sigma\Lambda} - [\frac{\sigma}{2} + (1 - \frac{\sigma}{2})e^{-\Lambda}]^2, \tag{18}$$

and hence that

$$\Lambda e^{-\sigma\Lambda/2} > \frac{\sigma}{2} + (1 - \frac{\sigma}{2})e^{-\Lambda}. \tag{19}$$

Figure 5 shows the parameter region where (18) has roots.

The exact location of the purely imaginary roots depend on ω and hence on ε, but numerical solutions with $\varepsilon \ll 1$ indicate that there are several branches of solution curves in the region defined by (19), and that there are solutions close to its boundary, indicating that positive eigenvalues can occur in almost the entire region. Castillo-Chavez et al. (1989) report that a closely related discrete time model has stable limit cycles for some parameter values in this region, confirming that there are eigenvalues with positive real part.

References

Anderson, R.M., and R.M. May. 1982a. Coevolution of hosts and parasites. *Parasitology*, **85**: 411–426.

Anderson, R.M., and R.M. May. 1982b. Directly Transmitted Infectious Diseases: Control by Vaccination. *Science*, **215**: 1053–1060.

Andreasen, V. 1988. *Dynamical models of epidemics in age-structured populations – Analysis and simplification.* Thesis, Cornell University.

Andreasen, V. 1990. Age dependent host mortality in the dynamics of endemic infectious diseases (submitted).

Bailey, N.T.J. 1986. Macro-modelling and prediction of epidemic spread at community level. *Math. modelling*, **7**: 689–717.

Bremermann, H.J., and H.R. Thieme. 1989. A competitive exclusion principle for pathogen virulence. *J. Math. Biol.*, **27**: 179–190.

Busenberg, S., K. Cooke, and M. Iannelli. 1988. Endemic thresholds and stability in a class of age-structured epidemics. *SIAM J. Appl. Math.*, **48**: 1379–1395.

Castillo-Chavez, C., H.W. Hethcote, V. Andreasen, S.A. Levin, and W. Liu. 1988. Cross-immunity in the dynamics of homogeneous and heterogeneous populations. In *Mathematical Ecology,* L. Gross, T.G. Hallam, and S.A. Levin (eds.), pp. 303–316. World Scientific Publishers, Singapore.

Castillo-Chavez, C., H.W. Hethcote, V. Andreasen, S.A. Levin, and W. Liu. 1989. Epidemiological models with age structure, proportionate mixing, and cross-immunity. *J. Math. Biol.*, **27**: 233–258.

Chakraverty, P., P. Cunningham, G.Z. Shen, and M.S. Pereira. 1986. Influenza in the United Kingdom 1982-1985. *J. Hyg., Camb.*, **97**: 347–358.

Chin, T.D.Y., J.F. Foley, I.L. Doto, C.R. Gravelle, and J. Weston. 1960. Morbidity and mortality characteristics of asian strain influenza. *Publ. Hlth. Rep., Wash.*, **75**: 149–158.

Couch, R.B., and J.A. Kasel. 1983. Immunity to influenza in man. *Ann. Rev. Microbiol.*, **37**: 529–549.

Davies, J.R., E.A. Grill, and A.J. Smith. 1984. Influenza A: infection and reinfection. *J. Hyg., Camb.*, **92**: 125–127.

Davies, J.R., E.A. Grill, and A.J. Smith. 1986. Infection with influenza A H1N1. 2. The effect of past experience on natural challenge. *J. Hyg., Camb.*, **96**: 345–352.

Diekmann, O., J.A.P. Heesterbeek, and J.A.J. Metz. 1989. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations (preprint).

Dietz, K. 1975. Transmission and control of arbovirus diseases. In *Epidemiology,* D. Ludwig and K.L. Cooke (Eds.), pp. 104–121. SIAM, Philadelphia.

Dietz, K. 1979. Epidemiologic interference of virus populations. *J. Math. Biol.*, **8**: 291–300.

Dietz, K., and D. Schenzle. 1985. Proportionate mixing models for age-dependent infection transmission. *J. Math. Biol.*, **22**: 117–120.

Dowdle, W.R., M.T. Coleman, and M.B. Gregg. 1974. Natural history of influenza type A in the United States, 1957-1972. *Progr. med. Virol.*, **17**: 91–135.

Dwyer, G., S.A. Levin, and L. Buttel. 1990. A simulation model of the population dynamics and evolution of myxomatosis (manuscript).

Elveback, L.R. 1982. Herd immunity. In *Influenza Models,* P. Selby (ed.), pp. 195–196. MTP Press, Lancaster.

Elveback, L., E. Ackerman, L. Gatewood, and J.P. Fox. 1971. Stochastic two-agent epidemic simulation models for a community of families. *Amer. J. Epidemiol.*, **93**: 267–280.

Fenner, F., and R.N. Ratcliffe. 1965. *Myxomatosis.* Cambridge University Press, London.

Fine, P.E.M. 1982a. Applications of mathematical models to the epidemiology of influenza: a critique. In *Influenza Models,* P. Selby (ed.), pp. 15–85. MTP Press, Lancaster.

Fine, P.E.M. 1982b. Herd immunity. In *Influenza Models,* P. Selby (ed.), pp. 189-194. MTP Press, Lancaster.

Fox, J.P., C.E. Hall, M.K. Cooney, and H.M. Foy. 1982. Influenzavirus infections in Seattle families, 1975-1979. *Amer. J. Epidemiol.*, **116**: 212–227.

Fraenkel-Conrat, H., P.C. Kimbal, and J.A. Levy. 1988. *Virology.* (2.ed) Prentice Hall, Englewood Cliffs.

Gill, P.W., and A.M. Murphy. 1976. Naturally acquired immunity to influenza type A. *Med. J. Aust.*, **2**: 329–333.

Glezen, W.P., R.B. Couch, and H.R. Six. 1982. The influenza herald wave. *Amer. J. Epidemiol.*, **116**: 589–598.

Greenhalgh, D. 1987. Analytical results on the stability of age-structured recurrent epidemic models. *IMA J. Math. Appl. Med. Biol.*, **4**: 109–144.

Hoppensteadt, F.. 1974. An age dependent epidemic model. *J. Franklin Inst.*, **297**: 325–333.

Kendal, A.P., J.M. Joseph, G. Kobayashi, D. Nelson, C.R. Reyes, M.R. Ross, J.L. Sarandria, R. White, D.F. Woodall, G.R. Noble, and W.R. Dowdle. 1979. Laboratory-based surveillance of influenza virus in the United States during the winter of 1977-1978. *Amer. J. Epidemiol.*, **110**: 449–461.

Larson, H.E., D.A.J. Tyrrell, C.H. Bowker, C.W. Potter, and G.C. Schild. 1978. Immunity to challenge in volunteers vaccinated with an inactivated current or earlier strain of influenza A(H3N2). *J. Hyg., Camb.*, **80**: 243–248.

Levin, S.A. 1970. Community equilibria and stability, and an extension of the competitive exclusion principle. *Amer. Nat.*, **104**: 413–423.

Levin, S.A., and D. Pimentel. 1981. Selection of intermediate rates of increase in parasite–host systems. *Amer. Nat.*, **117**: 308–315.

Longini, I.M., J.S. Koopman, A.S. Monto, and J.P. Fox. 1982. Estimating household and community transmission parameters for influenza. *Amer. J. Epidemiol.*, **115**: 736–751.

May, R.M., and R.M. Anderson. 1983. Epidemiology and genetics in the coevolution of parasites and hosts. *Proc. R. Soc. Lond.*, **B219**: 281–313.

Palese, P., and J.F. Young. 1982. Variation of influenza A, B, and C viruses. *Science*, **215**: 1468–1474.

Pease, C.M. 1987. An evolutionary epidemiological mechanism, with applications to type A influenza. *Theor. Popul. Biol.*, **31**: 422–452.

Potter, C.W., R. Jennings, K. Nicholson, D.A.J. Tyrrell, and K.G. Dickson. 1977. Immunity to attenuated influenza virus WRL 105 infection induced by heterologous, inactivated influenza A virus vaccines. *J. Hyg.,Camb.*, **79**: 321–332.

Saunders, I.W. 1981. Epidemics in Competition. *J. Math. Biol.*, **11**: 311–318.

Six, H.R., W.P. Glezen, J.A. Kasel, R.B. Couch, C. Griffis, and R.G. Webster. 1981. Heterogeneity of influenza viruses isolated from the Houston community during defined epidemic periods. In *Genetic Variation Among Influenza Viruses,* D.P. Nayak (ed.), pp. 505–513. Academic Press, New York.

Spicer, C.C. 1979. The mathematical modelling of influenza epidemics. *Brit. Med. Bull.*, **35**: 23–28.

Spicer, C.C., and C.J. Lawrence. 1984. Epidemic influenza in Greater London. *J. Hyg., Camb.*, **93**: 105–112.

Thacker, S.B. 1986. The persistence of influenza A in human populations. *Epidemiol. rev.*, **8**: 129–142.

Travis, C.C., and S.M. Lenhart. 1987. Eradication of infectious diseases in heterogeneous populations. *Math. Biosci.*, **81**: 191–198.

Webster, R.G., W.G. Laver, G.M. Air, and G.C. Schild. 1982. Molecular mechanisms of variation in influenza viruses. *Nature*, **296**: 115–121.

Yorke, J.A., N. Nathanson, G. Pianigiani, and J. Martin. 1979. Seasonality and the requirements for perpetuation and eradication of viruses in populations. *Amer. J. Epidemiol.*, **109**: 103–123.

1/78 "TANKER OM EN PRAKSIS" - et matematikprojekt.
Projektrapport af: Anne Jensen, Lena Lindenskov, Marianne Kesselhahn og Nicolai Lomholt.
Vejleder: Anders Madsen

2/78 "OPTIMERING" - Menneskets forøgede beherskelsesmuligheder af natur og samfund.
Projektrapport af: Tom J. Andersen, Tommy R. Andersen, Gert Krenøe og Peter H. Lassen
Vejleder: Bernhelm Boss.

3/78 "OPGAVESAMLING", breddekursus i fysik.
Af: Lasse Rasmussen, Aage Bonde Kræmmer og Jens Højgaard Jensen.

4/78 "TRE ESSAYS" - om matematikundervisning, matematiklæreruddannelsen og videnskabsrindalismen.
Af: Mogens Niss
Nr. 4 er p.t. udgået.

5/78 "BIBLIOGRAFISK VEJLEDNING til studiet af DEN MODERNE FYSIKS HISTORIE".
Af: Helge Kragh.
Nr. 5 er p.t. udgået.

6/78 "NOGLE ARTIKLER OG DEBATINDLÆG OM - læreruddannelse og undervisning i fysik, og - de naturvidenskabelige fags situation efter studenteroprøret".
Af: Karin Beyer, Jens Højgaard Jensen og Bent C. Jørgensen.

7/78 "MATEMATIKKENS FORHOLD TIL SAMFUNDSØKONOMIEN".
Af: B.V. Gnedenko.
Nr. 7 er udgået.

8/78 "DYNAMIK OG DIAGRAMMER". Introduktion til energy-bond-graph formalismen.
Af: Peder Voetmann Christiansen.

9/78 "OM PRAKSIS' INDFLYDELSE PÅ MATEMATIKKENS UDVIKLING". - Motiver til Kepler's: "Nova Stereometria Doliorum Vinariom".
Projektrapport af: Lasse Rasmussen.
Vejleder: Anders Madsen.

10/79 "TERMODYNAMIK I GYMNASIET".
Projektrapport af: Jan Christensen og Jeanne Mortensen.
Vejledere: Karin Beyer og Peder Voetmann Christiansen.

11/79 "STATISTISKE MATERIALER".
Af: Jørgen Larsen.

12/79 "LINEÆRE DIFFERENTIALLIGNINGER OG DIFFERENTIALLIGNINGSSYSTEMER".
Af: Mogens Brun Heefelt.
Nr. 12 er udgået.

13/79 "CAVENDISH'S FORSØG I GYMNASIET".
Projektrapport af: Gert Kreinøe.
Vejleder: Albert Chr. Paulsen.

14/79 "BOOKS ABOUT MATHEMATICS: History, Philosophy, Education, Models, System Theory, and Works of".
Af: Else Høyrup.
Nr. 14 er p.t. udgået.

15/79 "STRUKTUREL STABILITET OG KATASTROFER i systemer i og udenfor termodynamisk ligevægt".
Specialeopgave af: Leif S. Striegler.
Vejleder: Peder Voetmann Ckristiansen.

16/79 "STATISTIK I KRÆFTFORSKNINGEN".
Projektrapport af: Michael Olsen og Jørn Jensen.
Vejleder: Jørgen Larsen.

17/79 "AT SPØRGE OG AT SVARE i fysikundervisningen".
Af: Albert Christian Paulsen.

18/79 "MATHEMATICS AND THE REAL WORLD", Proceedings af an International Workshop, Roskilde University Centre, Denmark, 1978.
Preprint.
Af: Bernhelm Booss og Mogens Niss (eds.)

19/79 "GEOMETRI, SKOLE OG VIRKELIGHED".
Projektrapport af: Tom J. Andersen, Tommy R. Andersen og Per H.H. Larsen.
Vejleder: Mogens Niss.

20/79 "STATISTISKE MODELLER TIL BESTEMMELSE AF SIKRE DOSER FOR CARCINOGENE STOFFER".
Projektrapport af: Michael Olsen og Jørn Jensen.
Vejleder: Jørgen Larsen

21/79 "KONTROL I GYMNASIET-FORMÅL OG KONSEKVENSER".
Projektrapport af: Crilles Bacher, Per S.Jensen, Preben Jensen og Torben Nysteen.

22/79 "SEMIOTIK OG SYSTEMEGENSKABER (1)".
1-port lineært response og støj i fysikken.
Af: Peder Voetmann Christiansen.

23/79 "ON THE HISTORY AF EARLY WAVE MECHANICS - with special emphasis on the role af realitivity".
Af: Helge Kragh.

24/80 a+b "MATEMATIKOPFATTELSER HOS 2.C'ERE".
1. En analyse. 2. Interviewmateriale.
Projektrapport af: Jan Christensen og Knud Lindhardt Rasmussen.
Vejleder: Mogens Niss.

25/80 "EKSAMENSOPGAVER", Dybdemodulet/fysik 1974-79.

26/80 "OM MATEMATISKE MODELLER".
En projektrapport og to artikler.
Af: Jens Højgaard Jensen m.fl.

27/80 "METHODOLOGY AND PHILOSOPHY AF SCIENCE IN PAUL DIRAC's PHYSICS".
Af: Helge Kragh.

28/80 "DIELEKTRISK RELAXATION - et forslag til en ny model bygget på væskernes viscoelastiske egenskaber".
Projektrapport af: Gert Kreinøe.
Vejleder: Niels Boye Olsen.

29/80 "ODIN - undervisningsmateriale til et kursus i differentialligningsmodeller".
Projektrapport af: Tommy R. Andersen, Per H.H. Larsen og Peter H. Lassen.
Vejleder: Mogens Brun Heefelt.

30/80 "FUSIONSENERGIEN - - - ATOMSAMFUNDETS ENDESTATION".
Af: Oluf Danielsen.
Nr. 30 er udgået.

31/80 "VIDENSKABSTEORETISKE PROBLEMER VED UNDERVISNINGSSYSTEMER BASERET PÅ MÆNGDELÆRE".
Projektrapport af: Troels Lange og Jørgen Karrebæk.
Vejleder: Stig Andur Pedersen.
Nr. 31 er p.t. udgået.

32/80 "POLYMERE STOFFERS VISCOELASTISKE EGENSKABER - BELYST VED HJÆLP AF MEKANISKE IMPEDANSMÅLINGER MÖSSBAUEREFFEKTMÅLINGER".
Projektrapport af: Crilles Bacher og Preben Jensen.
Vejledere: Niels Boye Olsen og Peder Voetmann Christiansen.

33/80 "KONSTITUERING AF FAG INDEN FOR TEKNISK - NATURVIDENSKABELIGE UDDANNELSER. I-II".
Af: Arne Jakobsen.

34/80 "ENVIRONMENTAL IMPACT AF WIND ENERGY UTILIZATION".
ENERGY SERIES NO. I.
Af: Bent Sørensen
Nr. 34 er udgået.

35/80 "HISTORISKE STUDIER I DEN NYERE ATOMFYSIKS UDVIKLING".
Af: Helge Kragh.

36/80 "HVAD ER MENINGEN MED MATEMATIKUNDERVISNINGEN?".
Fire artikler.
Af: Mogens Niss.

37/80 "RENEWABLE ENERGY AND ENERGY STORAGE".
ENERGY SERIES NO. 2.
Af: Bent Sørensen.

38/81 "TIL EN HISTORIETEORI OM NATURERKENDELSE, TEKNOLOGI OG SAMFUND".
Projektrapport af: Erik Gade, Hans Hedal, Henrik Lau og Finn Physant.
Vejledere: Stig Andur Pedersen, Helge Kragh og Ib Thiersen.
Nr. 38 er p.t. udgået.

39/81 "TIL KRITIKKEN AF VÆKSTØKONOMIEN".
Af: Jens Højgaard Jensen.

40/81 "TELEKOMMUNIKATION I DANMARK - oplæg til en teknologivurdering".
Projektrapport af: Arne Jørgensen, Bruno Petersen og Jan Vedde.
Vejleder: Per Nørgaard.

41/81 "PLANNING AND POLICY CONSIDERATIONS RELATED TO THE INTRODUCTION OF RENEWABLE ENERGY SOURCES INTO ENERGY SUPPLY SYSTEMS".
ENERGY SERIES NO. 3.
Af: Bent Sørensen.

42/81 "VIDENSKAB TEORI SAMFUND - En introduktion til materialistiske videnskabsopfattelser".
Af: Helge Kragh og Stig Andur Pedersen.

43/81 1."COMPARATIVE RISK ASSESSMENT OF TOTAL ENERGY SYSTEMS".
2."ADVANTAGES AND DISADVANTAGES OF DECENTRALIZATION".
ENERGY SERIES NO. 4.
Af: Bent Sørensen.

44/81 "HISTORISKE UNDERSØGELSER AF DE EKSPERIMENTELLE FORUDSÆTNINGER FOR RUTHERFORDS ATOMMODEL".
Projektrapport af: Niels Thor Nielsen.
Vejleder: Bent C. Jørgensen.

45/82 Er aldrig udkommet.

46/82 "EKSEMPLARISK UNDERVISNING OG FYSISK ERKENDESE-
1+11 ILLUSTRERET VED TO EKSEMPLER".
Projektrapport af: Torben O.Olsen, Lasse Rasmussen og Niels Dreyer Sørensen.
Vejleder: Bent C. Jørgensen.

47/82 "BARSEBÄCK OG DET VÆRST OFFICIELT-TÆNKELIGE UHELD".
ENERGY SERIES NO. 5.
Af: Bent Sørensen.

48/82 "EN UNDERSØGELSE AF MATEMATIKUNDERVISNINGEN PÅ ADGANGSKURSUS TIL KØBENHAVNS TEKNIKUM".
Projektrapport af: Lis Eilertzen, Jørgen Karrebæk, Troels Lange, Preben Nørregaard, Lissi Pedesen, Laust Rishøj, Lill Røn og Isac Showiki.
Vejleder: Mogens Niss.

49/82 "ANALYSE AF MULTISPEKTRALE SATELLITBILLEDER".
Projektrapport af: Preben Nørregaard.
Vejledere: Jørgen Larsen og Rasmus Ole Rasmussen.

50/82 "HERSLEV - MULIGHEDER FOR VEDVARENDE ENERGI I EN LANDSBY".
ENERGY SERIES NO. 6.
Rapport af: Bent Christensen, Bent Hove Jensen, Dennis B. Møller, Bjarne Laursen, Bjarne Lillethorup og Jacob Mørch Pedersen.
Vejleder: Bent Sørensen.

51/82 "HVAD KAN DER GØRES FOR AT AFHJÆLPE PIGERS BLOKERING OVERFOR MATEMATIK ?"
Projektrapport af: Lis Eilertzen, Lissi Pedersen, Lill Røn og Susanne Stender.

52/82 "DESUSPENSION OF SPLITTING ELLIPTIC SYMBOLS".
Af: Bernhelm Booss og Krzysztof Wojciechowski.

53/82 "THE CONSTITUTION OF SUBJECTS IN ENGINEERING EDUCATION".
Af: Arne Jacobsen og Stig Andur Pedersen.

54/82 "FUTURES RESEARCH" - A Philosophical Analysis of Its Subject-Matter and Methods.
Af: Stig Andur Pedersen og Johannes Witt-Hansen.

55/82 "MATEMATISKE MODELLER" - Litteratur på Roskilde Universitetsbibliotek.
En biografi.
Af: Else Høyrup.

Vedr. tekst nr. 55/82 se også tekst nr. 62/83.

56/82 "EN - TO - MANGE" -
En undersøgelse af matematisk økologi.
Projektrapport af: Troels Lange.
Vejleder: Anders Madsen.

57/83 "ASPECT EKSPERIMENTET"-
Skjulte variable i kvantemekanikken?
Projektrapport af: Tom Juul Andersen.
Vejleder: Peder Voetmann Christiansen.
Nr. 57 er udgået.

58/83 "MATEMATISKE VANDRINGER" - Modelbetragtninger over spredning af dyr mellem småbiotoper i agerlandet.
Projektrapport af: Per Hammershøj Jensen og Lene Vagn Rasmussen.
Vejleder: Jørgen Larsen.

59/83"THE METHODOLOGY OF ENERGY PLANNING".
ENERGY SERIES NO. 7.
Af: Bent Sørensen.

60/83 "MATEMATISK MODEKSPERTISE"- et eksempel.
Projektrapport af: Erik O. Gade, Jørgen Karrebæk og Preben Nørregaard.
Vejleder: Anders Madsen.

61/83 "FYSIKS IDEOLOGISKE FUNKTION, SOM ET EKSEMPEL PÅ EN NATURVIDENSKAB - HISTORISK SET".
Projektrapport af: Annette Post Nielsen.
Vejledere: Jens Høyrup, Jens Højgaard Jensen og Jørgen Vogelius.

62/83 "MATEMATISKE MODELLER" - Litteratur på Roskilde Universitetsbibliotek.
En biografi 2. rev. udgave.
Af: Else Høyrup.

63/83 "CREATING ENERGY FUTURES:A SHORT GUIDE TO ENERGY PLANNING".
ENERGY SERIES No. 8.
Af: David Crossley og Bent Sørensen.

64/83 "VON MATEMATIK UND KRIEG".
Af: Berhelm Booss og Jens Høyrup.

65/83 "ANVENDT MATEMATIK - TEORI ELLER PRAKSIS".
Projektrapport af: Per Hedegård Andersen, Kirsten Habekost, Carsten Holst-Jensen, Annelise von Moos, Else Marie Pedersen og Erling Møller Pedersen.
Vejledere: Bernhelm Booss og Klaus Grünbaum.

66/83 "MATEMATISKE MODELLER FOR PERIODISK SELEKTION I ESCHERICHIA COLI".
Projektrapport af: Hanne Lisbet Andersen, Ole Richard Jensen og Klavs Frisdahl.
Vejledere: Jørgen Larsen og Anders Hede Madsen.

67/83 "ELEPSOIDE METODEN - EN NY METODE TIL LINEÆR PROGRAMMERING?"
Projektrapport af: Lone Biilmann og Lars Boye.
Vejleder: Mogens Brun Heefelt.

68/83 "STOKASTISKE MODELLER I POPULATIONSGENETIK"
- til kritikken af teoriladede modeller.
Projektrapport af: Lise Odgård Gade, Susanne Hansen, Michael Hviid og Frank Mølgård Olsen.
Vejleder: Jørgen Larsen.

69/83 "ELEVFORUDSÆTNINGER I FYSIK"
- en test i 1.g med kommentarer.
Af: Albert C. Paulsen.

70/83 "INDLÆRINGS - OG FORMIDLINGSPROBLEMER I MATEMATIK PÅ VOKSENUNDERVISNINGSNIVEAU".
Projektrapport af: Hanne Lisbet Andersen, Torben J. Andreasen, Svend Åge Houmann, Helle Glerup Jensen, Keld Fl. Nielsen, Lene Vagn Rasmussen.
Vejleder: Klaus Grünbaum og Anders Hede Madsen.

71/83 "PIGER OG FYSIK"
- et problem og en udfordring for skolen?
Af: Karin Beyer, Sussanne Blegaa, Birthe Olsen, Jette Reich og Mette Vedelsby.

72/83 "VERDEN IFØLGE PEIRCE" - to metafysiske essays, om og af C.S Peirce.
Af: Peder Voetmann Christiansen.

73/83 ""EN ENERGIANALYSE AF LANDBRUG"
- økologisk contra traditionelt.
ENERGY SERIES NO. 9
Specialeopgave i fysik af: Bent Hove Jensen.
Vejleder: Bent Sørensen.

74/84 "MINIATURISERING AF MIKROELEKTRONIK" - om videnskabeliggjort teknologi og nytten af at lære fysik.
Projektrapport af: Bodil Harder og Linda Szkotak Jensen.
Vejledere: Jens Højgaard Jensen og Bent C. Jørgensen.

75/84 "MATEMATIKUNDERVISNINGEN I FREMTIDENS GYMNASIUM"
- Case: Lineær programmering.
Projektrapport af: Morten Blomhøj, Klavs Frisdahl og Frank Mølgaard Olsen.
Vejledere: Mogens Brun Heefelt og Jens Bjørneboe.

76/84 "KERNEKRAFT I DANMARK?" - Et høringssvar indkaldt af miljøministeriet, med kritik af miljøstyrelsens rapporter af 15. marts 1984.
ENERGY SERIES No. 10
Af: Niels Boye Olsen og Bent Sørensen.

77/84 "POLITISKE INDEKS - FUP ELLER FAKTA?"
Opinionsundersøgelser belyst ved statistiske modeller.
Projektrapport af: Svend Åge Houmann, Keld Nielsen og Susanne Stender.
Vejledere: Jørgen Larsen og Jens Bjørneboe.

78/84 "JÆVNSTRØMSLEDNINGSEVNE OG GITTERSTRUKTUT I AMORFT GERMANIUM".
Specialrapport af: Hans Hedal, Frank C. Ludvigsen og Finn C. Physant.
Vejleder: Niels Boye Olsen.

79/84 "MATEMATIK OG ALMENDANNELSE".
Projektrapport af: Henrik Coster, Mikael Wennerberg Johansen, Povl Kattler, Birgitte Lydholm og Morten Overgaard Nielsen.
Vejleder: Bernhelm Booss.

80/84 "KURSUSMATERIALE TIL MATEMATIK B".
Af: Mogens Brun Heefelt.

81/84 "FREKVENSAFHÆNGIG LEDNINGSEVNE I AMORFT GERMANIUM".
Specialerapport af: Jørgen Wind Petersen og Jan Christensen.
Vejleder: Niels Boye Olsen.

82/84 "MATEMATIK - OG FYSIKUNDERVISNINGEN I DET AUTOMATISEREDE SAMFUND".
Rapport fra et seminar afholdt i Hvidovre 25-27 april 1983.
Red.: Jens Højgaard Jensen, Bent C. Jørgensen og Mogens Niss.

83/84 "ON THE QUANTIFICATION OF SECURITY":
PEACE RESEARCH SERIES NO. 1
Af: Bent Sørensen
nr. 83 er p.t. udgået

84/84 "NOGLE ARTIKLER OM MATEMATIK, FYSIK OG ALMENDANNELSE".
Af: Jens Højgaard Jensen, Mogens Niss m. fl.

85/84 "CENTRIFUGALREGULATORER OG MATEMATIK".
Specialerapport af: Per Hedegård Andersen, Carsten Holst-Jensen, Else Marie Pedersen og Erling Møller Pedersen.
Vejleder: Stig Andur Pedersen.

86/84 "SECURITY IMPLICATIONS OF ALTERNATIVE DEFENSE OPTIONS FOR WESTERN EUROPE".
PEACE RESEARCH SERIES NO. 2
Af: Bent Sørensen.

87/84 "A SIMPLE MODEL OF AC HOPPING CONDUCTIVITY IN DISORDERED SOLIDS".
Af: Jeppe C. Dyre.

88/84 "RISE, FALL AND RESURRECTION OF INFINITESIMALS".
Af: Detlef Laugwitz.

89/84 "FJERNVARMEOPTIMERING".
Af: Bjarne Lillethorup og Jacob Mørch Pedersen.

90/84 "ENERGI I 1.G - EN TEORI FOR TILRETTELÆGGELSE".
Af: Albert Chr. Paulsen.

91/85 "KVANTETEORI FOR GYMNASIET".
1. Lærervejledning
Projektrapport af: Biger Lundgren, Henning Sten Hansen og John Johansson.
Vejleder: Torsten Meyer.

92/85 "KVANTETEORI FOR GYMNASIET".
2. Materiale
Projektrapport af: Biger Lundgren, Henning Sten Hansen og John Johansson.
Vejleder: Torsten Meyer.

93/85 "THE SEMIOTICS OF QUANTUM - NON - LOCALITY".
Af: Peder Voetmann Christiansen.

94/85 "TREENIGHEDEN BOURBAKI - generalen, matematikeren og ånden".
Projektrapport af: Morten Blomhøj, Klavs Frisdahl og Frank M. Olsen.
Vejleder: Mogens Niss.

95/85 "AN ALTERNATIV DEFENSE PLAN FOR WESTERN EUROPE".
PEACE RESEARCH SERIES NO. 3
Af: Bent Sørensen

96/85 "ASPEKTER VED KRAFTVARMEFORSYNING".
Af: Bjarne Lilletorup.
Vejleder: Bent Sørensen.

97/85 "ON THE PHYSICS OF A.C. HOPPING CONDUCTIVITY".
Af: Jeppe C. Dyre.

98/85 "VALGMULIGHEDER I INFORMATIONSALDEREN".
Af: Bent Sørensen.

99/85 "Der er langt fra Q til R".
Projektrapport af: Niels Jørgensen og Mikael Klintorp.
Vejleder: Stig Andur Pedersen.

100/85 "TALSYSTEMETS OPBYGNING".
Af: Mogens Niss.

101/85 "EXTENDED MOMENTUM THEORY FOR WINDMILLS IN PERTURBATIVE FORM".
Af: Ganesh Sengupta.

102/85 OPSTILLING OG ANALYSE AF MATEMATISKE MODELLER, BELYST VED MODELLER OVER KØERS FODEROPTAGELSE OG - OMSÆTNING".
Projektrapport af: Lis Eilertzen, Kirsten Habekost, Lill Røn og Susanne Stender.
Vejleder: Klaus Grünbaum.

103/85 "ØDSLE KOLDKRIGERE OG VIDENSKABENS LYSE IDEER".
Projektrapport af: Niels Ole Dam og Kurt Jensen.
Vejleder: Bent Sørensen.

104/85 "ANALOGREGNEMASKINEN OG LORENZLIGNINGER".
Af: Jens Jæger.

105/85 "THE FREQUENCY DEPENDENCE OF THE SPECIFIC HEAT AF THE GLASS REANSITION".
Af: Tage Christensen.

"A SIMPLE MODEL AF AC HOPPING CONDUCTIVITY".
Af: Jeppe C. Dyre.
Contributions to the Third International Conference on the Structure of Non - Crystalline Materials held in Grenoble July 1985.

106/85 "QUANTUM THEORY OF EXTENDED PARTICLES".
Af: Bent Sørensen.

107/85 "EN MYG GØR INGEN EPIDEMI".
- flodblindhed som eksempel på matematisk modellering af et epidemiologisk problem.
Projektrapport af: Per Hedegård Andersen, Lars Boye, CarstenHolst Jensen, Else Marie Pedersen og Erling Møller Pedersen.
Vejleder: Jesper Larsen.

108/85 "APPLICATIONS AND MODELLING IN THE MATEMATICS CURRICULUM" - state and trends -
Af: Mogens Niss.

109/85 "COX I STUDIETIDEN" - Cox's regressionsmodel anvendt på studenteroplysninger fra RUC.
Projektrapport af: Mikael Wennerberg Johansen, Poul Kattler og Torben J. Andreasen.
Vejleder: Jørgen Larsen.

110/85 "PLANNING FOR SECURITY".
Af: Bent Sørensen

111/85 JORDEN RUNDT PÅ FLADE KORT".
Projektrapport af: Birgit Andresen, Beatriz Quinones og Jimmy Staal.
Vejleder: Mogens Niss.

112/85 "VIDENSKABELIGGØRELSE AF DANSK TEKNOLOGISK INNOVATION FREM TIL 1950 - BELYST VED EKSEMPLER".
Projektrapport af: Erik Odgaard Gade, Hans Hedal, Frank C. Ludvigsen, Annette Post Nielsen og Finn Physant.
Vejleder: Claus Bryld og Bent C. Jørgensen.

113/85 "DESUSPENSION OF SPLITTING ELLIPTIC SYMBOLS II".
Af: Bernhelm Booss og Krzysztof Wojciechowski.

114/85 "ANVENDELSE AF GRAFISKE METODER TIL ANALYSE AF KONTIGENSTABELLER".
Projektrapport af: Lone Biilmann, Ole R. Jensen og Anne-Lise von Moos.
Vejleder: Jørgen Larsen.

115/85 "MATEMATIKKENS UDVIKLING OP TIL RENÆSSANCEN".
Af: Mogens Niss.

116/85 "A PHENOMENOLOGICAL MODEL FOR THE MEYER-NELDEL RULE".
Af: Jeppe C. Dyre.

117/85 "KRAFT & FJERNVARMEOPTIMERING"
Af: Jacob Mørch Pedersen.
Vejleder: Bent Sørensen

118/85 "TILFÆLDIGHEDEN OG NØDVENDIGHEDEN IFØLGE PEIRCE OG FYSIKKEN".
Af: Peder Voetmann Christiansen

119/86 "DET ER GANSKE VIST - - EUKLIDS FEMTE POSTULAT KUNNE NOK SKABE RØRE I ANDEDAMMEN".
Af: Iben Maj Christiansen
Vejleder: Mogens Niss.

120/86 "ET ANTAL STATISTISKE STANDARDMODELLER".
Af: Jørgen Larsen

121/86 "SIMULATION I KONTINUERT TID".
Af: Peder Voetmann Christiansen.

122/86 "ON THE MECHANISM OF GLASS IONIC CONDUCTIVITY".
Af: Jeppe C. Dyre.

123/86 "GYMNASIEFYSIKKEN OG DEN STORE VERDEN".
Fysiklærerforeningen, IMFUFA, RUC.

124/86 "OPGAVESAMLING I MATEMATIK".
Samtlige opgaver stillet i tiden 1974-jan. 1986.

125/86 "UVBY,β - systemet - en effektiv fotometrisk spektralklassifikation af B-,A- og F-stjerner".
Projektrapport af: Birger Lundgren.

126/86 "OM UDVIKLINGEN AF DEN SPECIELLE RELATIVITETSTEORI".
Projektrapport af: Lise Odgaard & Linda Szkotak Jensen
Vejledere: Karin Beyer & Stig Andur Pedersen.

127/86 "GALOIS' BIDRAG TIL UDVIKLINGEN AF DEN ABSTRAKTE ALGEBRA".
Projektrapport af: Pernille Sand, Heine Larsen & Lars Frandsen.
Vejleder: Mogens Niss.

128/86 "SMÅKRYB" - om ikke-standard analyse.
Projektrapport af: Niels Jørgensen & Mikael Klintorp.
Vejleder: Jeppe Dyre.

129/86 "PHYSICS IN SOCIETY"
Lecture Notes 1983 (1986)
Af: Bent Sørensen

130/86 "Studies in Wind Power"
Af: Bent Sørensen

131/86 "FYSIK OG SAMFUND" - Et integreret fysik/historieprojekt om naturanskuelsens historiske udvikling og dens samfundsmæssige betingethed.
Projektrapport af: Jakob Heckscher, Søren Brønd, Andy Wierød.
Vejledere: Jens Høyrup, Jørgen Vogelius, Jens Højgaard Jensen.

132/86 "FYSIK OG DANNELSE"
Projektrapport af: Søren Brønd, Andy Wierød.
Vejledere: Karin Beyer, Jørgen Vogelius.

133/86 "CHERNOBYL ACCIDENT: ASSESSING THE DATA.
ENERGY SERIES NO. 15.
AF: Bent Sørensen.

134/87 "THE D.C. AND THE A.C. ELECTRICAL TRANSPORT IN AsSeTe SYSTEM"
Authors: M.B.El-Den, N.B.Olsen, Ib Høst Pedersen, Petr Viščor

135/87 "INTUITIONISTISK MATEMATIKS METODER OG ERKENDELSESTEORETISKE FORUDSÆTNINGER"
MASTEMATIKSPECIALE: Claus Larsen
Vejledere: Anton Jensen og Stig Andur Pedersen

136/87 "Mystisk og naturlig filosofi: En skitse af kristendommens første og andet møde med græsk filosofi"
Projektrapport af Frank Colding Ludvigsen
Vejledere: Historie: Ib Thiersen
Fysik: Jens Højgaard Jensen

137/87 "HOPMODELLER FOR ELEKTRISK LEDNING I UORDNEDE FASTE STOFFER" - Resume af licentiatafhandling
Af: Jeppe Dyre
Vejledere: Niels Boye Olsen og Peder Voetmann Christiansen.

138/87 "JOSEPHSON EFFECT AND CIRCLE MAP."

Paper presented at The International Workshop on Teaching Nonlinear Phenomena at Universities and Schools, "Chaos in Education". Balaton, Hungary, 26 April-2 May 1987.

By: Peder Voetmann Christiansen

139/87 "Machbarkeit nichtbeherrschbarer Technik durch Fortschritte in der Erkennbarkeit der Natur"

Af: Bernhelm Booss-Bavnbek
Martin Bohle-Carbonell

140/87 "ON THE TOPOLOGY OF SPACES OF HOLOMORPHIC MAPS"

By: Jens Gravesen

141/87 "RADIOMETERS UDVIKLING AF BLODGASAPPARATUR - ET TEKNOLOGIHISTORISK PROJEKT"

Projektrapport af Finn C. Physant

Vejleder: Ib Thiersen

142/87 "The Calderón Projektor for Operators With Splitting Elliptic Symbols"

by: Bernhelm Booss-Bavnbek og
Krzysztof P. Wojciechowski

143/87 "Kursusmateriale til Matematik på NAT-BAS"

af: Mogens Brun Heefelt

144/87 "Context and Non-Locality - A Peircan Approach

Paper presented at the Symposium on the Foundations of Modern Physics The Copenhagen Interpretation 60 Years after the Como Lecture. Joensuu, Finland, 6 - 8 august 1987.

By: Peder Voetmann Christiansen

145/87 "AIMS AND SCOPE OF APPLICATIONS AND MODELLING IN MATHEMATICS CURRICULA"

Manuscript of a plenary lecture delivered at ICMTA 3, Kassel, FRG 8.-11.9.1987

By: Mogens Niss

146/87 "BESTEMMELSE AF BULKRESISTIVITETEN I SILICIUM"

- en ny frekvensbaseret målemetode.

Fysikspeciale af Jan Vedde

Vejledere: Niels Boye Olsen & Petr Viščor

147/87 "Rapport om BIS på NAT-BAS"

redigeret af: Mogens Brun Heefelt

148/87 "Naturvidenskabsundervisning med Samfundsperspektiv"

af: Peter Colding-Jørgensen DLH
Albert Chr. Paulsen

149/87 "In-Situ Measurements of the density of amorphous germanium prepared in ultra high vacuum"

by: Petr Viščor

150/87 "Structure and the Existence of the first sharp diffraction peak in amorphous germanium prepared in UHV and measured in-situ"

by: Petr Viščor

151/87 "DYNAMISK PROGRAMMERING"

Matematikprojekt af:
Birgit Andresen, Keld Nielsen og Jimmy Staal

Vejleder: Mogens Niss

152/87 "PSEUDO-DIFFERENTIAL PROJECTIONS AND THE TOPOLOGY OF CERTAIN SPACES OF ELLIPTIC BOUNDARY VALUE PROBLEMS"

by: Bernhelm Booss-Bavnbek
Krzysztof P. Wojciechowski

153/88 "HALVLEDERTEKNOLOGIENS UDVIKLING MELLEM MILITÆRE OG CIVILE KRÆFTER"

Et eksempel på humanistisk teknologihistorie
Historiespeciale

Af: Hans Hedal

Vejleder: Ib Thiersen

154/88 "MASTER EQUATION APPROACH TO VISCOUS LIQUIDS AND THE GLASS TRANSITION"

By: Jeppe Dyre

155/88 "A NOTE ON THE ACTION OF THE POISSON SOLUTION OPERATOR TO THE DIRICHLET PROBLEM FOR A FORMALLY SELFADJOINT DIFFERENTIAL OPERATOR"

by: Michael Pedersen

156/88 "THE RANDOM FREE ENERGY BARRIER MODEL FOR AC CONDUCTION IN DISORDERED SOLIDS"

by: Jeppe C. Dyre

157/88 " STABILIZATION OF PARTIAL DIFFERENTIAL EQUATIONS BY FINITE DIMENSIONAL BOUNDARY FEEDBACK CONTROL: A pseudo-differential approach."

by: Michael Pedersen

158/88 "UNIFIED FORMALISM FOR EXCESS CURRENT NOISE IN RANDOM WALK MODELS"

by: Jeppe Dyre

159/88 "STUDIES IN SOLAR ENERGY"

by: Bent Sørensen

160/88 "LOOP GROUPS AND INSTANTONS IN DIMENSION TWO"

by: Jens Gravesen

161/88 "PSEUDO-DIFFERENTIAL PERTURBATIONS AND STABILIZATION OF DISTRIBUTED PARAMETER SYSTEMS:

Dirichlet feedback control problems"

by: Michael Pedersen

162/88 "PIGER & FYSIK - OG MEGET MERE"

AF: Karin Beyer, Sussanne Blegaa, Birthe Olsen,
Jette Reich , Mette Vedelsby

163/88 "EN MATEMATISK MODEL TIL BESTEMMELSE AF PERMEABILITETEN FOR BLOD-NETHINDE-BARRIEREN"

Af: Finn Langberg, Michael Jarden, Lars Frellesen

Vejleder: Jesper Larsen

164/88 "Vurdering af matematisk teknologi
Technology Assessment
Technikfolgenabschätzung"

Af: Bernhelm Booss-Bavnbek, Glen Pate med
Martin Bohle-Carbonell og Jens Højgaard Jensen

165/88 "COMPLEX STRUCTURES IN THE NASH-MOSER CATEGORY"

by: Jens Gravesen

166/88 "Grundbegreber i Sandsynligheds-regningen"

Af: Jørgen Larsen

167a/88 "BASISSTATISTIK 1. Diskrete modeller"

Af: Jørgen Larsen

167b/88 "BASISSTATISTIK 2. Kontinuerte modeller"

Af: Jørgen Larsen

168/88 "OVERFLADEN AF PLANETEN MARS"
Laboratorie-simulering og MARS-analoger undersøgt ved Mössbauerspektroskopi.

Fysikspeciale af:

Birger Lundgren

Vejleder: Jens Martin Knudsen
Fys.Lab./HCØ

169/88 "CHARLES S. PEIRCE: MURSTEN OG MØRTEL TIL EN METAFYSIK."

Fem artikler fra tidsskriftet "The Monist" 1891-93.

Introduktion og oversættelse:

Peder Voetmann Christiansen

170/88 "OPGAVESAMLING I MATEMATIK"

Samtlige opgaver stillet i tiden 1974 - juni 1988

171/88 "The Dirac Equation with Light-Cone Data"

af: Johnny Tom Ottesen

172/88 "FYSIK OG VIRKELIGHED"

Kvantemekanikkens grundlagsproblem i gymnasiet.

Fysikprojekt af:

Erik Lund og Kurt Jensen

Vejledere: Albert Chr. Paulsen og Peder Voetmann Christiansen

---

173/89 "NUMERISKE ALGORITMER"

af: Mogens Brun Heefelt

174/89 " GRAFISK FREMSTILLING AF FRAKTALER OG KAOS"

af: Peder Voetmann Christiansen

175/89 " AN ELEMENTARY ANALYSIS OF THE TIME DEPENDENT SPECTRUM OF THE NON-STATONARY SOLUTION TO THE OPERATOR RICCATI EQUATION

af: Michael Pedersen

176/89 " A MAXIUM ENTROPY ANSATZ FOR NONLINEAR RESPONSE THEORY"

af : Jeppe Dyre

177/89 "HVAD SKAL ADAM STÅ MODEL TIL"

af: Morten Andersen, Ulla Engström, Thomas Gravesen, Nanna Lund, Pia Madsen, Dina Rawat, Peter Torstensen

Vejleder: Mogens Brun Heefelt

178/89 "BIOSYNTESEN AF PENICILLIN - en matematisk model"

af: Ulla Eghave Rasmussen, Hans Oxvang Mortensen, Michael Jarden

vejleder i matematik: Jesper Larsen
biologi: Erling Lauridsen

179a/89 "LÆRERVEJLEDNING M.M. til et eksperimentelt forløb om kaos"

af: Andy Wierød, Søren Brønd og Jimmy Staal

Vejledere: Peder Voetmann Christiansen
Karin Beyer

179b/89 "ELEVHÆFTE: Noter til et eksperimentelt kursus om kaos"

af: Andy Wierød, Søren Brønd og Jimmy Staal

Vejledere: Peder Voetmann Christiansen
Karin Beyer

180/89 "KAOS I FYSISKE SYSTEMER eksemplificeret ved torsions- og dobbeltpendul".

af: Andy Wierød, Søren Brønd og Jimmy Staal

181/89 "A ZERO-PARAMETER CONSTITUTIVE RELATION FOR PURE SHEAR VISCOELASTICITY"

by: Jeppe Dyre

183/89 "MATEMATICAL PROBLEM SOLVING, MODELLING. APPLICATIONS AND LINKS TO OTHER SUBJECTS - State. trends and issues in mathematics instruction

by: WERNER BLUM, Kassel (FRG) og
MOGENS NISS, Roskilde (Denmark)

184/89 "En metode til bestemmelse af den frekvensafhængige varmefylde af en underafkølet væske ved glasovergangen"

af: Tage Emil Christensen

185/90 "EN NÆSTEN PERIODISK HISTORIE"
Et matematisk projekt
af: Steen Grode og Thomas Jessen
Vejleder: Jacob Jacobsen

186/90 "RITUAL OG RATIONALITET i videnskabers udvikling"
redigeret af Arne Jakobsen og Stig Andur Pedersen

187/90 "RSA - et kryptisk system"
af: Annemette Sofie Olufsen, Lars Frellesen og Ole Møller Nielsen

Vejledere: Michael Pedersen og Finn Munk

188/90 "FERMICONDENSATION - AN ALMOST IDEAL GLASS TRANSITION"
by: Jeppe Dyre

189/90 "DATAMATER I MATEMATIKUNDERVISNINGEN PÅ GYMNASIET OG HØJERE LÆREANSTALTER

af: Finn Langberg

190/90 "FIVE REQUIREMENTS FOR AN APPROXIMATE NONLINEAR RESPONSE THEORY"

by: Jeppe Dyre

191/90 "MOORE COHOMOLOGY, PRINCIPAL BUNDLES AND ACTIONS OF GROUPS ON C*-ALGEBRAS"

by: Iain Raeburn and Dana P. Williams