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# Epidemiologic Interference of Virus Populations*

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**Summary.** There are a few simulation studies for interference models in the literature but the present paper discusses an analytical model for the competition of two interfering virus populations in a community. The mathematical model consist of eight coupled differential equations which have up to four equilibrium points. Criteria for local stability are given.

**Key words:** Epidemiology — Virus epidemic — Virus interference.

## Introduction

The present paper was stimulated by the following articles: Elveback et al. (1964) extended the classical Reed–Frost model in order to investigate the effects of virus interference on the transmission and the size of epidemics. In the following this extension will be called Model II, as it is customary in the literature (see Bailey, 1975, page 346). A practical application of this interference phenomenon would be, e.g., the prevention of a Coxsackie B virus epidemic (against which there is no specific vaccine) by a vaccination campaign using polio life vaccine. The spreading of this vaccine by vaccination or by contact with vaccinated individuals could lower the susceptibility for the Coxsackie virus temporarily, and therefore slow down or prevent its transmission (Elveback et al., 1968, 1971). In order to study this question, numerous simulation studies have been performed. While Elveback and her coauthors are interested in the application of the interference phenomenon to the control of epidemics, Bang (1975) would like to interpret a series of epidemiologic observations from South-East Asia as a consequence of virus interference: 1. Several adenoviruses show a heterogeneous spatial distribution. E.g. type 1 could be demonstrated for 15 months at one end of a village, whereas type 2 predominated at the other end. In the center of the village, both types coexisted.

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2. Within a population, the epidemic appearance of one virus may suppress temporarily other types. 3. With respect to an individual, the appearance of a given virus infection and the resulting immunity may be delayed by interference with other viruses. This delay may lead, however, to an increase in disease prevalence, since the probability of developing the disease increases with age for many virus infections. Bang indicates that the minimum size of a population in which the virus can maintain itself as an endemic is reduced by the interference phenomenon.

In the present paper we consider a model which allows to explore some of these hypotheses. To this purpose we supply Model II of Elveback et al. (1964) with a continuous time parameter in order to apply the qualitative methods of differential equations.

## Description of the Model

For simplicity we use in Table 1 the same notation of the states as Elveback et al. (1964). The relations between the states is shown in Figure 1.

**Table 1**

| No. of the state | Description of the state |
|---|---|
| 1 | Susceptible to $A$ and $B$ |
| 2 | Susceptible to $A$, immune to $B$ |
| 3 | Susceptible to $B$, immune to $A$ |
| 4 | Immune to $A$ and $B$ |
| 5 | Infective to $A$, temporarily insusceptible to $B$ |
| 6 | Infective to $A$, immune to $B$ |
| 7 | Infective to $B$, temporarily insusceptible to $A$ |
| 8 | Infective to $B$, immune to $A$ |

The number of individuals in state $i$, $i = 1, \ldots, 8$, is denoted by $n_i$. In contrast to Model II we also take into account a birth-rate $\lambda$ and a death-rate $\mu$ in addition to the transition rates between the states. At birth all individuals are in state 1, i.e. the model ignores maternal antibodies. The death-rate $\mu$ is independent of the state

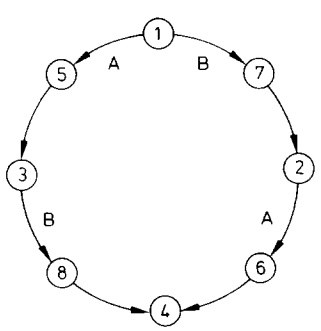


Fig. 1

$i$, $i = 1, \ldots, 8$, i.e. we restrict ourselves to the consideration of virus infections with negligible fatality rate. For simplicity the arrows for the transitions "birth" and "death" are not shown in Figure 1.

Our model is described by the following system of differential equations:

$$\begin{aligned}
\frac{dn_1}{dt} &= \lambda - [\beta_A(n_5 + n_6) + \beta_B(n_7 + n_8) + \mu]n_1, \\
\frac{dn_2}{dt} &= \gamma_B n_7 - [\beta_A(n_5 + n_6) + \mu]n_2, \\
\frac{dn_3}{dt} &= \gamma_A n_5 - [\beta_B(n_7 + n_8) + \mu]n_3, \\
\frac{dn_4}{dt} &= \gamma_A n_6 + \gamma_B n_8 - \mu n_4, \\
\frac{dn_5}{dt} &= \beta_A(n_5 + n_6)n_1 - (\gamma_A + \mu)n_5, \\
\frac{dn_6}{dt} &= \beta_A(n_5 + n_6)n_2 - (\gamma_A + \mu)n_6, \\
\frac{dn_7}{dt} &= \beta_B(n_7 + n_6)n_1 - (\gamma_B + \mu)n_7, \\
\frac{dn_8}{dt} &= \beta_B(n_7 + n_8)n_3 - (\gamma_B + \mu)n_8.
\end{aligned} \tag{1}$$

Here $\beta_A$ and $\beta_B$ are the infection rates of the two virus types $A$ and $B$. The corresponding immunization rates are denoted by $\gamma_A$ and $\gamma_B$. Setting one of the infection rates equal to zero, e.g. $\beta_B = 0$, the system (1) is reduced to the following system:

$$\begin{aligned}
\frac{dn_1}{dt} &= \lambda - [\beta_A n_5 + \mu]n_1, \\
\frac{dn_5}{dt} &= \beta_A n_5 - (\gamma_A + \mu)n_5, \\
\frac{dn_3}{dt} &= \gamma_A n_5 - \mu n_3.
\end{aligned} \tag{2}$$

These equations describe the classical model of the 'recurrent epidemic' which has been studied mainly by Bartlett (see Bailey, 1975, Chap. 7).

Adding all equations of system (1) and setting

$$n = \sum_{i=1}^{8} n_i, \tag{3}$$

one obtains the linear equation

$$\frac{dn}{dt} = \lambda - \mu n. \tag{4}$$

For $t \to \infty$, the size of the population tends to the limit

$$n^* = \lambda/\mu. \tag{5}$$

Since we are interested, above all, in the relative size of the quantities $n_i$, $i = 1, \ldots, 8$, we introduce the normalized variables

$$u_i = n_i/n^* \tag{6}$$

and assume that $n(0) = n^*$. Since

$$\sum_{i=1}^{8} u_i = 1, \tag{7}$$

one of the equations of (1) is superfluous. We eliminate in the following the equation for $u_4$. Hence (1) may be written:

$$\begin{aligned}
\frac{du_1}{dt} &= \mu - [\beta_A n^*(u_5 + u_6) + \beta_B n^*(u_7 + u_6) + \mu]u_1, \\
\frac{du_2}{dt} &= \gamma_B u_7 - [\beta_A n^*(u_5 + u_6) + \mu]u_2, \\
\frac{du_3}{dt} &= \gamma_A u_5 - [\beta_B n^*(u_7 + u_8)\mu]u_3, \\
\frac{du_5}{dt} &= \beta_A n^*(u_5 + u_6)u_1 - (\gamma_A + \mu)u_5, \\
\frac{du_6}{dt} &= \beta_A n^*(u_5 + u_6)u_2 - (\gamma_A + \mu)u_6, \\
\frac{du_7}{dt} &= \beta_B n^*(u_7 + u_8)u_1 - (\gamma_B + \mu)u_7, \\
\frac{du_8}{dt} &= \beta_B n^*(u_7 + u_8)u_3 - (\gamma_B + \mu)u_8.
\end{aligned} \tag{8}$$

**Equilibrium Points of the Model**

The system (8) has four equilibrium points $G_j$, $j = 1, \ldots, 4$. The point $G_1$ corresponds to the trivial solution

$$(u_1, \ldots, u_8) = (1, 0, \ldots, 0), \tag{9}$$

i.e. the total population is susceptible to both $A$ and $B$, and both virus types are absent. The two following equilibrium points describe the cases where only one of the two virus types is present. We introduce the following notation:

$$\begin{aligned}
R_A &= \beta_A n^*/(\gamma_A + \mu), \\
R_B &= \beta_B n^*/(\gamma_B + \mu), \\
q_A &= \mu/(\gamma_A + \mu), \\
q_B &= \mu/(\gamma_B + \mu).
\end{aligned} \tag{10}$$

The quantities $R_A$ and $R_B$ may be interpreted as the reproduction rates of the virus types $A$ and $B$, i.e. the number of the secondary cases which are produced by one infective case during his infectious period in a completely susceptible population of size $n^*$. The quantities $q_A$ and $q_B$ represent the fraction of the infectious period ($1/(\gamma_A + \mu)$, and $1/(\gamma_B + \mu)$ respectively) with respect to the life expectancy $1/\mu$ of an individual. For $R_A > 1 (R_B > 1)$, $G_2(G_3)$ is given by:

$$\begin{aligned} G_2&:(u_1, u_2, u_3, u_5, u_6, u_7, u_8) = \\ &(1/R_A, 0, (1 - 1/R_A)(1 - q_A), (1 - 1/R_A)q_A, 0, 0, 0), \\ G_3&:(u_1, u_2, u_3, u_5, u_6, u_7, u_8) = \\ &(1/R_B, (1 - 1/R_B)(1 - q_B), 0, 0, 0, (1 - 1/R_B)q_B, 0). \end{aligned} \tag{11}$$

For the determination of $G_4$ we introduce the auxiliary variables

$$\begin{aligned} \lambda_A &= \beta_A n^*(u_5 + u_6), \\ \lambda_B &= \beta_A n^*(u_7 + u_8). \end{aligned} \tag{12}$$

The quantity $\lambda_A(\lambda_B)$ represents the incidence of the infection of type $A(B)$. The components of $G_4$ could be determined by successive elimination and substitution in system (8). We shall, however, use another method where we express the components of $G_4$ first as functions of the incidences by using the relation between the $u_i$, $i = 1, \ldots, 8$ and the average sojourn times in the states $\{1, 2, \ldots, 8\}$. (We omit a detailed definition of the corresponding Markov process.) The life expectancy of an individual may be represented by the sojourn times $T_i$ in the individual states as follows:

$$\begin{aligned} 1/\mu = T_1 &+ p_{15}\{T_5 + p_{53}[T_3 + p_{38}(T_8 + p_{84}T_4)]\} \\ &+ p_{17}\{T_7 + p_{72}[T_2 + p_{26}(T_6 + p_{64}T_4)]\}. \end{aligned} \tag{13}$$

Here $p_{ij}$ is the probability of a transition out of state $i$ into the state $j$. The sojourn times and the transition probabilities are given by:

$$\begin{aligned} T_1 &= 1/(\lambda_A + \lambda_B + \mu), & T_5 &= 1(\gamma_A + \mu), \\ T_2 &= 1/(\lambda_A + \mu), & T_6 &= 1/(\gamma_A + \mu), \\ T_3 &= 1/(\lambda_B + \mu), & T_7 &= 1/(\gamma_B + \mu), \\ T_4 &= 1/\mu, & T_8 &= 1/(\gamma_B + \mu), \\ p_{15} &= \lambda_A/(\lambda_A + \lambda_B + \mu), & p_{17} &= \lambda_B/(\lambda_A + \lambda_B + \mu), \\ p_{53} &= \gamma_A/(\gamma_A + \mu), & p_{72} &= \gamma_B/(\gamma_B + \mu), \\ p_{38} &= \lambda_B/(\lambda_B + \mu), & p_{26} &= \lambda_A/(\lambda_A + \mu), \\ p_{84} &= \gamma_B/(\gamma_B + \mu), & p_{64} &= \gamma_A/(\gamma_A + \mu). \end{aligned} \tag{14}$$

Hence we obtain the desired expressions for the quantities $u_i$, $i = 1, \ldots, 8$:

$$
\begin{aligned}
u_1 &= \mu/(\lambda_A + \lambda_B + \mu),\\
u_5 &= \mu\lambda_A/[(\lambda_A + \lambda_B + \mu)(\gamma_A + \mu)],\\
u_3 &= \mu\lambda_A\gamma_A/[(\lambda_A + \lambda_B + \mu)(\gamma_A + \mu)(\gamma_B + \mu)],\\
u_8 &= \mu\lambda_A\gamma_A\lambda_B/[(\lambda_A + \lambda_B + \mu)(\gamma_A + \mu)(\lambda_B + \mu)(\gamma_B + \mu)],\\
u_7 &= \mu\lambda_B/[(\lambda_A + \lambda_B + \mu)(\gamma_B + \mu)],\\
u_2 &= \mu\lambda_B\gamma_B/[(\lambda_A + \lambda_B + \mu)(\gamma_B + \mu)(\lambda_A + \mu)],\\
u_6 &= \mu\lambda_B\gamma_B\lambda_A/[(\lambda_A + \lambda_B + \mu)(\gamma_B + \mu)(\lambda_A + \mu)(\gamma_A + \mu)],\\
u_4 &= \frac{\lambda_A\lambda_B\gamma_A\gamma_B}{(\lambda_A + \lambda_B + \mu)(\gamma_A + \mu)(\gamma_B + \mu)}\left(\frac{1}{\lambda_A + \mu} + \frac{1}{\lambda_B + \mu}\right).
\end{aligned}
\tag{15}
$$

We get a system of equations for $\lambda_A$ and $\lambda_B$ by substituting $u_1$, $u_2$, $u_3$ into the following simple equations

$$
\begin{aligned}
R_A(u_1 + u_2) &= 1,\\
R_B(u_1 + u_3) &= 1.
\end{aligned}
\tag{16}
$$

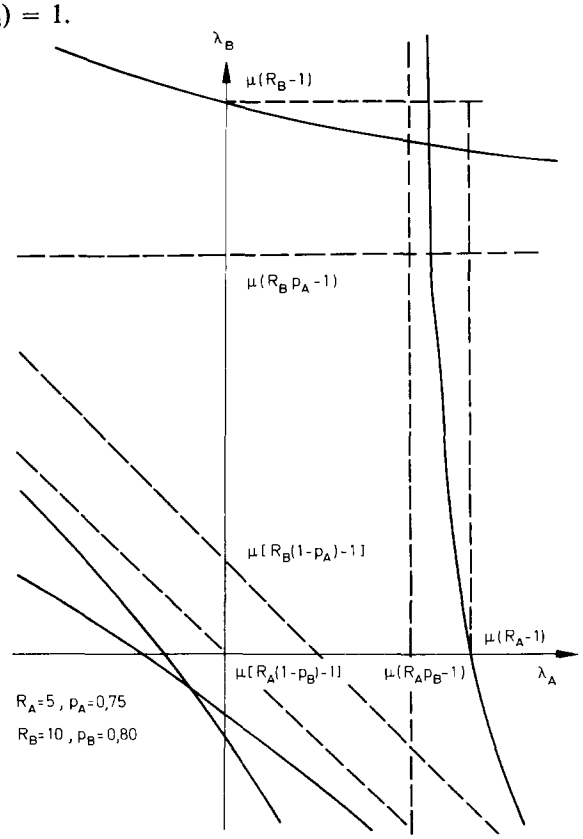


**Fig. 2**

Hence

$$(\lambda_A + \lambda_B + \mu)(\lambda_A + \mu) = \mu R_A(\lambda_A + \lambda_B p_B + \mu),$$

$$(\lambda_A + \lambda_B + \mu)(\lambda_B + \mu) = \mu R_B(\lambda_A p_A + \lambda_B + \mu), \tag{17}$$

where

$$p_A = 1 - q_A, \qquad p_B = 1 - q_B. \tag{18}$$

The equations (17) define two hyperbolas whose position with respect to each other may be seen in Figure 2.

The domain which yields solutions with positive $\lambda_A$ and $\lambda_B$ is given by the intersection of the sets

$$B_1 = \{R_B\colon R_B > R_A/[1 + (R_A - 1)p_A]\},$$

$$B_2 = \{R_A\colon R_A > R_B/[1 + (R_B - 1)p_B]\} \tag{19}$$

(See Fig. 3.)

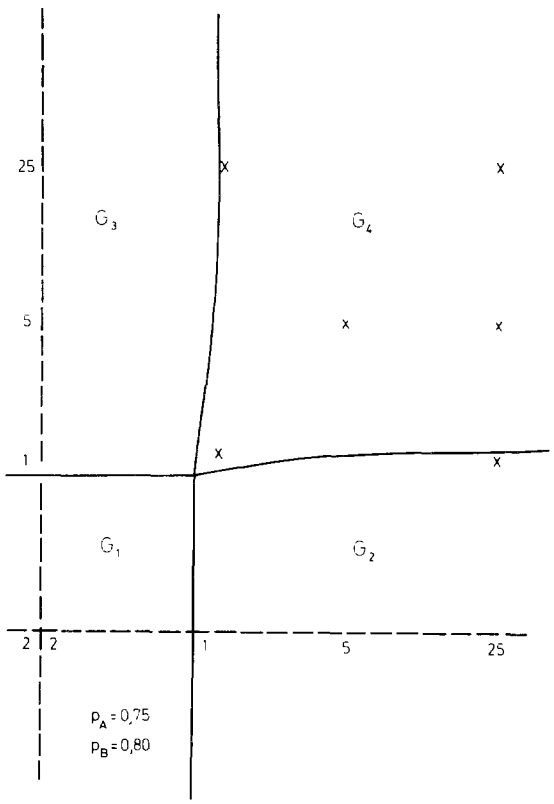


Fig. 3

The system (17) could be reduced to a cubic equation. For the numerical evaluation the following recursion formula is however more useful

$$\lambda_A^{(t+1)} = \mu\left[\frac{R_A(\lambda_A^{(t)} + \lambda_B^{(t)} p_B + \mu)}{\lambda_A^{(t)} + \lambda_B^{(t)} + \mu} - 1\right],$$

$$\lambda_B^{(t+1)} = \mu\left[\frac{R_B(\lambda_A^{(t)} p_A + \lambda_B^{(t)} + \mu)}{\lambda_A^{(t)} + \lambda_B^{(t)} + \mu} - 1\right]. \tag{20}$$

Table 2 gives the equilibrium solutions for the points drawn in Figure 3.

**Table 2.** $\mu = 0.02$, $p_A = 0.75$, $p_B = 0.80$

| $R_A$ | 5 | 25 | 25 | 1.30 | 1.3 | 25 |
|---|---|---|---|---|---|---|
| $R_B$ | 5 | 5 | 1.30 | 1.30 | 25 | 25 |
| $\lambda_A$ | 0.07141 | 0.46931 | 0.48000 | 0.00515 | 0.00102 | 0.43196 |
| $\lambda_B$ | 0.06886 | 0.05859 | 0 | 0.00489 | 0.47975 | 0.41793 |
| $u_1$ | 0.12479 | 0.03650 | 0.04000 | 0.66580 | 0.03994 | 0.02299 |
| $u_5$ | 0.11139 | 0.21414 | 0.24000 | 0.04289 | 0.00051 | 0.12414 |
| $u_3$ | 0.07521 | 0.16350 | 0.72000 | 0.10341 | 0.00006 | 0.01701 |
| $u_8$ | 0.05179 | 0.09579 | 0 | 0.00505 | 0.00029 | 0.07108 |
| $u_7$ | 0.08593 | 0.02139 | 0 | 0.03253 | 0.19161 | 0.09609 |
| $u_2$ | 0.07521 | 0.00350 | 0 | 0.10346 | 0.72929 | 0.01701 |
| $u_6$ | 0.06713 | 0.02051 | 0 | 0.00666 | 0.00928 | 0.09184 |
| $u_4$ | 0.40855 | 0.44468 | 0 | 0.04020 | 0.02902 | 0.55984 |
| $L_A$ | 20.141 | 3.518 | 2.083 | 200.125 | 994.544 | 8.462 |
| $L_B$ | 23.007 | 31.885 | $\infty$ | 213.237 | 2.120 | 10.864 |
| $1/[\mu(R_A - 1)]$ | 12.500 | 2.083 | 2.083 | 166.667 | 166.667 | 2.083 |
| $1/[\mu(R_B - 1)]$ | 12.500 | 12.500 | 166.667 | 166.667 | 2.083 | 2.083 |

### Stability of Equilibrium Points

In order to study the local stability of the equilibrium points $G_k$, $k = 1, \ldots, 4$, we have to check whether the eigenvalues of the matrix with the elements

$$\left\{\frac{\partial f_i(G_k)}{\partial u_j}\right\} \tag{21}$$

have positive real parts. Here $f_i$ denotes the right-hand side of the equation for $u_i$. We consider, for example, the equilibrium point $G_2$.

Table 3 gives the corresponding matrix whose characteristic polynomial is given by:

$$\begin{aligned}&(\mu + s)(\gamma_A + \mu + s)(R_A + s)[s^2 + R_A s + \mu(R_A - 1)(\gamma_A + \mu)]\\ &\{s^2 - s[\beta_B(R_A\gamma_A + \mu) - 2(\gamma_B + \mu)]\\ &\quad + (\gamma_B + \mu)[\gamma_B + \mu + \beta_B\gamma_A/\beta_A - \beta_B\gamma_A R_A/\beta_A - \beta_B(\gamma_A + \mu)/\beta_A]\}.\end{aligned} \tag{22}$$

From this we conclude that $G_2$ is locally stable if

$$R_B < R_A/[1 + (R_A - 1)p_A] \tag{23}$$

**Table 3**

| $i$ | $\frac{\partial f_i(G_2)}{\partial u_1}$ | $\frac{\partial f_i(G_2)}{\partial u_2}$ | $\frac{\partial f_i(G_2)}{\partial u_3}$ | $\frac{\partial f_i(G_2)}{\partial u_5}$ | $\frac{\partial f_i(G_2)}{\partial u_6}$ | $\frac{\partial f_i(G_2)}{\partial u_7}$ | $\frac{\partial f_i(G_2)}{\partial u_8}$ |
|---|---|---|---|---|---|---|---|
| 1 | $-R_A$ | 0 | 0 | $-(\gamma_A + \mu)$ | $-(\gamma_A + \mu)$ | $-\beta_B(\gamma_A + \mu)/\beta_A$ | $-\beta_B(\gamma_A + \mu)/\beta_A$ |
| 2 | 0 | $-R_A$ | 0 | 0 | 0 | $\gamma_B$ | 0 |
| 3 | 0 | 0 | $-\mu$ | $\gamma_A$ | 0 | $-\beta_B n^*(1 - 1/R_A)p_A$ | $-\beta_B n^*(1 - 1/R_A)p_A$ |
| 5 | $\mu(R_A - 1)$ | 0 | 0 | 0 | $(\gamma_A + \mu)$ | 0 | 0 |
| 6 | 0 | $\mu(R_A - 1)$ | 0 | 0 | $-(\gamma_A + \mu)$ | 0 | 0 |
| 7 | 0 | 0 | 0 | 0 | 0 | $\beta_B(\gamma_A + \mu)/\beta_A - (\gamma_B + \mu)$ | $\beta_B(\gamma_A + \mu)/\beta_A$ |
| 8 | 0 | 0 | 0 | 0 | 0 | $\beta_B n^*(1 - 1/R_A)p_A$ | $\beta_B n^*(1 - 1/R_A)p_A - (\gamma_B + \mu)$ |

and

$$R_A > 1 \tag{24}$$

The domains for local stability of the equilibrium points are shown in Figure 3.

## Discussion

We return to Bang's observations which were described in the Introduction and discuss to what extent they may be explained by the present model. The heterogeneous spatial distribution may be handled in the present model by spatial differences in the reproduction rates $R_A$ and $R_B$ if one assumes that the spatially distributed population is composed of mutually isolated subpopulations. A more satisfactory explanation would require an extension of the model by a spatial component. It is conceivable that this could result in spatially stable distribution patterns.

The second of Bang's remarks which is concerned with the temporal sequence of the two virus types requires to study the dynamic behavior of the present model. Already in the case of a single virus type marked oscillations of varying period and phase can occur for relatively small oscillations of the contact rates (Dietz 1976).

Finally, Bang's remark about the delay of the age at first infection in an individual may be easily investigated within the framework of the present model. Let the mean age at infection of type $A(B)$ be denoted by $L_A(L_B)$. Then one can easily deduce

$$\begin{aligned} L_A &= 1/\lambda_A + [\lambda_B/(\lambda_A + \lambda_B)]/\gamma_B, \\ L_B &= 1/\lambda_B + [\lambda_A/(\lambda_A + \lambda_B)]/\gamma_A. \end{aligned} \tag{25}$$

Table 2 gives a few numerical examples of the effect of interference on the age of infection.

In concluding it may be mentioned that differential mortality may easily be incorporated into the present model. This would result essentially in a reduction of the domain of stable coexistence of the two virus types.

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