

A mathematical model for the spread of infectious diseases based on a system of ordinary differential equations

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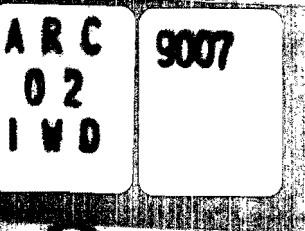
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Opleiding Wiskunde voor de Industrie Eindhoven

STUDENT REPORT 90-07

A MATHEMATICAL MODEL FOR THE SPREAD OF
INFECTIOUS DISEASES BASED ON A SYSTEM OF
ORDINARY DIFFERENTIAL EQUATIONS

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May 1990

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Contents

1.1	Introduction	1
1.2.	MEM diseases in the city of Bari	1
1.3.	Results and Advices	2
1.4.	Data analyses	5
2.1.	A mathematical model	6
2.2.	Analysis of the ODE-system	8
2.3.	A second mathematical model	13
3.	The non-autonomous model	15
4.	Estimation of the parameters	18
	4.1. Discretisation method	19
	4.2. Method with finite trigonometric series	20
	4.3. Computational results	21

1.1. Introduction

For the daily life of a human population living in a city or on an island, an infectious disease can have a dramatic impact. For example, a disease which causes death might lead to the extinction of the whole population, and even less dangerous diseases such as influenza can have important economic consequences when a large number of ill people is not able to go to work.

Therefore, it is important to know how to control the effects and the spread of infectious diseases. Although of course medical sciences play a very important role in combatting infectious diseases, mathematics can also give a contribution by means of a clear mathematical description of the spread of an infectious disease. Such a description can lead to identification of the essential causes of the spread and might render a strategy by which this spread can be controlled.

In this report mathematical models are presented which describe the spread of so-called Man-Environment-Man (MEM) diseases, i.e. diseases which spread is due to the interaction of a human population with the environment. In this case, we have a system with a population of infectious agents and a population of human infectives. On one hand, the infectious agents infect human beings and on the other hand, the infectives produce infectious agents bringing them into the environment. Moreover, agents disappear out of the environment and infectives recover from their disease. (See Fig. 1.)

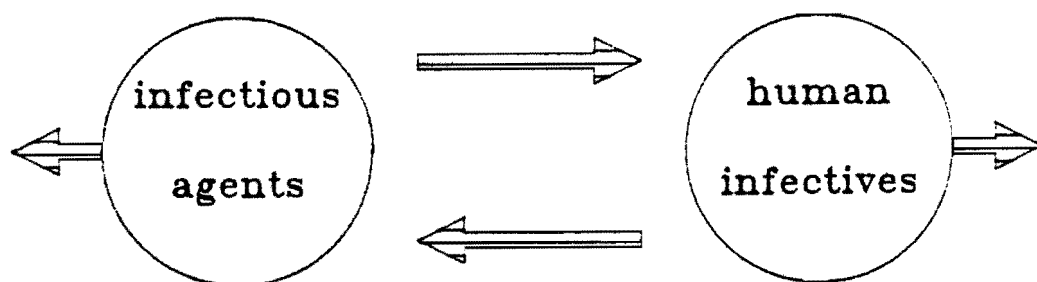


Figure 1. The interactions between the human population and the environment.

1.2. MEM diseases in the city of Bari

MEM diseases cause serious problems in the city of Bari in south-Italy. Especially during the summer and early autumn the city has to deal with a high number of infected people.

One of the diseases Bari suffers from is Hepatitis A. Hepatitis A is about in an endemic state in Bari. This means that on the average a constant number of people is infected. It is constant on the average because the number is highly seasonal dependent.

People are infected by eating contaminated raw fish. Via the human faces of infectives, infectious agents are brought into the sewerage system, which directly carries the bacteria into the sea. Subsequently, the fish is contaminated and can infect the people again.

This project has been originated by the authorities of Bari. They want to know how the number of infected people can be reduced efficiently.

The goal of this project is to formulate advices to the authorities of Bari. A mathematical model is developed to describe the interactions between man and environment.

The advices that can be formulated from the analyses of the model are discussed in the next section.

1.3. Results and Advices

In this section we formulate the main advices.

At a certain time point we have a number of people suffering from Hepatitis A. We refer to this number with capital S . Further we have a concentration of bacteria in the environment which is referred to with B .

The variable pair (B,S) completely describes the situation of the disease at a certain timepoint. This pair of variables can be plotted in a figure with on the horizontal axis the value of B and on the vertical axis the value of S . With the help of these figures the advices will be explained.

Advice 1:

Measures have to effect at the same time both the number of infected people (S) and the concentration of bacteria (B).

Explanation:

Analyses of the model showed that the (B,S) plane is divided into two regions by a line. If at a certain timepoint the combination (B,S) is above this line the disease will be in an endemic state or tend to it. On the other hand, if the combination (B^*,S^*) is below this line, the disease will tend to extinction.

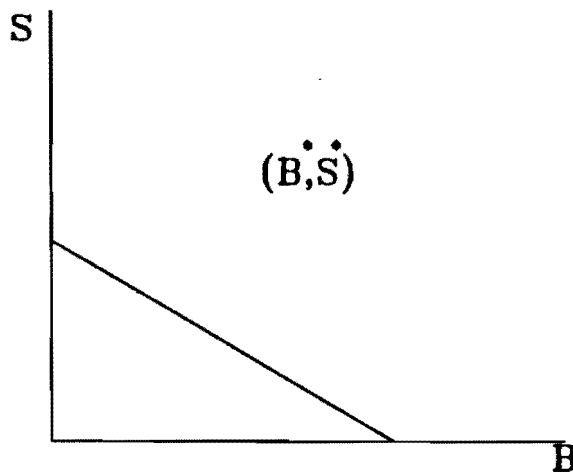


Figure 2. The (B,S) plane with an endemic disease.

In the figure 2. the combination (B^*, S^*) represents the situation of Hepatitis A.

Suppose the authorities succeed in reducing either the value of B or the value of S drastically. This approach will probably not have the desired result because the combination (B, S^*) or (B^*, S) will still lie above the critical line. A one-sided approach on B or S will therefore never be successful.

Advice 2:

If authorities can not reduce the values of B and S in such a way that the combination is below the critical line, then they better do nothing at all.

Explanation:

As long as the combination (B, S) is above the critical line, the disease will finally return to its endemic state. Authorities should be aware of this characteristic of the disease.

Another way to deal with a MEM disease, is to try to influence the interactions between B and S in stead of the levels of B and S .

The interactions are established through the consumption of contaminated fish and through the transport of contaminated faces to the sea by the sewerage system.

Advice 3:

"Reducing" the interaction between B and S will not only reduce the levels of B and S , but also move the critical line upwards in the (B, S) plane (see Fig. 3).

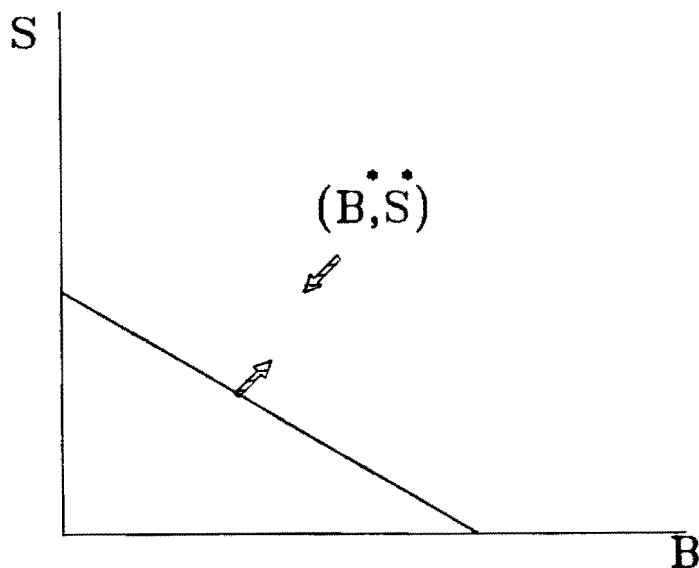


Figure 3. The consequence of the reduction of the interactions between B and S .

The advices 1-3 all have a "long-term" character. In this project however, we also looked at the "short-term" behaviour of a MEM disease. More concretely, we also analysed the causes of the

periodicity in the number of infectives.

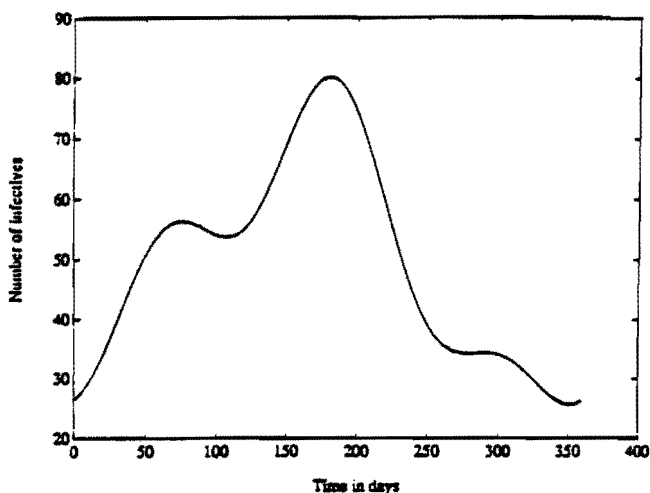


Figure 4. The number of infected people during the year (average from 1967-1984).

Figure 4 shows the average number of infected people during a year between 1967 and 1984.

The periodicity of Hepatitis A is mainly caused by periodically changing consumption habits of the human population. It is known that in the spring and early summer, the supply of fish is higher than in the rest of the year. In this project we translated this changing consumption pattern into a changing "force of infection". Data analysis gave us the following estimation of this force during the year.

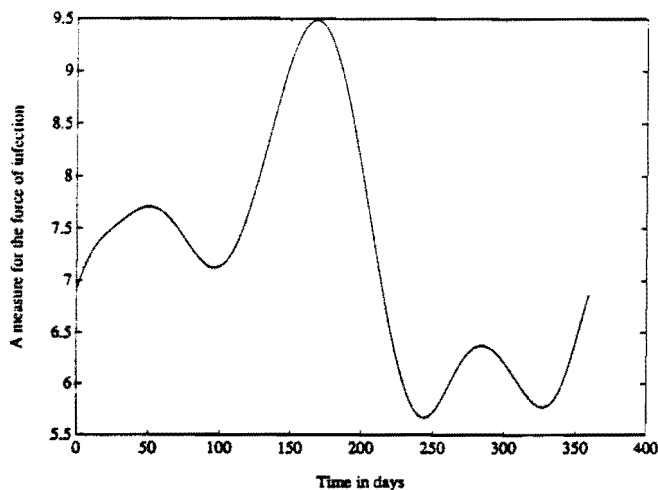


Figure 5. The force of infection during a year.

The peak in this figure during the spring and early summer precedes the peak in figure 4 by about 2 months.

Advice 4:

By counterbalancing the peak of the force of infection by an increased resistance of the population, the peak in the number of infected people during the summer and early autumn can be prevented.

Explanation:

This advice simply states that vaccination programs must be executed in the beginning of the year.

1.4. Data analyses

The data available for this project contained the number of infected people per month in the years 1967 till 1984.

There are two ways to look at these data. The first one is with a long term scope where you are interested in the development of the disease over the years. The second one is with a short term scope, where we are interested in the development of the disease within a year.

Long term

Figure 1 shows the average number of infected people per year in the period 1967-1984.

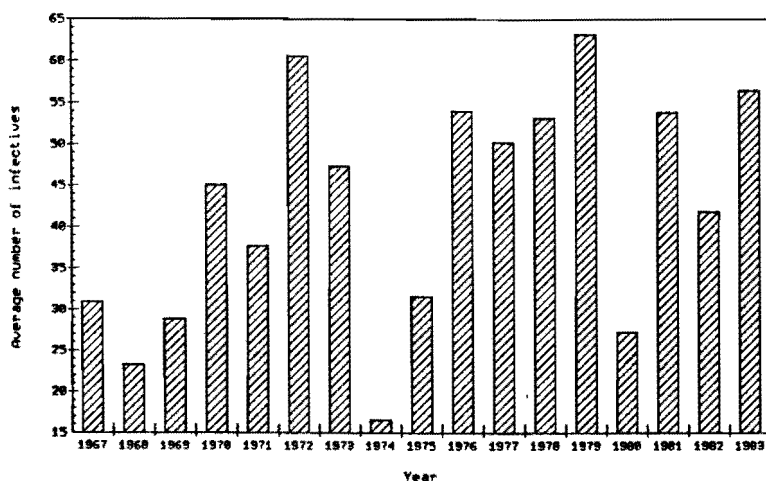


Figure 6. The number of infected people per year from 1967 and 1984 in Bari.

The upward trend of about 10% per year can be explained by the population growth. Therefore we can conclude that from 1967 till 1984 a constant percentage of the population was infected.

Short Term

On the short term, we are interested in what happens within a year. For this purpose, the available data were rescaled to the 1967 level by subtracting the trend from the original data. Subsequently, the rescaled data were averaged per month. Figure 2 shows the results.

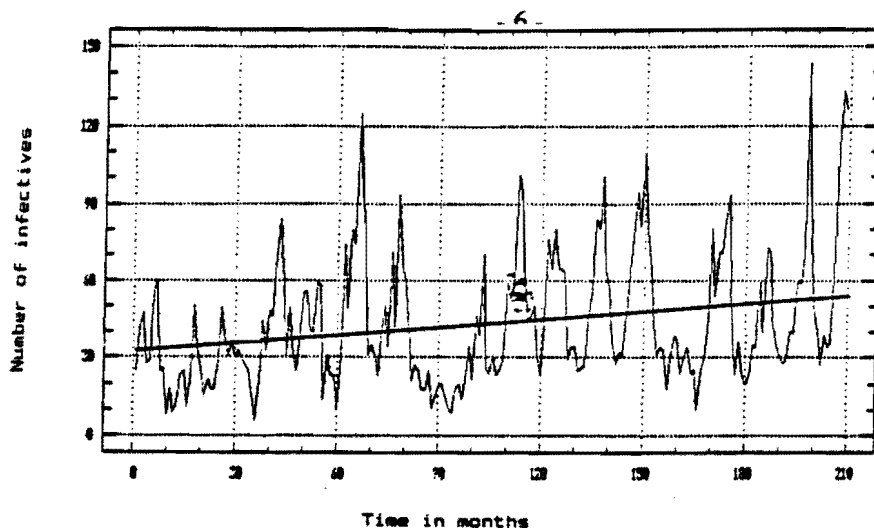


Figure 7. Average number of infected people per month between 1967 and 1984.

The conclusion is that during the summer and early autumn a peak in the number of infected people is observed.

2.1. A mathematical model

We now present a general mathematical model which describes the spread of infectious MEM-disease. The design of this model is based on several assumptions which we will try to motivate throughout this section.

First of all, we note that in the system of a MEM-disease we have two quantities which vary in time, viz. the concentration of infectious agents in the environment and the number of human infectives. We denote these by $z_1(t)$ and $z_2(t)$ respectively.

Due to the disappearance of infectious agents out of the environment $z_1(t)$ decreases. We assume that every infectious agent has the same (mean) "life-time" and that this "life-time" is constant in time, say $\frac{1}{a_{11}}$.

On the other hand, $z_1(t)$ increases due to the presence of human infectives. We assume that every human infective feeds the system with the same, constant concentration of infectious agents per unit of time, say a_{12} .

We now obtain:

$$(2.1) \quad z_1(t + \Delta t) \approx z_1(t) - a_{11} \Delta t z_1(t) + a_{12} \Delta t z_2(t).$$

Recuperation of infectives causes a decrease of $z_2(t)$. We assume that the (mean) infectious period of an infective is the same for every infective and that this (mean) infectious period is constant in time, say $\frac{1}{a_{22}}$.

Finally, $z_2(t)$ increases due to the presence of infectious agents. However, this "force of infection" is quite hard to model. Of course, absence of infectious agents implies absence of new infectives and an increasing concentration of infectious agents causes an increasing number of

new infectives, but in a situation with a very large concentration of infectious agents we expect that some kind of saturation takes place, i.e. even though the concentration of agents is very large, only a limited growth of infectives is to be expected. We assume that in a situation with an infinitely large concentration of infectious agents only a fraction $p(t)N$ of the total susceptible human population N gets infected per unit of time $0 < p(t) < 1$.

Now, if we denote the force of infection due to the presence of infectious agents, i.e. the number of new infectives per unit of time, by $g(z_1, t)$ then we have already made the following demands on g :

$$(2.2) \quad \begin{cases} g(0, t) = 0 \\ \frac{\partial g}{\partial z_1}(z_1, t) > 0 \\ \lim_{z_1 \rightarrow \infty} g(z_1, t) = p(t)N. \end{cases}$$

Looking at the data of reported new infectives per month in the city of Bari, one might say that considered over a large time-scale the number of new infectives per month is almost constant. Therefore, we assume that g does not explicitly depend on time t , i.e. we assume

$$(2.3) \quad g = g(z_1).$$

Finally, we expect that there is some critical value of the concentration of infectious agents such that for a situation with no infectives and a concentration of agents below this value the disease will become extinct and for a situation with no infectives and a concentration of agents higher than this value it will not. We also expect the existence of such a critical value for the number of infectives.

We now propose the following choice for g :

$$(2.4) \quad g = -\frac{N \alpha z_1^2}{1 + \beta z_1^2}.$$

Although this choice still seems quite arbitrary, we will show later on that this g has the desired properties.

For the variation of $z_2(t)$ in time t we now obtain:

$$(2.5) \quad z_2(t + \Delta t) \approx z_2(t) + g(z_1) \Delta t - a_{22} \Delta t z_2(t).$$

We now rewrite (2.1) and (2.5) as follows:

$$(2.6) \quad \frac{z_1(t + \Delta t) - z_1(t)}{\Delta t} \approx -a_{11} z_1(t) + a_{12} z_2(t),$$

$$(2.7) \quad \frac{z_2(t + \Delta t) - z_2(t)}{\Delta t} \approx g(z_1) - a_{22} z_2(t),$$

and by taking $\Delta t \rightarrow 0$ we end up with the following system of ODE's describing the spread of an infectious MEM-disease:

$$(2.8) \quad \begin{cases} \frac{dz_1}{dt} = -a_{11} z_1 + a_{12} z_2 \\ \frac{dz_2}{dt} = g(z_1) - a_{22} z_2 \end{cases}$$

where g is the force of infection, i.e. the number of new infectives per unit of time due to the infectious agents. (See also (2.4).)

We resume that all the parameters N , α , β , a_{11} , a_{12} and a_{22} are active and that they represent

- $\frac{1}{a_{11}}$: mean life time of an infectious agent
- $\frac{1}{a_{22}}$: mean infectious period of an infective
- q_{12} : concentration of infectious agents brought into the environment by an infective per unit of time
- (2.9) N : total susceptible human population
- $\frac{\alpha}{\beta} N$: the fraction of the human population that gets infected per unit of time in the presence of an infinitely large concentration of infectious agents.

We note that $\frac{\alpha}{\beta}$ can also be interpreted as the maximum probability that a human being is infected in 1 time unit.

The next section shows an analysis of the system (2.8).

2.2. Analysis of the ODE-system

The first step in our analysis of (2.8) consists of a rescaling in order to recognize the essential parameters of the problem scale the time t with $\frac{1}{a_{11}}$, i.e. we take $\tau = a_{11} t$; we scale z , with $\frac{a_{12}}{a_{11}}$ the concentration of agents brought into the environments by an infective during the life-time of an agent, i.e. we take $\frac{a_{11}}{a_{12}} z_1$. Also, we write $v_2(\tau) = z$ then (2.8) transforms into

$$(2.10) \quad \begin{cases} \frac{dv_1}{d\tau} = -v_1 + v_2 \\ \frac{dv_2}{d\tau} = \frac{a' v_1^2}{1 + \beta' v_1^2} - \delta v_2 \end{cases}$$

where

$$(2.11) \quad \delta = \frac{a_{22}}{a_{11}}, \quad \alpha' = \frac{1}{a_{11}} N \alpha \left[\frac{a_{12}}{a_{11}} \right]^2, \quad \beta' = \beta \left[\frac{a_{12}}{a_{11}} \right]^2.$$

Now, α'/β' stands for the maximum increase of infectives during the lifetime of an infectious agent, and δ is the ratio of the lifetimes of infectious agents and infectives.

Remark 1: In (2.10) only three parameters α' , β' and δ are left. It is possible to eliminate one more by means of a rescaling $u_1 = \alpha' v_1$ and $u_2 = \alpha' v_2$, but this does not really provide a better insight in the problem.

Remark 2: We look for positive solutions v_1 and v_2 , of course.

The horizontal and vertical isoclines of (2.10) are given by

$$(2.12) \quad v_2 = v_1$$

respectively,

$$(2.13) \quad v_2 = \frac{1}{\delta} \frac{\alpha' v_1^2}{1 + \beta' v_1^2} = \frac{\bar{\alpha} v_1^2}{1 + \beta' v_1^2} \quad (\bar{\alpha} = \alpha'/\delta).$$

If $\bar{\alpha}^2 - 4\beta' > 0$ then system (2.10) allows 3 steady states, namely $\underline{0} = (0,0)$, $\underline{p} = (p,p)$, $\underline{q} = (q,q)$, $q = \frac{\bar{\alpha} + \sqrt{\bar{\alpha}^2 - 4\beta'}}{2\beta'}$. (See Figure 8.)

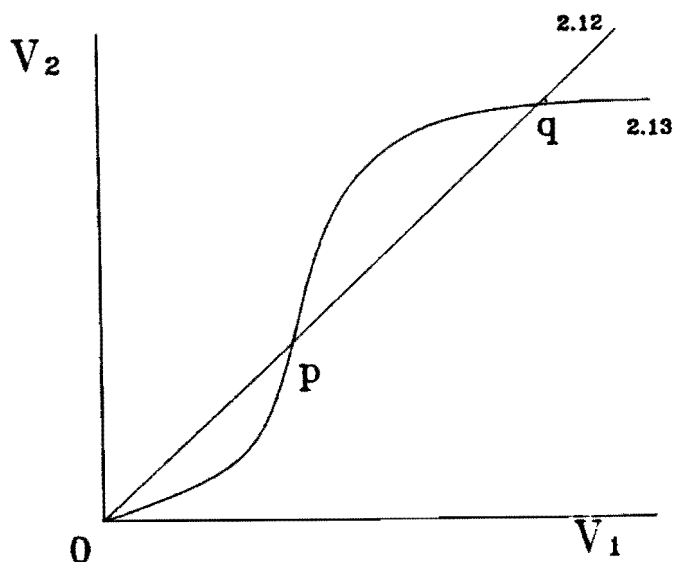


Figure 8. The isoclines of system (2.10)

It can be proven that $\underline{0}$ and \underline{q} are globally asymptotically stable and the \underline{p} is a saddle-point.

Remark 3: In real life $\underline{0}$ corresponds to extinction of the disease and \underline{q} to an endemic state of the disease. Although we have found a condition for the existence of \underline{q} , from now on we will impose that such an endemic state exists.

A typical phase plane portrait for system (2.10) is drawn below.

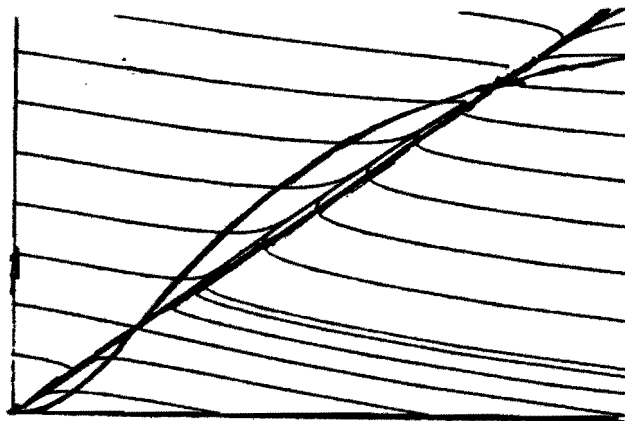


Figure 9. The phase plane of system (2.10)

The dotted line in the phase plane portrait is the separatrix. This separatrix, which corresponds with 3 solutions of the ODE-system (2.10), divides the positive cone $K = \mathbb{R}^+ \times \mathbb{R}^+$ into two regions. A solution \underline{y} with initial value \underline{v}_0 in the region below the separatrix will tend to $\underline{0}$, a solution \underline{y} with an initial value in the upper region will tend to \underline{q} .

Result (2.14): The separatrix cuts the axis $v_1 = 0$.

Proof:

Let $u_1 = v_1 - p$, $u_2 = v_2 - p$ and $f(x) = \frac{\alpha'(x+p)^2}{1 + \beta'(x+p)^2}$. Then (2.10) transforms into

$$(2.15) \quad \begin{cases} \frac{du_1}{d\tau} = -u_1 + u_2 \\ \frac{du_2}{d\tau} = f(u_1) - f(0) - \delta u_2. \end{cases}$$

Consider the line segment $u_2 = 0$, $u_1 \in [-p, 0]$. On this line segment $(-u_1 + u_2) \frac{du_2}{du_1} = 0$ and $f(u_1) - f(0) - \delta u_2 = f(u_1) - f(0) \leq 0$.

Consider also the line segment $u_2 = \gamma u_1$, $u_1 \in [-p, 0]$, $\gamma < 0$. On this line segment $(-u_1 + u_2) \frac{du_2}{du_1} = \gamma(\gamma - 1)u_1$. It is easy to see that $\gamma < 0$ exists such that $\gamma(\gamma + \delta - 1) \geq \max_{u_1 \in [-p, 0]} f'(u_1)$ and hence $\gamma(\gamma - 1)u_1 \leq f(u_1) - f(0) - \delta \gamma u_1$ for all $u_1 \in [-p, 0]$.

One can now verify that we have the following situation for the vector field defined by (3.1) ($\bar{p} = 1$). (See Figure 4.)

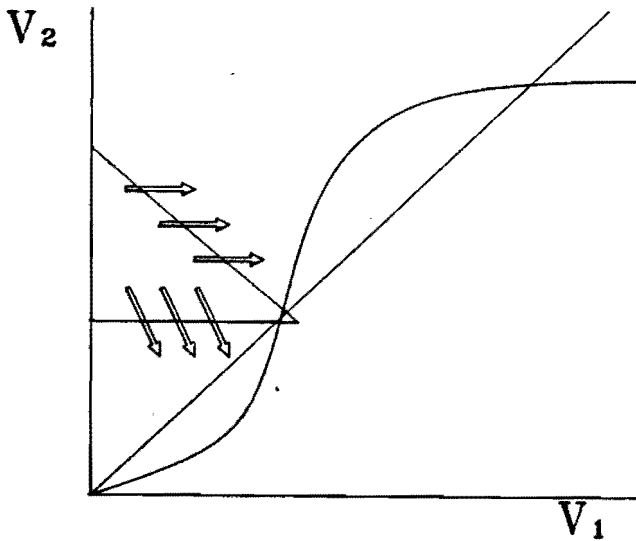


Figure 10. The vector field on the two line segments.

Hence, we conclude that the separatrix must be between the two line segments and therefore it cuts the axis $v_1 = 0$. □

Remark 4: In order to get a better estimation for the position of the cutting point of the separatrix and the axis $v_1 = 0$ one can prove a similar result taking other line segments or curves. The cutting point can also be computed numerically if the parameters of (2.10) are known.

Result (2.16). The separatrix cuts the axis $v_2 = 0$.

Proof:

Again, we start with a rescaling of system (2.10). Let $u_1 = \frac{v_1}{p}$, $u_2 = \frac{v_2}{p}$ and

$g(x) = \frac{\alpha' p x^2}{1 + \beta' p^2 x^2}$. Then (2.10) transforms into

$$(2.17) \quad \begin{cases} \frac{du_1}{d\tau} = -u_1 + u_2 \\ \frac{du_2}{d\tau} = g(u_1) - \delta u_2 \end{cases}$$

and the saddlepoint (p, p) moves to $(1, 1)$. (So, $g(1) = \delta > 0$).

Now, consider the following initial value problem

$$(2.18) \quad \begin{cases} (-u_1 + u_2) \frac{du_2}{du_1} = g(u_1) - g(1)u_2 \\ u_2(1) = 1. \end{cases}$$

One can easily verify that

$$(2.19) \quad \frac{du_2}{du_1}(1) = \frac{(1-g(1)) - \sqrt{(1-g(1))^2 + 4g'(1)}}{2} =: -\gamma < 0$$

and our goal is now to prove that $u_2(u_1) = 0$ for some u_1 , $1 \leq u_1 < +\infty$. Therefore, let $z = u_1 - u_2$. Then (2.18) transforms into

$$(2.20) \quad \begin{cases} z \frac{dz}{du_1} = (1+g(1))z - g(1)u_1 + g(u_1) \\ z(1) = 0 \\ \frac{dz}{du_1}(1) = 1 + \gamma > 1 \end{cases}$$

and our aim is to prove that $z(u_1)$ equals u_1 for some finite $u_1 \geq 1$. As a final transform we take $u_1 = 1 + x$. Then

$$(2.21) \quad \begin{cases} z \frac{dz}{dx} = (1+g(1))z - g(1)x + g(1+x) - g(1) \\ z(0) = 0 \\ \frac{dz}{dx}(0) = 1 + \gamma > 1 \end{cases}$$

and we have to prove that $z(x) = 1 + x$ for some finite $x \geq 0$. We first show that $z > x$ for $x > 0$.

Notice that $z(0) = 0$ and $\frac{dz}{dx}(0) > 1$. Moreover, for $\phi = x$ $\phi \frac{d\phi}{dx} = x$ and $(1+g(1))\phi - g(1)x + g(1+x) - g(1) - x + g(1+x) - g(1) > x$ for $x > 0$.

Hence, $z > x$ for $x > 0$.

Now, assume that $z < 1 + x$ for all $x > 0$. Then

$$\begin{aligned} \frac{dz}{dx} &= (1+g(1)) - g(1) \frac{x}{z} + \frac{g(1+x) - g(1)}{z} > (1+g(1)) - g(1) \frac{x}{x} + \frac{g(1+x) - g(1)}{1+x} \\ &= 1 + \frac{g(1+x) - g(1)}{1+x} \quad \text{for all } x > 0. \end{aligned}$$

So, for all $x \geq 1$: $\frac{dz}{dx} > 1 + \frac{g(2) - g(1)}{1+x}$, hence

$z(x) > z(1) + x - 1 + (g(2) - g(1)) \log \left[\frac{1+x}{2} \right]$. However, since the right hand side of the last

inequality is larger, than $1 + x$ for x sufficiently large, we find a contradiction with the assumption $z < 1 + x$. Hence, we conclude that $z(x) = 1 + x$ for some finite $x \geq 0$. \square

We resume the results for real life:

- i) the separatrix gives us a way to determine whether an initial situation will either tend to an endemic state or to extinction of the disease,
- ii) the cutting of the axes by the separatrix shows that our model is able to describe a real life situation in which critical values for the concentration of infectious agents and the number of human infectives exist such that situations with only one of the two populations present can be discriminated in either tending to an endemic state or to extinction.

2.3. A second mathematical model

In section 2.1 we mentioned that, looking at the data of reported new infectives per month in the city of Bari, one might say that considered over a large time-scale the number of new infectives per month is almost constant. However, if we look more carefully and compare several years then we see some kind of periodicity in the data. Every spring and summer the number of new infectives is higher than the number of new infectives during autumn and winter. Therefore, our assumption that the force of infection does not explicitly depend on time t does not seem very reasonable if we want to consider periods of a year.

In order to model this time-dependent force of infection, we mention that the eating of contaminated raw fish is the main cause of the spread of infectious Hepatitis A in the city of Bari, and therefore it seems quite obvious to choose

$$(2.22) \quad \bar{g}(z_1, t) = p(t) \frac{N \alpha z_1^2}{1 + \beta z_1^2}$$

where $p(t)$ is a periodic function with a period of one year and

$$(2.23) \quad 0 \leq p(t) \leq 1 .$$

We interpret p as the time-dependent probability to get infected.

In this way we find a new system of ODE's, viz.

$$(2.24) \quad \begin{cases} \frac{dz_1}{dt} = -a_{11} z_1 + a_{12} z_2 \\ \frac{dz_2}{dt} = p(t) \frac{N \alpha z_1^2}{1 + \beta z_1^2} - a_{22} z_2 \end{cases}$$

and again an analysis of the system is needed to see whether this system can be used to describe the spread of an infectious disease such as Hepatitis A in the city of Bari.

3. The non-autonomous model

The non-autonomous model contains a periodic function p . A condition is derived for the function p that guarantees the existence of a periodic solution of System (2.24).

The following lemma will be proved.

Lemma 1. $\exists C > 0$ such that when $\|p\| = \max_t |p(t)| \leq C$, then there exists a periodic solution of System (2.24).

Proof.

By introducing the variable transformation $\begin{pmatrix} u_1 \\ u_2 \end{pmatrix} = \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} - \begin{pmatrix} q \\ q \end{pmatrix}$ we get the following set of equations

$$(3.1) \quad \begin{cases} \frac{du_1}{dt} = -u_1 + u_2 \\ \frac{du_2}{dt} = -\delta q + f(q) + \hat{p}(t) f(q) + (1 + \hat{p}) f'(q) u_1 + (1 + \hat{p}(t)) f''(\xi) u_1^2 - \delta u_1. \end{cases}$$

Finally, by using vector notation, System (2.24) transforms into

$$(3.2) \quad \frac{d\underline{u}}{dt} = A(t)\underline{u} + \underline{r}(t) + \underline{f}(t, \underline{u})$$

where:

$$\underline{u} = \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} = \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} - \begin{pmatrix} q \\ q \end{pmatrix}$$

$$A(t) = \begin{bmatrix} -1 & 1 \\ f'(q)(1 + \hat{p}(t)) & -\delta \end{bmatrix}$$

$$\underline{r}(t) = \begin{bmatrix} 0 \\ \hat{p}(t) f(q) \end{bmatrix}$$

$$\underline{f}(t, \underline{u}) = \begin{bmatrix} 0 \\ (1 + \hat{p}(t)) h(u_1) \end{bmatrix}$$

$$\hat{p}(t) = p(t) - 1.$$

Remark 0. Since (3.1) has a stationary point in $(0,0)$, $-\delta q + f(q) = 0$.

Remark 1. The function $\hat{p}(t) = p(t) - 1$, represents the deviation of the relative probability from the average relative probability which is of course 1.

Remark 2. The function $h(u_1) = O(u_1^2)$.

Remark 3. The solution of $\dot{\underline{u}} = A(t)\underline{u}$ can be written in the form $\underline{u}(t) = Q(t)e^{Bt}\underline{u}_0$, where $Q(t)$ is a periodic matrix function. If the matrix B has negative eigenvalues, $\underline{u}(t)$ will tend to a periodic solution. We assume that B has negative eigenvalues.

Remark 4. The function $\underline{f}(t, \underline{u})$ in (3.2) can be seen as a perturbation factor that could prevent the existence of a periodic solution. Since we can write $\|\underline{f}\| \leq k_1 \|\underline{u}^2\|$, replacing \underline{f} by $k_1 \underline{u}^2$ only makes the perturbation factor larger. That is, if

$$(3.3) \quad \frac{d\underline{u}}{dt} = A(t)\underline{u} + \underline{r}(t) + k_1 \underline{u}^2$$

has a periodic solution then certainly System 2.24 has one.

Lemma 1 will be proved by deriving the condition for System (3.3) (see remark 4).

Assume that the function $k_1 \underline{u}^2$ is a known function of t . Then the general solution of (3.3) can be determined by applying Floquet's theorem (see remark 3)

$$(3.4) \quad \underline{u}(t) = Q(t)e^{tB} \left[\underline{u}_0 + \int_0^t e^{-\tau B} Q^{-1}(\tau) (\underline{r}(\tau) + k_1 \underline{u}^2) d\tau \right].$$

Since \underline{u} is a periodic solution and therefore is a bounded function,

$$\lim_{t \rightarrow -\infty} \left[\underline{u}_0 + \int_0^t e^{-\tau B} Q^{-1}(\tau) (\underline{r}(\tau) + k_1 \underline{u}^2) d\tau \right] = 0$$

because $\lim_{t \rightarrow -\infty} |\underline{u}(t)| < \infty$. Using this property, \underline{u}_0 can be determined and we end up with the following equation

$$(3.5) \quad \underline{u}(t) = Q(t)e^{tB} \int_{-\infty}^t e^{-\tau B} Q^{-1}(\tau) (\underline{r}(\tau) + k_1 \underline{u}^2) d\tau.$$

Define

$$(3.6) \quad \Phi(\underline{x}) = Q(t)e^{tB} \int_{-\infty}^t e^{-\tau B} Q^{-1}(\tau) (\underline{r}(\tau) + k_1 \underline{x}^2) d\tau.$$

If the function Φ has a fixed point periodic \underline{x}^* , then there exists a periodic solution. The Banach contraction theorem gives conditions which guarantee a fixed point. These conditions are

Condition 1. There must exist a set

$$V = \{ \underline{f} \in C(\mathbb{R}, \mathbb{R}^2) \mid \|\underline{f}\| \leq A, \underline{f} \text{ periodic with period 1 year} \}$$

for which holds that $\Phi : V \rightarrow V$. Where we define $\|\underline{f}\| = \sup_{t \in (0, T)} |f(t)|$ with T equal to one year.

Condition 2. For $\underline{x}, \underline{y} \in V \Rightarrow \|\Phi(\underline{x}) - \Phi(\underline{y})\| \leq L \|\underline{x} - \underline{y}\|$ where $0 \leq L < 1$.

If these conditions are fulfilled, then Φ has a fixed point.

Let us look if we can formulate the conditions in explicitly.

Condition 1:

We start with a few remarks.

Remark 5. Let $\|\underline{r}\| \leq \hat{B}$ where \hat{B} is a positive constant.

Remark 6. If α is the largest eigenvalue of B , then there exists a $0 < \sigma < -\alpha$ such that $\|e^{(t-\tau)B}\| \leq k_2 e^{(t-\tau)\sigma}$.

Remark 7. The elements of Q , $[Q(t)]_{ij}$, are continuous periodic functions. Therefore they have a maximum on the interval $[0, T]$. So, we can write $\|Q\| \leq k_3$, where k_3 is a positive constant.

Using Remark (5) to (7), we end up with the following relation when the condition 1 is applied.

$$(3.7) \quad \beta \hat{B} + \beta k_1 A^2 \leq A \Rightarrow \hat{B} \leq \frac{A(1 - \beta k_1 A)}{\beta}$$

where β is a positive constant.

Further, note that if \underline{x} is periodic $\Phi(\underline{x})$ is also periodic.

Condition 2:

The second condition in the Banach-contraction theorem states that

$$(3.8) \quad \forall \underline{x}, \underline{y} : \|\Phi(\underline{x}) - \Phi(\underline{y})\| \leq L \|\underline{x} - \underline{y}\|$$

where $0 \leq L < 1$. If this condition is worked out, we get

$$(3.9) \quad \|\Phi(\underline{x}) - \Phi(\underline{y})\| = \|k_1 Q(t) e^{tB} \int_{-\infty}^t e^{-\tau B} Q^{-1}(\tau) (\underline{x} - \underline{y}) (\underline{x} + \underline{y}) d\tau\|$$

$$\leq \beta k_1 2A \|\underline{x} - \underline{y}\|.$$

So, condition 2 results into the following relation

$$(3.10) \quad 2\beta k_1 A < 1 \Rightarrow A < \frac{1}{2\beta k_1}.$$

Combining the Relations (3.7) and (3.10) gives us the constant C we were looking for.

$$(3.11) \quad \|p\| \leq \frac{1}{4f(q)\beta^2 k_1} = C .$$

□

Numerical analysis showed that a periodic solution does exist. Therefore we assume that the function p fulfills the relation 3.11.

4. Estimation of the parameters

In this section we try to estimate the parameters of the model. This can be done partly by medical experience [1]. The model we consider is a slight variation of model 3.1

$$(4.1) \quad \begin{cases} \dot{v}_1(\tau) = -v_1(\tau) + v_2(\tau) \\ \dot{v}_2(\tau) = -\delta v_2(\tau) + g(v_1(\tau), \tau) \end{cases}$$

where $g(v_1(\tau), \tau)$ is the rate of *new* infectives per time unit, with

$$g(v_1(\tau), \tau) = \alpha(\tau) \frac{v_1^2(\tau)}{1 + \beta' \cdot v_1^2(\tau)}$$

and $\alpha(\tau) = \alpha' \bar{p}(\tau)$. From medical sources the following parameters can be obtained:

$$\frac{1}{a_{11}} = \text{mean lif-time of an infectious agent} \approx 3 \text{ days}$$

$$\frac{1}{a_{22}} = \text{mean infectious period of an infective} \approx 30 \text{ days}$$

$$\delta = \frac{a_{22}}{a_{11}} \approx \frac{1}{10}$$

d = incubation time ≈ 15 days

one time is $1/a_{11}$ days

the period P of $\alpha(t)$ is 360 days .

The only parameters left to be estimated are $\alpha(\tau)$ and β' . This must be done with the following empirical data:

$$N_i = \text{newly reported infectives}^1 \text{ during } [\tau_{i-1}^*, \tau_i^*) \quad i = 1, \dots, M$$

$\tau_0^* < \tau_1^* < \dots < \tau_M^*$. We assume that all new infectives are reported after a day (incubation time) of d time units. With the definition $\tau_i := \tau_i^* - d$ the following set of M equations can be

¹ See the *'s in figure 11.

found:

$$(4.2) \quad N_i = \int_{\tau_{i-1}}^{\tau_i} g(v_1(\tau), \tau) d\tau \quad i = 1, \dots, M.$$

The idea of both estimation methods is roughly the same:

1. Assume that the data N_i is the data the periodic solution of the system would have generated.
2. This data is about *new* infectives, thus $g(v_1(\tau), \tau)$ can be estimated.
3. Estimate $v_2(\tau)$, with use of the new infectives function g .
4. Solve $v_1(\tau)$ from differential equation 1.
5. Choose a β' , then $\alpha(\tau)$ can be calculated from

$$(4.3) \quad \alpha(\tau) = \frac{g(v_1(\tau), \tau) \cdot (1 + \beta' v_1^2(\tau))}{v_1^2(\tau)}.$$

4.1. Discretisation Method

1. **Assumption 1:** The rate of *new* infectives per time unit $g(v_1(\tau), \tau)$ at the half of period i equals the number of new infectives in that period times δ .
2. With assumption 1 we find $g(v_1(\frac{\tau_i - \tau_{i-1}}{2}), \frac{\tau_i - \tau_{i-1}}{2}) = N_i \delta$. Thus M values of g are obtained. With cubic splining this can be interpolated for all values of τ in a smooth function $N(\tau)$. See the dotted line in figure 11.
3. With the obtained approximation of the rate of new infectives per time unit $N(\tau)$ and the fact that the average duration of infectiveness is $a_{11}/a_{22} = \frac{1}{\delta}$ time units we approximate

$$v_2(\tau) = \int_{\tau-1/\delta}^{\tau} N(t) dt.$$

See the dotted line in figure 12.

4. To calculate $v_1(\tau)$ we use Euler backward on the first differential equation and find $v_1(\tau) - v_1(\tau-h) \approx -v_1(\tau)h + v_2(\tau)h$ which can be rewritten using the periodicity of v_1 and v_2 in

$$\begin{bmatrix} 1+h & & & -1 \\ -1 & 1+h & & \\ & \ddots & \ddots & \\ & & -1 & 1+h \end{bmatrix} \begin{bmatrix} v_1(0) \\ v_1(h) \\ \vdots \\ v_1(P-h) \end{bmatrix} \approx h \begin{bmatrix} v_2(0) \\ v_2(h) \\ \vdots \\ v_2(P-h) \end{bmatrix}.$$

See the dotted line in figure 13.

5. Finally if we assume $\beta' = 0.001$ then $\alpha(t)$ can be calculated with equation 4.3². See the dotted line in figure 14.

4.2. Method with finite trigonometric series

The following notation³ will be used: $f \in \text{FTS}(K, P)$ if

$$f(\tau) = a_0 + \sum_{i=1}^K (a_i \cos(i \frac{2\pi}{P} \tau) + b_i \sin(i \frac{2\pi}{P} \tau)).$$

1. **Assumption 2:** $v_1 \in \text{FTS}(K, P)$.

It is easily verified that this implies:

$$\dot{v}_1 \in \text{FTS}(K, P) \Rightarrow v_2 \in \text{FTS}(K, P) \Rightarrow \dot{v}_2 \in \text{FTS}(K, P) \Rightarrow g(v_1(\tau), \tau) \in \text{FTS}(K, P).$$

2. With the previous assumption that $g(v_1(\tau), \tau)$ is a *FTS* function with coefficients $a_0, \dots, a_K, b_1, \dots, b_K$ equation 4.2 can be rewritten as

$$(4.4) \quad A \cdot a + B \cdot b = N$$

with

$$A \cdot a = \begin{bmatrix} \int_{\tau_0}^{\tau_1} 1 dt & \int_{\tau_0}^{\tau_1} \cos(\phi\tau) dt & \cdots & \int_{\tau_0}^{\tau_1} \cos(K\phi\tau) dt \\ \vdots & \vdots & & \vdots \\ \int_{\tau_{M-1}}^{\tau_M} 1 dt & \int_{\tau_{M-1}}^{\tau_M} \cos(\phi\tau) dt & \cdots & \int_{\tau_{M-1}}^{\tau_M} \cos(K\phi\tau) dt \end{bmatrix} \cdot \begin{bmatrix} a_0 \\ a_1 \\ \vdots \\ a_K \end{bmatrix}$$

and

$$B \cdot b = \begin{bmatrix} \int_{\tau_0}^{\tau_1} \sin(\phi\tau) dt & \cdots & \int_{\tau_0}^{\tau_1} \sin(K\phi\tau) dt \\ \vdots & & \vdots \\ \int_{\tau_{M-1}}^{\tau_M} \sin(\phi\tau) dt & \cdots & \int_{\tau_{M-1}}^{\tau_M} \sin(K\phi\tau) dt \end{bmatrix} \cdot \begin{bmatrix} b_1 \\ \vdots \\ b_K \end{bmatrix} = N = \begin{bmatrix} N_1 \\ \vdots \\ N_M \end{bmatrix}.$$

Equation 4.4 can be solved in least square sense, which results in an estimation of $g(v_1(\tau), \tau)$. See the solid line in figure 11.

² See section 4.3 for an explanation of taking $\beta' = 0.001$.

³ See appendix.

3. $v_2(\tau)$ can be solved from the one dimensional differential equation $\dot{v}_2 = -\delta v_2 + g$ with only one FTS solution⁴. See the solid line in figure 12.
4. Similarly now $v_2(\tau)$ is known, $v_1(\tau)$ can be solved $\dot{v}_1 = -v_1 + v_2$. See the solid line in figure 13.
5. Finally if we take $\beta' = 0.001$ again, we can calculate $\alpha(\tau)$ from equation 4.3. See the solid line in figure 14.

4.3. Computational Results

We have applied both methods on the averaged data N_i given from the city of Bari. In the FTS method we have taken $K = 3$ and as indicated before, we have taken $\beta' = 0.001$. The results can be seen in figures 11 to 14. For the time scale of these figures we have chosen days with $t = 0$ being the first of january. Furthermore we have taken the length of all months to be 30 days.

The motivation for choosing $\beta' \geq 0.001$ is the following: For every time τ , α can be calculated from g , v_1 and β' . From figures 11 and 13 it follows that $g/\delta \approx v_1$, where $2 < g < 9$. We have taken g fixed and $v_1 = 10g$, so α is a function of β' . The stable attractor q can also be calculated now as a function of β' . We expect that $q \approx v_1$, since the periodic solution should lie close to the attractor. If we plot then ratio q/v_1 against β' , we see that for $\beta' < 0.001$ this fraction explodes (see figure 15). Thus it seems wise to choose $\beta' \geq 0.001$.

On the other hand β' should not be chosen too large, because if $\beta' v_1^2 \gg 1$ then $g(v_1, \tau) \approx \frac{\alpha(\tau)}{\beta'}$. In this case the rate of new infectives would not really depend on the number of infectious agents anymore, and the model wouldn't be of a MEM disease. With v_1 varying between 30 and 90, $\beta' v_1^2$ will vary between 3.6 and 32.4 if $\beta' = 0.004$. Thus it seems wise to choose $\beta' \leq 0.004$.

With these numerical values for $\alpha(\tau)$ and β' , we can test the validity of our model. We see that the fraction $\frac{\alpha(\tau)}{\beta'}$ varies between 5.5 and 10. This seems very reasonable since this fraction should equal the (maximum) rate of new infectives per 3 days (lifetime of an infectious agent), if the population of infectious agents is infinite. And in figure 11 we see that this rate varies between 2 and 9.

Another test for the validity of the model is a simulation. In general we see that $v_1(\tau)$ and $v_2(\tau)$ quickly converge to the calculated functions in figure 12 and 13. A nice feature is seen if v_1 and v_2 are taken as relatively small startvalues in the summer. In this case we see that the disease extincts, which could be what happened in 1974 and 1980. Of course the disease does not really extinct because of various other factors, but as a rough model for the phenomenon of a MEM disease, this model is quite satisfying.

⁴ See appendix

A Finite Trigonometric Series

Definition: A function f is called a finite trigonometric serie with period P (notation $f \in \text{FTS}(K,P)$) if

$$f(t) = a_0 + \sum_{i=1}^K (a_i \cos i\phi t + b_i \sin i\phi t)$$

with $\phi = 2\pi/P$.

Lemma: If $f \in \text{FTS}(K,P)$ with parameters a_0, \dots, a_K and b_1, \dots, b_K then

$$f'(t) = \sum_{i=1}^K (i\phi b_i \cos i\phi t - i\phi a_i \sin i\phi t).$$

Lemma: If $f \in \text{FTS}(K,P)$ with parameters a_0, \dots, a_K and b_1, \dots, b_K , the solution of the differential equation $u' = -\lambda u + f$ is

$$\frac{a_0}{\lambda} + \sum_{i=1}^K \frac{(a_i \lambda - b_i i\phi) \cos i\phi t + (b_i \lambda + a_i i\phi) \sin i\phi t}{\lambda^2 + (i\phi)^2} + ce^{-\lambda t}.$$

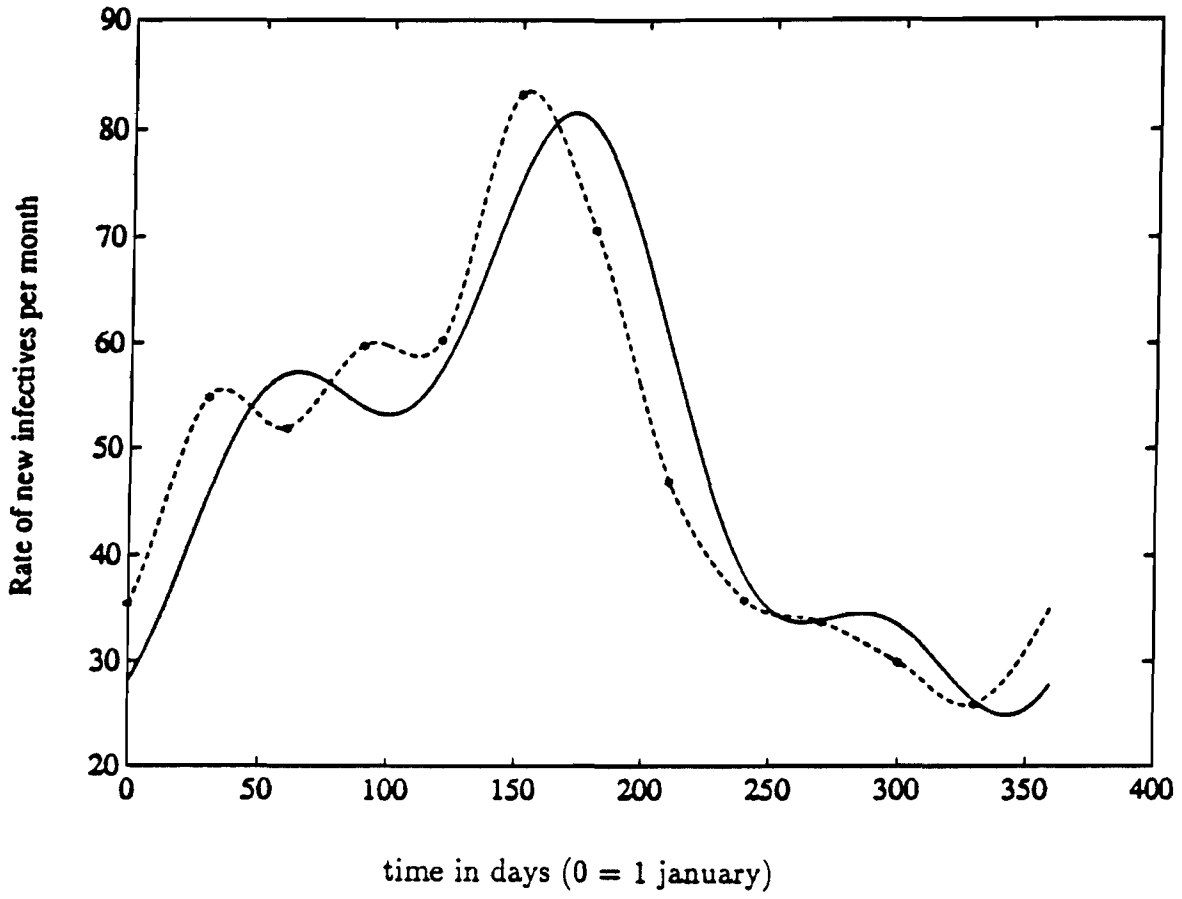


Figure 11.
Rate of new infectives per month.

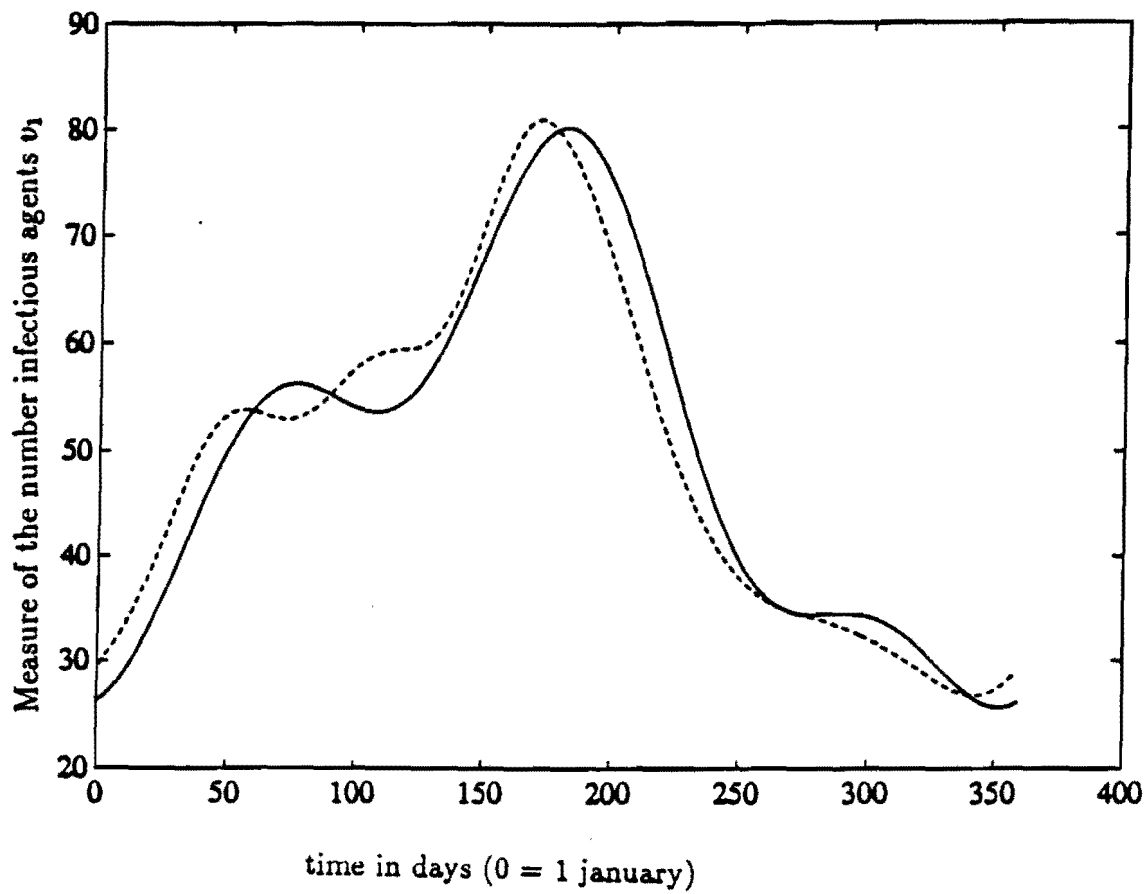


Figure 12.
Measure of the number of infectious agents.

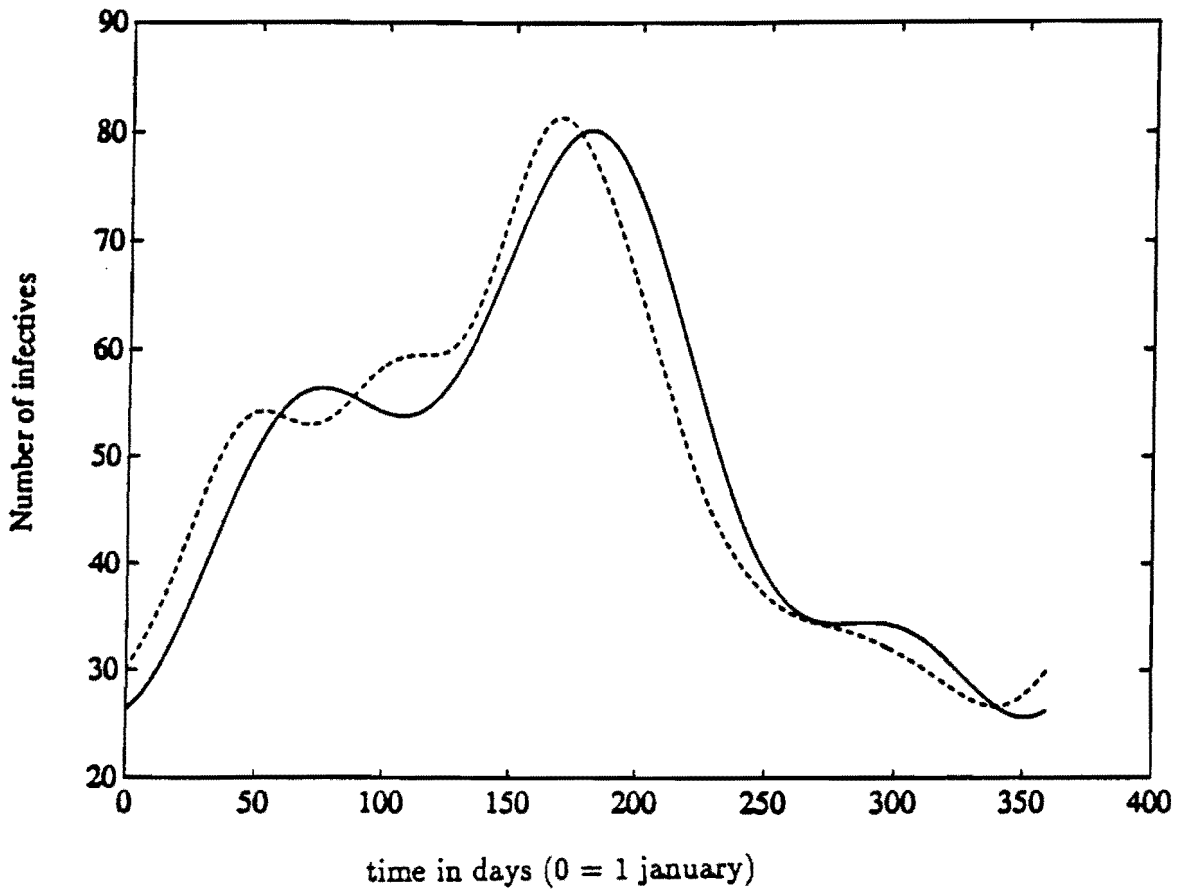


Figure 13.
The number of infectives during a year.

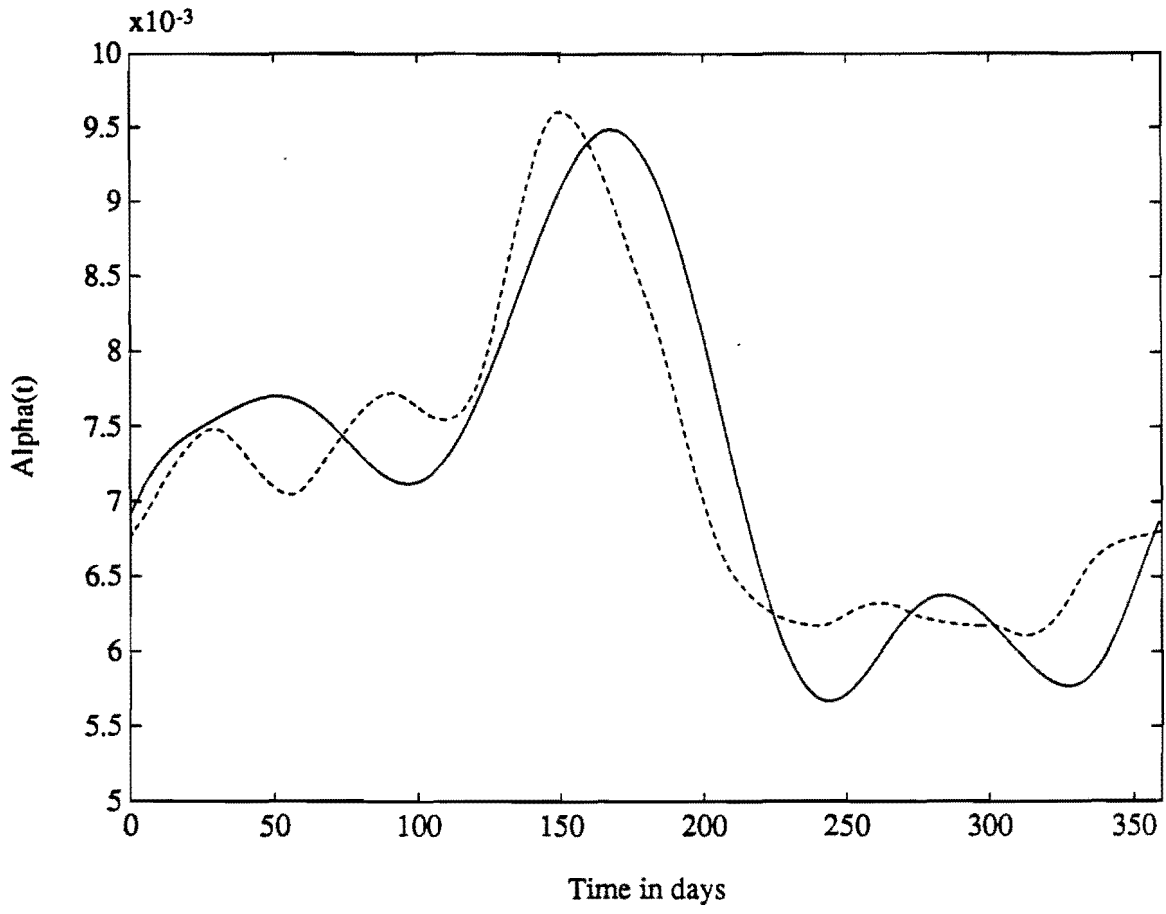


Figure 14.
Estimation of $\alpha(t)$.

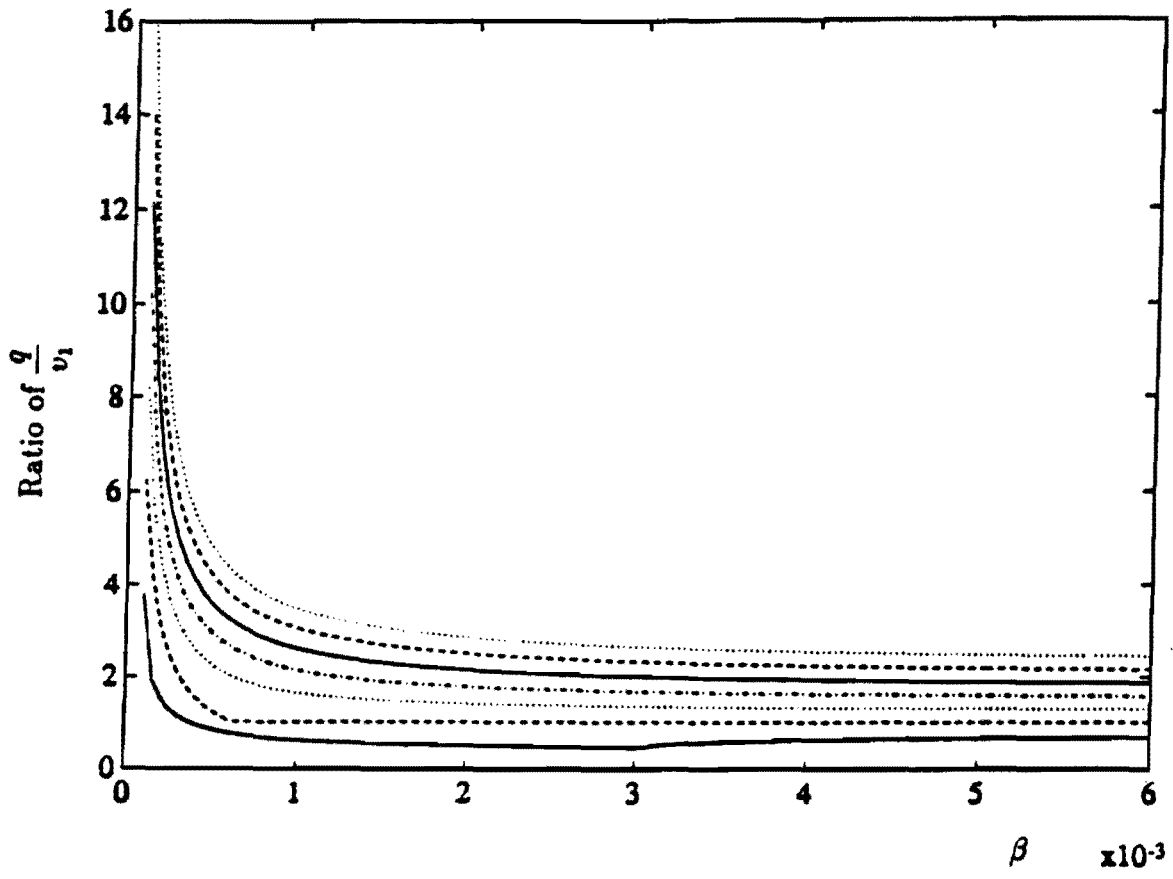


Figure 15.
Ratio of $\frac{q}{v_1}$ for $g = 3, \dots, q$ and $v_1 = 10 \cdot g$.

Acknowledgement

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