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NON-LINEAR DIFFERENTIAL EQUATIONS IN BIOLOGY*

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1. Introduction

In recent years there has been considerable growth in the range of mathematical sciences applied to biology and medicine. For many years the statistics of experimental design had been regarded as the main application in the life sciences, but with the advent of mathematical modelling, both deterministic and stochastic models (see Raymond Flood's lecture to the Easter 1983 Symposium [4]) are gaining widespread acceptance. The introduction of biotechnology courses in Ireland has led to interest in the partial differential equations which arise in biological process engineering, such as the reaction-diffusion equation. Workers in fluid dynamics have linked with medical doctors to consider the equations governing the flow of blood through the heart. Stochastic differential equations arise in population dynamics and interesting problems in branching of solutions of non-linear differential equations have come from transmission in nerve axons and from the study of reversible reactions.

The mathematics involved in biological problems can range from the very recent and sophisticated, such as the sledge-hammer of topological degree theory applied to branching problems, to the ingenious application of the most elementary *ad hoc* methods of classical analysis and geometry, as we shall see in Section 2. But whatever mathematics is used, the final results are only as good as the modelling process employed.

A typical modelling scheme is shown in Figure 1 overleaf. It is rare for this process to flow smoothly from one end to the other. Often the mathematical problem cannot be solved in its original form. A solution may be possible by adding

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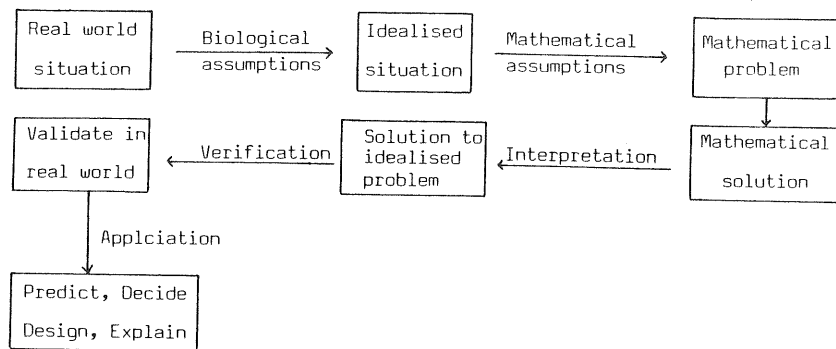


FIGURE 1: The Modelling Process

to the mathematical assumptions, but such assumptions may no longer be in line with the biological reality, with the consequence that the mathematical solution does not make sense when interpreted in the real world. There is an obvious "play-off" between mathematical tractability and biological reality in the model.

There is an enormous temptation for the academic mathematician to pursue only those problems of current, pure mathematical interest, but this should be subordinated to truly interdisciplinary studies, pursued in co-operation with clinical, laboratory and field research workers to provide fresh insight into problems whose solution has important practical consequences. At this time increasing numbers of applied mathematicians throughout the world are finding themselves employed on nuclear, military or defence-related projects. While there is no doubt that an active defence industry is good news for the employment and remuneration of mathematics graduates, many mathematicians in a neutral country would have moral reservations about working on such projects. In biological and medical problems, there exists the opportunity to deploy one's skills, not to add to human suffering, but to alleviate and prevent human misery through the eradication of want and disease.

2. The Predator-Prey Interaction

To give the flavour of biological applications, we present some classical work, carried out fifty years ago by the Italian mathematician, Vito Volterra, best known for his work on integral equations. This has also been used profitably as a case study for advanced undergraduates or master's degree students and appears in Braun's text on differential equations [1].

We consider an environment where a population of prey, numbering $x(t)$ at time t , interacts with a population of predators which numbers $y(t)$. We assume that there are ample resources of food for the prey, but that the prey are the sole source of food for the predators. In the absence of predators the prey population grows at a constant, positive rate a . The number of predator-prey contacts will be proportional to the numbers in each population: let b be the "success" rate, from the predator's viewpoint, of each contact, where b is a positive constant. Using dot for differentiation with respect to time, the rate of change in the prey population is thus

$$\dot{x} = ax - bxy \quad (2.1)$$

For the predators, let $c > 0$ be their natural constant rate of decrease in the absence of prey. But they will increase at a rate proportional to their present number and food supply. Thus

$$\dot{y} = -cy + dxy \quad (2.2)$$

where d is a positive constant.

Heuristic reasoning leads us to expect that, when prey are plentiful, the predators will multiply to a point at which prey are in short supply and starvation leads to a drop in predator numbers. When these have reached a sustainable number, the cyclic process will start again. Is this substantiated by the mathematics?

The equilibrium states of the system comprising (2.1) and (2.2) are clearly at (0,0) and (c/d, a/b). The state at the origin corresponds to no populations present. We restrict attention to the latter state (c/d, a/b), moving this state to the origin by the transformation $X = dx - c$, $Y = by - a$ to obtain

$$\begin{aligned} \dot{X} &= -(X + c)Y \\ \dot{Y} &= (Y + a)X. \end{aligned} \tag{2.3}$$

The corresponding linearised system is

$$\begin{aligned} \dot{X} &= -cY \\ \dot{Y} &= aX \end{aligned} \tag{2.4}$$

which has a pair of purely imaginary characteristic roots $\pm i\sqrt{ac}$. Hence (0,0) is a centre of the linearised system (2.4), and, by the asymptotic perturbation theorem [6, p. 87], will be either a centre or spiral point of the non-linear system (2.3). Fortunately we can find explicit solutions which enable us to distinguish these cases.

An explicit solution of (2.4) is $X(t) = K \cos \sqrt{ac} t$, $Y(t) = K\sqrt{ac} \sin \sqrt{ac} t$, for any constant K , which describes a system of confocal ellipses in the (X,Y)-plane as shown in Figure 2 below

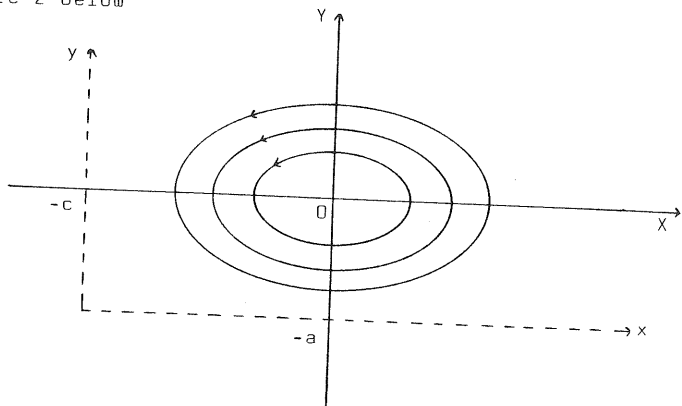


FIGURE 2: Phase-plane of the linear system

There is one for each value of K and the arrows denote the direction of increasing time.

Turning to the non-linear system (2.3), multiplying the equations by $X(Y+a)$ and $Y(X+c)$ respectively and adding yields

$$X(Y + a)\dot{X} + Y(X + c)\dot{Y} = 0.$$

Because both populations are required to be present, both $Y + a$ and $X + c$ are positive and we obtain

$$\frac{X}{X + c} \dot{X} + \frac{Y}{Y + a} \dot{Y} = 0,$$

which may be rearranged as

$$\dot{X} - \frac{c\dot{X}}{X + c} + \dot{Y} - \frac{a\dot{Y}}{Y + a} = 0$$

and integrated directly to give

$$e^{X+Y} = e^k (X + c)^c (Y + a)^a, \tag{2.5}$$

where again k is an arbitrary constant to be determined by the initial conditions. We shall show that this defines a family of closed curves, not spirals, the other possibility, in the positive quadrant.

Lemma 1. Equation (2.5) defines a family of closed curves in

$$X > -c, \quad Y > -a \quad (\text{that is, } x > 0, y > 0)$$

Proof: In original coordinates (2.5) may be written as

$$y^a x^c = K e^{by} e^{dx} \tag{2.6}$$

for some constant K . Define the functions $f(y) = y^a / e^{by}$, $g(x) = x^c / e^{dx}$. Then f vanishes at 0 and $+\infty$, is positive in between and has a single maximum at a/b with maximum value $M = (a/b)^a e^{-a}$. The function g has similar properties with a single maximum of height $m = (c/d)^c e^{-c}$ at c/d .

It follows at once that (2.6) has no solution with $x, y > 0$ if $K > mM$ and the unique solution $x = c/d, y = a/b$ if $K = mM$.

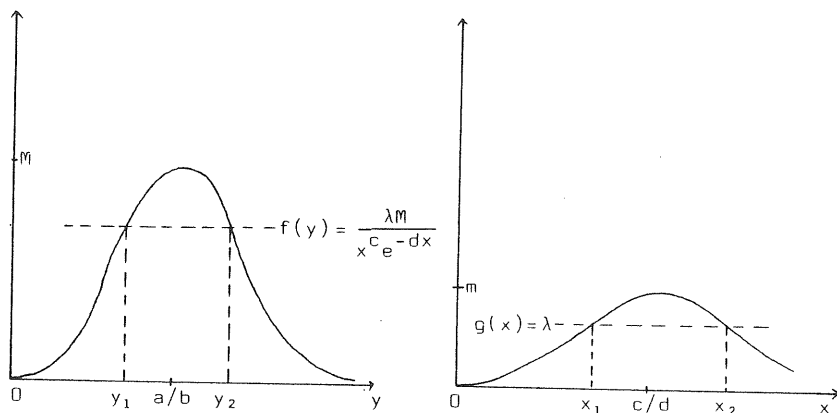


FIGURE 3: The functions f and g

Now let $K = \lambda M$, where $0 < \lambda < m$. We see from Figure 3 that the equation $g(x) = \lambda$ has exactly two solutions x_1 and x_2 lying on opposite sides of c/d . Rewriting the equation $f(y)g(x) = \lambda M$ as

$$f(y) = y^a e^{-by} = \left(\frac{\lambda}{x^c e^{-dx}} \right)^M$$

we see that this has: no solution y when $x < x_1$ or $x > x_2$; exactly one solution $y = a/b$ when $x = x_1$ or x_2 ; and two solutions $y_1(x), y_2(x)$ when $x_1 < x < x_2$. The smaller solution $y_1(x)$ is always less than a/b and $y_2(x)$ always greater. Both tend to a/b as $x \rightarrow x_1$ or x_2 . We note also that $y_2(x)$ is increasing for $x_1 < x < c/d$ and decreasing for $c/d < x < x_2$.

We now conclude that the curves defined by (2.6) are closed in $x > 0, y < 0$ and have the form shown overleaf in Figure 4.

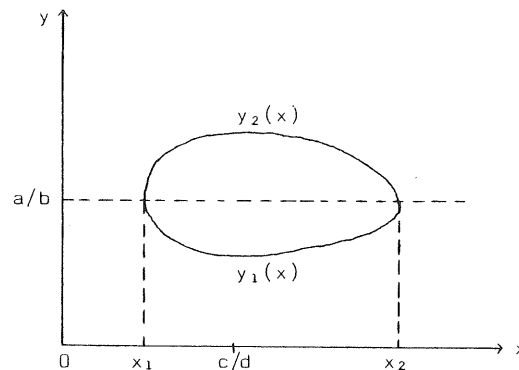


FIGURE 4: A trajectory of the non-linear system

Hence the solution curves of (2.5) are closed for $X > -c, Y > -a$ as required.

Corollary: All solutions of (2.1), (2.2) with positive initial conditions are periodic functions of time.

Lemma 2. Let $x(t), y(t)$ be a solution of (2.1), (2.2) with period $T > 0$. Define the mean values by

$$\bar{x} = \frac{1}{T} \int_0^T x(t) dt, \quad \bar{y} = \frac{1}{T} \int_0^T y(t) dt.$$

Then $\bar{x} = c/d, \bar{y} = a/b$, that is, the mean and equilibrium values coincide.

Proof: Dividing both sides of (2.2) by $y > 0$ and integrating yields

$$\frac{1}{T} \int_0^T \frac{\dot{y}}{y} dt = \frac{1}{T} \int_0^T (-c + dx) dt.$$

Since the left-hand side is zero by periodicity of y , the result $\bar{x} = c/d$ follows on evaluating the right-hand side.

The other result follows similarly by dividing (2.1) by x .

Thus the interpretation of the mathematical model is that the growth of each population can be described as regular increase and decrease around a mean level. From (2.1), if x ever vanishes, then it is zero for all future time. Since we know that for given initial conditions there is exactly one solution of (2.1), (2.2), we conclude that if x is ever positive then it will always remain positive. This means, under the assumptions preceding (2.1), that the prey population can never be wiped out by the predators.

Our next stage is to validate this model against sets of field observations. It may be that we have to modify the model to include more realistic interaction terms $p(x,y)$, $q(x,y)$ where p, q are polynomial functions, giving

$$\begin{aligned} \dot{x} &= ax + p(x,y) \\ \dot{y} &= -cy + q(x,y) \end{aligned}$$

The explicit phase-plane analysis given above holds only for the particularly simple forms of p, q in (2.1), (2.2). In general, it is possible to obtain spiral points, where the sizes of both populations oscillate about longterm equilibrium values.

3. The Effect of Harvesting

Volterra's contribution was to explain the effect of a reduction in fishing levels on fish stocks in the Adriatic, observed by the Italian biologist D'Ancona. He studied the interaction between the predatory selachians (sharks, skates and rays) and the food fish which formed their prey. The table below shows the percentage of selachians in the total catch recorded at the port of Fiume in the years 1914-1923.

1914	1915	1916	1917	1918	1919	1920	1921	1922	1923
11.9	21.4	22.1	21.2	36.4	27.3	16.0	15.9	14.8	10.7

Was the rise in percentage of selachians due to the decreased level of fishing during the First World War or simply part of the predator-prey cycle observed in Section 2?. As the selachians were not in demand for human consumption, there were important implications for the fishing industry.

D'Ancona's theory was that, when fishing was reduced, there were more prey available to the selachians, who flourished and multiplied. Unfortunately, it was found that the absolute numbers of food fish also increased in this period. The theory did not explain why a reduced level of fishing was more beneficial to the predators than their prey.

In [7], Volterra formulated predator-prey equations like (2.1), (2.2) with an extra term to describe the effects of fishing. Assume that fishing decreases the food fish population at rate $\epsilon x(t)$ and the selachian population at rate $\epsilon y(t)$, where ϵ describes the intensity of harvesting. This can be measured by the number of boats at sea or nets in the water: see Clark [2]. We then have

$$\begin{aligned} \dot{x} &= (a - \epsilon)x - bxy \\ \dot{y} &= -(c + \epsilon)y + dxy \end{aligned} \tag{3.1}$$

Provided $a > \epsilon$, the system (3.1) is identical to that of Section 2, with a replaced by $a - \epsilon$ and c by $c + \epsilon$. The mean values of x and y are given by Lemma 2 as

$$\bar{x} = \frac{c + \epsilon}{d}, \quad \bar{y} = \frac{a - \epsilon}{d} \tag{3.2}$$

The ratio of selachians to food fish is seen to be

$$\frac{a - \epsilon}{c + \epsilon} \cdot \frac{d}{b}$$

which increases as ϵ is reduced, accounting for the observed effect. The increase in percentage of selachians is due to a shift in the equilibrium values and not to cyclical variations. We observe also from (3.2) that a moderate amount of harvesting

($\epsilon < a$) actually increased the number of food fish and reduces the number of selachians. An excessive amount of fishing ($\epsilon > a$) leads to the eradication of both populations, with obvious implications for EEC fishing policies in Irish waters.

This result is known in biology as Volterra's principle. It is interesting to note that another distinguished analyst of the same period, G.H. Hardy, also better known to mathematicians in other fields, has his name enshrined in biology through the Hardy-Weinberg ratio in genetics.

4. Other Applications of the Model

The use of insecticides, which destroy both the insect predators and their prey, may have the undesired effect of increasing the population of insect pests kept under control by natural insect predators. The cottony cushion scale insect was accidentally carried from Australia to the U.S.A. in 1868 and spread to such proportions that it threatened the Californian citrus industry. To combat this, the ladybird beetle, a natural predator, was introduced from Australia and succeeded in keeping the scale insect in check. When the insecticide, DDT, was discovered, farmers applied it in an attempt to eradicate the scale insects. Instead they found that, as predicted by Volterra's principle, the scale insect population increased.

Similar effects have been observed in the spraying of lakes to kill off mosquito larvae, which also had the effect of reducing the population of natural predators on the larvae. Spraying of DDT had damaging longterm effects on the environment, while spraying with oil; to reduce the surface tension, causing the eggs to sink, led to pollution of water supplies. Mathematical work on alternative methods for mosquito control has been carried out by a former student, F.M. Dube [3], in 1982. Let $x(t)$, $z(t)$ and $p(t)$ denote the populations of adult female mosquitoes, immature mosquitoes (water-borne larvae) and aquatic predators respectively. The interaction of the two mosquito

populations, in the absence of predators, is shown in Figure 5 below.

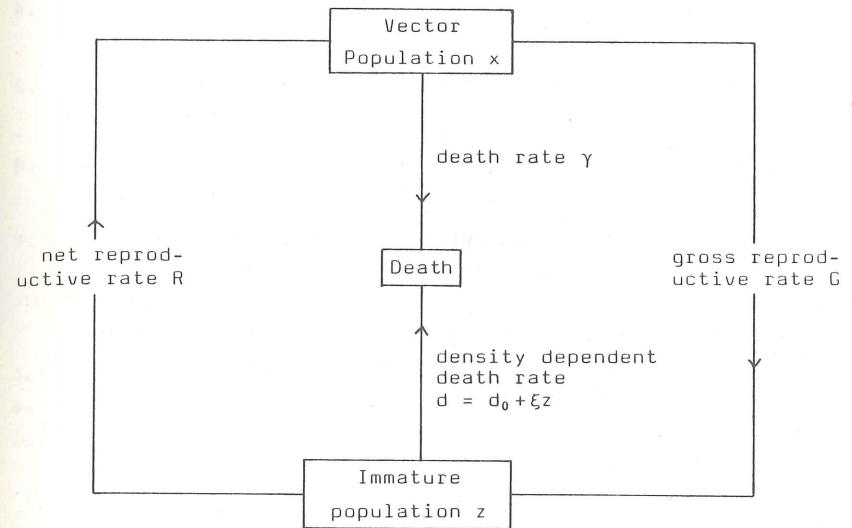


FIGURE 5: Interaction of mosquito population

This is described by the system of equations

$$\begin{aligned} \dot{x} &= -\gamma x + Rz \\ \dot{z} &= Gx - (d_0 + \xi z)z. \end{aligned} \tag{4.1}$$

A key parameter is the reproductive threshold $R_0 = GR/\gamma d_0$ which is interpreted as the average reproductive contribution of one female mosquito to the next generation, roughly the number of viable progeny.

We now introduce an aquatic predator population with carrying capacity (maximum sustainable population) κ , intrinsic growth rate α and rate of kill β . The system (4.1) is modified to:

$$\begin{aligned}\dot{x} &= -\gamma x + Rz \\ \dot{z} &= Gx - (d_0 + \beta p)z - \xi z^2 \\ \dot{p} &= \alpha p(1-p/\kappa) + \beta pz.\end{aligned}\quad (4.2)$$

This system has four equilibrium states

- E_0 : (0,0,0) ; no populations present
- E_1 : (0,0, κ) ; eradication of mosquitoes
- E_2 : ($\hat{x}, \hat{z}, 0$) ; predator fails to thrive
- E_3 : ($\bar{x}, \bar{z}, \bar{p}$) ; control of mosquito population

Let $\beta^* = d_0(R - 1)/\kappa$. It can be shown that, for $R_0 > 1$, the equilibrium states E_0 and E_2 are always unstable. If, in addition, $\beta > \beta^*$, then the equilibrium state E_1 is asymptotically stable, while E_3 (which is of no biological significance in this case) is unstable. Conversely, if $\beta < \beta^*$, then E_3 is asymptotically stable and E_1 is unstable. As $\beta \rightarrow \beta^*$, the states E_1 and E_3 coalesce. We conclude that, for a model with a density dependent death rate, β^* represents the threshold between control and eradication of the mosquito population.

This result has practical implications for the choice of natural predator introduced. For habitats with a low carrying capacity κ , the predatory worm of the genus *Mesostoma* has been found to reduce mosquito emergence by 70 to 90% [5]. In habitats with large κ , the introduction of predatory species of fish, with higher rate of kill β , will prove more effective.

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