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DIFFERENTIAL GROWTH MODELS FOR MICROBIAL POPULATIONS

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1. INTRODUCTION

A number of experimental and theoretical studies have been devoted to the dynamic behaviour of microbial evolution. In this note two basic approaches to deterministic models of microbial growth are discussed. The first one is the classical Monod model [12] in which the population coefficient is determined by a limiting substrate concentration in accordance with the Michaelis-Menten equation. This model was criticized and modified by many authors (see e.g. Edwards [2], Fencl [3], Herbert [6], Jerusalemskii [8], Kuzmin [9], Moser [13], Powell [15], Teissier [17], Young, Bruley, Bungay [19]). J. Monod supposed the substrate concentration to be decreasing proportionaly to the increment of the biomass concentration. In Section 2 we show that this assumption in a rather general setting leads to unrealistic conclusions (Proposition 1). I should like to point out here that all models are discussed mainly from an ecological point of view. As one cannot be sure where the time origin of growth is, the asymptotic behaviour of the models is interesting. This approach allows to reach only qualitative biological conclusions. Throughout this note a little attention is paid to the possibility of reconstruction of the models from experimental data but no comparisons with them are made as the author could not get any serious data to compare the models with reality. In Section 2 it is also mentioned that various modifications of the growth coefficient in the Monod model have the well known Pearl-Verhulst logistic model as the limit case. This last model will play an important role in the sequel for its simplicity though it is not probably very realistic.

The second basic approach which is due to S. N. Hinshelwood [7] takes account of inhibitory factors such as toxic products of metabolism. Although it is less used the author believes that it can yield more realistic results. In Section 3 we first show that the Hinshelwood model is equivalent to the above mentioned Pearl-Verhulst limit case of Monod models if it is supposed that the decrease of the substrate concentration is proportional to the total amount of cells which were produced during the cultivation. This equivalence justifies the use of the second assumption on the

decreasing of the substrate concentration in general models of the Monod type. Proposition 2 concerns their behaviour.

Both these approaches do not allow to describe such features of microbial evolution as oscillation which can be observed (see e.g. May et al. [11]). We mention that already V. Volterra and V. A. Kostitzin ([16], pp. 47–56) used integro-differential models to carry out a calculation based upon the accumulation of toxic products. We do not follow this idea but we try to explain this behaviour either by the lyse of dead cells in nutrient and toxic parts, or by cannibalism of bacteria. In Section 4 a model is deduced which involves a coefficient that measures the realization of toxic activity. If the toxic part is not killing for the population at finite time we show (Section 5) that biologically meaningful solutions have damping oscillations. In other cases the model under certain circumstances possesses unstable limit cycles. Such behaviour looks like biologically reasonable and it has been recently found in various situations (see Oster, Guckenheimer [14] and the references given there). The methods of Section 6 are well known in the bifurcation theory (see e.g. Marsden, McCracken [10]) but the author finds them more instructive than general theorems.

The last section is devoted to applying the preceding models to a chemostat. As a consequence of the multiplicative assumption on toxic activity it is shown that the limit concentration of inhibitory factors is a decreasing function of the dilution rate.

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2. MONOD MODEL

Let M denote the biomass concentration and S the limiting substrate concentration. Then the Monod model can be described by the couple of differential equations:

$$\frac{\mathrm{d}M}{\mathrm{d}t} \equiv \dot{M} = \mu_m \frac{S}{A + S} M , \tag{1}$$

$$\dot{S} + k\dot{M} = 0 , \tag{2}$$

where A, k are positive constants. Solving (2) with initial conditions $M(0) \equiv M_0 > 0$, $S(0) \equiv S_0 > 0$, and substituting in (1) we obtain the following equation of logistic type:

$$\dot{M} = \mu_m \frac{S_0 + k(M_0 - M)}{A + S_0 + k(M_0 - M)} M . \tag{3}$$

It easily follows that the solution M is increasing on the time interval $\langle 0, +\infty)$ and $M_\infty \equiv \lim_{t \to \infty} M(t) = S_0 k^{-1} + M_0$. By (2), the solution S is decreasing on this interval and $S_\infty = \lim_{t \to \infty} S(t) = 0$. In other words, a microbial population is still in-

creasing even if the substrate concentration is very small, and therefore the Monod model can be hardly valid on any large time interval.

In order to simplify the equation (3) we put $x = MM_\infty^{-1}$ and $a = kM_\infty(A + kM_\infty)^{-1}$, $\mu_0 = a\mu_m$. This allows to rewrite (3) in the form

$$\dot{x} = \mu_0 \frac{1 - x}{1 - ax} x . \tag{4}$$

We remark that the coefficients a, μ_0 in this equation can be determined from the inflection of M, i.e., the model can be reconstructed from experimental data. Simple calculation shows that for sufficiently small M_0 $(M_0 < S_0(A + S_0)(kA)^{-1})$ the biomass concentration has an inflection at a positive time t_i at which $M_i \equiv M(t_i) = M_\infty a^{-1}(1 - \sqrt{(1 - a)})$. The ratio $r = M_i M_\infty^{-1}$ is an increasing function of the parameter a with $r(0+) \equiv \lim_{a \to 0+} r(a) = 0{\cdot}5$ and $r(1-) \equiv \lim_{a \to 1-} r(a) = 1$. Moreover, $\dot{M}(t_i) M_\infty = \mu_0 M_i^2$. If M_0 is sufficiently small then t_i is also an increasing function of the parameter a. We also mention that the relative growth model (4) together with (2) is more general than the Monod model as it contains a non determined coefficient M_∞. It means that S_∞ is not necessarily equal to zero.

As has been mentioned in Introduction the classical Monod model was examined experimentally many times. Trying to get a fit with experimental data several authors (see Introduction) came to the conclusion that the growth coefficient in (1) ought to decrease faster and proposed various modifications. We mention two mathematically typical cases which we present in terms of the relative growth rate for the sake of simplicity. For A tending to infinity the relative Monod growth coefficient $f_a(x) = \mu_0(1 - x)(1 - ax)^{-1}$ goes to $f_0(x) = \mu_0(1 - x)$ and the equation (4) is the well known Pearl-Verhulst model which is sometimes used for the growth of batch culture (Brock [1], Williams [18]). The opposite (i.e. convex) relative growth coefficient is obtained by allowing the coefficient a in (4) to be negative (this implies that $M_i \in (0; 0{\cdot}5M_\infty)$), or, more generally, by putting $f(x) = \mu_0(1 - x^b)(1 - ax^b)^{-1}$, $b < 1$, $a < (1 - b)(1 + b)^{-1}$. The reconstruction of the last case from experimental data was examined by Fletcher [5] for $a = 0$ (i.e., for the Richards model) under other circumstances. For further purposes we rewrite the limit Verhulst case in the form

$$\dot{M} = (-\alpha + \beta S) M \tag{5}$$

and the equation (2),

where $\alpha = \beta S_\infty$, $\beta = 2(kM_\infty)^{-1}$, $k = (S_0 - S_\infty)(M_\infty - M_0)^{-1}$, $M_i = 0{\cdot}5M_\infty$.

It is not difficult to generalize various modifications of the Monod model. The general model of this type can be derived from the following two basic assumptions:

I. The growth coefficient for a microbial population depends on the substrate concentration only. No cell deaths and inhibitory factors are assumed.

II. The decrease of the substrate concentration is proportional to the increment of the biomass concentration.

These assumptions lead to a differential equation

$$\dot{M} = F(S)\, M \tag{6}$$

on a curve

$$S_0 - S = \varphi(M - M_0)\,. \tag{7}$$

Proposition 1. *Let F be an increasing continuous function on an interval $\langle 0, u)$ with a zero point u_1. Let φ be an increasing continuous function on an interval $\langle 0, v)$, $\varphi(0) = 0$. Suppose that for a given $S_0 \in (u_1, u)$ there is $x_1 \in (0, v)$ for which $\varphi(x_1) = S_0 - u_1$. Then for any $M_0 > 0$ there exists a uniquely determined maximal solution $[M, S]$ of the problem (6), (7) which satisfies the initial conditions $M(0) = M_0$, $S(0) = S_0$. This solution is defined on the interval $\langle 0, +\infty)$ on which M is non-decreasing and S is non-increasing. Moreover,* $\lim_{t\to\infty} M(t) = M_0 + x_1$, $\lim_{t\to\infty} S(t) = u_1$.

Proof. The problem (6), (7) reduces to the equation $\dot{M} = G(M)\, M$, where $G(M) = F(S_0 - \varphi(M - M_0))$. As the function G is continuous on the interval $\langle M_0, M_0 + x_1\rangle$ and positive on $\langle M_0, M_0 + x_1)$, there is a maximal interval $\langle 0, t_1)$ on which the solution M is increasing. Because of maximality of t_1, we have $G(M(t_1-)) = 0$, i.e. $M(t_1-) = M_0 + x_1$, and

$$t_1 = \int_{M_0}^{M_0 + x_1} \frac{\mathrm{d}x}{x\, G(x)}\,.$$

If $t_1 < \infty$ then $M(t) = M_0 + x_1$ for $t \geqq t_1$ is a solution. This proves the properties of the solution $[M, S]$. All maximal solutions are forward uniquely determined because the function F changes its sign at u_1.

Remark. We should like to point out the dependence of the limit value M_∞ of a microbial population on its initial value M_0 for a fixed initial value of the limiting substrate concentration S_0. According to our opinion this means that even the general model (6), (7) can be used only in a narow zone of the initial values of the biomass concentration.

3. HINSHELWOOD MODEL

It was mentioned in Introduction that the growth rate of the biomass concentration can be determined by the concentration of toxic products of metabolism of microbial cells. We now sketch a simple model of this type which is due to S. N. Hinshelwood [7]. Let P denote the concentration of toxic products and suppose that

$$\dot{P} = rM\,, \tag{8}$$

where r is a positive constant and the growth coefficient is a decreasing function of P; in the simplest case let

$$\dot{M} = \mu_0(1 - cP)\, M\,, \tag{9}$$

where μ_0, c are positive constants. We wish to find a solution of (8), (9) which satisfies initial conditions

$$P(0) = P_0 \geqq 0\,, \quad M(0) = M_0 > 0\,. \tag{10}$$

By (8), the P-coordinate of the solution is increasing on a maximal time interval $\langle 0, t_1)$ on which the M-coordinate is positive. Therefore

$$\frac{\mathrm{d}M}{\mathrm{d}P} = \frac{\mu_0}{r}(1 - cP)$$

along a part of the trajectory of the solution. It means that the curve $M = c\,\mu_0(2r)^{-1}(P_1 - P)(P - P_2)$, where $P_{1,2} = c^{-1}[1 \pm ((1 - cP_0)^2 + 2rc\mu_0^{-1}M_0)^{1/2}]$, contains this trajectory. Hence and by (8) we have

$$t_1 = \frac{2}{c\mu_0}\int_{P_0}^{P_1} \frac{\mathrm{d}P}{(P_1 - P)(P - P_2)} = +\infty$$

and $M_\infty = 0$, $P_\infty = P_1$. We further suppose that P_0 is rather small, namely that $cP_0 < 1$. Then the M-coordinate is increasing on an interval $\langle 0, t_0)$ $(P(t_0) = c^{-1})$ and it is decreasing on the interval $(t_0, +\infty)$. Hence

$$M_m \equiv \max\{M(t),\ t \in \langle 0, +\infty)\} = M(t_0) + \mu_0(2rc)^{-1}(1 - cP_0)^2\,.$$

Notice that this M_m has the same form as M_∞ for the general Monod model (see Proposition 1). Calculation of an inflection shows that it appears at the time at which $M_i = \frac{2}{3}M_m$ and $\dot{M}_i = \pm M_i^{3/2}(\mu_0 rc)^{1/2}$. For further purposes we denote the experimentally observed coefficient $(2\mu_0 rc)^{1/2}$ by μ. The equation (8) allows to state another interesting conclusion, namely, it follows from (8) that

$$\int_0^{t_0} M(t)\,\mathrm{d}t = \frac{1 - cP_0}{cr} = \frac{2}{\mu}(M_m - M_0)^{1/2}\,,$$

$$\int_{t_0}^{+\infty} M(t)\,\mathrm{d}t = \frac{P - P(t_0)}{r} = \frac{2}{\mu}M_m^{1/2}\,,$$

i.e., less microbial cells are produced during the increasing part of the cultivation then during the decreasing part.

We can also use the value M_m for showing that the equations (8), (9) are nothing else than a logistic equation (see also Finn [4]). Namely, if we put $M = M_m - \mu_0(2rc)^{-1}(1 - cP)^2$ in (9) we obtain

$$\dot{M} = \pm\mu(M_m - M)^{1/2}\, M\,.$$

It is quite obvious that we can proceed in the same way with the problem

$$\dot{M} = (-\alpha + \beta S)\, M\,, \tag{11}$$

$$\dot{S} = -\gamma M\,, \tag{12}$$

$$M(0) = M_0 > 0\,, \quad S(0) = S_0 > \alpha\beta^{-1}\,, \tag{13}$$

where α, β, γ are positive reals. Putting $\alpha = \mu_0 c(P_0 + S_0) - \mu_0$, $\beta = \mu_0 c$, $\gamma = r$ (or $\mu_0 = \beta(P_0 + S_0) - \alpha$, $c = \beta\mu_0^{-1}$) we obtain that the M-coordinate of a solution of (11)–(13) is equal to the M-coordinate of a solution of (8)–(10), while the second coordinates satisfy $S + P = S_0 + P_0$. It is therefore possible to account for the influence of inhibitory factors in the models of the Monod type by taking the equation (12) instead of (2). The coefficient γ would then be a measure of accumulation of inhibitory factors and the ratio $\Delta(S) = |F'(S)\,[F(S)]^{-1}|$, where F is the growth coefficient in (6), would be a measure of toxicity of inhibitory factors. For example, $\Delta(S) = c|1 - cP|^{-1}$ in the case of (11), and this is an increasing function of c. For the classical Monod model (1) we have $\Delta(S) = A[S(A + S)]^{-1}$ and thus the presence of toxic factors can be accounted for by increasing the coefficient A. This conclusion is in agreement with the purpose of the modifications of the growth coefficient which were mentioned in Section 2. By our opinion, the condition (12), which says that the decrement of the substrate concentration is proportional to the total amount of the produced biomass, is more realistic than the condition (7).

We conclude this section with an investigation of a general model of the Hinshelwood type, under which we mean the couple of equations

$$\dot{M} = F(S)\, M\,, \tag{14}$$

$$\dot{S} = -\gamma M\,. \tag{15}$$

Proposition 2. *Let F be a continuous and increasing function on an interval $\langle 0, u)$ with a zero point u_1. If $S_0 \in (u_1, u)$ and M_0 is a positive number then there exists a uniquely determined maximal solution $[M, S]$ of (14), (15), which satisfies the initial conditions $M(0) = M_0$, $S(0) = S_0$. This solution is defined on an interval $\langle 0, t_1)$, on which the S-coordinate is decreasing. Moreover, there is a point $t_0 \in \in (0, t_1\rangle$, such that the M-coordinate is increasing on the interval $(0, t_0)$ and decreasing on the interval (t_0, t_1). The end point t_1 is infinite if and only if*

$$\int_0^{S_0} F(S)\, \mathrm{d}S \leqq -\gamma M_0\,. \tag{16}$$

Only in this case $\lim_{t \to t_1 -} M(t) = 0$ *holds.*

Proof. The function F is continuous and therefore a maximal solution $[M, S]$ of (14), (15) exists for any mentioned initial conditions. As $M_0 > 0$, the S-coordinate

is decreasing on a maximal time interval $(0, t_1)$ and the M-coordinate is positive on it. Hence for the trajectory of this solution the condition

$$M = M_0 + \gamma^{-1} \int_S^{S_0} F(\sigma)\, \mathrm{d}\sigma \equiv H(S) \tag{17}$$

is true. By (15),

$$t = \gamma^{-1} \int_S^{S_0} \frac{\mathrm{d}\sigma}{H(\sigma)} . \tag{18}$$

Using this and the assumption on maximality of t_1 we can state that there exists a point $t_0 \in (0, t_1\rangle$ such that $S(t_0) = u_1$, i.e., the M-coordinate is increasing on the interval $(0, t_0)$ and decreasing on the interval (t_0, t_1). Put $M_1 = M(t_1 -)$ and $S_1 = S(t_1 -)$. There are two possibilities:

(i) $S_1 > 0$ and therefore, by maximality of t_1, $M_1 = 0$. As

$$\left.\frac{\mathrm{d}M}{\mathrm{d}S}\right| S = S_1 = -\gamma^{-1} F(S_1)$$

is finite, it follows from (18) that $t_1 = +\infty$. Moreover, the equality (17) yields

$$0 = M_1 = M_0 + \gamma^{-1} \int_{S_1}^{S_0} F(\sigma)\, \mathrm{d}\sigma \geqq M_0 + \gamma^{-1} \int_0^{S_0} F(\sigma)\, \mathrm{d}\sigma ,$$

i.e., the inequality (16) is fulfilled.

(ii) $S_1 = 0$. It is obvious that a solution $[M, S]$ cannot be extended beyond the time t_1. If the condition (16) is not satisfied, then, by (17), $M_1 = H(0)$ is positive and therefore t_1 is finite. If (16) holds then $M_1 = 0$ and the same method as above yields $t_1 = +\infty$.

Example. Consider the classical Monod equation (1) together with (15). As

$$\int_0^{S_0} \mu_m \frac{S}{A + S}\, \mathrm{d}S \geqq 0 ,$$

t_1 is finite. Moreover, $S_1 = 0$ and $M_1 = \max \{M(t);\ t \in \langle 0, t_1\rangle\}$. These conclusions show that this model is again unrealistic for long time intervals.

4. DERIVATION OF A MORE COMPLEX MODEL

The equivalence of the Hinshelwood model (8)–(10) and the model (11)–(13), which was expressed in terms of the substrate concentration, supplied – at least from the mathematical point of view – a treatment of influences of inhibitory factors as part of the substrate. But this approach does not take account of such features of the microbial evolution as the lyse of dead cells. In the sequel we suppose that dead cells

are desintegrated in two parts, namely into toxic substances and factors which stimulate the growth of the population. In order to avoid mathematical difficulties we further suppose, partly unrealistically, that this process of desintegration can be expressed by differential equations and therefore we shall use neither delay nor integrodifferential models.

Having in mind these phenomena we can treat the microbial evolution as three component model in which a biomass concentration M, a nutrious substrate concentration S and an inhibitory factors concentration F are considered. We normalize the unit of concentration by putting $M + S + F = 1$, intending to express that the other factors have no significance. We introduce influences of the nutriment by the equation (11). It is obvious that one can have many objections against this assumption but we introduce it for the sake of simplicity of mathematical discussion and because the equation (11) is the boundary case between concave and convex relative growth rates (see Section 2). We also point out the above mentioned equivalence with the Hinshelwood model. We are not sure in which form to present influences of toxic products. If the population is only inhibited with a constant rate ω then it either dissapears at a finite time or it is decreasing and exists for arbitrary long time intervals. The equation $\dot{M} = -\omega$ corresponds to the former case which we shall call additive. The latter – multiplicative – case can be realized by the equation $\dot{M} = -\omega M$.

Summarizing, we arrive at the following equations:

$$M + S + F = 1\,, \tag{19}$$

$$\dot{S} = -\gamma M + \varkappa F\,, \tag{20}$$

$$\dot{M} = (-\alpha + \beta S)\, M - \omega F \tag{21}$$

for the additive model. The multiplicative model consists of (19), (20) and

$$\dot{M} = (-\alpha + \beta S - \omega F)\, M\,. \tag{22}$$

Equations (21), (22) are special cases of the following more complex case:

$$\dot{M} = (-\alpha + \beta S - \omega_1 F)\, M - \omega_2 F\,. \tag{23}$$

It is obvious that the models can be reduced to the couple of differential equations for the concentrations M and S. We shall investigate these equations mainly in the set $\mathscr{B} = \{[M, S];\ M \geqq 0,\ S \geqq 0,\ M + S \leqq 1\}$, which is biologically meaningful. Further, we shall make two basic assumptions. We suppose that the vector field is directed into the set $\mathscr{B}$ on the part $\mathscr{B}_1 = \{[M, S];\ M + S = 1,\ M > 0,\ S > 0\}$ of the boundary of $\mathscr{B}$. Simple calculation shows that this assumption is equivalent to the inequality

$$\gamma \geqq \beta - \alpha \tag{24}$$

for all introduced models. It can be seen that the models have exactly two stationary points and the second assumption is concerned with the behaviour of solutions near

the stationary point $M_1 = 0$, $S_1 = 1$. We require this point to be a saddle point of the systems. It seems to be also biologically reasonable. By calculation, this hypothesis is equivalent to the assumption that the second stationary point $[M_2, S_2]$ belongs to the interior of the set $\mathscr{B}$ and leads to the condition

$$\varkappa(\beta - \alpha) > \omega_2 \gamma \,. \tag{25}$$

First of all we investigate the multiplicative model in the next section and postpone the general case to Section 6. By re-scaling the time parameter and values of concentration M and S one can come to the following couple of equations ($\tau = kt$ with $k = \omega_2 + \beta - \alpha > 0$):

$$\frac{\mathrm{d}x}{\mathrm{d}\tau} \equiv x' = (1 - y + ax)\, x - by \,, \tag{26}$$

$$y' = x - cy \,,$$

where our previous assumptions mean that $a \geqq 0$, $b \geqq 0$, $c > b$, $ac < 1$ and the stationary point $[0, 0]$ is a saddle point. We remark that $a = 0$ in the additive model and $b = 0$ in the multiplicative case.

5. MULTIPLICATIVE MODEL

This model has two stationary points, namely $M_1 = 0$, $S_1 = 1$, and

$$M_2 = \frac{\varkappa(\beta - \alpha)}{\beta(\gamma + \varkappa) + \omega\gamma} \,, \quad S_2 = \frac{\alpha(\gamma + \varkappa) + \omega\gamma}{\beta(\gamma + \varkappa) + \omega\gamma} \,. \tag{27}$$

If we put $x = \omega(M - M_2)$, $y = \omega(M - M_2) + (\beta + \omega)(S - S_2)$, eliminate F and denote $\varepsilon = \omega M_2 - \varkappa$, then the system (19), (20), (22) has the following form:

$$\dot{x} = y(x + \varepsilon + \varkappa) \,, \tag{28}$$

$$\dot{y} = -\frac{\varkappa}{\varepsilon + \varkappa}\, x(\beta - \alpha - y) + \frac{\varepsilon y}{\varepsilon + \varkappa}\,(x + \varepsilon + \varkappa) \,. \tag{29}$$

It is easy to see that, by omitting the second term in (29), we obtain the system with the first integral

$$W(x, y) = y + (\beta - \alpha)\log(\beta - \alpha - y) - \frac{\varkappa x}{\varepsilon + \varkappa} + \varkappa \log(x + \varepsilon + \varkappa) \tag{30}$$

in the domain $x > -\varepsilon - \varkappa$, $y < \beta - \alpha$, which contains the image of $\mathscr{B}$.

Lemma. *Let the function W be defined by* (30) *and* $\Gamma_c = \{[x, y];\ W(x, y) = c\}$. *Then Γ_c is a closed curve which tends to the origin with increasing c.*

Proof. Denote $\varphi(x) = -\varkappa(\varepsilon + \varkappa)^{-1} x + \varkappa \log(x + \varepsilon + \varkappa)$ and $\psi(y) = y + (\beta - \alpha) \log(\beta - \alpha - y)$. φ and ψ are evidently concave functions. As $\max \{W(x, y);\ x > -\varepsilon - \varkappa,\ y < \beta - \alpha\} = \varphi(0) + \psi(0)$, we have $\Gamma_c = \emptyset$ for $c > \varphi(0) + \psi(0)$ and $\Gamma_c = [0, 0]$ for $c = \varphi(0) + \psi(0)$. If $c < \varphi(0) + \psi(0)$ then there exist exactly two points $x_1 < 0 < x_2$ such that the inequality $\varphi(x) > c - \psi(0)$ holds if and only if $x \in (x_1, x_2)$. For any such x there exist exactly two points $y_1(x) < 0 < y_2(x)$ for which $W(x, y_i(x)) = c$, $i = 1, 2$. This proves that Γ_c is a closed curve. As x_1 is an increasing function of c and x_2 is a decreasing function of c, the curves Γ_c tend to the origin with c increasing to $\varphi(0) + \psi(0)$.

Proposition 3. *Let the conditions* $\gamma \geqq \beta - \alpha > 0$ *be satisfied. If* $[M(t), S(t)]$ *is a solution of* (19), (20), (22) *with an initial condition* $[M(0), S(0)] \in \mathscr{B}$, $M(0) > 0$, *then*

$$\lim_{t \to \infty} M(t) = M_2\,, \quad \lim_{t \to \infty} S(t) = S_2\,.$$

Proof. By expressing a solution $[M(t), S(t)]$ in terms of x, y we have

$$\frac{\mathrm{d}}{\mathrm{d}t} W(x(t), y(t)) = -\frac{\varepsilon}{\varepsilon + \varkappa} y^2(t) \frac{x(t) + \varepsilon + \varkappa}{\beta - \alpha - y(t)} > 0\,,$$

because $\varepsilon < 0$, $\varepsilon + \varkappa > 0$, and $x(t) > -\varepsilon - \varkappa$ (as $M(t) > 0$), $y(t) < \beta - \alpha$ (this follows from the form of the vector field and the coefficients inequalities). Therefore, the solution $[x(t), y(t)]$ crosses the curve Γ_c from the exterior to the interior. This fact together with the preceding lemma proves the statement.

We should like to point out that the asymptotic behaviour of a solution does not depend on the coefficients $\varkappa$, ω, whose meaning is rather obscure.

Remark on the determination of coefficients. The multiplicative model contains five coefficients. Two conditions on them are given by (27). Observing the first maximum and minimum values of M one can get two independent conditions on α, β, ω. The last condition on γ, $\varkappa$ can be obtained from the first minimum value of S. Unfortunately, the author was not able to get any serious experimental data to compare the model with reality.

6. GENERAL MODEL

The discussion of this model, i.e. the system (26), is more complicated and the results will not be so complete as for the multiplicative case. The stationary points of (26) are $[0, 0]$ and

$$x_2 = \frac{c - b}{1 - ac}\,, \quad y_2 = \frac{c - b}{c(1 - ac)}\,. \tag{31}$$

If we put $2\varepsilon = bc^{-1} + a(c - b)(1 - ac)^{-1} - c$ then the matrix of the linearized

system near the stationary point $[x_2, y_2]$ has the eigenvalues $\lambda_{1,2} = \varepsilon \pm (\varepsilon^2 + b - c)^{1/2}$. Thus the stationary point $[x_2, y_2]$ is locally asymptotical stable for $\varepsilon < 0$ and it is unstable for $\varepsilon > 0$. The following figure 1 shows the dependence of the asymptotic behaviour near to $[x_2, y_2]$ on the coefficients $\varkappa, \omega$ for the additive model (19)–(21).

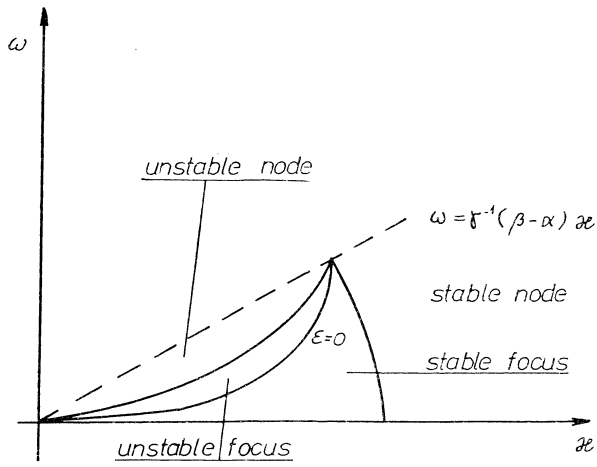

Fig. 1.

The case $\varepsilon = 0$ and existence of limit cycles for ε near zero will be studied by the standard bifurcation techniques (see e.g. Marsden, McCracken [10]). Instead of using the general Hopf theorem we shall show the main steps of the method. We restrict the parameter ε to the interval $(-(c - b)^{1/2}, (c - b)^{1/2})$ and put $v = (c - b - \varepsilon^2)^{1/2}$. Then the system (26) can be transformed into the following polar coordinate form:

$$r' = r[\varepsilon + r A(\varphi) \cos \varphi] = F_1(r, \varphi), \tag{32}$$

$$\varphi' = v - r A(\varphi) \sin \varphi = F_2(r, \varphi), \tag{33}$$

where $v A(\varphi) = [v \cos \varphi + (c + \varepsilon) \sin \varphi][av \cos \varphi + (a(c + \varepsilon) - 1) \sin \varphi]$.

We shall investigate the last system in the whole plane. It has the solution $r(\tau) = 0$, $\varphi(\tau) = v\tau$. Define the map

$$\Phi(\varrho, \tau, \sigma) = \begin{pmatrix} \varrho + \int_0^\tau F_1(r(t), \varphi(t))\, \mathrm{d}t - \sigma \\ \int_0^\tau F_2(r(t), \varphi(t))\, \mathrm{d}t - 2\pi \end{pmatrix},$$

where $[r(\tau), \varphi(\tau)]$ is a solution of (32), (33) which satisfies the initial condition $r(0) = \varrho$, $\varphi(0) = 0$. By the implicit function theorem, one can find $\varrho_0 > 0$, $\tau_0 > 0$,

$\sigma_0 > 0$ such that for any $\varrho \in (-\varrho_0, \varrho_0)$ there exists exactly one $\bar{\tau} \in (2\pi v^{-1} - \tau_0, 2\pi v^{-1} + \tau_0)$, and $\sigma \in (-\sigma_0, \sigma_0)$ for which $\Phi(\varrho, \bar{\tau}, \sigma) = 0$. It means that the above mentioned solution $[r(\tau), \varphi(\tau)]$ is defined on the interval $\langle 0, \bar{\tau} \rangle$ and $r(\bar{\tau}) = \sigma$, $\varphi(\bar{\tau}) = 2\pi$.

Denote by P the Poincaré map $P(\varrho, \varepsilon) = \sigma(\varrho, \varepsilon) - \varrho$. Positive ϱ-coordinates of zero points of P correspond to periodic solutions of (26). The φ-coordinate of a solution is increasing (see (33)) for a sufficiently small ϱ_0, and hence the time variable can be eliminated. So we have

$$\frac{\mathrm{d}r}{\mathrm{d}\varphi} = \frac{F_1(r, \varphi)}{F_2(r, \varphi)}, \quad r(0) = \varrho. \tag{34}$$

Moreover, ϱ_0 can be chosen so small that a solution $r(\varphi, \varrho)$ of (34) is an analytical function of ϱ, i.e.

$$r(\varphi, \varrho) = \sum_{n=1}^{\infty} a_n(\varphi, \varepsilon)\, \varrho^n .$$

Substituting this in (34) we obtain the following infinite system of differential equations:

$$\frac{\mathrm{d}a_1(\varphi)}{\mathrm{d}\varphi} = \varepsilon v^{-1}\, a_1(\varphi), \quad a_1(0) = 1,$$

$$\frac{\mathrm{d}a_2(\varphi)}{\mathrm{d}\varphi} = \varepsilon v^{-1}\, a_2(\varphi) + v^{-2} A(\varphi)(v \cos\varphi + \varepsilon \sin\varphi)\, a_1^2(\varphi), \quad a_2(0) = 0,$$

$$\frac{\mathrm{d}a_3(\varphi)}{\mathrm{d}\varphi} = \varepsilon v^{-1}\, a_3(\varphi) + v^{-2} A(\varphi)(v \cos\varphi + \varepsilon \sin\varphi) \cdot$$

$$\cdot [2\, a_2(\varphi) + v^{-1} A(\varphi)\, a_1^2(\varphi) \sin\varphi]\, a_1(\varphi), \quad a_3(0) = 0, \ldots .$$

As we are interested in the nonzero roots of $P(\varrho, \varepsilon)$, we put

$$f(\varrho, \varepsilon) = \left\langle \begin{array}{ll} \varrho^{-1} P(\varrho, \varepsilon) & \text{for } \varrho \neq 0 \\ \dfrac{\partial P}{\partial \varrho}(0, \varepsilon) & \text{for } \varrho = 0 \end{array} \right\rangle =$$

$$= \exp(2\pi v^{-1}\varepsilon) - 1 + \sum_{n=1}^{\infty} a_{n+1}(2\pi, \varepsilon)\, \varrho^n ,$$

and hence $f(0, 0) = 0$, $(\partial f/\partial \varepsilon)(0, 0) = 2\pi v^{-1} \neq 0$, $(\partial f/\partial \varrho)(0, 0) = a_2(2\pi, 0) = 0$. This allows to use the implicit function theorem which yields $\varrho_1 > 0$, $\varepsilon_1 > 0$ such that for every $\varrho \in (0, \varrho_1)$ there exists exactly one $\varepsilon \in (-\varepsilon_1, \varepsilon_1)$ satisfying $f(\varrho, \varepsilon) = 0$. It means that there is a closed trajectory of the system (26) passing through the point $[x_2 + \varrho, y_2]$. Further, we have $(\mathrm{d}\varepsilon/\mathrm{d}\varrho)(0) = 0$ and

$$\frac{\mathrm{d}^2\varepsilon}{\mathrm{d}\varrho^2} = -\left[\frac{\partial f}{\mathrm{d}\varepsilon}(0, 0)\right]^{-1} \cdot \frac{\partial^2 f}{\partial \varrho^2}(0, 0) = -\frac{v}{2\pi}\, 2a_3(2\pi, 0) = -\frac{b(1 - ac)}{2v^4 c}(1 - 2ac).$$

For example, if $2ac < 1$ (i.e. $\omega_1 \varkappa < \beta(\gamma + \varkappa)$) then the function $\varepsilon(\varrho)$ has a local maximum at $\varrho = 0$. It follows that periodic solutions of the system (19), (20), (23) occur for negative values of the parameter ε. Moreover, a continuity argument yields $\varrho_2 > 0$, $\varepsilon_2 > 0$ such that for any $\tilde{\varepsilon} \in (-\varepsilon_2, 0)$ there exists one and only one $\tilde{\varrho} \in (0, \varrho_2)$ for which $\tilde{\varepsilon} = \varepsilon(\tilde{\varrho})$.

In order to examine the stability of periodic solutions we fix $\bar{\varrho} \in (-\varrho_1, \varrho_1)$ and $\bar{\varepsilon} = \varepsilon(\bar{\varrho})$ and put $h(\bar{\varrho}) = (\partial P/\partial \varrho)(\bar{\varrho}, \varepsilon(\bar{\varrho}))$. As $h(0) = 0$, $h'(0) = 0$, $h''(0) = 4a_3(2\pi, 0)$ and

$$\lim_{\varrho \to \bar{\varrho}} \frac{\sigma(\varrho, \bar{\varepsilon}) - \bar{\varrho}}{\varrho - \bar{\varrho}} = 1 + h(\bar{\varrho}),$$

we can state that for $2ac < 1$ (i.e. $a_3(2\pi, 0) > 0$) and sufficiently small positive $\bar{\varrho}$ the corresponding periodic solution is unstable. Our investigation also shows that there is no small periodic solution for $\varepsilon \geqq 0$ in the case $2ac < 1$, $b > 0$. The following figures show typical cases of global behaviour of solutions in dependence on the increasing parameter ω_1.

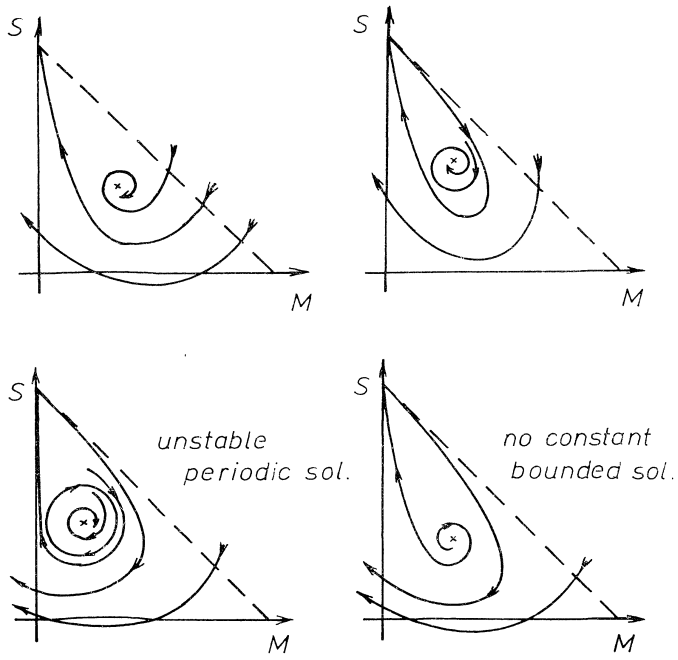

Fig. 2.

Analogously, opposite results hold for $2ac > 1$.

7. APPLYING THE MODELS TO A CHEMOSTAT

We suppose that a chemostat has a constant dilutation rate v and the evaluation for $v = 0$ can be described by the equations (19), (20), (23). As the study of the additive model is similar (although more complicated and not so complete) as in the multiplicative case, we shall be concerned with the last one only. The above assumptions lead to the equations

$$\begin{aligned} \dot{M} &= (-\alpha + \beta S - \omega F) M - vM , \\ \dot{S} &= -\gamma M + \varkappa F + v(1 - S) , \\ \dot{F} &= (\gamma + \omega F) M - \varkappa F - vF . \end{aligned} \tag{35}$$

Denoting $X = M + S + F$ and summing these equations, one obtains $\dot{X} = v(1 - X)$. If the initial condition $X(0) = 1$ is supposed, then $X(t) = 1$ for all positive t and therefore the system (35) can be rewritten in the form

$$\begin{aligned} \dot{M} &= [-(\alpha + \omega - v) + (\beta + \omega) S + \omega M] M , \\ \dot{S} &= v + \varkappa - (\gamma + \varkappa) M - (\varkappa + v) S . \end{aligned}$$

This system has two stationary points, namely $M_1 = 0$, $S_1 = 1$, and

$$M_2(v) = \frac{(v + \varkappa)(\beta - \alpha - v)}{\beta(\gamma + \varkappa) + \omega(\gamma - v)} , \tag{36}$$

$$S_2(v) = \frac{\alpha(\gamma + \varkappa) + \omega\gamma + v(\gamma + \varkappa - \omega)}{\beta(\gamma + \varkappa) + \omega(\gamma - v)} . \tag{37}$$

The same assumption on the direction of the vector field on the set $\mathscr{B}_1$ as in Section 4 gives also the condition (24) and, under this condition, the stationary point $[M_1, S_1]$ is a saddle point if and only if the dilutation rate fulfils the inequality

$$v < \beta - \alpha . \tag{38}$$

The conditions (24), (38) allow to proceed as in Section 5. The same transformation yields the equations

$$\begin{aligned} \dot{x} &= y(x + \varepsilon + \varkappa + v) , \\ \dot{y} &= -\frac{(\varkappa + v) x}{\varepsilon + \varkappa + v} (\beta - \alpha - v - y) + \frac{\varepsilon y}{\varepsilon + \varkappa + v} (x + \varepsilon + \varkappa + v) , \end{aligned}$$

where $\varepsilon = \omega M_2 - \varkappa - v < 0$, instead of (28), (29), and therefore Proposition 3 remains true. Having in mind the asymptotic behaviour of a chemostat we can ask how the steady state (36), (37) depends on the dilutation rate v. Obviously $(\partial S_2/\partial v) >$

> 0, and as

$$F_2(v) = 1 - M_2(v) - S_2(v) = \frac{\gamma(\beta - \alpha) - v(\gamma + \beta - \alpha - v)}{\beta(\gamma + \varkappa) + \omega(\gamma - v)},$$

we have

$$\frac{\partial F_2}{\partial v} = -\frac{\omega(v - v_1)(v - v_2)}{[\beta(\gamma + \varkappa) + \omega(\gamma - v)]^2},$$

where $\beta - \alpha < v_1 < v_2$, provided the condition (24) is satisfied. Thus $(\partial F_2/\partial v) < 0$ on the set (38). Similarly

$$\frac{\partial M_2}{\partial v} = -\frac{\omega(v - v_3)(v - v_4)}{[\beta(\gamma + \varkappa) + \omega(\gamma - v)]^2},$$

where $v_3 < \beta - \alpha < v_4$, and $v_3 > 0$ (i.e., the steady state M_2 assumes its maximum value at v_3) if and only if

$$\frac{\beta - \alpha}{\varkappa} > \frac{\beta(\gamma + \varkappa) + \omega\gamma}{(\beta + \omega)(\gamma + \varkappa)}. \tag{39}$$

Proposition 4. *Let the condition* (24) *be satisfied, let the dilutation rate* v *be constant and let* (38) *be fulfilled. Then for the initial conditions* $M(0) > 0$, $S(0) > 0$, $M(0) + S(0) \leqq 1$, *the dynamic behaviour of a chemostat* (35) *is such that*

$$\lim_{t \to \infty} M(t) = M_2(v), \quad \lim_{t \to \infty} S(t) = S_2(v),$$

where $M_2(v)$, $S_2(v)$ *are given by* (36), (37). *Moreover,* $\lim_{t \to \infty} F_2(t) = F_2(v)$ *is a decreasing function of* v *and* $M_2(v)$ *assumes its maximum value for the dilutation rate* $v_3 > 0$ *provided the condition* (39) *holds.*

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Souhrn

DIFERENCIÁLNÍ RŮSTOVÉ MODELY PRO MIKROBIÁLNÍ POPULACE

JAROSLAV MILOTA

Na základě studia modelů Monodova a Hinshelwoodova typu jsou v práci odvozeny dva modely mikrobiálního růstu, které uvažují rozklad mrtvých buněk v toxické složky a složky stimulující růst. Jsou dokázány asymptotické vlastnosti modelů a jsou rovněž použity pro popis kontinuální kultivace v chemostatu.

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