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REVIEW ARTICLE

STABILITY ANALYSIS OF MODELS OF CELL PRODUCTION SYSTEMS

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Abstract—We investigate the qualitative behaviour of the models of cell production systems, in the form of systems of nonlinear delay differential equations. Considered are three general models of a system involving the subpopulations of stem cells, precursor cells and mature cells, with different configurations of regulation feedbacks. The models correspond basically to the blood cell production process; however, other applications are possible. First, the simplified version (describable by ordinary differential equations) is considered. Fairly complete characterization of the trajectories is possible in this case, using the Lyapunov functions and phase plane techniques. Next, for the general models, the stability of equations linearized around the equilibria is investigated. Certain results can be obtained here, using both exact methods and numerical procedures based on an original lemma on the zeros of exponential polynomials. Then global properties (boundedness, attractivity, etc.) are examined for the nonlinear, delay case using a range of methods: Lyapunov functionals, Razumikhin functions and direct estimates on solutions. Certain special cases of our models reduce to previous literature models of blood production. Results of our analysis enable to exclude these configurations of regulation feedbacks which yield model behaviour not compatible with biological and medical observations. Techniques developed in this paper are applicable to a wide range of possible models of cell production systems.

1. INTRODUCTION

In this paper, we are going to present elements of a mathematical theory of cell production systems. We will be mainly preoccupied with the analysis of mathematical models in the form of systems of nonlinear difference-differential equations. However, we will derive the models based on their biological background and discuss the biological relevance of the results obtained. Our principal purpose will be to demonstrate in what way the model performance depends on the configuration of regulation feedbacks.

Cell production systems, as understood in this paper, are self-renewing cell populations which maintain the continuous supply of differentiated (functional) cells to various parts of a living organism. The dynamics of cell production systems attracted the attention of biologists and mathematicians a long time ago in the context of blood cell production (cf. Lajtha *et al.*[1]). Despite differences depending on the type of cells considered, certain common elements can be found in all the known cell production systems.

First, there exists a subpopulation of most primitive cells, called the stem cells, which is truly self-renewing. This means that stem cell divisions can produce both stem cells and cells of higher maturity, which will be called the precursor cells. The precursor cells, in turn, produce cells with an even more increased degree of maturity. After a certain

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number of maturation (differentiation) stages, the mature (differentiated) cells are produced. They usually do not have the ability to divide, and after fulfilling their specific tasks, are removed from the organism.

The above description applies, for example, to the blood production systems in animals and humans (see Wichmann[2] and the references therein) but also to the epidermis cell production (see Potten *et al.*[3]) and, possibly, to other systems.

In normal conditions, the cell production system should maintain a constant supply of differentiated mature cells. In the emergency cases when for some reasons the organism suffered from the loss of certain mature cells (like the loss of erythrocytes in a haemorrhage) the system should react, providing for an appropriate period of time an increased supply of cells. These two postulates imply that the system has at least one regulation feedback, detecting the perturbations in the number of mature cells and accordingly adjusting the production rate of the stem and precursor cells. We will call it the long-range feedback.

It is logical to suppose that there exists at least one more regulation feedback. Indeed, the long-range feedback would have a tendency towards "draining" the stem cell population to compensate for the loss. Then, if all the stem cells were committed towards maturation, the whole system would possibly collapse, since only the stem cells are truly self-renewing.

Therefore, another feedback should "cut off" the supply of precursor cells, if the number of stem cells decreases, preventing the system from extinction. This will be called a short-range feedback.

Based on ideas similar to these presented above, numerous mathematical models of cell production systems were constructed, mainly for various lines of the blood forming system in man and in experimental animals. The models vary from simple metaphores of real systems, described by a single equation and analyzed mathematically, to very complex, computer simulated structures. The simple models usually include only one feedback. Thus, for example, Mackey's model[4] describes the effects of a short-range feedback of the stem cell cycle, while Wazewska and Lasota's model[5] includes the long-range feedback only (see also discussion). The comprehensive computer models usually introduce additional feedbacks, corresponding to interactions between the stem and precursor cells, precursor and mature cells, etc. (see Wichmann[2] and Aarnaes[6], for example). These models reproduce details of cell production dynamics, under particular types of stresses, in a variety of experimental conditions.

The effort we undertake in this paper is directed towards understanding the influence of the configuration of the regulation feedbacks on the system performance. We deliberately consider a simplified situation involving the long- and short-range feedback only.

Doing so, we are able to characterize in a rigorous way the system dynamics. Our assumptions are qualitative only. This adds generality to the considerations and allows us to treat some previous models as special cases of our "generalized models."

We do not attempt to provide a complete literature review of the mathematical models of cell production systems. Instead, we refer the reader to an excellent review paper by Wichmann[7] who discusses models of blood cell production systems that constitute the vast majority of systems analyzed mathematically (see also a book by Wichmann[2]). Simple qualitative analysis of regulation functions for the blood stem cells differentiation was provided by Wichmann and Loeffler[8].

The structural model of the cell production system, which is a framework for three models of regulation feedback to be considered, is based on a model of red-blood-cell system introduced in Kimmel and Arino[9]. It is based on the following assumptions (cf. Fig. 1.1).

(1) Stem cell proliferation dynamics is represented by a cell cycle model consisting of two phases: active and passive. A stem cell leaving mitosis enters the passive phase, then

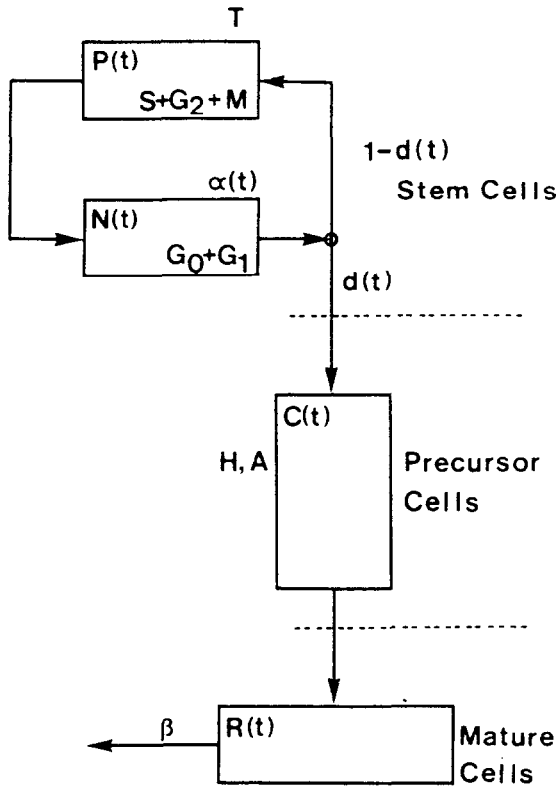

Fig. 1.1. Structural model of a cell production system. $P(t)$, $N(t)$, $C(t)$ and $R(t)$ are the number of active stem cells, passive stem cells, precursor cells and mature cells, respectively. $\alpha(t)$ is the exit rate from the passive stem cell compartment; T is the residence time in the active stem cell compartment; $d(t)$ is the fraction of differentiating stem cells. H and A are the transit time and amplification coefficient of the precursor cell compartment. β is the exit rate from the mature cell compartment.

it may either transform into a more mature precursor cell or enter the active phase (and then divide and enter the passive phase again). It is assumed that the cell residence time in the passive phase has the exponential distribution with parameter α (the reciprocal of the mean residence time in this phase). Such an hypothesis is consistent with the Smith–Martin[10] model of the cell cycle. The probability of stem cell differentiation (transformation) is denoted by d.

The residence time in the active phase is equal to T. As in biological terminology (see Mitchison[11]), we understand that our "active phase" is $S + G_2 + M$, where S stands for the DNA synthesis, G_2 for the premitotic phase and M for the cell division (mitosis). Our "passive phase" is assumed to be $G_0 + G_1$, where G_0 is the resting (quiescent or "storage") phase, while G_1 is the initial growth phase.

(2) Regulated factors are d-probability of stem cell differentiation and α-reciprocal of the mean residence time in the passive phase.

(3) Each stem cell, once differentiated, produces after time H an average number of A mature (completely differentiated) cells. Quantities A and H represent all the stages of the precursor cells maturation, division, etc.

(4) Mature cell life length is a random variable with exponential distribution with expected value $1/\beta$. This is a good approximation for, e.g., the red-blood-cell system (cf. Kimmel and Wazewska-Czyzewska[12, 13]).

Model structure implied by assumptions (1)–(4) is depicted in Figure 1.1. The equation for the stem cell number in $G_0 + G_1$ $[N(t)]$ takes the following form (cf. Kimmel and Arino[9] where a similar equation is derived step by step; also cf. Kimmel[14, 15] for

general methods of modeling the cell cycle kinetics):

$$\dot{N}(t) = -\alpha(t)N(t) + 2[1 - d(t - T)]\alpha(t - T)N(t - T). \tag{1.1}$$

The equation for the number $[R(t)]$ of mature cells is

$$\dot{R}(t) = -\beta R(t) + r(t), \tag{1.2}$$

where $r(t)$ is the rate of cell flow into the mature cell compartment. Assumption (3) implies that

$$r(t) = A\, d(t - H)\alpha(t - H)N(t - H), \tag{1.3}$$

so that

$$\dot{R}(t) = -\beta R(t) + A\,\alpha(t - H)d(t - H)N(t - H). \tag{1.4}$$

We may also compute the number $P(t)$ of cells present at time t in the active phase of the stem cell cycle:

$$P(t) = \int_{t-T}^{t} [1 - d(\tau)]\alpha(\tau)N(\tau)\, d\tau.$$

Equations (1.1) and (1.4) provide a complete description of the cell production system dynamics, if the regulated factors $\alpha(t)$ and $d(t)$ are specified.

In our paper, we will consider three versions of the regulation feedbacks (model 1, 2 and 3; Section 2). They correspond to various biological assumptions. We will try to answer basic questions concerning their qualitative behaviour. It is not easy, since the models are described by systems of two nonlinear difference-differential equations, with the two (generally different) delays T and H. We begin, in Section 3, by studying the special case of $T = H = 0$, i.e. the models reduced to systems of ordinary differential equations. The results of this section are fairly complete and allow us to characterize the model dynamics (also, to some extent, for the case of small delays T and H).

Which of these results can be extended to the general case of "large" T and H? We study this question in two sections. In Section 4 we present stability results for the linearized equations using both analytic methods and numerical studies. Section 5 contains boundedness and attractivity results for the general nonlinear equations. The most powerful tool for stability investigation of our models is provided by Lyapunov or quasi-Lyapunov functionals. For the delay systems, the analysis is very difficult and involved, while the results are only partial. However, even such results provide us with intuitions, important for understanding the cell production systems. Apart from biological interpretations, the equations considered in this paper are interesting from the purely mathematical viewpoint, since systems of difference-differential equations with more than one delay are still not very well understood. Interesting (sometimes more detailed) results can be obtained for special cases of model 1 (Section 6). Section 7 is a discussion containing a review of biological relevance of our models, as well as a summary of results.

2. MODELS 1, 2 AND 3: DEFINITIONS, ASSUMPTIONS AND POSITIVITY OF SOLUTIONS

We consider three versions of the regulating feedbacks. They correspond to various biological assumptions.

Model 1. The fraction $[d(t)]$ of differentiating stem cells is an increasing function of the number of passive $(G_0 + G_1)$ stem cells:

$$d(t) = g(N(t)).$$

The rate of the outflow from $G_0 + G_1$ stem cell compartment $[\alpha(t)]$ is a decreasing function of the number of mature cells:

$$\alpha(t) = h(R(t)).$$

Intuitively, the mature cell number is influencing the production rate of stem cells, while the contents of the "storage" $G_0 + G_1$ compartment controls the proportion of differentiating stem cells. For technical reasons, we assume the following:

$$h \in C^2(\mathbb{R}_+);\ h(0) = h^* > 0,\quad h(\infty) = 0;\ h'(u) < 0,\quad u > 0, \tag{h_1}$$

$$g \in C^2(\mathbb{R}_+);\ g(0) = 0,\ g(\infty) = 1,\ g'(u) > 0,\ u > 0. \tag{g_1}$$

Now the system (1.1) (1.4) takes the form of

$$\dot{N}(t) = -h(R(t))N(t) + 2[1 - g(N(t - T))]h(R(t - T))N(t - T), \tag{N_1}$$

$$\dot{R}(t) = -\beta R(t) + Ag(N(t - H))h(R(t - H))N(t - H). \tag{R_1}$$

Model 1 is an extension of the model by Wazewska and Lasota[5]. Model 1 has two equilibria: trivial $(N^*, R^*) = (0, 0)$ and nontrivial $(\tilde{N}, \tilde{R})$, such that

$$\begin{aligned} \tilde{N} &= g^{-1}(\tfrac{1}{2}), \\ \beta\tilde{R} &= (A/2)\tilde{N}h(\tilde{R}). \end{aligned} \tag{e_1}$$

Model 2. In this variant, both $\alpha(t)$ and $d(t)$ depend on the mature cell number:

$$\begin{aligned} d(t) &= g(R(t)), \\ \alpha(t) &= h(R(t)). \end{aligned}$$

with g and h being decreasing functions. The assumption that both feedbacks here are designed to "exploit" the stem cell population will cause system instability. Again, we assume

$$h \in C^2(\mathbb{R}_-);\ h(0) = h^* > 0;\ h(\infty) = 0;\ h'(u) < 0,\ u > 0, \tag{h_2}$$

$$g \in C^2(\mathbb{R}_-);\ g(0) = 1,\ g(\infty) = 0;\ g'(u) < 0,\ u > 0. \tag{g_2}$$

The system equations are

$$\dot{N}(t) = -h(R(t))\ N(t) + 2[1 - g(R(t - T))]h(R(t - T))N(t - T), \tag{N_2}$$

$$\dot{R}(t) = -\beta R(t) + Ag(R(t - H))h(R(t - H))N(t - H). \tag{R_2}$$

This model has also two equilibria: trivial $(N^*, R^*) = (0, 0)$ and nontrivial $(\tilde{N}, \tilde{R})$:

$$\begin{aligned} \tilde{R} &= g^{-1}(\tfrac{1}{2}), \\ \tilde{N} &= 2\beta\tilde{R}[Ah(\tilde{R})]^{-1}. \end{aligned} \tag{e_2}$$

Model 3. This is, in a sense, a reversal of model 1. The long-range feedback controls the differentiating stem cell fraction, while the "defensive" one, the exit rate from $G_0 + G_1$:

$$d(t) = g(R(t)),$$
$$\alpha(t) = h(N(t)),$$

where both g and h are decreasing. This model is analogous to a much more comprehensive computer model by Loeffler and Wichmann[16]. The system can be represented as follows:

$$\dot{N}(t) = -h(N(t))N(t) + 2[1 - g(R(t - T))]h(N(t - T))N(t - T),$$
$$\dot{R}(t) = -\beta R(t) + Ag(R(t - H))h(N(t - H))N(t - H),$$

where

$$g \in C^2(\mathbb{R}_+),\ g > 0,\ g' < 0,\ g(0) = 1,\ g(\infty) = 0, \tag{g_3}$$
$$h \in C^2(\mathbb{R}_+),\ h > 0,\ h' < 0,\ h(\infty) = 0. \tag{h_3}$$

It is more convenient to introduce the function $\Phi(N) = Nh(N)$, so that the system equations have the form

$$\dot{N}(t) = -\Phi(N(t)) + 2[1 - g(R(t - T))]\Phi(N(t - T)), \tag{N_3}$$
$$\dot{R}(t) = -\beta R(t) + Ag(R(t - H))\Phi(N(t - H)). \tag{R_3}$$

$\Phi(N)$ is not monotonous and can have quite a complicated form. We will assume the following:

$$\Phi'(N) > 0,\ N < N_0;\ \Phi'(N) < 0,\ N > N_0;\ \Phi(\infty) = 0. \tag{Φ_3}$$

Obviously, $\Phi(0) = 0$. Under (Φ_3), $\Phi(N)$ has a unique maximum at $N = N_0$. This system, (N_3), (R_3), has a trivial equilibrium $(N^*, R^*) = (0, 0)$ and can have 0, 1 or 2 nontrivial equilibria:

(1) $\Phi(N_0) < 2\beta g^{-1}(\frac{1}{2})/A$ (no nontrivial equilibrium),

(2) $\Phi(N_0) = 2\beta g^{-1}(\frac{1}{2})/A$ [single nontrivial equilibrium: $(N_0, \bar{R})$], where $\bar{R} = g^{-1}(\frac{1}{2})$,

(3) $\Phi(N_0) > 2\beta g^{-1}(\frac{1}{2})/A$ [two nontrivial equilibria: $(\bar{N}_1, \bar{R})$ and $(\bar{N}_2, \bar{R})$], where the $\bar{N}_i$ are the roots of the equation $\Phi(N) - 2\beta g^{-1}(\frac{1}{2})/A = 0$ $(\bar{N}_1 < N_0 < \bar{N}_2)$.

Though Models 1, 2 and 3 represent three simple and intuitively plausible versions of regulation feedbacks, they are by no means the only ones possible. Even in the framework of two regulated factors, α and d, we can consider much more generally: $\alpha = h(N, P, R)$ and $d = g(N, P, R)$. We will address this problem in Discussion.

Under assumptions introduced above, all the equations considered, have unique solutions on $\mathbb{R}_+$, given that continuous initial data $R|_{[-H, 0]}$, $N|_{[-H, 0]}$ are specified (see Hale[17]). However, we are interested only in non-negative solutions:

Proposition 2.1. Under Hypotheses (g_i), (h_i), $i = 1, 2, 3$, the solutions of Eqs. (N_i), (R_i), $i = 1, 2, 3$ (respectively) satisfy the following properties:

(1) If $R(t) \geq 0$, $N(t) \geq 0$, $t \in [-H, 0]$, then $R(t) \geq 0$, $N(t) \geq 0$, for $t > 0$.

(2) Moreover, if $N \not\equiv 0$ in $[-T, 0]$, then $N(t) > 0$, $t \geq T$; $R(t) > 0$, $t > H$.

(3) If $N = 0$ in $[-T, 0]$, then $R(t) = R(H - T)\, e^{-\beta(t-(H-T))}$, $t \geq H - T$.

Proof. We write down the "variation of constants" formula for the general system (1.1), (1.4):

$$N(t) = N(0)\, e^{-\int_0^t \alpha(\tau)\, d\tau} + 2\int_0^t [1 - d(\tau - T)]\alpha(\tau - T)N(\tau - T)e^{-\int_\tau^t \alpha(s)\, ds}\, d\tau,$$

$$R(t) = R(0)\, e^{-\beta t} + A\int_0^t \alpha(\tau - H)d(\tau - H)N(\tau - H)\, e^{-(t-\tau)\beta}\, d\tau.$$

These equations have non-negative solution since α, d, $1 - d \geq 0$ [see Hypotheses (g_1), (h_1); (g_2), (h_2) and (g_3), (h_3) for models 1, 2 and 3, respectively].

For part (2) of the lemma, it is enough to note the following estimates:

$$N(t) \geq 2 \min_{s\in[-T,t-T]} \alpha(s)(1 - d(s))\, e^{-th^*} \int_{-T}^{0} N(s)\, ds,\ t \geq T,$$

$$R(t) \geq A\, e^{-t\beta} \min_{s\in[-H,t-H]} \alpha(s) \int_{-T}^{0} d(s)N(s)\, ds,\ t \geq H,$$

and use the assumptions on functions h and g.

The last part is obtained by looking at the system (1.1), (1.4) and using the uniqueness of solutions. $N \equiv 0$ solves (1.1) for any R and then, after time $H - T$, Eq. (1.4) reduces to $\dot{R} = -\beta R$. □

Remark. Part (3) of the lemma illustrates the critical role of the stem cell population. If, namely, at some moment, say $t = -T$, all the stem cells are destroyed, then $N(t) = 0$, $t \in [-T, 0]$ (cf. Fig. 1.1). This, by Proposition 2.1, causes complete extinction of the system.

3. ORDINARY (NO DELAY) CASE

In this section, we will present the analysis of our models for the case $T = H = 0$, when they are described by ordinary differential equations. Biologically, $T = 0$ means that the duration of the $S + G_2 + M$ phase of the stem cells cycle is short compared to that of $G_0 + G_1$. This simplification is not unreasonable, since usually G_0 and G_1 are the longest cell cycle phases (see Mitchison[11]). Also, we may treat $N(t)$ as the total number of stem cells and assume that their generation time is exponentially distributed.

The second assumption, $H = 0$, is equivalent to the absence of the intermediate precursor cell compartment. Consequently, we should have $A = 1$. However, from the mathematical viewpoint, it is convenient to retain parameter A, because it is present in the general model.

Even if for given cell production system the above assumptions cannot be considered completely relevant, the ordinary case will provide intuitions about the type of behaviour to be expected in the general case. Also, in the vicinity of equilibria, the stability properties are unchanged for "small" delays T and H.

Model 1. The simplified version of Eqs. (N_1), (R_1) is now

$$\dot{N} = [1 - 2g(N(t))]N(t)h(R(t)), \tag{3.1}$$

$$\dot{R} = -\beta R + AN(t)g(N(t))h(R(t)) \tag{3.2}$$

Analysis of the linearized equations proves that the trivial equilibrium is unstable (saddle point), while the nontrivial equilibrium $(\bar{N}, \bar{R})$ is a stable (asymptotically) focal point. The

structure of the trajectories near $(\tilde{N}, \tilde{R})$ depends on systems parameters. Here we will analyse one of the two possible cases. The other case is analogous and corresponds to very similar behaviour.

Define $a_{11} = 2g'(\tilde{N})h(\tilde{R})$, $a_{21} = A(\frac{1}{2} + \tilde{N}g'(\tilde{N}))h(\tilde{R})$, and $a_{22} = \beta - \frac{1}{2}A\tilde{N}/h'(\tilde{R})$. We assume the following:

Hypothesis 3.1. $a_{22} > a_{11}$.

Now it is possible to prove that the trajectories (ξ, η) of the linearized version of system (3.1), (3.2) behave as depicted in Fig. 3.1.a.

Also, $\lim_{t\to\infty}[\eta(t)/\xi(t)] = a_{21}/(a_{22} - a_{11})$, except for the two trajectories located at the η axis.

To analyse the nonlinear version, let us define two functions: $\epsilon:\mathbb{R}_+ \to \mathbb{R}_-$, $\epsilon(R/h(R)) = R$ and $\psi:\mathbb{R}_+ \to \mathbb{R}_-$, $\psi(N) = \epsilon(A\beta^{-1}Ng(N))$.

We see that $\psi(0) = 0$, $\psi(\infty) = \infty$, $\psi' > 0$, $\psi(\tilde{N}) = \tilde{R}$. Also, $\psi'(\tilde{N}) = a_{21}/a_{22}$.

Proposition 3.1. Denote, for the system (3.1), (3.2), by $X_i(t) = [N_i(t), R_i(t)]$ the solution with trajectory corresponding to branch i ($i = 1, 2, 3, 4$) of Fig. 3.1.b and by $X_A(t)$, $X_B(t)$ and $X_C(t)$ a solution with trajectory inside region A, B and C of this figure (respectively). Then, under Hypothesis 3.1, all the solutions, except for $X_4(t)$, satisfy $X(\infty) = (\tilde{N}, \tilde{R})$, i.e. $(\tilde{N}, \tilde{R})$ is asymptotically stable with domain of attraction $(0, \infty) \times [0, \infty)$. Furthermore,

(1) $X_1(-\infty) = (\tilde{N}, \infty)$; $X_1(t) = [\tilde{N}, R_1(t)]$, $t \in \mathbb{R}$; $\dot{R}_1(t) < 0$.
(2) $X_2(t_2) = (\tilde{N}, 0)$, $X_2(t) = [\tilde{N}, R_2(t)]$, $R_2(t) > 0$, $t \geq t_2$; for some $t_2 \in \mathbb{R}$.
(3) $X_3(-\infty) = (0, 0)$; $N_3(t)$, $R_3(t) > 0$, $t \in \mathbb{R}$.
(4) $X_4(t) = [0, R_4(0)\, e^{-\beta t}]$, $t \in \mathbb{R}$.
(A) $N_A(t) > 0$, $t \in \mathbb{R}$; there exists $t_A \in \mathbb{R}$ such that $\dot{R}_A(t) < 0$, $t < t_A$ and $\dot{R}_A(t) > 0$, $t > t_A$ and $R_A(t_A) = \psi(N_A(t_A))$.
(B) $\dot{N}_B(t) > 0$, $\dot{R}_B(t) > 0$, $t \in \mathbb{R}$.
(C) $N_C(t) < 0$, $t \in \mathbb{R}$.

Remark. It does not seem easy to investigate the behaviour of $X_C(t)$ as $t \to -\infty$. For instance, it would require additional hypotheses on h and g to prove that all the trajectories in region C cross the line $N = \psi(R)$. Thus this part of Fig. 3.1.b displays only one of the possible variants.

Proof. Let us note that if $N > 0$, then $\dot{N} < 0$ iff $N > \tilde{N}$. Thus $N(t) \to \tilde{N}$, $t \to \infty$, if $N(t) > 0$. Therefore, we may look at limit equation $\dot{R} = -\beta R + (AN/2)h(R)$, and $R(t) \to \tilde{R}$, $t \to \infty$ follows. This proves that the region of attraction of $(\tilde{N}, \tilde{R})$ is $(0, \infty) \times [0, \infty)$. Behaviour of X_1, X_2 and X_4 is obvious. We have generally $\operatorname{sgn}(\dot{R}) = \operatorname{sgn}(\psi(N) - R)$ [and $\operatorname{sgn}(\dot{N}) = \operatorname{sgn}(\frac{1}{2} - g(N))$]. Also, $X_A(t)$ must cross the line $R = \psi(N)$ at least once (cf. the linearized version) say at $t = t_A$.

This explains the behaviour of $X_A(t)$, $t < t_A$. $X_A(t)$ cannot cross the line $R = \psi(N)$ after T_A. Indeed, suppose that $R_A(t') = \psi(N_A(t'))$, $t' > t_A$, and t' is first such moment. Then $\dot{R}_A(t')/\dot{N}_A(t') > 0$, since $\psi' > 0$. But on the other side $R_A(t') = 0$, which is a contradiction. Trajectories in region B cannot cross $R = \psi(N)$ (since they cannot cross the trajectories of A), which explains their geometry. Existence of $X_3(t)$ as a boundary between A and B is implied by the geometry of trajectories in A and B and by the fact that (0, 0) is a saddle point. Properties of $X_C(t)$ are obvious. □

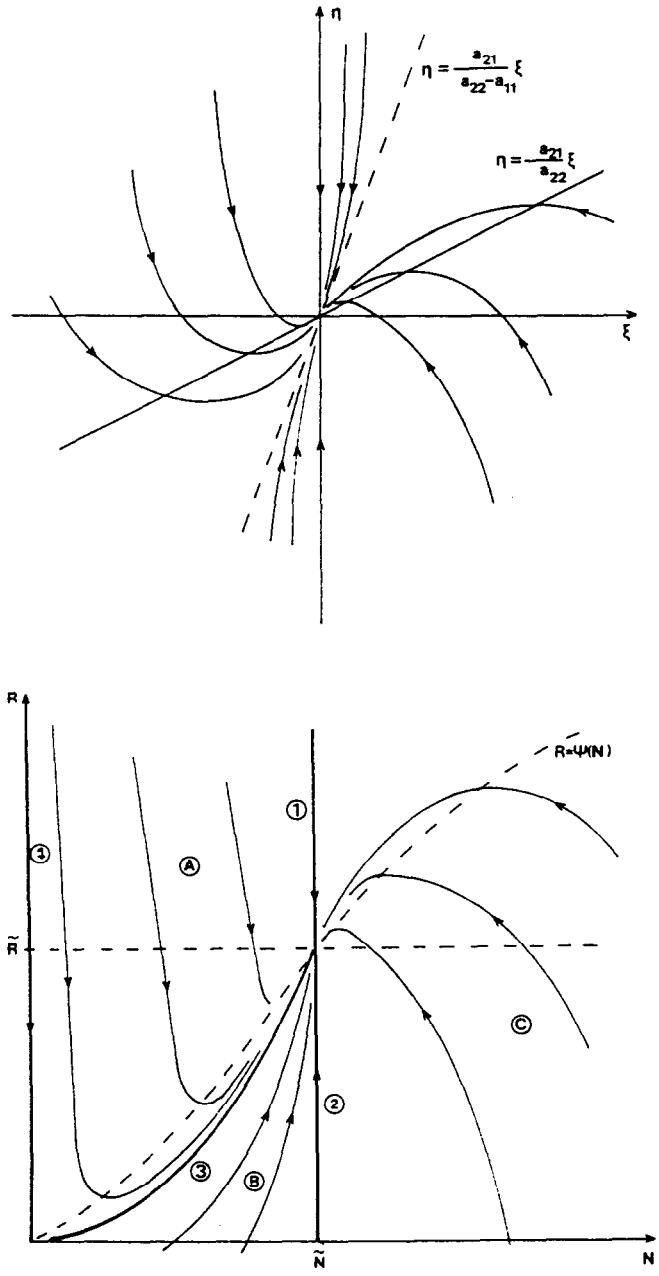

Fig. 3.1. Phase portraits of the trajectories of Model 1 (ordinary case). (a) Equations linearized around the nontrivial equilibrium. (b) The nonlinear equation system. Details in the text.

Model 2. The simplified version of Eqs. (N_2) and (R_2) is

$$\dot{N} = h(R)N(1 - 2g(R)), \tag{3.3}$$

$$\dot{R} = -\beta R + Ag(R)h(R)N. \tag{3.4}$$

Analysis of the linearized equations proves that (0, 0) is stable, while $(\tilde{N}, \tilde{R})$ is unstable (saddle point; eigenvalues: $\lambda_1 < 0 < \lambda_2$). In the vicinity of $(\tilde{N}, \tilde{R})$, trajectories behave as in the Fig. 3.2.a.

As for the global behaviour, the most important role is played by four solutions approaching $(\tilde{N}, \tilde{R})$ at $\pm\infty$, denoted by 1, 2, 3 and 4 in the Fig. 3.2.b. We omit the detailed description of the results which follows the same lines as in Proposition 3.1 and simply point out, as shown by Fig. 3.2.b, that the solutions either tend to (0, 0) or to $(+\infty, +\infty)$.

This behaviour hardly corresponds to any model of normal cell production. In an indirect way, this demonstrates that some kind of defensive, short-range feedback, which is missing in Model 2, is essential for stable performance of a cell production system.

Model 3. Equations (N_3) and (R_3) simplify to the form of

$$\dot{N}(t) = \Phi(N(t))[1 - 2g(R(t))], \tag{3.6}$$

$$\dot{R}(t) = -\beta R(t) + A\Phi(N(t))g(R(t)). \tag{3.7}$$

Analysis of the linearized equations proves that the trivial equilibrium is (asymptotically) stable. The first nontrivial equilibrium $(\tilde{N}_1, \tilde{R})$ is an unstable saddle point (trajectories, as depicted in Fig. 3.3.a), while the other equilibrium $(\tilde{N}_2, \tilde{R})$ is a stable focus.

For the case of only one nontrivial equilibrium $(N_0, \tilde{R})$, one of the eigenvalues is $\lambda_1 = 0$ (while $\lambda_2 < 0$), and nothing can be easily predicted for the nonlinear system. We will treat this case as marginal, noting that it is generated by a very special choice of parameters not likely to occur in any biological system. Therefore, we will concentrate on the two-equilibrium case.

Our results will concern the behaviour of system (3.6), (3.7) under additional assumption.

Hypothesis 3.2. $\Phi'(u) + \beta > 0$, $u \geq 0$.

Proposition 3.3. Under Hypothesis (3.2) all the solutions of the system (3.6), (3.7), starting from initial data $[N(0), R(0)]$; $N(0), R(0) \geq 0$, tend to one of the three equilibria: (0, 0), $(\tilde{N}_1, \tilde{R})$ or $(\tilde{N}_2, \tilde{R})$.

Proof. It is enough to demonstrate that there exists a Lyapunov function $V(N, R)$ bounded from below on $[0, \infty)^2$ and such that $\dot{V}$, the derivative of V down the solution of (3.6), (3.7) is non-negative and cancels only at (0, 0), $(\tilde{N}_1, \tilde{R})$ and $(\tilde{N}_2, \tilde{R})$. Then the assertion follows by Lemma 11.1 in [18].

We consider $V(N, R)$ of the form

$$V(N, R) = \frac{\beta R^2}{2} - A\frac{\Phi(N)R}{2} + \frac{\tilde{R}}{2}A[\beta N + \Phi(N)] - \frac{A^2}{4}\int_0^N \Phi(s)\,ds. \tag{3.8}$$

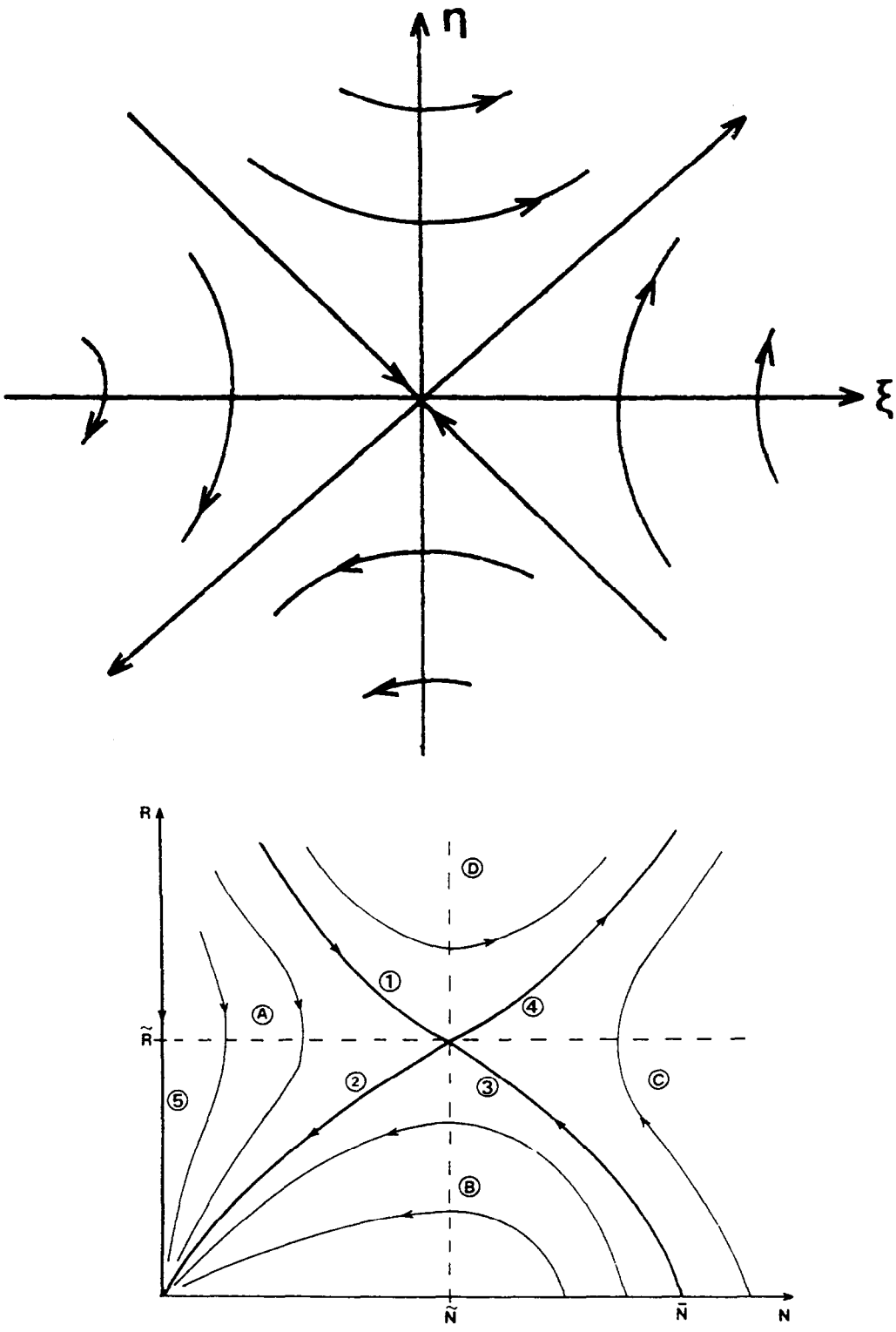

Fig. 3.2. Phase portraits of the trajectories of Model 2 (ordinary case). (a) Equations linearized around the nontrivial equilibrium. (b) The nonlinear equation system. Details in the text.

The derivative of V down the solutions of (3.6) and (3.7) is

$$\dot{V} = -\frac{A\Phi(N)}{2}[1 - 2g(R)](R - \tilde{R})[\beta + \Phi'(N)]$$
$$-\left(\beta R - \frac{A\Phi(N)}{2}\right)^2 \leq 0. \tag{3.9}$$

It has all the necessary properties. More detailed results can be proved under additional hypothesis.

Hypothesis 3.3.

$$\tilde{R} < \frac{1}{2}\left\{A + \frac{\beta}{\Phi(N_0)\max_{0\leq u\leq \tilde{R}} |g'(u)|}\right\}(\tilde{N}_2 - \tilde{N}_1) \underset{\text{def}}{=} C_3(\tilde{N}_2 - \tilde{N}_1).$$

Proposition 3.4. Denote for the system (3.6), (3.7) the subsets of solutions, depicted in Fig. 3.3.a, in a way analogous to that used in Proposition 3.1. Suppose that Hypotheses 3.2 and 3.3 hold. Then

(1) $X_1(-\infty) = (0, \infty)$; $X_1(\infty) = (\tilde{N}_1, \tilde{R})$; $\dot{N}_1(t) > 0$, $\dot{R}_1(t) < 0$, $t \in \mathbb{R}$.
(2) $X_2(-\infty) = (\tilde{N}_1, \tilde{R})$; $X_2(\infty) = (0, 0)$; $\dot{N}_2(t) < 0$, $R_2(t) < \tilde{R}$, $t \in \mathbb{R}$.
(3) $X_3(t_3) = (\overline{N}_3, 0)$, $\overline{N}_3 \in [\tilde{N}_1, \tilde{N}_2]$, for some $t_3 \in \mathbb{R}$; $X_3(\infty) = (\tilde{N}_1, \tilde{R})$; $\dot{N}_3(t) < 0$, $\dot{R}_3(t) > 0$, $t \geq t_3$.
(4) $X_4(-\infty) = (\tilde{N}_1, \tilde{R})$; $X_4(\infty) = (\tilde{N}_2, \tilde{R})$.
(A) $X_A(-\infty) = (0, \infty)$; $X_A(\infty) = (0, 0)$.; $\dot{N}_A(t) > 0$, $\dot{R}_A(t) < 0$, $R_A(t) > \tilde{R}$, $t < t_A$, $\dot{N}_A(t) < 0$, $R_A(t) < \tilde{R}$, $t > t_A$; for some $t_A \in \mathbb{R}$.
(B) $X_B(\infty) = (0, 0)$; $X_B(t_{B_1}) = (\overline{N}_B, 0)$, $\overline{N}_B < \overline{N}_3$, $\dot{N}_B(t) < 0$, $R_B(t) > 0$, $t \geq t_{B_1}$, for some $t_{B_1} \in \mathbb{R}$. Define function $\psi: \mathbb{R}_+ \to \mathbb{R}_+$, $\psi(N) = \gamma^{-1}[A\Phi(N)/\beta]$, where $\gamma(R) = R/g(R)$ (see Fig. 3.3.a). There exists $t_{B_2} > t_{B_1}$ such that $R_B(t_{B_2}) = \psi(N_B(t_{B_2}))$ and $R_B(t) > 0$, $t \in [t_{B_1}, t_{B_2})$.
(C) $X_C(\infty) = (\tilde{N}_2, \tilde{R})$.

Remark. Figure 3.3.a depicts the trajectories of Model 3 in the ordinary case. However, some details in this figure correspond to only one of the possible trajectory configurations. For instance, trajectory 2 could cross the line $R = \psi(N)$. The same is true for trajectories from regions A and B. Trajectories in region C could spiral around $(\tilde{N}_2, \tilde{R})$.

Proof. Let us note that

$$\operatorname{sgn}(\dot{N}) = \operatorname{sgn}(R - \tilde{R}), \tag{3.10}$$
$$\operatorname{sgn}(\dot{R}) = \operatorname{sgn}(\psi(N) - R). \tag{3.11}$$

From the linearized version (see Fig. 3.2.a) it follows that $X_1(\infty) = (\tilde{N}_1, \tilde{R})$ and $N_1(t) < \tilde{N}_1$, $R_1(t) > \tilde{R}$ for t large. Then, by (3.10) and (3.11), we see that $N_1(t) < \tilde{N}_1$, $R_1(t) > \tilde{R}$ for $t \in \mathbb{R}$. Therefore [by (3.10) and (3.11), again],

$$N_1(t) \downarrow \overline{N}_1 \geq 0, \; R_1(t) \uparrow \overline{R}_1 \leq \infty \text{ as } t \to -\infty.$$

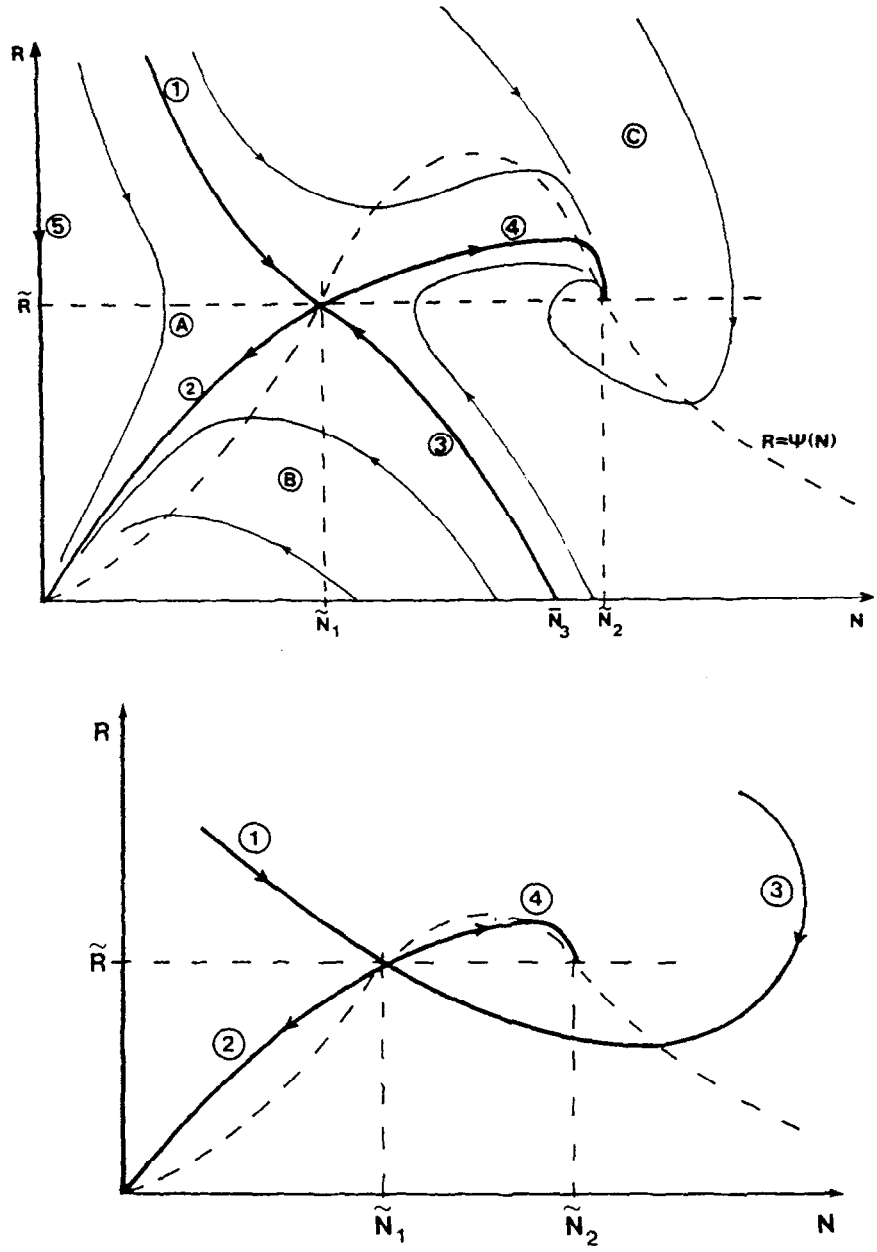

Fig. 3.3. Phase portraits of the trajectories of Model 3 (ordinary case). (a) Trajectories under Hypotheses 3.2 and 3.3. (b) Possible trajectories without Hypothesis 3.3. Details in the text.

It must be then $X_1(-\infty) = (0, \infty)$. Proof of (2) is similar. Also, in an analogous way, it can be proved that $X_3(\infty) = (\tilde{N}_1, \tilde{R})$ and that $R_3(t) < \tilde{R}$, $\dot{R}_3(t) > 0$ for t greater than some t_3.

We will prove that $R_3(t_3) = 0$. Indeed, consider the derivative dR/dN in the region $G = [\tilde{N}_1, \tilde{N}_2] \times [0, \tilde{R}]$:

$$\frac{dR}{dN} = -\frac{A}{2} + \frac{\beta(\tilde{R} - R)}{\Phi(N)[1 - 2g(R)]} + \frac{(A/2)\Phi(N) - \beta\tilde{R}}{\Phi(N)[1 - 2g(R)]} < -\frac{A}{2} + \frac{\beta(\tilde{R} - R)}{\Phi(N)[1 - 2g(R)]} \leq -C_3.$$

Thus Hypothesis 3.3 implies $|\,dR/dN\,| > \tilde{R}/(\tilde{N}_2 - \tilde{N}_1)$ in G. Therefore, $X_3(t_3) = (\overline{N}_3, 0)$, $\overline{N}_3 \leq \tilde{N}_2$ and (3) is proved. Remaining assertions follow by analogous considerations. □

Remarks. Dropping Hypothesis 3.3 with Hypothesis 3.2 holding, can affect the trajectory 3 and the trajectories in regions B and C. The qualitative picture might be then similar to that depicted in Fig. 3.3.b.

Dropping Hypothesis 3.2 is more unpredictable, since then the function defined in formula (3.8) ceases being a Lyapunov function for (N_3) and (R_3), and so Proposition 3.3 is not true. Thus it is not possible to exclude limit cycles around $(\tilde{N}_2, \tilde{R})$. There can be no cycles neither around $(\tilde{N}_1, \tilde{R})$, since it is a saddle point, nor around (0, 0) because of the positivity preservation.

Model 3 has a property that seems quite natural for the cell production systems. Forced into a certain region of initial data (regions A and B of Fig. 3.3.a), the system slides towards extinction. Therefore, Model 3 may be more relevant than the globally stable Model 1.

4. GENERAL (DELAY) CASE: LINEARIZED EQUATIONS AND NUMERICAL RESULTS

In this section, we will investigate the local stability properties of the equilibria of our three models. Wherever possible, we will give analytic results. In the case of nontrivial equilibria, however, the eigenvalue problems are so complex that it is necessary to resort to numerical studies.

Model 1. The system (N_1), (R_1) linearized around the trivial equilibrium (0, 0) assumes the form of

$$\dot{\xi}(t) = -h^*\xi(t) + 2h^*\xi(t - T), \tag{4.1}$$

$$\dot{\eta}(t) = -\beta\eta(t). \tag{4.2}$$

The characteristic equation associated to these equations is (cf., e.g. Hale[17])

$$(\lambda + \beta)(\lambda + h^* - 2h^* e^{-\lambda T}) = 0.$$

The root $\lambda_0 = -\beta$ is negative. For the equation $\delta(\lambda) = \lambda + h^* - 2h^* e^{-\lambda T} = 0$, we notice that $\delta(0) < 0$, $\delta(\infty) = \infty$ and $\delta'(\lambda) = 1 + 2h^*T e^{-\lambda T} > 0$, so that δ has exactly one positive real root.

Therefore (see Bellman and Cooke[19]), the trivial equilibrium is unstable for arbitrary values of the parameters. Linearization around $(\tilde{N}, \tilde{R})$ yields a system of two linear difference-differential equations with two delays, of the type considered in Appendix A (see the remark to Proposition A.1.) Unable to investigate it analytically, we applied Proposition A.1 to a version of the Model 1 with parameter values corresponding to data of the human erythropoietic system (see Arino and Kimmel[20] for details). Generally speaking, for given values of T, H, $\tilde{N}$, $\tilde{R}$, β and $h(\tilde{R})$, we varied the values of $h'(\tilde{R})$ and $g'(\tilde{N})$.

In these coordinates, we obtained an asymptotic stability region, depicted in Fig. 4.1. The interpretation is simple: As long as the "sensitivities" $h'(\tilde{R})$ and $g'(\tilde{N})$ of the feedbacks are not too high, the system returns to the equilibrium $(\tilde{N}, \tilde{R})$. If the system is "oversensitive" the equilibrium destabilizes. We will return to this problem in Discussion.

Let us only note that the instability of $(\tilde{N}, \tilde{R})$ is due to the existence of nonzero delays

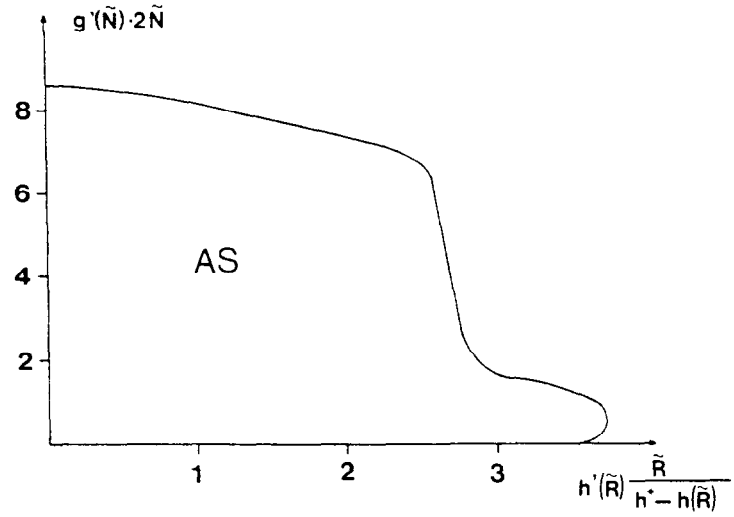

Fig. 4.1. The domain of sensitivities $g'(\tilde{N})$ and $h'(\tilde{R})$ of the regulation feedbacks of Model 1 (with two delays), for which the nontrivial equilibrium is asymptotically stable. Other parameters as in the model of human erythropoiesis.

T and H [in the ordinary case $(\tilde{N}, \tilde{R})$ is always asymptotically stable]. In Section 6 we will investigate the case of $T = 0$, $H > 0$, and show that the case H large enough results in stable oscillations.

Model 2. Linearization of (N_2), (R_2) around (0, 0) yields

$$\dot{\xi}(t) = -h^*\xi(t),$$
$$\dot{\eta}(t) = Ah^*\xi(t - H) - \beta\eta(t).$$

Only two eigenvalues exist and both are negative, so that the (0, 0) equilibrium is asymptotically stable.

Linearization around $(\tilde{N}, \tilde{R})$ yields the characteristic equation:

$$H(\lambda) \equiv \lambda^2 + \lambda\left\{\beta + h(\tilde{R})(1 - e^{-\lambda t}) - A\tilde{N}\left(\frac{h'(\tilde{R})}{2} + h(\tilde{R})g'(\tilde{R})\right)e^{-\lambda H}\right\}$$
$$+ h(\tilde{R})\beta(1 - e^{-\lambda T}) - Ag'(\tilde{R})[h(\tilde{R})]^2\tilde{N}\,e^{-\lambda H}(1 - 2\,e^{-\lambda T}) = 0.$$

But $H(0) < 0$, $H(\lambda) \to \infty$ as $\lambda \to \infty$. Thus there exists at least one positive eigenvalue and $(\tilde{N}, \tilde{R})$ is unstable. These results are identical to those for the nondelay case.

Model 3. Linearization of system (N_3), (R_3) around (0, 0) yields

$$\dot{\xi}(t) = -\Phi'(0)\xi(t),$$
$$\dot{\eta}(t) = A\Phi'(0)\xi(t - H) - \beta\eta(t).$$

The roots of the characteristic equation are both negative [$\lambda_1 = -\Phi'(0)$, $\lambda_2 = -\beta$], which implies the asymptotic stability of (0, 0). For the nontrivial equilibria $(\tilde{N}_i, \tilde{R})$, the char-

acteristic equation is

$$H_i(\lambda,\beta) = \lambda^2 + \lambda\{\alpha_i(\beta)(1 - e^{-\lambda T}) + \beta(1 + \gamma e^{-\lambda H})\} + \alpha_i(\beta)\beta\{(1 - e^{-\lambda T}) + \gamma(1 - 2e^{-\lambda T}) e^{-\lambda H}\}, \quad (4.3)$$

where $\gamma = -2\tilde{R}g'(\tilde{R}) > 0$ and $\alpha_i(\beta) = \Phi(\tilde{N}_i(\beta))$.

For $(\tilde{N}_1, \tilde{R})$, it is enough to note that $H(0) < 0$ and $H(\lambda) \to \infty$ as $\lambda \to \infty$ to conclude that $H(\lambda)$ has always a positive root. Thus $(\tilde{N}_1, \tilde{R})$ is unstable.

Analogous result does not hold for $(\tilde{N}_2, \tilde{R})$. We are able, however, to analyze the situation when the simple nontrivial equilibrium $(N_0, \tilde{R})$, existing for $\beta = \beta_0 = A\Phi(N_0)/2\tilde{R}$ splits into $(\tilde{N}_1, \tilde{R})$ and $(\tilde{N}_2, \tilde{R})$ for $\beta < \beta_0$. Thus we consider zeros of the exponential polynomial $H(\lambda) = H_i(\lambda, \beta)$ [corresponding to $(\tilde{N}_i, R)$, $i = 1, 2$] in a small interval $[\beta_0 - \epsilon, \beta_0]$.

Proposition 4.1. Denote by $\xi(\beta)$ the root of $\xi = -\beta H \tan(\xi)$, $\xi \in (\pi/2, \pi)$.

(1) If $\gamma < -\cos(\xi(\beta_0))[\xi^2(\beta_0)/H^2\beta_0^2 + 1]$, then there exists $\epsilon > 0$ such that for $\beta \in (\beta_0 - \epsilon, \beta_0)$, $(\tilde{N}_2, \tilde{R})$ is asymptotically stable.

(2) If $\gamma \geq -\cos(\xi(\beta_0))[\xi^2(\beta_0)/H^2\beta_0^2 + 1]$, then there exists $\epsilon > 0$ such that for $\beta \in (\beta_0 - \epsilon, \beta_0)$, $(\tilde{N}_2, \tilde{R})$ is unstable.

Sketch of the proof. If $\gamma \geq -\cos(\xi(\beta_0))[\xi^2(\beta_0)/H^2\beta_0^2 + 1]$, then $H_2(\lambda, \beta_0)$ has at least one root with positive real part (Hale[17], Theorem A.5), so that $H_2(\lambda, \beta)$ has such a root for β close to β_0.

If the opposite is true, then $H_2(\lambda, \beta_0)$ has a root $\lambda_0 = 0$ and the remaining roots with negative real parts. It is enough then to prove that $\lambda_0 = \lambda_0(\beta)[\lambda_0(\beta_0) = 0]$ is an increasing function of β in a vicinity of β_0. This can be done by looking at $\partial H_2/\partial\lambda$ and $\partial H_2/\partial\beta$ in the vinicity of $\beta = \beta_0$ and $\lambda_0 = 0$. □

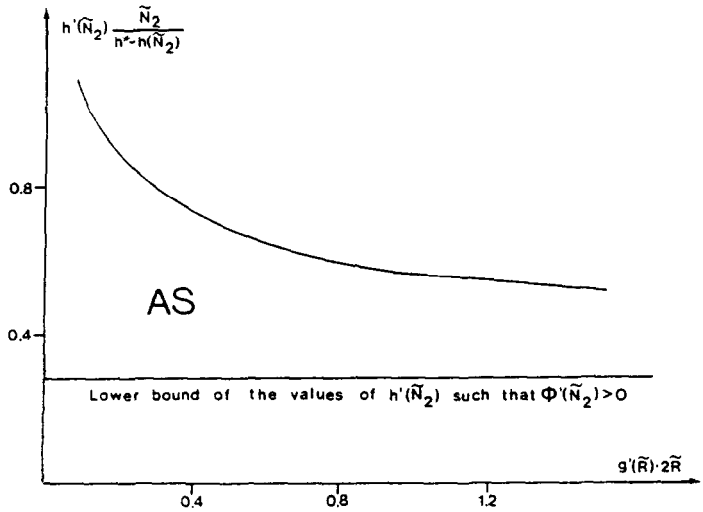

Fig. 4.2. The domain of sensitivities $g'(\tilde{R})$ and $h'(\tilde{N}_2)$ of the regulation feedbacks of Model 3 (with two delays) for which the nontrivial equilibrium $(\tilde{N}_2, \tilde{R})$ is asymptotically stable. Other parameters as in the model of human erythropoiesis.

To investigate the stability of $(\tilde{N}_2, \tilde{R})$ in a situation less restricted than that of Proposition 4.1, we performed numerical studies based on Proposition A.1 for the parameter values corresponding to the human erythropoiesis model (see this section, Model 1). Results are depicted in Fig. 4.2. The interpretation is similar to that of Model 1.

Concluding, the equilibria (0, 0) and $(\tilde{N}_1, \tilde{R})$ have the same properties as in the ordinary case. However, in the presence of delays, the nontrivial equilibrium $(\tilde{N}_2, \tilde{R})$ looses stability if the regulation feedbacks are too sensitive.

5. GENERAL (DELAY) CASE: BOUNDEDNESS AND ATTRACTIVITY FOR NONLINEAR EQUATIONS

In this section, we are interested in checking which global properties of the nonlinear systems (N_i), (R_i), $i = 1, 2, 3$ that are true for the ordinary case, are preserved in the (delay) case.

Based on the ordinary case, we would expect (perhaps under additional assumptions) to be able to prove boundedness of solutions of Models 1 and 3. Also, for Model 1, the nontrivial equilibrium should be globally asymptotically stable. Moreover, we could hope to estimate the regions of attraction for the stable equilibria of Models 2 and 3.

Most of the results are obtained, using Lyapunov and quasi-Lyapunov functionals, combined with additional estimates on solutions.

Model 1. We will introduce additional assumption.

Hypothesis 5.1. $\sup_{u \geq 0} [1 - g(u)]u < \infty$.

It can be imagined that in the real cell production system, g becomes equal to 1 for the argument large enough. In this context, Hypothesis 5.1 does not seem unreasonable.

To prove boundedness of solutions and global attractivity of $(\tilde{N}, \tilde{R})$, we will proceed through a series of interconnected lemmas. Remember that we are interested in nonnegative solutions only.

We adopt standard notation used in the theory of difference-differential equations (see Hale[17]). If $X(t)$ is a continuous n-vector function on $[t_0 - H, \infty)$ $(t_0 \geq -\infty)$, then $X_t(\cdot)$, $t \geq t_0$ will denote the element of $C([-H, 0], \mathbb{R}^n)$ (the Banach space of the bounded continuous functions from $[-H, 0]$ into $\mathbb{R}^n$) defined by $X_t(\tau) = X(t + \tau)$, $\tau \in [-H, 0]$.

First, we introduce a functional on the space $C([-T, 0], \mathbb{R}^2)$ which will play a role similar to the Lyapunov functionals (see Hale[17], Chap. 5):

$$W(\varphi, \psi) = \varphi(0) + 2 \int_{-T}^{0} [1 - g(\varphi(s))]\varphi(s)h(\psi(s))\, ds. \tag{5.1}$$

As usual, we define the derivative of W along the solutions of the system as $DW(\varphi, \psi) = (d^+/dt)\, W(N_t, R_t)|_{t=0}$, where (N, R) is the solution of the system starting from (φ, ψ) at time $t = 0$.

Lemma 5.1. $DW(\varphi, \psi) = [1 - 2g(\varphi(0))]\varphi(0)h(\psi(0))$.

Hence, for $\varphi, \psi \geq 0$, $DW(\varphi, \psi)(\tilde{N} - \varphi(0)) \geq 0$.

Proof. Standard.

Remark. Looking at Fig. 1.1, we note that $W(N_t, R_t)$ is equal to $N(t) + 2P(t)$, where $P(t)$ is the active stem cell number. Since each of the active stem cells produces two

passive stem cells, this expression has the meaning of a "potential" stored in the stem population. In physical systems, Lyapunov functionals are frequently interpreted as energies; we see that W has a similar interpretation.

We will now prove in several steps the boundedness of the solutions.
For function x defined on $\mathbb{R}^+$, we will denote

$$\bar{x} = \limsup_{t \to +\infty} x(t), \quad \underline{x} = \liminf_{t \to +\infty} x(t).$$

Lemma 5.2. Suppose that N is bounded. Then R is bounded, and the following estimates hold:

$$Ah\left(\frac{Ah^*}{\beta}\,\bar{N}g(\bar{N})\right)\underline{N}g(\underline{N}) \le \underline{R} \le \bar{R} \le \frac{Ah}{\beta}\,\bar{N}g(\bar{N}). \tag{5.2}$$

Proof. From the boundedness of N, it follows that for each θ, $\theta > 1$, there exists t_θ, such that for $t \ge t_\theta$,

$$\dot{R}(t) \le -\beta R(t) + Ah^*\theta\bar{N}g(\bar{N}).$$

By using the "variation of constants" formula for the inequality, we obtain

$$R(t) \le R(t_\theta)\,e^{-\beta(t-t_\theta)} + \frac{Ah^*\theta\bar{N}g(\bar{N})}{\beta}\,(1 - e^{-\beta(t-t_\theta)}).$$

Passing to the lim sup in both sides, it gives

$$\bar{R} \le (Ah^*/\beta)\theta\bar{N}g(\bar{N}), \text{ for each } \theta > 1,$$

so that $\bar{R} \le (Ah^*/\beta)\bar{N}g(\bar{N})$.
To prove the second inequality, we proceed in an analogous way. □

Lemma 5.3. Suppose that $N(t) \ge \tilde{N}$, $t \ge t_0$ [resp. $N(t) \le \tilde{N}$ and $N(t) \not\equiv 0$, $t \ge t_0$]. Then $N(t)$ tends to $\tilde{N}$ as t tends to the infinity.

Proof. From Lemma 5.1, the inequality $N(t) \ge \tilde{N}$, implies that $W(N_t, R_t)$ is nonincreasing in $t \ge t_0$; since $W(N_t, R_t) \ge N(t) \ge 0$, it implies that N is bounded. Thus from Lemma 5.2, R is bounded too.

Showing that $N(t)$ tends to $\tilde{N}$ is equivalent, in the case $N \ge \tilde{N}$, to showing that $DW(N_t, R_t)$ tends to zero as t tends to the infinity. But $W(N_t, R_t)$ tends to a limit and $DW(N_t, R_t)$ is uniformly continuous in t because of the boundedness of N and R. Thus the assertion follows. The case $N(t) \le N$ is proved in the same way. □

Lemma 5.4. Suppose that $N(t)$ is oscillating around $\tilde{N}$ [i.e. $N(t) = \tilde{N}$, for arbitrarily large t's]. Then

$$\frac{\tilde{N}}{1 + 2h^*T\,e^{h^*T}} \le \underline{N} \le \bar{N} \le \tilde{N} + CT, \tag{5.3}$$

where C, defined as $C = \sup_{u \ge 0} 2h^*u\,[1 - g(u)]$, is finite by Hypothesis 5.1.

Proof. Note that C is an upper bound of the derivative of N. We will look at N after the first point t_0 at which $N(t_0) = \bar{N}$.

Fix t, $t \geq t_0$ and $N(t) > \bar{N}$. Denote by t_1 the last point at which $N(t_1) = \bar{N}$ before t. Thus $N(s) > \bar{N}$, $t_1 < s < t$. $W(N_s, R_s)$ is nonincreasing in s, for $s \in [t_1, t]$; thus we have

$$N(t) \leq W(N_t, R_t) \leq W(N_{t_1}, R_{t_1}) \leq \bar{N} + CT.$$

For the other inequality, fix $t \geq t_0$, such that $N(t) < \bar{N}$. Denote by t_2 the last point in which $N(t) = \bar{N}$ before t.

Thus $N(s) < \bar{N}$, $t_2 < s < t$; $W(N_s, R_s)$ is nondecreasing in s in the interval $[t_2, t]$. Thus we have $W(N_{t_2}, R_{t_2}) \leq W(N_t, R_t)$. But $W(N_t, R_t) \leq N(t) + 2h^*T \sup_{t-T \leq s \leq t} N(s)$. We can estimate $\sup_{t-T \leq s \leq t} N(s)$ with respect to $N(t)$. From (N_1), we have $\sup_{t-T \leq s \leq t} N(s) \leq e^{h^*T} N(t)$. Using this fact and also that $\bar{N} \leq W(N_{t_2}, R_{t_2})$, the assertion follows. □

We can state all these results in a proposition.

Proposition 5.1. Under Hypothesis 5.1, let (N, R) be a non-negative solution, with $N(t) \not\equiv 0$, $-T \leq t \leq 0$; then

(a) $N(t)$ and $R(t)$ are bounded on $[0, +\infty)$, with ultimate bounds independent from the data given by formulae (5.2) and (5.3).
(b) If $N(t)$ does not tend to $\bar{N}$, as t tends to infinity, then it oscillates around $\bar{N}$.

Proof. (a) follows directly from Lemmas 5.2–5.3; (b) follows from Lemma 5.3.

In the remaining part of this section, we will consider the global attractivity and stability of the nonzero critical point $(\bar{N}, \bar{R})$. We will only consider the case of non-negative solutions, with $N(t)$ eventually positive (cf. Lemma 2.1.).

To simplify the statements, we will introduce the following definitions:

$$k(u) = 2[1 - g(u)]u,$$

$$h'^* = \sup_{u \geq 0} |h'(u)|,$$

$$k^* = \sup_{u \geq 0} k(u),$$

$$k'^* = \sup_{u \geq 0} |k'(u)|.$$

THEOREM 5.1. Suppose that the following conditions hold:

$$(A\bar{N}/2\beta)h'^* < 1, \tag{5.4}$$

$$2Th^* \left[k'^* + \frac{k^* h'^* A}{\beta - h'^*(AN/2)} (1 + \tfrac{1}{2}k'^*) \right] < 1. \tag{5.5}$$

Then $(\bar{N}, \bar{R})$ is a global attractor for the solutions [i.e. $N(t) \to \bar{N}$, $R(t) \to \bar{R}$, $t \to +\infty$].

Proof. We will show that (with notations introduced before Lemma 5.2) $\overline{N} = \underline{N}$, and then we will use the following inequality:

$$\overline{R} - \underline{R} \leq \frac{Ah^*/\beta}{1 - h'^* A\bar{N}/2\beta} [g(\overline{N})\overline{N} - g(\underline{N})\underline{N}] \text{ to obtain } \overline{R} = \underline{R}. \tag{5.6}$$

To prove (5.6), we notice the following inequalities:

$$\overline{R} \leq (A/\beta)h(\underline{R})\overline{N}g(\overline{N}),$$

$$\underline{R} \geq (A/\beta)h(\overline{R})\underline{N}g(\underline{N}).$$

These can be obtained by the method of Lemma 5.2. Substracting these inequalities side by side and using assumption (5.4) gives the desired result.

We prove now that $\overline{N} = \underline{N}$. First, notice that if $N(t)$ is eventually greater than $\hat{N}$ (resp. less than $\hat{N}$), then $N(t) \to \hat{N}$ (cf. lemma 5.3). Suppose now that $N(t)$ is oscillating around $\hat{N}$. There exists a sequence $(t_n)_{n\in\mathbb{N}}$, $t_n \to +\infty$, such that $N(t_n) \to N$, $N(t_n) > \hat{N}$. To each t_n, we can associate t_n^0, the last point before t_n at which $N(t_n^0) = \hat{N}$. The sequence $(t_n^0)_{n\in\mathbb{N}}$ tends also to the infinity. For each n, $N(t) > \hat{N}$, $t_n^0 \leq t \leq t_n$; thus, from Lemma 4.2, $W(N_t, R_t)$ is nonincreasing in t in the interval $[t_n^0, t_n]$. The gives the inequality

$$N(t_n) + \int_{-T}^{0} k(N(s + t_n))h(R(s + t_n))\,ds \leq \hat{N} + \int_{-T}^{0} k(N(s + t_n^0))k(R(s + t_n^0))\,ds.$$

Taking lim inf at the left side and lim sup at the right side, and noting that $\liminf_{n\to\infty} N(t_n) = \overline{N}$, we obtain the inequality:

$$\overline{N} + T\underline{k}h(\overline{R}) \leq \hat{N} + T\overline{k}h(\underline{R}), \tag{5.7}$$

where $\underline{k} = \inf_{\underline{N}\leq u\leq \hat{N}} k(u)$; $\overline{k} = \sup_{\underline{N}\leq u\leq \hat{N}} k(u)$ In exactly the same way using a sequence $(t_n)_{n\in\mathbb{N}}$, such that $N(t_n) \to \underline{N}$, we obtain

$$\underline{N} + T\overline{k}h(\underline{R}) \geq \hat{N} + T\underline{k}h(\overline{R}). \tag{5.8}$$

Substracting side by side these inequalities, it gives

$$\begin{aligned}\overline{N} - \underline{N} &\leq 2T[\overline{k}h(\underline{R}) - \underline{k}h(\overline{R})] \leq 2T[(\overline{k} - \underline{k})h^* + \overline{k}(h(\underline{R}) - h(\overline{R}))] \\ &\leq 2T\left[k'^*h^*(\overline{N} - \underline{N}) + \frac{k^*h'^*Ah^*}{\beta[1 - h'^*(A\hat{N}/2\beta)]}[g(\overline{N})\overline{N} - g(\underline{N})\underline{N}]\right].\end{aligned}$$

where this last step follows from (5.6). From $g(u)\,u = u - \frac{1}{2}k(u)$, it follows that $|\,(\mathrm{d}/\mathrm{d}u)[g(u)u]\,| \leq 1 + \frac{1}{2}k'^*$ and thus we obtain

$$\overline{N} - \underline{N} \leq 2Th^*\left[k'^* + \frac{k^*h'^*A}{\beta - h'^*(A\hat{N}/2)}(1 + \tfrac{1}{2}k'^*)\right](\overline{N} - \underline{N}).$$

Under the condition (5.5), this gives $\overline{N} = \underline{N}$. $\overline{R} = \underline{R}$ follows from (5.6). □

Let us note that assumptions of Theorem 5.1 are equivalent to certain requirements imposed on the sensitivities of regulation feedbacks (compare the numerical studies for linearized version). It is possible to demonstrate that under the assumptions of Theorem 5.1, the equilibrium $(\hat{N}, \hat{R})$ is not only a global attractor but also it is stable. (cf. Theorem 4.2 in [20]).

Model 2. We state, without a proof, an estimate under suitable assumptions of the domain of attraction of the trivial equilibrium (0, 0). The proof is a direct application of

the Lyapunov method (cf. Theorem 5.3.1 in [17]) with $V(\xi, \eta) = \xi(0) + \int_{-T}^{0} \xi(s)h(\eta(s))\,ds$ as a Lyapunov functional restricted to a convenient invariant set.

Proposition 5.2. Suppose that

$$\max_{0 \le u \le \bar{R}} (1 - g(u))h(u) \le h(\bar{R})/2. \tag{5.9}$$

Choose $\dot{N} > 0$ such that

$$\dot{N}/\bar{N} \le h(\bar{R})/2h^*. \tag{5.10}$$

Then the set $G = \{(\xi, \eta) \in C([-H, 0], [0, \bar{R}] \times [0, \dot{N}])$ is positively invariant w.r. to (N_2) and (R_2), and each solution of (N_2) and (R_2) which enters G tends to $(0, 0)$ at $+\infty$.

Model 3. We will begin with the boundedness of solutions.

Proposition 5.3. Solutions of (N_3) and (R_3) are bounded, for $t \in \mathbb{R}_-$.

Proof. We will use a Lyapunov-type functional on $C([-H, 0]; \mathbb{R}_-^2)$:

$$U(\xi, \eta) = \xi(0) + \int_{-T}^{0} 2[1 - g(\eta(s))]\Phi(\xi(s))\,ds. \tag{5.11}$$

The derivative $DU(\xi, \eta)$ down the solutions of (N_3, R_3) is equal to

$$DU(\xi, \eta) = [1 - 2g(\eta(t))]\Phi(\xi(t)). \tag{5.12}$$

Let us note that under assumption (Φ_3), two obvious properties hold:

$$\sup_{t \ge 0} R(t) = C < \infty, \tag{5.13}$$

$$\sup_{t \ge 0} |\dot{N}(t)| = C' < \infty. \tag{5.14}$$

Now choose a solution and suppose that $N(t) \to \infty$ as $t \to \infty$. Then it is possible to choose a sequence $t_n \to \infty$ such that $N(t_n) \uparrow \infty$. Since the derivative of N is bounded, it is also possible to associate with (t_n) another sequence (t_n') such that $t_n - t_n' \to \infty$,

$$N(t) \ge N(t_n)/2, \qquad t \in [t_n', t_n], \tag{5.15}$$

$$N(t_n') = N(t_n)/2. \tag{5.16}$$

Thus for $t \in [t_n' + H, t_n]$, we will have

$$R(t) \le e^{-\beta(t-(t_n'+H))} C + (A/\beta) \sup_{u \ge N'(t_n)/2} \Phi(u).$$

Therefore, it is possible to find a number $a > 0$ independent of n such that for n large enough $R(t) < g^{-1}(\frac{1}{2})$, $t \in [t_n' + a, t_n]$. By virtue of (5.12) this implies $D(N_t, R_t) \le 0$, $t \in [t_n' + a, t_n]$ what yields $U(N_{t_n}, R_{t_n}) \le U(N_{t_n'+a}, R_{t_n'-a})$. From this (using (5.11)) one can deduce

$$N(t_n) \le N(t_n' + a) + C'',$$

by (5.14),

$$N(t_n) \leq N(t_n') + aC' + C'',$$

while by (5.16),

$$N(t_n) \leq N(t_n)/2 + aC' + C''$$

which implies

$$N(t_n) \leq 2(aC' + C'').$$

This is a contradiction. □

Introducing a Lyapunov functional $V(\xi, \eta) = \xi(0) + \int_{-T}^{0} \Phi(\xi(s))\, ds$ and using the technique of Proposition 5.2, we obtain an estimate of the domain of attraction of (0, 0).

Proposition 5.4. Choose $\hat{R}$ and $\hat{N}$ such that

$$2[1 - g(\hat{R})] \leq h(\hat{N})/h(0), \tag{5.17}$$

$$A\Phi(\hat{N})/\beta \leq \hat{R}. \tag{5.18}$$

Then $G = C([-H, 0]; [0, \hat{R}] \times [0, \hat{N}]$ is positively invariant w.r. to (N_3) and (R_3). Moreover, each solution of (N_3) and (R_3) which enters G tends to (0, 0) at $+\infty$.

6. TWO SPECIAL MODELS RELATED TO MODEL 1

In this section we will consider two interesting models of cell production systems. The first one is a version of Model 1, with only one delay (H) present. It exhibits more complex behaviour than the model without delays, while being easier to analyze than the general two-delay version. Also, it can be viewed as a generalization of certain previous cell production models.

The second model is a version of Model 1 with the defensive feedback missing [i.e. $d(t) \equiv \frac{1}{2}$]. This version allows for a continum of equilibria, each of them attracting solutions from a certain subspace. It can serve as a model of a "defective" cell production system.

6.1. *Model 1 with one delay*

In 1976 Wazewska and Lasota[5] presented a model of the erythropoietic (red-blood-cell) system, in the form of one difference-differential equation:

$$\dot{u}(t) = -\sigma u(t) + e^{-u(t-H)}, \tag{6.1}$$

where $u(t)$ is the red cell number at t. Model (6.1) does not account for system extinction, since it has no trivial equilibrium. Solutions are always bounded: for some parameters the nontrivial equilibrium is globally asymptotically stable; for other parameters oscillations occur.

Equation (R_1) is very similar to (6.1). In the case $T = 0$ the analogy is quite complete: Equation (N_1) reduces to (3.1), and as we already know, $N(t) \to \tilde{N}$ no matter what happens to $R(t)$. Thus the asymptotic behaviour of $R(t)$ is the same as in the "limiting" equation:

$$\dot{R}(t) = -\beta R(t) + (A\tilde{N}/2)\, h(R(t - H)). \tag{6.2}$$

Lasota-Wazewska's equation is a special case of (6.2). This is also the case for two models by Mackey[4, 21]. From theorem 5.1, we obtain a sufficient condition for the global asymptotic stability of (6.2):

$$(A\tilde{N}/2\beta)h'^* < 1. \tag{6.3}$$

On the other side, the linearized version analysis gives local asymptotic stability iff

$$| h'(\tilde{R}) | < 2(a^2 + \beta^2 H^2)^{1/2} (HA\tilde{N})^{-1},$$

where $a \in (\pi/2, \pi)$ satisfies $a = -\beta H \tan(a)$ (see Bellman and Cooke[19], Theorem 13.8). If $H \to \infty$, then this condition takes the form

$$| h'(\tilde{R}) | < 2\beta/A\tilde{N},$$

which reduces to (6.3) if $h'(\tilde{R}) = h'^*$, i.e. when the slope of h is maximum at $\tilde{R}$. For such cases and H large, condition (6.3) is the best possible. Contrary to the general case, we were able to prove a criterion depending on H.

Proposition 6.1. Suppose that

$$(A\tilde{N}/2)Hh'^*[\beta + (A\tilde{N}/2)h'^*] < \beta.$$

Then (6.2) is globally asymptotically stable.

Proof. Denoting $X = R - \tilde{R}$, $f(X) = -\beta X + (A\tilde{N}/2)h_1(X)$, $h_1(X) = h(X + \tilde{R}) - h(\tilde{R})$ and performing some manipulations, we can rewrite (6.2) as

$$\dot{X}(t) = -f(X(t)) - \frac{A\tilde{N}}{2} \int_{t-H}^{t} h_1'(X(s)) \left(-\beta X(s) + \frac{A\tilde{N}}{2} h_1(X(s - H)) \right) ds,$$

or briefly as $\dot{X}(t) = -f(X(t)) + P_H(X_t)$, where P_H is defined on $C([-2H, 0], \mathbb{R})$, $P_H(0) = 0$ and $| P_H(X) | \leq | P_H | \, | X |$, where $| P_H |$ can be estimated as

$$| P_H | = (A\tilde{N}/2)Hh'^*[\beta + (A\tilde{N}/2)h'^*).$$

Suppose $| P_H | < \beta$. First, we prove the stability. Take a data X_0, $| X_0 | < \rho$ and $X(t_1) > 0$. Since $f'(X) \geq \beta$, we have $\dot{X}(t_1) \leq (-\beta + | P_H |) \rho < 0$. As $t_1 > 0$, this is a contradiction.

To prove the attractivity, let us take a sequence $t_n \to \infty$ such that $\pm X(t_n) \to \limsup_{s \to \infty} | X(s) |$ and then $\dot{X}(t_n) \to 0$. From the equality $\dot{X}(t_n) + f(X(t_n)) = P_H(X_{t_n})$ it follows that

$$\limsup_{n \to \infty} | f(X(t_n)) | = \limsup_{n \to \infty} | P(X(t_n)) | ,$$

which implies

$$\beta \limsup_{n \to \infty} | X(t_n) | \leq | P_H | \limsup_{n \to \infty} | X_{t_n} |$$

and

$$\beta \limsup_{t \to \infty} | X(t) | \leq | P_H | \limsup_{t \to \infty} | X(t) | .$$

But this yields $\limsup_{t \to \infty} | X(t) | = 0$. □

For the original Lasota-Wazewska's equation (6.1), Proposition 6.1 implies the asymptotic stability if $H < \sigma/(\sigma + 1)$. This condition is identical to that given in [5].

When roots of the characteristic equation of (6.2) have a positive real part, we see that the conditions given by Kaplan and Yorke[22] are verified. Thus (6.2) has a closed annulus in the phase plane $(R, \dot{R})$, which is globally attractive in the set of slowly oscillating solutions. Analogous property for the general system (N_1), (R_1) with two delays would be difficult to prove, although simulations suggest oscillations when the asymptotic stability is lost.

6.2. *Model* 1 *with* $d = \frac{1}{2}$

In this case, Eqs. (N_1) and (R_1) assume the form

$$\dot{N}(t) = -h(R(t))\,N(t) + h(R(t-T))\,N(t-T), \tag{6.4}$$

$$\dot{R}(t) = -\beta R(t) + (A/2)h(R(t-H))\,N(t-H). \tag{6.5}$$

First, observation is that the functional V: $C([-H, 0], \mathbb{R}_+^2)$ defined as

$$V(\xi, \eta) = \int_{-T}^{0} \xi(s)h(\eta(s))\,ds + \xi(0) \tag{6.6}$$

stays constant along the solutions of the system $V(N_t, R_t) = V(N_0, R_0)$, $t \geq 0$. Indeed, it is enough to integrate (6.4), side by side, on the interval $[0, t]$.

Consider now a solution of (6.4), (6.5) with initial data $(\varphi, \psi) = (N_0, R_0)$ and suppose that $[N(t), R(t)] \to (N_\infty, R_\infty)$. The equilibrium (N_∞, R_∞) depends on initial data, since (6.4) is satisfied by any pair of constant functions. Using (6.5) and the invariance of $V(.)$, we obtain

$$N_\infty = V(\varphi, \psi)/[1 + Th(R_\infty)], \tag{6.7}$$

and R_∞ is the unique solution of

$$R_\infty = [AV(\varphi, \psi)/2]\,\{h(R_\infty)/[1 + Th(R_\infty)]\}. \tag{6.8}$$

Biologically, $V(N_t, R_t) = N(t) + 2P(t)$ (see Section 1), i.e. it is equal to the number of stem cells in the passive phase plus twice the number of stem cells in the active phase. Thus $V(N_t, R_t) = V(\varphi, \psi)$ can be treated as a "potential" number of stem cells.

Let us consider a situation in which both $N(t)$ and $R(t)$ undergo a stepwise charge. This corresponds to the extinction of a part of stem and mature population. In the framework of our model this can be presented as follows: Suppose that for $t \in [-t_0 - H, 0)$ the system was evolving according to (6.4) and (6.5). Let us denote the corresponding solutions by $[n(t), r(t)]$, $t \in [-t_0 - H, 0)$. We consider then, solutions to system (6.4), (6.5), for $t \geq 0$, with initial data

$$[\varphi(\tau), \psi(\tau)] = \begin{cases} [n(\tau), r(\tau)], & \tau \in [-H, 0), \\ [N(0), R(0)], & \tau = 0, \end{cases} \tag{6.9}$$

where $[N(0), R(0)]$ is generally not equal to $[n(0-), r(0-)]$. It is possible to compute explicitly the difference $V(N_t, R_t) - V(n_{(0-)}, r_{(0-)})$ for $t \in [0, T]$ [by solving (6.4), (6.5) on $[0, T]$ with data (6.9) and substituting into (6.6)]. The result is

$$V(N_t, R_t) - V(n_{(0-)}, r_{(0-)}) = N(0) - n(0-)$$

for $t \in [0, T]$ and thus for $t \geq 0$. This proves that only extinction of stem cells can affect the system equilibrium in this model.

If $N(0) - n(0-) = 0$, then the equilibrium remains the same, no matter what $R(0)$ is.

After this discussion, let us address the question of attractivity of equilibrium (N_∞, R_∞), for solutions with $V(\varphi, \psi)$ given.

Suppose that $V(\varphi, \psi) = C$ and $t \geq H$. Then, by integrating (6.5) side by side on $[t - T, t]$ and noting that $V(N_{t-H}, R_{t-H}) = C$, we obtain

$$R(t) - R(t - T) = -\beta \int_{t-T}^{t} R(s)\, ds + \frac{A}{2}[C - N(t - H)].$$

Solving this for $N(t - H)$ and substituting into (6.5) we obtain

$$\dot{R}(t) = -\beta R(t) = \left(\frac{AC}{2} - \beta \int_{t-T}^{t} R(s)\, ds - R(t) + R(t - T)\right) h(R(t - H)). \quad (6.10)$$

If $[N(t), R(t)]$ is a solution of (6.4) and (6.5) on $[0, \infty)$, with $V(\varphi, \psi) = C$, then $R(t)$ satisfies (6.10) on $[H, \infty)$.

We are able now to state the following result.

Proposition 6.2. Suppose that condition

$$h^*(1 + \beta T) + \frac{\beta R_\infty}{h(R_\infty)} \max_{u \geq 0} \left| \frac{h(u) - h(R_\infty)}{u - R_\infty} \right| < k\beta \quad (6.11)$$

is satisfied for some $k < 1$. Then all the non-negative solutions of (6.4) and (6.5), with $V(\varphi, \psi) = C$, tend to (N_∞, R_∞) as $t \to \infty$.

Proof. Denote $r = R - \bar{R}$, $z(r) = h(r + R_\infty)$ if $r \geq -R_\infty$ and $z(t) = h^*$ if $r < -R_\infty$. Now $r(t)$ satisfies

$$\dot{r}(t) = -[\beta + z(r(t - H))]r(t) - \beta \int_{t-T}^{t} r(s)\, ds\, z(r(t - H))$$

$$+ r(t - T)z(r(t - H)) + r(t - H)\, \beta \frac{R_\infty}{h(R_\infty)} \frac{z(r(t - H)) - z(0)}{r(t - H)}. \quad (6.12)$$

It is enough to prove that $r \equiv 0$ is globally asymptotically stable. We will use a Razumikhin function method (Hale[17], Theorem 5.4.2).

The Razumikhin function V, satisfying assumptions of this theorem, can be chosen as $V(r) = r^2/2$ [with the auxiliary functions $u(r) = v(r) = r^2/2$]. Another function, $p(s)$, can be chosen as $p(s) = q^2 s$, for $q > 1$. Now we have to prove that the derivative $\dot{V}(\cdot)$ of $V(\cdot)$, down the solutions of (6.12), satisfies

$$\dot{V}(r(0)) \leq -\omega(|r(0)|) \quad (6.13)$$

(for some ω: $[0, \infty) \to [0, \infty)$ continuous, nondecreasing) if only r is chosen so that

$$V(r(\theta)) < p(V(r(\theta))), \theta \in [-H, 0]. \quad (6.14)$$

In our case, (6.14) is equivalent to

$$|r(\theta)| < q\,|r(0)|, \theta \in [-H, 0]. \quad (6.15)$$

It holds that $\dot{V}(r(0)) = -r(0)\dot{r}(0)$. After substituting for $\dot{r}(0)$ the right-hand side terms of (6.12) and using inequalities (6.11) and (6.15) we obtain

$$\dot{V}(r(0)) < -\beta(1 - qk)[r(0)]^2.$$

Choosing $q > 1$ such that $qk < 1$, we can define $w(s) = (1 - qk)s^2$ so that inequality (6.13) is satisfied. □

It is possible now to characterize the behaviour of solutions of this system if hypothesis (6.11) is satisfied. In "normal" conditions, system maintains an equilibrium. After a stepwise change in both R and N, the system returns to a new, generally different equilibrium.

If we assume that the stepwise change was caused by extinction of part of the stem and/or mature cells, we see by inspection of (6.1) and (6.8) that both R_∞ and N_∞ decrease. The amplitude of this decay, which is measure of the system performance deterioration, depends only on the extent to which the stem cell population was damaged.

7. DISCUSSION

The three models presented and analyzed in this paper provide interesting information on the hypothetical regulation mechanisms in multistage cell production systems. The basic observation is that models looking equally reasonable and being able to satisfy similar steady state properties can differ strikingly with respect to stability properties.

Before proceeding to details, let us address a fundamental issue. Recently, Wichmann[7] in a very comprehensive review article analyzed various concepts of mathematical models of blood cell production system. The postulates he states for models of this kind include (among others) the reproducibility of experimental data under various experimental conditions, possibility of reproducing the data in many compartments simultaneously and possibility of using the models to design new experiments. The approach of this paper is different. We look at a cell production system as at a dynamical system, trying to understand its behaviour as a function of assumptions in a possibly general way. Our models are simplified and so not exactly comparable to their complicated originals. However, since the models incorporate certain first principles of cell growth regulation in various configurations, their analysis can anticipate true system's behaviour in experiments that were never performed and that sometimes are not possible to perform.

The regulation functions of our models have quite a general form, so that they can be adjusted to various specific situations. For instance, the special case of Model 1 considered in Section 6.1 is a generalization of models presented in Refs. [4], [21] and [5]. However, there are some structural limitations that we would like to discuss here.

It seems that what we call a long-range feedback [which is sensitive to the number (R) of mature cells] is in fact composed (at least in the blood cell systems) of two parts. One of them controls the production of the precursor cells, based on the mature cell number (R); the other regulates the production of the stem cells, based on the precursor cell number (C) (see Loeffler and Wichmann[16], Wheldon[23], Aarnaes[6]). In our models, where the precursor cell populations is represented in a very simplified way, consideration of such a feedback would be difficult.

It can be imagined that all the regulated factors (α and d, in our models) can depend on the level of cells in more than one compartment [for instance $\alpha = h(N, P, R)$, $d = g(N, P, R)$. In fact, Loeffler and Wichmann[16] postulate $d = g(N + P, C)$ (in our notation) in their very well-documented model of the red blood cell system. However, such general dependencies would be very difficult to analyze, even in the ordinary (nondelay) cases of our models. (Also, it was suggested by Nečas and Neuwirt[24, 25] that the stem cell self-control feedback depends on the number of cells in the S phase).

Finally, it is possible (see Mackey and Dormer[26]) that the process of cell maturation is more continuous than discrete. Then our (and most of the authors') subdivision of the cell system into disjoint compartments would be disputable.

In this paper, the strategy of model analysis was to consider first the simplified version describable by ordinary differential equations. Then an attempt was made to examine which of the simplified model properties are valid for the general case. A variety of methods were used to achieve this purpose. We should mention here the Lyapunov functions (Proposition 3.3), Lyapunov functionals (Propositions 5.2 and 5.3), quasi-Lyapunov functionals (Proposition 5.3 and Theorem 5.1) and Razumikhin function (Proposition 6.2). These tools were used to prove attractivity of equilibria and boundedness of solutions. However, in almost each case, the application of Lyapunov or Razumikhin method had to be preceded by a painful preparatory analysis. It is extremely interesting that the quasi-Lyapunov functions used in Theorem 5.1 and Propositions 5.2, 5.3 and 5.4 are related to a "potential" number of the stem cells (see the discussion in Section 6.2).

In the ordinary case, most of the analysis was possible to carry out by means of traditional phase plane techniques. However, even in this case, the general form of the feedback functions increased the difficulties.

Also, for the purpose of numerical stability investigations of the linearized delay equations, it was necessary to prove an original result on the location of zeros of the exponential polynomials (Proposition A.1). This result is applicable to a wide class of models of cell production systems.

We will now review the results on the dynamical properties of the three models.

Model 1. In the ordinary (no delay) case, the nontrivial equilibrium of this model attracts all non-negative solutions, except for those with $N(0) = 0$ (corresponding to the total extinction of the stem cell population; see Proposition 3.1). In the general (two delay) case, the global attractivity (and stability) still holds, if the regulation functions are not too steep (see Proposition 3.1 and the numerical analysis of Section 4).

For the parameter values corresponding to the human blood cell system, numerical simulations (see Kimmel and Arino[9]) indicate that instability of the equilibrium results in stable oscillations with period of about 20 days.

This is similar to the period (16–17 days) of reticulocyte number oscillations in the auto-immuno hemolytic anemia (Mackey[21]) and to the period (17–28 days) of the neutrophil number oscillations in cyclic neutropenia (Mackey[4]). In fact, the one-delay version of Model 1 (Section 6.1) is a generalization of both Mackey's models, as well as of the pioneer model of Wazewska and Lasota[5] (see also Wazewska[27]). For the one-delay Model 1, the existence of stable oscillations can be proved based on results by Kaplan and Yorke[22] (see also Chow[28]); moreover, for this version, improved stability results are available (Proposition 6.1). Also, the general possibility of inducing oscillations by the means of "steepening" the regulation functions was indicated by Wichmann[7]. Model 1 was intended originally (Kimmel and Arino[9], Arino and Kimmel[20]) to generalize the models of Refs. [21] and [5] by incorporating the stem cell kinetics and short-range feedback. However, the dynamical effects observed do not seem to differ significantly from those reported in [21] and [5]. Specifically, the model fails to reproduce system decay when the perturbation is large enough.

Especially controversial is the version of Model 1 with $d \equiv \frac{1}{2}$ (Section 6.2), i.e. without regulation of the differentiating fraction of stem cells. Theory indicates that the consequence of this assumption is the possibility of existence of a continuum of equilibria, attracting solutions with initial conditions in various subspaces (Proposition 6.2). It is demonstrated in Section 6.2 that the system can change its equilibrium only if the per-

turbation affects directly the stem cell number. Then the cell system recovers, but never attains the previous production rate. According to Loeffler and Wichmann[16], who discussed similar questions, there is no experimental evidence supporting such possibility.

In our opinion, however, this model deserved discussion on the basis of its interesting dynamical properties.

Model 2. The main purpose of considering this model was to demonstrate that the absence of a short-range (defensive) feedback of the stem cell population destabilizes the system. This is clear from the simplified (no delay) case, in which practically all the trajectories either tend to the origin ($N = R = 0$) or escape to infinity (Proposition 3.2). Also, in the two-delay case, the nontrivial equilibrium is unstable (Section 4), while the trivial equilibrium is asymptotically stable with domain of attraction estimated in Proposition 5.2.

Model 3. This version seems to exhibit the most complex and interesting behaviour. In the simplified (no delay) case, all the solutions are attracted by one of the three existing equilibria (Proposition 3.3). One of the two nontrivial equilibria is unstable, while the other nontrivial equilibrium and the trivial equilibrium are asymptotically stable. Biologically it means that under some perturbations the system returns to the "normal" (nontrivial equilibrium), but if the number of mature and/or stem cells decreases below certain level, the system becomes extinct. This is exactly the effect predicted by a computer model (of red blood cell system) by Loeffler and Wichmann[16] (see their Fig. 6 and reference to Reincke[35]).

Similar family of responses was observed by Wazewska (unpublished experimental data) after inducing severe blood loss in rabbits.

In the general (two-delay) case, the model behaviour may change substantially, but certain essential features are saved.

All the solutions are bounded (Proposition 5.3). One of the nontrivial equilibria is unstable (see Section 4). The other one is stable at least when both nontrivial equilibria are close to each other (Proposition 4.1) and when the regulation feedbacks are not too steep (see Fig. 4.2). Attractivity domain of the stable trivial equilibrium is estimated in Proposition 5.4.

The above comparison indicates clearly that Model 3 or certain combinations of Model 1 and 3 describe correctly the basic features of normal cell production systems. Abnormalities in system feedback configuration result in "pathological" behaviour: unlimited growth, system extinction (Model 2) or permanent decrease in system output (Model 1 with $d \equiv \frac{1}{2}$).

Relevant experimental evidence concerning the cell production systems (in the sense used in this paper) was, until very recently, limited to the blood cell systems. Without any attempt to cover the subject, we can quote papers by Iscove[30], Lord[31], Nečas and Neuwirt[24, 25] and many others. However, recent papers by Potten *et al.*[3], Clausen *et al.*[32] and others indicate that similar structures and feedbacks are active in the mouse epidermis cells systems. The same seems to be true for the human epidermis cells in culture (Staiano-Coico *et al.*[33] and Kimmel *et al.*[34]). Therefore, it seems justified to explore the properties of mathematical models related to these important processes.

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APPENDIX

We provide a result on the zeros of exponential polynomials, which was used for the numerical investigation of asymptotic stability (Section 4). Although it has a technical character, it can be of interest since it enables analysis of a broad class of systems similar to those considered in this paper.

Proposition A.1. Given is the following exponential polynomial:

$$H(\lambda) = h(\lambda, e^{\lambda}) = \lambda^2 e^{\lambda(T+H)} + \lambda[\alpha_1 e^{\lambda(T+H)} + \beta_1 e^{\lambda T} + \gamma_1 e^{\lambda H} + \delta_1] + \alpha_0 e^{\lambda(T-H)} + \beta_0 e^{\lambda T} + \gamma_0 e^{\lambda H} + \delta_0,$$

where T and H are positive integers, $\alpha_i, \beta_i, \gamma_i, \delta \in \mathbb{R}$.

Suppose that $\alpha_0 + \beta_0 + \gamma_0 + \delta_0 \neq 0$, then a necessary and sufficient condition for all the zeros of $h(\lambda, e^{\lambda})$ to have negative real parts is that

(a) In the interval $[0, 2k_1\pi/(T + H)]$, the function $F(y) = \operatorname{Re} H(jy)$, $y \in \mathbb{R}$, $j = \sqrt{-1}$, has exactly $2k_1 + 1$ zeros and

(b) The condition $F'(y_0)\, G(y_0) < 0$, where $G(y) = \operatorname{Im} H(jy)$ is satisfied for the zeros y_0 in the interval $(0, 2k_1\pi/(T + H)]$, where k_1 is equal to $\max(k_0, k_0')$, where k_0 and k_0' are the smallest integers for which it holds:

$$B_k > \sqrt{2}\, A_k,\ k \geq k_0;\quad B_k > \sqrt{2}\, A_k',\ k \geq k_0',$$

with

$$A_k = \frac{2(k+1)\pi}{T+H}(|\alpha_1| + |\beta_1| + |\gamma_1| + |\delta_1|) + (|\alpha_0| + |\beta_0| + |\gamma_0| + |\delta_0|),$$

$$A_k' = \frac{2(k'+1)\pi}{(T+H)^2}(2 + (T+H)|\alpha_1| + T|\beta_1| + H|\gamma_1|) + \frac{|\alpha_1| + |\beta_1| + |\gamma_1| + |\alpha_0|(T+H) + |\beta_0|T + |\gamma_0|H}{T+H},$$

$$B_k = 4k^2\pi^2/(T+H)^2.$$

Suppose that $\alpha_0 + \beta_0 + \gamma_0 + \delta_0 = 0$; then $h(\lambda, e^{\lambda})$ is unstable.

Remark. The lemma applies to all the systems of form

$$\dot{y}_1(t) = a_{11}y_1(t) + a_{12}y_2(t) + b_{11}y_1(t - \omega_1) + b_{12}y_2(t - \omega_1),$$
$$\dot{y}_2(t) = a_{21}y_1(t) + a_{22}y_2(t) + b_{21}y_1(t - \omega_2) + b_{22}y_2(t - \omega_2),$$

if only ω_1/ω_2 is a rational number. In our system T/H should be rational, which can of course be safely assumed.

Proof. For our polynomial, the functions $F(y)$ and $G(y)$ take the form of

$$F(y) = -y^2\cos[y(T+H)] - y\{\alpha_1\sin[y(T+H)] + \beta_1\sin(yT) + \gamma_1\sin(yH)\} + \alpha_0\cos[y(T+H)] + \beta_0\cos(yT) + \gamma_0\cos(yH) + \delta_0, \tag{A.1}$$

$$G(y) = -y^2\sin[y(T+H)] + y\{\alpha_1\cos[y(T+H)] + \beta_1\cos(yT) + \gamma_1\cos(yH) + \delta_1\} + \alpha_0\sin[y(T+H)] + \beta_0\sin(yT) + \gamma_0\sin(yH). \tag{A.2}$$

We will also need $F'(y)$:

$$F'(y) = y^2(T+H)\sin(y(T+H)) - y\{2\cos(y(T+H)) + \alpha_1(T+H)\cos(y(T+H)) + \beta_1 T\cos(yT) + \gamma_1 H\cos(yH)\} - [\alpha_1 + \alpha_0(T+H)]\sin(y(T+H)) - (\beta_1 + \beta_0 T)\sin(yT) - (\gamma_1 + \gamma_0 H)\sin(yH). \tag{A.3}$$

We will be using the method described in Bellman and Cooke[19], Theorems 13.3 and 13.7. The

method requires that we verify if a certain function $\Psi^{*(T-H)}$ (defined in [19], Theorem 13.3) satisfies the condition

$$\Psi^{*(T-H)}(\epsilon + jy) \neq 0,$$

for every y in $\mathbb{R}$ and some real ϵ. It is easily checked that in our case $\Psi^{*(T-H)}(z) = -\cos(z(T + H))$, and thus if we take $\epsilon = 0$, the condition is verified.

Inspection of Theorems 13.3 and 13.7 of [19] gives in our case the following necessary and sufficient conditions for stability of $h(\lambda, e^{\lambda})$:

(1) The function $F(y)$ has exactly $4(T + H)k + 2$ real zeros in each interval $[-2k\pi, 2k\pi]$, beginning from some k.

(2) For each such zero y_0 of F, it holds that

$$F'(y_0)\, G(y_0) < 0.$$

Consider first the degenerate case, i.e. $\alpha_0 + \beta_0 + \gamma_0 + \delta_0 = 0$. We see that $F(0) = 0$. Thus, since F is an even function, it has an odd number of zeros in each symmetrical interval: this means that condition 1. cannot be satisfied. Hence $h(\lambda, e^{\lambda})$ is unstable.

Now assume that $\alpha_0 + \beta_0 + \gamma_0 + \delta_0 \neq 0$.

Let us start with the *sufficient condition*.

We introduce the following hypotheses:

(3) $F(y)$ has exactly one zero in each of the following intervals:

$$I_1^k = \left[\frac{2\pi k + \pi/4}{T + H}, \frac{2\pi k + 3\pi/4}{T + H}\right],$$

$$I_2^k = \left[\frac{2k\pi + 5\pi/4}{T + H} \quad \frac{2k\pi + 7\pi/4}{T + H}\right].$$

where k is greater or equal to k_1, and F has no other zeros in the interval $[2k\pi/(T + H), 2(k + 1)\pi/(T + H)]$.

(4) $G(y)$ is negative in I_1^k, positive in I_2^k, for $k \geq k_1$.

(5) $F'(y) > 0$ in I_1^k, $F'(y) < 0$ $\quad 0$ in I_2^k, for $k \geq k_1$.

First, we will prove that conditions (3)–(5) imply conditions (1) and (2), under the hypotheses (a) and (b) of the proposition.

Since F is even, $F(0) \neq 0$ and G is odd, it is sufficient when looking at 1 to prove that F has exactly $2(T + H)k + 1$ zeros in $(0, 2k\pi]$, for all k large enough, and looking at (2), to prove that $F'(y_0)\, G(y_0) < 0$, for the zeros in $(0, 2k\pi]$.

Proof of 1. We write the interval $(0, 2k\pi]$ as the union of $(0, 2k_1\pi/(T + H)]$ and of the intervals $[2l\pi/(T + H), 2(l + 1)\pi/(T + H)]$, $k_1 \leq l \leq k(T + H) - 1$. Using hypothesis (a) of the proposition and condition (3), we count exactly

$$2k_1 + 1 + 2[k(T + H) - k_1] = 2k(T + H) + 1$$

zeros in the interval $(0, 2k\pi]$.

Proof of 2. it is a direct consequence of conditions (4) and (5). The next step is to prove that (3)–(5) are true under the conditions of the proposition. The proof will be based on the fact that the terms involving the factor y^2 in F, G, F' dominate the remaining terms for y large enough. But because of the presence of $\cos y(T + H)$, the domination will only take place in intervals in which $\cos y(T + H)$ is far from zero. On the other hand, we will find a zero in intervals at the extremities of which $\cos y(T + H)$ takes opposite and far from zero values.

Let us take $k \geq k_0$: note that the value of $-y^2 \cos y(T + H)$ is less than $-B_k/\sqrt{2}$ (resp. greater than $B_k/\sqrt{2}$) on the left (resp. right) end of I_1^k, while A_k is the upper bound for the absolute value

of the sum of the remaining terms of $F(y)$. The same estimates are true for I_2^k. Moreover, in the set

$$\left[\frac{2k\pi}{T+H}, \frac{2(k+1)\pi}{T+H}\right] \setminus (I_1^k \cup I_2^k),$$

We have $|y^2 \cos y(T+H)| \geq B_k/\sqrt{2}$.

To conclude, F has at least one zero in each of the intervals I_1 and I_2 and has no zero in

$$\left[\frac{2k\pi}{T+H}, \frac{2(k+1)\pi}{T+H}\right] \setminus (I_1^k \cup I_2^k),\ k \geq k_0.$$

A similar argument applied to G shows that $G(y) < 0$ in I_1^k and $G(y) > 0$ in I_2^k, $k \geq k_0$, which is (4).

To complete the verification of (3), we have only to prove (5).

Looking at F' [formula (A.3)], we see that it is a combination of the same functions which appear in G, with other coefficients. Dividing F' by $T+H$, we can define a new A_k' and B_k as before. Thus from the preceding proof, it follows that the condition $B_k > 2\sqrt{A_k'}$, $k \geq k_0'$ (for some new constant k_0'), ensures that F' will stay positive in I_1^k and negative in I_2^k. That completes the proof of (3)–(5).

We pass to the necessary condition: Suppose that (a) does not hold. Then since $F(y)$ is even, we see that it has less than $4k(T+H)+2$ zeros in the interval $[-2k\pi, 2k\pi]$ for each k greater than some value. This in turn implies the instability of $h(\lambda, e^{\lambda})$ by condition (1). Similarly, if (b) does not hold, then $h(\lambda, e^{\lambda})$ is unstable by condition 2. □

Proposition A.1 provides a numerical method for checking the stability near the critical point (N, R) by undertaking the numerical search of the zeros of $F(y)$. Numerical computations were carried out partly using this method and partly a method introduced by Sikora and Kociecki[29]. This last method was modified and programmed by Miroslaw Sarnik, graduate student in the Institute of Automation of the Silesian Technical University in Gliwice, Poland.