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# STABILITY PROPERTIES OF PROLIFERATIVELY COUPLED CELL REPLICATION MODELS

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## ABSTRACT

To address the possibility that proliferative disorders may originate from interactions between multiple populations of proliferating and maturing cells, we formulate a model for this process as a set of coupled nonlinear first order partial differential equations. Using recent results for the asymptotic behaviour of the solutions to this model, we demonstrate that there exists a region of coupling coefficients, maturation rates, and proliferation rates that will guarantee the stable coexistence of coupled cellular populations. The analysis shows that increases in the coupling between populations may ultimately lead to a loss of stability. Furthermore, the analysis indicates that increases (decreases) in the maturation and/or proliferation rates above (below) critical levels will lead either to instability in the populations or the destruction of one population and the persistence of the other.

**Keywords.** Hematological diseases, first order partial differential equations, stability

## 1. INTRODUCTION

Hematological diseases have long served as model systems for the study of proliferative disorders in many tissues. Historically, this can be traced to the fact that it is relatively easy to monitor the number of mature end stage hematological cells, and as a consequence much information is available about the dynamics of these cells. Furthermore, because of the relative ease with which hematological systems may be

manipulated *in vivo* and studied *in vitro* there has been an explosive expansion in our knowledge of these systems (Metcalf, 1988).

In spite of the obvious differences at a functional level between various cell types, it has always been the hope that better understanding of the processes of differentiation, proliferation, and maturation within the hematological cell lines will give general precepts that can be exported to aid in the understanding of other tissue dynamics. Previous efforts to understand the dynamic origin of proliferative hematological disorders have focused either on destabilization of the control of pluripotential stem cell numbers (Mackey, 1978, 1979), or on the destabilization of a peripheral control loop (King-Smith & Morley, 1970 and Schmitz et al. 1989 are representative). These modeling studies (Milton & Mackey, 1989) have concentrated on the control of proliferative dynamics in these populations, and the appropriate models are usually framed as nonlinear differential or differential-delay equations (see Mackey & Milton, 1990 for a recent review). While there are formidable problems associated with the study of these equations, there are at least results giving necessary and sufficient conditions for the local stability of steady states.

However, there is evidence (see the next section) that there are significant interactions between various subpopulations of stem cells that ultimately give rise to mature circulating erythrocytes and white blood cells. This raises the alternative possibility that hematological diseases might occur because of a loss of stability in these interacting committed stem cell compartments in which there are powerful nonlinear interactions between cells that are both proliferating and maturing simultaneously. In this situation modeling problems change dramatically, because the mathematical models are most appropriately framed as nonlinear systems of first order partial differential equations. For partial differential equations appropriate for these problems, few stability results are available. This stems from the fact that in biologically realistic models the velocity of maturation is often estimated to be zero in the least mature cells of a given cell line. However, the results of Lasota (1981) and Brunowský (1983) offer some insight into the stability of equilibria of single cellular populations under this condition.

In this paper (section 2) we formulate a general model for the behaviour of multiple cellular populations undergoing both maturation and proliferation and coupled through the mutual interdependence of their proliferative activities. Though our considerations are general, our formulation of this problem is guided throughout by the known dynamic behaviors of various hematopoietic cell lines.

Loskot (1991) has given sufficient conditions for the local asymptotic stability of equilibria of coupled partial differential equations. These are presented in section 3 for our model, specialized to two coupled populations. In section 4 we use his results to examine the role of various biologically meaningful parameters in guaranteeing this stability condition. We show that bounds on maturation rates are just as important for the stability as bounds for the proliferation rates.

## 2. THE MODEL

### 2.1. Physiological considerations

The mammalian hematopoietic system, with its diversity of cell types, regulators, and kinetic behaviors, offers an ideal biological model with which the considerations of this paper can be motivated.

It is generally accepted that there is a population of pluripotential stem cells (PPSC) within the bone marrow that give rise to primitive stem cells committed to the production of erythrocytes, platelets, white blood cells, and lymphocytes. The committed stem cells for the erythroid series (CSC-E) are assayed *in vitro* by the primitive and mature burst forming units (BFU-E) and colony forming units (CFU-E). The committed stem cells for the white blood cells (CSC-G) have the colony forming units/granulocyte-macrophage (CFU-C) as their *in vitro* analogs (Quesenberry and Levitt, 1979).

Within the erythroid system there is a well established long range negative feedback humoral control mediated by erythropoietin. A fall in the number of circulating red blood cells is followed by a decrease in tissue $pO_2$ levels. This, in turn, stimulates the production and release of renal erythropoietin whose action is to increase the flux of cells from the PPSC into the CSC-E and/or the proliferative rate within the CSC-E. A similar control mechanism, mediated by the putative regulator granulopoietin (whose *in vitro* analog is colony stimulating factor, CSF), operates for the white blood cells.

In addition to these long range control mechanisms there seem to be local regulatory mechanisms over the proliferative rates within the PPSC, the CSC-E, and the CSC-G such that the proliferative rate is maximal at low cell numbers and monotonically decreases as cell numbers rise.

There is a host of *in vivo* data whose most conservative interpretation is that there exist significant interactions between the committed erythroid and granulocytic stem cells as well as the committed stem cells for the lymphocytes and platelets.

One piece of evidence comes from the secondary compensatory changes observed in white blood cells and their precursors in the presence of hypoxia and hyperoxia (Brookoff & Weiss, 1982; Iscove, 1977; Metcalf, 1969; Peschle et al. 1977; Smith et al. 1980a,b). Under experimental maneuvers expected to increase (decrease) the erythropoietin drive to the CSC-E, there is an accompanying decrease (increase) in the number of circulating white blood cells as well as their primitive precursors. This would indicate that an increased (decreased) proliferative activity in one population gives rise to a decreased (increased) proliferative activity in another.

There is strong *in vitro* evidence that this coupling of proliferative activity between cell populations is mediated by cell numbers. Van Zant and Goldwasser (1979) have shown that there are strong competitive interactions between erythropoietin and CSF in their actions on erythroid and neutrophil colonies growing in the same environment. Increased EPO (CSF) levels at constant CSF (EPO) concentrations lead to an increased erythroid (neutrophil) proliferation and a decreased neutrophil (erythroid) proliferation. These effects increase as cell population numbers increase, thus implying that there exists some sensing mechanism in each population that is responsive to the numbers of cells in other proliferative populations.

## 2.2. The model

From the comments of the previous section we may now turn to a mathematical formulation of our model of coupled cellular populations. A similar model for a single cellular population has previously appeared (Lasota et al., 1981).

We characterize every cell of the population by two internal variables: $a$, the age of the cell in the cell cycle, and $m$, the maturation level of the cell. At birth, cells

have age $a = 0$ and their age increases with a velocity $V_a$ until cell division occurs at age $a = a_D$. In terms of maturation, cells are assumed to first become identifiable members of the population under consideration at a maturation level $m = m_0$. These cells mature at a velocity $V_m$ until they reach the maturation level $m = m_1$ of a totally mature cell. During this entire process of maturation, the cells proliferate. It is important to emphasize that this process explicitly allows cellular movement through the cell cycle to proceed hand in hand with cellular maturation. The sufficiency of this hypothesis to explain existing hematopoietic cell kinetic data has been demonstrated by Mackey and Dörmer (1982).

For the $i^{th}$ population of cells, we denote the number of cells of age $a$ and maturation level $m$ at time $t$ by $n_i(t, m, a)$. By our above description of the assumed progression of cells through the age– maturation space, $n_i(t, m, a)$ must satisfy a continuity equation of the form

$$\frac{\partial n_i}{\partial t} + \frac{\partial (V_{m_i} n_i)}{\partial m} + \frac{\partial (V_{a_i} n_i)}{\partial a} = 0 \tag{1}$$

along with the mitotic condition

$$V_{a_i}(t, m, 0) n_i(t, m, 0) = 2 V_{a_i}(t, m, a_D) n_i(t, m, a_D). \tag{2}$$

At any given time $t$ and maturation level $m$ the total number of cells of all ages is simply

$$N_i(t, m) = \int_0^{a_D} n_i(t, m, a)\, da. \tag{3}$$

If the velocity of maturation, $V_{m_i}$, is independent of cellular position within the cell cycle, then equation (1) may be integrated over cellular age $a$ and the result combined with (2) and (3) to yield a corresponding continuity equation for $N_i$:

$$\frac{\partial N_i}{\partial t} + V_{m_i} \frac{\partial N_i}{\partial m} = \left[ p_i(t, m, N) - \frac{\partial V_{m_i}}{\partial m} \right] N_i. \tag{4}$$

In (4), the *relative proliferation rate* $p_i$ is defined by

$$p_i(t, m, N) = \frac{V_{a_i}(t, m, a_D) n_i(t, m, a_D)}{N_i(t, m)}.$$

The vector $N = (N_i)$ is included in the argument of the relative proliferation rate $p_i$ because it is through the dependence of $p_i$ on the numbers $N_j$ that coupling is achieved.

From the experimental evidence summarized in the previous section, if we had two populations of interacting cells then an expansion in the numbers $N_1$ of cells in population 1 would lead to a decrease in the proliferative rate of population 2, and *vice versa*. Furthermore, in terms of the autoregulatory control of a given population by itself, it is a common observation (Mackey, 1978; Mackey & Milton, 1990) that within a population the relative proliferative rate is a monotone decreasing function of the number of cells in the population. Both of these experimental observations are captured by making the specific assumption that the proliferative activity in the $i^{th}$

population of cells is a monotone decreasing function of some weighted average of all cell types. Thus, we assume that

$$p_i(t,m,N) = \nu_i(m)\frac{\theta_i^{\beta_i}(m)}{\theta_i^{\beta_i}(m) + \left[\sum_j B_{ij}(m)N_j\right]^{\beta_i}}, \tag{5}$$

where the $B_{ij}$ are weighting coefficients.

In this paper we assume that the maturation velocity $V_{m_i}$, as a function of maturation level $m$, is given by

$$V_{m_i}(t,m) = r_i(m - m_0), \qquad m \in [m_0, m_1], \tag{6}$$

where $r_i > 0$ is constant. Further, it is assumed that the functions $\nu_i$, $\theta_i$, and $B_{ij}$ are all $C^2$ and nonnegative, and that the $\beta_i$ are positive constants. These assumptions are consistent with the known physiology. Equations (4) through (6), in addition to the initial condition

$$N_i(0,m) = \widetilde{v}_i(m), \tag{7}$$

which we also assume to be at least $C^1$, complete the specification of our model.

Two of the parameters appearing in the model are superfluous and may be eliminated by a judicious choice of variables. To this end we first define a dimensionless maturation variable $x$ by

$$x = \frac{m - m_0}{m_1 - m_0}.$$

Thus for each population, $x \in [0,1]$. Secondly we scale the population numbers $N_i$ by $B_{ii}(x = 0) \equiv B_{ii}(0)$, setting $u_i = B_{ii}(0)N_i$, and define

$$\alpha_{ij}(x) = \frac{B_{ij}(x)}{B_{jj}(0)}.$$

With these conventions, equations (4) through (6) may be transformed and combined to yield

$$\frac{\partial u_i}{\partial t} + r_i x\frac{\partial u_i}{\partial x} = u_i\left\{\nu_i(x)\frac{\theta_i^{\beta_i}(x)}{\theta_i^{\beta_i}(x) + \left[\sum_j \alpha_{ij}(x)u_j\right]^{\beta_i}} - r_i\right\}, \qquad i = 1,\ldots,n, \tag{8}$$

with the associated initial conditions

$$u_i(0,x) = v_i(x), \qquad i = 1,\ldots,n. \tag{9}$$

The coefficients $\alpha_{ij}(x)$ [remember that $\alpha_{ii}(0) = 1$ for all $i$] may be interpreted as coupling coefficients measuring the strength of the influence of the $j^{th}$ population on the proliferative activity of the $i^{th}$ population.

## 3. A STABILITY RESULT

Recently Loskot (1991) has studied the stability of solutions of equations like our equation (8). Specifically he has examined the system

$$\frac{\partial u_i}{\partial t} + c_i(x)\frac{\partial u_i}{\partial x} = f_i(x,u), \qquad i = 1,\dots,n, \tag{10a}$$

where $u = (u_1,\dots,u_n)$, with the associated initial condition

$$\lim_{t\to 0} u_i(t,x) = v_i(x), \qquad i = 1,\dots,n \tag{10b}$$

for $t > 0$, $x \in (0,1]$. He assumed that

C1(a) $c_i$ and $f_i$ are $C^2$ functions defined for $0 \le x \le 1$ and $u \in R^n$;
C1(b) $c_i(x) > 0$ for $x \in (0,1]$, $c_i(0) = 0$, and $c_i'(0) > 0$; and
C1(c) $\partial_{u_j} f_i$ are bounded for all $i$ and $j$.

Conditions C1 guarantee the existence of a unique classical $C^1$ solution to the system (10).

Furthermore, we introduce the following conditions.

C2(d) There is some equilibrium point $u_{eq}$ such that $f(0,u_{eq}) = 0$; and
C2(e) If the matrix $A = (a_{ij})$ is defined with $a_{ij} = \partial_{u_j} f_i(0,u_{eq})$, then the diagonal matrix $B = (b_i)$, $b_i = 1/c_i'(0)$, is such that $C = BA$ is a negative definite matrix, i.e., $< BAz, z > \le -m|z|^2$ for some $m > 0$.

THEOREM 1. (LOSKOT, 1991).

*1. Conditions C1 plus C2 imply the existence of a unique solution $w(x)$ to the equation*

$$c_i(x)\frac{dw_i}{dx} = f_i(x,w), \qquad 0 < x \le 1; \quad i = 1,\cdots,n \tag{11}$$

*with $\lim_{x\to 0} w(x) = u_{eq}$, so $w(x)$ is a stationary solution of (10a); and*

*2. For every $\epsilon > 0$ there is a $\delta > 0$ such that for every initial $C^1$ function $v(x)$, $0 \le x \le 1$, satisfying*

$$|v(x) - w(x)| \le \delta, \qquad 0 < x \le 1$$

*there is a unique solution $u(t,x)$ of (10a,b) defined for $0 < x \le 1$, $t > 0$. Moreover, this solution satisfies*

$$|u(t,x) - w(x)| \le \epsilon, \qquad 0 < x \le 1, \quad t > 0 \tag{12a}$$

*and*

$$\lim_{t\to\infty} |u(t,x) - w(x)| = 0 \quad \text{uniformly for} \quad 0 < x \le 1. \tag{12b}$$

*Thus, $w(x)$ is a locally asymptotically stable solution of (10a).*

It is important to observe that the conditions necessary for this stability only involve properties of the functions $f_i(x,u)$ and $c_i(x)$ at the boundary $x = 0$, i.e., the values of $\partial_{u_j} f_i(0,u_{eq})$ and $c_i'(0)$. Further, if the cell populations described by (10a,b) are uncoupled from one another, i.e. $f_i$ is given by $f_i(x,u_i)$, then the results of Lasota

(1981, Theorem 2) show that the solutions of (10a,b) are globally asymptotically stable if $v(0) > 0$.

Observe that if $w(x)$ is a solution of (11) and $w(x)$ is continuous at $x = 0$, then using the condition $c_i(0) = 0$ it is easy to show that $f_i(0, w(0)) = 0$. In this proof we do not use any regularity conditions on the $f_i$, but only the boundedness of the composed functions $f_i(x, w(x))$. Thus if a $u_{eq}$ that satisfies $f(0, u_{eq}) = 0$ is unique, we know that $u_{eq} = w(0)$. In the next section we will apply these results to equations (8).

However, before discussing these equations a simple example of the significance of condition C2(e) will be illuminating.

Consider the first order equation

$$\frac{\partial u}{\partial t} + x\frac{\partial u}{\partial x} = bu, \qquad u(0,x) = v(x), \qquad x \in [0,1], \tag{13}$$

which has the solution

$$u(t,x) = e^{bt}v(xe^{-t}). \tag{14}$$

Condition C2(d) is evidently satisfied by $\bar{u} = 0$. If $b$ is negative, then (13) certainly satisfies condition C2(e). Furthermore, the solution of the stationary equation

$$\frac{dw}{dx} = \frac{bw}{x}, \qquad w(0) = \bar{u} = 0 \tag{15}$$

is nonincreasing in absolute value [since $(b/x)$ is negative] and therefore uniquely equal to 0. On the other hand, assume $b$ to be positive in which case condition C2(e) is violated.

Consider now the stationary solutions $w(x)$ of (15) with $b > 0$. A simple computation shows that $w(x) = px^b$ satisfies (15) with $w(0) = 0$, where $p$ is an arbitrary positive constant. Thus with the loss of condition C2(e) being satisfied we have lost the uniqueness of the stationary solution $w(x)$.

This loss of uniqueness of $w(x)$ has further consequences for the solution (14) of (13). Assume that the family of initial conditions satisfies

$$v_p(x) = \begin{cases} px^b & x \in [0,\epsilon] \\ \text{arbitrary} & x \in [\epsilon,1]. \end{cases} \tag{16}$$

Now consider the situation in which the time $t > \ln(1/\epsilon)$. Then $xe^{-t} < \epsilon x < \epsilon$, since $x \in [0,1]$, and thus from (14) it follows that the corresponding family of solutions is given by $u_p(t,x) = px^b$.

Take two different values, $p_1$ and $p_2$. Then it is possible to find $v_{p_1}$ and $v_{p_2}$ from (16) such that the corresponding difference in initial conditions satisfies

$$|v_{p_1}(x) - v_{p_2}(x)| \leq 2\epsilon^b |p_1 - p_2|.$$

Then from our previous considerations we have that

$$|u_{p_1}(t,1) - u_{p_2}(t,1)| = |p_1 - p_2|.$$

Therefore this nonuniqueness of stationary solutions implies a large instability in the eventual evolution of the system, since we may pick two initial conditions arbitrarily close to one another and find that this difference has become greatly magnified at $x = 1$ for large $t$.

These comments illustrate the following theorem which can be proved using the method of characteristics.

THEOREM 2. *Assume that the system (10a,b) satisfies conditions C1 and C2(d). Further assume that there are at least two different solutions* $w = (w_1, \ldots, w_n)$ *of the stationary system (11). Then there is a constant* $A > 0$ *such that for all* $\epsilon > 0$ *there are two solutions* $u^1$ *and* $u^2$ *of (10a,b) satisfying the following conditions:*

*1.)* $u^1(t,0) = u^2(t,0) = u_{eq}$;

*2.)* $|u^1(0,x) - u^2(0,x)| \leq \epsilon$; *and*

*3.)* $\sup_x |u^1(t,x) - u^2(t,x)| \geq A$ *for sufficiently large* $t$.

## 4. A COUPLED TWO CELL POPULATION MODEL

With the previous material in hand we now turn to a specific consideration of two populations of cells coupled through their relative proliferation rates. Denoting the populations by $i = 1, 2$, from (8) we have

$$\frac{\partial u_1}{\partial t} + r_1 x \frac{\partial u_1}{\partial x} = u_1 \left\{ \nu_1(x) \frac{\theta_1^{\beta_1}(x)}{\theta_1^{\beta_1}(x) + [\alpha_{11}(x)u_1 + \alpha_{12}(x)u_2]^{\beta_1}} - r_1 \right\}, \tag{17}$$

and

$$\frac{\partial u_2}{\partial t} + r_2 x \frac{\partial u_2}{\partial x} = u_2 \left\{ \nu_2(x) \frac{\theta_2^{\beta_2}(x)}{\theta_2^{\beta_2}(x) + [\alpha_{21}(x)u_1 + \alpha_{22}(x)u_2]^{\beta_2}} - r_2 \right\}, \tag{18}$$

with the initial conditions

$$u_1(0,x) = v_1(x) \qquad \text{and} \qquad u_2(0,x) = v_2(x).$$

According to the general assumptions in Section 2.2, we take all of the coefficients in equations (17) and (18) to be nonnegative. More precisely, we assume that $r_i$ and $\beta_i$ are positive constants, that $\theta_i$, $\alpha_{11}$, and $\alpha_{22}$ are positive $C^2$ functions, and that $\nu_i$, $\alpha_{12}$, and $\alpha_{21}$ are nonnegative $C^2$ functions (all defined for $0 \leq x \leq 1$). These assumptions imply that the right hand sides of (17) and (18) are $C^2$ functions for $0 \leq x \leq 1$, $u_i > 0$. If the $\beta_i$ are integers some of these conditions can be relaxed; for example, it is enough to assume that the $\theta_i$ are nonnegative.

We next turn to a determination of the equilibrium solutions $u_{eq}$ of $f_i(0,u) = 0$, $i = 1, 2$, required by the first of the (C2) conditions.

### 4.1. Determination of steady states

The equilibrium solutions $u_{eq} = (u_{1,eq}, u_{2,eq})$ are determined from the solutions of $f_i(0, u_{eq}) = 0$, $i = 1, 2$, or explicitly from

$$0 = u_1 \left\{ \nu_1 \frac{\theta_1^{\beta_1}}{\theta_1^{\beta_1} + [u_1 + \alpha_{12}u_2]^{\beta_1}} - r_1 \right\}, \tag{19}$$

and

$$0 = u_2 \left\{ \nu_2 \frac{\theta_2^{\beta_2}}{\theta_2^{\beta_2} + [\alpha_{21}u_1 + u_2]^{\beta_2}} - r_2 \right\}. \tag{20}$$

In writing equations (19) and (20) it is important to remember that $\nu_i(x), \theta_i(x)$, and $\alpha_{ij}(x)$, $(i,j = 1,2)$ are all evaluated at $x = 0$, and that $\alpha_{11}(0) = \alpha_{22}(0) = 1$. Further we always write $\nu_i$ for $\nu_i(0)$, etc.

Equations (19) and (20) have four solutions $u_{eq}$, which are easily found to be

$$u_{eq} = (0,0), \quad (0,\widetilde{u}_2), \quad (\widetilde{u}_1,0), \quad (\bar{u}_1,\bar{u}_2), \tag{21}$$

where

$$\widetilde{u}_1 = \theta_1 \left[\frac{\nu_1 - r_1}{r_1}\right]^{1/\beta_1}, \qquad \widetilde{u}_2 = \theta_2 \left[\frac{\nu_2 - r_2}{r_2}\right]^{1/\beta_2}, \tag{22}$$

and

$$\bar{u}_1 = \frac{\widetilde{u}_1 - \alpha_{12}\widetilde{u}_2}{1 - \alpha_{12}\alpha_{21}}, \qquad \bar{u}_2 = \frac{\widetilde{u}_2 - \alpha_{21}\widetilde{u}_1}{1 - \alpha_{12}\alpha_{21}}. \tag{23}$$

In these solutions it is important to note that $\widetilde{u}_i = \bar{u}_i$ if $\alpha_{12} = \alpha_{21} = 0$ (no coupling) and that the biologically meaningful situation of $\widetilde{u}_i \geq 0$ will only occur for $\nu_i \geq r_i$. If we define

$$L = \frac{\theta_2}{\theta_1}, \quad \text{and} \quad K_i = \frac{\nu_i}{r_i}, \quad i = 1,2,$$

then it is easy to show that the $\bar{u}_i$ will be positive if

$$1 + \left(\frac{\alpha_{21}}{L}\right)^{\beta_2} (K_1 - 1)^{\frac{\beta_2}{\beta_1}} < K_2 < 1 + \frac{(K_1 - 1)^{\frac{\beta_2}{\beta_1}}}{(\alpha_{12}L)^{\beta_2}} \tag{24}$$

and if $\alpha_{12}\alpha_{21} < 1$. (If $\alpha_{12}\alpha_{21} > 1$, then this inequality must be reversed to ensure the positivity of the $\bar{u}_i$.)

### 4.2. Examination of local stability criteria

We next turn to an examination of the condition C2(e) for the steady state solutions determined in the previous section. Of the four equilibrium solutions listed in (21), the last $(\bar{u}_1,\bar{u}_2)$ is the most interesting and will be discussed in detail last.

To consider the stability of the first three, observe that by our comments at the end of section 3, every stationary solution starts from one of the solutions in (21).

Suppose a solution starts from $(0,0)$. Of course, $u_1 = u_2 = 0$ is a solution, and if it is unique it is of little biological interest because it is trivial. If a second solution starts from $(0,0)$, then due to the lack of uniqueness none of the solutions starting from $(0,0)$ is asymptotically stable.

Now consider $(\widetilde{u}_1,0)$. In this case a stationary solution of (17) and (18) is given by the pair $(u_1(x), u_2 \equiv 0)$ where $u_1$ is a stationary solution of (17) with $u_2 \equiv 0$ satisfying the initial condition $\lim_{x\to 0} u_1(x) = \widetilde{u}_1$. Equation (17) with $u_2 \equiv 0$ describes a single population of cells and has been studied by Lasota (1981) and Brunowský (1983). Precisely the same comments pertain to the third equilibrium solution $(0,\widetilde{u}_2)$.

To discuss the stability of the final, and most interesting, case of both populations of cells having positive steady state values, we first calculate the matrix $A$ of condition C2(e):

$$A = \begin{pmatrix} -\kappa_1 & -\alpha_{12}\kappa_1 \\ -\alpha_{21}\kappa_2 & -\kappa_2 \end{pmatrix}, \tag{25}$$

where

$$\kappa_i = n_i \nu_i \left(\frac{\bar{u}_i}{\tilde{u}_i}\right) \left(\frac{r_i}{\nu_i}\right)^2 \left(\frac{\tilde{u}_i}{\theta_i}\right)^{\beta_i} \qquad i = 1, 2$$

and it is clear that the $\kappa_i$ are always strictly positive in the biologically important situation of positive cell numbers at the steady state $(\bar{u}_1, \bar{u}_2)$.

To check the local stability condition C2(e), first note that the diagonal matrix B has the simple form

$$B = \begin{pmatrix} \frac{1}{r_1} & 0 \\ 0 & \frac{1}{r_2} \end{pmatrix}$$

so $C = BA$ is just given by

$$C = \begin{pmatrix} -\frac{\kappa_1}{r_1} & -\frac{\alpha_{12}\kappa_1}{r_1} \\ -\frac{\alpha_{21}\kappa_2}{r_2} & -\frac{\kappa_2}{r_2}. \end{pmatrix}$$

For $C = (c_{ij})$ to be a negative definite matrix it is necessary and sufficient that the elements $c_{ij}$ satisfy

$$(c_{12} + c_{21})^2 < 4 c_{11} c_{22},$$

or more explicitly

$$\left[\alpha_{12}\frac{\kappa_1}{r_1} + \alpha_{21}\frac{\kappa_2}{r_2}\right]^2 < 4\frac{\kappa_1\kappa_2}{r_1 r_2}. \tag{26}$$

Define $z = \kappa_1 r_2 / \kappa_2 r_1$, which is clearly non-negative and can be written in the explicit form

$$z = \frac{\beta_1}{\beta_2}\frac{\nu_2}{\nu_1}\frac{\nu_1 - r_1}{\nu_2 - r_2}\left[\frac{1 - \alpha_{12}(\tilde{u}_2/\tilde{u}_1)}{1 - \alpha_{21}(\tilde{u}_1/\tilde{u}_2)}\right].$$

A complicated but elementary calculation shows that (26) is equivalent to $f(z) < 0$ where

$$f(z) = z^2 + \frac{2(\alpha_{12}\alpha_{21} - 2)}{\alpha_{12}^2} z + \left(\frac{\alpha_{21}}{\alpha_{12}}\right)^2. \tag{27}$$

The minimum of $f(z)$ is easily to found to occur at

$$z_{min} = \frac{2 - \alpha_{12}\alpha_{21}}{\alpha_{12}^2},$$

while

$$f(z_{min}) = -4\left(\frac{1 - \alpha_{12}\alpha_{21}}{\alpha_{12}^4}\right).$$

Thus we conclude that in order for condition C2(e) to be satisfied it is necessary that the product of the interaction coefficients $\alpha_{12}$ and $\alpha_{21}$ satisfy

$$\alpha_{12}\alpha_{21} < 1, \tag{28}$$

so that $f(z_{min}) < 0$. In this case it is also clear that $z_{min} > 0$.

Using these calculations we can state a result concerning the stability of the steady state solution corresponding to the point $(\bar{u}_1, \bar{u}_2)$. Consider the steady state equations

$$r_1 x \frac{dw_1}{dx} = w_1 \left\{ \nu_1(x) \frac{\theta_1^{\beta_1}(x)}{\theta_1^{\beta_1}(x) + [\alpha_{11}(x)w_1 + \alpha_{12}(x)w_2]^{\beta_1}} - r_1 \right\} \equiv f_1(x, w) \qquad (29)$$

and

$$r_2 x \frac{dw_2}{dx} = w_2 \left\{ \nu_2(x) \frac{\theta_2^{\beta_2}(x)}{\theta_2^{\beta_2}(x) + [\alpha_{21}(x)w_1 + \alpha_{22}(x)w_2]^{\beta_2}} - r_2 \right\} \equiv f_2(x, w) \qquad (30)$$

with the initial condition

$$\lim_{x \to 0} w_1(x) = \bar{u}_1, \qquad \lim_{x \to 0} w_2(x) = \bar{u}_2. \qquad (31)$$

From Theorem 1 we will derive the following.

COROLLARY. *If inequalities (24), (26), and (28) are satisfied (with $K_i = \nu_i / r_i > 1$) then the initial value problem (29)-(31) has a unique solution $(\hat{w}_1(x), \hat{w}_2(x))$, $0 < x \leq 1$. This solution is positive $(\hat{w}_i(x) > 0, i = 1, 2)$ and gives a stationary locally asymptotically stable solution of 17), (18).*

PROOF: The proof will be carried out in two steps.

I. First choose two numbers $m_1$ and $M_1$ such that

$$0 < m_1 < \min(\bar{u}_1, \bar{u}_2), \qquad \max(\bar{u}_1, \bar{u}_2) < M_1.$$

Since $m_1$ is positive, it is possible to find $C^2$ functions $\bar{f}_1(x, w), i = 1, 2$, defined for $0 \leq x \leq 1$, $w \in R^2$ with bounded derivatives $\partial f_i / \partial x_j$ and such that

$$\bar{f}_i(x, w) = f_i(x, w) \qquad \text{for} \quad 0 \leq x \leq 1, \quad m_1 \leq w_i \leq M_1, \quad i = 1, 2.$$

We consider the system (29)-(30) with $f_i$ replaced by $\bar{f}_i$ and the same initial conditions (31). For this new system all the assumptions of Theorem 1 are satisfied and it has a unique solution $(\bar{w}_1, \bar{w}_2)$. Due to conditions (31) there exists an $\eta > 0$ such that

$$m_1 < \bar{w}_i(x) < M_1 \qquad \text{for} \quad 0 < x \leq \eta, \quad i = 1, 2.$$

Consequently, for $0 < x \leq \eta$ we have $\bar{f}_i(x, \bar{w}(x)) = f_i(x, \bar{w}(x))$ and $(\bar{w}_1(x), \bar{w}_2(x))$ is a solution of the original system (29)-(30). Now observe that in the strip

$$\eta \leq x \leq 1, \quad 0 < w_i \qquad i = 1, 2,$$

the functions $(r_i x)^{-1} f_i(x, w)$ are $C^2$ and satisfy the inequalities

$$-\frac{M}{r_i \eta} w_i \leq \frac{1}{x r_i} f_i(x, w) \leq \frac{M}{r_i \eta} w_i, \qquad i = 1, 2, \qquad (32)$$

where $M = \max_{i,x} \nu_i(x)$. Thus the original system (29)-(30) has a unique solution $(\tilde{w}_1, \tilde{w}_2)$ in the interval $[\eta, 1]$ satisfying the initial conditions $\tilde{w}_i(x) = \bar{w}_i(x)$. Moreover, according to (32) this solution satisfies

$$m_1 e^{-M(\eta r_i)^{-1}(x-\eta)} < \tilde{w}_i(x) < M_1 e^{M(\eta r_i)^{-1}(x-\eta)}, \qquad \eta \le x \le 1, \quad i = 1,2.$$

The functions

$$\hat{w}_i(x) = \begin{cases} \bar{w}_i(x) & 0 < x \le \eta \\ \tilde{w}_i(x) & \eta < x \le 1, \end{cases}$$

$i = 1,2$, give a solution of the original initial value problem (29)-(31). The solution $(\hat{w}_1, \hat{w}_2)$ satisfies the inequality

$$m_1 e^{-M(\eta r_i)^{-1}} < \hat{w}_i(x) < M_1 e^{M(\eta r_i)^{-1}}, \qquad 0 \le x \le 1, \quad i = 1,2. \tag{33}$$

Observe that this solution of (29)-(31) is unique. This is a consequence of the fact that the functions $(r_i x)^{-1} f_i(x,w)$ are $C^2$ for $x > 0$, $w_i > 0$ and the branching point cannot occur for $x > 0$. Furthermore, nonuniqueness at $x = 0$ of the solution of the original problem (29)-(31) would imply the same property for the system with right hand sides $\bar{f}_i$ which is impossible.

II. Choose two numbers $m_2$ and $M_2$ such that

$$0 < m_2 < m_1 e^{-M(\eta r_i)^{-1}}, \qquad M_1 e^{M(\eta r_i)^{-1}} < M_2, \quad i = 1,2. \tag{34}$$

Again, since $m_2$ is positive it is possible to find $C^2$ functions $\bar{\bar{f}}_i(x,w)$ defined for $0 \le x \le 1$, $w \in R^2$ with bounded derivatives $\partial \bar{\bar{f}}_i / \partial w_j$ and such that

$$\bar{\bar{f}}_i(x,w) = f_i(x,w), \qquad 0 \le x \le 1, \quad m_2 \le w_i \le M_2, \quad i = 1,2. \tag{35}$$

Now consider the systems (29)-(30) and (17)-(18) in which the original right hand sides are replaced by $\bar{\bar{f}}_i$. For these systems, all assumptions of Theorem 1 are satisfied and $(\hat{w}_1, \hat{w}_2)$ is the unique stationary, locally asymptotically stable solution. Observe that the positive number $\epsilon$ in condition (12a) may be chosen small and in particular we may assume that

$$\epsilon < \min(m_1 e^{M(\eta r)^{-1}} - m_2, M_2 - M_1 e^{M(\eta r)^{-1}}),$$

where $r = \min(r_1, r_2)$. With such $\epsilon$, conditions (12a,b) for the systems with the right hand sides $\bar{\bar{f}}_i$ imply the same properties for the original systems ∎

The graph of (27) is a concave up parabola with roots $z_1, z_2$. From the forgoing discussion we know that for all $z \in (z_1, z_2)$ the stability criterion C2(e) is satisfied. Clearly, the larger the difference $1 - \alpha_{12}\alpha_{21}$, the larger is the range $z_2 - z_1$ of $z$ over which condition C2(e) is satisfied. Since, for any value of $z$ that falls in the interval $(z_1, z_2)$, we know that the local asymptotic stability criteria of section 3 are satisfied, we may examine the effects of systematically varying one parameter at a time on the stability of the solutions.

From equations 23 and 25 it follows that as the reciprocal coupling vanishes ($\alpha_{12} \to 0$ and $\alpha_{21} \to 0$), the values $\kappa_i$ converge to

$$\kappa_i^0 = \beta_i \nu_i \left(\frac{r_i}{\nu_i}\right)^2 \left(\frac{\nu_i - r_i}{r_i}\right).$$

Since it is always assumed that $\nu_i > r_i$, the $\kappa_i^0$ are strictly positive ($\kappa_i^0 > 0$). Thus, for every fixed $\beta_i, \theta_i, r_i$ and $\nu_i > r_i$, there is a sufficiently weak coupling between the populations ($\alpha_{12}$ and $\alpha_{21}$ small) such that the local stability condition (26) is satisfied.

Alternately, as the coupling between the populations increases so $\alpha_{12}\alpha_{21}$ is close to 1, the local stability condition (26) may be easily violated. Thus one origin of the loss of stability in the coupled system may be a very strong or tight coupling. Further, a large $\alpha_{12}$, for example, will lead to a dramatic decrease in the proliferative rate of the first population whenever the second population is large.

With respect to the effects of changes in the speed of maturation, $r_1$, on the stability, note that from (22) and (23) as $r_1$ increases and approaches $\nu_1$ from below, then $\bar{u}_1$ may become small and even negative when $\alpha_{12} > 0$. In this case either the solution $u_1(t,x), u_2(t,x)$ will not be positive and stable or $u_1$ will be too small to ensure survival of the population. Thus increases in the maturation velocity $r$ lead either to instability or to death.

Conversely, when $\alpha_{12} > 0$ a small $r_1$ (low maturation velocity) leads to a large $\widetilde{u}_1$ and a small or negative $\bar{u}_2$, again leading to either instability or death.

Completely analogous comments hold for changes in the maximal proliferation rates $\nu_i$ except they work in a way opposite to the $r_i$.

Thus the stable coexistence of coupled cellular populations imposes quite strict requirements on all of the parameters, in particular the maximal proliferation rates $\nu$ and velocities of maturation $r$.

## 5. CONCLUSIONS

In this paper, using recent results for the asymptotic behaviour of the solutions to this model, we have shown that there exists a region of coupling coefficients, maturation rates, and proliferation rates that will guarantee the stable coexistence of coupled cellular populations. The analysis demonstrates that increases in the coupling between populations may ultimately lead to a loss of stability. Furthermore, the analysis indicates that increases (decreases) in the maturation and/or proliferation rates above (below) critical levels will lead either to instability in the populations or the destruction of one population and the persistence of the other.

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