WHELDON MODEL OF CML REVISITED

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Abstract: The Wheldon model (1975) of a Chronic Myelogenous Leukemia (CML) dynamics is revisited in the light of recent discovery that this model has a major drawback. To reanimate the Wheldon model, we used late Wheldon's remarks and M. C. Mackey ideas to introduce a new mechanism. To further enrich the model, we introduced time-varying microenvironment and time-dependent drug efficacies. The resulting model is a special class of nonautonomous nonlinear system of differential equations with delays. The global existence and positiveness of the solutions of the Wheldon model are examined. Furthermore, via topological methods, the existence of positive periodic solutions is proved.

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1 WHELDON MODEL OF CML REVISITED

1.1 BACKGROUND

In 1974 T.E. Wheldon in the paper [14] introduced the following model of granulopoiesis (granulocyte production) (see also [13])

$$\begin{aligned} \frac{dM}{dt} &= \frac{\alpha}{1+\beta M^n(t-\tau)} - \frac{\lambda M(t)}{1+\mu B^m(t)} \\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1+\mu B^m(t)}, \end{aligned} \tag{1}$$

where all parameters are positive constants. In model (1), $M(t)$ is the number of cells in the marrow; $B(t)$ is the number of white blood cells; β is the coupling constant for cell production loop; α is the maximum rate of cell production; λ is the maximum rate of release of mature cells from marrow; μ is the coupling constant for release loop; ω is the constant rate for loss of granulocytes from blood to tissue; τ represents the mean time for stem cell maturity; n controls gain of cell production loop; m controls gain of release loop.
This model creates a time-delay loop triggering stem cell production and a fast loop regulating release of mature cells in the blood. Studies of the model imply that the oscillatory pattern in leukemia may be bring forth in two principal ways, either by an increased cell production rate or by an increased maturation time. The Wheldon model assumes that there is a direct negative feedback from mature (differentiated cells) to the precursors of those cells.
However this model has a major drawback, i.e., it describes a wrong mechanism. At the (unique) nontrivial equilibrium point (M_*, B_*) of system (1), we have:

$$\omega B_* = \frac{\alpha}{1+\beta M_*^n}. \tag{2}$$

Thus, the B-population in the Wheldon model is an inversely proportional to the M-population; the latter does not have any biological explanation.

1.2 NEW MODEL

To reanimate the Wheldon model, we used Wheldon's remarks in [13] p.294 and M. C. Mackey ideas to introduce a new mechanism:

$$\begin{aligned}\frac{dM}{dt} &= \frac{\alpha M(t)}{1+\beta M^n(t-\tau_1)} - \frac{\lambda M(t)}{1+\mu B^m(t-\tau_2)} \\ \frac{dB}{dt} &= -\omega B(t) + \frac{\lambda M(t)}{1+\mu(t) B^m(t-\tau_2)},\end{aligned} \tag{3}$$

The first term in (1) is a decreasing function of M

$$\frac{\alpha}{1+\beta M^n},$$

whereas in model (3)

$$\frac{\alpha M}{1+\beta M^n}$$

is a one-hump function, resulting in more realistic than in (2) relationship between stem cells and white blood cells

$$\omega B_* = \frac{\alpha M_*}{1+\beta M_*^n}. \tag{4}$$

Exposure to chemoradiation therapy will kill many of the rapidly dividing cells of the bone marrow ($B-$ cells), and will therefore suppress immune system [2], [3], [7], [9], [10], [11] and [12]. Existing data indicates that the oscillations in CML may exhibit chaos unless controlled by therapy. If we assume the drug combination is administered with a periodicity, then $p(t)$ and $q(t)$ can be expressed as exponential decaying functions in t during each period.

It is well recognized that tumor microenvironment changes with time and in response to treatment. These fluctuations can modulate tumor progression and acquired treatment resistance. Latest clinical studies on periodic hematological diseases suggest oscillations of some blood elements e.g., leukocytes, platelets, reticulocytes (see, for example, [7], [8] and [10]). Henceforth, to model changes that develop in the tumor microenvironment over time, we assume model parameters are time-varying functions.

Thus to enrich the model we incorporate time-dependent parameters

$$\begin{aligned}\frac{dM}{dt} &= \frac{\alpha(t) M(t)}{1+\beta(t) M^n(t-\tau_1)} - \frac{\lambda(t) M(t)}{1+\mu B^m(t-\tau_2)} - \delta p(t) M(t) \\ \frac{dB}{dt} &= -\omega(t) B(t) + \frac{\lambda(t) M(t)}{1+\mu(t) B^m(t-\tau_2)} - \delta q(t) B(t),\end{aligned} \tag{5}$$

where $p(t) = p(c)$ and $q(t) = q(c)$ are the varying effectiveness of the drug, and $c = c(t)$ is the drug concentration at time t. Traditionally, this pharmokinetic is modeled by linear functions, i.e., $p(c) = \alpha c(t)$ and $g(c) = \beta c(t)$ where α and β are the appropriate drug sensitivity parameters. Clearly $\alpha = \beta$ if the drugs are cycle-non-specific, i.e., it will be equally toxic to all types of cells. Some types of chemotherapy can be modeled based on a non-monotone one-humped functions- $p(c) = \alpha c(t) e^{-ac(t)}$ and $q(c) = \beta c(t) e^{-bc(t)}$. Throughout the paper, it shall be assumed that $\alpha(t), \beta(t), \omega(t), \lambda(t), \mu(t), p(t)$ and $q(t)$ are continuous, positive and T-periodic functions and $\tau_{1,2} > 0$ are fixed delays. The parameter δ is assumed to be 1 or 0 according the presence or absence of pharmacokinetics. By 'positive T-periodic solution' we mean a pair (M, B) of C^1 functions satisfying

$$M(t+T) = M(t) > 0, \qquad B(t+T) = B(t) > 0$$

for all $t \in \mathbb{R}$.

1.3 Existence of global solutions and equilibrium points

In first place, It is easy to prove that solutions of (3) with prescribed positive initial data are globally defined and remain positive for all t. Indeed, setting $R(t) = \ln M(t)$, the system becomes

$$\begin{aligned} R'(t) &= \frac{\alpha(t)}{1+\beta(t)e^{nR(t-\tau_1)}} - \frac{\lambda(t)}{1+\mu(t)B^m(t-\tau_2)} - \delta p(t) \\ B'(t) &= -\omega(t)B(t) + \frac{\lambda(t)e^{R(t)}}{1+\mu(t)B^m(t-\tau_2)} - \delta q(t)B(t). \end{aligned} \tag{6}$$

Suppose that $M(t)$ and $B(t)$ are defined and positive for $t < t_0$, then the inequalities $-\lambda(t) - \delta p(t) < R'(t) < \alpha(t)$ it is clear that $R(t)$ is defined up to t_0. Moreover, $B'(t) < \lambda e^{R(t)}$ and hence $B(t)$ is defined on t_0. Finally, if $B(t_0) = 0$ then $B'(t_0) > 0$, a contradiction.

To prove the existence of a nontrivial equilibrium, assume that all parameters in the previous system are constant and set

$$\begin{aligned} \tfrac{\alpha}{1+\beta e^{nR}} &= \tfrac{\lambda}{1+\mu B^m} + \delta p \\ (\omega + \delta q)B &= \tfrac{\lambda e^R}{1+\mu B^m}. \end{aligned} \tag{7}$$

Let

$$c(B) := \frac{B(1+\mu B^m)(\omega+\delta q)}{\lambda},$$

then system (7) has at least a positive solution if and only if the function $\varphi : [0, +\infty) \to \mathbb{R}$ given by

$$\varphi(B) := \frac{\alpha}{1+\beta c(B)^n} - \frac{\lambda}{1+\mu B^m} - \delta p$$

has at least a positive root. If $\delta = 1$, then direct computation shows that φ vanishes when $\alpha > \lambda$ and $n > \frac{m}{m+1}$. If $\delta = 1$, then $\varphi(0) = \alpha - \lambda - p$ and $\lim_{y\to+\infty} \varphi(y) = -p$, it follows that the system admits at least one positive equilibrium, provided that

$$\alpha > \lambda + p.$$

2 Existence of periodic solutions

2.1 Case 1: No pharmokinetic

Theorem 1 *Assume that $\alpha(t), \beta(t), \lambda(t), \mu(t)$ and $\omega(t)$ are continuous, positive and T-periodic. Furthermore, assume that:*

1. $n > \frac{m}{m+1}$.
2. $\alpha(t) > \lambda(t) > \omega(t)$ *for all* t.

Then system (3) *with $\delta = 0$ admits at least one positive T-periodic solution.*

Proof. **(Sketch of the proof:)**
Set $u(t) = \ln M(t)$ and $v(t) = \ln B(t)$, then (3) with $\delta = 0$ reads

$$u'(t) = \frac{\alpha(t)}{1+\beta(t)e^{nu(t-\tau_1)}} - \frac{\lambda(t)}{1+\mu(t)e^{mv(t-\tau_2)}}$$

$$v'(t) = -\omega(t) + \frac{\lambda(t)e^{u(t)-v(t)}}{1+\mu(t)e^{mv(t-\tau_2)}}$$

In order to prove the existence of T-periodic solutions of this system, we shall apply the continuation method. For simplicity, we divide the proof in two steps.

First step

Consider the function $F : \mathbb{R}^2 \to \mathbb{R}^2$ given by

$$F(u,v) := \frac{1}{T}\int_0^T \left(\frac{\alpha(t)}{1+\beta(t)e^{nu}} - \frac{\lambda(t)}{1+\mu(t)e^{mv}}, \frac{\lambda(t)e^{u-v}}{1+\mu(t)e^{mv}} - \Omega(t) \right) dt.$$

Let $\Omega_0 := (-R,R) \times (-R,cR) \subset \mathbb{R}^2$, where c is a fixed constant such that $\frac{1}{m+1} < c < \frac{n}{m}$. Taking $R > 0$ large enough, it is seen that F is homotopic to $-Id$, and hence $deg(F, \Omega_0, 0) = (-1)^2 = 1$, where 'deg' denotes the Brouwer degree.

Second step

Let C_T be the set of continuous and T-periodic real functions and let

$$\Omega := \{(u(t), v(t)) \in C_T \times C_T : \|u\|_\infty < R, -R < v(t) < cR\}.$$

We prove that if R is large enough then the T-periodic solutions of the system

$$u'(t) = \sigma \left(\frac{\alpha(t)}{1+\beta(t)e^{nu(t-\tau_1)}} - \frac{\lambda(t)}{1+\mu(t)e^{mv(t-\tau_2)}} \right)$$

$$v'(t) = \sigma \left(-\omega(t) + \frac{\lambda(t)e^{u(t)-v(t)}}{1+\mu(t)e^{mv(t-\tau_2)}} \right)$$

with $0 < \sigma \leq 1$ do not belong to $\partial\Omega$. Thus, by the standard continuation method we deduce the existence of a solution $(u,v) \in \Omega$.

□

2.2 Case 2: With pharmokinetic

Theorem 2 *Assume that $\alpha(t), \beta(t), \lambda(t), \mu(t), \omega(t), p(t)$ and $q(t)$ are positive and T-periodic. Furthermore, assume that:*

$$\alpha(t) - p(t) > \lambda(t) > \omega(t) + q(t)$$

for all t. Then system (3) *with $\delta = 1$ admits at least one positive T-periodic solution.*

Proof. The proof follows the general outline of the previous one. □

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