

Chemotherapeutic Effects on Hematopoiesis: A Mathematical Model

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Blood cell production is one of the major limiting effects of cell-cycle-specific chemotherapy. By studying the effects of the drugs on a mathematical model of hematopoiesis, a better understanding of how to prevent over-reduction of circulating blood cells may be investigated.

In this model we will use a delay-differential equation developed by Mackey and Glass (1977) to show acceptable chemotherapeutic doses (i.e. survival of the circulating blood cells) as a function of: the period which the drugs are administered; the strength of the dose; and the delay from initiation of blood cell production to its release into the blood stream. We then make qualitative comparisons to known effects of cell-cycle-specific chemotherapy on circulating blood cell elements. Finally, we also consider how the effects of hematopoietic growth factors alter the outcome of the therapy.

Keywords: Chemotherapy, hematopoiesis, delay-differential equation, hematopoietic growth factor, cancer

1 INTRODUCTION

One of the major limiting effects of cell-cycle-specific chemotherapy is its negative effects on bone marrow. In fact, in many cases the maximum dose needed to eradicate the cancer cells will also lead to over-destruction of bone marrow tissue and ultimately death to the patient. Therefore, there is a need to better understand the growth kinetics of blood cell production (hematopoiesis) so that we may develop more effective cell-cycle-specific chemotherapeutic regimens that prevent over-destruction of bone marrow tissue and thus circulating blood cells.

There are a variety of models that describe the various aspects of cell-cycle-specific chemotherapy and its effects on normal tissue such as bone marrow tissue. A cellular automaton model for hematopoiesis was developed by Mehr and Agur (1992). This model has a spatial aspect in that nearest neighbor bone marrow cells influence each other to divide, differentiate, etc. Their model shows that homeostasis can be maintained when drug administration is fully periodic, but when time intervals between administrations are stochastic the stem-cell pool of bone marrow is rapidly depleted. In the works by Agur, Arnon and Schechter (1988)

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and Cojocaru and Agur (1992), probabilistic models were developed that describe methods of reducing bone marrow damage. These models suggested that the chemotherapeutic drugs should be administered at integer multiples of the mean cell-cycle length of the normal tissue. They suggest that this method will be successful since the cancer cells have a longer mean cell-cycle time, thus placing them in the more sensitive phase while the normal tissue is not. Work similar to this has also been carried out by Webb (1990), and Webb (1995) who investigated resonance in the cell populations as a result of chemotherapy using age- and size-dependent differential equation models. A different approach was taken in Panetta and Adam (1995), Adam and Panetta (1995), and Panetta (1997). In these works we considered the effects of a resting phase (G_0) in the cell-cycle (phase which the cell-cycle-specific chemotherapeutic drugs are not effective, sometimes known as kinetic resistance) along with the effects of the drugs on normal tissue such as bone marrow. With these models, we calculated the optimal period in which to administer the drugs so that they would have the maximum effect on the cancerous tissue while preventing over-destruction of the normal tissue. We also briefly considered the effects hematopoietic growth factors (HGFs) have on the success of the chemotherapeutic regimen.

Here, we will consider a deterministic approach which includes some specific kinetics such as a natural fluctuation of mature circulating blood cells with a period of about 20 days. In particular, Mackey and Glass (1977) introduce two different first-order non-linear delay-differential equations which model the homogeneous population of mature circulating blood cells (see models in section 2) which possesses these dynamics. The reasoning for considering time delays in their model is that there is a time lag between when the bone marrow starts to produce blood cell elements and when the mature cells are released into the blood stream. This paper adds the effects of chemotherapy to Mackey and Glass's model and discusses both the mathematical and medical consequences. Chemotherapy affects all the different blood cell elements, each with varying

degrees. But, so that we can clearly observe the dynamics of the model, without the complexity of multiple circulating blood cell element compartments, we will only consider one homogeneous compartment of circulating blood cell elements. In the process some intriguing results, some qualitatively similar to Webb (1992a), Webb (1992b), Adam and Panetta (1995), and Panetta (1997) will be shown relating the period of treatment and the delay or time lag to the survival of the circulating blood cell elements. We will discuss what acceptable treatments (in terms of period) are such that the circulating blood cell levels will not be depleted. These mathematical results will also be qualitatively related to the medical literature such as: Klaassen, Wilke, Strumberg, Eberhardt, Korn and Seeber (1996), who suggest that shorter periods of treatment can be more effective at reducing the cancer; Wilson, Berg, Bryant, Wittes, Bates, Fojo, Steinberg, Goldspiel, Herdt, O'Shaughnessy, Balis and Chabner (1994) and Lopes, Adams, Pitts and Bhuyan (1993), who show increased duration of exposure to Taxol (a cell-cycle-specific drug) leads to significant increase to cytotoxicity of the cancer; and Hainsworth and Greco (1994) and ten Bokkel Huinink, Eisenhauer and Swenerton (1993), who note that shorter infusion times of cell-cycle-specific drugs are less myelosuppressive. In this process, we will also consider the use of (HGFs) to improve the recovery of blood cell production after the chemotherapeutic dose. From this, we hope to have a better understanding of the effects of the chemotherapy on the circulating blood cell elements and thus a better understanding on how to administer cell-cycle-specific chemotherapeutic drugs.

2 THE MODEL

The basic models that Mackey and Glass (1977) introduced to describe a homogeneous population of mature circulating blood cells are:

$$\frac{dP(t)}{dt} = \frac{\beta_0 \Theta^n}{\Theta^n + P^n(t - \tau)} - \gamma P(t) \quad (1)$$

$$\frac{dP(t)}{dt} = \frac{\beta_0 \Theta^n P(t - \tau)}{\Theta^n + P^n(t - \tau)} - \gamma P(t) \quad (2)$$

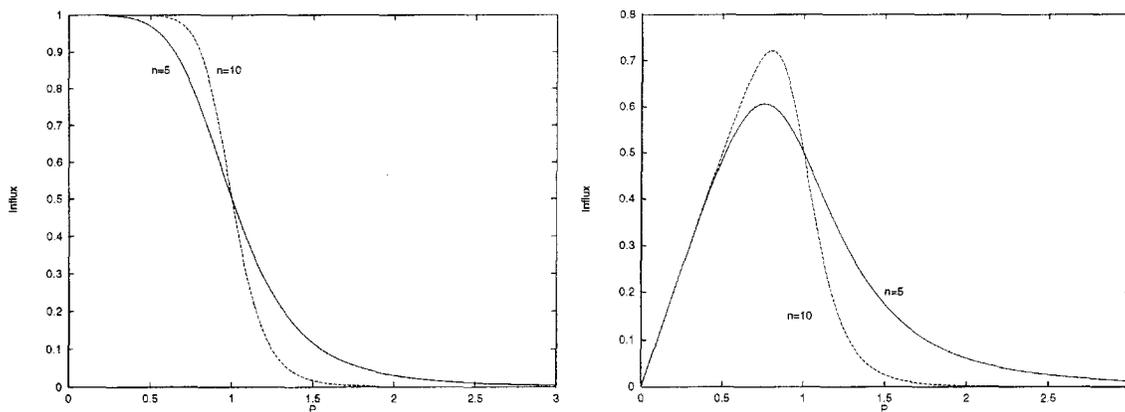


FIGURE 1 Influx Term: Model 1 on left, Model 2 on right.

where $P(t)$ are mature circulating blood cells, τ is the delay between the initiation of cellular production in the bone marrow and the release of mature cells into the blood, β_0 is the flux of cells into the blood, γ is the rate of random cell loss, Θ is a saturation parameter, and n relates to the rate of saturation (see Figure 1). The main difference between these two models is in the first term on the right hand side of equations (1) and (2) which describes the influx of mature circulating blood cells from the bone marrow. In the first model (1), the first term is a monotonic decreasing function of $P(t - \tau)$; that is, for very small $P(t - \tau)$ we have the largest influx of new mature circulating blood cells (see Figure 1, left). While in the second model (2), the influx term is a single-humped function of $P(t - \tau)$; that is, initially there is little influx of new mature circulating blood cells but then the influx increases to some maximum from where it monotonically decreases after that point (see Figure 1, right). Note that an increase in n has the effect of narrowing the range of cellular influx and gives a faster change from large influx to small influx.

As stated in Mackey and Glass (1977), some acceptable parameters for normal adult circulating granulocytes are: $\Theta = 1$, $\gamma = 0.1$, $\beta_0 = 0.2$, $n = 10$, and $\tau = 6$. The delay (parameter τ) refers to the fact that it takes the bone marrow about 6 days from the time it is signaled to produce and then release new circulating blood cell elements. These values will lead to **mild** oscillations of circulating levels

of granulocytes with period of about 20 days (see analysis in appendix A). For patients with chronic leukemia the delay is increased ($\tau = 20$) and we see a dramatic rise in the period (about 72 days) and **larger** periodic or aperiodic oscillations about the mean level.

Glass and Mackey (1979) and Mackey and Milton (1988) elaborate on the medical implications of these models to periodic hematological diseases while Gopalsamy, Kulenović and Ladas (1990) discuss the sufficient and necessary conditions for all positive solutions to oscillate about the steady states.

To simplify the calculations of models (1) and (2) we will scale them using methods like those found in Murray (1990). That is, let

$$x(t) = \frac{P(t)}{\Theta}, \quad t^* = \gamma t, \quad \tau^* = \gamma \tau$$

along with

$$\lambda^* = \beta_0 / (\Theta \gamma), \quad \lambda^* = \beta_0 / \gamma$$

in equations (1) and (2) respectively. The resulting equations (after dropping the *'s) are:

$$\frac{dx(t)}{dt} = \frac{\lambda}{1 + x^n(t - \tau)} - x(t) \quad (3)$$

$$\frac{dx(t)}{dt} = \frac{\lambda x(t - \tau)}{1 + x^n(t - \tau)} - x(t) \quad (4)$$

These will be the models that we work with in this paper though we will mostly consider model (4).

2.1 Stability

First, we will consider the stability of the equations without any chemotherapeutic effects.

2.1.1 Instantaneous model

When $\tau \equiv 0$ the steady state of equation (3) is the solution to

$$x^{n+1} + x - \lambda = 0 \tag{5}$$

shown in Figure (2, left) for various λ . The steady states to (4) are

$$x_u = 0, \quad x_s = \sqrt[n]{\lambda - 1} \tag{6}$$

and are shown in Figure (2, right). In the case of equation (4), x_s only exist for $\lambda > 1$ in which case it is stable, and x_u exist for all λ and is stable for $\lambda < 1$ and unstable for $\lambda > 1$. Therefore, we can interpret this as there will be a non-trivial mass of mature circulating blood cells if the growth rate is “big enough” or the saturation effects and decay rates are “small enough”.

2.1.2 Delay model

Now, let us consider how the delay affects the stability of the equations without considering the effects of chemotherapy.

First, consider model (4). The analysis for this model without chemotherapy can be followed from Murray (1990) and we will summarize that here. In the same manner as in the instantaneous case we will expand equation (4) about its non-zero equilibrium ($x_s = \sqrt[n]{\lambda - 1}$), using the expansion

$$x = x_s + \epsilon x_1 + \epsilon^2 x_2 + O(\epsilon^3), \quad 0 \leq \epsilon < 1 \tag{7}$$

we get the $O(\epsilon)$ equation to be

$$\dot{x}_1(t) = \frac{\lambda}{1 + x_s^n} x_1(t - \tau) - \frac{\lambda n x_s^{n-1} x_1(t - \tau)}{(1 + x_s^n)^2} - x_1(t) \tag{8}$$

$$= \left(1 - \frac{n(\lambda - 1)}{\lambda}\right) x_1(t - \tau) - x_1(t). \tag{9}$$

Defining

$$A = \left(1 - \frac{n(\lambda - 1)}{\lambda}\right) \tag{10}$$

we have

$$\dot{x}_1(t) = Ax_1(t - \tau) - x_1(t). \tag{11}$$

We will look for solutions to equation (11) of the form

$$x_1 = e^{\alpha t} \tag{12}$$

and determine when $\text{Re}(\alpha) < 0$ (i.e. when there is a stable solution).

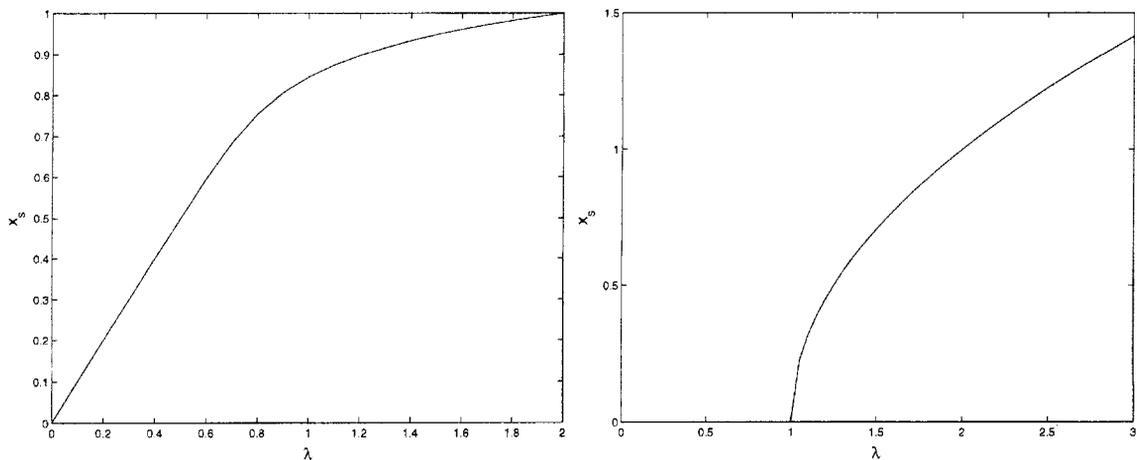


FIGURE 2 Instantaneous Bifurcation Diagram: x_s vs. λ . Left: equation 3; Right: equation 4.

Substituting equation (12) into equation (11) we obtain:

$$\alpha = Ae^{-\alpha\tau} - 1 \tag{13}$$

Let $\alpha = \mu + i\omega$ and comparing the real and imaginary parts of α we get

$$\mu = Ae^{-\mu\tau} \cos(\omega\tau) - 1 \tag{14}$$

$$\omega = -Ae^{-\mu\tau} \sin(\omega\tau) \tag{15}$$

After some manipulation of equations (14) and (15) we find the bifurcation ($\mu = 0$) to be

$$\tau_c = \frac{\cos^{-1}(1/A)}{\sqrt{A^2 - 1}}, \quad |A| = 1 \tag{16}$$

and for there to be a stable solution to model (4) ($\mu < 0$) the condition becomes

$$\tau < \frac{\cos^{-1} 1/A}{\sqrt{A^2 - 1}}, \quad |A| < 1 \tag{17}$$

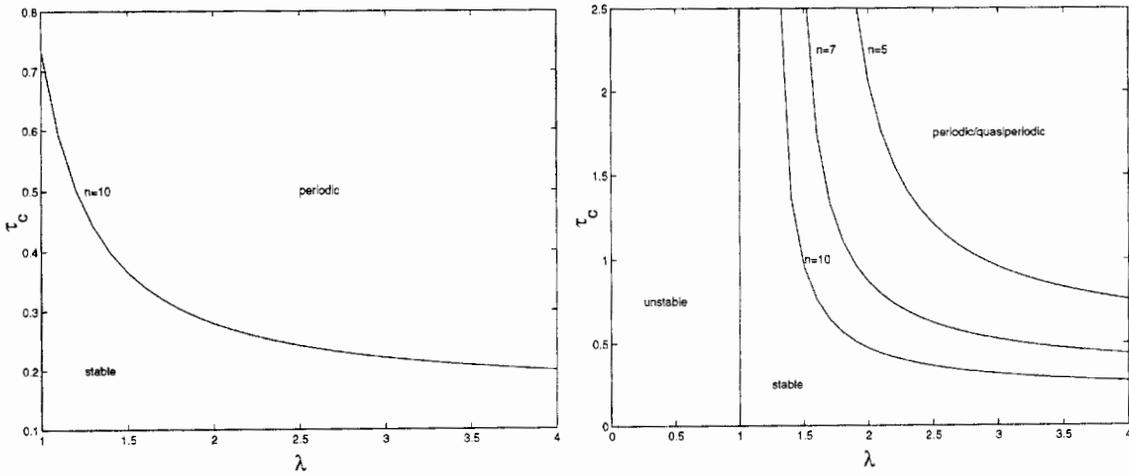


FIGURE 3 Bifurcation diagram: τ_c vs λ . Left — model 3, Right — model 4.

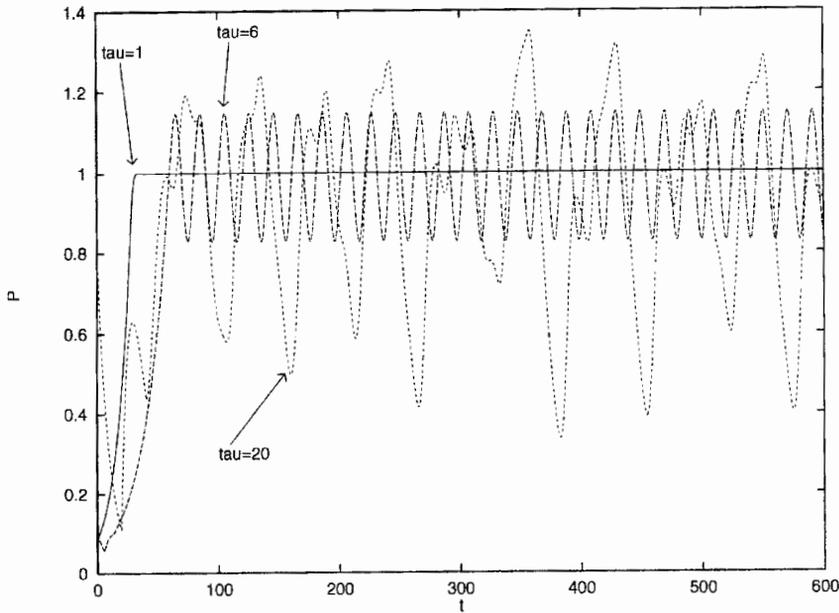


FIGURE 4 $\tau = 1, \tau = 6, \tau = 20$.

(see Figure 3, Right). If $A > 1$ then $\lambda < 1$ and the steady state x_u is stable for any τ . For $|A| < 1$ the steady state x_s is stable for any τ . Finally, if $A < -1$ and the first condition in (17) holds then the steady state x_s is stable otherwise the solution will be unstable and will lead to either periodic or quasiperiodic solutions (see Murray (1990) and Gopalsamy *et al.* (1990)). The most important fact to note is that from condition (17), it can be seen that either an increase in τ , λ , or n can have an unstabilizing effect that will lead to either periodic or quasiperiodic solutions. (See Figure 4 for the effects of increasing τ .)

Similar results are also obtained with model (3). In this case the analysis is similar to the previous case with the main difference being that A in equation (10) is of the form:

$$A = \frac{\lambda n x_s^{n-1}}{(1 + x_s^n)^2} \quad (18)$$

where x_s is the solution to equation (5). In this case the diagram showing the bifurcation from a stable equilibrium to periodic solutions is seen in Figure (3, Left). Note that this is similar to the bifurcation diagram in Figure (3, Right). Thus, for either model, an increase in τ will lead to periodic or quasiperiodic solutions.

3 CHEMOTHERAPEUTIC EFFECTS

We model the effects of the chemotherapy on the peripheral blood cell elements by a reduction in the parameter λ . As described in the previous section, λ is a scaled parameter which for model (4) is of the form β_0/γ (a ratio of cellular influx and decay) or net influx. Therefore, if the treatment has a direct effect on the peripheral blood cell elements then there is an increase in γ (cell decay) and thus a decrease in the parameter λ . Also, if the treatment reduces the influx of new peripheral blood cell elements due to destruction of bone marrow tissue then β_0 will decrease and again the parameter λ will

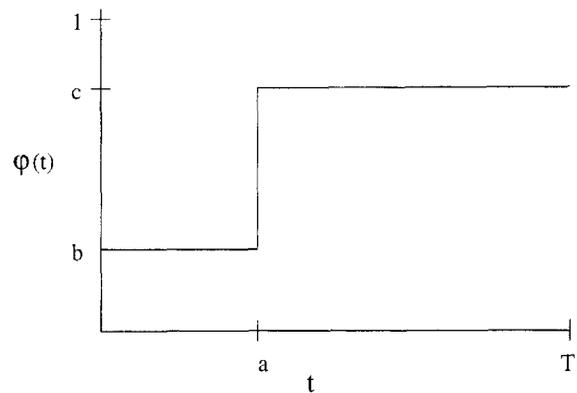


FIGURE 5 Step Function: $\phi(t)$ vs t . $\phi(t)$ represents the percentage of blood cell influx reduction due to the chemotherapy relative to the non-treatment influx.

decrease. So, the general effects of the chemotherapeutic treatment on the peripheral blood cell elements is a decrease in the parameter λ .

Therefore, to add the effects of periodic drug treatment to the model we will alter the parameter λ in equation (4) to be a periodic function of the form:

$$\lambda \equiv \lambda(t) = \bar{\lambda}\phi(t) \quad (19)$$

where $\bar{\lambda}$ is the net influx in the absence of treatment and $\phi(t)$ is a periodic step function with period T . Figure 5 shows one period of $\phi(t)$ where $0 \leq b \leq c \leq 1$ and $0 \leq a \leq T$. The parameter a represents the active phase of the treatment during which there is a $b\%$ decrease in circulating blood cell influx while c represents the percent reduction of influx during the remaining portion of the period. Therefore, b and c are proportional to the dose intensity, i.e. large doses of drug are modeled by smaller values of b and c while weaker doses are modeled by values of b and c near one. Also, if no treatment is given then $b = c = 1$. If the treatment is given continuously (or at least the drug concentration remains strong enough to actively destroy bone marrow during the full period) then $b = c$ is the percent reduction of the scaled influx term λ due to the treatment.

To help compare various treatments we define the mean value of the periodic treatment function $\phi(t)$ to be:

$$\langle \phi(t) \rangle = \frac{1}{T} \int_0^T \phi(t) dt. \quad (20)$$

Finally, we will also consider how changes in the parameter τ affect the stability of the circulating blood cell elements.

3.1 Numerical Results

We would like to define, in parameter space (dose/intensity etc.), acceptable drug regimens for model (4). Here, since we are modelling circulating blood cells, an acceptable regimen is one where the circulating blood cells are not destroyed. More specifically, we would like to have the model solution above some threshold, though for simplicity we will just determine whether the steady-state solution is non-zero. To do this we will fix parameters that are known (or use as good an estimate as is known) and determine how different doses and delays affect the outcome of the positive steady state. The parameters that are fixed are: $\beta_0 = 0.22$, $\gamma = 0.1$, $n = 10$, $\Theta = 1$ which are similar to those considered in Mackey and Glass (1977). The parameters for describing the drug effects are: $a = T/2$, $b = 0$, $c = 1$. Thus, the drug prevents influx of circulating blood cell elements for the first half of the period

and normal influx of circulating blood cell elements takes place during the second half of the period. Note that for these parameter values $\langle \lambda(t) \rangle = 1.1$ is near, and on the stable side of, the bifurcation for x_s in the *instantaneous* case. It should be observed that if $\langle \lambda(t) \rangle \ll 1$ then according to the stability analysis the system will be unstable for any choice of T , τ , and a and the circulating blood cell elements will decay to zero. Also note that as the period T is changed $\langle \lambda(t) \rangle$ does **not** change, thus, the mean value of the influx is constant for any period. Therefore, varying the period of the dose does **not** alter the total dose of the treatment, just when it is given. In fact, in the instantaneous case ($\tau = 0$), we observe that varying the period (T) or the active phase (a) will not change the stability of the solution. We will see below, this is **not** the case when delays are present.

3.1.1 The effects of varying the period

First, we consider how the model predicts changes in the period T affect the outcome of the treatment with the delay fixed at $\tau = 6$. From Figure 6, it can be

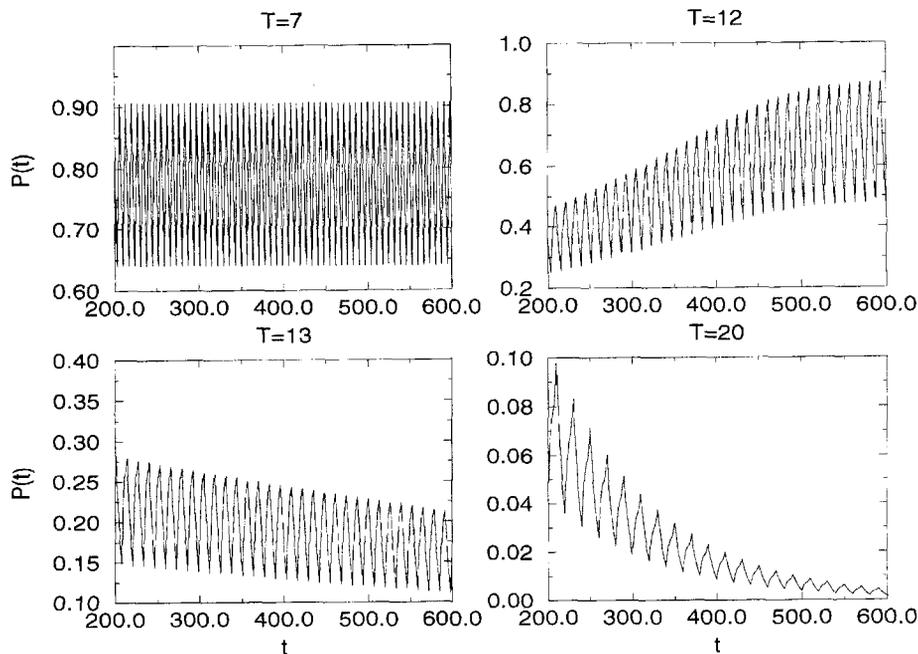


FIGURE 6 $P(t)$ vs t : $T = 7, 12, 13, 20$. There is circulating blood cell decay for $T \geq 13$.

observed that as the period is increased, the positive periodic solution is altered from stable to unstable (i.e. circulating blood cell elements decay), thus suggesting that treatments with shorter periods (but the same mean values as longer periods) could be better for circulating blood cells. This result is even more interesting when compared to results from Webb (1992a), Webb (1992b) and Panetta (1997). In modelling the cell-cycle-specific chemotherapeutic effects on proliferating and quiescent cell populations of cancerous tissue, they showed that in some cases shorter periods are better at eliminating the cancerous tissue. Thus, the result in this paper and those in Webb and Panetta would indicate that shorter periods not only can be better for the circulating blood cells but also are more effective in destroying cancerous tissue.

3.1.2 The effects of varying the delay

Next, we consider how the model predicts changes in the delay τ affects the outcome of the treatment. This is important to consider for several reasons. First, it has been observed that in some cancers such as chronic granulocytic leukemia and chronic myelogenous leukemia this delay is significantly increased (Mackey and Glass (1977)). It has also been observed that hematopoietic growth factors reduce this delay (see section 4). Finally, the chemotherapeutic treatment may increase the delay due to the treatment slowing down the cell-cycle time of the bone marrow. Also an increase in the delay can explain the chemotherapeutic induced periodic neutropenia discussed in Weldon, Kirk and Finlay (1974) and Mackey and Milton (1988). Holding the period fixed at $T = 10$, we find intervals

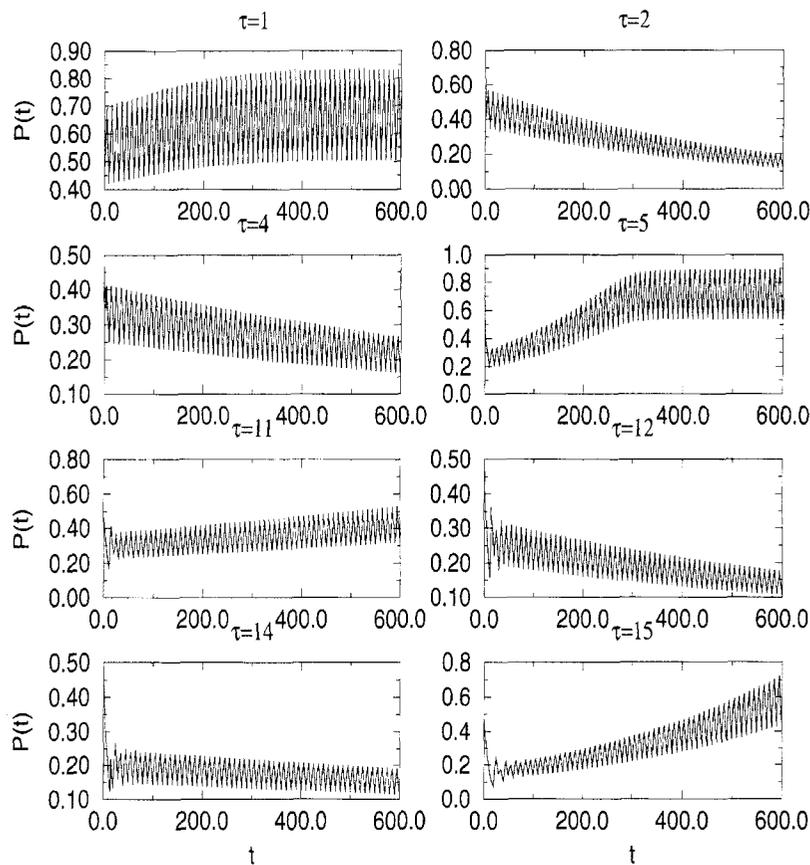


FIGURE 7 $P(t)$ vs t : $\tau = 1, 2, 4, 5, 11, 12, 14, 15$. The period is fixed in each graph $T = 10$. Note that as the delay increased, the circulating blood cell elements alternate between regions of positive growth ($0 \leq \tau \leq 1, 5 \leq \tau \leq 11, \dots$) and decay ($2 \leq \tau \leq 4, 12 \leq \tau \leq 14, \dots$).

(between $\tau = 2$ and $\tau = 4$ and also between $\tau = 12$ and $\tau = 14$) where the circulating blood cells decay (see Figure 7). It is also observed that these intervals in τ of decaying circulating blood cells repeat themselves for each multiple of the period. For instance, there is another decaying interval for the above case between approximately $\tau = 12 + 10$ and $\tau = 14 + 10$.

3.1.3 The T vs τ dynamics

For a more general picture of the dynamics of this system near $\langle \lambda(t) \rangle = 1$ we numerically calculate the $T - \tau$ bifurcation diagram showing where stable non-zero periodic solutions and unstable decaying solutions exist (see Figure 8). It should be noted that the bands of unstable decaying solution will keep repeating themselves every $\tau + T$ along the τ axis. This idea of unstable bands or “forbidden” zones in the $T - \tau$ parameter space is similar to those described in the cell-cycle-specific chemotherapy model for cancerous tissue by Adam and Panetta

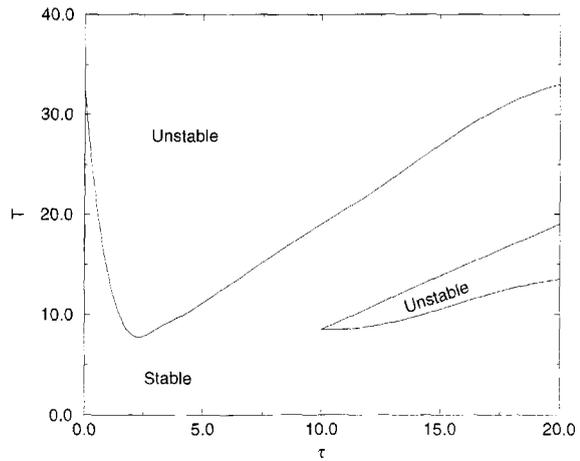


FIGURE 8 Bifurcation Diagram: T vs τ . Regions marked stable indicate stable circulating blood cell elements. Unstable regions are where the circulating blood cell elements decay to zero.

(1995). In that paper, unacceptable intervals in terms of dose and period with respect to cell-cycle-specific chemotherapy were also determined.

Furthermore, it should be noted that as the delay is increased (due to reasons given in the previous

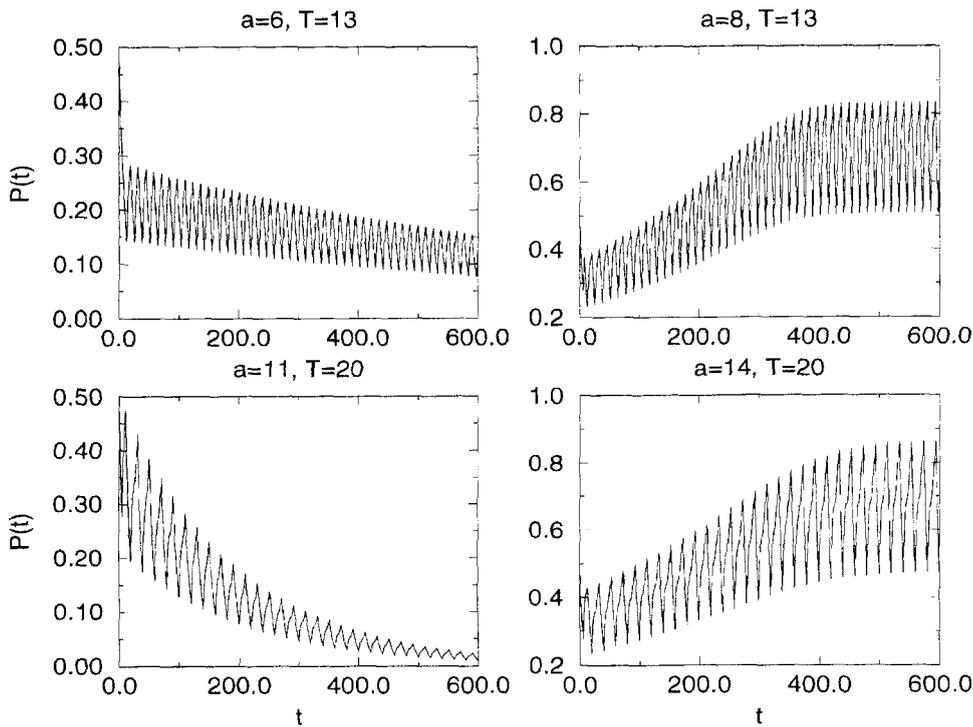


FIGURE 9 $P(t)$ vs t : Vary a . There is circulating blood cell decay for smaller values of a relative to T .

section) the dynamics of the system become more complex. For example, with delays below $\tau \approx 10$ there is just one interval where the circulating blood cells bifurcate from its positive periodic state to decaying, but if τ is increased above this point there are multiple regions of growth and decay making it much more difficult to determine an acceptable period.

3.1.4 The effects of varying the active time

Finally, we considered the case where the period T is fixed and we varied a (the active phase of the drug) and b (the percent reduction of circulating blood cell element influx due to the drugs) (see Figure 5). As a is varied we adjust b (with $c = 1$) such that $\langle \lambda(t) \rangle$ is constant, thus we compare equivalent treatments. For example, if the chemotherapeutic treatment is very myelosuppressive then the influx rate will be small ($b \ll 1$) while if the treatment is less myelosuppressive the influx rate will be larger and b will be closer to one. Thus, for $\langle \lambda(t) \rangle = \text{constant}$ the parameter a is set smaller for $b \ll 1$ than for b closer to one.

Here we observe that for fixed periods (T) we need a larger a with larger b (drug causes a smaller decrease in influx) to prevent total destruction of the circulating blood cells (see Figure 9).

4 HEMATOPOIETIC GROWTH FACTORS

The use of hematopoietic growth factors (HGFs) to accelerate hematopoiesis has become common practice in cancer treatment in recent years (see Engelhard and Brittinger (1994), Aglietta, Piacibello, Pasquino, Sanavio, Stacchini, Volta, Monteverde, Fubini, Morelli and Severino (1994), Hiddemann, Wörmann, Reuter, Schleyer, Zühlsdorf, Böckmann and Büchner (1994), Wörmann, Reuter, Zühlsdorf, Büchner and Hiddemann (1994), Willemsse, Boonstra and de Vries (1994), Bhalla, Holladay, Arlin, Grant, Ibrado and Jasiok (1991), Demetri (1994) to list only a few). If given appropriately, they allow

the clinician to adhere to the planned chemotherapeutic regimen or allow them to deliver higher doses of chemotherapy while preventing extreme detrimental effects to the bone marrow. In fact Lindley (1994) and Demetri (1994) state that these HGFs allow larger doses of chemotherapy to be safely given because of the increased circulating leukocytes. Typically, HGFs are given to a patient after they receive a chemotherapeutic treatment to help reduce chemotherapeutic-induced febrile neutropenia. Therefore, we consider the effects of HGFs have on our models.

Lindley (1994) observes that HGFs “accelerate hematopoiesis by expanding the mitotic pool of committed progenitor cells and shorting the period of time spent in the postmitotic pool from 5 to 6 days down to 1 day”. In terms of the model in this paper, a **decrease** in n (a stabilizing change) has the effect of expanding the mitotic pool and a *decrease* in the delay τ (a stabilizing change) has the effect of shorting the period of time spent in the postmitotic pool. In particular, this model shows, through changes in the parameters described above, how the use of HGFs can help in improving circulating blood cell recovery by seeing increased circulating blood cells and less oscillations. For example, if we consider that the HGFs reduce the parameter τ then the period and amplitude of the oscillations of the circulating blood cells will be reduced or even eliminated (see Figure 4) which is a positive affect that allows the patient to receive more treatment sooner. Also, we observe from Figure 8 that as τ is decreased, the system with chemotherapy becomes more stable, i.e. circulating blood cell elements are less likely to decay.

Currently, clinicians are not clear on how to optimally schedule HGFs. Since there are some toxic side effects to HGFs and if given too soon after the chemotherapeutic treatment is stopped then there will be detrimental affects to the bone marrow, models are needed to help determine optimal usage of HGFs. In fact, it is commonly recommended by some pharmaceutical companies that produce HGFs that they be given 24 hours post-chemotherapy while others suggest that a longer

waiting period is needed, e.g. "Because the nadir with most chemotherapeutic agents does not occur until 10 to 14 days after administration, the question of whether CSFs can be postponed until the neutrophil count begins to decrease has been raised." (see Oncolink). One might ask, what is an acceptable period. This model cannot answer these questions, and more sophisticated models are needed (see the conclusions).

5 CONCLUSIONS

The model presented in this paper gives one method of explicitly determining the toxic effects of chemotherapeutic drugs on circulating blood cells. To accomplish this, a mathematical model that was originally designed to describe the dynamics of the circulating blood cells is modified to also account for negative chemotherapeutic effects.

This model, which shows some very complex dynamics readily observed in mature blood cells without the chemotherapeutic modifications, also describes some interesting and clinically relevant results when the chemotherapy is considered. These results include the following. (1) Shorter periods allow circulating blood cell elements to be maintained while longer periods can cause reductions in the blood cells. This is complimentary to the mathematical results of Webb (1992b), Webb (1992a) and Panetta (1997) along with the clinical results by Klaassen *et al.* (1996), Lopes *et al.* (1993), and Wilson *et al.* (1994) which show that shorter periods can be more effective against cancers. (2) Intervals or bands exist in the $T - \tau$ parameter space where the drugs cause circulating blood cell decay which is similar to Adam and Panetta (1995). (3) Longer active phase a with a smaller reduction of influx due to treatment (b) are less detrimental to circulating blood cells. This is also seen mathematically in Panetta (1997) and clinically by Hainsworth and Greco (1994) and ten Bokkel Huinink *et al.* (1993) who show that for cell-cycle-specific drugs such as Paclitaxel short strong doses are less myelosuppressive. For example, with a fixed period of 21 days,

one day infusions are less myelosuppressive (i.e. larger b , thus larger a) than 3 day infusions (smaller b , thus smaller a). (4) Altering appropriate parameters, related to the use of HGFs, has positive stabilizing effects on the model.

Not only does this model show some interesting dynamics, it also poses the following questions. 1.) Are these dynamics clinically relevant? Due to the fact that clinicians have not considered the possibility of some of these dynamics (such as periodic fluctuations in circulating blood cell elements) and because of the clinical impracticality of testing some of these results (for example, clinicians cannot directly alter the delay like they can alter the period) the clinical relevance is in general not known. But, in some cases, general clinical observations have been made such as reduced or periodic fluctuating circulating blood cells due to chemotherapy and the fact that shorter periods can be better. 2.) What is a better protocol for delivering HGFs? Currently it is recommended that they be given 24 hours post-chemotherapy, but this is not necessary correct. Some suggest a longer delay before the HGFs be used. To help answer this question some modifications to the model are needed. A more sophisticated two-compartment model describing proliferating and quiescent cells in the bone marrow such as those by Mackey (1978) and MacDonald (1978) with the added terms to describe the effects of cell-cycle-specific chemotherapy might be able to help answer this question. This is because it would explicitly model the effects of the chemotherapy and HGFs on the bone marrow. Thus, by altering when the HGFs are given, it could be determined which protocols would be effective. 3.) Finally, how should clinicians determine when the next dose should be given? Due to the oscillating nature of blood cell counts, only a few blood samples may **not** be enough to clearly show the big picture of how the chemotherapy is affecting the patient. Therefore, a blood cell count above some threshold may not be an appropriate measure of determining when the next dose should be given. Models such as the ones posed here can help in determining how to schedule cell-cycle-specific chemotherapy.

A PERIOD OF OSCILLATIONS NEAR THE BIFURCATION

Here we will show how to obtain an estimate for the period of oscillations close to the bifurcation given in equation 16. To do this we will follow ideas given in Murray (1990). First, define

$$\tau = \tau_c + \epsilon + O(\epsilon^2), \quad (21)$$

where τ_c is defined in equation 16. Also, define ω_c as the value of ω when $\tau = \tau_c$ and also note that $\mu = 0$ at $\tau = \tau_c$. Therefore, near the bifurcation

$$\mu = \epsilon\mu_1 + O(\epsilon^2) \quad (22)$$

$$\omega = \omega_c + \epsilon\omega_1 + O(\epsilon^2). \quad (23)$$

Substituting equations (21, 22, 23) into (12) we get that the solution will oscillate with period

$$\frac{2\pi}{\omega_c + \epsilon\omega_1} \quad (24)$$

to $O(\epsilon)$. Note that

$$\omega_1 = \frac{(1 + \tau_c - \omega_c^2 \tau_c)\omega_c}{(1 - \tau_c + \omega_c^2 \tau_c)}. \quad (25)$$

In terms of the parameters listed in section (2) we see that to $O(1)$ the period is about 20.67 days which is close to the actual period of 20 days. Note that in some cases it is useful to know the period in terms of the delay. That is, the period (24) is equivalent to

$$\frac{2\pi\omega_c}{\omega_c + \epsilon\omega_1 \cos^{-1}(1/A)} \tau \quad (26)$$

to $O(\epsilon)$.

References

- Adam, J. A. and Panetta, J. C. (1995) 'A simple mathematical model and alternative paradigm for certain chemotherapeutic regimens', *Mathl. Comput. Modelling*, **22**(8), 49–60.
- Aglietta, M., Piacibello, W., Pasquino, P., Sanavio, F., Stacchini, A., Volta, C., Monteverde, A., Fubini, L., Morelli, S. and Severino, A. (1994) 'Rational for the use of granulocyte-macrophage colony-stimulating factor in oncology', *Seminars in Oncology*, **21**(6, Suppl 16), 5–9.
- Agur, Z., Arnon, R. and Schechter, B. (1988) 'Reduction of cytotoxicity to normal tissues by new regimens of cell-cycle phase-specific drugs', *Math. Biosci.*, **92**(1), 1–15.
- Bhalla, K., Holladay, C., Arlin, Z., Grant, S., Ibrado, A. M. and Jasiok, M. (1991) 'Treatment with interleukin-3 plus granulocyte-macrophage colony-stimulating factors improves the selectivity of ara-c in vitro against acute myeloid leukemia blasts', *Blood*, **78**(10), 2674–2679.
- Cojocaru, L. and Agur, Z. (1992) 'A theoretical analysis of interval drug dosing for cell-cycle-phase-specific drugs', *Math. Biosci.*, **109**(1), 85–97.
- Demetri, G. D. (1994) 'The use of hematopoietic growth factors to support cytotoxic chemotherapy for patients with breast cancer', *Hematology and Oncology Clinics of North America*, **8**(1), 233–249.
- Engelhard, M. and Brittinger, G. (1994) 'Clinical relevance of granulocyte-macrophage colony-stimulation factor', *Seminars in Oncology*, **21**(6, Suppl 16), 1–4.
- Glass, L. and Mackey, M. C. (1979) *Bifurcation Theory and Applications in Scientific Disciplines*, Ann. N. Y. Acad. Sci., chapter Pathological Conditions Resulting From Instabilities in Physiological Control Systems, **316**, pp. 214–235.
- Gopalsamy, K., Kulenović, M. R. S. and Ladas, G. (1990) 'Oscillations and global attractivity in models of hematopoiesis', *Journal of Dynamics and Differential Equations*, **2**(2), 117–132.
- Hainsworth, J. D. and Greco, F. A. (1994) 'Paclitaxel administered by 1-hour infusion', *Cancer*, **74**(4), 1377–1382.
- Hiddemann, W., Wörmann, B., Reuter, C., Schleyer, E., Zühlsdorf, M., Böckmann, A. and Büchner, T. (1994) 'New perspectives in the treatment of acute myeloid leukemia by hematopoietic growth factors', *Seminars in Oncology*, **21**(6, Suppl 16), 33–38.
- Klaassen, U., Wilke, H., Strumberg, D., Eberhardt, W., Korn, M. and Seeber, S. (1996) 'Phase I study with a weekly 1 h infusion of paclitaxel in heavily pretreated patients with metastatic breast and ovarian cancer', *European Journal of Cancer*, **32A**(3), 547–549.
- Lindley, C. M. (1994) Update on colony-stimulating factors, <http://www.oncolink.upenn.edu/specialty/chemo/colony.html>.
- Lopes, M. M., Adams, E. G., Pitts, T. W. and Bhuyan, B. K. (1993) 'Cell kill kinetics and cell cycle effects of taxol on human and hamster ovarian cell lines', *Cancer Chemother. Pharmacol.*, **32**, 235–242.
- MacDonald, N. (1978) *Time Lags in Biological Models, Lecture Notes in Biomathematics*, Springer-Verlag, New York, **27**.
- Mackey, M. C. (1978) 'Unified hypothesis for the origin of aplastic anemia and periodic hematopoiesis', *Blood*, **51**(5), 941–956.
- Mackey, M. C. and Glass, L. (1977) 'Oscillation and chaos in physiological control systems', *Science*, **197**, 287–289.
- Mackey, M. C. and Milton, J. G. (1988) *Perspectives in Biological Dynamics and Theoretical Medicine*, Ann. N. Y. Acad. Sci., chapter Dynamical Diseases, **504**, pp. 16–32.
- Mehr, R. and Agur, Z. (1992) 'Bone marrow regeneration under cytotoxic drug regimens: behaviour ranging from homeostasis to unpredictability in a model for hemopoietic differentiation', *BioSystems*, **26**, 231–237.
- Murray, J. D. (1990) *Mathematical Biology*, Springer-Verlag, New York.
- Oncolink (n.d.), Oncolink, the university of pennsylvania cancer center resource, <http://cancer.med.upenn.edu/>.
- Panetta, J. C. (1997) 'A mathematical model of breast and ovarian cancer treated with paclitaxel', *Math. Biosci.*, **146**(2), 89–113.
- Panetta, J. C. and Adam, J. A. (1995) 'A mathematical model of cycle-specific chemotherapy', *Mathl. Comput. Modelling*, **22**(2), 67–82.
- ten Bokkel Huinink, W. W., Eisenhauer, E. and Swenerton, K. (1993) 'Preliminary evaluation of a multicenter randomized comparative study of TAXOL (paclitaxel) dose and infusion length in platinum-treated ovarian cancer', *Cancer Treatment Reviews*, **19**(Supplement C), 79–86.

- Webb, G. F. (1990) 'Resonance phenomena in cell population chemotherapy models', *Rocky Mountain Journal of Mathematics*, **20**(4), 1195-1216.
- Webb, G. F. (1992a) 'A nonlinear cell population model of periodic chemotherapy treatment', *Recent Trends in Ordinary Differential Equations, Series in Applicable Analysis*, World Scientific Publishing Company, **1**, 569-583.
- Webb, G. F. (1992b) 'A cell population model of periodic chemotherapy treatment', *Biomedical Modeling and Simulation*, Elsevier Science Publishers, pp. 83-92.
- Webb, G. F. (1995) Resonances in periodic chemotherapy scheduling, in 'Proceedings of the First World Congress of Nonlinear Analysts'. To Appear.
- Weldon, T. E., Kirk, J. and Finlay, H. M. (1974) 'Cyclical granulopoiesis in chronic granulocytic leukemia: A simulation study', *Blood*, **43**(3), 379-387.
- Willemsse, P. H. B., Boonstra, H. and de Vries, E. G. E. (1994) 'Chemotherapy dose-escalation with hemopoietic growth factor support in ovarian cancer', *Seminars in Oncology*, **21**(6, Suppl 16), 44-50.
- Wilson, W. H., Berg, S. L., Bryant, G., Wittes, R. E., Bates, S., Fojo, A., Steinberg, S. M., Goldspiel, B. R., Herdt, J., O'Shaughnessy, J., Balis, F. M. and Chabner, B. A. (1994) 'Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: a phase I/II trial of 96-hour infusion'. *Journal of Clinical Oncology*, **12**(8), 1621-1629.
- Wörmann, B., Reuter, C., Zühlendorf, M., Büchner, T. and Hiddemann, W. (1994) 'Experimental basis for the use of recombinant human granulocyte-macrophage colony-stimulating factor in patients with acute myeloid leukemia', *Seminars in Oncology*, **21**(6, Suppl 16), 39-43.