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Neutrophil dynamics in response to chemotherapy and G-CSF

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ABSTRACT

We have used a mathematical model of the combined dynamics of the hematopoietic stem cells and the differentiated neutrophil progeny to examine the effects of periodic chemotherapy in generating neutropenia, and the corresponding response of this system to granulocyte colony stimulating factor given to counteract the neutropenia. We find that there is a significant period of chemotherapy delivery that induces resonance in the system (at a period twice the average neutrophil lifespan from commitment to death) and a corresponding neutropenia suggesting that myelosuppressive protocols should avoid this period to minimize hematopoietic damage. The response to G-CSF is highly variable.

1. Introduction

Chemotherapy is frequently accompanied by hematopoietic side effects due to the myelosuppressive character of the drugs used. These side effects commonly include neutropenia (accompanied by fever and possible infection) and, to a lesser extent, thrombocytopenia and/or anemia. In an effort to circumvent these side effects, hematopoietic cytokines are frequently used as an adjunct to chemotherapy, for example granulocyte colony stimulating factor (G-CSF) to deal with neutropenia (Crawford et al., 2003; Foley and Mackey, 2009).

Relatively speaking, a great deal of energy has been expended on efforts to clinically determine the most efficacious way to administer G-CSF (Bennett et al., 1999; Clark et al., 2005; Fukuda et al., 1993; Holmes et al., 2002; Koumakis et al., 1999), as well as to examine this question using a variety of mathematical modeling techniques (Engel et al., 2004; Foley and Mackey, 2009; Friberg et al., 2002; Scholz et al., 2005; Shochat et al., 2007; Vainstein et al., 2005). However, the period of repeated chemotherapy treatments is known to have effects on the hematopoietic response (Thatcher et al., 2000; Tjan-Heijnen et al., 2002), but there seems to be virtually no literature examining the nature of these effects from a clinical perspective.

In this paper, using a relatively simple but physiologically realistic mathematical model for the hematopoietic stem cells and the differentiated neutrophils, we examine the dependence of neutrophil response on the period of simulated chemotherapy and the secondary response to G-CSF administration. Detailed mathematical calculations that lead to our details are contained in Appendices A and B.

2. The model

2.1. Model assumptions and dynamical equations

Fig. 1 illustrates the mathematical model of neutrophil production studied in this paper. This model contains the hematopoietic stem cell (HSC) compartment, as well as a neutrophil compartment. The neutrophil compartment is further divided into three sub-compartments corresponding to proliferating, maturating, and circulating neutrophils, respectively. The erythrocytes and platelets are not included in the model other than to assume that the total differentiation rate of HSCs into these two cell lines is a constant κ_δ (days^{-1}).

HSCs are classified as quiescent (Q) or proliferative phase cells. Quiescent phase HSCs can either enter the proliferative phase at a rate β, or differentiate into any of the three cell lines, leukocytes, erythrocytes, or platelets. The proliferating HSCs are assumed to undergo mitosis at a fixed time τ_S after entry into proliferation, and to be lost randomly at a rate $\gamma_S(t)$ during the proliferating phase (Mackey, 1996). Each proliferative cell generates two quiescent phase cells following mitosis.

After differentiation from Q, the neutrophil precursors enter a proliferative phase for a period of time τ_{NP} (days), during which they proliferate at a rate $\eta_{NP}(t)$ (days^{-1}). Following the

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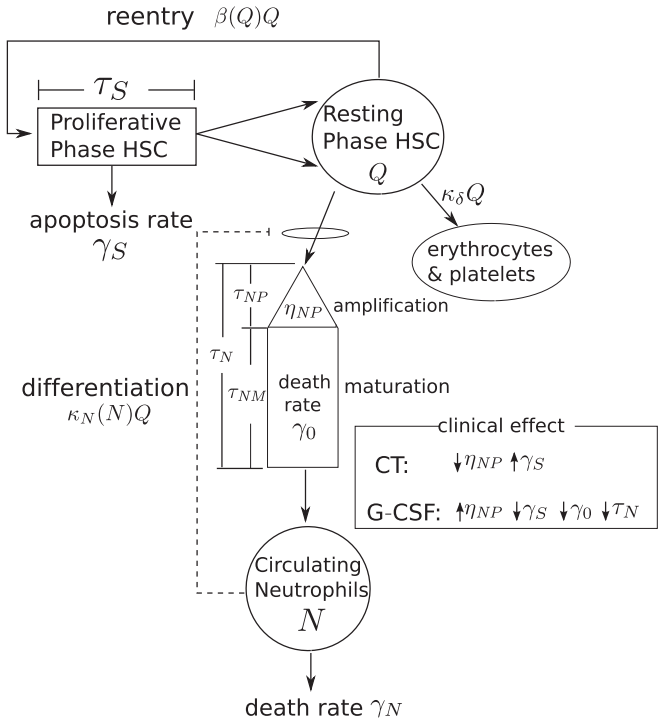

Fig. 1. A cartoon representation of the model of neutrophil production investigated here. The model dynamics include those of the hematopoietic stem cells (HSC) as well as differentiated cells committed to the neutrophil line. Quiescent (resting phase) HSCs can either remain in Q, exit into the proliferative HSC phase at a rate β, or differentiate into the committed neutrophil compartment at a rate κ_N, or into the combined megakaryocyte/erythrocyte lines at a rate κ_δ. Cells in the HSC proliferative phase are assumed to undergo apoptosis at a rate γ_S and the duration of the proliferative phase is taken to be τ_S. Cells in the neutrophil pathway are amplified by successive divisions for a time τ_{NP}, and then enter a purely maturation (no proliferation) compartment for a period of time τ_{NM} before they enter the circulation. The circulating neutrophils (N) die at a random rate γ_N so their average lifespan is γ_N^{-1}. The differentiation rate of HSC to neutrophils is controlled by the circulating neutrophil population through the differentiation rate κ_N, while the HSC proliferation is controlled by the resting HSC population with proliferation rate β.

proliferative phase, cells become non-proliferative and mature for a period of time τ_{NM}. During this time it is assumed that they die randomly at a rate $\gamma_0(t)$. At the end of the maturation phase the surviving cells are released as mature neutrophils into the circulation where they die randomly at a rate γ_N. Thus, the total duration of the proliferation and maturation phases of a neutrophil precursor is $\tau_N=\tau_{NP}+\tau_{NM}$, and the amplification rate of neutrophil precursors at a time t is given by

$$A_N(t)=\exp\left[\int_0^{\tau_{NP}}\eta_{NP}(t-\tau_N+s)\,ds-\int_{\tau_{NP}}^{\tau_N}\gamma_0(t-\tau_N+s)\,ds\right]. \quad (1)$$

If the proliferation rate η_{NP} and apoptosis rate γ_0 are constants, then $A_N=\exp(\eta_{NP}\tau_{NP}-\gamma_0\tau_{NM})$. The circulating neutrophils have an average lifespan of γ_N^{-1}.

The mathematical formulation for this abstraction of the neutrophil production system consists of a pair of delay differential equations (DDEs) (see Bernard et al., 2003b; Foley and Mackey, 2009 for details) governing the dynamics of the quiescent phase stem cells (Q) and the circulation neutrophils (N). Both populations are measured in units of cells/kg body weight. Each of these equations takes into account the balance between the net production and loss rates of HSCs and circulating neutrophils. There are two important delays in this model and they are τ_S (the duration of the HSC proliferative phase) and τ_N (the total duration of the proliferative and maturation phases of the differentiated neutrophils). In the dynamic equations describing this model we always use the convention that a variable delayed by a time τ, *e.g.* $x(t-\tau)$ is denoted by x_τ, i.e. $x(t-\tau)\equiv x_\tau$. With this convention, the equations describing the dynamics of this model are given by

$$\begin{cases} dQ/dt=-(\beta(Q)+\kappa_N(N)+\kappa_\delta)Q+A_Q(t)\beta(Q_{\tau_S})Q_{\tau_S},\\ dN/dt=-\gamma_N N+A_N(t)\kappa_N(N_{\tau_N})Q_{\tau_N}\end{cases} \quad (2)$$

and

$$\kappa_N(N)=f_0\theta_1^{s_1}/(\theta_1^{s_1}+N^{s_1}),$$

$$\beta(Q)=k_0\theta_2^{s_2}/(\theta_2^{s_2}+Q^{s_2}),$$

$$A_Q(t)=2\exp\left[-\int_0^{\tau_S}\gamma_S(t-\tau_S+s)\,ds\right],$$

$$A_N(t)=\exp\left[\int_0^{\tau_{NP}}\eta_{NP}(t-\tau_N+s)\,ds-\int_{\tau_{NP}}^{\tau_N}\gamma_0(t-\tau_N+s)\,ds\right],$$

$$\tau_N=\tau_{NP}+\tau_{NM}. \quad (3)$$

For hematologically normal individuals, the rate γ_S,η_{NP} and γ_0 are constants (refer Table 1), and therefore

$$A_Q=2e^{-\gamma_S\tau_S},\quad A_N=\exp(\eta_{NP}\tau_{NP}-\gamma_0\tau_{NM}). \quad (4)$$

A detailed derivation of these equations starting from a more fundamental age-structured model has been given in Foley and Mackey (2009) and Lei and Mackey (2011).

2.2. Model parameters

An extensive series of studies provide excellent estimates for the parameters of this model for hematologically normal humans, and these have been validated for patients with periodic chronic myelogenous leukemia (Colijn and Mackey, 2005a), cyclical neutropenia (Colijn and Mackey, 2005b), and periodic thrombocytopenia (Apostu and Mackey, 2008). The estimates (for

Table 1
Parameters for hematologically normal individuals.

Parameter	Value	Unit	Sources
Stem cell compartment			
Q_*	1.1	$\times 10^6$ cells/kg	1
γ_S	0.07	days^{-1}	1, 2
$\gamma_S^{\min}$	0.03	days^{-1}	1
$\gamma_S^{\max}$	0.20	days^{-1}	10
τ_S	2.8	days	1, 2
k_0	8.0	days^{-1}	1, 3
θ_2	0.3	$\times 10^6$ cells/kg	2, 9
s_2	4	(none)	1
Neutrophil compartment			
N_*	6.3	$\times 10^8$ cells/kg	4
γ_N	2.4	days^{-1}	1, 5
τ_{NP}	5	days	6
τ_{NM}	6	days	4
τ_N	11	days	9
η_{NP}	2.5420	days^{-1}	1, 9
$\eta_{NP}^{\min}$	2.0420	days^{-1}	9
$\eta_{NP}^{\max}$	3.0552	days^{-1}	1, 9
γ_0	0.27	days^{-1}	7
$\gamma_0^{\min}$	0.12	days^{-1}	7
f_0	0.40	days^{-1}	1
θ_1	0.36	$\times 10^8$ cells/kg	9
s_1	1	(none)	1
Other cell compartments			
κ_δ	0.01	days^{-1}	8, 9

Sources: 1=(Bernard et al., 2003b), 2=(Mackey, 2001), 3=(Bernard et al., 2003a), 4=(Dancey et al., 1976), 5=(Haurie et al., 2000), 6=(Israels and Israels, 2002), 7=(Mackey et al., 2003), 8=(Colijn and Mackey, 2005b), 9=Calculated, 10=BioNumbers (http://bionumbers.hms.harvard.edu/).

a hematologically normal individual) listed in Table 1 are taken from the works of Bernard et al. (2003b), Colijn and Mackey (2005a,b), Foley and Mackey (2009) and Lei and Mackey (2011):

- The cellular loss rates are estimated to be $\gamma_S = 0.07$ days^{-1}, $\gamma_N = 2.4$ days^{-1} and $\gamma_0 = 0.27$ days^{-1}.
- *Duration of different functional cellular phases*: The duration of the proliferative phase of the HSC is $\tau_S = 2.8$ days, the duration of the proliferative phase for neutrophil precursors is $\tau_{NP} = 5$ days and the neutrophil maturation phase duration is $\tau_{NM} = 6$ days.
- *Differentiation rates*: The parameters for the differentiation rate κ_N are $f_0 = 0.40$ days^{-1}, $\theta_1 = 0.36 \times 10^8$ cells/kg, and $s_1 = 1$. The differentiation rate from the HSC compartment into the erythrocyte line is on the order of 10^{-3} days^{-1}, while the corresponding rate into the platelet line is on the order of 10^{-2} days^{-1}. Thus, $\kappa_\delta \simeq 0.01$ days^{-1}.
- The parameters for the reentry rate β of stem cells from the quiescent phase into the proliferative phase are $k_0 = 8.0$ days^{-1}, $\theta_2 = 0.3 \times 10^6$ cells/kg, $s_2 = 4$.
- The amplification rate A_N is taken as $A_N \simeq 6.55 \times 10^4$ (Bernard et al., 2003b) from which the proliferation rate is $\eta_{NP} = 2.5420$ days^{-1}.
- Steady states values are $Q_* = 1.1 \times 10^6$ cells/kg, and $N_* = 6.3 \times 10^8$ cells/kg.

2.3. Simulating chemotherapy and G-CSF

Chemotherapy is often administered with a fixed period T (days). Neutropenia is a common side effect, and G-CSF is frequently administrated as an adjunct some days (denoted by T_1) after chemotherapy. In this study, we assume that both the effects of the chemotherapy and G-CSF are maintained for one day. (An expanded model with more realistic chemotherapy and G-CSF dynamics will be presented in Brooks et al., in preparation.)

Chemotherapy increases apoptosis in both proliferative HSCs and proliferative neutrophil precursors (Hannun, 1997). We use the maximum apoptosis rate $\gamma_S^{\max} = 0.2$ days^{-1} of HSCs as estimated by Foley and Mackey (2009). Moreover, it has been reported that chemotherapy can induce oscillations in the blood neutrophil count (Kennedy, 1970). Thus, we choose the minimal proliferation rate of neutrophil precursors such that the model displays oscillations. Since the proliferation rate is minimal during chemotherapy, we denote it as $\eta_{NP}^{\min} = 2.0420$ day^{-1}. From (3), these is a delay τ_{NM} between a change in η_{NP} and its effect in the neutrophil population.

Three effects of G-CSF are considered in this model (Bernard et al., 2003b; Foley and Mackey, 2009):

(1) Decrease of apoptosis in neutrophil precursors leading to a decrease of γ_0 to the minimum value $\gamma_0^{\min} = 0.12$ days^{-1}, and an increase of the proliferative rate η_{NP} to the maximum value of $\eta_{NP}^{\max} = 3.0552$ days^{-1}, in accordance with the estimated maximum amplification rate $A_N^{\max} = 2^{21}$ (Foley and Mackey, 2009).
(2) Decrease of apoptosis γ_S of HSCs to the minimum value $\gamma_S^{\min} = 0.03$ days^{-1}.
(3) Decrease of the neutrophil precursor maturation time. The maturation time τ_{NM}^{gcsf} in the presence of G-CSF depends on the dose of G-CSF administered, *e.g.* 2.9 days with 300 μg/kg/day G-CSF and 4.3 days with 30 μg/kg/day (Price et al., 1996). The exact dependence on dosage remains, however, unknown.

To idealize the effects of chemotherapy and G-CSF, we assume square wave temporal functions for the loss rates γ_S, γ_0, the neutrophil precursor proliferative rate η_{NP}, and the neutrophil precursor maturation time τ_{NM} of the following form:

$$\gamma_S(t) = \begin{cases} \gamma_S^{\max} & \text{if } 0 \le t - kT < 1, \\ \gamma_S^{\min} & \text{if } T_1 \le t - kT < T_1 + 1, \\ \gamma_S & \text{otherwise,} \end{cases} \tag{5}$$

$$\gamma_0(t) = \begin{cases} \gamma_0^{\min} & \text{if } T_1 \le t - kT < T_1 + 1, \\ \gamma_0 & \text{otherwise,} \end{cases} \tag{6}$$

$$\eta_{NP}(t) = \begin{cases} \eta_{NP}^{\min} & \text{if } 0 \le t - kT < 1, \\ \eta_{NP}^{\max} & \text{if } T_1 \le t - kT < T_1 + 1, \\ \eta_{NP} & \text{otherwise} \end{cases} \tag{7}$$

and

$$\tau_{NM} = \begin{cases} \tau_{NM}^{\text{gcsf}} & \text{if } T_1 \le t - kT < T_1 + 1, \\ \tau_{NM} & \text{otherwise.} \end{cases} \tag{8}$$

Here k is an integer.

3. Results

We first study the response of the neutrophil dynamics alone to chemotherapy and then examine how that is modified by G-CSF. We then turn to an examination of the full model response.

3.1. Neutrophil compartment dynamics

To study the neutrophil response to chemotherapy, and the effect of G-CSF administration after chemotherapy, we focus on the population dynamics of neutrophils assuming HSC numbers to be held constant ($Q(t) \equiv Q_*$). Therefore, we have a single equation for the neutrophil dynamics

$$dN/dt = -\gamma_N N + A_N(t)\kappa_N(N_{\tau_N})Q_*. \tag{9}$$

In this one-dimensional delay differential equation, chemotherapy acts to decrease the amplification rate $A_N(t)$, while G-CSF increases $A_N(t)$ and decreases the delay τ_N temporarily.

3.1.1. Chemotherapy at a period T and resonance

We varied T from 1 to 40 days and, for each value, solved (9) for $t = 1000$ days using the initial condition $N(t) = N_*$ for $t < 0$. To obtain the long term effect of chemotherapy for each simulation result the last 400 days are used to obtain both the temporal amplitude in neutrophil fluctuations as well as the nadir in the neutrophil level.

Fig. 2a shows both the amplitude and nadir in the neutrophil level as a function of the chemotherapy period T (as well as the predicted system response function, see below). Fig. 2a shows that the numerically determined amplitude has a peak, and the nadir a minimum, when the chemotherapy period is 23 days in accordance with the results in Fig. 2b. In Fig. 2b we show computed time series for the neutrophils at two different periods of chemotherapy administration. The model predicts substantial differences in the dynamic response of the system as severe neutropenia was produced in the model at $T=23$ days but not at $T=18$ days. Moreover, the first-cycle neutrophil nadir is reached at about 10 days after chemotherapy in agreement with clinical observations (range from 7 to 14 days).

A possible reason for the occurrence of a significant peak in the amplitude and minimum in the nadir at a specific T is resonance between the perturbation to the system (due to the periodic chemotherapy) and the intrinsic characteristic frequency in the neutrophil production dynamics.

To examine this possibility, we study the linear frequency response function of the system (9) with respect to the period T of

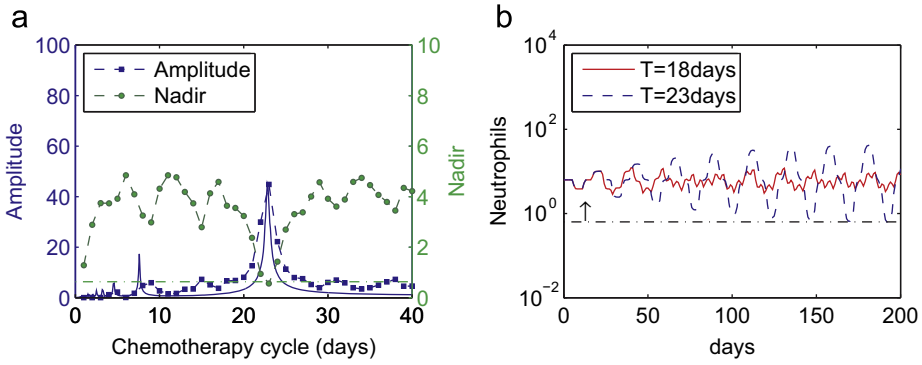

Fig. 2. Numerical simulation results for the neutrophil compartment model with chemotherapy alone. (a) The amplitude (left hand ordinate) in neutrophil response (blue squares connected with a dashed blue line) as well as the nadir (right hand ordinate and green circles connected with a dashed green line) as a function of the period T of chemotherapy. The horizontal green dash-dot line indicates the level for severe neutropenia (0.63×10^8 cells/kg). Note that the major peaks in the amplitude coincide with the minima in the nadir. The solid blue line is the computed linear frequency response function determined from (10) (rescaled to compare with the amplitude). (b) Simulated neutrophil levels from (9) in response to chemotherapy with a period of either T=18 days or 23 days. Neutrophil levels are in units of 10^8 cells/kg, the dashed-dot horizontal line again indicates the level for severe neutropenia, and the arrow shows the first neutrophil nadir. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the chemotherapy. The chemotherapy is assumed to perturb the amplification such that $A_N(t)$ is expressed as $A_N(t) = A_N + \xi(t)$, where A_N is the normal amplification rate as given by (4), and $\xi(t)$ is the perturbation to the amplification factor (see Appendix A.1). The linear frequency response function $F(\omega)$ measures the gain in neutrophil amplitude in response to a periodic perturbation $\xi(t)$ (with frequency $\omega = 2\pi/T$), and is given by (see Appendix A.1 for the derivation)

$$F(\omega) = \left|\kappa_N(N_*)Q_*/(i\omega+\gamma_N+Be^{-i\omega\tau_N})\right|, \tag{10}$$

where $B = -A_N Q_* \kappa'_N(N_*)$.

In Fig. 2a we have also plotted the linear response function F with parameter values taken from Table 1. There is a prominent resonant peak at $T \approx 22.8$ (days), consistent with the numerical simulation results from (9). This provides strong support for the hypothesis that large amplitudes in the neutrophil fluctuation level, as well as the minima in the neutrophil nadir, originate from a resonance between the chemotherapy period and the dynamics of the neutrophil regulatory system. The fundamental resonant period, using the parameters in Table 1, is computed to be 22.8 days and it is precisely this period of chemotherapy administration that leads to severe neutropenia in the model.

In Appendix A.3, we have shown that from the gain of the transfer function, the dominant resonant period is approximately

$$T \approx 2.0 \times (\tau_N + \gamma_N^{-1}). \tag{11}$$

Note that τ_N is the transit time for the entire neutrophil precursor stage (proliferation plus maturation), and γ_N^{-1} is the average life time of circulating neutrophils. Thus (11) suggests that the dominant resonant period of chemotherapy is about twice the average life time of marrow plus circulating neutrophils starting from when they differentiated from the HSC.

The density of the distribution of τ_N is not a delta function, as has been assumed above and in the derivation of (10), but rather is distributed with a density $g(\tau_N)$ closely approximated by the density of the gamma distribution (Hearn et al., 1998; Price et al., 1996). We have extended the above calculations for the linear response function to this case in Appendix A.2, and the observation that the dominant resonant period for chemotherapy depends linearly on the total neutrophil life time also holds in this case (Fig. 8 in Appendix A).

From Price et al. (1996), cells spend 3–6 days in the mitotic pool under normal physiological conditions, the transit time through the postmitotic pool is between 6 and 8.4 days, and the circulating neutrophil death rate is $1.7 < \gamma_N < 2.4$ days^{-1}. Thus $9 < \tau_N <$ 14.4 days and (11) indicates that for hematologically normal individuals the resonant period in response to chemotherapy is about $18.8 < T < 29.7$ days. This estimate suggests that if the period T of chemotherapy is outside this range it should be possible to avoid resonance, and therefore severe neutropenia.

3.1.2. *One day G-CSF administration T_1 days after chemotherapy*

From the previous section, the total neutrophil life time appears to be a major determinant of the response to chemotherapy. G-CSF administration is known to increase the neutrophil production rate (by interfering with apoptosis and thus increasing amplification within the proliferative neutrophil precursor pool) and also decrease the neutrophil maturation time. Thus, G-CSF administration after chemotherapy might be expected to eliminate the large amplitude neutrophil level oscillations that are triggered by chemotherapy, but one would suspect that its timing, relative to the chemotherapy, may be critical. This suspicion is confirmed by the numerical solutions in Fig. 3 where administration of G-CSF with $T_1 = 1$ days has a profoundly different effect than $T_1 = 10$ days on the response to periodic chemotherapy with T=23 days.

To study the effect of G-CSF, we fixed the period of chemotherapy at T=23 days to coincide with the resonant period, and then varied the day T_1 of G-CSF administration after chemotherapy. To also study the effect of the duration of the neutrophil maturation time $\tau_{NM}^{\mathrm{gcsf}}$ during G-CSF administration, we changed $\tau_{NM}^{\mathrm{gcsf}}$ in the range from 0 to 6 days. Results are in Fig. 3a, which shows the contour plot of the nadir in neutrophil levels as a function of $\tau_{NM}^{\mathrm{gcsf}}$ and the day T_1 of G-CSF administration. The results clearly show that the most beneficial response (minimizing the neutropenia) occurs when G-CSF administration is given early (1–2 days) after chemotherapy, but there are also broad ranges of T_1 (7–21 days after chemotherapy) during which G-CSF will actually augment the neutropenia induced by the chemotherapy. Two representative computed neutrophil time series illustrate these two points in Fig. 3b. The effects are insensitive to the value of $\tau_{NM}^{\mathrm{gcsf}}$.

3.2. *Behavior of the full model*

In this section we investigate the response of the full model given by Eq. (2). We first examine the response to chemotherapy alone, and then the response to G-CSF following chemotherapy. The results will show that our previous conclusions from

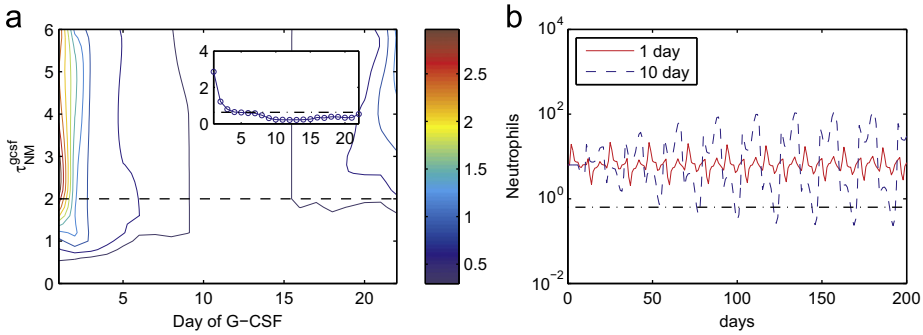

Fig. 3. The simulated effect of one day G-CSF administration on neutrophil dynamics alone with periodic chemotherapy and $T=23$ days to coincide with the resonant period. Neutrophil levels are in units of $\times 10^8$ cells/kg throughout. (a) Contour plot of the nadir in the neutrophil level as a function of neutrophil precursor maturation time τ_{NM}^{gcsf} (ordinate) and the day T_1 of G-CSF after chemotherapy. Dashed line shows $\tau_{NM}^{gcsf}=2.0$ days. Inset shows the dependence of nadir with the day of G-CSF administration, along the dashed line with $\tau_{NM}^{gcsf}=2.0$ days. Dashed dot line in the inset shows the threshold for severe neutropenia (0.63×10^8 cells/kg). (b) Simulated neutrophil response with one day G-CSF administration 1 or 14 days after chemotherapy, respectively. Here $\tau_{NM}^{gcsf}=2.0$ days. The horizontal dotted line indicates the level of severe neutropenia (0.63×10^8 cells/kg).

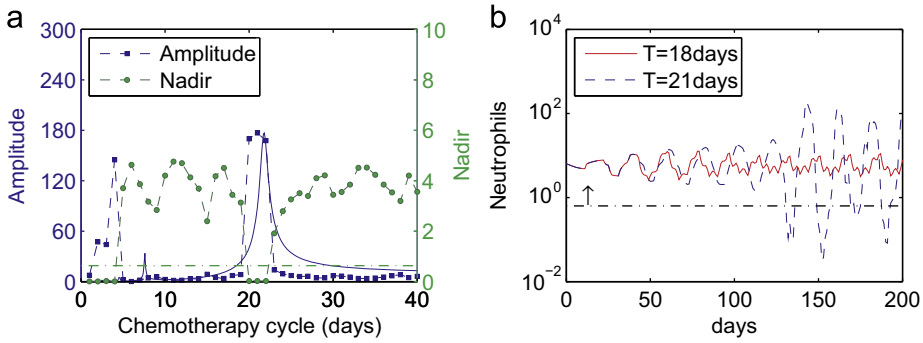

Fig. 4. Numerical simulation results for the full two compartment model with only chemotherapy. All nomenclatures as in Fig. 2 except that the linear frequency response function are determined from (B.5) in Appendix B, and the simulations are for chemotherapy with a period of either $T=18$ days or 21 days.

consideration of the neutrophil dynamics alone remain generally valid in this case.

3.2.1. *Chemotherapy*

We first examine the response to chemotherapy alone by varying the period T of chemotherapy administration from 1 to 40 days, and examine how the amplitude and nadir in neutrophil count numbers depend on T. Fig. 4a shows the simulation results from which the existence of a prominent resonance in the amplitude and nadir with a chemotherapy period of 21 days is obvious. This is slightly smaller than that we found in our examination of the neutrophil dynamics alone. This resonant period is intrinsic to the dynamics of the full model and can be satisfactorily explained by examining the maximum in the gain determined from the frequency response function of the full model (see Appendix B), which gives 21.8 days (Fig. 4a). We also found that there is a peak in the amplitude response and minimum in the nadir at $T=4$ days that cannot be explained by resonance. The mechanism for the occurrence of this peak remains unknown.

This resonance, dependent on the period T of the chemotherapy, is seen in the two simulated neutrophil time series shown in Fig. 4b for $T=18$ days at which severe neutropenia is not induced, and $T=21$ days which is at the resonant period and which predicts severe neutropenia.

In the previous section where we studied the dynamics of the neutrophils alone, we obtained an estimate for the resonant period of chemotherapy which was twice the average neutrophil life time. As shown in Appendix B, precisely the same conclusion for the full model holds. Namely that the resonant period depends linearly on the neutrophil life time in spite of the appearance of many other parameters. Fig. 5 shows the numerical results of computing the resonant period as a function of neutrophil life

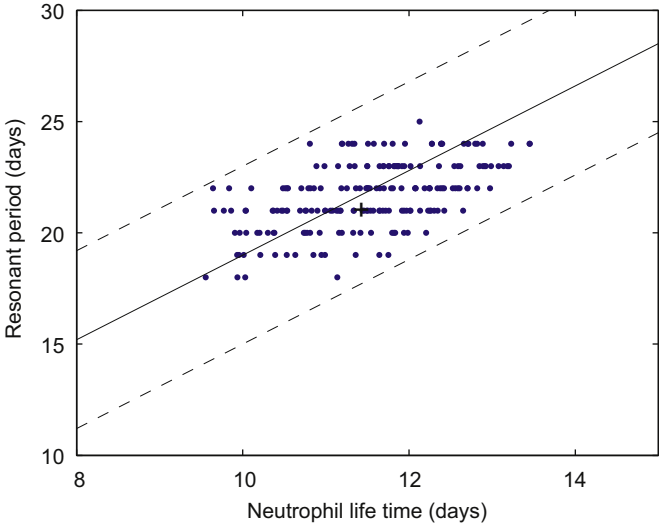

Fig. 5. Numerical simulation results of resonant period T as a function of neutrophil life time in the full model. In the simulations, we randomly varied the parameters τ_{NP}, τ_{NM}, γ_N and f_0 over the range of $\pm 20\%$ of their default values given in Table 1. Resonant periods were obtained by the day of maximum amplitude of neutrophil variation. Solid line shows the graph of $T=1.9(\tau_N+\gamma_N^{-1})$, and the two dashed lines show errors of ± 4 (days). The black cross shows the neutrophil life time of 11.4 days and the resonant period of 21 days as in Fig. 2.

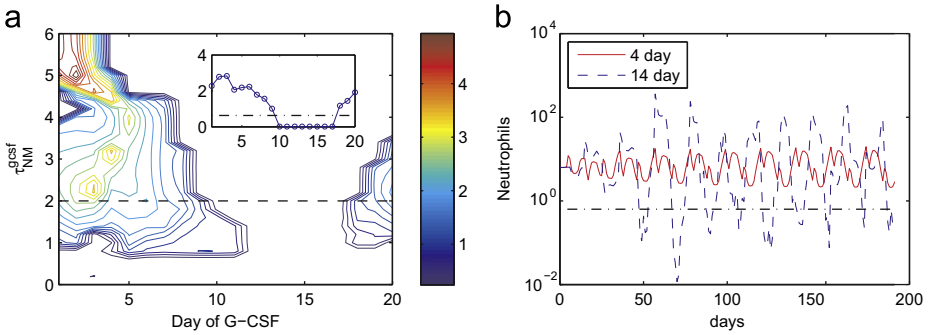

Fig. 6. The simulated effect of one day G-CSF administration in the full model with periodic chemotherapy and $T=21$ days to coincide with the resonant period. All other nomenclatures as in Fig. 3. The simulated neutrophil response is for one day G-CSF administration 4 or 14 days after chemotherapy.

time, with parameters $\tau_{NP}, \tau_{NM}, \gamma_N$ and f_0 taken randomly over a range of $\pm 20\%$ of their default values given in Table 1. The results show that approximately

$$\text{Resonant period} = 1.9 \times \text{Neutrophil life time} \pm 4 \text{ days}. \quad (12)$$

3.2.2. One day G-CSF administration T_1 days after chemotherapy

Now, we study the effect of one day G-CSF administration T_1 days after chemotherapy. As in the examination of the neutrophil response alone, we change τ_{NM}^{gcsf} from 0 to 6 days and study the system response to G-CSF administration on different days T_1 after chemotherapy. In these simulations, we fixed the period of chemotherapy at 21 days which we found to be the resonant period in the presence of periodic chemotherapy alone. The results are shown in Fig. 6.

The results presented in Fig. 6a indicate that it is possible to completely overcome the neutropenia caused by chemotherapy if the G-CSF is given early ($1 \le T_1 \le 4$ days) after chemotherapy, irrespective of the value of τ_{NM}^{gcsf}. The optimal timing of G-CSF administration depends on τ_{NM}^{gcsf}. Moreover, our simulations show that administering G-CSF 8 days after chemotherapy can actually worsen the neutropenia. Even latter administration (18 days after chemotherapy) can also overcome the neutropenia, but the effect depends on the neutrophil life time τ_{NM}^{gcsf}, which may differ between patients. These results are in agreement with clinical observations (Butler et al., 1992; Koumakis et al., 1999; Meisenberg et al., 1992; Morstyn et al., 1989). Fig. 6b shows the numerically computed time course of the neutrophils when one day G-CSF is used either 4 or 14 days after chemotherapy (here $\tau_{NM}^{gcsf}=2$), respectively. The results show that G-CSF 4 days after chemotherapy is able to abolish neutropenia, but G-CSF 14 days after chemotherapy actually *worsens* the neutropenia (compare with Fig. 4)! These results indicate that the timing of G-CSF administration after chemotherapy is crucial for a positive outcome and indeed that improper timing of G-CSF may have deleterious effects.

4. Discussion

Using a relatively simple mathematical model for the HSC-neutrophil dynamics, we have investigated the effects of the periodicity of chemotherapy alone, and then the effects of G-CSF as an adjunct to chemotherapy with respect to the timing of G-CSF delivery.

If chemotherapy is given alone every T days, then for parameters typical for a hematologically normal human the model results display a clear and dramatic resonance at $T=23$ days for the neutrophil dynamics alone, and $T=21$ days for the full model. This numerical observation is easily understood from an analysis of the linear response function of either situation (see the Appendix and Figs. 2a and 4a), which predicts that the resonant period for the model is given by twice the average neutrophil lifetime (defined as the average time τ_N spent in marrow proliferation and maturation/differentiation following commitment from the HSC plus the average lifetime γ_N^{-1} in the circulation). Symbolically, $T \approx 2.0 \times (\tau_N + \gamma_N^{-1})$, and we have found that this relation holds in all situations we examined. The clear implication of this observation is that it is prudent to avoid protocols for chemotherapy administration that call for an approximate 21 day cycle, and indeed our numerical simulations indicate that deviating from this range of 21–23 days, *e.g.* to 18 days (see Figs. 2b and 4b), could be beneficial. If this simple relationship is found to hold then it offers a way to tailor chemotherapy for individuals. Namely using the techniques employed by Price et al. (1996), determine τ_N and γ_N for a specific patient, and then compute the resonant period T to be avoided in any delivery of myelosuppressive agents.

Protocols for the administration of many common chemotherapy agents (such as cisplatin, cydophosphamide, docetaxel, paclitaxel, *etc.*) call for a three week ($T=21$ days) cycle (Skeel and Roland, 2007). However, if the parameters used in this study are typical for hematologically normal individuals then the conclusions we have reached suggest that this is perhaps the worst choice that could be made since the modeling results indicate that it will be accompanied by severe neutropenia with the accompanying secondary effects (Rahman et al., 1997; Vainstein et al., 2005). Our simulations suggest that a simple change in the period T of chemotherapy to, for example, every 18 days, would effectively avoid these problems (see Fig. 4b).

If chemotherapy is given at a period T in conjunction with G-CSF T_1 days later then the results are interesting. We conducted numerical experiments for the neutrophil model alone and the full model assuming that chemotherapy was being delivered at the worst possible period (23 and 21 days, respectively). In both cases, the timing of G-CSF (*i.e.* the value of T_1) has a significant effect on the outcome. Namely, there are specific times T_1 in the chemotherapy cycle when G-CSF can have positive effects in terms of ameliorating or even eliminating severe neutropenia (see Figs. 3a and 6a specifically). However, there are also broad ranges of T_1 that will lead to a worsening by G-CSF of the neutropenia induced by the chemotherapy (see Figs. 3 and 6). These results are in general agreement with the initial results presented in Foley and Mackey (2009) but await confirmation until more realistic G-CSF kinetics are included in the modeling (Brooks et al., in preparation). Understanding these effects of G-CSF is difficult since G-CSF is known to affect the neutrophil maturation time in the bone marrow. Unfortunately, the detailed dependence of neutrophil maturation time on G-CSF is unknown (though it is known that the maturation time is a decreasing function of increasing G-CSF (Price et al., 1996)), and further

clinical investigations are needed to characterize this important facet of neutrophil regulation. Without this knowledge it seems that it will be difficult to design more intelligent protocols for the delivery of G-CSF following chemotherapy. Fortunately, newer techniques are now available to collect this type of data available in Price et al. (1996) and the experiment has recently been redone on healthy human volunteers using deuterium as a tracer (Prof. D. Dale, personal communication). The availability of this newer technique makes it feasible to undertake a more extensive determination of the dependence of the maturation time on G-CSF levels and make the model physiologically realistic.

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Appendix A. Transfer function and frequency response function

In control theory, the transfer function simply relates the output of a linear time-invariant system to a perturbing input. Here, we develop the transfer function for our model(s) to obtain insight into the resonance effects of chemotherapy.

A.1. Neutrophil dynamics: discrete delay

In the equation

$$dN/dt = -\gamma_N N + A_N(t)\kappa_N(N_{\tau_N})Q_* \tag{A.1}$$

for the neutrophil compartment alone, chemotherapy is a periodic perturbation with period T of the amplification factor so $A_N(t)$ can be expressed as $A_N(t) = A_N + \xi(t)$, where A_N is the normal amplification rate as given by (4), and $\xi(t)$ is the periodic perturbation.

Let $N(t)$ be the solution of (A.1) assuming the population of neutrophils is at a steady state (*i.e.* $N(t) = N_*$) when $t < 0$. Then when the deviation from the steady state $y(t) = N(t) - N_*$ is quite small and of order $\epsilon \ll 1$ it will satisfy the linear differential delay equation

$$dy/dt = -\gamma_N y - B y_{\tau_N} + \xi(t)\kappa_N(N_*)Q_*, \tag{A.2}$$

where $B = -A_N Q_* \kappa_N'(N_*)$.

The transfer function of (A.2) is the ratio between the Laplace transforms of $y(t)$ and the input $\xi(t)$ assuming zero initial conditions (Marshall, 1979). Let $\hat{f}(s)$ be the Laplace transform of $f(t)$, defined as

$$\hat{f}(s) = \int_0^\infty e^{-st} f(t)\, dt,$$

so we easily obtain the transfer function

$$H(s) = \hat{y}(s)/\hat{\xi}(s) = \kappa_N(N_*)Q_*/(s + \gamma_N + Be^{-s\tau_N}). \tag{A.3}$$

For a linear system at a stable steady state, the response to a periodic input at a frequency ω is expressed in terms of the gain $F(\omega)$ of the system and the phase shift $\phi(\omega)$. Both are related to the transfer function $H(s)$ through

$$F(\omega) = |H(i\omega)|, \quad \phi(\omega) = \arg H(i\omega). \tag{A.4}$$

Resonance occurs when ω is such that $F(\omega)$ has a maximum.

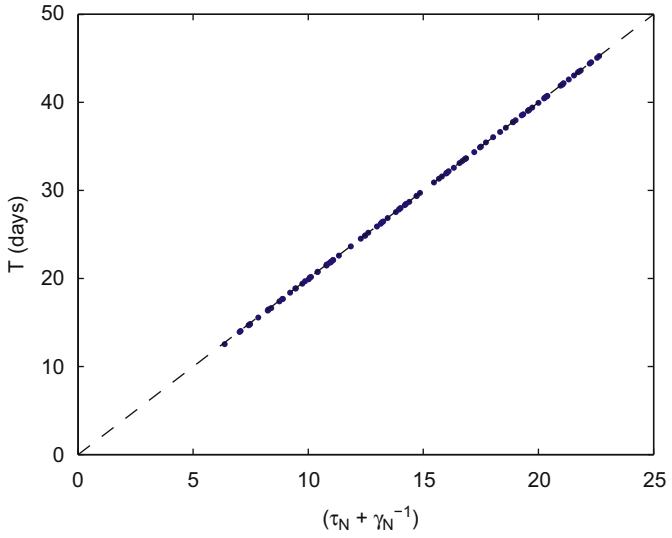

Fig. 7. Resonant period obtained from the frequency response function (A.4). Blue dots show the resonant period T as a function of the neutrophil life time $(\tau_N + \gamma_N^{-1})$, obtained from the maximization of the frequency response function, with parameters τ_N, γ_N and B taken randomly in the range from half to twice their default values $(\tau_N, \gamma_N, B) = (11, 2.4, 2.34)$. The dashed line is the graph of $T = 2(\tau_N + \gamma_N^{-1})$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 7 shows the resonant period obtained from (A.4) with randomly selected parameters, and illustrates the linear relationship with the neutrophil life time (to be detailed below).

A.2. Neutrophil dynamics: distributed delay

In a similar fashion it is easy to obtain the transfer function in the case where the delay is distributed with a density $g(\tau)$. Since $g(\tau)$ is a density, it is normalized by definition: $\int_0^\infty g(u)\, du = 1$. Then the transfer function is given by

$$H(s) = \kappa_N(N_*)Q_*/(s + \gamma_N + B\hat{g}(s)), \tag{A.5}$$

where $\hat{g}$ is the Laplace transform of the density function.

We have taken $g(\tau)$ to be the density of the gamma distribution shifted by a minimal delay τ_m since Hearn et al. (1998) have shown that it provides an excellent fit to a number of data sets. Thus we take

$$g(\tau) = \begin{cases} 0, & \tau \le \tau_m, \\ (a^{m+1}/\Gamma(m+1))(\tau - \tau_m)^m e^{-a(\tau-\tau_m)}, & \tau > \tau_m \end{cases} \tag{A.6}$$

with $a, m \ge 0$. With this choice it is easy to show that

$$F(\omega) = |H(i\omega)| = |\kappa_N(N_*)Q_*/(i\omega + \gamma_N + B(1 + i\omega/a)^{-(m+1)}e^{-i\omega\tau_m})|. \tag{A.7}$$

The parameters m, a, and τ_m in the density of the gamma distribution can be related to certain easily determined statistical quantities. The average of the *unshifted* density is given by

$$\tau_2 = \int_{\tau_m}^\infty \tau g(\tau)\, d\tau = (m+1)/a, \tag{A.8}$$

and thus the average total delay as calculated from (A.6) is given by

$$\langle \tau_N \rangle = \tau_m + \tau_2 = \tau_m + (m+1)/a. \tag{A.9}$$

The variance (denoted by σ^2) is given by

$$\sigma^2 = (m+1)/a^2. \tag{A.10}$$

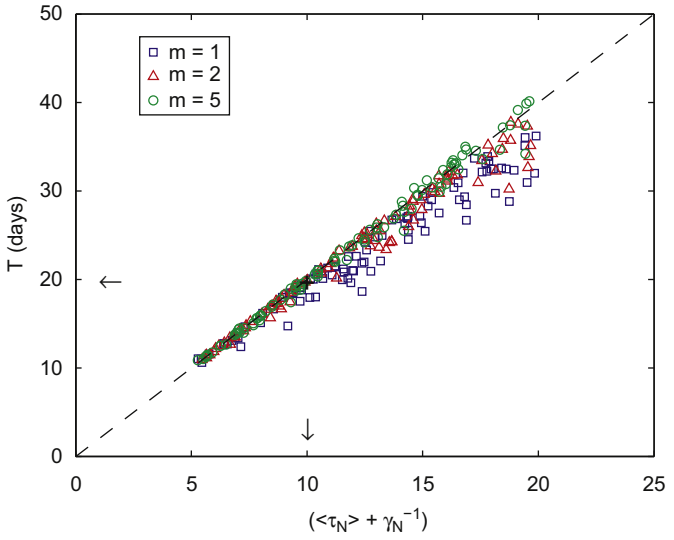

Fig. 8. Dependence of the resonant period on the neutrophil life time assuming the distribution of τ_N has a gamma density (A.6). The figure shows the resonant period obtained from the maximization of the frequency response function (A.7), with $\langle\tau_N\rangle$, τ_m, γ_N and B taken randomly in a range from half to twice their default values ($\langle\tau_N\rangle,\tau_m,\gamma_N,B$) = (11,3.8,2.4,2.34), and different m as indicated. The dashed line is the graph of $T=2(\langle\tau_N\rangle+\gamma_N^{-1})$. Arrows show the average neutrophil life time of 10.1(=9.7+1/2.4) days for a normal human (Hearn et al., 1998), and the corresponding resonant period of 20.2 days (also shown by the black cross).

Given the expressions in (A.8)–(A.10) in terms of the gamma distribution parameters m and a, we may easily solve for these parameters in terms of τ_2 and σ^2 to give

$$a=\tau_2/\sigma^2 \tag{A.11}$$

and

$$m+1=\tau_2^2/\sigma^2. \tag{A.12}$$

Fig. 8 shows the resonant period obtained from the frequency response function (A.7) with randomly selected parameters as a function of the neutrophil life time.

A.3. Neutrophil dynamics: resonant period

From the above development, the resonant frequencies ω are given by the frequencies that maximize the frequency response function $F(\omega)=|H(i\omega)|$. In the case of discrete delay, from (A.3), in order to obtain the dependence of the resonant period on system parameters, we only need to find the minimum value of

$$h(\omega)=\left|i\omega+\gamma_N+Be^{-i\omega\tau_N}\right|^2, \tag{A.13}$$

which is given by the solution of

$$h'(\omega)=\omega-B(\gamma_N\tau_N+1)\sin(\omega\tau_N)-B\omega\tau_N\cos(\omega\tau_N)=0. \tag{A.14}$$

If the parameters B, τ_N, γ_N satisfy

$$B\tau_N(\gamma_N\tau_N+1)>\pi/2, \tag{A.15}$$

it is easy to verify that

$$h^{(3)}(\omega)>0 \text{ when } 0<\omega<\pi/(2\tau_N)$$

and

$$h'(0)=0,\quad h'(\pi/(2\tau_N))<0,\quad h'(\pi/(\tau_N))>0.$$

Therefore, we have $h'(\omega)<0$ when $0<\omega<\pi/(2\tau_N)$, and there is at least one solution of the equation $h'(\omega)=0$ that satisfies $\pi/(2\tau_N)<\omega<\pi/\tau_N$. This solution is the minimum positive root that corresponds to the dominant resonant frequency.

Now we can solve (A.14) to obtain the dominant resonant frequency $\omega\in(\pi/(2\tau_N),\pi/\tau_N)$. To do this, we use the approximations

$$\sin(\omega\tau_N)\approx\pi-\omega\tau_N,\quad(\cos\omega\tau_N)\approx-1$$

and therefore (A.14) becomes

$$\omega-B(\gamma_N\tau_N+1)(\pi-\omega\tau_N)+B\omega\tau_N\approx0, \tag{A.16}$$

which yields

$$\omega\approx\pi B(\gamma_N\tau_N+1)/(1+B\tau_N(\gamma_N\tau_N+2)). \tag{A.17}$$

Now, the dominant resonant period is given approximately as

$$T=2\pi/\omega\approx2[\tau_N+(B\tau_N+1)/(B(\tau_N\gamma_N+1))]. \tag{A.18}$$

From the parameter values for hematologically normal individuals (Table 1), we have

$$B\tau_N\gg1,\quad\tau_N\gamma_N\gg1. \tag{A.19}$$

Therefore, (A.18) becomes

$$T\approx2(\tau_N+\gamma_N^{-1}) \tag{A.20}$$

under normal physiological conditions. We also note that the conditions (A.19) also yield (A.15), and $\omega\approx\pi$ according to (A.17). Thus, when (A.19) is satisfied, the first resonant period can be approximated by (A.20), which shows good agreement with the numerical results (Fig. 7).

In the case of a gamma distributed delay as discussed above, note that $a=\tau_2/(m+1)$. Thus, if we have approximately

$$(1+i\omega/a)^{-(m+1)}\approx e^{-i(\omega/a)(m+1)}=e^{-i\omega\tau_2},$$

then the above argument also holds and the approximation (A.20) is also valid, by simply replacing τ_N in (A.20) with $\tau_m+\tau_2$ (Fig. 8).

Appendix B. Full model: transfer function and frequency response

In a manner similar to the preceding arguments, we can calculate the transfer function of frequency response function of the full model (2). If

$$x=Q-Q_*,\quad y=N-N_*, \tag{B.1}$$

then considering periodic perturbations in the apoptosis rates due to chemotherapy, and linearizing (2) around the steady state, we obtain the following linear differential delay equations:

$$\begin{cases} dx/dt=a_1x+a_2y-a_3x_{\tau_S}+\xi_1(t),\\ dy/dt=-\gamma_Ny-By_{\tau_N}+b_3x_{\tau_N}+\xi_2(t),\end{cases} \tag{B.2}$$

where $\xi_1(t),\xi_2(t)$ are the periodic chemotherapy perturbation terms, and

$$a_1=-(\beta'(Q_*)Q_*+\beta(Q_*)+\kappa_N(N_*)+\kappa_\delta),$$

$$a_2=-Q_*\kappa_N'(N_*),$$

$$a_3=-2e^{-\gamma_S\tau_S}(\beta'(Q_*)Q_*+\beta(Q_*)),$$

$$b_3=A_N\kappa_N(N_*).$$

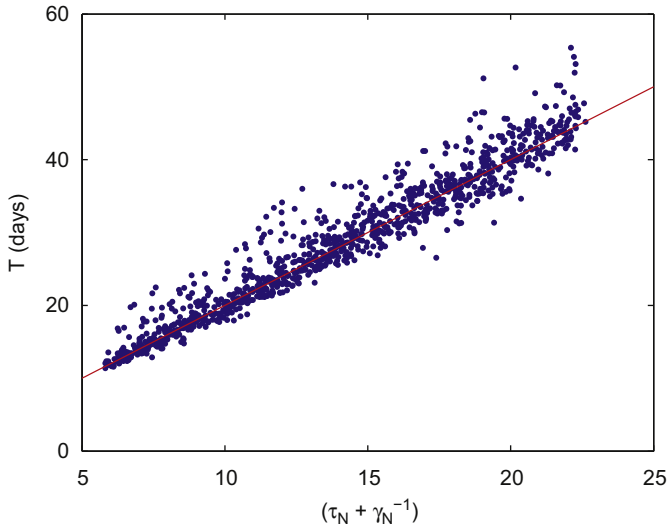

Fig. 9. Resonant period obtained from the frequency response function (B.5). Blue dots show resonant period T as a function of neutrophil life time $(\tau_N+\gamma_N^{-1})$. These were obtained by finding the local maximum of the response function $F(2\pi/T)$ defined by (B.5) with parameters $(a_1,a_2,a_3,\gamma_N,B,b_3,\tau_S,\tau_N)$ taken randomly over the range from half to twice of their default values $(a_1,a_2,a_3,\gamma_N,B,b_3,\tau_S,\tau_N)=(0.1,3.6\times10^{-5},0.2,2.4,2.34,1.416\times10^{3},2.8,11)$. The solid red line shows the fit with $T=2(\tau_N+\gamma_N^{-1})$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

For the parameters of Table 1, we have $(a_1,a_2,a_3,b_3)=(0.1,3.6\times10^{-5},0.22,1416.49)$.

Taking the Laplace transform of (B.2) with zero initial conditions, we obtain the system

$$\begin{bmatrix} s-a_1+a_3e^{-s\tau_S} & -a_2 \\ -b_3e^{-s\tau_N} & s+\gamma_N+Be^{-s\tau_N} \end{bmatrix}\begin{bmatrix}\hat{x}\\ \hat{y}\end{bmatrix}=\begin{bmatrix}\hat{\xi}_1\\ \hat{\xi}_2\end{bmatrix}. \tag{B.3}$$

The transfer function is given by

$$H(s)=\begin{vmatrix} s-a_1+a_3e^{-s\tau_S} & -a_2 \\ -b_3e^{-s\tau_N} & s+\gamma_N+Be^{-s\tau_N} \end{vmatrix}^{-1}$$
$$=[(s-a_1+a_3e^{-s\tau_S})(s+\gamma_N+Be^{-s\tau_N})+a_2b_3e^{-s\tau_N}]^{-1}. \tag{B.4}$$

The frequency response function is defined by

$$F(\omega)=|H(i\omega)|. \tag{B.5}$$

The resonant frequencies are obtained by maximizing the response function $F(\omega)$, and the resonant periods are given by $T=2\pi/\omega$ from the resonant frequencies.

Fig. 9 shows the resonant period of the full model obtained from the frequency function (B.5). The results are consistent with our previous conclusion that the resonant periods are approximately twice the neutrophil life time in spite of the appearance of many additional parameters.

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