Journal of Physical Mathematics
ISSN: 2090-0902

Ma and Lei, J Phys Math 2016, 7:1
DOI: 10.4172/2090-0902.1000154

Research Article Open Access

Parametric Resonance Applications in Neutrophil Dynamics

Suqi Ma[1] and Jinzhi Lei[2]*

[1]Department of Mathematics, Chinese Agricultural University, Beijing 100083, China
[2]Zhou Pei-Yuan Center for Applied Mathematics, Tsinghua University, Beijing 100083, China

Abstract

The profound effects of chemotherapy on the combined dynamics of the hematological stem cells and their differentiated neutrophils is examined. G-CSF is often used to deal with this neutropenia and the response is highly variable. To shape the neutrophil response to chemotherapy and G-CSF, periodic parametric resonance is discussed. Periodic oscillation in neutrophil levels and the subharmonic 1:2 resonance phenomena are observed with the assumption of periodic chemotherapy is given. The work is aim to stimulate further investigations and the practical applications.

Keywords: Parametric resonance; Neutrophils; Hematological stem cells

Introduction

In the treatment of malignant tumors, chemotherapy is frequently accompanied by hematopoietic side effects due to the myelosuppressive character of drugs used. A common neutropenia(accompanied by fever and possible infection), to a lesser extent, thrombocytopenia and anemia are frequently observed. To circumvent these side effects, an effective administration of granulocyte colony stimulating factor (G-CSF) is suggested in clinic practice [1-7], and now a standard post-chemotherapy treatment for neutropenia. Mathematically, people try to understand G-CSF control by a variety of models [3,8-12].

A significant G-CSF support in clinic perspective is periodically repeated treatment of chemotherapy, and neutrophil is highly responsive and dependent on timing and protocol of the drug's administration [13,14]. Experiment have reported that chemotherapy increases apoptosis in both proliferative HSCs (hematopoietic stem cells) and proliferative neutrophil precursors [15]. To idealize the effects of chemotherapy and G-CSF, a square wave temporal functions for the loss rates,neutrophil precursor proliferative rate are used, explained in reference [16]. The resonance between the perturbation due to the periodic chemotherapy and the intrinsic characteristic frequency in the neutrophil production have been discussed. The periodic damped oscillation in neutrophil levels [17] are also reported with the assumption of single dose of chemotherapy, which is simulated by exponential mathematically.

In this paper, we explain the hematopoietic dynamics with the pharmacokinetics of chemotherapy and G-CSF by periodic parametric excitation. The dependence of the neutrophil response on the stimulation frequency is examined and resonance phenomena is discussed.

The Model Equations

The combined dynamics of hematopoietic stem cells and neutrophil production is illustrated in Figure 1 and generally described by the following equations

$$\frac{dQ}{dt} = -(\beta(Q) + k_N(N) + k_\delta)Q + A_Q(t)\beta(Qt - \tau_s)Qt - \tau_s$$
$$\frac{dN}{dt} = -\gamma_N N + A_N(t)k_N(Nt - \tau_N)Qt - \tau_N \quad (1)$$

where Holling function

$$k_N(N) = fracf_0\theta_1\theta_1 + N, \qquad \beta(Q) = frack_0\theta_2^2\theta_2^2 + Q^2$$

and rates

$$A_Q(t) = 2exp\left[-\int_0^{\tau_s} r_s(t - \tau_s + s)ds\right],$$
$$A_N(t) = exp\left[\int_0^{\tau_{NP}} \eta_{NP}(t - \tau_N + s)ds - \int_{\tau_{NP}}^{\tau_N} \gamma_0(t - \tau_N + s)ds\right] \quad (2)$$

The neutrophil system (1) consists of DDEs(delay differential

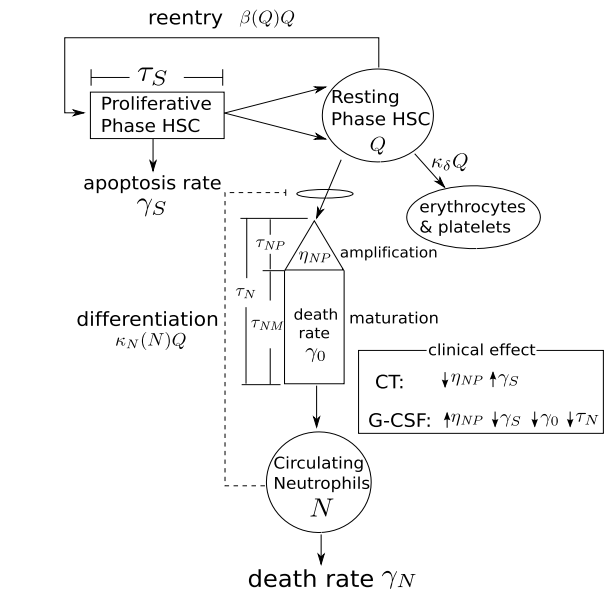

Figure 1: A cartoon representation of system.

***Corresponding author:** Jinzhi Lei, Zhou Pei-Yuan Center for Applied Mathematics, Tsinghua University, China, Tel: 86 10 6279 3001; E-mail: cau-masuqi@163.com

Received December 08, 2015; **Accepted** January 19, 2016; **Published** January 25, 2016

Citation: Ma S, Lei J (2016) Parametric Resonance Applications in Neutrophil Dynamics. J Phys Math 7: 154. doi:10.4172/2090-0902.1000154

equations) with two delays. These two equations takes into account the balance between the net production and loss terms of HSCs and circulating neutrophils, where Q and

N (both with unit cells/kg)are respectively hematopoietic stem cells and neutrophils. HSCs differentiate into the committed neutrophil compartment with term $k_N(N)Q$. Delay τ_s denotes their duration days of proliferative phase of HSCs. HSCs either remain in the resting phase or enter into the proliferative phase at a rate $\beta(Q)$. The differentiation of HSCs to neutrophil is controlled by $k_N(N)$ (the differentiated rate of circulating neutrophils), and HSCs proliferation is controlled by the resting HSCs population with proliferation rate $\beta(Q)$. r_s represents the apoptosis rate during the proliferation phase of HSCs. The circulating neutrophils survive with their averaged lifespan γ_N^{-1} and thus with the ature death $\gamma_N N$. Cells in the neutrophil lines experience a successive division with time period τ_{NP} and then enter into a purely maturation compartment with time period τ_{NM}, and the total time period $\tau_N = \tau_{NP} + \tau_{NM}$. η_{NP} denotes the proliferative rate of neutrophils and γ_o denotes their death rate before neutrophils enter into the circulation. The parameter values in System (1).

Suppose chemotherapy is administrated periodically. Neutropenia is a common side-effect, and G-SCF is also administrated after chemotherapy. Both the effects of chemotherapy and G-SCF are maintained for several days. Chemotherapy increases apoptosis in both proliferative HSCs and proliferative neutrophil precursors. The perturbation of parameter values are supposed to be

$$\begin{aligned} r_s(t) &= min\{r_s^{min}, r_s + \delta_1 \cos(\omega_1 t)\}, \\ \eta_{NP}(t) &= max\{\eta_{NP}^{max}, \eta_{NP} + \delta_2 \cos(\omega_2 t)\}, \\ \gamma_0(t) &= min\{\gamma_0^{min}, \gamma_0 + \delta_3 \cos(\omega_3 t)\} \end{aligned} \tag{3}$$

Normally, the rates r_s, η_{NP} and γ_o are constants, and therefore

$$A_Q = 2e^{-r_s \tau_s} \quad and \quad A_N = e^{\eta_{NP}\tau_{NP} - \gamma_0 \tau_{NM}} \tag{4}$$

Resonance

The response of neutrophil to chemotherapy, and the effect of G-CSF adminstration always can be strong as varying excitation frequency near natural frequency. Under the excited vibration of parameters r_s, η_{NP} and γ_o, resonance oscillation can be initiated in the interval of the excitation frequency due to the nonlinearity. It is well known, system can be unstable due to the action of parametric excitation. In certain intervals of frequency Ω lying,system(1) may have phase lock solutions. Set $\omega_1 = \omega_2 = \omega_3 = \Omega$, and then let $\Omega = \frac{p}{q}\omega$, in general, there exist intervals of excitation frequency Ω with bigger width to induce 1:1 primary resonance or 1:2 subharmonic resonance phenomena. The combination parametric resonance can be triggered which induce the periodic solutions with large amplitude. To perform bifurcation analysis, we choose Ω as bifurcation parameter, then define $\mu := (\Omega, \tau_s)$, and set $\varphi_\mu(Q,N;t)$ to be solution flow of system (1) with initial values $Q(t-\tau) = Q^*, N(t-\tau) = N^*$ for $\tau \le t \le 0$, where $\tau = max(\tau_s, \tau_N)$. Since $\Omega : \omega_{=1:1}$, every point on its orbit is a period point. Define the amplitude $\| N\|$ to describe the difference between the maximal period point and the minimal period point. We varied Ω widely and, for each value, solved DDEs (1) for $t_{=1200}$ days using initial values $Q = Q^*, N = N^*$ for $t - \tau_N \le t \le 0$ due to delays $\tau_s < \tau_N$ satisfied. The long term effect of chemotherapy and G-CSF for each simulation the last 400 days are used to obtain the amplitude in neutrophil fluctuations. $\| N\|$ continue to a bigger value to form the resonance in a widely varying scope of excitation frequency. The 1:1 resonance regime in parameter space (Ω, τ_s)plane is formed in a shaded regime as shown in Figure 2a. In special, choose $\tau_s = 3.2$, the response of neutrophil numbers near 1 (the ratio of Ω/ω) are denoted by its amplitude exhibits large values continuously. The amplitude response corresponding to the ratio of Ω/ω is drawn in Figure 2b.

Vary excitation frequency Ω near ω/2 with ω being natural frequency, the 1:2 subharmonic resonance regime in parameter space (,τ) plane is also formed by shaded regime in Figure 3a. In special, choose $\tau_s = 3.2$, the response of neutrophil numbers near 0.5 (the ratio of Ω/ω) are drawn which exhibits 1:2 subharmonic resonance phenomena as shown in Figure 3b. The amplitude response exhibits large values continuously.

Conclusion

In a physiologically realistic point view, a two compartment model combined the dynamics of hematopoietic stem cells and the differentiated neutrophils with its response dependence on the period chemotherapy and G-CSF adminstration are given. The combined parametric excitation resonance phenomena are discussed. When the ratio between excitation frequency and eigenfrequency are rational, both 1:1 primary resonance and 1:2 subharmonic resonance are tracked which respectively form a resonance regime on plane of parameters.

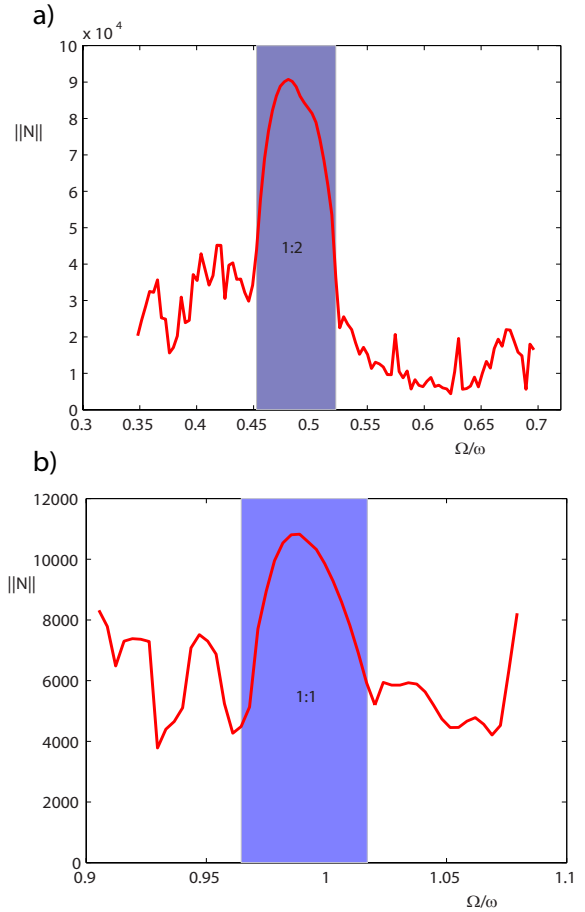

Figure 2: Primary resonance phenomena in system (a) Resonance regime of 1:1 primary resonance formed in parameter space. The shaded regime is the called 1:1 resonance regime. (b)The amplitude response of neutrophils versus varying ratio Ω/ω.

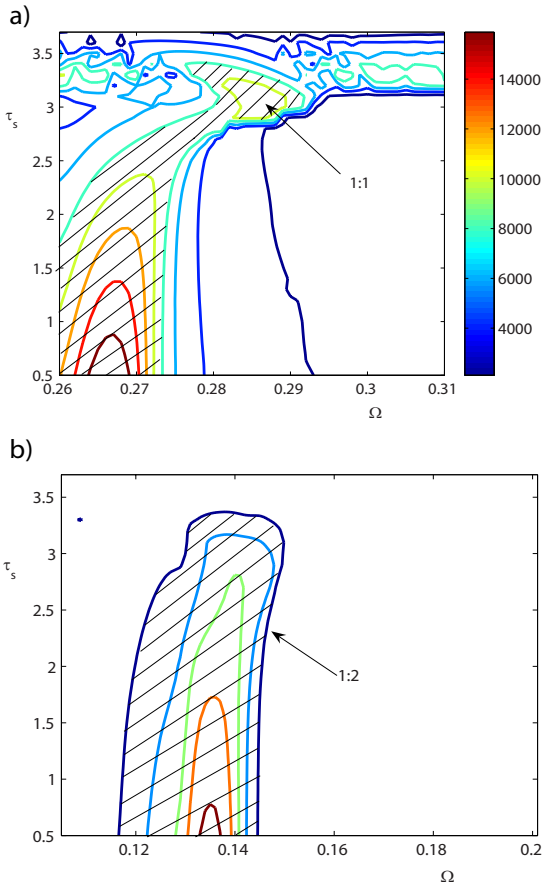

Figure 3: Ubharmonic resonance phenomena in system (a) resonance regime of 1:2 subharmonic resonance formed in (Ω,τ) parameter space. The shaded regime is the called 1:2 resonance regime. (b)The amplitude response of neutrophils versus varying ratio Ω/ω.

References

1. Crawford J, Dale DC, Lyman GH (2003) Chemotherapy induced neutropenia: Risks, consequences, and new directions for its management. Cancer 100: 228-237.
2. Foley C, Mackey MC (2009) Mathematical model for G-CSF administration after chemotherapy. J Theor Biol 257: 27-44.
3. Bennett CL, Weeks JA (1999) Use of hematopoietic colony-stimulating factors: Comparison of the 1994 and 1997 American Society of Clinical Oncology surveys regarding ASCO clinical practice guidelines, Health Services Research Committee of the American Society of clinical Oncology. J Clin Oncol 17: 3676-3681.
4. Clark OA, Lyman GH, Castro AA, Clark LG, Djulbegovic B (2005) Colony-stimulating factors for chemotherapy-induced febrile neutropenia: A meta-analysis of randomized controlled trials. J Clin Oncol 23: 4198-4214.
5. Fukuda M, Nakato M, Kinoshita A (1993) Optimal timing of G-CSF adminstration in patients receiving chemotherapy for non-small cell lung cancers.Am Soc Clin Oncol 12: 1549.
6. Holmes FA, O'Shaughnessy JA (2002) Blinded, randomized,multicenter study to evaluate single adminstration Peg-filgrastim once per cycle versus daily Filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 20: 727-731.
7. Koumakis G, Vassilomanolakis M (1999) Optimal Timing(Preemptive versus Supportive) of Granulocyte colony-stimulating factor administration following High-Dose Cyclophosphanide. Oncology 56: 28-35.
8. Engel C, Scholz M, Loeffler MA (2004) Computational model of human granulopoiesis to stimulate the hematotoxic effects of multicycle polychemotherapy. Bloo d104: 2323-2331.
9. Friberg LE, Henningsson A, MassH, Nguyen L, Karlsson MO (2002) Model of chemotherapy-induced myleosuppression with parameter consistency across drugs. J Clin Oncol 20: 4713-4721.
10. Scholz M, Engel C, Loeffler M (2005) Modelling human granulopoiesis under poly-chemotherapy with G-CSF support. J Math Biol 50: 397-439.
11. Schochat E, Rom-KedarV, Segel LA (2007) G-CSF control of neutrophil dynamics in the blood. Bull Math Biol 69: 2299-2338.
12. Vainstein V (2005) The complex effect of granulocyte colony-stimulating factor on human granulopoiesis analyzed by a new physiologically-based mathematical model. J Theor Biol 234: 311-327.
13. Bogges D, Boggs S, Saxe D, Gress L, Canfield D (1982) Hematopoietic stem cells with high potential assay of their concentration in marrow by the frequency and duration of cure of W/Wv mice. J Clin Invest 70: 242-253.
14. Leavey PJ (1998) In vivo treatment with granulocyte colony-stimulating factor results in divergent effects on neutrophil functions measured in vitro Blood 92: 4366-4374.
15. Fogli S, Danesi R (2001) Drug distribution and pharmacokinetic/pharmacodynamic relationship of practaxel and gemciabine in patients with non-small-cell lung cancer. Ann Oncol 12: 1553-1559.
16. Changjing Zh, Jinzhi L, Mackey MC (2012) Neutrophil dynamics in response to chemotherapy and G-CSF. J Theor Biol 293:111-120.
17. Grace B, Gabriel PL, Jinzhi L, Mackey MC (2012) Neutrophil dymamics after chemotherapy and G-CSF: The role of pharmacokinetics in shaping the response. J Theor Biol 315: 97-109.