ELSEVIER

EXPERIMENTAL HEMATOLOGY

Experimental Hematology 27 (1999) 1139–1148

Hematopoietic dynamics in grey collies

Caroline Haurie[a], Richard Person[c], David C. Dale[c], and Michael C. Mackey[a,b]

[a]*Department of Physiology and* [b]*Departments of Physics & Mathematics, Centre for Nonlinear Dynamics, McGill University, Montreal, Canada;* [c]*Division of Hematology, Department of Medicine, University of Washington, Seattle, WA*

(Received 4 December 1998; revised 18 February 1999; accepted 25 February 1999)

Using Lomb periodogram analysis we have quantified variations in the peripheral neutrophil and platelet counts of the cyclical neutropenia animal model–the grey collie. We found that the amplitudes of the oscillations in these two cell lineages vary concomitantly. Further, the power spectrum and the shape of the oscillations in the absolute neutrophil counts vary together with the amplitude of the oscillations. As the amplitude of the oscillations increases, the height of the second subharmonic increases, giving rise to a distorted oscillation with two peaks per cycle. The particular dynamics of the absolute neutrophil counts can be reproduced by a combination of a delayed peripheral feedback, representing the peripheral control of granulopoiesis through granulocyte colony stimulating factor, together with a sinusoidal input representing an oscillatory input from the pluripotential stem cells to the granulocytic lineage. The same pluripotential stem cell input is probably responsible for the sinusoidal oscillations observed in the other cell lineages.

Keywords: **Oscillation—Cyclic—G-CSF—Neutropenia—Periodic**

Introduction

Normally, the regulation of hematopoiesis maintains functional levels of white blood cells (WBC), red blood cells (RBC), and platelets in the blood. Though these cells play separate and independent functions, it has been shown that they all arise ultimately from a common primitive pluripotential stem cell (PPSC) population. Most disorders of hematopoiesis regulation lead to chronic failures of the production of either all the blood cell types or only one cell type. Models of these disorders are based on the existence of either lineage specific regulators [e.g., erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF), thrombopoietin (TPO)] or multilineage regulators such as stem cell factor (SCF).

Offprint requests to: Michael C. Mackey, Ph.D., Departments of Physiology, Physics, & Mathematics, Centre for Nonlinear Dynamics, McGill University, 3655 Drummond Street, Room 1124, Montreal, Quebec, CANADA H3G 1Y6; E-mail: mackey@cnd.mcgill.ca

Cyclical neutropenia (CN) is a peculiar disorder that does not correspond to either of these categories. It is characterized, in humans and in grey collies (GCs), by recurring episodes of neutropenia occurring at regular intervals. It is, thus, a dynamical disorder [1] rather than a chronic defect. Moreover, other cell types (platelets, reticulocytes, monocytes, and more rarely, lymphocytes and eosinophils) often oscillate with the same period as the neutrophils [2]. The monocyte, eosinophil, platelet, and reticulocyte oscillations are generally from normal to high levels; in contrast to the neutrophils that oscillate from near normal to extremely low levels. Thus, this disorder affects several cell lineages in different ways.

Transplantation studies suggest that the origin of the defect in CN is resident in one of the stem cell populations of the bone marrow [3–8]. Studies of bone marrow cellularity throughout a complete cycle in humans with CN show that there is an orderly cell density wave that extends back into the CFU-G [9], the CFU-E [10–13] as well as in the BFU-E and CFU-GM [12,14]. Studies in the grey collie [15,16] and in humans [17,18] show that the responsiveness of granulocyte committed progenitor cells to G-CSF is greatly attenuated in CN compared to normal. In CN, the levels of colony stimulating activity (CSA, related to G-CSF) fluctuate inversely with the circulating neutrophil levels [19–21]. It is unclear if this is related to the cause of CN or is a consequence of the neutrophil oscillations.

The complex aspects of CN have led to conflicting hypotheses about its origin and have generated a variety of mathematical modeling studies. One group of models hypothesizes a destabilization of the peripheral control of granulopoiesis mediated by granulocyte colony stimulating factor (G-CSF) to be the origin of the periodic episodes of neutropenia [22–36]. There is evidence that G-CSF mediates a negative feedback loop controlling granulopoiesis [37]. However, a recent modeling study indicates that this peripheral control is probably stable in CN and, thus, cannot account for the occurrence of oscillations [38]. A second group of models proposes that there is a destabilization of a pluripotential stem cell population because oscillations occur in all the blood cell lineages. Mackey [39,40] proposed that there could be a loss of stability in the stem cell popula-

0301-472X/99 $–see front matter.
PII S0301-472X(99)00051-X

tion independent of feedback from peripheral circulating cell types. The existence of cell-to-cell interactions mediated by cytokines that control the growth of hematopoietic stem cells (HSC) in vitro, such as interlukin-3 (IL-3) and stem cell factor (SCF), supports the hypothesis of an autoregulation of hemopoietic stem cells [41–53]. In Morley et al. [54], a combination of several feedback control loops acting on different compartments of hematopoiesis was considered.

To better understand the relationship between the regulation of the different blood cell lineages in CN, we analyzed serial blood counts from nine GCs. We used power spectral

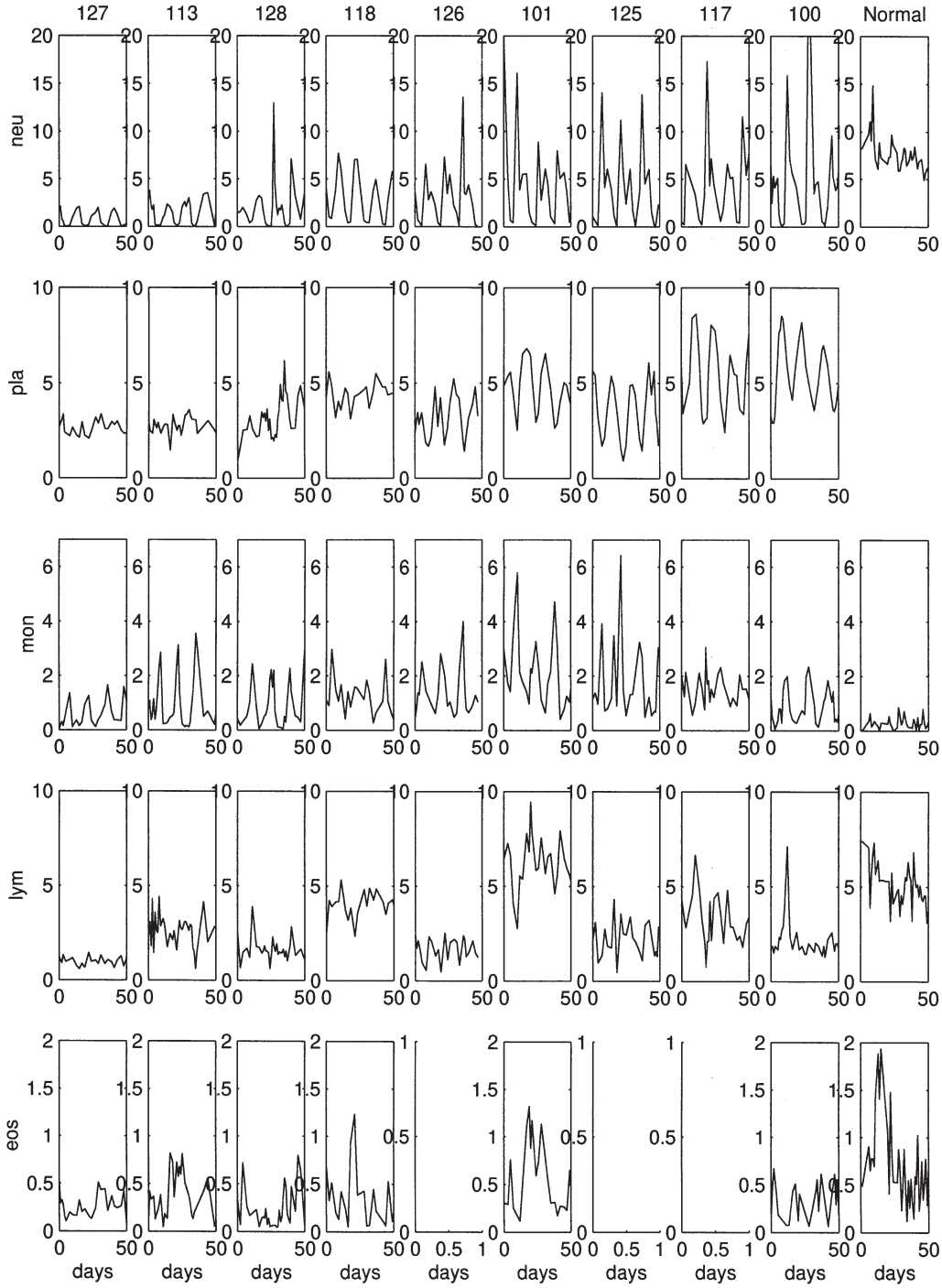

Figure 1. Differential blood counts in nine grey collies and one normal dog. Units: Cells $\times 10^{-5}$ per mm^3 for the platelets and Cells $\times 10^{-3}$ per mm^3 for the other cell types. Neu = neutrophils, Pla = platelets, Mon = monocytes, Lym = lymphocytes, Eos = eosinophils.

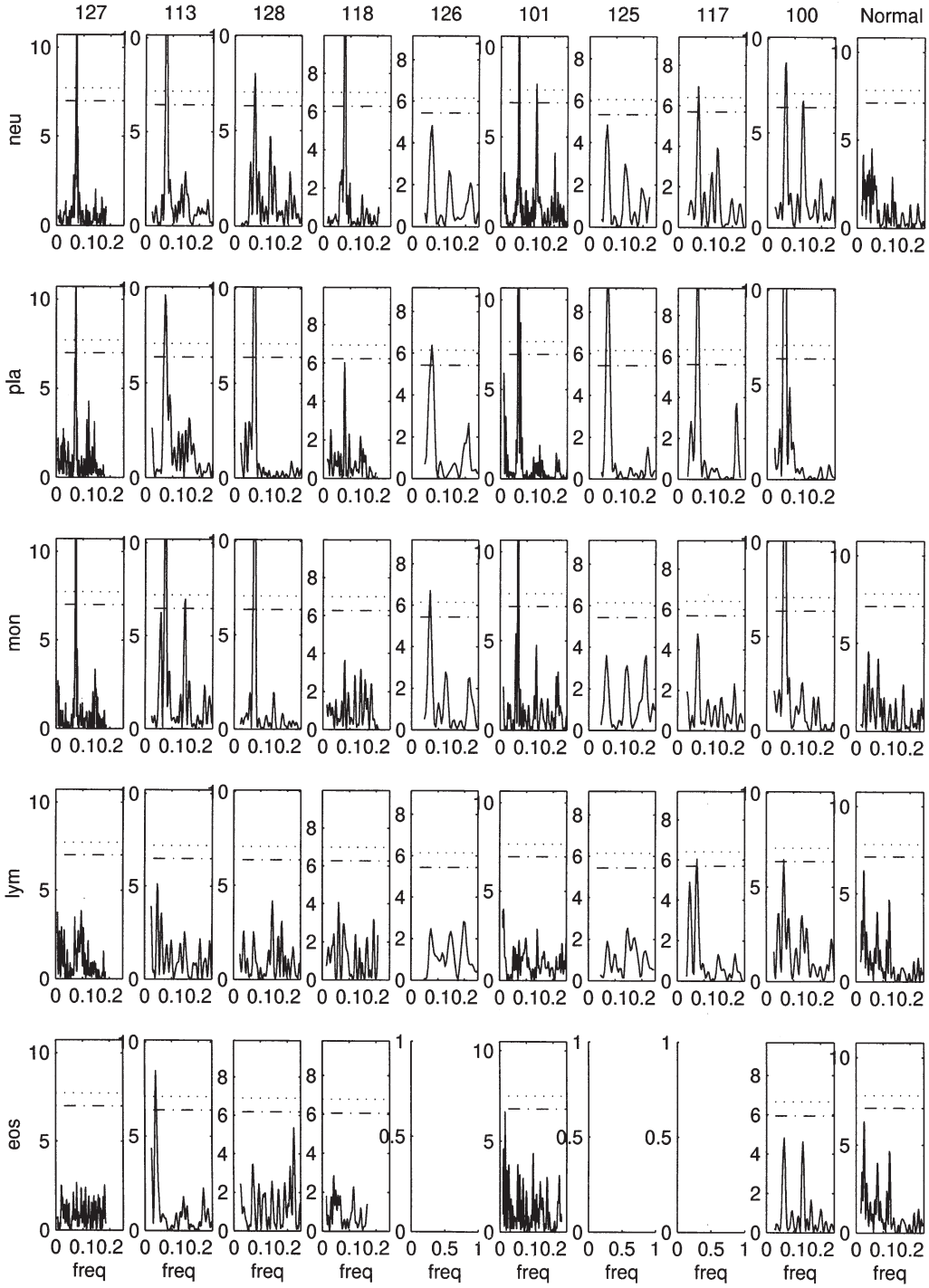

Figure 2. Lomb periodogram of the differential blood counts in nine grey collies.

analysis to detect and quantify the periodic components of the serial counts. We show that the dynamics of the serial blood counts in GCs can be understood by a model including an oscillatory output from the PPSC common to all the cell lineages and a peripheral feedback specific to the neutrophils.

Data collection and methods

The GC dogs were housed in individual cages and temperature-controlled quarters for these studies. Normal mongrel dogs served as the controls. Blood specimens were routinely drawn from the cephalic vein of unanesthetized dogs between 8:30 and 9:30 AM. White blood cell and platelet counts were performed on EDTA amticoagulated blood specimens with a Coulter Counter (Coulter

Electronics, Hialeah, FL). One-hundred cell differential counts were performed on air dried, Wright stain smears. Purified rhG-CSF and rcG-CSF provided by AMGen Inc (Thousand Oaks, CA) were administered subcutaneously once daily.

We used the Lomb periodogram to detect periodicity in the blood counts [55], as has been described previously in [56]. The Lomb periodogram is equivalent to Fourier power spectral analysis, but is tailored for unevenly sampled data sets [55,57]. In the case of discrete time series, the periodogram is calculated for a discrete number of frequencies. The statistical significance (p value) of any peak in the periodogram can be calculated [57]. For each frequency, the value taken by the periodogram is inversely correlated with the distance between the data set and a sinusoidal wave with frequency f. The presence of a significant peak at one of the frequencies f implies that the data set is periodic with a period $T = 1/f$.

We implemented an adaptation of the procedure proposed by Weiden et al. [58] using Matlab. Copies of this program are available from the authors for the analysis of analogous data for non-commercial purposes. Integrations of the model were done by the Euler method using XPP.

Analysis of serial blood counts in grey collies

Pattern of oscillations in different cell types

Figures 1 and 2 show the differential blood counts and the Lomb periodogram of the differential blood counts for nine GCs and one normal dog. Periodogram analysis shows periodicity of the absolute neutrophil count (ANC) and the platelet counts in all the GCs, and of the monocyte counts in eight of the nine GCs, with frequencies (f) between 0.065 ($T = 12.5$ days) and 0.080 ($T = 14.5$ days). We detected significant periodic oscillation of the lymphocyte and/or eosinophil counts in only two dogs (GC 117 and 100). There was no significant periodicity in the serial blood count of the three normal dogs analyzed (data shown for one normal dog only).

The periodogram analysis shows the presence of harmonics in the ANC of GC 128 to 100, represented by peaks at twice the main frequency (f), and sometimes at three times the main frequency (GC 128, 126, 125, and 100). The presence of these harmonic components implies that the pattern of the oscillations can be represented by a sum of sinusoidal waves with frequencies f, $2f$, $3f$, etc. Figure 3 shows the periodogram of GC 101 and the fitting of the serial ANC using the primary frequency and the second and third harmonics. We estimated the amplitude of the first (α_1), second (α_2), and third (α_3) harmonic components of the ANC by fitting the serial counts to the sum of three sine waves with frequencies f, $2f$, and $3f$, respectively.

Peaks at the harmonic frequencies occur in some GCs in the other granulocytic lineages (e.g., monocytes and eosinophils) but never in the periodogram of the platelet counts. The platelet oscillations can thus be fit by a single sinusoidal.

Variability of the dynamics in different grey collies

The presence of harmonics in the periodogram is not related to the period of the oscillations. We estimated the amplitude of the first (a_1) and second (a_2) harmonic components of the

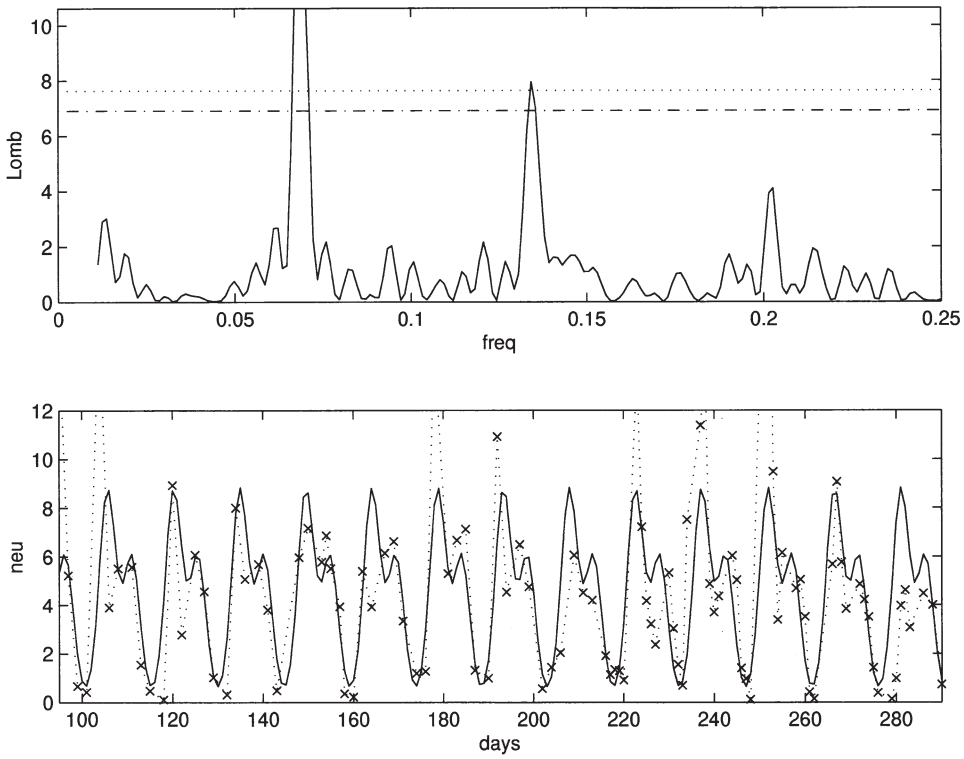

Figure 3. Lomb periodogram and fit of the ANC of GC 101. The function used to fit the data is $X(t) = 4.6 + 3\sin(2\pi f t - 0.6) + 1.8\sin(4\pi f t - 0.6) + 0.6\sin(6\pi f t - 3.2)$, with $f = 0.07(\mathrm{d}-1)$.

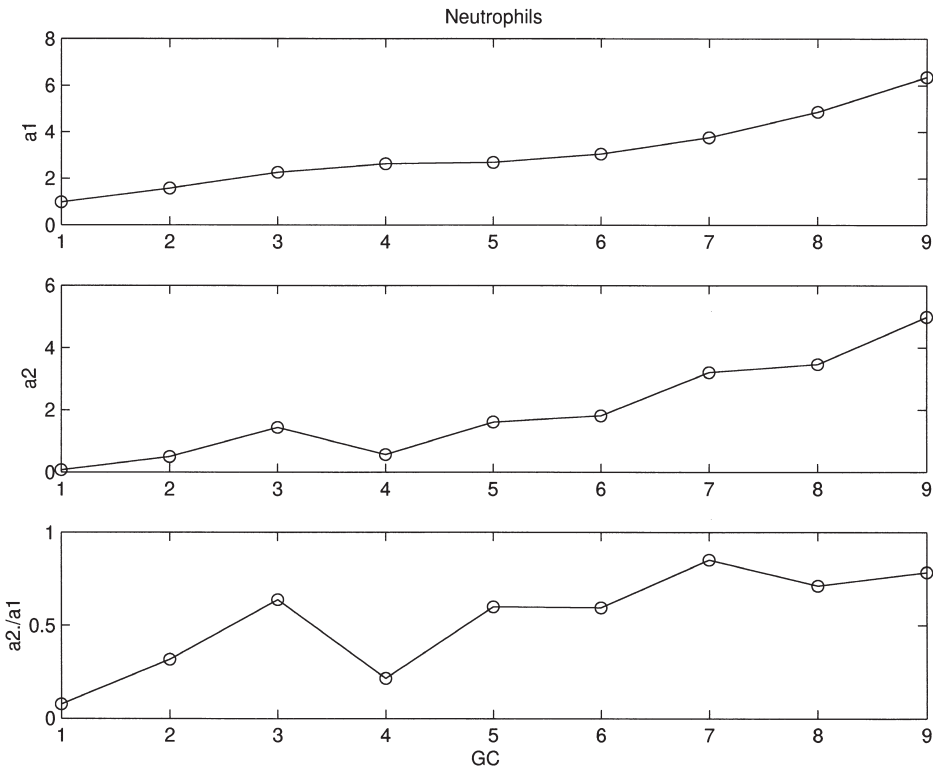

Figure 4. Variations of the amplitude of the first harmonic (α_1) and the second harmonic (α_2) in the absolute neutrophil counts (ANC) of the nine grey collies.

oscillations in the ANC in each dog by fitting the serial counts to the sum of two sine waves with frequencies *f* and 2*f*; a_1 and a_2 both increase with the mean ANC, as does the ratio a_2/a_1 (Fig. 4). Thus, there is a transformation of the oscillations in the ANC from a single sinusoid to a more complex oscillation, which is correlated with the mean level of ANC and the amplitude of the oscillations (a_1). Such correlation was not found for the other granulocytic cell lineages. The amplitude of the oscillations in the the neutrophils and the platelets are also positively correlated ($p \leq 0.10$). The changes in the amplitude of the oscillations is, thus, not specific to the dynamics of the neutrophils, but is common to both cell lineages.

Variations in the amplitude of the oscillations not only occur in different GCs but can also occur in a single dog. Figure 5 shows the ANC and the platelet counts of GC 128 during a period where the dog was not receiving any treatment. A transition occurs at the third cycle in the ANC, from a low to high amplitude oscillation with the characteristic second bump. This transition is accompanied by an increase in the amplitude of the oscillations in the platelet counts. Individual GCs can thus express consecutively different dynamics of cyclic hematopoiesis during different temporal epochs.

Effect of G-CSF

As observed previously [59], G-CSF either abolished the cycling or decreased the period of the oscillations in all the cell lineages. In the latter case, the mean and amplitude of the oscillations was increased in the ANC and more mildly in the monocytes, whereas the mean and amplitude of the oscillations in the platelets was unchanged. In the dogs where the ANC showed subharmonics (second bump), the latter disappeared during G-CSF administration (see Fig. 6). In one dog, which was administered G-CSF for an extended period, we observed an abolition of the oscillations in all the cell lineages more than 200 days after the treatment was started (see Fig. 6). Thus, the dynamics of the serial blood counts during G-CSF administration is variable.

Model explanation of the neutrophil dynamics in grey collies

Given the occurrence of oscillations with the same period in all cell types in GCs, we assumed that the output from the PPSC is oscillating in GCs and that the oscillations propagate equally to all the blood cell lineages (see Fig. 7). Because the oscillations in the platelet counts could be fit with a sinusoid, we assumed that the output from the PPSC was sinusoidal. The input from the PPSC to the granulocytic compartment is modulated by a peripheral feedback controlling the proliferation of the granulocyte precursors [37,38]. This feedback is mediated by G-CSF, which enhances the amplification of the granulocytic progenitors and is inversely correlated with the levels of mature cells in the blood [60]. The amplification in the granulocytic compartment is, thus, a decreasing function of the number of mature neutrophils. Because of the time taken for granulocytic pre-

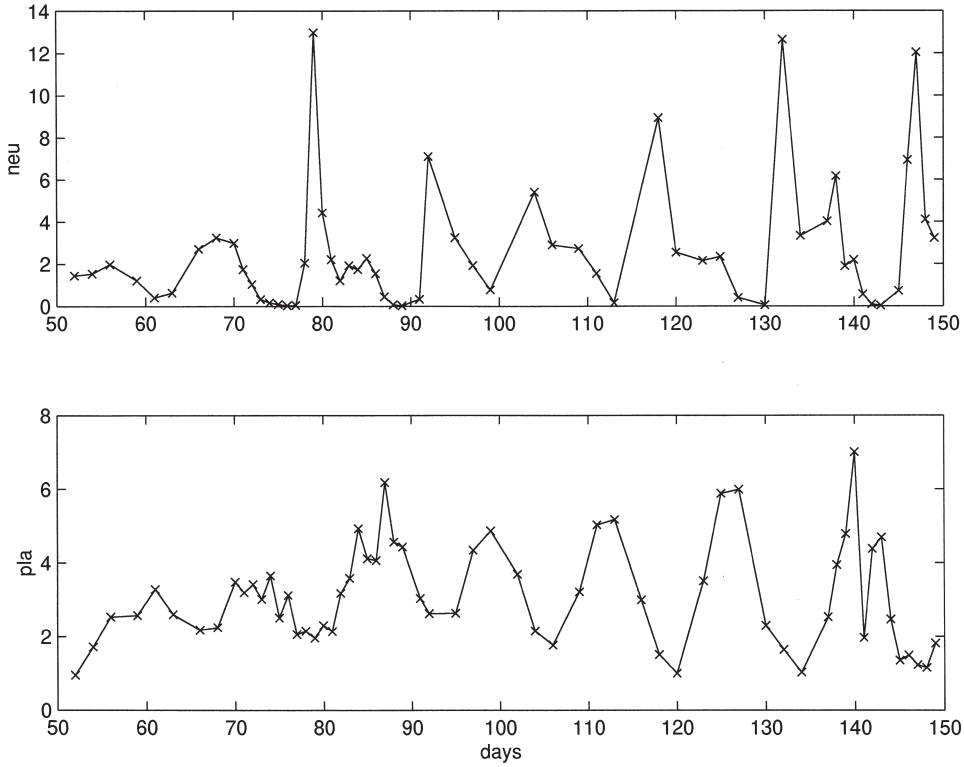

Figure 5. Neutrophil ($\times 10^{-3}$ per mm^3) and platelet counts ($\times 10^{-5}$ per mm^3) of GC 128. The data can be separated into two parts which have different dynamics.

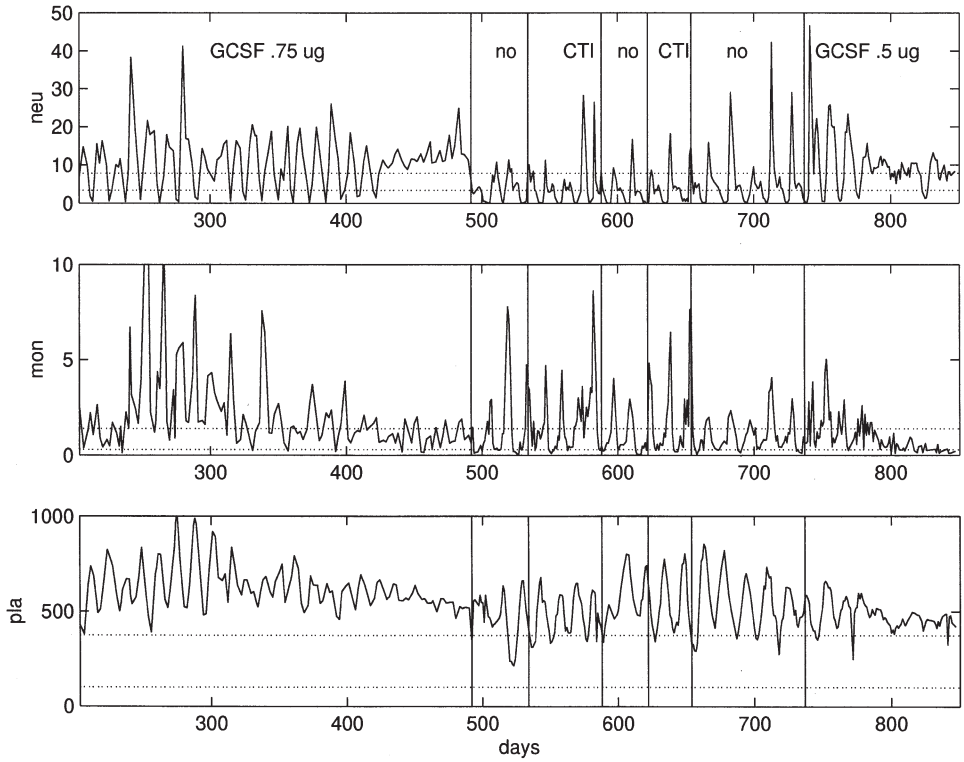

Figure 6. Serial blood counts of GC 100, during treatment with G-CSF, CTI (CT-1501, provided by Cell Therapeutic Inc.) or no treatment. Dotted lines show normal ranges. Units: Cells $\times 10^{-5}$ per mm^3 for the platelets and Cells $\times 10^{-3}$ per mm^3 for the other cell types. Neu = neutrophils, Mon = monocytes, Pla = platelets.

cursors to mature in the bone marrow, the effect of G-CSF on the peripheral density of neutrophils is delayed. The output from the granulocytic compartment into the blood is, therefore, a function of the sinusoidal input from the PPSC modified by a delayed negative feedback controlled by G-CSF. The delay represents the granulocytic maturation time, which ranges between 2.7 and 3.3 days [38].

There are also peripheral feedback loops controlling the amplification of the progenitors committed to the other cell lineages (for example, mediated by EPO in the reticulocytes and TPO in the megakaryocytes). However, because the cell density in these compartments oscillates within normal ranges, it is likely that the levels of regulators do not vary significantly (Fig. 8).

Results

The result of combining a sinusoidal input with the peripheral feedback control of granulopoiesis is shown in Fig. 9. We used an exponential decreasing feedback with a delay of 3 days within the context of the model of WBC peripheral control presented in [38].

We used the same feedback function for simulating the ANC in GC 127 and GC 101. For an input with a small amplitude, the predicted oscillations in the neutrophil compartment are close to sinusoidal and fit the ANC of GC 127. When the amplitude of the input is increased, the shape of the oscillations in the circulating neutrophils is transformed by the feedback function, giving the characteristic two peaks observed in the neutrophil counts of GC 128 to 100. The correlation between the model's prediction and the fit of the ANC using periodogram analysis is 0.95 for GC 127, and 0.90 for GC 101.

Absence of significant variations in the levels of TPO and other lineage-specific regulators implies that, unlike the ANC, the sinusoidal input to the megakaryocytes will not be distorted by the peripheral feedback. The amplitude of the oscillations in the peripheral blood counts will, however, increase with the amplitude of the input. This is consistent with the sinusoidal oscillations observed in the platelet counts and the positive correlation between the amplitude of the platelets oscillations and the amplitude of the neutrophils oscillations.

The increase in the mean and amplitude of the oscillations in the ANC during G-CSF administration can be explained by an increased amplification in granulocyte progenitors compartment. The decrease in the period of the oscillations in all the cell lineages suggests that G-CSF also affects the dynamics of PPSC. The fact that the mean and amplitude of the oscillations in the platelets are not modified by G-CSF suggests that both effects are independent and further supports the hypothesis of the cycling of PPSC independently from the peripheral control of granulocyte.

Discussion

The Lomb periodogram analysis allowed us to quantify variations in the dynamics of hematopoiesis in the GC, in particular in the neutrophils and the platelets. The amplitudes of the oscillations in these two cell lineages vary concomitantly. The power spectrum and the shape of the oscillations in the ANC vary together with the amplitude of the oscillations. As the amplitude of the oscillations increases, the height of the second subharmonic increases, giving rise to a distorted oscillation with two peaks per cycle.

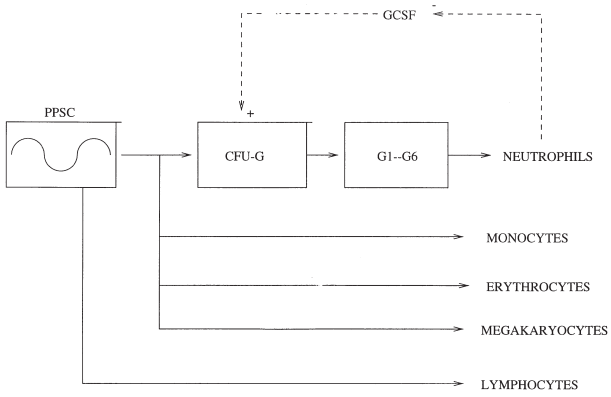

Figure 7. Scheme of granulopoiesis. The efflux from the pluripotential stem cells (PPSC) compartment differentiates towards granulopoiesis, erythropoiesis, megakaryopoiesis and lymphopoiesis. The granulopoietic lineage is represented by the colony forming unit committed to the granulocytes and the monocytes (CFU-G) and by the recognizable proliferating precursors myeloblasts (G1), promyelocytes (G2), myelocytes (G3) and the post-mitotic precursors metamyelocytes (G4), bands (G5) and segmented neutrophils (G6). Mature neutrophils are released in the granulocytic compartment in the peripheral blood. The proliferation of CFU-G is regulated by a feedback loop via granulocyte colony stimulating factor (G-CSF). The level of G-CSF is inversely correlated with the density of neutrophils in the blood.

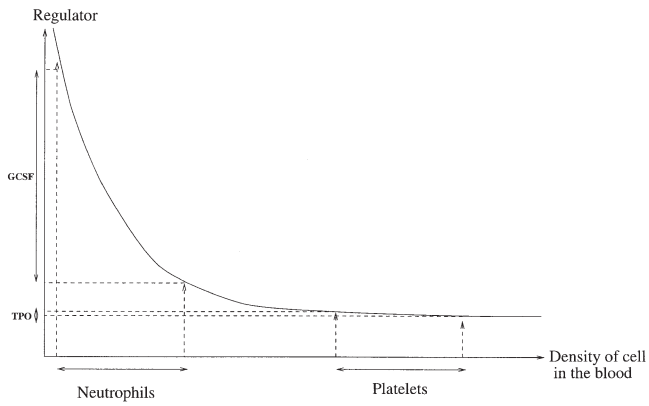

Figure 8. Illustration of the prediction of the model in Fig. 7 regarding the variations of lineage-specific peripheral regulators in GCs, as a function of the density of cells, for the neutrophils and the platelets.

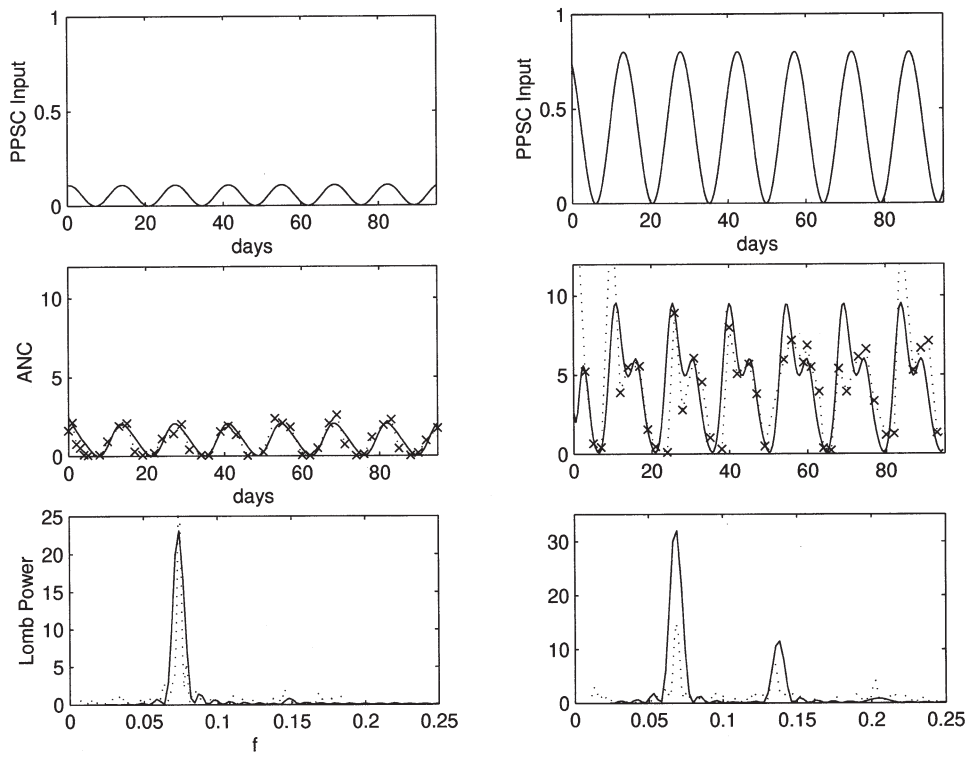

Figure 9. Simulations of the model of granulopoiesis. By varying the amplitude of the input from the PPSC, the predicted oscillations fit either the serial ANC of GC 127 (left panel) or GC 101 (right panel); solid lines are simulations of the model, dotted lines and 'x' are data points.

We showed that the particular dynamics of the ANC can be reproduced by a combination of a delayed peripheral feedback, representing the peripheral control of granulopoiesis through G-CSF, together with a sinusoidal input representing an oscillatory input from the PPSC to the granulocytic lineage. The distortion of the sinusoidal input by the peripheral feedback increases with the amplitude of the input. Thus, the model predictions and the data are entirely consistent.

The absence of distortion of the oscillations in the platelet counts can be explained by the absence of effective feedback in this cell lineage, that is the absence of significant variations in the levels of thrombopoietic regulators. This is consistent with the fact that the platelet counts oscillate within normal ranges. On the other hand, the ANC oscillate from normal to very low values, which induces dramatic changes in the levels of G-CSF. The other granulocytic cells and the monocytes may be also affected by the variations in G-CSF, although more moderately.

Previous models of CN in the GCs did not take into account the differences in the dynamics of the different cell lineages and their variations. The present modeling study suggests that the peripheral feedback controlling granulocytosis is responsible for the distortion of the oscillations observed in the ANC. We could reproduce the dynamics of the different cell lineages by assuming a sinusoidal oscillation propagating from the PPSC into the different cell lineages independent of the peripheral regulation of the committed granulocytic progenitors. All the cell counts are oscillating within normal ranges except the neutrophil counts, which are lower than normal. This is consistent with the defect observed in the growth of granulocytic progenitors in vitro, in GCs, and in humans with congenital CN. The investigation of the precise mechanism that generates oscillations in the PPSC requires data on the kinetics of stem cell populations in the bone marrow to allow us to extend the original work in Necas et al. [39,40].

Acknowledgments

This work was supported by the Natural Sciences and Engineering Research Council (NSERC Grant No. OGP-0036920, Canada), the National Institutes of Health (NIH Grant No. 18951, USA), Le Fonds pour la Formation de Chercheurs et l'Aide à la Recherche (FCAR Grant No. 98ER1057, Québec), and the École Normale Supérieure de Paris.

References

1. Glass L, Mackey MC (1988) From clocks to chaos: the rhythms of life. Princeton, NJ: Princeton University Press
2. Guerry D, Dale DC, Omine M, Perry S, Wolff SM (1973) Periodic hematopoiesis in human cyclic neutropenia. J Clin Invest 52:3220

3. Dale DC and Graw RG (1974) Transplantation of allogenic bone marrow in canine cyclic neutropenia. Science 183:83
4. Jones JB, Lange RD, Yang TJ, Vodopick H, Jones ES (1975) Canine cyclic neutropenia: erythropoietin and platelet cycles after bone marrow transplantation. Blood 45:213
5. Jones JB, Yang TJ, Dale JB, Lange RD (1975) Canine cyclic haematopoiesis: marrow transplantation between littermates. Br J Haematol 30:215
6. Weiden PL, Robinett B, Graham TC, Adamson J, Storb R (1974) Canine cyclic neutropenia. J Clin Invest 53:950
7. Krance RA, Spruce WE, Forman SJ, Rosen RB, Hecht T, Hammond WP, Blume G (1982) Human cyclic neutropenia transferred by allogeneic bone marrow grafting. Blood 60:1263
8. Patt HM, Lund JE, Maloney MA (1973) Cyclic hematopoiesis in grey collie dogs: a stem-cell problem. Blood 42:873
9. Jacobsen N, Broxmeyer HE (1979) Oscillations of granulocytic and megakaryocvtic progenitor cell populations in cyclic neutropenia in man. Scand J Haernatol 23:33
10. Dunn CDR, Jones JB, Lange RD (1977) Progenitor cells in canine cyclic hematopoiesis. Blood 50:1111
11. Dunn CDR, Jolly JD, Jones JB, Lange RD (1978) Erythroid colony formation in vitro from the marrow of dogs with cyclic hematopoiesis: interrelationship of progenitor cells. Exp Hematol 6:701
12. Hammond WP, Dale DC (1982) Cyclic hematopoiesis: effects of lithium on colony forming cells and colony stimulating activity in grey collie dogs. Blood 59:179
13. Jones JB, Jolly JD (1982) Canine cyclic haematopoiesis: bone marrow adherent cell influence of CFU-C formation. Br J Haematol 50:607
14. Abkowitz JL, Holly RD, Hammond WP (1988) Cyclic hematopoiesis in dogs: studies of erythroid burst-forming cells confirm an early stem cell defect. Exp Hematol 16:941
15. Avalos BR, Broudy VC, Ceselski SK, Druker BJ, Griffin JD, Hammond WP (1994) Abnormal response to granulocyte colony stimulating factor (GCSF) in canine cyclic hematopoiesis is not caused by altered GCSF receptor expression. Blood 84:789
16. Lothrop CD, Warren DJ, Souza LM, Jones JB, Moore MAS (1988) Correction of canine cyclic hematopoiesis with recombinant human granulocyte colonystimulating factor. Blood 72:1324
17. Hammond WP, Chatta GS, Andrews RG, Dale DC (1992) Abnormal responsiveness of granulocyte committed progenitor cells in cyclic neutropenia. Blood 79:2536
18. Wright DG, LaRussa VF, Salvado AJ, Knight RD (1989) Abnormal responses of myeloid progenitor cells to granulocyte macrophage colony stimulating factor in human cyclic neutropenia. J Clin Invest 83:1414
19. Dale DD, Brown C, Carbone P, Wolff SM (1971) Cyclic urinary leukopoietic activity in gray collie dogs. Science 173:152
20. Guerry D, Adamson DJW, Dale C, Wolff SM (1974) Human cyclic neutropenia: urinary colony-stimulating factor and erythropoietin levels. Blood 44:257
21. Moore MA, Spitzer G, Metcalf D, Penington DG (1974) Monocyte production of colony stimulating factor in familial cyclic neutropenia. Br J Haematol 27:47
22. Kazarinoff ND, van den Driessche P (1979) Control of oscillations in hematopoiesis. Science 203:1348
23. King-Smith EA, Morley A (1970) Computer simulation of granulopoiesis: normal and impaired granulopoiesis. Blood 36:254
24. MacDonald N (1978) Cyclical neutropenia: models with two cell types and two time lags. In: AJ Valleron, PDM Macdonald (eds) Biomathematics and cell kinetics. Amsterdam: Elsevier/North-Holland, 287
25. Morley A, Stohlman F (1970) Cyclophosphamide induced cyclical neutropenia. N Engl J Med 282:643
26. Morley A (1970) Periodic diseases, physiological rhythms and feedback control—a hypothesis. Australas Ann Med 3:244
27. Morley A (1979) Cyclic hemopoiesis and feedback control. Blood Cells 5:283
28. Reeve J (1973) An analogue model of granulopoiesis for the analysis of isotopic and other data obtained in the nonsteady state. Br J Haematol 25:15
29. von Schulthess GK, Mazer NA (1982) Cyclic neutropenia (CN): a clue to the control of granulopoiesis. Blood 59:27
30. Shvitra D, Laugalys R, Kolesov YS (1983) Mathematical modeling of the production of white blood cells. In: G Marchuk, LN Belykh (eds) Mathematical modeling in immunology and medicine. Amsterdam: North-Holland, 211
31. Schmitz S (1988) Ein mathematisches Modell der zyklischen Haemopoese (Ph.D. thesis). Koln: Universitat Koln
32. Schmitz S, Franke H, Brusis J, Wichmann HE (1993) Quantification of the cell kinetic effects of G-CSF using a model of human granulopoiesis. Exp Hematol 21:755
33. Schmitz S, Franke H, Loeffler M, Wichmann HE, Diehl V (1994) Reduced variance of bone-marrow transit time of granulopoiesis: a possible pathomechanism of human cyclic neutropenia. Cell Prolif 27:655
34. Schmitz S, Franke H, Wichmann HE, Diehl V (1995) The effect of continuous G-CSF application in human cyclic neutropenia: a model analysis. Br J Haematol 90:41
35. Schmitz S, Loeffler M, Jones JB, Lange RD, Wichmann HE (1990) Synchrony of bone marrow proliferation and maturation as the origin of cyclic haemopoiesis. Cell Tissue Kinet 23:425
36. Wichmann HE, Loeffler M, Schmitz S (1988) A concept of hemopoietic regulation and its biomathematical realization. Blood Cells 14:411
37. Haurie C, Mackey MC, Dale DC (1998) Cyclical neutropenia and other periodic hematological diseases: a review of mechanisms and mathematical models. Blood 92:2629
38. Hearn T, Haurie C, Mackey MC (1998) Cyclical neutropenia and the peripheral control of white blood cell production. J Theor Biol 192:167
39. Mackey MC (1978) A unified hypothesis for the origin of aplastic anernia and periodic haematopoiesis. Blood 51:941
40. Mackey MC (1996) Mathematical models of hematopoietic cell replication and control. In: HG Othmer, FR Adler, MA Lewis, IC Dallon (eds) The art of mathematical modeling: case studies in ecology, physiology and biofluids. New York: Prentice Hall, 149
41. Necas E, Hauser F (1988) Simulation of CFU-s kinetics after irradiation. Cell Tissue Kinet 21:81
42. Necas E, Znojil V (1988) Bone marrow response to single small doses of irradiation: implications for stem cell functional organization. Exp Hematol 16:871
43. Necas E, Znojil V (1988) Non-circadian rhythm in proliferation of haematopoietic stem cells. Cell Tissue Kinet 21:73
44. Necas E, Znojil V, Vacha J (1988) Stem cell number versus the fraction synthesizing DNA. Exp Hematol 16:231
45. Good PI (1973) Alternative mechanisms for homeostatic regulation of mammalian cell populations. J Theor Biol 40:543
46. Grudinin MM, Klochko AV, Lukshin IuV, Klochko EV (1978) Study of the kinetics of the functioning of a population of haernopoietic stem cells using analogue modeling devices. Biophysics 23:343
47. Gruzdev GP, Monichev Y (1975) Model of the regulation of the rate of multiplication of the stem cells of the bone marrow. Biophysics 20:308
48. Nazarenko VG (1997) Influence of delay on auto-oscillations in cell populations. Biophysics 21:352
49. Nazarenko VG (1978) Modification of the model of a cell population depressing its mitotic activity. Biophysics 23:337
50. Newton CM (1965) Computer simulation of stem-cell kinetics. Bull Math Biophys 27(Suppl):275
51. Rotenberg M (1979) Stability analysis of the two compartment model of cell proliferation. J Theor Biol 77:51
52. Rotenberg M (1982) Theory of distributed quiescent state in the cell cycle. J Theor Biol 96:495
53. Rotenberg M (1983) Transport theory for growing cell populations. J Cell Biol 103:181
54. Morley A, King-Smith EA, Stohlman F (1969) The oscillatory nature

of hemopoiesis. In: F Stohlman (ed) Hemopoietic cellular proliferation. New York: Grune & Stratton, 3
55. Lomb NR (1976) Least-squares frequency analysis of unequally spaced data. Astrophys Space Sci 39:447
56. Haurie C, Mackey MC, Dale DC (1999) Occurrence of periodic oscillations in the differential blood counts of congenital, idiopathic, and cyclical neutropenic patients before and during treatment with G-CSF. Exp Hematol 27:401
57. Scargle JD (1982) Studies in astronomical time series analysis. II. Statistical aspects of spectral analysis of unevenly spaced data. Astrophys J 263:835
58. Press WH, Flannery BP, Vetterling WT, Teukolsky SA (1993) Numerical recipes in C, 2nd edition. Cambridge: Cambridge University Press
59. Hammond WP, Boone TC, Donahue RE, Souza LM, Dale DC (1990) Comparison of treatment of canine cyclic hematopoiesis with recombinant human granulocyte-macropliage colony stimulating factor (GM-CSF), G-CSF, Interleukin-3, and Canine G-CSF. Blood 76:523
60. Layton JE, Hockman H, Sheridan WP, Morstyn G (1989) Evidence for a novel in vivo control mechanism of granulopoiesis: mature cell-related control of a regulatory growth factor. Blood 74:1303