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Parameter Estimation Modeling for the Analysis of CN Diseases by Alternative G-CSF Treatment.

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ABSTRACT

The FFT (Fast Fourier Transform) simulation develops the dynamics of circulating blood cells before and after the granulocyte colony stimulating factor (G-CSF) treatment. We review different modeling approaches in hematology, mainly based on the study of periodic hematological disorders. In particular, modeling of cyclical neutropenia (CN) and analysis of its dynamical properties has provided insights on the origin of the disease and potentially helped in the design of new G-CSF treatment regimens. We proposed alternative G-CSF treatment strategies for cyclical neutropenia using a combination of analytical and numerical tools. There are fitting parameters to evaluate the estimation of seven set of dogs. It is also essential and necessary to model more samples for increase in Neutrophil amplification. It may reduce the amount of G-CSF for required potential maintenance. Sometimes, it may even improve the treatment effects too. This model gives us good result in treatment. After this (Absolute Neutrophil Count) ANC base, the neutrophil levels then increase. Treatment protocols prescribe daily G-CSF treatment (starting dose of 5μg/kg) beginning at least 12 hours after treatment. It should be administered daily for up to 14 days or until the ANC has reached normal levels following the neutrophil base. Nevertheless, it is not clear what would be the best schedule for giving G-CSF following treatment. A few studies have considered alternative G-CSF regimens in order to find optimal G-CSF timing**.** However, the results and conclusions vary from one study to another.

Keywords: CN, G-CSF, FFT, ANC.

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INTRODUCTION

The analytical features of the use of G-CSF for treating low blood counting levels of white blood cells are also introduced. In a normal individual, the number of circulating neutrophils is relatively constant with an average of about 2.0× 10^9 cells/L (Matthew E *et al.*, 2006). Neutropenia is a term that designates a low number of neutrophils, thus indicating that the individual is less effective at fighting infections (Koury M *et al.*, 1991-1992, Hoffman R *et al.*, 1989). CN is characterized by oscillations in the number of neutrophils from normal to very low levels (less than 0.5 × 10^9 cells/L) (Price T *et al.*, 1996). The period of these oscillations is usually around 3 weeks for humans, although periods up to 45 days have been observed. The period in which the ANC is very low usually lasts for about a week in humans (Ritchie A *et al.*, 1997, Kaushansky K *et al.*, 1996). This period is associated with symptoms such as mouth ulcers, periodic fever, pharyngitis, sinusitis, otitis and other infections, some of which can sometimes be life-threatening (Lord B. I *et al.*,1989, Basu S *et al.*, 2002, Kearns C. M *et al.*, 1993). Fortunately, CN is effectively treated with daily administration of the growth factor G-CSF, which has the effect of reducing the period of the oscillations and increasing both the oscillation amplitude and the value of the ANC base. This has the overall effect of decreasing the period of severe neutropenia (Shochat E *et al.*, 2007, Roeder I *et al.*, 2006).

Understanding of CN has been greatly aided by the existence of a similar disease in grey collies (street dogs) (Haurie C *et al.*, 1998-2000). The canine disorder shows the same characteristics as in humans, except that the period of the oscillations is usually between 11 and 15 days (Foley C *et al.*, 2008). The existence of this animal model has allowed the collection of a variety of data that would have been difficult, if not impossible, to obtain in humans. A major characteristic of CN is that the oscillations are not only present in neutrophils, but also in platelets, monocytes and reticulocytes, which is the reason CN is sometimes referred to as periodic hematopoiesis. This observation suggests that the source of the oscillations may lie in the stem cell compartment. Although it is a rare disorder, CN is probably the most extensively studied periodic hematological disorder (Hearn T *et al.*, 1998).

Explicit functions used for modeling the effects of G-CSF on the amplification factor, the post mitotic transit time and the apoptosis rates. The effects of G-CSF reduction, but for CN are studied. G-CSF stimulates neutrophils production and is used analytically for treating neutropenia (low neutrophil levels). G-CSF can either increase or the amplitude of the oscillations (Meisenberg B. R *et al.*, 1992). These results suggest that administration of G-CSF can affect the dynamical behavior of the granulopoiesis system. Indeed, G-CSF is widely used in oncological practice for treating neutropenia and preventing infections that often follow G-CSF treatment (Scholz M *et al.*, 2005). Using a combination of analysis and FFT simulations tools, it was used this model to study the effects of G-CSF treatment following for two recombinant forms of G-CSF (Tissue G-CSF and Circulating G-CSF). The consequences of varying the duration of G-CSF drug reduction and study some dynamical properties of the system is examined (Colijn C *et al.*, 2007).

In this paper, we try to find out and investigate the "Fast Fourier Transform model and G-CSF Treatment of CN (Cyclical Neutropenia)", in detail. For this analysis of G-CSF treatment of 'Neutropenia', we get animal model for CN. They are grey collies (street dogs). We resolve these issues by proposing a comprehensive model of the mammalian hematopoietic system that couples the pharmacokinetics of G-CSF to the hematopoietic stem cell, neutrophil, platelet, and erythrocyte dynamics (Koumakis G *et al.*, 1999). We study the effects of varying the treatment initiation time, and whether injections are given daily, every other day, or every three days. All blood cells are derived from hematopoietic stem cells. These stem cells are called 'undifferentiated cells' (Fukuda M *et al.*, 1993). They have high proliferative potential in nature. This multipotent stem cells which often regulates cytokines, erythropoietin, erythrocyte, thrombopoietin, platelets as well as granulocyte colony stimulating factor and regulates leukocyte numbers (Butler R. D *et al.*, 1992)**.** We examine cyclical neutropenia which rarely leads to hematological disorder characterized by "oscillations" in the circulating neutrophil count. Sometimes the oscillation level may fall. The period of oscillation time may be of 19 to 21days in humans, even though it has been observed to 40 days (Belair J *et al.*, 1995). These 'oscillations' are generally accompanied by platelets, lymphocytes and reticulocytes (Orr J. S *et al.*, 1968). Cyclical neutropenia also occurs in grey collies when the periods on the order may be of 11 to 16 days. This is called 'animal model'. It has provided extensive analytical approach**.** It enriched our understanding of cyclical neutropenia.

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MATERIALS AND METHODS

All of these dogs showed statistically significant cycling in neutrophils or platelets, according to the FFT analysis carried out**.** The FFT is equivalent to power spectrum analysis. It is used to detect periodicity in the blood counts before and during treatment with G-CSF. Simulations for neutrophils, erythrocytes and platelets were available both for untreated dogs as well as dogs receiving daily G-CSF. We have developed a model that couples the pharmacokinetics of G-CSF to the hematopoietic stem cell, neutrophil, platelet and erythrocyte dynamics. In the hematological portion of the present model was fitted to observed polynomial for cyclical neutropenic dogs and human patients, both untreated and receiving G-CSF treatment. Both the platelet and neutrophil counts were matched for dogs with untreated cyclical neutropenia, and for dogs undergoing daily treatment with G-CSF injections (Bennett C. L *et al.*, 1999).

The results were that three of the models parameters were identified as the most crucial in simulating the effects of cyclical neutropenia and its treatment with G-CSF: the amplification in the proliferating neutrophil precursors, the rate of apoptosis in the proliferating HSC's, and the maximal rate of differentiation from the HSC's into the neutrophil line(Clark O. A *et al.*, 2005). Interestingly, it was consistently necessary to change all of these to account for the features of the method. In this analysis we used the fits for 7 set of dogs without G-CSF treatment from CN**.** For three of these, we then used the simulated FFT procedure to minimize the least squares difference between the simulation and the treated polynomial fit, changing only the four most critical parameters. We then estimated, without fitting, the treated parameters for the remaining 4 dogs. At this point, the parameter sets successfully match the model simulations to polynomial, without the new G-CSF compartment.

We add the pharmacokinetic G-CSF compartment, to obtain our full model. The quality of the fits is preserved; in other words, the polynomial fit difference between the model and simulations is as good, as or better, with the G-CSF compartment than without, though the parameters were estimated for the model without it. At this point, having determined both the untreated and treated parameter values we are in a position to use simulation to explore the effects of different treatment strategies. We experiment with simulating treatment every day, every second day, and every three days, for each of the dogs. We also examine the effect of changing the time in the cycle when treatment is first initiated.

The model we have developed includes the hematopoietic stem cells, the neutrophils, platelets and erythrocytes, as well as tissue G-CSF levels and circulating G-CSF in the blood (Vainstein V *et al.*, 2005). The stem cells are pluripotential and self-renewing, and can differentiate into the leukocyte, erythrocyte or platelet lines. The stem cell compartment model is based on the original work**.** The neutrophil, erythrocyte and platelet compartments are modeled after earlier efforts**.** G-CSF, meanwhile, is injected into the tissue compartment and enters the circulation from there (Mempel K *et al.*, 1991). It is cleared from the circulation by two processes: a random loss, and a linear neutrophil mediated clearance representing the fact that neutrophils take up circulating G-CSF at very high G-CSF levels the neutrophil mediated clearance is saturable, but at the concentrations relevant here, a linear approximation is accurate.

The Fast Fourier Transform simulation analysis allowed us to quantify variations in the dynamics of hematopoiesis in the GC (Grey Collies), in particular in the neutrophils and the platelets. The amplitudes of the oscillations in these two cell lineages vary parallel.

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 sub harmonic increases, giving rise to a distorted oscillation with two peaks per cycle. 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 simulated input representing an oscillatory input from the CN to the granulocytic cell lineages (Takatani H *et al.*, 1996). The distortion of the simulated input by the peripheral feedback increases with the amplitude of the input. Thus, the model predictions and the simulations are entirely consistent (Watari K *et al.*, 1989). 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.

G-CSF Drug Level Reduction

G-CSF is a hematopoietic growth factor that stimulates the bone marrow to increase the production of neutrophils (MacDonald N *et al.*, 1978). Thus, this is the treatment of choice for neutropenia. It is produced naturally in the body, but recombinant forms of G-CSF (Neupogen, lenograstim and Neulasta) are used as drugs to accelerate recovery from neutropenia**.** Another drug is the same molecule as G-CSF drug but to which a 20 kDa polyethylene glycol moiety has been added. This addition changes its pharmacokinetic properties and virtually eliminates renal clearance. Hence, whereas G-CSF drug is rapidly cleared after a subcutaneous dose, another drug, a bigger molecule, has a much longer half-life. Therefore, only a single administration after each cycle of treatment is necessary for CN instead of a number of daily injections for drug, thereby reducing cost and inconvenience to the patient (Moore M. A *et al.*, 1991)**.**

It is usually given subcutaneously (injection under the skin) because the increase in neutrophil count is higher and the stimulated duration is longer than with an intravenous administration of the same dose**.** In this study, we only consider the use of G-CSF following myelosuppressive drug on patients suffering from nonmyeloid types of cancer, e.g. we are assuming that a model of regulation of neutrophil production can be taken to represent a hematological normal individual (Ratajczak M. Z *et al.*, 1995). Neupogen's clinical guidance for cancer patients receiving myelosuppressive drug recommends a starting dose of 5 µg/kg/day, subcutaneously. Doses may be increased in increments of 5 µg/kg for each drug cycle, according to the duration and severity of the ANC base**.** Neupogen should be administered no earlier than 24 hours after the administration of cytotoxic drug and it should be administered daily for up to 2 weeks, until the ANC has reached normal levels following the expected induced neutrophil (Santillan M *et al.*, 2000). The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per drug cycle. Neulasta should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic drug.

RESULTS

The parameter sets for the first three dogs are given in the first three columns of in the Table 1. In each case, we found that the neutrophil amplification increases substantially under G-CSF treatment, as does the rate of stem cell apoptosis, and the differentiation into the neutrophil line. We therefore predict similar changes for the remaining dogs. There is some redundancy in the model, in that increasing the neutrophil amplification and the differentiation into the neutrophil line from the stem cells has similar effects. This is not unexpected, since the primary effect of both changes is to raise neutrophil levels. It shows the fit of the untreated and treated data for Dogs 100, 118 and 127. This confirms that the new model, with the G-CSF coupled to the cell population dynamics, is capable of reproducing the new results. The least squares differences between the FFT analysis and the simulations were not significantly less than the reported values. Thus, we are able to match observed results without automated parameter fitting based simply on an examination of the treated data and the parameter changes for Dogs 100, 118 and 127 in Table1. For each dog, we performed simulations comparing daily treatment, treatment every other day, and every three days. We find that particularly for Dogs 100, 101,118 and 127, changing the period of the treatment can significantly affect the nature of the oscillations. It shows the results of treating Dog 118 every other day, rather than every day.

We have also explored the effects of changing the time at which the treatment is initiated. In most cases, this did not significantly change the long-term behavior. However, for Dog 127 the amplitude of the oscillations was significantly reduced when the treatment was initiated in the latter half of the cycle in Table 1. More specifically, measured from day 1, we find that smaller oscillations occur if treatment is initiated on day 8 or afterwards, or on days 2 or 5. When treatment was initiated on other days, larger oscillations in the model resulted. It should also be noted that increasing the G-CSF dosage in the model sometimes helped to stabilize oscillations (Dog 127), but in several cases (Dogs 100, 128 and 101) a dosage increase from 5 µg/kg to a dosage in the range 15-25 µg/kg caused some other analysis to fail. In that analysis, the differentiation rate out of the stem cells was so high, and the apoptosis rate in the stem cells was so high, that the stem cell population was no longer able to maintain itself. For the other dogs, there was always a dosage that was sufficiently higher than to terminate the FFT analyze, but it was sometimes the factor 10 times higher than the actual dosage given.

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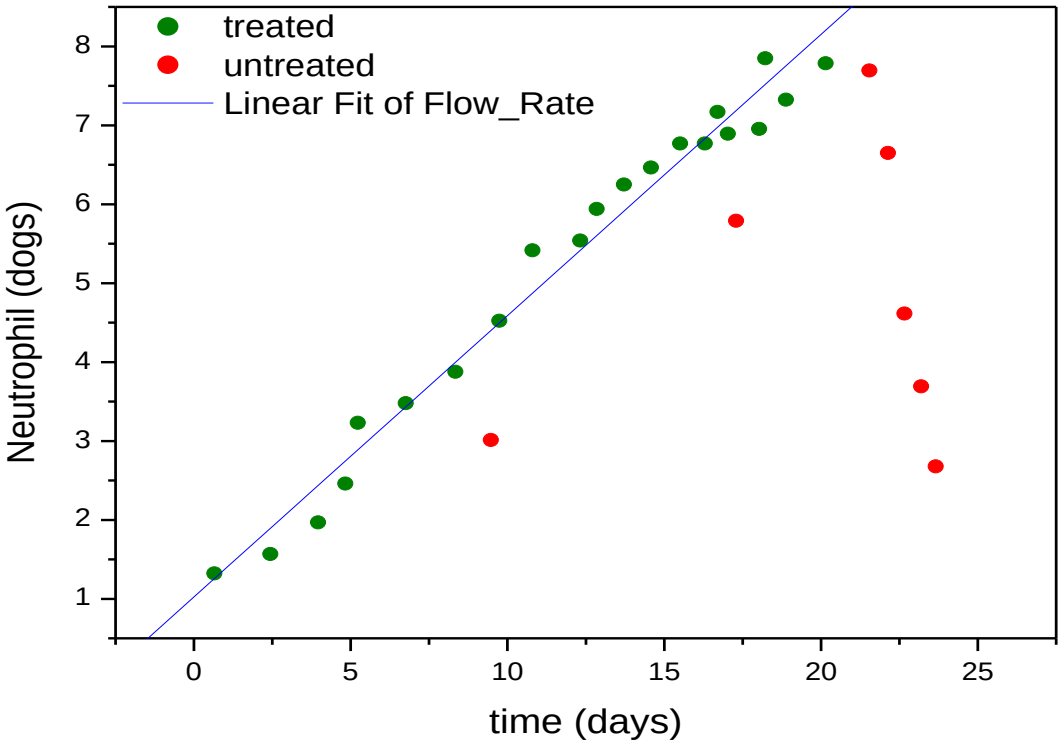
The result of combining a simulation input with the peripheral feedback control of granulopoiesis is shown**.** We used an exponential decreasing feedback with a delay of 3 days within the context of the model of WBC peripheral control presented. We used the same feedback function for simulating the ANC in GC 127 and GC 101. For an input with small amplitude, the predicted oscillations in the neutrophil compartment are close to FFT 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. For example the simulation between the model's prediction and the fit of the ANC using FFT analysis is 10^6 to $10^7$for GC 127 (0 to 6 days) and 10^2 to 10^3 for GC 101(0 to 30 days).

Table 1: Parameters used for computation each dog.

S. No.	Dog 100	Dog 118	Dog 127	Dog 101	Dog 113	Dog 117	Dog 128
1	488	73.4	18.8	135.8	51	6.59	100
2	912.4	866.4	68.3	900	200	2000	800
3	0.36	0.36	0.36	0.36	0.36	0.36	0.8
4	2.0	4.1	2.1	4	4	4	5
5	0.03	0.03	0.005	0.05	0.01	0.05	0.08
6	0.17	0.15	0.05	0.18	0.055	0.1	0.18
7	2.8	20.8	2.8	2.52	2.45	2.52	2.52
8	1.45	1.21	1.34	1.03	1.5	1.59	1.90
9	0.3	0.69	1.44	0.81	0.48	0.17	0.5
10	5.63	5.63	5.63	5.80	5.63	5.8	5.63
11	7	7	7	6.9	5.27	6.9	7
12	21.63	49.38	30.88	91.74	6.15	14.0	21.0
13	1.38	1.16	0.26	0.32	3.48	0.69	0.90
14	3.41	10.82	2.46	8.01	11.66	3.79	4.0
15	0.008	0.0038	0.0083	0.008	0.01	0.008	0.005

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.



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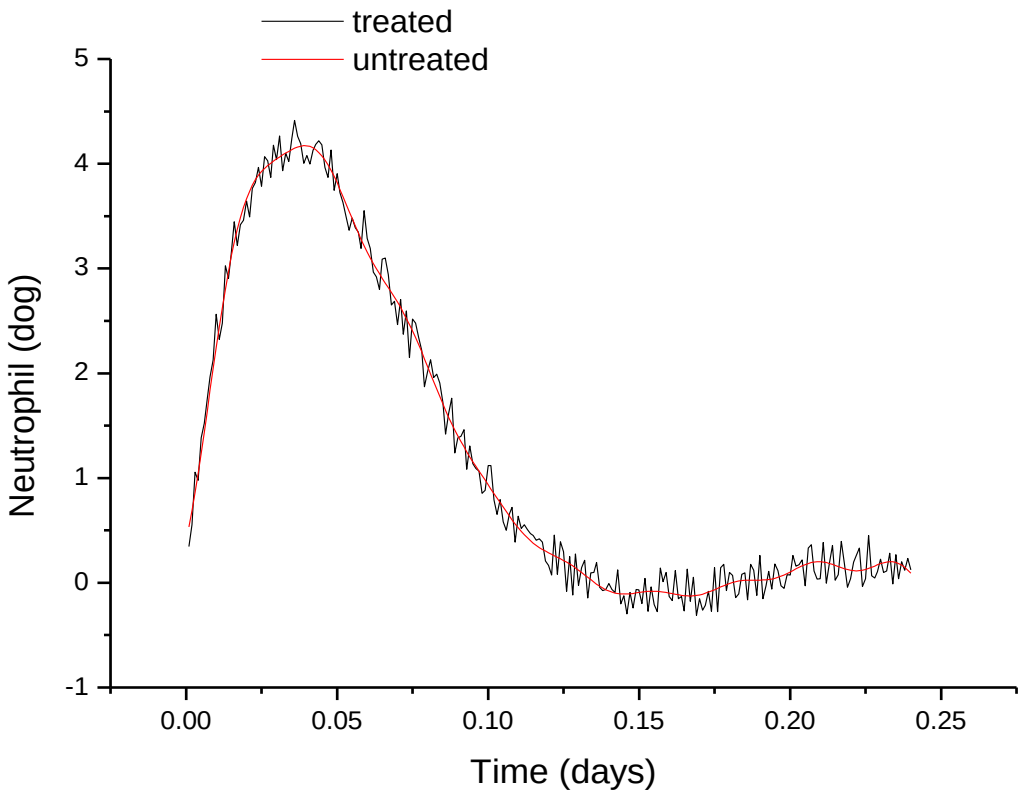

Figure 1: Neutrophil count (green circles and red circles) are taken from simulation. G-CSF treatment was given for a period of 25 days.

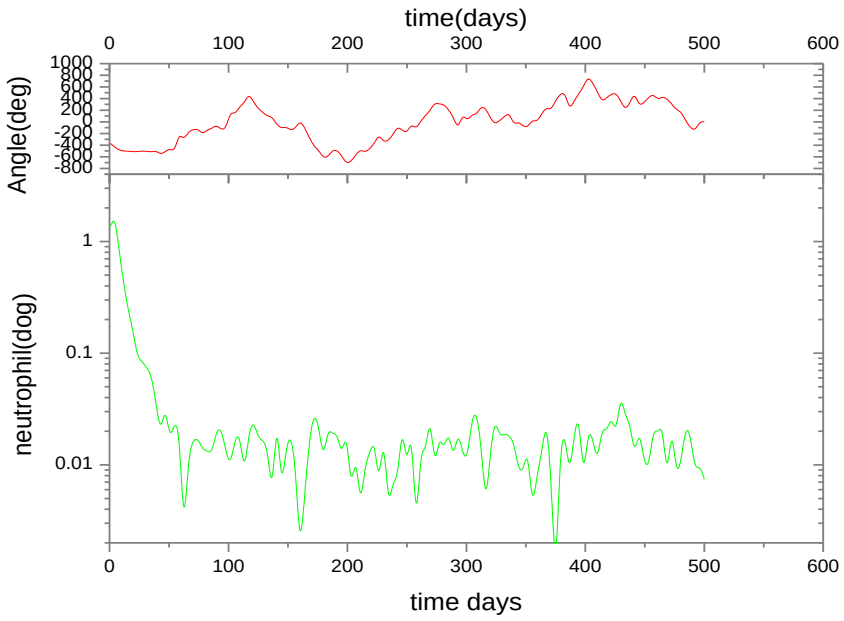

Figure 2: FFT low pass filter effects of G-CSF treatment.

As discussed above, it has been suggested that delayed initiation of G-CSF could successfully reduce neutropenia while being cost-effective. We found that changing the starting day of G-CSF administration could result in important qualitative changes in the ANC levels. Figure 1 show the effects of starting 1 day and 8 days after treatment. Our model leads to very different responses in the ANC levels. Early administration of CN

results in a large response in the neutrophil levels, followed by a decrease to low ANC. CN was simulated to stop when the neutrophil levels were back to normal following this base. Conversely, initiation of 8 days after treatment leads to a very different qualitative response. Neutrophil levels increased but remained relatively stable around normal levels during G-CSF treatment without falling to very low values. Starting G-CSF treatment leads to a reduced maximum ANC during G-CSF treatment. Interestingly, delaying treatment of one week also coincides with higher neutrophil base during the treatment.

These results are in agreement with those reported and suggest that late G-CSF administration method should be efficient in reducing the neutropenic period, provided that neutropenia does not occur prior to the start of treatment. Since the ANC increases rapidly after CN administration, this suggests that G-CSF could be efficiently used as supportive treatment, i.e. starting G-CSF only at the onset of neutropenia. Moreover, this could result in a more stable ANC response and avoid the typical decrease in neutrophil count. However, we do not take into account the use of antibiotics in this model, which is a criterion that was in favor of a proactive treatment. Also, in a clinical setting, there are several factors to consider when administering G-CSF to patients, such as the type of cancer, the intensity of the chemotherapy, the age and general health of the subject, the history of febrile neutropenic episodes, etc. All these factors can influence the response to CN treatment. Therefore, our results should be looked at from a qualitative point of view. Our model suggests that two different types of response (large amplitude followed by low base and a relatively stable ANC) can be obtained by G-CSF administration. We believe that this may be due to the existence of multiple stable solutions in the system.

Relation between G-CSF Reduction and Neutrophil Counts

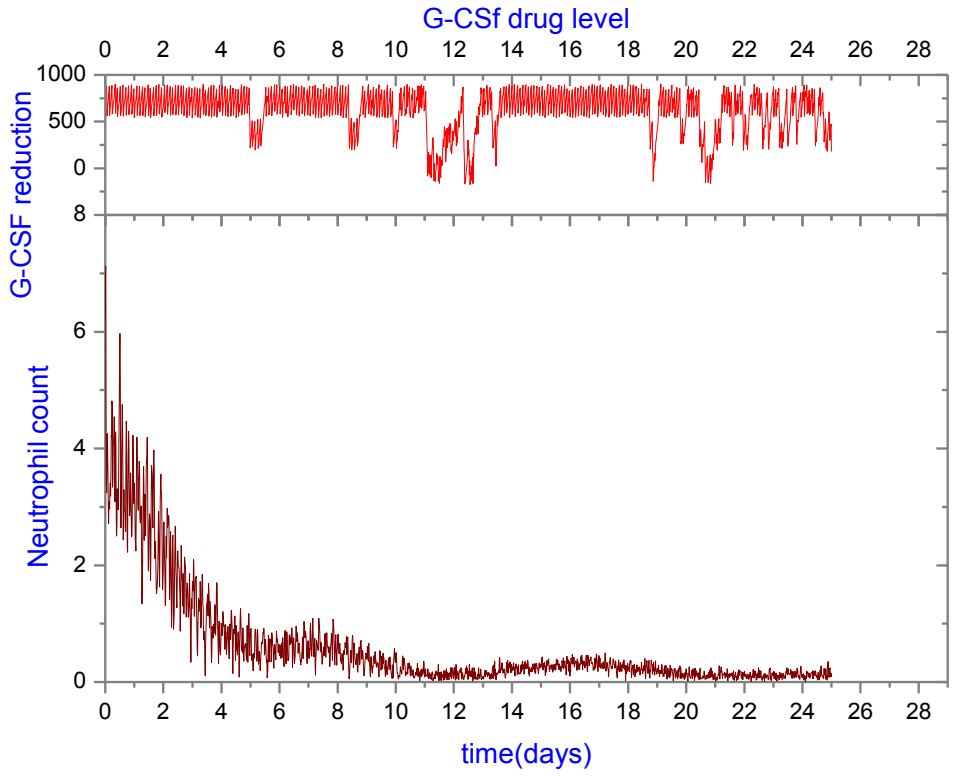

Figure 3: The Relation between G-CSF reduction and Neutrophil counts are shown. It shows Neutrophil count in units, versus time in days.

We study the effects of varying the duration of G-CSF treatment. Since clinical guidelines suggest starting on day 1 and stopping its administration when the neutrophil levels are back to normal values following the expected base, we chose to always simulate the start of treatment on the day and only vary the end of G-CSF treatment. Figure 3 shows the simulations when treatment is given for 28 days. When starting treatment on day 1, one can see that a rapid rise in neutrophil occurs, followed by the decrease and a second increase in ANC. The amplitude of this second increase as well as the depth of the expected base varies with

the length of treatment. For each, duration of treatment from 0 to 25 days, we computed the base and maximum neutrophil counts of the second ANC increase over 2 cycles of G-CSF in Figure 3**.** We found that the longer the treatment, the higher are the maximum neutrophil levels. More interestingly, depths of the base are similar for treatment duration of more than 8 days. With this model, administering for 8 days correspond to stopping it just before the expected neutrophil pits whereas ending G-CSF when ANC are back to a normal after the base corresponds to duration of 12 days of treatment. Therefore, our simulations suggest that the duration of treatment could be reduced by stopping treatment when the base is reached, instead of waiting for the ANC to get back to normal levels.

It is worth noting that only one day of treatment given the day method leads to a reduced increase of the ANC and a higher neutrophil base, as shown in Figure 2 & 3. As in the case of delayed treatment discussed above, the ANC response remains relatively stable around normal values, without falling down to very low neutrophil levels. We make the hypothesis that this reflects the existence of another stable solution in the system. From a mathematical point of view, many factors influence the response of the model, among which the historical values of all variables (stem cells, precursors, neutrophils) as well as the choice of parameters. The bases and maximum values with respect to the duration of treatment have similar behavior for both cycles, except that the bases are lower and maximums are higher for the second cycle. We do not have a clear explanation for that difference. However, since we are mainly interested in the dynamical properties of the model, we believe that this quantitative aspect is of less importance and focus on the fact that the same types of variations in bases and maximum values hold for both cycles.

Table 2: G-CSF drug level reduction (min-max) recovery from CN

G-CSF (x)	Max	Min	ANC (y)	G-CSF Injection=y/x
0.11	2.401	0.753	1.078	9.8
0.1	2.393-3.546	0.760-0.578	1.031-1.614	10.31-16.14
0.05	2.342-3.060	0.778-0.645	0.7515-1.095	15.03-21.91
0.02	2.300-2.681	0.776-0.698	0.5234-0.692	26.17-34.58
0.005	2.260-2.410	0.765-0.736	0.34555-0.402	69.11-80.47
0.001	2.237-2.293	0.762-0.753	0.26014-0.277	260.14-277.12
0.0001	2.223-2.245	0.763-0.759	0.2221-0.226	2220.9-2260.6
0.00002	2.220-2.236	0.763-0.760	0.21476-0.217	10738-10841.6

Table 3: G-CSF drug level reduced in minimum

Circulating C-CSF (x)	Max	Min	ANC (y)	G-CSF Injection=y/x
0.11	2.401	0.753	1.078	**9.8**
0.1	2.393	0.578	1.031	10.31
0.05	2.342	0.645	0.7515	15.03
0.02	2.300	0.698	0.5234	26.17
0.005	2.260	0.736	0.34555	69.11
0.001	2.237	0.753	0.26014	260.14
0.0001	2.223	0.759	0.2221	2220.9
0.00002	2.220	0.760	0.21476	10738

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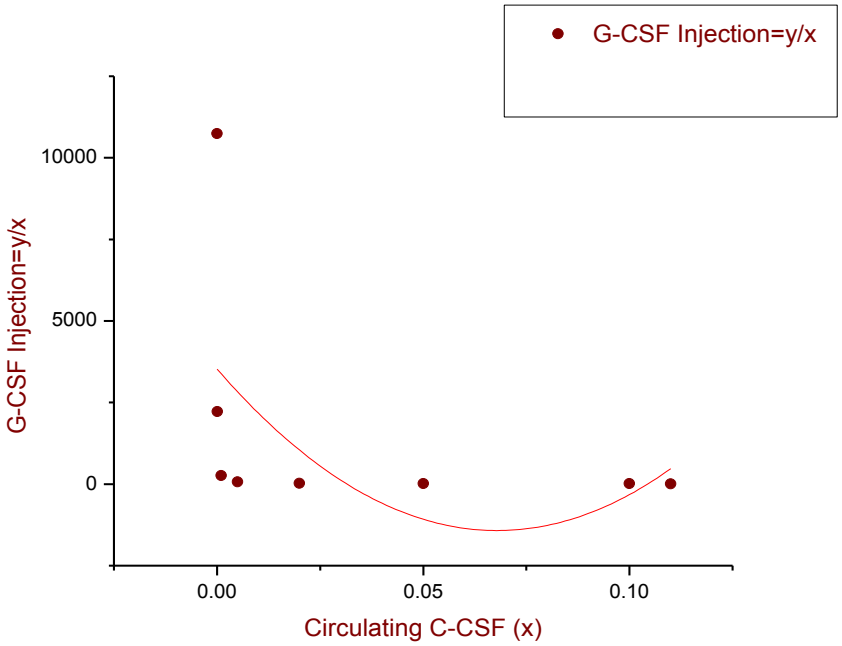

Figure 4: G-CSF drug level reduced in minimum

Table 4: G-CSF drug level reduced in maximum

Circulating C-CSF (x)	Max	Min	ANC (y)	G-CSF Injection=y/x
0.11	2.401	0.753	1.078	9.8
0.1	3.546	0.760	1.614	16.14
0.05	3.060	0.778-	1.095	21.91
0.02	2.681	0.776	0.692	34.58
0.005	2.410	0.765	0.402	80.47
0.001	2.293	0.762	0.277	277.12
0.0001	2.245	0.763	0.226	2260.6
0.00002	2.236	0.763	0.217	**10841.6**

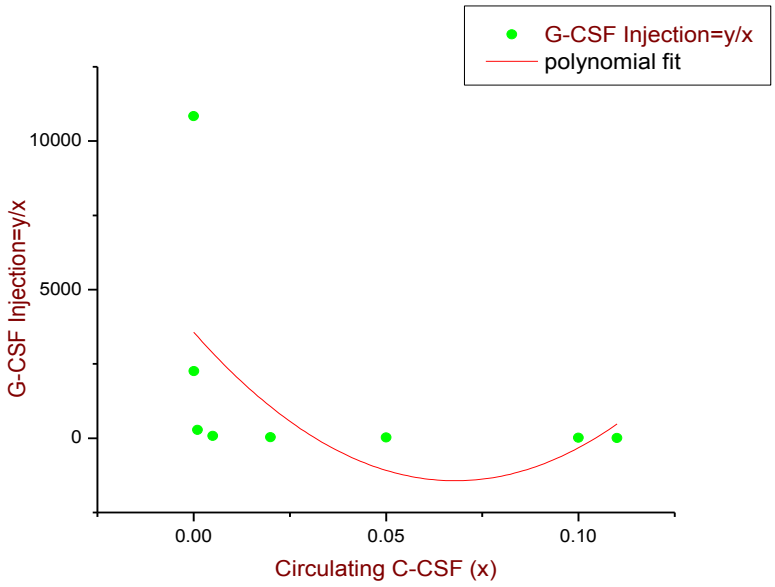

Figure 5: G-CSF drug level reduced in maximum

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Table 5: The computations for counting days were made simulation

Dog	Polynomial fit	Day^{-1}	Days
127	-0.10	0.465	0
113	-0.05	0.470	0
128	-2.00	0.464	5.39
118	-0.50	0.500	0
101	-1.50	0.426	3.27
117	-1.70	0.438	4.49
100	-1.80	0.418	5.20

Finally, we compared various timing schedules of G-CSF treatment drug reduction in Table 2, Table 3 and Table 4. In this study, we will only consider the reduction of drug (see Figure 4 & 5). G-CSF drug is a small molecule which is rapidly filtered by the kidney and cleared from the blood, necessitating daily administrations. Then it shows the data and analysis for the other four dogs, again with daily treatment in Table 5. Recall that these were the estimated, not fitted, values for the treated parameters and note the quality of the fits. In particular, since a common side effect of many G-CSF drugs is a reduction in the number of white blood cells, G-CSF is often given after treatment to elevate the white blood cell production.

DISCUSSION

We review previous clinical attempts to optimize G-CSF drug administration following treatment. There are basically two main lines of thought concerning the timing of G-CSF administration. Some authors consider that the duration of neutropenia and the neutrophil base are not significantly different whether G-CSF is given as early as 24 hours or even as late as 8 days after treatment**.** However, others have concluded that it is preferable to start G-CSF administration early after drug treatment because it reduces the number of infections and hospitalization days. Next, we briefly discuss the main results of studies based on these two premises. We showed that beginning daily treatment (5 μg/kg) on either days 1, 3, 5 or 7 after G-CSF all reduce neutropenia. They demonstrated that the duration of G-CSF treatment could be reduced considerably by delaying G-CSF initiation. They also observed that early G-CSF led to a more rapid recovery of myeloid progenitor cells and an earlier onset of neutropenia than delayed treatment. We also studied the effects of delaying G-CSF treatment following simulation and of reducing its duration of administration. They suggest that the amplitude in the ANC levels in response to G-CSF could vary depending on the starting day of G-CSF administration.

In particular, maximal neutrophil levels are higher when starting G-CSF treatment on the day following drug reduction and lower when starting 7 days after CN. It demonstrated that starting G-CSF 7 days after treatment still has the effect of rapidly raising the ANC levels, although the neutrophil response is typically of smaller amplitude. They also concluded that it was not necessary to continue G-CSF for more than 7 days.

We administered G-CSF starting on days 4 or 11 during intensive treatment for CN. They found that patients who were given G-CSF on day 4 had fewer days of neutropenia, hospitalization and antibiotic days while having similar duration the G-CSF treatment. These results are in agreement with another study**,** which also showed that early G-CSF administration following treatment was more beneficial than late administration, when the number of neutropenic days and the depth of the base were considered. They were interested in investigating the dependence of the optimal time of G-CSF initiation on criteria such as incidence of febrile neutropenia, antibiotic use, duration and cost of G-CSF administration. Preemptive treatment involves starting G-CSF shortly after treatment whereas in supportive therapy, G-CSF is started later and only when neutropenia occurs. However, the incidence of antibiotic use and febrile episodes was less when G-CSF was started early. For these reasons, they recommended preemptive rather than therapeutic administration of G-CSF for subjects receiving chemotherapy. In this paper we use our model to study the days of G-CSF administration with respect to the starting day of administration and the duration of treatment.

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CONCLUSION

In this paper, we have studied alternative G-CSF treatment strategies for induced cyclical neutropenia using a modeling approach and a combination of analysis and computer simulations. To mimic the effects of G-CSF on cyclical neutropenia dogs, five relevant parameters were changed: the amplification and apoptosis rates, the transit times in the proliferative and differentiating phases and a neutrophil count that was part of a negative feedback function. Two sets of parameters (one for CN and another one for G-CSF) were taken into account and simulating G-CSF effects was carried out by switching from one set of parameters to the other. Three parameters were modified to mimic the effects of treatment: the amplification in the proliferating neutrophil precursors, the rate of apoptosis in the proliferating hematopoietic stem cells, and the maximal rate of differentiation from the HSCs into the neutrophil line. The model parameters were successfully fit for seven set of cyclical neutropenia dogs before and during treatment. We found that varying either the starting day of G-CSF treatment or its duration could result in two qualitatively different responses: a large neutrophil increase followed by a deep base or a smaller ANC increase that remains relatively stable and does not go to very low levels. We estimated a normal blood neutrophil count higher than previous work.

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