ISCA Journal of Biological Sciences ISSN 2278-3202
Vol. **1(2),** 55-60, June **(2012)** *ISCA J. Biological Sci.*

Stability of the Six Equilibrium States between CN and G-CSF with Infectives Growth Rate Progression: A FFT Study

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Available online at: www.isca.in
(Received 1st June 2012, revised 7th June 2012, accepted 8th June 2012)

Abstract

In this paper we have investigated a stability of the equilibrium states between CN (Cyclical Neutropenia) and G-CSF (granulocyte-colony stimulating factor) with infective growth rate progression. Mathematical models and FFT (fast fourier transform) simulations can be used as experimental tools for testing the control- measures and determining sensitivities of changes in parameter values. The paper deals with an investigation on a four parameters estimates consisting of cure rate (c), infective rate (I), absolute neutrophil count (A_N) and total carrying capacity (K) only. All six equilibrium points for this model are identified and their stability criteria are analyzed. Mathematical modelling of epidemics can lead to and motivate new results in mathematics.

Keywords: Cure rate in infective, infective rate in neutropenia population, absolute neutrophil count, total carrying capacity.

Introduction

Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1500/micro L. The ANC is equal to the product of the white blood cell count and the fraction of polymorph nuclear cells and band forms noted on the differential analysis[1]. The term neutropenia describes the situation where the number of neutrophils in the blood is too low. Neutrophils are very important in defending the body against bacterial infections, and therefore, a patient with too few neutrophils is more susceptible to bacterial infections[2]. People with neutropenia get infections easily and often. Most of the infections occur in the lungs, mouth and throat, sinuses and skin. Painful mouth ulcers, gum infections, ear infections and periodontal disease are common. Most cases of neutropenia are acquired and are due to decreased granulocyte production or less often increased destruction. Neutropenia is a blood disorder that can affect anyone. White blood cells are just as important, but for a very different reason. One of their jobs is to protect you from infection. There are several kinds of white cells. Each has a special function. It is a condition in which an individual has an abnormally low number of a type of white blood cell called a neutrophil. Neutrophils are a specific kind of white blood cell that helps to prevent and fight off infections[3]. There function is to eat up the bad microorganisms that enter your body. Neutrophils make up fifty to seventy percent of the circulating white blood cells in the body. In cyclic neutropenia considerable evidence from human studies and from investigations of an analogous disease in collie dogs indicate that a regulatory defect at the hematopoietic stem cell level leads to oscillations in production of all types of blood cells. People of any age group can be affected by this disease[4]. In this Paper we examine the spread of CN among the G-CSF and establish Criteria for stability of the equilibrium states. Mathematical models can be used to compare and optimize control programs. The modelling process can contribute to the design of public health surveys, especially by suggesting data that should be collected. The process of formulating a mathematical model clarifies the assumptions and provides qualitative results such as thresholds[5]. And also we have solved a pair of differential equations which represents the growth rates of population and infective by employing the FFT. And solution graphs are presented for all possible cases. This model is characterized by a pair of First Order ordinary differential Equations reflecting the balances of growth rates of cure and infective in a neutropenia population[6].

Basic notations: Q - total number of hematopoietic stem cells (10^6 cells/kg), X- number of tissue levels of G-CSF, g_r- growth rate in population, I_c - inhibition coefficient, c- cure rate in infective, I – infective rate in neutropenia population, k - total carrying capacity (g_r/I_c), A_N - initial number of absolute neutrophil counts, K_T, K_B – transfer rates, K_{T_0}, K_{B_0} - initial transfer rates, t-the time of dominates over the infective and cure rates.

Material and Methods

Equation for Total number of hematopoietic stem cells (10^6 cells/kg) (Q): Rate of change in total number of hematopoietic stem cells (Q) = growth rate in population (g_r) - reduction in population (Q)

$$\frac{dQ}{dt} = (g_r - I_c Q)Q \text{---------} (1)$$

Equation for Number of tissue levels of G-CSF (X): Rate of change in number of tissue levels of G-CSF (X) = increasing of infective due to contract between susceptible and infective - decrease in the number of Infective due to death.

$$\frac{dX}{dt} = I(Q - X)X - cX ----------(2)$$

Equilibrium points: The system under investigation has three equilibrium points:

1. $\overline{Q} = 0$, $\overline{X} = 0$

Fully washed out stage.

2. $\overline{Q} = k$, $\overline{X} = 0$

Healthy State. In this state healthy population can survive and infective population washed out.

3. $\overline{Q} = k$, $\overline{X} = \frac{Ik - c}{I}$

Coexistence state. In this state both healthy and infective population can survive, it could happen only when I $k > c$. When Ik = *c this* becomes same as 2.

Stability of the Equilibrium States: This method affords stability information directly without solving the differential equations occupied in the system. This method is based on the main characteristic of constructing a scalar function. The stability behavior of solutions of linear and non-linear system is done by using the techniques of variation of constants formulae and integral inequalities. So this analysis is restricted to a small neighborhoods of operating point i.e., local stability. Further, the techniques used there in require explicit knowledge of solutions of corresponding linear systems[7].

Stability of the Equilibrium State 1: We consider the transfer rates K_T, K_B from study state (*Q, X) i.e.*

$$Q = \overline{Q} + K_T, X = \overline{X} + K_B$$

Here K_T, K_B is so small that the terms other than their first order can be neglected. Substituting in above equations (1), (2) and neglecting products and higher powers of K_T, K_B we get

$$\frac{dK_T}{dt} = g_r K_T, \frac{dK_B}{dt} = -cK_B ---(3)$$

The characteristic equation for which is $(\lambda - g_r)(\lambda + c) = 0$. The roots of which are g_r , -c and these are of opposite signs. Hence the state is unstable[8].

Case 1.1:- When $K_{T_0} > K_{B_0}$

When $K_{T_0} > K_{B_0}$, Total number of hematopoietic stem cells (Q) increases over the Number of tissue levels of G-CSF (X) in growth as well as its population strength.

Stability of the Equilibrium State 2: The corresponding linearized perturbed equations are

$$\frac{dK_T}{dt} = -g_r K_T, \frac{dK_B}{dt} = (Ik - c)K_B ---(4)$$

The characteristic equation is

$$(\lambda + g_r)(\lambda - (Ik - c)) = 0 \quad ----- (5)$$

where roots are $-g_r$ *and Ik-c.*

Case2.1:- When $k > \frac{c}{I}$

The roots of the above equation are one is positive and the other is negative. Hence the state is unstable.

Case2.2:- when $K_{T_0} > K_{B_0}$

When $K_{T_0} > K_{B_0}$, Population decreasing and the infective are increasing, after some time total population becomes infected and starts decay with population[9].

Case 2.3:- When $K_{T_0} > K_{B_0}$

Here no change in Number of tissue levels of G-CSF(X) and infective population declines.

$$t^* = \frac{1}{g_r} \log\left[\frac{K_{T_0}}{K_{B_0}}\right]$$

Case2.4:- When $k < \frac{c}{I}$

The roots of the equation (5) are both negative. Hence the state is stable. By solving the equation (4) we get

$$K_T = K_{T_0} e^{-g_r t}, K_B = K_{B_0} e^{-(c - IK)t}$$

Case 2.5:- When $K_{T_0} > K_{B_0}$

When $K_{T_0} > K_{B_0}$ and g_r = (c – Ik) here the total population and infective both are decreasing.

Stability of the equilibrium state 3: ($\overline{Q} = k$, $\overline{X} = \frac{Ik - c}{I}$)

This state exist only when I$k > c$, The corresponding differential equations are

$$\frac{dK_T}{dt} = -g_r K_T, \frac{dK_B}{dt} = (Ik - c)(K_T - K_B) ---(6)$$

The characteristic equation is $(\lambda + g_r)(\lambda + (Ik - c)) = 0$. The roots of this equation are $-g_r$ and *-(I k - c)* both negative. Hence the state is stable.

Case 3.1:- when $K_{T_0} > K_{B_0}$

When $K_{T_0} > K_{B_0}$, and $g_r = (Ik - c)$, here the total population and infective both are decreasing.

A solution of differential equations: We get the differential equation representing the growth rate of infective.By solving the equation (3) we get, $K_T = K_{T_0} e^{g_r t}, K_B = K_{B_0} e^{-ct}$

where K_{T_0} , K_{B_0} are initial values of K_T and K_B respectively. By solving the equation (4) we get, $K_T = K_{T_0} e^{-g_r t}, K_B = K_{B_0} e^{(IK-c)t}$

By solving the equation (6) we get.

$$K_T = K_{T_0} e^{-g_r t}, K_B = K_{B_0} e^{-(Ik-c)t} + \frac{Ik-c}{(Ik-c)-g_r}\left[K_{T_0} e^{-g_r t} - e^{-(Ik-c)t}\right]$$

Numerical solution of this equation is obtained by FFT method of transform for investigate the behaviour of the infective of this model[10].

Parameter estimation values of CN and G-CSF

Parameter Name	Value Used	Unit	Sources
Q	1.1	10^6 cells/kg	C. Foley
A_N	<1500-7700	µI	S. Bernard
X	0.1	mg/kg	M. Mackey
G	0	mg/ml	(calculated)
k_T	0.07	hours^{-1}	(calculated)
k_B	0.25	hours^{-1}	(calculated)
I_C	0.01	µI	T. Hearn,
g_r			(calculated)

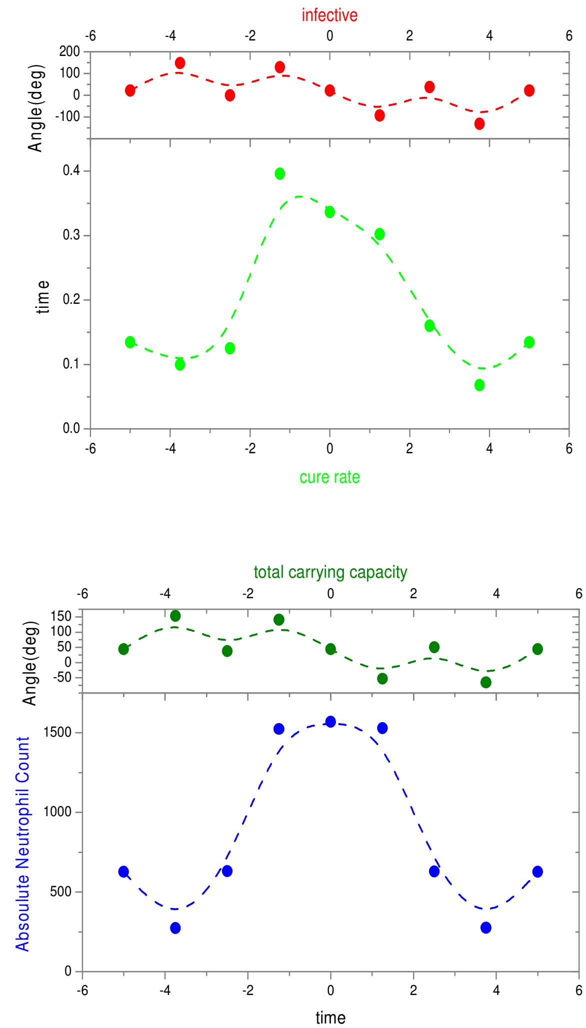


Figure-1
Cure rate is greater than infective rate when Initial number of absolute neutrophil count greater than total carrying capacity

Results and Discussion

Case (1): when c >I and A_N > k: Computations have been carried for FFT of values for the system parameters as shown in the table 1 to estimate the strength of the infective (I).

Table-1

t	c	I	A_N	k
0.1	0.3	0.2	1600	1550
0.2	0.4	0.2	1700	1650
0.3	0.5	0.2	1800	1750
0.4	0.6	0.2	1900	1850
0.5	0.7	0.2	2000	1950

Case (2): when c > I and A_N = k: Computations have been carried for FFT of values for the system parameters as shown in the table.2 to estimate the strength of the infectives (I)

Table-2

t	c	I	A_N	k
0.1	0.3	0.2	1600	1600
0.2	0.4	0.2	1700	1700
0.3	0.5	0.2	1800	1800
0.4	0.6	0.2	1900	1900
0.5	0.7	0.2	2000	2000

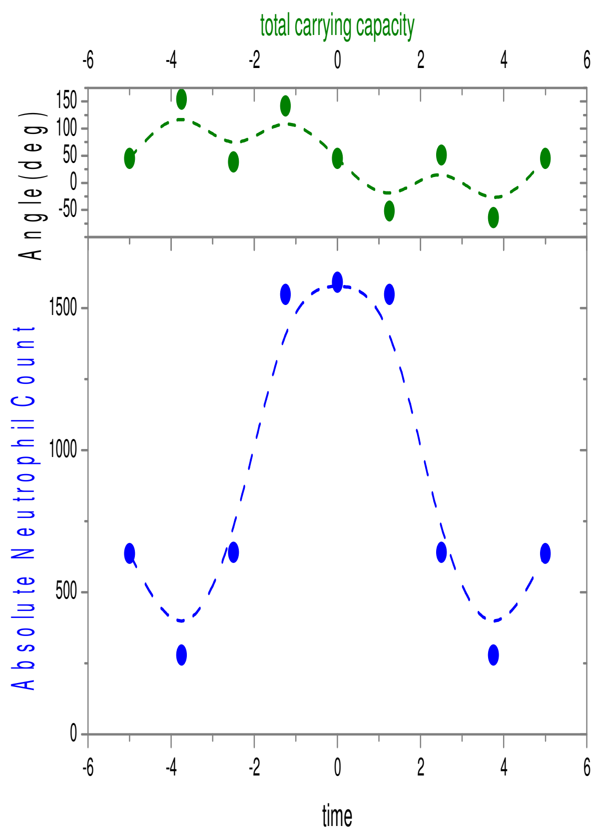


Figure-2
Initial number of absolute neutrophil count is equal to total carrying capacity

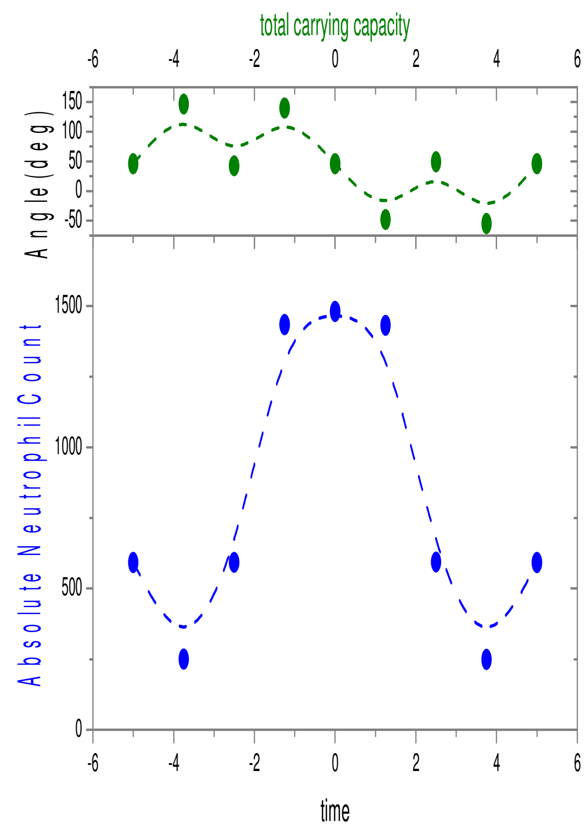


Figure-3
Initial number of absolute neutrophil count is less then total carrying capacity

Case (3): when c > I and A_N < k: Computations have been carried for FFT of values for the system parameters as shown in the table 3 to estimate the strength of the infectives (I).

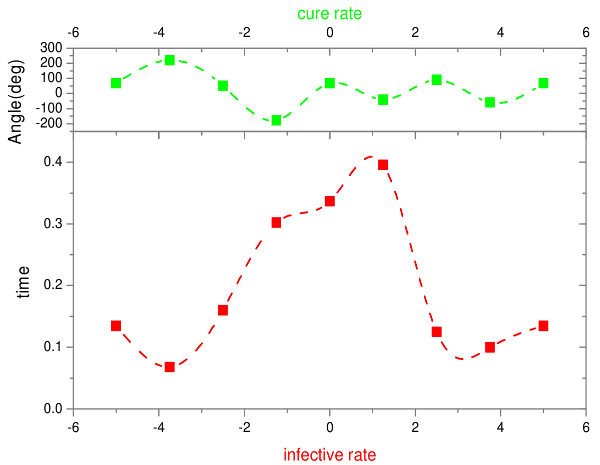
Table-3

t	c	I	A_N	k
0.1	0.3	0.2	1550	1600
0.2	0.4	0.2	1600	1650
0.3	0.5	0.2	1650	1700
0.4	0.6	0.2	1700	1750
0.5	0.7	0.2	1750	1800

Case (4): when c < I and A_N > k: Computations have been carried for FFT of values for the system parameters as shown in the table 4 to estimate the strength of the infectives (I).

Table-4

t	c	I	A_N	k
0.1	0.2	0.3	1200	1150
0.2	0.2	0.4	1250	1200
0.3	0.2	0.5	1300	1250
0.4	0.2	0.6	1350	1300
0.5	0.2	0.7	1400	1350



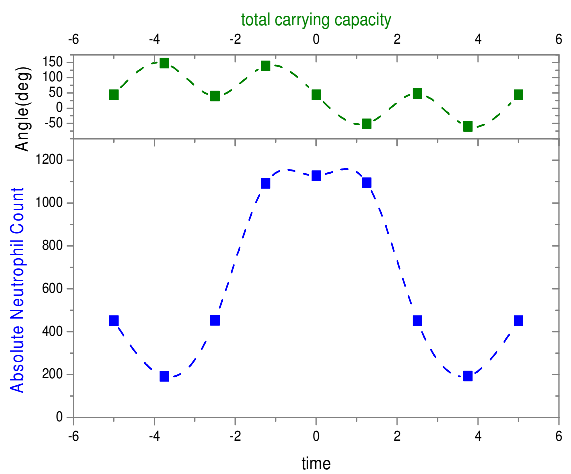


Figure-4
Cure rate is less than infective rate in susceptible when Initial number of absolute neutrophil count greater than total carrying capacity

Case (5): when c < I and A_N = k: Computations have been carried for FFT of values for the system parameters as shown in the table 5 to estimate the strength of the infective (I).

Table-5

t	c	I	A_N	k
0.1	0.2	0.3	1200	1200
0.2	0.2	0.4	1250	1250
0.3	0.2	0.5	1300	1300
0.4	0.2	0.6	1350	1350
0.5	0.2	0.7	1400	1400

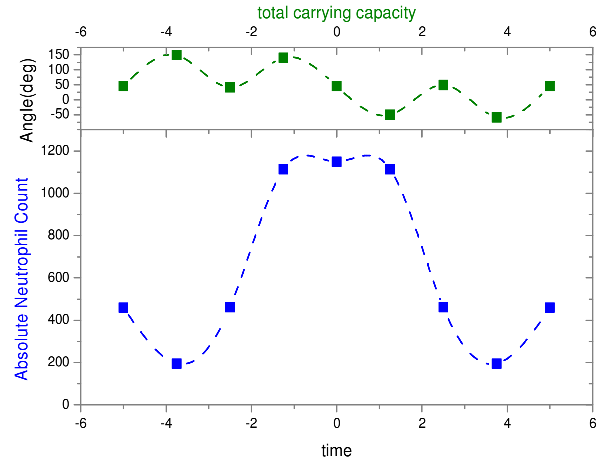


Figure-5
Absolute Neutrophil Count is equal to total carrying capacity

Case (6): when c < I and A_N < k: Computations have been carried for FFT of values for the system parameters as shown in the table 6 to estimate the strength of the infective (I).

Table-6

t	c	I	A_N	k
0.1	0.2	0.3	1200	1250
0.2	0.2	0.4	1250	1300
0.3	0.2	0.5	1300	1350
0.4	0.2	0.6	1350	1400
0.5	0.2	0.7	1400	1450

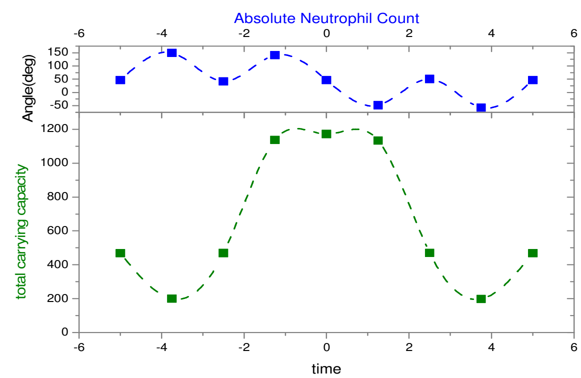


Figure-6
Absolute Neutrophil Count is less than total carrying capacity

The objective of the paper is to examine the stability case in a mathematical model of CN between four factors in which a delayed G-CSF is comprised[11]. Six equilibrium points of the model are discovered. The cure rate is greater than the infective rate and the Initial number of absolute neutrophil count are greater than total carrying capacity (freg(X)= 2.5, Real(Y)= 0.125, Imag(Y)= 0.1, r(Y)= 0.16008, Phi(Y)= 38.65981, Power(Y)= 0.0032 and freg (X)= 1.25, Real(Y)= 920.86309, Imag(Y)= -1221.75144, r(Y)= 1529.92334, Phi(Y)= -52.9938, Power(Y)= 292583.17814 from figure1). The cure rate is greater than the infective rate and the Initial number of absolute neutrophil count is equal to total carrying capacity (freg(X)= 1.25, Real(Y)= 951.04076, Imag(Y)= -1221.75144, r(Y)= 1548.27489, Phi(Y)= -52.10195, Power(Y)= 299644.39014 from figure 2). The cure rate is greater than the infective rate and the Initial number of absolute neutrophil count is less than total carrying capacity (freg(X)= 1.25, Real(Y)= 958.36309, Imag(Y)= -1063.54076, r(Y)= 1431.635, Phi(Y)= -47.97779, Power(Y)= 256197.3472 from figure 3).The cure rate is less than the infective rate and the Initial number of absolute neutrophil count are greater than total carrying capacity (freg(X)= -1.25, Real(Y)= -0.30178, Imag(Y)= -0.01464, r(Y)= 0.30213, Phi(Y)= -177.22172, Power(Y)= 0.01141 and freg(X)= -1.25, Real(Y)= -822.11941, Imag(Y)= 716.94174, r(Y)= 1090.81886, Phi(Y)= 138.90945, Power(Y)= 148735.72208 from figure 4). The cure rate is less than the infective rate and the Initial number of absolute neutrophil count is equal to total carrying capacity (freg(X)= -1.25, Real(Y)= -852.29708, Imag(Y)= 716.94174, r(Y)= 1113.73954, Phi(Y)= 139.92987, Power(Y)= 155051.9705 from figure 5). The cure rate is less than the infective rate and the Initial number of absolute neutrophil count is less than total carrying capacity (freg(X)= -1.25, Real(Y)= -882.47475, Imag(Y)= 716.94174, r(Y)= 1136.99918, Phi(Y)= 140.90884, Power(Y)= 161595.89185 from figure 6).

Conclusion

In this paper we have investigated some results on the stability of equilibrium in a mathematical model of CN and G-CSF by FFT analysis. Some observations are made from the relationship between the cure rate of CN and G-CSF through the growth rates. Each and every one six stability of equilibrium points for this mathematical differential equation model are identified and their stability criteria are discussed. Under the limited and unlimited resources for first and second factors respectively, if the cure rate is greater than the infective rate for both the models, it is found that there are six equilibrium cases. The equilibrium point of this model is traced and the stability criteria at this equilibrium point are calculated.

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