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# Mathematical Model of the Behaviors of T, B and Natural Killer Cells in the Absence of Viral Infections

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The immune system is our major defense against viruses, tumors and other 'foreign invaders'. The issue of humans' defense against viral infections and the reaction of immune system to these infections are the main problems in practical immunology. To understand the integrated behaviour of the immune system, there is no alternative to Mathematical modeling. This current study seeks to extend the one system of two differential equations originally developed by a system of three differential equations. The system was used to model the behaviour of lymphoid cells in the absence of viruses. The steady states and the stability for this differential model were deduced. The model permitted the existence of two types of stationary states. These are a stable state and an unstable state. It was found from the study that a stable state represents the pre-programmed state of the matured lymphoid cells to attack pathogens which may invade the organism. The unstable state represents immuno-deficiency as a result of one or more cells within the immune system not operating properly or the cells are absent altogether.

**Key words:** Immune system, lymphoid cells, viral infections, pre-programmed state, mathematical modeling and differential equations

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## INTRODUCTION

The immune system is composed of two major subdivisions, the innate or nonspecific which is our first line of defense against invading pathogens right from birth and function without requiring prior exposure to microorganism or its antigens. The adaptive immune system acts as a second line of defense and is triggered when an infection eludes or overwhelms the innate defense mechanisms and generates a threshold dose of antigens. When the adaptive immune response is activated, it culminates in the production of antibodies and effector T cells. T cells, B cells and natural killer cells play important roles in immunity against viral infections. The functions of these cells include the uptake and killing of intracellular pathogens, lysis of infected host cells and presentation of antigens to T cells and release of cytokines. Natural killer cells are capable of killing virus infected or virus transformed cells. For example, NK cells play an important role in the nonspecific immune response against cytomegalovirus infection and play an initial role in controlling viral replication in altered self target cells particularly, in the fields of anti: HIV, HBV and HCV infections (Dominik, 2004).

In the absence of viral infections, the cells of the immune system grow and get ready to attack should a pathogen gets into the system. It is therefore important to study the dynamics of these cells in the absence of infection.

The construction of mathematical models to enhance our understanding of the dynamics of chronic viral infections has proved fruitful (Perelson, 2002; Nowak *et al*., 1996; Hews *et al*., 2010). Using mathematical models to interpret experimental and clinical results has made a significant contribution to the fields of anti-, HIV, HBV and or HCV infections (Perelson *et al*., 1996; Lau *et al*., 2000; Smith and Leenheer, 2003).

Most of these researches have looked at the immune responses to particular viral infection but have not studied the behavior of these effector cells in the absence of viruses. The original model discussed by Anderson and May (1992) consisted of the behaviour of two effector cells (T and B lymphocytes) in the absence of viruses. These two effector cells were representative of the generic lymphocytes which do not provide first line of defense in viral infections. Thus in this study, we couple the two equations from Anderson and May (1992) representing the two lymphocytes that do not provide the first line of defense with a third equation that represents the NK cells which provide the first line of defense to give us a set of equations of mixed lymphocyte types.

Vaccines against most viral infections are not currently available. This makes it very important for researchers to focus on preventive measures through information and education on the effect of viral infections and measures that will help fight viral infections.

The mathematical techniques which help us to understand, forecast and control the spread of infectious diseases like viral infections are diverse and growing rapidly (Dimitrov and Nedialko, 2010). Some techniques have been newly developed, whereas others build upon existing methods from diverse fields including dynamical systems (Alfio, 2002), stochastic processes (Arakaki *et al*., 2012), statistical physics (Anderson *et al*., 1995), graph theory (Chudnovsky and Plumettaz, 2013), statistics (Le Palud, 2007), operations research (Lee, 2005), mathematical modeling and high-performance computing. There are several population growth models which have been used for modeling disease progress curves.

The logistic growth model was chosen because of its simplicity and the many real world applications it has. It can be applied in biology, ecology, statistics, neural networks, reaction models (chemistry) and in medicine.

## MATERIALS AND METHODS

A logistic growth model was used to represent the behaviour of three lymphoid cells (T, B and NK cells) in the absence of viral infections. These cells were considered since they are very effective in fighting most viral infections. The growth rates of these lymphoid cells were assumed to be the same. The constants reproduction rates, the self-reproduction rate, death rates and the rate at which they interact to saturate were considered in the models, the equilibrium points and their stability for the system of the extended differential equations were analyzed and the stability of the linearized equations was determined. Time histories of this system of differential equations were also used to analyze the system. MATLAB code solver 'ode45' was written to evaluate the numerical solutions of this system of differential equations. Parameter values which had been estimated by Anderson and May (1992) were extended based on the assumptions made for the current study.

**The model:** The model described the behaviour of lymphocytes in the absence of viruses. Anderson and

May (1992) first discussed this model by considering two effector cells (T and B cells). Research has shown the important role that Natural Killer cells play in fighting viral infections but this effector cell was not considered in the model of Anderson and May (1992). Data indicate that there are two important components of Nk cell response (Daniels *et al*., 2001; Busa *et al*., 2001). First, many of the NK cells which exist before the infection can kill virus-infected cells because the virus cells are recognized by a number of different receptors on the NK cells. Second, NK cells bearing specific receptors can expand in response to antigenic stimulation. This study has included the dynamics of this third effector cell (Natural Killer Cells). Therefore, the parameters involved in this model are the three lymphoid populations denoted by T(t), B(t) and N(t). There exist three lymphoid populations T(t), B(t) and N(t). In the absence of the virus, there is a limited number of each of these population types and these populations are regulated by the interactions between them. The following assumptions were made as an extension of the work of Anderson and May (1992):

- New lymphoid cells of type T, B and NK cells are produced by the bone marrow at constant rates of $A_t$, $A_b$ and $A_n$, respectively
- Lymphoid cells of type T, B and NK cells die at a per capita rate of $\mu_t$, $\mu_b$ and $\mu_n$, respectively
- Lymphoid cells of the three types proliferate due to contact with one another at a rate that saturates for large values of T, B and NK

The assumptions lead to this system of differential equations:

$$T' = A_t - \mu_t T + \frac{a_t TBN}{(1 + b_t TBN)} \quad (1)$$

$$B' = A_b - \mu_b B + \frac{a_b TBN}{(1 + b_b TBN)} \quad (2)$$

$$N = A_n - \mu_n N + \frac{a_n TBN}{(1 + b_n TBN)} \quad (3)$$

$A_t$ in Eq. 1 corresponds to the constant production rate of T cells; $\mu_t T$ represents self-reproduction of T cells and $a_t$ TBN/1+$b_t$TBN corresponds to the logistic growth rate of these effector cells. The interaction between the three populations of lymphoid cells saturates, that is, approaches $a_t/b_t$ as TBN→∞.

It is assumed that the production rates of the three effector cells are equal which implies:

$$T = B = NK$$

**Existence of steady states:** By system of Eq. 1-3, we obtained steady states by putting derivatives to zero. We obtained (T* B* N*) = (0 0 0) as a trivial steady state of the system. We obtained the characteristics equation of the system (1-3).

$$\frac{a_t TBN}{1 + b_t TBN} A_t - \mu_t T + \frac{a_t TBN}{(1 + b_t TBN)} = A_b - \mu_b B + \frac{a_b TBN}{(1 + b_b TBN)} = A_n - \mu_n N_n \frac{a_t TBN}{(1 + b_n TBN)} = 0 \quad (4)$$

But T = B = N also:

$$\begin{pmatrix} a = a_t = a_b = a_n \\ b = b_t = b_b = b_n \\ \mu = \mu_t = \mu_b = \mu_n \end{pmatrix} \quad (5)$$

$$\Rightarrow A - \mu T + \frac{aT^3}{(1 + bT^3)} = 0 \quad (6)$$

$$\Rightarrow b\mu T^4 - (Ab + a)T^3 + \mu T - A = 0) \quad (7)$$

The linearized matrix of system (1-3) is:

$$J(T,B,N) = \begin{pmatrix} -u_t + \frac{a_t BN}{(1 + b_t TBN)^2} & \frac{a_t TN}{(1 + b_t TBN)^2} & \frac{a_t TB}{(1 + b_t TBN)^2} \\ \frac{a_b BN}{(1 + b_b TBN)^2} & -\mu_b + \frac{a_b TB}{(1 + b_b TBN)^2} & \frac{a_b TB}{(1 + b_b TBN)^2} \\ \frac{a_n BN}{(1 + b_n TBN)^2} & \frac{a_n TN}{(1 + b_n TBN)^2} & -\mu_n + \frac{a_n TB}{(1 + b_n TBN)^2} \end{pmatrix} \quad (8)$$

$$T^4 - 26T^3 + 125T - 100 = 0 \quad (9)$$

## RESULTS

The results of the study and the numerical methods used to study the mathematical model are presented. We present the time histories of this system of differential equations and analyze the system qualitatively. MATLAB codes were written to find the equilibrium points, Jacobian matrices and eigenvalues in order to ascertain the behavior of these effector cells and determine the immune state. MATLAB ordinary differential equation solver 'ode45' is used to compute the numerical solution of the system of differential equations.

Data is from (Anderson and May, 1992) and by assumption, we have added the third row.

Table 1: Parameters values supplied by Anderson and May (1992)

| Lymphoid cells | Initial Production | Rate of increase | Rate of decrease | Death rate |
|---|---|---|---|---|
| T | $A_t$= 1 | $a_t$= 0.252 | $b_t$= 0.008 | $\mu_t$= 1.25 |
| B | $A_b$= 1 | $a_b$= 0.252 | $b_b$= 0.008 | $\mu_b$= 1.25 |
| N | $A_n$= 1 | $a_n$= 0.252 | $b_n$= 0.008 | $\mu_n$= 1.25 |

Table 1 shows the parameter values used in the models.

Parameter values in row 2 and row 3 are due to Anderson and May (1992). We chose for row 4 same parameter values as Anderson and May (1992) so as to have comparative results.

The data were substituted in Eq. 8 to get a 3 by 3 matrix. MATLAB codes were written to find the equilibrium points and their corresponding eigenvalues. The eigenvalues were then classified into either a stable point or an unstable point.

**Behaviour of steady states in the absence of viruses:** We substitute parameter values into (8) which yields:

$$T^4-26T^3+125T-100 = 0 \quad (10)$$

The roots of this quartic equation were found using MATLAB codes written by the authors and the roots are:

25.8183, -2.4193, 1.6010, 1.0000

It has already been shown that T = B = N, it then shows that there exits four equilibrium points at:

$$\begin{pmatrix} T^* \\ B^* \\ N^* \end{pmatrix} = \begin{pmatrix} 25.82 \\ 25.82 \\ 25.82 \end{pmatrix}, \begin{pmatrix} -2.4 \\ -2.4 \\ -2.4 \end{pmatrix}, \begin{pmatrix} 1.6 \\ 1.6 \\ 1.6 \end{pmatrix} \text{ and } \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} \quad (11)$$

Substituting the parameters of Table 1, into Eq. 8, we get:

$$J(T,B,N) = \begin{pmatrix} -1.25+\frac{0.252BN}{(1+0.008TBN)^2} & \frac{0.252TN}{(1+0.008TBN)^2} & \frac{0.252TB}{(1+0.008TBN)^2} \\ \frac{0.252BN}{(1+0.008TBN)^2} & -1.25+\frac{0.252TN}{(1+0.008TBN)^2} & \frac{0.252TB}{(1+0.008TBN)^2} \\ \frac{0.252BN}{(1+0.008TBN)^2} & \frac{0.252TN}{(1+0.008TBN)^2} & -1.25+\frac{0.252TB}{(1+0.008TBN)^2} \end{pmatrix} \quad (12)$$

At (T* B* N*) = (1 1 1), we obtain:

$$J(1,1,1) = \begin{pmatrix} -1.25+\frac{0.252BN}{(1+0.008TBN)^2} & \frac{0.252TN}{(1+0.008TBN)^2} & \frac{0.252TB}{(1+0.008TBN)^2} \\ \frac{0.252BN}{(1+0.008TBN)^2} & -1.25+\frac{0.252TN}{(1+0.008TBN)^2} & \frac{0.252TB}{(1+0.008TBN)^2} \\ \frac{0.252BN}{(1+0.008TBN)^2} & \frac{0.252TN}{(1+0.008TBN)^2} & -1.25+\frac{0.252TB}{(1+0.008TBN)^2} \end{pmatrix} \quad (13)$$

Table 2: Classification of the equilibrium points

| Equilibrium point | Eigenvalues | Classification |
|---|---|---|
| (1, 1, 1) | $\lambda_1$= - 1.25, $\lambda_2$= -1.25, $\lambda_3$= -1.25 | Asymptotically stable |
| (1.6, 1.6, 1.6) | $\lambda_1$= -1.25, $\lambda_2$= 0.50, $\lambda_3$= 4.25 | Unstable Point |
| (25.8, 25.8, 25.8) | $\lambda_1$= -1.25, $\lambda_2$= - 1.25, $\lambda_3$= 4312642.00 | Unstable Point |
| (-2.4,-2.4,-2.4) | $\lambda_1$= -1.25, $\lambda_2$= - 1.25, $\lambda_3$= 4.25 | Unstable Point |

$$J(1,1,1) = \begin{bmatrix} -1.00198 & 0.248017 & 0.248017 \\ 0.248017 & -1.00198 & 0.248017 \\ 0.248017 & 0.248017 & -1.00198 \end{bmatrix} \quad (14)$$

The eigenvalues were obtained to be $\lambda_1$ = -1.2500, $\lambda_2$ = -1.2500 and $\lambda_3$ = -0.5059.

At (T*, B*, N*) = (1.6, 1.6, 1.6) we obtain:

$$J(1.6,1.6,1.6) = \begin{bmatrix} -0.645168 & 0.604832 & 0.604832 \\ 0.604832 & -0.64568 & 0.604832 \\ 0.604832 & 0.604832 & -0.645168 \end{bmatrix} \quad (15)$$

The eigenvalues were found to be; $\lambda_1$ = -1.2500, $\lambda_2$ = -1.2500 and $\lambda_3$ = 0.5645.

At (T*, B*, N*) = (-2.4, -2.4, -2.4) we obtain:

$$J(-2.4,-2.4,-2.4) = \begin{bmatrix} 0.584935 & 1.83494 & 1.83494 \\ 1.83494 & 0.584935 & 1.83494 \\ 1.83494 & 1.83494 & 0.584935 \end{bmatrix}$$

The eigenvalues were found to be $\lambda_1$ = -1.2500, $\lambda_2$ = -1.2500 and $\lambda_3$ = 4.2548.

At (T*, B*, N*) = (25.8, 25.8, 25.8) we obtain:

$$J(25.8,25.8,25.8) = \begin{bmatrix} 112.9214 & 114.1714 & 114.1714 \\ 114.1714 & 112.9214 & 114.1714 \\ 114.1714 & 114.1714 & 112.9214 \end{bmatrix}$$

The eigenvalues were found to be; $\lambda_1$ = -1.2500, $\lambda_2$ = -1.2500 and $\lambda_3$ = 431.2642.

Table 2 shows the equilibrium points, their corresponding eigenvalues and the classifications of these equilibrium points as indicated in Eq. 11.

The classification of the equilibrium points allows us to qualitatively describe the behaviour of the system for all initial values. There is one stable point (nodal sink) that will attract solution curves that begin near it and that around this point are three saddle points that will "bend" solution curves that begin near them. We can therefore predict that there will be one basin of attraction, for this nodal sink which is bounded by three unstable solution curves that pass through the nodal sink.

It is observed that all the eigen values corresponding to the equilibrium point:

$$\begin{pmatrix} T^* \\ B^* \\ N^* \end{pmatrix} = \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix}$$

Are the same and are negative as well. That is:

$\lambda_1 = -1.25$, $\lambda_2 = -1.25$ and $\lambda_3 = -1.25$

We say that this point is asymptotically stable. This means that all solution curves will tend towards this point for all initial conditions in its neighborhood. This equilibrium point is also called a sink since all of the eigenvalues have negative real part. This is the point where the system is stable.

The eigenvalues corresponding to the equilibrium point:

$$\begin{pmatrix} T^* \\ B^* \\ N^* \end{pmatrix} = \begin{bmatrix} 1.6 \\ 1.6 \\ 1.6 \end{bmatrix}$$

Are $\lambda_1 = -1.25$, $\lambda_2 = 0.50$ and $\lambda_3 = 4.25$

Since the eigenvalues are real with mixed signs (one negative and the other two positive), we say that this equilibrium point is unstable and it is also called a saddle point for the same reason of at least having one of its eigenvalues as negative real part and one as a positive real part.

The eigenvalues corresponding to the equilibrium point:

$$\begin{bmatrix} T^* \\ B^* \\ N^* \end{bmatrix} = \begin{vmatrix} 25.8 \\ 25.8 \\ 25.8 \end{vmatrix}$$

Are $\lambda_1 = -1.25$, $\lambda_2 = -1.25$ and $\lambda_3 = 4.25$

This equilibrium point is also unstable since its eigenvalues are of opposite signs.

The eigenvalues corresponding to the equilibrium point:

$$\begin{bmatrix} T^* \\ B^* \\ N^* \end{bmatrix} = \begin{vmatrix} -2.4 \\ -2.4 \\ -2.4 \end{vmatrix}$$

Are $\lambda_1 = -1.25$, $\lambda_2 = -1.25$ and $\lambda_3 = 4.25$

which is also an unstable point for the same reason given above.

Figure 1 Illustrates the behaviour of lymphocytes in the absence of the virus cells. The growth rates of T, B and Natural Killer cells were considered to be the same. The curve shows that all the lymphocyte population types increase with time when viruses have not invaded the human body. We observe that the cells (T, B and Nk) grow exponentially and reach a constant endemic value of 25 which represent the carrying capacity. This confirms the logistic growth nature of the lymphocytes population.

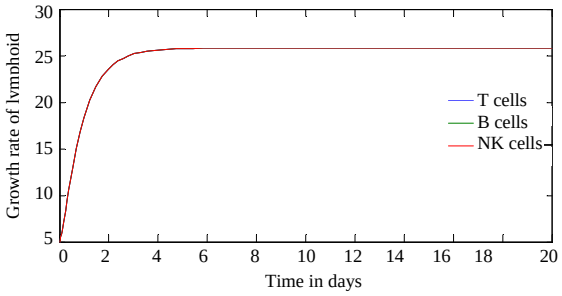


Fig. 1: Growth nature of lymphoid cells in the absence of viruses (equal growth rates)

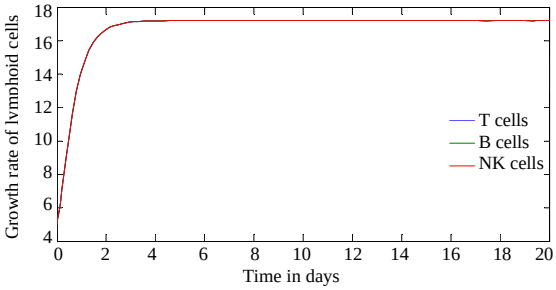


Fig. 2: Growth nature of lymphoid cells in the absence of viruses (equal but higher growth rates)

Figure 2 illustrates the behaviour or growth nature of the three lymphoid cells (T, B and Nk) in the absence of viruses. It is observed that there is exponential growth rate at the initial stage and reaches a certain endemic constant value which represents the carrying capacity of the population types.

Figure 3 illustrates the growth nature of T, B and Nk cells in the absence of viral infections. With equal growth rates of T and B cells and different growth rate of NK cells, it is observed that the growth nature still follows the logistic pattern.

Figure 4 illustrates the behaviour of lymphoid cells in the absence of viral infections. We observed that as time increases all the lymphoid cells increase but at different

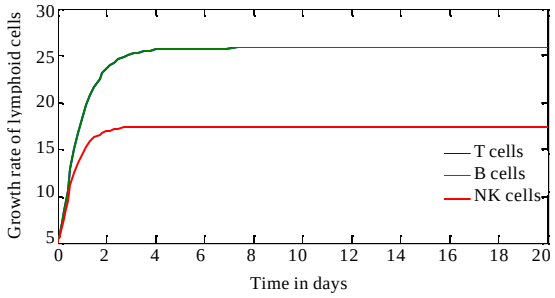


Fig. 3: Growth nature of lymphoid cells in the absence of viruses (equal growth rates of T and B but different growth rate of kn cells)

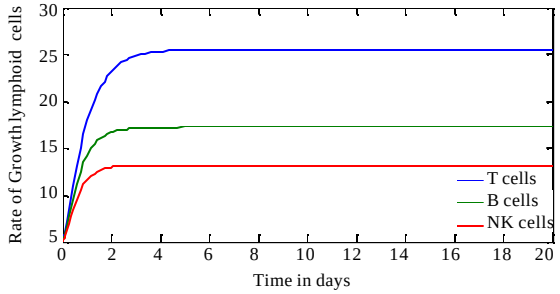


Fig. 4: Growth nature of lymphoid cells in the absence of viruses (different growth rates)

growth rates. All the three cells increase exponentially at the initial stages to reach a saturation point where there is no sharp increase. This constant endemic value (saturation point) represents the carrying capacity of the population types.

## DISCUSSION

The characteristics of the NK cells is to provide the first line of defense to viral infections. However, it is observed from the study that their growth pattern is similar to those lymphocytes that do not provide the first line of defense. The results of this study are in conformity with the study of Anderson and May (1992) who considered the behaviour of two lymphocytes population types (T and B). The growth nature of (T and B) lymphocytes in the absence of viral infections which was considered by Anderson and May (1992) is similar to the third lymphoid cell (NK) which was considered as an extension to the work of these previous authors. It could be predicted that there would be differences in the growth nature of these three lymphoid cells as soon viruses invade the human system. This is because the (NK) cells will provide the first line of defense as (T and B) cells get ready to attack.

Thus until there is viral infection, their growth activity cannot be separated. We observed from all the figures that as time increases, there is always the production of lymphoid cells. The lymphoid cells grow exponentially in the initial stages and they approach a certain constant value which represent the carrying capacity of their population. This is the state where the interaction between the lymphoid cells types saturate in the immune state. At this point, the lymphoid cells are said to be pre-programmed to react with any invading organism for that matter viruses that get into the immune system. It was found from the study that the stable state corresponded to the equilibrium point:

$$\begin{pmatrix} T^* \\ B^* \\ N^* \end{pmatrix} = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix}$$

The other three equilibrium points corresponded to unstable states. It was found from the study that NK cells should be given priority if any immunotherapy is to be made since it provides the first line of defence and these cells do not also require more days to react with invading viruses. The model, therefore, displays all of the major macroscopic characteristics of the human immune response to viral infections.

## CONCLUSION

By numerical simulation analysis, the cells (T, B and NK) grow exponentially and reach a carrying capacity as time (t) increases. We were expecting that the NK cells' growth pattern in the absence of viral infection would be different from the lymphocyte types used by Anderson and May (1992). However, we determined otherwise. Thus before the inception of viral infection the growth dynamics of the three types of cells are the same. The growth nature of the Natural killer cells will be different as viruses enter the human body. The model permits the existence of two types of stationary states. There is a stable state in the immune system and an unstable state. The stable state represents the pre-programmed state of the lymphoid cells to attack invaders should they enter the system.

The unstable state represents immuno-deficiency as a result of one or more cells within the immune system not operating properly or the cells are absent altogether.

It can be concluded that the lymphoid cells in a persons' immune state should be ready to fight invaders if there are no deformities of the immune cells. It is

recommended that further research be carried out on variable sensitivity analysis and bifurcation to determine which of the immune cells is so critical to be pre-programmed to fight viral infections when viruses invade the human body. It is also recommended that this study applied to a specific viral infection in the near future.

## APPENDIX

MATLAB codes for numerical solutions and simulations

```
p= [1,-26, 125,-100];
r=roots (p)
p= [1,-26, 125,-100];
r=roots (p)
A=[-1.25,0.05,0,0,0;0,-0.08,0,0,0;0,0,-1.0505,0.1996,0.04;0,0,0.1996,-
1.0505,0;0,0,0,0,-0.9];
Lambda=eig (A)
B=[-1.21,0.05,0,0,0;-0.008,-1.24,0,0,0;0,0,-1.25,0,0.04;0,0,0,-
1.25,0;0,0,0,0,0.99];
Lambda=eig (B)
C=[-1.21,0.05,0,0,0;-0.008,-6.25,0,0,0;0,0,-1.25,0,0.25;0,0,0,-
1.25,0;0,0,0,0,0.05];
Lambda=eig(C)
D=[-1.21,1,0,0,0;-0.008,-24.99,0,0,0;0,0,-1.25,0,1;0,0,0,-1.25,0;0,0,0,0,-
0.1];
Lambda=eig (D)
function yprft =yprft(t,y)
yprft(1) =1-1.25*y(1)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
yprft(2) =1-1.25*y(2)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
yprft(3) =1-1.25*y(3)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
yprft = [yprft(1) yprft(2) yprft(3)]';
function nk =nk(t,y)
nk(1) =1-1.25*y(1)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
nk(2) =1-1.25*y(2)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
nk(3)  =1.5-1.875*y(3)+0.378*y(1)*y(2)*y(3)/(1.5+0.012*y(1)*y(2)*y(3));
nk = [nk(1) nk(2) nk(3)]';
function paper =paper(t,y)
paper(1) = 1.5-
1.875*y(1)+0.378*y(1)*y(2)*y(3)/(1.5+0.012*y(1)*y(2)*y(3));
paper(2) = 1.5-
1.875*y(2)+0.378*y(1)*y(2)*y(3)/(1.5+0.012*y(1)*y(2)*y(3));
paper(3) = 1.5-
1.875*y(3)+0.378*y(1)*y(2)*y(3)/(1.5+0.012*y(1)*y(2)*y(3));
paper = [paper(1) paper(2) paper(3)]';
function var =var(t,y)
var(1) =1-1.25*y(1)+0.252*y(1)*y(2)*y(3)/(1+0.008*y(1)*y(2)*y(3));
var(2)  =1.5-1.875*y(2)+0.378*y(1)*y(2)*y(3)/(1.5+0.012*y(1)*y(2)*y(3));
var(3) =2-2.5*y(3)+0.504*y(1)*y(2)*y(3)/(2+0.016*y(1)*y(2)*y(3));
var = [var(1) var(2) var(3)]';
```

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