A Discrete Time Mathematical Model on Lung Cancer Incorporating Smokers and Non Smokers

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Abstract— Cancer epidemiology is the branch of epidemiology concerned with the disease cancer. Cancer epidemiology uses epidemiological methods to find the cause of cancer and to identify and develop improved treatments. In this paper, we construct and analyze a discrete time mathematical model on lung cancer involving smokers and non smokers. We derive the two equilibrium points namely smoke free and smoke induced equilibrium and analyze the conditions in which the equilibrium points are stable or unstable. We derive the basic reproduction number of the model. Finally, we prove our theoretical results using numerical simulations through MATLAB.

Keywords: *Difference equations, Disease-free and endemic equilibria, Basic reproduction number, Lung Cancer.*

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I. INTRODUCTION

A mathematical model is a description of a system using mathematical concepts. Epidemic models are used as a tool to analyze the behaviors of biological diseases and how they spread. Lung cancer is the leading cause of cancer deaths worldwide. The WHO reports that over 1.1 million people die of Lung cancer each year. As a result, WHO has identified Lung cancer as one of the new problems facing the world in this new century.

Lung cancer develops when cells that line the lungs sustain genetic damage. Scientists have identified several different chemicals and environmental factors that are capable of causing the kind of genetic damage that can lead to lung cancer. Majority of lung cancer occur in people who are either current or former smokers. While the relationship between smoking and lung cancer is well established, other factors also came into play. The health risks of tobacco smoke are not limited to smokers. The lungs of anyone who breathes the air that contains tobacco smoke are exposed to its carcinogens. Therefore, exposure to smoky air in the home, workplace, or in public can increase a person's risk of lung cancer. This kind of exposure is called second-hand smoke, side-stream smoke, environmental tobacco smoke or passive smoke. Some of the most common lung carcinogens are asbestos, radon, arsenic, chromium and nickel.

- The risk of developing lung cancer from smoking is influenced by many factors including the age at which the person began smoking. The effect of carcinogens accumulate over time.
- Genes control how a person's body handle carcinogens, how susceptible it is to genetic damage, and how capable it is of repairing the damage that occurs. One of the most striking features of lung cancer cells is the large number of genetic changes present in them.
- While we know that the total amount of exposure is one factor that governs whether someone develops lung cancer, we also know that it is not the only factor. Most of the lifelong smokers never develop lung cancer and a significant number of people with no known personal or environmental risk factors develop lung cancer. These facts make it obvious that, it is not only what we are exposed to, but also how our bodies handle the exposures that determine whether the lung cancer develops.

Taking these factors into consideration, we construct a mathematical model involving smokers and non smokers and analyze the system. We consider exponential rate for production of cancer cells. As one of the most striking features of lung cancer cells is the large number of genetic changes present in them. Often 10 to 20 genetic mutations are found, indicating a genetic instability in lung cancer cells.

Mathematical model of tumor growth and treatment was studied by Heiko Enderling and Mark A.J. Chaplain. Nonlinear modelling of cancer: bridging the gap between cells and tumours was studied by J S Lowengrub, H B Frieboes, F Jin, Y-L Chuang, X Li, P Macklin, S M Wise, and V Cristini. Mathematical modeling of tumor therapy with oncolytic viruses was analyzed by Georgy P. Karev , Artem S. Novozhilov, Eugene V. Koonin. Mathematical Modelling of Cancer Invasion of Tissue was analyzed by M.A.J Chaplain and G. Lolas.

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II. MODEL FORMULATION

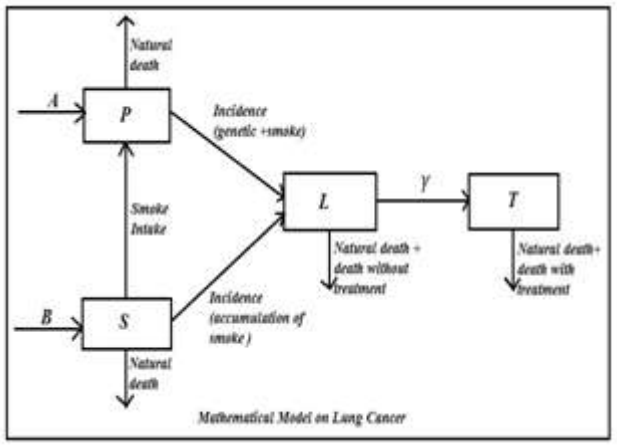

Fig.: Mathematical Model on Lung Cancer

We construct a mathematical model using a system of Differential equations which is given below:

$$\begin{aligned}
\frac{dP(t)}{dt} &= pA+\beta P(t)S(t)-\left(Ke^{-\frac{r}{\varepsilon_D}}+d\right)P(t)\\
\frac{dS(t)}{dt} &= (1-p)A-\beta P(t)S(t)-(\theta+d)S(t)\\
\frac{dL(t)}{dt} &= \theta S(t)+Ke^{-\frac{r}{\varepsilon_D B}}P(t)-(\gamma+d+\delta)L(t)\\
\frac{dT(t)}{dt} &= \gamma L(t)-(d+\delta_1)T(t)
\end{aligned} \qquad (1)$$

$P(t)$ is the population of non smokers at time t. $S(t)$ is the population of smokers at time t. $L(t)$ is the population affected by lung cancer at time t. $T(t)$ is the population getting treatment for lung cancer at time t. A is the constant population. p is the rate of population who do not smoke. β is the rate of passive smoke intake by non smokers when they come in contact with smokers. d is the natural death rate. γ is the rate at which treatment for lung cancer is provided. δ is the death rate due to lung cancer without treatment. δ_1 is the death rate due to lung cancer with treatment.

Following the Strehler and Mildvan model for mortality, we assume that an organism has a certain capacity to stay healthy ie) to have no tumors at age x. The capacity or 'vitality' is defined as linear function of age.

$$V(x)=V_0(1-Bx)$$

where the parameter B characterises the slope of the vitality curve. V_0B can be interpreted as rate of physiological aging. Suppose that the intensity of events associated with external stress does not depend on age ie) $K(x)=K$. Let ε_D be the average magnitude of stress. Under these assumptions the observed cancer incidence rates are

$$u(x)=Ke^{-\frac{V(x)}{\varepsilon_D}}$$

We take $V(x)=r$. That is, the vitality at age x is taken to be a constant. This is taken as the incidence rate for non smokers. Whereas, the incidence rate for smokers is taken as θ. Doctors refer to this risk in terms of pack-years of smoking.

We discretize the model (1) using Backward Euler method:

$$\begin{aligned}
P(t+1) &= P(t)+pA+\beta P(t+1)S(t+1)-\left(Ke^{-\frac{r}{\varepsilon_D}}+d\right)P(t+1)\\
S(t+1) &= S(t)+(1-p)A-\beta P(t+1)S(t+1)-(\theta+d)S(t+1)\\
L(t+1) &= L(t)+Ke^{-\frac{r}{\varepsilon_D}}P(t+1)+\theta S(t+1)-(\gamma+d+\delta)L(t+1)\\
T(t+1) &= T(t)+\gamma L(t+1)-(d+\delta_1)T(t+1)
\end{aligned} \qquad (2)$$

Let us take $N(t)=P(t)+S(t)+L(t)+T(t)$, Adding all the equations of the model, we get

$$\begin{aligned}
N(t+1) &= N(t)+A-dN(t+1)-\delta L(t)-\delta_1 T(t)\\
&\le N(t)+A-dN(t+1)
\end{aligned} \qquad (3)$$

For our model, we get the equilibrium point $N^*=\frac{A}{d}$, which is globally asymptotically stable as $\lim_{t\to\infty}N(t)=N^*$.

The initial conditions are given by,

$$P(0)\ge 0, S(0)\ge 0, L(0)\ge 0, T(0)\ge 0 \qquad (4)$$

Let us assume that the following condition holds:

$$0<Ke^{-\frac{r}{\varepsilon_D}}+d, \beta P^0+\theta+d, \gamma+\delta+d<2 \qquad (5)$$

We can reduce the system (2) as follows:

$$\begin{aligned}
P(t+1) &= P(t)+pA+\beta P(t+1)S(t+1)-\left(Ke^{-\frac{r}{\varepsilon_D}}+d\right)P(t+1)\\
S(t+1) &= S(t)+(1-p)A-\beta P(t+1)S(t+1)-(\theta+d)S(t+1)\\
L(t+1) &= L(t)+Ke^{-\frac{r}{\varepsilon_D}}P(t+1)+\theta S(t+1)-(\gamma+d+\delta)L(t+1)
\end{aligned} \qquad (6)$$

III. EQUILIBRIUM POINTS

The system has two equilibrium points namely the smoke free equilibrium and the smoke induced equilibrium [4].

A. Smoke-free Equilibrium

Smoke free equilibrium is the condition in which there is no passive intake of smoke. $E^0=(P^0,0,0)$, where

$$P^0=\frac{pA}{Ke^{-\frac{r}{\varepsilon_D}}+d}$$

B. Smoke Induced Equilibrium

Smoke Induced equilibrium is the condition in which there is passive intake of smoke. $E^*=(P^*,S^*,L^*)$

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$$P^* = \frac{A}{\left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)}, S^* = \frac{(1-p)A\left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)}{\beta A + \left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)(\theta + d)}$$

$$L^* = \frac{AKe^{-\frac{r}{\varepsilon_D}}\left[\beta A + \left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)(\theta + d)\right] - \theta(1-p)A\left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)^2}{\left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)\left[\beta A + \left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)(\theta + d)\right](\delta + \gamma + d)}$$

C. Basic Reproduction Number

In epidemiology, the basic reproduction number, denoted by R_0, is a significant epidemiological quantity, which plays an important role in the dynamics of disease transmission. We find the basic reproduction number of the system (6) to be

$$R_0 = \frac{AKe^{-\frac{r}{\varepsilon_D}}\left[\beta A + \left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)(\theta + d)\right]}{\theta(1-p)A\left(Ke^{-\frac{r}{\varepsilon_D}} + d\right)^2} \quad (7)$$

IV. Stability Analysis

Theorem 1:
The smoke free equilibrium is locally asymptotically stable if condition (5) holds and $R_0 \leq 1$.

Proof:
The Jacobian matrix of System (6) at E^0 is given by

$$J(E^0) = \begin{pmatrix} 1-\left(Ke^{-\frac{r}{\varepsilon_D}} + d\right) & \beta P^0 & 0 \\ 0 & 1-\beta P^0 - (\theta + d) & 0 \\ Ke^{-\frac{r}{\varepsilon_D}} & \theta & 1-(\gamma + \delta + d) \end{pmatrix} \quad (8)$$

The eigen values of this matrix is given by

$$\lambda_1 = 1-\left(Ke^{-\frac{r}{\varepsilon_D}} + d\right), \lambda_2 = 1-\beta P^0 - (\theta + d), \lambda_3 = 1-(\gamma + \delta + d)$$

The modulus of the eigen values is less than one if the conditions $0 < Ke^{-\frac{r}{\varepsilon_D B}} + d, \beta P^0 + \theta + d, \gamma + \delta + d < 2$ are satisfied. Hence the smoke free equilibrium is locally asymptotically stable.

Theorem 2:
The smoke induced equilibrium is locally asymptotically stable if $R_0 > 1$ and

$$2 + \beta S^* > \beta P^* + Ke^{-\frac{r}{\varepsilon_D B}} + \theta + 2d$$

$$\left[\left(1 + \beta S^* - \left(Ke^{-\frac{r}{\varepsilon_D B}} + d\right)\right) - \left(1 - (\theta + d) - \beta P^*\right)\right]^2 > 4\beta^2 P^* S^*$$

Otherwise unstable.

Proof:
The Jacobian matrix of system (6) at E^* is given by

$$J(E^*) = \begin{pmatrix} 1+\beta S^* - \left(Ke^{-\frac{r}{\varepsilon_D}} + d\right) & \beta P^* & 0 \\ -\beta S^* & 1-(\theta + d) - \beta P^* & 0 \\ Ke^{-\frac{r}{\varepsilon_D}} & \theta & 1-(\gamma + \delta + d) \end{pmatrix} \quad (9)$$

One of the eigen values of the matrix is given by

$$\lambda = 1-(\gamma + \delta + d)$$

The remaining matrix can be written as,

$$J(E^*) = \begin{pmatrix} 1+\beta S^* - \left(Ke^{-\frac{r}{\varepsilon_D}} + d\right) & \beta P^* \\ -\beta S^* & 1-(\theta + d) - \beta P^* \end{pmatrix} \quad (10)$$

The characteristic equation of the matrix is given by,

$$\varphi(\lambda) = \lambda^2 + a_1\lambda + a_2 = 0 \quad (11)$$

where

$$a_1 = -\left[Ke^{-\frac{r}{\varepsilon_D B}} + \theta + 2(d-1) + \beta(P^* - S^*)\right]$$

$$a_2 = \left[1 + \beta S^* - \left(Ke^{-\frac{r}{\varepsilon_D B}} + d\right)\right]\left[1-(\theta + d) - \beta P^*\right] + \beta^2 P^* S^*$$

We see that characteristic equation (10) has positive roots if $R_0 > 1$ and

$$2 + \beta S^* > \beta P^* + Ke^{-\frac{r}{\varepsilon_D B}} + \theta + 2d$$

$$\left[\left(1 + \beta S^* - \left(Ke^{-\frac{r}{\varepsilon_D B}} + d\right)\right) - \left(1 - (\theta + d) - \beta P^*\right)\right]^2 > 4\beta^2 P^* S^*$$

V. Global Stability

Theorem 3:
Under the conditions of theorem (3), if there are positive number δ and n satisfying the following inequalities:

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$$i)\left[\left(Ke^{-\frac{r}{\varepsilon_D B}}+d\right)-\beta S^*\right]n_1-k_1\left(n_2\beta+n_3Ke^{-\frac{r}{\varepsilon_D B}}\frac{1}{k_3}\right)>\delta$$

$$ii)n_2\left[\beta P^*+\left(Re^x+d\right)\right]-k_2\left(n_1\beta+Re^x\frac{1}{k_3}\right)>\delta$$

$$iii)n_3\left(\gamma+d+\delta\right)>\delta$$

Then the positive equilibrium E^* is globally stable.

Proof:

We make translation transformations,

$$u(t)=P(t)-P^*$$
$$v(t)=S(t)-S^*$$
$$w(t)=L(t)-L^*$$

Substituting it into (6), getting that $(u(t),v(t),w(t))$ changed by $(P(t),S(t),L(t))$, we have

$$P(t+1)-P(t)=pA+\left(P(t)+P^*\right)\left[\beta\left(S(t)+S^*\right)-\left(Ke^{-\frac{r}{\varepsilon_D B}}+d\right)\right]$$
$$S(t+1)-S(t)=(1-p)A-\left(S(t)+S^*\right)\left[\beta\left(P(t)+P^*\right)+\left(Re^x+d\right)\right]$$
$$L(t+1)-L(t)=Ke^{-\frac{r}{\varepsilon_D B}}\left(P(t)+P^*\right)+Re^x\left(S(t)+S^*\right)-\left(\gamma+d+\delta\right)\left(L(t)+L^*\right) \quad (12)$$

Where $(0,0,0)$ is an equilibrium point of (12). Make Taylor expanding the right side of (12) on the equilibrium point $(0,0,0)$, we have

$$P(t+1)=P(t)\left[1+\beta S^*-\left(Ke^{-\frac{r}{\varepsilon_D B}}+d\right)\right]+\beta P^*S(t)+g_1\left(n,P(t),S(t),L(t)\right)$$
$$S(t+1)=S(t)\left[1-\beta P^*-\left(Re^x+d\right)\right]-\beta S^*P(t)+g_2\left(n,P(t),S(t),L(t)\right)$$
$$L(t+1)=L(t)\left(1-\left(\gamma+d+\delta\right)\right)+Ke^{-\frac{r}{\varepsilon_D B}}P(t)+Re^xS(t)+g_3\left(n,P(t),S(t),L(t)\right) \quad (13)$$

where $X_n=(P(t),S(t),L(t))$ and $\|X_n\|=|P_n|+|S_n|+|L_n|$. If $\|X_n\|\to 0$, then

$$\frac{\left|g_2\left(n,P(t),S(t),L(t)\right)\right|}{\|X_n\|}\to 0 \quad (14)$$

For every $n\in N$, they are consistent $(i=1,2)$. Then (13) can be written as follows:

$$P(t+1)-P(t)=P^*\left[\beta S^*-\left(Ke^{-\frac{r}{\varepsilon_D B}}+d\right)\right]\frac{P(t)}{P^*}+P^*\left\{\beta S^*\frac{S(t)}{S^*}+g_1\left(n,P(t),S(t),L(t)\right)\right\}$$
$$S(t+1)-S(t)=S^*\left[-\beta P^*-\left(Re^x+d\right)\right]\frac{S(t)}{S^*}+S^*\left\{-\beta P^*\frac{P(t)}{P^*}+g_2\left(n,P(t),S(t),L(t)\right)\right\}$$
$$L(t+1)-L(t)=-L^*\left(\gamma+d+\delta\right)\frac{L(t)}{L^*}+L^*Ke^{-\frac{r}{\varepsilon_D B}}\frac{P^*}{L^*}\frac{P(t)}{P^*}+L^*\left\{Re^x\frac{S^*}{L^*}\frac{S(t)}{S^*}+g_3\left(n,P(t),S(t),L(t)\right)\right\} \quad (15)$$

$$P(t+1)-P(t)=P^*\left[\beta S^*-\left(Ke^{-\frac{r}{\varepsilon_D B}}+d\right)\right]\frac{P(t)}{P^*}+P^*\left\{\beta k_2\frac{S(t)}{S^*}+g_1\left(n,P(t),S(t),L(t)\right)\right\}$$
$$S(t+1)-S(t)=S^*\left[-\beta P^*-\left(Re^x+d\right)\right]\frac{S(t)}{S^*}+S^*\left\{-\beta k_1\frac{P(t)}{P^*}+g_2\left(n,P(t),S(t),L(t)\right)\right\}$$
$$L(t+1)-L(t)=L^*Ke^{-\frac{r}{\varepsilon_D B}}\frac{k_1}{k_3}\frac{P(t)}{P^*}+L^*Re^x\frac{k_2}{k_3}\frac{S(t)}{S^*}+L^*\left\{-\left(\gamma+d+\delta\right)\frac{L(t)}{L^*}++g_3\left(n,P(t),S(t),L(t)\right)\right\} \quad (16)$$

where $k_1=\dfrac{pA}{Ke^{-\frac{r}{\varepsilon_D B}}+d-\beta S^*}$, $k_2=\dfrac{(1-p)A}{Re^x+d+\beta P^*}$ and $k_3=\dfrac{Re^xS^*+Ke^{-\frac{r}{\varepsilon_D B}}P^*}{\mu+\delta+d}$.

We have the following Lyapunov function:

$$V(P(t),S(t),L(t))=n_1\left|\frac{P(t)}{P^*}\right|+n_2\left|\frac{S(t)}{S^*}\right|+n_3\left|\frac{L(t)}{L^*}\right| \quad (17)$$

By condition(i)(ii)(iii) and (16), we get the difference of Lyapunov function as follows:

$$\Delta V(P(t),S(t),L(t))\le n_1\left[\beta S^*-\left(Ke^{-\frac{r}{\varepsilon_D B}}+d\right)\right]\left|\frac{P(t)}{P^*}\right|+n_1\beta k_2\left|\frac{S(t)}{S^*}\right|+n_1\left|\frac{g_1\left(n,P(t),S(t),L(t)\right)}{P^*}\right|$$

$$+n_2\left[-\beta P^*-\left(Re^x+d\right)\right]\left|\frac{S(t)}{S^*}\right|+n_2\beta k_1\left|\frac{P(t)}{P^*}\right|$$

$$+n_2\left|\frac{g_2\left(n,P(t),S(t),L(t)\right)}{S^*}\right|$$

$$+n_3\left[-\left(\gamma+d+\delta\right)\right]\left|\frac{L(t)}{L^*}\right|+n_3Ke^{-\frac{r}{\varepsilon_D B}}\frac{k_1}{k_3}\left|\frac{P(t)}{P^*}\right|$$

$$+Re^x\frac{k_2}{k_3}\left|\frac{S(t)}{S^*}\right|+n_3\left|\frac{g_3\left(n,P(t),S(t),L(t)\right)}{L^*}\right|$$

$$=-\left\{\left[\left(Ke^{-\frac{r}{\varepsilon_D B}}+d\right)-\beta S^*\right]n_1-k_1\left(n_2\beta+n_3Ke^{-\frac{r}{\varepsilon_D B}}\frac{1}{k_3}\right)\right\}\left|\frac{P(t)}{P^*}\right|$$

$$-\left\{n_2\left[\beta P^*+\left(Re^x+d\right)\right]-k_2\left(n_1\beta+Re^x\frac{1}{k_3}\right)\right\}\left|\frac{S(t)}{S^*}\right|$$

$$-n_3\left(\gamma+d+\delta\right)\left|\frac{L(t)}{L^*}\right|+n_1\left|\frac{g_1\left(n,P(t),S(t),L(t)\right)}{P^*}\right|$$

$$+n_2\left|\frac{g_2\left(n,P(t),S(t),L(t)\right)}{S^*}\right|+n_3\left|\frac{g_3\left(n,P(t),S(t),L(t)\right)}{L^*}\right|$$

As if $\|X_n\|\to 0$, then $\left|g_2\left(n,P(t),S(t),L(t)\right)\right|/\|X_n\|\to 0(i=1,2)$. If n is great enough, then there exists a positive δ such that $\Delta V\le -\delta\|X_n\|/2$. So, if the interior equilibrium $(0,0,0)$ of the system (12) is globally stable, then the interior equilibrium (P^*,S^*,L^*) of the system(6) is also globally stable.

VI. Numerical Simulation

According to the World Health Organisation(WHO), despite India's regulation on public smoking, 30% adults are found exposed to second hand tobacco smoke at work, the study said. WHO has also declared that there are approximately 120 million smokers in India. ie. India is home for 12% smokers worldwide. According to National Institute of Cancer Prevention and Research in 2012, the cancer incidence among both sexes is 70,000 and the mortality rate is 64,000.

From these information, we have

$$p=0.7,\beta=0.4,\delta=0.9,\gamma=0.8,d=0.748$$

Let us take a population size of 100. That is $A=100$.

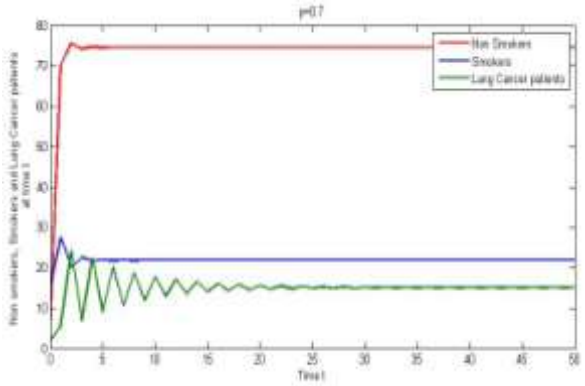

Figure 1. Dynamical Behaviour of System (6) with p=0.7

We consider the dynamical behaviour of the system for different values of p, that is, the rate of population who do not smoke.

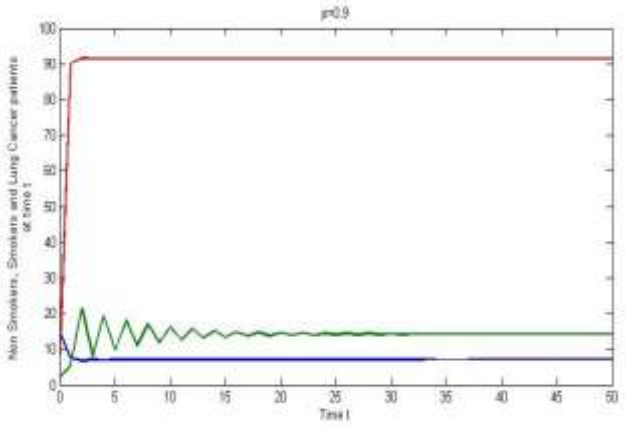

Figure 2. Dynamical Behaviour of System (6) with p=0.9

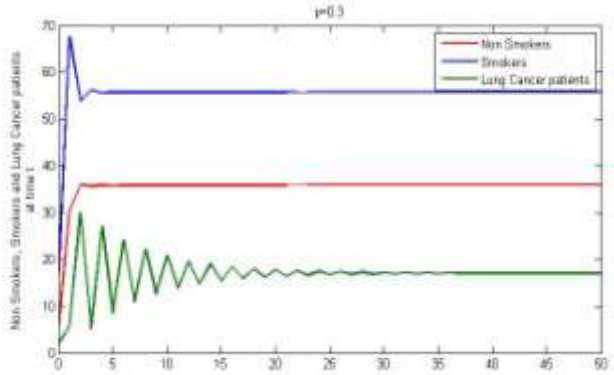

Figure 3. Dynamical Behaviour of System (6) with p=0.3

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