Mathematical Modeling on Interrelation between Ultraviolet Radiation and Skin Cancer

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Abstract

Cancer has become the second main cause of death in the world. Various types of cancers take place in human body. Among them skin cancer is a malignant cancer of the skin. It is the most common type of cancer in fair-skinned populations in many parts of the world. There are two main types of skin cancer such as melanoma and non-melanoma skin cancer. Skin cancer (Melanoma of skin) Deaths in Bangladesh reached 320 among 472 new cases, according to the latest WHO data published in 2018. So, it is a matter of concern also for Asian. The leading environmental risk factor for this type of fatal cancer is over-exposure of ultraviolet radiation. This paper deals with nonlinear dynamical systems in the form of mathematical modeling to elucidate the relationship between ultraviolet radiation and skin cancers. In particular, the model is expanded with the help of the concentration of the basic reproduction number and involved stability analysis for the disease-free and endemic equilibrium points. The aim is to show the relation between over exposure of UV radiation and skin cancer. This model is observed both analytically and numerically and the numerical simulations are carried out to explain the analytical finding.

Keywords
Ultraviolet radiation, skin cancer, stability, mathematical model, numerical analysis.

1. Introduction
Cancer is a generic name that refers to a group of diseases. Skin cancer is the out-of-control growth of abnormal cells in the epidermis. About 2 to 3 million non-melanoma skin cancers and 132,000 melanoma skin cancers occur globally each year (WHO, 2017). If we diagnose three cancers affected people then one parson is skin cancer affected, one American among five Americans develop skin cancer in their life. It is the most common type of cancer in fair-skinned populations in many parts of the world. It also takes place in dark-skinned people. It greatly affects quality of life, and it can be disfiguring or even deadly. Medical treatment for skin cancer creates massive health care costs for the nation. In 2018, 287,723 cases of melanoma skin cancer and 1,042,056 of non-melanoma skin cancer were diagnosed globally. 60,712 people died of melanoma skin cancer and 65,155 of non-melanoma skin cancer (WHO, 2018). Melanoma skin cancer deaths in Bangladesh reached 320 among 472 new cases (WHO, 2018).

Stratospheric ozone layer is decreasing 0.4 to 0.8 percent each year from 2012 (OWD, 2018), the atmosphere loses more and more of its protective filter function and more solar UV radiation reaches the Earth's surface. Newman et al. (2009) predicted that due to global reduction of stratosperic ozone layer dangerous UV index will be increased three times of its standard scale. Additional 300,000 non-melanoma and 4,500 melanoma skin cancer cases are caused by the 10 percent decay of ozone layer (WHO, 2017). Average temperature of Bangladesh will raise by 1.0° C to 1.5° C by 2050 even if resistant methods are taken by us. If we do not take any measure, then the country's average temperatures will increase by 1.0° C to 2.5° C (UNFCCC).

Ultraviolet radiation (UVR) is part of electromagnetic spectrum with wavelengths 100-400 nm emitted by the sun and by artificial sources (e.g. sunbeds, tanning devices). Reductions in stratospheric ozone (O_3) are expected to allow more solar ultraviolet-B to reach the earth surface. Consequently, more UV radiation that come from sun and sunbeds can harm the DNA in the skin cells. If enough DNA damage increases day by day, it can cause skin tumor, which can lead to skin cancer. Considering all the fatalities of skin cancer as well as the effect of ultraviolet radiation on skin

cancer, theory based as well as statistics study on skin cancer was discussed by many researchers. Fears et al. (1977) formulated a mathematical model considering the effect of age and UV on the outbreak of skin cancer among fair skinned people in the United States. De Grulil and Leun (1979) constructed a dose-response model, based on the results of animal experiments, presented for skin cancer induction in a human population by chronic exposure to ultraviolet radiation. Moan and Dahlback (1993) represented the effects of ultraviolet radiation on skin cancer in their theory based study. Shore (2001) discussed about radiation-induced skin cancer in humans. He also discussed the treatment options for skin cancer. Bharath and Turner (2009) represented the impact of climate change on skin cancer. Bishop et al. (2011) explained the relationship between sun exposure and melanoma risk for tumors in different body sites in a large case-control study in a temperate climate. Greinert et al. (2014) explored the effects of ultraviolet radiation on cancer. The research study of Kim and He (2014) represented the ultraviolet radiation-induced non-melanoma skin cancer as well as regulation of DNA damage repair and inflammation. Berwick and Garcia (2020) discussed about the solar UV exposure and mortality from skin tumors. Patel and Nagl (2010) and Allen et al. (2014) represented Surgery, chemotherapy, radiation therapy, hormonal therapy, hyperthermia, targeted therapy and ketogenic diet amongst other therapeutics as to inhibit tumor growth or kill the tumor cells in the body. However, each treatment has side effects attributed to it, for example, hair loss, vomiting, nausea and fatigue. Adverse effects occur as a result of chemotherapy, which is not able to differentiate between normal cells and tumor cells, consequently killing both of them. There is a large body of work to develop mathematical models and optimal control policies of infectious diseases. Biswas (2014) (see also Biswas *et al*., 2014) investigated and analyzed the treatment of most devastating infectious diseases independently in which mathematical modeling and optimal control strategy was the key tool. Taking the above discussions into account, we propose a model to study the dynamics of skin cancer transmission. Many theoretical as well as statistics models of skin cancer have been proposed by researchers. But this is a newly proposed differential equation mathematical model of skin cancer on the basis of some basic assumptions. Our goal is to study the disease dynamics of skin cancer due to the over exposure of ultraviolet radiation.

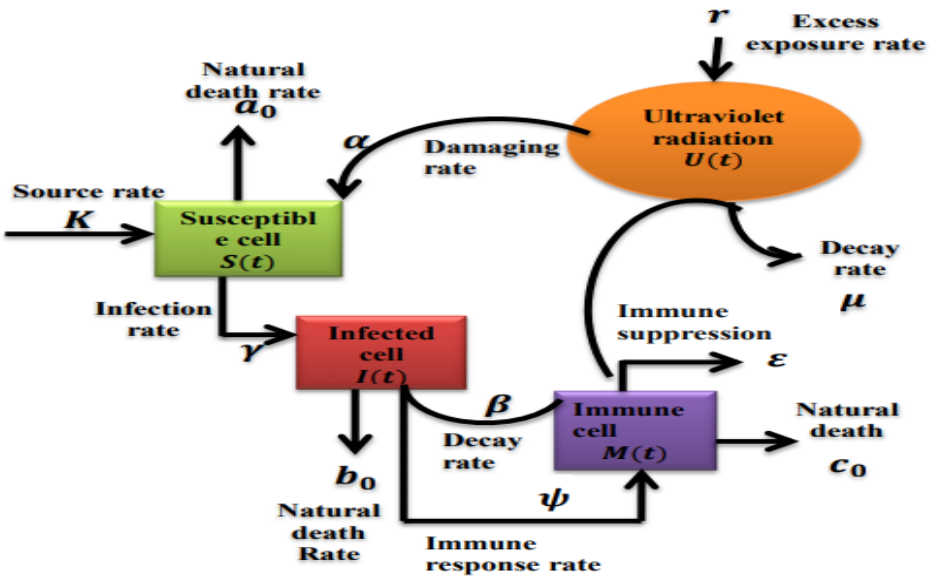

Figure 1: Diagram of the relation between ultraviolet radiation and Skin cancer

2. Mathematical model of skin cancer

There is no clinical documentation that close contact can spread skin cancer from one people to another. It is a non-communicable disease. Mathematical model is the most significant tools to analyze the transmission dynamics of non-communicable disease. Mathematical model of non-communicable disease help us to understand the mechanisms of different cell population. Our aim is to formulate a mathematical model of skin cancer and investigate the effect of ultraviolet radiation on skin cells. In this study, we represent a four compartmental model of skin cancer. Among them the first three compartments are cell population and the last one is environmental risk factor (ultraviolet radiation).

Susceptible cells are denoted by $S(t)$ which are mainly epidermis, the outer layer of our skin. Infected cells are denoted by $I(t)$ which are manly skin cancer stem cells and the immune cells are denoted by $M(t)$. Natural Killer (NK) cells, CD4+ T and CD8+ T cells are the main immune cells for this cancer which are created in bone marrow and matured in thymus gland. The main risk factor of skin cancer ultraviolet radiation is denoted by $U(t)$. Let K is the recruitment rate of susceptible cells, r is the excess exposure rate of Ultraviolet radiation that at first damage skin cell and then create cancer. The parameter s α is the rate at which ultraviolet light infecting or damaging the susceptible cells, γ is the rate at which susceptible cell infected in contact with infected cells, β is decay rate of infected cells in contact with immune cells, ψ is Immune response rate due to infected cells, ε is immunosuppression rate due to ultraviolet radiation and μ is decay rate of ultraviolet radiation. Also the parameters a_0, b_0 and c_0 are the natural death rate of susceptible, infected and immune cells.

According to the model diagram in Figure 1 and parameters described above, the mathematical model of skin cancer can be written in the form of following nonlinear system of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= K - (\alpha U + \gamma I)S - a_0 S \\
\frac{dI}{dt} &= (\alpha U + \gamma I)S - \beta IM - b_0 I \\
\frac{dM}{dt} &= \psi I - \varepsilon MU - c_0 M \\
\frac{dU}{dt} &= r - \mu U
\end{aligned} \tag{1}$$

With $S(0) = S_0 > 0$, $I(0) = I_0 \geq 0$, $M(0) = M_0 \geq 0$ and $U(0) = U_0 > 0$.

2.1 Properties of solutions

Boundedness of solutions:

In this section we investigate the boundedness of the solutions of the model (1). The model (1) describes the evolution of a cell population. Hence, the cell numbers should remain non negative and bounded.

Lemma 1 The solutions of the model (1) are uniformly bounded within the region

$$\phi = \left\{ (S, I, M) \in \mathbb{R}^3_+ : X(t) = S(t) + I(t) + M(t), 0 < X(t) \leq \frac{\chi}{\hbar} \right\}$$

Where $\hbar = \rho c_0$ and $\chi = Kc_0 + \psi K$.

Proof: Let $A(t) = S(t) + I(t)$

$$i.e. A \leq \frac{K}{\rho}\left(1 - e^{-\rho t}\right) + A_0 e^{-\rho t}$$

At $t \to \infty$

$$0 < A \leq \frac{K}{\rho}$$

From third equation of model (1) we get,

$$\frac{dM}{dt} = \psi I - \varepsilon MU - c_0 M$$

$$i.e. \frac{dM}{dt} + c_0 M \leq \psi I$$

$$S(t)+I(t)\le\frac{K}{\rho}$$

Since,

$$i.e. I(t)\le\frac{K}{\rho}$$

So, we can write

$$\frac{dM}{dt}+c_0M\le\frac{\psi K}{\rho}$$

$$i.e. M\le\frac{\psi K}{\rho c_0}\left(1-e^{-c_0t}\right)+M_0e^{-c_0t}$$

At $t\to\infty$

$$0<M\le\frac{\psi K}{\rho c_0}$$

Assume,

$$X(t)=S(t)+I(t)+M(t)=A(t)+M(t)$$

Now,

$$0+0<A(t)+M(t)\le\frac{K}{\rho}+\frac{\psi K}{\rho c_0}$$

$$\Rightarrow 0<X(t)\le\frac{Kc_0+\psi K}{\rho c_0}$$

$$i.e. 0<X(t)\le\frac{\chi}{\hbar}$$

Where $\chi=Kc_0+\psi K$ and $\hbar=\rho c_0$

Hence, the solutions of the model (1) is bounded in the region ϕ.

2.2 Model analysis

Existence of the equilibrium points of the system

The equilibrium points of the model (1) are obtained by equating $\frac{dS}{dt}=\frac{dI}{dt}=\frac{dM}{dt}=\frac{dU}{dt}=0$.

At disease free equilibrium point (DFE), $I=M=U=0$.

So, the disease free equilibrium point (DFE) is $E_0\left(\frac{K}{a_0},0,0,0\right)$.

Let, the endemic equilibrium point is $E^*\left(S^*,I^*,M^*,U^*\right)$.

Here, all state variables are non zero.After calculating we get the endemic equilibrium point is $E^*\left(S^*,I^*,M^*,U^*\right)=\left(\phi_2,\frac{\alpha r\phi_1\phi_2}{\mu\left(\beta\phi_1+b_0\phi-\gamma\phi_1\phi_2\right)},\frac{\psi\alpha r\phi_2}{\mu\left(\beta\phi_1+b_0\phi-\gamma\phi_1\phi_2\right)},\frac{r}{\mu}\right)$.

2.3 Basic reproduction number

A very important threshold quantity is the basic reproduction number, sometimes called the basic reproductive number or basic reproductive ratio, which is usually denoted by R_0. The epidemiological definition of R_0 is the average

number of secondary cases produced by one infected individual introduced into a population of susceptible individuals, where an infected individual has acquired the disease, and susceptible individuals are healthy but can acquire the disease. In reality, the value of R_0 for a specific disease depends on many variables. In our study we use the next generation matrix approach to find the basic reproduction number.

We obtain the Basic Reproduction Number $R_0 = \frac{\gamma S_0}{b_0}$.

The disease free equilibrium point (DFE) is $E_0\left(\frac{K}{a_0}, 0, 0, 0\right)$. So, $S_0 = \frac{K}{a_0}$

Thus we get,

$$R_0 = \frac{\gamma K}{a_0 b_0}$$

2.4 Stability analysis

Stability of DFE point

In this section, we want to found the stability at DFE point is locally stable providing the Theorem 1.

Theorem 1: The DFE point E_0 of the model (1) is locally asymptotically stable if $R_0 < 1$ and $R_0 > 1$, then it is unstable.

Proof: Let, $\frac{dS}{dt} = P, \frac{dI}{dt} = Q, \frac{dM}{dt} = R, \frac{dU}{dt} = T$

Then the model (1) becomes,

$$P = K - (\alpha U + \gamma I)S - a_0 S \tag{2}$$

$$Q = (\alpha U + \gamma I)S - \beta IM - b_0 I \tag{3}$$

$$R = \psi I - \varepsilon MU - c_0 M \tag{4}$$

$$T = r - \mu U \tag{5}$$

The Jacobian matrix of the system (2)-(5) can be written as,

$$J = \frac{\partial(P,Q,R,T)}{\partial(S,I,M,U)} = \begin{bmatrix} \frac{\partial P}{\partial S} & \frac{\partial P}{\partial I} & \frac{\partial P}{\partial M} & \frac{\partial P}{\partial U} \\ \frac{\partial Q}{\partial S} & \frac{\partial Q}{\partial I} & \frac{\partial Q}{\partial M} & \frac{\partial Q}{\partial U} \\ \frac{\partial R}{\partial S} & \frac{\partial R}{\partial I} & \frac{\partial R}{\partial M} & \frac{\partial R}{\partial U} \\ \frac{\partial T}{\partial S} & \frac{\partial T}{\partial I} & \frac{\partial T}{\partial M} & \frac{\partial T}{\partial U} \end{bmatrix} = \begin{bmatrix} -(\alpha U + \gamma I + a_0) & -\gamma S & 0 & -\alpha S \\ \alpha U + \gamma I & \gamma S - \beta M - b_0 & -\beta I & \alpha S \\ 0 & \psi & -(\varepsilon U + c_0) & -\varepsilon M \\ 0 & 0 & 0 & -\mu \end{bmatrix} \tag{6}$$

At point $E_0\left(\frac{K}{a_0}, 0, 0, 0\right)$ the Jacobian matrix becomes,

$$E_0 = \begin{bmatrix} -a_0 & -\frac{\gamma K}{a_0} & 0 & -\frac{\alpha K}{a_0} \\ 0 & \frac{\alpha K}{a_0} - b_0 & 0 & \frac{\alpha K}{a_0} \\ 0 & \psi & -c_0 & 0 \\ 0 & 0 & 0 & -\mu \end{bmatrix} \tag{7}$$

Using elementary row operation in equation (7) we obtain,

$$J_{E_0} = \begin{bmatrix} -a_0 & -\frac{\gamma K}{a_0} & 0 & -\frac{\alpha K}{a_0} \\ 0 & \frac{\alpha K - a_0 b_0}{a_0} & 0 & \frac{\alpha K}{a_0} \\ 0 & 0 & -c_0 & -\frac{\alpha K \psi}{\gamma K - c_0 b_0} \\ 0 & 0 & 0 & -\mu \end{bmatrix}$$

This is an 4×4 upper triangular Jacobian matrix.

So, the eigenvalues of J_{E_0} are $\lambda_1 = -a_0, \lambda_2 = \frac{\gamma K - a_0 b_0}{a_0} = b_0 \left(R_0 - 1 \right), \lambda_3 = -c_0$ and $\lambda_4 = -\mu$

The equilibrium point E_0 will be locally asymptotically stable when all the eigenvalues of J_{E_0} will be negative,

According to cell biology all the parameters of the model (1) is positive. So, clearly all the eigenvalues of J_{E_0} is negative except λ_2.

λ_2 is negative when $R_0 < 1$.

So, the equilibrium point E_0 is locally asymptotically stable when $R_0 < 1$, otherwise unstable.

Hence, the theorem 1 is proved.

Stability of endemic equilibrium point E^*

Here, we investigate the stability of endemic equilibrium point E^* using Theorem 2.

Theorem 2: The endemic equilibrium point $E^* \left(S^*, I^*, M^*, U^* \right)$ is locally asymptotically stable when $\left(\gamma S^* - \beta M^* - b_0 \right) \left(\alpha U^* + \gamma I^* + a_0 \right) < \gamma S^* \left(\alpha U^* + \gamma I^* \right)$ and $\psi \beta I^* \left(\alpha U^* + \gamma I^* + a_0 \right) < \left(\varepsilon U^* + c_0 \right) \left(\left(\gamma S^* - \beta M^* - b_0 \right) \left(\alpha U^* + \gamma I^* + a_0 \right) - \gamma S^* \left(\alpha U^* + \gamma I^* \right) \right)$ otherwise unstable.

Proof: Using equation (6) the Jacobian matrix at endemic equilibrium point $E^* \left(S^*, I^*, M^*, U^* \right)$ becomes,

$$J_{E^*}=\begin{bmatrix} -\left(\alpha U^*+\gamma I^*+a_0\right) & -\gamma S^* & 0 & -\alpha S^* \\ \alpha U^*+\gamma I^* & \gamma S^*-\beta M^*-b_0 & -\beta I^* & \alpha S^* \\ 0 & \psi & -\left(\varepsilon U^*+c_0\right) & -\varepsilon M^* \\ 0 & 0 & 0 & -\mu \end{bmatrix} \quad (8)$$

Using elementary row operation in equation (8) we obtain,

$$J_{E^*}=\begin{bmatrix} -\left(\alpha U^*+\gamma I^*+a_0\right) & -\gamma S^* & 0 & -\alpha S^* \\ 0 & C_2 & -\beta I^* & C_3 \\ 0 & 0 & D_2 & D_3 \\ 0 & 0 & 0 & -\mu \end{bmatrix}$$

The characteristic equation of this Jacobian matrix is,

$$\left|J_{E^*}-\lambda I\right|=\begin{vmatrix} -\left(\alpha U^*+\gamma I^*+a_0\right)-\lambda & -\gamma S^* & 0 & -\alpha S^* \\ 0 & C_2-\lambda & -\beta I^* & C_3 \\ 0 & 0 & D_2-\lambda & D_3 \\ 0 & 0 & 0 & -\mu-\lambda \end{vmatrix}=0$$

So, the eigenvalues of J_{E^*} are $\lambda_1=-\left(\alpha U^*+\gamma I^*+a_0\right), \lambda_2=C_2, \lambda_3=D_2$ and $\lambda_4=-\mu$.

Now, J_{E^*} will be stable if $C_2<0$ and $D_2<0$

Here,

$$C_2=\frac{\left(\gamma S^*-\beta M^*-b_0\right)\left(\alpha U^*+\gamma I^*+a_0\right)-\gamma S^*\left(\alpha U^*+\gamma I^*\right)}{\left(\alpha U^*+\gamma I^*+a_0\right)}$$

So, when

$C_2<0$

$$\frac{\left(\gamma S^*-\beta M^*-b_0\right)\left(\alpha U^*+\gamma I^*+a_0\right)-\gamma S^*\left(\alpha U^*+\gamma I^*\right)}{\left(\alpha U^*+\gamma I^*+a_0\right)}<0$$

$$\left(\gamma S^*-\beta M^*-b_0\right)\left(\alpha U^*+\gamma I^*+a_0\right)<\gamma S^*\left(\alpha U^*+\gamma I^*\right)$$

Then, J_{E^*} will be stable.

Here,

$$D_2=\frac{-\left(\varepsilon U^*+c_0\right)\left(\left(\gamma S^*-\beta M^*-b_0\right)\left(\alpha U^*+\gamma I^*+a_0\right)-\gamma S^*\left(\alpha U^*+\gamma I^*\right)\right)+\psi\beta I^*\left(\alpha U^*+\gamma I^*+a_0\right)}{\left(\gamma S^*-\beta M^*-b_0\right)\left(\alpha U^*+\gamma I^*+a_0\right)-\gamma S^*\left(\alpha U^*+\gamma I^*\right)}$$

So, when

$$D_2 < 0$$

$$D_2 = \frac{-\left(\varepsilon U^* + c_0\right)\left(\left(\gamma S^* - \beta M^* - b_0\right)\left(\alpha U^* + \gamma I^* + a_0\right) - \gamma S^*\left(\alpha U^* + \gamma I^*\right)\right) + \psi\beta I^*\left(\alpha U^* + \gamma I^* + a_0\right)}{\left(\gamma S^* - \beta M^* - b_0\right)\left(\alpha U^* + \gamma I^* + a_0\right) - \gamma S^*\left(\alpha U^* + \gamma I^*\right)} < 0$$

$$\psi\beta I^*\left(\alpha U^* + \gamma I^* + a_0\right) < \left(\varepsilon U^* + c_0\right)\left(\left(\gamma S^* - \beta M^* - b_0\right)\left(\alpha U^* + \gamma I^* + a_0\right) - \gamma S^*\left(\alpha U^* + \gamma I^*\right)\right)$$

Then, J_{E^*} will be stable otherwise, unstable.

Hence the Theorem 2 is proved.

3. Numerical Analysis

We perform numerical simulations of our model proposed in (1) by the ODE45-solver using MATLAB programming. To solve the epidemic model (1), we consider the initial values as $S(0) = 145,\ I(0) = 45,\ M(0) = 5,\ U(0) = 10,$ and all the values of the parameters used in Table 1. We perform simulations for the fixed final time 100 days.

Table 1: Parameter specifications of model (1)

Parameter	Description	Value
K	Recruitment rate of susceptible cells	5.07 day^{-1}
α	The rate at which ultraviolet light damaging the susceptible cells	0.001 day^{-1}
γ	The rate at which susceptible cells infected due to infected cells	0.02 day^{-1}
a_0	Natural death rate of susceptible cells	0.003 day^{-1}
β	Decay rate of infected cells in contact with immune cells	0.0034 day^{-1}
b_0	Natural death rate of infected cells	0.04 day^{-1}
ψ	Immune response rate due to infected cells	0.5 day^{-1}
ε	Immune Suppression rate due to ultraviolet radiation	0.002 day^{-1}
c_0	Natural death rate of immune cells	0.039 day^{-1}
R	Excess exposure rate of ultraviolet radiation	12 $uvindex$
μ	Decay rate of ultraviolet radiation	0.01 day^{-1}

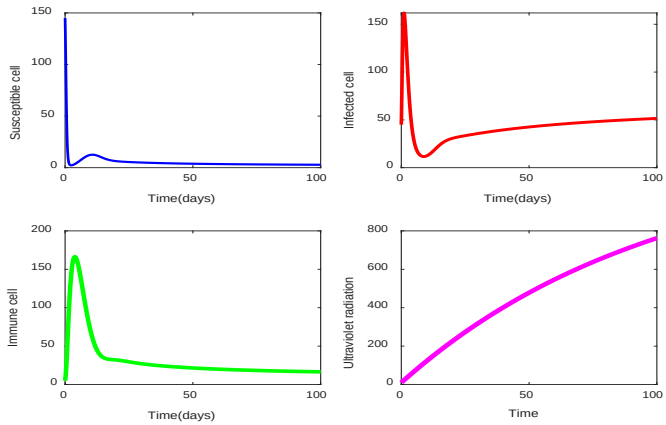

Figure 2: Time series graph of Susceptible cell, Infected cell, Immune cell and Ultraviolet Radiation

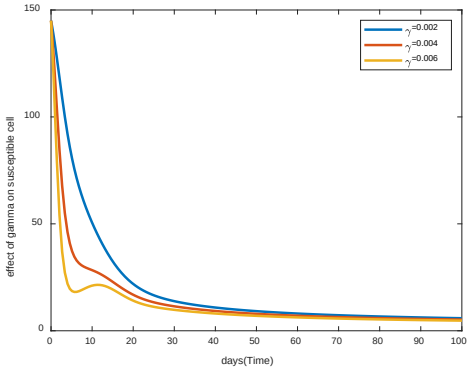

Figure 3: Effect of γ on susceptible cell

In this figure, we see that in the increase of values of γ the density of susceptible cell decrease respectively.

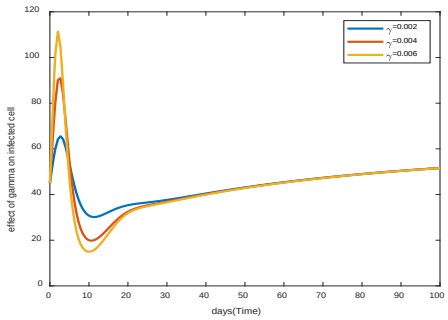

Figure 4: Effect of γ on infected cell

Here, we observe that, 0 to 5 days the density of infected cell increase with increase the values of γ, but 5 to 30 days the density decrees with increase the values of γ and 30 to 100 days there is no change in the density of infected cell with the increase the values of γ.

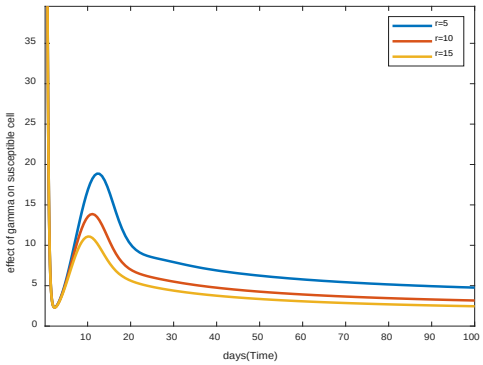

Figure 5: Effect of r on susceptible cell

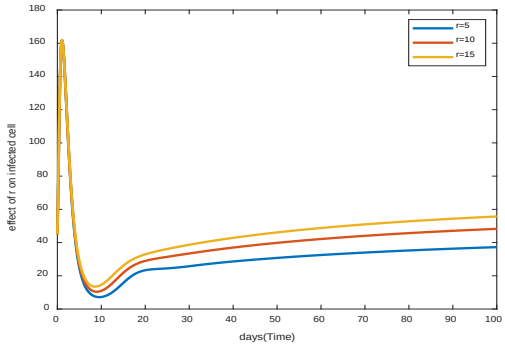

Figure 6: Effect of r on infected cell

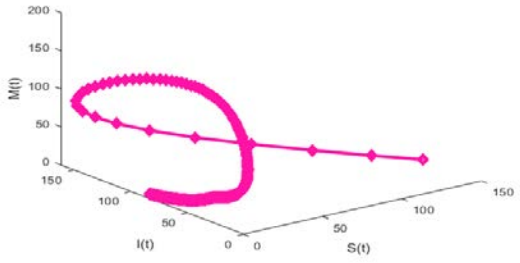

Figure 7: Variation of Susceptible cells, Infected cells and Immune cells when $R_0 > 1$

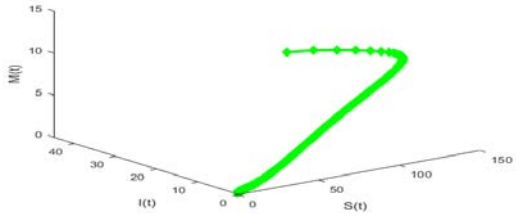

Figure 8: Variation of Susceptible cells, Infected cells and Immune cells when $R_0 < 1$

4. Conclusion

If we can't detect early, skin cancer becomes malignant. In this paper, a four compartmental model has been proposed to study the spread of Skin cancer. We first determine the basic reproduction number and perform the stability analysis of equilibria (disease free and endemic point). We find that the disease free equilibrium point is locally asymptotically stable if $R_0 < 1$ and endemic equilibrium is locally asymptotically stable if $R_0 > 1$. Therefore, it is time to take proper steps to make sure of universal access to this immunotherapy all over the world and save the global human life.

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