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THE EFFECT OF OBESITY AND CANCER STEM CELLS IN TUMOR MODEL WITH TIME DELAY

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Abstract: In this paper, the obesity and tumor model with cancer stem cells has been analyzed. We aim to show that all solutions of the model are non-negative and bounded. Next, we find all equilibria of the models. We also investigate the conditions for the existence of positive equilibria for the model. Next, the local of the positive equilibrium is determined by the linearization method. Finally, we illustrate the numerical results using some advantages of mathematical software to support the analytic results and show the effect of some parameters for the model.

Keywords: Obesity, Stem cells, Tumor model, Time delay, Stability Analysis

I. INTRODUCTION

A tumor is formed in body due to abnormal cellular growth, and it becomes cancer when the tumor is malignant. It is one of the most serious world health problems [1]. There are many common causes of tumor, such as, smoking and tobacco, diet and physical activity, sun and other types of radiation, viruses and other infections. Recently, many previous works [2 – 6] show that obesity is a risk factor for many serious diseases such as type-II-diabetes, hypertension, hearth problem, including tumor and cancer. Therefore, the relationship between obesity and tumor growth is an interested topic for many researchers.

Observing several experimental studies between cancer and obesity, [7, 8] the International Agency for Research on Cancer (IARC) has reported linkages between cancer and obesity in cases of colorectal cancer, breast cancer in postmenopausal women, endometrium cancer, renal cancer, and esophagus cancer [9]. In previous work [8 – 10], it has been found that obesity and excess weight are two major health problems in countries around the world. These problems are mostly caused by a sedentary lifestyle and excess eating. Obesity occurs when excessive amounts of fat cells are stored in the body. It is well known that the fat cell population increases rapidly during childhood. In adulthood, the fat cell population remains almost constant or increases slowly unless there is a dramatic weight gain or loss [11].

In the tumor, we also find that the cancer stem cell which states that malignant tumor cell populations are developed and maintained by a population of tumor cells. The cancer stem cell act similarly to adult stem cells. These specialized cancer cells, known as cancer stem cells, are believed to repopulate tumor cell populations. The population of cancer stem cells is generally small which makes it harder to detect and therefore, harder to eradicate. Because the tumor cell

population may be repopulated by cancer stem cells, it is important to eliminate both tumor cells and cancer stem cells to prevent cancer recurrence [12].

In theoretical cancer researches, mathematical modeling is one of the more successful methodologies by applying experimental data to create mathematical equations with describing tumor growth. In 2013, Okwan-Duodu et al. [13] studied simulation models to assess the effect of obesity on mortality of cancer patients. In 2016, Ku-Carrillo et al. [10] assumed that the obesity of an individual is directly proportional to the carrying capacity of their body to store fat which means that the obesity degree of an individual can carrying in the organism which tumor can be occurred, so obesity can carry in tumor.

In 2003, Villasana et al. [14] developed the logistic growth function with time delay for studying the effect of drug to the tumor cells by tumor-growth model. In 2014, Rihan et al. [15] had shown that a time delay between the interactions of the immune cells and the tumor cells and the growth rate of the immune cells are important for developing a suitable response after recognizing the tumor cells.

In 2017, Abernathy et al. [16] presented the system of ordinary differential equations with cancer stem cells which have increased in tumor cells.

Table- I: The meaning and unit of parameters for the obesity and stem cells in tumor model

Parameter	Meaning	Unit
s	A constant rate of migration of immune cells into the tumor.	$Density.mL^{-1}\cdot day^{-1}$
ρ	A positive constant	day^{-1}
α	A positive constant	$Density.mL^{-1}$
d_1	The natural death rate of the immune cells.	day^{-1}
d_2	The natural death rate of the tumor cells.	day^{-1}
r_1	The growth rate for the cancer cells.	day^{-1}
r_2	The growth rate for the normal cells.	day^{-1}
r_3	The growth rate for the density of fat cells.	day^{-1}
r_4	The growth rate for the density of cancer stem cells.	day^{-1}
r_5	The growth rate for the density of tumor cells by cancer stem cells.	day^{-1}
b_1	The inverse of the carrying capacity for the tumor cells.	$Density.mL$
b_2	The inverse of the carrying capacity for the normal cells.	$Density.mL$
b_3	The inverse of the carrying capacity for the density of fat.	$Density.mL$
b_4	The inverse of the carrying capacity for the cancer stem cells.	$Density.mL$
b_5	The inverse of the carrying capacity for the density of the tumor cells by cancer stem cells.	$Density.mL$
c_1	The competition coefficients between immune cells and tumor cells.	$Density.mL\cdot day^{-1}$
c_2	The competition coefficients between tumor cells and immune cells.	$Density.mL\cdot day^{-1}$
c_3	The competition coefficients between tumor cells and normal cells.	$Density.mL\cdot day^{-1}$
c_4	The competition coefficients between normal cells and tumor cells.	$Density.mL\cdot day^{-1}$
c_5	The competition coefficients between tumor cells and fat cells.	$Density.mL\cdot day^{-1}$
c_6	The competition coefficients between immune cells and cancer stem cells.	$Density.mL\cdot day^{-1}$
c_7	The competition coefficients between cancer stem cells and fat cells.	$Density.mL\cdot day^{-1}$

Note that all variables are assumed to be non-negative and allparameters are assumed to be positive.

In this work, we extend the model interaction between tumor cells and obesity represented by the positive nonlinear growth term for the immune cells $\frac{\rho I(t-\tau)T(t-\tau)}{\alpha+T(t-\tau)}$ and the competition between immune cells and tumor cells $c_1 I(t-\tau)T(t-\tau)$ with a time delay (τ). We also add population of cancer stem cells in the model. Hence, we generalized the model for the interaction between tumor and obesity with cancer stem cells as

$$\begin{aligned}
\dot{C}(t) &= r_4 C(t)(1-b_4 C(t)) - c_6 I(t)C(t) + c_7 C(t)F(t),\\
\dot{I}(t) &= s + \frac{\rho I(t-\tau)T(t-\tau)}{\alpha+T(t-\tau)} - c_1 I(t-\tau)T(t-\tau) - d_1 I(t),\\
\dot{T}(t) &= r_1 T(t)\left(1-b_1 T(t)\right) - c_2 I(t)T(t) - c_3 T(t)N(t)\\
&\quad - d_2 T(t) + r_5 C(t)\left(b_4 C(t)(1-b_5 T(t))\right)\\
&\quad + c_5 T(t)F(t),\\
\dot{N}(t) &= r_2 N(t)\left(1-b_2 N(t)\right) - c_4 T(t)N(t),\\
\dot{F}(t) &= r_3 F(t)\left(1-b_3 F(t)\right),
\end{aligned} \tag{1}$$

where $C(t)$ is the density of cancer stem cells at time t, $I(t)$ is the density of immune cells at time t, $T(t)$ is the density of cancer - tumor cells at time t, $N(t)$ is the density of normal cells at time t, $F(t)$ represents the density of fat cells at time t and $\tau \geq 0$. The parameters of the model (1) are in the Table I.

II. Non-Negativity and Boundedness of Solutions

In this section, we aim to show that all solutions of the model are non-negative and bounded.

Theorem 1 *All solutions of the model (1) with any positive initial conditions are non-negative and bounded for all* $t > 0$.

Proof: If any population becomes negative, then there must be one population which is the first population to become

zero and the time derivative of the population at the zero point must be negative. We prove that this necessary condition is not possible for any of the populations.

First, we assume that C is the first population becomes zero at time t_C with all other populations non-negative. Then, from (1), we have

$$\frac{dC}{dt} = r_4 C(t_C)(1-b_4 C(t_C)) - c_6 I(t_C)C(t_C) + c_7 C(t_C)F(t_C) = 0.$$

Hence, $C(t)$ is non-negative for all $t > 0$. Similarly, we also show that $N(t)$ and $F(t)$ are non-negative for all $t > 0$.

Next, we assume that T is the first populationbecomes zero at time t_T with all other populations non-negative. Then, from (1), we have

$$\begin{aligned}\dot{T(t)} &= r_1 T(t_T)\left(1-b_1 T(t_T)\right) - c_2 I(t_T)T(t_T) - c_3 T(t_T)N(t_T) \\ &\quad - d_2 T\left(t_T\right) + r_5 C\left(t_T\right)(b_4 C\left(t_T\right)(1 - b_5 T\left(t_T\right))) \\ &\quad + c_5 T\left(t_T\right)F\left(t_T\right) > 0.\end{aligned}$$

Hence, $T(t)$ is non-negative for all $t > 0$.

Finally, we assume that I is the first population to become zero at time $t_I - \tau$ with all other population non-negative. Then, from(1), we have

$$\frac{dI}{dt} = s - d_1 I(t_I) > 0,$$

with the condition $I(\mathrm{t}_I) < s/d_1$.

Hence, $I(t)$ is non-negative for all $t > 0$ .Then, all solutions of the model (1) with any positive initial conditions are non-negative for all $t > 0$.

We next to show that all solutions of (1) are uniformly ultimately bounded. From the last equation of (1), it provides

$$\frac{dF(t)}{dt} \le r_3 F(t)(1-b_3 F(t))$$

which gives

$$F(t) \le \frac{1}{b_3}.$$

We also apply this process and show that the first and forth equations of the model (1), give

$$N(t) \le \frac{1}{b_2} \text{ and } C(t) \le \frac{r_4 b_3 + c_7}{r_4 b_3 b_4}.$$

Similarly, from the third equation of the model (1), we obtain

$$\begin{aligned}\frac{dT(t)}{dt} &\le r_1 T(t)(1-b_1 T(t)) + r_5 C(t)(b_4 C(t))(1-b_5 T(t)) \\ &\quad + c_5 T(t)F(t), \\ &\le r_1 T(t)(1-b_1 T(t)) + r_5 b_4 \left(\frac{r_4 b_3 + c_7}{r_4 b_3 b_4}\right)^2 (1-b_1 T(t)) \\ &\quad + \frac{c_5}{b_3} T(t), \\ &\le r_1 T(t) - r_1 b_1 T^2(t) + M_1,\end{aligned}$$

which gives

$$T(t) \le \frac{1}{2b_1}\left(1 + \sqrt{\frac{r_1 + 4b_1 M_1}{r_1}}\right),$$

where

$$M_1 = r_5 b_4 \left(\frac{r_4 b_3 + c_7}{r_4 b_3 b_4}\right)^2.$$

Finally, we also show that $I(t)$ of the second equation of (1) is uniformly bounded by using the generalized Gronwall Lemma [17]. From the first equation of the model(1), we obtain

$$\begin{aligned}I(t) &= e^{-d_1 t}\Big(I(0) + \int_0^t \Big(s + \frac{\rho I(u-\tau)T(u-\tau)}{\alpha + T(u-\tau)} \\ &\quad - c_1 I(u-\tau)T(u-\tau)\Big)e^{d_1 u}du\Big).\end{aligned}$$

Since $T/(\alpha+T) < 1$ and $e^{-d_1 t} \in (0,1]$, we get

$$\begin{aligned}I(t) &\le I(0) + \frac{s}{d_1}e^{d_1 t} + \int_0^t \rho I(u-\tau)e^{d_1 u}du, \\ &< I(0) + \frac{se^{d_1 t}}{d_1} + \int_0^t \Big(\rho e^{d_1(u+\tau)}\Big(I(0) + \frac{se^{d_1 u}}{d_1}\Big)e^{\int_u^t \rho e^{d_1(\xi+\tau)}d\xi}\Big)du \\ &= M_2.\end{aligned}$$

The generalized Gronwall Lemma gives $I(t) < M_2$ where M_2 is uniformly bounded, then $I(t)$ is uniformly bounded.

III. Analysis of Equilibria

In this section, we derive conditions for the existence of equilibrium populations $(C^*, I^*, T^*, N^*, F^*)$. From the last equation of (1), it is obvious that $F^* = 0$ or $1/b_3$. We also show that $N^* = 0$ or $N^* = (r_2 - c_4 T^*)/r_2 b_2$ from the forth equation of (1). From the first equation of (1), the solutions are $C^* = 0$ and $C^* = (r_4 - c_6 I^* + c_7 F^*)/r_4 b_4$. We can find the solutions of I^* from the second equation of(1), the solutions are $I^* = s/d_1$ when $T^* = 0$ and $I^* = \dfrac{s(\alpha + T^*)}{c_1 (T^*)^2 + (c_1\alpha + d_1 - \rho)T^* + d_1\alpha}$ when $T^* = 0$. If $F^* = 0$, i.e., no fat inside the tumor. The equilibrium points as follows:

For $N^* = 0$ and $C^* = 0$, then the equilibrium points are

$$E_1 = \left(0, \frac{s}{d_1}, 0, 0, 0\right) \text{ and } E_2 = \left(0, I^*, T^*, 0, 0\right),$$

where $T^* = \dfrac{r_1 - c_2 I^* - d_1}{r_1 b_1}$.

For $N^* = (r_2 - c_4 T^*)/r_2 b_2$ and $C^* = 0$, then the equilibrium points are

$$E_3 = \left(0, \frac{s}{d_1}, 0, \frac{1}{b_2}, 0\right) \text{ and } E_4 = \left(0, I^*, T^*, \frac{r_2 - c_4 T^*}{r_2 b_2}, 0\right),$$

where $T^* = \dfrac{r_2 b_2 (r_2 b_2 - c_3 - d_2 b_2 - c_2 b_2 I^*)}{r_1 r_2 b_1 b_2 - c_3 c_4}$.

For $N^* = 0$ and $C^* = (r_4 - c_6 I^*)/r_4 b_4$, then the equilibrium point is

$$E_5 = \left(\frac{r_4 - c_6 I^*}{r_4 b_4}, I^*, T^*, 0, 0\right),$$

where

$$T^* = \frac{r_5 ((r_4 - c_6 I^*)/r_4 b_4)^{*2}}{r_1 b_1 b_4 + c_2 b_4 I^* + d_2 b_4 - r_1 b_4 + \dfrac{r_5}{b_5}((r_4 - c_6 I^*)/r_4 b_4)^{*2}}.$$

For $N^* = (r_2 - c_4 T^*)/r_2 b_2$ and $C^* = (r_4 - c_6 I^*)/r_4 b_4$, then the equilibrium point is

$$E_6 = \left(\frac{r_4 - c_6 I^*}{r_4 b_4}, I^*, T^*, \frac{r_2 - c_4 T^*}{r_2 b_2}, 0\right).$$

The value of T^* satisfies the quadratic equation

$$T^{*2} + a_1 T^* + \frac{r_2 r_5 b_2 b_4}{c_3 c_4 - r_1 r_2 b_1 b_2}((r_4 - c_6 I^*)/r_4 b_4)^2 = 0,$$

where

$$a_1 = \frac{r_2 b_2}{c_3 c_4 - r_1 r_2 b_1 b_2}\left(r_1 - \frac{c_3}{b_2} - d_2 - c_2 I^* - r_5 b_4 b_5 \left(\frac{r_4 - c_6 I^*}{r_4 b_4}\right)^2\right).$$

As noted above, $F^* = 1/b_3$ is positive value. Repeating the steps given above, then the equilibrium points can be solved as follows:

For $N^* = 0$ and $C^* = 0$, then the equilibrium points are

$$E_7 = \left(0, \frac{s}{d_1}, 0, 0, \frac{1}{b_3}\right) \text{ and } E_8 = \left(0, I^*, T^*, 0, \frac{1}{b_3}\right),$$

where $T^* = \dfrac{r_1 b_3 + c_5 - b_3 d_2 - b_3 c_2 I^*}{r_1 b_1 b_3}$.

For $N^* = (r_2 - c_4 T^*)/r_2 b_2$ and $C^* = 0$, then the equilibrium points are

$$E_9 = \left(0, \frac{s}{d_1}, 0, \frac{r_2 - c_4 T^*}{r_2 b_2}, \frac{1}{b_3}\right),$$

and

$$E_{10} = \left(0, I^*, T^*, \frac{r_2 - c_4 T^*}{r_2 b_2}, \frac{1}{b_3}\right),$$

where

$$T^* = \frac{r_2 \left(b_3 c_3 + b_2 b_3 d_2 - b_2 c_5 - b_2 b_3 r_1 + b_2 b_3 c_2 I^*\right)}{b_3 (c_3 c_4 - r_1 r_2 b_1 b_2)}.$$

For $N^* = 0$ and $C^* = (r_4 - c_6 I^* + c_7/b_3)/r_4 b_4$, then the equilibrium point is

$$E_{11} = \left(\left(r_4 - c_6 I^* + \frac{c_7}{b_3}\right)/r_4 b_4, I^*, T^*, 0, 1/b_3\right),$$

where

$$T^* = \frac{r_5 (C^*)^2}{r_1 b_1 b_4 + d_2 b_4 + c_2 b_4 I^* + \dfrac{r_5}{b_5}(C^*)^2 - r_1 b_4 - \dfrac{b_4 c_5}{b_3}}.$$

For $N^* = \dfrac{r_2 - c_4 T^*}{r_2 b_2}$ and $C^* = (r_4 - c_6 I^* + c_7/b_3)/r_4 b_4$, then the equilibrium point is

$$E_{12} = \left(\frac{r_4 - c_6 I^* + c_7/b_3}{r_4 b_4}, I^*, T^*, \frac{r_2 - c_4 T^*}{r_2 b_2}, \frac{1}{b_3}\right).$$

The value of T^* satisfies the quadratic equation

$$T^{*2} + a_2 T^* + \frac{r_2 r_5 b_2 (r_4 - c_6 I^* + c_7/b_3)^2}{r_4^2 b_4 (c_3 c_4 - r_1 r_2 b_1 b_2)} = 0,$$

where

$$a_2 = \frac{r_2 b_2 \left(r_1 - \dfrac{c_3}{b_2} - d_2 - c_2 I^* + \dfrac{c_5}{b_3} - r_5 b_4 b_5 C^{*2}\right)}{c_3 c_4 - r_1 r_2 b_1 b_2}.$$

In summary, the equilibrium points E_1, E_3, E_7 and E_9, the tumor cell populations were zero. These states were therefore medically desirable tumor-free states. In the equilibrium points E_2, E_4, E_5, E_6, E_8, E_{10}, E_{11} and E_{12}, the tumor cell populations were nonzero. These were therefore endemic equilibrium states.

IV. STABILITY OF THE MODEL

In this section, we study the local stability of the model (1) about each equilibria by the linearization method [18]. Let $W(t) = (C(t), I(t), T(t), N(t), F(t))^T$, then the linearized of (1) about equilibrium $(C^*, I^*, T^*, N^*, F^*)$ is given as follows

$$\dot{\mathbf{W}}(\mathbf{t}) = \begin{bmatrix} w_{11} & -c_6C^* & 0 & 0 & c_7C^* \\ 0 & -d_1 & 0 & 0 & 0 \\ w_{31} & -c_2T^* & w_{22} & -c_3T^* & c_5T^* \\ 0 & 0 & -c_4N^* & w_{44} & 0 \\ 0 & 0 & 0 & 0 & w_{55} \end{bmatrix} \mathbf{W}(\mathbf{t}) + \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & \dfrac{\rho T^*}{\alpha + T^*} - c_1T^* & \dfrac{\alpha\rho I^*}{(\alpha + T^*)^2} - c_1I^* & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \mathbf{W}(\mathbf{t}-\tau), \tag{1}$$

where

$$\begin{aligned} w_{11} &= r_4 - 2r_4b_4C^* - c_2I^* + c_7F^*, \\ w_{31} &= 2r_5b_4C^*(1 - b_5T^*), \\ w_{33} &= r_1 - 2r_1b_1T^* - c_2I^* - c_3N^* + c_5F^* - d_2 - r_5b_4b_5C^{*2}, \\ w_{44} &= r_2 - 2r_2b_2N^* - c_4T^*, \\ w_{55} &= r_3 - 2r_3b_3F^*. \end{aligned}$$

At all equilibria with $F^* = 0$, then the characteristics equation of the model (1)are given by

$$(\lambda - r_3)\begin{vmatrix} e_{11} - \lambda & -c_6C^* & 0 & 0 \\ 0 & e_{22}e^{-\lambda\tau} - d_1 - \lambda & e_{23}e^{-\lambda\tau} & 0 \\ e_{31} & -c_2T^* & e_{33} - \lambda & -c_3T^* \\ 0 & 0 & -c_4N^* & e_{44} - \lambda \end{vmatrix} = 0,$$

where

$$\begin{aligned} e_{11} &= r_4 - 2r_4b_4C^* - c_2I^*, \\ e_{22} &= \frac{\rho T^*}{\alpha + T^*} - c_1T^*, \\ e_{23} &= \frac{\alpha\rho I^*}{(\alpha + T^*)^2} - c_1I^*, \\ e_{31} &= 2r_5b_4C^*(1 - b_5T^*), \\ e_{33} &= r_1 - 2r_1b_1T^* - c_2I^* - c_3N^* - d_2 - r_5b_4b_5C^{*2}, \\ e_{44} &= r_2 - 2r_2b_2N^* - c_4T^*. \end{aligned}$$

It is obvious that one of eigen value is $\lambda = r_3 > 0$, which is a positive. Hence, the equilibrium E_1, E_2, E_3, E_4, E_5 and E_6 are unstable for $\tau \geq 0$. Moreover, we can show that the equilibrium E_7 is unstable for $\tau \geq 0$ as follows

$$(\lambda + r_3)(\lambda - r_2)\begin{vmatrix} f_{11} - \lambda & 0 & 0 \\ 0 & d_1 - \lambda & \left(\dfrac{\rho s - \alpha s c_1}{\alpha d_1}\right)e^{-\lambda\tau} \\ 0 & 0 & f_{33} - \lambda \end{vmatrix} = 0,$$

where

$$\begin{aligned} f_{11} &= r_4 - \frac{c_2 s}{d_1} + \frac{c_7}{b_3}, \\ f_{33} &= r_1 - \frac{c_2 s}{d_1} + \frac{c_5}{b_3} - d_2. \end{aligned}$$

It is obvious that one of eigen value is $\lambda = r_2 > 0$, which is a positive. Hence, the equilibrium E_7 is unstable for $\tau \geq 0$.

Next, we investigate local stability of the equilibrium E_8. From (1), the characteristic equation of (1) at E_8 is

$$\begin{aligned} (\lambda + r_3)\left(\lambda - r_2 + c_4T^*\right)\left(\lambda - r_4 + c_2I^* - \frac{c_7}{b_3}\right) \\ \times \begin{vmatrix} g_{22}e^{-\lambda\tau} - d_1 - \lambda & g_{23}e^{-\lambda\tau} \\ -c_2T^* & g_{33} - \lambda \end{vmatrix} = 0, \end{aligned} \tag{2}$$

where

$$\begin{aligned} g_{22} &= \frac{\rho T^*}{\alpha + T^*} - c_1T^*, \\ g_{23} &= \frac{\alpha\rho I^*}{(\alpha + T^*)^2} - c_1I^*, \\ g_{33} &= r_1 - 2r_1b_1T^* - c_2I^* + \frac{c_5}{b_3} - d_2. \end{aligned}$$

The characteristic equation of (2)is given by

$$\begin{aligned} \left(\lambda^2 + (d_1 - g_{33})\lambda - g_{33}d_1 + (c_2g_{23}T^* + g_{22}g_{33} - g_{22}\lambda)e^{-\lambda\tau}\right) \\ \times (\lambda + r_3)\left(\lambda - r_2 + c_4T^*\right)\left(\lambda - r_4 + c_2I^* - \frac{c_7}{b_3}\right) = 0. \end{aligned} \tag{3}$$

In case $\tau = 0$, all eigen values of the characteristic of (3) are

$$\lambda = -r_3, r_4 + \frac{c_7}{b_3} - c_2I^*, r_2 - c_4T^*, \frac{-g_5 \pm \sqrt{g_5^2 - 4(g_{22}g_{33} + c_2g_{23}T^* - g_{33}d_1)}}{2},$$

where $g_5 = d_1 - g_{22} - g_{33}$.

Therefore, the conditions of stability of non-delay case for E_8 are given by the following theorem.

Theorem 2 *If* $T^* > \frac{r_2}{c_4}$, $I^* > \frac{r_4 b_3 + c_7}{c_2}$, $d_1 > g_{22} + g_{33}$ *and* $c_2 g_{23} T^* > g_{33}(d_1 - g_{22})$, *then* E_8 *of the model (1) is locally asymptotically stable where*

$$g_{22} = \frac{\rho T^*}{\alpha + T^*} - c_1 T^*, \; g_{23} = \frac{\alpha \rho I^*}{(\alpha + T^*)^2} - c_1 I^*$$

and $g_{33} = r_1 - 2 r_1 b_1 T^* - c_2 I^* + \frac{c_5}{b_3} - d_2$.

Similarity, we also find local stability of the equilibrium E_9. From (1), the characteristic equation of (1)at E_9 is

$$\begin{vmatrix} h_{11} - \lambda & 0 & (\lambda + r_3)\left(\lambda + r_2 - 2c_4 T^*\right) \\ 0 & -d_1 - \lambda & \left(\frac{\rho s - \alpha s c_1}{\alpha d_1}\right) e^{-\lambda \tau} \\ 0 & 0 & h_{33} - \lambda \end{vmatrix} = 0, \quad (4)$$

where

$$h_{11} = r_4 - c_2 I^* + \frac{c_7}{b_3},$$

$$h_{33} = r_1 - \frac{c_2 s}{d_1} - c_3 \left(\frac{r_2 - c_4 T^*}{r_2 b_2}\right) + \frac{c_5}{b_3} - d_2.$$

Hence, all eigenvalues of the characteristic of (4) are

$$\lambda = -r_3, r_4 + \frac{c_7}{b_3} - c_2 I^*, -d_1, 2c_4 T^*,$$

$$r_1 - \frac{c_2 s}{d_1} - c_3 \left(\frac{r_2 - c_4 T^*}{r_2 b_2}\right) + \frac{c_5}{b_3} - d_2.$$

Then, the conditions of stability of E_9 are given by the following theorem.

Theorem 3 *If* $T^* > \frac{r_2 b_3^2 c_3^2 d_1^2 - r_2 b_2}{b_3 c_3 c_4 d_1}(r_1 b_3 d_1 - b_3 c_2 s + c_5 d - b_3 d_1 d_2)$, *and* $T^* < \frac{r_2}{2c_4}$, $I^* > \frac{r_4 b_3 + c_7}{b_3 c_2}$ *then* E_9 *of the model (1)is locally asymptotically stable for all* $\tau \geq 0$.

V. Numerical Simulation Results

In this section, we implement mathematical programs of Maple software package to simulate numerical results for local stability, necessary conditions of behavior of bifurcation and effecting some parameters for tumor model (1). The parameter values in Table II and the initial conditions

$$C(0) = 1, \; I(0) = 0.52, \; T(0) = 0.94, \; N(0) = 1.3$$

and $F(0) = 1.1$, which gives the endemic equilibrium point is $E_8 = (0, 0.505541473, 0.9206153173, 0, 1)$.

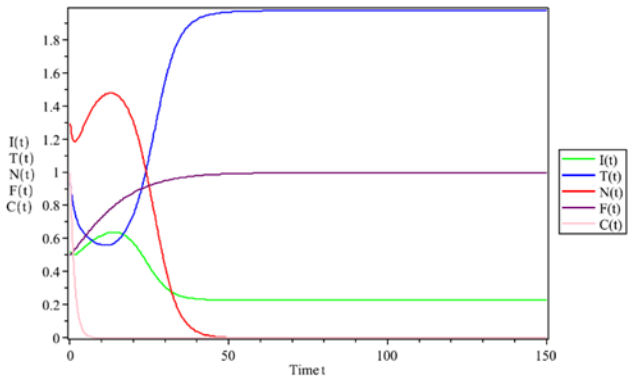


Fig. I: The numerical simulation of Cancer stem cells, Immune cells, Tumor cells, Host cells and Fat cells.

Graphs in Fig. I shows that all numerical solutions for the host population classes converge to E_8. Those results agree with the theoretical results provided in Theorem 2, which show that the equilibrium point E_8 is asymptotically stable.

Next, we provide the numerical simulation of the model (1)with the parameter values in Table III and the initial conditions

$$C(0) = 1, \; I(0) = 0.52, \; T(0) = 0.94, \; N(0) = 1.3$$

and $F(0) = 1.1$, which gives the endemic equilibrium point is $E_9 = (0, \; 4.00, \; 0, \; 2.39, \; 1)$.

Table- II: The value of parameters for the obesity and stem cells in tumor model

Parameter	Values used	Unit	Reference
s	0.22	$Density.mL^{-1} \cdot day^{-1}$	[10]
ρ	0.01	day^{-1}	[10]
α	0.1	$Density.mL^{-1}$	[10]
d_1	0.1	day^{-1}	[10]
d_2	0.42	day^{-1}	Estimated
r_1	1	day^{-1}	Estimated
r_2	0.9	day^{-1}	[10]
r_3	0.1	day^{-1}	Estimated
r_4	0.01	day^{-1}	Estimated
r_5	0.1	day^{-1}	Estimated
b_1	0.8	$Density.mL$	[10]
b_2	0.42	$Density.mL$	Estimated
b_3	1	$Density.mL$	Estimated
b_4	0.5	$Density.mL$	Estimated
b_5	0.1	$Density.mL$	Estimated
c_1	0.44	$Density.mL \cdot day^{-1}$	[10]
c_2	0.5	$Density.mL \cdot day^{-1}$	Estimated
c_3	0.5	$Density.mL \cdot day^{-1}$	[10]
c_4	0.6	$Density.mL \cdot day^{-1}$	[10]
c_5	0.8	$Density.mL \cdot day^{-1}$	Estimated

c_6	1.5	$Density.mL \cdot day^{-1}$	Estimated
c_7	0.01	$Density.mL \cdot day^{-1}$	Estimated

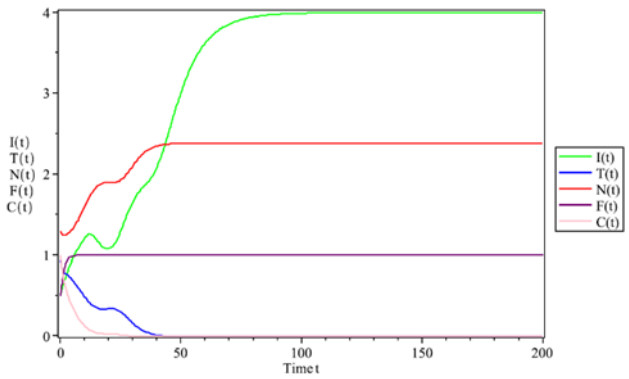


Fig. II The numerical simulation of Cancer stem cells, Immune cells, Tumorcells, Host cells and Fat cells.

Graphs in Fig. II shows that all numerical solutions for the host population classes converge to E_9. Those results agree with the theoretical results provided in Theorem 3, which show that the equilibrium point E_9 is asymptotically stable.

Table- III: The second value of parameters for the obesity and stem cells in tumor model

Parameter	Values used	Unit	Reference
s	0.4	$Density.mL^{-1} \cdot day^{-1}$	[10]
ρ	0.01	day^{-1}	[10]
α	0.1	$Density.mL^{-1}$	[10]
d_1	0.2	day^{-1}	[10]
d_2	0.2	day^{-1}	Estimated
r_1	1.5	day^{-1}	Estimated
r_2	1	day^{-1}	[10]
r_3	1	day^{-1}	[10]
r_4	0.79	day^{-1}	Estimated
r_5	0.1	day^{-1}	Estimated
b_1	0.8	$Density.mL$	[10]
b_2	0.42	$Density.mL$	Estimated
b_3	1	$Density.mL$	Estimated
b_4	0.99	$Density.mL$	Estimated
b_5	0.1	$Density.mL$	Estimated
c_1	0.5	$Density.mL \cdot day^{-1}$	[10]
c_2	0.5	$Density.mL \cdot day^{-1}$	Estimated
c_3	0.5	$Density.mL \cdot day^{-1}$	[10]
c_4	0.6	$Density.mL \cdot day^{-1}$	[10]
c_5	0.5	$Density.mL \cdot day^{-1}$	Estimated
c_6	0.95	$Density.mL \cdot day^{-1}$	Estimated
c_7	0.21	$Density.mL \cdot day^{-1}$	Estimated

Finally, we provide the numerical simulations of the model (1) with the parameter values in Table IV and the initial conditions

$$C(0) = 1,\ I(0) = 0.52,\ T(0) = 0.94,\ N(0) = 1.3$$

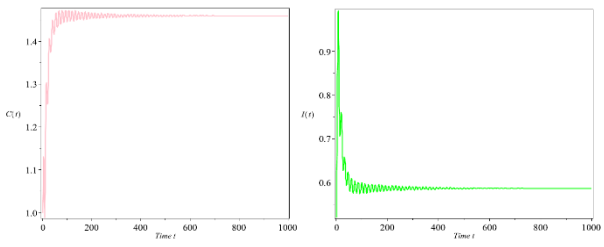
and $F(0) = 1.1$, which gives the endemic equilibrium point is $E_{12} = (1.45,\ 0.58,\ 1.18,\ 0.69,\ 1)$.

All numerical solutions for the host population classes converge to E_{12} for all time delays τ. Graphs of numerical solutions in Fig. III are decreasingly oscillated to the equilibrium point which gives asymptotically stability, when $\tau = 4.2$. For Fig. IV, $\tau = 4.6$ the solutions of cancer stem cells, immune cells, tumor cells and normal cells are widely oscillated about the equilibrium E_{12}.

Moreover, if obese people are tumors, the density of fat cells are rapidly decreasing, while the density of tumor cells are constantly oscillating and changing any time t.

Table- IV: The third value of parameters for the obesity and stem cells in tumor model

Parameter	Values used	Unit	Reference
s	0.4	$Density.mL^{-1} \cdot day^{-1}$	[10]
ρ	0.01	day^{-1}	[10]
α	0.1	$Density.mL^{-1}$	[10]
d_1	0.1	day^{-1}	[10]
d_2	0.1	day^{-1}	Estimated
r_1	1.5	day^{-1}	Estimated
r_2	1	day^{-1}	[10]
r_3	1	day^{-1}	Estimated
r_4	0.79	day^{-1}	Estimated
r_5	0.1	day^{-1}	Estimated
b_1	0.8	$Density.mL$	[10]
b_2	0.42	$Density.mL$	Estimated
b_3	1	$Density.mL$	Estimated
b_4	0.99	$Density.mL$	Estimated
b_5	0.1	$Density.mL$	Estimated
c_1	0.5	$Density.mL \cdot day^{-1}$	[10]
c_2	0.5	$Density.mL \cdot day^{-1}$	Estimated
c_3	0.5	$Density.mL \cdot day^{-1}$	[10]
c_4	0.6	$Density.mL \cdot day^{-1}$	[10]
c_5	0.5	$Density.mL \cdot day^{-1}$	Estimated
c_6	0.95	$Density.mL \cdot day^{-1}$	Estimated
c_7	0.91	$Density.mL \cdot day^{-1}$	Estimated



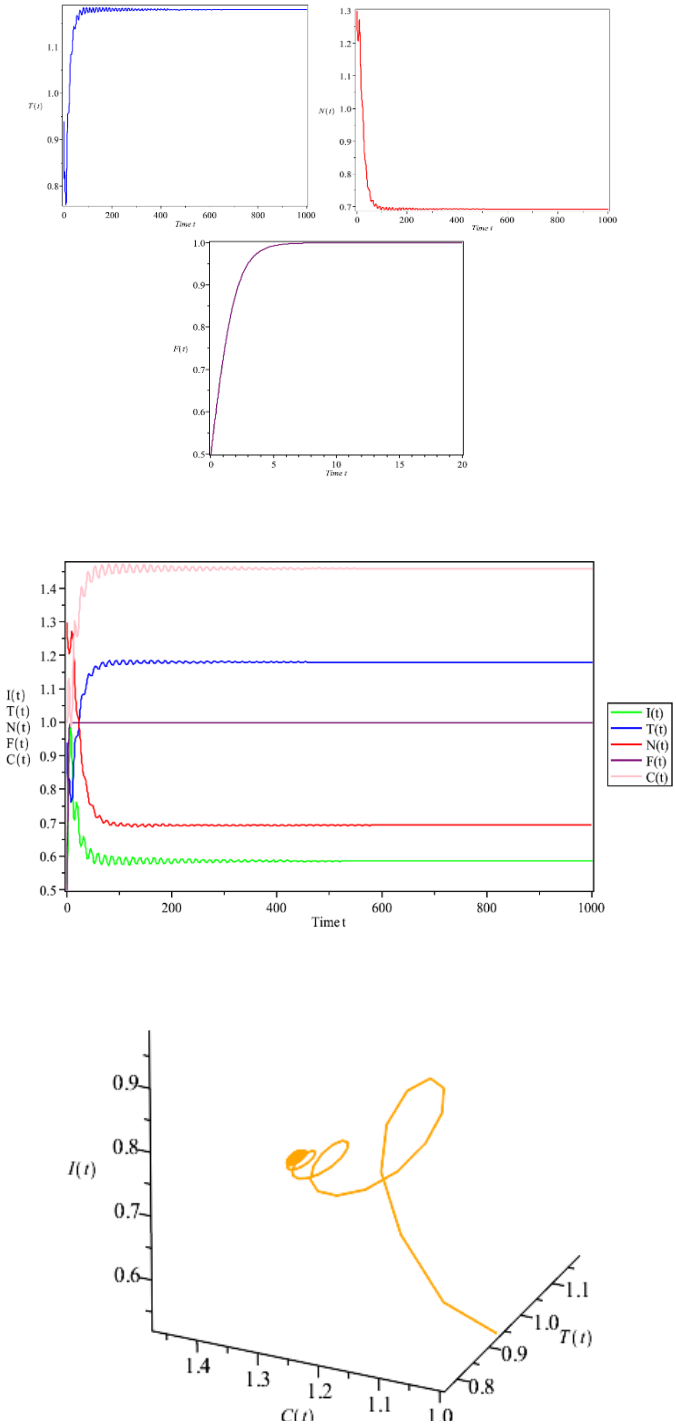
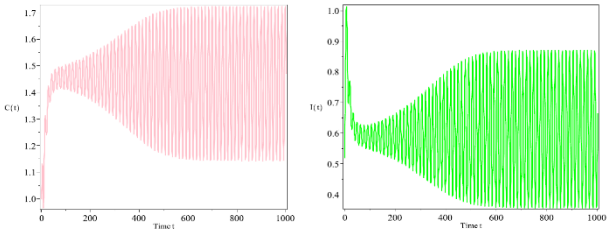


Fig. III: The numerical simulation of Immune cells, Tumor cells and Fat cells when $\tau = 0.42$.



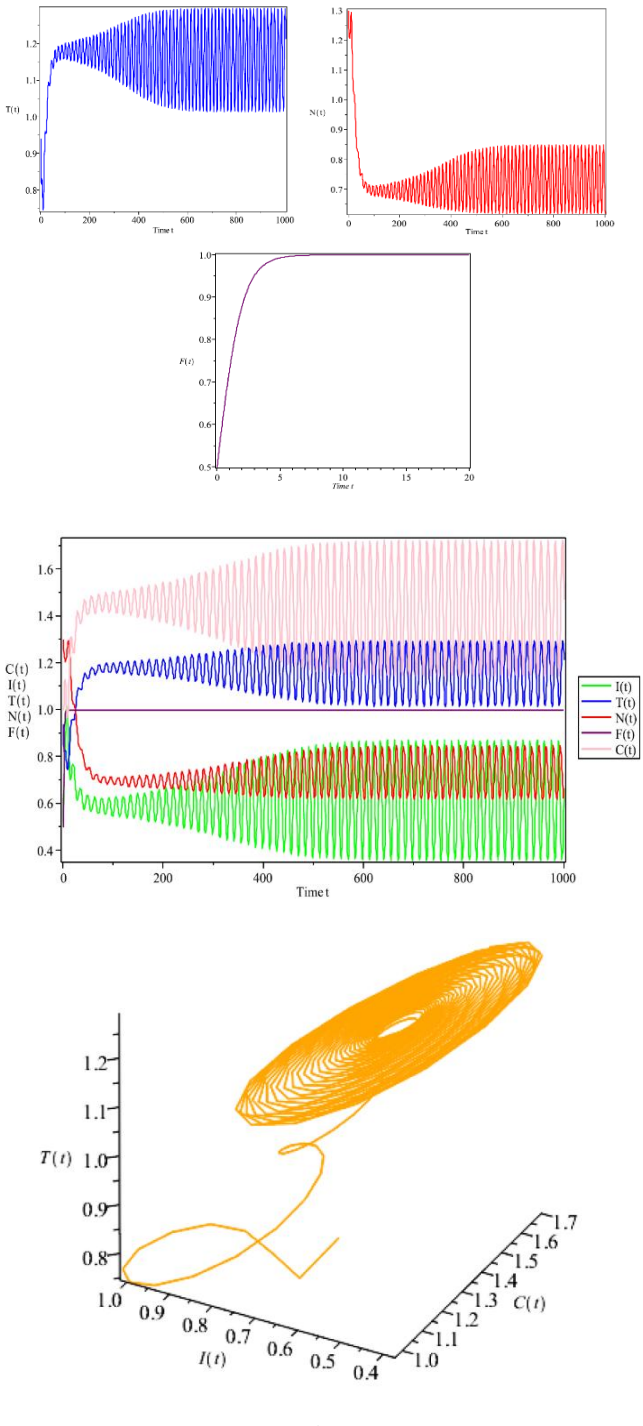


Fig. IV: The numerical simulation of Immune cells, Tumor cells and Fat cells when $\tau = 0.46$.

VI. CONCLUSIONS

In this paper, we presented an analysis of the obesity and tumor model with cancer stem cells with time delay. We first show the non-negative and bounded of model with time delay for positive values of model parameters. The generalized Gronwall Lemma applied for finding the bounds of immune cells of model with time delay which is uniformly bounded. For stability of equilibrium points, we found that equilibrium points E_1, E_2, E_3, E_4, E_5, E_6 and E_7

of the model with a time delay is always unstable. Next, the statement and determining of the conditions for local stability of E_8 with zero-time delay is given in Theorem 2. Also, the conditions for the local stability of E_9 is stated and investigated in Theorem 3. In the numerical simulations, we used biologically reasonable values of parameters to test our analytical results, which the numerical simulations converged to the equilibrium point E_8 and E_9 for choices of parameter values satisfying the conditions in Theorem 2-3. The numerical simulations also showed convergence to E_{12} for less time delays τ and limit cycle behavior for large time delays τ. It can be concluded that the obesity, cancer stem cells and time delay affect the growth of tumors.

VII. ACKNOWLEDGMENT

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