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Dynamic Simulation for Analyzing the Effects of the Intervention of Vitamins on Delaying the Growth of Tumor Cells

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ABSTRACT The natural sources of the vitamins, which come from a balanced diet (as recommended by the World Cancer Research Fund and the American Institute for Cancer Research) contribute to protecting the body from advancing progressive of cancer stages. Thus, in this study, we analyze the effect of the intervention of vitamins on delaying the growth of cancer cells based on the dynamics of a normal cell cycle when the tumor cells appear in a tissue as a resulting for progressing abnormal cells due to the weak response of the immune system. We developed a mathematical model, called tumor–normal–vitamins model (TNVM), which is governed by a system of ordinary differential equations and refers to two main populations normal cells and tumor cells. This model considers the intervention of vitamins as a moderating factor within thirty days. The models are discussed analytically and numerically by utilizing the Runge–Kutta method to simulate them. The results of the analysis and simulation of free model illustrate that the model will be stable if the tumor cells succeed in eliminating normal cells in the tissue. Whereas, the analysis and simulation of the TNVM showed a case of coexistence between normal cells and tumor cells occur if an individual consumes a regular rate of vitamins that have been simulated to be 87% per day from a natural food source. Even though the response of the immune system is weak, the daily consumption of enough vitamins can play an essential role in delaying the development of an early stage of cancer. This study contributes to the increasing awareness regarding a healthy diet to reduce the risk of some deadly diseases, especially cancer.

INDEX TERMS Dynamic system, numerical simulation, tumor-normal model, healthy diet.

I. INTRODUCTION

Cancer is classified as a civilization disease nowadays, where GLOBOCAN 2018 database estimated that 9.6 million cases of death have occurred owing to cancer. The number of new cases of cancer is predicted to be about 18.1 million [1]. Lung cancer is common for both sexes. A previously conducted study indicated that the mortality rate of lung cancer is about 18.4% of the total mortality rate of cancer, and the percentage of new cases of cancer is about 11.6% of the total cancer cases. This is followed by breast cancer among females, with a mortality rate of about 11.6% compared to 7.1% of prostate cancer among males. In 2018, Australia and New Zealand recorded the highest mortality rate of 94.2% due to cancer, which comprised 571.2 per 100000 male and 362 per 100000 female deaths compared to 95.6 per 100000 males in Western Africa. Among females, the mortality rates are 362 and 96.2 per 100000 in Australia, New Zealand, and South–Central Asia, respectively. In general, the mortality rate of cancer among males is higher than that among females. However, in Eastern Europe, the mortality rate due to cancer is about 171 per 100000 males and about 92 per 100000 females [1]. Note that this disease rarely occurred in the early history of humanity, when humans lived as hunter–gatherers [2]. The study indicated that only about $5-10\%$ of cancers occur because of internal factors, such as inherited mutations, hormones, and immunity conditions, while $90-95\%$ of cancers occur due to some inappropriate lifestyle and environmental factors [3]. Civilization is the key factor for understanding the causes of increasing cases of cancer. A disadvantage of the development of society is that our dietary habits have changed to fast food or processed food. These types of diets contain low fiber, low carbohydrates, more proteins, and high calories in comparison with a healthy diet, which is rich in natural sources of minerals, such as vitamins, fiber, and carbohydrates, as needed by the

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body [4]. Cancer has been studied biologically, nutritionally, medically, and clinically. Several mathematical models have been proposed to demonstrate the interaction between the immune system and tumor cells [5] and prognosis cancer and its treatment plan [6]. Most of the mathematical cancer models refer to three populations: normal, tumor, and immune cells [7], [8] and aimed to answer the following questions: how can we measure cancer [9]? and how can we treat cancer [10]?. Recently, a strong dynamical relation has been observed between the tumor and normal cells, where these cells depend on each other and may be mutually tuned. The investigation of dynamic cells has contributed to the development of the therapy method and determination of an appropriate time for eliminating and inhibiting tumor cells. In 1982, the first mathematical model that illustrated the mutual interaction between tumor and normal cells was proposed by Witten [11]. Based on this model, several other models have been proposed to evaluate the dynamic system by applying various therapeutical types, such as virotherapy, chemotherapy, and immunotherapy [12]–[15]. In addition, the mathematical and numerical models are applied to investigate the effect of resistant-deferent levels of a drug on the cells and determine the tumor cells that respond and those that are resistant to drugs [16]–[19]. In 1966, Burton [20] observed that nutrient consumption might limit the growth of solid tumor. Based on Burton's result, some models were developed, which discussed the characteristics of spatiotemporal interactions between the population of tumor cells and nutrients [21], [22]. Other study showed that a dynamically modified diet is more healthy and can avoid abnormal cells from developing into tumor cells [23] such that the simulation model refer to [23] indicated that the consumption of a regular rate and sufficient vitamins which has been simulated to be 16% per day, as suggested by [24]–[26], can boost the immune system.

The tissues and organs of the body are formed from 10^{13} tiny cells. There is a one-to-one correspondence between cells and the body growth. The more increased the number of cells, the more tissue grows. The cells between conception and adulthood divide and grow very quickly [27]. Yet, the functions of these cells vary, and as a result the division and growth of the cells depend on their functions. Concerning the multiplication of cells, it is possible for them to multiply as many as 60 times before dying, as a result of the signals that control cellular growth and death [28], [29]. Conversely, they can become damaged during the process of division, which can lead to self-elimination. This process is known as apoptosis and it protects the body from cancer. Conversely,cell division is sometimes abnormal when there is damage during cell division, with very unique characteristics [27]–[29]. Thus, Cancer results from an abnormal division of the normal cells that failed to be destroyed automatically [27]–[29]. The process by which abnormal cells develop into tumor cells, and then, cancer takes ten years and above [27]–[29]. However, it is affected by numerous internal factors, such as immunity, maturation, and hormones, in addition to some external factors, such as diet, physical activity, stress, and sleeping habits [30]–[32].

The diet pattern is classified as one of the main risk factors that cause cancer due to civilization. These days, most people depend on processed and frozen food, which is readily available anytime and everywhere. Such foods impact the response of the immune system to avoid abnormal cells from growing and dividing as cancer cells [33]–[36]. In 2019, Alharbi and Rambely inferred dynamically that an unhealthy diet, such as a Western diet, can weaken the functions of the immune system, which play a crucial role in protecting the body from developing cancer [37]. This challenge motivated us to develop the tumor–normal model (TNM) by using the ordinary differential equations, which shows that when the immune system is very weak, the development of abnormal cells into tumor cells might impact the dynamics of normal cells. This model, which contains two main populations tumor cells and normal cells, will be discussed mathematically, analytically and numerically. It is known that some cells have been competing for nutrients as a cellular-growth requirement. Thus, modifying the dynamics behavior of the TNM by considering the intervention of vitamins as an external factor which comes from switching back to the healthy diet (TNVM) will be analyzed and simulated to show the effect of the intervention of vitamins on the growth of tumor cells. This study contributes to reducing the number of cases of cancer and deaths by raising awareness of healthy habits and promotes healthy eating, especially among youth. Also, it opens the door for conducting more research regarding the disadvantages of modern life on our health and determining a perfect result for avoiding cancer risk based on civilization and technology.

The rest of this paper is organized as follows. Section 2 describes the developed free model, and section 3 analyzes the model and discusses the stability of the equilibrium points. In section 4, the modification of the behavior of the dynamic TNM by the intervention of vitamins is presented. The analysis of the model and the study of the stability of equilibrium points are presented in section 5. The simulation of the model is illustrated in section 6, and the conclusion is presented in section 7.

II. FREE MODEL

In this study, we developed a TNM based on a model presented in [37], which is called immune-unhealthy diet model (IUNHDM), expressed as follows:

$$\begin{aligned} \frac{dN}{dt} &= rN[1-\beta N]-\eta NI, \\ \frac{dI}{dt} &= \sigma-\delta I-\frac{\rho NI}{m+N}-\mu NI, \end{aligned} \tag{1}$$

with initial values $N(0) = 1$ and $I(0) = 1.22$, where the dependent variables N and I represent the population of normal cells and immune cells, respectively. The parameters $r, \beta, \eta, \sigma, \delta, \rho, m$, and μ are real and positive. Additionally, we made the following hypothesis in our model:

cell population has significantly grown up, and a competition exists between normal and tumor cells. In our model, the entire cell population of human tissues is split up at any interval of time given. We denote a normal cell by $N(t)$, which tends to grow or die as it involves a stable deoxyribonucleic acid (DNA) that rules out all the cell activities. Therefore, normal cells will not live longer because they have been targeted and inhabited by tumor cells that have grown up. The following ordinary differential equation describes the behaviors of normal cells:

$$\frac{dN}{dt} = rN(1 - \beta_1 N) - \gamma NT.$$

Here, r denotes the normal cells that have grown up, β_1, denotes the rate of division of the normal cells into abnormal ones, and γ denotes the rate of the inhibition or attack on the normal cells made by developing tumor cells. DNA alteration is the main cause of cancer cells containing an uninhibited cycle [38]. The independent variable, T, denotes the tumor cell compartment depicted by an abnormal mass of tissue. Moreover, one of the signs of cancer is inflammation, which can be classically grouped into two types: benign and malignant. These names are reflection names of the tissues that grow up in different parts of the body, such as breast or brain cancer [27]–[29]. The following differential equation illustrates the behavior of tumor cells:

$$\frac{dT}{dt} = \alpha_1 T(1 - \alpha_2 T) + \beta_2 NT.$$

This equation demonstrates that the limited growth of tumor cells mainly depends on the rate of the parameter, which is denoted by α_1. The second term, α_2, denotes the reduction in the tumor cells which is due to the ingrown tumor from the body during metabolism in the diet. In addition, the third term, β_2, denotes the rate of conversion of abnormal cells into tumor cells. For instance, an excess estrogen causes DNA transfer due to dietary types that increase the production of tumor cells [31]. Thus, A TNM is expressed as follows:

$$\begin{aligned} \frac{dN}{dt} &= rN(1 - \beta_1 N) - \gamma NT, \\ \frac{dT}{dt} &= \alpha_1 T(1 - \alpha_2 T) + \beta_2 NT. \end{aligned} \tag{2}$$

Remark 1: According to the physiological meaning of cell cycle life, we can deduce that the rate of division normal cell as abnormal cells is very small compared with the rate of the natural divide of cell.

III. MODEL ANALYSIS

A. BOUNDARIES AND POSITIVITY OF SOLUTIONS

The dynamic system of TNM demonstrated by (2) was proposed to illustrate the cellular population behavior of the normal and tumor cells. Thus, the variables $N(t)$ and $T(t)$ and all parameters are real, nonnegative and less than or equal one. The feasible region is defined as follows:

$$\Omega = \{(N, T) \in R_+^2\}.$$

An objective of this study is to compare the behavior of normal and tumor cells. Therefore, we assume that the initial values are equal and given as follows:

$$N(0) = T(0) = 1.$$

Furthermore, the solutions of the nonnegative conditions are also nonnegative for all time, t. Consequently, we obtain the following theorem:

Theorem 1: The region of the dynamic system of TNM, $\Omega \subset R_+^2$, is nonnegativity-invariant, and there exists a nonnegative solution for all time, t.

Proof: Let

$$\Omega = \Omega_c := \{(N, T) \in R_+^2, N = \frac{1}{\beta_1} \text{ and } T = \frac{1}{\alpha_2}\}.$$

Thus, all solutions $(N(t), T(t))$ of TNM (2) are nonnegative for all time, t. From the first population of TNM (2), we have

$$\frac{dN}{dt} \leq rN(t) - r\beta_1 N^2(t). \tag{3}$$

By applying Bernoulli's method, the solution of equation (3) is given as

$$N(t) \leq \frac{1}{\beta_1 + ce^{-rt}}.$$

As $t \to \infty$, the solution is given by

$$N(t) \leq \frac{1}{\beta_1}.$$

Similarly, the solution of the second population of TNM (2) is nonnegative for all time, t, and given by

$$T(t) \leq \frac{1}{\alpha_2}.$$

B. EQUILIBRIUM POINTS OF FREE MODEL

The steady states occur when the left hand side of the dynamic system of TNM presented in (2) is set to zero, as follows:

- $\frac{dN}{dt} = 0 \Leftrightarrow$

$$N(r(1 - \beta_1 N(t)) - \gamma T(t)) = 0. \tag{4}$$

- $\frac{dT}{dt} = 0 \Leftrightarrow$

$$T(\alpha_1(1 - \alpha_2 T(t)) + \beta_2 N(t)) = 0. \tag{5}$$

Thus, the equilibrium points of TNM (2) compute by solving the equation (4) and (5), as follows:

First, the solutions of the equation (4) for N, are given by,

$$N = 0, \quad \text{or } N = \frac{r - \gamma T}{r\beta_1}.$$

Now, substitute $N = 0$ into the equation (5) and we get

$$T = 0 \quad \text{or } T = \frac{1}{\alpha_2}.$$

Thus, the first two equilibrium points are represented by

$$p_0 = (0, 0) \quad \text{and } p_1 = (0, \frac{1}{\alpha_2}).$$

Next, substitute $N = \frac{r-\gamma T}{r\beta_1}$ into the equation (5) and we get

$$T = 0 \quad \text{or } T = \frac{r(\alpha_1\beta_1 + \beta_2)}{r\alpha_1\alpha_2\beta_1 + \gamma\beta_2}$$

Thus, the others equilibrium points are represented by

$$p_2 = (\frac{1}{\beta_1}, 0)$$

and

$$p_3 = (\frac{\alpha_1(r\alpha_2 - \gamma)}{r\alpha_1\alpha_2\beta_1 + \gamma\beta_2}, \frac{r(\alpha_1\beta_1 + \beta_2)}{r\alpha_1\alpha_2\beta_1 + \gamma\beta_2}).$$

Remark 2: Since the feasible region of the TNM (2) is defined as $\Omega = \{(N, T) \in R^2_+\}$. Thus,

$$p_3 \notin R^2_+ \quad \text{where } \alpha_1(r\alpha_2 - \gamma) < 0.$$

Hence, the TNM has only three types of dead equilibrium points in the feasible region, p_0, p_1, and p_2, which are classified based on their biological meaning, where the tumor cells are in stage I or II as follows:

1) Type 1 dead equilibrium point: The dead equilibrium points of TNM imply that the cell death is related to the compartment populations of the normal and tumor cells. In this case, if the tumor cells begin to appear in a tissue, the death of the normal cells occurs due to the attack from the tumor cells [31]. If there does not exist any tumor cell, then the death of the normal cells occurs due to metabolic equilibrium, where the death of the tumor cells probably means that the abnormal cells are yet to develop into tumor cells [27]–[29], [37]. Furthermore, the death of the tumor cells can be a result of internal factors, such as glucose rate in the blood, where the tumor cells do not have dying property automatically in comparison with the normal cells [27]–[29]. This equilibrium point is called the origin point, and is denoted by $p_0 = (0, 0)$.
2) Type 2 dead equilibrium point (free normal cells): This equilibrium point shows that tumor cells begin to attack normal cells in tissues, and the DNA mutation stimulates the abnormal cells to develop into tumor cells. Moreover, this process is associated with the food pattern and the high level of estrogen [38]. This equilibrium point is denoted by $p_1 = (0, \frac{1}{\alpha_2})$.
3) Type 3 dead equilibrium point (free tumor cells): This equilibrium point illustrates that there are internal factors that inhibit the abnormal cells from developing into tumor cells due to the effect of diet and lifestyle factors. These factors play a central role in indirectly protecting our body from pathogen attack, as illustrated dynamically by [7], [37]. This equilibrium point is denoted by $p_2 = (\frac{1}{\beta_1}, 0)$.

C. STABILITY OF THE EQUILIBRIUM POINTS OF THE FREE MODEL

This section analyzes the behavior of an equilibrium point of TNM (2) by applying the Hartman–Grobman theorem, which states that the hyperbolic equilibrium point in the neighborhood and a nonlinear dynamical system is topologically equivalent to its linearization [39]. For studying the behavior of the aforementioned equilibrium points, we evaluate the Jacobian matrix of TNM (2) as follows:

$$J[N, T] = \begin{bmatrix} F_N[N, T] & F_T[N, T] \\ G_N[N, T] & G_T[N, T] \end{bmatrix}, \tag{6}$$

where $F[N, T] = \frac{dN}{dt}$ and $G[N, T] = \frac{dT}{dt}$.

Theorem 2: The type 1 *dead equilibrium point, p_0, of TNM equation* (2) *is unstable for all time t.*

Proof: To study the behavior of the equilibrium point, p_0, the Jacobian matrix equation (6) at p_0 is given by

$$J[N, T]_{p_0} = \begin{bmatrix} r & 0 \\ 0 & \alpha_1 \end{bmatrix}. \tag{7}$$

Since $tr(J[N, T]_{p_0})$ and $det(J[N, T]_{p_0})$ are positive, the dead equilibrium point p_0 is unstable.

The instability of this point is physiologically considered as a risk case if and only if there exist some tumor cells that can be activated as a consequence of the failure of the internal factors to retard the growth of tumor cells.

Theorem 3: The type 2 *dead equilibrium point, p_1, of TNM* (2) *is asymptotically stable if and only if $\gamma > r\alpha_2$; otherwise, the point is unstable.*

Proof: To study the behavior of the equilibrium point, p_1, we compute the Jacobian matrix (6) at p_1 as follows:

$$J[N, T]_{p_1} = \begin{bmatrix} \frac{r\alpha_2 - \gamma}{\alpha_2} & 0 \\ \frac{\beta_2}{\alpha_2} & -\alpha_1 \end{bmatrix}. \tag{8}$$

The eigenvalues are given by $\lambda_i = \frac{r\alpha_2 - \gamma}{\alpha_2}, -\alpha_1$, for $i = 1, 2$. It is obvious that the equilibrium point p_1 is stable if and only if $\gamma > r\alpha_2$; otherwise, the equilibrium point is unstable, for all $t \leq 0$. Since

$$tr(J[N, T]_{p_1}) = \frac{r\alpha_2 - \gamma}{\alpha_2} - \alpha_1 < 0,$$
$$det(J[N, T]_{p_1}) = -\frac{\alpha_1(r\alpha_2 - \gamma)}{\alpha_2} > 0,$$

and

$$\begin{aligned} \Delta &= (tr(J[N, T]_{p_1}))^2 - 4det(J[N, T]_{p_1}) \\ &= (\frac{r\alpha_2 + \alpha_1\alpha_2 - \gamma}{\alpha_2})^2 - 4(-\frac{\alpha_1(r\alpha_2 - \gamma)}{\alpha_2}) \\ &= r^2 + 2r\alpha_1 + \alpha_1^2 - \frac{2\,r\gamma}{\alpha_2} - \frac{2\gamma\alpha_1}{\alpha_2} + \frac{\gamma^2}{\alpha_2^2} \\ &= (\frac{r\alpha_1 + \alpha_1\alpha_2 - \gamma}{\alpha_2})^2 \\ &> 0. \end{aligned}$$

then the eigenvalues are real, distinct and have the same sign where $0 < det(J[N, T]_{p_1}) < \frac{(tr(J[N,T]_{p_1}))^2}{4}$. This shows that the equilibrium point p_1 is asymptotically stable node if and only if $\gamma > r\alpha_2$.

The existence of tumor cells physiologically demonstrates that they are capable of attacking the other cells in a tissue. In addition, their number increases through DNA mutation. One of the reasons for the occurrence of this mutation is excess estrogen, which repopulates the tumor cells [31]. Consequently, the population of tumor cells is denoted by $\frac{1}{\alpha_2}$.

Theorem 4: The type 3 *dead equilibrium point,* p_2*, of the TNM equation* (2) *is unstable for all time* t.

Proof: To study the behavior of the equilibrium point, p_2, we compute the Jacobian matrix (6) at p_2 as follows:

$$J[N,T]_{p_2} = \begin{bmatrix} -r & \frac{\gamma}{\beta_1} \\ 0 & \frac{\alpha_1\beta_1+\beta_2}{\beta_1} \end{bmatrix}. \tag{9}$$

Since the rate of normal cell division with respect to abnormal cells is very small ($0 < \beta_1 < 0.1$), then

$$tr(J[N,T]_{p_2}) = -\frac{(r-\alpha_1)\beta_1-\beta_2}{\beta_1} > 0,$$
$$det(J[N,T]_{p_2}) = -\frac{r(\alpha_1\beta_1+\beta_2)}{\beta_1} < 0,$$

and

$$\begin{aligned}\Delta &= (tr(J[N,T]_{p_2}))^2 - 4\,det(J[N,T]_{p_2}) \\ &= (\frac{(\alpha_1-r)\beta_1+\beta_2}{\beta_1})^2 + \frac{4\,r(\alpha_1\beta_1+\beta_2)}{\beta_1} \\ &> 0.\end{aligned}$$

Thus, the eigenvalues are real and have opposite sign where $\Delta(J[N,T]_{p_2}) > 0$ and $det(J[N,T]_{p_2}) < 0$. This shows that the dead equilibrium point p_2 is unstable.

Remark 3: Note that there exists a correspondence between the mathematical results and physiological properties, where the model does not have a coexistence point when the immune system is very weak. The coexistence case means that the tissue can include both normal and tumor cells without any side-effect [7]. In addition, the model is stable if the tumor cells succeed in attacking all normal cells in a tissue. The behavior of all equilibrium points is shown in FIGURES 1 and 2.

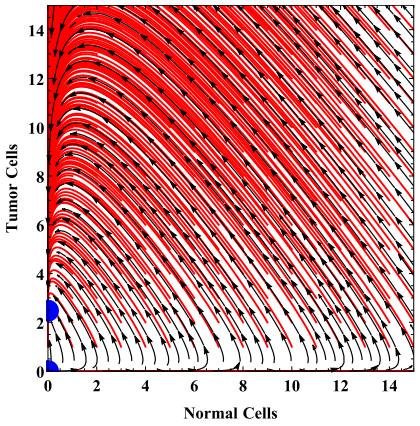

FIGURE 1. Phase portrait of TNM and its solutions around the origin point and free normal cell equilibrium points.

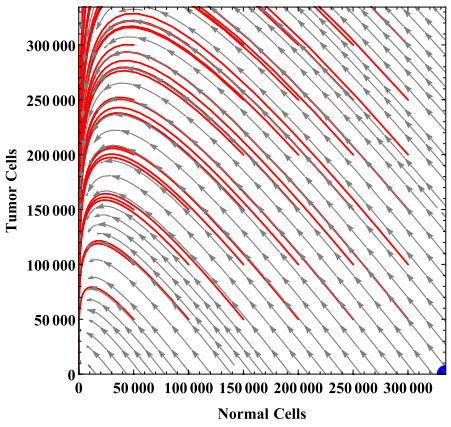

FIGURE 2. Phase portrait of TNM and its solutions around the free tumor cell equilibrium points.

IV. MODIFICATION OF A FREE MODEL BY THE INTERVENTION OF VITAMINS

Based on the model of Alharbi *et al.* [23], we developed the behavior of the free model by the intervention of a regular rate of vitamins. These authors amended the diet pattern to be more healthy, as recommended by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) [25]. As shown by the food pyramid in FIGURE 3, Alharbi *et al.* [23] deduced that the food contains at least 16% of vitamins, which can support the immune system and protect the body from cancer. Glucose is necessary for the growth of a cell but there is a difference between the metabolic glucose of cancer cells and that of normal cells [40]. Here, we investigate the effect of the intervention of vitamins when a tissue has a tumor cell from stages I, II. By consuming a moderate rate of glucose and vitamins from a natural or supplemental source (external factor), we can support the growth of normal cells, where the rate of the affected vitamins of the normal cells is denoted by c_1. In addition, to maintain a regular rate of glucose in the blood, we should inhibit the growth of tumor cells, where the rate of the affected vitamins of tumor cells is denoted by c_2. Consequently, the developed model is called tumor–normal–vitamins model (TNVM), which is given by

$$\begin{aligned}\frac{dN}{dt} &= rN[1-\beta_1 N] - \gamma NT + c_1 NV, \\ \frac{dT}{dt} &= \alpha_1 T[1-\alpha_2 T] + \beta_2 NT - c_2 TV, \\ \frac{dV}{dt} &= k_1 - k_2 V,\end{aligned} \tag{10}$$

where the last equation demonstrates the intervention of vitamins as an external factor denoted by the variable V. The parameters k_1 and k_2 are positive, where k_1 denotes the rate of the external vitamins, while k_2 denotes the rate of vitamins that affects the behavior of the model.

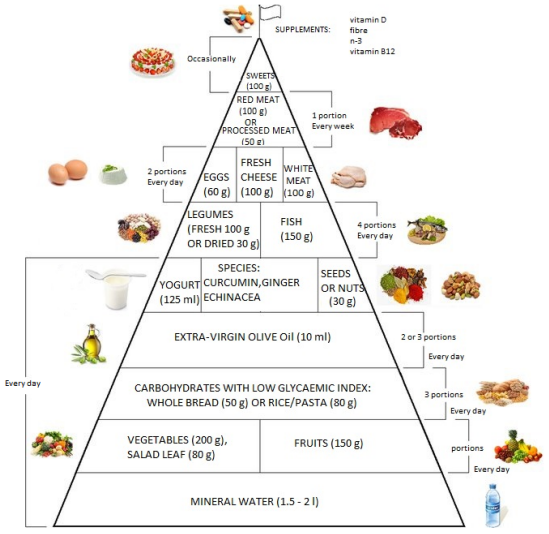

FIGURE 3. Management of a diet based on the recommendation by WCRF and AICR, where the amounts of food are estimated by nutritional and practical considerations.

V. MODEL ANALYSIS

A. BOUNDARIES AND POSITIVITY OF SOLUTIONS

Since the dynamic of TNVM (10) illustrates the behavior of normal and tumor cells by considering the intervention of vitamins as an external factor, the variables $N(t)$, $T(t)$, and $V(t)$ are real and nonnegative. Hence, the feasible region is given by

$$\Omega = \{(N, T, V) \in R^3_+\}.$$

To determine the initial values of vitamins, we conduct an experiment by utilizing Mathematica software and observe that the best response occurs when $V(0) = 5$. Hence, the initial value of the dynamic TNVM (10) is given by

$$N(0) = T(0) = 1, \quad \text{and } V(0) = 5.$$

In addition, all solutions with positive conditions are positive for $0 \le t < \infty$. Then, we obtain the following theorem based on Theorem 1:

Theorem 5: The region $\Omega \subset R^3_+$ is nonnegativity invariant with respect to the model (10), and there exists a nonnegative solution for $0 \le t < \infty$.

Proof: Let

$$\Omega = \Omega_d = \{(N, T, V) \in R^3_+, N = \frac{1}{\beta_1}, T = \frac{1}{\alpha 2}, \text{and } V = 1\}.$$

Then, the solutions $(N(t), T(t), V(t))$ of TNVM (10) are positive for all time t with $0 \le t < \infty$. The positivity of the solutions of N and T can be shown by applying Theorem 1. Now, we show that the solution is $V(t) = 1$. Since

$$\frac{dV}{dt} \le k_1 - k_2 V(t) \tag{11}$$

and by applying the separable method, the solution of (11) is given by

$$V(t) \le 1 + ce^{-kt}.$$

As $t \to \infty$, we obtain that

$$V(t) \le 1.$$

Since the feasible region of TNVM is denoted by $\Omega = \{(N, T, V) \in R^3_+\}$, we have $V(t) = 1$ as $t \to \infty$.

B. EQUILIBRIUM POINTS OF FREE MODEL

The steady states occur when the left hand side of the dynamic system of TNVM presented in (10) is set to zero, as follows:

- $\frac{dN}{dt} = 0 \Rightarrow$

$$N(r(1 - \beta_1 N) - \gamma T + c_1 V) = 0. \tag{12}$$

- $\frac{dT}{dt} = 0 \Rightarrow$

$$T(\alpha_1(1 - \alpha_2 T) + \beta_2 N - c_2 V) = 0. \tag{13}$$

- $\frac{dV}{dt} = 0 \Rightarrow$

$$k_1 - k_2 V = 0$$
$$V = \frac{k_1}{k_2}. \tag{14}$$

Thus, the equilibrium points of TNVM (10) compute by solving the equations (12), (13) and (14), as follows:

First, the solutions of the equation (12) for N, are given by,

$$N = 0, \quad \text{or } N = \frac{r + c_1 V - \gamma T}{r\beta_1}.$$

Now, substitute $N = 0$ into the equation (13). We get

$$T = 0, \quad \text{or } T = \frac{\alpha_1 - c_2 V}{\alpha_1 \alpha_2} = \frac{\alpha_1 k_2 - c_2 k_1}{\alpha_1 \alpha_2 k_2}.$$

Thus, the first equilibrium points is represented by

$$q_1 = (0, 0, \frac{k_1}{k_2}) \quad \text{and } q_2 = (0, \frac{\alpha_1 k_2 - c_2 k_1}{\alpha_1 \alpha_2 k_2}, \frac{k_1}{k_2}).$$

Next, substitute $N = \frac{r + c_1 V - \gamma T}{r\beta_1}$ into the equation (13). We get

$$T = 0,$$

or

$$T = \frac{(\alpha_1 - c_2 V) r\beta_1 + (r + c_1 V - \gamma T)\beta_2}{(r\alpha_1\alpha_2\beta_1 + \gamma\beta_2)k_2} = \frac{(\alpha_1\beta_1 + \beta_2) rk_2 + (c_1\beta_2 - c_2 k_1)}{(r\alpha_1\alpha_2\beta_1 + \gamma\beta_2)k_2}.$$

Thus, the others equilibrium points are represented by

$$q_3 = (\frac{c_1 k_1 + rk_2}{rk_2\beta_1}, 0, \frac{k_1}{k_2})$$

and

$$q_4 = (\frac{(c_1 k_1 + rk_2)\alpha_1\alpha_2 + (c_2 k_1 - \alpha_1 k_2)\gamma}{(r\alpha_1\alpha_2\beta_1 + \gamma\beta_2)k_2}, \frac{(\alpha_1\beta_1 + \beta_2) rk_2 + (c_1\beta_2 - rc_2\beta_1)k_1}{(r\alpha_1\alpha_2\beta_1 + \gamma\beta_2)k_2}, \frac{k_1}{k_2}).$$

Remark 4: As a resulting of the intervention of vitamins, the TNVM (10) does not have a type 2 dead equilibrium point comparing by the equilibrium point of the TNM (1) such that

the type-2 dead equilibrium point illustrates that the normal cells die when tumor cells become active. This point is given by

$$q_2 = \left(0, \frac{\alpha_1 k_2 - c_2 k_1}{\alpha_1 \alpha_2 k_2}, \frac{k_1}{k_2}\right).$$

An obvious reason for the intervention of vitamins is to moderate the level of glucose and estrogen hormone in the blood, considered as a healthy medium to simulate the growth of tumor cells [41]–[43]. Hence,

$$q_2 \notin R^3_+ \quad \text{where } c_2 k_1 > \alpha_1 k_2.$$

Thus, the TNVM has only two types of dead equilibrium points in the feasible region which are given by

$$q_1 = (0, 0, \frac{k_1}{k_2})$$

and

$$q_3 = (\frac{c_1 k_1 + r k_2}{r k_2 \beta_1}, 0, \frac{k_1}{k_2}).$$

The coexistence equilibrium point occurs based on a special case and is given by

$$q_4 = (\frac{(c_1 k_1 + r k_2)\alpha_1 \alpha_2 + (c_2 k_1 - \alpha_1 k_2)\gamma}{(r\alpha_1\alpha_2\beta_1 + \gamma\beta_2)k_2}, \frac{(\alpha_1\beta_1 + \beta_2)r k_2 + (c_1\beta_2 - r c_2 \beta_1)k_1}{(r\alpha_1\alpha_2\beta_1 + \gamma\beta_2)k_2}, \frac{k_1}{k_2}).$$

Therefor, the equilibrium points of The TNVM (10), q_1, q_3 and q_4, are classified based on their biological meaning as the following:

1) Type 1 dead equilibrium point: This equilibrium point demonstrates that both normal and tumor cells die when vitamins enter the body. By comparing with type 1 dead equilibrium point of TNM (2), we deduce that the modification of this equilibrium point causes vitamins to appear in the blood. This equilibrium point is given by

$$q_1 = (0, 0, \frac{k_1}{k_2}).$$

2) Type 3 dead equilibrium point: This equilibrium point differs from the type 3 dead equilibrium point of TNM (2), where the population of the normal cells changes due to the intervention of vitamins. This point is positive everywhere, and is given as

$$q_3 = (\frac{c_1 k_1 + r k_2}{r \beta_1 k_2}, 0, \frac{k_1}{k_2}).$$

3) Coexistence equilibrium point: The coexistence equilibrium point is considered as an emergency equilibrium point, which means the success for survival of the tumor cells with the normal cells, and may spread into the tissue. In addition, tumor cells have a higher chance of invasion than the neighboring tissues, as shown by the following equation:

$$q_4 = (\frac{A}{(r\alpha_1\alpha_2\beta_1 + \gamma\beta_2)k_2}, \frac{B}{(r\alpha_1\alpha_2\beta_1 + \gamma\beta_2)k_2}, \frac{k_1}{k_2}),$$

where

$$A = (c_1 k_1 + r k_2)\alpha_1\alpha_2 + (c_2 k_1 - \alpha_1 k_2)\gamma,$$
$$B = (\alpha_1\beta_1 + \beta_2)r k_2 + (c_1\beta_2 - r c_2\beta_1)k_1.$$

The studies conducted on cancer have revealed an association between the dietary pattern and cancer. According to them, the consumption of the Western diet leads to insulin resistance, which increases the level of glucose, obesity, and cancer [33]–[35]. Hence, switching back to a healthy diet, which includes a sufficient amount of vitamins, which dented by k_1 and k_2, can moderate the level of glucose in the blood and affect the behavior of tumor growth [41]–[43]. Thus, based on these studies, an appropriate coexistence occurs when

$$c_2 k_1 - \alpha_1 k_2 > 0.$$

C. STABILITY OF THE EQUILIBRIUM POINTS OF MODIFIED FREE MODEL WITH THE INTERVENTION OF VITAMINS

This section discusses the stability of equilibrium points for investigating the effect of the intervention of vitamins as an inhibitor of tumor cells. The following is the Jacobian matrix of TNVM (10):

$$J[N,T,V] = \begin{bmatrix} F_N[N,T,V] & F_T[N,T,V] & F_V[N,T,V] \\ G_N[N,T,V] & G_T[N,T,V] & G_V[N,T,V] \\ H_N[N,T,V] & H_T[N,T,V] & H_V[N,T,V] \end{bmatrix}, \quad (15)$$

where

$$F[N,T,V] = \frac{dN}{dt},$$
$$G[N,T,V] = \frac{dT}{dt}$$

and

$$H[N,T,V] = \frac{dV}{dt}.$$

Theorem 6: The type 1 *dead equilibrium point, q_1, of the TNVM (11) is an unstable point for all time t*

Proof: To study the behavior of this equilibrium point, we compute the following Jacobian matrix (15) at q_1:

$$J[N,T,V]_{q_1} = \begin{bmatrix} \frac{c_1 k_1 + r k_2}{k_2} & 0 & 0 \\ 0 & \frac{\alpha_1 k_2 - c_2 k_1}{k_2} & 0 \\ 0 & 0 & -k_2 \end{bmatrix}, \quad (16)$$

where the eigenvalues of the matrix (16) are given by

$$\lambda_i = -k_2, \frac{\alpha_1 k_2 - c_2 k_1}{k_2}, \frac{c_1 k_1 + r k_2}{k_2}, \quad \text{for } i = 1, 2, 3.$$

From the condition of the type 1 dead equilibrium point, $\alpha_1 k_2 - c_2 k_1 < 0$, it is obvious that $\lambda_{1,2} < 0$ and $\lambda_3 > 0$. Thus, the type 1 dead equilibrium point, q_1, is unstable for all time t.

$$J[N,T,V]_{q_3}=\begin{bmatrix} -\dfrac{c_1k_1+rk_2}{k_2} & -\dfrac{(c_1k_1+rk_2)\gamma}{r\beta_1k_2} & \dfrac{c_1(c_1k_1+rk_2)}{r\beta_1k_2} \\ 0 & \dfrac{(\alpha_1k_2-c_2k_1)r\beta_1+(c_1k_1+rk_2)\beta_2}{r\beta_1k_2} & 0 \\ 0 & 0 & -k_2 \end{bmatrix}. \tag{17}$$

A comparison of the type 1 dead equilibrium point of models (2) and (10) shows that both of them are unstable points, but the death of q_1 is considered as positive, where the death of the cells occurs by switching back to a healthy diet and intake of sufficient vitamins. Our model also assumes that the effect of the immune system is very weak, and there is a cycle life for normal cells. An instability of q_1 is a natural case, which physiologically means that the body can avoid tumor cells from developing.

Theorem 7: The type 3 *dead equilibrium point, q_3, of the TNVM (10) is an unstable for all time of t.*

Proof: To study the behavior of this equilibrium point, we compute the Jacobian matrix (15) at q_3 as (17), as shown at the top of this page.

To find the eigenvalue of the matrix (17), we compute the $det(J[N,T,V]_{q_3}-\lambda I)$ as follows

$$\begin{aligned} &det(J[N,T,V]_{q_3}-\lambda I)\\ &\quad=(-k_2-\lambda)(-\frac{c_1\,k_1+rk_2}{k_2}-\lambda)\\ &\qquad\times(\frac{(\alpha_1\,k_2-c_2\,k_1)r\beta_1+(c_1k_1+rk_2)\beta_2}{r\beta_1\,k_2}-\lambda). \end{aligned}$$

Then, the characteristic equation is given by

$$\begin{aligned} &(-k_2-\lambda)(-\frac{c_1k_1+rk_2}{k_2}-\lambda)\\ &\quad\times(\frac{(\alpha_1k_2-c_2k_1)r\beta_1+(c_1k_1+rk_2)\beta_2}{r\beta_1k_2}-\lambda)=0. \end{aligned} \tag{18}$$

Therefore, the solution of (18) shows that the matrix (17) has three distance eigenvalues are given by

$$\begin{aligned} \lambda_1&=-k_2,\\ \lambda_2&=-\frac{c_1\,k_1+rk_2}{k_2},\\ \lambda_3&=\frac{(\alpha_1\,k_2-c_2\,k_2)r\beta_1+(c_1k_1+rk_2)\beta_2}{r\beta_1\,k_2}. \end{aligned}$$

To determine the stability case of the type 3 dead equilibrium point, q_3 we need to examine the sign of λ_i. It is clear that $\lambda_{1,2}<0$. Physiologically, the rate of division normal cells as abnormal cells is very small compare with the rate of conversion of abnormal cells into tumor cells. This leads that $(c_1k_1+rk_2)\beta_2>(\alpha_1\,k_2-c_2\,k_2)r\beta_1$ then $\lambda_3>0$. Hence, this type of dead equilibrium point is an unstable point.

Theorem 8: The coexistence of the equilibrium point, q_4, of the TNVM (10) is a stable point.

Proof: To study the behavior of this equilibrium point, the Jacobian matrix (15) at q_4 is computed as follows:

$$J[N,T,V]_{q_4}=\begin{bmatrix} -\dfrac{r\beta_1A}{C} & -\dfrac{\gamma A}{C} & \dfrac{c_1A}{C} \\ \dfrac{\beta_2B}{C} & -\dfrac{\alpha_1\alpha_2B}{C} & -\dfrac{c_2B}{C} \\ 0 & 0 & -k_2^2 \end{bmatrix}, \tag{19}$$

where

$$\begin{aligned} A&=(c_1\,k_1+rk_2)\alpha_1\alpha_2+(c_2\,k_1-\alpha_1\,k_2)\gamma,\\ B&=(\alpha_1\beta_1+\beta_2)rk_2+(c_1\beta_2-rc_2\beta_1)k_1\\ C&=(r\alpha_1\alpha_2\beta_1+\gamma\beta_2)k_2. \end{aligned}$$

To find the eigenvalue of the matrix (19), we collected $det(J[N,T,V]_{q_4}-\lambda I)$ as follows

$$\begin{aligned} &det(J[N,T,V]_{q_4}-\lambda)\\ &\quad=(-k_2-\lambda)[(\frac{-r\beta_1A}{C}-\lambda)(\frac{-\alpha_1\alpha_2B}{C}-\lambda)+\frac{\gamma\beta_1AB}{C}]\\ &\quad=(-k_2-\lambda)(\lambda^2+\frac{r\beta_1A+\alpha_1\alpha_2B}{C}\lambda\\ &\qquad+\frac{(\gamma^2\beta_2k_2+(1+\gamma\beta_1k_2)r\alpha_1\alpha_2)\beta_1AB}{C^2}). \end{aligned} \tag{20}$$

Then, the characteristic equation is given by

$$\begin{aligned} &(-k_2-\lambda)(\lambda^2+\frac{r\beta_1A+\alpha_1\alpha_2B}{(r\alpha_1\alpha_2\beta_1+\gamma\beta_2)k_2}\lambda\\ &\qquad+\frac{(\gamma^2\beta_2k_2+(1+\gamma\beta_1k_2)r\alpha_1\alpha_2)\beta_1AB}{(r\alpha_1\alpha_2\beta_1+\gamma\beta_2)^2k_2^2})=0. \end{aligned} \tag{21}$$

Using the Remark 1, the simplified form of the characteristic equation (21) is written as follows

$$k_2^2\gamma\lambda^3+D\lambda^2+F\lambda+k_2F=0, \tag{22}$$

where

$$\begin{aligned} D&=\gamma k_2^3+r\alpha_1\alpha_2k_2^2+\alpha_1\alpha_2c_1k_1k_2\\ F&=[\gamma c_2\,k_1+\alpha_1\alpha_2c_1k_1\\ &\quad+((r+k_2)\alpha_2-\gamma)\alpha_1\,k_2](c_1k_1+rk_2)\\ &>0 \end{aligned}$$

Now, we apply the Routh-Hurwitz theorem for (22), giving

$$\begin{vmatrix} \lambda^3 & \gamma k_2^2 & F \\ \lambda^2 & D & k_2F \\ \lambda^1 & \dfrac{F(D-\gamma k_2^3)}{D} & 0 \\ \lambda^0 & k_2F & 0 \end{vmatrix}.$$

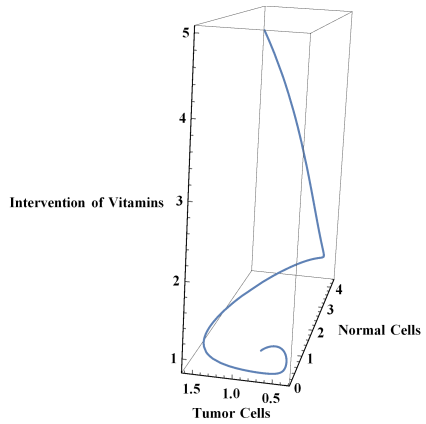

FIGURE 4. Parametric solution of TNVM.

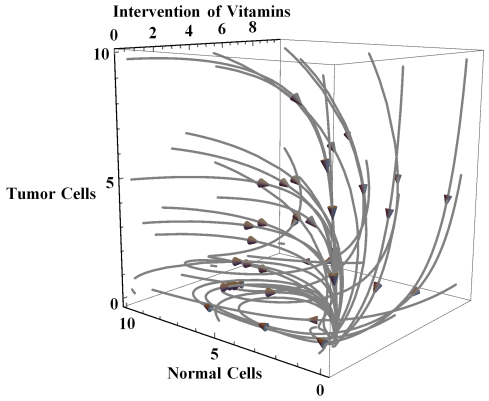

FIGURE 5. The behavior solutions of TNVM around the equilibrium points.

Since,

$$D - \gamma k_2^3 = r\alpha_1\alpha_2 k_2^2 + \alpha_1\alpha_2 c_1 k_1 k_2 > 0.$$

Therefore, it is obvious that the sign of elements in first column is positive. This shows that the coexistence of the equilibrium point, q_4, of the TNVM (10) is a stable point.

Remark 5: The effect of switching back to a healthy diet, which includes sufficient vitamins, on the dynamic system of TNM can be deduced as follows:

- The intervention of vitamins plays a role in supporting normal cells to survive even when tumor cells have appeared.
- There is no equilibrium when tumor cells begin to react and attack normal cells. In other words, the intervention of vitamins is an unsuitable medium for the survived survival tumor cells.
- TNVM is stable when the combined cells survive together.

The behavior of all equilibrium points is shown in FIGURES 4 and 5.

VI. NUMERICAL SIMULATION OF THE MODELS

We have used Software Mathematica 11.0 with command NDSolve to simulate the two models TNM (2) and TNVM (10). This simulation was designed by applying

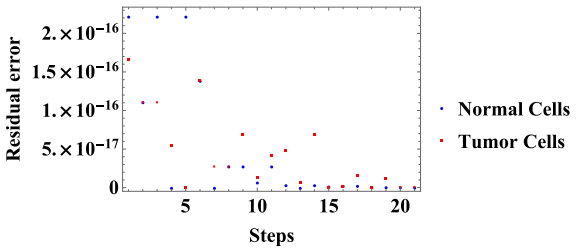

FIGURE 6. Residual error at various steps for TNM.

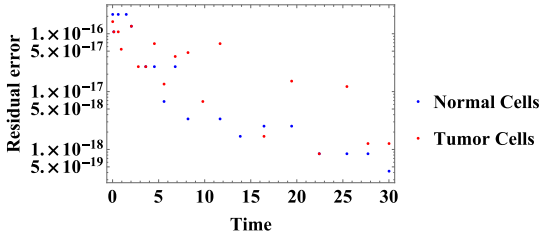

FIGURE 7. Residual error at time t for TNM.

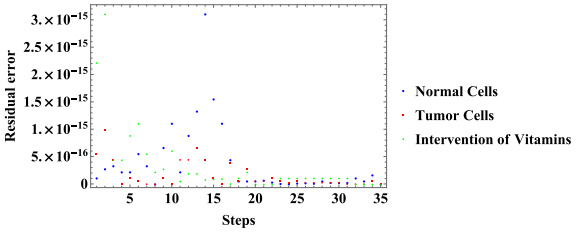

FIGURE 8. Residual error at various steps for TNVM.

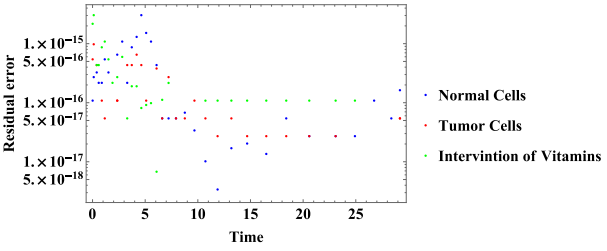

FIGURE 9. Residual error at time t for TNVM.

NDSolve using a fourth–order Runge–Kutta method for getting a more stable and easily convergent solution. The simulation of TNM and TNVM were done by choosing an individual time as thirty days and an integration step $\frac{1}{10000}$. This simulation deduced that switching from an unhealthy diet to a healthy diet has a significant impact on inhibiting the growth of tumor cells and might support the normal cells to survive for a long time if the function of the immune system is very weak or fails to recognize the activities of tumor cells. As depicted in FIGURES 6–9, the residual error validates the accuracy and reliability of the proposed method. The simulation results of two models TNM (2) and TNVM (10) were compared with the numerical results of assessing the effect of estrogen on the dynamics of breast cancer [7].

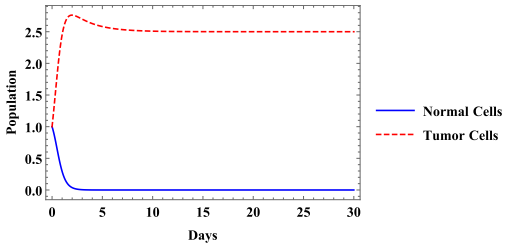

FIGURE 10. Behavior of TNM within thirty days where $r = 0.4312$, $\beta_1 = 2.99 * 10^{-6}$, $\gamma = 0.9314$, $\alpha_1 = 0.4426$, $\alpha_2 = 0.4$, $\beta_2 = 1.1891$.

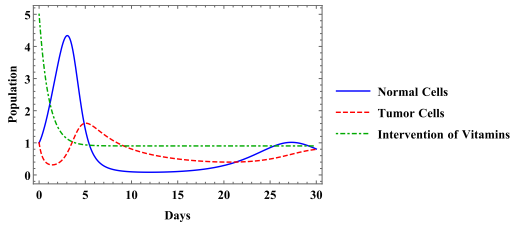

FIGURE 11. Effect of intervention of vitamins on the behavior of tumor and normal cells where $r = 0.4312$, $\beta_1 = 2.99 * 10^{-6}$, $\gamma = 0.2291$, $\alpha_1 = 0.4426$, $\alpha_2 = 0.4$, $\beta_2 = 0.9817$, $c_1 = 0.2215$, $c_2 = 0.4975$, $k_1 = 0.8976$, $k_2 = 0.9611$.

The result of TNM simulation indicated that when the tumor cells began to grow rapidly, the growth of normal cells was retarded but continued to divide horizontally. Horizontal division of normal cells indicates that normal cells divide and grow by following the signals of control cellular growth and death [28], [37]. Based on the physiological meaning of the growth cells, we can deduce that the growth status of cells is affected when $\gamma = 0.9314$ and $\beta_2 = 1.1891$ cells per day. These parameters demonstrate the ability of tumor cells to attack normal cells and develop abnormal cells into tumor cells. The behavior of the tumor and normal cells of TNM is illustrated in FIGURE 10.

The result of TNVM simulation indicated that the intervention of vitamins has a significant impact on moderating the dynamic of TNM. To substitute for the absence of the function in the immune system, a significant response occurs when most of the vitamins interact. In this case, the rate of development of abnormal cells into tumor cells is retarded from 1.1891 to 0.9817. This can retard the rate of growth of tumor cells. The rate of activities of tumor cells under consideration is decreased, where we deduced that the rate of attack on the normal cells decreased by 75% after the intervention of vitamins within thirty days.

When tumor cells are retarded but the rate of the retardation of the normal cell growth is simulating the tumor cell to grow, the normal cells grow significantly during the first four days from the intervention of vitamins. Note that there are no new tumor cells emerging due to the abnormal cells. Hence, there is an asymmetric relation between these results and those of analyzing the effect of intervention of vitamins on the function of the immune system [23]. Herein, we show that the intervention of vitamins does not allow the development of the abnormal cells appearing in the tissue for several years. Based on the results of the TNVM simulation, the simulated rate of consuming a sufficient amount of vitamins is $k_1 = 0.8677\%$ per day, where the simulated rate of vitamins that react with the cells is $k_2 = 0.9611\%$. The retarded growth of tumor cells occurs by enabling vitamins to moderate the level of glucose in the blood [26]. Hence, the vitamin rate is affected by the tumor cells, i.e., $c_2 = 0.4975$, while the rest is affected by the normal cells, i.e., $c_1 = 0.2215$. The effect of the intervention of vitamins on the behavior of the tumor and normal cells is demonstrated in FIGURE 11.

VII. CONCLUSION

Alharbi and Rambely [37] indicated dynamically that the function of the immune system is affected by the type of diet. They deduced that the people who observe an unhealthy diet are at higher risk of being affected by cancer as compared to those who observe a healthy diet. In 2019, Alharbi *et al.* [23] showed numerically that switching back to a healthy diet from an unhealthy diet, such as the Western diet, can retard or eliminate the abnormal cells. In this study, we proposed the TNM to investigate the effect of the development of abnormal cells into tumor cells due to the malfunctioning of the immune system on the dynamics of normal cells cycle dynamically, analytically, and numerically. In addition, we formulated the TNVM by assuming that the person started to change his/her diet, as depicted by the food pyramid in FIGURE 3. By comparing the results of the analysis and simulation of both TNM and TNVM, we deduced that the appearance of tumor cells in a tissue, as well as their activities, affects the dynamics of the cycle of normal cells. If the rate of development of abnormal cells to tumor cells is higher than that of the growth of the normal cells, the TNM model is stable and retards the activities of tumor cells based on internal factors in the body. This implies that the tumor cells were at high risk of attacking and eliminating the normal cells in the tissue, which possibly enabled them to affect the neighboring tissues. Clearly, the dynamics of TNM were moderated by considering that a person started to consume a sufficient amount of vitamins daily. These moderates summarized by disappearing the type 2 dead of equilibrium points, which probably means that the activity of the tumor cells was decreased by interring the vitamins. Since tumor cells do not die automatically, the intervention of vitamins could support the tumor and normal cells to survive together. This may delay the development of tumor cells and cancer. Based on the simulation of both models, we deduced that the consumption of a regular rate of vitamins simulated to at least 87% can dynamically change the early stage of the tumor cells. In this study, the proposed models presented the general dynamics of the normal cells when the tumor cells started to be in the tissue and moderate their dynamics by consuming the intervention of vitamins. Mathematical models are useful for understanding the natural science and can be extensively applied to discuss the dynamics of different types of diseases, but it is difficult to consider and account for the effects of all variables. Our proposed

models contribute to highlighting the effect of intervention of vitamins on the dynamics of normal cells and tumor cells in a tissue, and we discussed the dynamics of both TNM and TNVM by adding some constraints. To investigate the results of our mathematical models and obtain more accurate results, it is important we conduct more clinical experiments by considering real-life problems and classify the foods that can retard the growth of tumor cells in early stages of cancer. In the future, we hope to develop this study by examining drugs that are resistant to vitamins and their effects on the dynamic model of the tumor–normal cells. Finally, the results of this study will be applied to manage several common types of cancer.

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