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STABILITY ANALYSIS OF MATHEMATICAL MODEL ON THE EFFECT OF MODERN LIFESTYLES TOWARDS THE IMMUNE SYSTEM

(Analisis Kestabilan Model Matematik bagi Kesan Cara Hidup Moden Terhadap Sistem Imun)

SANA ALHARBI & AZMIN SHAM RAMBELY

ABSTRACT

During the last century, lifestyles have changed globally not only in the western countries but also in the developing countries. As a result, the percentages of common fatal diseases, such as obesity, diabetes, cardiovascular disease, and cancer, have dramatically increased, especially in youth. This paper aims to mathematically examine the impact of modern lifestyle on health. Furthermore, we formulate a dynamical model for the impact of a balanced diet, regular exercise and sufficient sleep on the immune system and its processes. We present a stability model of the immune system that includes a cycle of phase-specific vitamins. Ordinary differential equations are used to model the system to describe the functioning of immune cells. The model considers three populations: normal cells, immune cells, and vitamin interventions. The results show that a balanced diet and a healthy lifestyle can boost the immune system and improve its processes to protect a human body from pathogens. In conclusion, a balanced diet and physical activity reduce the percentage of fatal disease risk. Furthermore, it is vital to raise awareness about healthy habits and promote healthy eating, especially for the youth.

Keywords: malnutrition; supplement dietary; bout exercises; malfunction in immune system; unhealthy body

ABSTRAK

Semenjak abad lalu, gaya hidup telah berubah secara global bukan sahaja di negara barat tetapi juga di negara sedang membangun. Akibatnya, peratusan penghidap penyakit maut yang lazim, seperti obesiti, diabetes, penyakit kardiovaskular dan kanser, telah meningkat secara dramatik, terutamanya dalam kalangan belia. Kajian ini dijalankan dengan tujuan untuk mengkaji secara matematik kesan gaya hidup moden terhadap kesihatan. Selain itu, rumus model dinamik untuk kesan diet seimbang, senaman yang kerap dan tidur yang mencukupi pada sistem imun dan prosesnya dibincangkan. Satu model kestabilan sistem imun yang merangkumi kitaran vitamin fasa khusus dibentuk. Persamaan pembezaan biasa digunakan untuk memodelkan sistem untuk menggambarkan fungsi sel imun. Model ini mempertimbangkan tiga populasi: sel normal, sel imun, dan penggunaan vitamin. Hasilnya menunjukkan bahawa diet seimbang dan gaya hidup yang sihat dapat meningkatkan sistem imun dan memperbaiki prosesnya untuk melindungi tubuh manusia dari patogen. Sebagai kesimpulan, diet yang seimbang dan aktiviti fizikal dapat mengurangkan peratusan risiko penyakit maut. Tambahan pula, adalah penting untuk meningkatkan kesedaran mengenai tabiat yang sihat dan menggalakkan pemakanan yang sihat, terutamanya untuk kalangan belia.

Kata kunci: malnutrisi; makanan tambahan; senario senaman; malfungsi dalam sistem imun; badan tidak sihat

1. Introduction

In the human body, there are about 10^{13} tiny cells that form the tissues and organs. Increases in the number of cells leads to growth of body tissues. The conception and adulthood cells divide and grow very quickly. However, division and growth depend on their functions, and some cells such as blood and skin cells divide continuously. Some cells have specialised functions in

the body and do not multiply often. At most, a human cell can multiply as many as 60 times before dying naturally.

A cell division cycle has four principal phases. The first phase is *Gap*1 (*G*1 phase), in which a cell grows and determines when to divide. The second phase is synthesis (*S* phase), in which the cell copies its DNA and then checks if all of its DNA has been copied correctly in *Gap*2 (*G*2 phase). The final phase is mitosis (*M* phase), in which the cell divides into two cells. During this phase, the cell shares DNA copies equally between two new cells. This results in two identical copies of the cells, with the two cells separating the duplicated chromosomes into two full sets.

Sometimes, cells become damaged during the process of growth and division, and in that case, they typically destroy themselves. This process is called apoptosis, which helps to prevent the body from developing cancer. On the other hand, cell division is sometimes abnormal when there is damage during cell division. Such cells have different properties from those of normal cells. In this case, the immune system responds by attacking them for protecting the human body by preventing them from growing into a tumour.

A human body has many elements to protect itself. The first is the outer creatine layer on the skin and another is its biochemical body units (Karacabey & Ozdemir 2012). The human immune system is the second line of defence against infection of the body, which also influences other physiological systems and processes, including metabolism, tissue repair, fatigue and sleep, mental health and thermal regulation (Peake 2013). The protection of the immune system consists of the lymph nodes, thymus, spleen and some specific immune cells (Coico & Sunshine 2015). If a pathogen enters a human body, the immune system reacts and generates an immune response (Karacabey & Ozdemir 2012).

The immune system has two principal parts, the innate or natural and the acquired, also called the adaptive immune system. The first line of defence against infections is the innate immunity mechanism. This is more responsive and evolutionarily reserved to non-specific molecular pathogen patterns. On the other hand, the adaptive immune system especially consists of highly specific B and T cells. These are necessary for building immunological long-term memory against specific pathogens (Rowe *et al*. 2007; Lendor *et al*. 2008; Abbas *et al.* 2014; Male *et al*. 2014;).

The structure of the immune system is similar to that of the nervous system. One of its most important features is its ability to recognise and distinguish millions of different threats. With this characteristic, functional cells detect an unfamiliar object, memorise it and recognise it later. The immune system begins to work if features of a pathogen enter a human body. Then, the immune response determines a reaction and defence that is used by the immune system against the pathogen (Jornayvaz 2011; Coico & Sunshine 2015).

The immune system is a complex mechanism in sanitation and defence against diseases (Başoğlu & Turnagöl 2004; Saygin *et al*. 2006; Palmer 2011; Cantorna *et al.* 2012). It contains different cells distributed in many locations in the body, between which the cells move in the lymph and bloodstream. These organised cells are in separate lymphoid organs classified as primary lymphocytes (bone marrow and thymus), where immune cells mature. Secondary lymphoid organs include lymph nodes, spleen and gut-associated lymphoid tissue, where immune cells mature, respond and interact with antigens (Abbas *et al.* 2014; Male *et al.* 2014). A potential response of the immune system against body cells themselves is called an autoimmune reaction, which causes autoimmune disorders (Başoğlu & Turnagöl 2004; Saygin *et al.* 2006; Palmer 2011; Cantorna *et al.* 2012).

However, immune cells require substrates of energy fuels such as glucose, amino acids and fatty acids. Multiple nutrients support the immune cells to produce and divide protective chemicals; destroy, engulf and move pathogens and produce proteins such as cytokines and immunoglobulins. In addition, immune cells are required for specific critical roles in enzyme

systems for vitamins (A, D, C, E, B_{12} and B_6), zinc, iron, copper, selenium, magnesium and others. Vitamins play various roles in an immune function. For example, vitamins A and D and their metabolism are regulators of gene expression directly in the immune cell. In addition, they play the principal role in the maturation, differentiation and response of immune cells (Calder 2013). Vitamin B_{12} is important for red blood cell formation, DNA synthesis during cell division and preserving the myelin sheath around neurons. Deficiency of vitamin B_{12} is associated with diseases such as dementia (Pin 2016), neurodegenerative disorders cancer, cardiovascular disease and pernicious anaemia (Watanabe 2007).

The resistance of immunity against microorganism functions normally involves a complex mechanism, but mostly in cooperation. There are many factors affecting natural resistance, such as nutrition, obesity, age, physical activity, hormones, consumption of alcohol and genetics (Nieman 2000; Başoğlu & Turnagöl 2004; Coico & Sunshine 2015).

2. Previous Study on Modelling of Tumour Cells

Many researchers have studied the behaviour of human disease by modelling the immune system. Mayer *et al.* (1995) described the dynamic process of interaction of the immune system with a target population, formulating their system in terms of a system of two ordinary differential equations, as follows:

$$\frac{dT}{dt} = rT - kTE, \tag{1}$$

$$\frac{dE}{dt} = f(T) + g(E) - dE, \tag{2}$$

where equation (1) represents a temporal change in the target population, T. The second term represents the elimination of the targets as a result of interaction with specific immune component effectors E and r, k are positive rate constants. The equation (2) describes immune competence. It is formulated in terms of three factors, $f(T)$ denotes targets that trigger processes in the immune system leading to competence against them, where $f(T) = \rho\frac{T^u}{m^v+T^v}$ such that ρ, m, u and v are positive constants, and $u \leq v$. The immune reaction, $g(E)$ is given by $s\frac{E^n}{c^n+E^n}$ and the finite lifetime of an immune competent cell is given by $-dE$, where a positive constant d is the dying rate of the immune system (Mayer *et al.* 1995). However, several mathematical techniques have been applied in the study of therapy effect types on the behaviour of tumour growth using the immune system. Researchers modified the immune system model formulated by Kirschner and Panetta through the use of delay differential equations and used numerical simulations where periodic solutions can arise through Hopf bifurcations (Villasana & Radunskaya 2003). A model of this system is as follows:

$$\begin{aligned}
T_I' &= 2a_4T_M - (c_1I + d_2)T_I - a_1T_I(t-\tau),\\
T_M' &= a_1T_I(t-\tau) - d_3T_M - a_4T_M - c_3T_MI - k_1\left(1 - e^{-k_2u}\right)T_M,\\
I' &= k + \frac{\rho I(T_I+T_M)^n}{\alpha+(T_I+T_M)^n} - c_2IT_I - c_4T_MI - d_1I - K_3(1 - e^{-K_4u})I,\\
u' &= -\gamma u \qquad ,
\end{aligned}$$

where

$$\begin{aligned}
T_I(t) &= \phi_1(t) \text{ for } t \in [-\tau; 0],\\
T_M(t) &= \phi_2(t) \text{ for } t \in [-\tau; 0],
\end{aligned}$$

$$I(t) = \phi_3(t) \text{ for } t \in [-\tau; 0],$$
$$u(0) = u_0,$$

where T_I' is the tumour cell population during the interphase at time t, T_M' is the tumour population during mitosis at time t, I' is the immune system population at time t, u' is the amount of drug present at time t and τ is the resident time of cells in the interphase (Villasana & Radunskaya 2003). Mufudza *et al.* (2012) uses the immune dynamics system to show that there is a negative relation between the effects of estrogen and tumour cell growth in breast cancer. Previous studies have discussed the relation between disease pathogenesis, effects on the body (Mayer *et al.* 1995; Mufudza *et al.* 2012) and their treatments (Swan 1985; De Pillis & Radunskaya 2003; Villasana & Radunskaya 2003). In this part, we describe the interaction of the immune system with an unhealthy body before the body is infected by any disease.

In summary, the objective of this paper is to formulate a model which dynamically describes the bad effects of diet patterns on immune processes and adult health and to discuss the relation between the logistic growth of the normal cell and boosting the immune system.

3. Modelling of Unhealthy Lifestyle Model

Many diet patterns and lifestyle changes have occurred in contemporary society, especially for youth. As a result, the percentages of common fatal diseases, such as obesity, diabetes, cardiovascular diseases and cancer, have increased dramatically (Riboli *et al.* 2002; Shridhar *et al.* 2015). Moreover, malnutrition causes the deaths of six million children each year. Nutritional deficiency can cause immune system malfunctions (Chandra 2003).

In this section, we illustrate the immune system model which shows the relationship between a change in diet and lifestyle on a healthy body. According to the logistic growth of cells, the normal cell division is about 50 - 60 times before dying naturally. However, during these processes, some cells are damaged and this is known as abnormal division. These abnormal cells are dormant for one to two years, at this stage the immune system eliminates them from growing before they turn into tumour cells (by attacking and repairing processes). But sometimes the immune system fails to recognize these abnormal cells as a foreign cells which lead them to attack the immune cells and grow into tumour cells. Such as interaction of an unhealthy lifestyle (external factors) and the immune response is shown in Figure 1. Thus the immune model is represented as follows:

$$\frac{dN}{dt} = \alpha N[1 - \beta N] - \eta NI,$$
$$\frac{dI}{dt} = \sigma + \frac{\rho NI}{m+N} - \delta I - \mu NI, \tag{3}$$

with initial values $N[0] = 1$ (Mufudza *et al.* 2012) and $I[0] = 1.22$ (Shan *et al.* 2012), where the first equation represents the change in the normal cell population, where N is a normal cell. The parameters α and β represent the growth and dying rates, respectively. The second equation describes the immune competence, where I denotes the immune cells. The number of immune cells is given by σ and the finite lifetime of immune competence is given by $-\delta I$, where a positive constant δ is the dying rate of the immune system. The Michaelis-Menten term $\frac{\rho NI}{m+N}$ (Mayer *et al.*1995) demonstrates growth of immune cells as a result of the stimulation of abnormal cells, where ρ is the rate of immune response and m is the threshold rate of the immune cells (Mufudza *et al.* 2012). Finally, the interaction of the immune system and abnormal cells can be described in two manners (which are shown as a two-way arrow),

repaired and attacked processes at a rate η and the results of the interaction model decrease the number of cells at the rate μ.

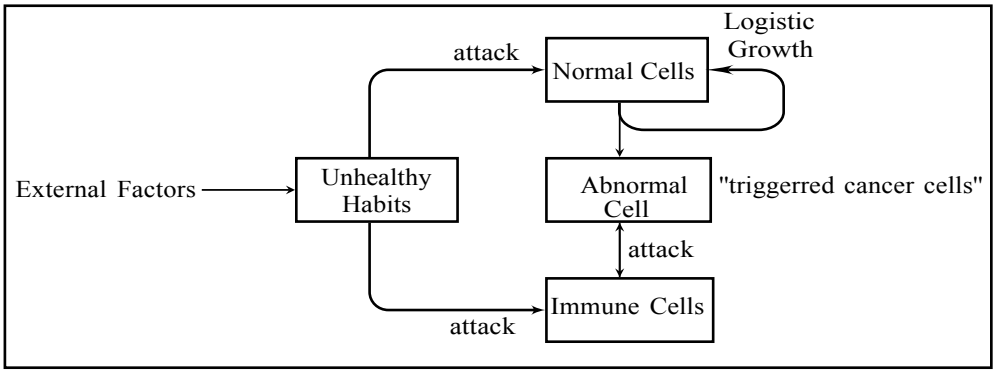

Figure 1: The interaction of normal cells, abnormal cells and immune cells under unhealthy habits

3.1. *Equilibrium points*

Equilibrium points are stable if they remain constant over time or continually balance change in one direction by that in another. Subpopulations of tissue cells N and I are positive or equal to zero for all $t \geq 0$. Stable situations occur when the ordinary differential equations equal zero at the same time (Mufudza *et al.* 2012), where

$$\frac{dN}{dt} = \frac{dI}{dt} = 0.$$

The model system has the folowing two stable situations:

3.1.1. *Case 1 dead equilibrium - E_d*

The model has a death equilibrium point, E_d if and only if the normal cells have died off. Consequently, there are no recovered normal cells damaged since they have been forced into extinction (Mufudza *et al.* 2012). Hence, the equilibrium point is as follows:

$$E_d = (N_1, I_1) = \left(0, \frac{\sigma}{\delta}\right)$$

where (N_1, I_1) is the first equilibrium point of (3). It is clear that $E_d \geq 0$, where $\sigma \geq 0$ and $\delta > 0$.

3.1.2. *Case 2 co-existence equilibrium point - E_c*

The model has a coexistence equilibrium point, E_c if and only if the population of cells N and I has survived the competition, as they coexist (Mufudza *et al.* 2012). Then, the equilibrium point is as follows:

$$E_c = (N_2, I_2) = \left(\frac{\alpha - \eta I}{\alpha\beta}, \frac{\sigma}{\delta + \mu N_2 - \frac{\rho N_2}{m + N_2}}\right)$$

where (N_2, I_2) is the second equilibrium point of (3). Since N_2 and I_2 are positive then $E_c > 0$.

3.2. *Stability analysis for equilibrium points*

We discussed the stability of equilibrium points using the Hartman-Grobman Theorem, which states that the hyperbolic equilibrium point in the neighbourhood of a nonlinear dynamical system is topologically equivalent to its linearization. To discuss the stability equilibrium points, we found the Jacobian of (3) given by

$$J(N,I) = \begin{pmatrix} \alpha - 2\alpha\beta N - \eta I & -\eta N \\ \frac{m\rho I}{(m+N)^2} - \mu I & \frac{\rho N}{m+N} - \delta - \mu N \end{pmatrix}. \tag{4}$$

3.2.1. *Local stability of dead equilibrium - E_d*

We evaluated the stability of death equilibrium points, with Jacobian at E_d which is given by

$$J_{E_d} = \begin{pmatrix} \alpha - \eta I_1 & -0 \\ \frac{m\rho I_1}{m^2} - \mu I_1 & -\delta \end{pmatrix}. \tag{5}$$

This system has two eigenvalues, namely $\lambda_1 = \alpha - \eta I_1$ and $\lambda_2 = -\delta$. Since $\lambda_2 < 0$, the system has a stable dead equilibrium point if $\alpha < \eta I_1$. This means that the immune system can repair and fight damage to normal cells. However, since the patient has a malfunction in the immune system due to nutritional deficiency (Saygin *et al.* 2006) and has no regular physical activity, the immune response is weak in this case. This implies the growth of abnormal cells (damage of normal) and $\alpha > \eta I_1$. Hence, the equilibrium point E_d is an unstable saddle point. This is shown in Figure 1, where the immune system cells attack the abnormal cells which is shown by the first two-way arrow. However, for unhealthy lifestyle the abnormal cells will be triggerred to become cancer cells.

3.2.2. *Local stability of coexisting equilibrium point - E_c*

In this case, we analyse the behaviour of the system around a coexisting equilibrium point, E_c where the Jacobian at E_c is given by

$$J_{E_c} = \begin{pmatrix} \alpha - 2\alpha\beta N_2 - \eta I_2 & -\eta N_2 \\ \frac{m\rho I_2}{(m+N_2)^2} - \mu I_2 & \frac{\rho N_2}{m+N_2} - \delta - \mu N_2 \end{pmatrix}. \tag{6}$$

The characteristic equation of (6) is given by

$$\lambda^2 - U_1\lambda + U_2 = 0,$$

where

$$U_1 = \alpha - 2\alpha\beta N_2 - \eta I_2 + \frac{\rho N_2}{m+N_2} - \delta - \mu N_2 < 0$$

such that

$$\delta + \mu N_2 + \eta I_2 + 2\alpha\beta N_2 > \alpha + \frac{\rho N_2}{m+N_2}\,.$$

In addition, we set U_2 as

$$U_2 = (\alpha - 2\alpha\beta N_2 - \mu N_2)\left(\frac{\rho N_2}{m+N_2} - \delta - \mu N_2\right) + \eta N_2\left[\frac{m\rho I_2}{(m+N_2)^2} - \mu I_2\right]$$

where

$$\alpha - 2\alpha\beta N_2 - \eta I_2 = -\alpha + \eta I_2 < 0 \qquad .$$

However,

$$\frac{\rho N_2}{m+N_2} - \delta - \mu N_2 < 0$$

where $\frac{\rho N_2}{m+N_2}$ represents Michaelis-Menten as a result of reaction processes of the model. This is very small because the body is unhealthy. Hence,

$$(\alpha - 2\alpha\beta N_2 - \mu N_2)\left(\frac{\rho N_2}{m+N_2} - \delta - \mu N_2\right) > 0 \ .$$

Moreover,

$$\eta N_2\left[\frac{m\rho I_2}{(m+N_2)^2} - \mu I_2\right] < 0$$

where $\frac{m\rho I_2}{(m+N_2)^2} < \mu I_2$. Then,

$$U_2 > 0 \quad \text{where } (\alpha - 2\alpha\beta N_2 - \mu N_2)\left(\frac{\rho N_2}{m+N_2} - \delta - \mu N_2\right) > \eta N_2\left[\frac{m\rho I_2}{(m+N_2)^2} - \mu I_2\right].$$

Now, the two eigenvalues of λ are given by

$$\lambda_{1,2} = \frac{-U_1 \pm \sqrt{U_1^2 - 4U_2}}{2} \qquad .$$

Since $U_1 < 0$ and $U_2 > 0$ and if $\Delta = U_1^2 - 4U_2 > 0$, then the equilibrium point, E_c is a stable node. However, the equilibrium point, E_c is a stable spiral if $\Delta = U_1^2 - 4U_2 < 0$. This means in this case the immune cells growth are greater than abnormal cells to have a stable system.

4. Modelling of Unhealthy Lifestyle with Intervention of Vitamins

Exercise on a regular basis, having a proper sleep and following a healthy diet pattern influence the immune processes. In this section we will see this influence in the immune cells in the model (3) by assuming that a person keeps a regular schedule of exercising twice per week, gets approximately 6-8 hours of sleep and eats a balanced diet based on the food pyramid for boosting the immune system. Previous studies have clinically observed that there is a significant difference in the immune function between consistently and moderately active persons

(Schmidt *et al.* 2017). Studies have found that there is an increase in the production of reactive oxygen species, and that some immune cell functions can be affected by an excess of free radicals during exercise (Niess *et al.* 1999). Repeated exercise on the same day (Field *et al.* 1991; Nielsen *et al.* 1996; Rohde *et al.* 1998; Severs *et al.* 1996) or for more than several days (Hoff man-Goetz *et al.* 1990) shows different changes in the number of circulating, natural killer (NK) cells, NK cell cytotoxic activity (NKCA) and lymphocyte proliferation. Subsequent research examined changes in other immune responses after repeated exercise on the same day for a short period of time versus prolonged recovery and days to months of intense training.

Circulating leukocytes comprise 50 – 60 % of netruphils. Netruphils are considered the first microbicidal line of defence and are involved in inflammatory responses (Peake 2002). A single exercise period changes the number of leukocytes in the blood, which most likely remain for a long time in exercise. All major populations of leukocytes are increased during exercise activity owing to effects on the circulatory system (Witard *et al.* 2012). There is a significant increase in the number of circulating leukocytes and their sizes are associated with both intensity and duration of exercise (Steensberg *et al.* 2000). However, the activity of netruphils is significantly influenced during an intensified exercise. For example, cycling for one hour at 50 %vs. 80% of $V_{0_{2\max}}$ increases the production of neutrophil oxidative burst activity (Robson *et al.* 1999). During the initial stage of recovery after an exercise, the activity of bactericidal neutrophils continues to increase after 40 min to 1 h of a moderately intense exercise, whereas it remains impaired after prolonged or exhaustive exercise activity (Robson *et al.* 1999).

Moreover, the number of circulating NK cells increases temporarily as a result of acute exercise. For a couple of hours after the exercise, it decreases to less than one half of the normal. Typically, normal resting values are restored within 24 h (Shephard & Shek 1999). During a short recovery after an exercise session, NKCA remains unchanged on a per cell basis (Shephard & Shek 1999), particularly if a session is prolonged (Gleeson & Bishop 2005). After intensive and prolonged endurance exercise, NKCA is reduced by 40%−60% for at least 6 h (Shinkai *et al.* 1993; Nieman 1997; Nieman *et al.* 1997). This reduction is greater and longer lasting than that after an exercise period of less than one hour and the redistribution of cortisol induced by blood NK lymphocyte cells from the blood to other tissues (Nieman 1997). The reduction in NKCA closely parallels the drop in concentration of blood NK cells, meaning that each NK cell retains normal function (Nieman 2000).

However, sleep and the biological clock system have a strong regulatory impact on the immune function. A regular sleep cycle shows that immunological parameters such as the number of undifferentiated naive T cells and the production of pro-inflammatory cytokines show peaks during early night sleep while circulating the immune cells with immediate responder functions, such as NKCA, as well as the activity of anti-inflammatory cytokine peaks during daytime vigilance (Besedovsky *et al.* 2012).

There is a significant relation between nutrition and the immune system (Karacabey & Ozdemir 2012). Balanced nutrition, including intake of adequate vitamins, minerals and especially protein, promotes resistance against infection (Chandra 1997). Some elements of nutrition, such as zinc and especially antioxidant proteins, benefit immune functions. We have stronger immune systems if we take care of healthy nutrition (Karacabey & Ozdemir 2012). Moreover, studies prove that balanced nutrition supports the immune system (Chandra 1997).

Carbohydrates are necessary for fuelling immune system cells. It has been observed that anaerobic glycolysis causes an increase in the number of lymphocytes. However, the formation of methanogen indicates an increase in glucose as a fuel. During the spread of lymphocytes, the use of carbohydrates for energy decreases. In this case, glycolytic mid-products are directed to purine and pyrimidine nucleotide synthesis for growth cell (Sayan 1999; Chandra 2003; Başoğlu & Turnagöl 2004). The consumption of carbohydrates (30 and $60 g/h$) during cycling

for 2.5 reduces the suppression of lymphocyte T cells such as $CD4^+$ and $CD8^+$, which produce and express $IFN\gamma$ following the exercise (Lancaster *et al.* 2005). Carbohydrates are found largely in plant foods containing hydrogen, oxygen and carbon molecules (Sayan 1999; Başoğlu & Turnagöl 2004).

In the following section, we discuss the stability of cases of the previous model (3) with vitamin intervention and lifestyle habit changes see Figure 2. The new model is as follows:

$$\frac{dN}{dt} = \alpha N[1-\beta N] - \eta NI + c_1 NV,$$
$$\frac{dI}{dt} = \sigma + \frac{\rho NI}{m+N} - \delta I - \mu NI + c_2 IV,$$

$$\frac{dv}{dt} = k_1 - k_2 V, \tag{7}$$

with initial values $N[0] = 1$ (Mufudza *et al.* 2012) and $I[0] = 1.22$ (Shan *et al.* 2012) and $V[0] = 2$, where c_1 and c_2 are the rates of interaction of vitamins with normal and immune cells, respectively. The constant k_1 is the vitamin intervention rate. Loss of vitamins causes a reaction between vitamins and cells at rate k_2.

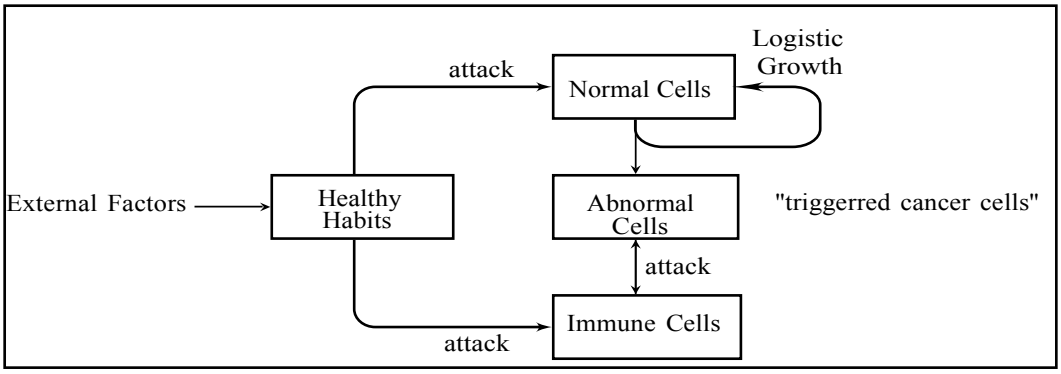

Figure 2: The interaction of normal cells, abnoraml cells and immune cells under healthy habits

4.1. *Equilibrium points*

The model given by equation (7) has two equilibrium points, the dead and coexisting equilibrium points.

4.1.1. *Dead equilibrium point* - ψ_d

We can say that an equilibrium point, ψ_d is dead if the normal cell population is zero. In this case, the equilibrium point is given by

$$\psi_d = (N_1, I_1, V_1) = \left(0, \frac{\sigma}{\delta - c_2 V}, \frac{k_1}{k_2}\right)$$

where (N_1, I_1, V_1) is the first equilibrium point of (7). It is clear that $\psi_d > 0$ if and only if $V < \frac{\delta}{c_2}$.

4.1.2. *Coexisting equilibrium point - ψ_c*

There is a state of coexisting equilibrium point, ψ_c if the entire population of cells would have survived the competition. This is given by

$$\psi_c = (N_2, I_2, V_2) = \left(\frac{\alpha - \eta I + c_1 V}{\alpha\beta}, \frac{\sigma}{\delta + \mu N_2 - \frac{\rho N_2}{m+N_2} - c_2 V}, \frac{k_1}{k_2} \right),$$

where (N_2, I_2, V_2) is the second equilibrium point of (7). Since N_2, V_2 and I_2 are positive then the equilibrium state of ψ_c is feasible.

4.2. *Stability analysis of equilibrium points*

We use linearization of the dynamical system to discuss the state of equilibrium points. The Jacobian of the system (7) is given by

$$J(N,I,V) = \begin{pmatrix} \alpha - 2\alpha\beta_1 N - \eta I + c_1 V & -\eta N & c_1 N \\ \frac{m\rho I}{(m+N)^2} - \mu I & \frac{\rho N}{m+N} - \delta - \mu N + c_2 V & c_2 I \\ 0 & 0 & -k_2 \end{pmatrix} \quad . \tag{8}$$

4.2.1. *Stability of dead equilibrium point - ψ_d*

We check on the behaviour of dead equilibrium point stability in terms of vitamin intervention and lifestyle habit changes. The Jacobian (8) at equilibrium point ψ_d is given by

$$J_{\psi_d} = \begin{pmatrix} \alpha - \eta I_1 + c_1 V_1 & 0 & 0 \\ \frac{\rho I_1}{m} - \mu I_1 & -\delta + c_2 V_1 & c_2 I_2 \\ 0 & 0 & -k_2 \end{pmatrix} \quad .$$

The system has three eigenvalues λ_i at ψ_d which are given by

$$\lambda_1 = -k_2,$$
$$\lambda_2 = -\delta + c_2 V_1,$$
$$\lambda_3 = \alpha - \eta I_1 + c_1 V_1.$$

Since the body is unhealthy, vitamin intervention supports the immune system more in repairing cell damage than in promoting cell growth. Then, the equilibrium point, ψ_d is stable if and only if $\delta > c_2 V_1$ and $\eta I_1 > \alpha - c_1 V_1$. However, if balanced nutrition and regular exercise are maintained for a long time, the immune system is strengthened with $c_2 > c_1$.

4.2.2. Stability of Coexisting Equilibrium Point-ψ_c

We evaluate the Jacobian of the system (8) at $\psi_c = (N_2, I_2, V_2)$, which is given by

$$J_{\psi_c} = \begin{pmatrix} \alpha - 2\alpha\beta N_2 - \eta I_2 + c_1 V_2 & -\eta N_2 & c_1 V_2 \\ \frac{m\rho I_2}{(m+N_2)^2} - \mu I_2 & \frac{\rho N_2}{m+N_2} - \delta - \mu N_2 + c_2 V_2 & c_2 I_2 \\ 0 & 0 & -k_2 \end{pmatrix}. \tag{9}$$

The characteristic equation of (9) is given by

$$(-k_2-\lambda)\left[(\alpha-2\alpha\beta N_2-\eta I_2+c_1V_2-\lambda)\left(\frac{\rho N_2}{m+N_2-\delta-\mu N_2+c_2V_2}-\lambda\right)+\eta N_2\left[\frac{m\rho I_2}{(m+N)^2}-\mu\right]\right]=0.$$

This system has three eigenvalues. The first eigenvalue is given by $\lambda_1=-k_2 \;\; where \;\; \lambda_1<0$. We obtain the other eigenvalues by solving the following equation:

$$(\alpha-2\alpha\beta N_2-\eta I_2+c_1V_2-\lambda)\left(\frac{\rho N_2}{m+N_2}-\delta-\mu N_2+c_2V_2-\lambda\right)+\eta N_2\left[\frac{m\rho I_2}{(m+N_2)^2}-\mu I_2\right]=0. \quad (10)$$

We rewrite (10) as

$$\lambda^2+U_1\lambda+U_2=0$$

where

$$U_1=2\alpha\beta N_2+\eta I_2+\delta+\mu N_2-\alpha-c_2V_2-c_1V_2-\frac{\rho N_2}{m+N_2}$$

and

$$U_2=(\alpha-2\alpha\beta N_2-\eta I_2+c_1V_2)\left(\frac{\rho N_2}{m+N_2}-\delta-\mu N_2+c_2V_2\right)+\eta N_2\left[\frac{m\rho I_2}{(m+N_2)^2}-\mu I_2\right]$$

.

According to previous studies, there is a significant correlation between the immune system and its function with diet pattern and lifestyle habits. Then, with an alteration in patterns and continuous exercise, there is an increase in immune system response, and hence, the immune system can detect an unfamiliar object, memorise it and recognise it later. Hence, $U_1>0$ where

$$2\alpha\beta N_2+\eta I_2+\delta+\mu N_2>\alpha+c_1V_2+c_2V_2+\frac{\rho N_2}{m+N_2} \quad .$$

Also, $U_2>0$ where

$$(\alpha-2\alpha\beta N_2-\eta I_2+c_1V_2)\left(\frac{\rho N_2}{m+N_2}-\delta-\mu N_2+c_2V_2\right)+\eta N_2\left[\frac{m\rho I_2}{(m+N_2)^2}-\mu I_2\right]>0\,.$$

Then, the eigenvalues $\lambda_{1,2}=\frac{-U_1\pm\sqrt{U_1^2-4U_2}}{2}$ have two cases. In the first case, if $\lambda_{1,2}\in \mathrm{R}$, then $\sqrt{U_1^2-4U_2}>0$ and $\lambda_{1,2}<0$. Hence, the equilibrium point ψ_c is stable. In the second case, if $\lambda_{1.2}\in \mathrm{C}$ then ψ_c is stable where the real parts of $\lambda_{1.2}$ are negative.

5. Numerical Solution

Mathematica software 10.0 is used to solve both models and show the behaviour model of the immune system that includes moderate the lifestyle. All values of parameters are obtained from the literature, see Table1 except for value of δ. This parameter is evaluated as follows:

$$\delta = \frac{\sigma}{I(0)} = \frac{0.7}{1.22} = 0.573$$

with values of and are obtained by Jacqueline *et al*. (2016) and Shan *et al.* (2012), respectively. The numerical solutions illustrated modern lifestyle had an impact on the immune system function and the division of the normal cells when the pathogen had begun to attack the body, see Figure 3 and 4.

Table 1: Parameters of the model and references

Parameter	Value	Definition and reference
r	0.431201	Rate of growth normal cells (Aziz *et al*. 2015)
β	$2.99 * 10^{-6}$	Rate turn normal cells to abnormal cells (Roach *et a*l. 2010)
η	0.2	Rate of repaired abnormal cells (Villasana & Radunskaya 2003)
σ	0.7	Fixed of immune source (Jacqueline *et al*. 2016)
δ	0.57	Rate natural death of immune cells
ρ	0.003	Response rate of immune cells (Aydar *et al*. 2002)
m	0.427	Threshold rate of immune cells (Jacqueline *et al.* 2016)
μ	0.82	Rate in decreasing of immune cells as result of interaction with abnormal cells (Aziz *et al*. 2015)
a	0.7	Amplitude of immune alteration (Jacqueline *et al*. 2016)

6. Discussion

The ability of the immune system to protect the human body from pathogens has been discussed in terms of a system of ordinary diff erential equations. The stability of the equilibrium points shows that there is a positive relation between lifestyle (diet pattern, physical activity and sleep) and the immune system and its response. The unhealthy model proved that the system can only be stable if the immune cells are greater than the abnormal cells. In this case, the immune system can eff ectively compete with the abnormal cell. But vitamin deprivation, stable physics and irregular sleep have a deleterious eff ect on the ability of the immune system to recognise an object (virus, bacteria or abnormal cell) as foreign and attack it, just as previous studies have shown that a deficiency in nutritional elements causes malfunctioning of the immune system (Chandra 2003). There is a strong relationship between acute and chronic inflammation and loss of sleep. Restriction and deprivation of sleeping causes changes in anti-inflammatory and pro-inflammatory, cytokine soluble receptors, inflammatory signalling pathways and innate immunity (Dinges *et al.* 1994; Irwin 2002; Lekander *et al.* 2013). Hence, in the modern era, diet pattern and lifestyle habits are factors in human health risk.

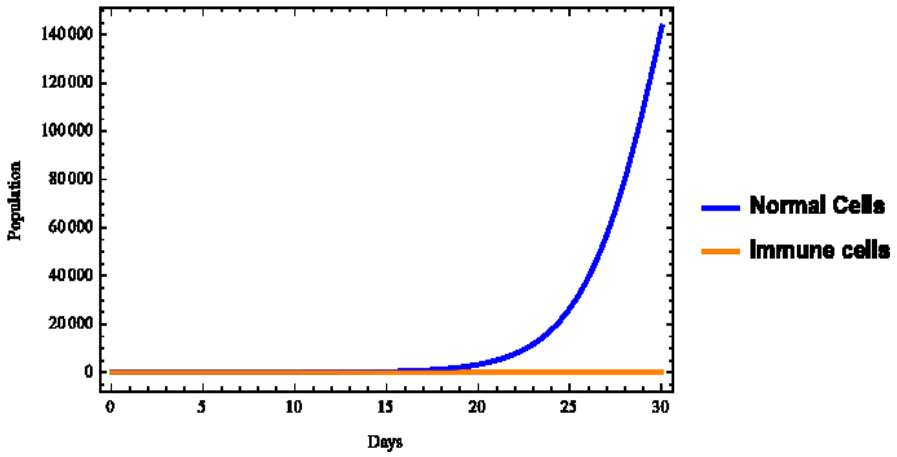

Figure 3: The behaviour of the model with unhealthy habits within 30 days

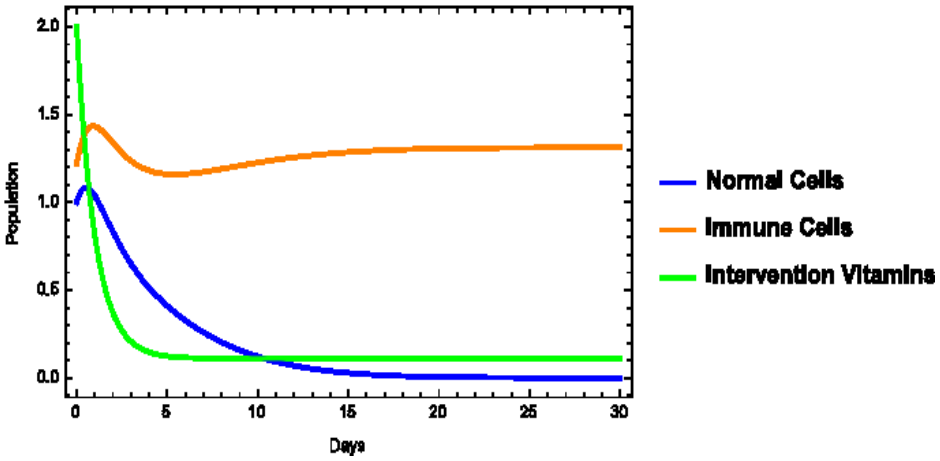

Figure 4:The behaviour of the model with healthy habits within 30 days

However, the behaviour of the immune system and its response begins to be more stable with changes in diet pattern, lifestyle habits and balanced consumption of vitamins with the eff ect that the body becomes healthier. These results support the findings of previous studies. There is a significant correlation between the immune system and its functioning with diet pattern and lifestyle habits. With alterations in diet pattern and continuous exercise, we observed that there is an increase in immune system response, and as a result, the immune system can detect an unfamiliar object, memorise it and recognise it later.

Consequently, nutrition specialists can encourage their patients to boost their immune systems by following the below guidelines:

- Eat a balanced diet to decrease the amount of fat, sugar and salt in their meals,
- Consume balanced amounts of complementary vitamins and minerals,
- Drink substantial amounts of water,
- Avoid junk food,
- Attain an ideal weight,
- Maintain a regular exercise schedule every day or at least once a week,
- Try to be more relaxed to reduce stress on the immune system function,
- Get sufficient sleep.

7. Conclusion

Adequate nutrition and a balanced diet are essential in enabling the immune system to repair damaged tissue and fight pathogens. In this study, we observed that a balanced diet and moderate physical activity have a significant impact on immune system response. We showed mathematically that the equilibrium points are unstable in an unhealthy model owing to weakness in the immune system, and hence, it cannot recognise pathogens as foreign objects and attack them. On the other hand, the behaviour of the immune system becomes stable through the influence of supplemental vitamins, a balanced diet, exercise and sleep. Thus, it is vital to raise awareness of healthy habits and promote healthy eating habits, especially among youth.

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References

Abbas A.K., Lichtman A.H. & Pillai S. 2014. *Cellular and Molecular Immunology*. 8th Ed. Philadelphia, PA: Elsevier Saunders.

Aydar Y., Balogh P., Tew J.G. & Szakal A.K. 2002. Age-related depression of FDC accessory functions and CD21 ligand-mediated repair of co-stimulation. *European Journal of Immunology* **32**(10): 2817–2826.

Aziz F., Yang X. Wen Q. & Yan Q. 2015. A method for establishing human primary gastric epithelial cell culture from fresh surgical gastric tissues. *Molecular Medicine Reports* **12**(2): 2939– 2944.

Başoğlu S. & Turnagöl H. 2004. Egzersiz ve immün sistem: Karbonhidratlarin etkisi. *Spor Bilimleri Dergisi* **15**(2): 100–123.

Besedovsky L., Lange T. & Born J. 2012. Sleep and immune function. *Pflügers Archiv: European Journal of Physiology* **463**(1): 121–137.

Calder P.C. 2013. Feeding the immune system. *Proceedings of the Nutrition Society* **72**(3): 299-309.

Cantorna M.T., Zhao J. & Yang L. 2012. Vitamin D, invariant natural killer t-cells and experimental autoimmune disease. *Proceedings of the Nutrition Society* **71**(1): 62–66.

Chandra R.K. 1997. Nutrition and the immune system: an introduction. *The American Journal of Clinical Nutrition* **66**(2): 460S–463S.

Chandra R.K. 2003. Nutrient regulation of immune functions. *Forum of Nutrition* **56**: 147-148.

Coico R. & Sunshine G. 2015. *Immunology: A Short Course*. West Sussex: John Wiley & Sons.

De Pillis L.G. & Radunskaya A. 2003. The dynamics of an optimally controlled tumor model: A case study. *Mathematical and Computer Modelling* **37**(11): 1221–1244.

Dinges D.F., Douglas S.D. & Zaugg L., Campbell D.E., McMann J.M., Whitehouse W.G., Orne E.C., Kapoor S.C., Icaza E. & Orne M.T. 1994. Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. *The Journal of Clinical Investigation* **93**(5): 1930–1939.

Field C.J., Gougeon R. & Marliss E.B. 1991. Circulating mononuclear cell numbers and function during intense exercise and recovery. *Journal of Applied Physiology* **71**(3): 1089–1097.

Gleeson M. & Bishop N.C. 2005. The T cell and NK cell immune response. *Annals of Transplantation* **10**(4): 44–49.

Hoffman-Goetz L., Simpson J.R., Cipp N., Arumugam Y. & Houston M.E. 1990. Lymphocyte subset responses to repeated submaximal exercise in men. *Journal of Applied Physiology* **68**(3): 1069–1074.

Irwin M. 2002. Effects of sleep and sleep loss on immunity and cytokines. *Brain, Behavior, and Immunity* **16**(5): 503–512.

Jacqueline C., Bourfia Y., Hbid H., Sorci G., Thomas F. & Roche B. 2016. Interactions between immune challenges and cancer cells proliferation: timing does matter! *Evolution, Medicine, and Public Health* **1**: 299–311.

Jornayvaz F.R. 2011. Diet, lifestyle, and long-term weight gain. *The New England Journal of Medicine* **365**(11): 1058–1059.

Karacabey K. & Ozdemir N. 2012. The effect of nutritional elements on the immune system. *Journal Obesity and Weight Loss Therapy* **2**(9): 1-6.

Lancaster G.I., Khan Q., Drysdale P.T., Wallace F., Jeukendrup A.E., Drayson M.T. & Gleeson M. 2005. Effect of prolonged exercise and carbohydrate ingestion on type 1 and type 2 T lymphocyte distribution and intracellular cytokine production in humans. *Journal of Applied Physiology* **98**(2): 565–571.

Lekander M., Andreasson A.N., Kecklund G., Ekman R., Ingre M., Akerstedt T. & Axelsson J. 2013. Subjective health perception in healthy young men changes in response to experimentally restricted sleep and subsequent recovery sleep. *Brain, Behavior, and Immunity* **34**: 43–46.

Lendor C., Johnson A., Perzanowski M., Chew G.L., Goldstein I.F., Kelvin E., Perera F. & Miller R.L. 2008. Effects of winter birth season and prenatal cockroach and mouse allergen exposure on indoor allergen-specific cord blood mononuclear cell proliferation and cytokine production. *Annals of Allergy, Asthma & Immunology* **101**(2): 193–199.

Male D., Brostoff J., Roth D.B. & Roitt I.M. 2014. *Imunologia*. 8th Ed. Sao Paulo: Elsevier.

Mayer H., Zaenker K. & Der Heiden U. 1995. A basic mathematical model of the immune response. *Chaos: An Interdisciplinary Journal of Nonlinear Science* **5**(1): 155–161.

Mufudza C., Sorofa W. & Chiyaka E.T. 2012. Assessing the effects of estrogen on the dynamics of breast cancer. *Computational and Mathematical Methods in Medicine* **2012**: 1-14.

Nielsen H.B., Secher N.H., Christensen N.J. & Pedersen B.K. 1996. Lymphocytes and NK cell activity during repeated bouts of maximal exercise. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* **271**(1): R222–R227.

Nieman D.C. 1997. Immune response to heavy exertion. *Journal of Applied Physiology* **82**(5): 1385–1394.

Nieman D.C., Henson D.A., Garner E.B., Butterworth D.E., Warren B.J., Utter A., Davis J.M., Fagoaga O.R. & Nehlsen-Cannarella S.L. 1997. Carbohydrate affects natural killer cell redistribution but not activity after running. *Medicine and Science in Sports and Exercise* **29**(10): 1318–1324.

Nieman D.C. 2000. Exercise effects on systemic immunity. *Immunology & Cell Biology* **78**(5): 496–501.

Niess A., Dickhuth H., Northoff H. & Fehrenbach E. 1999. Free radicals and oxidative stress in exercise–immunological aspects. Exercise Immunology Review **5**: 22–56.

Palmer A.C. 2011. Nutritionally mediated programming of the developing immune system. *Advances in Nutrition* **2**(5): 377–395.

Peake J. 2002. Exercise-induced alterations in neutrophil degranulation and respiratory burst activity: possible mechanisms of action. *Exercise Immunology Review* **8**: 49–100.

Peake J. 2013. Interrelations between acute and chronic exercise stress and the immune and endocrine systems. In: *Endocrinology of Physical Activity and Sport*: 259-280. New York: Springer/Hamana Press.

Pin N. 2016. Cognitive health of older persons in longitudinal ageing cohort studies. *Sains Malaysiana* **45**(9): 1351–1355.

Riboli E., Hunt K., Slimani N., Ferrari P., Norat T., Fahey M., Charrondiere U., Hemon B., Casagrande C. & Vignat J, et al. 2002. European prospective investigation into cancer and nutrition (epic): study populations and data collection. *Public Health Nutrition* **5**(6b): 1113–1124.

Roach J.C., Glusman G., Smit A.F., Huff C.D., Hubley R., Shannon P.T., Rowen L., Pant K.P., Goodman N. & Bamshad M. et al. 2010. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. *Science* **328**(5978): 636–639.

Robson P., Blannin A., Walsh N., Castell L. & Gleeson M. 1999. Effects of exercise intensity, duration and recovery on in vitro neutrophil function in male athletes. *International Journal of Sports Medicine* **20**(2): 128–130.

Rohde T., MacLean D.A. & Pedersen B.K. 1998. Effect of glutamine supplementation on changes in the immune system induced by repeated exercise. *Medicine and Science in Sports and Exercise* **30**(6): 856–862.

Rowe J., Kusel M., Holt B.J., Suriyaarachchi D., Serralha M., Hollams E., Yerkovich S.T., Subrata L.S., Ladyman C, Sadowska A. et al. 2007. Prenatal versus postnatal sensitization to environmental allergens in a high-risk birth cohort. *Journal of Allergy and Clinical Immunology* **119**(5): 1164–1173.

Sayan A. 1999. Beslenme alışkanlıkları ve temel besin gereksinimleri. *Atatürk Üniversitesi HemGirelik Yüksekokulu Dergisi* **2**(2): 53–65.

Saygin O., Karacabey K., Ozmerdivenli R., Zorba E., Ilhan F. & Bulut V. 2006. Effect of chronic exercise on immunoglobin, complement and leukocyte types in volleyball players and athletes. *Neuroendocrinology Letters* **27**(1-2): 271–276.

Schmidt T., Hermes A. & Weisser B. 2017. Physical training influences the immune system of breast cancer patients. *Deutsche Zeitschrift für Sportmedizin* **68**(3): 53–60.

Severs Y., Brenner I., Shek P. & Shephard R. 1996. Effects of heat and intermittent exercise on leukocyte and sub-population cell counts. *European Journal of Applied Physiology and Occupational Physiology* **74**(3): 234–245.

Shan L., Deng K., Shroff N.S., Durand C.M., Rabi S.A., Yang H.C., Zhang H., Margolick J.B., Blankson J.N. & Siliciano R.F. 2012. Stimulation of HIV-1-specific cytolytic t lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. *Immunity* **36**(3): 491–501.

Shephard R.J. & Shek P.N. 1999. Effects of exercise and training on natural killer cell counts and cytolytic activity. *Sports Medicine* **28**(3): 177–195.

Shinkai S., Kurokawa Y., Hino S., Hirose M., Torii J., Watanabe S., Shiraishi S., Oka K. & Watanabe T. 1993. Triathlon competition induced a transient immunosuppressive change in the peripheral blood of athletes. *The Journal of Sports Medicine and Physical Fitness* **33**(1): 70–78.

Shridhar G., Rajendra N., Murigendra H., Shridevi P., Prasad M., Mujeeb M., Arun S., Neeraj D., Vikas S., & Suneel D. et al. 2015. Modern diet and its impact on human health. *Journal of Nutrition & Food Sciences* **5**(6): 430–432.

Steensberg A., Hall G., Osada T., Sacchetti M., Saltin B. & Pedersen B.K. 2000. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *The Journal of Physiology* **529**(1): 237–242.

Swan G.W. 1985. Optimal control applications in the chemotherapy of multiple myeloma. *Mathematical Medicine and Biology: A Journal of the IMA* **2**(3): 139–160.

Villasana M. & Radunskaya A. 2003. A delay differential equation model for tumor growth. *Journal of Mathematical Biology* **47**(3): 270–294.

Watanabe F. 2007. Vitamin B_{12} sources and bioavailability. *Experimental Biology and Medicine* **232**(10): 1266–1274.

Witard O.C., Turner J.E., Jackman S.R., Tipton K.D., Jeukendrup A.E., Kies A.K. & Bosch J.A. 2012. High-intensity training reduces CD8+ T-cell redistribution in response to exercise. *Medicine & Science in Sports & Exercise* **44**(9): 1689–1697.

[1]*Department of Mathematics & Statistics*
Taibah University
College of Science
Yanbu, 41911, SAUDI ARABIA
E-mail: s.n.a.2013@hotmail.com

[1,2]*School of Mathematical Sciences*
Faculty of Science and Technology
Universiti Kebangsaan Malaysia
43600 UKM Bangi
Selangor DE, MALAYSIA
E-mail: asr@ukm.edu.my[*]

[*] Corresponding author