ON CONFORMABLE MATHEMATICAL MODEL OF IMMUNE SYSTEM COUPLED WITH INTESTINAL MICROBIOME

by

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Sometimes, an increased reaction is caused by an immune system of the body to a non-toxic agent (e. g. eggs, dust, pollens or some drugs). This is called allergy or hypersensitivity. The regulatory T cells decrease these allergic reactions. Nowadays, it is noticed that immune system has a deep relationship with micro-organism present in the intestine, that can be explained by the example, that some bacteria of intestine increase production of Treg cells by producing butyric acid like fatty acids. This can also understand that sufficiently different types of T cell receptors of Treg cells are needed to stop the inflammatory response produced by intestinal bacteria. In this study, the dynamic relation of T helper cells, intestinal bacteria and Treg cells are illustrated by a conformable mathematical model. Memory effects are figured out and displayed through graphs. Different plots also show the effects of increasing/decreasing amount of Treg induction efficiency on the whole system.

Key words: *intestinal microbiome, conformable derivative, immune system, initial value problem, non-linear differential equations*

Introduction

Immune systems of a human body start working at the age of six months till death. Other few subsystems of the body have a direct link with this immune system [1]. The more recent relation between intestine microbes and the immune system was highlighted by Fujimura and Lynch [2]. In a human body, by producing a few types of metabolites, Treg cells can be produced by a group of intestinal microbes [3]. Regulatory T cells decrease these allergic reactions [4]. The early stages of life are very important for the colonization of intestinal micro-organism because during this time the development of the immune system has a strong relation with these microbes [5]. Significant changes and reduction in intestinal micro-organism diversity, in neonatal and infant periods, could be the reason for disturbance in the immune system, which can cause asthma and atopy [4]. As heat transfer due to the climate changes effects the health of humans badly and risk of allergy attacks is very high during this time period. One of the major reasons for allergies is the thermal change in the environment so, from the health perspective of humans, one must understand the thermal comfort [5].

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A mathematical model related to the process of differentiation of Treg cells and Th cells was presented by Hara and Lwasa [6]. This model was combined with a simple model of intestinal micro-organism in a recent study by Hara and Lwasa in [7]. They presented a coupled model and discussed its stable and unstable conditions. After a keen literature review, we came to know that the solution for the particular model has not yet been found.

Fractional calculus has a very significant role in understanding the real-life phenomena [8-10]. Khalil [11] proposed a new definition for fractional order derivative (having all the properties of classical derivative). So, there were no more complexities in using this definition and we adopted the same for the investigation of the mathematical model of the immune system coupled with intestinal micro-organism. By using this approach, the memory effects have been observed, which was not possible by using a classical approach of derivatives. The obtained results are new and not reported before in the literature.

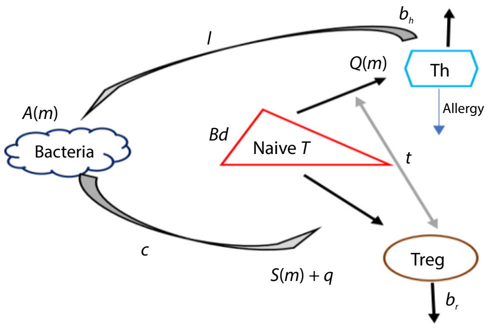

Figure 1. Procedural diagram

Mathematical formulation

A flow chart is always a helping tool for better understanding of any phenomena. Let us use it for the considered problem, fig. 1.

The previous fig. 1, help us to constru ct the following system of non-linear differential equations:

$$\frac{dQ(m)}{dm} = Bd\left[\frac{g}{1+cA(m)}\right]\left\{\frac{1}{t\left[S(m)+q\right]}\right\} - b_h Q(m) \tag{1}$$

$$\frac{dS(m)}{dm} = Bd\left[1-\frac{g}{1+cA(m)}\right] - b_r S(m) \tag{2}$$

$$\frac{dA(m)}{dm} = xA(m)\left[1-\frac{A(m)}{K}\right] - lQ(m)A(m) \tag{3}$$

In the previous system of equations m is denoting time. The Q, S, and A are number of Th cells, number of Treg cells and number of bacteria, respectively. First, two equations in the aforementioned system are describing the immune system, in which naive T cells are differentiated into Treg cells (allergy suppressor) and Th cells (allergy trigger), that is also presented in [6]. Here, B is the abundance of antigen and against it the antibodies are made by naive T cells with efficiency d. The Treg cells induction efficiency by microbiota is denoted here by c and g is the base level of differentiation. The $(g/1 + cA)$ is showing the fraction of naive T cells which are differentiated into T helper cells and other cells, along with the differentiation of $(1 - g/1 + cA)$ fraction into T regulatory cells. The term corresponds to the induction of Treg cells by intestinal bacteria is $(1 + cA)$ [3]. These fractions show that as the value of $cA(m)$ increases/decreases the number of Treg cells also increases/decreases and the number of Th cells decreases/increases. The $t[S(m) + q]$ highlights the Th cells suppression by Treg cells. The last terms of the first two equations of the previous system are, respectively describing decay in Th and Treg cells, by representation of d_h and d_r as rates of decaying, respectively.

Equation (3) is physically illustrating the dynamical changes in the population of micro-organism present in the intestine, which can induce Treg cells [3]. The logistic growth pattern is followed by the biomass of this group of microbes. Suppression of microbes is illustrated by the second term, with l, K, and x as rates of reduction of microbes per Th cell, carrying capacity and natural increase, respectively. Table 1 is provided below for the illustration of parameters which have been used in the aforementioned model.

Table 1. Description of parameters

Physical significance	Symbols	Units
Th_2 (allergic symptoms indicator) cells population	$Q(m)$	Cell
iTreg cells population	$S(m)$	Cell
Population of bacteria	$A(m)$	Bacteria
Quantity of antigen	B	Antigen/day
Naive T cells sensitivity to differentiate into Treg or Th cells	d	Cell/antigen
Base level of differentiation into T helper cells	g	1
Natural decay of T helper cells	b_h	1/day
Natural decay rate of iT regulatory cells	b_r	1/day
Treg suppression effect	t	1/cell
Population nTreg cells	q	Cell
Treg induction efficiency	c	1/bacteria
Effect of suppression on bacteria	l	1/cell day
Bacteria growth rate	x	1/day
Carrying capacity of bacteria	K	Bacteria

Let us develop the fractional form of the model, eqs. (1)-(3), by using the definition of Khalilzadeh's conformable derivative [11]:

$$\aleph_\Omega(Q)(m) = Bd\left[\frac{g}{1+cA(m)}\right]\left\{\frac{1}{t\left[S(m)+q\right]}\right\} - b_h Q(m) \tag{4}$$

$$\aleph_\Omega(S)(m) = Bd\left[1-\frac{g}{1+cA(m)}\right] - b_r S(m) \tag{5}$$

$$\aleph_\Omega(A)(m) = xA(m)\left[1-\frac{A(m)}{K}\right] - lQ(m)A(m) \tag{6}$$

Here, in the aforementioned system (4)-(6), $\aleph_\Omega$ is used as the operator and Ω – the order of the conformable derivative, for $\Omega \in (0, 1]$.

Now use the transformation of Khalilzadeh's in the previous system of differential equations to convert it in the following form:

$$\aleph^{1-\Omega}(Q)'(m) = Bd\left[\frac{g}{1+cA(m)}\right]\left\{\frac{1}{t\left[S(m)+q\right]}\right\} - b_h Q(m) \tag{7}$$

$$\aleph^{1-\Omega}\left(S\right)'\left(m\right)=Bd\left[1-\frac{g}{1+cA\left(m\right)}\right]-b_{r}S\left(m\right) \tag{8}$$

$$\aleph^{1-\Omega}\left(A\right)'\left(m\right)=xA\left(m\right)\left[1-\frac{A\left(m\right)}{K}\right]-lQ\left(m\right)A\left(m\right) \tag{9}$$

Results and discussion

The system of differential eqs. (4)-(6), has been solved numerically to get an approximate solution. The solution is painted with the help of graphs that are presented below, figs. 2-10. These figures are drawn to show the memory effects for different values of Ω, by using initial conditions as, $Q(0) = 7.29$, $S(0) = 576$, and $A(0) = 16$, the values of other parameters as $B = 1$, $d = 1$, $b_h = 0.1$, $b_r = 0.001$, $c = 0.001$, $g = 0.7$, $t = 0.001$, $x = 0.01$, $K = 10$, $q = 1$, and $l = 0.001$. Indeed, the use of fractional order discovers the hidden phenomena because of the memory effects, that cannot be seen in the mathematical models with Ω = 1. The beauty of the fractional order is that the solution of the fractional model (4)-(6), tends to the solution of the classic model (1)-(3), as the value of Ω tends to 1.

We can observe in figs. 2-9 that the change in the value of Treg inducing efficiency causes a very big effect on the change of population of Treg cells and Th cells. As the value of *c* (Treg inducing efficiency) is increasing, the amount of Treg cells are increasing with a decrease in the amount of Th cells.

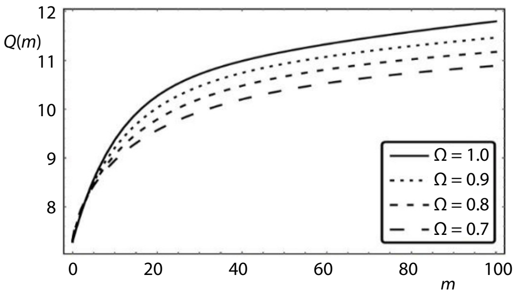

Figure 2. Dynamical changes in *Q*(*m*), for different fractional values with *c* = 0.01

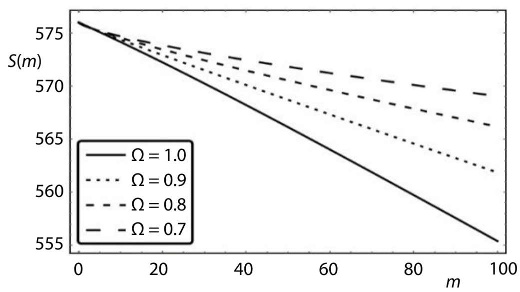

Figure 3. Dynamical changes in *S*(*m*), for different fractional values with *c* = 0.01

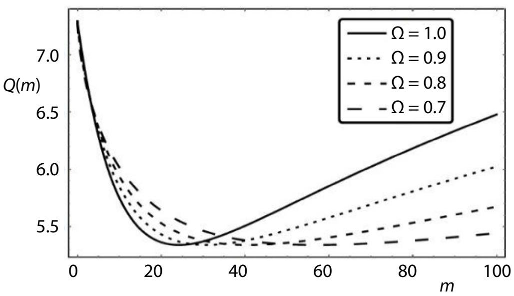

Figure 4. Dynamical changes in *Q*(*m*), for different fractional values with *c* = 0.1

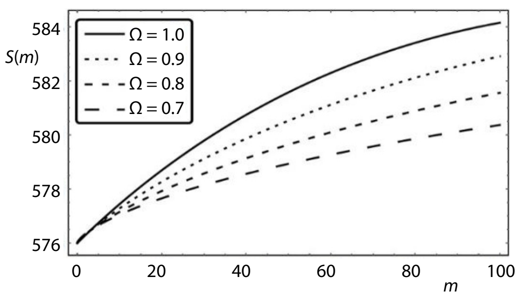

Figure 5. Dynamical changes in *S*(*m*), for different fractional values with *c* = 0.1

For *c* = 0.01 Th cells are increasing while Treg cells population have a clear decrease over 100 days. But as we increase the value of *c*, the opposite behaviors in the population of both Treg cells and Th cells occur that can be seen in the following graphs.

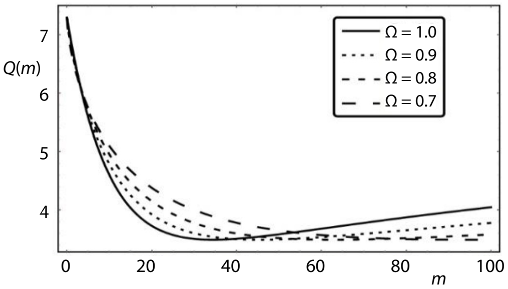

Figure 6. Dynamical changes in *Q*(*m*), for different fractional values with *c* = 0.2

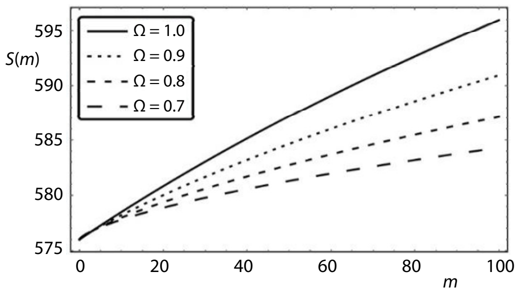

Figure 7. Dynamical changes in *S*(*m*), for different fractional values with *c* = 0.2

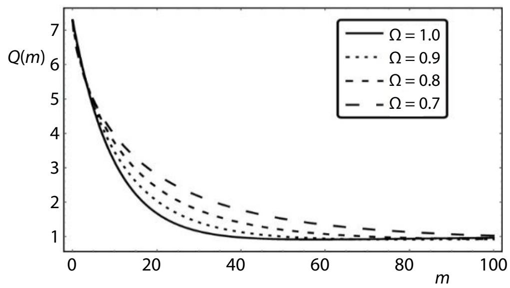

Figure 8. Dynamical changes in *Q*(*m*), for different fractional values with *c* = 1

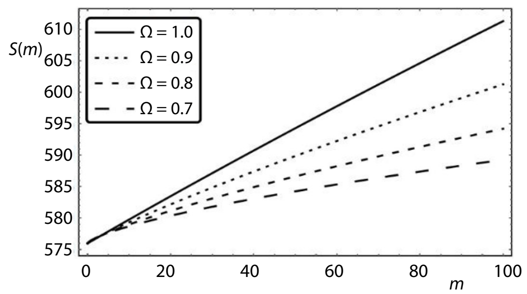

Figure 9. Dynamical changes in *S*(*m*), for different fractional values with *c* = 1

As the last class of the model (Bacteria) do not affect the change in the Treg inducing efficiency so, it will have the same behavior in all scenarios. Figure 10 is describing the change in the number of bacteria over the time of 100 days. The population of bacteria is continuously decreasing with the time passing.

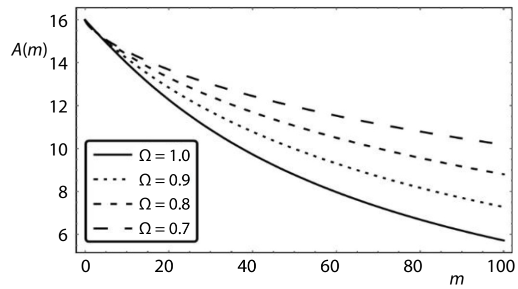

Figure 10. Dynamical changes in *Q*(*m*), for different fractional values

Conclusion

A conformable mathematical model has been proposed to generalize the study on the model of the immune system (that is directly connected with the intestinal microbes). We concluded that the main factor affecting the whole system is the Treg inducing efficiency. Its decreasing values cause a decrease in the number of Th cells while increasing the population of Treg cells. This behavior has been painted in the graphs to predict the changes and their effects in the immune system. Also, the recording of the memory effects for the under-study phenomena has been shown which are the backbone of biological problems.

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