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A MATHEMATICAL MODEL OF IMMUNE-MEDIATED DISORDER IN INFLAMMATORY BOWEL DISEASE

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Abstract. Inflammatory Bowel Disease(IBD) is chronic, relapsing, immune mediated disorder. The exact cause of IBD is still unknown. The immune system is known to play important role in the dynamics of IBD. We focus on relation between T cells and cytokines in immune system that leads to IBD. In this paper, we propose a mathematical model describing IBD under considering immune mediated disorder by using ordinary differential equations. The existence and stability of the model are established, where an applicable basin of attraction are calculated and examined. Some numerical simulations are presented to verify the proposed results and as changing parameter values given by sensitivity analysis, we show how to change dynamic behaviors of the model.

1. Introduction

Inflammatory Bowel Disease(IBD) is a chronic, relapsing, immune mediated disorder. The prevalence of IBD rapidly increased in Europe and North America in the second half of the twentieth century and is becoming more common in the rest of the world as different countries adopt a Western lifestyle([1],[2]). The main forms of IBD are divided into Crohns disease(CD) and Ulcerative colitis(UC).

The exact cause of IBD is still unknown. It is estimated that both environmental and genetic factor cause IBD. It is assumed that the change of our lifestyle augments this kind of disease. Above all since people use large amount of antibiotics and vaccine, our lifestyle has become more and more hygienic[2]. Also, a diet high in protein, particular animal protein, may be associated with increased risk of IBD and relapses[3].

The immune system is known to play an important role in the dynamics of IBD[4]. There are many studies that deal with mathematical models about

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immunopathogenesis and also diseases arise from an inappropriate immune system. In [5], the authors described a mathematical model about skin disease related with the densities of immune cells(Dendritic cells and Helper T cells) and Keratinocytes[5]. Moorea *et.al.*(2004) analyzed a mathematical model for chronic myelogenous leukemia (CML), a cancer of the blood[6].

Some researchers have concentrated on cytokine-mediated inflammatory processes rather than the densities of immune cells. Seymour and Henderson(2001) described the behavior of IL-1 and IL-10, with TNF-α as an external stimulus for IL-1, using a six-variable ODE model([7],[8]). However there are not so much research papers about IBD dealing with mathematical models. In 2006, Wendelsdorf *et al.* found the positive inflammatory feedback loop by inflammatory M1 macrophage activation of T-cells under the immunopathology of IBD[9]. In Lo *et al.*[10], they extend the model to include Treg cells.

In this work, we focus on relation between T cells and cytokines in immune system that leads to IBD. In particular, we considered the interaction between Naive T cells, Helper T cells, and cytokines secreted by Helper T cells in the body because the three compartment are important role in immune system. Thus we first present a mathematical model describing IBD by using ordinary differential equations. We observe the existence of solutions of the model, stability of equilibria for the model and some numerical simulations. Conditions for local stability and global stability of the equilibrium are determined. The equilibrium demonstrates the case of how the T cells proferate and attain a particular equilibrium level in IBD patient.

The rest of this paper is organized as follows. In Section 2 we set up mathematical modeling for IBD in detail and the existence of solutions and a positive equilibrium of the IBD model are established. In Sections 3 and 4, some other the techniques and theories useful in the study of the model are introduced. Some numerical simulations are presented to verify the proposed results and by changing parameter values, we show how to change dynamics of the model. Finally, the conclusion is given in Section 5.

2. A Mathematical Model

Pathophysiology of IBD is related to the immune. Immunity is a process to protect body from non-self such as bacteria or virus[4]. Normally, if bacteria or virus intrude from outside, body is protected by immune response. In severe case, inflammatory reaction occurs. The inflammatory reaction disappears when the causes such as bacteria or virus are removed. However, the case of IBD is different. In this case, even though the causes which stimulate immune response are removed, it is unrestrained various substances that mediate inflammation such as Type 1 T-helper lymphocyte(Th1) activation, Type 2 T-helper lymphocyte(Th2) activation and cytokines release. Cytokines release are associated with the generation of activated matrix metalloproteinases(MMP), which

are essential mediators of tissue destruction. Additionally, cytokines act on neutrophils and phagocytes, which contribute to amplification of the inflammatory response and further tissue damage[11].

Th1 cells produce high levels of IFN-γ whereas Th2 cells secrete too much interleukin-4(IL-4) and other interleukins, including IL-10, IL-5 and IL-13. Th1 cells play important role in immune responses to intracellular pathogens, such as viruses and intracellular bacteria[12]. By contrast, Th2 responses are more appropriate for targeting parasites and worms, and for enabling antibody responses.

Specifically, overexpression of proinflammatory Th1 cytokines such as tumor necrosis factor(TNF), IL-6, IL-12 and IFN-γ is a main factor of Crohn's disease, and Th2 cytokines IL-4 and IL-13 cause ulcerative colitis. The Th1 cytokine profile, which includes IFN-γ and IL-12, is dominant in patients with Crohn's disease. IFN-γ production is stimulated by IL-12, which is produced by antigen-presenting cells(APCs). Most experimental colitis models also have a dominant TH1 response. However, in some models, Th1 responses can be changed into Th2 responses as the inflammatory process matures. In Th2 responses, IL-4 and IL-5 are normally elevated. Also, in ulcerative colitis tissues, the concentrations of IL-4 and IL-5 are variable[1].

Naive T cells are divided into subsets that are commonly defined by the cytokines that they secrete[13]. These cytokines are responsible for T-cell-effector function and allow for the development of other immune responses, or have direct effects on tissues. The long-standing paradigm for Th differentiation is the Th1 and Th2 model[14]. Th1 cells produce high levels of IFN-γ whereas Th2 cells express IL-4 and other interleukins, including IL-10, IL-5 and IL-13.

Our purpose is to use some of the best ideas in these model, but to keep the model as simple as possible while incorporation the most important concepts of IBD dynamics together with the feature of cytokines dynamics. Therefore, we define three population. The model comprises initially 3 variables, namely the concentration of Naive T cells $N(t)$, the concentration of Helper T cell $T(t)$ including Th1 and Th2, the cytokines secreted by Helper T cell denoted by $S(t)$ including many kinds of cytokines(see Figure 1).

The complete model is described by the following the system of differential equation:

$$\begin{cases} \dfrac{dN}{dt} &= bN\left(1-\dfrac{N}{K}\right)-(\gamma S+c)N-\mu_1 N \\ \dfrac{dT}{dt} &= \alpha_1\gamma SN+\alpha_2 cN-\mu_2 T \\ \dfrac{dS}{dt} &= \omega T-\beta NS-\mu_3 S. \end{cases} \tag{1}$$

All parameters are assumed to be strictly positive constant.

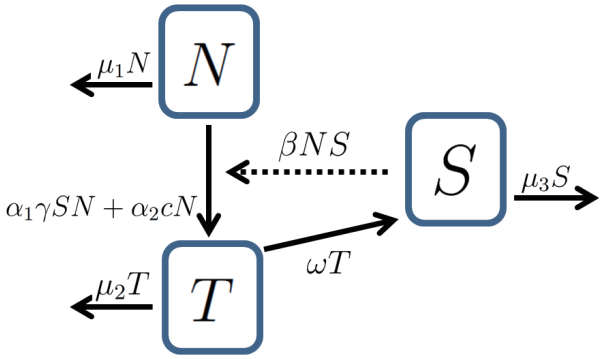

FIGURE 1. Schematic diagram of Inflammatory Bowel Disease

Notation	Description of parameter
b	The growth rate of Naive T cell.
K	Carrying capacity.
γ	Coefficient, represents the loss of N due to encounters S.
c	The rate of internal production for T differentiation.
α_1	The rate of proliferation and differentiation into N by S.
α_2	The rate of proliferation and differentiation into N by c.
ω	The rate of S production from T.
β	Coefficient, represents the loss of S due to encounters N.
μ_1	The rate of excretion and elimination of N.
μ_2	The death rate constant for T.
μ_3	The death rate constant for cytokines S.

TABLE 1. Description of parameters for the model (1).

2.1. Existence and Invariance

In this section, we show that the model (1) is positively invariant and has the solution.

Theorem 2.1. *Let* $(t_0, \Psi_0) \in \mathbb{R} \times \mathbb{R}^3$, *where* $\Psi_0 = (N(t_0), T(t_0), S(t_0))$ *be given. Then there exists a unique solution* $(N(t), T(t), S(t))$ *of the model (1).*

Proof. Put

$$\Psi := \begin{pmatrix} N \\ T \\ S \end{pmatrix}.$$

Then

$$\frac{d\Psi}{dt} = A\Psi + B(\Psi),$$

where $A = \begin{pmatrix} b-c-\mu_1 & 0 & 0 \\ \alpha_2 c & -\mu_2 & 0 \\ 0 & \omega & b-\mu_3 \end{pmatrix}$ and $B(\Psi) = \begin{pmatrix} \frac{b}{K}N^2 - \gamma SN \\ \alpha_1\gamma SN \\ -\beta NS \end{pmatrix}$.

For some given $a, b > 0$, we denote by $\Gamma = \{(t,\Psi) \in \mathbb{R}\times\mathbb{R}^3 \mid |t-t_0| \le a, \|\Psi-\Psi_0\| \le b\}$. Define $F : \Gamma \to \mathbb{R}^3$ by $F(t,\Psi) = A\Psi + B(\Psi)$ for all $(t,\Psi) \in \Gamma$. For any $\Psi_1 = (\bar{N},\bar{T},\bar{S})^T$ and $\Psi_2 = (\hat{N},\hat{T},\hat{S})^T$, we have

$$\begin{aligned}
&\|F(t,\Psi_1) - F(t,\Psi_2)\| \\
&= \|A(\Psi_1-\Psi_2) + (B(\Psi_1) - B(\Psi_2))\| \\
&\le \|A\|\|\Psi_1-\Psi_2\| + \|B(\Psi_1) - B(\Psi_2)\| \\
&\le (|b-c-\mu_1| + |\alpha_2 c| + |\mu_2| + |\mu_3|)(|\bar{N}-\hat{N}| + |\bar{T}-\hat{T}| + |\bar{S}-\hat{S}|) \\
&\quad + \left|\left(\frac{b}{K}\bar{N}^2 - \gamma\bar{S}\bar{N}\right) - \left(\frac{b}{K}\hat{N}^2 - \gamma\hat{S}\hat{N}\right)\right| + |\alpha_1\gamma\bar{S}\bar{N} - \alpha_1\gamma\hat{S}\hat{N}| \\
&\quad + |\beta\bar{N}\bar{S} - \beta\hat{N}\hat{S}| \\
&\le M(|\bar{N}-\hat{N}| + |\bar{T}-\hat{T}| + |\bar{S}-\hat{S}|) + \frac{b}{K}|\bar{N}+\hat{N}||\bar{N}-\hat{N}| \\
&\quad + (\gamma + \alpha_1\gamma + \beta)(|\bar{S}||\bar{N}-\hat{N}| + |\bar{N}||\bar{S}-\hat{S}|), \\
&\le L_1|\bar{N}-\hat{N}| + L_2|\bar{T}-\hat{T}| + L_3|\bar{S}-\hat{S}|, \\
&\le L[|\bar{N}-\hat{N}| + |\bar{T}-\hat{T}| + |\bar{S}-\hat{S}|], \\
&\le L\|\Psi_1-\Psi_2\|,
\end{aligned}$$

where $M = |b-c-\mu_1| + |\alpha_2 c| + |\mu_2| + |\mu_3|$, $L_1 = M + \frac{b}{K}|\bar{N}+\hat{N}| + (\gamma+\alpha_1\gamma+\beta)|\bar{S}|$, $L_2 = M$, $L_3 = M + (\gamma+\alpha_1\gamma+\beta)|\hat{N}|$, and $L = \max\{L_1, L_2, L_3\}$.
By the Picard-Lindelöf theorem, we are done. □

The feasible region $\mathbb{B} = \{(N,T,S) \in \mathbb{R}^3 \mid N,T,S \ge 0\}$ for the model (1) is the non-negative cone $\mathbb{R}^3$, which can be shown to be positively invariant with respect to the model (1). Given non-negative initial data, solutions exist and have non-negative components for all $t \ge 0$, and thus the model is well posed.

Theorem 2.2. *The model* (1) *is positively invariant. In other word, if the initial conditions lie in* $\mathbb{B}$*, the system of equation has a unique solution that remains in* $\mathbb{B}$ *for all time* $t \ge 0$*.*

Proof. By Theorem 2.1, the model (1) with initial value (t_0, Ψ_0) has a unique solution and the right hand side of the model (1) is continuous with continuous partial derivatives in $\mathbb{B}$. Moreover, if $N(t) = 0$ then $\frac{dN}{dt} = 0$; if $T(t) = 0$ then

$\frac{dT}{dt} = \alpha_1\gamma SN + \alpha_2 cN \geq 0$; if $S(t) = 0$ then $\frac{dS}{dt} = \omega T \geq 0$. Therefore, none of the orbits can leave $\mathbb{B}$ for all time. □

3. Stability of an Equilibrium

In this section, stability of the 3-dimensional equilibrium with respect to solutions initiating in *int* $\mathbb{B}$ will be established.

3.1. Equilibria of Model

The equilibria of the model (1) are obtained by solving the system of equations:

$$\begin{aligned} bN\left(1-\frac{N}{K}\right) - (\gamma S + c)N - \mu_1 N = 0,\\ \alpha_1\gamma SN + \alpha_2 cN - \mu_2 T = 0,\\ \omega T - \beta NS - \mu_3 S = 0, \end{aligned} \tag{2}$$

where we see that

$$-bAN^2 + (ABK - b\mu_2\mu_3 - K\gamma\alpha_2\omega c)N + \mu_2\mu_3 KB = 0,$$

with $A = \mu_2\beta - \omega\alpha_1\gamma$ and $B = b - c - \mu_1$.
The solutions of the above equation are

$$N = \frac{H \pm \sqrt{H^2 + 4bKAB\mu_2\mu_3}}{2bA},$$

where $H = ABK - b\mu_2\mu_3 - K\gamma\alpha_2\omega c$.

From the first equation of (2),

$$\begin{aligned} & bN\left(1-\frac{N}{K}\right) - (\gamma S + c)N - \mu_1 N = 0,\\ \iff & N(b - \frac{N}{K} - \gamma S - c - \mu_1) = 0,\\ \iff & N(B - \frac{N}{K} - \gamma S) = 0, \text{ where } B = b - c - \mu_1. \end{aligned}$$

Therefore $N = 0$ or $B = \frac{N}{K} + \gamma S$. By feasibility condition of the model (1), we shall assume $B > 0$.
We need to handle each sign of A case by case.

Case 1. Suppose $A = 0$.

Then the model (1) has one positive equilibrium $E_1 = (N_1^*, T_1^*, S_1^*)$
$= \left(\frac{\mu_2\mu_3 KB}{b\mu_2\mu_3 + K\gamma\alpha_2\omega c}, \frac{\beta\mu_2\mu_3 cK^2B^2}{(b\mu_2\mu_3 + K\gamma\alpha_2\omega c)^2} + \frac{\mu_3\alpha_2 cKB}{b\mu_2\mu_3 + K\gamma\alpha_2\omega c}, \frac{w\alpha_2 cKB}{b\mu_2\mu_3 + K\gamma\alpha_2\omega c}\right)$.

Case 2. Suppose $A \neq 0$.

There are two equilibria E_2 and E_3.

$$E_2 = (N_2^*, T_2^*, S_2^*) = \left(\frac{P}{2bA}, \frac{\beta P^2 \alpha_2 c}{2bA^2(P + 2b\mu_2\mu_3)} + \frac{\mu_3 \alpha_2 cP}{A(P + 2b\mu_2\mu_3)}, \frac{\omega \alpha_2 cP}{A(P + 2b\mu_2\mu_3)} \right),$$

$$E_3 = (N_3^*, T_3^*, S_3^*) = \left(\frac{F}{2bA}, \frac{\beta F^2 \alpha_2 c}{2bA^2(F + 2b\mu_2\mu_3)} + \frac{\mu_3 \alpha_2 cF}{A(F + 2b\mu_2\mu_3)}, \frac{\omega \alpha_2 cF}{A(F + 2b\mu_2\mu_3)} \right),$$

where $P = H + \sqrt{H^2 + 4bKAB\mu_2\mu_3}$, $F = H - \sqrt{H^2 + 4bKAB\mu_2\mu_3}$.
If $0 < F + 2b\mu_2\mu_3$ and $0 < P + 2b\mu_2\mu_3$, then the model (1) has two positive equilibria. Otherwise the model (1) has one positive equilibrium. But $F + 2b\mu_2\mu_3$ is always negative value. Suppose $0 < F + 2b\mu_2\mu_3$. Then,

$0 < F + 2b\mu_2\mu_3$,

$0 < H - \sqrt{H^2 + 4bKAB\mu_2\mu_3} + 2b\mu_2\mu_3$, where $F = H - \sqrt{H^2 + 4bKAB\mu_2\mu_3}$,

$\sqrt{H^2 + 4bKAB\mu_2\mu_3} < H + 2b\mu_2\mu_3$,

$H^2 + 4bKAB\mu_2\mu_3 < H^2 + 4Hb\mu_2\mu_3 + (2b\mu_2\mu_3)^2$,

$4bKAB\mu_2\mu_3 < 4Hb\mu_2\mu_3 + (2b\mu_2\mu_3)^2$,

$0 < 4b\mu_2\mu_3(H + b\mu_2\mu_3 - KAB)$,

$0 < 4b\mu_2\mu_3(ABK - b\mu_2\mu_3 - K\gamma\alpha_2\omega c + b\mu_2\mu_3 - KAB$,

where $H = ABK - b\mu_2\mu_3 - K\gamma\alpha_2\omega c$,

$0 < 4b\mu_2\mu_3(-K\gamma\alpha_2\omega c)$,

$0 < -4b\mu_2\mu_3 K\gamma\alpha_2\omega c$.

It's contradiction of the assumption. And it's similar to prove that $0 < P + 2b\mu_2\mu_3$ is always true.
Since $F + 2b\mu_2\mu_3 < 0$ and $0 < P + 2b\mu_2\mu_3$, E_3 is a negative equilibrium. And the model (1) has one positive equilibrium E_2.

In summary, we have two kinds of positive equilibria as follows.

Theorem 3.1. (i) *If $A = 0$, then the model* (1) *has one positive equilibrium $E_1 = (N_1^*, T_1^*, S_1^*)$.*
(ii) *If $A \neq 0$, then the model* (1) *has one positive equilibrium $E_2 = (N_2^*, T_2^*, S_2^*)$.*

3.2. Local Stability of Equilibria

Next, we analyze local stability of equilibria E_i, $i = 1, 2$.

Theorem 3.2. *The positive equilibrium $E_1 = (N_1^*, T_1^*, S_1^*)$ is locally asymptotically stable if $(\frac{b}{K}N_1^* + I)(\frac{b}{K}N_1^* I - \beta S_1^* \gamma N_1^*) + I\mu_2\mu_3 - \gamma N_1^* \omega \alpha_2 c > 0$, and otherwise unstable.*

Proof. To show the local stability of the equilibrium E_1, the Jacobian matrix at E_i, $i = 1, 2$ for the model (1) is given by

$$J(E_i) = \begin{pmatrix} b - \frac{2b}{K}N_i^* - \gamma S_i^* - c - \mu_1 & 0 & -\gamma N_i^* \\ \alpha_1\gamma S_i^* + \alpha_2 c & -\mu_2 & \alpha_1\gamma N_i^* \\ -\beta S_i^* & \omega & -\beta N_i^* - \mu_3 \end{pmatrix}.$$

The characteristic polynomial of the matrix $J(E_i)$ is

$$\det\left(J(E_i) - \lambda I\right) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3, \tag{3}$$

where

$$\begin{aligned} a_1 &= -(b - \frac{2b}{K}N_i^* - \gamma S_i^* - c - \mu_1 - \mu_2 - \beta N_i^* - \mu_3), \\ a_2 &= (b - \frac{2b}{K}N_i^* - \gamma S_i^* - c - \mu_1)(-\mu_2) + (b - \frac{2b}{K}N_i^* - \gamma S_i^* - c - \mu_1) \\ &\quad (-\beta N_i^* - \mu_3) - (-\gamma N_i^*)(-\beta S_i^*) + (-\mu_2)(-\beta N_i^* - \mu_3) - (\alpha_1\gamma N_i^*\omega), \\ a_3 &= -(b - \frac{2b}{K}N_i^* - \gamma S_i^* - c - \mu_1)\{(-\mu_2)(-\beta N_i^* - \mu_3) - (\alpha_1\gamma N_i^*\omega)\} \\ &\quad -(-\gamma N_i^*)\{\omega(\alpha_1\gamma S_i^* + \alpha_2 c) - (-\mu_2)(-\beta S_i^*)\}. \end{aligned}$$

Put $I = \mu_2 + \beta N_1^* + \mu_3$. Then we get that

$$\begin{aligned} a_1 &= \frac{b}{K}N_i^* + I, \\ a_2 &= \frac{b}{K}N_i^* I + N_i^* A - \beta S_i^*\gamma N_i^*, \\ a_3 &= \frac{b}{K}N_i^*(\mu_2\mu_3 + N_i^* A) + \gamma N_i^*(\omega\alpha_2 c - S_i^* A). \end{aligned}$$

Then

$$a_1 = \frac{b}{K}N_1^* + \mu_2 + \beta N_1^* + \mu_3 > 0,$$

and since $A = 0$, we obtain that

$$\begin{aligned} a_3 &= \frac{b}{K}N_1^*\mu_2\mu_3 + \gamma N_1^*\omega\alpha_2 c > 0, \\ a_1a_2 - a_3 &= (\frac{b}{K}N_1^* + I)(\frac{b}{K}N_1^* I + \mu_2\mu_3 - \beta S_1^*\gamma N_1^*) - (\frac{b}{K}N_1^*\mu_2\mu_3 + \gamma N_1^*\omega\alpha_2 c) \\ &= (\frac{b}{K}N_1^* + I)(\frac{b}{K}N_1^* I - \beta S_1^*\gamma N_1^*) + I\mu_2\mu_3 - \gamma N_1^*\omega\alpha_2 c. \end{aligned}$$

Thus $a_1 > 0$, $a_3 > 0$ and $a_1a_2 > a_3$. By the Routh-Hurwitz Criteria, the positive equilibrium E_1 is locally asymptotically stable. □

Example 1. *$b = 0.8$, $c = 0.3177$ $\mu_1 = 0.32$, $\mu_2 = 0.58$ $\beta = 0.02$, $\alpha_1 = 0.58$, $\omega = 0.1$, $\gamma = 0.2$, $\alpha_2 = 0.68$, $K = 3500$, $\mu_3 = 0.5$, then $a_1 = 1.2970 > 0$, $a_3 = 0.2261 > 0$ and $a_1a_2 - a_3 = 0.1097 > 0$. Hence, from Theorem*

3.2 the equilibrium $E_1 = (10.7287, 6.5182, 0.7992)$ *of the model* (1) *is locally asymptotically stable.*

Theorem 3.3. *The positive equilibrium* $E_2 = (N_2^*, T_2^*, S_2^*)$ *is locally asymptotically stable if*
(i)$\frac{b}{K}N_2^*(\mu_2\mu_3 + N_2^*A) + \gamma N_2^*(\omega\alpha_2 c - S_2^*A) > 0,$
(ii)$(\frac{b}{K}N_2^* + I)(\frac{b}{K}N_2^*I - \beta S_2^*\gamma N_2^*) + I(\mu_2\mu_3 + N_2^*A) - \gamma N_2^*(\omega\alpha_2 c - S_2^*A)\} > 0,$
and otherwise unstable.

Proof. Since $A \neq 0$, it follows from (3) that

$$a_3 = \frac{b}{K}N_2^*(\mu_2\mu_3 + N_2^*A) + \gamma N_2^*(\omega\alpha_2 c - S_2^*A).$$

And put $I = \mu_2 + \beta N_2^* + \mu_3$,

$$\begin{aligned} a_1a_2 - a_3 &= (\frac{b}{K}N_2^* + I)(\frac{b}{K}N_2^*I + N_2^*A + \mu_2\mu_3 - \beta S_2^*\gamma N_2^*) \\ &\quad - \{\frac{b}{K}N_2^*(\mu_2\mu_3 + N_2^*A) + \gamma N_2^*(\omega\alpha_2 c - S_2^*A)\} \\ &= (\frac{b}{K}N_2^* + I)(\frac{b}{K}N_2^*I - \beta S_2^*\gamma N_2^*) + I(\mu_2\mu_3 + N_2^*A) \\ &\quad - \gamma N_2^*(\omega\alpha_2 c - S_2^*A). \end{aligned}$$

Thus $a_1 > 0$, $a_3 > 0$ and $a_1a_2 > a_3$. By the Routh-Hurwitz Criteria, the positive equilibrium E_2 is locally asymptotically stable. □

3.3. Global Stability of Equilibria

Theorem 3.4. *If the equilibrium* $E_i(i = 1, 2)$ *exists, then it is globally asymptotically stable provided the following conditions are satisfied in* $\mathbb{B}$,
(i)$(\gamma + \beta S_i^*)^2 < \frac{b}{K}\mu_3,$
(ii)$(\alpha_2\gamma S_i^* + \alpha_2 c)^2 < \frac{b}{K}\mu_2,$
(iii)$(\alpha_1\gamma K + \omega)^2 < \mu_2\mu_3.$

Proof. Consider the positive definite function about E_i,

$$V = \left(N - N_i^* - N_i^* \ln\frac{N}{N_i^*}\right) + \frac{1}{2}(T - T_i^*) + \frac{1}{2}(S - S_i^*).$$

The derivative of V along the solution of the system (1) can be written as,

$$\frac{dV}{dt} = \frac{(N - N_i^*)}{N}\frac{dN}{dt} + (T - T_i^*)\frac{dT}{dt} + (S - S_i^*)\frac{dS}{dt}.$$

After some algebraic calculations we get,

$$\begin{aligned}\frac{dV}{dt} =& -\frac{b}{K}(N-N_i^*)^2 - \mu_2(T-T_i^*)^2 - (\beta N+\mu_3+\mu_3)(S-S_i^*)^2 \\ &+ (\alpha_1\gamma S_i^* + \alpha_2 c)(N-N_i^*)(T-T_i^*) + (\alpha_1\gamma N+\omega)(T-T_i^*)(S-S_i^*) \\ &- (\gamma+\beta S_i^*)(S-S_i^*)(N-N_i^*).\end{aligned}$$

Thus, for dV/dt to be negative definite the following sufficient conditions must be satisfied,

$$(\gamma+\beta S_i^*)^2 < \frac{b}{K}\mu_3, \tag{4}$$

$$(\alpha_2\gamma S_i^* + \alpha_2 c)^2 < \frac{b}{K}\mu_2, \tag{5}$$

$$(\alpha_1\gamma k+\omega)^2 < \mu_2\mu_3. \tag{6}$$

Under conditions (4),(5) and (6), dV/dt will be negative definite showing that V is a Lyapunov function with respect to E_i, whose domain contains $\mathbb{B}$. □

Example 2. *Let* $b = 0.8$, $c = 0.04$ $\mu_1 = 0.04$, $\mu_2 = 0.4$ $\beta = 0.01$, $\alpha_1 = 0.000174$, $\omega = 0.01$, $\gamma = 0.00174$, $\alpha_2 = 0.1$, $K = 14600$, $\mu_3 = 0.5$. *Hence, from Theorem 3.4 the equilibrium* $E_1 = (13140, 130.1376, 0.01)$ *of the model* (1) *is globally asymptotically stable.*

4. Numerical Simulations

In this section, we will verify the proposed by doing some simulations. We carried out simulations using MATLAB. In order to have an understanding of the detailed dynamics of the model comprising of three different compartments, we do numerical simulations of the model (1).

Parameter	Value	Parameter	Value
b	1	K	14600
γ	0.0174	c	0.04
α_1	0.0174	α_2	0.1
ω	0.5	β	0.015
μ_1	0.04	μ_2	0.04
μ_3	0.11		

TABLE 2. Values of parameters for the model (1).

For the purpose numerical values of the model parameters are standardized based on available clinical date, reflections from analytical solutions of the model. Another option is to use a logarithmic scale. The model parameters, as standardized are given in Table 2[15]. Initial values of the variables are chosen as $N(0) = 2790$, $T(0) = 1000$, $S(0) = 50$.

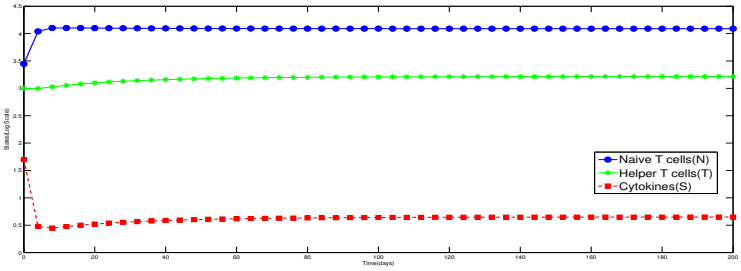

FIGURE 2. The dynamics of model (1). Parameters are as in Table 2.

A numerical simulation in Figure 3 illustrates the dynamics of model (1), when the conditions of locally asymptotically stable(Theorem 3.2) are satisfied. One thing noticeably in Figure 2 is the timing of extremum, that is, valleys at the beginning. That means that cytokines S help differentiation of T cell.

One clinical feature of IBD is that proinflammatory cytokines is upregulated, unlike normal person's cytokines level. The best way to treat IBD is to reduce the level of cytokines since the exact cause of IBD is unknown. If the factor which makes cytokines increase is figured out, we can suggest another way to treat IBD.

Numerical parameter sensitivity analysis show the greatest effect parameter on model result. The method is that changing each of the model parameter by $\pm 25\%$. And whenever we try simulation, all parameter fixed expect only one parameter. The parameters are satisfied condition of local stable. In Figure 3, we plot the percent change in concentration of cytokine. We can appreciate what parameter to be more sensitive than other parameters. The parameter ω, the rate of S production from T influence the level of cytokines S. We expect if the treatment can control the ω, the rate of S production from T, then that is the best way for helping to relieve IBD.

5. Conclusions

In the analytical study, we presented the model (1) by using an ordinary differential equation and we focus on the qualitative aspects within the model (1).

We observed that the solutions of the model (1) with the initial values $(N(t_0), T(t_0), S(t_0))$ exist and unique, and the solutions of the dynamical variables N(naive T cell), T(Helper T cell), S(Cytokines are secreted by T) holds in the positive where we assume all the model parameters are positive.

In this model (1), there were two equilibria E_1 and E_2 when the condition is satisfied each $A = 0$ and $A \neq 0$. We found the condition under which

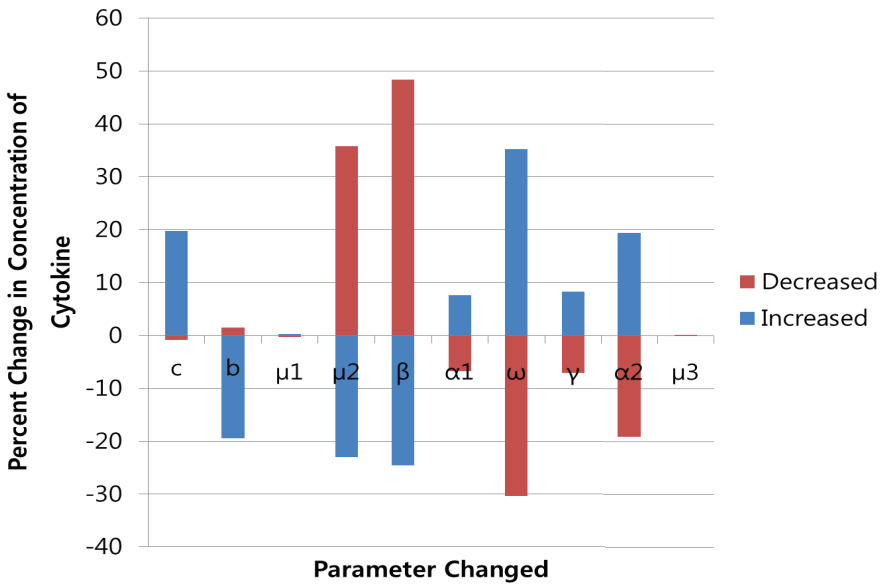

FIGURE 3. Numerical sensitivity analysis.

the solution of the model (1) becomes locally stable each equilibrium E_1 and E_2. In Section 4, to understand how different model parameters control the dynamical behavior of the model (1), we changed their parameters.In Figure 4, we saw that dynamics of S gets progressively upgraded with the increase the rate of S production from T, ω. So we expect that ω is an important factor in understanding pathogenesis of IBD. However, the change of b, the growth rate of Naive T cell or μ_3, the death rate of S do not influence.
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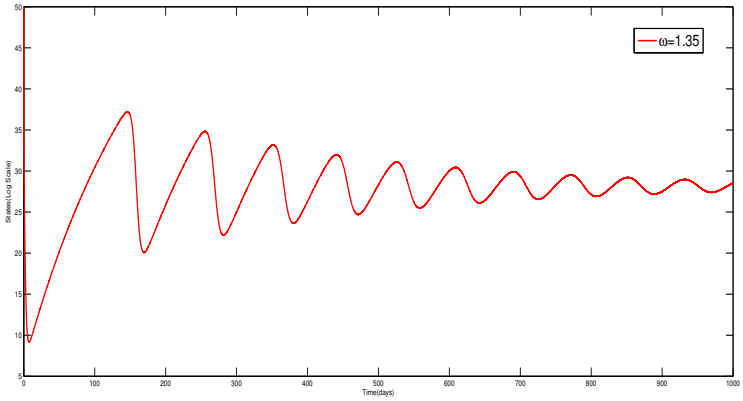
We present the following Figure 4 to support the future work. We provide the same stimulus to Naive T cells(see Figure 4). The times series of Figure 4(a) shows an oscillation of the concentration of cytokines S, which slows down and eventually stops. But the Figure 4(b) is not. This means that the values of ω is sensitive to stimulus. We'll be interesting to see how results correlate with IBD. In further work, we will find sensitive parameters to stimulus and present cause of IBD and another treatment strategy.

[Dynamics of S when $\omega = 1.35$]



[Dynamics of S when $\omega = 0.5$]

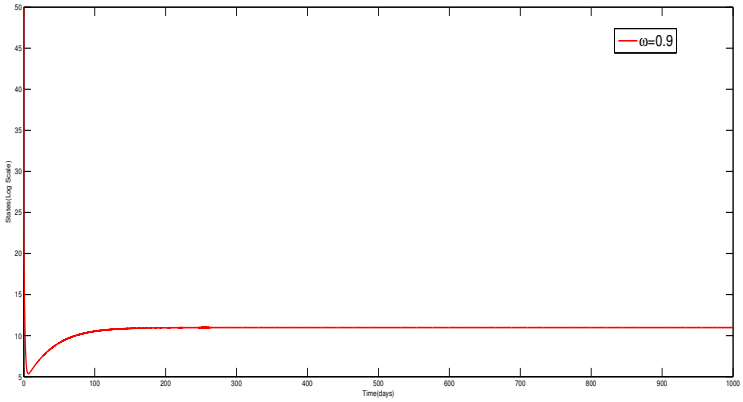


FIGURE 4. Dynamics of compartment S changing ω when Naive T cell(N) are stimulated. Other parameters are as in Table 2.

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