Available online at http://scik.org
Commun. Math. Biol. Neurosci. 2023, 2023:33
https://doi.org/10.28919/cmbn/7879
ISSN: 2052-2541

THE ROLE OF ANTIBIOTICS AND PROBIOTICS SUPPLEMENTS ON THE STABILITY OF GUT FLORA BACTERIA INTERACTIONS

MUSTAFA AHMED, SHIREEN JAWAD*

Department of Mathematics, College of Science, University of Baghdad, Iraq

Abstract: Dyspepsia is a significant public health issue that affects the entire world population. In this work, we formulate and analyze a deterministic model for the population dynamics of Gut bacteria in the presence of antibiotics and Probiotic supplements. All the possible equilibria and their local stability are obtained. The global stability around the positive equilibrium point is established. Numerical simulations back up our analytical findings and show the temporal dynamics of gut microorganisms.

Keywords: stability analysis; probiotic bacteria; the impact of antibiotic.

2020 AMS Subject Classification: 92C75.

1. INTRODUCTION

The human large intestine consists not just of cells but is also an ecosystem such as "gut flora," one of the trillion different types of bacteria. The majority of these microorganisms have advantages. A portion of the small and large intestines is home to friendly bacteria. Bacteria cannot develop in the stomach's acidic environment. The body's gut microorganisms play a variety of

*Corresponding author
E-mail address: shireen.jawad@sc.uobaghdad.edu.iq
Received January 07, 2023

functions. For instance, gastrointestinal bacteria create the vitamins K and B_{12}. Limit the spread of dangerous organisms. Toxins are broken down in the big intestine. Break down the fiber and some carbohydrates and sugars in meals that cannot be absorbed. Enzymes made by bacteria break down the carbohydrates in plant cell walls.

Without these bacteria, most of the nutritional content of plant matter would be lost. These facilitate the digestion of plant meals like spinach [1]. Some of the human gut's microorganisms are pathogens that can cause sickness. Other bacteria are beneficial and give a wide range of health advantages. Bacteria in the gut play a crucial part in digestion by assisting your body in breaking down food and absorbing nutrients [2]. It is an integral part of the human body. Gut bacteria are essential to human health by delivering crucial nutrients, generating vitamin K, aiding cellulose digestion, and stimulating angiogenesis and enteric nerve activity. Due to the alteration in their composition brought on by the gut ecosystem's aberrant alterations by disease, antibiotics, ageing, stress, lifestyle choices, and poor dietary practices can also be potentially dangerous. Numerous chronic disorders, such as cancer, inflammatory bowel disease, autism, and obesity, can be brought on by dysbiosis of the gut bacterial communities [3]-[4]. We are also nourishing the microorganisms in our guts when we eat. These bacteria like feasting on proteins, carbs and milk sugars just as we do. The human and the bacteria in our gut gain through this symbiotic eating connection [5].

Recent research has illuminated the collateral damage that antibiotics due to the bacteria in the human gut. These medications have been proven to have immediate and occasionally long-lasting impacts that affect the human gut bacteria's taxonomic, genomic, and functional capabilities. While increasing and decreasing the membership of particular native taxa, broad-spectrum antibiotics reduce bacterial diversity [6].

Probiotics are living bacteria that exist naturally in the human body. Our body is continually infected with both healthy and dangerous microorganisms. When you acquire an illness, more nasty bacteria enter your system, throwing your system off balance. Good bacteria aid in the elimination of excess harmful bacteria, restoring equilibrium. Probiotic supplements are a way to supply your body with beneficial microorganisms which help the human body digest food [7]. Mathematical modelling is a procedure that involves translating issues from the actual world into mathematical terms, solving them in a symbolic system, and then testing the results in the original system. Mathematical models such as biology, ecosystem, and physics are utilized in the natural sciences. Extensive studies have used mathematical modelling to solve problems describing a system, investigate the consequences of various elements, and forecast behavior [1], [8]–[14][4]. In this paper, the mathematical model describes the interplay of bacteria in the human gut in the presence of antibiotic and Probiotic supplements is offered. The rest of the article is set as follows. The structure of the proposed model is described in Sect. 2. The existence of the possible equilibria is shown in Sects. 3. The stability property of the equilibria is investigated in Sects. 4. Some examples and their numeric simulations are presented in Sect. 5 to show the feasibility of the main results. We end this paper with a brief discussion.

2. MATHEMATICAL MODELLING

Suppose an ecosystem in the large intestine contains two symbiotic bacteria. Let $b_1(t)$ and $b_2(t)$ are the population sizes of probiotic and pathogenic at time t. $c(t)$ is the non-decomposing toxins in the large intestine at time t. $a(t)$ is the concentration of dissolved antibiotics at time t. Under the above assumptions, the following set of ordinary differential equations is obtained:

$$\begin{aligned}
\frac{db_1}{dt} &= r_1 b_1\left[1-\frac{(b_1+\alpha_1 b_2)}{k}\right]+\beta_0 b_1-(\beta_1+\gamma_1)ab_1-\mu_1 b_1 = f_1(b_1,b_2,c,a),\\
\frac{db_2}{dt} &= r_2 b_2\left[1-\frac{(b_2+\alpha_2 b_1)}{k}\right]+\beta_1\, ab_1-\gamma_2\, ab_2-\gamma_0 b_2-\mu_2 b_2 = f_2(b_1,b_2,c,a),\\
\frac{dc}{dt} &= (c_0-c)d+q_1 b_2 c-q_2 b_1 c = f_3(b_1,b_2,c,a),\\
\frac{da}{dt} &= \omega-\mu_0 a = f_4(b_1,b_2,c,a),
\end{aligned} \tag{1}$$

with the initial conditions $b_1(0)\geq 0, b_2(0)\geq 0, c(0)\geq 0$ and $a(0)\geq 0$. All parameters for model (1) are assumed to be positive and are clearly described in table 1.

Table 1 Explanation of system's (1) parameters.

PARAMETER	EXPLANATION
$\boldsymbol{r_1}$	Growth rate of b_1.
$\boldsymbol{r_2}$	Growth rate of b_2.
$\boldsymbol{k}$	Carrying capacity of b_1 and b_2.
$\boldsymbol{\beta_0}$	The rate of effectiveness of Probiotic supplements.
$\boldsymbol{\beta_1}$	The transfer rate of good bacteria to harmful bacteria is due to mutations of good bacteria exposed to antibiotics.
$\boldsymbol{\gamma_1}$	The rate of eliminating good bacteria by an antibiotic.
$\boldsymbol{\gamma_2}$	The rate of eliminating harmful bacteria by antibiotics.
$\boldsymbol{\mu_1}$	The natural death rate of b_1.
$\boldsymbol{\mu_2}$	The natural death rate of b_2.
$\boldsymbol{\gamma_0}$	The elimination rate of harmful bacteria by the immune system.
$\boldsymbol{c_0}$	The constant intake of non-decomposing toxins in the large intestine.
$\boldsymbol{d}$	The natural degradation of non-decomposing toxins in the large intestine.
$\boldsymbol{q_1}$	The increased rate of non-decomposing toxins due to a large amount or quantity of harmful bacteria.
$\boldsymbol{q_2}$	The decreased rate of non-decomposing toxins due to a large amount or quantity of good bacteria.
$\boldsymbol{\omega}$	The concentration rate of antibiotics.
$\boldsymbol{\mu_0}$	The degradation rate of antibiotics.

Further, Fig.1 illustrates the schematic sketch of the system (1) under examination.

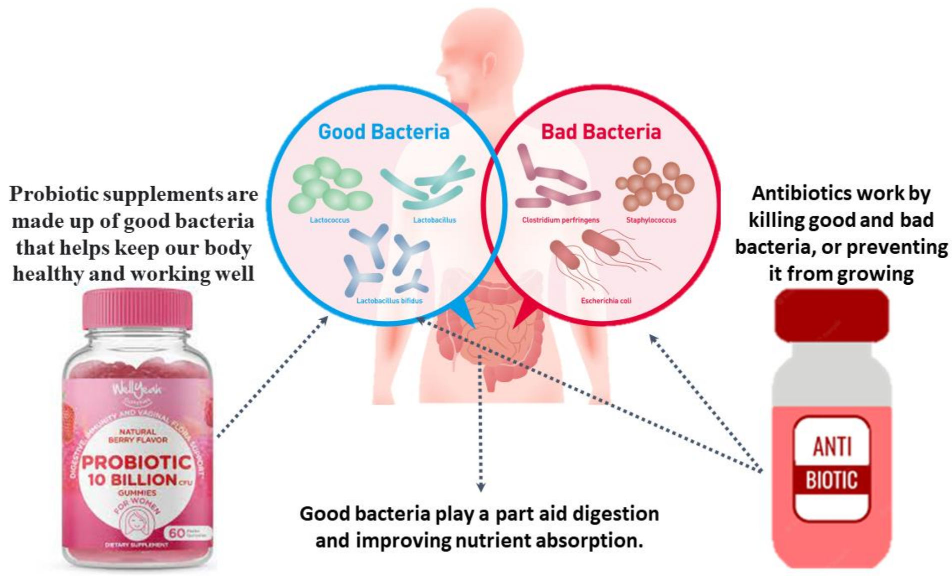

Figure 1 the schematic sketch of the system (1)

Theorem 1. All system's (1) solutions $b_1(t), b_2(t), c(t)$ and $a(t)$ that start with positive initial conditions $(b_1(0), b_2(0), c(0), a(0))$ are also positive.

Proof. By integrating the right-hand functions of the model (1) for $b_1(t), b_2(t), c(t)$ and $a(t)$, we get

$$b_1(t)=b_1(0)\, exp\left\{\int_0^t \left[r_1\left[1-\frac{(b_1(s)+\alpha_1 b_2(s))}{k}\right]+\beta_0-(\beta_1+\gamma_1)a(s)-\mu_1\right]ds\right\},$$

$$b_2(t)=b_2(0)\, exp\left\{\int_0^t \left[r_2\left[1-\frac{(b_2(s)+\alpha_2 b_1(s))}{k}\right]+\frac{\beta_1\, a(s) b_1(s)}{b_2(s)}-\gamma_2\, a(s)-\gamma_0-\mu_2\right]ds\right\},$$

$$c(t)=c(0)\, exp\left\{\int_0^t \left[\frac{dc_0}{c(s)}-d+q_1 b_2(s)-q_2 b_1(s)\right]ds\right\},$$

$$a(t)=a(0)\, exp\left\{\int_0^t \left[\frac{\omega}{a(s)}-\mu_0\right]ds\right\}.$$

Then $b_1(t) \geq 0, b_2(t) \geq 0, c(t) \geq 0$ and $a(t) \geq 0$ for all $t > 0$. Therefore, the interior of R_+^4 is an invariant set.

Theorem 2. All solutions $b_1(t), b_2(t), c(t)$ and $a(t)$ with the initial values $(b_1(0), b_2(0), c(0), a(0))$ which start in $\zeta \subset \mathrm{R}_+^4$ and satisfy $q_2 > q_1$ are uniformly bounded.

Proof: Let $b_1(t), b_2(t), c(t)$ and $a(t)$ be an arbitrary system (1) solution with a non-negative initial condition. Then, for $B(t) = b_1(t) + b_2(t) + c(t) + a(t)$, we have:

$$\frac{dB}{dt} = \frac{db_1}{dt} + \frac{db_2}{dt} + \frac{dc}{dt} + \frac{da}{dt}$$

$$\frac{dB}{dt} = r_1 b_1\left[1-\frac{(b_1+\alpha_1 b_2)}{k}\right]+\beta_0 b_1-(\beta_1+\gamma_1)ab_1 - \mu_1 b_1 + r_2 b_2\left[1-\frac{(b_2+\alpha_2 b_1)}{k}\right] + \beta_1\, ab_1 - \gamma_2\, ab_2 - \gamma_0 b_2$$
$$- \mu_2 b_2 + (c_0 - c)d + q_1 b_2 c - q_2 b_1 c + \omega - \mu_0 a$$

Hence, $\frac{dB}{dt} + \delta B \leq r_1 b_1 + \beta_0 b_1 r_2 b_2 + c_0 d + \omega = \varphi$, where $\delta = min.\{\mu_1 b_1 + (\gamma_0 + \mu_2), d, \mu_0\}$.

Then, by applying Gronwall's Inequality, the following is obtained:

$$0 \leq B\big(b_1(t), b_2(t), c(t), a(t)\big) \leq \frac{\varphi}{\delta}\left(1 - e^{-\delta t}\right) + B(0)e^{-\delta t}$$

Hence, $0 \leq \limsup_{t\to\infty} B(t) \leq \frac{\varphi}{\delta}$

Thus, all system (1) solutions that are initiated in R_+^4 are attracted to the region $\zeta = \left\{(b_1, b_2, c, a) \in R_+^4 : B = b_1 + b_2 + c + a \leq \frac{\varphi}{\delta}\right\}$.

3. EXISTENCE OF EQUILIBRIA

System (1) has twelve non-negative equilibrium points, namely:

1. $s_1 = (\tilde{b}_1, 0,0,0)$, where $\tilde{b}_1 = \frac{k(r_1+\beta_0-\mu_1)}{r_1}$ exists when

$$r_1 + \beta_0 > \mu_1. \tag{2}$$

2. $s_2 = (0, b_2^{;}, 0,0)$, where $b_2^{;} = \frac{k(r_2-\gamma_0-\mu_2)}{r_2}$ exists when

$$r_2 > \gamma_0 + \mu_2\,. \tag{3}$$

3. $s_3 = \left(\ddot{b}_1, 0,0, a^*\right)$, where, $\ddot{b}_1 = \frac{k\left[r_1+\beta_0-(\beta_1-\gamma_1)\frac{\omega}{\mu_0}-\mu_1\right]}{r_1}$ and, $a^* = \frac{\omega}{\mu_0}$ exists when

$$r_1 + \beta_0 > (\beta_1 + \gamma_1)\frac{\omega}{\mu_0} + \mu_1 \tag{4}$$

4. $s_4 = \left(0, b_2^{\dagger}, c^{\dagger}, 0\right)$, where, $b_2^{\dagger} = \frac{k(r_2-\gamma_0-\mu_2)}{r_2}$ and $c^{\dagger} = \frac{c_0 d}{d-q_1 b_2^{\dagger}}$. For $b_2^{\dagger}$ and $c^{\dagger}$ to be positive, the following would be the case:

$$r_2 > \gamma_0 + \mu_1,$$
$$d > q_1 b_2^{\dagger}. \tag{5}$$

5. $s_5 = \left(\dddot{b}_1, 0, \ddot{c}, 0\right)$, where $\dddot{b}_1 = \frac{k(r_1+\beta_0-\mu_1)}{r_1} > 0$ if condition (2) is satisfied, and $\ddot{c} = \frac{c_0 d}{c(d-q_1\dddot{b}_1)} > 0$ if

$$d > q_1 b_2^{\dagger} \tag{6}$$

6. $s_6 = \left(0, b_2'', 0, a^*\right)$, where $b_2'' = \frac{k(r_2 - \gamma_2 a^* - \gamma_0 - \mu_2)}{r_2}$ and $a^* = \frac{\omega}{\mu_0}$. For b_2'' to be positive, the following should be the case

$$r_2 > \gamma_2 a^* + \gamma_0 + \mu_2 \tag{7}$$

7. $s_7 = \left(\hat{b}_1, \hat{b}_2, 0, 0\right)$, where $\hat{b}_2 = \frac{r_2\alpha_2 k\mu_1 + kr_1(r_2+\mu_2) - kr_1\gamma_0 - r_2\alpha_2 k(r_1+\beta_0)}{r_1 r_2(1-\alpha_1\alpha_2)}$, and $\hat{b}_1 = \frac{-r_1\gamma_1\hat{b}_2 + k(r_1+\beta_0-\mu_1)}{r_1}$. Clearly, $\hat{b}_1 > 0$ if the following condition holds:

$$k(r_1 + \beta_0) > r_1\gamma_1\hat{b}_2 + k\mu_1 \tag{8}$$

It should also be noted that for $\hat{b}_2 > 0$ to be positive, one of the following conditions must be the case:

$$\left.\begin{matrix} r_2\alpha_2\mu_1 + r_1(r_2+\mu_2) > r_1\gamma_0 + r_2\alpha_2(r_1+\beta_0) \\ 1 > \alpha_1\alpha_2 \end{matrix}\right\} \tag{9}$$

$$\left.\begin{matrix} r_2\alpha_2\mu_1 + r_1(r_2+\mu_2) < r_1\gamma_0 + r_2\alpha_2(r_1+\beta_0) \\ 1 < \alpha_1\alpha_2 \end{matrix}\right\} \tag{10}$$

8. $s_8 = \left(\breve{b}_1, 0, \check{c}, a^*\right)$, where $\breve{b}_1 = \frac{k[r_1+\beta_0-(\beta_1+\gamma_1)a^*-\mu_1]}{r_1} > 0$ if condition (4) is satisfied, $\check{c} = \frac{c_0 d}{d + q_2\breve{b}_1}$ and $a^* = \frac{\omega}{\mu_0}$.

9. $s_9 = (0, b_2', c', a^*)$, where $b_2' = \frac{k(r_2\mu_0 - \gamma_2\omega - \gamma_0\mu_0 - \mu_2)}{r_2}$, $c' = \frac{c_0 d}{d - q_1 b_2'}$ and $a^* = \frac{\omega}{\mu_0}$. For b_2' and c' to be positive, the following must be validated:

$$r_2\mu_0 > \gamma_2\omega + \gamma_0\mu_0 + \mu_2 \tag{11}$$
$$d > q_1 b_2'$$

10. $s_{10} = (b_1^-, b_2^-, c^-, 0)$, where $b_2^- = \frac{-r_2\alpha_2 k(r_1+\beta_0-\mu_1) - r_2\alpha_2 kr_1^2(r_2-\gamma_0-\mu_2)}{(\alpha_2\alpha_1+1)r_2 r_1}$, $b_1^- = \frac{-r_1\gamma_1 b_2^- + k(r_1+\beta_0-\mu_1)}{r_1}$ and $c^- = \frac{c_0 d}{d - q_1 b_2^- + q_2 b_1^-}$. Clearly, for b_2^-, b_1^- and c^- to be positive, the following conditions must be satisfied:

$$r_2\alpha_2 k\mu_1 + r_2\alpha_2 kr_1^2(\gamma_0 + \mu_2) > r_2\alpha_2 k(r_1 + \beta_0) + r_2^2\alpha_2 kr_1^2, \tag{12}$$

11. $s_{11} = (b_1', b_2', 0, a^*)$ where $b_1' = \frac{-r_1\gamma_1 b_2' + k\left[r_1+\beta_0-(\beta_1+\gamma_1)\frac{\omega}{\mu_0}\right]}{r_1}$, $a^* = \frac{\omega}{\mu_0}$ and b_2' is the root of

the following equation

$$A\,b_2^2 + Bb_2 + c = 0, \quad (14)$$

here

$A = r_2(\alpha_1\alpha_2 - r_1)$

$B = r_2\left[r_1 k - \frac{\alpha_2 k\omega\ (\beta_1+\gamma_1)}{\mu_0} + \alpha_2\mu_1\right] - k\left[r_2\alpha_2(r_1+\beta_0) + 2\gamma_2\frac{\omega}{\mu_0} + \mu_2 + \alpha_1\beta_1\frac{\omega}{\mu_0}\right]$

$C = \frac{\beta_1\omega k}{\mu_0}\left[k(k+\beta_0) - \left[\frac{\omega k}{\mu_0}(\beta_1+\gamma_1) + \mu_1\right]\right]$

Using Descartes's rule of sign [15], Eq. (14) has a unique positive root b_2' if one of the following conditions is satisfied:

1. $A > 0$ and $C < 0$,
2. $A < 0$ and $C > 0$.

Further, for b_1' to be positive, the following must be the case

$$r_1\gamma_1 b_2' < k\left[r_1 + \beta_0 - (\beta_1+\gamma_1)\frac{\omega}{\mu_0}\right] \quad (15)$$

12. $s_{12} = (b_1^*, b_2^*, c^*, a^*)$, where b_1^*, b_2^*, a^*have the same formula as in number 11, and $c^* = \frac{c_0 d}{d - q_1 b_2^* + q_2 b_1^*}$. For c^* to be positive, the following must be the case:

$$d + q_2 b_1^* > q_1 b_2^* \quad (16)$$

3. STABILITY ANALYSIS

This section explores the local stability behavior of the system (1) 's equilibrium points.

The Jacobin matrix of system (1) at any point, say (b_1, b_2, c, a), can be written as:

$$J = \begin{bmatrix} \frac{\partial b_1}{\partial f_1} & \frac{\partial b_2}{\partial f_1} & \frac{\partial c}{\partial f_1} & \frac{\partial a}{\partial f_1} \\ \frac{\partial b_1}{\partial f_2} & \frac{\partial b_2}{\partial f_2} & \frac{\partial c}{\partial f_2} & \frac{\partial a}{\partial f_2} \\ \frac{\partial b_1}{\partial f_3} & \frac{\partial b_2}{\partial f_3} & \frac{\partial c}{\partial f_3} & \frac{\partial a}{\partial f_3} \\ \frac{\partial b_1}{\partial f_4} & \frac{\partial b_2}{\partial f_4} & \frac{\partial c}{\partial f_4} & \frac{\partial a}{\partial f_4} \end{bmatrix} = (a_{ij})_{4\times4},$$

where, $a_{11} = r_1 + \frac{2r_1 b_1 - r_1\alpha_1 b_2}{k} + \beta_0 - (\beta_1+\gamma_1)a - \mu_1$, $a_{12} = \frac{-r_1\alpha_1 b_1}{k}$, $a_{13} = 0$, $a_{14} =$

$-(\beta_1+\gamma_1)b_1$, $a_{21} = \frac{-r_1\alpha_2 b_2}{k} + \beta_1 a$, $a_{22} = r_2 - \frac{2r_2 b_2 - r_2\alpha_2 b_1}{k} - \gamma_2 a - \gamma_0 - \mu_2$, $a_{23} = 0$, $a_{24} = \beta_1 b_1 - \gamma_2 b_2$, $a_{31} = -q_2 c$, $a_{32} = q_1 c$, $a_{33} = -d + q_1 b_2 - q_2 b_1$, $a_{34} = 0$, $a_{41} = a_{42} = a_{43} = 0$, $a_{44} = -\mu_0$.

Consequently, the following is obtained.

1. The Jacobian matrix at $s_1 = (\tilde{b}_1, 0,0,0)$ is given as:

$$J(s_1) = \begin{bmatrix} \frac{-r_1\tilde{b}_1}{k} & \frac{-r_1\alpha_1\tilde{b}_1}{k} & 0 & -(\beta_1+\gamma_1)\tilde{b}_1 \\ 0 & r_2 - \frac{r_2\alpha_2\tilde{b}_1}{k} - \mu_2 & 0 & \beta_1\tilde{b}_1 \\ 0 & 0 & -d - q_2\tilde{b}_1 & 0 \\ 0 & 0 & 0 & -\mu_0 \end{bmatrix}.$$

Then, $J(s_1)$ has the eigenvalues

$\lambda_{11} = \frac{-r_1\tilde{b}_1}{k} < 0,$

$\lambda_{12} = r_2 - \frac{r_2\alpha_2\tilde{b}_1}{k} - \mu_2,$

$\lambda_{13} = -d - q_2\tilde{b}_1 < 0,$

$\lambda_{14} = -\mu_0 < 0.$

Then s_1 is a locally asymptotic stable if

$$r_2 < \frac{r_2\alpha_2\tilde{b}_1}{k} + \mu_2 \tag{17}$$

otherwise, s_1 is a saddle point.

2. The Jacobian matrix at $s_2 = (0, b_2^{;}, 0,0)$can be written as:

$$J(s_2) = \begin{bmatrix} r_1 - \frac{\alpha_1 r_1 b_2^{;}}{k} + \beta_0 - \mu_1 & 0 & 0 & 0 \\ \frac{-r_2\alpha_2 b_2^{;}}{k} & \frac{-r_2 b_2^{;}}{k} & 0 & -\gamma_2 b_2^{;} \\ 0 & 0 & -d + q_1 b_2^{;} & 0 \\ 0 & 0 & 0 & -\mu_0 \end{bmatrix}$$

Then, $J(s_2)$ has the following eigenvalues

$\lambda_{21} = r_1 - \frac{\alpha_1 r_1 b_2^{;}}{k} + \beta_0 - \mu_1,$

$\lambda_{22} = \frac{-r_2 b_2^{;}}{k} < 0,$

$\lambda_{23} = -d + q_1 b_2^{;},$

$\lambda_{24} = -\mu_0 < 0.$

That means s_2 is a locally asymptotical stable point if, and only if, the following conditions are satisfied:

$$r_1 < \frac{\alpha_1 r_1 b_2^{;}}{k} + \beta_0 + \mu_1, \qquad (18)$$

$$q_1 b_2^{;} < \text{d}.$$

3. The Jacobian matrix at $s_3 = (\ddot{b}_1, 0,0, a^*)$ can be written as:

$$J(s_3) = \begin{bmatrix} -\frac{r_1\ddot{b}_1}{k} & \frac{-r_1\alpha_1\ddot{b}_1}{k} & 0 & -(\beta_1+\gamma_1)\ddot{b}_1 \\ \beta_1 a^* & r_2 - \frac{r_2\alpha_2\ddot{b}_1}{k} - \gamma_2 a^* - \gamma_0 - \mu_2 & 0 & \beta_1\ddot{b}_1 \\ 0 & 0 & -d - q_2\ddot{b}_1 & 0 \\ 0 & 0 & 0 & -\mu_0 \end{bmatrix}.$$

Then, $J(s_3)$ has the eigenvalues

$\lambda_{31} + \lambda_{32} = -\frac{r_1\ddot{b}_1}{k} + r_2 - \frac{r_2\alpha_2\ddot{b}_1}{k} - \gamma_2 a^* - \gamma_0 - \mu_2,$

$\lambda_{31}.\lambda_{32} = \frac{r_1\ddot{b}_1}{k}\left(-r_2 + \frac{r_2\alpha_2\ddot{b}_1}{k} + \gamma_2 a^* + \gamma_0 + \mu_2 + \beta_1\alpha_1 a^*\right),$

$\lambda_{33} = -\text{d} - q_2\ddot{b}_1 < 0$

$\lambda_{43} = -\mu_0 < 0.$

That means s_3 is a locally asymptotical stable point if, and only if, the following conditions hold:

$$r_2 < min.\left\{\frac{r_2\alpha_2\ddot{b}_1}{k} + \gamma_2 a^* + \gamma_0 + \mu_2 + \beta_1\alpha_1 a^*, \frac{r_1\ddot{b}_1}{k} + \frac{r_2\alpha_2\ddot{b}_1}{k} + \gamma_2 a^* + \gamma_0 + \mu_2\right\}. \qquad (19)$$

4. The Jacobian matrix at $s_4 = (0, b_2^{\dagger}, c^{\dagger}, 0)$ can be written as:

$$J(s_4) = \begin{bmatrix} r_1 - \frac{r_1\alpha_1 b_2^{\dagger}}{k} + \beta_0 - \mu_1 & 0 & 0 & 0 \\ \frac{-r_1\alpha_2 b_2^{\dagger}}{k} & -\frac{r_2 b_2^{\dagger}}{k} & 0 & -\gamma_2 b_2^{\dagger} \\ -q_2 c & q_1 c & -d + q_1\ddot{b}_2 & 0 \\ 0 & 0 & 0 & -\mu_0 \end{bmatrix}.$$

Then, $J(s_4)$ has the following eigenvalues

$\lambda_{41} = r_1 - \frac{r_1\alpha_1 b_2^{\dagger}}{k} + \beta_0 - \mu_1,$

$\lambda_{42} = -\frac{r_2 b_2^{\dagger}}{k} < 0,$

$\lambda_{43} = -d + q_1 b_2^{\dagger},$

$\lambda_{44} = -\mu_0 < 0.$

That means s_4 is a locally asymptotical stable point provided that:

$$r_1 + \beta_0 < \frac{r_1 b_2^{\dagger}}{k} + \mu_1, \qquad q_1 b_2^{\dagger} < \text{d}. \tag{20}$$

5. The Jacobian matrix at $s_5 = (\dddot{b}_1, 0, \ddot{c}, 0)$ can be written as:

$$J(s_5) = \begin{bmatrix} \frac{-r_1 \ddot{b}_1}{k} & 0 & 0 & -(\beta_1 + \gamma_1)\dddot{b}_1 \\ 0 & r_2 - \frac{r_2 \alpha_2 \ddot{b}_1}{k} - \gamma_0 - \mu_2 & 0 & \beta_1 \ddot{b}_1 \\ -q_2 \ddot{c} & q_1 \ddot{c} & -d - q_2 \dddot{b}_1 & 0 \\ 0 & 0 & 0 & -\mu_0 \end{bmatrix}.$$

The eigenvalues of $J(s_5)$ can be written as follows:

$\lambda_{51} = \frac{-r_1 \ddot{b}_1}{k} < 0,$

$\lambda_{52} = r_2 - \frac{r_2 \alpha_2 \ddot{b}_1}{k} - \gamma_0 - \mu_2,$

$\lambda_{53} = -\text{d} - q_2 \dddot{b}_1 < 0,$

$\lambda_{54} = -\mu_0 < 0.$

That means s_5 is a locally asymptotical stable point if

$$r_2 < \frac{r_2 \alpha_2 \ddot{b}_1}{k} + \gamma_0 + \mu_2. \tag{11}$$

6. The Jacobian matrix at $s_6 = (0, b_2'', 0, a^*)$ can be written as:

$$J(s_6) = \begin{bmatrix} r_1 - \frac{r_1 \alpha_1 b_2''}{k} + \beta_0 - (\beta_1 + \gamma_1)a^* - \mu_1 & 0 & 0 & 0 \\ \frac{-r_2 \alpha_2 b_2''}{k} + \beta_1 a^* & -\frac{r_2 b_2''}{k} & 0 & -\gamma_2 b_2'' \\ 0 & 0 & -d + q_1 b_2'' & 0 \\ 0 & 0 & 0 & -\mu_0 \end{bmatrix}$$

Then the eigenvalues of $J(s_6)$ are given by

$\lambda_{61} = r_1 - \frac{r_1\alpha_1 b_2^{''}}{k} + \beta_0 - (\beta_1 + \gamma_1)a^* - \mu_1,$

$\lambda_{62} = -\frac{r_2 b_2^{''}}{k} < 0\,,$

$\lambda_{63} = -d + q_1 b_2^{''},$

$\lambda_{64} = -\mu_0 < 0.$

That means s_6 is a locally asymptotical stable point provided that the following conditions are satisfied

$$q_1 b_2^{''} < d,$$
$$\frac{r_1\alpha_1 b_2^{''}}{k} + (\beta_1 + \gamma_1)a^* + \mu_1 > r_1 + \beta_0. \quad (22)$$

7. The Jacobian matrix at $s_7 = \left(\hat{b}_1, \hat{b}_2, 0,0\right)$ can be written as:

$$J(s_7) = \begin{bmatrix} -\frac{r_1\hat{b}_1}{k} & \frac{-r_1\gamma_1\hat{b}_1}{k} & 0 & -(\beta_1+\gamma_1)\hat{b}_1 \\ \frac{-r_2\alpha_2\hat{b}_2}{k} & -\frac{r_2\hat{b}_2}{k} & 0 & \beta_1\hat{b}_1 - \gamma_2\hat{b}_2 \\ 0 & 0 & -d + q_1\hat{b}_2 - q_2\hat{b}_1 & 0 \\ 0 & 0 & 0 & -\mu_0 \end{bmatrix}.$$

Then, the eigenvalues of $J(F_7)$ are given by

$\lambda_{71} + \lambda_{72} = -\frac{r_1\hat{b}_1}{k} - \frac{r_2\hat{b}_2}{k} < 0,$

$\lambda_{71}.\lambda_{72} = \frac{r_1 r_2\hat{b}_1\hat{b}_2}{k^2}[1 - \alpha_1\alpha_2],$

$\lambda_{73} = -d + q_1\hat{b}_2 - q_2\hat{b}_1,$

$\lambda_{74} = -\mu_0 < 0.$

That means s_7 is a locally asymptotical stable point provided that:

$$1 > \alpha_1\alpha_2$$
$$q_1\hat{b}_2 < d + q_2\hat{b}_1 \quad (22)$$

8. The Jacobian matrix at $S_8 = \left(\check{b}_1, 0, \check{c}, a^*\right)$ can be written as:

$$J(s_8) = \begin{bmatrix} -\frac{r_1\check{b}_1}{k} & \frac{-r_1\alpha_1\check{b}_1}{k} & 0 & -(\beta_1+\gamma_1)\check{b}_1 \\ \beta_1 a^* & r_2 - \frac{r_2\alpha_2\check{b}_1}{k} - \gamma_2 a^* - \gamma_0 - \mu_2 & 0 & \beta_1\check{b}_1 \\ -q_2\check{c} & q_1\check{c} & -d - q_2\check{b}_1 & 0 \\ 0 & 0 & 0 & -\mu_0 \end{bmatrix}$$

Then, the eigenvalues of $J(s_8)$ are given by

$$\lambda_{81}+\lambda_{82}= r_2-\frac{r_1\breve{b}_1}{k}-\frac{r_2\alpha_2\breve{b}_1}{k}-\gamma_2 a^*-\gamma_0-\mu_2,$$

$$\lambda_{81}.\lambda_{82}=\frac{r_1\breve{b}_1}{k}\left(-r_2+\frac{r_2\alpha_2\breve{b}_1}{k}+\gamma_2 a^*+\gamma_0+\mu_2+\alpha_1\beta_1 a^*\right),$$

$$\lambda_{83}=-d-q_2\breve{b}_1<0,$$

$$\lambda_{84}=-\mu_0<0.$$

Clearly, s_8 is a locally asymptotical stable point provided that:

$$r_2<min.\left\{\frac{r_1\breve{b}_1}{k}+\frac{r_2\alpha_2\breve{b}_1}{k}+\gamma_2 a^*+\gamma_0+\mu_2,\frac{r_2\alpha_2\breve{b}_1}{k}+\gamma_2 a^*+\gamma_0+\mu_2+\alpha_1\beta_1 a^*\right\}. \tag{23}$$

9. The Jacobian matrix at $s_9=(0,b_2{}',c',a^*)$ can be written as:

$$J(s_9)=\begin{bmatrix} r_1-\frac{r_1\alpha_1 b_2{}'}{k}+\beta_0-(\beta_1+\gamma_1)a^*-\mu_1 & 0 & 0 & 0\\ \frac{-r_2\alpha_2 b_2{}'}{k}+\beta_1 a & \frac{-r_2 b_2{}'}{k} & 0 & -\gamma_2 b_2{}'\\ -q_2c' & q_1c' & -d+q_1\, b_2{}' & 0\\ 0 & 0 & 0 & -\mu_0\end{bmatrix}$$

Then, the eigenvalues of $J(s_9)$ are given by

$$\lambda_{91}=r_1-\frac{r_1\alpha_1\, b_2{}'}{k}+\beta_0-(\beta_1+\gamma_1)a^*-\mu_1,$$

$$\lambda_{92}=-\frac{r_2 b_2{}'}{k}<0,$$

$$\lambda_{93}=-d+q_1 b_2{}',$$

$$\lambda_{94}=-\mu_0<0.$$

That means s_9 is a locally asymptotical stable point if

$$r_1+\beta_0<\frac{r_1\alpha_1 b_2{}'}{k}+(\beta_1+\gamma_1)a^*+\mu_1, \tag{25}$$

$$q_1 b_2'<d.$$

10. The Jacobian matrix at $s_{10}=(b_1^-,b_2^-,c^-,0)$can be written as:

$$J(s_{10})=\begin{bmatrix} \frac{-r_1b_1^-}{k} & \frac{-r_1\alpha_1 b_1^-}{k} & 0 & -(\beta_1+\gamma_1)b_1^-\\ \frac{-r_2\alpha_2 b_2^-}{k} & -\frac{r_2b_2^-}{k} & 0 & \beta_1b_1^- -\gamma_2 b_2^-\\ -q_2c^- & q_1c^- & -\frac{c_0}{c^-} & 0\\ 0 & 0 & 0 & -\mu_0\end{bmatrix}.$$

Then, the eigenvalues of $J(s_{10})$ are given by

$$\lambda_{10,1}+\lambda_{10,2}=-\frac{r_1b_1^-}{k}-\frac{r_2b_2^-}{k}<0,$$

$\lambda_{10,1}.\lambda_{10,2} = \frac{r_1 r_2 b_1^- b_2^-}{k^2}(1-\alpha_1\alpha_2)$,

$\lambda_{10,3} = -\frac{c_0}{c^-} < 0,$

$\lambda_{10,4} = -\mu_{\ 0} < 0.$

That s_{10} is a locally asymptotical stable point if:

$$1 > \alpha_1\alpha_2. \tag{26}$$

11. The Jacobian matrix at $s_{11} = (b_1^=, b_2^=, 0, a^*)$ can be written as:

$$J(s_{11}) = \begin{bmatrix} -\frac{r_1 b_1^=}{k} & \frac{-r_1\alpha_1 b_1^=}{k} & 0 & -(\beta_1+\gamma_1)b_1^= \\ \frac{-r_1\alpha_2 b_2^=}{k} + \beta_1 a^* & -\frac{\beta_1 a^* b_1^=}{b_2^=} - \frac{r_2 b_2^=}{k} & 0 & \beta_1 b_1^= - \gamma_2 b_2^= \\ 0 & 0 & -d + q_1 b_2^= - q_2 b_1^= & 0 \\ 0 & 0 & 0 & -\mu_{\ 0} \end{bmatrix}$$

Then,

$\lambda_{11,2} + \lambda_{11,1} = -\frac{r_1 b_1^=}{k} - \frac{\beta_1 a^* b_1^=}{b_2} - \frac{r_2 b_2^=}{k} < 0,$

$\lambda_{11,1} \ . \ \lambda_{11,2} = \frac{r_1 b_1^=}{k}\left(\frac{a^*\beta_1 b_1^=}{b_2^=} + \frac{r_2 b_2^=}{k} - \frac{r_1\alpha_1\alpha_2 b_2^=}{k} - a^*\alpha_1\beta_1\right),$

$\lambda_{11,3} = -d + q_1 b_2^= - q_2 b_1^=,$

$\lambda_{11,4} = -\mu_{\ 0} \ < 0.$

Then, the stability s_{11} is a locally asymptotical stable point if:

$$\begin{gathered} \frac{a^*\beta_1 b_1^=}{b_2^=} + \frac{r_2 b_2^=}{k} > \frac{r_1\alpha_1\alpha_2 b_2^=}{k} + a^*\alpha_1\beta_1 \\ q_1 b_2^= < d + q_2 b_1^=. \end{gathered} \tag{27}$$

12. The Jacobian matrix at $S_{12} = (b_1^*, b_2^*, c^*, a^*)$ can be written as:

$$J(s_{12}) = \begin{bmatrix} -\frac{r_1 b_1^*}{k} & \frac{-r_1\alpha_1 b_1^*}{k} & 0 & -(\beta_1+\gamma_1)b_1^* \\ \frac{-r_1\alpha_2 b_2^*}{k} + \beta_1 a^* & -\frac{\beta_1 a^* b_1^*}{b_2} - \frac{r_2 b_2^*}{k} & 0 & \beta_1 b_1^* - \gamma_2 b_2^* \\ -q_2 c^* & q_1 c^* & -\frac{c_0}{c^*} & 0 \\ 0 & 0 & 0 & -\mu_{\ 0} \end{bmatrix}.$$

Then,

$\lambda_{12,1} + \ \lambda_{12,2} = -\frac{r_1 b_1^*}{k} - \frac{\beta_1 a^* b_1^*}{b_2} - \frac{r_2 b_2^*}{k} < 0$

$\lambda_{12,1} \cdot \lambda_{12,2} = \frac{r_1 b_1^*}{k}\left[\frac{r_2 b_2^*}{k} + \frac{a^* \beta_1 b_1^*}{b_2^*} - \frac{r_2 \alpha_1 \alpha_2 b_2^*}{k} + a^* \alpha_1 \beta_1\right],$

$\lambda_{12,3} = -\frac{c_0}{c^*} < 0,$

$\lambda_{12,4} = -\mu < 0.$

Then, the stability of S_{12} a locally asymptotical stable point if:

$$\frac{r_2 b_2^*}{k} + \frac{a^* \beta_1 b_1^*}{b_2^*} + a^* \alpha_1 \beta_1 > \frac{r_2 \alpha_1 \alpha_2 b_2^*}{k} \tag{28}$$

Now, Using the Lyapunov approach [16], this section delves into the requirements that must be met for the global stability property of the system to exist (1) at the positive equilibrium point.

Theorem 3. $s_{12} = (b_1^*, b_2^*, c^*, a^*)$ is globally asymptotically stable if the following conditions

$$\left[\frac{-r_1 \alpha_1}{k} - \frac{r_2 \alpha_2}{k} + \frac{\beta_1 a b_2^*}{b_2 b_2^*}\right]^2 \leq \frac{r_1 r_2}{4k^2}\left(\frac{\beta_1 b_1^* a^*}{b_2 b_2^*}\right)^2,$$

$$\frac{c_0}{4kcc^*} \geq max.\left\{\frac{q_1^2}{r_2}, \frac{q_2^2}{r_1}\right\}, \tag{29}$$

$$\left[\frac{\beta_1 - \gamma_2}{b_2}\right]^2 \leq \frac{r_2 \omega}{4kaa^*},$$

are satisfied.

Proof: Define:

$$L_{12} = c_1\left(b_1 - b_1^* - b_1\, ln\frac{b_1}{b_1^*}\right) + c_2\left(b_2 - b_2^* - b_2\, ln\frac{b_2}{b_2^*}\right) + c_3\left(c - c^* - c\, ln\frac{c}{c^*}\right)$$
$$+ c_4\left(a - a^* - a^* \ln\frac{a}{a^*}\right)$$

Therefore,

$$\frac{dL_{12}}{dt} = -\frac{c_1 r_1 (b_1 - b_1^*)^2}{k} + \left[\frac{c_2 \beta_1 a}{b_2} - \frac{c_2 r_2 \alpha_2}{k} - \frac{c_1 r_1}{k}\right](b_1 - b_1^*)(b_2 - b_2^*)$$
$$- c_1(\beta_1 + \gamma_1)(a - a^*)(b_1 - b_1^*) - \left[\frac{c_2 r_2}{k} + \frac{c_2 \beta_1 b_1^* a^*}{b_2 b_2^*}\right](b_2 - b_2^*)^2$$
$$- \left[\frac{c_2 \beta_1 b_1^*}{b_2} + c_2 \gamma_2\right](a - a^*)(b_2 - b_2^*) - \frac{c_3 c_0}{cc^*}(c - c^*)^2 + c_3 q_1 (b_2 - b_2^*)(c - c^*)$$
$$- c_3 q_2 (b_1 - b_1^*)(c - c^*) - \frac{c_4 \omega}{aa^*}(a - a^*)$$

By choosing the positive constants as: $c_1 = c_3 = c_4 = 1, c_2 = \frac{b_1(r_1 d + r_2\alpha_2)}{k}$, the following is obtained:

$$\frac{dL_{12}}{dt} = -\frac{r_1(b_1 - b_1^*)^2}{2k} - (\beta_1 + \gamma_1)(a - a^*)(b_1 - b_1^*) - \frac{\omega}{2aa^*}(a - a^*) - \frac{c_2 r_2}{k}(b_2 - b_2^*)^2$$
$$- \left[\frac{c_2\beta_1 b_1^*}{b_2} + c_2\gamma_2\right](a - a^*)(b_2 - b_2^*) - \frac{\omega}{2aa^*}(a - a^*) - \frac{c_0}{2cc^*}(c - c^*)^2$$
$$+ q_1(b_2 - b_2^*)(c - c^*) - \frac{c_2\beta_1 b_1^* a^*}{b_2 b_2^*}(b_2 - b_2^*)^2 - \frac{c_0}{2cc^*}(c - c^*)^2$$
$$- q_2(b_1 - b_1^*)(c - c^*) - \frac{r_1(b_1 - b_1^*)^2}{2k}$$

According to condition (29), the following is obtained:

$$\frac{dL_{12}}{dt} =\leq -\left(\sqrt{\frac{r_1}{2k}}(b_1 - b_1^*) + \sqrt{\frac{c_0}{2cc^*}}(c - c^*)\right)^2 - \left(\sqrt{\frac{r_1}{2k}}(b_1 - b_1^*) + \sqrt{\frac{\omega}{2aa^*}}(a - a^*)\right)^2$$
$$- \left(\sqrt{\frac{r_2}{2k}}(b_2 - b_2^*) + \sqrt{\frac{c_0}{2cc^*}}(c - c^*)\right)^2 - \left(\sqrt{\frac{r_2}{2k}}(b_2 - b_2^*) + \sqrt{\frac{\omega}{2aa^*}}(a - a^*)\right)^2$$

Then, $\frac{dL_{12}}{dt} \leq 0$ thus, F_{12} is Lyapunov stable. Therefore, s_{12} is a globally stable point in the interior of R_+^4.

4. NUMERICAL ANALYSIS

Through the use of numerical simulations, the purpose of this part is to identify the essential parameters of the system that have an impact on the behaviour of the proposed system. The dynamics of model (1) can be acquired by the numerically solving system (1) with the help of MATLAB and the Runge-Kutta method. This will give you the model's dynamics. After that, the time series of the solutions of system (1) for many cases is drawn for the sets of parameters that are as follows:

$$r_1 = 0.2, r_2 = 0.4, k = 40, \alpha_1 = 0.1, \alpha_2 = 0.1, \delta_1 = 0.16, \delta_2 = 0.16, \beta_0 = 0.14, \beta_1 = 0.016, \gamma_1 = 0.018, \gamma_2 = 0.017, \gamma_0 = 0.18, d = 0.32, c_0 = 4, q_1 = 0.012, q_2 = 0.014, \omega = 0.6, \ \mu_0 = 0.118. \quad (30)$$

Three instances will be considered to comprehend the system (1) model's dynamic behavior and evaluate antibiotic and probiotic supplementation's effect on the gastrointestinal tract's performance. The outcomes of the four instances will then be compared.

- Case 1: the behavior of the system (1) without antibiotic and probiotic supplementation

In this scenario, we examine the behavior of the system (1) in the absence of antibiotic $(\omega = 0)$ and probiotic supplementation $(\beta_0 = 0)$. Figure 2 illustrates the behaviour of the data given in (30) with $\beta_0 = \omega = 0$. It demonstrates the solution settling asymptotically to s_{10} in $R^3_{+(b_1,b_2,c)}$ for different initial values. It's clear that the big intestine's non-decomposing toxins and harmful bacteria are vast. In this particular scenario, there is a significant risk of gut wall inflammation. It is also conceivable for harmful bacteria to be transferred from the lumen into the tissue compartment or circulation.

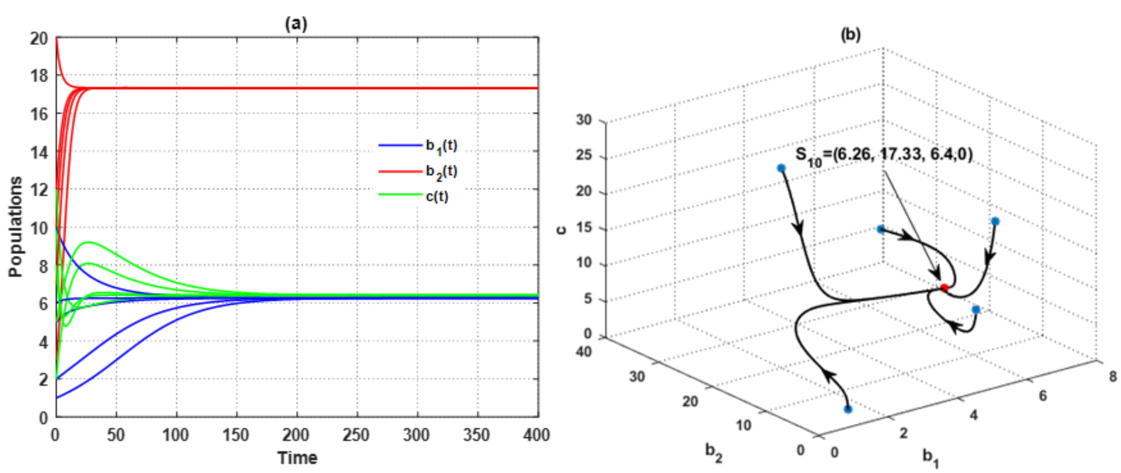

Figure 2 Dynamics of the system (1) with the data given by (30) with $\beta_0 = \omega = 0$ *and different initial values.*

- Case 2: the behavior of the system (1) with probiotic supplementation and without antibiotic

In this case, system (1) is studied with probiotic supplementation and without antibiotics. Figure 3 explains the behavior of the data given in (30) with $(\omega = 0)$. It determines the solution approaching asymptotically to s_{10} in $R^3_{+(b_1,b_2,c)}$ for different initial values with significant decreases in non-decomposing toxins and harmful bacteria.

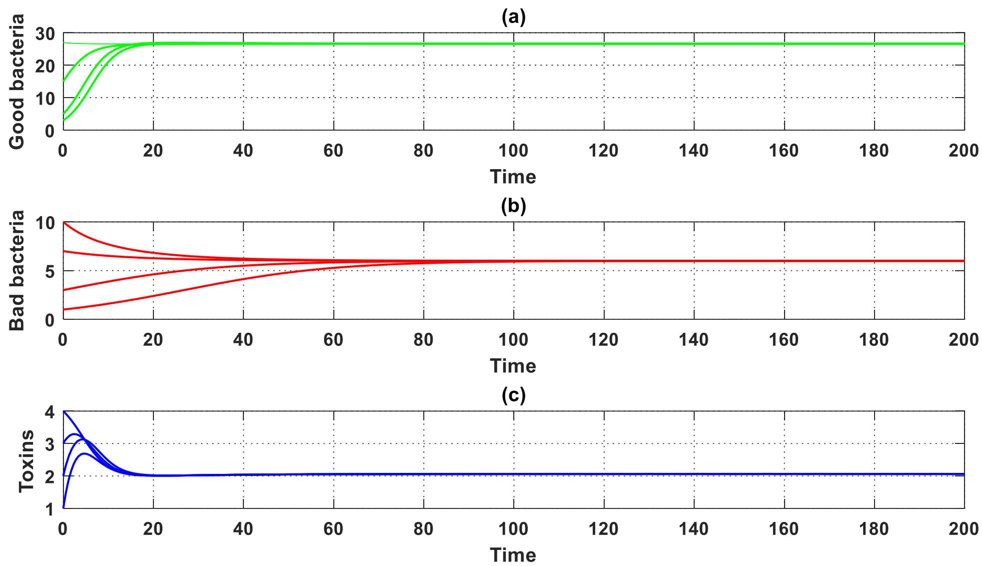

Figure 3 Dynamics of the system (1) for the data given by (30) with $\omega = 0$.

➢ Case 3: the behavior of the system (1) with probiotic supplementation and antibiotic

Clearly, for different sets of initial values, the solution of system (1) approach asymptotically to the globally stable point $s_{12} = (b_1^*, b_2^*, c^*, a^*) = (23.13, 12.51, 2.58, 5.08)$ (see Figure 4).

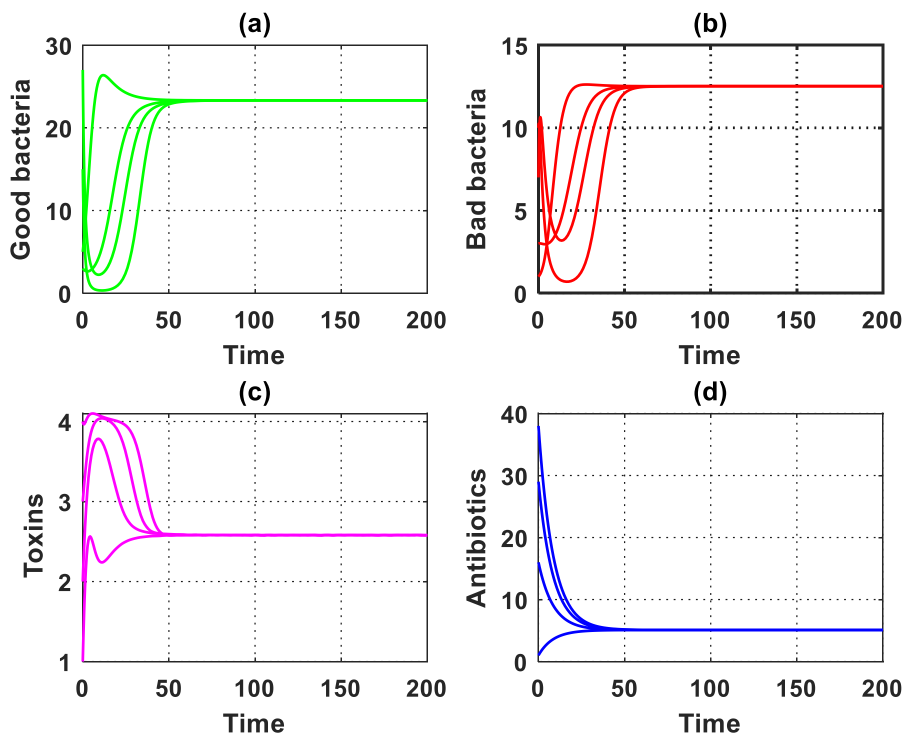

Figure 4 Dynamics of the system (1) with the data given by (30).

5. Conclusion

A model consisting of good bacteria, harmful bacteria, toxins and antibiotics in the large intestine has been studied. The terms of probiotic supplementation of the good bacteria have been included. The theoretical analysis of the proposed mathematical model shows the existing conditions of the twelve non-negative equilibrium points. Based on the Routh-Hurwitz stability criteria, the positive equilibria $s_{12} = (b_1^*, b_2^*, c^*, a^*)$ Showed asymptotically stable behavior under certain conditions. Further, using the Lyapunov method, the appropriate states that guarantee the global stability of the positive equilibria have been established. According to the numerical simulation results, system movement always happens around the positive equilibria if the system stability conditions are met. In contrast, the absence of probiotic supplements will increase toxins in the large intestine. That means the beneficial bacteria play a role in digestion and the enhancement of nutrient absorption.

Conflict of Interests

The author(s) declare that there is no conflict of interests.

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