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Optimal Control Strategies Applied to Slow Down the Multiple Antibiotic Resistances in Human Body

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Abstract

The use of antibiotics in large quantities and in a very fast way is currently a very hot topic. Doctors and health workers all over the world are conducting various activities to create awareness about the use of antibiotics. It is sometimes necessary to apply more than one antibiotic at a time to a patient and if it is not taken as prescribed; it causes antibiotic resistance, which is harmful to them. And once antibiotics are resisted, there's no other treatment. So, we need to treat infectious diseases by avoiding antibiotic resistance. For this, we are suggesting boosting the immune system to treat infections rather than antibiotics. In this study, we observed a patient's resistance to antibiotics and its effect on our body and immune system. Although no effective and boosting method has yet been discovered in medicine, experts recommend a wide range of ways to boost the immune system to treat infection rather than using antibiotics. We have developed a mathematical model to show antibiotic resistance of bacteria in the human body and then suggested some precautions to avoid this disaster. We have shown how effective our model is by correctly solving and illustrating the dynamics of antibiotic when it's consumed inside the human body.

Keywords

Multiple Antibiotic Resistance, Mathematical Modeling of Antibiotic Resistance, Controlling Antibiotic Resistance, Optimal Control.

1. Introduction

Bacterial resistance to antibiotics is the leading problem of recent time in human health care sectors. Scientists are warning that if we do not take necessary steps to minimize bacterial resistance, we could soon return to the "dark age of medicine", where all of our available drugs become ineffective against even the most basic infection.
In recent years it is seen that the increase in antimicrobial resistance has caused additional cost in health care sector. Now-a-days the traditional medicine is no longer effective to these multi-resistance micro-organisms and the infection due to these micro-organisms can only be treated with more expensive or more toxic drugs. In some cases even the available antibiotics are not sufficient. As more strains of bacteria become resistant to antibiotics,
The nature and evolution of tolerance and resistance of microbes against antibiotics has been documented in some 200000 scientific articles. According to these articles three types of mechanism can cause these rise of resistance:

1. Adaptation of the regular cellular machinery.
2. Mutation that make the target insensitive.
3. Transfer of so called resistance genes.

Once any of these has occurred, further exposure to antibiotic will select for the specific trait. Though we have detailed knowledge about the mechanism of antibiotic resistance, the rate of increase and decrease of resistance with respect to arrival and removal of antibiotic is not known quantitatively.
This build up and decline of antibiotic resistance depend on a large number of factors. Important components are,

1. Initial acquisition of resistance by a single cell.
2. Initial acquisition of resistance by at most a few cells.
3. Subsequent positive selection of this resistant cell.

Infections have been the leading cause of most diseases in the history of mankind (NIH 2018). Especially bacterial infections are more prevailing among these. The most common procedure known to fight bacterial infection is

through antibiotic therapy applied to individuals. The release of each new class of antibiotics for treatment, shortly after, has been followed by the emergence of new strains of bacteria which are resistant to this class.
In this respect, developing new treatment strategies for bacterial infections is very important (Caron and Mousa2010). According to its properties, antibiotics have the bacteriostatic action to stop the growth of bacteria and bactericidal action to wipe out the bacteria. However, the distinction between these properties is not explicit, as it depends on the drug concentration used and the type and the growth stage of bacteria (Massad et al. 2008).
The immune system is expressed as a system of biological structures and processes in an organism protecting the body from likely harmful substances via recognizing and responding to antigens. In this context, the reactions of different hosts against the same infection can be different due to immune system's response given by host.
Antibiotics are some of the biochemical drugs that destroy microorganisms (especially bacteria). The natural substance that has the ability to cure. In 1881, British microbiologist John Tyndall observed that fungus has the ability to resist the germ. The first antibiotic discovered in 1927 by the physiologist Alexander Fleming. While working at St. Mary's Hospital in London, Fleming observed that in Solid culture medium staphylococcus aureus cannot grow up with the presence of fungus. Fleming was interested in identifying the species of that fungus and testing its antibiotic properties. The fungus was penicillium and its species is Penicilliumchrysogenum. Fleming named the substance penicillin because it was derived by penicillium. In 1945 Fleming, Ernest Chain, and Floor received the Nobel Prize for their contributions to medical science.
On 12 February 1941, the first penicillin was applied to the human body. A police officer from Oxford was hospitalized as he was attacked by Staphylococcus. His condition was improved. This invention of Fleming attracted the attention of American scientists. In America, scientists have been able to prepare approximately 900 (unit / milliliter) penicillin. During this time many other antibiotics are invented. Rene Dubos discovered Gramicidin and Tyrosine, which works on Gram-Positive Bacteria. Many antibiotics are still being discovered today.
One of the challenges for treating bacterial disease like TB is the emergence of drug-resistant bacteria. This complicates any program of control and prevention, especially for developing countries where the surveillance for measuring the presence of drug-resistant strains is inadequate. The predictions are based on observed data that suggests that more than 50 million people in the world are carrying resistant strains. This resistance to drugs develops spontaneously through mutation, which is a rare event. Therefore, its genesis is independent of drug exposure. The mutations occur at a predictable rate and its magnitude varies among antibacterial drugs.
While antibiotic research and development is one way to target the spread of microbial resistance, it is just as true that current drugs could be more efficacious if used more appropriately, with greater attention to their pharmacokinetic (PK) and pharmacodynamics (PD) properties and avoidance of overuse. In addition, measures such as proper hygiene and barrier precautions, environmental cleaning, prophylaxis and topical decolonization, infection control and reduced antibiotic overuse can be very successful in ensuring the long-term preservation of antimicrobial efficacy. Mostly appropriate use of antibiotics and preventative measures can result in dramatic health care savings by eradicating drug-resistant microbes that arise due to careless antibiotic exposure (Bonten et al. 2001).
Mathematical models are one of the significant tools used in both analyzing the spread of infectious diseases in a population of individuals, and predicting the timing and expansion of infection and possible reinfection processes in an individual.
In this study, we have constructed a continuous time model considering the immune response of the host and the basic mechanisms of bacterial resistance to antibiotics. Our aim is to find specific parameters determining the change in the concentrations of the immune system's cells produced in host to fight these and the sensitive sub-populations and resistant sub-populations that has either arisen through random mutation and clonal enlargement or through cross-contamination in a special infection and under an appropriate treatment regimen.
Mathematical models are used to create a simplified representation of infection spread in a population and to understand how an infection may progress in the future. These predictions can help us to use public health resources such as hospital space or a vacation program more effectively(Bootsma et al. 2012). Consequently, results on reproduction of sensitive and resistant bacteria to antibiotics are obtained in various researches (Barrie 2012); definitions of factors responsible for resistance prevalence are studied in (Austin et al. 1997), bacteria behavior under different antibiotic treatments is examined in (Alavez 2006); optimization results and design of control measures are investigated in (Butler and Buss2006); biological cost and persistence of antibiotic resistance are analyzed in (André andGandon2006); dynamics between pathogens and immune response are given in (Arya2007).

In this context, a mathematical model defining population dynamics of both the specific immune cells produced according to the properties of bacteria by host and the bacteria exposed to multiple antibiotics synchronically, presuming that resistance is gained through mutations due to exposure to antibiotic. Qualitative analysis found out infection-free equilibrium point and other equilibrium points where resistant bacteria and immune system cells exist,

only resistant bacteria exists and sensitive bacteria, resistant bacteria and immune system cells exist. As a result of analysis, the model highlights the fact that when an individual's immune system weakens, he/she suffers more from the bacterial infections which are believed to have been confined or terminated.

2. Mathematical Model Formulation:

Let us consider the five variables as,

$S(t)$ = Population size of Sensitive Bacteria at time t

$R(t)$ = Population size of Resistance Bacteria at time t

$I(t)$ = Population size of Immune cells at time t

$A(t)$ = Antibiotic concentration

If we assume that, bacteria follow a logistic growth model with carrying capacity C. Let, β_s and β_r be the birth rate of sensitive and resistance bacteria respectively. The time rate of change of sensitive and resistance bacteria depends on a number of parameters. Number of sensitive bacteria is increased due to the birth rate of sensitive bacteria β_s until the number of bacteria is gone beyond the carrying capacity. This is denoted by the term $\beta_s S\left(1-\frac{S+R}{C}\right)$. Number of sensitive bacteria decreased due to the immune response of the host body which is λSI ; where, λ is per capita death rate of sensitive bacteria. Sensitive bacteria also decreased as a result of antibiotic concentration in the host body which is, $\overline{\sigma}SA$. Where, $\overline{\sigma}$ is the death rate of sensitive bacteria due to the exposure of given antibiotic. Finally sensitive bacteria decreased as a result of the mutation of sensitive bacteria to resistance bacteria due to exposure of the given antibiotic which is given by the term $\overline{\alpha}SA$, where $\overline{\alpha}$ is the mutation rate. Hence the equation will be,

$$\frac{dS}{dt}=\beta_s S\left(1-\frac{S+R}{C}\right)-\lambda SI-\overline{\alpha}SA-\overline{\sigma}SA$$

Again, the number of resistance bacteria is increased due to the birth rate of resistance bacteria β_R until the number of bacteria is gone beyond the carrying capacity. So this is denoted by the term $\beta_r R\left(1-\frac{S+R}{C}\right)$. Resistance bacteria also increased as the result of the mutation of sensitive bacteria to resistance bacteria due to exposure of the given antibiotic. Which is, $\overline{\alpha}SA$. Number of resistance bacteria decreased due to the immune response of the host body which is λRI ; where, λ per capita death rate of resistance bacteria is. So the equation will be,

$$\frac{dR}{dt}=\beta_r R\left(1-\frac{S+R}{C}\right)-\lambda RI+\overline{\alpha}SA$$

Now as we are using a logistic term, immune cells are recruited to the region of infection at a rate β_m and carrying capacity of these is as ω fold of amount of present bacteria. This is biologically very significant in term of proliferation of specific immune cells. Also these interact can be expressed as a generalized model of a local bacteria function such as Mycobacterium tuberculosis. The equation is,

$$\frac{dI}{dt}=\beta_m I\left(1-\frac{I}{\omega(S+R)}\right)$$

Again if δ be the constant rate at which antibiotic concentration is supplied and μ be the per capita rate at which antibiotic concentration is taken up then the time rate of change of antibiotic concentration will be,

$$\frac{dA}{dt} = \delta - \mu A$$

Hence we obtain the following system of Ordinary Differential Equation as,

$$\frac{dS}{dt} = \beta_s S\left(1 - \frac{S+R}{c}\right) - \lambda SI - \bar{\alpha} SA - \bar{\sigma} SA$$

$$\frac{dR}{dt} = \beta_r R\left(1 - \frac{S+R}{c}\right) - \lambda RI + \bar{\alpha} SA$$

$$\frac{dI}{dt} = \beta_m I\left(1 - \frac{I}{\omega(S+R)}\right)$$

$$\frac{dA_n}{dt} = \delta - \mu A_n$$

Where

$$\beta_S, \beta_S, \beta_m, \mathrm{C}, \lambda, \bar{\alpha}, \bar{\sigma}, \omega, \tau, \mu, \delta > 0$$

We can reduce the parameters by changing the variable as,

$$A = \frac{S}{c}, B = \frac{R}{c}, C = \frac{I}{\omega c}\ ,\ D = \frac{An}{\frac{\delta}{\mu}}$$

So by using these new variable our system of ordinary differential equations become,

$$\frac{d}{dt}A(t) = -a_7 A(t)C(t) - a_1 A(t)\big(A(t) + B(t) - 1\big) - A(t)D(t)\big(a_3 + a_4\big)$$

$$\frac{d}{dt}B(t) = a_3 A(t)D(t) - a_7 B(t)C(t) - a_2 B(t)\big(A(t) + B(t) - 1\big)$$

$$\frac{d}{dt}C(t) = -a_9 C(t)\left(\frac{C(t)}{A(t) + B(t)} - 1\right)$$

$$\frac{d}{dt}D(t) = -\mu\big(D(t) - 1\big)$$

Where, $\alpha = \bar{\alpha}\left(\frac{\delta}{\mu}\right)$, $\sigma = \bar{\sigma}\left(\frac{\delta}{\mu}\right)$ and $\eta = \lambda\omega T$

2.1 Equilibrium Points:

We have the mathematical model of system of ODEs

To find the equilibrium points (s^*, r^*, m^*, a^*) let us consider,

$$\frac{dA^*}{dt} = \frac{dB^*}{dt} = \frac{dC^*}{dt} = \frac{dD^*}{dt} = 0$$

That is,

$$-a_7 A(t)C(t) - a_1 A(t)\big(A(t) + B(t) - 1\big) - A(t)D(t)\big(a_3 + a_4\big) = 0$$

$$a_3 A(t)D(t) - a_7 B(t)C(t) - a_2 B(t)\big(A(t) + B(t) - 1\big) = 0$$

$$-a_9 C(t)\left(\frac{C(t)}{A(t) + B(t)} - 1\right) = 0$$

$$-\mu\left(D(t)-1\right)=0$$

So we have obtained five equilibrium points e_1, e_2, e_3, e_4 and the equilibrium points are,

$$\mathrm{E}_1 = -\frac{a_2 a_3{}^2 + 2a_2 a_3 a_4 - a_1 a_2 a_3 + a_2 a_4{}^2 - a_1 a_2 a_4}{a_1\left(a_2 a_3 - a_1 a_3 + a_2 a_4\right)}$$

$$\mathrm{E}_2 = \frac{a_3\left(a_3 - a_1 + a_4\right)}{a_2 a_3 - a_1 a_3 + a_2 a_4}$$

$$\mathrm{E}_3 = 0$$

$$\mathrm{E}_4 = 1$$

2.2 Stability Analysis:

The model is,

$$\frac{d}{dt}A(t) = -a_7 A(t)C(t) - a_1 A(t)\left(A(t)+B(t)-1\right) - A(t)D(t)\left(a_3+a_4\right)$$

$$\frac{d}{dt}B(t) = a_3 A(t)D(t) - a_7 B(t)C(t) - a_2 B(t)\left(A(t)+B(t)-1\right)$$

$$\frac{d}{dt}C(t) = -a_9 C(t)\left(\frac{C(t)}{A(t)+B(t)}-1\right)$$

$$\frac{d}{dt}D(t) = -\mu\left(D(t)-1\right)$$

The Jacobian matrix J of the model is given by,

$$J = \begin{bmatrix} -Aa_1 - Ca_7 - a_1(A+B-1) - D\left(a_3+a_4\right) & -Aa_1 & -Aa_7 & -A\left(a_3+a_4\right) \\ Da_3 - Ba_2 & -Ba_2 - Ca_7 - a_2(A+B-1) & -Ba_7 & Aa_3 \\ \frac{C^2 a_9}{(A+B)^2} & \frac{C^2 a_9}{(A+B)^2} & -a_9\left(\frac{C}{A+B}-1\right) - \frac{Ca_9}{A+B} & 0 \\ 0 & 0 & 0 & -\mu \end{bmatrix}$$

Now will examine whether the equilibrium points of the model e_1, e_2, e_3, e_4 are stable or not.

$$J\left(e_2\right) = \begin{bmatrix} \frac{a_2\left(a_3+a_4\right)\left(a_3-a_1+a_4\right)}{a_2 a_3 - a_1 a_3 + a_2 a_4} & \frac{a_2\left(a_3+a_4\right)\left(a_3-a_1+a_4\right)}{a_2 a_3 - a_1 a_3 + a_2 a_4} & \frac{a_2 a_7\left(a_3+a_4\right)\left(a_3-a_1+a_4\right)}{a_1\left(a_2 a_3 - a_1 a_3 + a_2 a_4\right)} & \frac{a_2\left(a_3+a_4\right)^2\left(a_3-a_1+a_4\right)}{a_1\left(a_2 a_3 - a_1 a_3 + a_2 a_4\right)} \\ \frac{a_1 a_3\left(a_2-a_3\right)}{a_2 a_3 - a_1 a_3 + a_2 a_4} & \frac{a_2\left(a_1{}^2 a_3 - 2a_1 a_3{}^2 - 2a_1 a_3 a_4 + a_2 a_3{}^2 + 2a_2 a_3 a_4 + a_2 a_4{}^2\right)}{a_1\left(a_2 a_3 - a_1 a_3 + a_2 a_4\right)} & -\frac{a_3 a_7\left(a_3-a_1+a_4\right)}{a_2 a_3 - a_1 a_3 + a_2 a_4} & -\frac{a_2 a_3\left(a_3+a_4\right)\left(a_3-a_1+a_4\right)}{a_1\left(a_2 a_3 - a_1 a_3 + a_2 a_4\right)} \\ 0 & 0 & a_9 & 0 \\ 0 & 0 & 0 & -a_6 \end{bmatrix}$$

Let λ be the eigen value and I be the identity matrix, then the characteristic equation is,

$$\lambda_1 = -a_9$$

$$\lambda_2 = -\mu$$

$$\lambda_3 = \frac{-a_1^{\,2}a_2a_4 - a_1a_2a_3^{\,2} + a_1a_2a_4^{\,2} + a_2^{\,2}a_3^{\,2} + 2a_2^{\,2}a_3a_4 + a_2^{\,2}a_4^{\,2'} + \Psi}{2a_1a_2a_3 - 2a_1^{\,2}a_3 + 2a_1a_2a_4}$$

$$\lambda_4 = \frac{-a_1^{\,2}a_2a_4 - a_1a_2a_3^{\,2} + a_1a_2a_4^{\,2} + 2a_2^{\,2}a_3a_4 + a_2^{\,2}a_4^{\,2}}{2a_1a_2a_3 - 2a_1^{\,2}a_3 + 2a_1a_2a_4} - \sqrt{\Psi} + a_2^{\,2}a_3^{\,2'}$$

$$\Psi = \sqrt{a_2\begin{pmatrix} a_1^{\,4}a_2a_4^{\,2} + 4a_1^{\,4}a_3^{\,3} + 4a_1^{\,4}a_3^{\,2}a_4 - 8a_1^{\,3}a_2a_3^{\,3} - 14a_1^{\,3}a_2a_3^{\,2}a_4 \\ -8a_1^{\,3}a_2a_3a_4^{\,2} - 2a_1^{\,3}a_2a_4^{\,3} - 4a_1^{\,3}a_3^{\,4} - 8a_1^{\,3}a_3^{\,3}a_4 - 4a_1^{\,3}a_3^{\,2}a_4^{\,2} + 4a_1^{\,2}a_2^{\,2}a_3^{\,3} \\ +10a_1^{\,2}a_2^{\,2}a_3^{\,2}a_4 + 8a_1^{\,2}a_2^{\,2}a_3a_4^{\,2} + 2a_1^{\,2}a_2^{\,2}a_4^{\,3} + 9a_1^{\,2}a_2a_3^{\,4} + 24a_1^{\,2}a_2a_3^{\,3}a_4 \\ +22a_1^{\,2}a_2a_3^{\,2}a_4^{\,2} + 8a_1^{\,2}a_2a_3a_4^{\,3} + a_1^{\,2}a_2a_4^{\,4} - 6a_1a_2^{\,2}a_3^{\,4} - 20a_1a_2^{\,2}a_3^{\,3}a_4 \\ -24a_1a_2^{\,2}a_3^{\,2}a_4^{\,2} - 12a_1a_2^{\,2}a_3a_4^{\,3} - 2a_1a_2^{\,2}a_4^{\,4} + a_2^{\,3}a_3^{\,4} + 4a_2^{\,3}a_3^{\,3}a_4 + 6a_2^{\,3}a_3^{\,2}a_4^{\,2} + 4a_2^{\,3}a_3a_4^{\,3} + a_2^{\,3}a_4^{\,4} \end{pmatrix}}$$

Since all the values of λ are negative, it implies that the equilibrium is stable.

3. Numerical Simulation:

Numerical analysis is the study of algorithms that use numerical approximation for problems of mathematical analysis. After all the analytical study in previous section, numerical analysis will help us to understand the model more accurately.

In this section, the model has been solved numerically based on the respective parameters. We have conducted some numerical computations using Runge-Kutta method in MATLAB(R2017a). We have used the following set of parameter values which are given in the table (1). By using these parameters we have solved the model numerically in order to describe the dynamics of sensitive and resistant bacteria and the effect of antibiotic and immune cells on these bacteria in time.

Table 1: Description of parameters and their respective values for the model.

Parameter	New Variables	Description	Value
β_s	a_7	Growth rate of sensitive bacteria	0.8 day-1
β_r	a_2	Growth rate of resistant bacteria	0.4-0.1 day-1
β_m	a_9	Growth rate of immune cells	0.6 day-1
η		Rate of bacteria destroyed by immune cells	0.3 day-1
ω		Rate of the amount of present bacteria of carrying capacity of immune cells	1
α	a_3	Mutation rate of sensitive bacteria	10-6mut×gen
σ	a_4	Elimination rate of sensitive bacteria	0.0039 day-1
δ		Daily dose of antibiotic	5 mg/kg/day
μ		Uptake rate of antibiotic	0.06 day-1
C		Carrying capacity of bacteria	109 bacteria

At first we have solved the model numerically by using the parameters value as in the table (1). We have studied that in general cases most of the patients has been prescribed antibiotic for different bacterial diseases at about 14 days. Some patients who are less affected by bacteria has been prescribed antibiotic for 5-7 days. Patients who are

seriously affected by the bacteria has been prescribed antibiotic for 3-4 weeks depending on the laboratory test reports. As most of the patients have to take antibiotic for 2 weeks that is 14 days. So we are solving the model numerically for 14 days' time period. We also assume that the patient will take 3 doses of antibiotic per day at an interval of 8 hours.

We have considered the initial value of sensitive bacteria (s), resistant bacteria(r), immune cells in the body (m) is positive. That is $s(0) = 0.8, r(0) = 0.1, m(0) = 0.3$ and at the start of antibiotic course $a(0) = 0$.

We have also observed that, antibiotics which are available in the market have different dose power such as 5mg, 50mg, or even 500mg. The respective doctor will decide which one is suitable for that respective patient according to patient age, health, and infection quality. Here first we are solving the model for lower power dose of antibiotic and next we will do it for higher power dose. For higher dose of antibiotic the value of δ will be high, which results higher value of antibiotic consumption rate μ.

Now in the Figure 4.1 we have used lower antibiotic dose based uptake rate $\mu = 0.06 day^{-1}$ and growth rate of immune response $\beta_m = 0.6 day^{-1}$. All other parameters value will be same as in the Table-1.

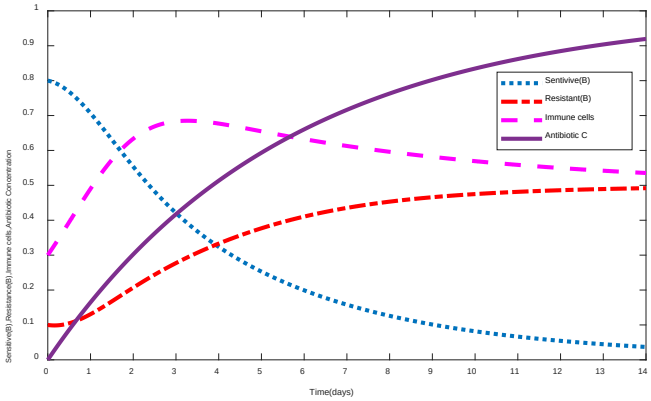

Figure 1: Sensitive bacteria, resistant bacteria, Immune cells and Antibiotic concentration from 1-14 days at antibiotic uptake rate $\mu = 0.06 day^{-1}$

From the figure it is evident that, antibiotic concentration is increasing from 1-14 days with respect to time and sensitive bacteria is decreasing as the result of antibiotic effect. Which is congruence with our description because antibiotic kills sensitive bacteria with time. As we have used the antibiotic of less power in this figure, so the number of sensitive bacteria is decreasing slowly from 0.8 to 0.03(approximately) at the end of the 14 days course.

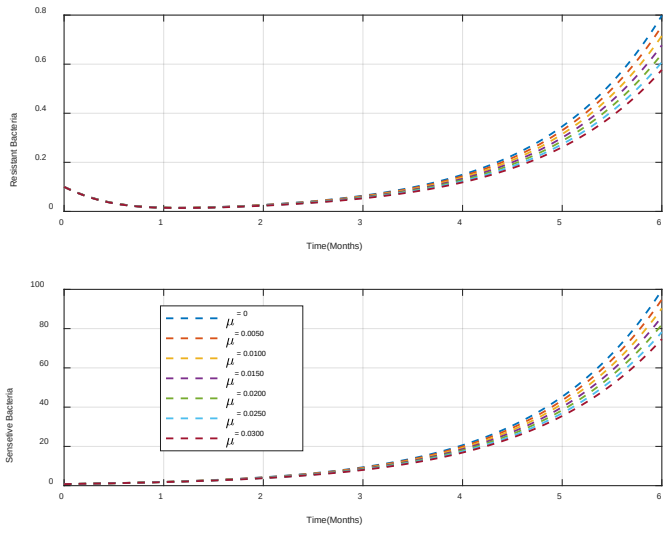

Figure 2: Effect of different antibiotic uptake rate $\mu = 0.06, 0.09, 0.12, 0.15, 0.20 day^{-1}$ on sensitive bacteria

For 6 months.

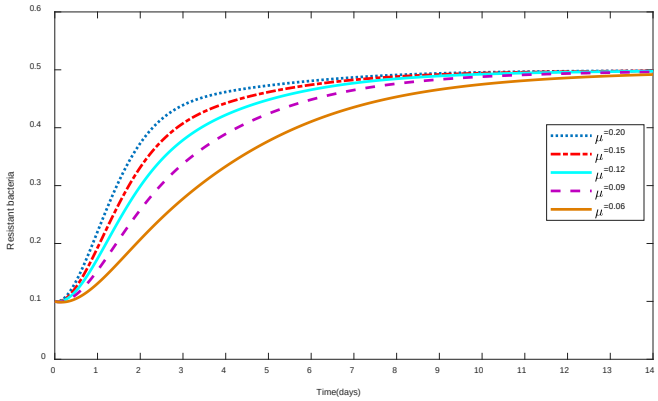

Figure 3: Effect of different antibiotic uptake rate on resistant bacteria where,

$$\mu = 0.06, 0.09, 0.12, 0.15, 0.20 day^{-1}$$

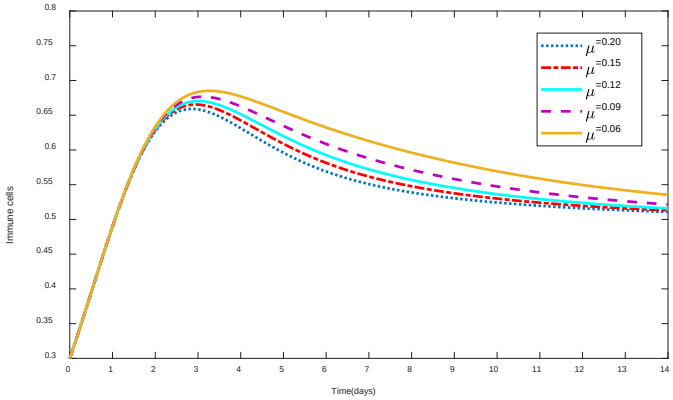

Figure 4: Effect of antibiotic uptake rate $\mu = 0.06, 0.09, 0.12, 0.15, 0.20 day^{-1}$ on our body immune system.

This Figure (4) shows that, immune cells are reducing at a considerable number in the same period of time when we are taking higher dose of antibiotic. As we said earlier that antibiotic kills the good micro-organism living in our intestine and thus reduces the growth rate of immune cells. As a result total immune response is decreasing as we have observed in Figure 4. From the figure we can see that, number of immune cells is minimum when we took maximum power dose antibiotics.

3.1 Over-dose of Antibiotics:

Over dose of antibiotics means taking antibiotics more than the doctor prescribed. Suppose a doctor prescribe antibiotics for 14 days. If the patient take the antibiotics more than 14 days than it is termed as over-dose of antibiotics.

Now we can modify our model for over-dose of antibiotics. Let us consider over-dose of antibiotics decrease the immune cells at a rate φ. So we get our modified model as,

$$\frac{d}{dt}A(t) = -a_7 A(t)C(t) - a_1 A(t)\big(A(t) + B(t) - 1\big) - A(t)D(t)\big(a_3 + a_4\big)$$

$$\frac{d}{dt}B(t) = a_3 A(t)D(t) - a_7 B(t)C(t) - a_2 B(t)\big(A(t) + B(t) - 1\big)$$

$$\frac{d}{dt}C(t) = -a_9 C(t)\left(\frac{C(t)}{A(t) + B(t)} - 1\right)$$

$$\frac{d}{dt}D(t) = -\mu\left(D(t) - 1\right)$$

Now we consider the model for patients, who took over-dose of antibiotics.

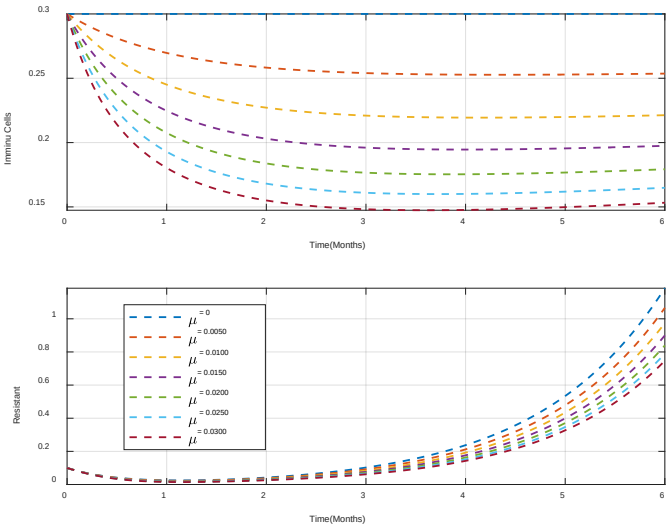

Figure 5: State trajectories after Antibiotic Overdose

From Figure 5 above we can see that as the concentration of antibiotics gradually increases the cells of the human body's immune system decrease and the amount of resistant bacteria increases. So from this we can conclude that if the human body takes in the right amount, it damages the human body's immune system. We see that no system changes when no antibiotics are taken. This means that taking more or less antibiotics for the human body's immune system is largely responsible.

The figure above also shows us at what rate our immune system changes when we take antibiotics. So from this study we can see how the immune system is damaged as a result of the application of antibiotics.

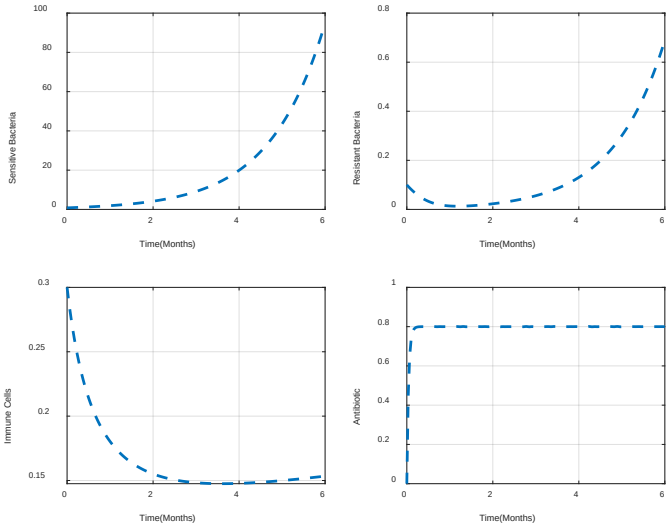

Figure 6:State trajectories after Antibiotic Overdose

Over-dose of antibiotics causes problem in human body in several ways. First of all over-dose of antibiotics decrease human immune cells at a considerable number. As we describe before in this paper, antibiotics kill some good bacteria living in human intestine. These good bacteria produce human immune cells and make the immune system stronger. Antibiotics weaken the immune system by killing those bacteria. This process begins when

antibiotic is started. But the process gets acceleration when over-dose of antibiotics is consumed. Hence over-dose of antibiotics weakens the human immune system.
At the same time, over-dose of antibiotics increase resistant bacteria. We know that antibiotics cannot kill bacteria but human immune system can do it. As over-dose of antibiotics weakens the immune system, hence it increases the number of resistant bacteria.

4. Conclusion:

In this research, we have come to learn that the antibiotic prescribed by doctors should be taken according the schedule. Taking it for a long time or short time apart from the prescription can lead to antibiotic resistance so the optimal control of antibiotic resistance should be the authorized procedure suggested by the doctor. No matter if that's a single antibiotic or more than one, the misuse of antibiotics will always lead to the same results, in one hand we'll push the sensitive bacteria to the road of resistance and on the other hand, our immune system will collapse at some point because of this. We showed the effect of one antibiotic in our model,but in case ofmore than one antibiotic the effects of antibiotic resistant will be more severe. It'll multiply the damage in human body compared to bacteria resistant to one antibiotic. We should not take antibiotic as we please. The most efficient and effective way of avoiding multiple antibiotic resistance is to consume antibiotics as the authorized doctor or certified health worker suggested. The government of the developing countries should take appropriate steps to control the antibiotic consumption of their countries. Or else it could lead us to a global problem of antibiotic resistance, which can be a very hard problem for us to avoid. Antibiotic resistance inside human body often leads to death. It'll affect our future generations too, they'll have to suffer more than us because of the severity of normal infections caused by resistant bacteria. So, we should be more careful about taking antibiotics. We should not take antibiotics for normal diseases without the doctor's suggestion. We should encourage the people around us to take antibiotics as authorized to ensure a better world for the future generations.

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