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BIOLOGICAL AND ECONOMIC DYNAMICS FOR ANTIBIOTICS IN PERFECTLY COMPETITIVE MARKET

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Abstract. In this paper, we study the production and circulation of antibiotics in a perfectly competitive market. An incentive function is constructed to measure the macroscopic regulation of the government with respect to the environmental disruption caused by overuse of antibiotics. The demand-supply ODE with an explicit solution reflects the circulation of antibiotics in market economy. A fully nonlinear biological system reveals the evolutionary mechanism of antibiotic bacteria where distinct types of bacterial strains interact with each other. The parameter analysis follows up numerical simulations to show the flexible controllability of management from the government.

1. Introduction

In 1928, Alexander Fleming discovered modern penicillin, although antibiotic use dated from old times as specific applications of moldy bread. Penicillin was finally available for widespread use due to the help from other biochemists during wartime. Nowadays, antibiotics have become standard antimicrobial substances to prevent and fight against bacterial infections. However, antibiotics are not effective against viruses such as common cold or influenza. Unfortunately, easy access and effectiveness also led to their overuse, and moreover some bacteria have developed resistance.

Since 1950s, the overuse of antibiotics including penicillin and erythromycin has issued a problem of antibiotic resistance. The drug resistance restricted use of antibiotics in the UK (1970) and the EU (2003). The misuse of antibiotics has led to astonishing development of antimicrobial resistance, which can beat antibiotics while resisting the drugs and immune system and therefore they are difficult to exterminate [7], [14]. Moreover, many organizations including the World Health Organization (WHO), the National Academy of Sciences (NAS), the U.S. Food and Drug Administration (FDA), and the National Institutes of Health (NIH) prompted restrictions on antibiotic use in food production [10], [17]. Abuse of antibiotic is also a problem in aquaculture, poultry farming and animal husbandry. Antibiotics help animals grow faster by killing most bacteria in their body. However, the quantity of drug-against strain of bacteria (super bug) will multiply. The antibiotics use on farm animals is increasing every year, in spite of the reduction or elimination of the meat product from antibiotics-fed animals [16]. The World Health Organization

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(WHO) has classified antimicrobial resistance as a serious threat and it has the potential to affect anyone [23].

In order to cut out the overuse of antibiotics, one firstly needs to predominate the production and circulation of antibiotics as well as the mechanism how antimicrobial resistance evolves. Differential-equation (DE) models and Individual-based (IB) models have both been adopted to analyze the transmission dynamics of antibiotic-resistant bacteria. Specifically, DE models divide patients and health-care workers into different groups: infected patients and uninfected ones, contaminated health-care workers and uncontaminated ones. The clusters are supposed to be homogeneous and mutually interacted. IB models are constructed in a different way. They regard patient and health-care worker as a single agent, and simulations reveal the heterogeneity of their behaviors. Quite some microscopic analysis of population-level adopt DE models, taking the immune systems into account. Meanwhile, IB models are extensively applied to various biological problems in recent years.

On mathematical aspect, various theories and tools have been adopted to investigate antibiotic resistance. Leenheer et al [4] constructed a model consisting of four nonlinear parabolic PDEs for the bacteria living in bio-film communities. The existence of solutions to this model was shown via a positivity criterion. In [5], D'Agata et al built a two-strain ODE system satisfying the recombination and reversion processes. They found existence conditions for three possible equilibria and investigated the asymptotic behavior of the solutions to the model with respect to these equilibria. Recently, Knopoff et al [9] proposed a mathematical model for antibiotic resistance from kinetic theory. A computational analysis and simulations were performed to show interactions between bacterial and immune cells. A recent focus on dynamics of bacterial population level was followed by several authors, where cells of distinct ages or pathological statistics of various groups of patients are taken into account [3], [20].

In this paper, we study production and clinical applications of antibiotics in a perfectly competitive market from macroscopic regulation to microscopic mechanism. The intrinsic properties of a perfectly competitive market permit us to exploit the nature of developments and enhance the supervision from the government. The process is carried out through three mathematical models. In section 2, we first construct an incentive function to measure how much the government would undertake the cost of the civil use of antibiotics. It could help the government establish the total amount of antibiotics issued into circulation. Next we exploit the interest chain of antibiotics on a perfectly competitive market, where patients (farmers) with alternative medicine (PAM) will reduce or stop using antibiotic as its price rises, while patients stuck to antibiotics (PA) will keep on using it. A demand-supply differential model follows up this property in section 3, and the sensitivity of parameters are explicitly illustrated. In section 4, we aim to expose a fundamental reproduction-transmission process of antibiotic-resistant bacteria. As is known in appropriate circumstances, normal bacteria could turn into drug-resistant bacteria, but there is a ceiling for the total amount of the bacteria, including normal and drug-resistant bacteria. We simulate the evolutionary process with different sets of the parameters.

2. Incentive policy on antibiotics

In this section, we consider the antibiotics from a macroscopic aspect. Our main objective is to indicate the least cost that the government has to pay for the use of antibiotic in farming animals.

2.1. **Perfectly competitive market.** Firstly, we mention the economic background of perfectly competitive market. It shares the following features throughout the whole text.

(1) There are sufficiently many buyers and sellers in this market.
(2) Perfect information. The information is completely open and it transfers instantly.
(3) Homogeneous products. No differences on external appearance and qualitative properties for the same type of merchandize.
(4) Everyone accepts the price instead of deciding it.
(5) There is no market barrier.
(6) Equilibrium state. Supply equals demand on the market.

Next, we set a dependent variable y to represent the government's total input which consists of two parts, the incentive funds and the environmental damage caused by using antibiotic. The argument x represents the amount of government incentives, and it affects the total input of the government. We next list another four parameters and set the values for numerical illustration.

- c_1 represents environmental damage caused by use of antibiotics. The damage is measured by a certain amount of currency.
- c_2 represents farmers' loss without using antibiotics. The loss is measured by output and price in contrast to normal use of antibiotics.
- α represents farmers' sensitivity to the incentive policy on nonuse of antibiotics. It reflects farmers' acceptance level to the bonus.
- β represents the environmental damages caused by different sorts of antibiotics. It reflects environmental sensitivity to antibiotics.

2.2. **Construction of incentive function.** We are now at the stage to construct an incentive function. In order to characterize the environmental damage caused by antibiotics, we notice that the function

$$f_1(x) = \frac{1}{2} + \frac{1}{\pi} \arctan\left(\frac{x - c_2}{\alpha}\right)$$

represents the scale of farmers still using antibiotics even under the incentive policy of government, and hence the function

$$f_2(x) = c_1 f_1^{\beta}(x)$$

indicates government's input to fix the environmental damage caused by use of antibiotic on farms.

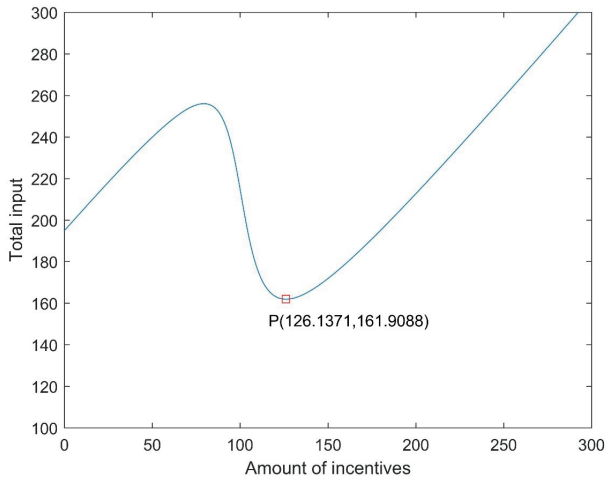

FIGURE 1. Curve of incentive function for $c_1 = 200$, $c_2 = 100$, $\alpha = 10$, $\beta = 0.8$

We account that the establishment of incentive funds is determined by the effectiveness of policy. The revenue of this policy is determined by the cost of the incentive policy, as well as the environmental damage caused by antibiotics. Finally, we yield an incentive function

$$y = x + c_1 \left[\frac{1}{2} + \frac{1}{\pi} \arctan \left(\frac{x - c_2}{\alpha} \right) \right]^{\beta}$$

and plot its curve by setting

$$c_1 = 200, \qquad c_2 = 100, \qquad \alpha = 10, \qquad \beta = 0.8$$

as in Figure 1.

From Figure 1, it is apparent that the government could reach the minimum total input 161.9088 units as the incentive amount takes 126.1371 units.

3. Demand and supply of antibiotics

In this section, we set up a demand and supply (DS) model to reflect the interest chain of antibiotics. The parameters in the model are about to be fixed for regulative purpose.

3.1. **A deterministic DS model driven by pricing.** The suppliers are pharmaceutical companies, while the consumers mainly include hospital (patients) and animal husbandry (farmers). In particular, patients are classified by those who must use antibiotics (PA) and those have alternative medicine (PAM) as illustrated in Figure 2. In hospital, antibiotics are used to prevent or cure bacterial infections, and on farm the forage with antibiotics could help animals grow fast and strong. In the perfectly competitive market, we suppose that the minimum demand of antibiotic equals to its minimum supply.

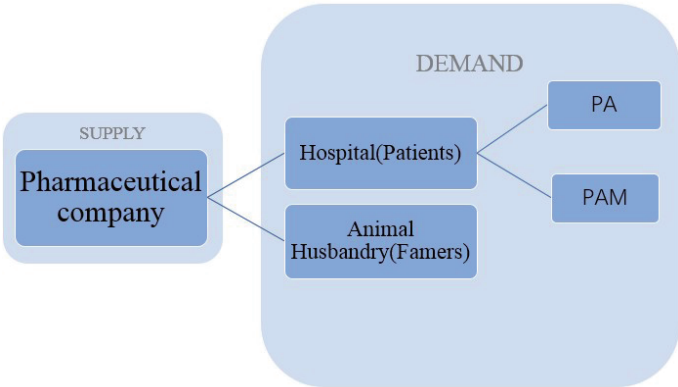

FIGURE 2. The interest chain of antibiotics.

TABLE 1. Notations for demand and supply model of antibiotics

Symbol	Definition
$P(t)$	Price of antibiotics at time t
P_0	Initial price of antibiotics
$S(t)$	Supply of antibiotics at time t
S_m	The maximum supply of antibiotics
γ	The decreasing rate of supply as the price falls
$D(t)$	Demand of antibiotics at time t
D_0	The minimum demand of antibiotics
η	The increasing rate of demand as the price falls
ε	The price factor of antibiotics associated to demand and supply

We introduce some necessary notations in Table 1.

It is well known that the demand increases while the supply decreases as the price falls in the merchandize trade. Of a great amount of literature, one assumes that the demand and supply functions are linearly dependent on price. Readers may consult [2] and [15] as well as the references therein. Therefore, we respectively take demand function $D(t) = D_0 + \eta P(t)$ and supply function $S(t) = S_m - \gamma P(t)$ in the following initial problem for the first-order ODE model complying with fundamental economic principle [12]

$$\begin{cases} \dfrac{dP}{dt} = \varepsilon[S(t) - D(t)] \\ P(0) = P_0 \end{cases}.$$

The solution of the above initial value problem reads as

$$P(t) = \left(P_0 - \frac{S_m - D_0}{\gamma + \eta}\right) e^{-\varepsilon(\gamma+\eta)t} + \frac{S_m - D_0}{\gamma + \eta}.$$

TABLE 2. The Values of parameters in DS model

Parameter	Value 1	Value 2	Value 3	Value 4	Value 5
P_0 (CNY)	3	3	3	3	3
S_m (unit)	146.41	141.41	141.41	141.41	141.41
D_0 (unit)	92.50	92.50	92.50	92.50	92.50
γ	1	2	1	1	2
η	2	2	4	2	4
ε	0.05	0.05	0.05	0.1	0.1
Color	Blue	Green	Black	Red	Yellow

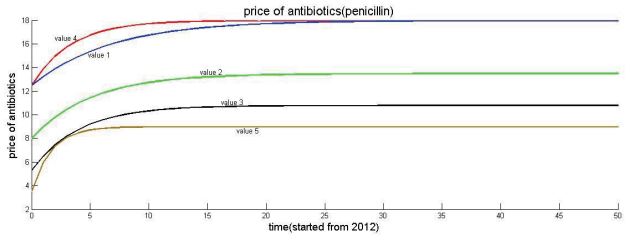

FIGURE 3. Curves for the price function of antibiotics with different values of parameters.

3.2. **Sensitivity of parameters.** Taking penicillin as an example, we set its unit as 1.6 million. The initial price of penicillin is assumed to be 3.00 CNY. We regard the production and the forecast production in 2012 as the basic demand and the maximum supply in 2019 respectively. Table 2 lists the values we take for the other parameters.

The curves of the solutions with parameters to the demand-supply model are illustrated in Figure 3.

We now compare the price functions of antibiotics with different values of parameters illustrated in Figure 3. For curve 1, we set $\gamma = 1$, $\eta = 2$ and $\varepsilon = 0.05$. Then we increase γ to 2 and remain the values of other parameters on curve 2, the ascending trend is more flat than that of curve 1 and the value of price is lower. Next on curve 3, η increases to 4, and the variation tendency of price is similar to curve 2 with lower value. On subsequent curve 4, ε increases to 1, and the variation tendency of price remains similar to curve 2 but the price value reaches the highest. For last curve 5 with parameters taking $\gamma = 2$, $\eta = 4$ and $\varepsilon = 0.1$, the ascending trend is the steepest but the price value of antibiotic is the lowest.

4. EVOLUTION OF ANTIBIOTIC BACTERIA

A deep knowledge of the physiological process of resistant bacteria helps one effectively control antibiotic resistance. We set up a combined nonlinear system based on the pathological mechanism of antibiotic resistance in this section.

TABLE 3. Parameters in reproduction-transmission system

Parameter	Definition
X	Total volume of metabolism
K	Total carrying capacity
K_1	Carrying capacity of sensitive bacteria
K_2	Carrying capacity of resistant bacteria
A_m	Saturation rate of isoniazid (INH)
ν	Reproduction rate of sensitive bacteria
f	Mutation index of sensitive bacteria
ν_1	Reproduction rate of resistant bacteria
q_n	Natural mutation rate
$\bar{\lambda}$	The transfer rate of resistant plasmids among bacteria
γ	Sensitive and resistant bacteria are eliminated by host immune system at per capita rate.
μ_s	Natural mortality of sensitive bacteria
μ_r	Natural mortality of resistant bacteria
l	The ratio of the concentration of resistant bacteria and antibiotics

The clinical evidence shows that key factors arise from the accumulation of resistance determinants (RD) in a same bacterial strain. Most bacterial resistance comes essentially either from genetic mutation or resistant plasmid. A long-term propagation of extra-chromosomal molecules leads to antibiotic resistance, where infectious agents received by plasmid make the treatments increasingly tough [6]. Loosely speaking, bacterial infection is a complex process as the most important part is related to the response of the immune system [11].

4.1. **A reproduction-transmission system of antibiotic bacteria.** Super bug is supposed to have drug-resistance by nature and it can produce resistance plasmid, with response of the immune system and acquisition of resistance in different ways fully accounted. Enlightened by the interacting process of antibiotic bacteria [8], we focus on the concentration of bactericidal antibiotics which leads to an essentially different system. The frequently used notations are listed in Table 3.

We consider that an infected patient is medicated with bactericidal antibiotics. $S(t)$ represents the sensitive bacteria and $R(t)$ denotes the resistant bacteria at time t . Sensitive bacteria have a reproduction rate ν , and their carrying capacity K_1 means the maximum amount of sensitive bacteria for an infected individual to support. An intrinsic biological cost in mutating resistance to antibiotics reflects on f by the decrease of reproductive ability or competitive ability of bacteria [1]. Assuming resistant strains are proportionate to sensitive ones, we yield the reproduction rate of resistant bacteria $\nu_1 = f\nu$ with f confined to the interval $(0, 1)$. The total volume of metabolism, total carrying capacity and carrying capacity of resistant bacteria are given by X, K and K_2 respectively.

During treatment, antibiotic resistance mutates from permeability barriers at a rate q_n [21], with sensitive bacteria eliminated by bactericidal antibiotic at a rate $\bar{\alpha}$ and resistant bacteria multiplying by mutation at a rate q. Meanwhile, bacterial conjugation of resistant plasmid transfers at a rate $\bar{\lambda}$, and host immune system eliminates sensitive and resistant bacteria at per capita rate γ. Natural mortality of sensitive and resistant bacteria are respectively given by μ_s and μ_r, with $\mu_s \leqslant \mu_r$. Let $A(t)$ be the concentration of medicament with respect to time t, while A_m denotes the saturation of medicament and represents the ratio of the concentration of resistant bacteria and antibiotic.

In order to record the concentration of sensitive and drug-resistant bacteria, we assume the model is in the perfectly competitive market. The government will not interfere the decisions made by markets as long as there is profit to seek, and pharmaceutical companies will keep manufacturing antibiotics. In a word, there is no limits to the use of antibiotics except for the medical aspect. Under the assumptions mentioned above, we obtain the following fully nonlinear dynamical system

$$\begin{cases} \dfrac{dS}{dt} = \nu S\left(1-\dfrac{S}{K_1}\right) - \nu q_n S - (\bar{q}+\bar{\alpha})\,AS - \bar{\lambda}SR - (\gamma+\mu_s)S \\ \dfrac{dR}{dt} = \nu_1 R\left(1-\dfrac{R}{K_2}\right) + \nu q_n S + \bar{q}AS + \bar{\lambda}SR - (\gamma+\mu_r)R \\ \dfrac{dA}{dt} = l\left(\dfrac{S}{K_1}+\dfrac{R}{K_2}-\dfrac{X}{K}\right)(A_m - A) \end{cases} . \tag{4.1}$$

Clinical statistics shows that K_1 and K_2 approximately equal to K for most individual, and hence we assume $K_1 = K_2 = K$. Taking a change of variables

$$s = \frac{S}{K}, \quad r = \frac{R}{K}, \quad x = \frac{X}{K}, \quad a = \frac{A}{A_m},$$

one reduces the system (4.1) to

$$\begin{cases} \dfrac{ds}{dt} = \nu s(1-s) - \nu q_n s - (q+\alpha)as - \lambda sr - (\gamma+\mu_s)s \\ \dfrac{dr}{dt} = \nu_1 r(1-r) + \nu q_n s + qas + \lambda sr - (\gamma+\mu_r)r \\ \dfrac{da}{dt} = l(s+r-x)(1-a) \end{cases} , \tag{4.2}$$

where $q = \bar{q}A_m$, $\alpha = \bar{\alpha}A_m$, $\lambda = \bar{\lambda}K$. The system (4.2) behaves regularly in the biological region $0 \leqslant s \leqslant 1$, $0 \leqslant r \leqslant 1$, $0 \leqslant a \leqslant 1$.

4.2. **Simulative evolution of sensitive and resistant bacteria.** In this subsection, we carry out numerical simulations to the fully nonlinear evolution system of sensitive and resistant bacteria. As a compared result to the partially nonlinear system in [8], we refer to take Mycobacterium tuberculosis (MTB) as our simulation object and assign the same values to the parameters in reproduction-transmission system (4.1).

TABLE 4. Simulation of reproduction-transmission system

Parameter	Value
K	10^9 bact.
K_1	10^9 bact.
K_2	10^9 bact.
ν	0.4/day
$\bar{\alpha}$	0.0039/day
q_n	$10^{-21} - 10^{-22}$
$\bar{\lambda}$	9×10^{-11}/bact. day
γ	$0 - 0.8$/day
μ_s	0.012/day
A_m	300mg/kg

To a large extent, Tuberculosis (TB) is caused by MTB. Unfortunately in many countries, TB is still a long standing issue in public health, and effective strategies are taken priority to stop it [22]. Most TB treatments nowadays are highly hazardous to patients [18], and the dosage usually continues for more than six months. The initial purpose of these treatments is to deracinate MTB, however inappropriate therapy has resulted in increasingly resistant to the available drugs [13]. There is a common sense that drug resistance in MTB is due to primary mutations of chromosomal [19].

In the following, we simulate therapies of bactericidal antibiotic against MTB, and the values of parameters are listed in Table 4.

When it comes to the other parameters, we assume the medicine mutations rate $q = 0.07$, the removal rate of MTB by immune system $\gamma = 0.15$, the death rate of MTB resistant $\mu_r = 0.024$, the ratio of concentration of bacteria and medicine $l = 0.05$ and the inherent biological cost $f = 0.5$, thus $\nu_1 = f\nu = 0.2$.

To simulate the development trend towards sensitive and resistant bacteria, we set the initial values as $s_0 = 0.01$, $r_0 = 0.005$ and $a_0 = 0.24$ respectively.

In Figure 4, we find that the density of the sensitive bacteria declines quickly in the first 20 days, and on the 35th day, the density remains only 10% of the initial value. On the contrary, the density of the resistant bacteria ascends rapidly in Figure 5 and it even hits 10 times of the initial value on the 91th day. Similarly, the density of antibiotics also climbs fast. We conclude that the quantity of sensitive bacteria declines evidently with the treatment of antibiotics, but the resistant bacteria also aggravate drastically.

4.3. **Sensitivity of the parameters.** For the evolution model of sensitive and resistant bacteria, one could adjust the values of two parameters, the mutation rate q and the removal rate α. The differences are shown in the following figures.

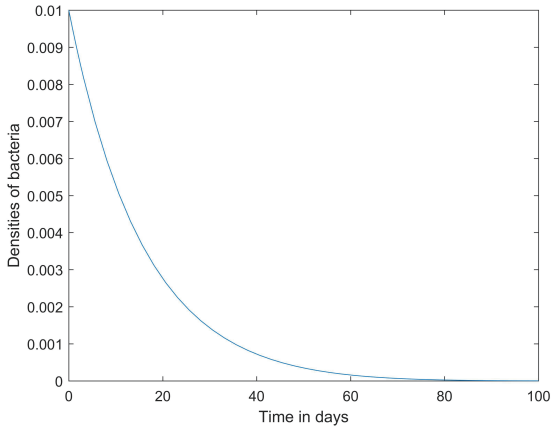

FIGURE 4. Evolution curve of sensitive bacteria

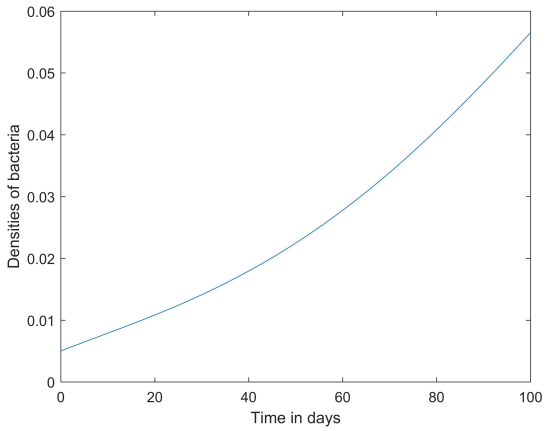

FIGURE 5. Evolution curve of resistant bacteria

Comparing Figure 8 with Figure 10, we find that the curve in Figure 10 grows slower than that in Figure 8 as q decreases. Comparing Figure 7 with Figure 11, we find that the curve in Figure 11 grows slower than that in Figure 7 as α increases. The curves in Figure 12 and Figure 8 show the similar differences as the Figure 8 and Figure 10. We conclude that the decrease of the mutation rate q reduces the growth of resistant bacteria, while the increase of the removal rate α reduces the both growth of sensitive bacteria and resistant bacteria.

5. CONCLUSIONS

The incentive function is used to evaluate the validity of the management and control from the government. We lay particular emphasis on antibiotic damage to environment, and one variable function is surely intuitional and simple for the holistic estimation of it. Generally, a multi-factor and multi-effect incentive function

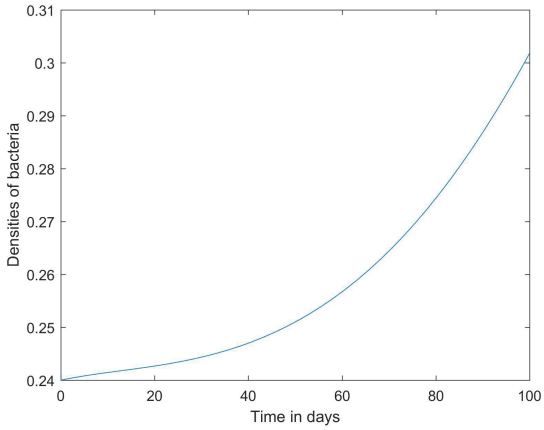

FIGURE 6. Evolution curve of the density of bactericidal antibiotics

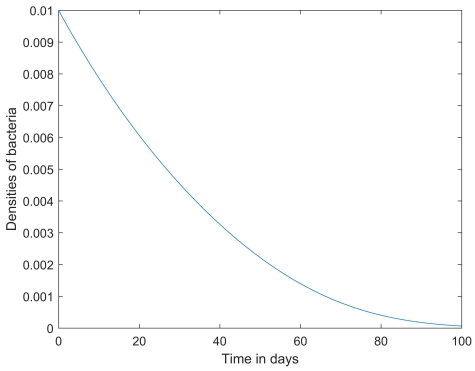

FIGURE 7. The densities of sensitive bacteria with parameters $q = 0.07$ and $\alpha = 1.0$

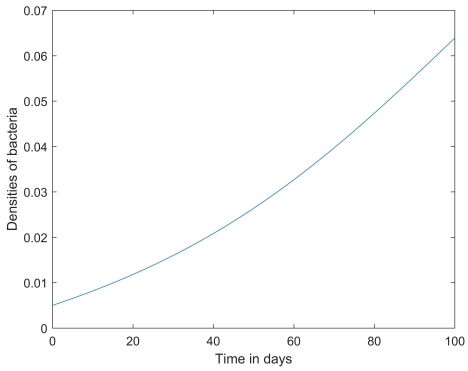

FIGURE 8. The densities of resistant bacteria with parameters $q = 0.07$ and $\alpha = 1.0$

has a potential to enhance applicability and wide serviceability. The demand-supply model is extensively adaptable to commodity transaction in perfectly competitive market. The demand-supply function does not necessarily depend linearly on price. Moreover the price, demand and supply could be functions of time t and interact with each other. In evolutionary model, distinct sorts of antibiotic bacteria interact with each other and it makes the dynamical system fully nonlinear. Our numerical simulations show the controllability of observational parameters for the mutation rate and the removal rate. A qualitative analysis of the system is about to clarify the behavior of the equilibrium point of different types. We would pursue all such generalizations in subsequent research work.

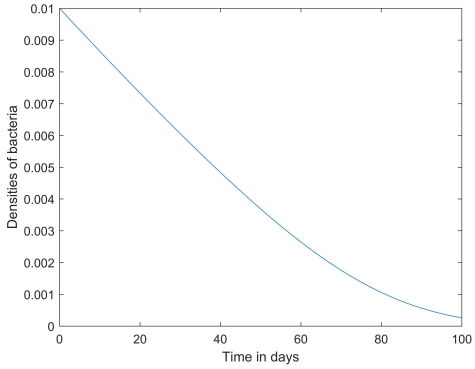

FIGURE 9. The densities of sensitive bacteria with parameters $q = 0.03$ and $\alpha = 1.0$

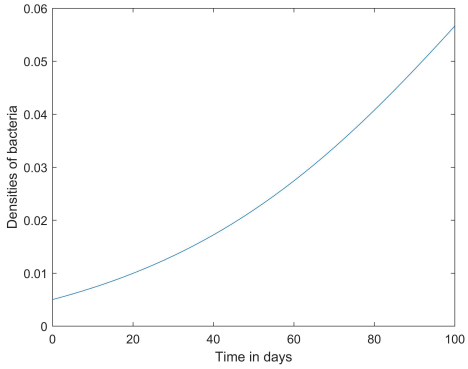

FIGURE 10. The densities of resistant bacteria with parameters $q = 0.03$ and $\alpha = 1.0$

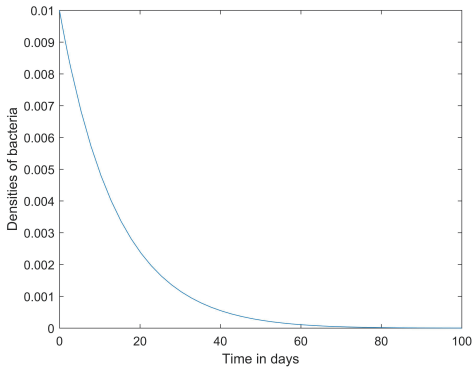

FIGURE 11. The densities of sensitive bacteria with parameters $q = 0.07$ and $\alpha = 1.2$

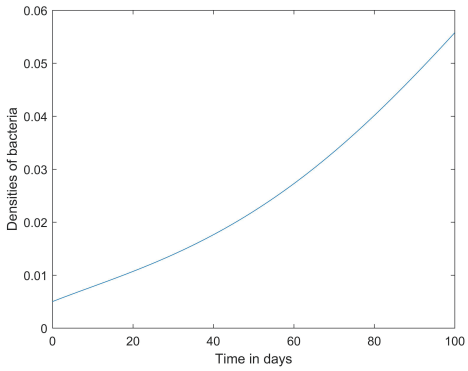

FIGURE 12. The densities of resistant bacteria with parameters $q = 0.07$ and $\alpha = 1.2$

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