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A Mathematical Model For Population Dynamics of Antibiotic Treatment

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A MATHEMATICAL MODEL FOR POPULATION DYNAMICS OF ANTIBIOTIC TREATMENT

by

SIYU TIAN

Under the Direction of Yi Jiang, PhD

ABSTRACT

The objective of the thesis is to model the behavior of the reaction between two species of bacteria and antibiotics by building an ordinary differential equation (ODE) system under a list of assumptions. With the ODE, we analyze equilibrium points and the stability of these equilibrium points to forecast the trend of each species of bacteria and antibiotics. We test the validity of the model assumptions. Based on these outcomes, we show that: 1. Both equilibrium points and eigenvalues differ in orders of magnitude. 2. Some figures which were generated using different initial values do not make any sense. 3. There were abnormal values of the variables sensitivity.

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INDEX WORDS: Ordinary Differential Equations, Population dynamics, Multiple species Bacteria, Antibiotics, Simulation, Equilibrium Points.

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1 INTRODUCTION

1.1 Explanation of data and experiment

The data used for this analysis came from Dr. Eric Gilbert's lab of the Biology department at Georgia State University. In this experiment, two bacterial population of E.coli were prepared. One is referred to as the "Amp^r" strain (bacteria-A) which is sensitive to spectinomycin (antibiotic-A) and resistant to ampicillin (antibiotic-B). Another is referred to as the "Spt^r" (bacteria-B) and it is sensitive to ampicillin and resistant to spectinomycin. "*For chemostat experiments, inocula of the* Amp^r *or* Spt^r *strain were grown overnight in a shaking incubator at 37°C and 200 rpm in LB broth containing either 400 ppm ampicillin or 100 ppm spectinomycin, respectively*."[4]

A 250-mL well-sealed sidearm flasks which contained a Pharmed tube for the intake of air was used for chemostat experiments. A 2L Pyrex bottles which contained recourse and antibiotics incubated in a 37°C water bath and pumped into the chemostat. The chemostat was maintained the temperature within $37^\circ C \pm 0.5^\circ C$. A magnetic was used to keep contents well mixed and a Bunsen burner was used to maintain aseptic conditions. A sample was collected to measure, centrifuged, resuspended and stored under certain condition at each time point. Meanwhile, the ampicillin flow was maintained at $4.5 ml \cdot \min^{-1}$, and the spectinomycin flow was maintained at $3.8 ml \cdot \min^{-1}$.

In Dr.Gilbert's paper, he made a conclusion that:" *In well-mixed planktonic cultures, cells that cannot coaggregate move past one another and do not establish interactions that have a spatial component.*" [4]

1.2 Model background

1.2.1 Population Dynamics Model

In wildlife management, people use population dynamics model as a tool to keep track of four factors of population dynamics. The four factors are birth(B), death(D), immigration(I) and emigration(E). So the population dynamics model can be noted as:

$$N_1 = N_0 + B - D + I - E$$

Where N_0 is the number of population at time 0.

1.2.2 Bacterial Growth Model

To describe the bacterial growth, a simplest model could be used is:

$$\frac{dN}{dt} = rN \ ,$$

N is the bacterial density, r is the growth rate. If r > 0 , we can get $N(t) = N_0 e^{rt}$ with initial condition $N(0) = N_0$. This model is under the assumption of infinite resources for bacteria to grow.

1.2.3 Lotka-Volterra Model

Our model is based on the Lotka-Volterra equations, which is also known as the predator-prey equations. Lotka-Volterra equations are first-order, non-linear and ODE equations. This model was built by Alfred J. Lotka in 1910. It is always used to simulate the dynamical systems for biology, especially for the interaction between two species, one for fox and another one for rabbit.

The populations of two species change over time to two equations:

$$\frac{dx}{dt} = x(\alpha - \beta y)$$

$$\frac{dy}{dt} = -y(\gamma - \delta x)$$

Where,

x is the size of population of the rabbits;

y is the size of population of the foxes;

t represents the time;

α , β , $\delta$and γ are the parameters describing the relationship between two species.

In order to use this system of equations, we have certain assumptions on the environment and the change of the rabbits and foxes population are under certain assumptions:

1. There are sufficient foods available for the rabbits all the time.
2. The size of population of foxes only depends on the population of rabbits.
3. The growth rate of population is proportional to its size.
4. There is no limit for foxes' appetite.

1.3 Purpose of the Study

This report provides a differential equations model to simulate and understand the dynamics of commensal or mutualistic bacterial interaction in the presence of antibiotics.

This text aims to answer question like “If I change the density of bacteria at time 0, how will it behave?”, “How sensitive are the parameters to the whole system?” “If my model is wrong, how could I change it?”, and some more.

2 MATERIALS AND METHODS

2.1 Model Explanation

2.1.1 The Original Model

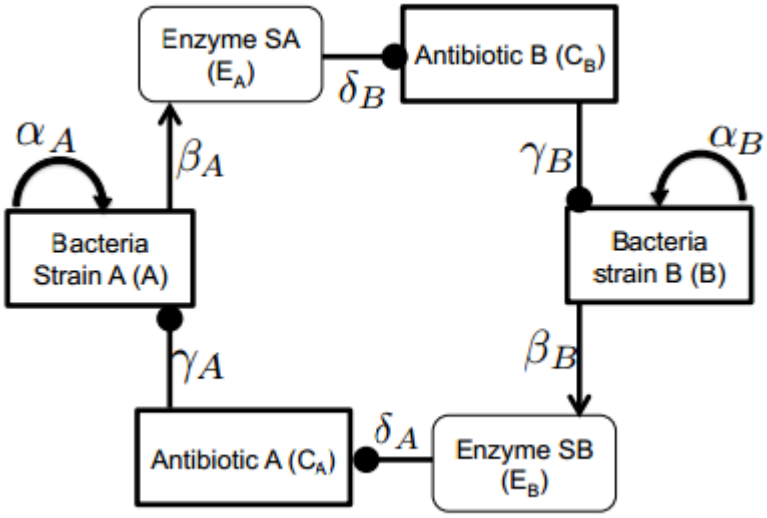


Figure 1 The original model

Two strains of bacteria, bacteria-A (A) and bacteria-B (B), are growing in the same dish at the rates of α_A and α_B respectively. In the meantime, two types of antibiotics, Antibiotic-A (C_A) and Antibiotic-B(C_B), are added into the dish. Antibiotic-A kills Bacteria-A at the rate of γ_A, and Antibiotic-B kills Bacteria-B at the rate of γ_B. Antibiotics A and B are provided at a constant rate, with ω_A for Antibiotic-A and ω_B for Antibiotic-B. Furthermore, Bacteria-A secretes at rate β_A Enzyme SA (E_A) , which degrades Antibiotic-B at rate δ_B. Similarly, Bacteria-B secretes at rate β_B Enzyme SB (E_B) , which degrades Antibiotic-A at rate δ_A.

We assume that the reaction is a first-order reaction, which means that the rate only depends on one reactant concentration. The differential equation describing first order kinetics is: Rate = d[A]/dt=k[A]. So the chemical reaction between bacteria and antibiotic is: A + $C_A \rightarrow$ 0, B + $C_B \rightarrow$0, E_A + $C_B \rightarrow$0 and E_B+$C_A \rightarrow$0.

2.1.2 The Simplify Model

For the original model, we assumed that antibiotics disappear when they kill bacteria, and in the degradation process, antibiotics disappear as well. So we can effectively skip the enzymes to reduce 2 parameters.

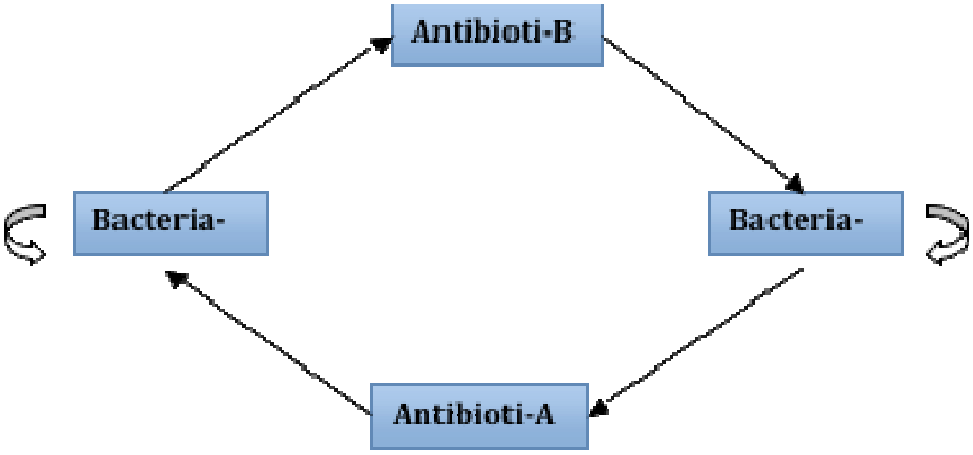


Figure 2 The diagram of the simplified model

2.2 Establishment of equations

2.2.1 Setting up the equations for the population of bacteria

According to the model, the population of bacteria is determined by the reproduction of itself and the killing effect of Antibiotic. So the equations for bacteria-A and bacteria-B are as follows:

— (1)

— (2)

2.2.2 Setting up the equations for the population of antibiotic

In the same model we have mentioned, the population of antibiotic has three components, such as the constant inflow rate, the consumption of killing correlative

bacteria and inhibition by another bacteria. So the equations for antibiotic-A and antibiotic-B can be set up as the following:

$$\frac{dC_B}{dt} = \omega_B - \gamma_B \cdot B \cdot C_B - K_B \cdot C_B \cdot A \qquad (3)$$

$$\frac{dC_A}{dt} = \omega_A - \gamma_A \cdot A \cdot C_A - K_A \cdot C_A \cdot B \qquad (4)$$

2.3 Standardized the units in the System

2.3.1 *Standard units of measurement*

The unit of time is 1 minute (min). The unit of mass is 1 gram (g). The unit of capacity is milliliter (ml).

2.3.2 Standard units of parameters

To develop the model, the first step is to equalize and define meaningful units for both sides of each equation. The units of each parameter are as follows:

[A]=[B]= #/mL

$[C_A\ ]$=$[C_B]$= #/mL

$\left[\frac{dA}{dt}\right] = \left[\frac{dB}{dt}\right]$ = #/(mL min)

$[\omega_A]$=$[\omega_B]$=#/(mL min)

$[\alpha_A]$=$[\alpha_B]$= 1/min

$[\gamma_A]$=$[\gamma_B]$= mL/(# min)

Table 1 Variables and parameters' definition and unit

Variables or parameters	Definition	units
Variables		
A	The population of bacteria-A	#/mL
C_A	The population of antibiotic-A	#/mL
B	The population of bacteria-B	#/mL
C_B	The population of antibiotic-B	#/mL
Parameters		
α_A	The growth rate of bacteria-A	min^{-1}
α_B	The growth rate of bacteria-B	min^{-1}
γ_A	The killing rate of antibiotic-A	mL/(#*min)
γ_B	The killing rate of antibiotic-B	mL/(#*min)
ω_A	The flow-in rate of antibiotic-A	#/(mL*min)
ω_B	The flow-in rate of antibiotic-B	#/(mL*min)
K_A	The inhibition of bacteria-A	mL/(#*min)
K_B	The inhibition of bacteria-B	mL/(#*min)

2.4 Convert the experimental data and Calculate the unknown Parameters

The conversion of unit becomes necessary due to the difference between the units of experimental data and the units we set in the above equations. As the equilibrium point

is the value of dx/dt if dx/dt=0 for all t, we can then calculate the rest of the unknown parameters.

Table 2 Variables and parameters' value

Variables or parameters	Values
Variables	
A	2×10^{7}
C_A	0.27576×10^{20}
B	2×10^{8}
C_B	0.543596×10^{20}
Parameters	
α_A	0.028333
α_B	0.0216667
γ_A	0.102746×10^{-20}
γ_B	3.9858×10^{-22}
ω_A	4.3088×10^{17}
ω_B	7.1725×10^{17}
K_A	6.5972×10^{-10}
K_B	7.8125×10^{-11}

2.5 Rescale and Nondimensionalize the System's Equation

Substantial differences between each variable and parameter's order of magnitude are represented by the data shown in Table 2. To reduce the number of variables and analyze the behavior of the system we simplified the system by rescaling and nondimensionalizing it.

The calculation process is as follows:

Write the differential equation system in terms of the new variables:

$$A = A^* \cdot a$$

$$C_A = C_A^* \cdot C_a$$

$$B = B^* \cdot b$$

$$C_B = C_B^* \cdot C_b$$

Apply the chain rule, to get:

$$\frac{da}{dt} = \alpha_A \cdot a - \gamma_A \cdot a \cdot C_A^* \cdot C_a \quad (5)$$

$$\frac{dC_a}{dt} = \frac{\omega_A}{C_A^*} - \gamma_A \cdot a \cdot A^* \cdot C_a - K_B \cdot B^* \cdot C_a \cdot b \quad (6)$$

$$\frac{db}{dt} = \alpha_B \cdot b - \gamma_B \cdot b \cdot C_B^* \cdot C_b \quad (7)$$

$$\frac{dC_b}{dt} = \frac{\omega_B}{C_B^*} - \gamma_B \cdot b \cdot B^* \cdot C_b - K_A \cdot A^* \cdot C_b \cdot a \quad (8)$$

Table 3 Parameters' value after Nondimensionalize

Parameters	Values
α_A^*	0.028333
α_B^*	0.0216667
γ_A^*	0.0283
γ_B^*	0.0217
ω_A^*	0.0156
ω_B^*	0.0132
K_A^*	0.0156
K_B^*	0.0132

3 RESULTS

3.1 Stability of the Solution

3.1.1 equilibrium points for the nondimensionalized equations system

Set equations (5)-(8) equals to 0,

$$\alpha_A \cdot a - \gamma_A \cdot a \cdot C_A^* \cdot C_a = 0$$

$$\frac{\omega_A}{C_A^*} - \gamma_A \cdot a \cdot A^* \cdot C_a - K_B \cdot B^* \cdot C_a \cdot b = 0$$

$$\alpha_B \cdot b - \gamma_B \cdot b \cdot C_B^* \cdot C_b = 0$$

$$\frac{\omega_B}{C_B^*} - \gamma_B \cdot b \cdot B^* \cdot C_b - K_A \cdot A^* \cdot C_b \cdot a = 0$$

There are three solutions:

$$\left(a_1, C_{a_1}, b_1, C_{b_1}\right) = (7.6038 * 10^{11}, 1\ , 0\ , 1.13151 * 10^{-12})$$

$$\left(a_2, C_{a_2}, b_2, C_{b_2}\right) = (\ 0\ , 6.0416 * 10^{-12}\ , 1.6552 * 10^{11}\ , 1\ )$$

$$\left(a_3, C_{a_3}, b_3, C_{b_3}\right) = (1, 1\ , 1\ , 1)$$

3.1.2 solve the eigenvalues

Use Jacobian of the system to find the eigenvalue of each equilibrium point.

Table 4 The eigenvalues for each equilibrium points

equilibrium point	eigenvalues
$(a_1, C_{a_1}, b_1, C_{b_1})$ $(7.6038 * 10^{11}, 1, 0, 1.13151 * 10^{-12})$	(0.0217, -1.0033*10^10, 0.0146, -0.0303)
$(a_2, C_{a_2}, b_2, C_{b_2})$ $(0, 6.0416 * 10^{-12}, 1.6552 * 10^{11}, 1)$	(-2.5862*10^9, 0.0283, 0.0116, -0.0247)
$(a_3, C_{a_3}, b_3, C_{b_3})$ $(1, 1, 1, 1)$	(-0.0072-0.0174i, -0.0072 + 0.0174i, 0.0130, -0.0274)

As we can see, eigenvalues from the first and the second equilibrium points both have a quite small negative number on the order of 9 and 10.

Because we have nondimensionalized the system, the third equilibrium point is matter-of-course, we ignore this one for now.

3.2 Variables Sensitivity Analysis

As we know even the most accurate ode system still cannot predict or reproduce it its parameter values are not correct.

The goal of doing variables sensitivity analysis is to determine the parameter vector that decreases the difference between the data from experiment and the ODE system.

If a model is sensitive to a parameter's value, then no matter what value of that parameter is closely regulated, or uncertainties in the parameter will translate into unstable in the predicted system behavior.

The sensitivities at Steady-State can be calculated using a forward difference approximation:

$$S_{ij}(t) = \frac{y_i(p_j + \Delta p_j, t) - y_i(p_j, t)}{\Delta p_j},$$

where S is the sensitivity, y is the vector of variables, p is the parameter.

One percent of each parameter value was selected as the step size.

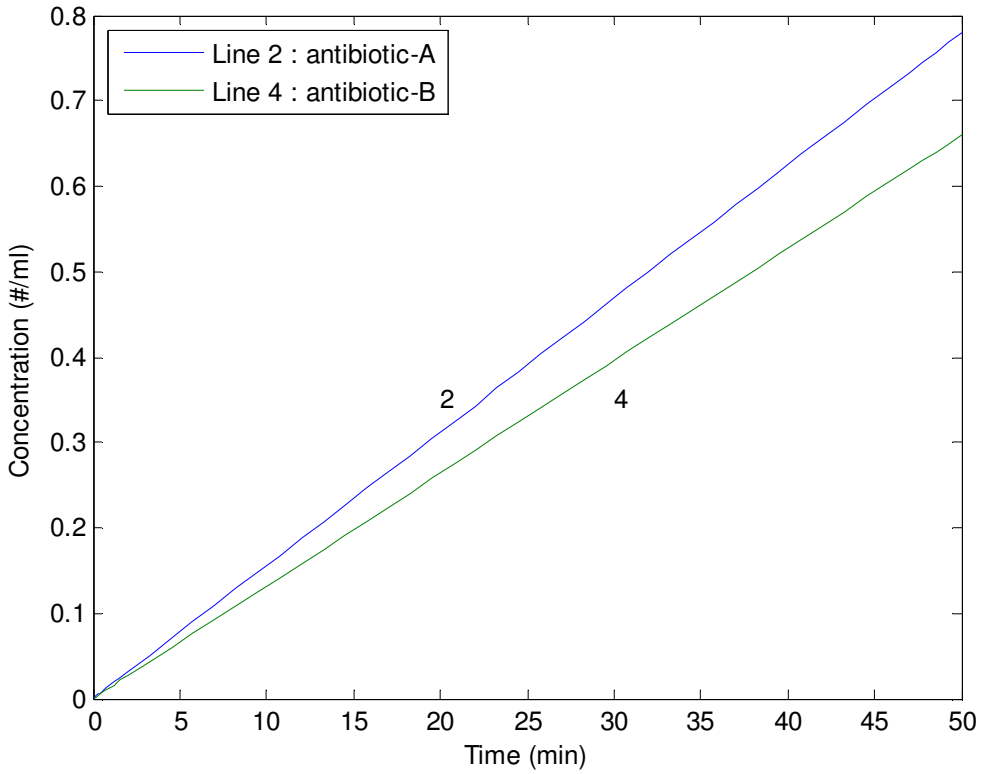
Table 5 Parameter sensitivity

	A	C_A	B	C_B
α_A	0	1	-1	0
α_B	-1	0	0	1
ω_A	0	0	1	0
ω_B	1	0	0	0
γ_A	0	-1	1	0
γ_B	1	0	0	-1
K_A	-1	0	0	0
K_B	0	0	-1	0

There three distinct values in the table, they are 1, 0, -1.

If the result is 0, which means the variable and the corresponding parameter independent. The positive result means the value of equilibrium point of the variable increased by enlarging the corresponding parameter. Similarly, the negative result shows value of equilibrium point of the variable decreased by enlarging the corresponding parameter. But only three distinct results in the table is abnormal and meaningless to analysis.

3.3 Plots for different initial conditions



Initial value: $A = 0, C_A = 0,\ B = 0, C_B = 0$

Figure 3 Absence of bacteria

The purpose of this simulation is to check the flow-in rate for both antibiotic-A and antibiotic-B. As we can see they increased linearly. After 50 minutes, antibiotic-A (Line-2) reached a value of 0.78 (number per ml), and antibiotic-B (Line-4) reached a value of 0.66 (number per ml).

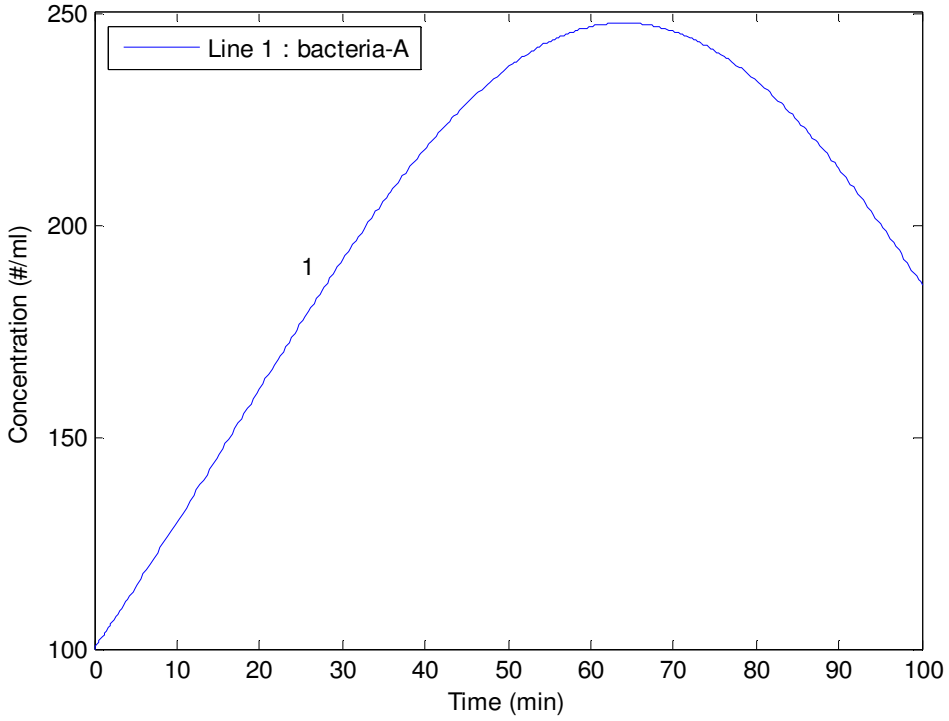
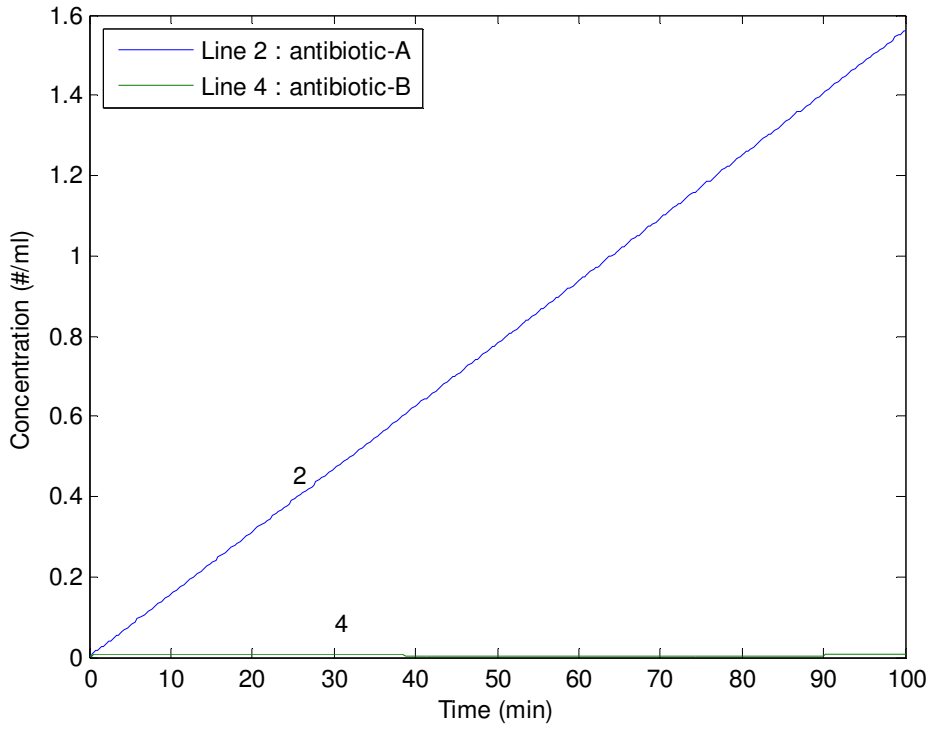


Figure 4 Concentration of bacteria-A with absence of bacteria-B



Initial value: $A = 100, C_A = 0, B = 0, C_B = 0$

Figure 5 Concentration of antibiotic with absence of bacteria-A

The concentration of bacteria-A (Line-1) reached a maximum around 247 (number per ml) at approximately 65 minutes. In the same instant the concentration of antibiotic-A (Line-2) reached 1(number per ml) and the concentration of antibiotic-B was very close to zero. This means that at 65 minutes, bacteria-A and antibiotic-A reached equilibrium. Antibiotic-A declined afterwards because antibiotic-B was provided continuously. But it is worthwhile to note that the concentration of antibiotic-A was mostly unaffected. We conjecture that the antibiotic has a high killing rate.

We got a similar result when we set the initial value of bacteria-B is equal 100, and rest set to 0.

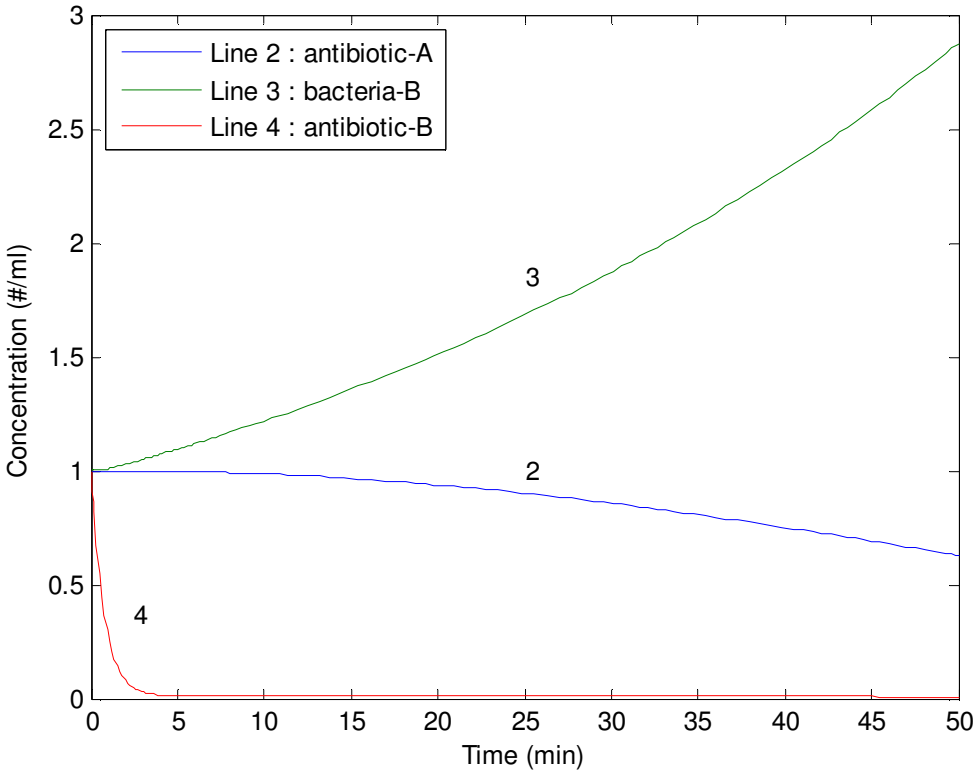
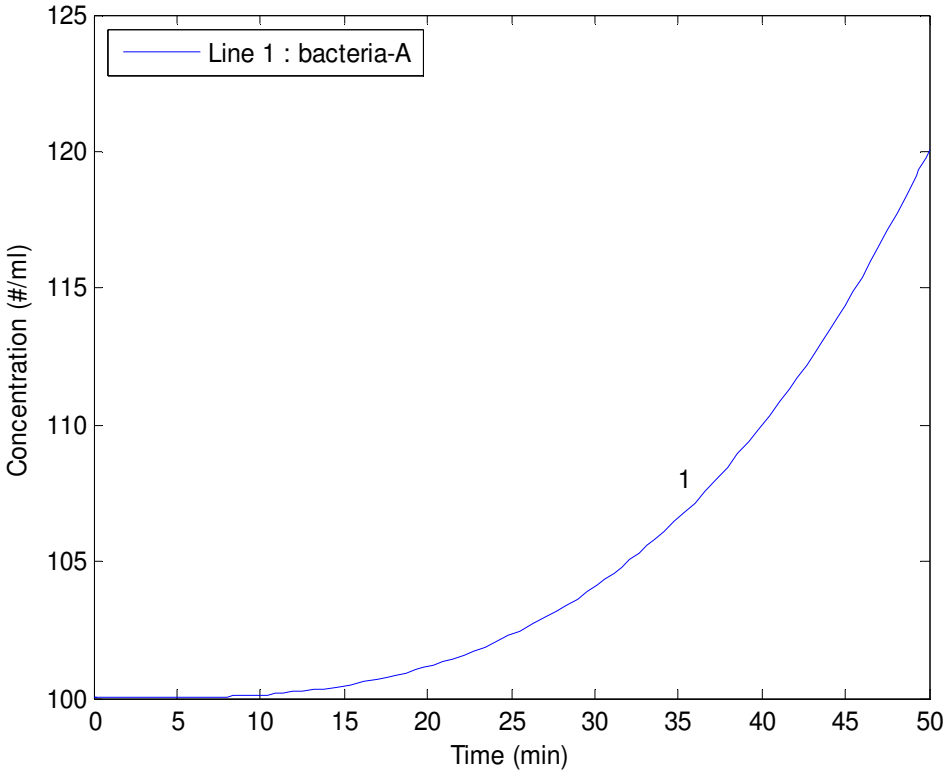


Figure 6 A large amount of bacteria-A



Initial value: $A = 100$, $C_A = 1$, $B = 1$, $C_B = 1$

Figure 7 Concentration of bacteria-A with a large initial value

With a large amount of bacteria-A, antibiotic-B (Line-4) was severely depressed and reduced to a low concentration in a very short time (4 minutes). The low concentration of antibiotic-B caused bacteria-B (Line-3) to grow linearly at first, but started growing exponentially around 35 minutes. The reason for the fall in the concentration of antibiotic-A (Line-2) was the same as for antibiotic-B, but the process was slower because the bacteria-B had a lower initial value. It is not difficult to understand why bacteria-A (Line-1) was growing rapidly from the beginning. This is similarly true for a large amount of bacteria-B.

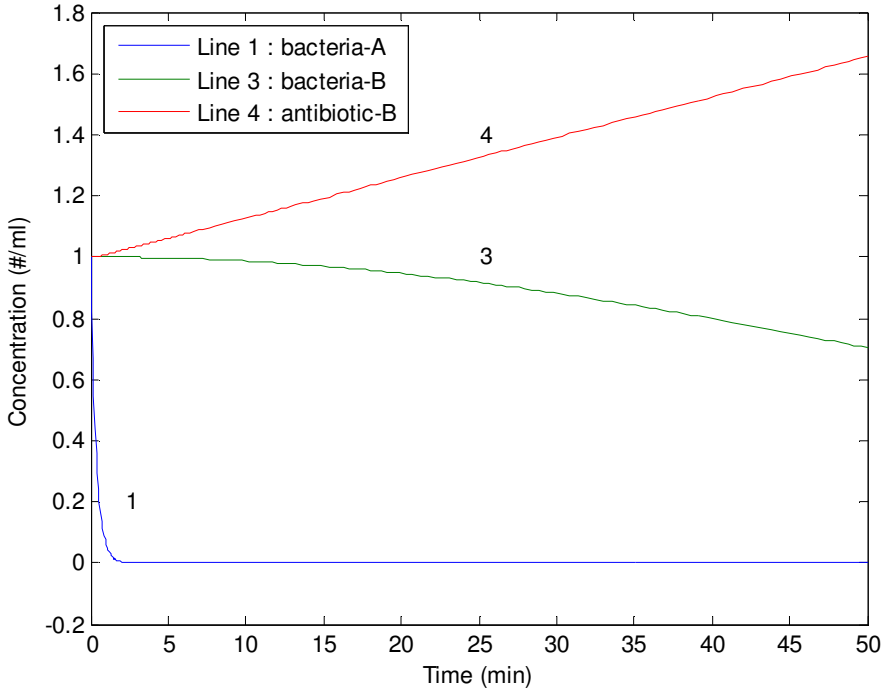
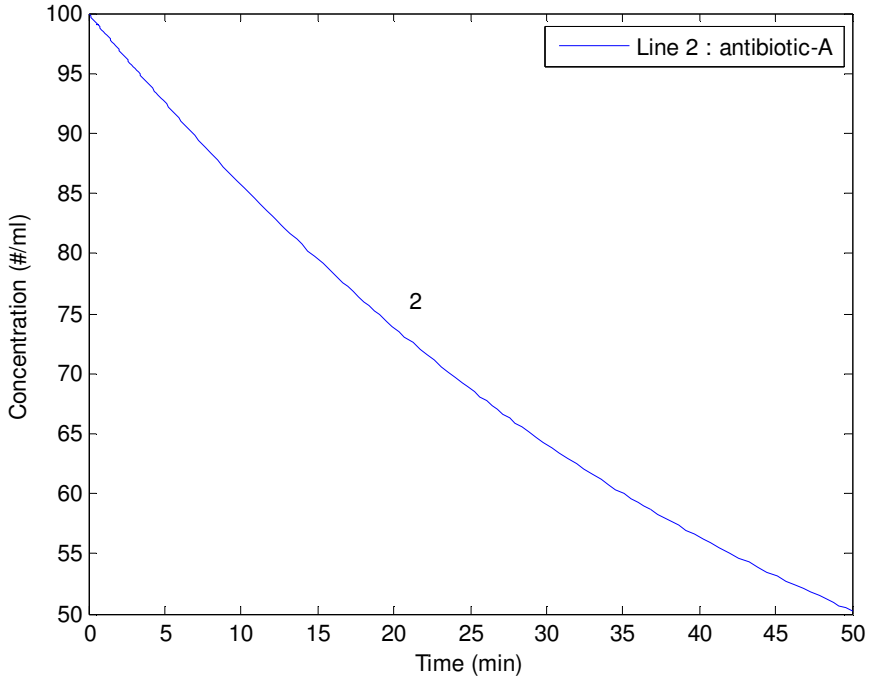


Figure 8 A large amount of antibiotic-A



Initial value: $A = 1, \quad C_A = 100, \quad B = 1, \quad C_B = 1$

Figure Error! Bookmark not defined. 9 **Concentration of antibiotic**

– A with a large inital value

As the initial value of antibiotic-A was assigned a very high number, the bacteria-A (Line-1) was killed within 2 minutes leading to an increase of antibiotic-B (Line-4). Then as the antibiotic-B kept soaring, the decrease of bacteria-B (Line-3) was an inevitable result.

But the trend of antibiotic-A (Line-2) was unexpected. The decrease of bacteria-A as bacteria-B was provided continuously was supposed to increase the concentration of antibiotic-A. This result runs counter to the forecast. So we infer that the inhibition of bacteria-B is much higher than the flow-in rate of antibiotic-B.

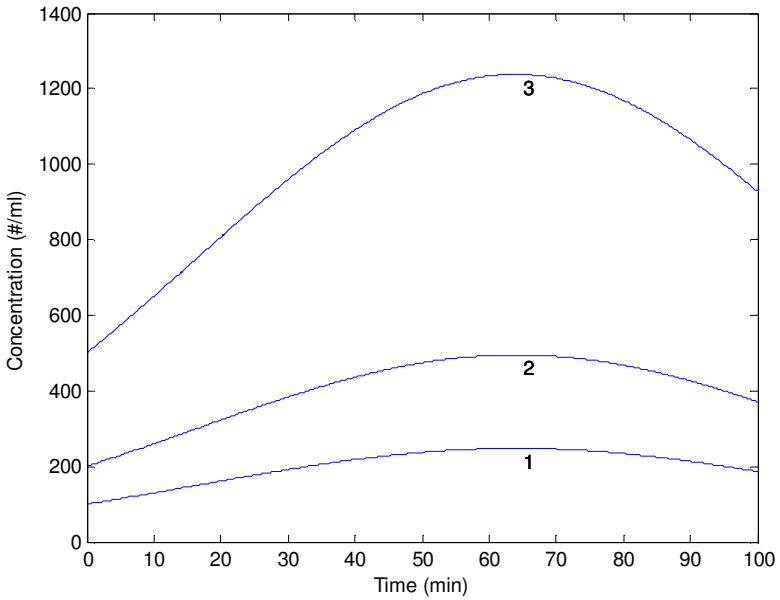


Figure 9 Concentration of bacteria-A with different initial value

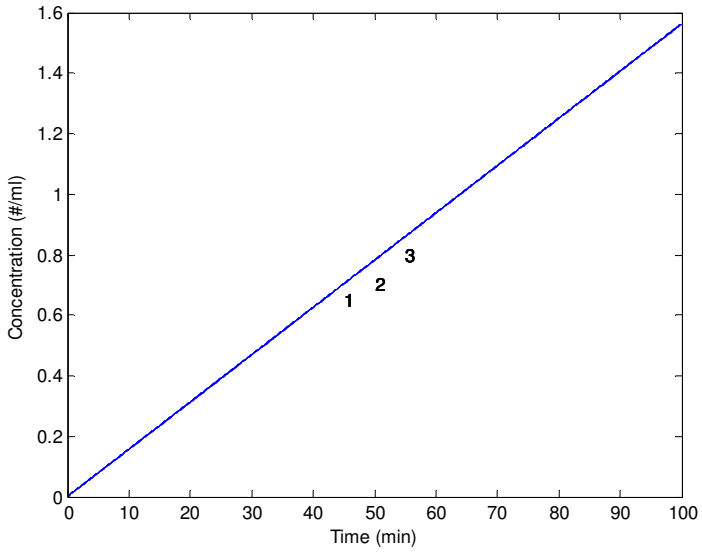


Figure 10 Concentration of antibiotic-A with different initial value to bacteria-A

FIG 7.1 and FIG 7.2 have the same initial values with bacteria-A = 100, 200, 500 and bacteria-B = antibiotic-A = antibiotic-B = 0;

FIG 7.1 is the plot of concentration of bacteria-A.

FIG 7.2 is the plot of concentration of antibiotic-A.

Bacteria-A = 100 (Line 1), bacteria-A = 200 (Line 2), bacteria-A = 500 (Line 3).

In this condition, as the concentration level of bacteria-A increases and eventually reaches equilibrium the concentration level of antibiotic –A will become lower over time. But in the FIG 1.1 these three lines reached the peak at the same time. In FIG 1.2 these three lines which represent concentration of antibiotic-A are almost entirely overlapped.

This problem happened in the similar situation when initial values to bacteria-B are set at different amount such as100,200, 500 and the remaining values at zero.(FIG 8.1 & 8.2)

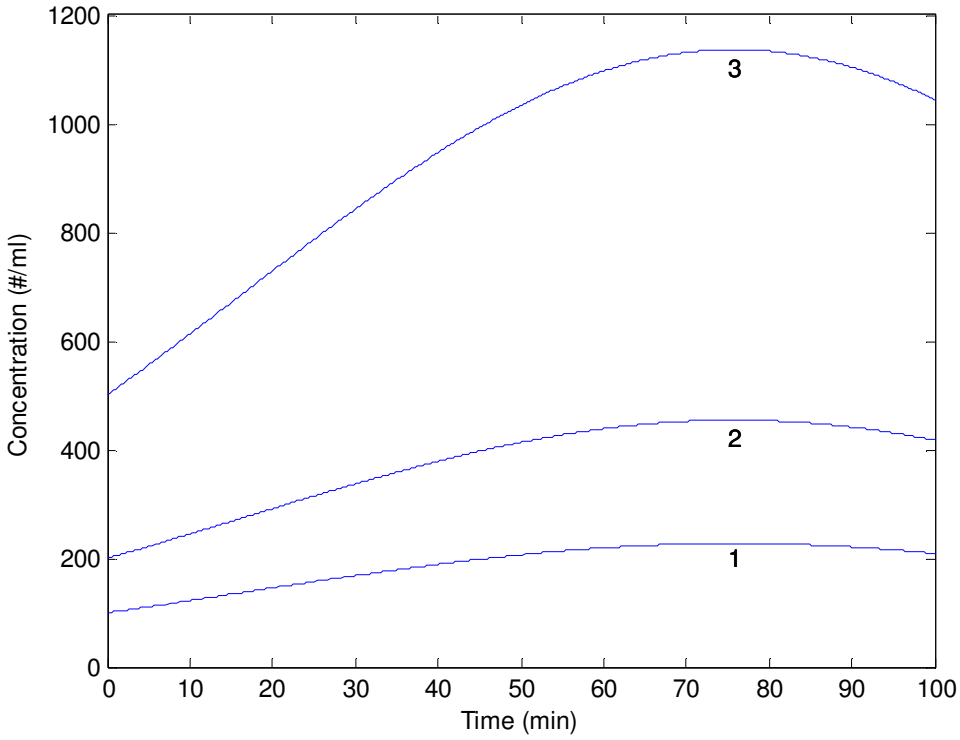


Figure 11 Concentration of bacteria-B with different initial value

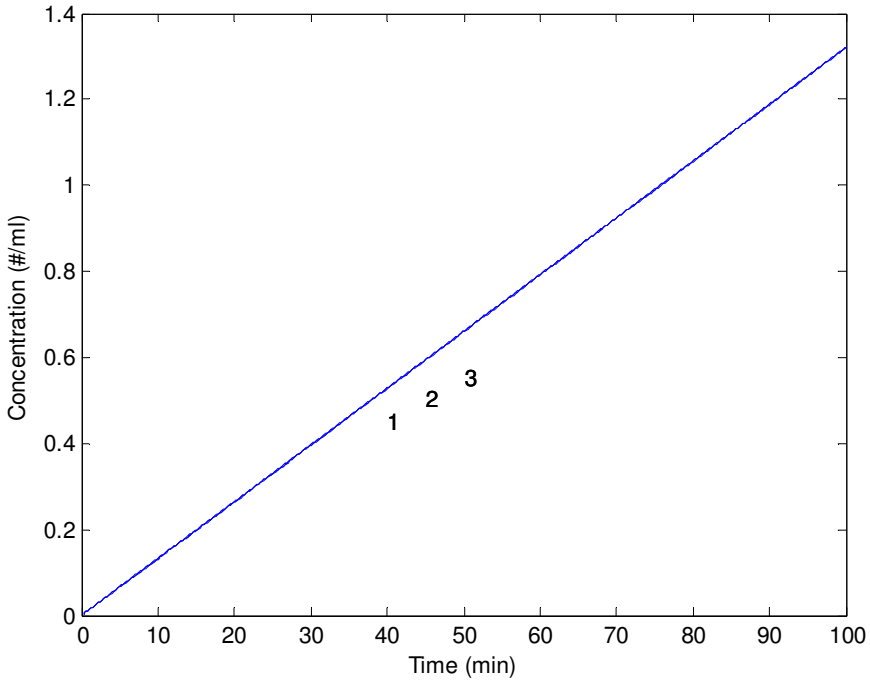


Figure 12 Concentration of antibiotic-B with different initial value of bacteria-B

4 CONCLUSIONS

Despite some interesting figures and some reasonable explanations for them, the OED model was wrong.

The reasons why we reached this conclusion are:

1. Both equilibrium points and eigenvalues differ in orders of magnitude.
2. Some figures which were generated using different initial values do not make any sense. The increase in the concentration of the corresponding bacteria did not cause a reduction in the concentration of the antibiotic.
3. There were abnormal values of the variables sensitivity.

We think the main problem may lie in the assumptions:

1. The growth rate of bacteria is resource concentration-independent.
2. The killing rate of antibiotic is bacteria density-independent.
3. The inhibition rate of bacteria is antibiotic density-independent.

So we need to adjust one or more of these assumptions to reissue the model.

We should develop a more complex model to simulate population dynamics of antibiotic reaction.

4.1 Developing Model

In order to re-describe the relationship between the killing rate of the antibiotic and the concentration of the bacteria, the Hill function was introduced.

So that,

$$\gamma_A^{'} = \gamma_A \cdot \frac{A}{A + H_A},$$

where γ_A is antibiotic-A killing rate from the last model, H_A is the ligand concentration producing half occupation related to bacteria-A, and A is the concentration of the bacteria-A.(Set the Hill coefficient to 1).

Similarly, the relationship between the concentration of the antibiotic-A and inhibition ratio of bacteria-B is,

$$K_A^{'} = K_A \cdot \frac{C_A}{C_A + H_{C_A}}$$

In this developing model, the growth rate of bacteria was the same as the last model. Then, the developing model is

$$\frac{dA}{dt} = \alpha_A \cdot A - \gamma_A \cdot \frac{A}{A + H_A} \cdot C_A$$

$$\frac{dB}{dt} = \alpha_B \cdot B - \gamma_B \cdot \frac{B}{B + H_B} \cdot C_B$$

$$\frac{dC_A}{dt} = \omega_A - \gamma_A \cdot \frac{A}{A + H_A} \cdot C_A - K_A \cdot \frac{C_A}{C_A + H_{C_A}} \cdot B$$

$$\frac{dC_B}{dt} = \omega_B - \gamma_B \cdot \frac{B}{B + H_B} \cdot C_B - K_B \cdot \frac{C_B}{C_B + H_{C_B}} \cdot A$$

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