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# Mathematical analysis of multi-antibiotic resistance

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ABSTRACT

*Background:* Multi-antibiotic resistance in bacterial infections is a growing threat to public health. Some experiments were carried out to study the multi-antibiotic resistance.
*Methods:* The changes of the multi-antibiotic resistance with time were achieved by numerical simulations and the mathematical models, with the calculated temperature field, velocity field, and the antibiotic concentration field.
*Results:* The computed results and experimental results are compared.
*Conclusions:* Both numerical simulations and the analytic models suggest that minor low concentrations of antibiotics could induce antibiotic resistance in bacteria.

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## 1. Introduction

Antibiotics resistance has accompanied with the introduction of antibiotics since shortly after penicillin was first introduced. Continued evolution of new, multi-antibiotic resistant bacteria has been considered as major threat to public health. Such bacterial strains are already present in different bacteria species and treating them is more difficult and often accompanied by a period of ineffective treatment, resulting in increased patient mortality [1]. Moreover, the development of new antibiotic is declining in the past decade, leaving few treatment alternatives for treating the increasing multi-resistant bacteria. Since such resistance is especially prevalent in hospitals, various treatment strategies have been suggested to facilitate better responses to resistant bacteria induced infections and to minimize the emergence of new multi-resistant bacteria [2–6].

Cycling, mixing and combining are three prominent strategies of antibiotic treatment. Under a cycling regime, all patients are treated with the same antibiotic drug at a given period of time, and the drug used is periodically switched. The rationale behind cycling is that each time an alteration of drug is administered; the pathogens resistant to the previously used drug are attacked and are expectatively susceptible to the new drug [7]. In the mixing strategy, patients receive a randomly selected antibiotic. Mixing has the advantage of creating a heterogeneous stress environment for the bacterial population. Combining is the administration of several drugs to the same patient [8]. By applying several antibiotics at once, combining is designed to diminish the chance of evolving resistance by eradicating any bacteria resistant to just one type of antibiotics. As a result, more antibiotics are used in combining than in mixing or cycling. This could lead to higher antibiotic-related toxicity and increased treatment costs [9].

## 2. Numerical simulation of multi-antibiotic resistance

We perform some numerical simulations to investigate an individual receiving a mixture of multi-antibiotic treatment against bacteria. Let us denote by $S(t)$ and $R(t)$ the population sizes of sensitive, and resistant bacteria to multiple antibiotics at time $t$, respectively; and by $C_i(t)$ the concentration of the $i$th antibiotic, $i = 1,2,\ldots,n$.

We assume that bacteria follow a logistic growth with carrying capacity $K$. Let $\beta_s$ and $\beta_r$ the birth rate of sensitive and resistant bacteria, respectively. Specific mutations conferring resistance to chemicals often have an inherent fitness cost which may be manifested through reduced reproductive capacity or competitive ability [10]. We quantify the fitness cost as a reduction on the reproduction rate of the resistant strain, therefore $\beta_r \le \beta_s$. During the administration of the $i$th antibiotic, a number of resistant bacteria to it can emerge due to mutations of exposed sensitive bacteria to such antibiotic, we model this situation by the term $\overline{q}_i C_i S$, where $q_i$ is the mutation rate of sensitive bacteria due to exposure to $i$th antibiotic.

Sensitive and resistant bacteria have per capita natural death rates $\mu_s$ and $\mu_r$, respectively. Sensitive bacteria can be killed by the antibiotics, and we assume that the rate at which they are killed by the $i$th antibiotic

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is equal to $\overline{\alpha}_i SC_i$. Finally, the $i$th antibiotic concentration is supplied at a constant rate $\Lambda_i$, and is taken up at a constant per capita rate $\mu_i$.

Under the assumptions aforementioned, we obtain the following system of $(n+2)$ ordinary differential equation:

$$\frac{dS}{dt} = \beta_s S\left(1-\frac{S+R}{K}\right) - \sum_{i=1}^{n}(\overline{q}_i + \overline{\alpha}_i)C_i S - \mu_s S$$

$$\frac{dR}{dt} = \beta_r R\left(1-\frac{S+R}{K}\right) + \sum_{i=1}^{n}\overline{q}_i C_i S - \mu_r R$$

$$\frac{dC_i}{dt} = \Lambda_i - \mu_i C_i$$

where $i=1,2,\ldots,n$.

To reduce the number of parameters, we introduce the following change of variables

$$s = \frac{S}{K}, r = \frac{R}{K} \text{ and } c_i = \frac{C_i}{\Lambda/\mu_i}.$$

In the new variables, the normalized system is given by

$$\frac{ds}{dt} = \beta_s s[1-(s+r)] - \sum_{i=1}^{n}(q_i+\alpha_i)c_i s - \mu_s s$$

$$\frac{dr}{dt} = \beta_r r[1-(s+r)] - \sum_{i=1}^{n} q_i c_i s - \mu_r r$$

$$\frac{dc_i}{dt} = \mu_i - \mu_i c_i, \quad i = 1,2,\ldots,n$$

with $q_i = \overline{q}_i(\Lambda_i/\mu_i)$, and $\alpha_i = \overline{\alpha}_i(\Lambda_i/\mu_i)$. The region of biological interest is given by the set

$$\Omega = \left\{(s,r,c_1,\ldots,c_n)\in R^{n+2} : 0\le s+r\le 1, 0\le c_i\le 1, i=1,\ldots,n\right\}.$$

Then we can get that the equilibria of the above equations are given by the solutions of the system of the following algebraic equations

$$\beta_s s[1-(s+r)] - \sum_{i=1}^{n}(q_i+\alpha_i)\,c_i s - \mu_s s = 0$$

$$\beta_r r[1-(s+r)] - \sum_{i=1}^{n} q_i c_i s - \mu_r r = 0$$

$$\mu_i - \mu_i c_i = 0$$

where $i = 1,2,\ldots,n$.

From the last $n$ equations of the above equations, we have $c_i = 1, i = 1,2,\ldots,n$. Replacing $c_i$ in the above first two equations, we obtain.

$$\beta_s s - \beta_s(s+r)s - \sum_{i=1}^{n}(q_i+\alpha_i)s - \mu_s s = 0$$
$$\beta_r r - \beta_r(s+r)r + \sum_{i=1}^{n} q_i s - \mu_r r = 0.$$

Then, we have $s = 0$, or $\beta_s - \beta_s(s+r) - \sum_{i=1}^{n}(q_i+\alpha_i) - \mu_s = 0$ holds. This condition is equivalent to

$$\frac{S_0-1}{S_0} = s + r$$

where $S_0 = \frac{\beta_s}{\sum_{i=1}^{n}(q_i+\alpha_i)+\mu_s}$..

It is easy to see that

$$\beta_r r - \beta_r r^2 - \mu_r r = 0$$

which implies $r=0$ or $r = \frac{R_r-1}{R_r}$, where $R_r = \frac{\beta_r}{\mu_r}$.

Therefore, we obtain the solutions

$$E_0 = (0,0,1,\ldots,1)$$
$$E_1 = \left(0, \frac{R_r-1}{R_r}, 1, \ldots, 1\right).$$

In which $E_0$ represents the state that both sensitive and resistant bacteria are eliminated, whereas $E_1$ is the equilibrium that only resistant bacteria persist. Then a necessary condition for $r>0$ is $R_r>1$, and $E_1$ has biological sense if and only if $R_r>1$. Assuming $s\neq 0$, then we have

$$s = \frac{S_0-1}{S_0} - r.$$

Therefore, a necessary and sufficient condition for $s$ to be positive is

$$r < \frac{S_0-1}{S_0}.$$

Then we obtain.

$$r = \frac{\sum_{i=1}^{n} q_i(S_0-1)}{(\sum_{i=1}^{n} q_i+\mu_r)(S_0-(\mu_r/\sum_{i=1}^{n} q_i+\mu_r)R_r)}..$$

If $r>0$, then

$$S_0 > \frac{\mu_r}{\sum_{i=1}^{n} q_i + \mu_r} R_r.$$

Therefore, a necessary condition for $s$ and $r$ to be positive is $S_0 > R_r$. It can be seen that

$$s + r = \frac{S_0-1}{S_0} = 1 - \frac{1}{S_0} \le 1$$

which implies that $S_0 \ge 1$.

Suppose that $E_0 = (0,0,1,\ldots,1), E_1 = (0, \frac{R_r-1}{R_r}, 1, \ldots, 1), E_2 = (\overline{s}, \overline{r}, 1, \ldots, 1)$, then we get that the local stability of the infection-free equilibrium $E_0$ is determined by the eigenvalues of the matrix

$$J(E_0) = \begin{pmatrix} \phi(E_0) & 0 & 0 & \cdots & 0 \\ \sum_{i=1}^{n} q_i & \mu_r(R_r-1) & 0 & \cdots & 0 \\ 0 & 0 & -\mu_1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & -\mu_n \end{pmatrix}$$

where $J(E_0)$ denotes the derivative of the vector field $F$, and

$$\phi(E_0) = \left[\sum_{i=1}^{n}(q_i+\alpha_i) + \mu_s\right](S_0-1)$$

The eigenvalues of $J(E_0)$ are

$$\lambda_1 = \phi(E_0)$$
$$\lambda_2 = \mu_r(R_r-1)$$
$$\lambda_{i+2} = -\mu_i, \quad i = 1,\cdots,n.$$

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