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Mathematical modeling on bacterial resistance to multiple antibiotics caused by spontaneous mutations

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ABSTRACT

We formulate a mathematical model that describes the population dynamics of bacteria exposed to multiple antibiotics simultaneously, assuming that acquisition of resistance is through mutations due to antibiotic exposure. Qualitative analysis reveals the existence of a free-bacteria equilibrium, resistant-bacteria equilibrium and an endemic equilibrium where both bacteria coexist.

1. Introduction

Infections have been the major cause of disease throughout the history of human population. With the introduction of antibiotics it was thought that this problem should disappear. However, bacteria have been able to evolve and become resistant to antibiotics (Mahmoud et al., 1999). Bacterial resistance to antibiotics is defined as the ability of bacteria to resist the effects of antibiotics designed to eliminate or control them (Arya, 2008). Resistance is generated both by evolutionary pressures derived of antibacterial therapy, as well as the indiscriminate application of such treatments (McMichael, 1995; Mahmoud et al., 1999). This growing phenomenon has enormous social and economic implications reflected in a growing morbidity and mortality due to infectious diseases, as well as the increment of treatment costs and hospital resources (Mahmoud et al., 1999).

Resistance has an intrinsic genetic substratum (natural), or can be acquired by biochemical mechanisms. Thus, it can be studied as a purely biological phenomenon or from the biochemical viewpoint (Ammor et al., 2007). Natural resistance is the one that is genetically determined, and it is not correlated with increasing doses of the antibiotic (e.g. the resistance of *Pseudomonas aerogenous* to the benzylpenicillin, trimethylene and sulphamethoxazole; aerobic Gram-negative bacilli resistant to clindamycin) (Ammor et al., 2007). Acquired resistance occurs due to specific changes in the DNA (mutation) or through contact with external sources such as plasmids, transposons, or integrons (Devirgiliis et al., 2011).

From molecular and biochemical viewpoint there are basically three mechanisms for acquisition of resistance: (i) alteration of the target site, (ii) inactivation of the antibiotic and (iii) formation of permeability barriers. The first one alteration of the target site, inactivation of the antibiotic and formation of permeability barriers. The former may arise due to altering some specific sites of the cellular anatomy (e.g. cell wall, subunit 50s, ribosomal 30s, etc). The second may arise from the production of enzymes that hydrolyze the antibiotic (e.g. β-lactamase, β-lactamase broad spectrum, erythromycin estereasa and aminoglycoside modifying enzymes, chloramphenicol, lincosamides and streptogramins). The third occurs by permeation of the external or internal bacterial

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membrane. It is important outline that all of these mechanisms can occur simultaneously (Burke, 2000).

It is said that an antibiotic has bacteriostatic action when its function is to inhibit the growth of bacteria and bactericidal when its function is to kill the bacteria. However, this distinction is not absolute because it depends on the drug concentration, the species of bacteria and the growth stage (Zhang, 2009).

In general, the bacterial infection is a complex process in which not only the infectious bacteria plays an important role (Carvalho et al., 2012), but also the host. In fact, a significant role in the development of the infection is played by the immune system (Linares and Martinez, 2005).

The evolving public health threat of antimicrobial resistance (AMR) is driven by both appropriate and inappropriate use of anti-infective medicines for human and animal health and food production, together with inadequate measures to control the spread of infections. Recognizing the public health crisis due AMR, several nations, international agencies, and many other organizations worldwide have taken action to counteract it through strategies applied in the relevant sectors. Among them, foster innovations, mathematical models and research and development of new tools (World Health Organization, 2012). Mathematical modeling has been extensively used on the understanding of the biological mechanisms underlying the acquisition of antibiotic resistance. Thus, in Wiesch et al. (2011), Romero et al. (2011), Bonten et al. (2007) and Austin et al. (1997), the authors obtain results on propagation of sensitive and resistant bacteria to antibiotics. Identification of factors responsible for resistance prevalence is given in Opatowski et al. (2011), Rodrigues et al. (2007), Austin and Anderson (1999); bacteria behavior under different antibiotic treatments is modeled in Bootsma et al. (2012), Sun et al. (2010), D'Agata et al. (2007), Alavez et al. (2006) and Bonhoeffer et al. (1997); optimization results and design of control measures are given in Sotto and Lavigne (2012), Massad et al. (2008), Haber et al. (2010) and Bonten et al. (2007); biological cost and persistence of antibiotic resistance are analyzed in Johnson and Levin (2013), Antia et al. (1996), Andersson et al. (2001) and Andersson and Levin (1999), respectively.

We proceed to derive a continuous time model considering the basic mechanisms of bacterial resistance to antibiotics. The main objective is to obtain parameter dependent threshold conditions determining the development of resistant and sensitive bacteria population.

2. Model formulation

We model a situation where an individual receives a cocktail of multi-drug treatment against bacteria (like in the case of *Mycobacterium tuberculosis*). 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 ith antibiotic, $i = 1, \ldots, n$.

We assume that bacteria follow a logistic growth with carrying capacity K. Let β_s and β_r the birth rate of sensitive and resistant bacteria, respectively. Specific mutations that confer resistance to chemical control often have an inherent fitness cost which may be manifested through reduced reproductive capacity or competitive ability (Alavez et al., 2006). We quantify fitness cost as a reduction on the reproduction rate of the resistant strain, therefore $\beta_r \leq \beta_s$. During the administration of the ith 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 $\overline{q}_i$ is the mutation rate of sensitive bacteria due to exposure to ith antibiotic.

Sensitive and resistant bacteria have per capita natural death rates μ_s and μ_r, respectively. Sensitive bacteria also die due to the action of the antibiotics, and we assume that the rate at which they are killed by the ith antibiotic is equal to $\overline{\alpha}_i S C_i$. Finally, the ith antibiotic concentration is supplied at a constant rate Λ_i, and is taken up at a constant per capita rate μ_i.

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

$$\begin{aligned}
\frac{dS}{dt} &= \beta_s S\left(1 - \frac{S+R}{K}\right) - \sum_{i=1}^{n}(\overline{q}_i + \overline{\alpha}_i)C_i S - \mu_s S\\
\frac{dR}{dt} &= \beta_r R\left(1 - \frac{S+R}{K}\right) + \sum_{i=1}^{n}\overline{q}_i C_i S - \mu_r R\\
\frac{dC_i}{dt} &= \Lambda_i - \mu_i C_i, \quad i = 1, 2, \ldots, n.
\end{aligned} \tag{1}$$

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

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

In the new variables, the normalized system is given by

$$\begin{aligned}
\frac{ds}{dt} &= \beta_s s[1-(s+r)] - \sum_{i=1}^{n}(q_i + \alpha_i)c_i s - \mu_s s\\
\frac{dr}{dt} &= \beta_r r[1-(s+r)] + \sum_{i=1}^{n} q_i c_i s - \mu_r r\\
\frac{dc_i}{dt} &= \mu_i - \mu_i c_i, \quad para \quad i = 1, 2, \ldots, n,
\end{aligned} \tag{2}$$

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

$$\Omega = \left\{(s, r, c_1, \ldots, c_n) \in \mathbb{R}^{n+2} : 0 \leq s, r \leq 1, 0 \leq s+r \leq 1,\ 0 \leq c_i \leq 1,\ i = 1, \ldots, n\right\}. \tag{3}$$

The following proposition assures that system (2) is well posed in the sense that solutions with initial conditions in Ω remain there for all $t \geq 0$, and therefore they have biological meaning.

Proposition 2.1. *The region Ω defined in (3) is positively invariant with respect system (2).*

Proof. The vector field of system (2) restricted to the boundary of Ω does not point to the exterior of it, therefore, solutions starting in Ω remain there for all $t \geq 0$. □

3. Qualitative analysis of the model

We characterize the existence and stability of equilibria of the system (2).

3.1. Equilibrium points

The equilibria of system (2) are given by the solutions of the system of algebraic equations

$$\begin{aligned}
&\beta_s s[1-(s+r)] - \sum_{i=1}^{n}(q_i + \alpha_i)c_i s - \mu_s s = 0\\
&\beta_r r[1-(s+r)] + \sum_{i=1}^{n} q_i c_i s - \mu_r r = 0\\
&\mu_i - \mu_i c_i = 0, \quad i = 1, \ldots, n.
\end{aligned} \tag{4}$$