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SIMPLE MATHEMATICAL MODELS OF ANTIMICROBIAL RESISTANCE

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Abstract. A fractional order dynamical system model of antimicrobial resistance is presented. The healthy equilibrium is found to be unstable. This can interpret the reappearance of some eradicated diseases. Also, a multi-objective optimization approached is discussed. Both models ensure the persistent of antibiotic resistance.

1. Introduction

Recently [1] some diseases that were thought to have disappeared, have reappeared. A possible reason is vaccination waning. Another possible reason is antimicrobial resistance (AMR) [2]. According to World Health Organisation, AMR and vaccination waning are among the ten most important threats to human health in 2019 [3].

Antibiotics are widely used to treat both small infections and dangerous human diseases. On another hand, antibiotics are extensively used for animal farming and for agricultural purposes. Antibiotics have been frequently and successfully used to control both human and animal epidemic outbreaks. Also, antibiotics play an important role in many medical procedures.

Unfortunately, over time bacteria built up AMR. Some of the reasons are [4]: first, naturally during the bacteria replication process. Second, misuse of antibiotics in both humans and animals is accelerating the process. Third, less investment in both hospital infection control and scientific researching for discovering new types of antibiotics. Forth, the absence of crucial governmental regulations on medical facilities in some regions of the world. Fifth, pollution has a strong role in increasing AMR development.

AMR is one of the complicated threats to global health, food security, economics, and development today. Some of the reasons are: first, antibiotics are globally used. Second, the non-locality of the problem, where AMR developed in a certain region of the world can be exported to another regions. This makes AMR can affect anyone, of any age, in any country.

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Mathematical models have played an important role in improving the understanding of several biological phenomena [5]. Many mathematical models are developed for exploring several aspects of epidemics, see [6]-[8], as examples. Integer order dynamical systems are used to model optimization of antibiotic use [9]. Moghadas [10] developed a model of the effect of imperfect vaccines on disease epidemology. Generally, the theory of dynamical systems is one of the most important approaches to the mathematical models in biology [5].

Both AMR and waning vaccination depend on the exposure time. Hence memory effects are crucial for both phenomena. Consequently, fractional order formulation [11] is quite relevant. An important question is the existence of backward bifurcation in their models. Fractional order dynamical systems are used to model several systems [11, 7].

Multi-objective optimization [12] is an important branch of mathematical programming. It studies the decision problems of multiple conflicting objective functions that are to be optimized over a set of decisions. Multi-objective optimization has many applications in different areas [12].

Here we study two mathematical models for MAR. In Section 2, a fractional order dynamical system of AMR is developed. The stability of the healthy equilibrium is studied. In Section 3, a multi-objective optimization approach is presented. Some conclusions and recommendations are summarized in Section 4.

2. A Fractional Order Dynamical System Approach

Dynamical system models are widely applied for studying biological phenomena [5]. The positive correlation between the intensity of use of a given antibiotic and the prevalence of resistant strains leads to a great dilemma in using antibiotics. When there is an infection with a sensitive strain, the less infected individuals you treat, the higher the mortality rates and the longer the hospitalization time of infected individuals that could be successfully treated. On the other hand, the more you treat, more individuals infected with resistant strains appears that causes higher mortality and longer the hospitalization time too [9]. Here, we give a fractional order dynamical system model for AMR.

Consider a given population that faces a given bacterial infection. Let $S(t)$ be fraction of susceptible population, $I_1(t)$ be fraction of infected and treated population, $I_2(t)$ be fraction of infected and not treated population, and $R(t)$ be fraction of infected population with resistant strain. This process is described by a fractional order dynamical system as follows:

$$D^{\alpha}S(t) = -b_1 S(t)[I_1(t) + I_2(t)] - b_2 S(t)R(t) + b_3 S(t)[1 - S(t)], \tag{1}$$

$$D^{\alpha}I_1(t) = pb_1 S(t)[I_1(t) + I_2(t)] - b_4 I_1(t), \tag{2}$$

$$D^{\alpha}I_2(t) = (1-p)b_1 S(t)[I_1(t) + I_2(t)] - b_5 I_2(t), \tag{3}$$

$$D^{\alpha}R(t) = b_2 S(t)R(t) + b_6 I_1(t) - b_7 R(t), \tag{4}$$

where D^{α} is Caputo fractional order differentiation, p is the rate treatment with antibiotics, b_1 is the infection rate of sensitive strains, b_2 is the infection rate of resistant strains, b_3 is the growth rate of susceptible individuals, b_6 is the rate of evolution of resistance, b_4, b_5, and b_7 are discharge rates in infected and treated, infected and not treated, and infected with resistant strains individuals, respectively.

The healthy equilibrium is represented by $S = 1, I_1 = I_2 = R = 0$. It is direct to see that the healthy equilibrium is unstable. Hence infective individuals have to exist. This can explain the reappearance of some diseases that were thought to have disappeared.

3. A Multi-Objective Optimization Approach

The general form of a multi-objective optimization problem [12] is

$$\begin{aligned} &\min f(f_1(x), f_2(x), ..., f_p(x)), \\ &\text{subject} \quad \text{to} \quad x \in X \subset \Re^n, \end{aligned} \tag{5}$$

where f is a vector-valued objective function composed of p real valued objective functions ($f_k : \Re^n \longrightarrow \Re, k = 1, 2, ..., p$), X is the feasible set of decision vectors that is defined by some constraint functions, and $\Re^n$ is an Euclidean vector space corresponds to the decision space.

In the weighted-sum approach, the function f is a weight sum of the objective functions. Now, we use the weighted-sum approach of multi-objective optimization to model AMR.

Consider a treatment plan with two objectives: The first is to minimize the antibiotic dose to reduce antibiotic resistance. But this will increase treatment time and risk disease increase. The second objective is to increase antibiotic dose. But this will increase antibiotic resistance. We assume the two objectives in the following form (close to radiotherapy case):

$$\begin{aligned} f_1 &= a_1 D - b_1 D^2, \\ f_2 &= a_2 D - b_2 D^2, \end{aligned} \tag{6}$$

where D represents the dose of an antibiotic, and a_1, a_2, b_1, and b_2 are constants.

Giving a weight w $(0 < w < 1)$ to the first objective and $1 - w$ to the second, then the objective is to minimize:

$$f = w[a_1 D - b_1 D^2] + (1 - w)[a_2 D - b_2 D^2]. \tag{7}$$

Applying the weighted-sum approach of multi-objective optimization [12], we get

$$D_{min} = \frac{a_1 w - a_2(1 - w)}{2[b_1 w - b_2(1 - w)]}, \tag{8}$$

where

$$w > \frac{b_2}{b_1 + b_2}. \tag{9}$$

This result means that AMR is going to persist, in agreement with the result of Section 2.

4. Conclusions and Recommendations

A simple fractional order dynamical system model is developed and used for explaining the reappearance of some disappeared diseases. A multi-objective optimization approach is used. The resistance to antibiotics is found to be going to persist.

We suggest the following solutions: Adjusting the antibiotics doses accurately. Offering the sufficient investment in research for new types of antibiotics. Presenting more effort towards hospital infection control. Controlling all types of pollution. Dividing antibiotics into two classes: expensive and less expensive. This will make expensive ones less prone to AR. Administering the antimicrobal alternatively. Finally, crucial governmental regulations on medical facilities are required.

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