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# What should be considered in the treatment of bacterial infections by multi-drug therapies: A mathematical perspective?

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ABSTRACT

Bacterial infections are a global health concern with high levels of mortality and morbidity associated. The resistance of pathogens to drugs is one leading cause of this problem, being common the administration of multiple drugs to improve the therapeutic effects.

This review critically explores diverse aspects involved in the treatment of bacterial infections through multi-drug therapies, from a mathematical and within-host perspectives. Five recent models were selected and are reviewed. These models fall into the following question: which drugs to select, the respective dose, the administration period to effectively eradicate the infection in the shortest period of time and with reduced side effects? In this analysis, three groups of variables were considered: pharmacokinetics, pharmacodynamics and disturbance variables. To date, there is no model that fully answers to this issue for a living organism and it is questionable whether this would be possible for any case of infection.



## 1. Introduction

The discovery of antibiotics in the twentieth century, along with the improvement of hygiene conditions, has significantly reduced the mortality associated to bacterial infections (Davies, 2006). However, infections are again a public health concern due to the growing number of microorganisms resistant to antibiotics. To contextualize the dimension of this problem, two numbers respective to the Europe Union are presented: the cost that antibiotic-resistant infections pose yearly is 1.5 billion €, with 25,000 associated deaths (Kirby, 2012).

In the development of new drugs, there may be a significant time lapse between the synthesis/discovery of a new compound and its approval and clinical use. Furthermore, antibiotics are usually derived from microbial metabolites (pure or modified) and half of the antibiotics currently in use were discovered along the antibiotics golden age, 1950–1960 (Davies, 2006), although novel approaches are underway (Coates and Hu, 2007). The mitigation of antibiotic resistance has been accomplished through the use of new antimicrobial compounds, by the combination of existing compounds (Boucher et al., 2013) and also through a more rational use of antimicrobials (Bartlett et al., 2013). However, the combination of existing drugs seems to be a more rapid and accessible solution.

In the treatment of an infection by the combination of drugs – multi-drug therapy – it should be defined a set of parameters related to the strategy to be used: which drugs, in what concentration, and using which algorithm of administration (Fig. 1)? The selection of these parameters should ideally take into account several variables, which are classified in this work as: pharmacodynamics, pharmacokinetics, and disturbance variables (Fig. 1). This procedure is applied to achieve a set of established goals, such as to completely eradicate the population of pathogens (although resistance may emerge along the treatment, drug resistant bacteria should be eliminated to accomplish this goal; avoid drug resistance could also be a goal if epidemiologic considerations were applied, which is note the case) and to minimize the eradication time and side effects (renal effects, intestinal effects, cardiac effects, among others, according to McKinnon and Davis, 2004) (Fig. 1). Yet, a given therapy often requires a compromise between these three objectives, since fulfilling one may imply a deviation from the others. The challenge is to define a strategy that allows to the highest closeness of all three goals.

In Fig. 1, it is assumed that all the information needed on the infection to be treated is known. However, a detailed analysis of each individual case of infection is often impractical, whether due to the urgency raised by the situation (technological limitations) or by

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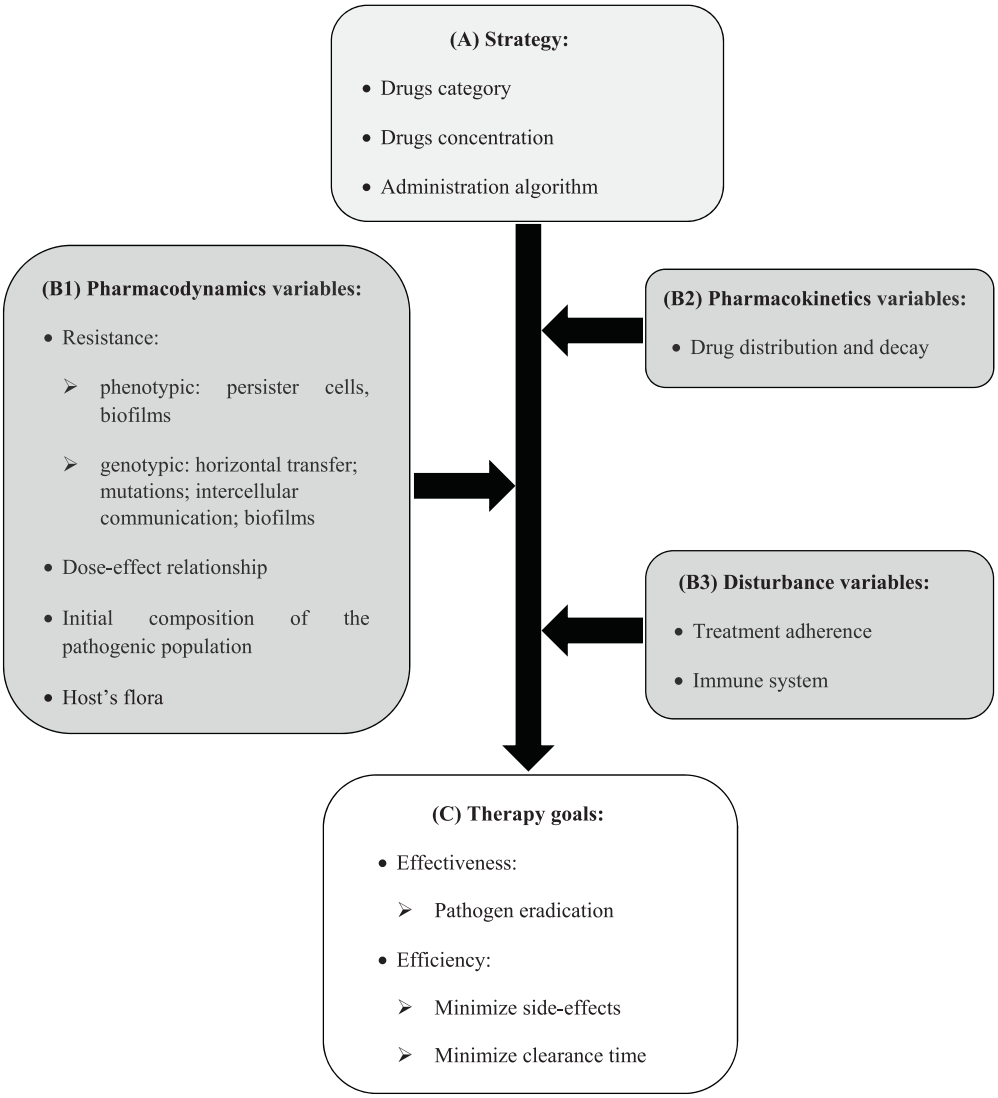


**Fig. 1.** Infection treatment approach in a living organism, using a multi-drug therapy, from a mathematical perspective. A multi-drug therapy is defined by (A): the drugs to be used (including the route of administration), the respective concentration and the time at which each drug should be administered (as well as the therapy duration). The interaction established between both drugs (type and intensity) depends on the type and concentration of each drug. These three inputs of a therapy should be defined taking into account three groups of variables: (B1) pharmacodynamics (related with the effect of the drug on the pathogen), (B2) pharmacokinetics (related with the effect of the organism on the drug) and (B3) disturbance (these are variables that, although they can be modeled, there is a high uncertainty degree associated with them). Note that these variables are inter-associated (for instance, the non-compliance with the therapy may increase the level of resistance). The ultimate goal of the therapy is to attain (C) an effective (all pathogens are cleared) and efficient (side effects and clearance time are minimized) treatment of the infection. The scheme offers a holistic view of a therapy, although other topics could be added. Epidemiologic aspects were not considered in the present within-host analysis, although they are of utmost importance in a real clinical situation (the inclusion of epidemiology would have effects on the three groups of variable depicted in the figure).

the unavailability of material/economic resources. Thus, available information is generally limited and it is quite common to follow guidelines for drugs administration, which are based on established policies, apparent symptoms and in the patient past records (Deresinski, 2007; Houck et al., 2004). Some of these guidelines still follow the old and very popular: "hit early, hit hard" (Ehrlich, 1913). This empirical-based protocol may suggest, *a priori*, a rapid and complete eradication of the infection, but actually there are situations in which this approach is not the most appropriate, particularly nowadays, since many infections are caused by pathogens with pre-acquired resistance to some drugs. A more rational protocol may be based on PK/PD (pharmacokinetics/pharmacodynamics) indices, as the MIC (minimal inhibitory concentration) of an antibiotic, but several important factors are omitted in these indices (Udekwu and Levin, 2012). This work is focused on PK/PD models (with population dynamics included) as an alternative to empirical and indices-based protocols, since they can potentially accommodate all aspects presented in Fig. 1, being a holistic (also complex and sometimes difficult) approach to the problem.

There are several models devoted to the study of pharmacokinetics (*e.g.*, Nielsen et al., 2011) and disturbance (*e.g.*, Mayer et al., 1995) variables. There are also specific models that give a mathematical form to the relationship between the killing agent and the infectious agent (pharmacodynamics variables), from an *in vitro* perspective (Iranzo et al., 2011; Landersdorfer et al., 2013; Pena-Miller et al., 2012, 2013; Torella et al., 2010; Wang et al., 2003; Wood et al., 2012). However, there are few holistic pharmacokinetic/pharmacodynamics (PK/PD) models and the number is even smaller if one consider only those models on multi-drug strategies. Lipsitch and Levin (1997) and Ankomah et al. (2013) explored such a model, based on the previous work of Levin and Udekwu (2010).

In this review, basic concepts concerning drug interactions are firstly presented. Secondly, five recent models were selected to illustrate the process depicted in Fig. 1, although most of them