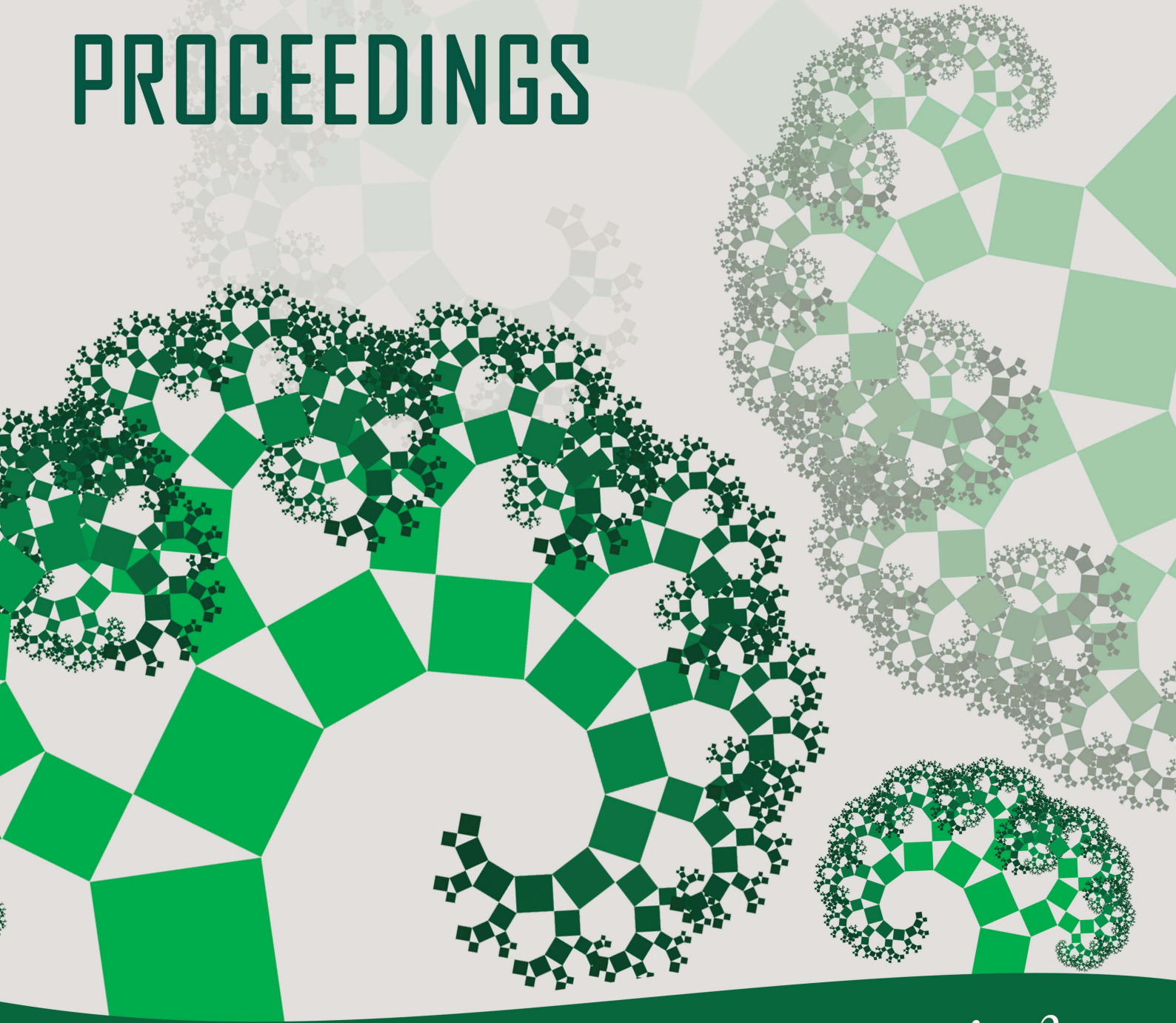
MODELLING FOR ENGINEERING & HUMAN BEHAVIOUR 2022

PROCEEDINGS



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Impact of antibiotic consumption on the dynamic evolution of antibiotic resistance: the colistin-resistant *Acinetobacter baumannii* case

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1 Introduction

One of the major public health threats today is antibiotic resistance, i.e. the ability of certain bacteria to genetically adapt and resist antibiotic treatment [12, 14]. The evolution of antibiotic resistance has been particularly worrying in recent years, and the latest forecasts estimate that by the year 2050, resistance will cause around 10 million deaths annually and an annual cost of 100 billion USD [7]. In the face of this challenge, mathematical modeling can provide great value in predicting, monitoring and aiding public health policy decisions.

On the evolution of the dynamics of antibiotic resistance, is well-known that antibiotic consumption increases bacterial resistance [3]. This evidence is based on the fact that, in an environment with the presence of antibiotic, resistance is a competitive advantage for the bacteria and, consequently, resistant bacteria survive in greater proportion than sensitive bacteria [9]. However, in the absence of antibiotic, there is no clear consensus on whether maintaining resistance is a disadvantage for the resistant bacteria and, then, whether antibiotic resistance can be reversed [2, 10].

In this work, a general random mathematical model that describes the evolution over time of the proportion of a resistant microorganism against an antibiotic have been proposed. The equation depends on the antibiotic consumption. Using real available data on antibiotic consumption and the proportion of resistance, the random model parameters have been calibrated using the Multi-Objective Particle Swarm Optimization (MOPSO) bio-inspired evolutionary algorithm [5] and the Monte Carlo method. In this way, the probability distributions of the parameters that best capture the uncertainty of the time series of data have been obtained.

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2 Methods

2.1 Model description

The proposed random mathematical model describes the evolution of bacterial resistance to an antibiotic in a population over time. This equation has been derived from a compartmental microbiological model with three species (subpopulations): resistant bacteria, sensitive bacteria and free space left by dying bacteria [11]. The random equation for the proportion of resistant bacteria in a population is given by:

$$p(t) = \frac{e^{\tau A(t) - \Delta\kappa t + \theta_0}}{e^{\tau A(t) - \Delta\kappa t + \theta_0} + 1} \in (0, 1), \tag{1}$$

where $\tau \in \mathbb{R}^+$ is the antibiotic kill rate, $\Delta\kappa \in \mathbb{R}^+$ is the difference between resistant and sensitive bacterial mortality rates, and $\theta_0 \in \mathbb{R}$ is the ratio $\theta(t)$, which is defined as $\theta(t) = \log\left(\frac{p(t)}{1-p(t)}\right)$, at time $t = 0$. The three parameters are considered in this model as random variables. The cumulative antibiotic consumption function, defined as $A(t) = \int_0^t a(u)du \in \mathbb{R}^+$ (where $a(t)$ is the antibiotic consumption registered at time t), is considered as a known deterministic function.

2.2 Data

The random model has been applied to study the resistance evolution of the *Acinetobacter baumannii* (or *A. baumannii*) bacterium, which is one of the most problematic microorganisms in hospitals. As antibiotic, we have chosen colistin because is one of the last efective antibiotics against *A. baumannii* [4, 8]. For our application, the data series of interest have been *(i)* the proportion $\hat{\mathbf{p}} = \{\hat{p}_t : \ t = 0, 1, \ldots, 107\}$ of *A. baumannii* colistin-resistant monthly cases in the 2012-2020 period [13], and *(ii)* the yearly colistin consumption $\hat{\mathbf{a}} = \{\hat{a}_t : \ t = 47, \ldots, 107\}$ [1] in the 2016-2020 period. As consumption data between 2012 and 2015 are not registered in antibiotic consumption database, and a linear growth have been observed, the 2012-2015 period monthly consumption data have been interpolated by a linear regression model, obtaining an estimation function $\hat{a}(t) = \beta_1 t + \beta_0 = 0.000525t + 0.031625$ for the 2012-2020 entire period.

2.3 Model calibration

The first step in the calibration process is to specify the family distribution of the model parameters. From the data we do not have any information about the effect of decreased resistance to a reduction in consumption. Consequently, we assume the worst possible scenario: resistance is not a competitive disadvantage in the absence of antibiotic, or, $\Delta\kappa = 0$. On the other hand, the remaining parameters $\tau \in \mathbb{R}^+$ and $\theta_0 \in \mathbb{R}$ can be considered as random variables with log-normal and Gaussian distributions respectively, so that

$$\tau \sim \text{log-}\mathcal{N}(\mu_\tau, \sigma_\tau), \quad \theta_0 \sim \mathcal{N}(\mu_{\theta_0}, \sigma_{\theta_0}),$$

Once defined the random model parameters, the calibration goal is to find the parameter set $\pi = (\mu_\tau, \mu_{\theta_0}, \sigma_\tau, \sigma_{\theta_0})$ that best captures the uncertainty of the data within a specific $(1-\alpha)$-confidence region. A significance level of $\alpha = 0.05$ has been chosen. To calibrate the model, the Multi-Objective Particle Swarm Optimization (MOPSO) bioinspired evolutionary algorithm have been applied [5]. The algorithm follows these steps:

1. Generate L particles. Each particle represents a set of parameters $\pi = (\mu_\tau, \mu_{\theta_0}, \sigma_\tau, \sigma_{\theta_0})$, which characterizes $\tau \sim \text{log-}\mathcal{N}(\mu_\tau, \sigma_\tau)$ and $\theta_0 \sim \mathcal{N}(\mu_{\theta_0}, \sigma_{\theta_0})$ random model parameters.

2. Generate a set $P = \{p^i(t;\pi) :\ t = 0,\dots,107;\ i = 1,\dots,n\}$ of n model simulations using the random model in Equation (1) with n sampled pairs $\{\tau, \theta_0\}_{i=1}^n$ from the model parameters distributions (Monte Carlo sampling), and considering $\Delta\kappa = 0$.

3. Compute the objetive functions with set P and real data $\hat{\mathbf{p}}$, and the time instants set $T = \{0,\dots,107\}$. Two orthogonal or antagonistic objective functions have been applied:

   - *Inside-outside error function*: if we define $q_t = q(t;P)$ and $Q_t = Q(t;P)$ as the $\alpha/2$ and $1-\alpha/2$ quantiles, respectively, of the set $\{p^i(t;\pi)\}_{i=1}^n$ given a time instant t, the inside-outside error function F_{io} is defined as

$$F_{io}\left(\hat{\mathbf{p}}, P\right) = \sum_{t\in T} \min\left\{|\hat{p}_t - q_t|, |\hat{p}_t - Q_t|\right\} \mathbb{1}_{\hat{p}_t \notin [q_t, Q_t]}\ , \tag{2}$$

     where $\mathbb{1}_{\hat{p}_t \notin [q_t,Q_t]}$ is the indicator function.
   - *Standard deviation error function*: if we define $\sigma_t = \sigma(t;P)$ as the standard deviation of the set $\{p^i(t;\pi)\}_{i=1}^n$ given a time instant t, the standard deviation error function F_σ is defined as

$$F_\sigma(P) = \sum_{t\in T} \sigma(t;P). \tag{3}$$

     As both functions are orthogonal, we are facing a multi-objective optimization problem.

4. Check if $\left[F_{io}\left(\hat{\mathbf{p}}, P\right), F_\sigma(P)\right]$ is a local best and/or a global best. It is considered as local best if the particle is not Pareto dominated by any of the previous local bests, and global best if the solution is not Pareto dominated by any of the previous global bests.

5. Update particle randomly or via the velocity term, using the classical PSO implementation [6].

6. Repeat from 2 until convergence is achieved.

Generally, the result of optimization a set of solutions (the Pareto front) called Pareto-optimal solutions, which are not dominated by any other solution.

3 Results

After the application of the optimization algorithm on the model and the data, a Pareto front has been obtained, from which a good solution has been chosen, preferring solutions with a low inside-outside error F_{io}, ensuring that the majority of the data are within the 95%-confidence interval. Based on these criteria, the chosen solution has been

$$\begin{aligned} &\pi^* = (\mu_\tau, \sigma_\tau, \mu_{\theta_0}, \sigma_{\theta_0})^* = (-1.1507, 0.0210, -3.9327, 0.4523)\,, \\ &\tau \sim \text{log-}\mathcal{N}(-1.1507, 0.0210),\ \theta_0 \sim \mathcal{N}(-3.9327, 0.4523), \\ &[F_{io}^*, F_\sigma^*] = [0.3233, 2.6597]. \end{aligned} \tag{4}$$

The probability distributions of the model parameters and the fit to the data are shown in Figure 1.

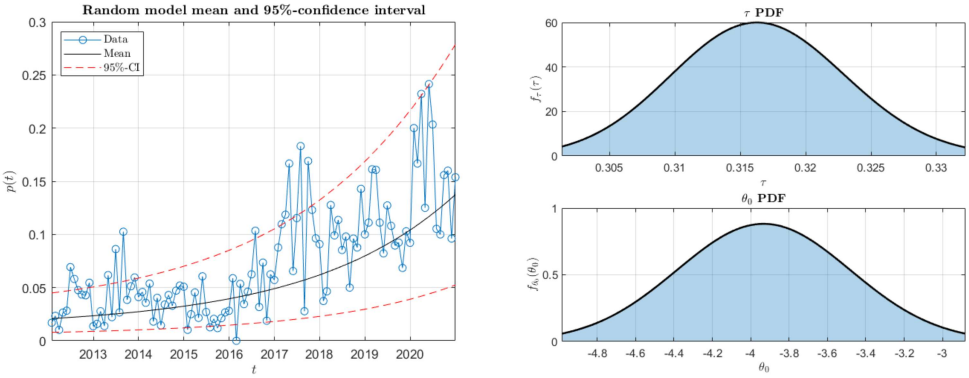

Figure 1: Random model expected value and 95%-confidence interval (left) and model parameters PDFs (right).

4 Conclusions

A general model for antibiotic resistance proportion dynamics considering antibiotic consumption have been analyzed and successfully applied to a real-world case of antibiotic resistance: the colistin-resistant *A. baumannii*. Additionally, a complete random calibration method based on the MOPSO algorithm and Monte Carlo method have been performed to find the random model parameters that best fit to real resistance data series, successfully capturing the randomness within a 95%-confidence interval.

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