Training of Neural Networks to Optimise Drug Dosage and Minimise Proliferation of Multidrug Resistant Bacteria

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Introduction

Bacterial infections, which are most commonly treated via administration of multiple antibiotics, inevitably lead to multi-drug resistance. In order to effectively formulate an optimal dosage strategy that minimises multi-drug resistance, many models have been made to attempt to achieve these objectives. These approaches include the application of approaches such as Levenberg-Marquardt Algorithms, Multilayer Perception (MLP) models, and Bayesian fitting procedures to produce the most realistic models.

The purpose of this project was to model the mathematical system of ODEs to mimic the growth of sensitive and resistant bacteria and the effect of multiple antibiotics on their growth, create a zero-dimensional model and use neural networks to optimise the drug dosage.

Abstract

The purpose of this project is to generate an optimal dosage strategy in order to minimise the effects of multi-drug resistance of bacteria. The growth of sensitive and resistant bacteria, and their respective drug uptake rates are mathematically modelled in MAPLE. This model involves the application of a Gaussian dosage model, and mimics a realistic form of periodic drug injection. Using a minimal number of parameters, a database of several virtual input and output parameters is generated, which is then used to train the neural network.

System of ODEs for Bacterial Growth Model

The model consists of two components: a basic system of equations, and a Gaussian dosage model. The basic system of equations models the treatment of a host infected with both, sensitive and resistant bacteria, through multiple antibiotic treatment. A minimal number of parameters are used. **Table 1** summarises what each of the parameters represent.

Parameter	Description
c_i	Concentration of i_{th} antibiotic where i=1, 2, 3, 4.
du	Concertation at which mutation begins.
m_i	Uptake rate of each antibiotic
μ_i	Position of the centre of the peak in pulsed injection
$r_1(t)$	Population size of sensitive bacteria at time t
$r_2(t)$	Population size of resistive bacteria at time t
σ_i	Width of pulsed injection
A_i	Amplitude of pulsed injection

Table 1: A summary of descriptions of each of the parameters.

$$\frac{dr_1}{dt} = -r_1(r_1+r_2) - r_1\sum_{i=1}^{4}\frac{c_i}{1+c_i} \qquad \frac{dr_2}{dt} = -r_2(r_1+r_2) + r_1\sum_{i=1}^{4}\left[\frac{c_i}{1+c_i}\cdot\frac{\max(0,c_i-du)}{c_i-du}\right]$$

(a) (b)

Figure 1: (a) Equation 1 describes the evolution of sensitive bacteria, which experiences natural birth and death rates of $r_1(1-r_1-r_2)$ and $-r_1$ respectively.
(b) Equation 2 models the evolution of resistant bacteria, with its natural birth rate and death rate described by $r_2(1-r_1-r_2)$ and r_2 respectively. The growth in population sizes of the resistant bacteria as a result of the antibiotic treatment is indicated by the second term in the equation.

A Gaussian dosage model is observed in order to mimic realistic methods of drug administration as opposed to a continuous injection of drugs described in Equation 3. This method observes the injection of the drug in periodic pulses, modelled with a Gaussian function of amplitude A_i, standard deviation σi, and the centered position of the peak at μ_i. This model is depicted in **Figure 2.**

$$f_i = \frac{1}{\sqrt{2\pi}\cdot\sigma_i}\cdot e^{\frac{(t-\mu_i)^2}{2\cdot\sigma_i^2}}$$

Figure 2: In the Gaussian Dosage Model, the equations regarding the population sizes of sensitive and resistant bacteria remain the same, but the concentration of antibiotic within the host is given by this equation.

Database Formulation

A database of virtual test cases on the input and output parameters was generated using nested for loops in MAPLE, with each loop representing the iterations through each parameter. Such a database was necessary to form a basis for the reduced order modelling of bacterial evolution.The steady-state values of the ODEs were obtained by evaluating the MAPLE code (**Figure 2)** for the numerical solutions of the ODEs as they approached infinity. The code was evaluated at time t = 7, 14, 21, 28 and 60 and the values of the input and output parameters generated after completing all iterations through the nested loops were stored in a text file.

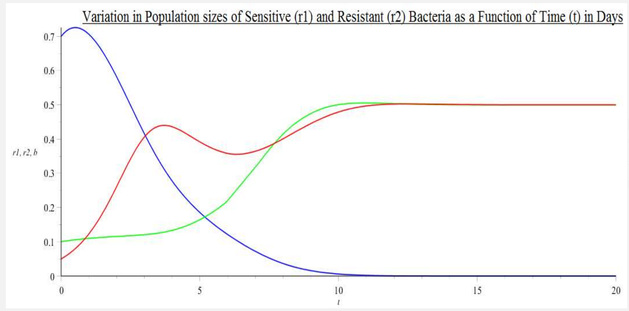

Figure 3: Changes in population sizes of Sensitive and resistant bacteria with a sample set of initial conditions, plotted against time in days.

Neural Network Training

Test cases of files with number of hidden units (nH) ranging from 5 to 20 were run on MATLAB in order to train the neural network. A range of mean square error (MSE) values were retrieved for each of the 5 cases that were run on each value of nH.
Validation:
Regression plots were retrieved **(Figure 3),** denoting a high degree of efficiency and accuracy in the execution, since the majority of the values lie along the general linear trend.

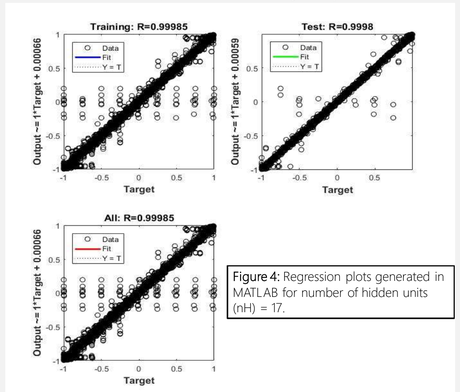

Figure 4: Regression plots generated in MATLAB for number of hidden units (nH) = 17.

Results

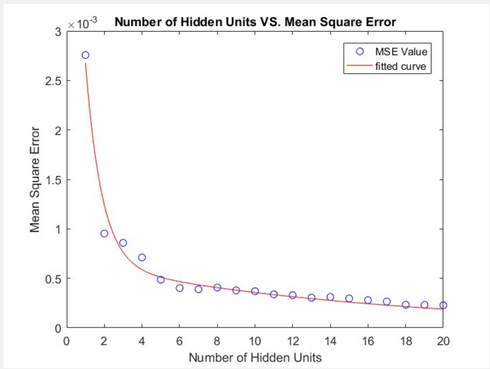

Figure 5: The Number of Hidden Units Plotted Against the Mean Square Error for 20 test cases of nH.

The Gaussian dosage model applied to this model that mimics realistic methods of drug administration. The regression plots and the training of the neural network resulted in an efficient model of bacterial growth, as displayed in Figures 3 to 5, which can then be used to further build the zero-dimensional model.

Closing Statements

Upon the completion of the zero-dimensional model for the neural network, this framework can be used to determine an optimal dosage strategy to evaluate the best dosages of multiple antibiotics to be administered so as to minimise the proliferation of resistant strains of bacteria.
The ultimate goal is to use a zero-dimensional model to allow a fully trained neural network to generate and assess optimal dosages for treatment of bacterial infections using multiple antibiotics.

References

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