AIP Conference Proceedings

RESEARCH ARTICLE | JULY 10 2018

Parameter fitting in models of biofilm resistance to antibiotics

E. Cebrián ✉; A. Carpio

Check for updates

AIP Conf. Proc. 1978, 350003 (2018)
https://doi.org/10.1063/1.5043956

View Online Export Citation CrossMark

09 January 2024 13:05:22

AIP Publishing

Parameter Fitting in Models of Biofilm Resistance to Antibiotics

E. Cebrián[1, a)] and A. Carpio[2, b)]

[1]*Departamento de Matemáticas y Computación, Universidad de Burgos, 09001 Burgos, Spain.*
[2]*Departamento de Matemática Aplicada, Universidad Complutense, 28040 Madrid, Spain.*

[a)]Corresponding author: elenac@ubu.es
[b)]carpio@mat.ucm.es

Abstract. Biofilms are communities formed by bacteria attached to surfaces and protected from antibiotic attacks by a polymeric matrix (EPS). Dynamic Energy Budget (DEB) models take into account the diversity of the mechanisms involved in biofilm resistance to antibiotics and allow us to study their effects on bacteria. These models involve sets of unknown parameters, which must be fitted to experimental data in such a way that the model predictions are consistent with experiments. Varying these parameters in a simplified model, we are able to calibrate their values and understand their influence on different bacterial distributions.

09 January 2024 13:05:22

INTRODUCTION

Bacterial biofilms are embedded in a self-produced polymeric matrix which creates a favorable environment for their development. Bacterial resistance to antibiotics in a biofilm contributes to chronic infections. Mathematical modeling can assist in the interpretation of experimental data, help to understand the causes of resistance and predict new behaviors.

DEB models take into account different types of energies within the biofilm to study the effect of antibiotics. In Ref. 1, it is adapted a DEB model to analyze antibiotic effects on Pseudomonas aeruginosa biofilms. In this DEB model, the fundamental energies characterizing the bacterium growth and its EPS production (energy density, cell volume and volume of EPS) are established, taking into account spatial variations in the concentration equations of oxygen and antibiotics and in the environmental degradation. In addition, spatial variations affect the diffused concentration of EPS associated to the EPS matrix which envelops and shelters all the biofilm cells. When the bacterial energy density is larger than a value e_{eps-a}, the cell is active and does not produce EPS matrix. Cell division happens when a threshold maintenance energy e_d is surpassed and the length cell, related to its volume, is bigger than a threshold length l_d. A cell becomes an EPS matrix producer if its energy density verifies $e_{eps-n} \le e \le e_{eps-a}$ and its aging acceleration q is large enough to exclude newborn cells. The survival probability p and the hazard rate h determine when cells die. The equations that govern the previous model involve many parameters whose values must be calibrated to reproduce experimentally observed tendencies. Their study is important to understand how they influence the distribution of bacterial types (active, dormant, dead). In Ref. 1, it is fitted parameter values to reproduce the number of viable cells after bactericidal action by four antibiotics, as quantified in Ref. 2. However, there are several values that offer acceptable results for the survival probability and approximate the experimental results. To select adequate values, it is necessary to take into account other aspect like the distribution of dead cells.

International Conference of Numerical Analysis and Applied Mathematics (ICNAAM 2017)
AIP Conf. Proc. 1978, 350003-1–350003-4; https://doi.org/10.1063/1.5043956
Published by AIP Publishing. 978-0-7354-1690-1/$30.00

MATHEMATICAL MODEL

Let us start simplifying the DEB model presented in Ref. 1. First, we consider constant the concentration of antibiotic C_a in the biofilm. Assuming that all cells are non EPS producers, we set the oxygen concentration C_o equal to the stationary solution of the diffusion equation

$$\frac{dC_o}{dt} = d_o \Delta C_o \tag{1}$$

taking the oxygen diffusion coefficient d_o like in Ref. 1. The boundary conditions are $C_o = C_{o,out}$ at the interface with the oxygen providing fluid and a no-flux condition $\partial C_o = 0$ at the interface with the substratum on which the biofilm grows.

Each bacterium and its EPS production are characterized by the following energies:

- Scaled energy density e:

$$\frac{de}{dt} = \nu\left(f - e\right), \qquad f = \frac{C_o}{C_o + K_o} \tag{2}$$

  where ν is the energy conductance and K_o is the oxygen half saturation. We do not take into account toxic effects on conductance here.

- Dimensionless cell volume v:

$$\frac{d\mathrm{v}}{dt} = (r - h)\,\mathrm{v}, \qquad r = \left(\frac{\nu e - m_\kappa g_\kappa}{e + g_\kappa}\right)^+ \tag{3}$$

  where r is the bacterial production rate, m_κ is the maintenance rate, and g_κ is the investment ratio. We are considering the acclimation energy density constant and equal to the target acclimation energy. h is the hazard rate (eq.(5)).

- Dimensionless volume of EPS matrix produced v_e:

$$\frac{d\mathrm{v}_e}{dt} = r_e \mathrm{v}, \qquad r_e = kr + k' \tag{4}$$

  where k and k' are, respectively, the growth associated yield and the non growth associated yield. This matrix remains attached to the cell, we neglect the diffused concentration of EPS here.

The hazard rate is governed by the equation:

$$\frac{dh}{dt} = q - \left(r + r_e\right)h \tag{5}$$

Together with the hazard rate, to decide when a cell dies, we need the survival probability p and the aging acceleration q:

$$\frac{dp}{dt} = -ph \tag{6}$$

09 January 2024 13:05:22

$$\frac{dq}{dt} = e\left(s_q \rho_x \nu q + h_a\right)(\nu - r) + f(e) k_{qA}^I \left[C_{IN}\right] - \left(r_e + r\right) q \tag{7}$$

where ρ_x, s_q, h_a and k_{qA}^I are cell density, multiplicative stress coefficient, Weibull aging acceleration and dissolved antibiotic toxicity. The term $f(e)$ allows us to take into account the action of different antibiotic types, targeting active or dormant cells. The antibiotic cellular density $\left[C_{IN}\right]$ is obtained solving

$$\frac{d\left[C_{IN}\right]}{dt} = k_A^I C_a - k_A^O \left[C_{IN}\right] \tag{8}$$

with the coefficients of antibiotic influx k_A^I and of antibiotic efflux k_A^O.

PARAMETER' INFLUENCE

In this section we illustrate the importance of giving adequate values to the parameters of the equations that form the DEB model to reproduce the expected behavior of antibiotics on bacteria in biofilms. For this, we solve the model using a numerical scheme based on two-stage Runge-Kutta method. We do not intend to fit values to actual experiments but to show the influence of the parameters on the results so that, when real data is available, we know how to act.

In order to simplify the exposition we work with the values selected in Ref. 1. (table 2, see Refs. 2, 3, 4 and 5) except when explicitly are mentioned.

Aging acceleration parameters

We show that controlling the parameters in equation (7) for the aging acceleration is essential for the distribution of dying cells. For example, Figure 1 illustrates that for different choices of the term $f(e)$ cells die first in the outer active biofilm layer or in the inner dormant core, which corresponds to the action of different antibiotic types. Figure 2 shows the influence of the multiplicative stress coefficient in the distribution of dead cells.

Figure 1 reproduces the distribution of cell types after 30 min when $C_a = 1.56 \mu g\, ml^{-1}$, $h(0) = 0.4 h^{-1}$, $k' = 0.29 \frac{mg\ polymer}{mg\, cell\ h}$ and $h_a = 1.4192 \cdot 10^{-4} h^{-2}$ for two different choices of $f(e)$.

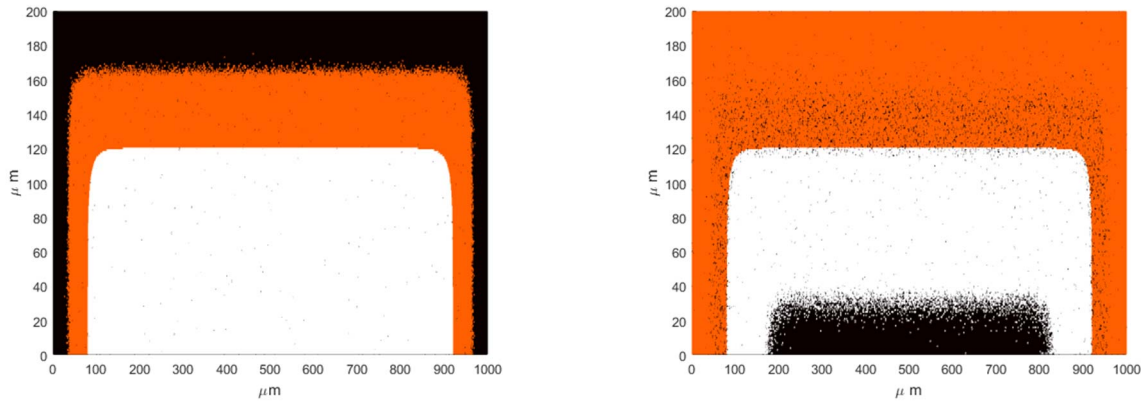
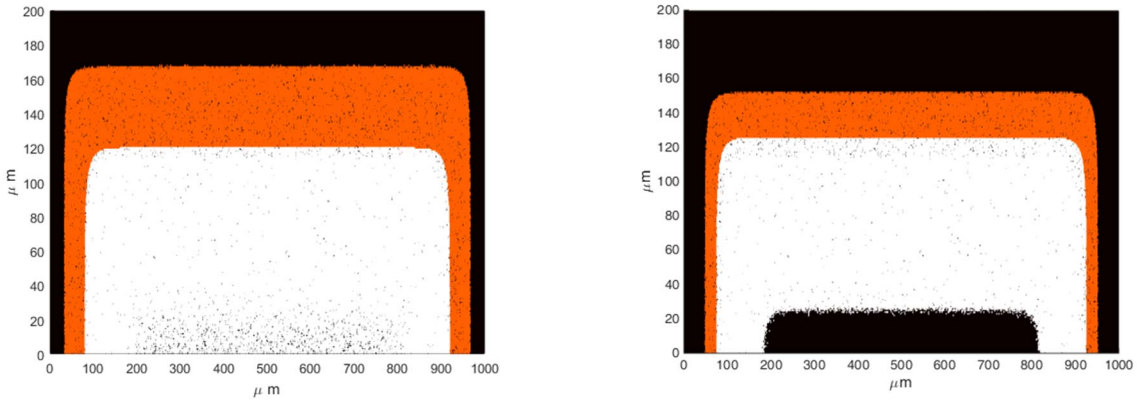


FIGURE 1. Distribution of cell types. (a) $f(e) = \frac{e}{0.1 median(e_{st})}$, (b) $f(e) = 10 \frac{median(e_{st})}{e}$ both for $s_q = 0.96259 Cmol^{-1} l$.

White regions are occupied by EPS producers, orange regions by non EPS producers and black regions by dead cells.

09 January 2024 13:05:22

Figure 2 considers $f(e)=10\dfrac{median(e_{st})}{e}$ and $s_q=70\cdot 0.96259 Cmol^{-1}l$ at different times. To obtain Figures 1b) and 2a) we have only modified the value of the multiplicative stress coefficient, but the different behavior is clear.



(a) (b)

FIGURE 2. Distribution of cell types for $f(e)=10\dfrac{median(e_{st})}{e}$ and $s_q=70\cdot 0.96259 Cmol^{-1}l$. (a) after 30 min (b) after 60 min.

CONCLUSION

We have illustrated the importance of educated simulations to select appropriate values for the model parameters. There are many other aspects of the action of antibiotics on bacteria which should be controlled through parameter variations. For example, the influence of non growth associated polymer yield on the relation between m_κ, g_κ, k and k' that is selected in Ref. 1 considerably affects the percentage of live cells. In addition, it is necessary to asses if the conclusions obtained from the study of simplified situations persist when considering the complete model.

ACKNOWLEDGMENTS

Research partially supported by MINECO grant No. MTM2014-56948-C2-1-P.

REFERENCES

1. B. Birnir et al., Communications in Nonlinear Science and Numerical Simulation **54**, 70-83 (in press).
2. H. Ishida et al., Antimicrobial Agents and Chemotherapy **42**, No. 7, 1641–1645 (1998).
3. T. Klanjscek et al., PLoS ONE **7** (issue 2) e26955 (2012).
4. P. S. Stewart, Antimicrobial Agents Chemotherapy **38** 1052–1058 (1994).
5. E. Werner et al., Applied and Environmental Microbiology **70** (10) 6188-6196 (2004).

09 January 2024 13:05:22