Pharmacodynamic Model of Tobramycin and Colistin Activity Against *Pseudomonas Aeruginosa* Biofilms

Swarnima Roychowdhury[1] and Charles M. Roth[1,2]

[1]*Department of Biomedical Engineering,* [2] *Department of Chemical & Biochemical Engineering, Rutgers University*

Abstract

- Chronic infection by gram-negative bacteria such as *Pseudomonas aeruginosa* is the leading cause of morbidity and mortality in cystic fibrosis patients who experience overabundant mucus and bacterial biofilm formation thereby negatively impacting drug delivery and effectiveness.
- Pharmacokinetic-pharmacodynamic modeling of biofilm treatment can be used to determine drug delivery strategies to control bacterial lung infections.
- A detailed pharmacodynamic model was developed to model the treatment of *P. aeruginosa* in response to frontline antibiotics tobramycin (TOB) and colistin (CST). This model was validated using a detailed dataset of killing dynamics.

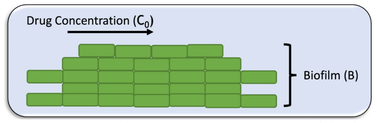
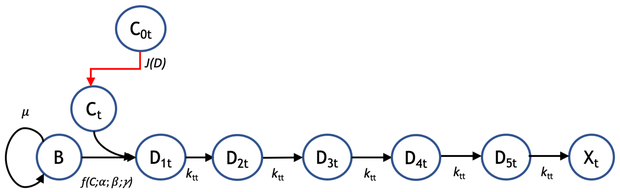


Figure 1: The pharmacodynamic model assumes drug diffusion to the biofilm as well as nonlinear drug concentration effects on the viability of the biofilm cells.

Methods

- A compartmental model was developed which includes diffusion of the drug to the bacteria and passage of the bacteria through multiple transit states before becoming completely nonviable.
- Colistin, which acts by disrupting bacterial membranes, has a fast-acting mechanism when compared to tobramycin, a ribosomal inhibitor, so only one compartment was used.



$$\frac{dB^*}{dt} = B^* \cdot \left[\mu \cdot (1 - B^* - D_1^* - D_2^* - D_3^* - D_4^* - D_5^* - X^*) - k_s(\alpha,\beta)C_0^{\gamma}\right]$$
$$\frac{dD_1^*}{dt} = k_s(\alpha,\beta)C_0^{\gamma} \cdot B^* - k_t \cdot D_1^*$$
$$\frac{dD_2^*}{dt} = k_t \cdot (D_1^* - D_2^*)$$
$$\frac{dD_3^*}{dt} = k_t \cdot (D_2^* - D_3^*)$$
$$\frac{dD_4^*}{dt} = k_t \cdot (D_3^* - D_4^*)$$
$$\frac{dD_5^*}{dt} = k_t \cdot (D_4^* - D_5^*)$$
$$\frac{dX^*}{dt} = k_t \cdot D_5^*$$

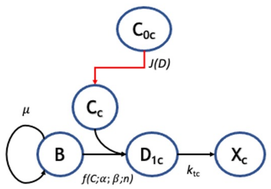


Figure 2: Tobramycin was fit to a 5-compartment model as indicated with subscript 't', whereas colistin was fit to a 1-compartment model, as indicated with subscript 'c'. Mass balances on each compartment formed a set of ordinary differential equations, which were solved in MATLAB for a given set of parameters.

Results

Table 1: Pharmacodynamic Parameter Values

Parameter	Description	Units	TOB Value	CST Value
μ_B	Growth rate of biofilm population	h^{-1}	0.0321	0.0001
α	Rate constant for drug effect on biofilm cells	$(\mu g/mL)^{\gamma-1}\ h^{-1}$	0.0002	0.0082
β	Normalized drug diffusivity	h^{-1}	0.2088	0.3986
γ	Cooperativity in drug effect on biofilm	-	3.5330	4.4313
k_t	Intercompartmental transit rate of drug	h^{-1}	0.5424	1.8924

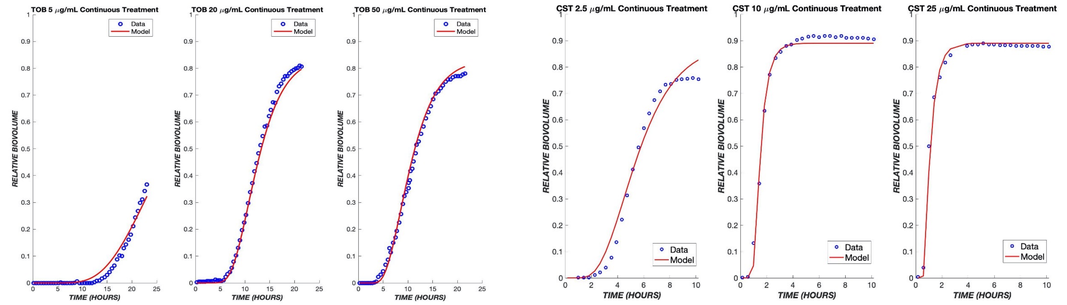


Figure 3: The model was first fit to data from Musken et al.[1] in three different tobramycin concentration dosages of 5, 20, and 50 μg/mL, in which the drug was administered continuously. The same drug exposure times were used for colistin, and the concentration dosages were 2.5, 10, and 25 μg/mL.

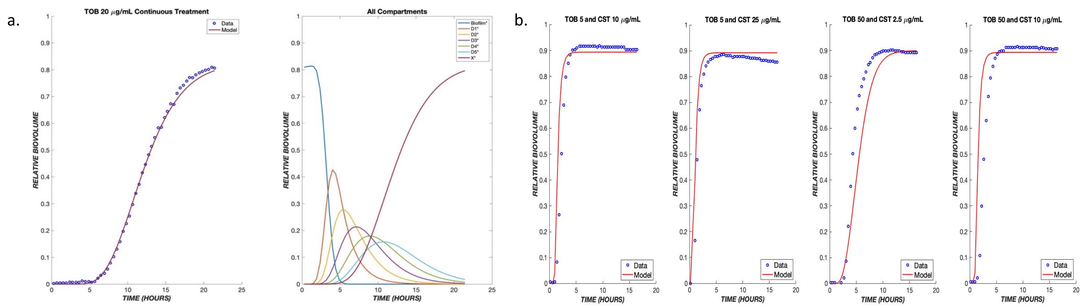


Figure 4: (a)Healthy biofilm bacteria are acted upon by tobramycin at a given concentration of 20 μg/mL, causing the cells to traverse multiple transit compartments D_1, D_2, D_3, D_4, and D_5 before reaching death, as represented by the *X* population. The initial delay in killing represents the drug diffusion through a concentration boundary layer in order to reach the biofilm.
(b) Combination treatments were tested using various dose combinations of tobramycin and colistin over the course of 24 hours.

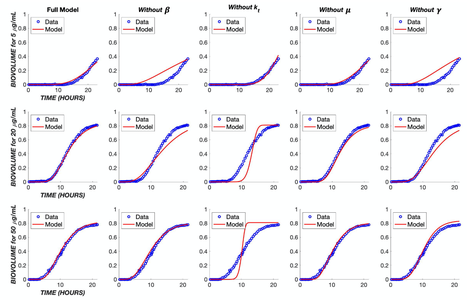


Figure 5: The tobramycin continuous data was used to analyze the effects of each parameter separately. The model was fit to the data without one of the indicated parameters. The column titled 'Full Model' shows the fit with the original parameter values found in Table 1.

Discussion

- The key components of the pharmacodynamic model include the diffusion of drug through a boundary layer and the usage of transit compartments which represented a cascade specific to the mechanism of action of the drug.
- The delay in killing time for both the tobramycin and colistin was consistent with the diffusion time.
- Tobramycin had an extended lag time in comparison to colistin, which is consistent with the mechanism of action of the drug.
- The intercompartmental transit rate of each drug played the greatest role in dictating the shape of the model.
- The current model does not address detachment of the bacteria and regrowth, which was seen to have occurred in transient exposure treatments around 20 hours. Moreover, the experimental data used to validate the model were collected over a period of 24 hours, so pharmacologic effects occurring beyond this time point may have not been addressed by the model.

Future Work

- Combining this pharmacodynamic model with an in vivo pharmacokinetic description will allow for more insight on drug administration strategies and overall drug effects on the system.
- Alginate beads can be inoculated with *P. aeruginosa* bacteria to simulate infection in an in vitro system. The bacteria-filled beads can then be put through a perfusion bioreactor in which drug can be administered at different time points (in continuous or transient treatment). Data involving bacteria concentration can be collected, and the developed pharmacodynamic model can be validated using this data set as well.

Acknowledgements

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References

[1]Musken, M.; Pawar, V.; Schwebs, T.; Bahre, H.; Felgner, S.; Weiss, S.; Haussler, S., Breaking the Vicious Cycle of Antibiotic Killing and Regrowth of Biofilm-Residing Pseudomonas aeruginosa. *Antimicrob Agents Chemother* **2018,** *62* (12).