Pharmacokinetic-Pharmacodynamic Modeling for Treatment Analysis of Lung Infections

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Introduction

- *P. aeruginosa* is a resistant pathogen due its formation of biofilm. Therefore, method of delivery of the treatment has effects on the efficacy in eradicating the pathogen.
- Currently, cystic fibrosis patients are given tobramycin via inhalation by nebulizer.
- A pharmacokinetic model was used to determine the best method of drug delivery, and the pharmacodynamic model was used to evaluate the effect of drug distribution on bacteria in different states.
- The PK model utilized the lung, blood, and peripheral tissue compartments. The PD model focused on the bacterial agar, planktonic, biofilm, and latent states.

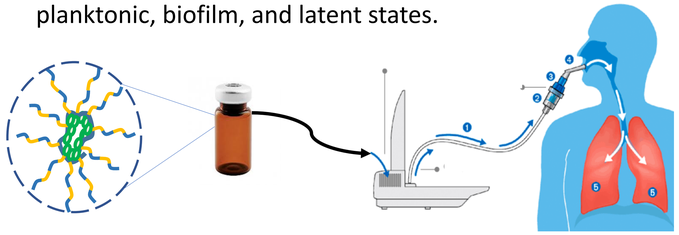
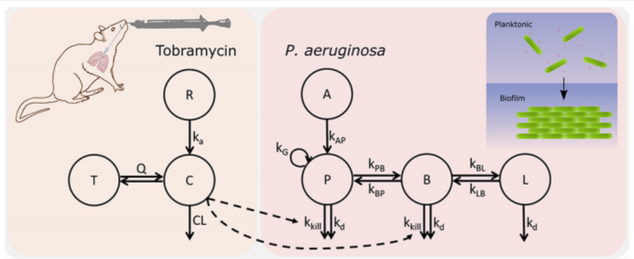


Figure 1: Our laboratory is interested in developing nanomedicine to improve the effectiveness of antibiotics in lung infections.

Methods



[1]**Figure 2**: Schematic of PKPD model used to create formulae. Matlab code utilizing the ODE15 solver was used to evaluate the solutions to these equations.

Pharmacodynamic Model

$$\frac{dA}{dt} = -k_{atA0}t \cdot A$$

$$\frac{dP}{dt} = k_{atA0}t \cdot A + k_g\left(\frac{B_{max}}{A+P+B+L}\right)P + k_{BP}B - k_{PB0}\left(\frac{A+P+B+L}{B_{max}}\right)P - k_dP - \sigma C_pP$$

$$\frac{dB}{dt} = k_{PB0}\left(\frac{A+P+B+L}{B_{max}}\right)P - k_{BP}B - k_{BL}B - k_dB - \sigma C_pB + k_{LB}\,L$$

$$\frac{dL}{dt} = k_{BL}B - k_{LB}L - k_dL$$

Pharmacokinetic Model

$$\frac{dC_p}{dt} = \frac{1}{V_c}\begin{bmatrix} k_{a0}e^{-k_{at}(t-t_a)} \cdot R - CL \cdot C_p \\ -QC_p + QC_t \end{bmatrix}$$

$$\frac{dC_t}{dt} = \frac{Q}{V_t}(Cp - Ct)$$

$$\frac{dR}{dt} = -k_{a0}e^{-k_{at}(t-t_a)} \cdot R$$

Nanoparticle Equations

$$\frac{dR}{dt} = \frac{M_\infty K}{[K+(t-t_a)]^2} - k_{a0}e^{-k_{at}(t-t_a)} \cdot R$$

$$\frac{dN}{dt} = -\frac{M_\infty K}{[K+(t-t_a)]^2}$$

In the PD model, the equations track the bacteria in the agar (A), planktonic (P), biofilm (B), and latent (L) states during the initial infection and following drug treatment. In the PK model, the drug is tracked in the lungs (R), plasma (C), and the tissues (T). The nanoparticle model incorporates all equations from PD and PK model, but the lung concentration equation was changed and an equation tracking the nanoparticle was added.

Results

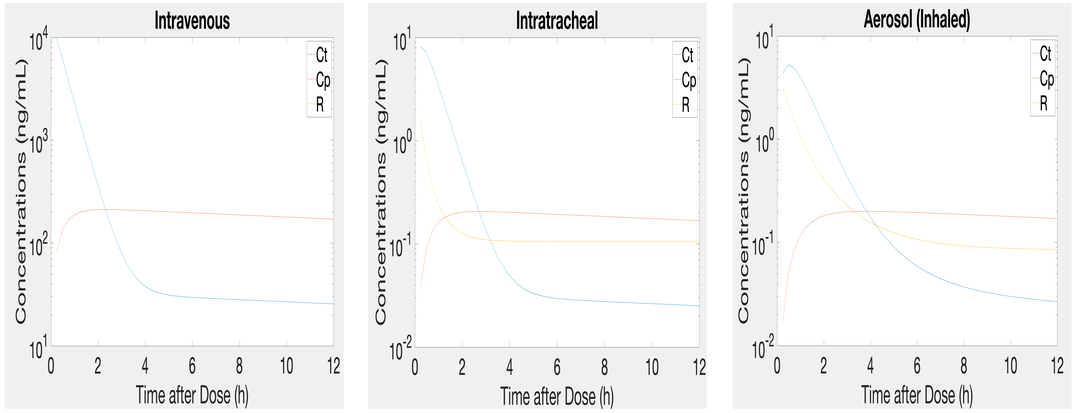


Figure 3: These graphs show the results from the different drug administrations in the PK model. As shown in the graphs, the intratracheal and nebulizer methods of administration have slightly delayed but similar absorption rates as the intravenous administration.

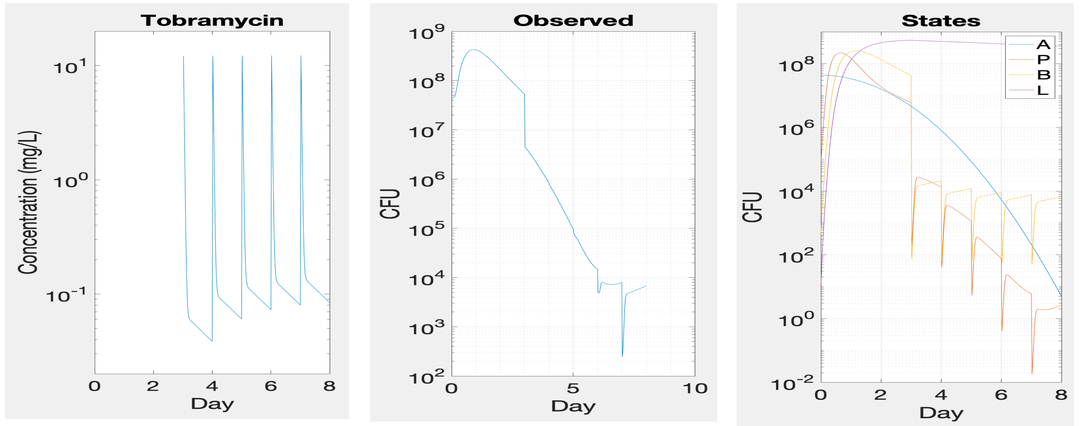


Figure 4: These three graphs show the drug profile and bacterial populations following tobramycin administration from days 3-8. The drug was administered through a nebulizer. Left: Tobramycin pharmacokinetics. Center: The 'Observed' graph shows the sum of the agar, biofilm, and planktonic states of the bacteria. Right: Individual bacterial populations over time.

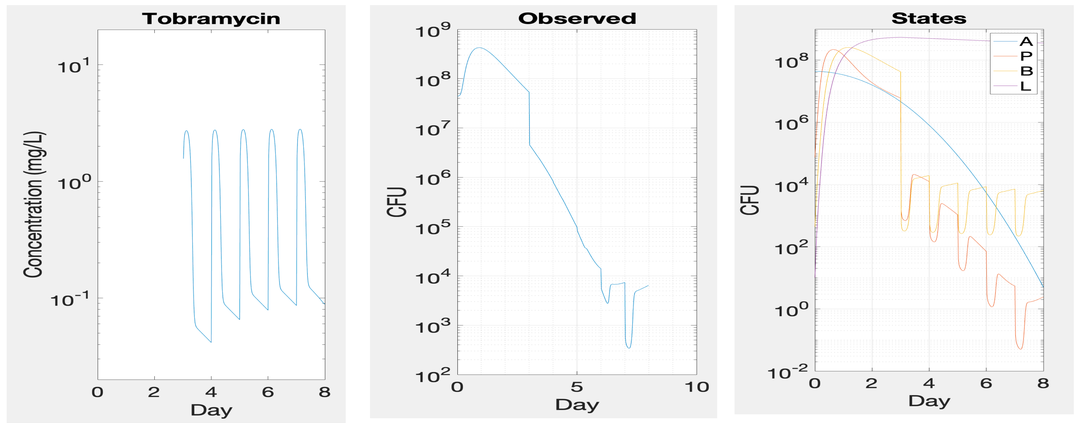


Figure 5: These three graphs show the drug profile and bacterial populations following tobramycin administration from days 3-8, where the drug was delivered through nanoparticles, which carries the drug to the lungs and releases it in a sustained manner.

Discussion and Future Work

- It was determined, from the PK model, that the nebulizer would be the most effective for direct delivery of the drug to the site of infection. Therefore, the nebulizer conditions were used in the PD model.
- The nanoparticle gradually releases the drugs, as compared to the nebulizer.
- The model does not address the saturation effect of the drug. A high concentration of drug can often be toxic, so higher concentration is not always good.
- Nanoparticles would be the most favored method of drug administration because gradually releasing the drug reduces chances of reaching toxic concentrations.
- Each day, a decrease in the planktonic and biofilm states is observed. However, the bacteria are always able to repopulate because of the latent (persister) population.
- This experiment has only been done through simulations in MATLAB, so far, so we hope to do in vitro and in vivo testing to see if the simulation results hold true.
- The PKPD model represents our current understanding of lung infections in cystic fibrosis and can be used to further investigate the efficacy of other treatments of biofilms in other chronic infections.

Acknowledgements

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References

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