Cost-Effective Techniques for Creating QSP Models

Quantitative systems pharmacology (QSP) modeling can be an effective tool to solve a variety of drug development questions including understanding a drug's mechanism of action, determining a drug's biomarkers, and much more. Since this method of modeling is relatively new, there is a common misconception that all QSP models must be built from scratch and that an enormous amount of effort is required in creating, validating, and applying QSP models.

The availability of QSP models in peer-reviewed literature, platforms for sharing open-source models, and publicly available data, can often serve as a starting point for QSP model development. Leveraging existing research and literature sources is a great way to reduce the time and costs associated with developing QSP models. Here, we summarize a recent example showing this approach in action.

Question to be Addressed: While the standard ratios of area under the curve (AUC) to minimum inhibitory concentrations (MIC) were available, the following question arose: "What combination of antibiotics should be given with colistin to reduce the lung injury associated with Acinetobacter baumannii-induced pneumonia?"

Using Published Literature to Conduct QSP Modeling

In order to study the effect that antibiotics, administered concomitantly with colistin, would have on bacterial load, we needed to also understand the mechanism through which colistin by itself acts. QSP models enable researchers to simulate these mechanistic interactions to predict the antibiotic's effects on lung injury.

In this example our QSP modeling team implemented a pre-existing model originally developed by Diep et al. simulating the immune system response to the bacterium, Acinetobacter baumannii, and subsequent lung injury caused by pneumonia. Data published by Liu et al. was then used to extend the model to include the effect of the antibiotic, colistin, in reducing bacterial load in addition to the immune response.

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Base QSP Model

Figure 1 illustrates the base model for host-pathogen interaction published by Diep et al. The model simulates the reduction in the number of colony-forming units (CFU) of the bacteria due to the immune response. The bacterial load of Acinetobacter baumannii – an opportunistic gram-negative pathogen, known to cause pneumonia in various settings is administered to the model.

The model describes simulation of the production of pro-inflammatory cytokines IL-1β and TNF-α and anti-inflammatory cytokines as part of the host immune response. TNF-α stimulates the cytokine-induced neutrophil chemoattractant 1 production. Neutrophil recruitment is triggered by IL-1β and CINC-1. Neutrophils, along with neutrophil signaling, promote reduction of the bacterial load. In this model, neutrophil signaling is non-specific and can be representative of processes such as the recruitment of other immune cells. Lung injury is characterized by albumin leakage and is driven by IL-1β.

The model showed that lung injury increases with increasing initial bacterial load. Therefore, reducing the number of bacteria in the body is one way in which to decrease lung injury.

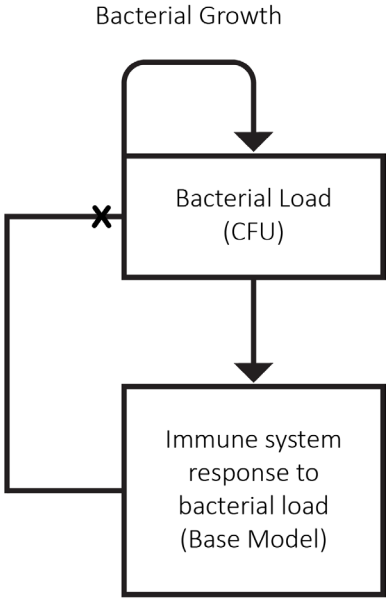

Figure 1 Simplified model schematic. Immune System response in the model consists of complex cell signaling network involving multiple immune system cells and signaling molecules

Extending the Base Model

The model was expanded to explain how bacterial load can be depleted by using antibiotics. Antibiotics either kill bacteria or slow their growth letting the immune system kill the bacteria. It is important to understand the mechanism through which an antibiotic operates to predict its efficacy in different scenarios.

Colistin has become a new treatment regimen for *A. baumannii* infections as antibiotic resistance to more common treatments becomes pervasive. Colistin targets the bacterial cell membrane which kills the bacteria. Figure 2 shows the updated model that includes the action of colistin on bacterial load. Now bacterial load can be reduced either through the action of the immune system or through the action of the antibiotic.

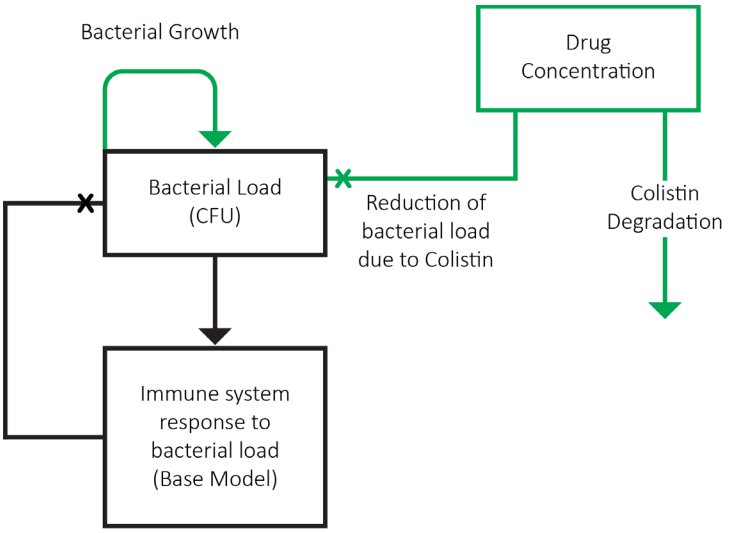

Figure 2 Updated base model to include colistin antibiotic intervention

Parameter Estimation and Validation

The next step is to estimate the model parameters for the additional pathway we have introduced in the model. Previous experiments performed by Liu et al. showed various treatment regimens of colistin and other antibiotics and their effect on the bacterial load of *A. baumannii* over time. Both control and treatment data from the publication were digitized and used for model fitting. The bacterial growth rate was estimated using the data from the control experiment.

The final two parameters – the interaction between colistin and bacterial load and the degradation of colistin in the experimental system – were then estimated using the treatment data from Liu et al. The data for a colistin treatment of 0.25 µg/ml (equivalent to ½ MIC for *A. baumannii*) was used to parameterize the model. The model results were validated by simulating a treatment condition of 0.125 µg/ml and comparing it against experimental data. Adding the antibiotic intervention to the pre-existing immune response model only necessitated adding three new parameters as opposed to 41 parameters if the entire model were to be constructed from scratch.

A key advantage to the model was the fact that it was developed using R-Shiny (an R based program producing graphics and tables of results that can be easily digested across audiences). This R-Shiny app allows for simulations to be conducted using different assumptions to test the combination of different antibiotics so the magnitude of improvement with a combination drug could be illustrated.

Conclusions

The development of a QSP model that started with a previously-published model was able to address drug development questions associated with picking the optimal antibiotic to be used in combination with colistin to decrease Acinetobacter baumannii-induced pneumonia. Implementing this model into an R-Shiny app (an interactive web-based resource) resulted in easily understandable graphics that could be interpreted by a variety of audiences including technical scientists, nontechnical scientists, and stakeholders.

Nuventra can integrate pre-existing models and previously published literature data to develop QSP models that can be used for solving a variety of drug development questions for our clients. This approach can improve decision making and save both time and resources. Contact us today to learn more about our QSP modeling services or to speak with one of our QSP modeling experts about your program.

REFERENCES

Diep JK, Russo TA, Rao GG. Mechanism-Based Disease Progression Model Describing Host-Pathogen Interactions During the Pathogenesis of Acinetobacter baumannii Pneumonia. CPT Pharmacometrics Syst Pharmacol. 2018 Aug;7(8):507-516. doi: 10.1002/psp4.12312. Epub 2018 Aug 24. PMID: 29761668; PMCID: PMC6118322.

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