A More Robust Assessment of Antibiotic Combinations by Dynamic Susceptibility Model

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Background

- Bacterial **resistance** to **antibiotics**: Rising threat to global health
- **Enzymatic resistance** treated with **combination** therapy:
  - Active **antibiotic**
  - Bacterial enzyme **inhibitor**
- **Current practice** for therapeutic dosing decisions:
  Maintain antibiotic concentration in the body above minimum inhibitory concentration for % of dosing period, T
  - $\%\mathbf{T} > \mathbf{MIC}$
- **Problem** with current practice:
  Does not account for **fluctuating inhibitor concentrations** in the body

Objective

- Develop a **robust computational tool** to help identify the most **effective combination therapy** options

Materials

- Clinical bacterial strain:
  Klebsiella pneumoniae expressing CTX-M15 (Kp3)
- Active antibiotic: Piperacillin
- Enhancing inhibitor: Avibactam

Methods

- Obtained bacterial susceptibility to antibiotic (**MIC**) at **varying concentrations of inhibitor**
- Fit **dynamic susceptibility model** $\log_2 \mathrm{MIC}_i = \log_2 \mathrm{MIC}_0 - I_{max}\left(\frac{I^H}{I^H + I_{50}^H}\right)$ to data
- Combined model with typical fluctuating drug concentrations in the body for better **criterion** of **bacterial susceptibility to antibiotic-inhibitor combination**: $\boxed{\%\mathbf{T} > \mathbf{MIC}_i}$

Results

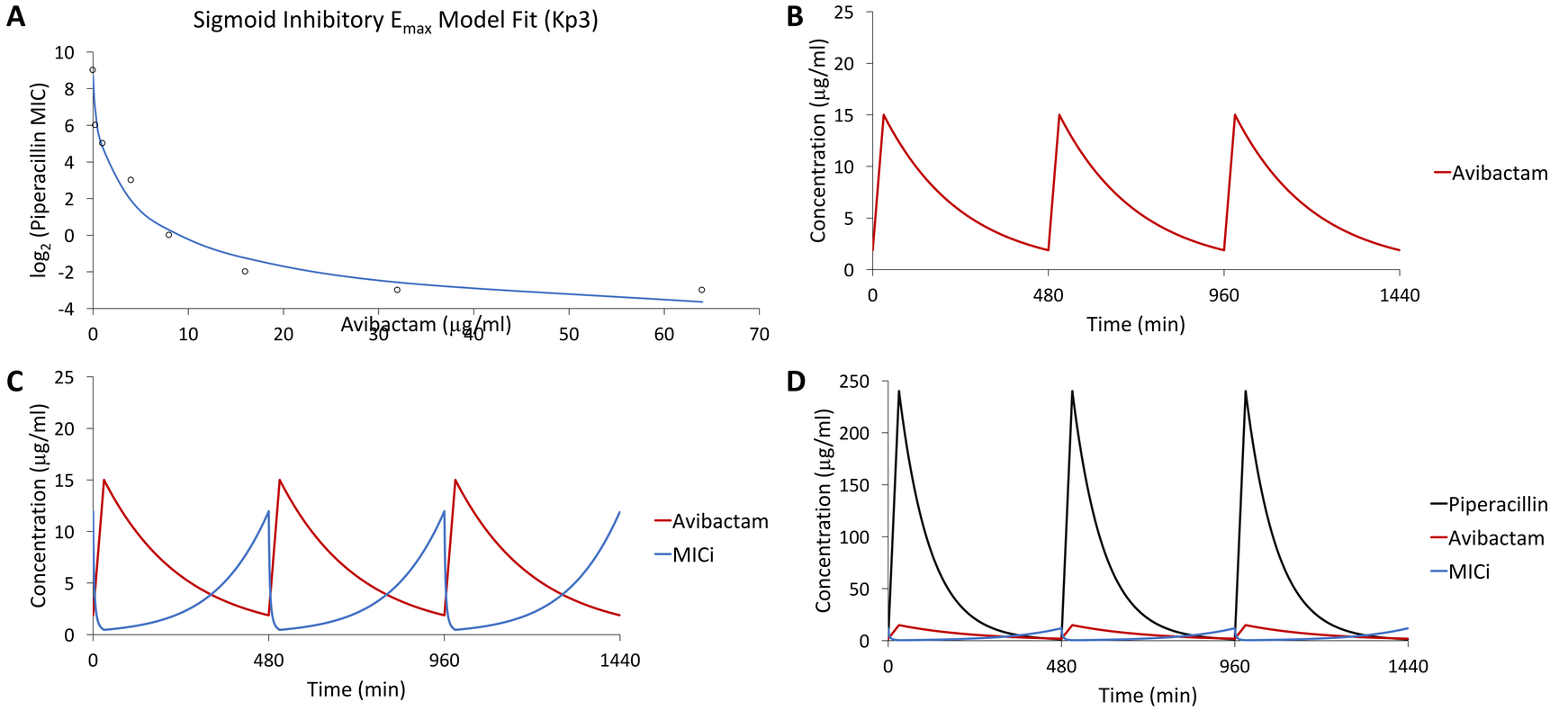

Fig. A: Piperacillin MICs for clinical isolate Kp3, determined at Avibactam concentrations 0-64 µg/ml. Resulting data fit to a sigmoid inhibitory E_{max} model for each isolate.
Fig. B: Pharmacokinetic model of a 24-hour dosing period for Avibactam with a dose of 0.5 g every 8 hours.
Fig. C: Estimate of isolate-specific MIC_i profile from dynamic susceptibility model, illustrating bacterial susceptibility fluctuation inversely to concentration of Avibactam.
Fig. D: $\%T>MIC_i$ estimated at 75% from model generated in fig. C and pharmacokinetic model for Piperacillin over the same 24-hour dosing period with a dose of 4g/8h.

Discussion

- Formulated a model to characterize dynamic susceptibility of bacterial strain over time
- Future work: Predict bacterial suppression in pre-clinical infection model for various strains
- Utility: Refined and validated computational tool may help clinicians to choose the best available treatment for their patients