



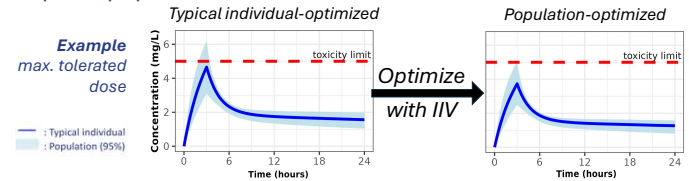
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Introduction

Population Treatment Optimization

- Treatment optimization can improve the probability of achieving therapeutic objectives¹
- Involving inter-individual variability (IIV) in optimization could improve population outcomes
- Multi-objective optimization**
 - Maximize efficacy
 - Limit toxicity and exposure
 - Prevent resistance/tolerance



Case Study

- Ciprofloxacin (CIP) and tobramycin (TOB)
- Pseudomonas aeruginosa* infection
- Treatment objectives**
 - Achieve target endpoint bacterial density
 - Avoid sepsis
 - Avoid drug toxicity (C_{max} and exposure)

Objective

- Propose a treatment optimization method for a patient **population** by considering **IIV** for **multiple treatment objectives**
- Case study: design of a **combination antibiotic therapy** to **prevent antibiotic resistance**

Methods

PK-PD model

- PopPK models from literature
- PD model from experiment
- Monte Carlo** simulation (n=1000)

Cost function

- Equal weight** to all targets
- Individual cost (i) for each target (x_i)

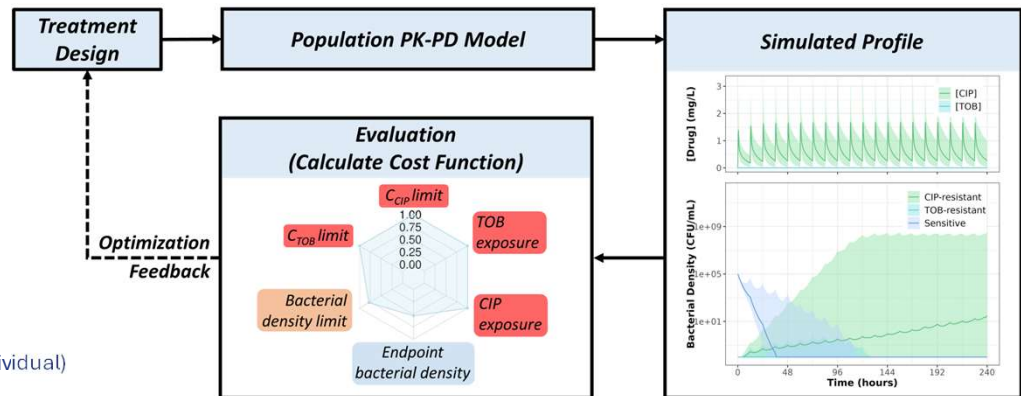
$$Cost_i = \frac{1}{J} \sum_{j=1}^J \frac{1}{1 + e^{-\varphi(x_j/x_{target,i}-1)}}; \varphi \equiv 50$$

- Population = mean individual cost

Optimization Algorithm: PSO+BFGS²

Method Comparisons

- Optimization without IIV (typical individual)
- Other algorithms (SA and GA)



Results

- Population-optimized** therapy achieved treatment objectives in **93.4%** of the population
 - Standard **monotherapy** : **≤ 50.8%**
 - Typical individual-optimized** : 75.8%
- Other optimization algorithms
 - Simulated annealing (SA) : 81.2%
 - Genetic algorithm (GA) : 83.1%

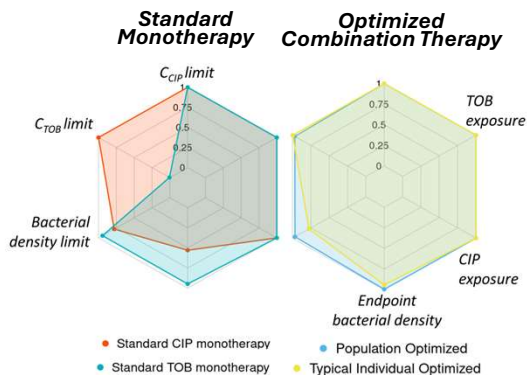


Fig. 1 | Target attainment probability of standard monotherapy and optimized combination therapy

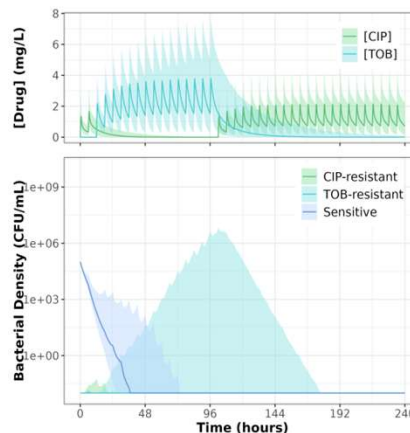


Fig. 2 | Population-optimized combination therapy

Discussion

- Multi-criteria decision analysis to **assign weight** in cost function
- Disadvantages of this method
 - Computationally heavy
 - Objective has to be a **range**

Conclusions

- Involving **IIV in optimization** could yield better population outcomes
- In this case study, **PSO+BFGS strategy²** was the most effective for identifying optimal treatment design
- The presented method can be used to **optimize dosing schedule** for a patient **population**

References

1. Bachmann, et al. (2023). Computing optimal drug dosing with OptiDose: implementation in NONMEM. JPKPD, 50(3), 173-188.
2. Shutao Li, et al. (2011). A Hybrid PSO-BFGS Strategy for Global Optimization of Multimodal Functions. IEEE, 41(4), 1003-1014.