Towards an integrated mPBPK/PD model for drug-optimization and prediction of relapse after treatment of tuberculosis in mice

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Motivations and Objectives

The treatment of tuberculosis (TB), one of the most harmful infectious diseases killing millions of people worldwide [1], still needs to be improved to shorten its duration and reduce relapse events. In pursuit of this objective, combining experimental data from mouse model treatments with simulation tools offers a strategic approach to identifying the most effective treatments for eradicating Mycobacterium tuberculosis infection. We present the extension of a recently published minimal physiologically based pharmacokinetic (mPBPK) model [2] with pharmacodynamic (PD) effects on bacteria populations. This enhanced model provides mechanistic insights into a drug's bactericidal and bacteriostatic action.

Methods

- PD expansion of the mPBPK model by adding one population of growing bacteria in the lung
- Modeling of bacteriostatic and bactericidal effects acting on the bacterial population
  - Bacteria quantified, at every simulated time point, as colony forming units (CFU)
  - Current version with literature values [3], ongoing development with more drugs
- R [4] and LSODA in rxode2 [5] implementation of the mPBPK-PD model
- R Shiny web-app interface where the drug PK/PD properties can be manipulated to inspect the behavior of the system

Results

Bacterial burden reduction exploration with anti-TB drugs

A mPBPK/PD modeling framework was developed leveraging a published mPBPK model and a disease model. The modeling framework tracks the path of a drug from the intake to its bactericidal and bacteriostatic effects in the lung compartment.

Informed by literature data, this integrated modeling approach allows for evaluating the sterilizing efficacy of several single drug therapies in terms of bacterial burden reduction, including, for example, rifampicin (Figure 1) and bedaquiline (Figure 2).

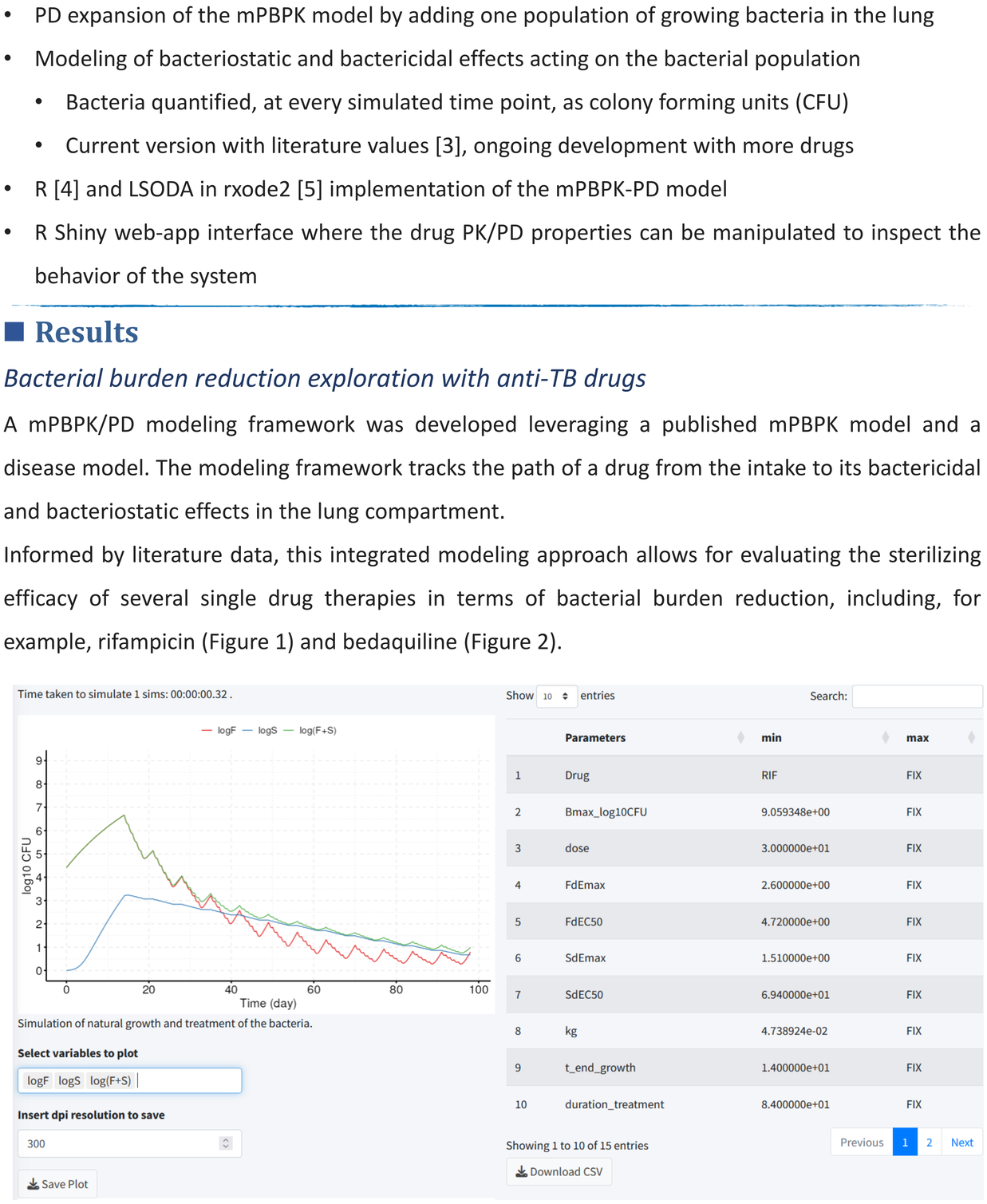

Figure 1: A screenshot of a mPBPK/PD simulation of a 84-day treatment with 30 mg/kg of rifampicin, 5 daily consecutive doses per week, after 14 days of natural growth of the bacteria.

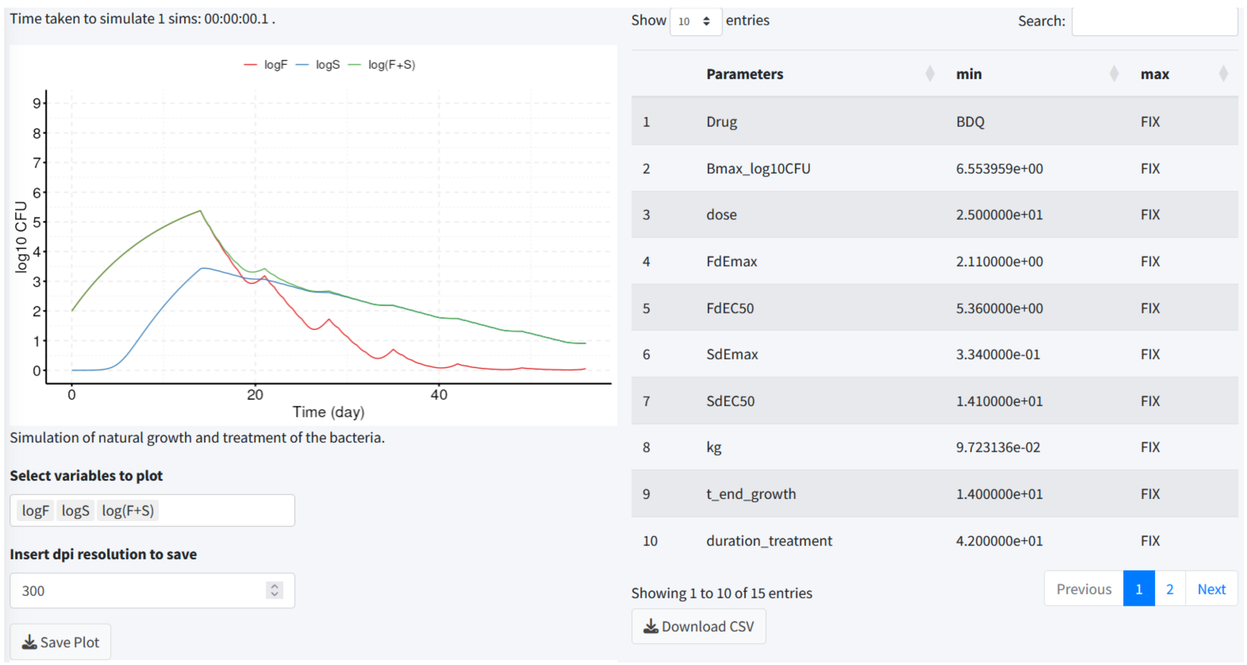

Figure 2: A screenshot of a mPBPK/PD simulation of a 42-day treatment with 25 mg/kg of bedaquiline, 5 daily consecutive doses per week, after 14 days of natural growth of the bacteria.

Simulation of a virtual experiment

The user can simulate and visualize the bacteria population profile over time with parameters sampled in a user-defined range (Figure 3). Further, the user can simulate the efficacy of a custom new drug by selecting bactericidal and bacteriostatic potency, different doses, frequencies of the doses, and treatment length (Figure 4).

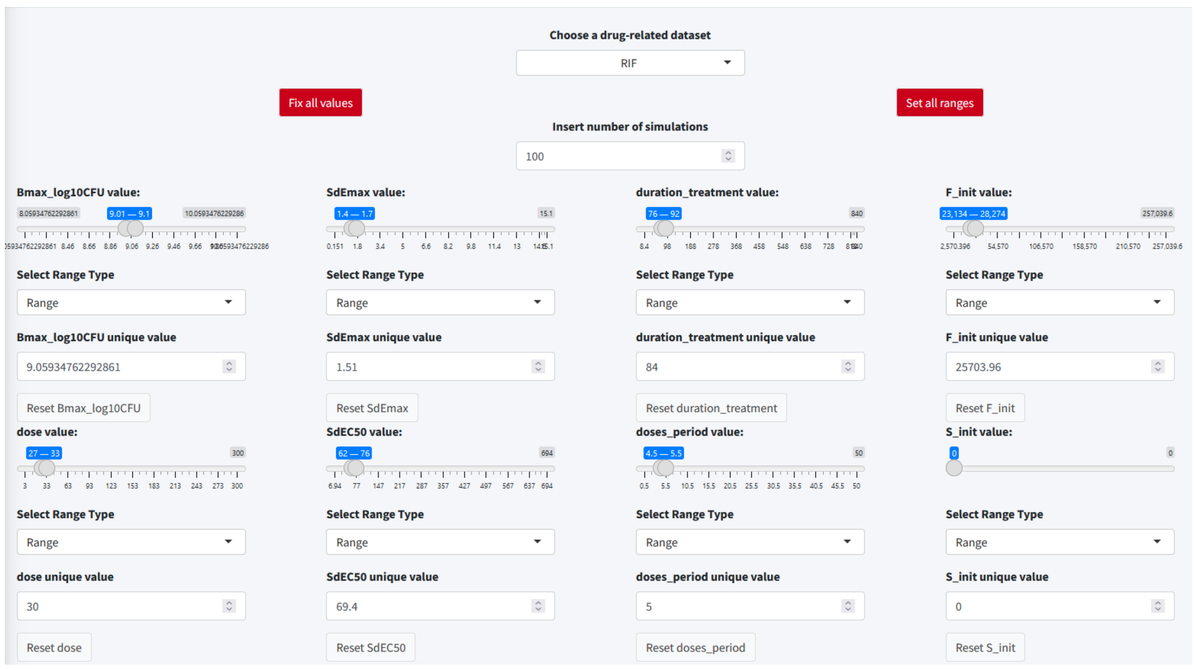

Figure 3: A screenshot of the Shiny web interface showing some of the simulation parameters. The user can choose to select single or multiple simulations, fix model parameter values or define custom ranges within a predefined set of values. It is also possible to simulate treatments with different duration, number of doses per week and different initial conditions of the bacteria.

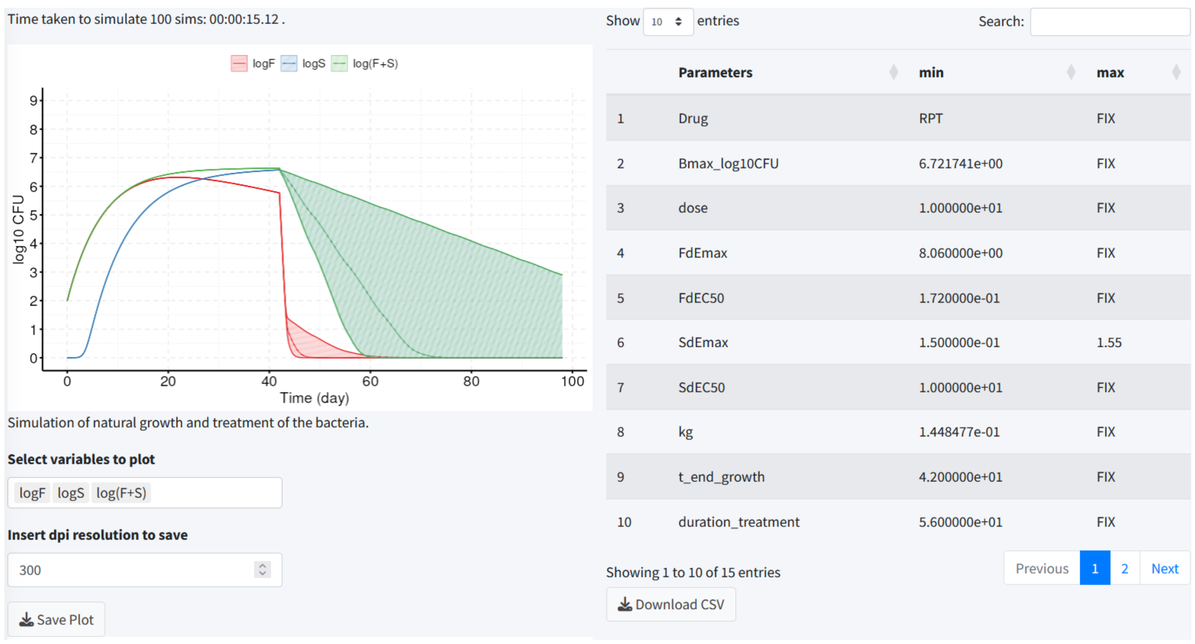

Figure 4: A screenshot of 100 mPBPK/PD simulations of a 56-day treatment with 10 mg/kg of rifapentine (RPT), 5 daily consecutive doses per week, after 42 days of natural growth of the bacteria. One parameter (*SdEmax*, the drug maximum killing rate against slow-growing population S) randomly varied between 0.15 and 1.55 1/day and another parameter (*SdEC50*, the drug potency against S) was set to a custom fixed value of 10 mg/L; the other parameters were fixed to their predefined values. The shaded areas are the 5th and 95th percentile of the 100 simulations.

Conclusions

- ✓ The proposed combined mPBPK/PD approach effectively enhances the preclinical and translational stages of drug development against tuberculosis by dynamically quantifying the potency and efficacy of a single drug.
- ✓ The parameters used in the model can be linked to relevant PK/PD indices, e.g., the minimal inhibitory or bactericidal concentration (MIC and MBC).
- ✓ We are currently investigating the addition of a post-antibiotic effect (PAE) with a compartment to include the long-term action of the drug.
- ✓ This platform will be further expanded to evaluate combination therapies, enabling additional optimization of the current regimens.
- ✓ The platform will assist in shortening treatment duration by potentially indicating specific modes of action to include in new regimens.

References

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