INDIVIDUALLY DESIGNED OPTIMUM DOSING STRATEGIES

User Manual

Basic Functions

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Introduction

Individually Designed Optimum Dosing Strategies (ID – ODS™; http://www.optimum-dosing-strategies.org/) is a therapeutic drug monitoring and simulation tool powered by the R® software (version 3.3.0; Institute for Statistics and Mathematics [http://www.r-project.org/]). Based on patient demographic information readily available at the bedside, ID – ODS™ incorporates Monte Carlo simulation and inverse Bayesian modeling into the design of personalized dosing regimens. Drug concentration-time profiles are simulated using Monte Carlo simulation and inverse modeling based on linear 1 and 2-compartment intravenous or oral infusion models written in the R® language using the published, validated population pharmacokinetic parameter values and respective inter-individual variability. This manual presents background information for the Basic functionality.

Citing ID-ODS™

Web: in text of document as: http://www.optimum-dosing-strategies.org/id-ods/

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and use such content and information in accordance with applicable personal data privacy laws.

System Requirements and Installation

The Web Application runs in our hosted environment and accessible from mobile or desktop devices via any standard web browser and is available from the http://www.optimum-dosing-strategies.org/id-ods/ site. **Google Chrome or Mozilla Firefox with HTML5 and CSS3 support are recommended. THIS IS GREAT FOR iOS users!**

The platform is also available as a service, via the use of a standardized table format for data load, so can be integrated in any online application via a link or into a frame.

Getting Help and Updates

The web application is updated by the ID-ODS™ team in our hosted environment, so thus always runs the most recent version of the ID-ODS™ platform. In order to get help with profile specific questions the user should download all input by clicking on the Help button and send the zip file to odsadmin@optimum-dosing-strategies.org.

ID-ODS™ Components

Monte Carlo Simulation

A Monte Carlo simulation is a mathematical model developed in the early 1940s to produce scenarios that require the generation of random numbers. It has many applications in physics, finance and business, and artificial intelligence. In the setting of antibiotic therapy, Monte Carlo simulations can combine pharmacokinetic and microbiological data to predict the likelihood an antimicrobial regimen will achieve a therapeutic target. This is called the probability of target attainment (PTA) where the target to be achieved is an optimal pharmacodynamic parameter for bacterial killing when considering only MICs of single values versus it is called Cumulative Fraction of Response (CFR) when considering an entire population of microorganisms. This technique is often useful in instances where the option of therapeutic drug monitoring is not available for certain antimicrobial agent.

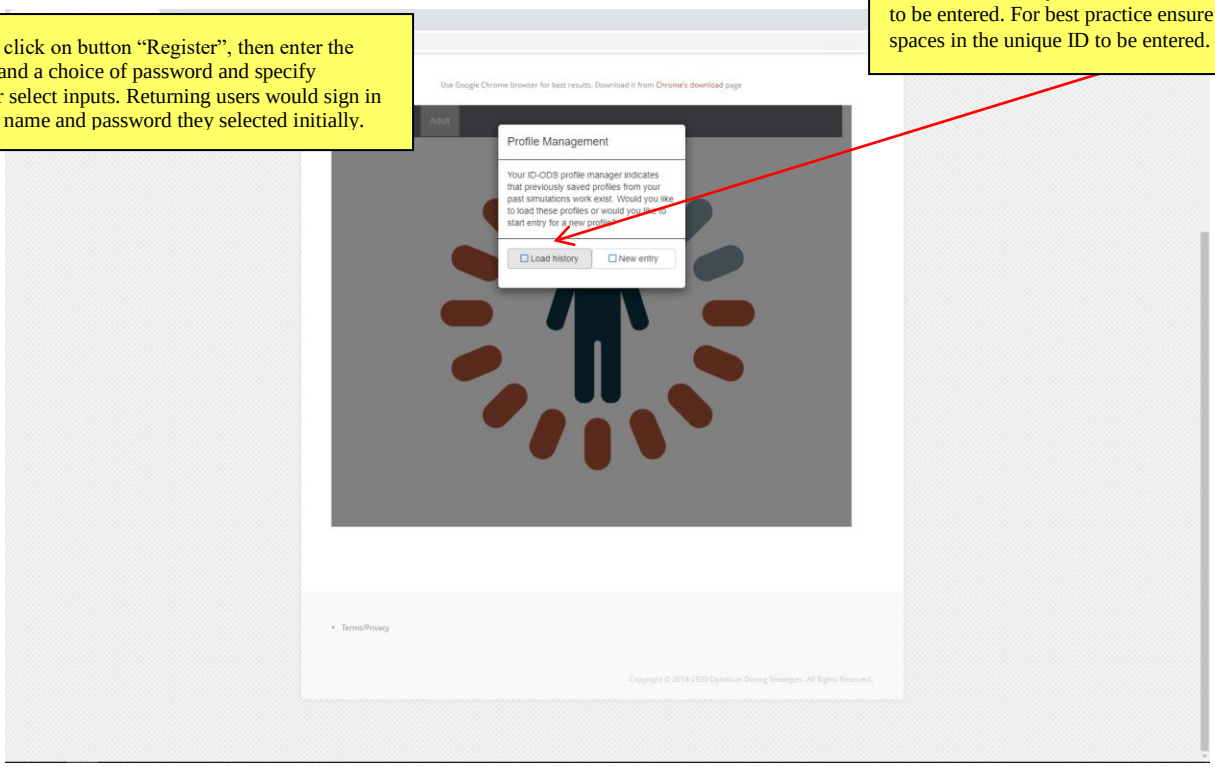
Inverse Bayesian modeling

The selection of antibiotic dosage regimen in the absence of measured concentrations (ie., a priori dosing) is based on estimates of the patient's pharmacokinetic parameters adjusted for patient covariates or known demographics (ie., weight, age, sex, serum creatinine). During inverse modelling, the use of measured drug levels (ie. a posteriori dosing) is to estimate the patient's pharmacokinetic parameters from the measured antibiotic concentrations with relying on the population model. This Bayesian approach incorporates both sets of data (ie: the actual measured concentration and the population pharmacokinetic model) for estimating the patient specific pharmacokinetic parameters. It uses the a priori pharmacokinetic parameters of the population model as some starting estimate for the patient; it then adjusts these estimates based on the patient's measured antibiotic levels, taking into consideration the inter-individual variability of the population parameters and the variability of the serum level measurement. During the procedure, the serum level data is interpreted by incorporating both the variability of the population model and the variability of the serum level measurement itself. Bayes' theorem tells us quantitatively just how important every piece of information is, however it is not always able to tell whether a piece of information is relevant to the actual patient care.

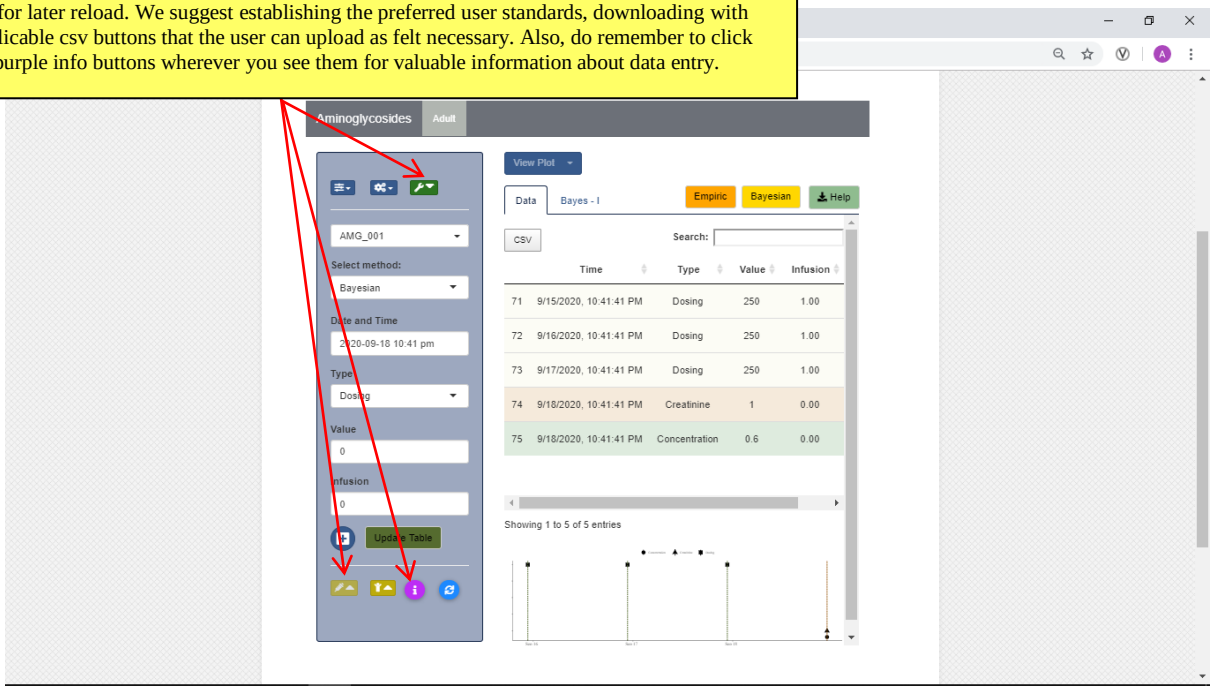
First time users sign up to the app and general settings options

First time user click on button “Register”, then enter the email address and a choice of password and specify preferences for select inputs. Returning users would sign in with their user name and password they selected initially.

Once logged in, users may load previously saved profiles or start entry for a new profile. Past profiles will automatically be purged from active use in the system if no simulations were done on them in the past 14 days. If “New entry” is selected then the system will ask for a unique ID to be entered. For best practice ensure no empty spaces in the unique ID to be entered.



Next step after log in is naturally to review simulation settings by clicking on the following buttons to set your simulation preferences. Some -but not all- of these settings will be saved in the profile for later reload. We suggest establishing the preferred user standards, downloading with the applicable csv buttons that the user can upload as felt necessary. Also, do remember to click on the purple info buttons wherever you see them for valuable information about data entry.

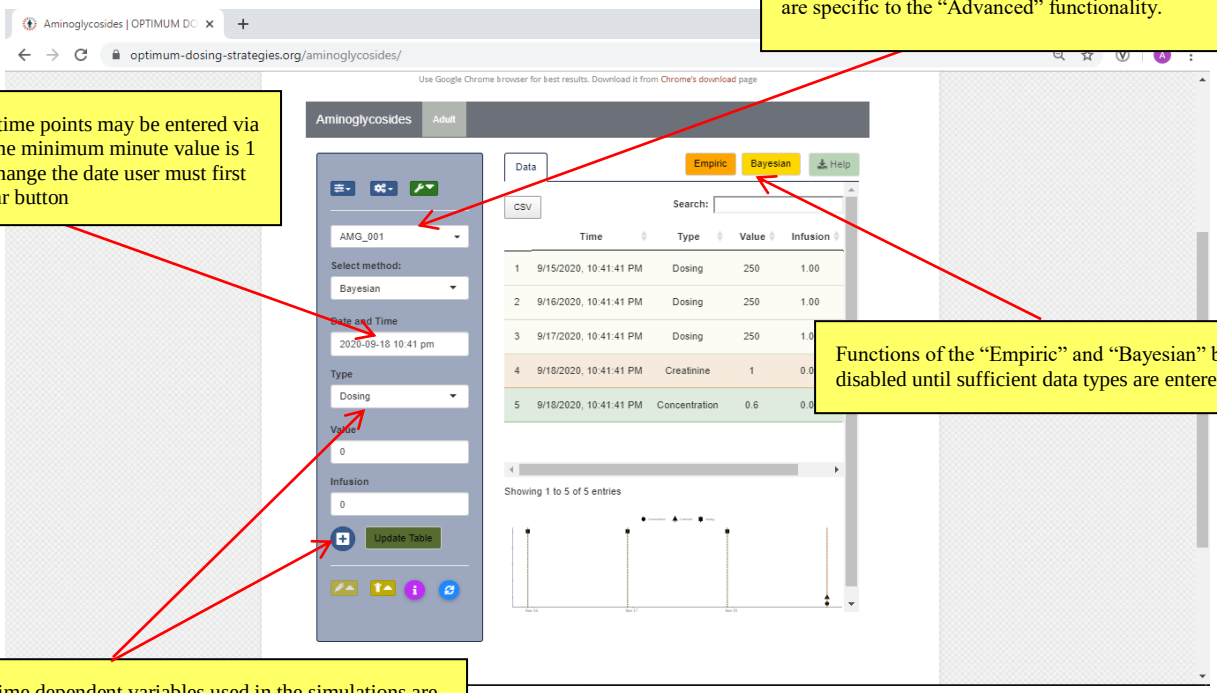


General overview of the a priori dosing and the Bayesian user interface using the Aminoglycosides example

I. User Interface and data input

User will select previously saved profiles via the search space. Each profile saved refers to a data set entered for Bayesian or Monte Carlo simulation routines. Some Monte Carlo profiles are specific to the "Advanced" functionality.

All date and time points may be entered via the picker. The minimum minute value is 1 minute. To change the date user must first press the clear button

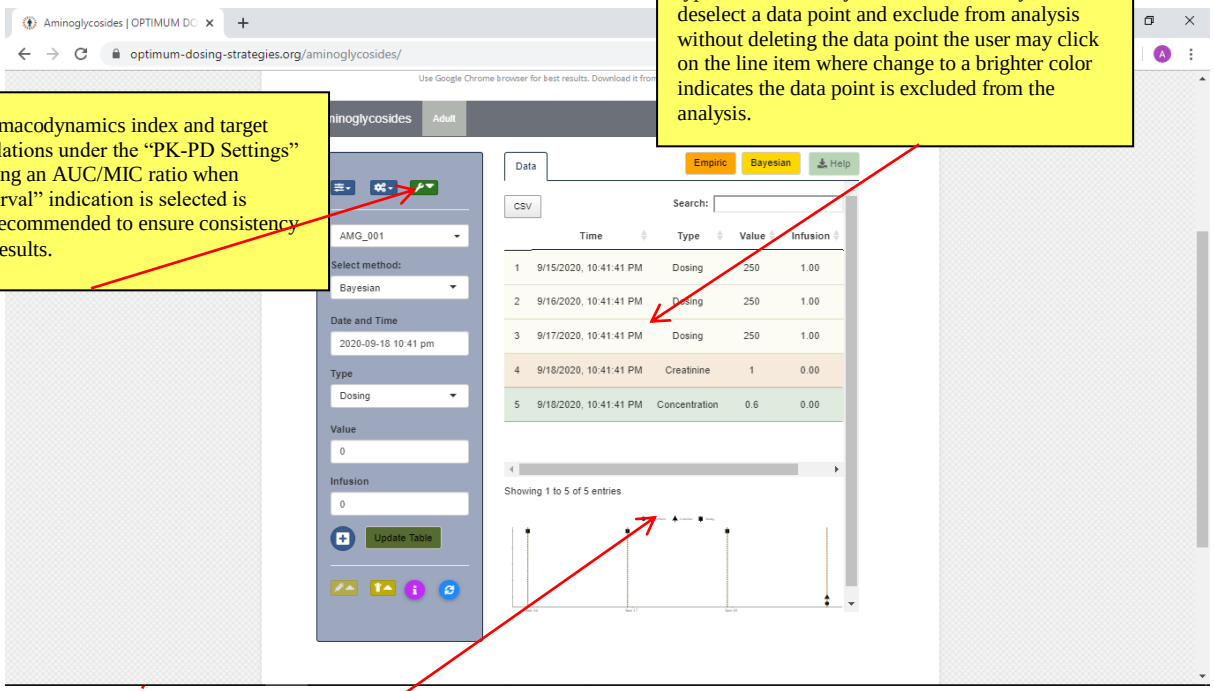


Functions of the "Empiric" and "Bayesian" buttons are disabled until sufficient data types are entered.

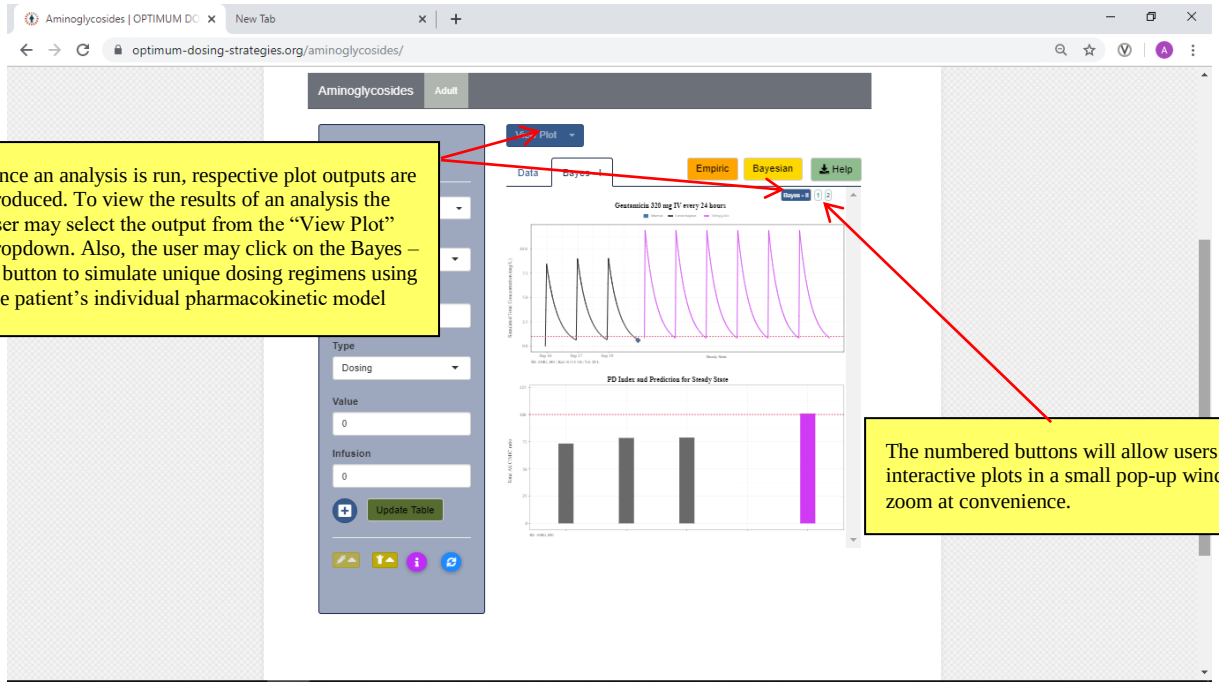
All time dependent variables used in the simulations are labeled with a type, User to select as appropriate. To enter multiple inputs at set intervals the user should use the "Quick-Add" button. Press the "Update Table" button to add selection to the table.

The table will show inputs color coded. Any data type entered initially is selected for analysis. To deselect a data point and exclude from analysis without deleting the data point the user may click on the line item where change to a brighter color indicates the data point is excluded from the analysis.

Set target pharmacodynamics index and target value for simulations under the "PK-PD Settings" button. Targeting an AUC/MIC ratio when "Extended interval" indication is selected is generally not recommended to ensure consistency of simulation results.



The plot show visual representation of the data points entered above in the table

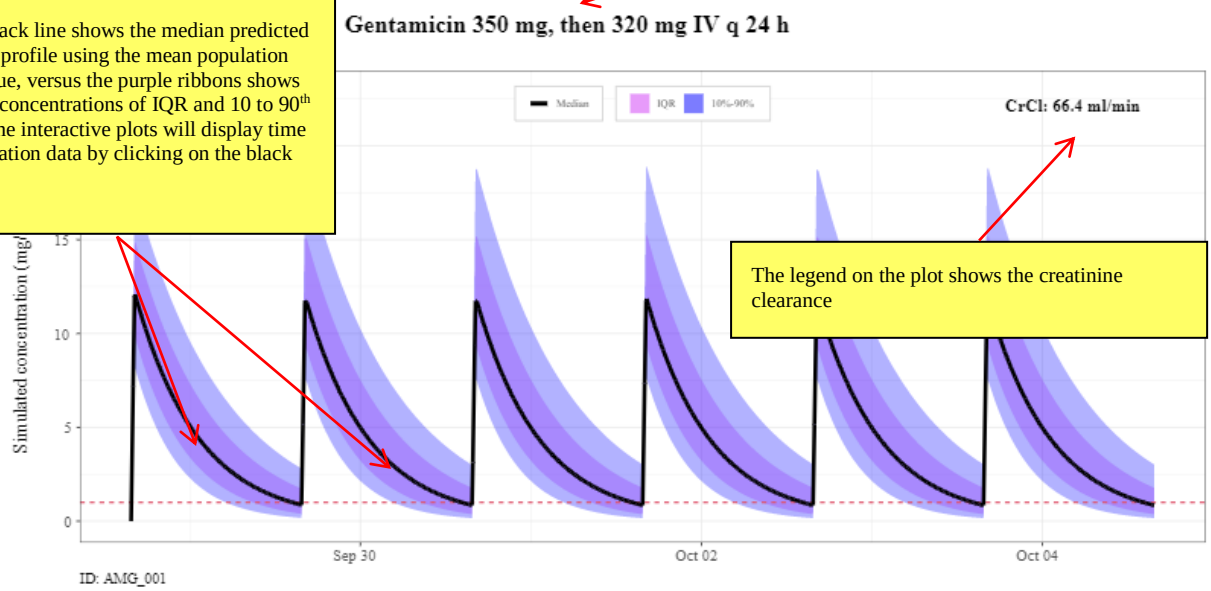


II. Output plots

A. A – priory dosing

The plot title displays the calculated drug's name, the loading dose, and the subsequent maintenance dose, followed by the dosing interval.

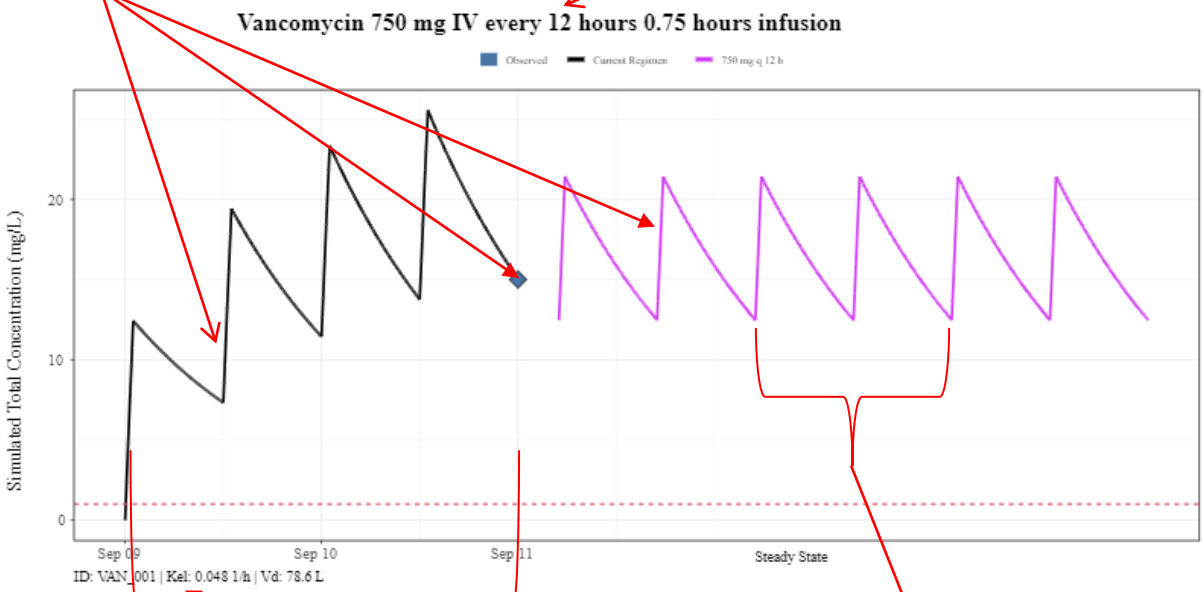
The plotted black line shows the median predicted concentration profile using the mean population parameter value, versus the purple ribbons shows the simulated concentrations of IQR and 10 to 90th percentiles. The interactive plots will display time specific simulation data by clicking on the black line



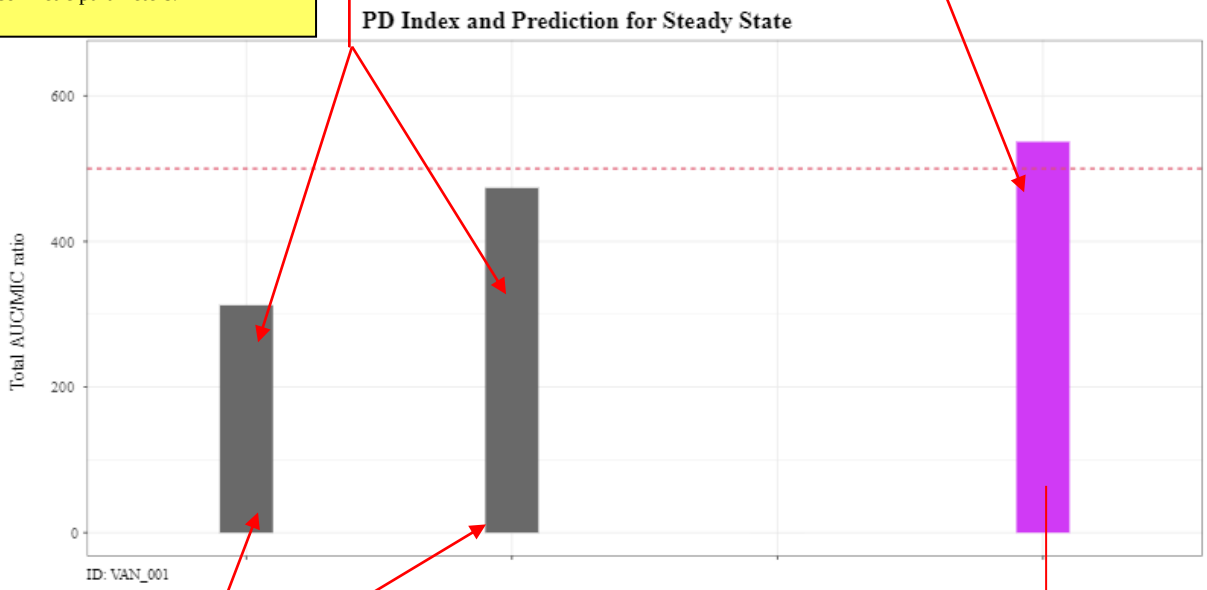
B. A – posteriori dosing

The plotted black line shows the predicted concentration - time profile using the individual pharmacokinetic parameter values established by fitting the measured concentrations (blue dots) with the Bayesian system. The purple line represents predicted steady state concentration for the optimal regimen.

The plot title displays the calculated drug's name, the optimal dose (rounded), followed by the optimal dosing interval designed to achieve the target concentrations. The calculation is based on the assumption of steady state.

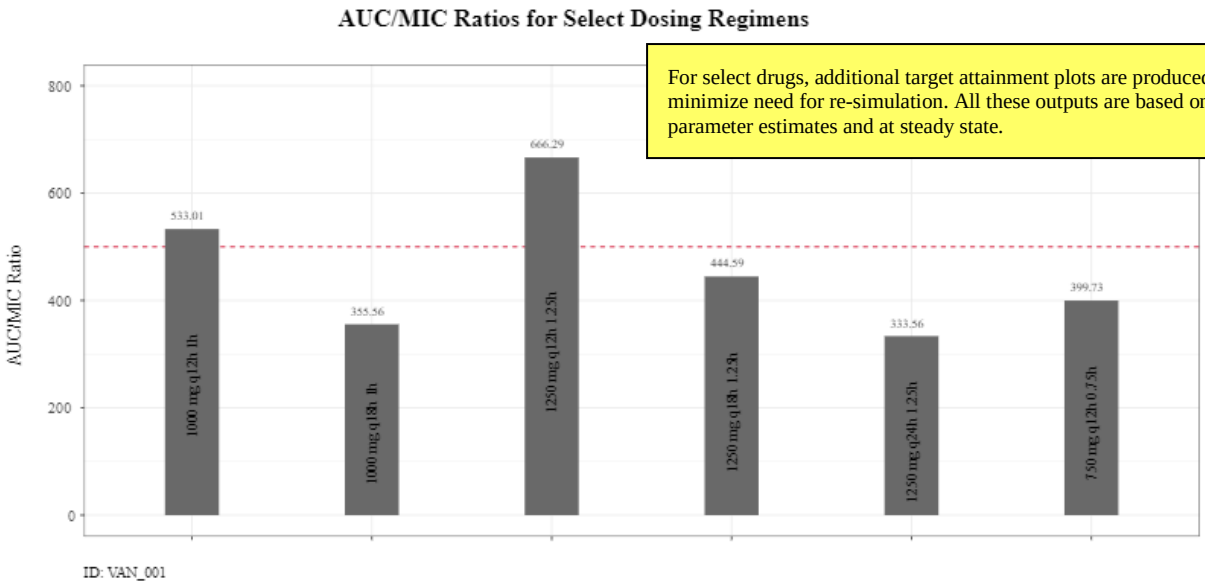


The footnote on the plot shows the individual specific pharmacokinetic parameters.



The calculated daily AUCs labelled as "SS" or Steady State is estimated for 24 hours of the recommended steady state dose.

The calculated daily AUCs are estimated for the full time frame under the black concentration-time profile displayed in plot on top. In the example here, we plotted approximately 48 hours' worth of concentration profile; hence the AUCs are calculated for 2 full days. A fractional AUC on the last day/s will be calculated if the full time course can not be divided into full 24 h intervals..

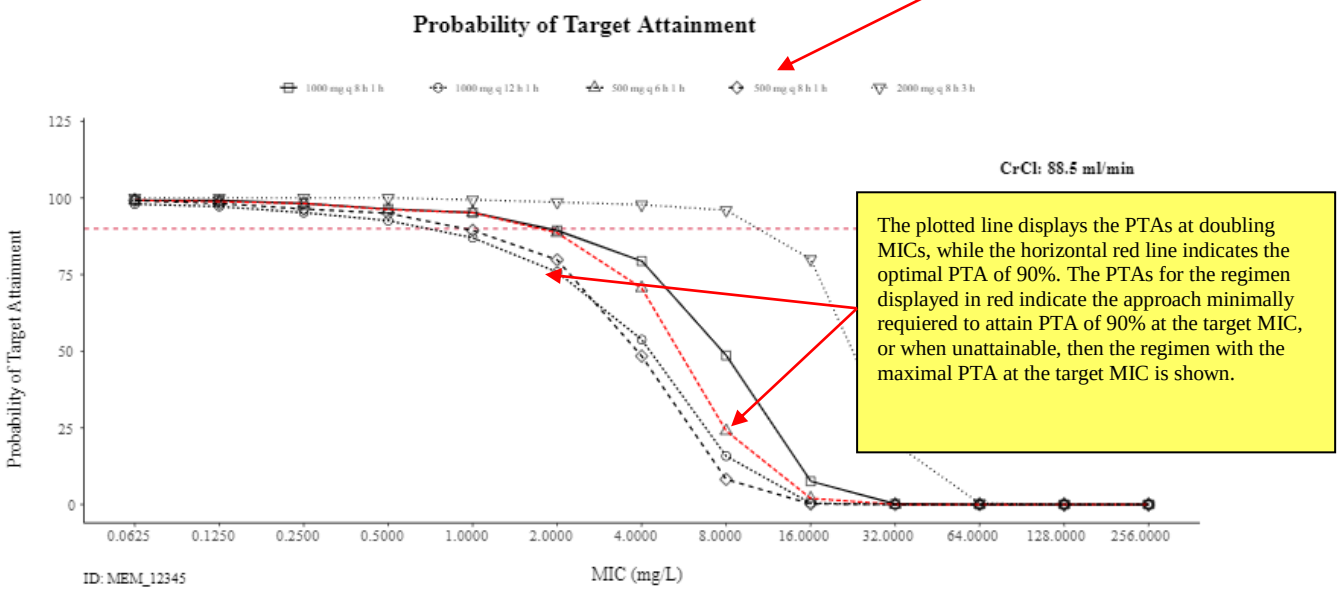


General overview of the Monte Carlo Simulation user interface using the Meropenem example

I. Output plots

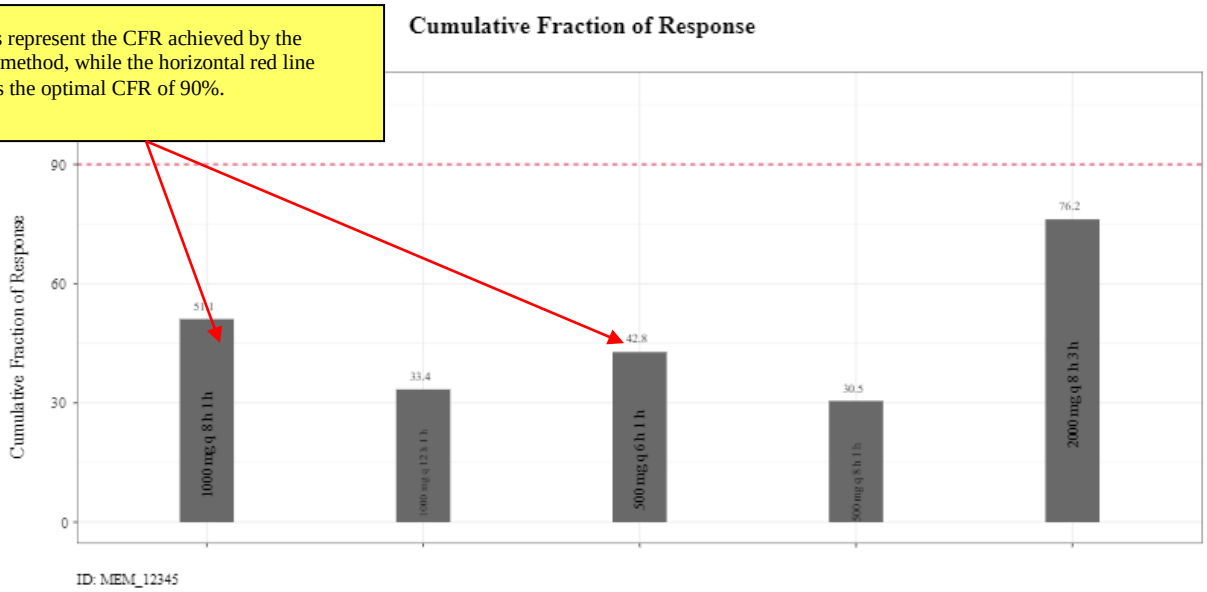
The plot legend displays the various simulated drug's dose, followed by the dosing interval and infusion time.

A. Probability of target Attainment (PTA) plots



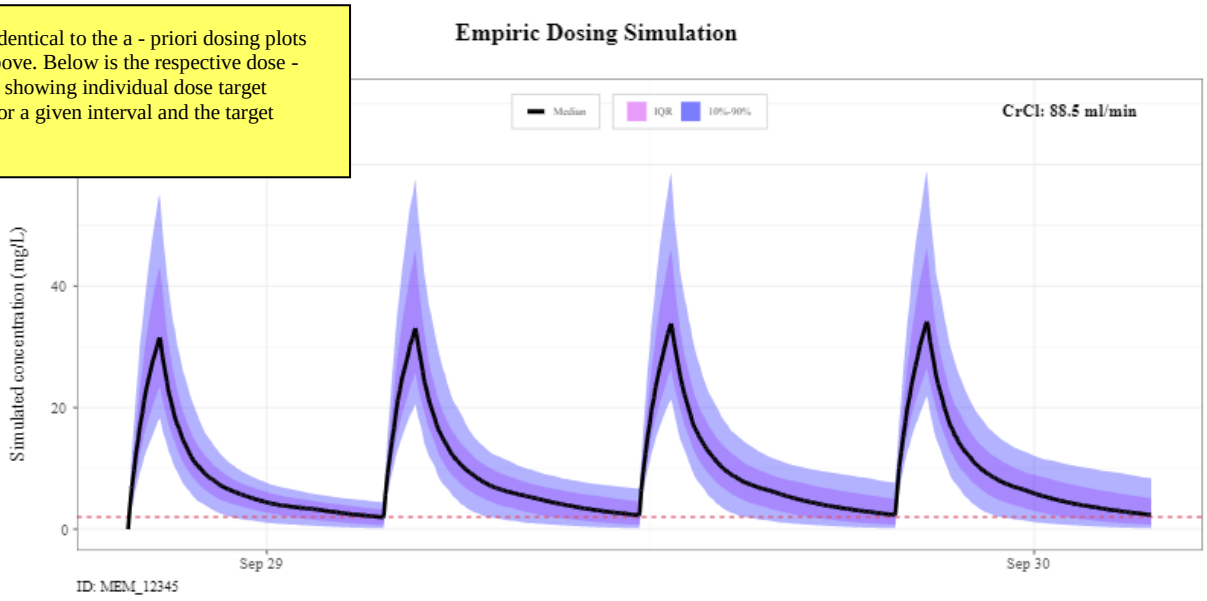
B. Cumulative Fraction of Response (CFR) plots

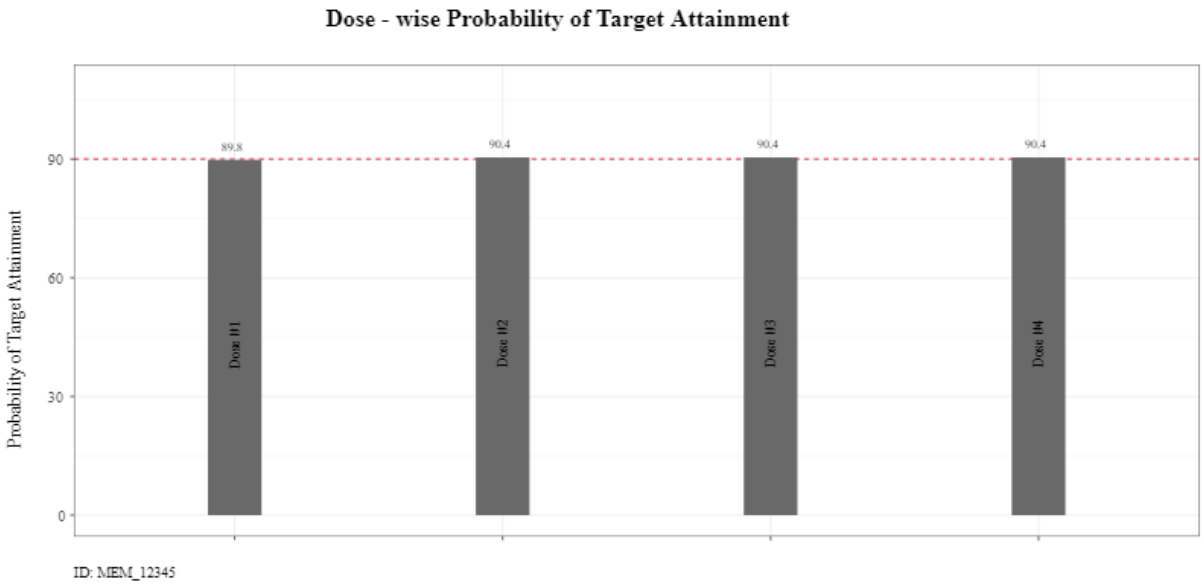
The bars represent the CFR achieved by the specific method, while the horizontal red line indicates the optimal CFR of 90%.



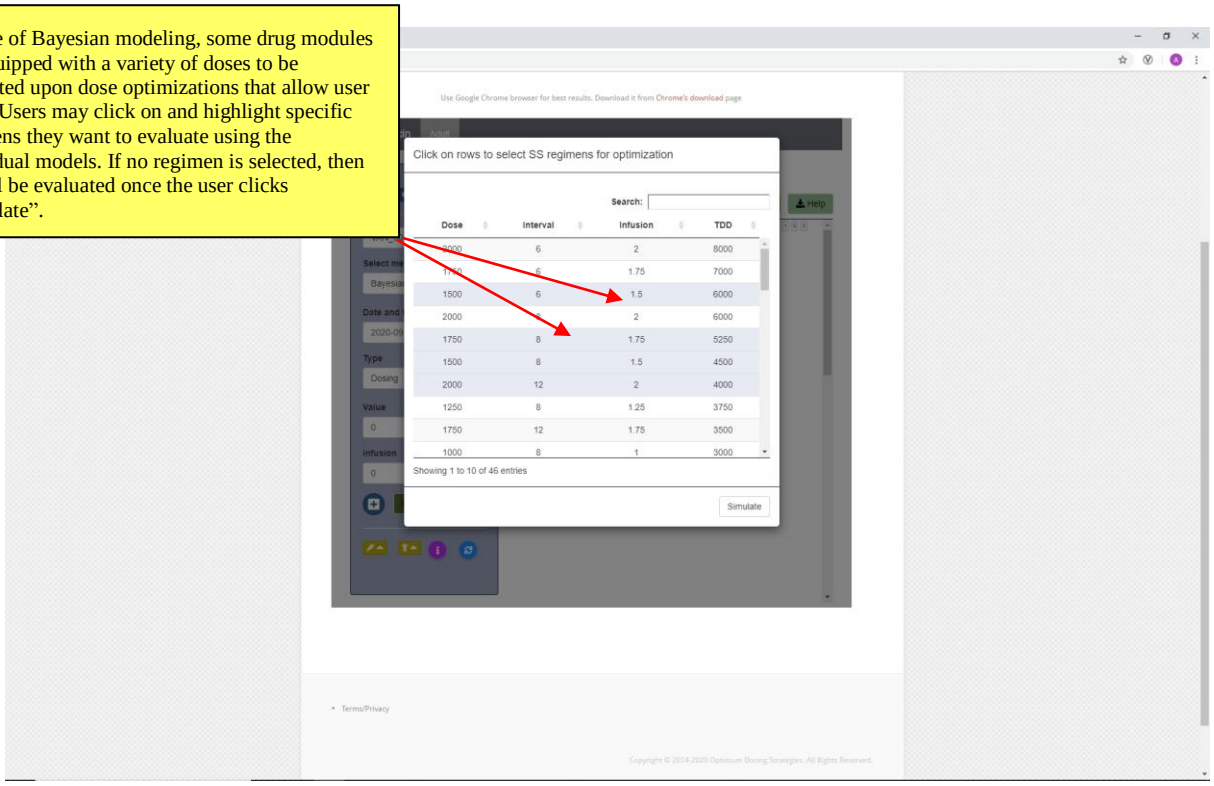
C. Single Dose Exposure plots

The plot is identical to the a - priori dosing plots described above. Below is the respective dose - wise barplot showing individual dose target attainment for a given interval and the target specified.





In case of Bayesian modeling, some drug modules are equipped with a variety of doses to be evaluated upon dose optimizations that allow user input. Users may click on and highlight specific regimens they want to evaluate using the individual models. If no regimen is selected, then all will be evaluated once the user clicks "Simulate".



Drug models

ID – ODS^{TM} system utilizes peer reviewed, published pharmacokinetic models in the calculation of drug specific kinetic and dynamic indices. The list of antibiotics and respective pharmacokinetic models coded in the application are as follows:

1. *Aminoglycosides*

Pai MP, Nafziger AN, Bertino JS. Simplified Estimation of Aminoglycoside Pharmacokinetics in Underweight and Obese Adult Patients. Antimicrobial Agents and Chemotherapy. 2011;55(9):4006-4011. doi:10.1128/AAC.00174-11.

2. *Cefepime*

Nicasio AM, Ariano RE, Zelenitsky SA, et al. Population Pharmacokinetics of High-Dose, Prolonged-Infusion Cefepime in Adult Critically Ill Patients with Ventilator-Associated Pneumonia . Antimicrobial Agents and Chemotherapy. 2009;53(4):1476-1481. doi:10.1128/AAC.01141-08.

3. *Ceftazidime*

Georges B, Conil J-M, Seguin T, et al. Population Pharmacokinetics of Ceftazidime in Intensive Care Unit Patients: Influence of Glomerular Filtration Rate, Mechanical Ventilation, and Reason for Admission . Antimicrobial Agents and Chemotherapy. 2009;53(10):4483-4489. doi:10.1128/AAC.00430-09.

4. *Ceftriaxone - soon to come back*

Garot D, Respaud R, Lanotte P, et al. Population pharmacokinetics of ceftriaxone in critically ill septic patients: a reappraisal. British Journal of Clinical Pharmacology. 2011;72(5):758-767. doi:10.1111/j.1365-2125.2011.04005.x.

5. *Ciprofloxacin- soon to come back*

Khachman, D., Conil, J., Georges, B., Saivin, S., Houin, G., Toutain, P., & Laffont, C. M. (2011). Optimizing ciprofloxacin dosing in intensive care unit patients through the use of population pharmacokinetic-pharmacodynamic analysis and Monte Carlo simulations. Journal of Antimicrobial Chemotherapy, 66(8), 1798-1809. doi:10.1093/jac/dkr220

6. *Daptomycin- soon to come back*

Dvorchik B, Arbeit RD, Chung J, Liu S, Knebel W, Kastrissios H. Population Pharmacokinetics of Daptomycin. Antimicrobial Agents and Chemotherapy. 2004;48(8):2799-2807. doi:10.1128/AAC.48.8.2799-2807.2004.

7. Levofloxacin- soon to come back

Preston SL, Drusano GL, Berman AL, et al. Levofloxacin Population Pharmacokinetics and Creation of a Demographic Model for Prediction of Individual Drug Clearance in Patients with Serious Community-Acquired Infection. Antimicrobial Agents and Chemotherapy. 1998;42(5):1098-1104.

8. Meropenem

Crandon, J. L., Ariano, R. E., Zelenitsky, S. A., Nicasio, A. M., Kuti, J. L., & Nicolau, D. P. (2010). Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Medicine, 37(4), 632-638. doi:10.1007/s00134-010-2105-0

9. Piperacillin and tazobactam

Felton TW, Roberts JA, Lodise TP, et al. Individualization of Piperacillin Dosing for Critically Ill Patients: Dosing Software To Optimize Antimicrobial Therapy. Antimicrobial Agents and Chemotherapy. 2014;58(7):4094-4102. doi:10.1128/AAC.02664-14.

Patel N, Scheetz MH, Drusano GL, Lodise TP. Identification of Optimal Renal Dosage Adjustments for Traditional and Extended-Infusion Piperacillin-Tazobactam Dosing Regimens in Hospitalized Patients . Antimicrobial Agents and Chemotherapy. 2010;54(1):460-465. doi:10.1128/AAC.00296-09.

10. Polymixin- soon to come back

Sandri, A. M., Landersdorfer, C. B., Jacob, J., Boniatti, M. M., Dalarosa, M. G., Falci, D. R., Zavascki, A. P. (2013). Population Pharmacokinetics of Intravenous Polymyxin B in Critically Ill Patients: Implications for Selection of Dosage Regimens. Clinical Infectious Diseases, 57(4), 524-531. doi:10.1093/cid/cit334

11. Telavancin- soon to come back

Samara E, Shaw J-P, Barriere SL, Wong SL, Worboys P. Population Pharmacokinetics of Telavancin in Healthy Subjects and Patients with Infections. Antimicrobial Agents and Chemotherapy. 2012;56(4):2067-2073. doi:10.1128/AAC.05915-11.

12. Tigecycline- soon to come back

Van Wart SA, Owen JS, Ludwig EA, Meagher AK, Korth-Bradley JM, Cirincione BB. Population Pharmacokinetics of Tigecycline in Patients with Complicated Intra-Abdominal or Skin and Skin Structure Infections . Antimicrobial Agents and Chemotherapy. 2006;50(11):3701-3707. doi:10.1128/AAC.01636-05.

Rubino CM, Forrest A, Bhavnani SM, et al. Tigecycline Population Pharmacokinetics in Patients with Community- or Hospital-Acquired Pneumonia . Antimicrobial Agents and Chemotherapy. 2010;54(12):5180-5186. doi:10.1128/AAC.01414-09.

13. Vancomycin

Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. Antimicrobial Agents and Chemotherapy. 1984;25(4):433-437.

Goti V, Chaturvedula A, Fossler MJ, Mok S, Jacob JT. Hospitalized Patients With and Without Hemodialysis Have Markedly Different Vancomycin Pharmacokinetics: A Population Pharmacokinetic Model-Based Analysis. Ther Drug Monit. 2018 Apr;40(2):212-221.

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