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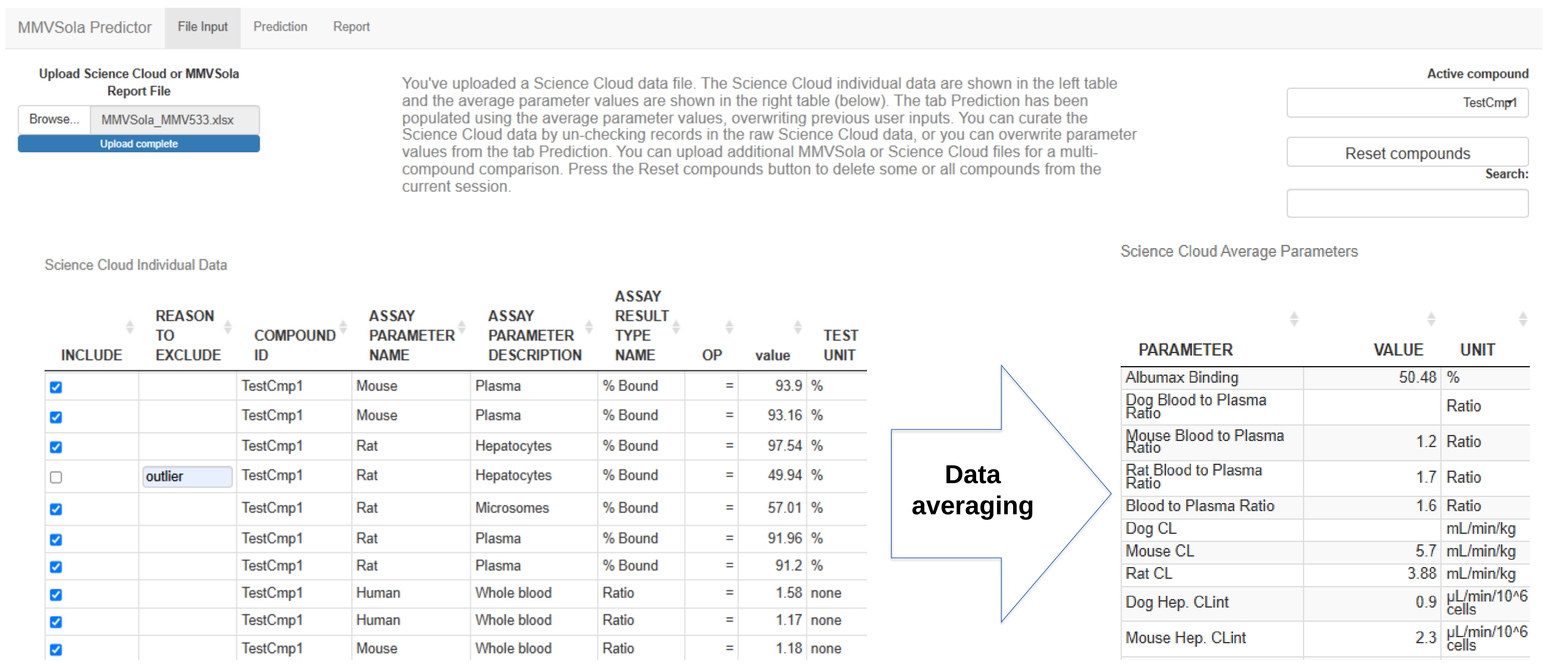
MMVSola

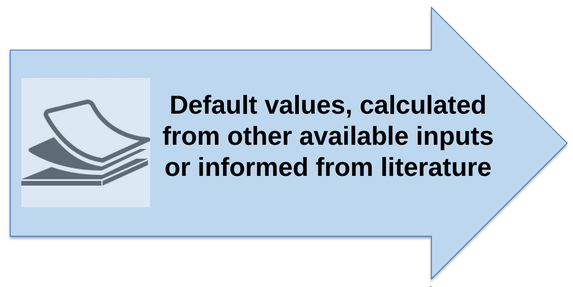
An Early PK/PD and Dose Predicting Tool for Antimalarial Drug Development

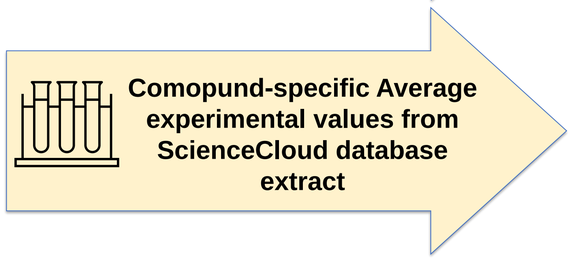
MMVSola[1] is a web-based open access pharmacokinetic (PK)/ pharmacodynamic (PD) application for early prediction of (i) human PK and (ii) estimation of the dose required to deliver a defined reduction in parasitemia or to guarantee chemoprevention for a defined period. The tool assists teams in Lead Optimization to optimize compounds, without the need for specialist PK/PD simulation scientists, and reducing the necessity for numerous mice experiments. The application can be securely accessed at www.MMVSola.org

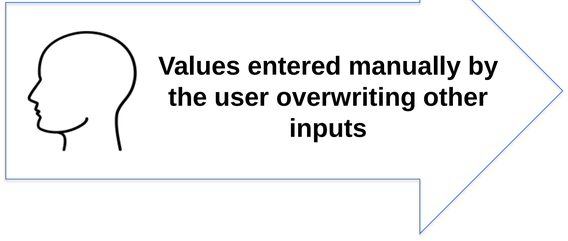
Input

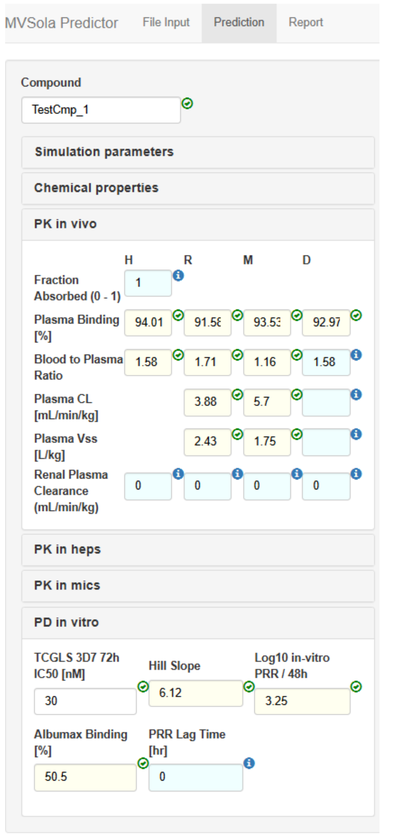
From the File Input tab, the user inputs in-vitro or mouse experimentally derived parameters, by uploading a ScienceCloud data-base extract file or a previously generated MMVSola Excel report. The user can review and curate this data by excluding individual records from the input averaging.











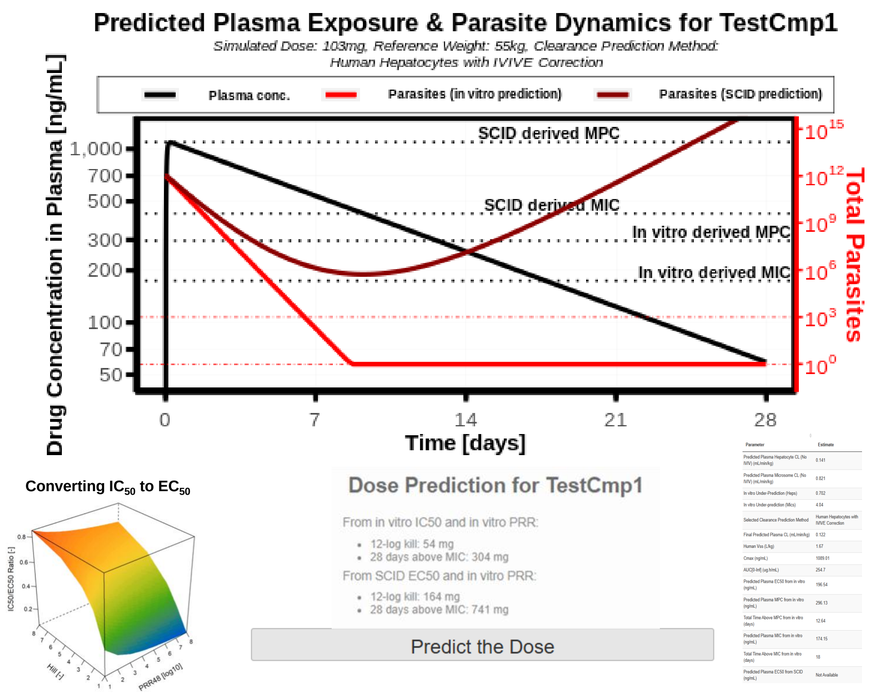
It is possible to upload multiple files. Each input file may contain data for multiple test compounds. At any time, the data for a single “active” compound is displayed in the web interface.

Prediction

The Prediction tab summarizes the PK/PD and dose prediction for the selected active compound and allows the user to interactively test changing the values of any input parameter.

Human Pharmacokinetics:

- **PK is a function of Volume of distribution, Clearance (Vd, CL)[2]**
- **MMVSola predicts the human plasma concentration-time profile based on:**
  - *a one-compartment in-vivo model*
  - *in-vitro to in-vivo extrapolation (IVIVE) from hepatocyte and/or microsome intrinsic clearance (CLint) data (the assay with best $IVIVC_{m,r,d}$ is selected)*
  - *well-stirred liver model with full in-vitro and in-vivo binding correction*
  - *Volume of distribution ($Vd_{ss,u}$) and fraction absorbed estimated from animal data, i.e. Hu $Vd_{ss,u} = \mu\, Vd_{ss,u}(m,r,d)$*
  - *any known underprediction of clearance observed in the animal species*
  - *defined single or multiple doses*



Human Pharmacodynamics:

Parasite counts are computed dynamically using parasite growth and death kinetics and free drug concentrations, which are changing over time, using a direct E_{max} PD model.[3] Parasite death depends on free drug concentrations via a sigmoid function with E_{max} (maximum kill rate), EC_{50} (half-E_{max} drug concentration) and Hill slope.

- **E_{max} is measured in vitro using a standardized parasite reduction ratio (PRR) assay**
- **EC_{50} and Hill slope can be determined in-vitro from a 72h TCGLS 3D7 assay (IC_{50}), or in-vivo from modelled mouse data**
- **MPC (max parasiticidal concentration) is calculated from EC_{50} and Hill.**
- **Dose is calculated for defined PD endpoints (for a 55Kg adult):**
  - *12-log_{10} kill (treatment, i.e. TCP1-TPP1)[4]*
  - *t > MIC for 28d (prophylaxis, i.e. TCP1-TPP2)[4]*
- **Predictions for single or multiple dose are possible.**

Report

The Report tab allows to customize the generation of a report. This is a multi-sheet Excel document providing details on the predictions as well as coloured tables comparing the predictions for multiple candidate antimalarial drugs. An MMVSola Excel report can be uploaded as input file.

Implementation

MMVSola[1] was developed in a collaboration between MMV and IntiQuan AG, using the R-packages MMVshiny[5], IQRtools[6], and MMVmalaria[5]. MMVshiny orchestrates the high-level user interface, the specification of input parameters, and rule-based imputation of default values for missing inputs. IQRtools and MMVmalaria are the backbone of MMV’s PK/PD modeling and simulation framework. These packages are available under open-source licenses[5,6].

Conclusions

MMVSola represents a significant advancement in the field of antimalarial drug development. Its ability to provide actionable insights early in the development process makes it an invaluable resource for researchers and pharmaceutical companies. By leveraging preclinical data in an efficient way, MMVSola contributes to the global effort to combat malaria.

References:
(1) www.MMVSola.org was named to commemorate Suresh Solapure, a scientist at MMV who passed away in 2016. Suresh was an early champion of pharmacokinetic and pharmacodynamic data modelling to predict human dose. (2) Pharmacokinetics and Metabolism in Drug Design. Smith, D. A.; Allerton, C.; Kalgutkar, A. S.; Waterbeemd, Han van de.; Walker, D. K. Wiley, 2012, ISBN: 978-3-527-32954-0. (3) Pharmacokinetic/pharmacodynamic modelling of the antimalarial effect of Actelion-451840 in an induced blood stage malaria study in healthy subjects. Krause, A. et. al. British Journal of Clinical Pharmacology 2016; 82: 412. (4) New developments in anti-malarial target candidate and product profiles. J.N. Burrows et.al.. Malaria Journal. 2017; 16: 26. (5) https://github.com/MMVverse (6) https://iqrtools.intiquan.com

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