H3D Foundation and Ersilia Present

Bringing data science and AI/ML tools to infectious disease research

Session 3: Skills session

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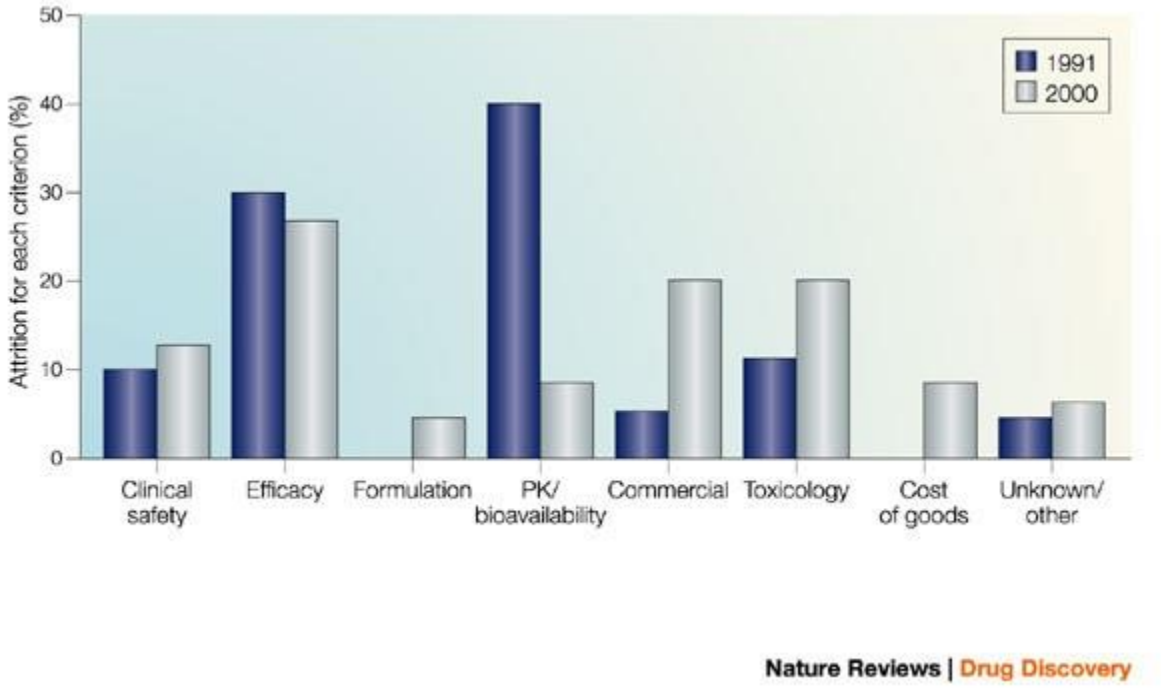
CS&S Code for Science & Society

Evolution of DMPK



1950s – 1980s
Pharmacodynamic drug discovery

1990s
High throughput DMPK driven by revolution in analytical tools and robotics

2000s
Assay refinement for IVIVC + QSAR + mechanistic models

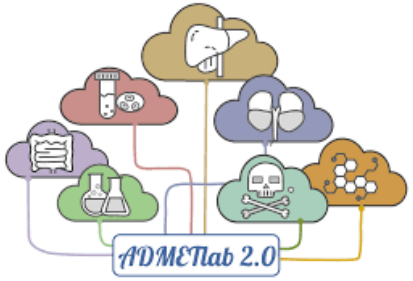
Modern era
High throughput DMPK + Modelling and Simulation + AI/ML-based predictions for compound design etc

Computational Tools in DMPK

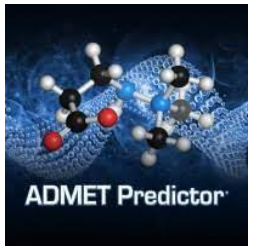
Ersilia

H3D FOUNDATION

Screening | Hit Validation | Formal Hit Assessment | Hit to Lead | Lead Optimisation | Candidate Profiling | Pre-clinical development | Clinical development



StarDrop™



PK-Sim®

MD

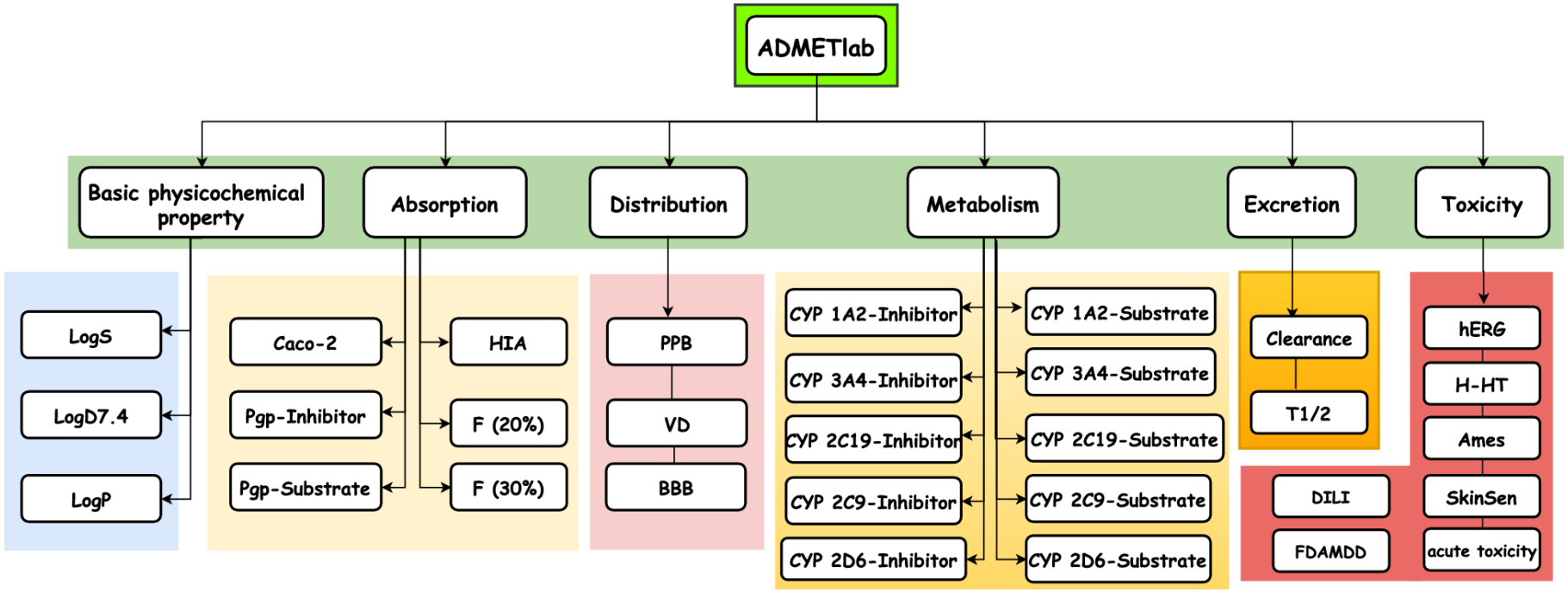
PK-Sim®

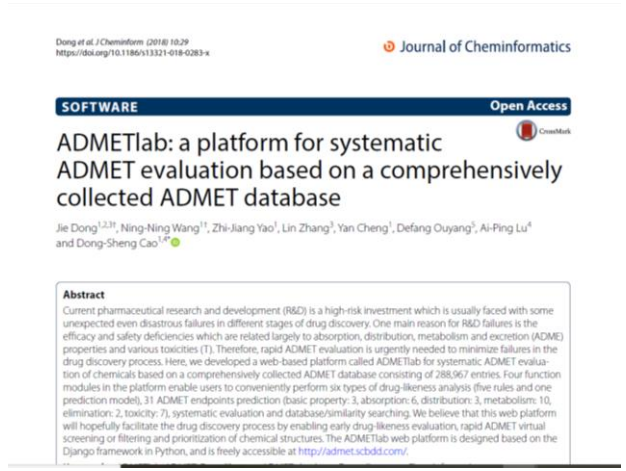
Scientastic

SIB Swiss Institute of Bioinformatics

SwissADME

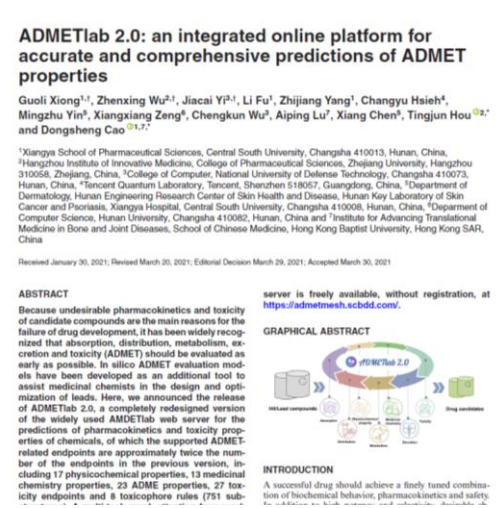
ADMETLab




Journal of Cheminformatics

SOFTWARE Open Access

ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database


ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties

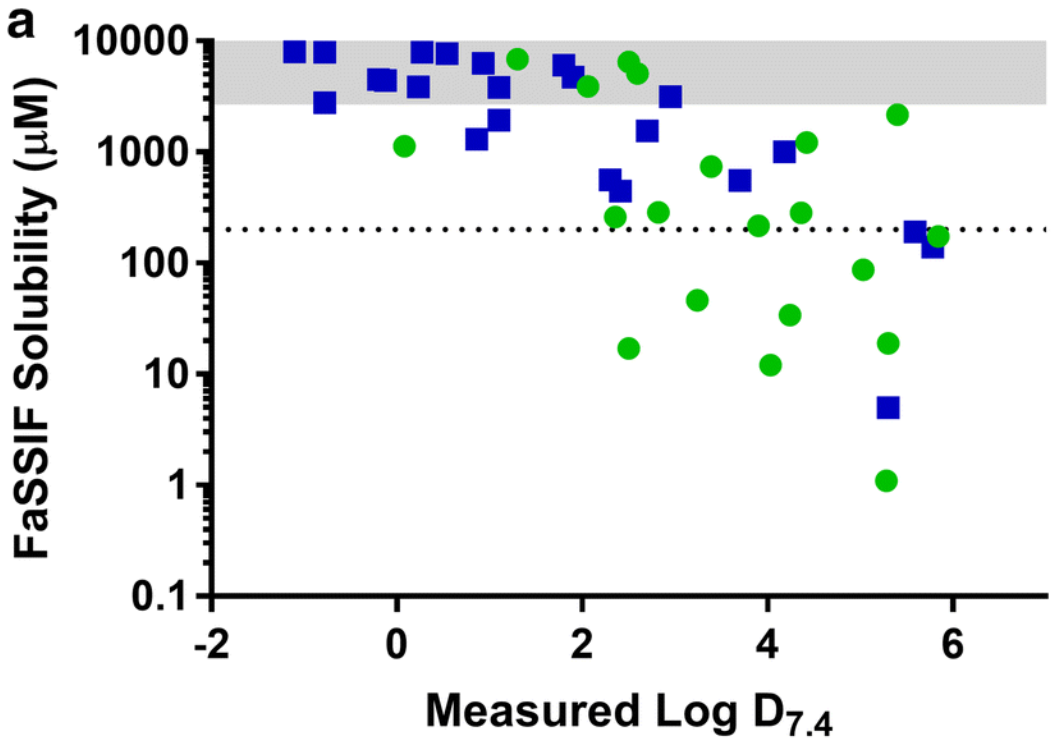
- ADMETLab is implemented on the Ersilia Model Hub (eos2re5)

ADMETLab skills workshop

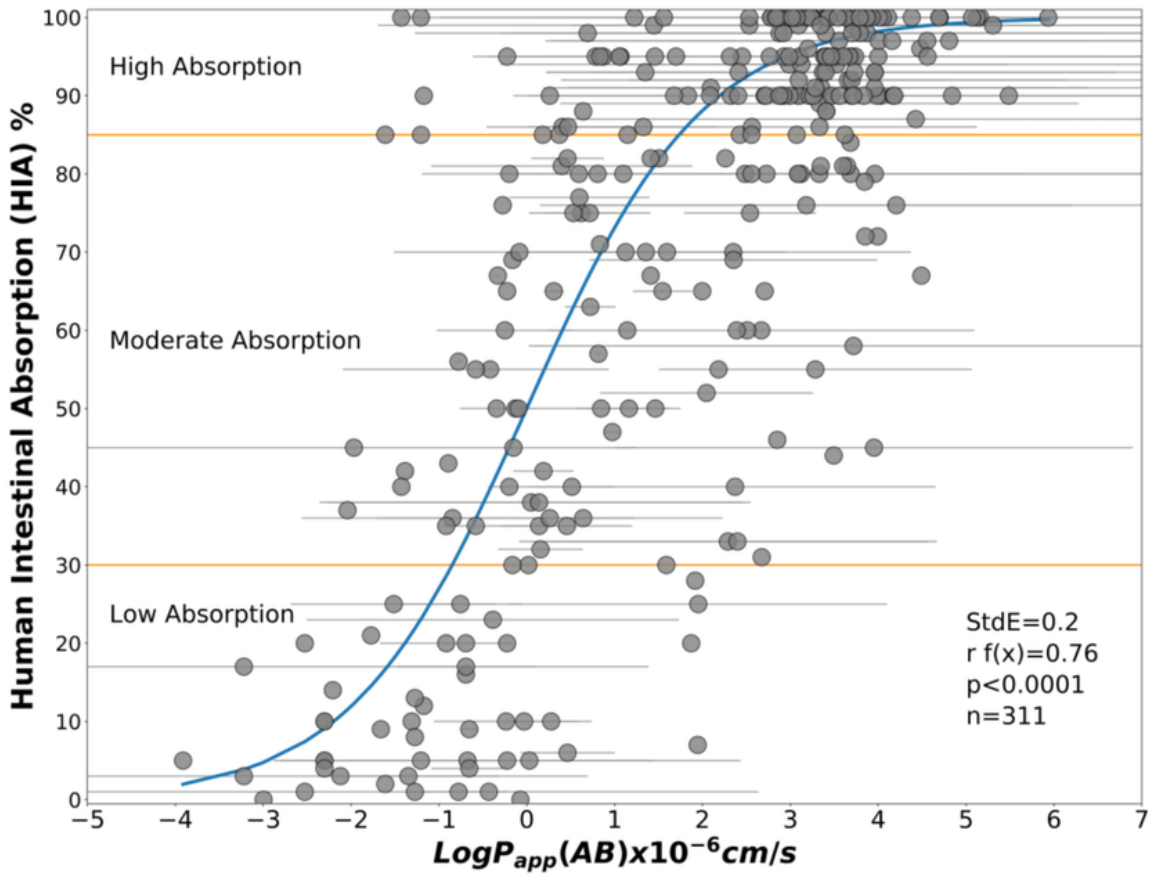
- We will now evaluate the ADMET properties of a series of clinically used drugs to demonstrate the process

Quinine
Chloroquine
Amodiaquine
Desethylamodiaquine
Artemether
Lumefantrine
Amlodipine
Nifedipine
Ritonavir

Solubility and Log D



Caco-2 vs HIA



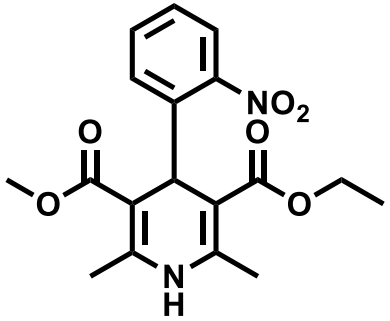
DOI:10.2174/1568026619666181130140350

Clearance and unbound clearance

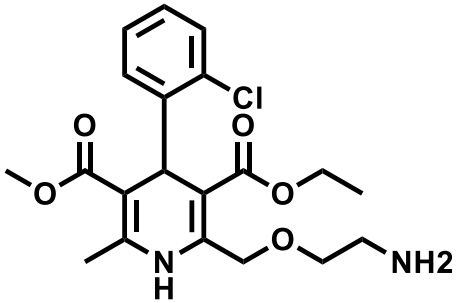
- Unbound clearance and its use for compound ranking

	CL	Fu	CLu
Quinine	3.3	18.49%	17.9
Chloroquine	5.8	25.79%	22.6
Amodiaquine	7.5	1.42%	529.5
Desethylamodiaquine	5.4	7.63%	70.7
Artemether	15.9	3.64%	436.3
Lumefantrine	5.6	0.67%	832.5
Amlodipine	6.9	42.93%	16.1
Nifedipine	10.1	19.50%	51.6
Ritonavir	6.4	0.74%	867.2

VD, half-life and dose



Nifedipine
Vd_u 19.5 L/kg
CLu 175 ml/min/kg
$t_{½}$ 1.8h
Dose: 10 mg x 3 times a day

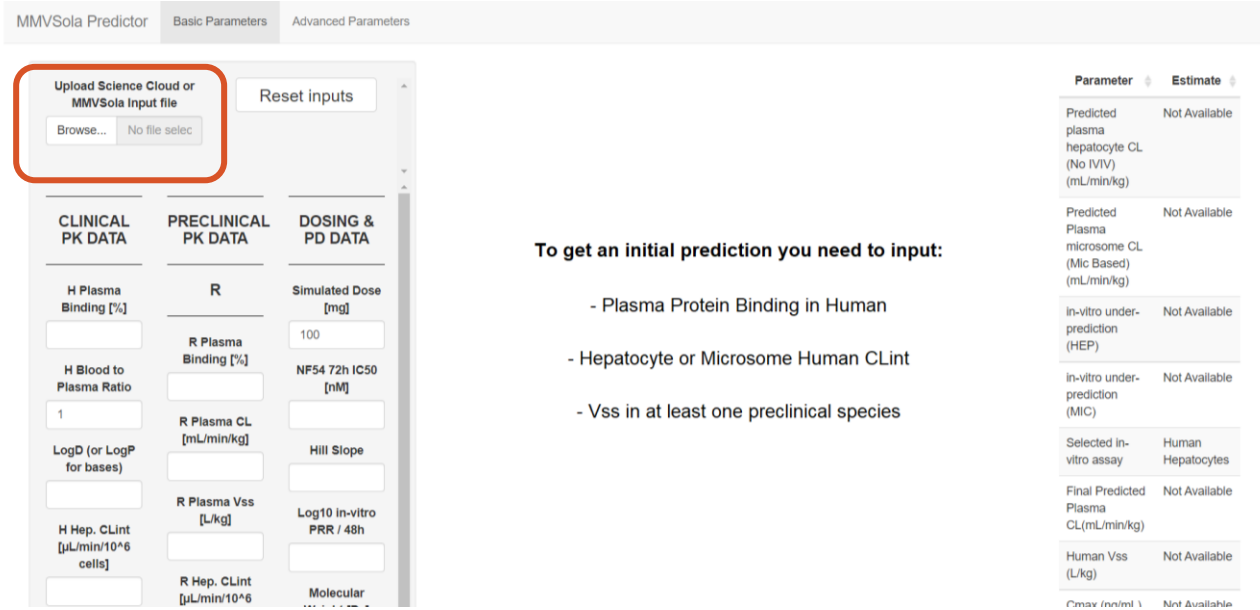


Amlodipine
Vd_u 228 L/kg
CLu 85 ml/min/kg
$t_{½}$ 40h
Dose: 10 mg once a day

$$t_{1/2} = \frac{\ln 2 * Vd}{CL}$$

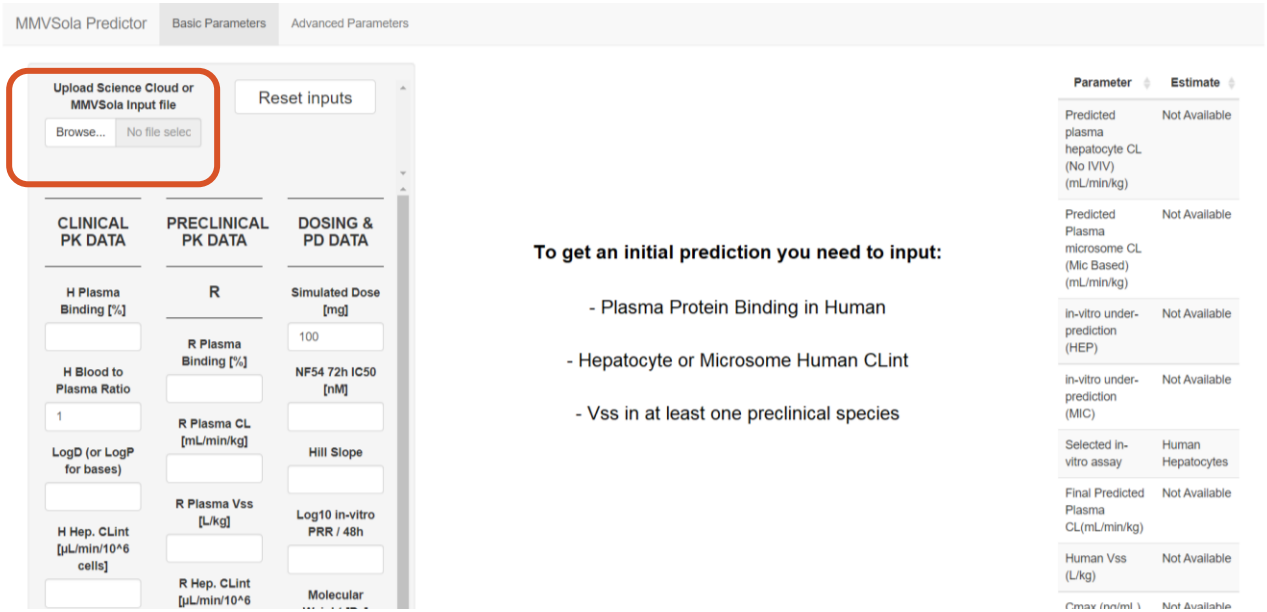
Dose prediction on MMVSola

- The impact of ADME/PK on the clinical efficacy of a compound can be described using mathematical equations allowing human dose prediction from *in vitro* data.
- Let's explore this using ADME/PK data of a hypothetical compound.
- Navigate to https://www.mmvsola.org/

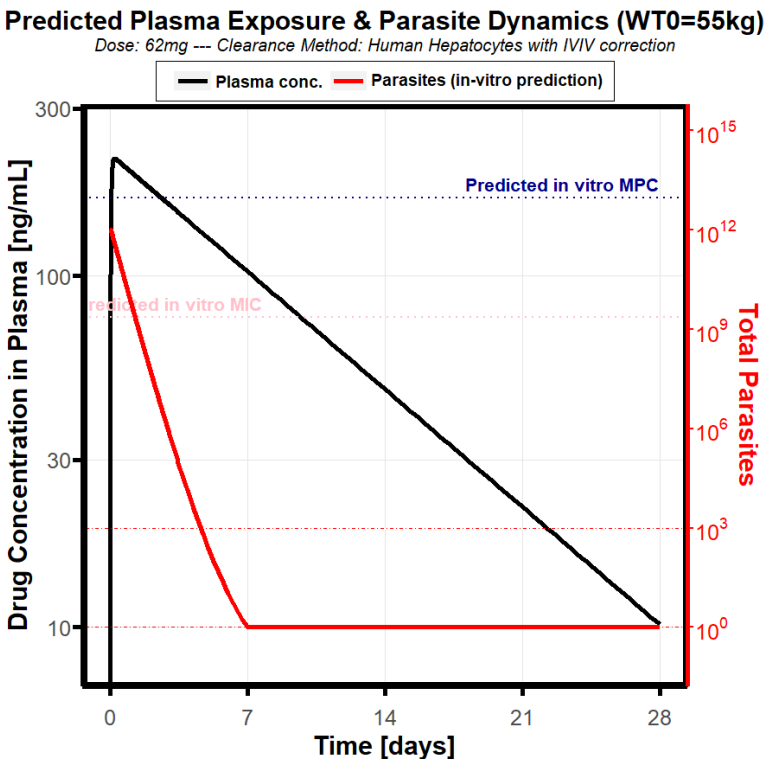


Dose prediction on MMVSola

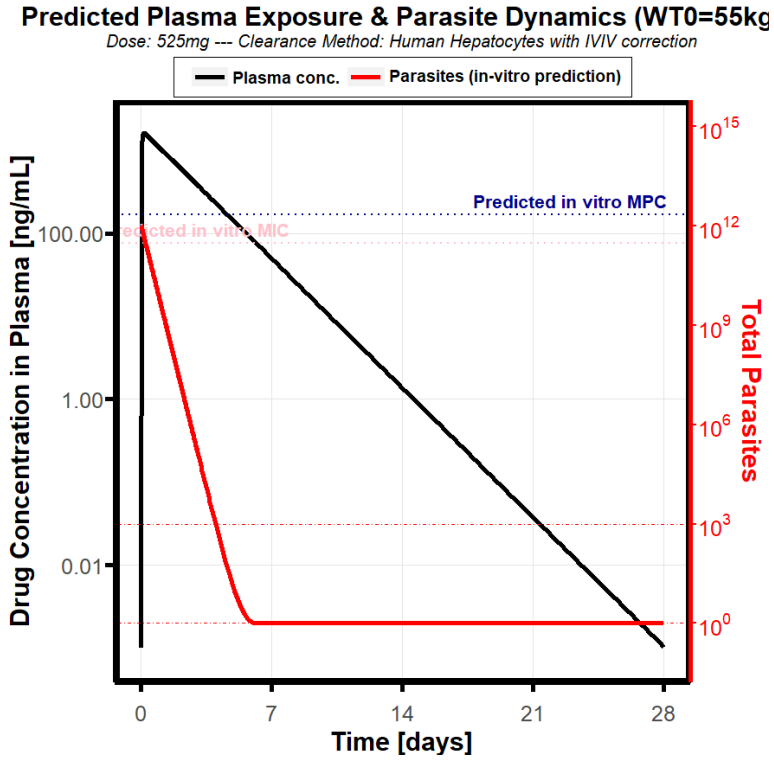
- Navigate to https://www.mmvsola.org/
- Load the data saved under your project folder



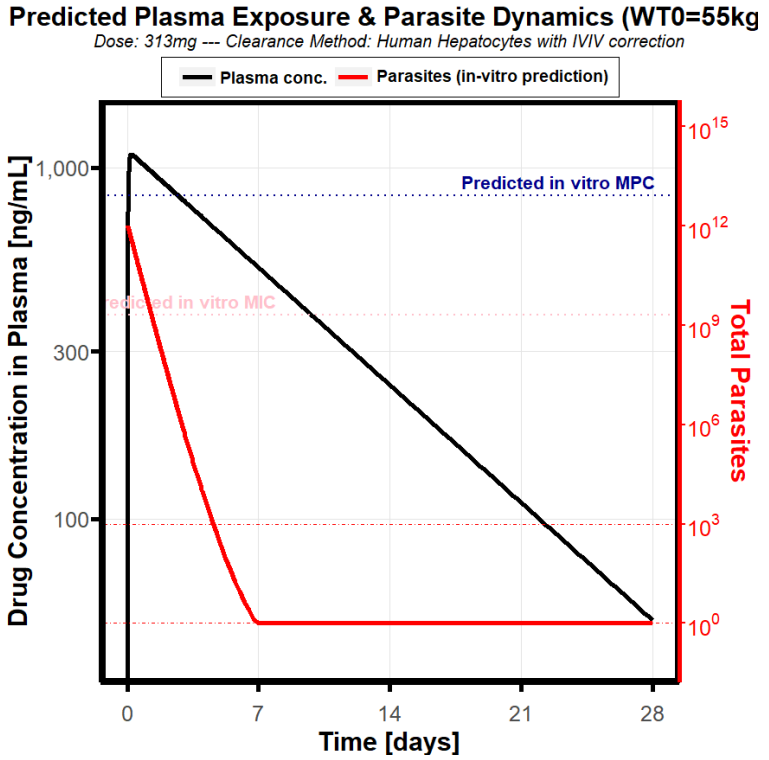
MMVSola dose prediction



Heps CL_{int}: 1 µl/min/e6 cells
NF54: 20 nM
Predicted dose: 62 mg



Heps CL_{int}: 5 µl/min/e6 cells
NF54: 20 nM
Predicted dose: 525 mg



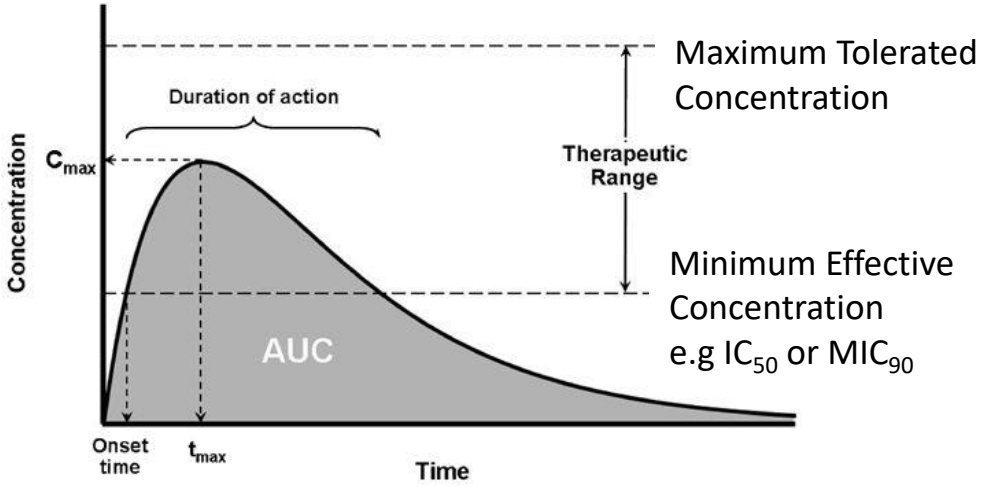
Heps CL_{int}: 1 µl/min/e6 cells
NF54: 100 nM
Predicted dose: 313 mg

ADME/PK and Dose

- The unbound Area Under the Curve (AUC_u) is one of the key measures of how much compound is in circulation

- For an oral drug;

$$\mathrm{AUC}_u = \mathrm{F}_{abs} \cdot \mathrm{F}_{gut} \cdot \frac{\mathrm{Dose}}{\mathrm{CL}_{int,u}}$$



Therefore:

$$Dose = \mathrm{F}_{abs} \cdot \mathrm{F}_{gut} \cdot \frac{\mathrm{AUC}_u}{\mathrm{CL}_{int,u}}$$

- Increasing clearance increases the dose since more compound is required to achieve a similar AUC
- With an increase in IC_{50} and increase in exposure levels is required resulting in an increased dose.