DILIsym® User Training - Defining RNS/ROS Toxicity Parameter Values in DILIsym®

DILI-sim Team

Goal for This Training Session

Participants should understand the following general concepts:

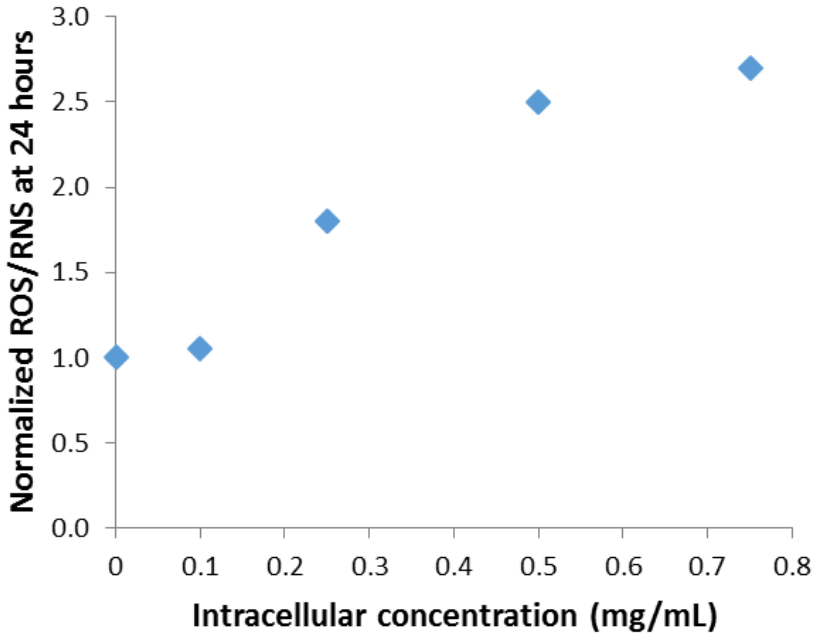
- Methods used to parameterize and to simulate disturbances in the reactive oxygen species balance in DILIsym®

Modeling Compounds that Disturb the Reactive Oxygen Species Balance

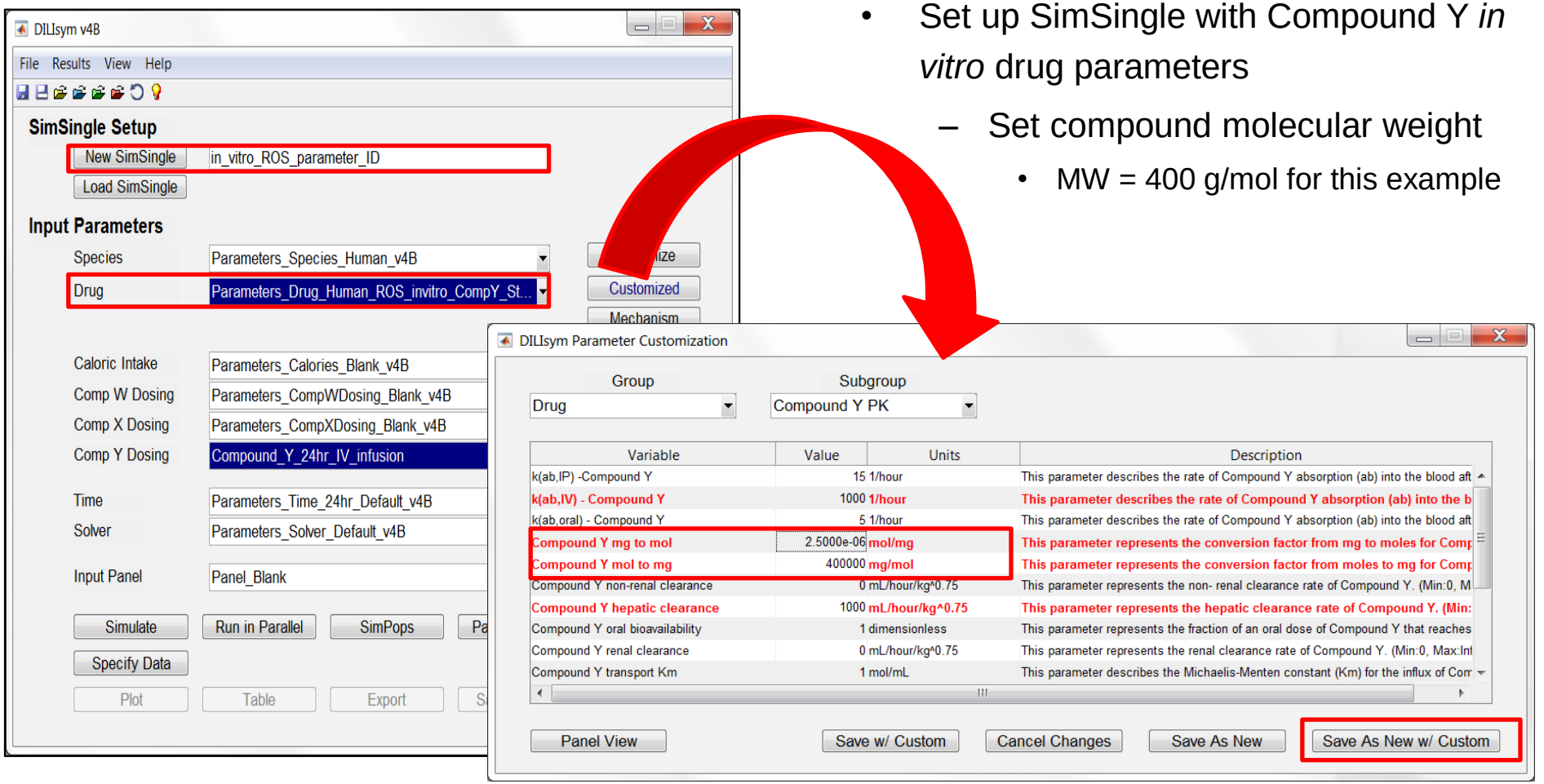
- Outline of method used to translate *in vitro* ROS/RNS data to DILIsym® parameters
  - Establish a dose response to use for the optimization
    - Dose response comparing RNS/ROS to producer concentration
    - Intracellular concentration preferred
  - Implement an '*in vitro*' like environment within DILIsym® using Compound Y
    - '*in vitro*' Compound Y drug parameters available in DILIsym® v4B
      - "Parameters_Drug_Human_ROS_invitro_CompY_SteadyState"
  - Optimize the simulations to match the *in vitro* data
    - Use Parameter Sweep tool to find value of RNS_ROS_prod_const that produces appropriate amount of RNS/ROS at most concentrations
    - Requires some iteration in order to match all concentrations

Example of Determining ROS Production Toxicity Parameter Value in DILIsym®

- Objective: determine ROS production toxicity parameter value for the following mock RNS/ROS data

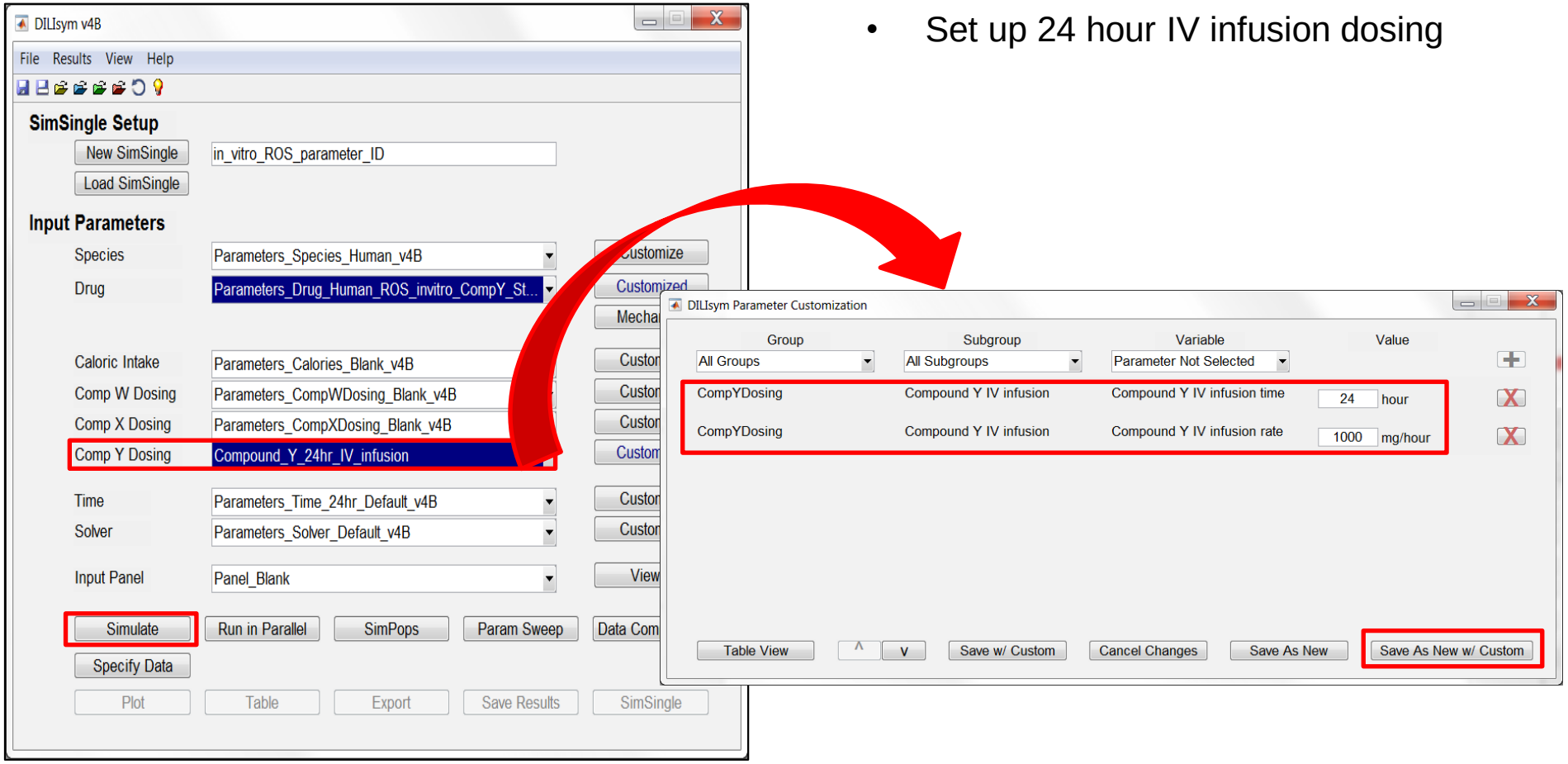


Setup an "*in vitro*–like" Simulation within DILIsym® Using Compound Y



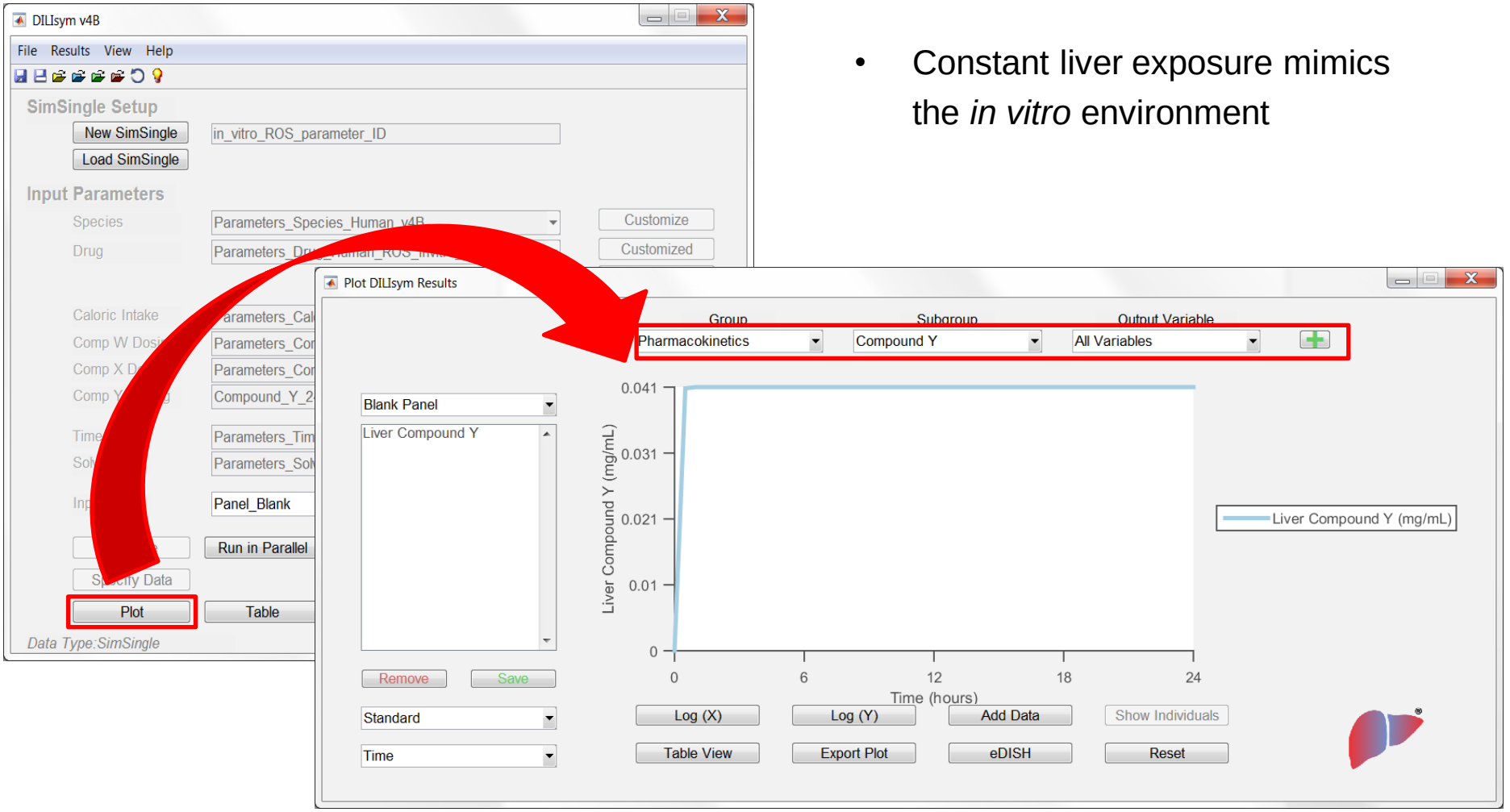
- Set up SimSingle with Compound Y *in vitro* drug parameters
  - Set compound molecular weight
    - MW = 400 g/mol for this example

Setup an "*in vitro*–like" Simulation within DILIsym® Using Compound Y



- Set up 24 hour IV infusion dosing

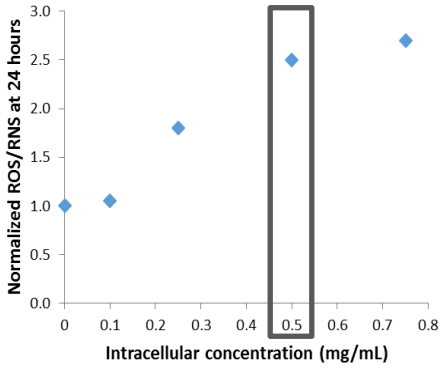
Constant Liver Exposure Achieved with "*in vitro*–like" Setup

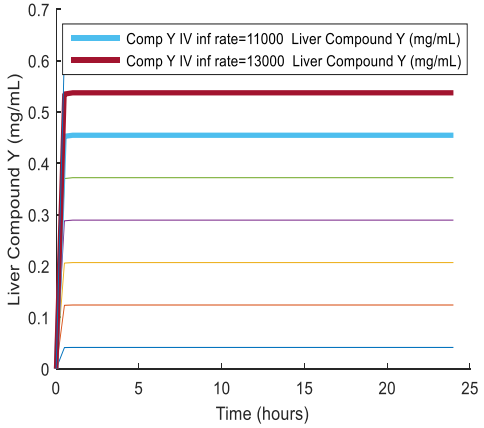


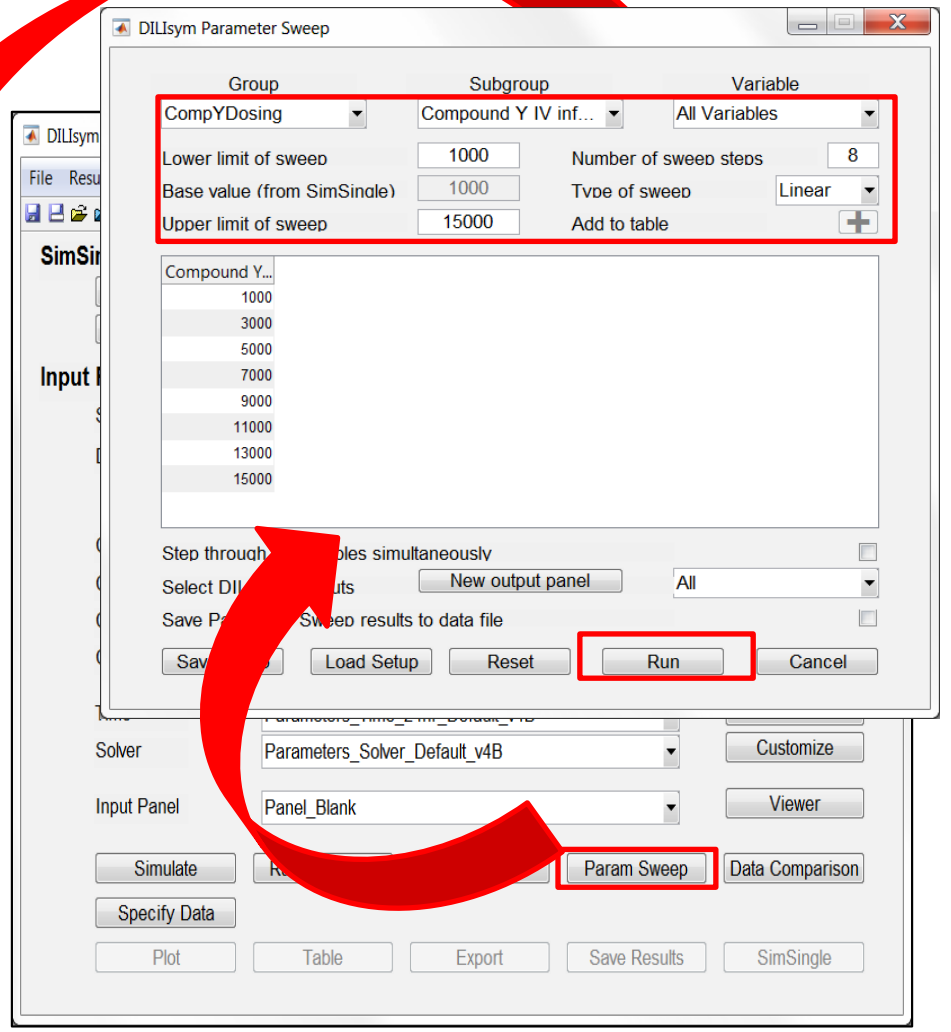
- Constant liver exposure mimics the *in vitro* environment

Tune Compound Y Infusion Rate to Approximate Liver Exposure

- Pick an exposure level: 0.5 mg/mL
- Tune the Compound Y infusion rate to get exposures in the **liver** in the range of the *in vitro* exposure estimates
  - 12000 mg/hour in our example



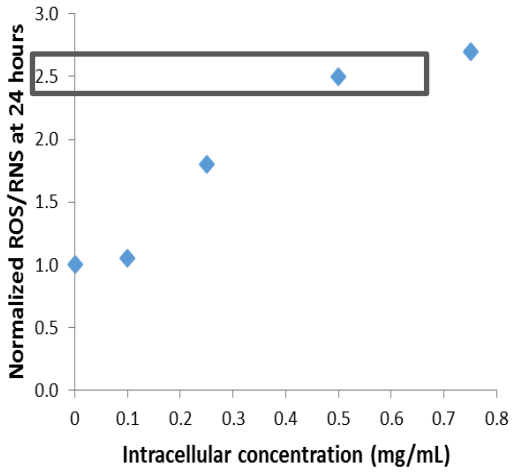


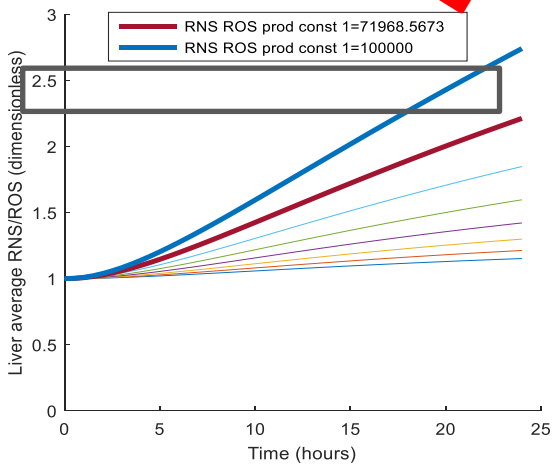


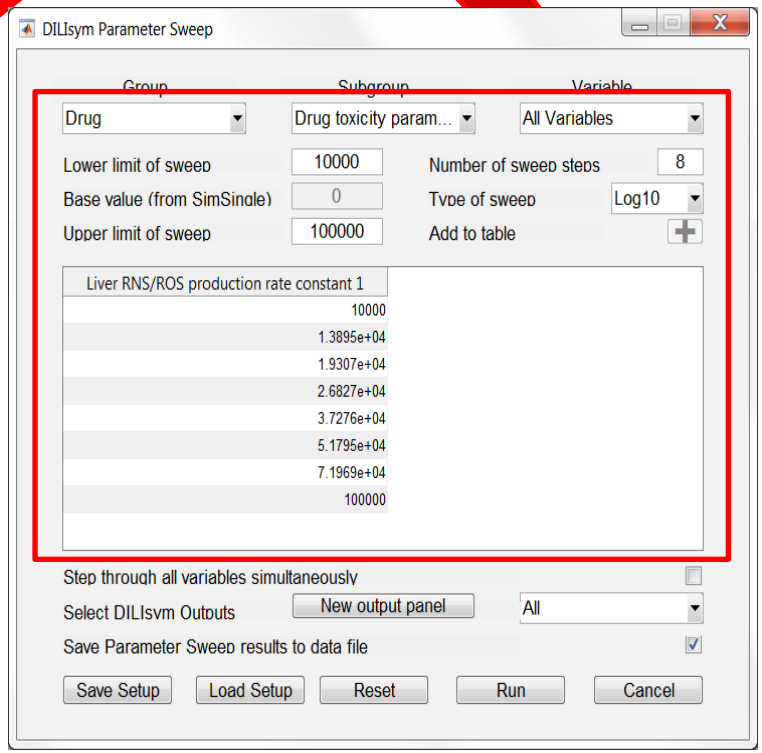
Theoretical Preclinical Data and Simulation Results

Using the Parameter Sweep Tool for RNS/ROS Production Rate Constant 1

- For the selected exposure level (.5 mg/mL concentration), use the parameter sweep tool within DILIsym® to find a Liver RNS/ROS production rate constant 1 value that gives a reasonable level of ROS (i.e. ~2.5x) at the corresponding time point (24 hrs)
  - Make sure to update Compound Y infusion rate to 12000 mg/hr
  - Output to use for ROS is 'Liver average RNS/ROS'
  - For our case, value is roughly 80,000

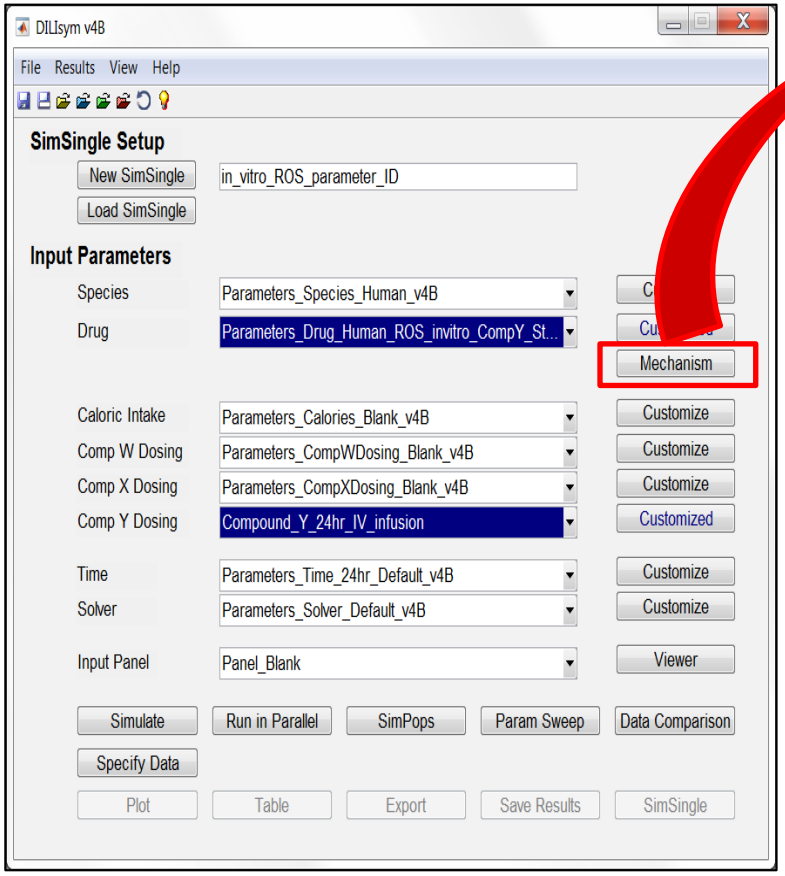


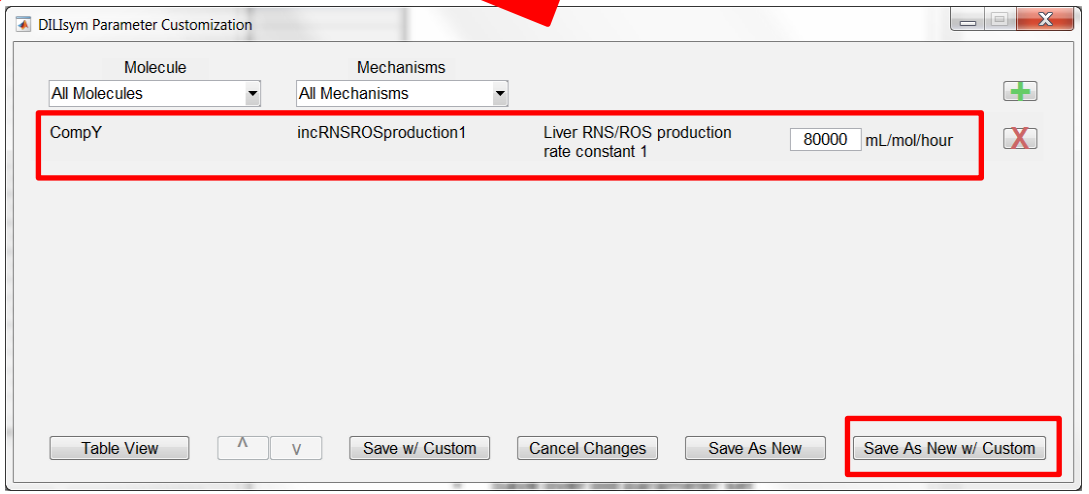




Theoretical Preclinical Data and Simulation Results

Setup SimSingle™ with New RNS/ROS Production Rate Constant 1

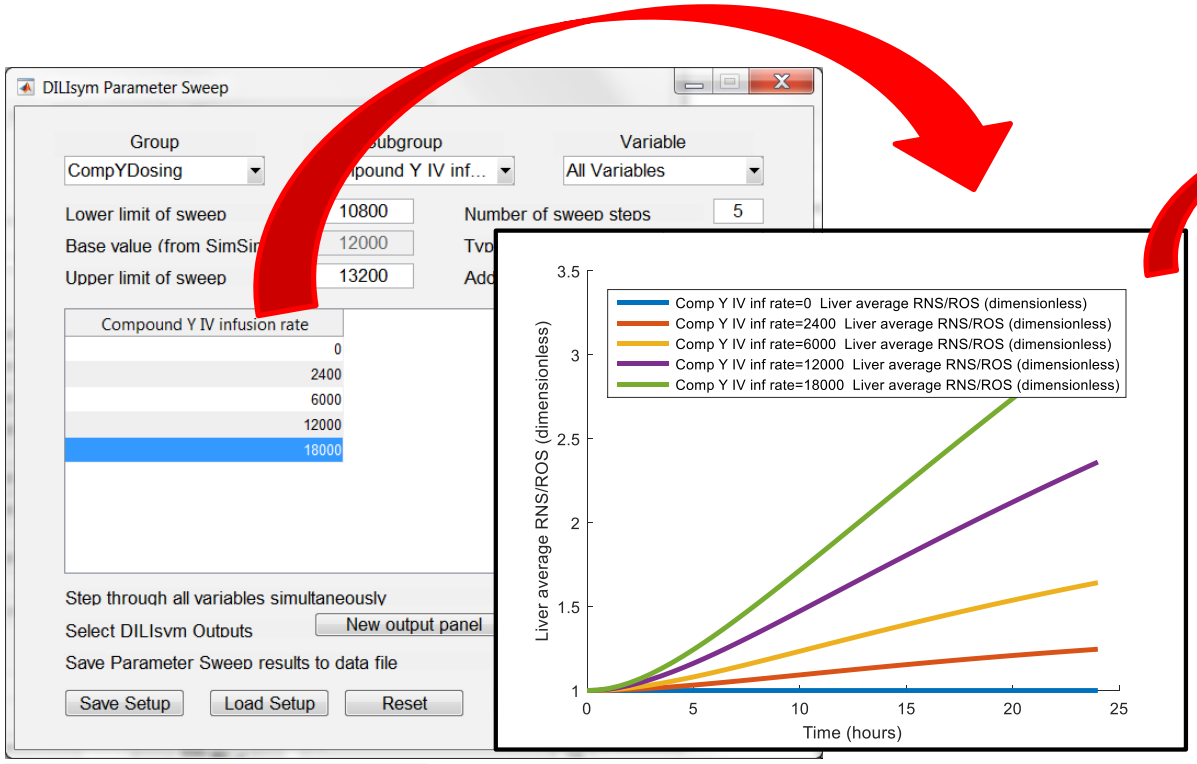


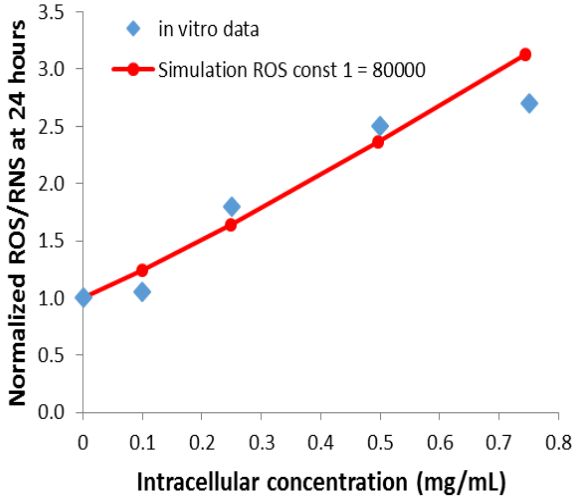


- Return to SimSingle™ setup
- Change RNS/ROS Production Rate Constant 1 to new value in drug parameters
- Save drug parameter set

Parameter Sweep on *In Vitro* Dose

- Run dose sweep over entire exposure range measured in *in vitro* experiments
  - Dose scales with *in vitro* intracellular concentration
- Compare simulated results with experimental results
- Iterate if necessary using different ROS production rate constants
  - Not necessary here





Theoretical Preclinical Data and Simulation Results