

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

DILI-sim Team

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# Goal for This Training Session

*Participants should understand the following general concepts:*

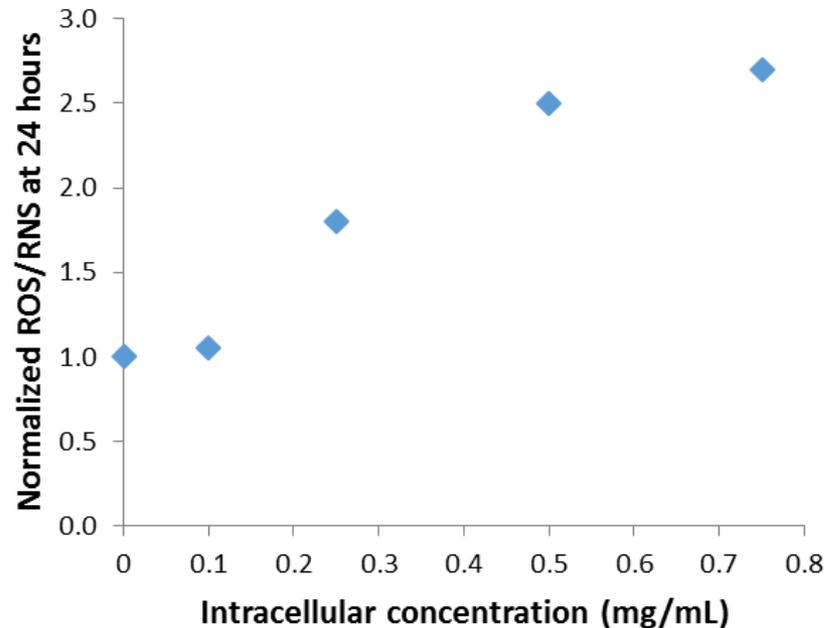
- Methods used to parameterize and to simulate disturbances in the reactive oxygen species balance in DILIsym<sup>®</sup>

# Modeling Compounds that Disturb the Reactive Oxygen Species Balance

- Outline of method used to translate *in vitro* ROS/RNS data to DILIsym<sup>®</sup> 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<sup>®</sup> using Compound Y
    - '*in vitro*' Compound Y drug parameters available in DILIsym<sup>®</sup> 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<sup>®</sup>

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



# Setup an “*in vitro*–like” Simulation within DILIsym<sup>®</sup> Using Compound Y

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

**SimSingle Setup**

New SimSingle: in\_vitro\_ROS\_parameter\_ID

Load SimSingle

**Input Parameters**

Species: Parameters\_Species\_Human\_v4B

Drug: Parameters\_Drug\_Human\_ROS\_invitro\_CompY\_St...

Caloric Intake: Parameters\_Calories\_Blank\_v4B

Comp W Dosing: Parameters\_CompWDosing\_Blank\_v4B

Comp X Dosing: Parameters\_CompXDosing\_Blank\_v4B

Comp Y Dosing: Compound\_Y\_24hr\_IV\_infusion

Time: Parameters\_Time\_24hr\_Default\_v4B

Solver: Parameters\_Solver\_Default\_v4B

Input Panel: Panel\_Blank

Buttons: Simulate, Run in Parallel, SimPops, Specify Data, Plot, Table, Export

**DILIsym Parameter Customization**

Group: Drug, Subgroup: Compound Y PK

Variable	Value	Units	Description
k(ab,IP) -Compound Y	15	1/hour	This parameter describes the rate of Compound Y absorption (ab) into the blood at
k(ab,IV) - Compound Y	1000	1/hour	This parameter describes the rate of Compound Y absorption (ab) into the b
k(ab,oral) - Compound Y	5	1/hour	This parameter describes the rate of Compound Y absorption (ab) into the blood at
Compound Y mg to mol	2.5000e-06	mol/mg	This parameter represents the conversion factor from mg to moles for Comp
Compound Y mol to mg	400000	mg/mol	This parameter represents the conversion factor from moles to mg for Comp
Compound Y non-renal clearance	0	mL/hour/kg <sup>0.75</sup>	This parameter represents the non- renal clearance rate of Compound Y. (Min:0, M
Compound Y hepatic clearance	1000	mL/hour/kg <sup>0.75</sup>	This parameter represents the hepatic clearance rate of Compound Y. (Min:
Compound Y oral bioavailability	1	dimensionless	This parameter represents the fraction of an oral dose of Compound Y that reaches
Compound Y renal clearance	0	mL/hour/kg <sup>0.75</sup>	This parameter represents the renal clearance rate of Compound Y. (Min:0, Max:Inf
Compound Y transport Km	1	mol/mL	This parameter describes the Michaelis-Menten constant (Km) for the influx of Cor

Buttons: Panel View, Save w/ Custom, Cancel Changes, Save As New, Save As New w/ Custom

# Setup an “*in vitro*–like” Simulation within DILIsym<sup>®</sup> Using Compound Y

- Set up 24 hour IV infusion dosing

**SimSingle Setup**

New SimSingle: in\_vitro\_ROS\_parameter\_ID

Load SimSingle

**Input Parameters**

Species: Parameters\_Species\_Human\_v4B

Drug: Parameters\_Drug\_Human\_ROS\_invitro\_CompY\_St...

Caloric Intake: Parameters\_Calories\_Blank\_v4B

Comp W Dosing: Parameters\_CompWDosing\_Blank\_v4B

Comp X Dosing: Parameters\_CompXDosing\_Blank\_v4B

Comp Y Dosing: **Compound\_Y\_24hr\_IV\_infusion**

Time: Parameters\_Time\_24hr\_Default\_v4B

Solver: Parameters\_Solver\_Default\_v4B

Input Panel: Panel\_Blank

Buttons: Simulate, Run in Parallel, SimPops, Param Sweep, Data Com...

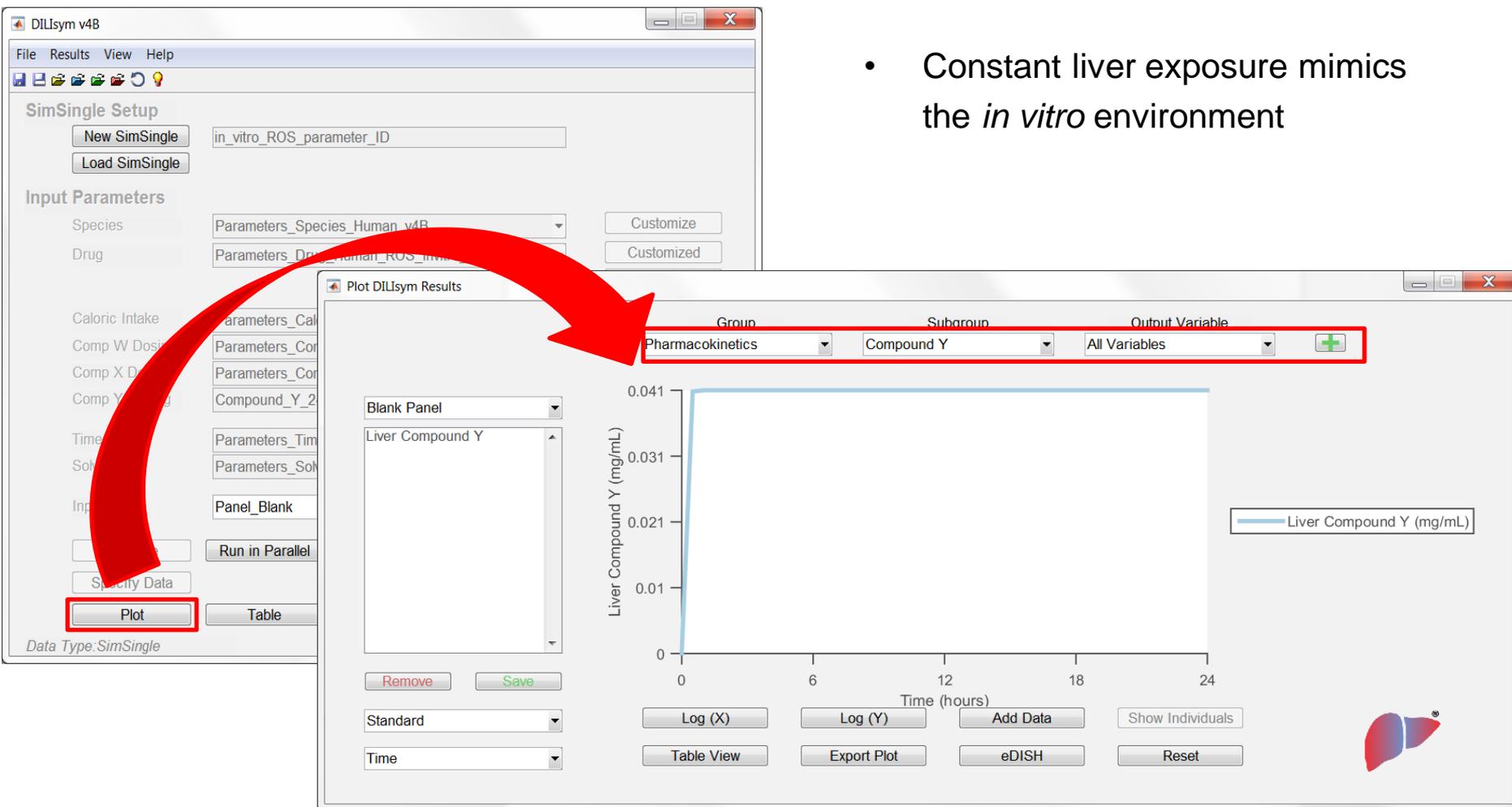
Buttons: Plot, Table, Export, Save Results, SimSingle

Group	Subgroup	Variable	Value
All Groups	All Subgroups	Parameter Not Selected	
CompYDosing	Compound Y IV infusion	Compound Y IV infusion time	24 hour
CompYDosing	Compound Y IV infusion	Compound Y IV infusion rate	1000 mg/hour

Buttons: Table View, ^, v, Save w/ Custom, Cancel Changes, Save As New, **Save As New w/ Custom**

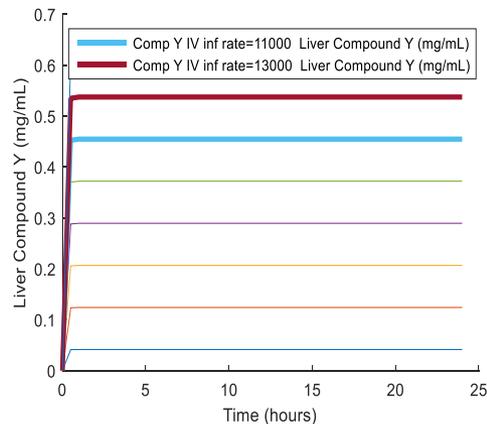
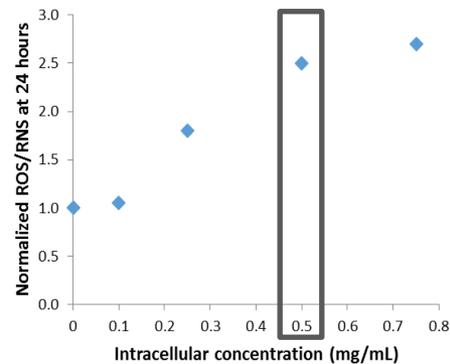
# Constant Liver Exposure Achieved with “*in vitro*–like” Setup

- 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



DILIsym Parameter Sweep

Group	Subgroup	Variable
CompYDosing	Compound Y IV inf...	All Variables

Lower limit of sweep: 1000  
Base value (from SimSingle): 1000  
Upper limit of sweep: 15000

Number of sweep steps: 8  
Type of sweep: Linear

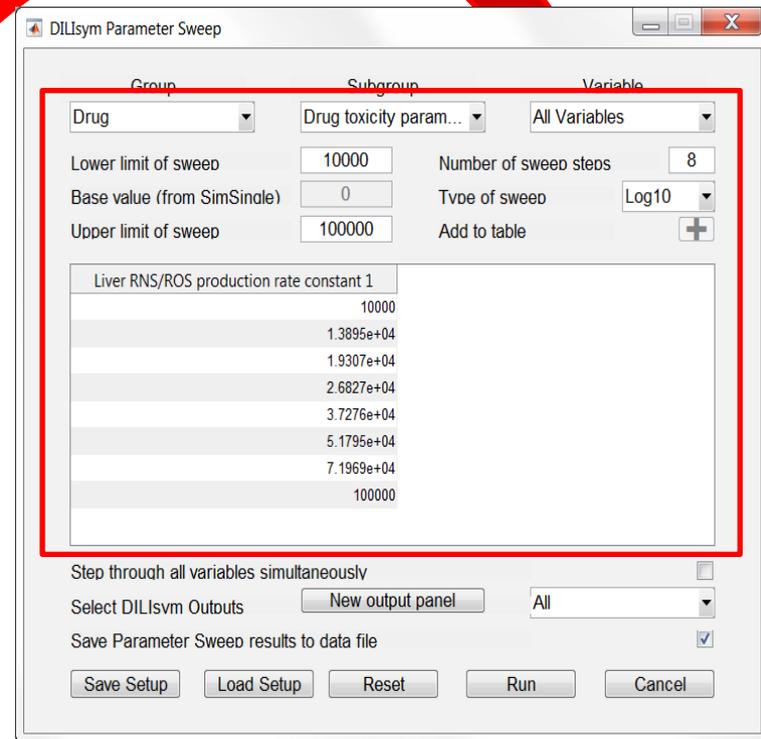
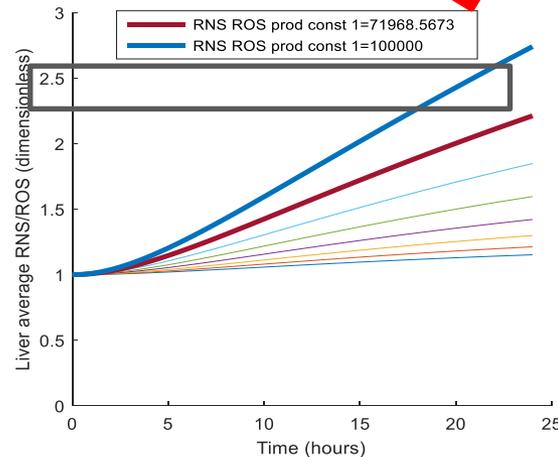
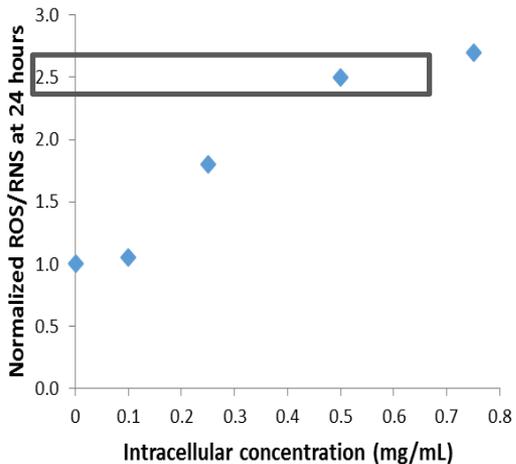
Step through variables simultaneously:   
Select DILIsym outputs:  All  
Save Parameters: Sweep results to data file:

Solver: Parameters\_Solver\_Default\_v4B   
Input Panel: Panel\_Blank

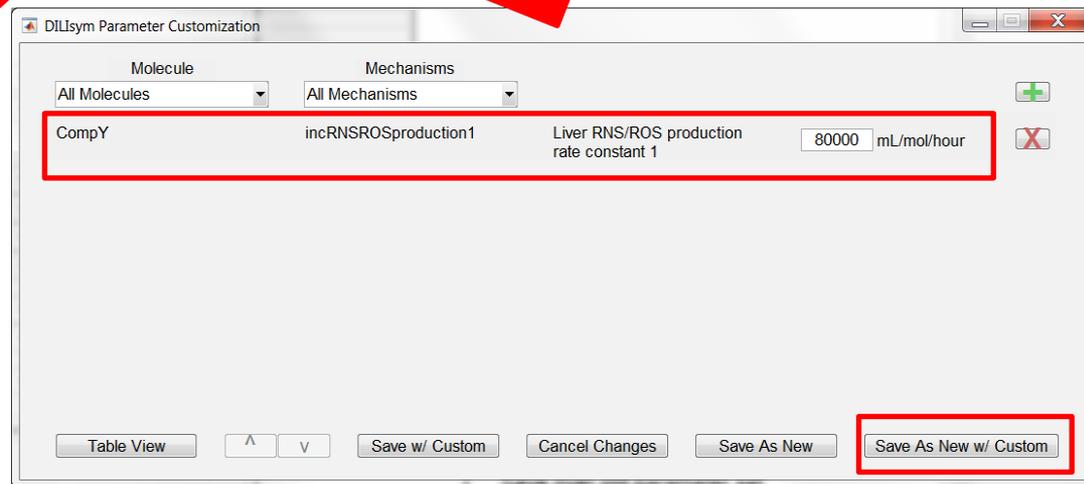
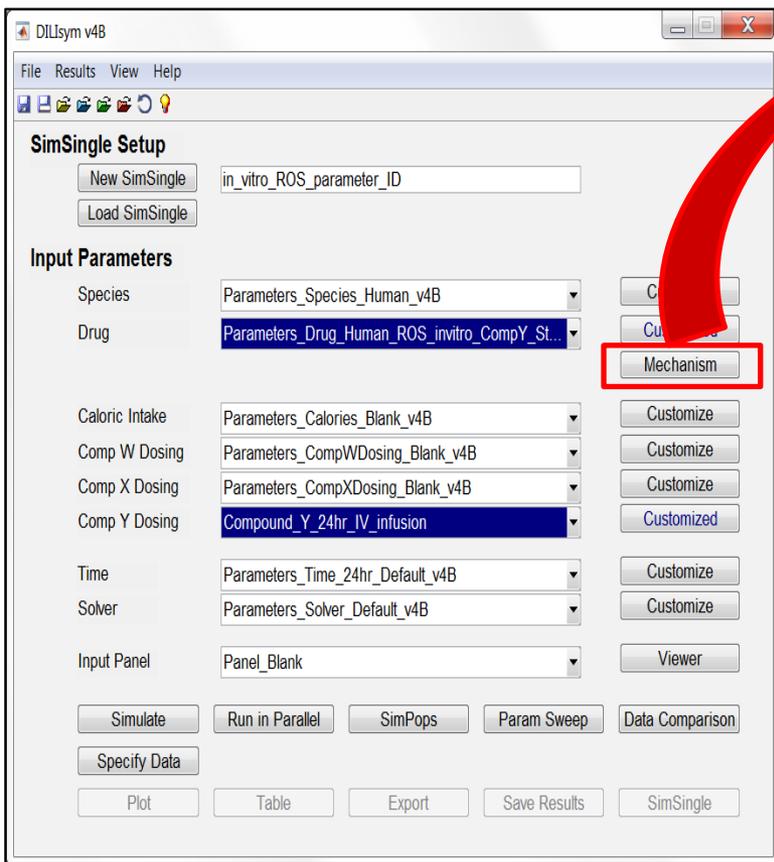
Theoretical Preclinical  
Data and Simulation  
Results

# 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<sup>®</sup> 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



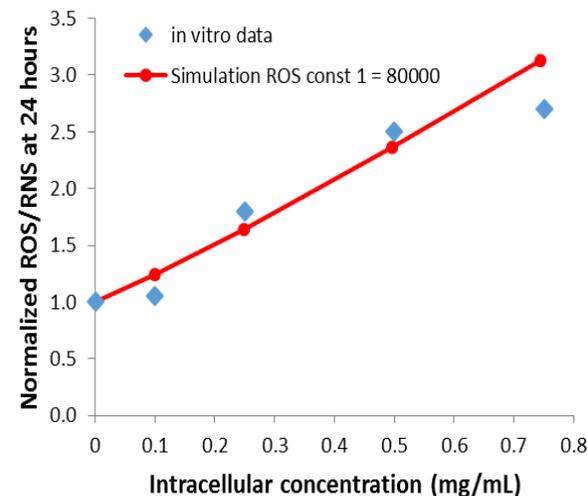
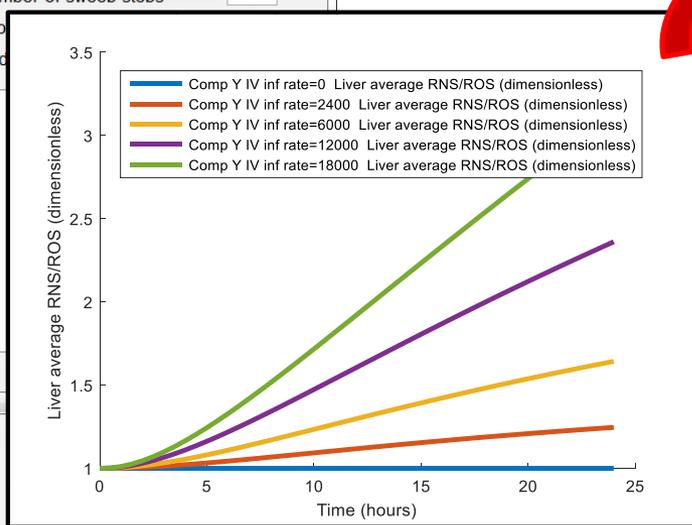
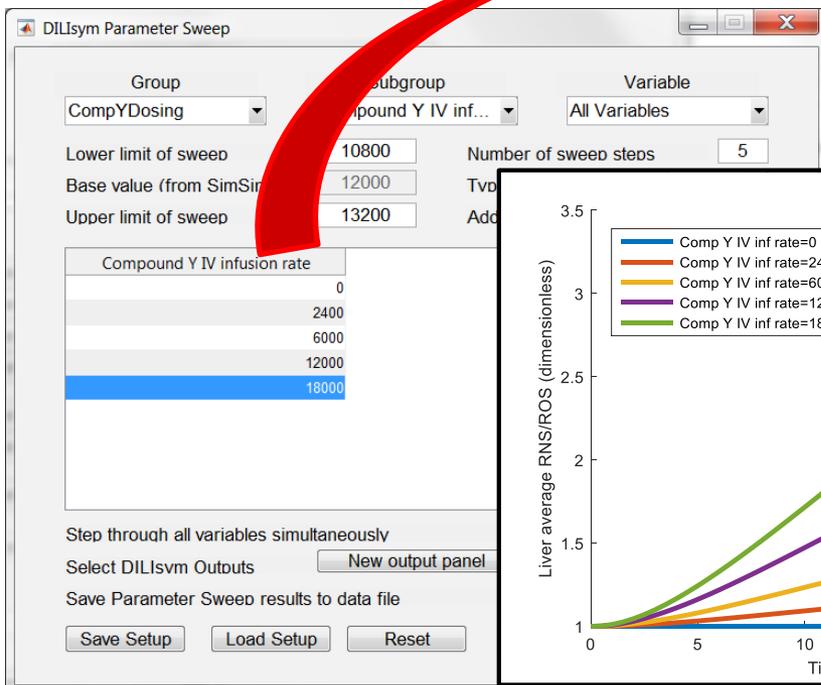
# Setup SimSingle™ with New RNS/ROS Production Rate Constant 1



- 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  
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