DILIsym Services

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DILIsym User Training –

Introduction to the DILIsym Software Environment

DILIsym Development Team

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Goals for the DILIsym Software Environment Introduction Training Session

Participants should understand the following general concepts:

- Use of the DILIsym user interface within the following areas:
    - Directory structure overview
    - DILIsym home screen startup and use
    - Input panels and Output panels
    - SimSingle – setup and results structure
    - Run in Parallel feature
    - Data comparisons
    - Plotting tool
    - Table tool
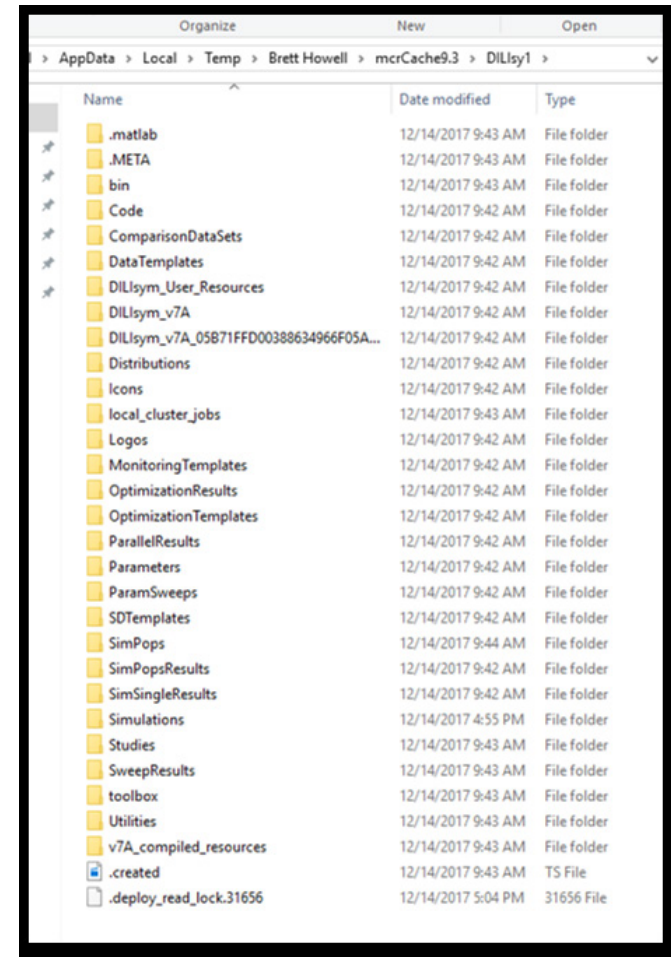   - Export to Excel

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DILIsym Directory Structure is Accessible for Adding and Sharing Setup and Results Files

- DILIsym installs into location within Windows user profile by default

  - Installation path can be altered by user

- To find location of directory structure, simply navigate to any "Load" command within DILIsym Results menu

- Various directories store results, simulations, SimPops files, etc.

  - SimPops directory contains SimPops parameters and values

  - Code directory contains SimPops initial conditions files

  - Parameters directory contains inventory of parameter sets issued with DILIsym

  - Various other setup and results directories

- www.DILIsymHelp.com contains DILIsym user guide which describes specifics of directories

- Users will become familiar with several of the directories during the training

Name	Date modified	Type
.matlab	12/14/2017 9:43 AM	File folder
.META	12/14/2017 9:43 AM	File folder
bin	12/14/2017 9:43 AM	File folder
Code	12/14/2017 9:42 AM	File folder
ComparisonDataSets	12/14/2017 9:42 AM	File folder
DataTemplates	12/14/2017 9:42 AM	File folder
DILIsym_User_Resources	12/14/2017 9:42 AM	File folder
DILIsym_v7A	12/14/2017 9:42 AM	File folder
DILIsym_v7A_05B71FFD00388634966F05A...	12/14/2017 9:42 AM	File folder
Distributions	12/14/2017 9:42 AM	File folder
Icons	12/14/2017 9:42 AM	File folder
local_cluster_jobs	12/14/2017 9:43 AM	File folder
Logos	12/14/2017 9:42 AM	File folder
MonitoringTemplates	12/14/2017 9:42 AM	File folder
OptimizationResults	12/14/2017 9:42 AM	File folder
OptimizationTemplates	12/14/2017 9:42 AM	File folder
ParallelResults	12/14/2017 9:42 AM	File folder
Parameters	12/14/2017 9:42 AM	File folder
ParamSweeps	12/14/2017 9:42 AM	File folder
SDTemplates	12/14/2017 9:42 AM	File folder
SimPops	12/14/2017 9:44 AM	File folder
SimPopsResults	12/14/2017 9:42 AM	File folder
SimSingleResults	12/14/2017 9:42 AM	File folder
Simulations	12/14/2017 4:55 PM	File folder
Studies	12/14/2017 9:43 AM	File folder
SweepResults	12/14/2017 9:43 AM	File folder
toolbox	12/14/2017 9:43 AM	File folder
Utilities	12/14/2017 9:43 AM	File folder
v7A_compiled_resources	12/14/2017 9:43 AM	File folder
.created	12/14/2017 9:43 AM	TS File
.deploy_read_lock.31656	12/14/2017 5:04 PM	31656 File

Organize   *New*   *Open*

> AppData > Local > Temp > Brett Howell > mcrCache9.3 > DILIsy1 >

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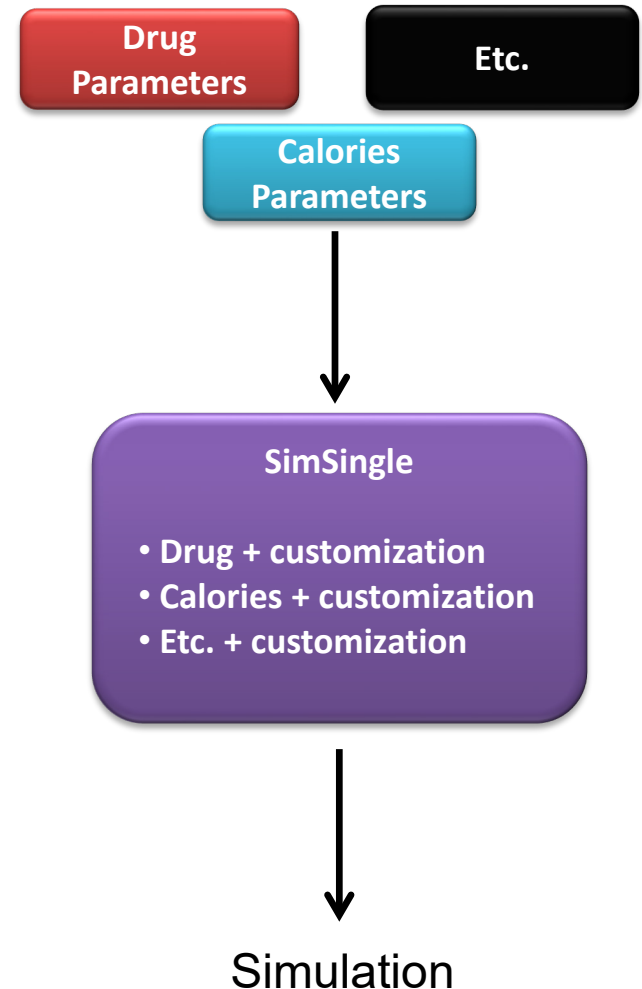
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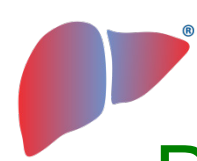# Simulation Setup (SimSingle) Organization Within DILIsym

- Simulations are run using SimSingles, which define a single simulation setup completely

  – The parameter subsets (drug, species, time, etc.) are only there for the purposes of organizing and creating SimSingles

  – SimSingles are a snapshot of subset choices, plus any customization (saved or unsaved), at the time of running the simulation or saving

- Simulation outputs are placed into one larger structure with attributes for each output

  – All output types, including state variables and algebraic expressions, are included in the results structure (SimResult)

Drug Parameters

Etc.

Calories Parameters

SimSingle

- • Drug + customization
- • Calories + customization
- • Etc. + customization

Simulation

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DILIsym – Operation and Workflow Details

- Classes are used within MATLAB for outputs and inputs within the DILIsym interface

  – Include additional information for a 'parameter' or 'output', such as data type and range, annotation, group and subgroup, etc.

- Relative changes can be tracked if desired and are indicated with colors and location

  – For example, user can see how someone altered a parameter set relative to the original

- Panels allow for easy customization of input and output lists for training and model use, as well as output selection and analysis

  – Can plot and export results from selected outputs only

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Getting Started in DILIsym – Load the Application
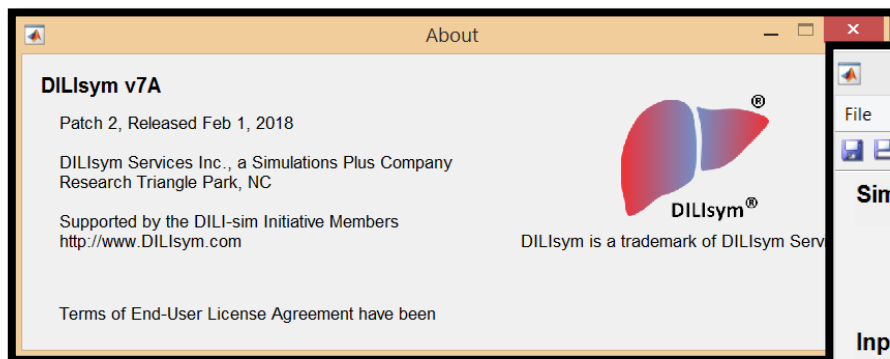
- Ensure Flexera license management is set up according to provided instructions
  - Can be standalone installation or network based
  - License file needed from DILIsym Services to activate software
- Open DILIsym application from Start menu in Windows
- Follow similar process for MITOsym
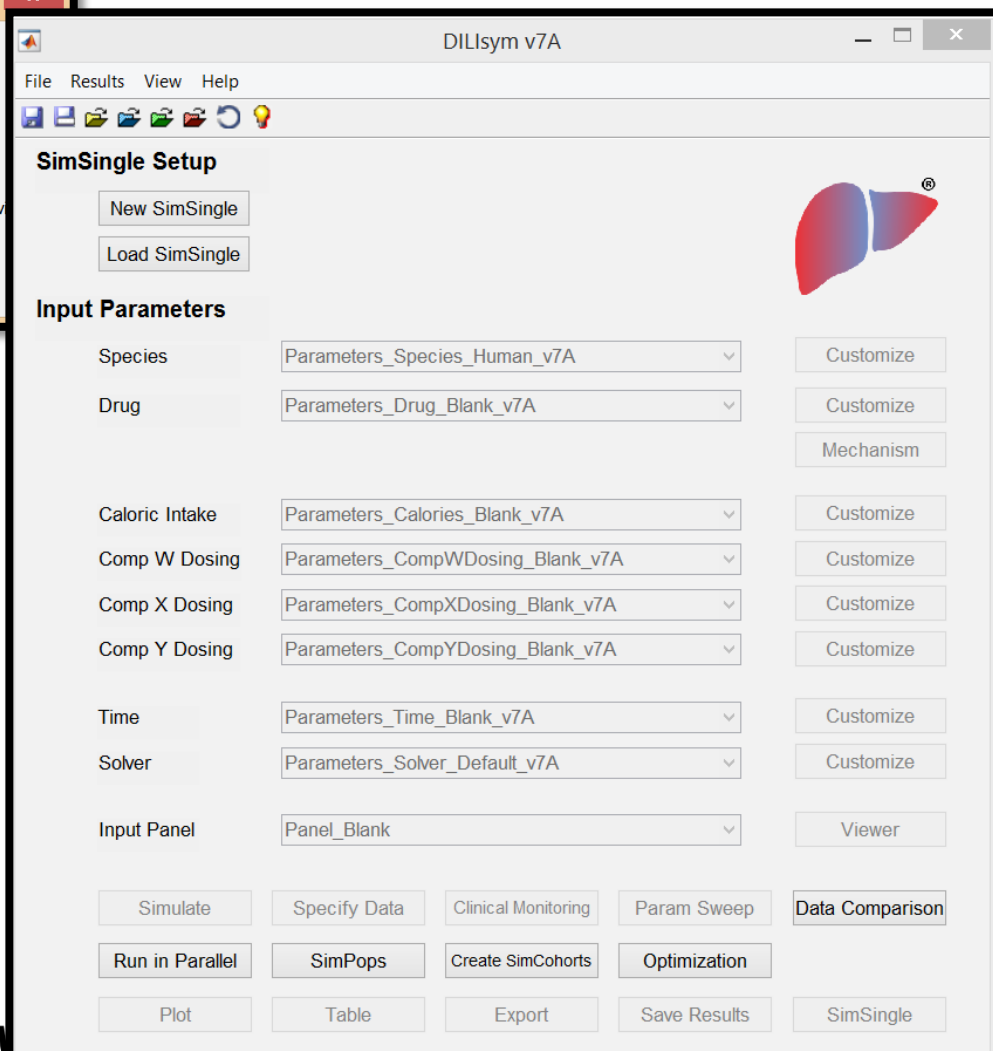
DILIsy

DILIsym Home Screen – Basic Setup

- DILIsym is centered around concept of SimSingles, or simulation setup units

- Start by selecting either 'New SimSingle' or 'Load SimSingle'

- DILIsym options are organized into parameter set groups

- In order to select a parameter set, choose one from the drop-down menu

- SimSingles combine parameters selected from all drop-down menus

  – Saved SimSingle captures parameters as a snapshot-in-time (no auto-update)

  – SimSingles are saved as one file with all parameters in it, but maintains the original, individual parameter set names, parameter contents, and customization

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Customizing a Parameter Set – Multiple Options Available for Viewing and Tracking

- To customize parameters, select the "Customize" button next to the parameter of interest

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Customizing a Parameter Set – Multiple Options Available for Viewing and Tracking

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- View parameter:
  - Select a group, subgroup, variable

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- Add parameters to the panel:
  - Change the variable value
  - Add the parameter by clicking the green "**+**"

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Customizing a Parameter Set – Multiple Options Available for Viewing and Tracking

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- Save parameter values with customization, as new, as new w/custom
  - Customization flag tracks changes
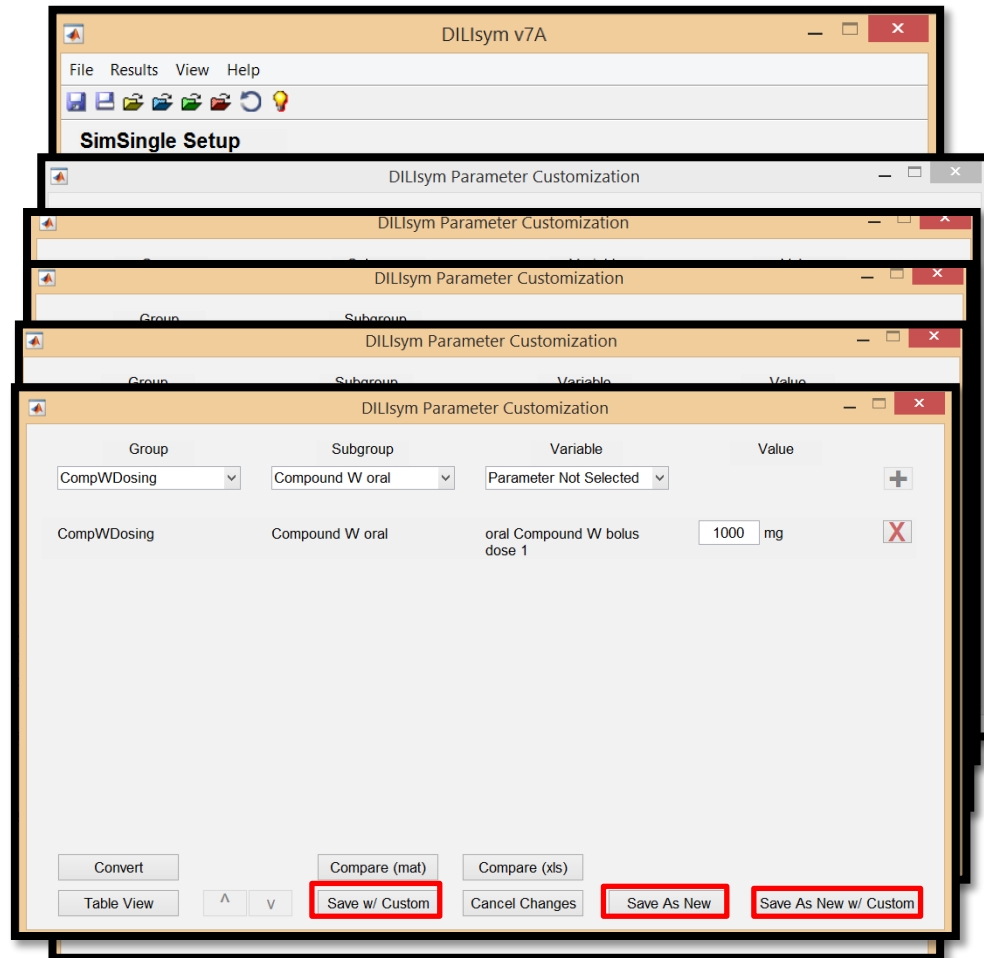
Parameter Set Attribute	Save w/Custom	Save as New	Save as New w/Custom
Name	No change	User-defined name	User-defined name
Appearance in Home Screen	Blue	White	Blue

Saving a Customized Parameter Set

Customized parameter set appears blue

Save w/Custom

Parameter set name does not change
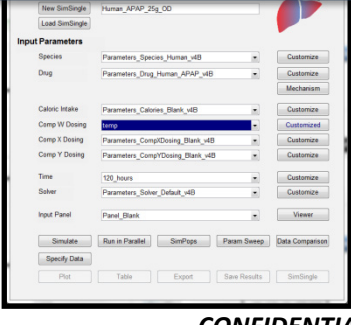

Customized parameter set appears white
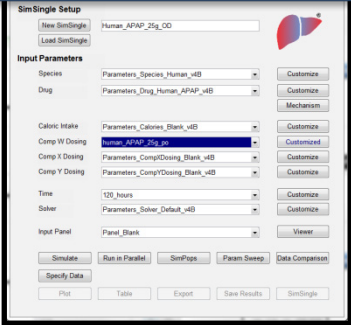
Save as New

User specifies new parameter set name

Customized parameter set appears blue
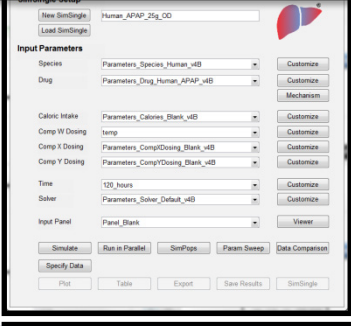
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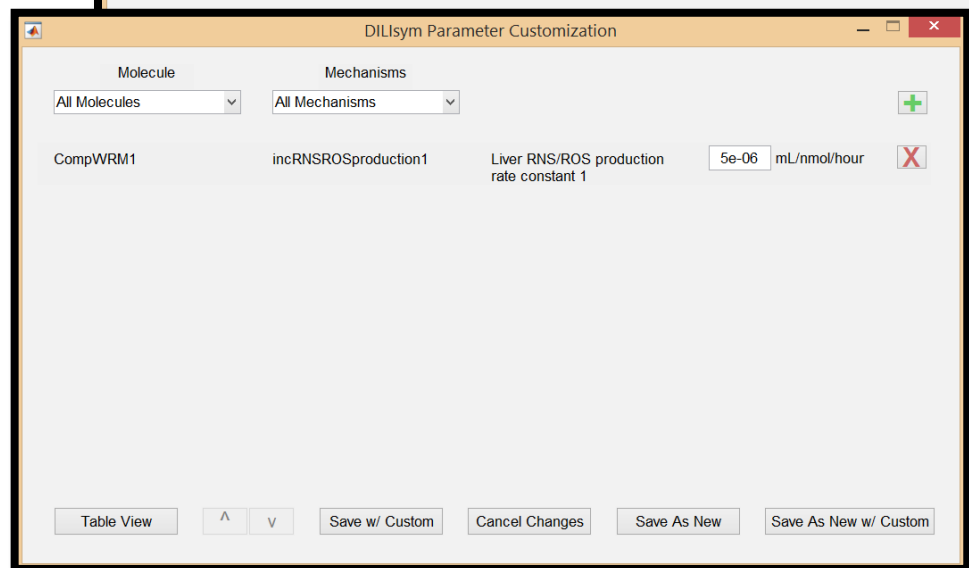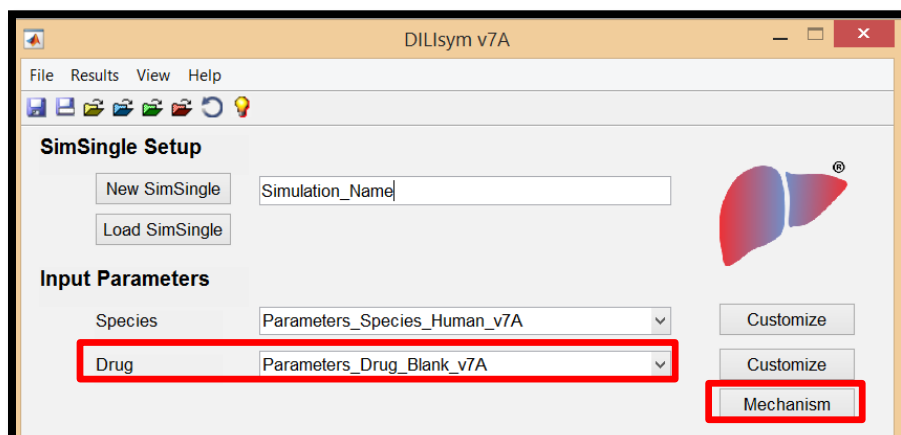# Customized Parameter Sets in the Context of SimSingles

- Regardless of mode of saving the parameter set, it will **NOT** be updated in the SimSingle unless the SimSingle is re-saved
  - Save, Save As options
  - Simulation can be run without saving, which will resave it automatically

- Similarly, <u>other SimSingles that use this parameter set</u> will **NOT** reflect changes until they are re-constituted and re-saved (*i.e.*, no auto-updating)

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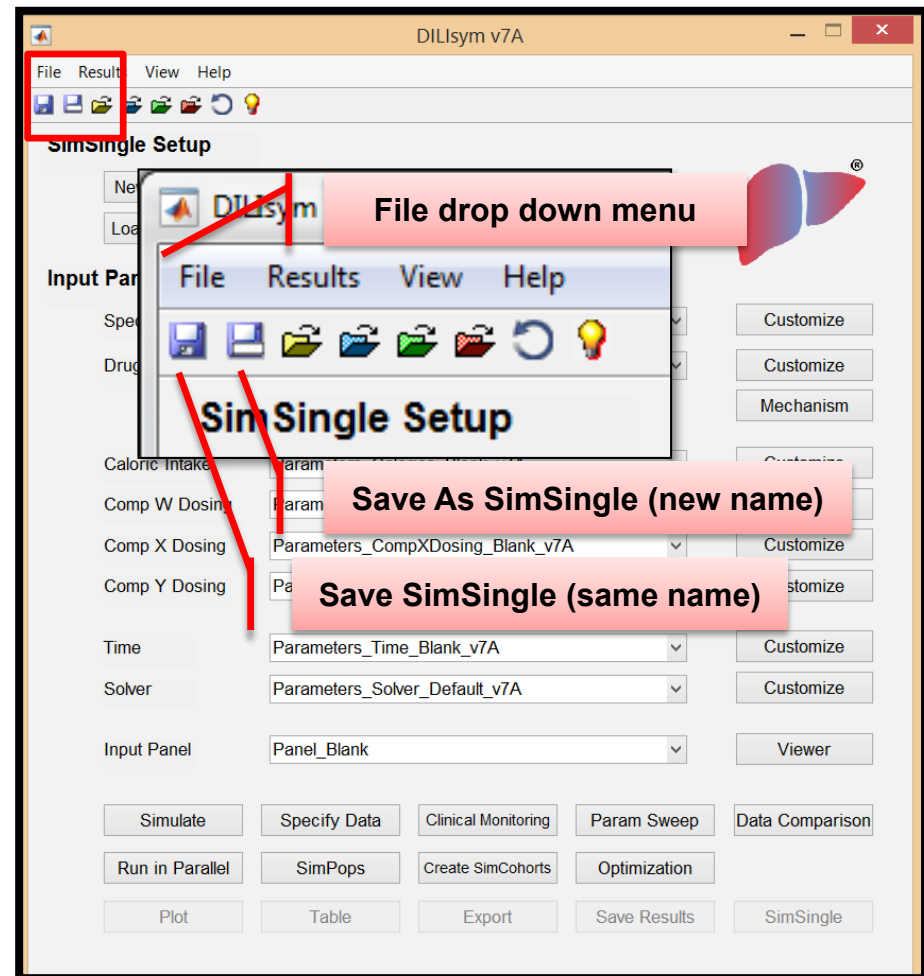
Selection of Mechanism of Hepatotoxicity and Parameter Inputs for a Molecule

- Mechanism viewer allows you to view only those parameters associated with a particular toxicity mechanism

- Add a new mechanism:
  - Select a molecule from the first drop-down menu
  - Select a mechanism from the second list and click the green "+"
  - The parameters you need to fill in are now listed in the panel
  - Table view also available

- View the mechanism of an existing compound:
  - Select the compound and click on the "mechanism" button
  - The panel viewer will display the relevant mechanisms
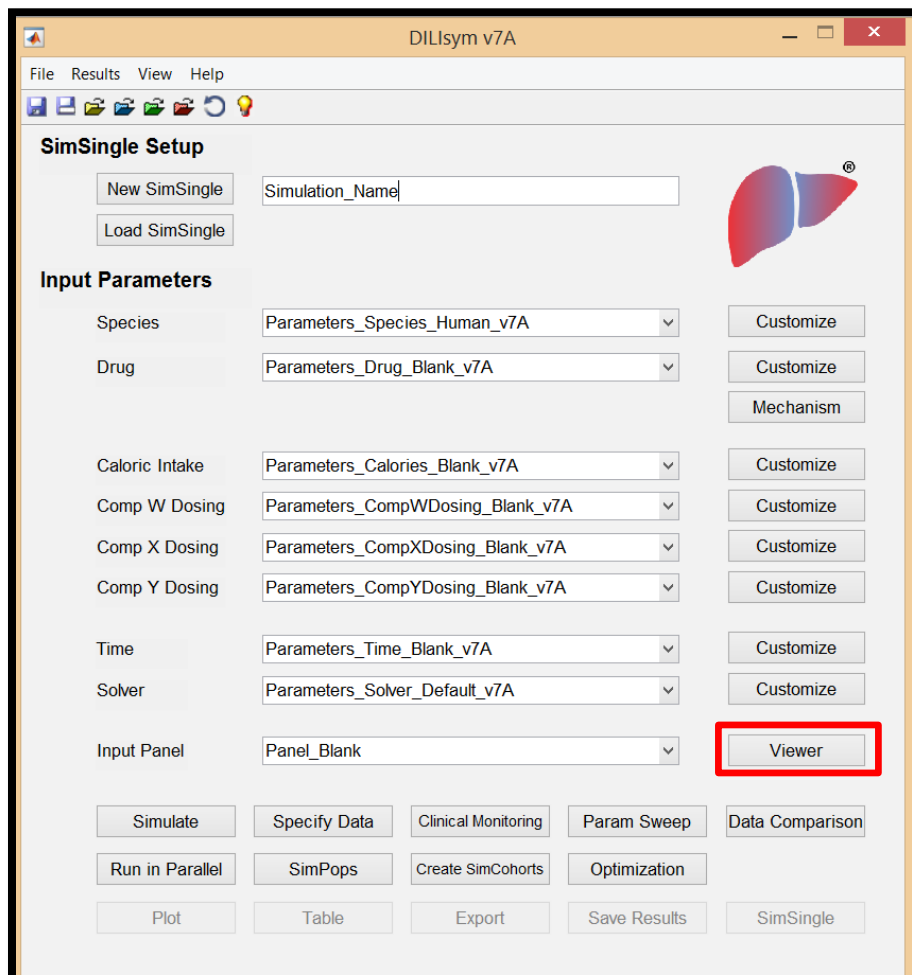

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DILIsym Parameter Input Panel Viewer

- Input Panel Viewer exists to display user-defined sets of parameters

- Custom Input Panels with parameters that span multiple parameter sets can be created:
  - Select Viewer
  - Select Group, Subgroup, Parameter
  - Add Parameter of interest

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DILIsym Parameter Input Panel Viewer

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- Use Input Panels to:
  - Compare parameters of interest between SimSingles
  - Modify parameters within a SimSingle
  - Note: Input Panels are **NOT** saved/specific to any one SimSingle, but are collections of parameters grouped for viewing of values within SimSingles

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Using DILIsym Input Panel Viewer - Important Use Notes

- Input Panels are **NOT** saved/specific to any one SimSingle

  – Permits comparison of the same parameters between SimSingles easily, as well as grouping of parameters from different mechanistic areas of DILIsym for quick access

- Input Panels are **NOT** saved automatically; save a panel after constructing it

- Input Panel Viewer **closes** when you hit Apply Changes

  – Changes made to a newly created and unsaved Input Panel will only appear in the **parameter sets**

  – If changes included zero-ing a parameter with a default value of zero, the parameter will have disappeared from list

- Parameter changes made from the Input Panel Viewer must be saved in the parameter set or SimSingle to be maintained

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DILIsym Parameter Input
Panel Viewer – Hands On Exercise

1. Open New SimSingle

2. Click "Viewer" next to Input Panel

3. Add *Drug -> BA canalicular efflux (BSEP) ->* **Compound W BSEP inhibition constant** to Panel

4. Save As New Panel

5. Open Panel with various Drug parameter sets selected and view value

   – Human APAP

   – Human erythromycin

   – Human tolvaptan

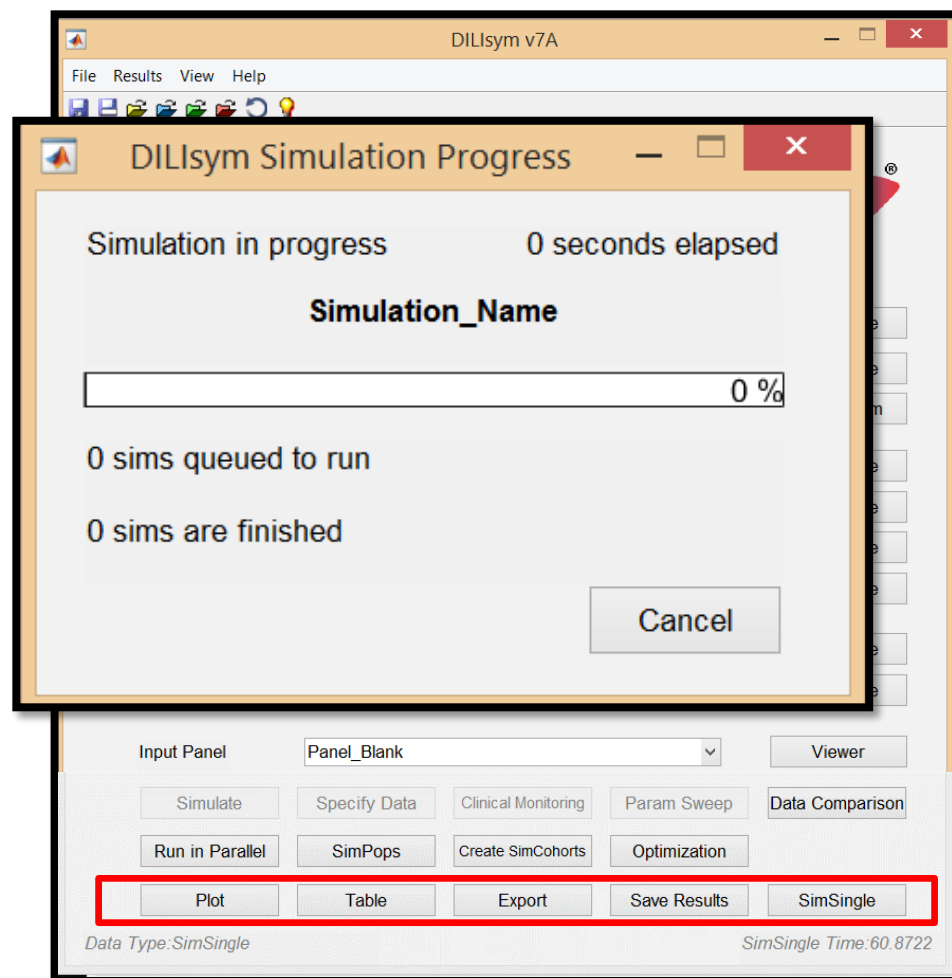# DILIsym SimSingle Results Options

- Run a SimSingle by selecting the Simulate button
  - Progress window appears
  - Save results window appears as an automatic option
- Home Screen gives multiple analysis options (plot, table, export)
- GUI results analysis using Plot or Table
- Export for analysis in MS Excel
- Save Results for additional opportunity to save the results
- SimSingle to view simulation setup

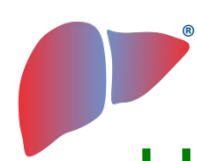# Using the Plot Function for Results Analysis

- Plot function can be used to visualize DILIsym outputs

- Outputs can be examined in ad hoc manner
  - Select group, subgroup, output variable

Plot Window

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- Plot customization
  - Log or linear axes
  - Add Data for comparison

Plot Window

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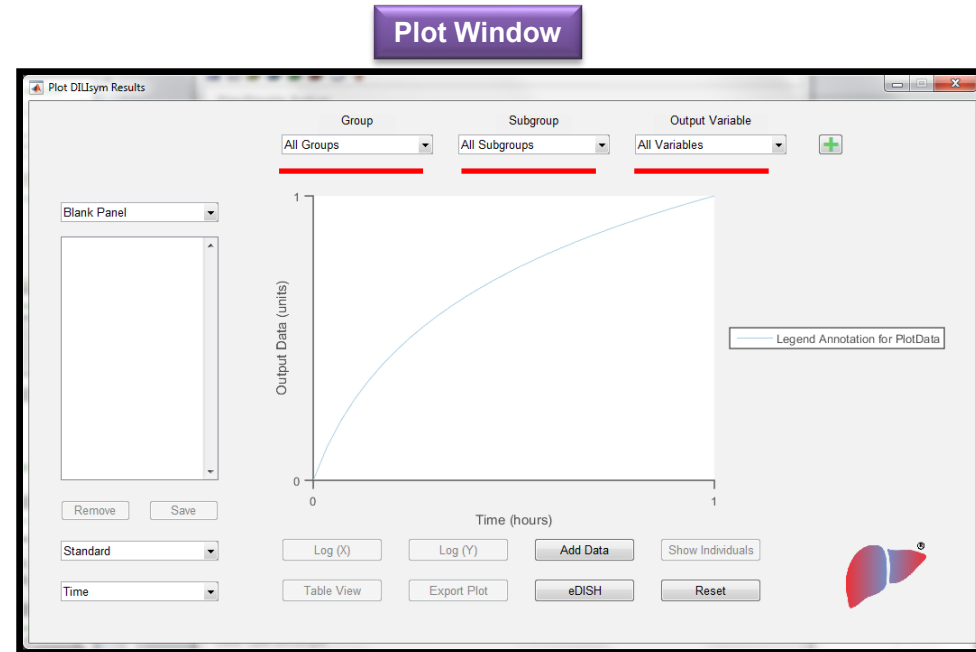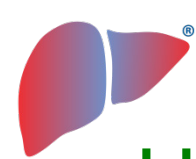
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  - Export Plot
  - eDISH

Plot Window

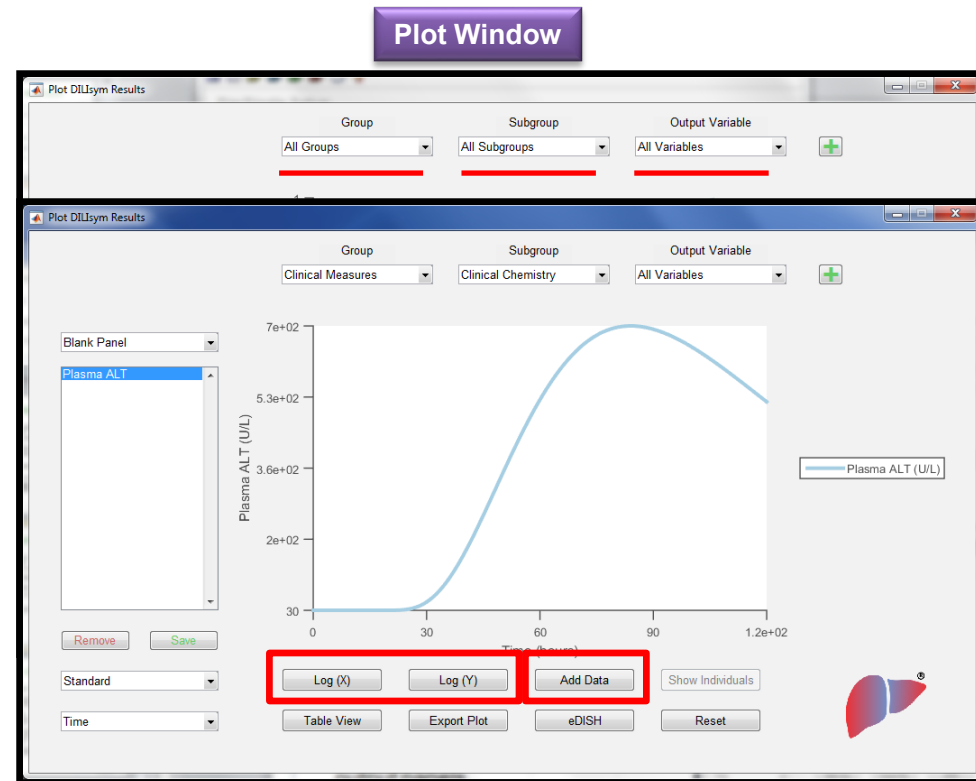# Using the Plot Function for Results Analysis

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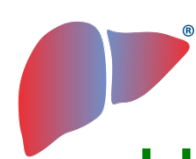
- Toggle to Table View

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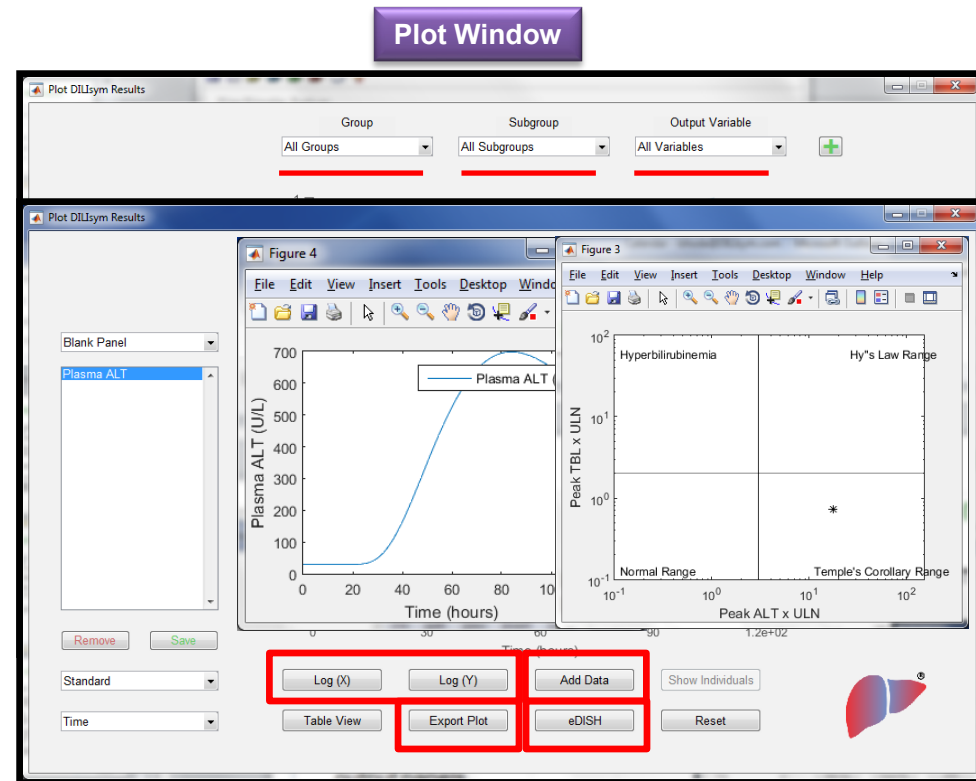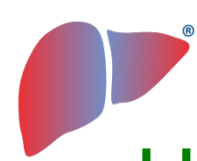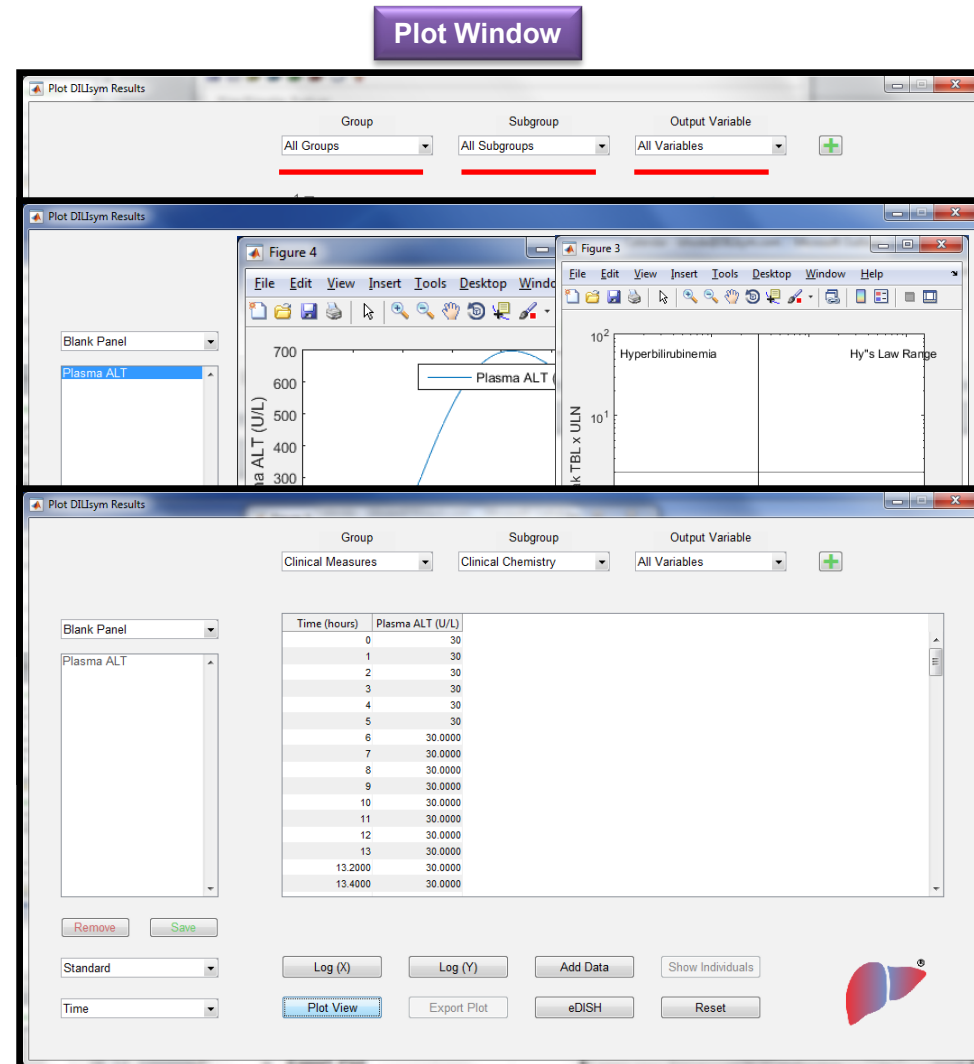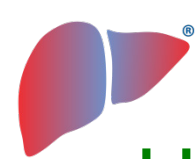# Using the Plot Function for Results Analysis

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- Toggle to Table View

- Outputs can be organized into output panels
  - Default output panels
  - Custom output panels (user-defined)

Plot Window
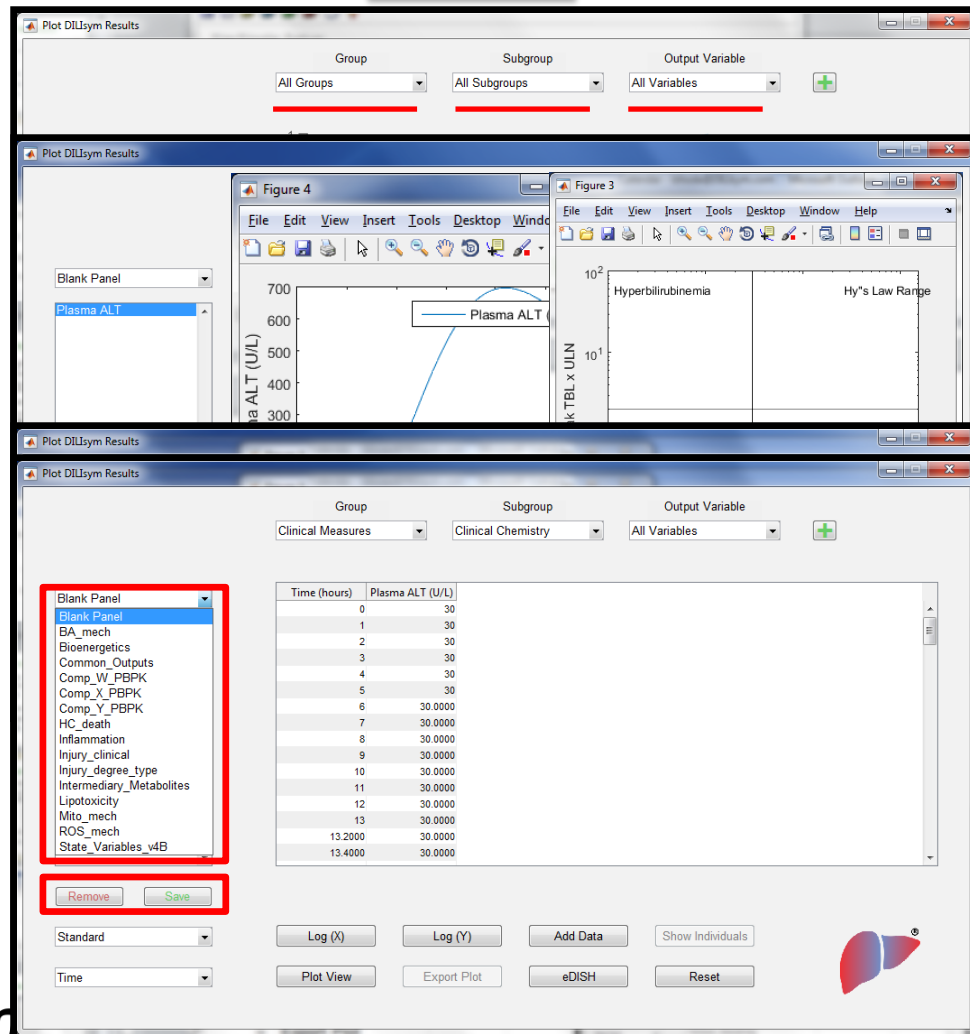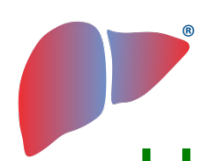
Using the Plot Function for Results Analysis

- For parameter sweeps and SimPops results, can use the plotting tool to investigate individuals

  – Select an individual or series of individuals from the plotting window

  – Select the "Show Individuals" button

Plot Window

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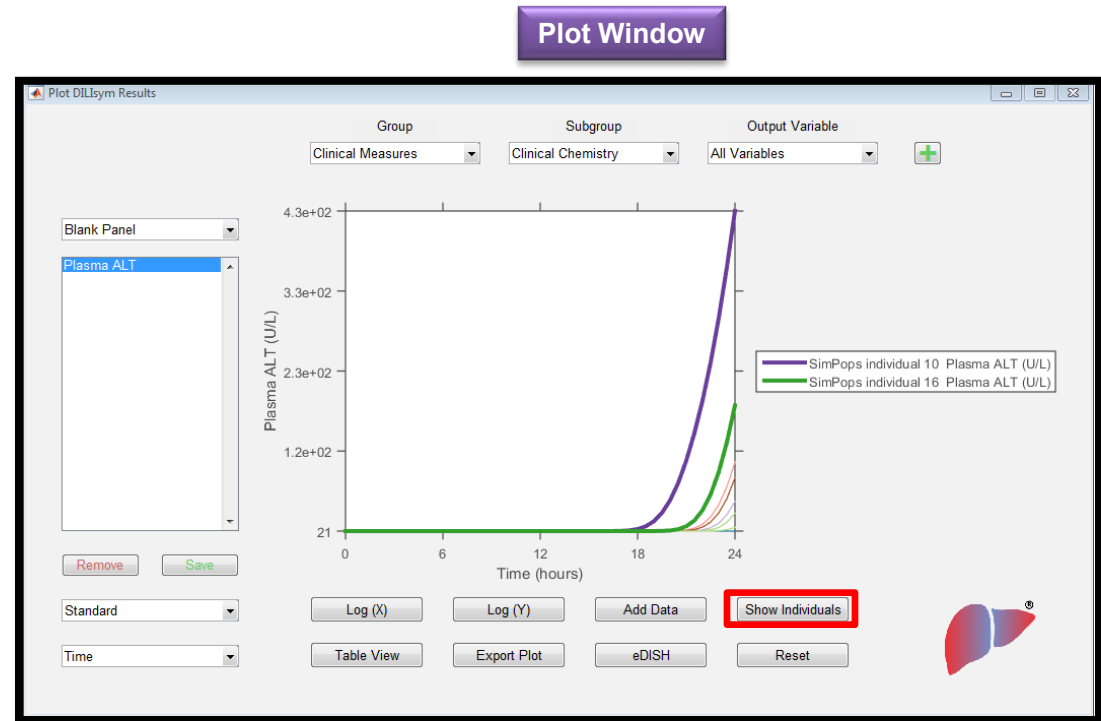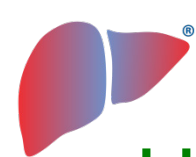
Using the Plot Function for Results Analysis

Plot Window

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  - Select an individual or series of individuals from the plotting window

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- Individuals (parameters) can be exported to Excel for further manipulation

- Parameter set can be created for a selected individual for more simulations

- SimCohorts can be created for selected groups of individuals for more simulations
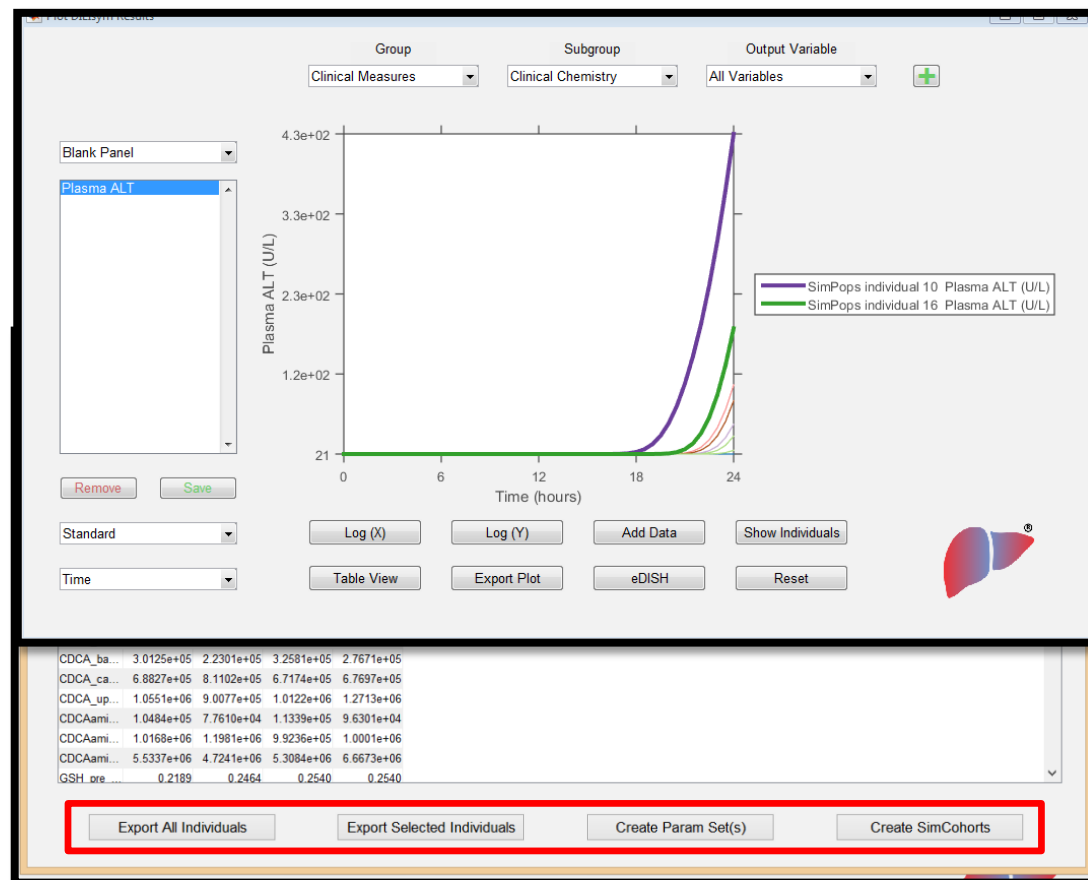
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Adding Data for Comparison

- Add Data
  - Permits the overlay of user-defined data on simulation results

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- Opens the Input Data window
  - Select Group, Subgroup, Output Variable

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  - Add Output Variable
  - Select Create Data Template

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  - Select Group, Subgroup, Output Variable
  - Add Output Variable
  - Select Create Data Template
    - Creates excel file template

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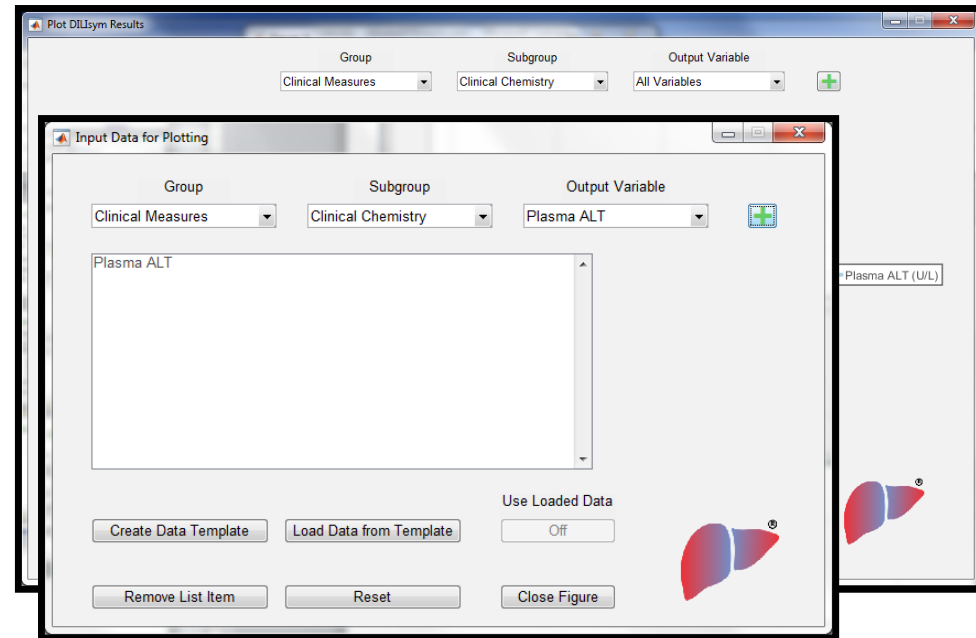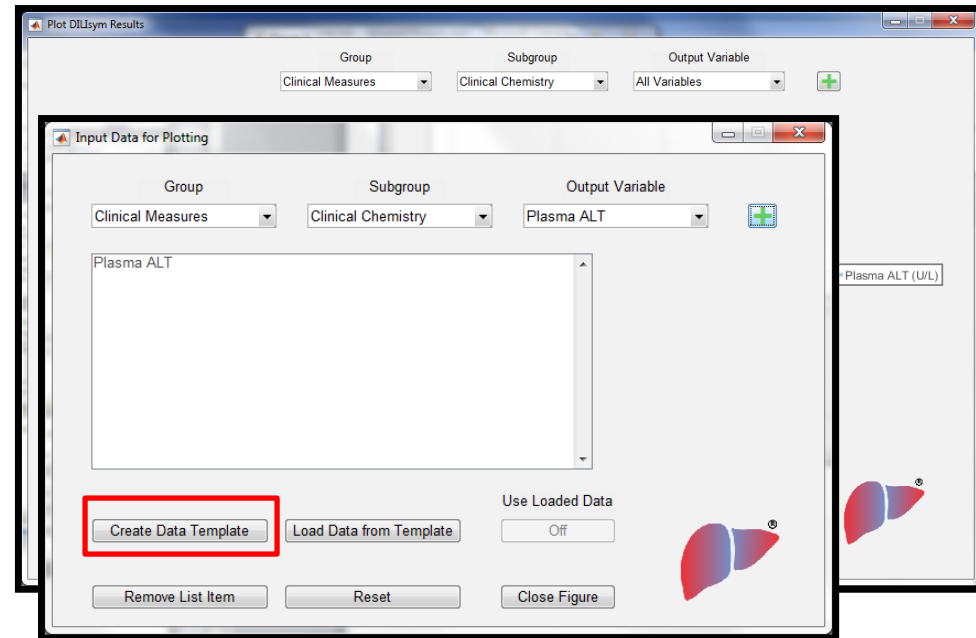
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    - Fill in data; save and close file

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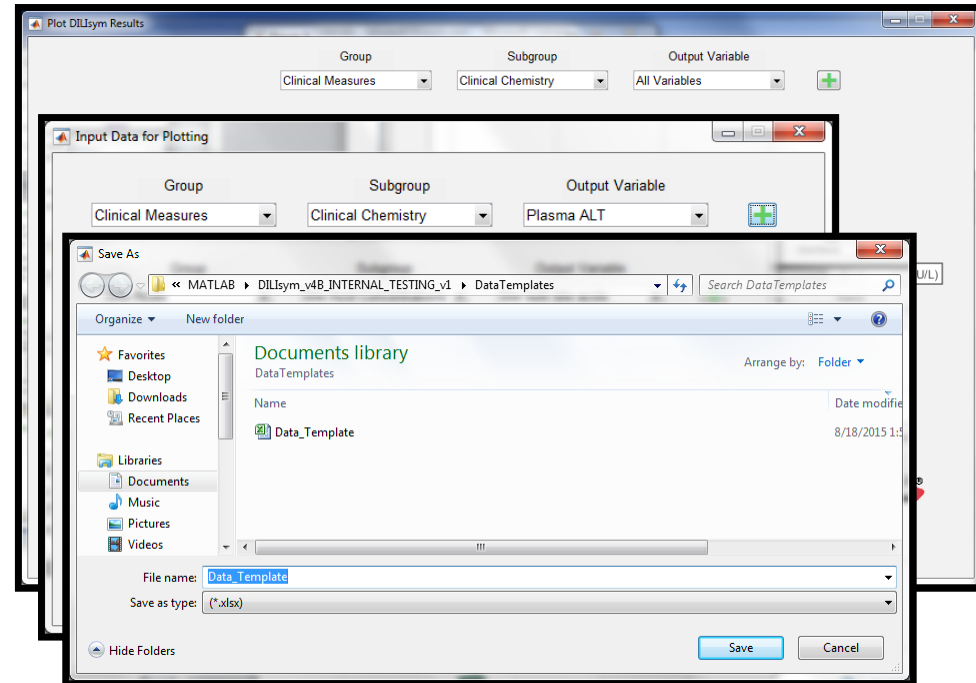# Adding Data for Comparison

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    - Creates excel file template
    - Fill in data; save and close file
  - Select Load Data Template
    - Select excel file of interest

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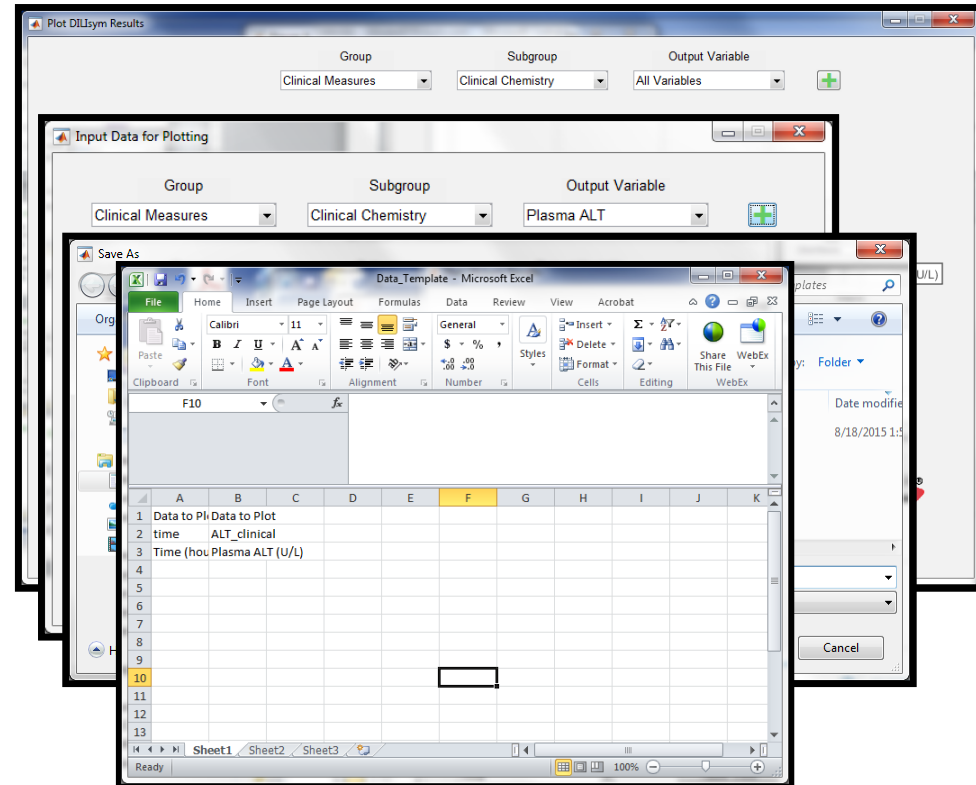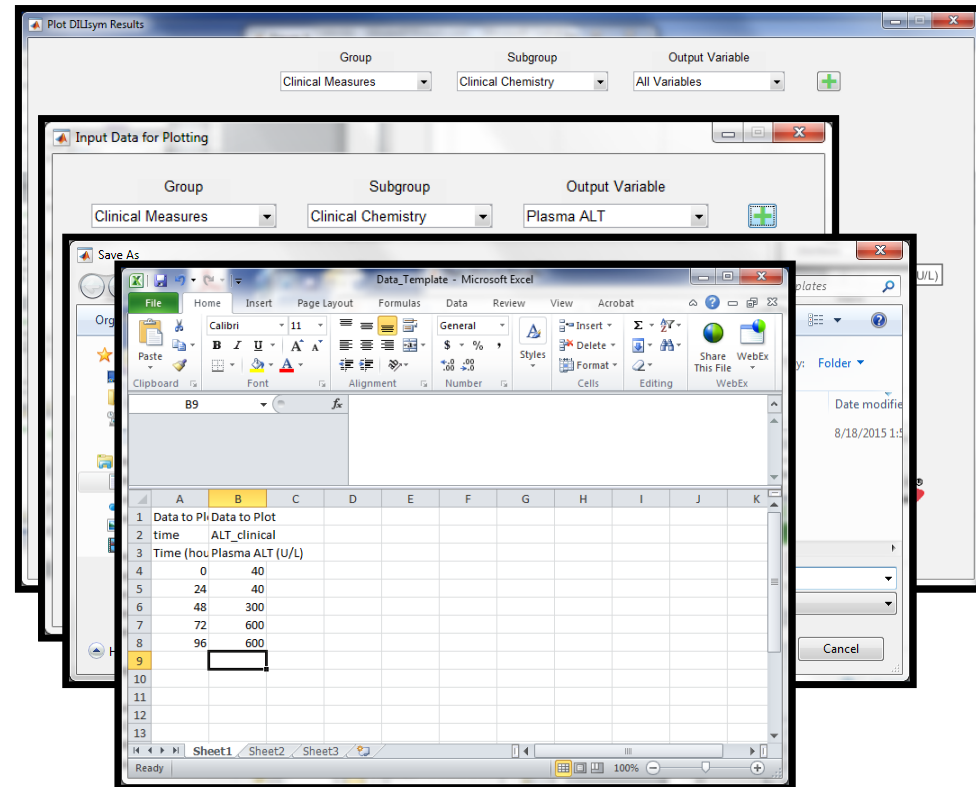# Adding Data for Comparison

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  - Select Load Data Template
    - Select excel file of interest

  - Toggle Use Loaded Data to ON

  - Select Close Figure

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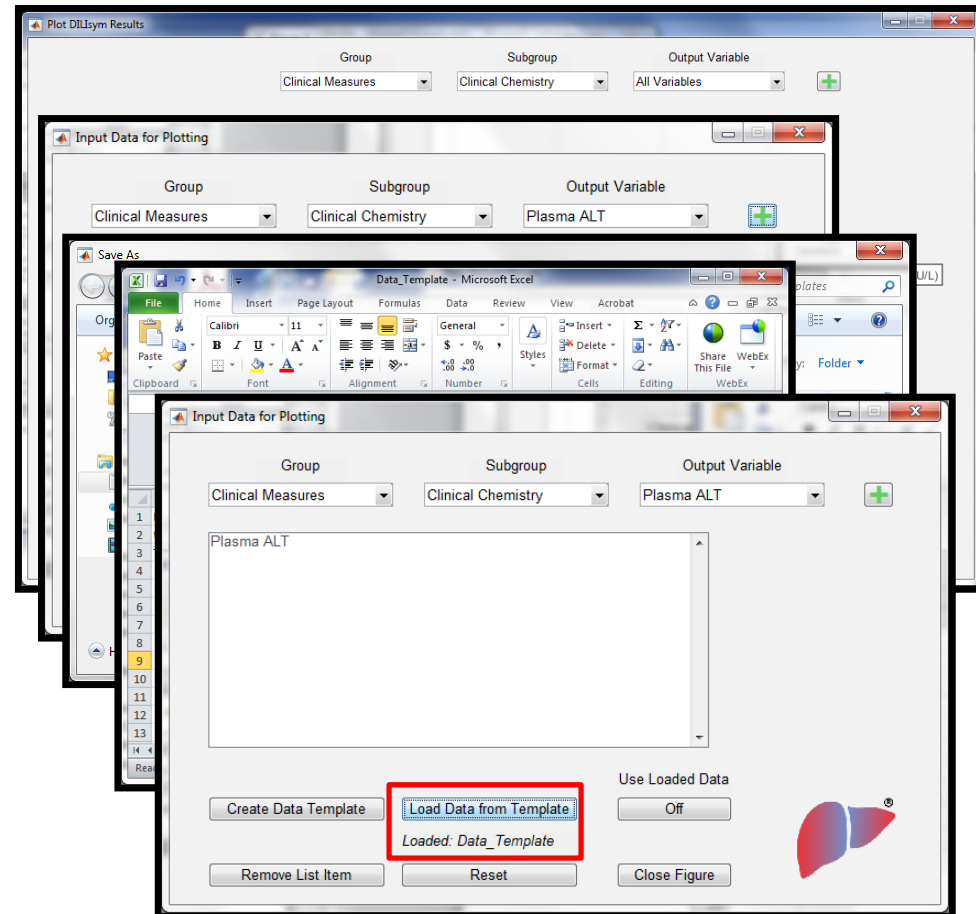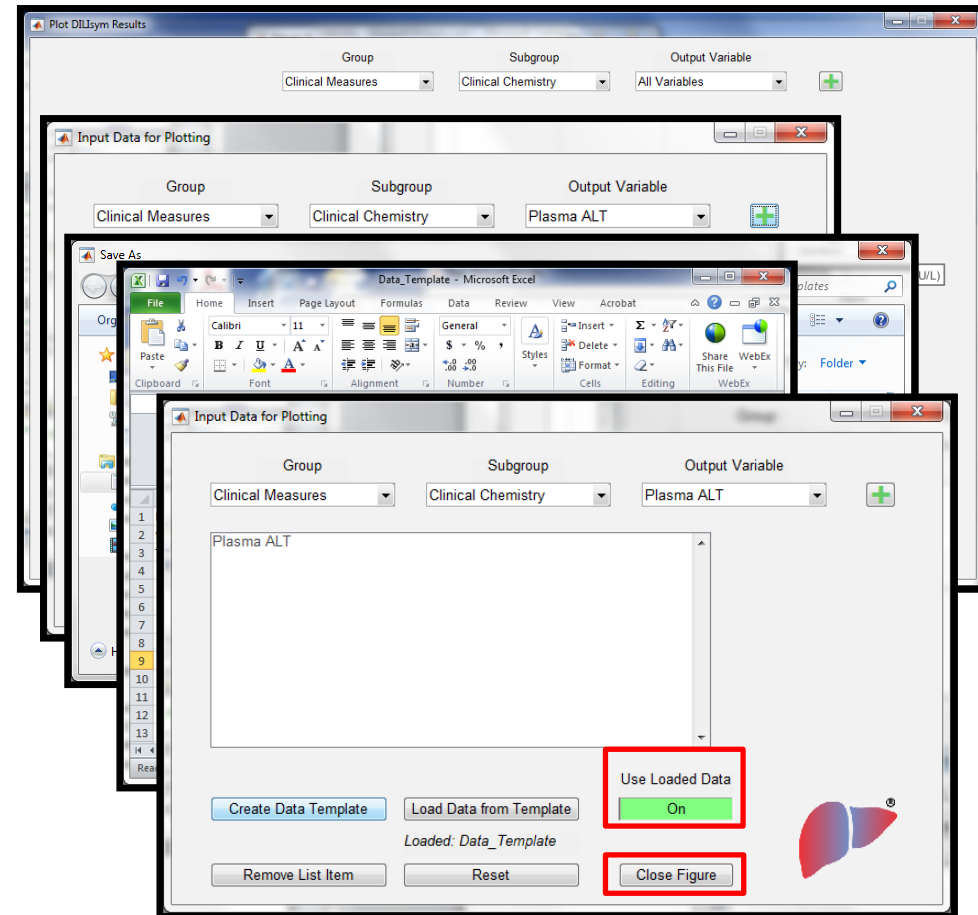
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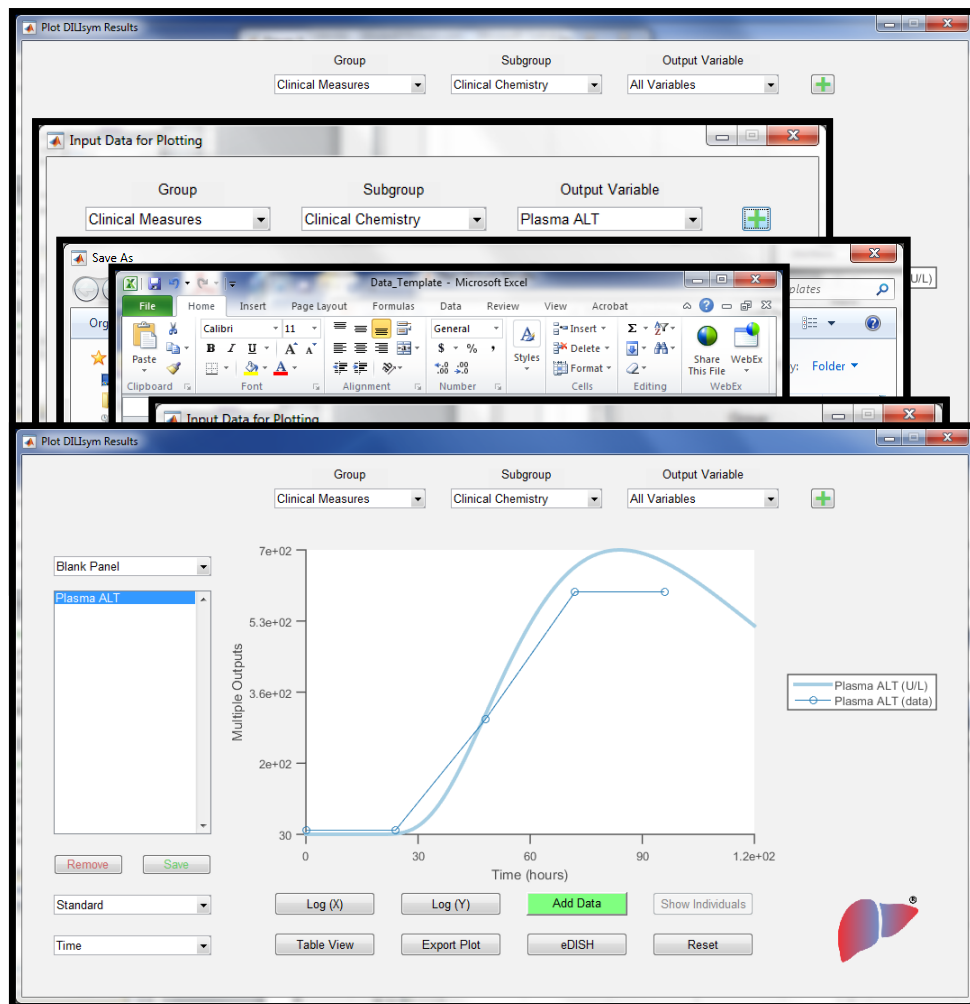 - Toggle Use Loaded Data to ON
  - Select Close Figure

- ## Data are displayed with simulation

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Creating Output Panels for Use in Large Simulations

- Saving all DILIsym outputs is memory intensive
  - Limiting outputs to only what you need for a large simulation (e.g., SimPops, Run in Parallel, Parameter Sweep) is highly recommended
  - Use Output Panel selection to limit outputs

- Output Panel setup within SimPops, Run in Parallel or Parameter Sweep windows:

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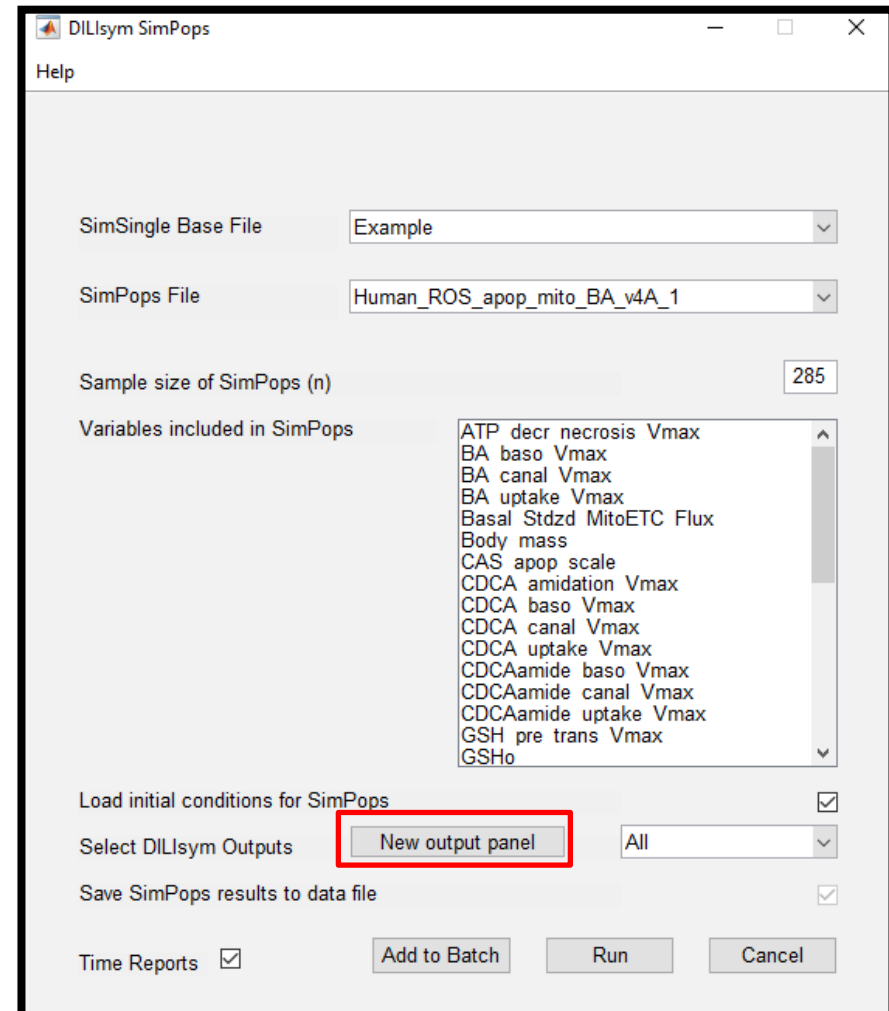 - Similar to setup in SimSingle Plot window
  - Allows adding an entire Subgroup

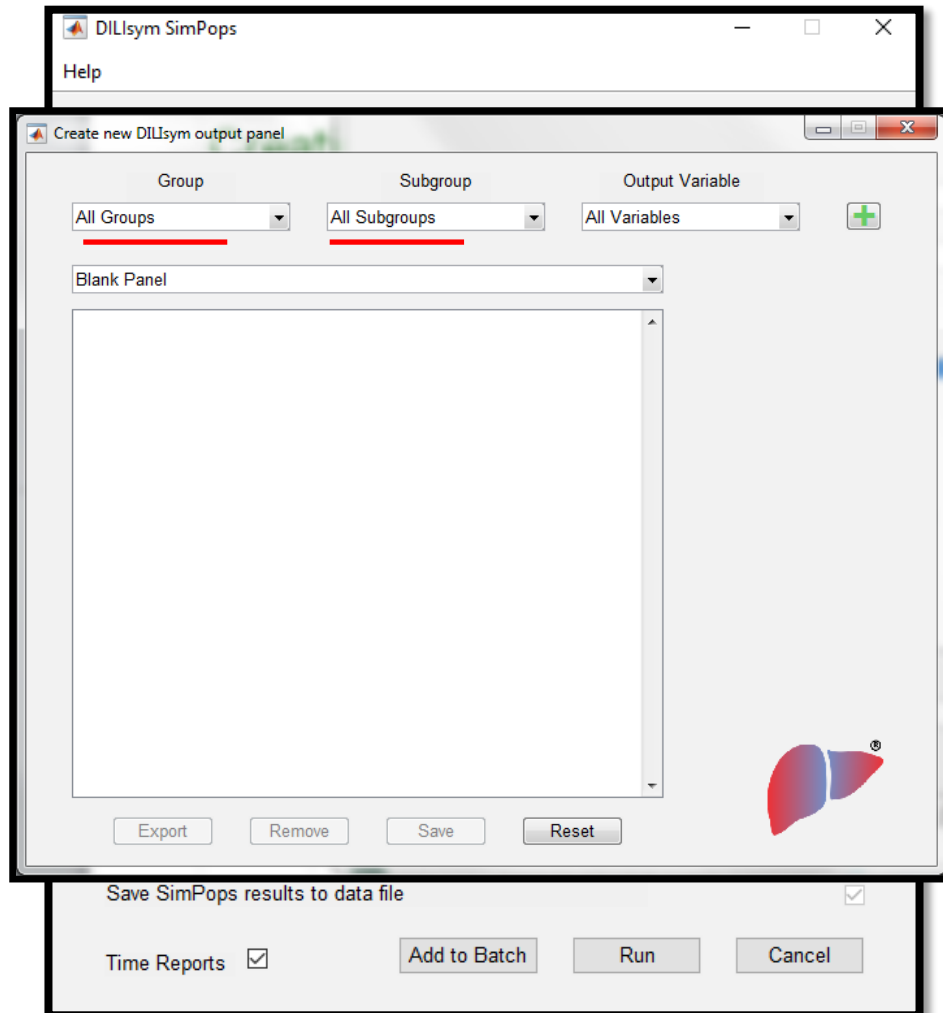# Creating Output Panels for Use in Large Simulations

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- Output Panel setup within SimPops, Run in Parallel or Parameter Sweep windows:
  - Similar to setup in SimSingle Plot window
  - Allows adding an entire Subgroup
  - Once desired outputs are added, save and close

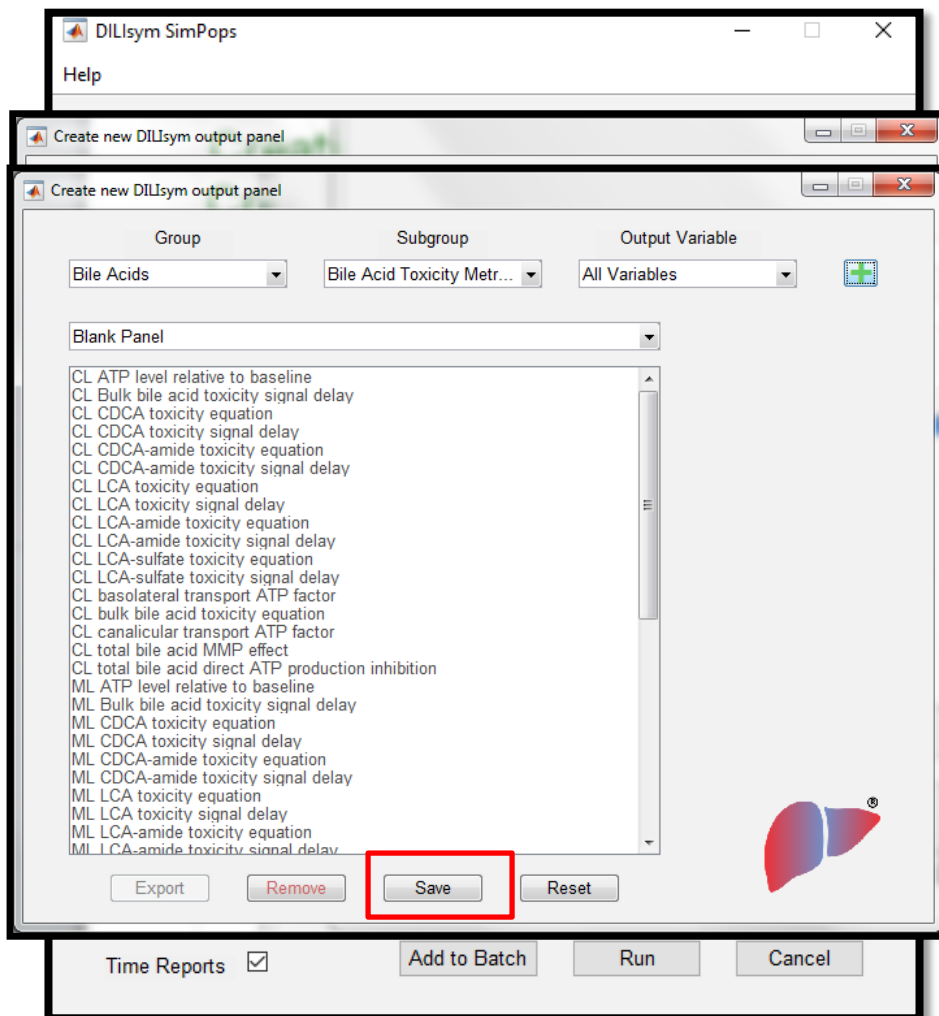# Creating Output Panels for Use in Large Simulations

- Saving all DILIsym outputs is memory intensive
  - Limiting outputs to only what you need for a large simulation (e.g., SimPops, Run in Parallel, Parameter Sweep) is highly recommended
  - Use Output Panel selection to limit outputs

- Output Panel setup within SimPops, Run in Parallel or Parameter Sweep windows:
  - Similar to setup in SimSingle Plot window
  - Allows adding an entire Subgroup
  - Once desired outputs are added, save and close

- Default and customized Output Panels can be selected from simulation and results windows
  - SimPops, Run in Parallel, Parameter Sweep
  - Plot and Table View§

§ Output Panels with many outputs may not be very meaningful to visualize in the Plot View
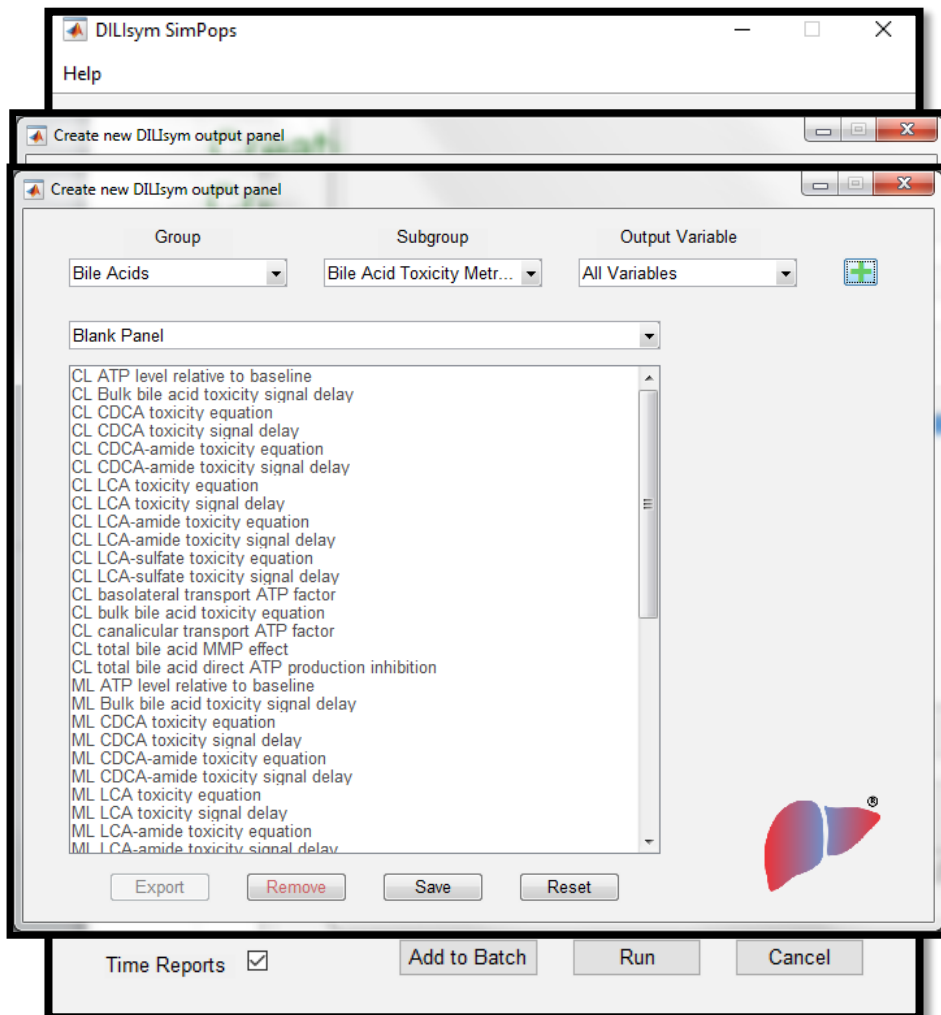
DILIsym Services

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Using the DILIsym Data Comparisons Tool

- Data Comparison tool includes combinations of simulation setups and results used as calibration or validation data that user can run and review
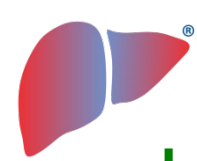

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Using the DILIsym Data Comparisons Tool

- Data Comparison tool includes combinations of simulation setups and results used as calibration or validation data that user can run and review

- To launch the data comparisons:
  - Select the species of interest from the checkbox menu
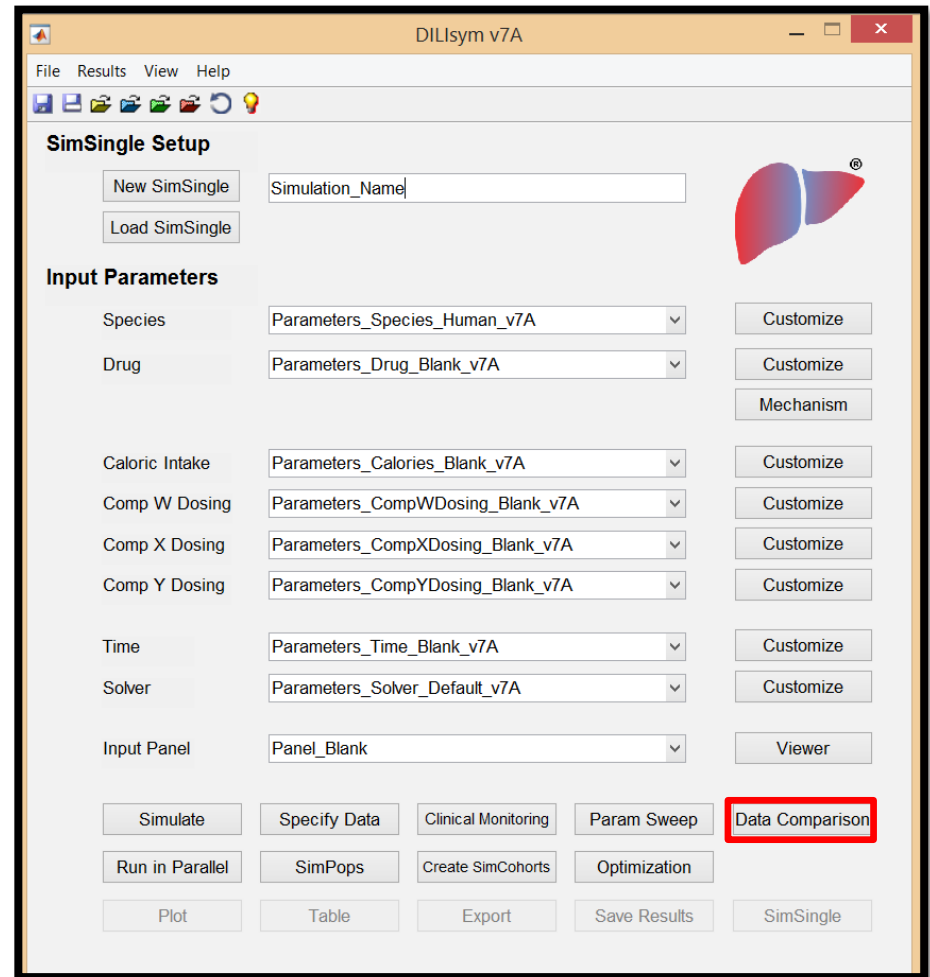 - Select data comparisons by checking box next to the comparison you wish to run

DILIsym Services

Using the DILIsym Data Comparisons Tool

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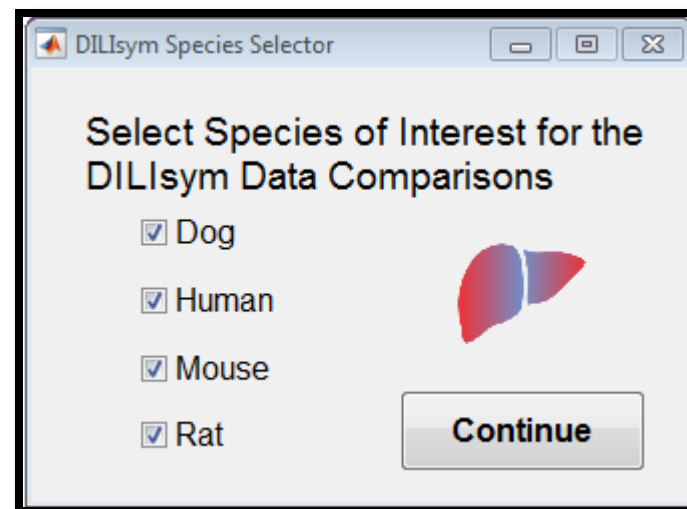 - Select data comparisons by checking box next to the comparison you wish to run
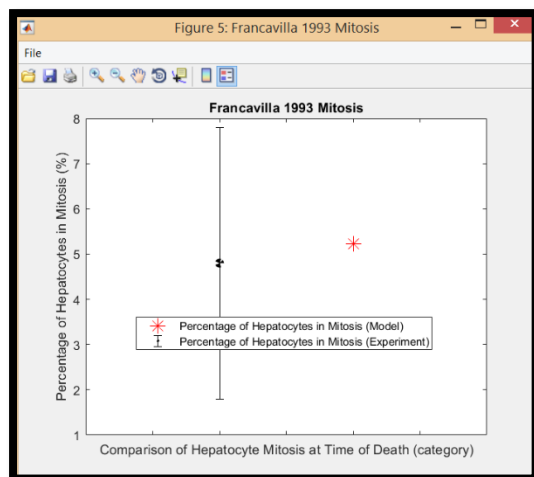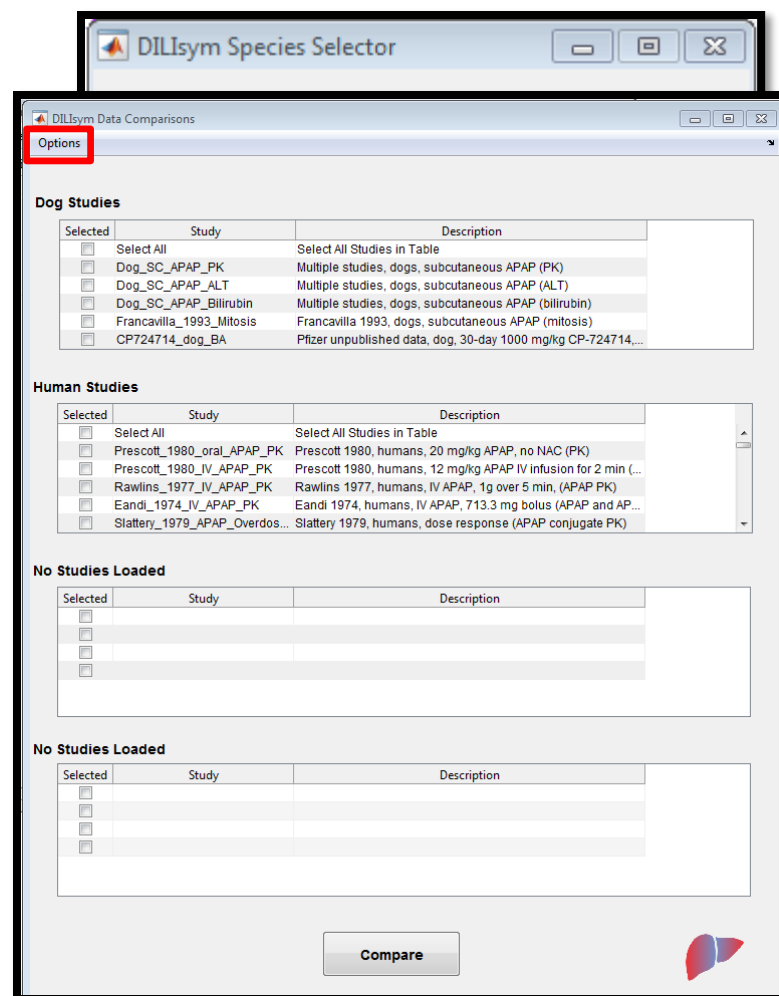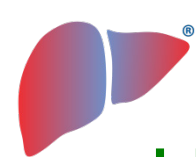
Using the DILIsym Data Comparisons Tool

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- To launch the data comparisons:
  - Select the species of interest from the checkbox menu
  - Select data comparisons by checking box next to the comparison you wish to run

- Can create SimSingle for each data comparison by selecting "Create SimSingle File" from the "Options" menu on the menu bar

DILIsym Species Selector

DILIsym Data Comparisons

Options

Dog Studies

Selected	Study	Description
☐	Select All	Select All Studies in Table
☐	Dog_SC_APAP_PK	Multiple studies, dogs, subcutaneous APAP (PK)
☐	Dog_SC_APAP_ALT	Multiple studies, dogs, subcutaneous APAP (ALT)
☐	Dog_SC_APAP_Bilirubin	Multiple studies, dogs, subcutaneous APAP (bilirubin)
☐	Francavilla_1993_Mitosis	Francavilla 1993, dogs, subcutaneous APAP (mitosis)
☐	CP724714_dog_BA	Pfizer unpublished data, dog, 30-day 1000 mg/kg CP-724714,...

Human Studies

Selected	Study	Description
☐	Select All	Select All Studies in Table
☐	Prescott_1980_oral_APAP_PK	Prescott 1980, humans, 20 mg/kg APAP, no NAC (PK)
☐	Prescott_1980_IV_APAP_PK	Prescott 1980, humans, 12 mg/kg APAP IV infusion for 2 min (...
☐	Rawlins_1977_IV_APAP_PK	Rawlins 1977, humans, IV APAP, 1g over 5 min, (APAP PK)
☐	Eandi_1974_IV_APAP_PK	Eandi 1974, humans, IV APAP, 713.3 mg bolus (APAP and AP...
☐	Slattery_1979_APAP_Overdos...	Slattery 1979, humans, dose response (APAP conjugate PK)

No Studies Loaded

Selected	Study	Description
☐		
☐		
☐		
☐		

No Studies Loaded

Selected	Study	Description
☐		
☐		
☐		
☐		

Compare

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Using the Output Table Tool within DILIsym

- DILIsym contains an output table that will perform basic calculations for simulation results

- Population level results for ALT, bilirubin, and Hy's Law are automatically displayed for SimPops, parameter sweeps, and SimSingles in parallel

Group	Subgroup	Output Variable	Metric	Value	Units
All Groups	All Subgroups	None Selected	None Selected		
Outcomes	Outcomes	Number of deaths	Count		0 dimensionless
Outcomes	Outcomes	ALT at or over 3x ULN	Count		0 dimensionless
Outcomes	Outcomes	Bilirubin over 2x ULN	Count		0 dimensionless
Outcomes	Outcomes	Hy's Law cases	Count		0 dimensionless

- In order to use the table tool:
  - Press the "Table" button on the DILIsym home screen
  - Select the output and desired metric to calculate
  - Press the 'Calculate' button

- To capture output table results, copy rows and paste into Excel or take screen shot of table

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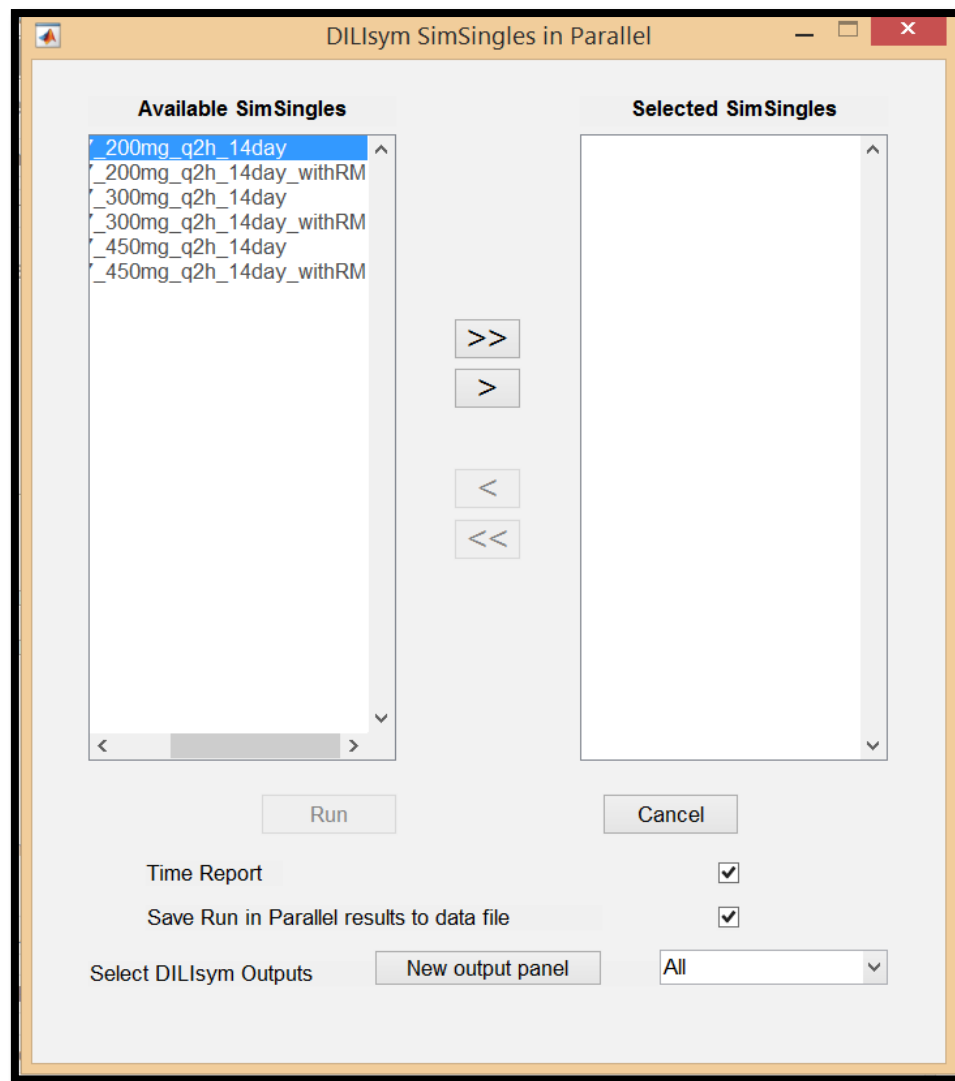
Using the Export Tool within DILIsym

- DILIsym contains an export tool that creates an Excel spreadsheet of simulation results
- Export is available for all simulation results, including parallel applications
- Each tab is an output for parallel applications

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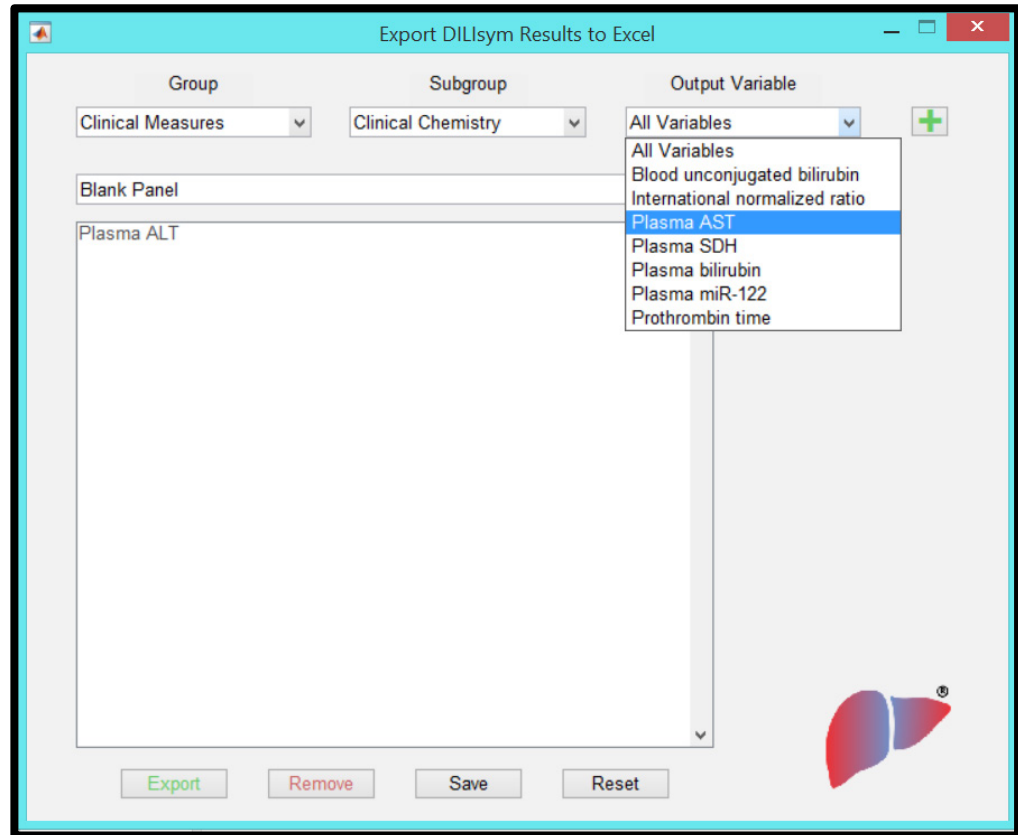
Using the Run in Parallel Tool in DILIsym

- The "Run in Parallel" interface allows for running several SimSingles in parallel

- Utilizes all local cores up to 512, reducing simulation time

- Nice alternative to parameter sweep or SimPops if odd or unique collection of simulation setups is needed

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