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# **DILIsym User Training –**

# **SimPops in DILIsym - Step By Step Instructions and a Hands-on Example**

**DILIsym Development Team**

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# Goals for This Training Session

***Participants should understand the following general concepts:***

- The practical workflow for running SimPops and SimCohorts
- The concept of loading initial conditions for SimPops simulations

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# Overview of SimPops Training Session

- Step by step instructions for using the SimPops feature
- Hands-on example using the SimPops feature



# DILIsym SimPops Tool – Critical Components

1. SimSingle (simulation setup) within DILIsym via the home screen
  - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
  - A simulation needs to be set up, during which the overwriting with the population parameters will occur
2. Select SimPops of choice
  - Same species as SimSingle should be chosen
  - Parameters will be shown once chosen
3. Select simulation options and run simulation (or add to batch and run a batch of simulations)

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# DILIsym SimPops Tool – Step By Step Instructions

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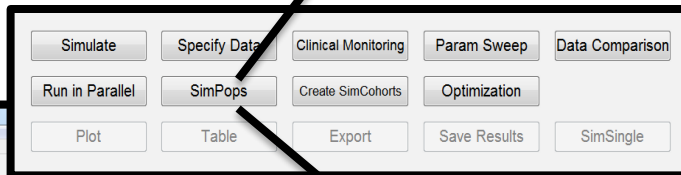
# DILIsym SimPops Tool – Step By Step Instructions

1. SimSingle (simulation setup) within DILIsym via the home screen
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# The DILIsym SimPops Feature is Accessed from the DILIsym Home Screen

- The SimPops window has two main sections:
  - SimSingle and SimPops selection
  - Simulation options selection



DILIsym SimPops

Help

SimSingle Base File

SimPops File: Dog\_ROS\_apop\_mito\_v3B\_3

Sample size of SimPops (n): 0

Variables included in SimPops

Load initial conditions for SimPops: ☒

Select DILIsym Outputs: New output panel | All

Save SimPops results to data file: ☒

Time Reports: ☒

Add to Batch Run Cancel

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# Select the SimSingle and Corresponding SimPops from the Dropdown Menus

- Setting up a SimPops:
  - Select SimSingle from drop-down menu
  - Select SimPops from drop-down menu
  - The number of individuals in the SimPops and the parameters varied will appear in the window

The screenshot shows the 'DILIsym SimPops' window with the following settings:

- SimSingle Base File:** Example
- SimPops File:** Human\_ROS\_apop\_mito\_BA\_v4A\_1
- Sample size of SimPops (n):** 285
- Variables included in SimPops:** A list of parameters including ATP decr necrosis Vmax, BA baso Vmax, BA canal Vmax, BA uptake Vmax, Basal Stdzd MitoETC Flux, Body mass, CAS apop scale, CDCA amidation Vmax, CDCA baso Vmax, CDCA canal Vmax, CDCA uptake Vmax, CDCAamide baso Vmax, CDCAamide canal Vmax, CDCAamide uptake Vmax, GSH pre trans Vmax, and GSHo.
- Load initial conditions for SimPops:** Checked
- Select DILIsym Outputs:** New output panel, All
- Save SimPops results to data file:** Checked
- Time Reports:** Checked
- Buttons:** Add to Batch, Run, Cancel





# DILIsym SimPops Tool – Step By Step Instructions

1. SimSingle (simulation setup) within DILIsym via the home screen
  - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
  - A simulation needs to be set up, during which the overwriting with the population parameters will occur
2. Select SimPops of choice
  - Same species as SimSingle should be chosen
  - Parameters will be shown once chosen
3. Select simulation options and run simulation (or add to batch and run a batch of simulations)



# Select the Simulation Options for Each SimPops Simulation Set

1. “Load initial conditions for SimPops” option allows loading of initial conditions for all default SimPops and SimCohorts
  - **Highly recommend leaving this option selected unless you are an advanced user very familiar with initial condition process for DILIsym SimPops**
2. Select DILIsym Outputs desired
  - Including **all** DILIsym outputs will lead to very large file size
  - Choose smaller output panel that fits needs or create custom output panel
3. Saving SimPops results is mandatory
  - Files are automatically named
  - This facilitates use of the batch processor
4. Decide on time reporting option
  - If checked, Excel file will be saved with simulation time information
  - Time reports are very helpful with planning future SimPops runs

DILIsym SimPops

Help

SimSingle Base File: Example

SimPops File: Human\_ROS\_apop\_mito\_BA\_v4A\_1

Sample size of SimPops (n): 285

Variables included in SimPops:

- ATP decr necrosis Vmax
- BA baso Vmax
- BA canal Vmax
- BA uptake Vmax
- Basal Stdzd MitoETC Flux
- Body mass
- CAS apop scale
- CDCA amidation Vmax
- CDCA baso Vmax
- CDCA canal Vmax
- CDCA uptake Vmax
- CDCAamide baso Vmax
- CDCAamide canal Vmax
- CDCAamide uptake Vmax
- GSH pre trans Vmax
- GSHo

1 Load initial conditions for SimPops ☒

2 Select DILIsym Outputs  All

3 Save SimPops results to data file ☒

4 Time Reports ☒

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# Automated Equilibration Simulation Loading Is Incorporated Into DILIsym

- What are equilibration simulations and how are they used?
  - Equilibration is the process of running a simulation within DILIsym (typically without drug) prior to running the simulation specified by the user (a 'pre-simulation')
  - They are used to generate stored initial conditions for SimSingles and SimPops
- What is accomplished with equilibration?
  - Equilibration allows DILIsym outputs (state variables and algebraic expressions) to reach new steady state values that are different than the initial starting values, due to the oscillatory nature of many aspects of DILIsym, including meals, and due to the difficulty in calculating the correct steady state values for every output *a priori* with a large equation set for simulated patients and animals with variability in species parameters
  - Loading stored steady state values is the default option for users
- ***Loading initial conditions is highly recommended to reduce simulation time and should only be turned off for specific applications***
- ***If users create custom SimPops de novo, excluding SimCohorts creation from existing SimPops using the DILIsym interface tool, they will need to also include new initial conditions***

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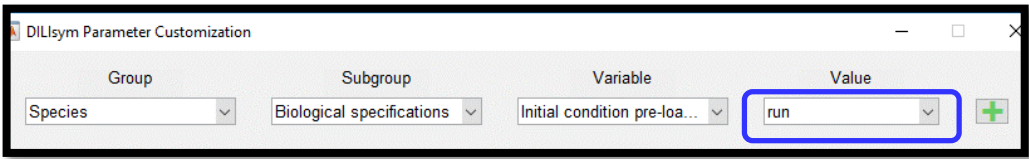
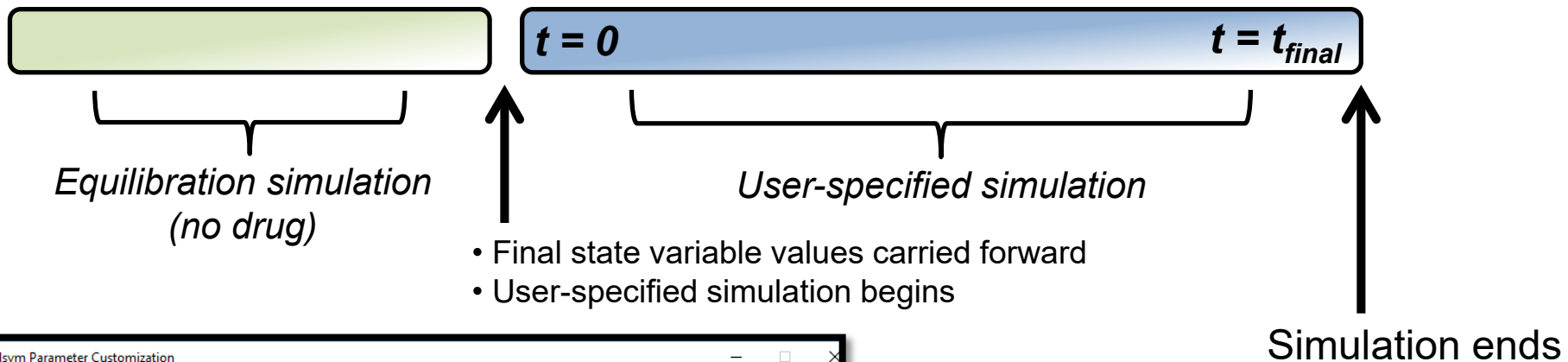
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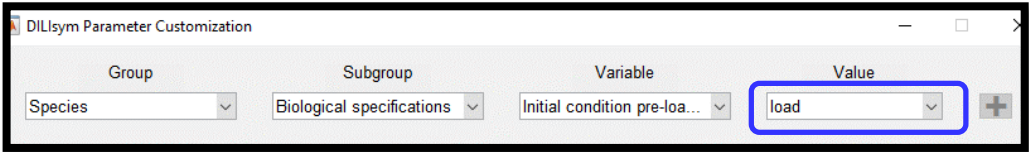
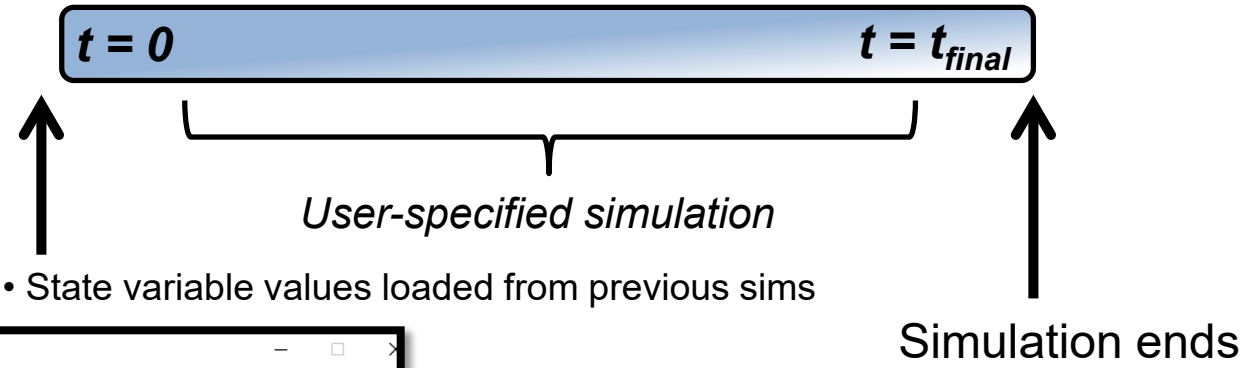


# A Chronological View of Equilibration in DILIsym

## Running an equilibration simulation



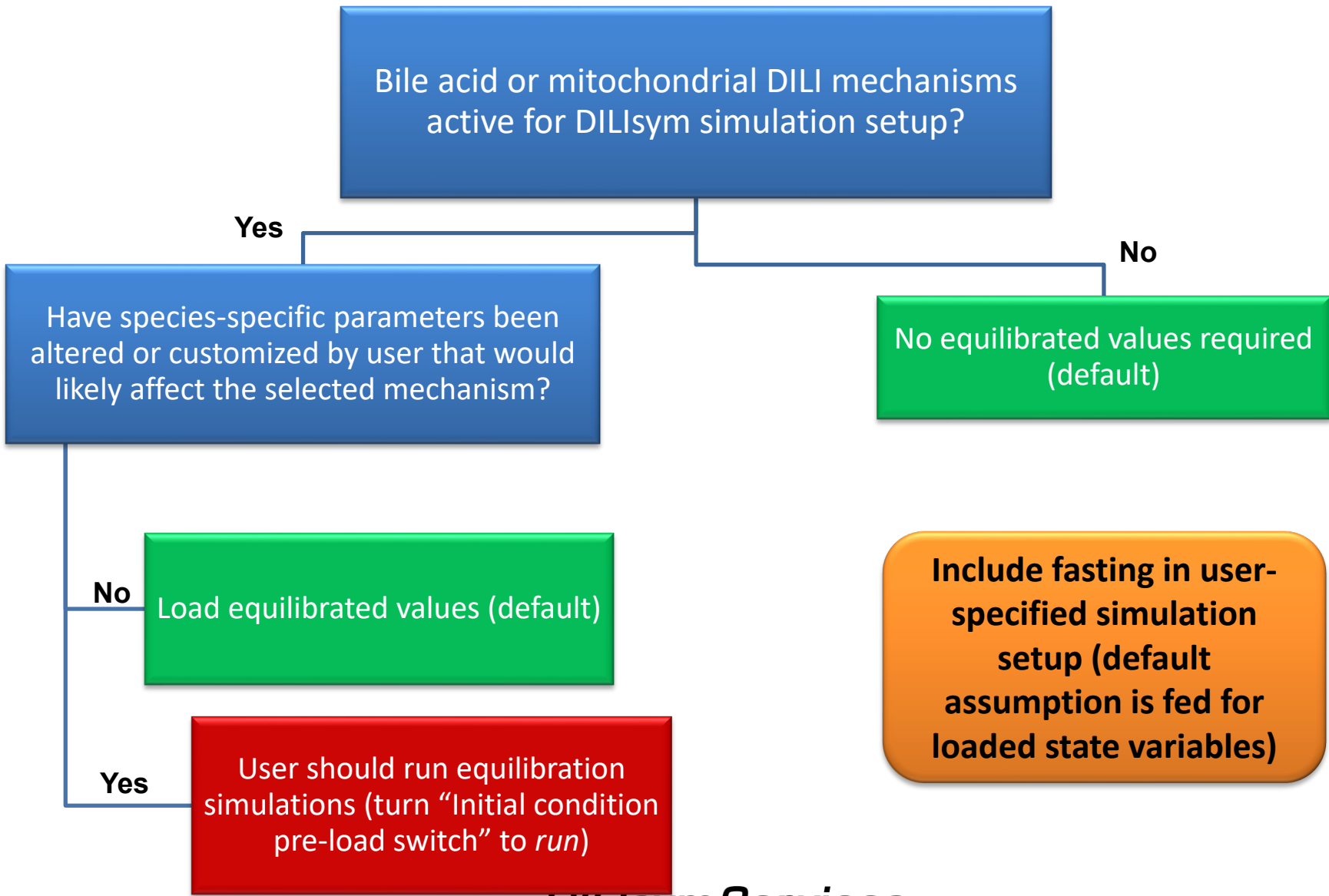
## Loading equilibrated initial conditions (default)



**ices**



# DILIsym Equilibration Decision Tree



**Include fasting in user-specified simulation setup (default assumption is fed for loaded state variables)**



# Custom SimPops Constructed By Users Within MATLAB Should Also Include Accompanying Saved Initial Conditions for Loading

- Advanced DILIsym users have the ability to create their own, in-house SimPops files
  - Could be customized to include PK of particular drug
  - Could be focused on group not included in current version of DILIsym software
- All SimPops simulations, including user-defined custom SimPops, should include loading of initial conditions
  - Simulation time requirements for equilibration simulations for every simulation with a given SimPops would be overly burdensome and unnecessary
- Once a SimPops is created, follow these general steps to include your loaded initial conditions:
  1. Run the SimPops without drug for long enough to ensure that key indicators have reached steady state (e.g. triglycerides, ATP, hepatocyte cell count, etc.)
    - Required simulation time ranges from 10 days to 2 years
    - Be sure to save All Outputs or at least the State Variables output panel
  2. Convert state variable value results at last time step from SimResults.mat format to simple MATLAB array format within MATLAB
  3. Place saved initial conditions array in proper folder
  4. Update SimPops initial conditions key file to link SimPops and initial conditions
- See DILIsym user guide, “DILIsym Directory Structure” section, for more details – advanced training may also be necessary



# After Selecting All Options, Run SimPops or Add to Batch of SimPops Runs

- Clicking “**Run**” will lead to simulations for 1 SimPops chosen
- Clicking “**Add to Batch**” will add simulation to a batch of SimPops simulations
  - ***Be certain that the options for each SimPops, including the SimSingle selected and the options below, are correct before adding to batch***
    - Cannot see options once added to batch
  - Each SimPops results file is saved automatically after completion in between batch simulations
  - Use the Load feature to load in results for analysis
- **It highly recommended that CPU's with multiple cores and advanced processors be used for DILIsym simulations**
  - **SimPops simulations will take substantial time**

The image shows two overlapping screenshots of the DILIsym SimPops software interface. The top window is titled 'DILIsym SimPops' and has a 'Help' button. It contains two dropdown menus: 'SimSingle Base File' set to 'Example' and 'SimPops File' set to 'Human\_ROS\_apop\_mito\_BA\_v4A\_1'. The bottom window is also titled 'DILIsym SimPops' and has a 'Help' button. It contains the same 'SimSingle Base File' dropdown set to 'Example'. The 'SimPops File' dropdown is set to 'Human\_ALT\_SimPops\_v6A\_1'. To the right of these dropdowns is a 'SimPops Batch Processor' section with two rows of example entries, each with a red 'X' icon: 'Human\_ROS\_apop\_mito\_BA\_v4A\_1' and 'Human\_ALT\_SimPops\_v6A\_1'. Below this is a 'Sample size of SimPops (n)' input field set to '300'. A list box titled 'Variables included in SimPops' contains the following text: 'HC necr ALT release', 'HGF prod LSEC Vmax', 'HGF regen Vmax', 'interm ALT h', 'interm ALT serum ALT rate', 'liver ALT h', 'liver ALT interm ALT rate', and 'serum ALT h'. At the bottom of the window, there are several checkboxes and buttons: 'Load initial conditions for SimPops' (checked), 'Select DILIsym Outputs' (with a 'New output panel' button and a 'Common\_Outputs' dropdown), 'Save SimPops results to data file' (checked), 'Time Reports' (checked), and three buttons: 'Add to Batch' (highlighted with a red box), 'Run Batch', and 'Cancel'. There are also 'Cancel Batch' buttons at the bottom right.

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# Overview of SimPops Training Session

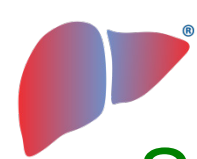
- Step by step instructions for using the SimPops feature
- Hands-on example using the SimPops feature





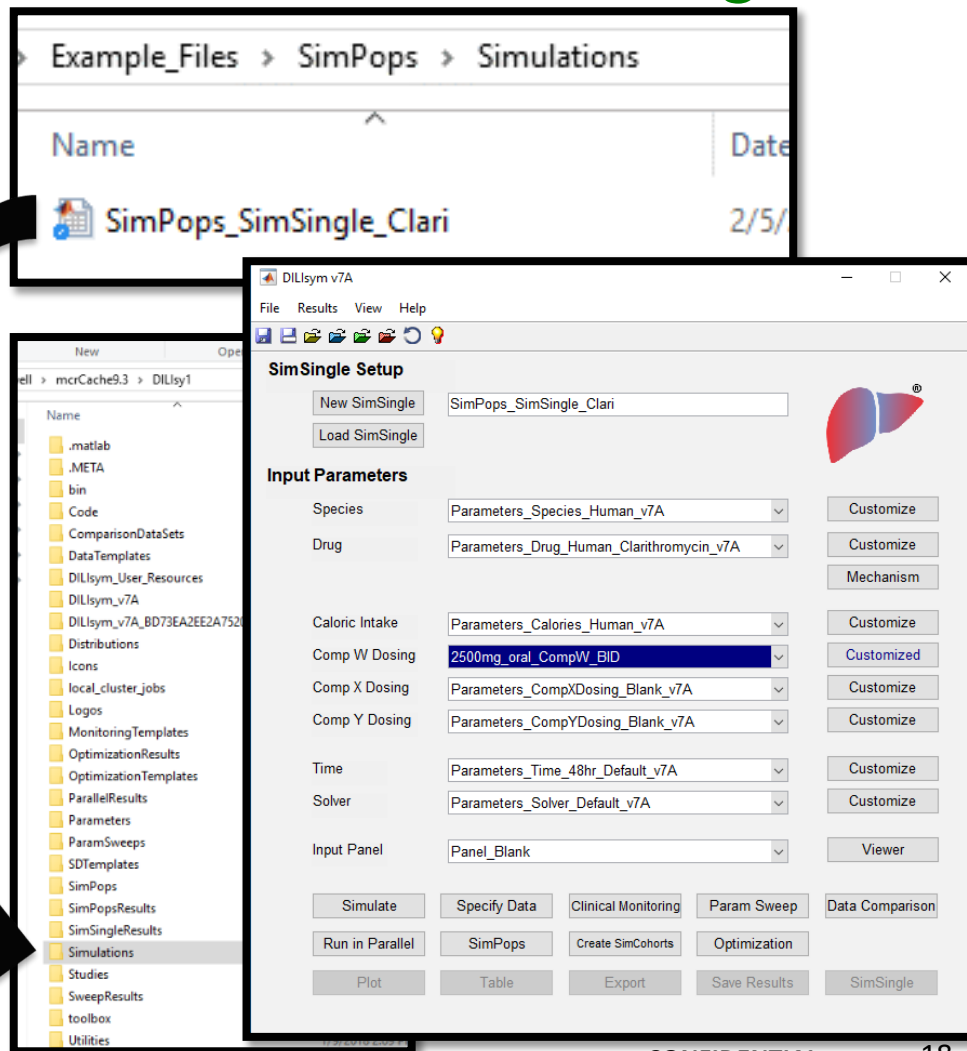
# Hands-on SimPops Example – Simulations in SimCohorts Sensitive to Mitochondrial Toxicity

- Goal is to run standard SimCohorts and user-defined SimCohorts created within DILIsym using the SimCohorts customization tool
- Clarithromycin will be used as exemplar drug for example
  - *SimSingle for example includes higher dose than used clinically, for illustration purposes only*
- You will learn how to set up SimPops simulation
- You will learn how to extract individuals from existing SimPops or SimCohorts and create new SimCohorts with subset desired



# Hands-on SimPops Example – *Step 1 – Place Provided SimSingle Setup in Simulations Folder and Review SimSingle*

- Find Simulations directory by clicking any load option within DILIsym and copying location from Windows Explorer
- Copy one provided SimSingle into your Simulations directory
- Explore SimSingle
  - Human species
  - Human clarithromycin drug file selected
  - Human meal pattern selected
  - 2500 mg dosed orally, BID, for Compound W
  - 2 day simulation time





# Hands-on SimPops Example – Step 2 – *Select SimPops Options as Shown Below*

- Open SimPops interface from DILIsym home screen
  - Select  
“***Human\_ROS\_apop\_mito\_BA\_v4A\_1\_SensMito***” as SimPops File
  - Select “***Common\_Outputs***” panel with drop down menu as shown at right
    - Including all DILIsym outputs will lead to very large file size
  - Leave loading and time reporting options as default
  - Click “***Run***”

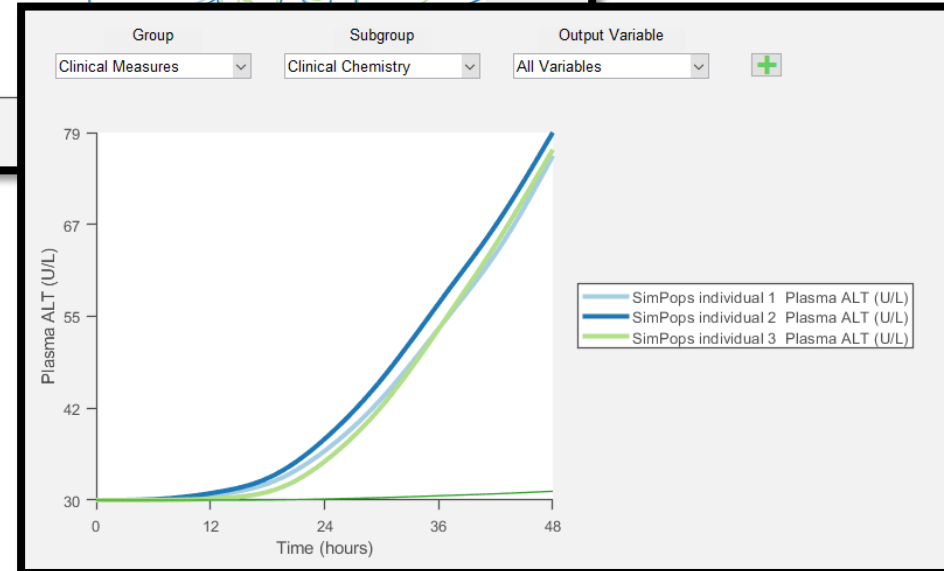
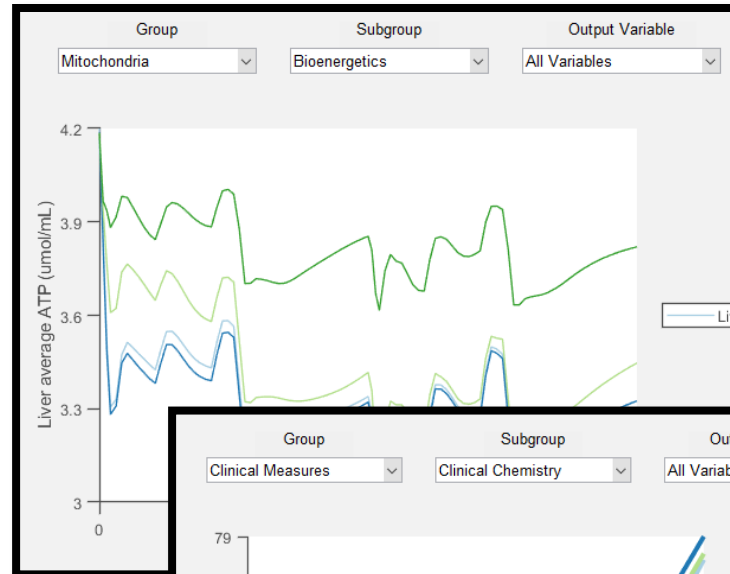
The screenshot shows the DILIsym SimPops window with the following settings:

- SimSingle Base File:** SimPops\_SimSingle\_Clari
- SimPops File:** Human\_ROS\_apop\_mito\_BA\_v4A\_1\_SensMito (highlighted with a blue box)
- Sample size of SimPops (n):** 4
- Variables included in SimPops:** A list of variables including ATP, BA, CDCA, and GSH, with a scroll bar on the right.
- Load initial conditions for SimPops:** ☒
- Select DILIsym Outputs:** A dropdown menu showing "New output panel" and "Common\_Outputs" (highlighted with a blue box).
- Save SimPops results to data file:** ☒
- Time Reports:** ☒
- Buttons:** "Add to Batch", "Run" (highlighted with a blue box), and "Cancel".



# Hands-on SimPops Example – Step 3 – *Analyze SimPops Results and Select Custom SimCohorts Based on Responses*

- Note variability in liver ATP levels
  - *Mitochondria* ->  
*Bioenergetics* -> **Liver  
average ATP**
- Note variability in Plasma ALT
  - *Clinical Measures* ->  
*Clinical Chemistry* -> **Plasma ALT**
- *Select 3 traces with  
highest ALT*





# Hands-on SimPops Example – Step 4 – Create Custom SimCohorts Based on Responses Using Built-in Feature

- After selecting 3 traces with highest ALT
  - Click “**Show Individuals**”
  - Click “**Create SimCohorts**”
  - Click “**Create Custom SimCohorts**”
- Save SimCohorts as:
  - **v4A\_1\_SensMITO\_3Responders**

SimPops/Parameter Sweep Simulated Individuals

Variables	Individual 1	Individual 2	Individual 3
ATP_decr_n...	0.4355	0.3751	0.3746
BA_baso_V...	1.9542e+06	1.1613e+06	1.7585e+06
BA_canal_V...	1.9453e+07	1.5768e+07	1.8597e+07
BA_uptake_...	2.2248e+06	2.4749e+06	3.5868e+06
Basal_Stdz...	26.6835	25.2033	24.4491
Body_mass	50	50	50.0127
CAS_apop_...	0.1297	0.1051	0.0922
CDCA_amida...	5.3719e+11	1.1349e+11	6.0524e+11
CDCA_baso...	7.3934e+05	4.3934e+05	6.6529e+05
CDCA_canal...	8.0799e+05	6.5493e+05	7.7244e+05
CDCA_uptak...	6.5547e+05	7.2916e+05	1.0568e+06
CDCAamide_...	2.5730e+05	1.5290e+05	2.3153e+05
CDCAamide_...	1.1936e+06	9.6752e+05	1.1411e+06
CDCAamide_...	3.4376e+06	3.8241e+06	5.5423e+06
GSH_nre_tra	0.1873	0.1988	0.2436

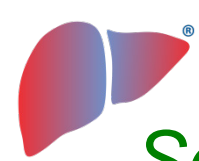
Create Custom SimCohorts

Use Selected Individuals ☒

Input Individual Indexes  (Enter sequential indexes using a colon and non-sequential indexes separated by a comma, e.g. 1,5,6,9,30,38)

Choose Source SimPops Human\_ROS\_apop\_mito\_BA\_v4A\_1\_SensMito

Create Custom SimCohorts



# Hands-on SimPops Example – Step 5 – *Select Newly Created SimCohorts and Options and Run Simulations as Shown Below*

- Open SimPops interface from DILIsym home screen
  - Select newly created SimCohorts with same SimSingle as before
    - “**v4A\_1\_SensMITO\_3Responders**”
  - Select “**Common\_Outputs**” panel
  - Leave loading and time reporting options as default
  - Click “**Run**”

The screenshot shows the DILIsym SimPops window with the following settings:

- SimSingle Base File:** SimPops\_SimSingle\_Clari
- SimPops File:** v4A\_1\_SensMITO\_3Responders
- Sample size of SimPops (n):** 3
- Variables included in SimPops:** A list of variables including ATP, BA, CDCA, and GSH, with checkboxes for various parameters like Vmax, baso, canal, uptake, and flux.
- Load initial conditions for SimPops:** ☒
- Select DILIsym Outputs:** New output panel (selected) and Common\_Outputs
- Save SimPops results to data file:** ☒
- Time Reports:** ☒
- Buttons:** Add to Batch, Run, and Cancel



# Hands-on SimPops Example – Step 6 – *Analyze SimCohorts Results with 3 Responders*

- Note variability in Plasma ALT
  - *Clinical Measures* ->  
*Clinical Chemistry* ->  
**Plasma ALT**
- Non-responder is no longer present

