

DILIsymServices

ST A SIMULATIONS PLUS COMPANY

DILlsym User Training – Using the DILlsym Optimization Feature

DILIsym Development Team

* DILIsym[®], NAFLDsym[®], and MITOsym[®] are registered trademarks and SimPops[™] and SimCohorts[™] are trademarks of DILIsym[®] Services Inc. for computer modeling software and for consulting services.

CONFIDENTIAL

Goals for the Optimization Training Session

Participants should understand the following general concepts:

- Applications of the Optimization feature within DILIsym
- The critical components necessary for optimization within DILIsym
- Key concepts behind creating a fitness function
- Key concepts behind the genetic algorithm optimization routine
- The practical workflow for completing an optimization within DILIsym



DILIsym Optimization - General Introduction

- Optimization is the process of making changes to DILIsym parameters so that one or more simulation outcomes better align with user-defined endpoints (optimization target data sets)
- Optimization is an art form, with endless possibilities, so this is an introduction to the interface tool in general, but not a comprehensive review of all possible optimization setups
- Optimization of complex data sets and many parameters will take time to learn and time to simulate (iteration typically required)
- DILIsym (as of version 7A) contains an optimization interface, allowing users to set up and run complex optimizations without code manipulation



Some Applications of DILIsym Optimization

- 1. DILIsym toxicity parameter identification based on in vitro data
 - oxidative stress (or reactive oxygen species, ROS) production parameters
 - mitochondrial effects, such as V_{max} identification for saturable ETC inhibition pathways
- 2. Physiologically based pharmacokinetic (PBPK) model construction to fit user-defined data sets using the DILIsym PBPK model framework
 - Note that when importing PK time courses from GastroPlus or other PBPK platforms to drive toxicity predictions, PBPK optimization for those models is done in the program of origin, not DILIsym
- 3. Identification of new SimPops, or simulated humans or animals, to fit user-defined data sets
 - In this case, the user would typically be optimizing **Species** parameters related to fundamental processes, rather than **Drug** parameters related to exposure or toxicity pathways





- 1. <u>SimSingles (simulation setups) within DILIsym via the home screen</u>
 - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
 - Simulations need to be set up for all scenarios pertaining to the optimization target data set(s)
- 2. <u>Constructing a fitness function using the DILIsym Optimization interface</u>
 - Goal is comparison(s) between a given simulation result and data
 - Tailored to fit the needs of each optimization by the user
 - Can be very complex or very simple
- 3. <u>Utilizing an optimization routine, the genetic algorithm, to conduct the</u> <u>comparisons and iterations toward best fits</u>
 - DILIsym version 7A only includes the genetic algorithm optimization routine option
 - Future versions may include different fitting algorithms, if desired by users



ST A SIMULATIONS PLUS COMPANY

The Flow of Information Within a DILIsym Optimization

- The optimization routine begins the process with parameter information
- The fitness function is the intermediary between the optimization tool and the simulation engine
- The cycle runs iteratively for the <u>number of generations</u> defined by the user



Genetic Algorithm Defined – MATLAB Documentation

- A genetic algorithm (GA) is a method for solving both constrained and unconstrained optimization problems based on a natural selection process that mimics biological evolution.
- The algorithm repeatedly modifies a population of individual solutions. At each step, the genetic algorithm randomly selects individuals from the current population and uses them as parents to produce the children for the next generation. Over successive generations, the population "evolves" toward an optimal solution.
- You can apply the genetic algorithm to solve problems that are not well suited for standard optimization algorithms, including problems in which the objective function is discontinuous, nondifferentiable, stochastic, or highly nonlinear.
- The genetic algorithm differs from a classical, derivative-based, optimization algorithm in two main ways, as summarized in the following table.

Classical Algorithm	Genetic Algorithm
Generates a single point at each iteration. The sequence of points approaches an optimal solution.	Generates a population of points at each iteration. The best point in the population approaches an optimal solution.
Selects the next point in the sequence by a deterministic computation.	Selects the next population by computation which uses random number generators.

DILIsymServices

The Genetic Algorithm Allows for Efficient Exploration of Parameter Space

- The genetic algorithm is an optimization method based on choosing the best parameter set fit to a specific fitness function
 - Best parameter sets are kept from generation to generation; other parameter sets created for each generation
- Genetic algorithms allow for the efficient exploration of a multidimensional parameter space
- DILIsym is utilizing the MATLAB global optimization toolbox for its genetic algorithm
- DILIsym contains nonlinear equations that can take time to solve, so the GA is a good fit





Choosing Parameter Ranges for the Genetic Algorithm



- There are many ways to choose parameter bounds and distributions
- Different consideration applied to "data-derived" vs "fitted" parameters
 - Prior information can be used to inform the optimized ranges of "data-derived" parameters (such as tissues' PC, Vmax Km)
 - "fitted" parameters should be tested in wide-range to allows the optimization scheme to sweep out as much of the parameter space as possible in order to find the best fit
 - Parameter ranges can be narrowed iteratively if the first fit is not ideal



Fitness Functions Are Used During Optimization to Evaluate Relative Performance

- The fitness function is the tool used by the optimization routine to evaluate performance relative to a target
- The fitness function contains several critical components:
 - Information for one or more simulations
 - Data to be compared with simulation results, along with method for comparison
 - Parameter probability distribution scoring, if included
- Two primary ways of evaluating a given parameter solution within DILIsym
 - Difference between data point and simulation result, such as least squares fit, etc.
 - Combined probability of parameter values selected compared to assumed or known distributions, if applicable



Setting Up an Optimization in DILIsym – Step by Step Instructions

- 1. Set up SimSingles (simulation setups) within DILIsym via the home screen
 - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
 - Simulations need to be set up for each scenario from which each optimization target data set is provided
- 2. <u>Construct your fitness function using the DILIsym Optimization interface</u>
 - Goal is comparison(s) between a given simulation result and data
 - Tailored to fit the needs of each optimization
 - Can be very complex or very simple
- 3. <u>Run the optimization routine (which then utilizes the genetic algorithm in</u> <u>the background) to conduct the comparisons and iterations toward best fits</u>
 - DILIsym version 7A only includes the genetic algorithm optimization routine option
 - Future versions may include different fitting algorithms, if desired by users



Setting Up an Optimization in DILIsym – Step by Step Instructions

- 1. <u>Set up SimSingles (simulation setups) within DILIsym via the home screen</u>
 - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
 - Simulations need to be set up for each scenario from which each optimization target data set is provided
- 2. <u>Construct your fitness function using the DILIsym Optimization interface</u>
 - Goal is comparison(s) between a given simulation result and data
 - Tailored to fit the needs of each optimization
 - Can be very complex or very simple
- 3. <u>Run the optimization routine (which then utilizes the genetic algorithm in</u> <u>the background) to conduct the comparisons and iterations toward best fits</u>
 - DILIsym version 7A only includes the genetic algorithm optimization routine option
 - Future versions may include different fitting algorithms, if desired by users



The DILIsym Optimization Feature is Accessed from the DILIsym Home Screen

The optimization window has four main sections:

DILIsym Optimization

Optimization Parameters

- 1. Optimization Parameters
- 2. Parameter Constraints (Covariates)
- 3. SimSingles, or simulation setups

4. Comparison Da	ata	P Subgroup	Variable		A V
simulate Specify Data Clinical Monitoring Param	Para Vari Sweep Data Con	ameter Constraints (Covariates) able1 Relation Multiplier	Variable2		A V
in Parallel SimPops Create SimCohorts Optimiz Plot Table Export Save R ex SimSingle example and SimSingle example	zation Sim Lesults SimSi Sim Pop	Single(s) Single Selection	10		A V
Parameters Outomics ecites Parameters_Species_Mana_17A Customics ga Parameters_Drug_Bank_17A Customics daris Machanism Machanism daris Parameters_Calories_Blank_17A Customics mp V Dosing Parameters_CanoryDosing_Blank_17A Customics mp X Dosing Parameters_ComprOrosing_Blank_17A Customics mp Y Dosing Parameters_ComprOrosing_Blank_17A Customics me Parameters_Time_Blank_17A Customics	Con Wei Sim Con	pparison Data ght 1 Single Reference parison Method Add Comparison D	+ ~ ata		A V
Parameter Parameter Default Image: Control of the co	Pro (pe bas	bability nalty for unlikely occurrence red on distribution)	Save Setu	p Load Setup	

Add Your Intended Optimization Parameters to the Optimization Parameters Table

Optimization Parameters					
Group Subgroup	Variable	Compound W biliary excretion Vmax	100	1000 Load X	
Drug Compound W PBPK	Compound W gut 💌				
Lower Bound 100 Upper Bound	1000				۸
Add Distribution Type					V

- The parameter name is input in the drop-down menus marked "Group", "Subgroup", and "Variable"
- Upper and lower bounds are input into the text box
- Note that dependent parameters, or covariates of other optimization parameters, need to be added as well
- The next step is adding the Distribution Type for the parameter, which must be done before the parameter can be added to the table of parameters being optimized



Set Up the Distribution Desired for Each Optimization Parameter

- The selected parameter value at each iteration will be selected from the distribution provided
- DILIsym includes normal, lognormal, Poisson, exponential, and uniform stochastic distributions
- Distribution can be symmetric or asymmetric
- Fill in the mean value, standard deviation (if applicable), distribution type

Different Left and	d Right Distributions				
Same Distribution	I	Left Distribution		Right Distribution	on
Mean Value	Distribution Type	Mean Value	Distribution Type	Mean Value	Distribution Type
Standard Deviation		Standard Deviation		Standard Deviati	on
		Save Distrib	ution Load	Saved Distribution	Use Current Distributio

- Once a distribution has been created, it must be saved and then loaded
- Click on the "Load Saved Distribution" button, select a distribution, and load
- Click beneath the words "Use Current Distribution" to turn on or off loaded distribution
- Close the Distribution window and note that the "Add Distribution Type" button has now turned green, if turned on

ed on	Optimization Param			
	Group Drug	Subgroup Compound W PB ~	Variable Compound W acti ~	
	Lower Bound 1	Upper Bound Add Distribution Type	5	
,	S + A SIM	IULATIONS P	LUS COMPAN	NY

CONFIDENTIAL 15

Parameter Constraints (Covariation) Can Be Added, if Desired

Parameter Constra	iints (Covaria	tes)					
Variable1	Relation	Multiplier Variable2		Vmax(Compound W m =	3	Vmax(Compound W m 🔀	
	•		• +				V

- Allows constraint of two parameters that should be covariates or otherwise related
- Choose the two parameters you wish to constrain with the two drop-down menus labeled "Variable 1" and "Variable 2"
- Choose a relationship (either =, <, or >) from the "Relation" drop-down menu
- The "Multiplier" input box allows constraint of a parameter to a multiple of another parameter's value
- Click the green plus button next to the constraint inputs



Select the SimSingles to Include in the Optimization Process and the Population and Generation Sizes

SimSingle(s)	example X]
SimSingle Selection		Λ
Population # 200 Generation 10		V

- A SimSingle can be added to the optimization by selecting a SimSingle from the drop-down menu and clicking the green plus next to the drop-down menu
- The Population and Generation options are located beneath the SimSingles Selection menu
 - The population size represents the number of parameter sets, or simulations, conducted within each generation
 - Population size is important, as larger populations will provide better coverage of the solution space
 - The number of generations represents the number of times that each population will be generated and simulated after the initial condition simulations are complete (total generations is generations requested by the user plus one (e.g., the setup shown above would be 11 generations total))
 - <u>Generation number is important, as a sufficient number of generations is critical for the optimization</u> routine to successfully progress
 - We recommend at least 5-10 generations, with a population size of roughly 20-200, depending on the simulation time required
 - Note that depending on the application, more or less individuals and generations may be needed



Use the Comparison Data Section to Add the Data for Comparison to Simulation Results

Comparison Data		
Weight 1	+	
SimSingle Reference	example 💌	Δ
Comparison Method	sum of least square	
	Add Comparison Data	V

Each comparison data set has four components:

- 1. Weight
 - The weight given to a particular data set can be modulated by changing the input in the "Weight" input box
 - Each data set is normalized to the data results so that the inclusion of results that are in different orders of magnitude will not skew the comparison
- 2. SimSingle Reference, which must be chosen from the SimSingles added above
- 3. Comparison method
 - User can select absolute difference, least-squares, or logarithmic absolute comparison method for each data set
- 4. Data itself click "Add Comparison Data" to add the data



Data Is Added by Clicking on the "Add Comparison Data" Button Which Opens the Template Generation Tool

- Using the drop down menus, add the DILIsym output that is analogous to the data to be added for comparison
- For AUC or C_{max} entries, the AUC and/or C_{max} check boxes should be highlighted and bounds for the AUC/ C_{max} input into the appropriate input box
- For time-course data, leave both AUC and C_{max} check boxes empty
- Once variables are added to the window, click "Create Data Template"
- Note that a data template will be required for each SimSingle desired for comparison
 - e.g., if 4 SimSingles are desired with 4 unique simulation scenarios, at least 4 data templates will be required, each one corresponding to a particular SimSingle

▲ Input Data for Comparison Data Se	t Parameter Const	nainta (Covariates)	
Group	Subgroup	Output Variable	_
Pharmacokinetics -	Compound W	▼ Plasma Compound W ▼	
Plasma Compound W (no AL Plasma Compound W Metab	JC or Cmax) olite A (AUC)	AUC All Time F from to	Points
		From to	Points
		Use Loaded Data	M
Create Data Template	Load Data from Template		
Remove List Item	Reset	Close Figure	



Add Your Data to the Template via the Time Course Tab (1^{st}) or the AUC and/or C_{max} Tabs (next tabs)

- Input the time vector into the column labeled "Time" and the time course data into their respective columns
- The AUC and C_{max} sheets are similar; input the AUC or C_{max} beneath the appropriate label
 - Located on separate tabs
- **Do not** create a template with both time course information and AUC / C_{max} information for the same output
- **Do not alter** the other areas of the template, as the optimization tool will use the template information

	А	В	С
1	Data Set to Compa	re Data Set to Compare	
2	time	plasma_compound_W	
3	Time (hour)	Plasma Compound W (ug/mL)	
4		0 0	
5		1 0.05	
6		2 0.21	
7		3 0.14	
8		4 0.054	
9		5 0.043	
10		6 0.027	
11		8 0.017	
12		12 0.0064	
13		24 0.0048	
	А	В	
1	AUC to Compare	AUC to Compare	
2		plasma_CompW_MetA	
3		Plasma Compound W Metabo	lite A (ug/mL)
4	AUC Value		45000
5	Time Range	All Time Points	
6			
7			

Click the "Use Loaded Data" Button and Close the Template Generator Tool to See the "Add Comparison Data" Button Turn Green

Create Data Template Load Data from Template Loaded: BloodXtest2 Remove List Item Reset	Use Loaded Data	
	Comparison Data Weight 1 SimSingle Reference Comparison Method Add Comparison Data Probability (penalty for unlikely occurrence based on distribution) Run	Save Setup Load Setup Cancel

Once a template has been fully completed with data:

- 1. Click "Load Data from Template" to load in a fully specified data template
 - User should see "Loaded: Template_Name" beneath the button
- 2. Click the "Use Loaded Data" button (it should turn green)
- 3. Close the template generator tool
- 4. The Comparison Data section should now show the "Add Comparison Data" button as green and the comparison data set can be added to the list with the plus sign
- 5. Repeat for all desired comparison data sets



An Optional Penalty Can Be Assessed for the Likelihood of Parameter Value Occurrence Based on the Provided Distributions

- The selection of parameter values as the optimization routine progresses will depend on the fitness scores but distributions provided will initially bias the selection towards more likely values
- Checking the Probability box causes the fitness score to include an additional component not based on simulation comparison to data, but based on the likelihood of that value truly occurring based on the distribution
- Normalized to number of data points and units
- Formula used for probability component shown at right
 - PDF = probability density function value, computed for each parameter for each value of the parameter selected compared to the provided distribution, always between 0 and 1
 - n = number of parameters included in optimization
 - Data Score Component = value from comparison between simulation outcomes and data provided based on comparison method selected by user
 - Score is equal to Data Score Component alone if
 Probability box unchecked







Setting Up an Optimization in DILIsym – Step by Step Instructions

- 1. <u>Set up SimSingles (simulation setups) within DILIsym via the home screen</u>
 - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
 - Simulations need to be set up for each scenario from which each optimization target data set is provided
- 2. <u>Construct your fitness function using the DILIsym Optimization interface</u>
 - Goal is comparison(s) between a given simulation result and data
 - Tailored to fit the needs of each optimization
 - Can be very complex or very simple
- 3. <u>Run the optimization routine (which then utilizes the genetic algorithm in</u> <u>the background) to conduct the comparisons and iterations toward best fits</u>
 - DILIsym version 7A only includes the genetic algorithm optimization routine option
 - Future versions may include different fitting algorithms, if desired by users

	Add Comparison Data		V	
	Probability (penalty for unlikely occurrence Run based on distribution)	Save Setup Cancel]	CONFIDENTIAL
-		SP A SIMULATIONS PLUS COMPANY		CONFIDENTIAL

The Optimization Results Display Includes Parameter Values and Fitness Function Scores

- Optimization Results window initially shows two things
 - 1. the best-fit parameter set
 - 2. fitness function score for best-fit parameter set
- "Display All Parameter Sets" displays a table with all parameter sets run during optimization and all fitness function scores
- The "Export Results to Excel" button creates Excel spreadsheet containing
 - 1. parameter sets and their scores
 - 2. separate sheet with just the best-fit parameter set
 - 3. third sheet that contains the optimization settings
- "Create Optimized Parameter Set" button allows the user to create a parameter set using the parameters from the overall best fit
 - User selects an existing parameter set to modify; this is the parameter set into which the parameters will be placed (overwritten to) for the new parameter set
- Previously saved optimization results can be loaded from the "Results" drop-down menu on the main DILIsym screen

Death Eit	Vmax(Compound)	W metabolite A) Vmax(Comp	ound W metabolite B)		
Best Fit		850.1810	969.1413		
Best fit scor	e: 5294074.6285				
Display	All Parameter Sets	Export Res	sults to Excel	Create Optin	nized Parameter Set
Display	All Parameter Sets	Export Res	sults to Excel	Create Optin	nized Parameter Set
Display	All Parameter Sets	Export Res	sults to Excel	Create Optin	nized Parameter Set
Display	All Parameter Sets	Export Res	sults to Excel	Create Optin	nized Parameter Set
Display	All Parameter Sets	415 6991 964 738	sults to Excel	Create Optir 716 9821 5 3616e	nized Parameter Set
Display	All Parameter Sets	415 6991 364 7338 849 1810	sults to Excel	Create Optir 716 9821 5 3616e 577 5664 5 3875e 637 7412 5 3523e	nized Parameter Set
Display	All Parameter Sets	415 6991 364 7338 849 1810 401.7802	sults to Excel	Create Optir 716 9821 5 3616e 577 5664 5 3875e 637 7412 5 3623e 369 3025 5 4206e	nized Parameter Set
Display	All Parameter Sets	415 6991 364 738 849,1810 401.7802	sults to Excel	Create Optir 716 9821 5 3616e 577 5664 5 3875e 637 7412 5 3523e 369 3025 5 4206e	nized Parameter Set
Display	All Parameter Sets	415 6991 364 738 849 1810 401.7802	sults to Excel	Create Optir 716 9821 5 3616e 577 5664 5 3875e 637 7412 5 3523a 369 3025 5 4206e	nized Parameter Set
Display	All Parameter Sets	415 6991 364 7338 849 1810 401.7802	sults to Excel	Create Optir 716 9821 5 3616e 577 5664 5 3875e 637 7412 5 3523e 369 3025 5 4206e	nized Parameter Set
Display	All Parameter Sets	Export Res 415 6991 364 7338 849 1810 401.7802	sults to Excel Export Results	Create Optin 716 9821 5 3616e 577 5664 5 3875e 369 3025 5 4206e to Excel	nized Parameter Set

Hands-on Optimization Example – Optimizing to an Oxidative Stress Data Set

- Goal is to determine an RNS/ROS parameter value that will reproduce exposureresponse shown at right
- Assume data was generated for human – will use human species for simulations
- Data was collected after 6 hours of incubation at concentrations leading to intracellular concentrations shown
- Example is simplified for the purposes of illustration



Theoretical Preclinical Data

symServices

Hands-on Optimization Example – Step 1 – Review Specified Data Excel Files Provided to Understand Exposure Setup

- Open Specified Data templates provided
 - Liver_CompW_1point5_uM
 - Liver_CompW_5_uM
 - Liver_CompW_10_uM
- Each template sets all 3 zones of liver to constant intracellular concentration value of 1.5, 5, or 10 ug/mL
- In vitro like Drug parameter file could also be used for this purpose
 - Both methods accomplish rapid steady state in liver tissue

Organiz	e	New	Open		Select	
2018 > Ex	kample_Files > Optin	nization > SDTemplates	~	ن Se	arch SDTe	mp
r	Name	^	Date modifie	ed	Туре	
	Liver_CompW_1po	int5_uM	1/12/2018 9:	52 AM	Microsoft	Ex
<i>*</i>	🚹 Liver_CompW_5_u	M	1/12/2018 9:	52 AM	Microsoft	Ex
*	Liver_CompW_10_0	Mu	1/12/2018 9:	53 AM	Microsoft	Ex
*						_
Clipboard 🖓	Font	ra Align	ment	Fai	Number	
i13 • : ×	√ f _x					
A	В	с		D	E	
DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT D	ELETE ROW		
DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT D	ELETE ROW		
Specified Data - C	Specified Data - C	Specified Data - C	Specified	Data - C		
Individual 1	cl_liver_compound_w	CL liver Compound W (ug/m	L)	1.5	i	
Individual 1	ml_liver_compound_w	ML liver Compound W (ug/n	nL)	1.5	;	
Individual 1	pp_liver_compound_w	PP liver Compound W (ug/m	nL)	1.5	5	



Hands-on Optimization Example – Step 2 – Place Provided SimSingle Setups in Simulations Folder and Review SimSingles

- Find Simulations directory by • clicking any load option within **DILIsym and copying location** from Windows Explorer
- Copy three provided SimSingles into your Simulations directory
- Explore SimSingles
 - Human species selected
 - Drug parameter file:
 - molecular weight of 300 g/mol ٠
 - RNS/ROS pathway 1 turned on
 - No meals (to save simulation time)
 - No drug dosing
 - 6 hour simulation time
 - Specified data used to set Compound W liver concentrations



Hands-on Optimization Example – Step 3 – Add "Liver RNS/ROS Production Rate Constant 1" Parameter as Optimization Parameter

Open Optimization interface	DILIsym Optimization
rom DILIsym home screen	Optimization Parameters
 Select Drug -> Drug toxicity parameters -> Liver RNS/ROS 	Drug v Drug toxicity para v Liver RNS/ROS pr v Lower Bound 0.01 Upper Bound 0.1 + Add Distribution Type v
<i>production rate constant 1</i> from drop down menus	Parame Distribution Variable Same Distribution Throughout Different Left and Right Distributions V A
- Bounds: 0.01 to 0.1	SimSing Same Distribution Left Distribution Right Distribution SimSing Mean Value Distribution Type Mean Value Distribution Type A
 Distribution: uniform 	Populatic Standard Deviation Standard Deviation V
 Same distribution throughout 	Compar Weight Use Current Distribution
Save distribution	SimSing Save Distribution On Companie Loaded:Uniform_Distribution A
 Load distribution 	Reset Close Figure V Probability
 Turn "Use Current Distribution" button on so it's green 	(penalty for unlikely occurrence Run Save Setup Load Setup Cancel based on distribution)

- Close Figure
- Add parameter to table with green "+" sign



Hands-on Optimization Example – Step 4 – Add Three Provided SimSingles

- No parameter constraints (covariates) included in example
- Select each of the SimSingles and add them to table using green "+" sign
 - ROS_Human_IVIVE_10_UM
 - ROS_Human_IVIVE_5_UM
 - ROS_Human_IVIVE_1point5_UM
- Set Population size to 4
- Set Generation size to 5

an syn optimization			^
Optimization Parameters			
Group Subgroup Variable	Liver RNS/ROS production rate const 0.01 0.1 Load	X	
Drug 🗸 Drug toxicity para 🗸			
Lower Bound Upper Bound		Λ	
Add Distribution Type		V	
Parameter Constraints (Covariates)		•	
Variable1 Relation Multiplier Variable2			
v v •		V	
SimSingle(s)	ROS Human IVIVE 10 UM	X	
SimSingle Selection	ROS_Human_IVIVE_5_UM	X	
	ROS_Human_IVIVE_1point5_UM	X	۰.
Population # 4 Generation # 5		V	
Comparison Data			
Weight 1			
SimSingle Reference			
		Λ	
Add Comparison Data		V	۰.
Probability			
(penalty for unlikely occurrence Run San	ve Setup Load Setup Can	cel	



Hands-on Optimization Example – Step 5 – Place Provided Comparison Data Excel Files in ComparisonDataSets Folder and Review Data

- Find ComparisonDataSets directory by clicking any load option within DILIsym and copying location from Windows Explorer
- Copy three provided Excel files into your ComparisonDataSets directory
- Explore Excel files
 - Each file has ROS value at 0 and 6 hours for each zone of the liver at the three respective intracellular concentrations
 - 1.5 uM = 1.8 fold change ROS
 - 5 uM = 3 fold change ROS
 - 10 uM = 4.2 fold change ROS

lipbo	ard	Organize	1	New	Open
~~	Example_Files > Optimizati	on > Compariso	nDataSets		
^	Name		Date modified	Туре	Size
	👔 Ox_Stress_1point5_uM_A	II_Zones	1/12/2018 1:27 PM	Microsoft Excel W	
	Ox_Stress_5_uM_All_Zon	es	1/12/2018 1:27 PM	Microsoft Excel W	
	Ox_Stress_10_uM_All_Zo	nes	1/12/2018 1:28 PM	Microsoft Excel W	
	ISPO . L/DEI	SHEET &			
vell >	mcrCache9.3 > DILlsy1 v 진	Search DILIsy			
	Name	Date mo			
	matlab	1/9/2018			
Я	.META	1/9/2018			
#	📙 bin	1/9/2010			
	Code	1/9/2018			
	ComparisonDataSets	1/12/201			
14	DataTemplates	1/9/2010			
1	DILIsym_User_Resources	1/9/2018			
	DILIsym_v/A	1/9/2018			
	Diclisym_v/A_BD/3EA2EE2A/320EAF30	1/12/2010			
		1/ 12/20			
^	B		C		D
t to Compar	re Data Set to Compare	Data Set	to Compare	Data Set to Com	pare
	cl rns ros balance	ml rns	ros balance	pp rns ros bala	ance
our)	CL RNS-ROS balance (dimen	sionless) ML RNS-	ROS balance (dimension	less) PP RNS-ROS bala	ance (dimension
	0	1		1	,
	6	1.8		1.8	
	SimPops	1/9/2018			
	SimPopsResults	1/9/2018			
	SimSingleResults	1/12/201			
	Simulations	1/12/20			
	Sween Percette	1/9/201			
	toolbox	1/9/201			
		11 21 22 11			

Hands-on Optimization Example – Step 6 – Add 3 Comparison Data Sets

- Leave Weight at 1
- Select each SimSingle reference for each exposure level
- Select "sum of least square" method for method
- Click "Add Comparison Data"
 - Load data for the SimSingle selected using the "Load Data from Template" button
 - Be sure template selected for loading matches the exposure level in SimSingle selected
 - Click "Use Loaded Data" button (should turn green)
 - Close window
- Click green "+" sign
- Repeat for other two SimSingles
 - When comparison data window opens for the second time, the data from the first run will still be in the window
 - Load in new data set

	Input Data for Comparison Data Se	et		- 🗆 X
	Group	Subgroup	Output Variable	
	All Groups ~	All Subgroups ~	All Variables	~
DILIsym Optimization			AUC fror to	All Time Points
Optimization Parameters			Cmax	All Time Points
Group Subgroup			from	n
Drug v Drug toxi			✔ to	
Lower Bound L Add Dis	Create Data Template	Load Data from Template	Jse Loaded Data On	
Parameter Constraints (Covariat		Loaded: Ox_Stress_5_uM_All_Zone	es	
Variable1 Relation	Remove List Item	Reset	Close Figure	
SimSingle(s)		ROS Human IVIVE 10 UM		X
SimSingle Selection	~ +	ROS_Human_IVIVE_5_UM		X
Population # 4 Generation #	5	ROS_Human_IVIVE_1point5_UM		X
Comparison Data		Ox Stress 10 JM All Zones	1.03	
Weight 1	+	CA_Diless_IV_UNI_AI_ZUILES	Lua	
SimSingle Reference ROS_Human	_IVIVE_5_UM ~			۸
Comparison Method sum of least	square ~			
Add Comparis	on Data)		V
Probability (penalty for unlikely occurrence based on distribution)	Run S	Save Setup Load S	ietup	Cancel

.lsymServices



Hands-on Optimization Example – Step 7 – Start Optimization with Run Button

- Fully defined optimization:
 - Parameter added
 - 3 SimSingles added
 - 3 Comparison Data sets added
- Save Setup before running
- Do NOT check
 "Probability" initially
- Click "Run"

DILIsym Optimization		-		×
Optimization Parameters Group Subgroup Variable	Liver RNS/ROS production rate const 0.01 0.1 Load	X]	
Lower Bound Upper Bound Add Distribution Type			۸ V	
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2			۸ ۷	1
SimSingle(s) SimSingle Selection Population # 4 Generation # 5	ROS_Human_IVIVE_1point5_UM ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM	X X X	A V	1
Comparison Data Weight 1 SimSingle Reference Comparison Method Add Comparison Data	Ox_Stress_1point5_uM_All_Zones Load Ox_Stress_5_uM_All_Zones Load Ox_Stress_10_uM_All_Zones Load	X X X	۸ V	1
Probability (penalty for unlikely occurrence Run Saw based on distribution)	e Setup	ncel		



Hands-on Optimization Example – Step 8 – Explore Results Once Complete

- The "Display Optimization Results" window will appear
- Explore the buttons available
 - Display all sets
 - Export results to Excel
 - Create Optimized set of parameters from existing set
- Note example fit to data shown at right with solution value of <u>0.0512</u> for *Liver RNS/ROS production rate constant 1*



Theoretical Preclinical Data and Simulation Results

DILIsymServices

Hands-on Optimization Example – Step 9 – Load Setup and Add Probability Component

- First, remove Liver RNS/ROS production rate constant 1 parameter and add back with same bounds
 - Bounds: 0.01 to 0.1
- Add Distribution Type as shown at right, instead of Uniform
 - Same Throughout
 - Mean = 0.05
 - Stnd Dev = 0.15
 - Type = normal
- Check Probability box and save
- · Once complete, Export results to Excel and compare results to those without Probability
- Notice difference in fitness score values
- Did solution value change? •

Distribution			_ □	``
Distribution				
Same Distribution Throughout 🗹 Different Left and Right Distributions				
Same Distribution Left Distribution		Right Distribution		
Agan Value Distribution Type Mean Value	Distribution Type	Mean Value	Distribution Tv	De
0.05 normal				
itandard Deviation Standard Deviatio	n 1	Standard Deviation		
0.15				
			Use Current Dis	tributi
Save Dist	ribution Load S	Saved Distribution	On	1
	Looded	Normal Ont Exam		
	Loaded.	vorna_Opt_Exam		
		Reset	Close Figu	re
				-
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2				∧ V
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 Sim Single(s)	BOS Human IMVE 1noid5	IIM		∧ V
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 SimSingle(s) SimSingle Selection	ROS_Human_IVIVE_1point5 ROS_Human_IVIVE_5_UM	LUM	X	A V
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 SimSingle(s) SimSingle Selection	ROS_Human_IVIVE_1point5 ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM	ĹſM		۸ V
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 Variable3 SimSingle(s) SimSingle Selection Population # 4 Generation # 5	ROS_Human_IVIVE_1point5 ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM	LUM	X X X	Λ V Λ V
Parameter Constraints (Covariates) Variable 1 Relation Multiplier Variable 2 SimSingle(s) SimSingle Selection Population # 4 Generation # 5 Comparison Data	ROS_Human_IVIVE_1point5 ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM	UM		∧ ∨ ∧ ∨
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 SimSingle(s) SimSingle Selection ** Population # 4 Generation # 5 Comparison Data ** **	ROS_Human_IVIVE_1point5 ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM Ox_Stress_1point5_uM_AII_ Ox_Stress 5_uM_AII_Zones	_UM Zones	X X X X	Λ V Λ V
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 SimSingle(s) Image: Comparison Data Weight 1 SimSingle Reference Image: Comparison Data	ROS_Human_IVIVE_1point5 ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM Ox_Stress_1point5_uM_AII_ Ox_Stress_5_uM_AII_Zones Ox_Stress_10_uM_AII_Zones	LUM Zones	X X X X Load X Load X	Λ V Λ V
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 SimSingle(s) Image: Comparison Data Weight 1 SimSingle Reference Image: Comparison Method	ROS_Human_IVIVE_1point5, ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM Ox_Stress_1point5_uM_All_ Ox_Stress_5_uM_All_Zones Ox_Stress_10_uM_All_Zone	_UM Zones	X X X X Load X Load X	А V А V
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 SimSingle(s) SimSingle Selection • Population # 4 Generation # 5 Comparison Data • • • Weight 1 • • SimSingle Reference • • • Comparison Method Add Comparison Data • •	ROS_Human_IVIVE_1point5 ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM Ox_Stress_1point5_uM_AII_ Ox_Stress_5_uM_AII_Zones Ox_Stress_10_uM_AII_Zone	_UM Zones	Load X Load X	А V V V V
Parameter Constraints (Covariates) Variable1 Relation Multiplier Variable2 Sim Single(s) Image: Comparison Data Population # 4 Generation # 5 Comparison Data Image: Comparison Method Image: Comparison Data Probability Image: Comparison Data Image: Comparison Data Probability Image: Comparison Data Image: Comparison Data Probability Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data Image: Comparison Data	ROS_Human_IVIVE_1point5 ROS_Human_IVIVE_5_UM ROS_Human_IVIVE_10_UM Ox_Stress_1point5_uM_AII_ Ox_Stress_5_uM_AII_Zones Ox_Stress_10_uM_AII_Zone	_UM Zones s	Load X Load X Load X	А У У Х У