DILIsym®

DILIsym® User Training – DILIsym® v5A Updates Overview

July 2016

DILIsym® Development Team

CONFIDENTIAL

Goal for This Training Session

Participants should understand the following general concepts:

- The most notable updates included in DILIsym® v5A as compared to v4B
- Some practical considerations for utilizing DILIsym® v5A as compared to v4B

MATLAB 2015a is Recommended for DILIsym® v5A Simulations

- MATLAB made internal changes as of MATLAB 2015b that cause variables declared within a parent function and accessed from a nested function to use much more memory and therefore take much longer to access
  - Related to Just in Time (JIT) compiler feature
- MathWorks has assured DILIsym Services that they are working on possible solutions for MATLAB for Spring of 2017
- In the meantime, the DILIsym Services team recommends using DILIsym® v5A on **MATLAB 2015a** until MATLAB resolves the problem
- DILIsym® v5A will run properly on MATLAB 2016a, but simulation time is increased (speed is decreased) in some cases

DILIsym® Documentation is Moving to the Web

Stage 1: Conversion of current DILIsym® documentation to web-based site

Current Status:

Completed for v4B

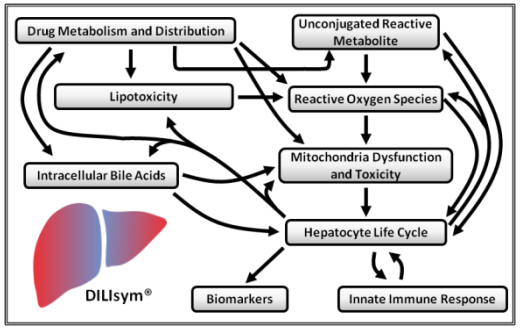
- DILIsym® User Guide
- DILIsym® Notes
- DILIsym® Design Diagrams

Updating for v5A

Goal for completion: By Q3 of 2016, the documentation files currently distributed within DILIsym® will be available within a new, web-based documentation system.

Highlights of DILIsym® v5A (Released Summer 2016)

- Several new validation compounds included with varying clinical presentations
  - TAK875 (Takeda) represented in humans, rats, and dogs (dog representation primarily used for DILIsym® development purposes)
    - Additional data collection on-going to better define parameter values
  - MK0536 (Merck) represented in humans and rats
    - Additional data collection on-going to better define parameter values
  - CKA (AstraZeneca) represented in humans and rats
  - AMG853 (Amgen) represented in humans and rats (backup candidate to AMG009)



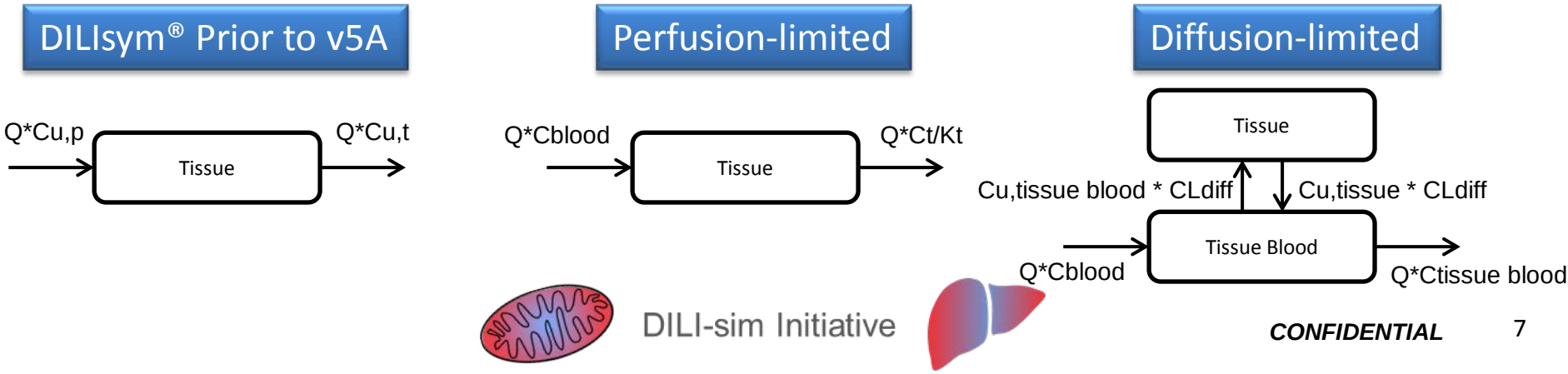
- Mitochondrial DNA depletion mechanism added with FIAU as exemplar compound
  - Mitochondrial biogenesis equations also added as mode of adaptation for exploration
- Non-alcoholic fatty liver disease (NAFLD) SimPops™ added
- Mechanistic representation of bilirubin transport and metabolism added
  - Indinavir and CKA serve as exemplar compounds

Expanded Capabilities and Features of DILIsym® v5A

- PBPK representation updates:
  - v5A includes classic, flow-limited organ uptake of drugs (protein binding restriction removed), with option for transporter mediated uptake into liver
  - Inverse molecular weight entry requirement removed from PBPK sub-models and MW units altered to g/mol
  - Several additional PBPK updates: see subsequent slide and July 2016 DILIsym® Review session for details
- New graphical user interface (GUI) tools added to allow users to:
  - Convert old parameter sets from v4B to be compatible with v5A
  - Systematically compare parameter sets for value differences in various formats (.mat and Excel)
- Mitochondrial electron transport chain (ETC) inhibition mechanism updated to include new third parameterization spot (ETC inhibition 3) with saturable capability
  - Also updated for MITOsym® v3A
- Several new human SimCohorts™ added for v4A_1 and v5A_1 (NAFLD) SimPops™
- All transporter inputs are now in units of uM instead of mg/mL
- MATLAB profile viewer no longer used during simulations to improve simulation speed (simulation times printed to the MATLAB command window)
- 'startup.m' function renamed to 'startDILIsym.m' to avoid MATLAB system file issues
- Compound W and X IV infusion protocols updated with more options
- Expanded Zotero reference database (contact us for real-time access)
- Various bug fixes and enhancements to improve performance, speed, and user-friendliness

PBPK Sub-model Updates in DILIsym® v5A

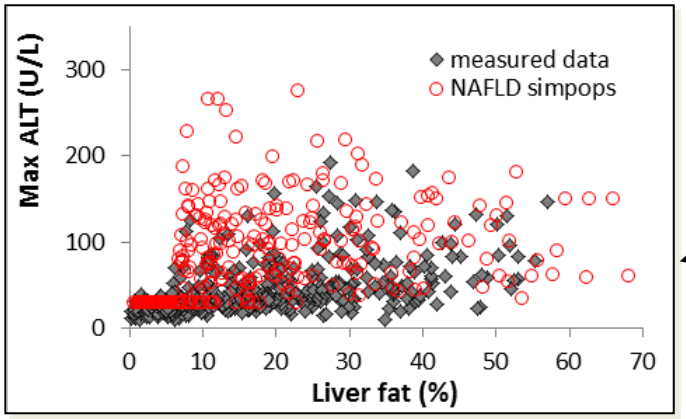
- Tissue distribution was updated, as of DILIsym® v5A, to represent classic, perfusion rate-limited kinetics, unless user selects active (transporter-mediated) liver uptake
  - Prior to v5A, rate of tissue distribution was limited by protein binding rather than blood flow
  - As of v5A, perfusion rate-limited tissue distribution has been employed to be consistent with the widely-accepted concept; conversion factors were added to make the current exemplar parameters compatible
- Hepatic transport processes are now based on the unbound plasma (for uptake) and liver concentration (for biliary excretion)
  - Saturable biliary excretion included using the Michaelis-Menten equation
- Intestinal metabolism and transport added for Compound W and X
- Hepatic inlet concentration (the weighted average of portal vein concentration and hepatic artery concentration) was added and is now used for OATP inhibition in the bilirubin sub-model
- The user is now able to input experimentally measured/user-defined fu_L (fraction unbound liver), in addition to allowing the static calculations to calculate the value of fu_L, if desired
  - Fractions unbound for other organs are now automatically calculated in static calculations (partition coefficients drive distribution)
- Further details discussed at the DILIsym® review session in July of 2016



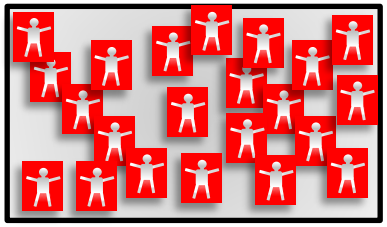
DILI-sim Initiative

Pathophysiologic Variability Represented in NAFLD (v5A_1) SimPops™

- SimPops™ are population samples with variability in NAFLD pathophysiology
- Multiple parameters were varied to produce 275 diverse simulated patients with steatosis +/- lipotoxicity
- SimPops™ compared with reported clinical data where available
- Variability in NAFLD pathophysiology responsible for varied DILI responses



Maximos 2015



Variables Used to Construct the NAFLD SimPops™
Body weight
Adipose FA release
De novo lipogenesis
RNS-ROS clearance
Mitochondria function
VLDL-TG secretion rates
Bile acid transporter expression
Plasma glucose
Hepatic glucose uptake
Plasma TG clearance
Apoptotic sensitivity to RNS-ROS
Necrotic sensitivity to ATP reductions
Hepatocyte regeneration

Clinical Data and Simulation Results

DILI-sim Initiative

DILIsym® v5A Includes New SimCohorts™ from the Human v4A_1 SimPops™

- SimCohorts™ were generated for screening purposes
  - Smaller groups consisting of subsets of simulated individuals from existing SimPops™
  - Computationally less-expensive for testing multiple hypotheses prior to full SimPops™

SimCohorts™ ID	Population Sample Size	Description
Human_ROS_apop_mito_BA_v4A_1_SensBAMITO	4	Individuals with high sensitivity to combined bile acid transport inhibition and mitochondrial dysfunction
Human_ROS_apop_mito_BA_v4A_1_SensMulti	4	Sensitive individuals in the areas of oxidative stress, mitochondrial dysfunction, BA transport inhibition, and combined BA inhibition and mitochondrial dysfunction
Human_ROS_apop_mito_BA_v4A_1_Multi16	16	SimCohorts™ with the baseline human and 13 individuals with high sensitivity and 2 individuals with low sensitivity in the areas of oxidative stress, mitochondrial dysfunction, BA transport inhibition, and combined BA inhibition and mitochondrial dysfunction
Human_ROS_apop_mito_BA_v4A_1_FIAU_15	15	Individuals with body weight approximately 80 kg and initial respiratory reserve scalar between 2.2 and 6.02

DILIsym® v5A Includes NAFLD SimCohorts™ from the Newly Included v5A_1 NAFLD SimPops™

- SimCohorts™ generated from new NAFLD SimPops™
  - Smaller groups consisting of subsets of individuals in the full (n=275) NAFLD SimPops™ included in DILIsym® v5A

SimCohorts™ ID	Population Sample Size	Description
Human_NAFLD_ROS_apop_mito_BA_v5A_1_RS16, _RS36, _RS100, RS_138a, RS_137b	16, 36, 100, 138, 137	Random sample of individuals from full SimPops™
Human_NAFLD_ROS_apop_mito_BA_v5A_1_low_ALT	99	Individuals with baseline plasma ALT < 50 U/L
Human_NAFLD_ROS_apop_mito_BA_v5A_1_high_ALT	176	Individuals with baseline plasma ALT ≥ 50 U/L
Human_NAFLD_ROS_apop_mito_BA_v5A_1_low_BMI	231	Individuals with BMI < 40
Human_NAFLD_ROS_apop_mito_BA_v5A_1_high_BMI	44	Individuals with BMI ≥ 40
Human_NAFLD_ROS_apop_mito_BA_v5A_1_low_FPG	221	Individuals with fasting plasma glucose < 7 mM
Human_NAFLD_ROS_apop_mito_BA_v5A_1_high_FPG	54	Individuals with fasting plasma glucose ≥ 7 mM

More Complicated Mitochondrial Data is Reproducible with the DILIsym® Update

- Data from recent project demonstrates modest, saturable inhibition at low concentrations, with more marked effects at higher concentrations
  - May represent differential inhibition of multiple ETC complexes (e.g., complex I and II)
- Original equations only reproduce a single non-saturable effect
- New equations allow reproduction of both behaviors – ETC inhibition 3