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gQSPSim: a SimBiology®-based GUI for standardized QSP model development and application

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Acknowledgments

Genentech

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- **Kapil Gadkar,** Principal Scientist

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- **Sietse Braakman,** Application Engineer Computational Biology
- **Ricardo Paxson,** Director of Computational Biology
- **Fulden Buyukozturk,** Engineer and Product Manager, MathWorks

Our Objectives for Designing the App

To facilitate the development, exploration, and distribution of QSP models using an interactive graphical environment

- Streamlined **calibration of QSP models** simultaneously to data collected across multiple experimental conditions
- Exploration of parameter uncertainty and biological variability via **generation of virtual populations**
- Generation of robust **model-based predictions** with virtual populations aided by interactive visualizations.
- gQSPSim works with **SimBiology-built models**
- **Cross-platform compatible sessions** files that can be easily shared between modelers
- **Documentation** of the workflow for reproducibility and transparency
- **Open-source platform:** users who would like to contribute to the development of gQSPSim are invited to contact us.
- **Review** of all model based analyses via GUI for non-modelers

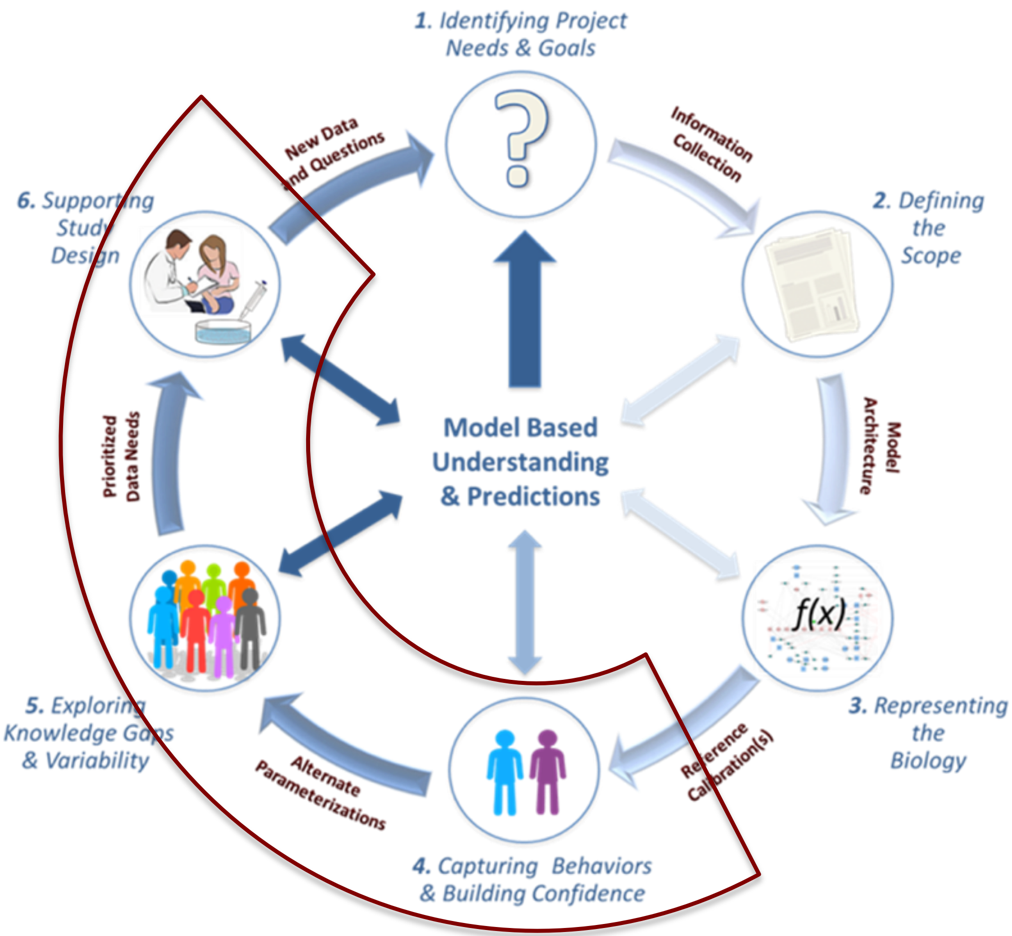
Agenda

- Introduction
  - Workflow for QSP model development and utilization
  - Overview of gQSPSim framework, building blocks and functionalities

- Demo
  - Showcase features of gQSPSim with TMDD model

Workflow & Technical Methodologies:

Six Stages of QSP model development and Implementation



Gadkar et al, CPT-PSP 2016

Six stages of QSP model development & implementation

1. Identifying project needs & goals
2. Defining model and project scope
3. Representing the biology
4. Capturing behaviors
5. Explore knowledge gaps & variability
6. Supporting experimental & clinical design

- *Typically an iterative process*
- *Needs to be adapted to specific project*
- *Model based "value" addition at each stage*

Using Virtual Subjects to Represent Uncertainty & Variability

Virtual subject (VS)

Single structure & parameterization of the model yielding *virtual measurements* within ranges of corresponding data

- subject = animal, human, cell, pathway, …

Reference virtual subject (Ref VS)

Virtual subject with virtual measurements representative of corresponding real-world data in a specified patient phenotype

- e.g., severe vs. moderate vs. mild disease activity

Virtual Cohort

Collection of "candidate" virtual subjects with alternate structures or parameterizations each yielding measurements consistent with corresponding data

Virtual Population (VPop)

Set of virtual subjects (from a virtual cohort) that is selected and statistically *weighted* to reproduce selected statistical features of corresponding data

- e.g., mean and std. dev. of biomarker measurements

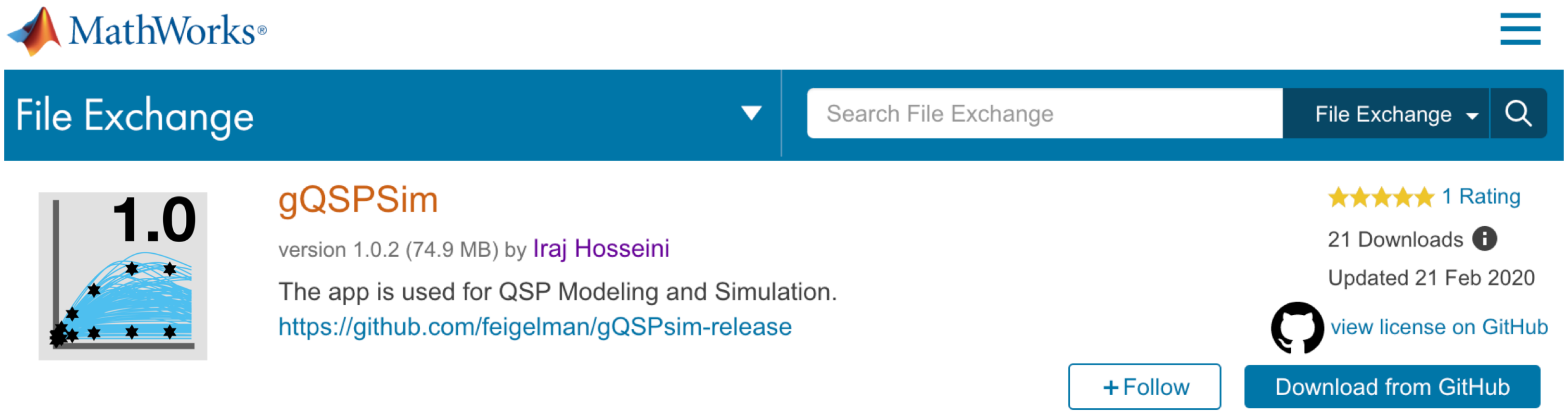
gQSPSim Resources

- **QSPC2021 Workshop**
- **Journal Publication:** https://www.ncbi.nlm.nih.gov/pubmed/31957304

gQSPSim: A SimBiology-Based GUI for Standardized QSP Model Development and Application

Iraj Hosseini, Justin Feigelman, Anita Gajjala, Monica Susilo, Vidya Ramakrishnan, Saroja Ramanujan, Kapil Gadkar ✉

- **Matlab Central:** https://www.mathworks.com/matlabcentral/fileexchange/73631-gqspsim



gQSPSim

version 1.0.2 (74.9 MB) by Iraj Hosseini

The app is used for QSP Modeling and Simulation.
https://github.com/feigelman/gQSPsim-release

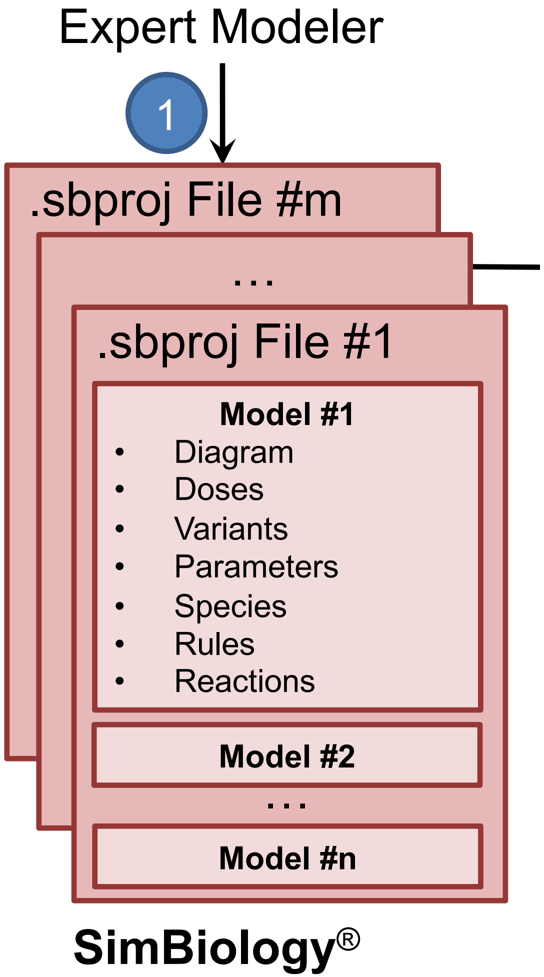
★★★★★ 1 Rating

21 Downloads

Updated 21 Feb 2020

view license on GitHub

Workflow of How Modelers Employ SimBiology® and gQSPSim



Expert Modeler

1

.sbproj File #m

…

.sbproj File #1

Model #1

- Diagram
- Doses
- Variants
- Parameters
- Species
- Rules
- Reactions

Model #2

…

Model #n

SimBiology®

1. The modeler builds models and projects in SimBiology®

gQSPSim performs “Functionalities” using “Building Blocks” as input

gQSPSim (Genentech QSP Simulator)

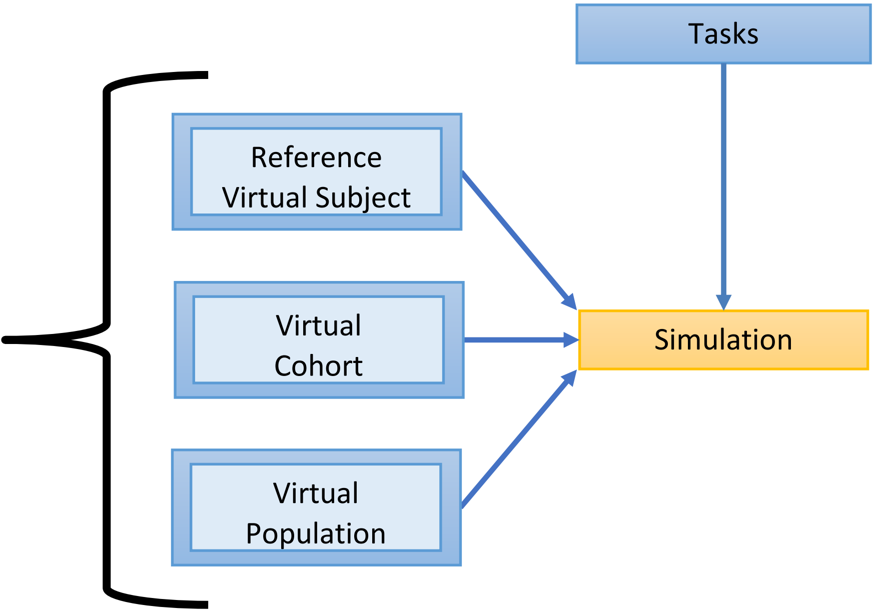
Functionalities

1. ***Simulation***: simulates one or more virtual subjects for the desired scenarios
2. ***Optimization/Calibration***: produces reference virtual subject
3. ***Virtual cohort generation***: produces a collection of virtual subjects
4. ***Virtual population generation***: weights virtual subjects to match data

Building blocks

1. ***Tasks*** (used for all functionalities)
2. ***Parameters*** (used for cohort generation, optimization)
3. ***Optimization dataset*** (used for optimization)
4. ***Acceptance criteria*** (used for cohort generation)
5. ***Target statistics*** (used for virtual population generation)
6. ***Virtual populations*** (used for simulation)

The simulation functionality requires task(s) and virtual subject(s) as inputs to generate desired model outputs

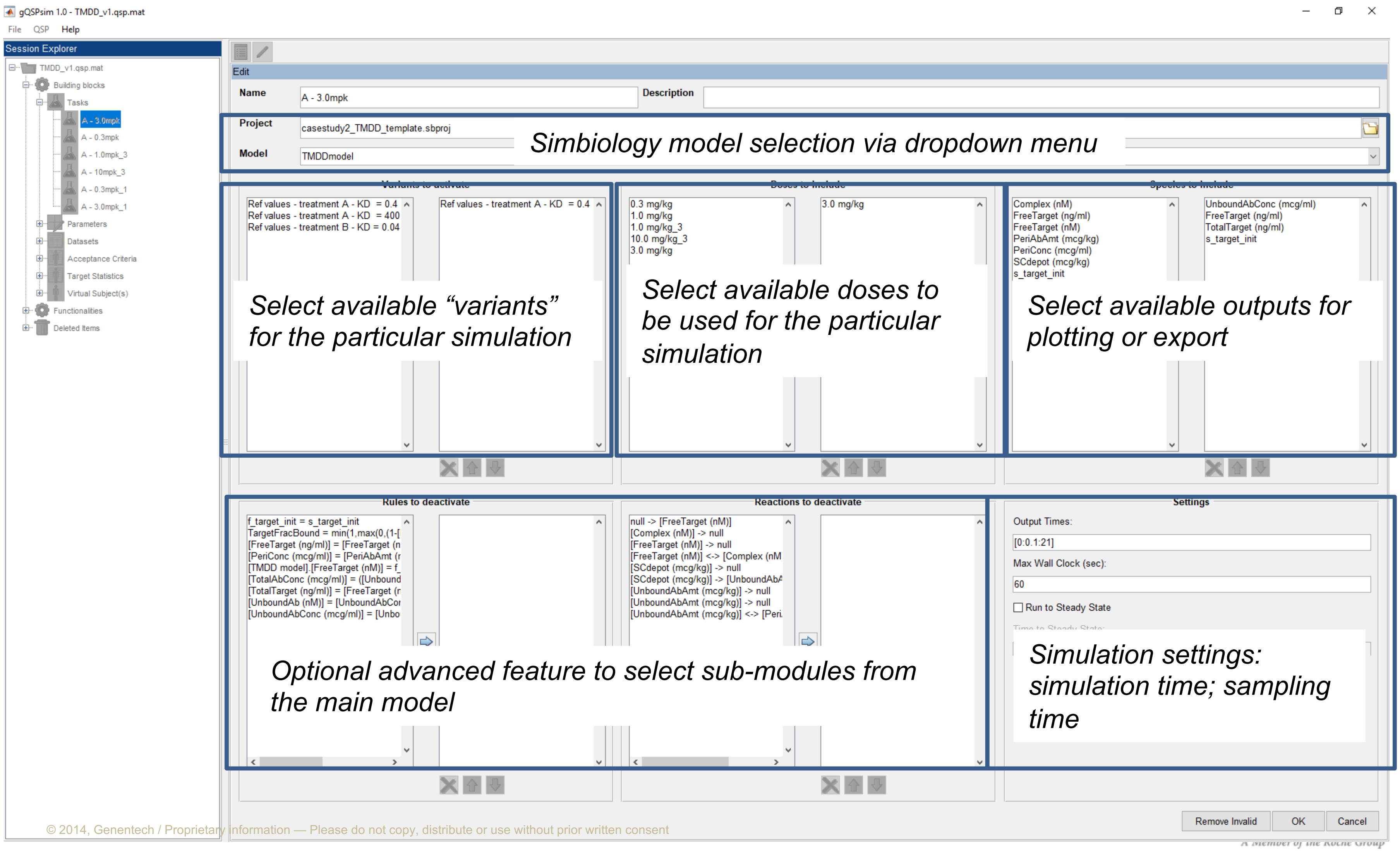


A list of scenarios to be simulated for the model

Either one of these are required inputs and we will refer to this as "Virtual subjects"

Screenshot of the basic building block of “Task”

“Task” is a virtual experiment corresponding to a specific real experiment



Name A - 3.0mpk

Description

Project casestudy2_TMDD_template.sbproj

Model TMDDmodel

Simbiology model selection via dropdown menu

Variants to activate:

Ref values - treatment A - KD = 0.4
Ref values - treatment A - KD = 400
Ref values - treatment B - KD = 0.04

Ref values - treatment A - KD = 0.4

Select available “variants” for the particular simulation

Doses to include:

0.3 mg/kg
1.0 mg/kg
1.0 mg/kg_3
10.0 mg/kg_3
3.0 mg/kg

3.0 mg/kg

Select available doses to be used for the particular simulation

Species to include:

Complex (nM)
FreeTarget (ng/ml)
FreeTarget (nM)
PeriAbAmt (mcg/kg)
PeriConc (mcg/ml)
SCdepot (mcg/kg)
s_target_init

UnboundAbConc (mcg/ml)
FreeTarget (ng/ml)
TotalTarget (ng/ml)
s_target_init

Select available outputs for plotting or export

Rules to deactivate:

f_target_init = s_target_init
TargetFracBound = min(1,max(0,(1-[
[FreeTarget (ng/ml)] = [FreeTarget (n
[PeriConc (mcg/ml)] = [PeriAbAmt (r
[TMDD model].[FreeTarget (nM)] = f_
[TotalAbConc (mcg/ml)] = ([Unbound
[TotalTarget (ng/ml)] = [FreeTarget (r
[UnboundAb (nM)] = [UnboundAbCor
[UnboundAbConc (mcg/ml)] = [Unbo

Reactions to deactivate:

null -> [FreeTarget (nM)]
[Complex (nM)] -> null
[FreeTarget (nM)] -> null
[FreeTarget (nM)] <-> [Complex (nM
[SCdepot (mcg/kg)] -> null
[SCdepot (mcg/kg)] -> [UnboundAbA
[UnboundAbAmt (mcg/kg)] -> null
[UnboundAbAmt (mcg/kg)] -> null
[UnboundAbAmt (mcg/kg)] <-> [Peri.

Optional advanced feature to select sub-modules from the main model

Settings:

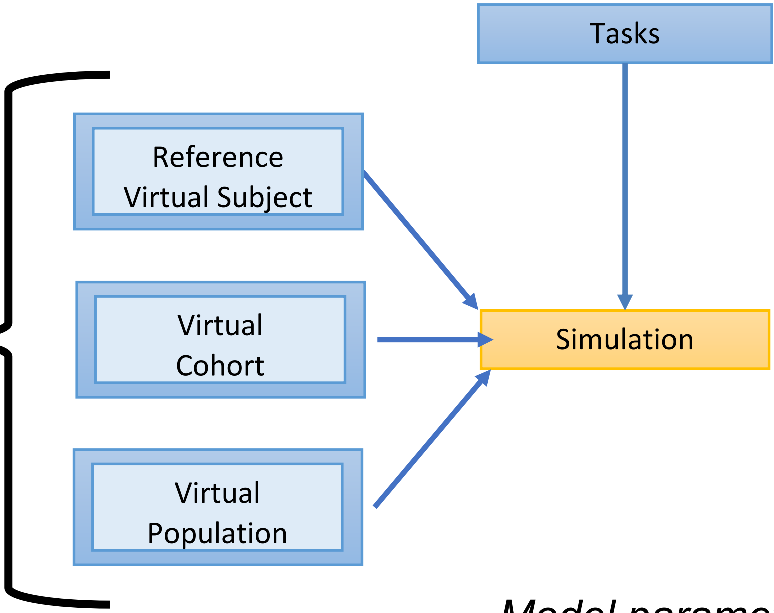
Output Times: [0:0.1:21]

Max Wall Clock (sec): 60

☐ Run to Steady State

Simulation settings: simulation time; sampling time

The simulation functionality requires task(s) and virtual subject(s) as inputs to generate desired model outputs



A list of scenarios to be simulated for the model

Tasks

Reference Virtual Subject

Virtual Cohort

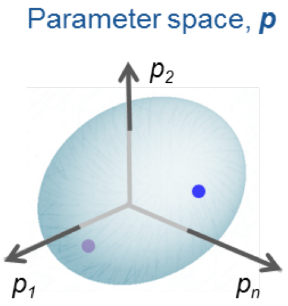
Virtual Population

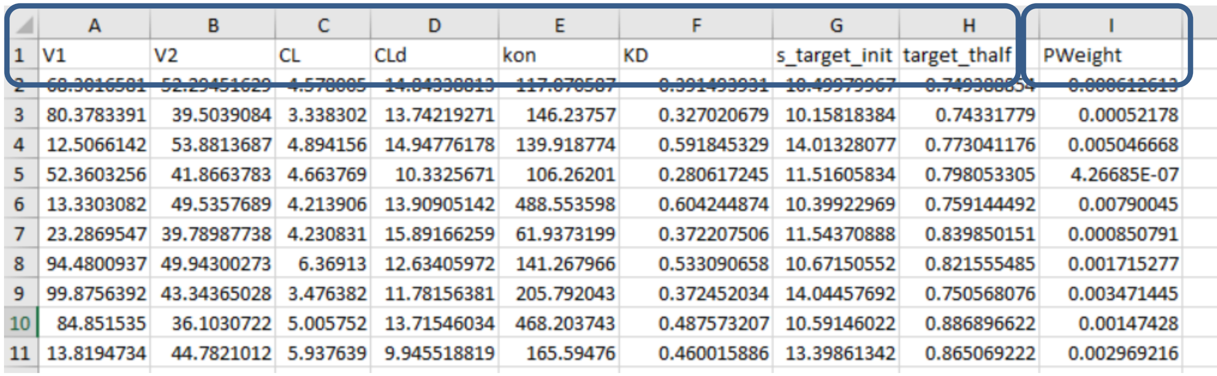
Simulation

Either one of these are required inputs and we will refer to this as "Virtual subjects"

Optional prevalence weight

Model parameters

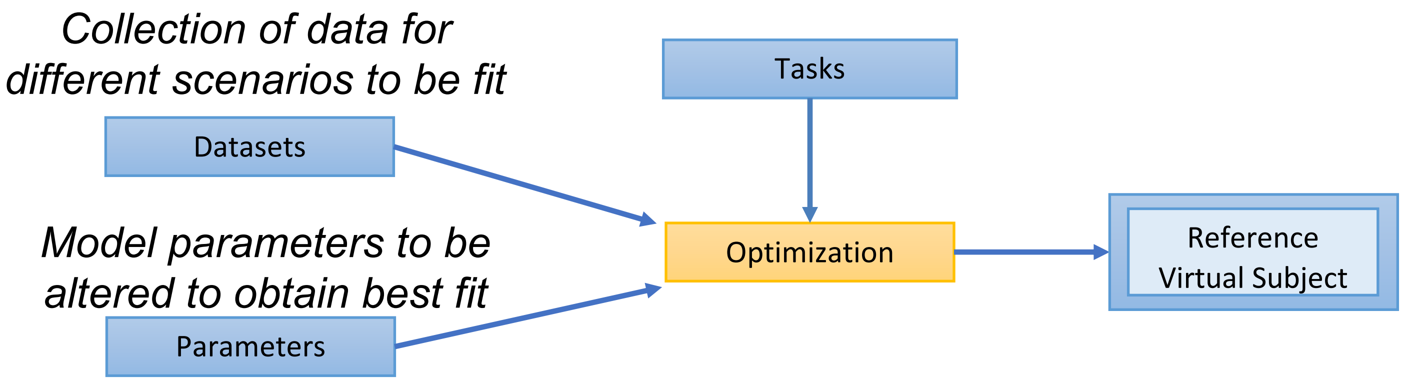




	A	B	C	D	E	F	G	H	I
1	V1	V2	CL	CLd	kon	KD	s_target_init	target_thalf	PWeight
2	68.3016581	52.29451629	4.578005	14.84338813	117.070587	0.391493931	10.49979967	0.749388854	0.000612613
3	80.3783391	39.5039084	3.338302	13.74219271	146.23757	0.327020679	10.15818384	0.74331779	0.00052178
4	12.5066142	53.8813687	4.894156	14.94776178	139.918774	0.591845329	14.01328077	0.773041176	0.005046668
5	52.3603256	41.8663783	4.663769	10.3325671	106.26201	0.280617245	11.51605834	0.798053305	4.26685E-07
6	13.3303082	49.5357689	4.213906	13.90905142	488.553598	0.604244874	10.39922969	0.759144492	0.00790045
7	23.2869547	39.78987738	4.230831	15.89166259	61.9373199	0.372207506	11.54370888	0.839850151	0.000850791
8	94.4800937	49.94300273	6.36913	12.63405972	141.267966	0.533090658	10.67150552	0.821555485	0.001715277
9	99.8756392	43.34365028	3.476382	11.78156381	205.792043	0.372452034	14.04457692	0.750568076	0.003471445
10	84.851535	36.1030722	5.005752	13.71546034	468.203743	0.487573207	10.59146022	0.886896622	0.00147428
11	13.8194734	44.7821012	5.937639	9.945518819	165.59476	0.460015886	13.39861342	0.865069222	0.002969216

Virtual subject(s) is an excel file

Optimization functionality generates a reference VS such that it matches the available datasets across different scenarios

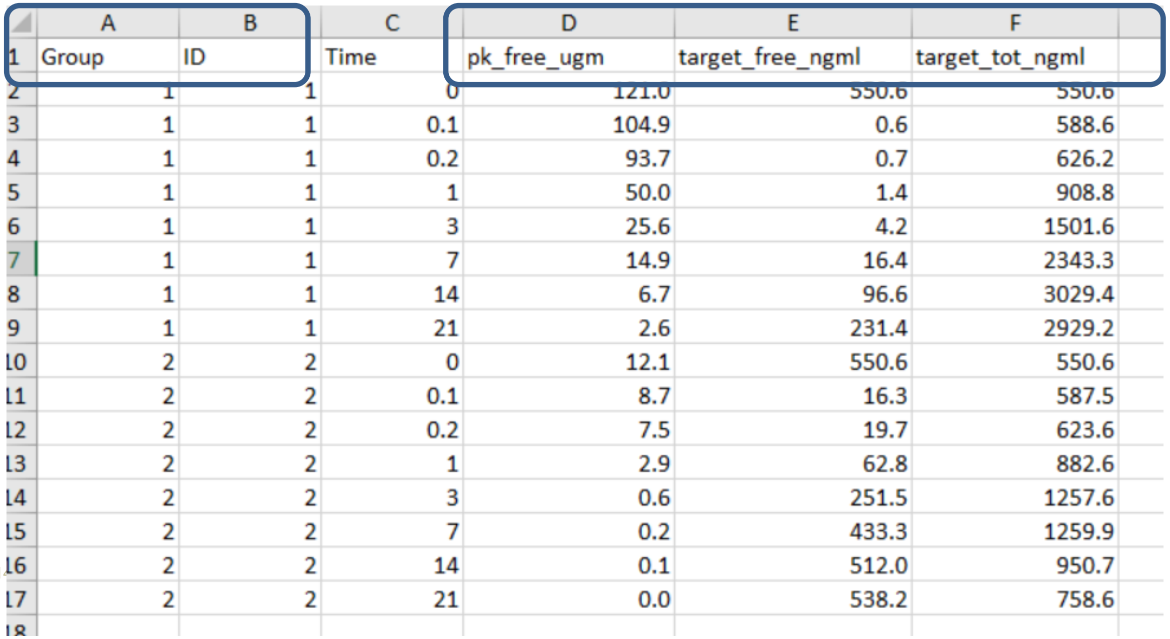


Collection of data for different scenarios to be fit

Model parameters to be altered to obtain best fit

Group/ID indicators to map to different tasks

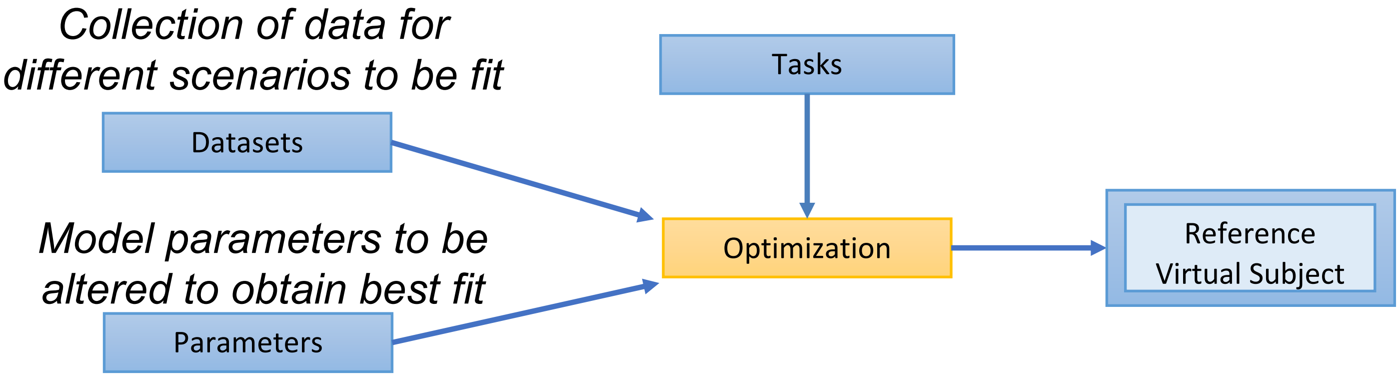
Output data (time matched)



	A	B	C	D	E	F
1	Group	ID	Time	pk_free_ugm	target_free_ngml	target_tot_ngml
2	1	1	0	121.0	550.6	550.6
3	1	1	0.1	104.9	0.6	588.6
4	1	1	0.2	93.7	0.7	626.2
5	1	1	1	50.0	1.4	908.8
6	1	1	3	25.6	4.2	1501.6
7	1	1	7	14.9	16.4	2343.3
8	1	1	14	6.7	96.6	3029.4
9	1	1	21	2.6	231.4	2929.2
10	2	2	0	12.1	550.6	550.6
11	2	2	0.1	8.7	16.3	587.5
12	2	2	0.2	7.5	19.7	623.6
13	2	2	1	2.9	62.8	882.6
14	2	2	3	0.6	251.5	1257.6
15	2	2	7	0.2	433.3	1259.9
16	2	2	14	0.1	512.0	950.7
17	2	2	21	0.0	538.2	758.6

Dataset is an excel file

Optimization functionality generates a reference VS such that it matches the available datasets across different scenarios



Collection of data for different scenarios to be fit

Datasets

Model parameters to be altered to obtain best fit

Parameters

Tasks

Optimization

Reference Virtual Subject

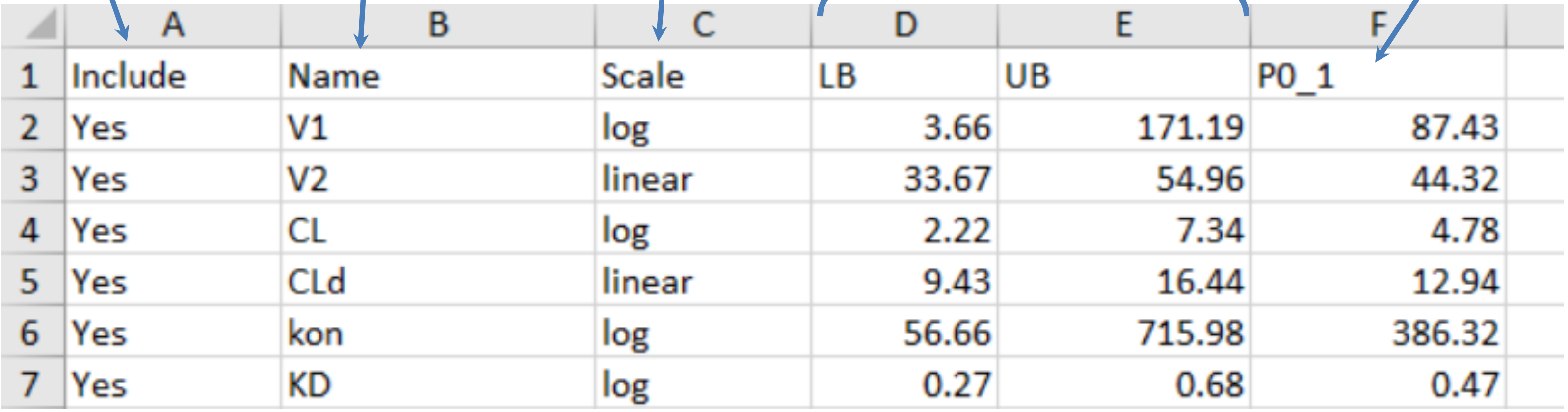
Include in fitting? Yes/No

Parameter name

Scale for exploration

Range of exploration

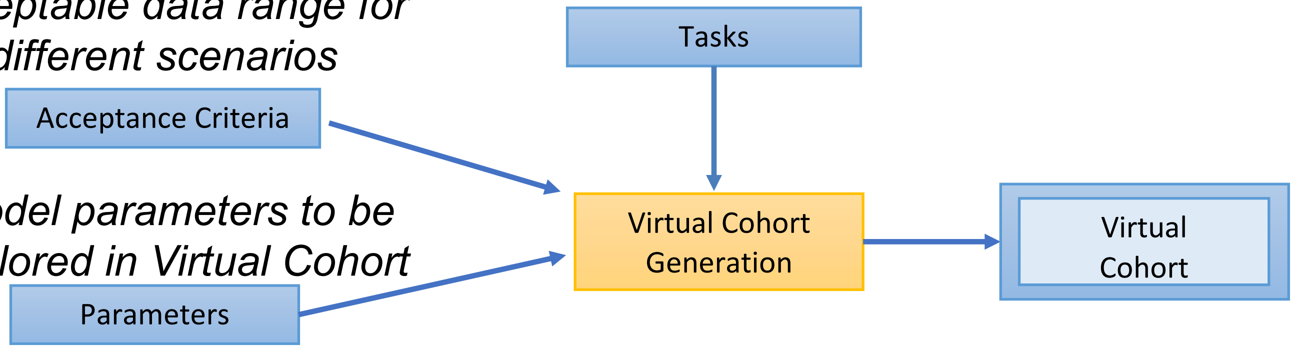
Initial guess



	A	B	C	D	E	F
1	Include	Name	Scale	LB	UB	P0_1
2	Yes	V1	log	3.66	171.19	87.43
3	Yes	V2	linear	33.67	54.96	44.32
4	Yes	CL	log	2.22	7.34	4.78
5	Yes	CLd	linear	9.43	16.44	12.94
6	Yes	kon	log	56.66	715.98	386.32
7	Yes	KD	log	0.27	0.68	0.47

Parameters file is an excel file

Parameter variability is explored to develop a Virtual Cohort constrained to be within the desired Acceptance Criteria



Acceptable data range for different scenarios

Acceptance Criteria

Model parameters to be explored in Virtual Cohort

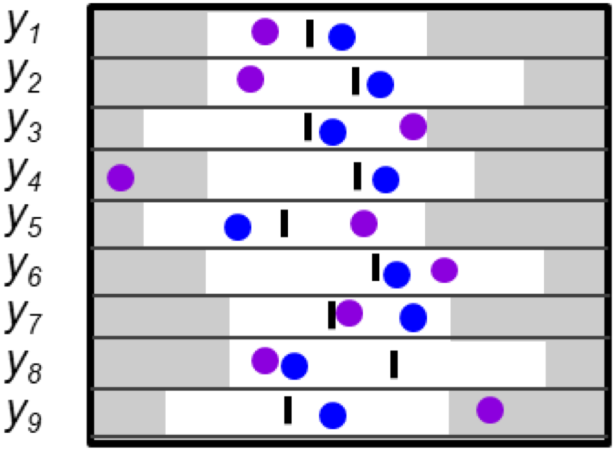
Parameters

Tasks

Virtual Cohort Generation

Virtual Cohort

Physiological outcomes "Acceptance" Criteria

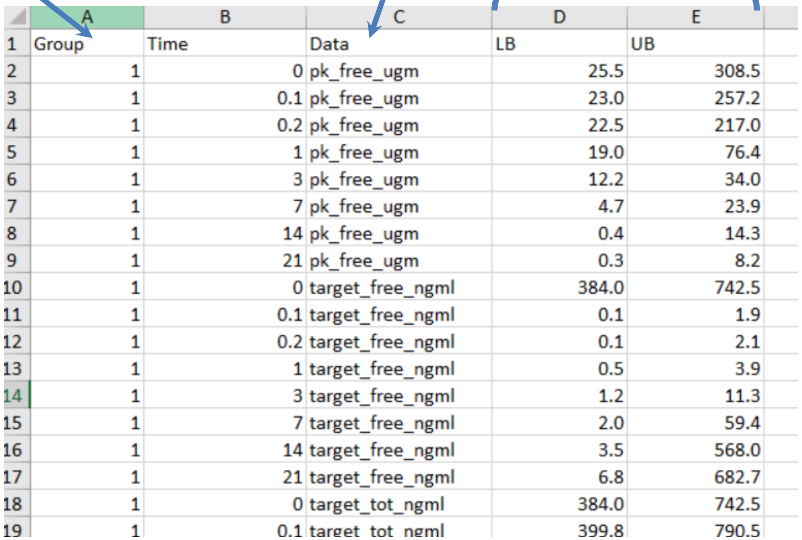


blue is a valid VS;
purple is an invalid one.

Group/ID indicators to map to different tasks

Output names

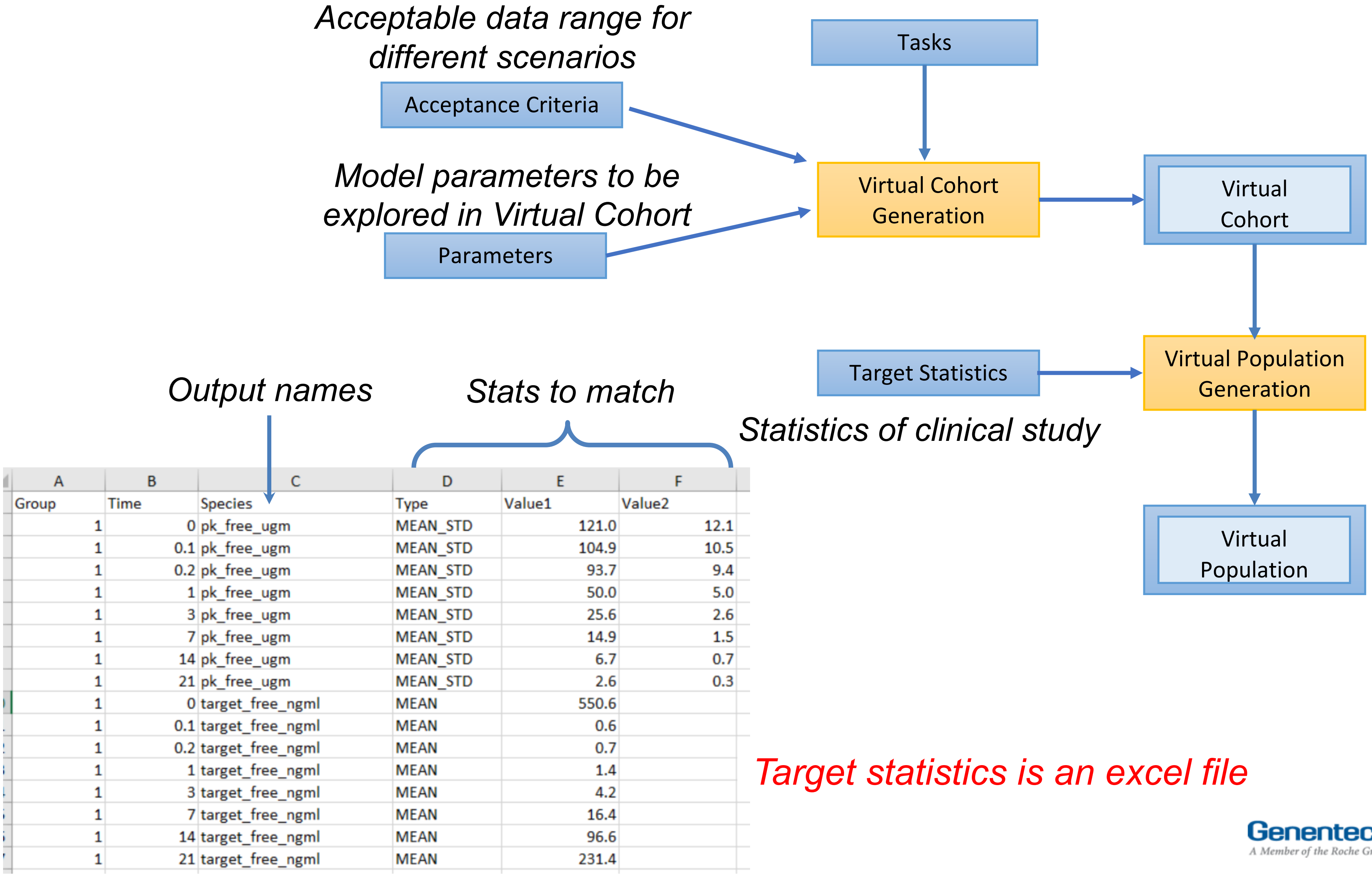
Range of data



	A	B	C	D	E
1	Group	Time	Data	LB	UB
2	1	0	pk_free_ugm	25.5	308.5
3	1	0.1	pk_free_ugm	23.0	257.2
4	1	0.2	pk_free_ugm	22.5	217.0
5	1	1	pk_free_ugm	19.0	76.4
6	1	3	pk_free_ugm	12.2	34.0
7	1	7	pk_free_ugm	4.7	23.9
8	1	14	pk_free_ugm	0.4	14.3
9	1	21	pk_free_ugm	0.3	8.2
10	1	0	target_free_ngml	384.0	742.5
11	1	0.1	target_free_ngml	0.1	1.9
12	1	0.2	target_free_ngml	0.1	2.1
13	1	1	target_free_ngml	0.5	3.9
14	1	3	target_free_ngml	1.2	11.3
15	1	7	target_free_ngml	2.0	59.4
16	1	14	target_free_ngml	3.5	568.0
17	1	21	target_free_ngml	6.8	682.7
18	1	0	target_tot_ngml	384.0	742.5
19	1	0.1	target_tot_ngml	399.8	790.5

Acceptance criteria is an excel file

Virtual Cohort is prevalence weighted to produce a Virtual Population that represents the statistics of a “real” clinical study



Acceptable data range for different scenarios

Model parameters to be explored in Virtual Cohort

Statistics of clinical study

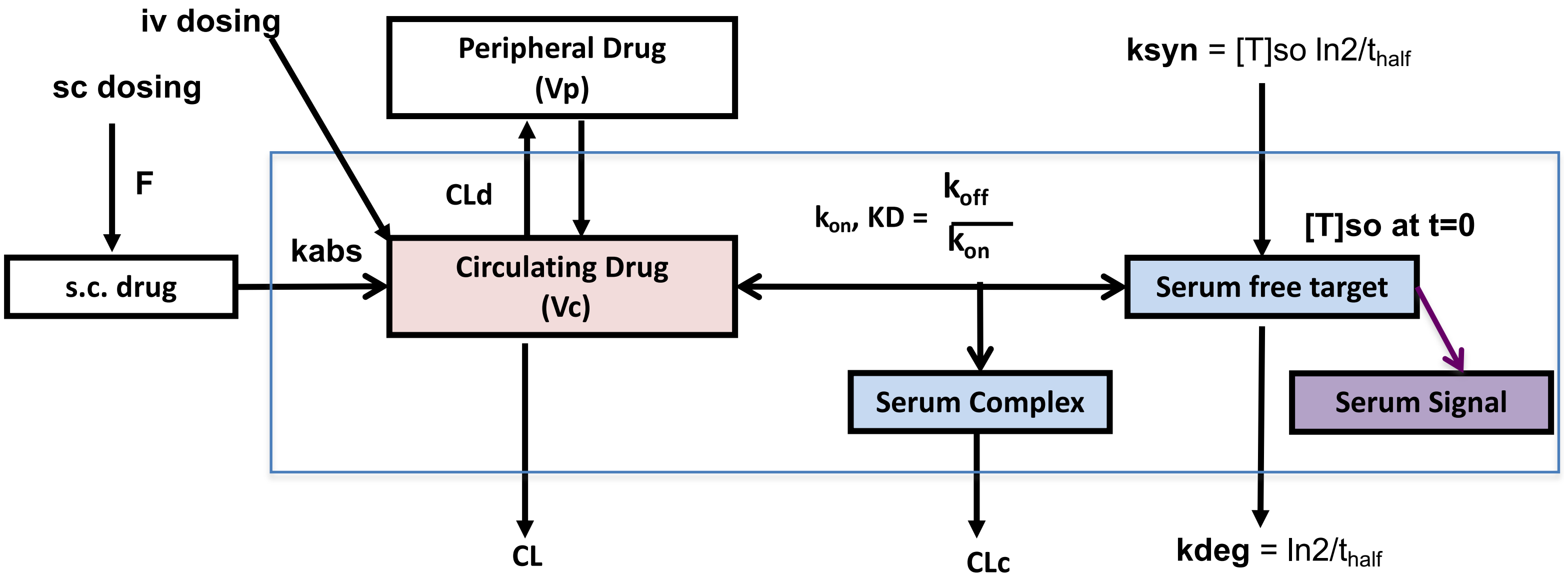
Output names

Stats to match

A	B	C	D	E	F
Group	Time	Species	Type	Value1	Value2
1	0	pk_free_ugm	MEAN_STD	121.0	12.1
1	0.1	pk_free_ugm	MEAN_STD	104.9	10.5
1	0.2	pk_free_ugm	MEAN_STD	93.7	9.4
1	1	pk_free_ugm	MEAN_STD	50.0	5.0
1	3	pk_free_ugm	MEAN_STD	25.6	2.6
1	7	pk_free_ugm	MEAN_STD	14.9	1.5
1	14	pk_free_ugm	MEAN_STD	6.7	0.7
1	21	pk_free_ugm	MEAN_STD	2.6	0.3
1	0	target_free_ngml	MEAN	550.6	
1	0.1	target_free_ngml	MEAN	0.6	
1	0.2	target_free_ngml	MEAN	0.7	
1	1	target_free_ngml	MEAN	1.4	
1	3	target_free_ngml	MEAN	4.2	
1	7	target_free_ngml	MEAN	16.4	
1	14	target_free_ngml	MEAN	96.6	
1	21	target_free_ngml	MEAN	231.4	

Target statistics is an excel file

Today's Case Study: TMDD Model



Available Data

1. Unbound antibody concentration
2. Free Target concentration
3. Total Target concentration

To Estimate

1. PK parameters
2. Antibody K_D

Today’s Case Study: TMDD Model

Data from a single-dose study

- **Dose:** 3 mg/kg and 0.3 mg/kg
- **In vitro Measured affinity:** 0.4 nM
- **Duration:** 21 days
- **Stats:** average, min and max of measurements

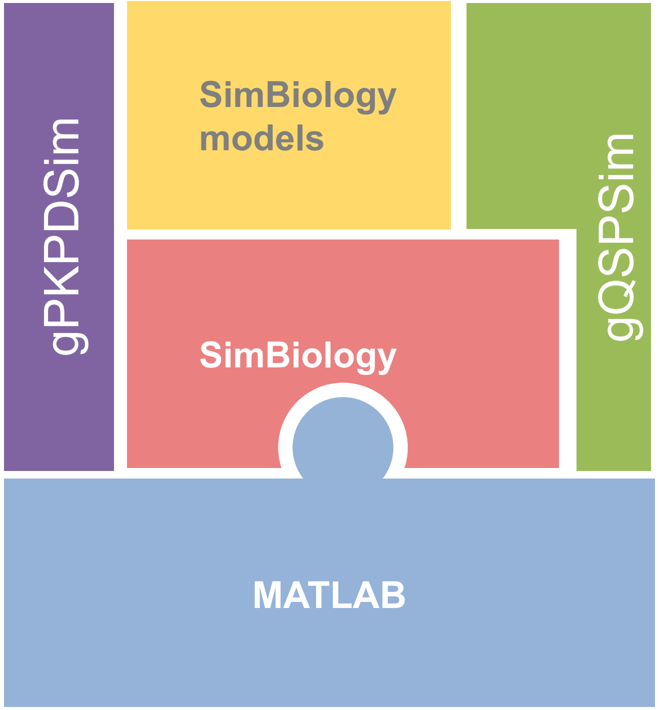
Demo

- Creating appropriate tasks
- Simulating model default values
- Parameter estimation (SS, PSO) and using “hand-calibration” features
- Generating a virtual cohort of valid patients
- Generating a virtual population of valid patients

THANK YOU

Questions? Contact hosseini.iraj@gene.com

SimBiology and the MATLAB ecosystem



- Developed by end-users
- Projects promote continuity and traceability of results
- Graphical model representation
- MATLAB and SimBiology infrastructure ensure reproducibility

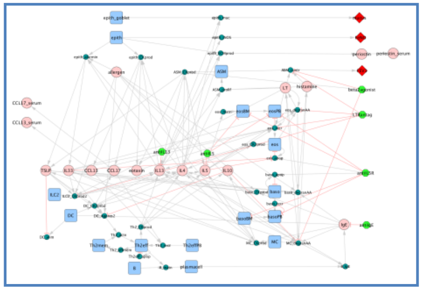
- MATLAB toolbox
- Graphical and programmatic workflows
- Comprehensive set of built-in analysis tools
- Accelerate models by compiling to C-code

- Programming language
- Versatile platform
- Maintained and updated
- Rigorous testing framework to ensure quality of platform

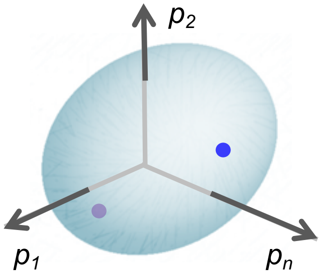
- **Where does gQSPSim sit in this ecosystem?**
- **How is gPKPDSim different from gQSPSim?**
  - Deployed vs Developing models
  - Non-modelers vs Expert modelers

Workflow and considerations for Reference Subject calibration

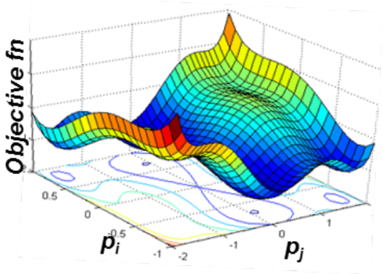
Structural Model



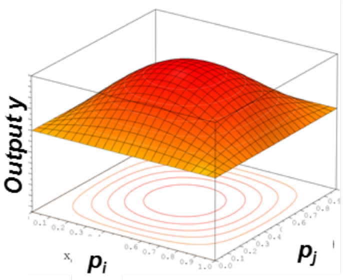
Parameter space, ***p***



Parameter Optimization

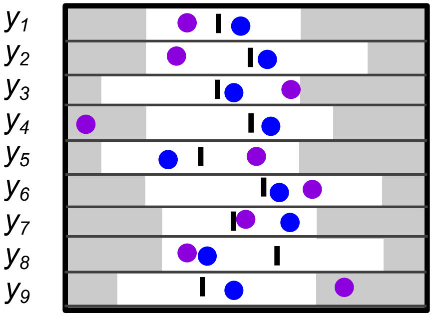


Model Analysis



Parameter Sensitivity

Physiological outcomes
“Acceptance” Criteria



Virtual Subjects

Reference Virtual Subject

Invalid Virtual Subject

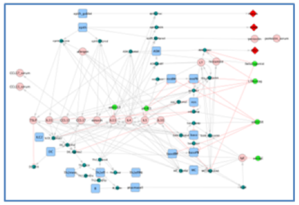
Considerations

- Defining the objective function is non-trivial & critical for efficient Reference Subject calibration
- Iteration on QSP model representation is critical at this stage: (i) modifications to mathematical representation; (ii) expansion/reduction of biology included; (iii) alternate hypothesis testing
- Developing a suite of algorithms/tools specific for to QSP models is of high value

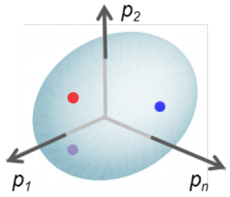
Workflow for developing a Virtual Population

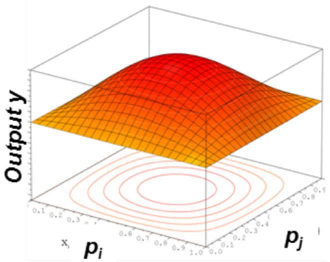
Developing the Virtual Cohort

Structural Model



Parameter space, ***p***

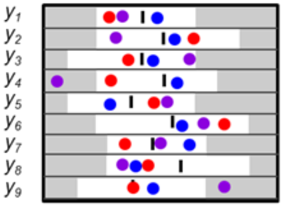




Parameter Sensitivity

Model Analysis

Physiological outcomes
“Acceptance” Criteria



Virtual Subjects

Reference Virtual Subject

(Alternate) Virtual Subject

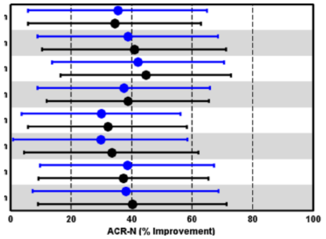
Invalid Virtual Subject

Virtual Cohort

Developing the Virtual Population

Virtual Cohort

Clinical Statistics

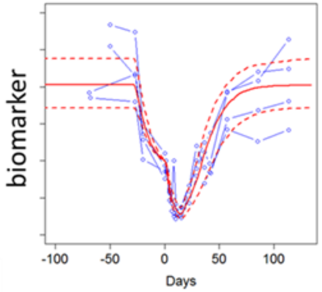


Statistical weighting

Weighting algorithm

Virtual Population

Predictive Simulations



Genentech
A Member of the Roche Group

Statistically weighed virtual population enables robust quantitative representation of a “real” clinical population

Each Virtual Subject in the Virtual Population assigned a “weight” corresponding to the probability of finding similar measurements in the clinical population

- The virtual population as a whole captures the observed statistics of the “true” clinical population of interest

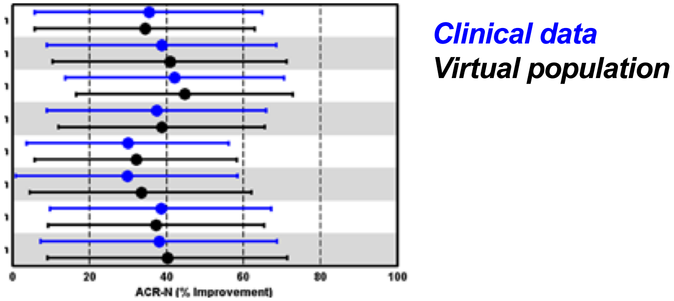
The key statistics captured include:

- Mean and distribution of clinical measurements both as baseline and responses to interventions
- Observed correlations (or lack thereof) between measurements

The weights could either be binary (include/exclude) or be continuous (range from 0-1)

- Calculated using constrained optimization techniques to match the desired statistics

Virtual Population matching means & distributions of clinical populations



Virtual Population captures correlation between biomarkers observed in clinical data