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A Six-Stage Workflow for Robust Application of Systems Pharmacology

Kapil Gadkar

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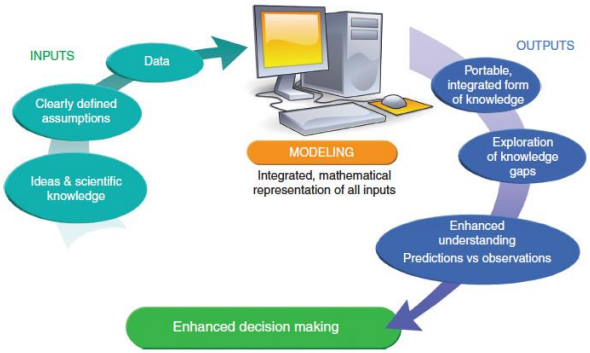
Workflows in QSP: Bridging Conceptual Workflows and Execution?

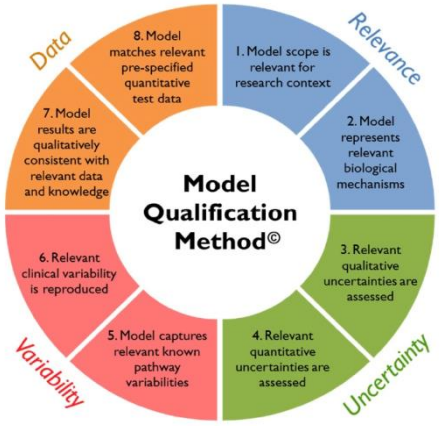
Descriptive workflows

e.g., Visser et al CPTPSP 2015



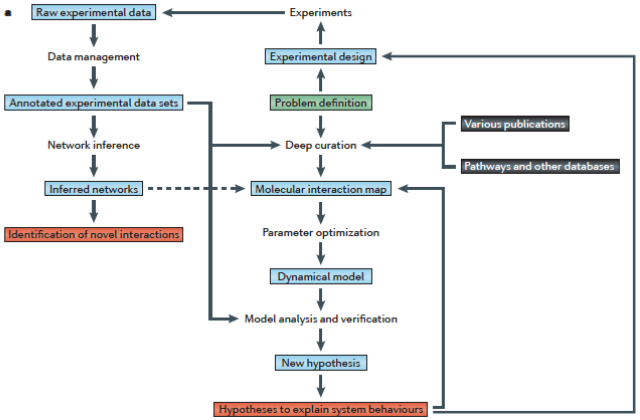
Qualification Workflows

e.g., ROSA MQM© Friedrich et al CPTPSP 2016



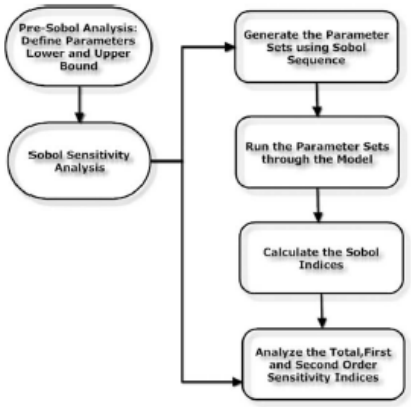
Computational workflows

e.g., Ghosh et al 2011, Nature Revs- Genetics



Workflows for specific analyses

e.g., Zhang et al 2015, CPTPSP



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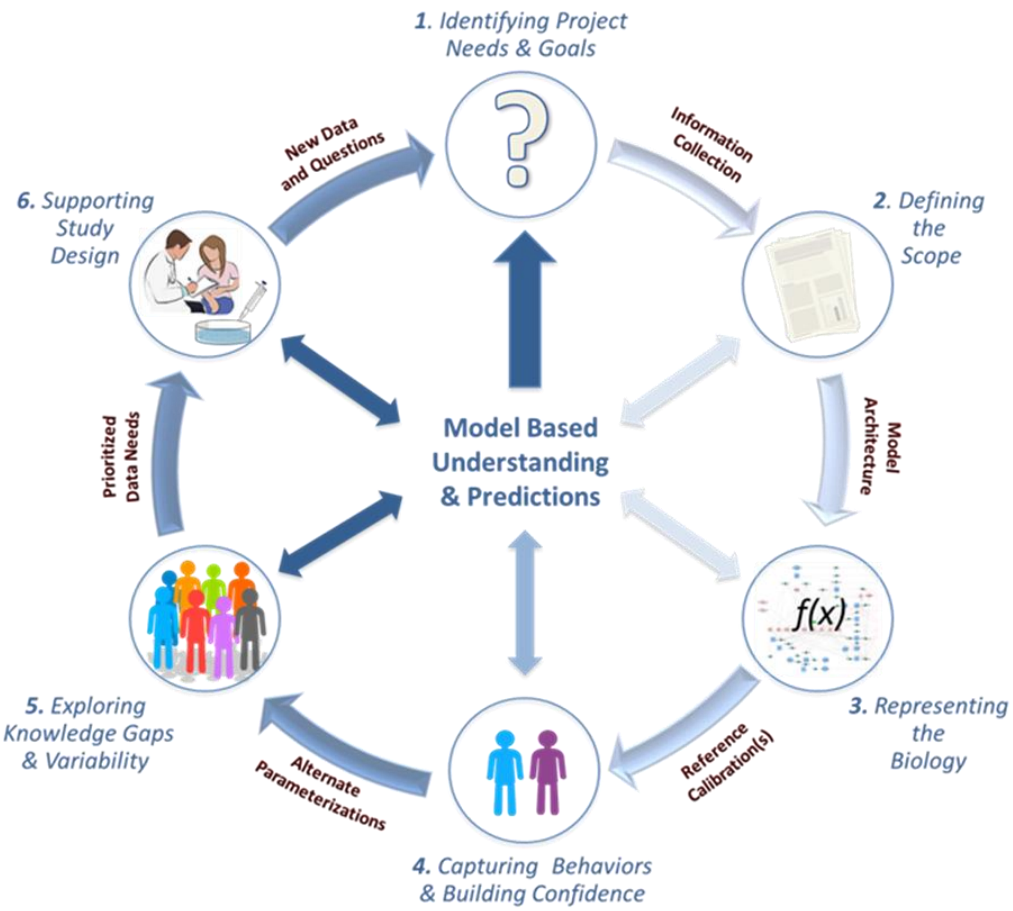
Workflow & Technical Methodologies:
Six Stages of QSP model development and Implementation



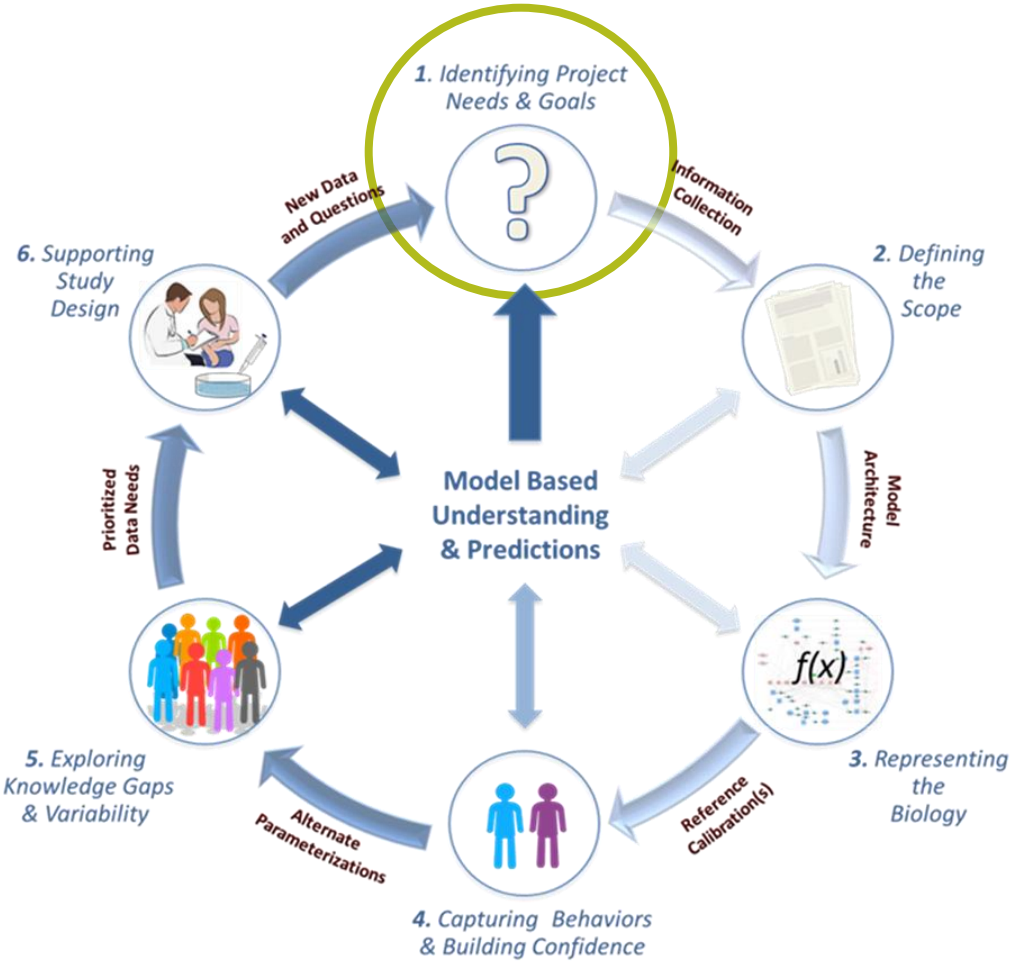
Six stages of QSP model development & implementation

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*

Gadkar et al, CPT-PSP 2016

Stage 1: Clear understanding of the project needs & goals is primary to the ultimate success of any QSP effort

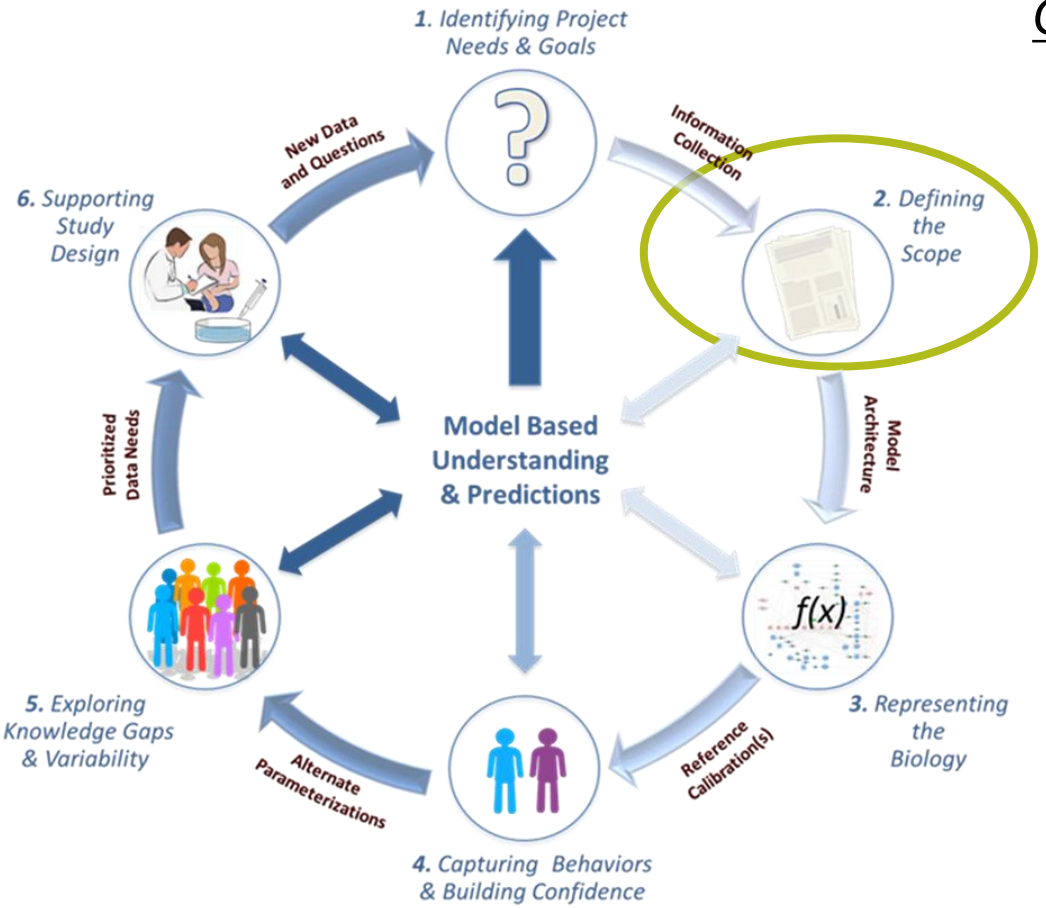


Gadkar et al, CPT-PSP 2016

Considerations & Activities

- Careful evaluation of problem context and specification of the needs to be met
- Clear understanding of the decisions that will be potentially impacted
- Deadlines & time frame for decisions and milestones
- Evaluation of whether QSP is the right approach
- Identification and interaction with key stakeholders and collaborators

Stage 2: A robust model scoping effort lays the platform for efficient execution and success of QSP project



Considerations & Activities

Gadkar et al, CPT-PSP 2016

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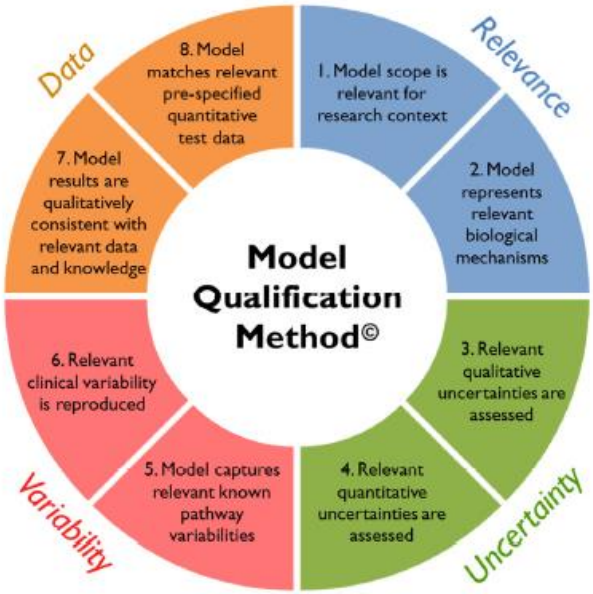
Stage 2: A robust model scoping effort lays the platform for efficient execution and success of QSP project

Considerations & Activities

- Extensive review & organization of information & data from varied sources
- Identify key knowledge gaps

	KOLs	Literature & Abstracts	Databases (eg)	"in-house" data
General Understanding	Disease biology and clinical experts	Review papers		
Mechanistic understanding and data	Disease biology & target experts	in vitro and in vivo studies	Pathways Molecular	In vitro and in vivo studies
Clinical understanding and data	Clinical experts	Clinical reports and study results	Trials	Summary & Patient-level data
Modeling Approaches	QSP, PKPD, bioinformatics, and statistics experts	Prior art	Model repositories	PKPD & Statistical models

Stage 2: A robust model scoping effort lays the platform for efficient execution and success of QSP project



Considerations & Activities

- Extensive review & organization of information & data from varied sources
- Identify key knowledge gaps
- Specification of the QSP model qualification criteria[1]

1. *Friedrich et al; Facilitating Drug Discovery and Development with Mechanistic Physiological Models that are "Fit for Purpose": Introducing a Model Qualification Method 2012*

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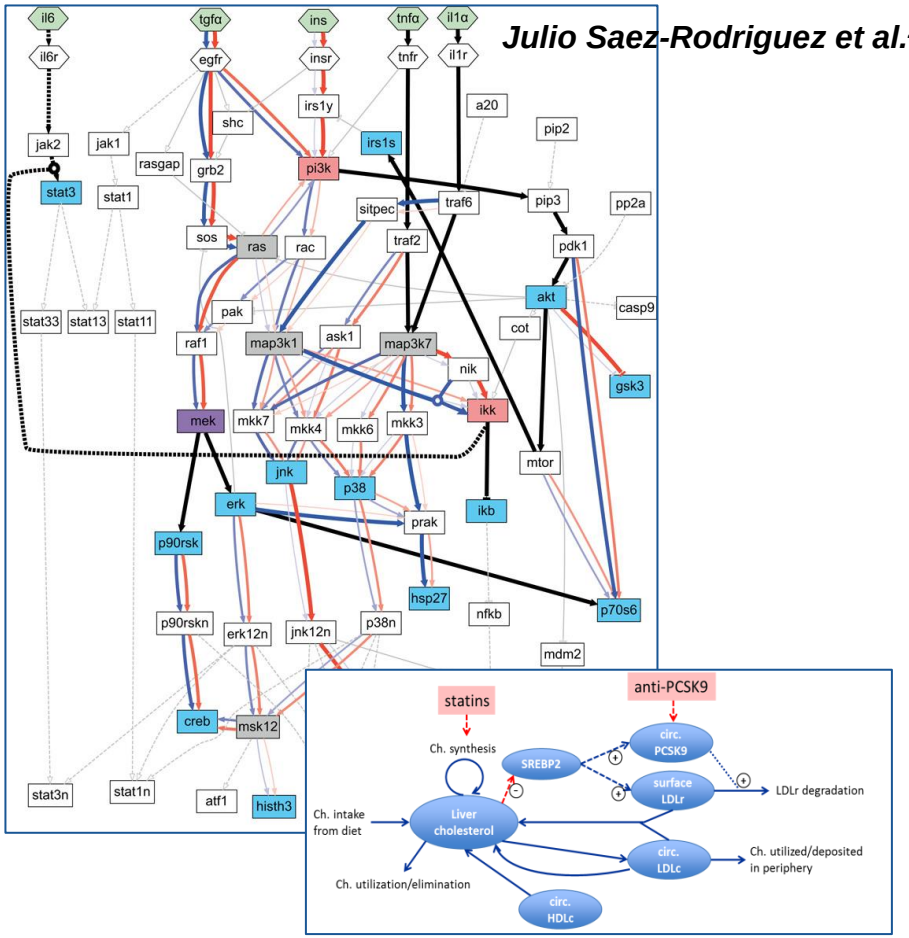

Julio Saez-Rodriguez et al.[2]

Gadkar et al.[3]

Considerations & Activities

- Extensive review & organization of information & data from varied sources
- Identify key knowledge gaps
- Specification of the QSP model qualification criteria[1]
- Visual map of the biology of scope with tools such as Cytoscape, JDesigner, others

1. *Friedrich et al; Facilitating Drug Discovery and Development with Mechanistic Physiological Models that are "Fit for Purpose": Introducing a Model Qualification Method 2012*
2. *Julio Saez-Rodriguez et al. "Comparing signaling networks between normal and transformed hepatocytes using discrete logical models" Cancer Res 2011;71:5400-5411*
3. *Gadkar et al. "A Mechanistic Systems Pharmacology Model for Prediction of LDL Cholesterol Lowering by PCSK9 Antagonism in Human Dyslipidemic Populations" CPT-PSP, 2014; Nov. 3(11)*

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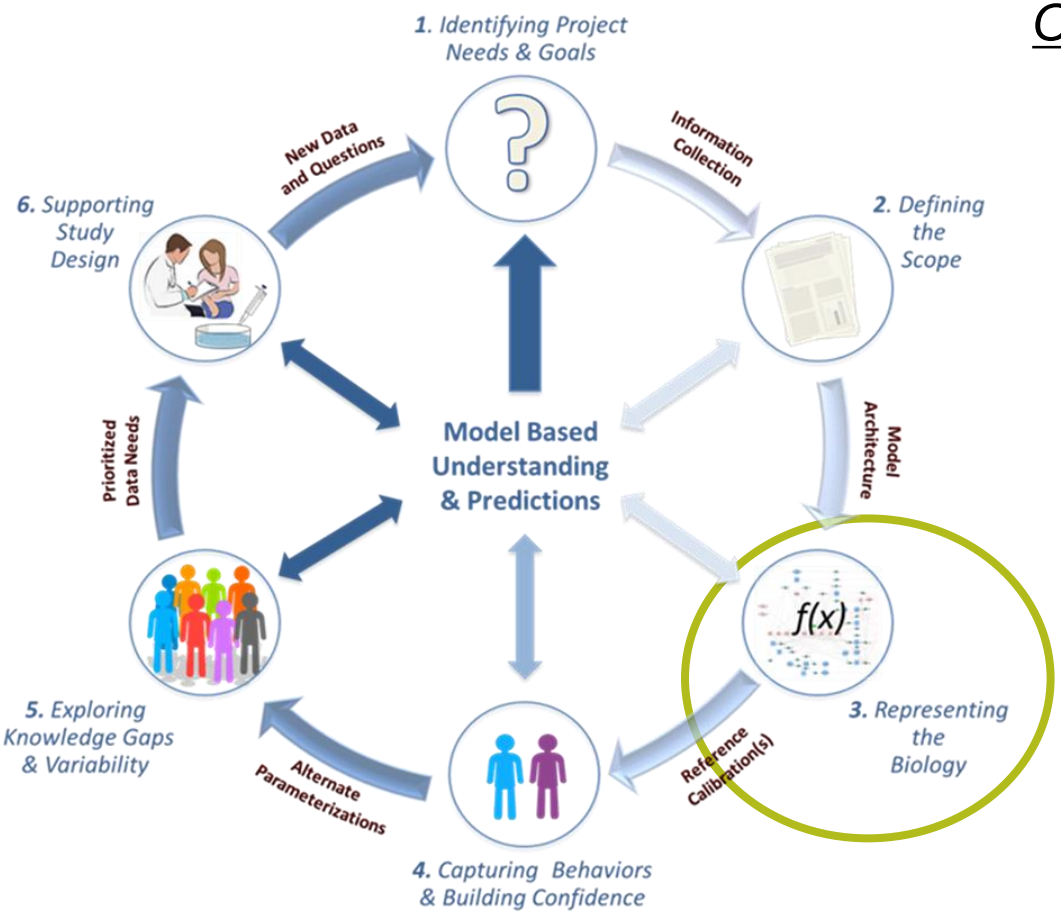
Stage 3: Selection from various options for mathematical representation of the biology of interest is case specific



Considerations & Activities

Gadkar et al, CPT-PSP 2016

Stage 3: Selection from various options for mathematical representation of the biology of interest is case specific

Considerations & Activities

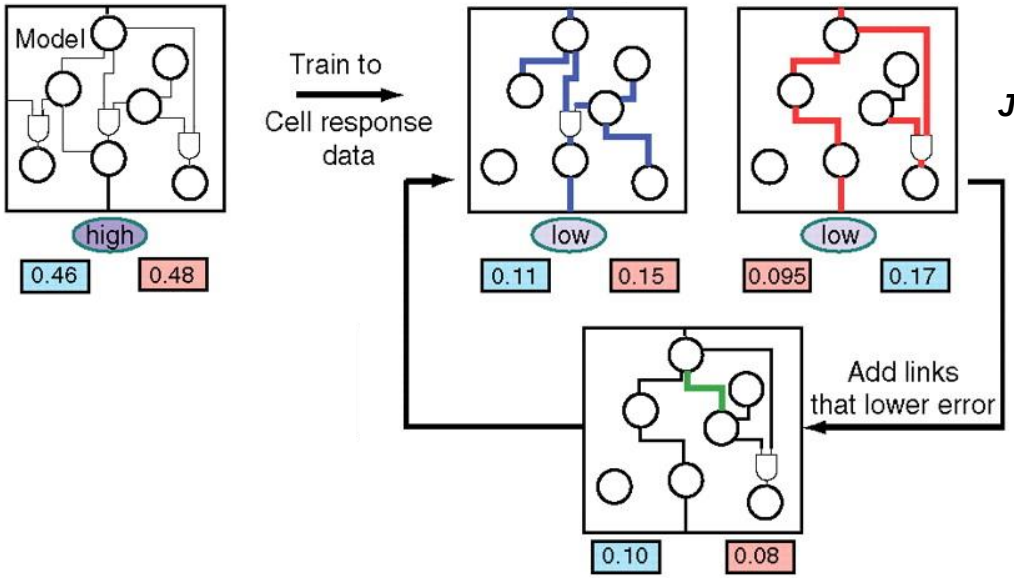
- Choice of mathematical formalism & implementation of equations

Method	Common application	Strengths	Caveats
ODEs	Various	Continuous dynamics	Needs data or understanding of kinetics
Logic based	signaling	Intuitive rules	Less kinetic richness
PDEs	Tumor heterogeneity	Continuous spatial dynamics	Complex and computationally expensive
Cellular automata & agent based	Tumor cells, immune cells, infectious agents	Emergent behaviors & spatial dynamics	Complex and computationally expensive
Statistical	various	Data-driven biology elucidation	Less mechanistic

Stage 3: Selection from various options for mathematical representation of the biology of interest is case specific

Considerations & Activities

- Choice of mathematical formalism & implementation of equations
- Alternate model structures and/or topologies



***Julio Saez-Rodriguez et al.*[1]**

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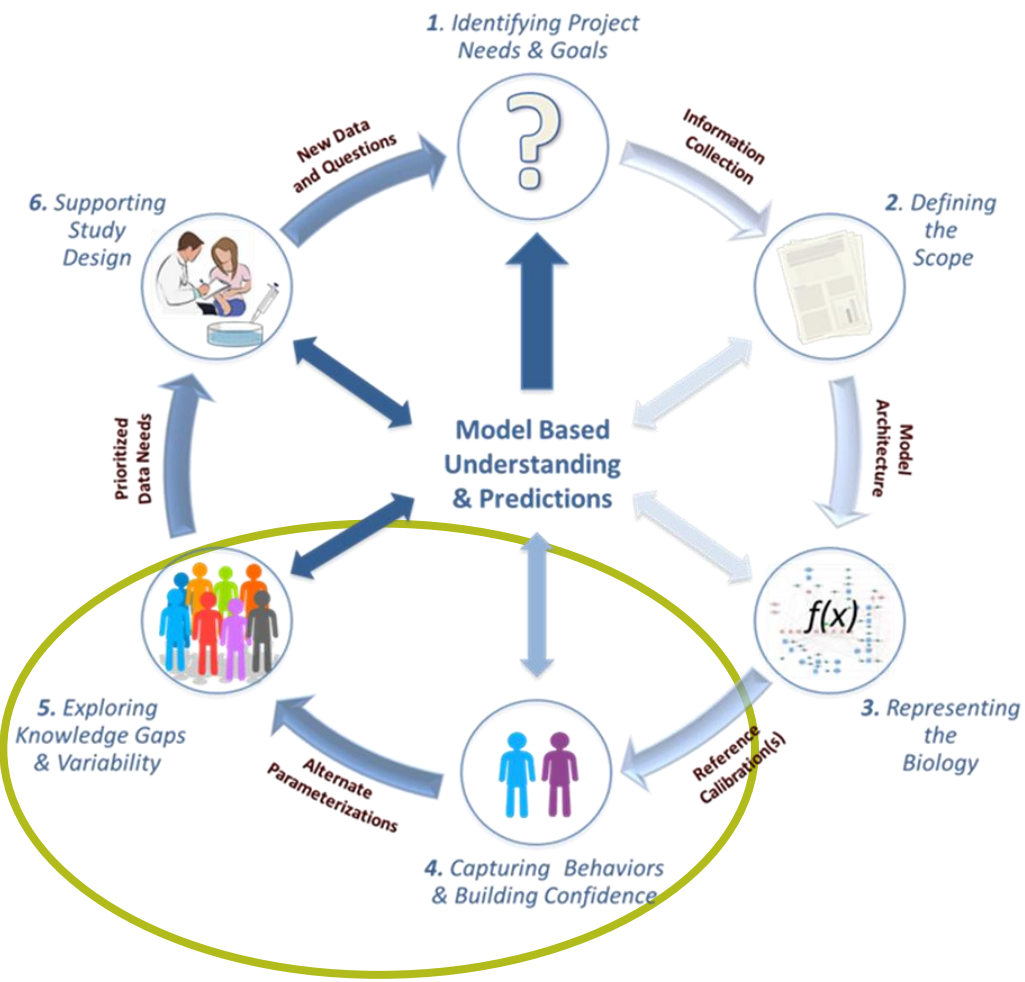
Workflow & Technical Methodologies: Six Stages of QSP model development and Implementation



Gadkar et al, CPT-PSP 2016

Stage 4: Capturing "Reference" behavior

- Overview of tools

Stage 5: Virtual populations (Vpops) as a means to explore variability & uncertainty

- A methodology for developing Vpops

Case studies demonstrating application of the tools and workflows

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

Stage 4: “Reference” calibration indicative of high likelihood of success for QSP model

Considerations & Activities

- A “reference” calibration ensures topology and mathematical representation sufficient

Stage 4: "Reference" calibration indicative of high likelihood of success for QSP model

Considerations & Activities

- A "reference" calibration ensures topology and mathematical representation sufficient
- Sensitivity analysis (local vs. global)[1,2]

	Commonly used global sensitivity analysis methods				
Criteria for comparison	**Weighted average of local sensitivity analysis (WALS)**	**Partial rank correlation coefficient (PRCC)**	**Multi-parametric sensitivity analysis (MPSA)**	**Fourier amplitude sensitivity analysis (FAST)**	**Sobol**
Discrete inputs	Yes	Yes	Yes	Yes	Yes
Model independence	No	No	No	Yes	Yes
Non-linear, input-output relationship	Yes	Yes	Yes	Yes	Yes
Non-monotonic input-output relationship	Yes	No	Yes	Yes	Yes
Robustness	Yes	Yes	Yes	Yes	Yes
Reproducibility	Yes	Yes	Yes	Yes	Yes
Ability to apportion the output variance	No	No	No	Yes	Yes
Higher order interaction of parameters	No	No	No	Yes	Yes
Quantitative measure for ranking	Yes	Yes	Yes	Yes	Yes
Computational efficiency	Yes	Yes	Yes	No	No

Zhang et al.[2]

1. *Marino, S., I. B. Hogue, et al. (2008). "A methodology for performing global uncertainty and sensitivity analysis in systems biology." J Theor Biol 254(1): 178-196*
2. *Zhang et. Al. (2015). "Sobol Sensitivity Analysis: A Tool to Guide the Development and Evaluation of Systems Pharmacology Models", CPT-PSP, Feb.*

Stage 4: “Reference” calibration indicative of high likelihood of success for QSP model

Considerations & Activities

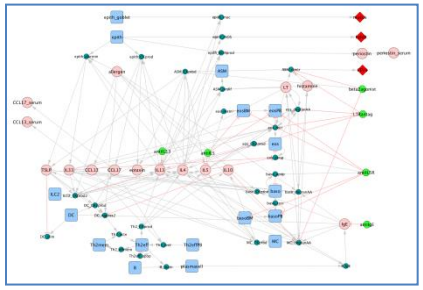
- A “reference” calibration ensures topology and mathematical representation sufficient
- Sensitivity analysis (local vs. global)[1,2]
- Parameter estimation via optimization[3,4]

Optimization approach	Example algorithms	Strengths	Caveats	Example prior applications
Local	Levenberg-Marquardt	Simplicity, Computational efficiency	Local minimum only; Requires convex, smooth objective function	Multiple
Deterministic Global	Branch and Bound	Guaranteed global min	Computationally expensive	Metabolic systems
Stochastic Global	Simulated Annealing, Genetic Algorithms, Evolutionary Programming, Evolutionary Strategies, Particle Swarm, Scatter Search	Computational efficiency; Near global minimum	Global minimum not guaranteed	Blood coagulation Signal transduction
Hybrid	Combinations of the above	Leverages strengths of local and global approaches	Fewer and less widely tested algorithms available	Lipid metabolism

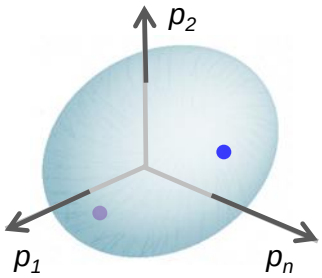
1. *Marino, S., I. B. Hogue, et al. (2008). "A methodology for performing global uncertainty and sensitivity analysis in systems biology." J Theor Biol 254(1): 178-196*
2. *Zhang et. Al. (2015). “Sobol Sensitivity Analysis: A Tool to Guide the Development and Evaluation of Systems Pharmacology Models”, CPT-PSP, Feb.*
3. *Sun, J., V. Palade, et al. (2014). "Biochemical systems identification by a random drift particle swarm optimization approach." BMC Bioinformatics 15 Suppl 6: S1*
4. *Rodriguez-Fernandez et al. (2006). "Novel metaheuristic for parameter estimation in nonlinear dynamic biological systems." BMC Bioinformatics 7: 483*

Stage 4: Workflow and considerations for Reference Subject calibration

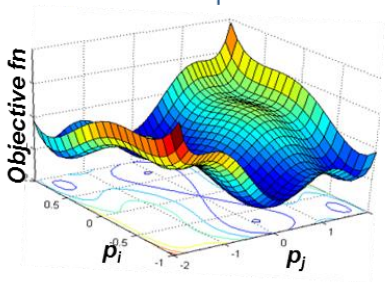
Structural Model



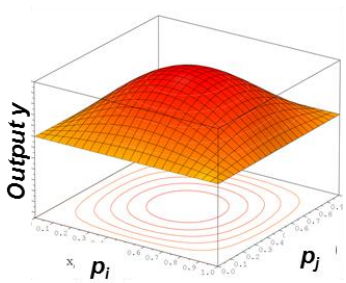
Parameter space, ***p***



Parameter Optimization

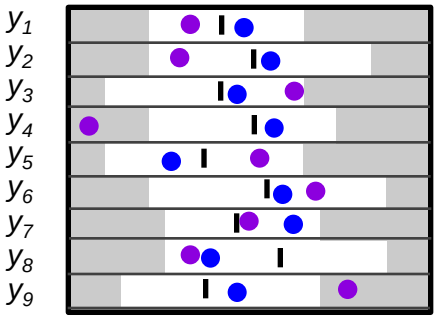


Model Analysis



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

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Stage 5: Exploration of variability and knowledge gaps an extremely important aspect of QSP-based work

Considerations

- Kinds of uncertainty & variability include:
  - Insufficient or imperfect mechanistic knowledge
  - Quantitative uncertainty in the available data
  - Known inter-subject or intra-subject (spatial or time) variability
- Knowledge gaps typically explored via alternate model structures or alternate parameterizations; each instance a Virtual Subject
- Multiple Virtual Subjects may “behave” similarly to the known data– i.e, non-unique
- Collective available data utilized to develop the Virtual Population
- Testing against “new” data establishes predictive capability
- “Typical” QSP models are “sloppy”[1]: focus on ranges of predictions rather than parameter values

Outcomes/learnings

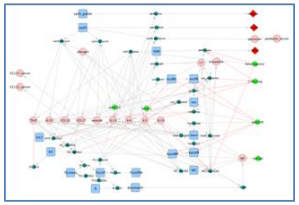
- Robust QSP-based findings grounded in quantitative biology

1. *Gutenkunst, R. N., J. J. Waterfall, et al. (2007). "Universally sloppy parameter sensitivities in systems biology models." PLoS Comput Biol **3**(10): 1871-1878.*

Workflow for developing a Virtual Population

Developing the Virtual Cohort

Structural Model



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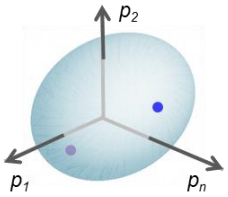
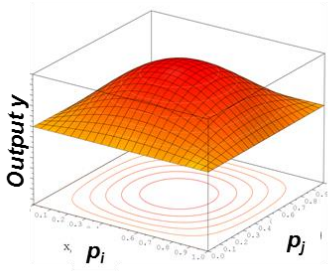
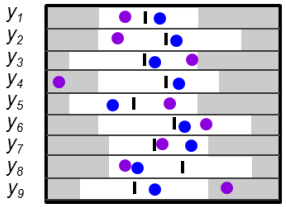




Parameter Sensitivity

Model Analysis

Physiological outcomes
"Acceptance" Criteria



Virtual Subjects

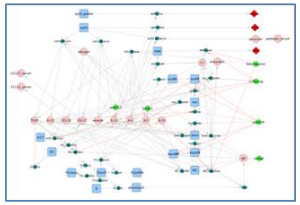
Reference Virtual Subject

Invalid Virtual Subject

Workflow for developing a Virtual Population

Developing the Virtual Cohort

Structural Model



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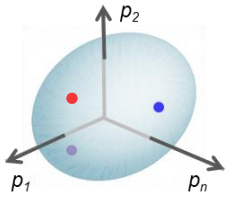
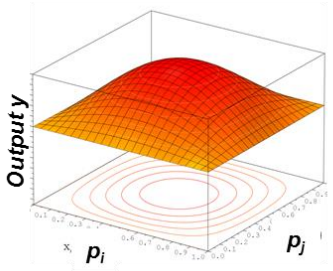
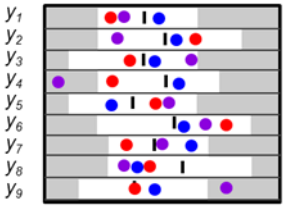




Parameter Sensitivity

Model Analysis

Physiological outcomes "Acceptance" Criteria



Virtual Subjects

Reference Virtual Subject

(Alternate) Virtual Subject

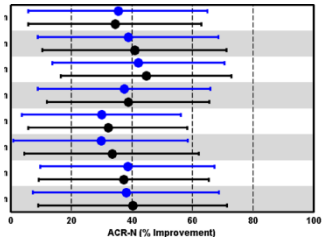
Invalid Virtual Subject

Virtual Cohort

Developing the Virtual Population

Virtual Cohort

Clinical Statistics

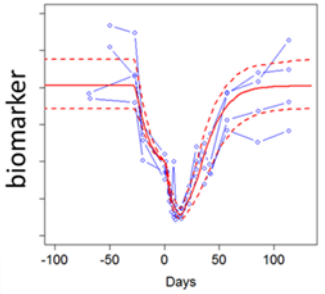


Statistical weighting

Weighting algorithm

Virtual Population

Predictive Simulations



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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

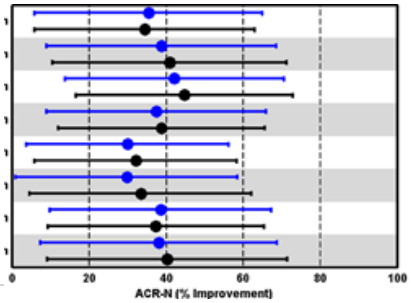
The key statistics captured include:

- 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)

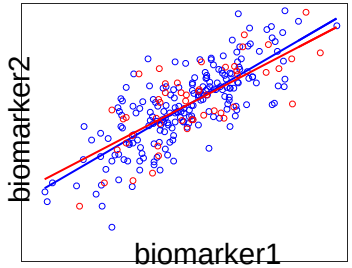
- Calculated using constrained optimization techniques to match the desired statistics

Virtual Population matching means & distributions of clinical populations



Clinical data
Virtual population

Virtual Population captures correlation between biomarkers observed in clinical data



Clinical data
Virtual population

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Example: Mechanism based Asthma disease model supporting Genentech pipeline for target validation, molecule selection & biomarker evaluation

Stage 1: Project goals

- Mechanistic underlying relating cell biology to airway physiology in terms of FEV1
- Predictions of changes in underlying biology and endpoints for untested novel therapies
- Evaluation of potential biomarkers
- Support patient population selection for clinical trials
- Evaluate impact of co-meds/background therapies on response to novel drug
- Evaluation of new targets

Stage 2: Scoping

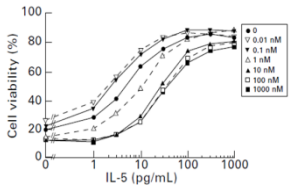
Key Biological mechanisms & scope

- Activation /recruitment of innate immune cells: eosinophils, basophils, dendritic cells, ILC2s, mast cells, neutrophils
- Activation of adaptive immune cells: Th2, B, plasma, Th17
- Production & effects of soluble mediators
- Airway response: Epithelial cell mediator & mucus production, ASM contraction

Clinical Scope

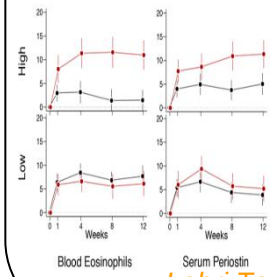
- Clinical endpoints: FEV1, FeNO
- Patients types: healthy, asthmatics (range of disease severity), eosinophilic vs. neutrophil dominant
- Interventions: anti-IL5, anti-IL13, anti-IgE, steroids, anti-IL4Rα, others

Mechanistic in-vitro & preclinical data

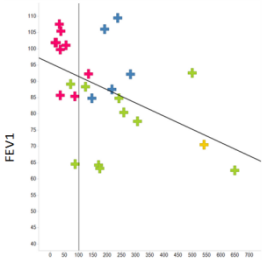


Public lit.

Published & in-house clinical data Repository (50+ clinical studies)



Lebri Team



Public lit.

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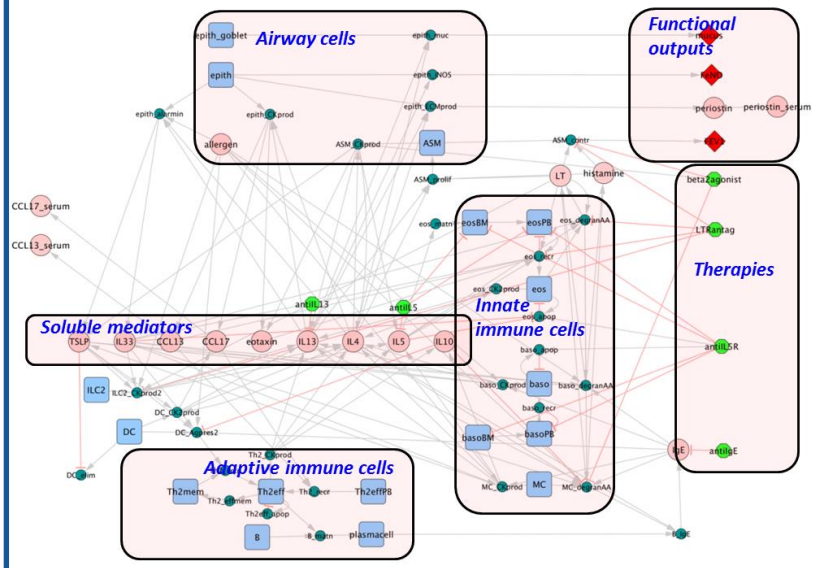
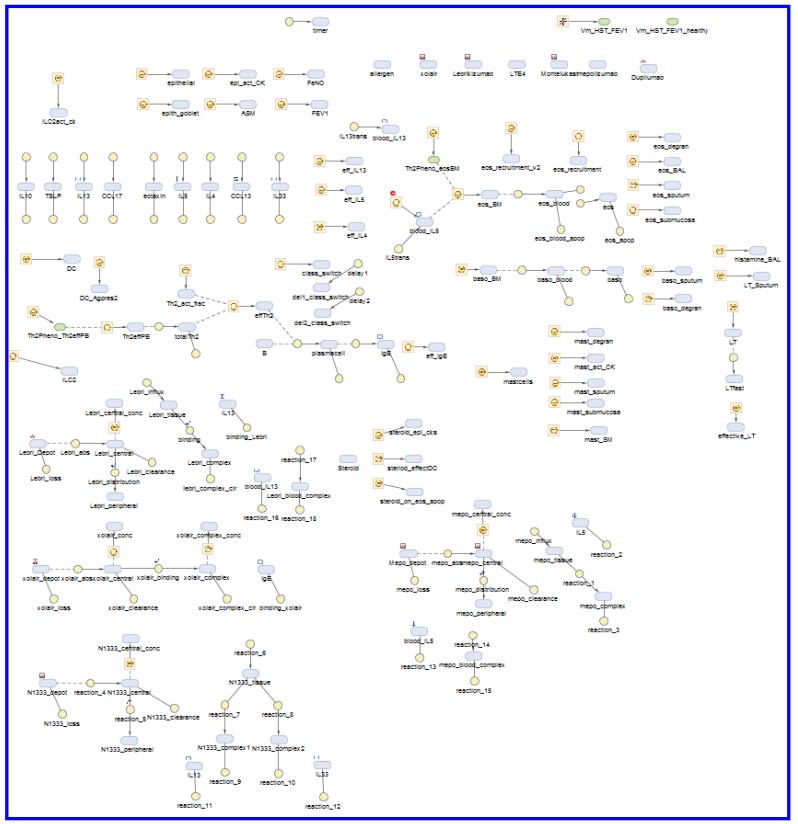
Stage 2 & 3: Model schematic in Cytoscape translated to a an ODE based model represented in Simbiology/MATLAB

Model connectivity map



Model diagram/equations in Simbiology



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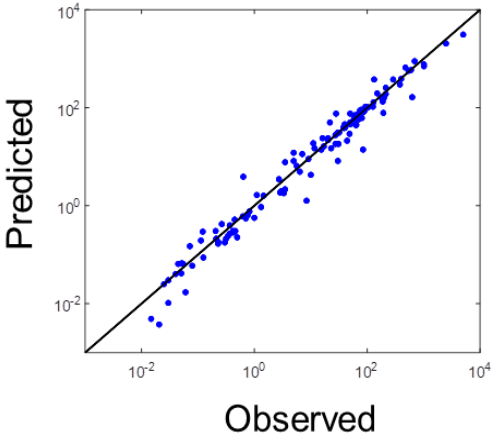
Stage 4: Application of stochastic global optimization for Reference Subject(s) calibrations in the Asthma QSP platform

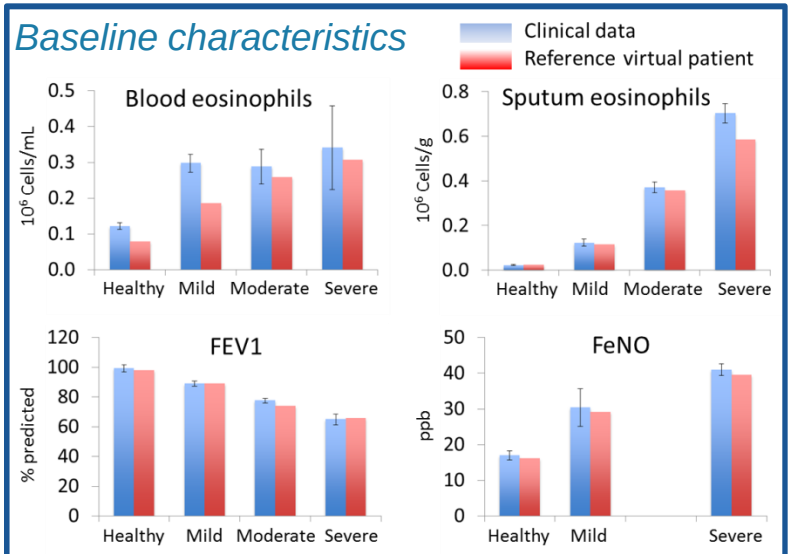
Implementation Considerations

- Data for different patient phenotypes (variability in mechanistic drivers, disease severity)
- Data across multiple cell types, mediators & clinical readouts for multiple therapies/interventions
  - Appropriate data normalization
  - Simultaneous simulations of all interventions for objective function evaluation
- Several mechanistic limitations of model identified in this step and model updated accordingly



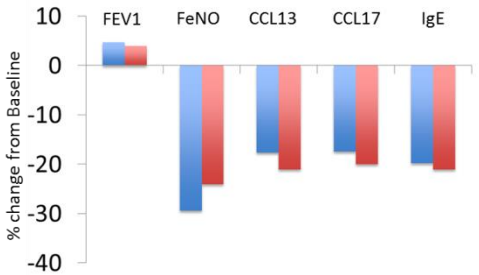
Capturing the "reference" behavior

Baseline characteristics

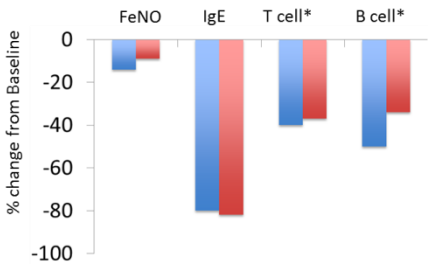


Response to therapies (severe reference subject)

Lebrikizumab (anti-IL13)[1]



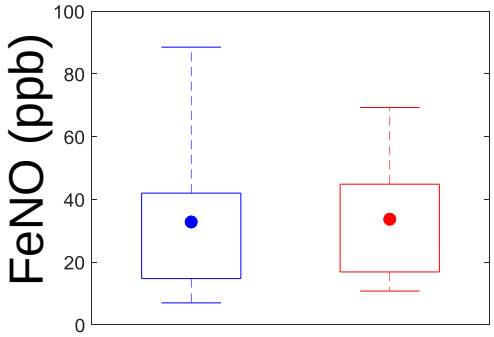
Omalizumab (anti-IgE)[2,3]

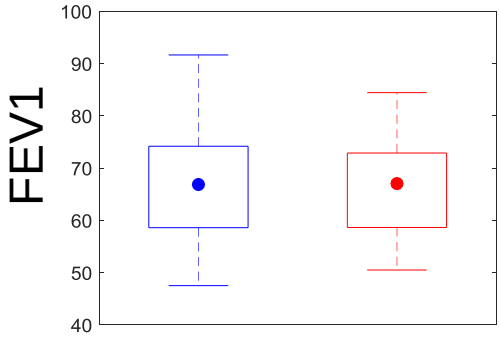


(1) Corren J et al. Lebrikizumab treatment in adults with asthma. N Engl J Med. 2011 Sep 22;365(12):1088-98
(2) Hanania NA, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med. 2011 May 3;154(9):573-82
(3) Djukanović R, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med. 2004 Sep 15;170(6):583-93

Stage 5: Variability at baseline and responses to intervention represented in virtual population

Baseline characteristics

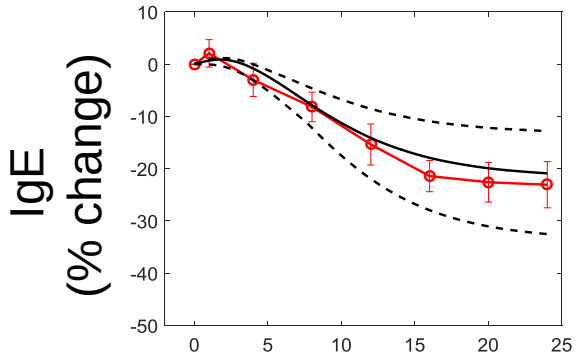


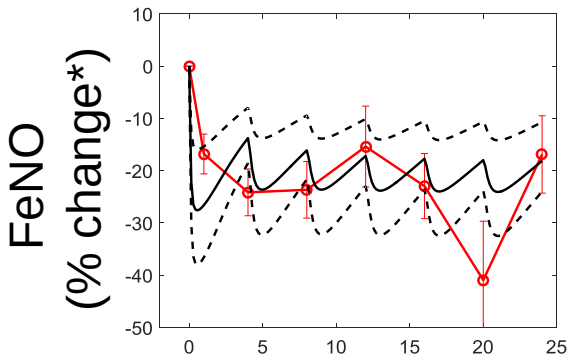


Blue: clinical data
Red: Virtual population

Solid circle is mean
Box is 25-75 percentile
Error bars is range

Response to interventions





Clinical data (response to anti-IL13)
Virtual population

Research application of this Asthma QSP model is presented in poster (IV-18) presented by Sid Sukumaran

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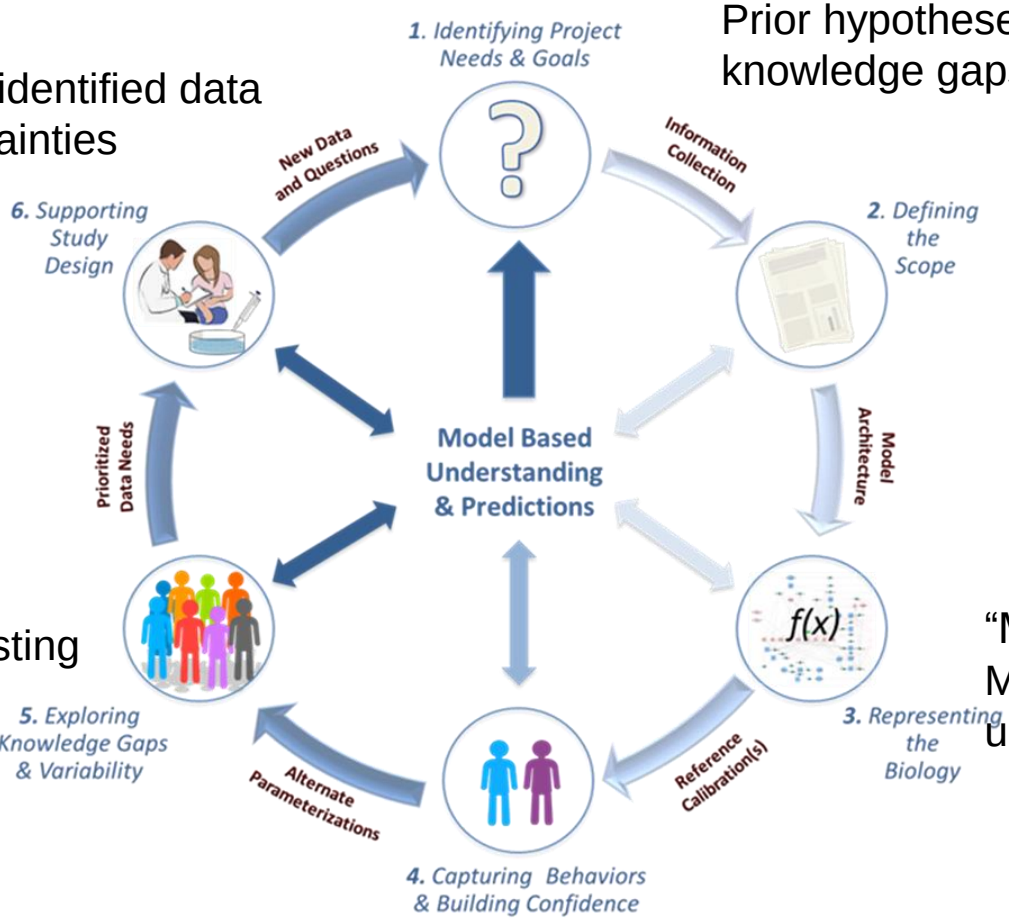
Don Mager

Workflow & Technical Methodologies:
Six Stages of QSP model development and Implementation

Addressing identified data gaps/uncertainties

Prior hypotheses and knowledge gaps



Data gaps and inconsistencies

Generating and testing Alternate solutions

"Mathematical" formulation
Mechanistic/topological uncertainty

Verifying structural model can capture key phenotypes/data within ranges of uncertainty and variability

Gadkar et al, CPT-PSP 2016

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Backup slides

What kinds of uncertainty and variability do we commonly encounter

Insufficient or imperfect mechanistic knowledge

- Alternate hypotheses? Conflicting data? Missing data?
- Translational relevance?

Quantitative uncertainty

- Lack of quantitative prior information on modeled entities and/or process parameters (e.g. what is the level or rate of X)

Known inter-subject or intra-subject (spatial or time) Variability

- Can be either qualitative or quantitative

Backup slides

Common distinguishing features of QSP approaches

- A coherent mathematical representation of key biological connections in the system of interest, consistent with the current state of knowledge
- A general prioritization of necessary biological detail over parsimony potentially including detail at the genetic, protein, cellular, tissue, organ, and whole-body scales
- Consideration of complex systems dynamics resulting from biological feedbacks, cross-talk, and redundancies
- Integration of diverse data, biological knowledge, and hypotheses
- A representation of the pharmacology of relevant therapeutic interventions
- The ability to perform quantitative hypothesis exploration and testing via biology-based simulation in virtual "subjects" (e.g., humans, animals, cells)

Ramanujan, Gadkar, Kadambi 2015

Frequently Asked Questions of QSP models in the context of uncertainty & variability

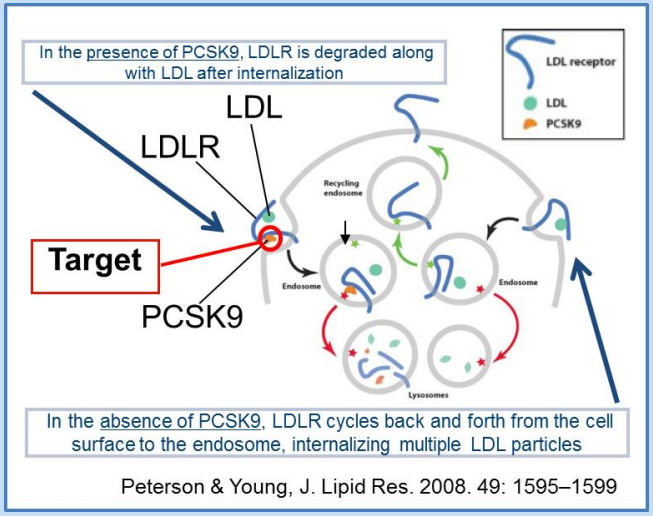
- *How can you build a model of biology we don't quite understand? What about competing hypotheses? Conflicting data?*

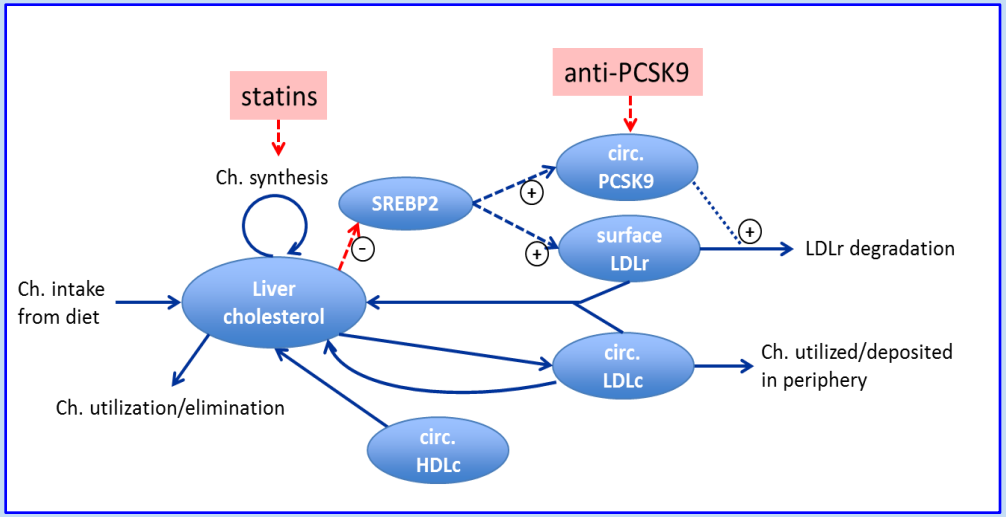
- *With enough parameters you can fit an elephant. The model is underspecified and the parameters are not identifiable.*

- *How do we evaluate and interpret this work? To what extent should we trust the predictions?*

Robust scoping effort determines the biology to be included in the QSP model & collection of diverse data sets for development

Model schematic developed from current knowledge & input from biology experts





Biological Mechanisms & Behaviors

- Untreated hepatic cholesterol balance
- LDLr synthesis/degradation including regulation by PCSK9
- LDL synthesis and uptake via LDLr
- SREBP2 regulation of PCSK9 & LDLr expression
- Anti-PCSK9 binding of PCSK9
- Statin inhibition of cholesterol synthesis

Available data

Preclinical data

- Impact of pcsk9 on LDLr in vitro
- Regulation of pcsk9 and LDLr via SREBP2 in vitro
- LDLr specific vs non-specific LDL clearance in animal models

Patient populations

- pcsk9 & LDLc levels in dyslipidemia, familial hypercholesterolemia
- Kinetics of hepatocyte cholesterol regulation, apoB-100 particle dynamics, etc

Statin clinical data (Jupiter & TNT studies)

- Change in LDLc with statins
- Changes in pcsk9 levels on statins and correlations with other biomarkers

Anti-pcsk9 clinical data (Genentech Phase I study)

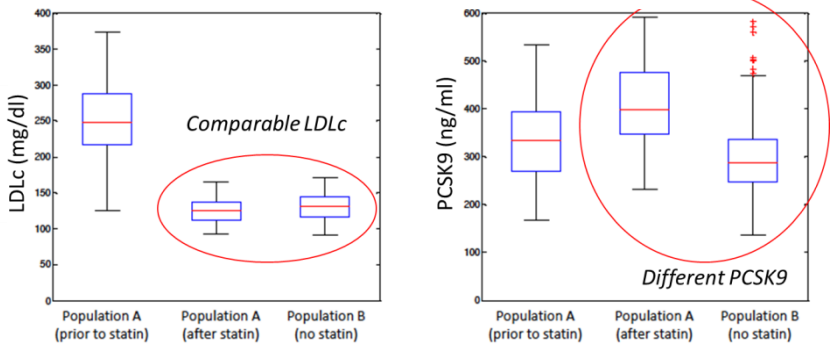
- Phase I clinical data for anti-pcsk9, total pcsk9, LDLc profiles for monotherapy and combo with statins

Virtual Populations to address impact of background statin therapy to response to anit-PCSK9 and support trial design

- Inclusion criteria for Phase II available for Virtual Population development
  - Expected LDLc for clinical population: Mean ±SD = 125 ± 25 mg/dL
  - Patients with/without statin background expected (two Vpops developed)
- Variability in response (both LDLc & PCSK9) to statin treatment for clinical population available

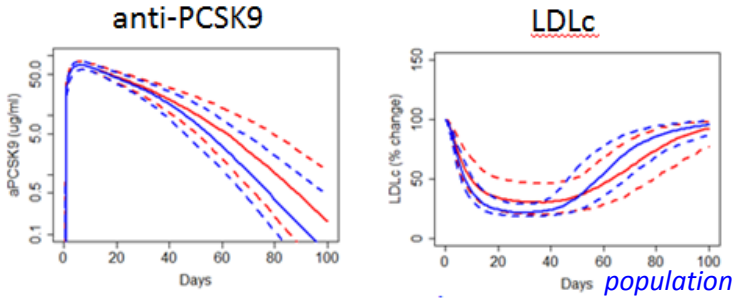
Virtual population: development

Baseline measures for virtual populations



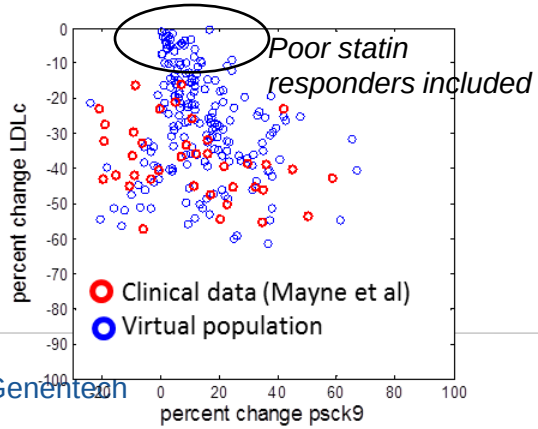
Virtual population: application in research

Evaluation of statin background on response to anti-pcsk9

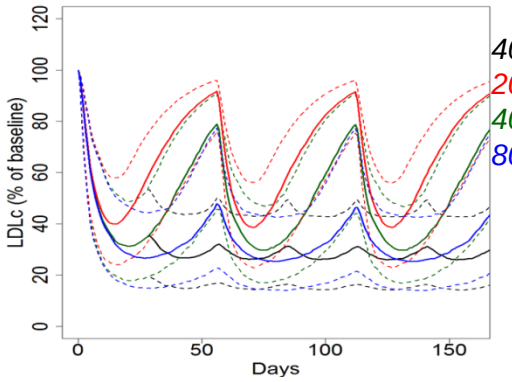


population A, statin background
population B, no statin

Response to low dose atorvastatin



Predictions for proposed Phase II dosing protocols



400 mg Q4W
200 mg Q8W
400 mg Q8W
800 mg Q8W

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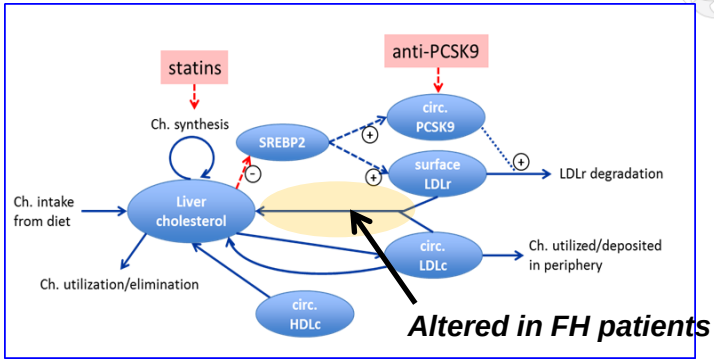
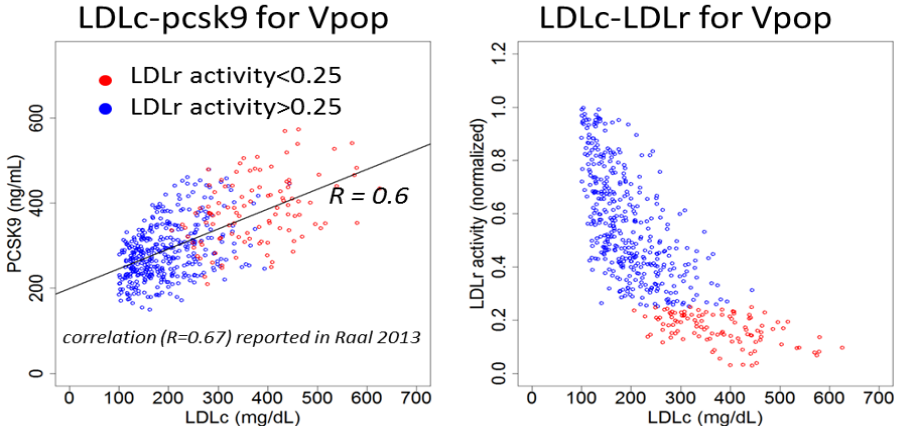
Virtual Populations developed to evaluate response to anti-PCSK9 for a specific patient sub-phenotype

- The most common genetic defects in Familial hypercholesterolemia (FH) patients are *LDLr* mutations
  - Function LDLr activity in heterozygous FH is 10-25%
  - Function LDLr activity in homozygous FH is <5%
- FH patients have high LDLc levels
- Correlations of baseline LDLc & PCSK9 levels reported in literature (Raal et al. 2003)

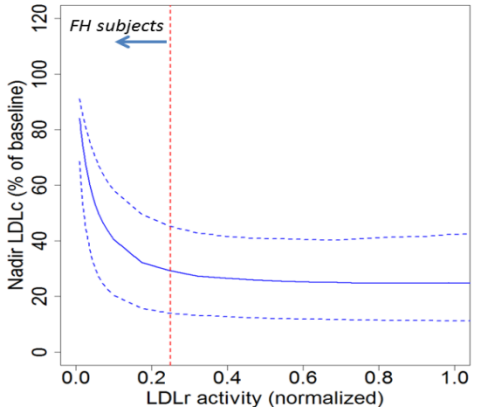


Virtual population: development



- Range of clinical measures (LDLc, PCSK9) at baseline consistent with expected enrollment in potential clinical study

Virtual population: application in research



- QSP model predicts that response to anti-pcsk9 is compromised for FH subjects with LDLr activity less than 10% of normal

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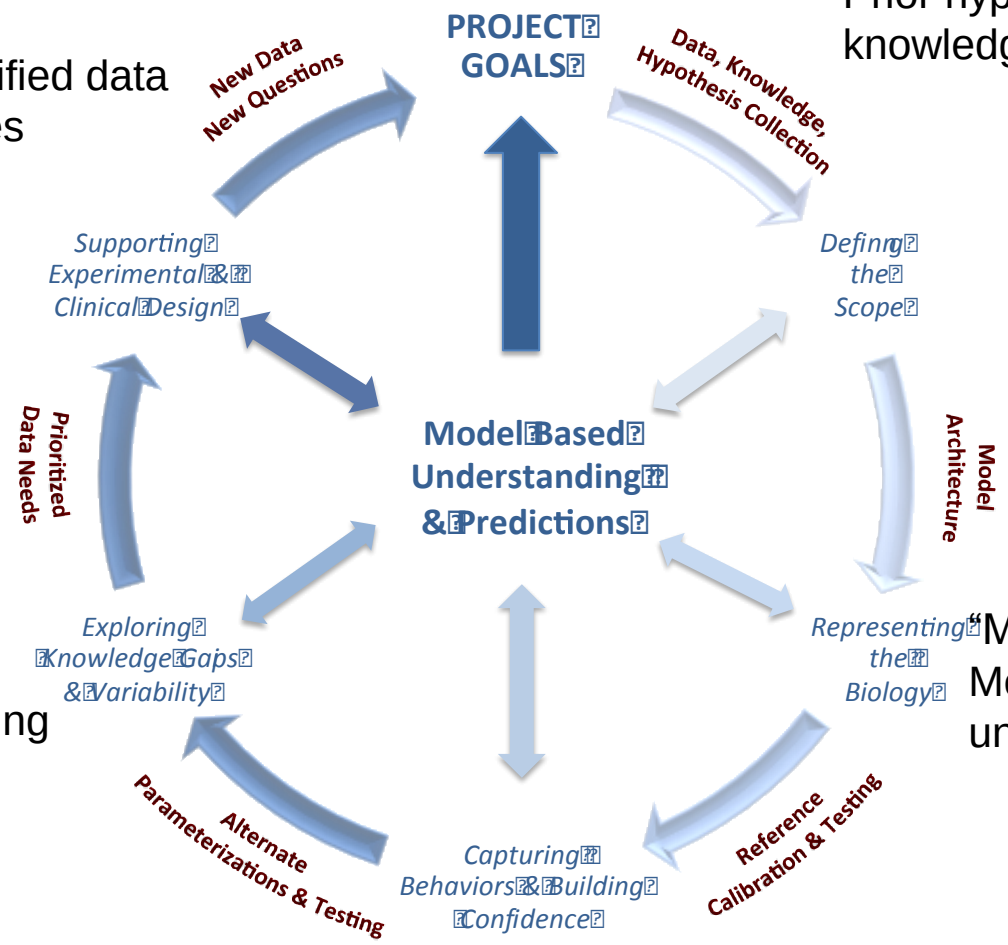
Workflow & Technical Methodologies: Six Stages of QSP model development and Implementation

Prior hypotheses and knowledge gaps

Addressing identified data gaps/uncertainties



Data gaps and inconsistencies

"Mathematical" formulation
Mechanistic/topological uncertainty

Generating and testing Alternate solutions

Verifying structural model can capture key phenotypes/data within ranges of uncertainty and variability

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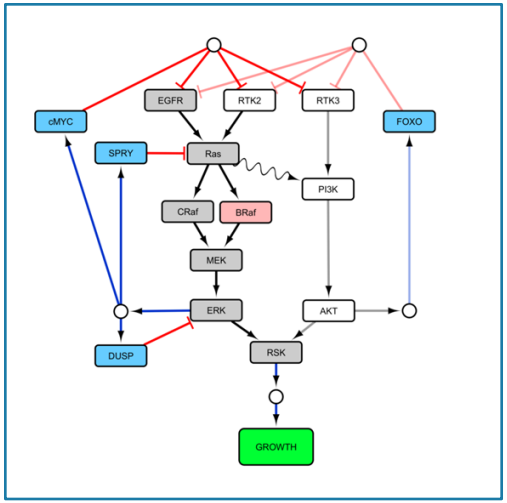
Quantitative Systems Pharmacology: Terminology for this talk

Term	Definition	Attributes
QSP Model (for tools described in this presentation)	ODE based: $\dot{X} = f(X,p,t)$ Logic/algebraic based: $X = f(X,p,t)$	X: states/species p: parameters
Physiological Outcome	Any quantity calculated from model for which experimental data available	
Virtual Subject	A single parameterization of the model	All physiological outcomes are within available data
Reference Subject	A Virtual Subject that exhibits simulated behaviors representative of a specific phenotype	
Virtual Cohort	A collection of virtual subjects	
Virtual Population	A collection of virtual subjects that is selected to match a “real” population	A subset of the Virtual Cohort that is selected or weighted to match statistical properties of experimental or clinical data
Statistical (prevalence) Weighting	Assignment of weights to different Virtual Subjects in a Virtual Population	The resulting weighted simulation results capture statistical features of experimental data
Variability	Subject to subject differences in mechanistic biology and/or phenotypic behaviors	
Uncertainty or Knowledge Gap	Areas of qualitative or quantitative uncertainty in mechanistic biology, phenotypic profiles	

Case studies demonstrate implementation of proposed QSP workflow for Virtual Population

MAPK signaling model

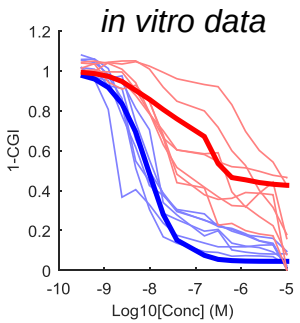
- 15 states; 35 parameters
- Model developed primarily using in-vitro & preclinical data sets:
  - Protein signaling dynamics (e.g. pERK, pMEK) in response to inhibitor treatment in vitro
  - In vitro cell growth responses to inhibitors across panels of genetically diverse cell lines
  - In vivo (xenograft) responses to drug combos
- Limited clinical data available: Patient-level tumor growth response data from Phase1 clinical trials

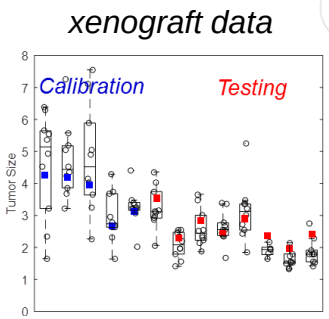


Kirouac, ACoP 2015

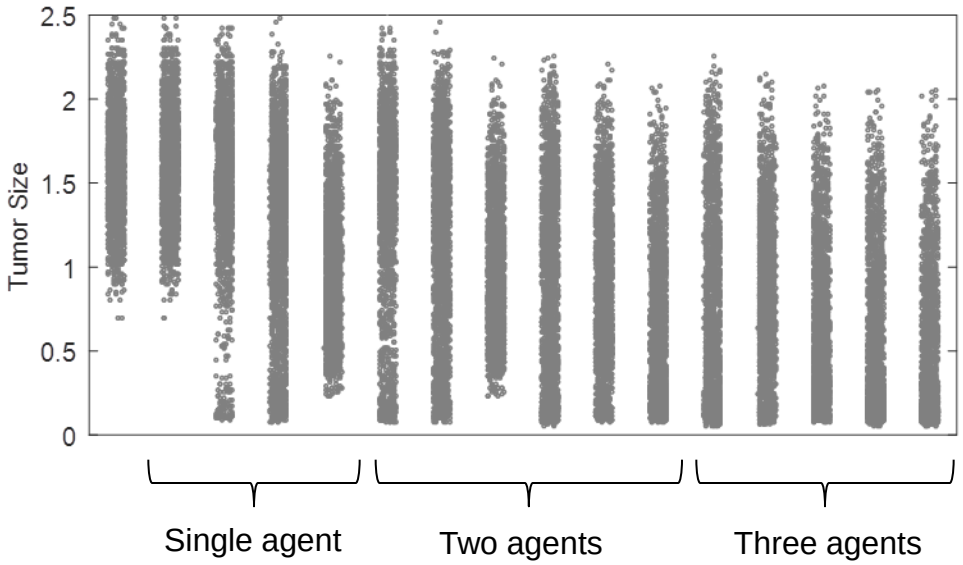
Comparison across multiple single and combination therapies for MAPK pathway inhibitors

- Model developed using in-vitro & preclinical data
- Model translation to predict tumor size for a clinical population
  - Uncertainty in translation included
  - Greater intersubject tumor heterogeneity
  - Pharmacokinetic variability included





Representative figures for model calibration & testing



- *Limited confidence in predictive capability with Virtual Cohort*

- *Virtual Subjects*

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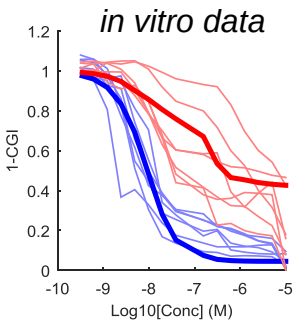

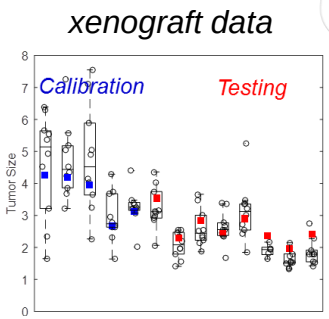

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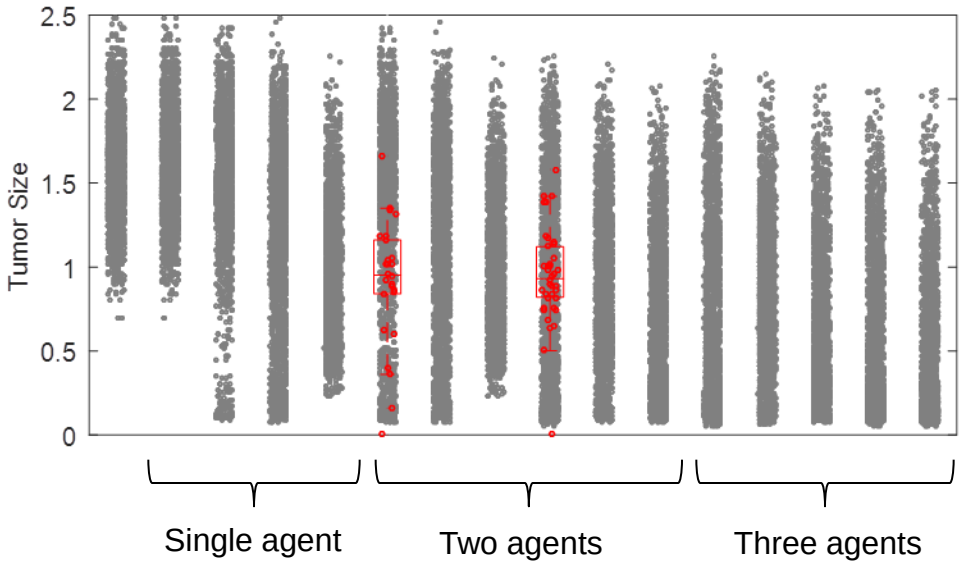

- *Limited confidence in predictive capability with Virtual Cohort*
- *Clinical data available for two protocols utilized for weighting to generate the Virtual Population*

- *Virtual Subjects*
- *Clinical data*

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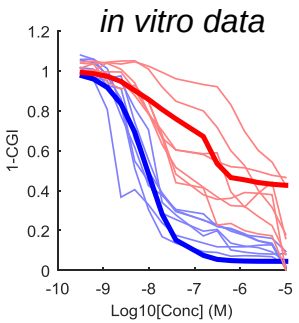

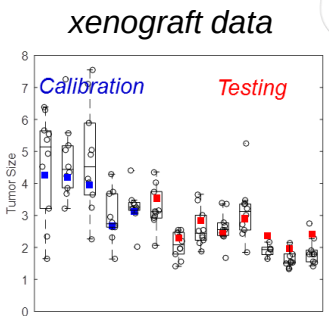

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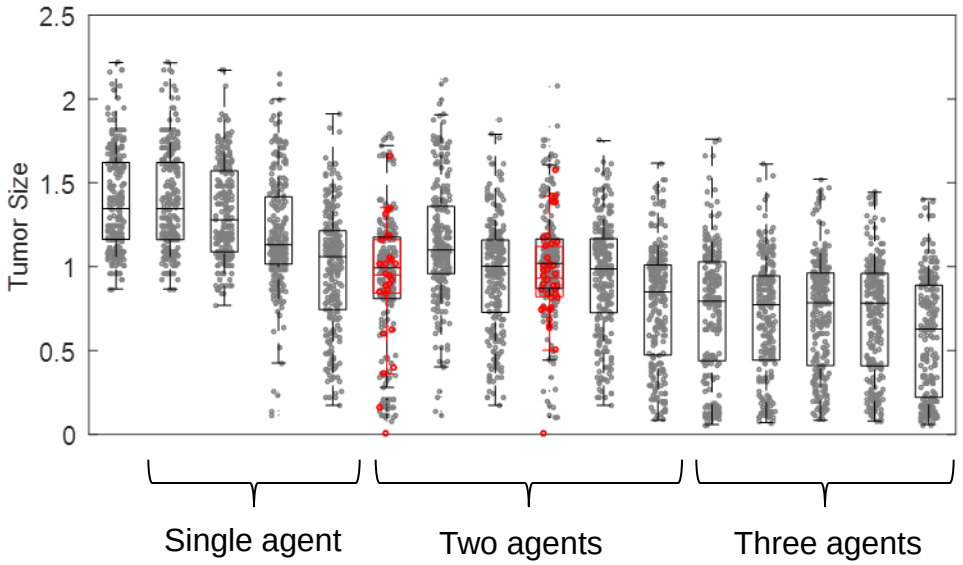

- *Limited confidence in predictive capability with Virtual Cohort*
- *Clinical data available for two protocols utilized for weighting to generate the Virtual Population*
- *Increase in quantitative confidence in predictions with Virtual Population*

- *Virtual Subjects*
- *Clinical data*

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