Context-Dependent Assessment of QSP Models: *industry perspective & a proposed approach*

ASCPT 2019 - QSP preconference

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A Flexible Approach for QSP Model Assessment

Rationale for "Assessment Approach"

- Need ways to *assess confidence* in model predictions and appropriate interpretation/use
- Need a *common approach* to support broad applicability and consistent use and interpretation

But this must also be:

- *Consistent* with and synthesized from existing best practices in QSP
- *Customizable* to the diversity of applications of interest ("context") & modeling approaches

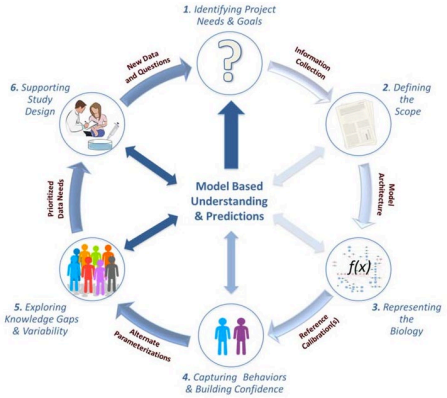
Subgroup of IQ consortium CPLG-QSP reviewed/discussed past models, guidances, etc to distill an overarching flexible approach for context-dependent assessment of QSP models

- *invited perspective piece submitted to CPT-PSP special issue*

Build on Current Guidances & Best Practices

Workflow Stages

1. Identifying goals
2. Defining scope
3. Representing biology
4. Capturing behaviors
5. Exploring variability
6. Supporting studies



Qualification Criteria

- **Relevance**
- **Uncertainty**
- **Variability**
- **Data**

[1]*Gadkar et al, 2016, CPTPSP*
[2]*Friedrich, 2016, CPTP-PSP*

Different “Areas” of QSP Models Require Assessment

Workflow Stages

1. Identifying goals
2. Defining scope
3. Representing biology
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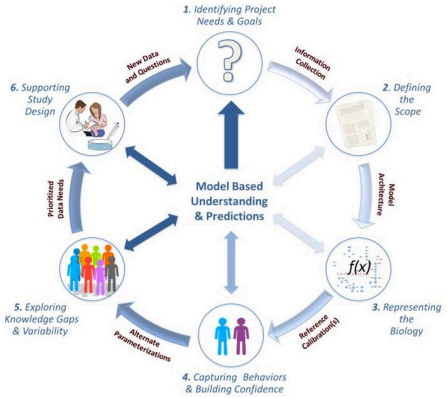

Qualification Criteria

- Relevance
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[1]Gadkar et al, 2016, CPTPSP
[2]Friedrich, 2016, CPTP-PSP

Assessment Areas

Biology (1-2)	• Are the biological mechanisms, hypotheses, and data relevant to the question at hand considered? • Are the assumptions and hypotheses plausible and appropriate? • Are alternate hypotheses considered?
Implementation (3)	• Are the model structure and parameter ranges appropriate for the question at hand? • Was there technical QA/QC of the implementation and testing of the model structure? • Can the model capture the appropriate range of behaviors?
Simulation (4-5)	• Does the model exhibit appropriate behaviors and sensitivities to parameters or perturbations? • Does the model reproduce “calibration/training” data? • Can the model predict behaviors or data it was not calibrated against (validation/testing)?
Robustness (5-6)	• Has the robustness of the predictions to potential biological uncertainty and variability been explored?

Different “Areas” of QSP Models Require Assessment

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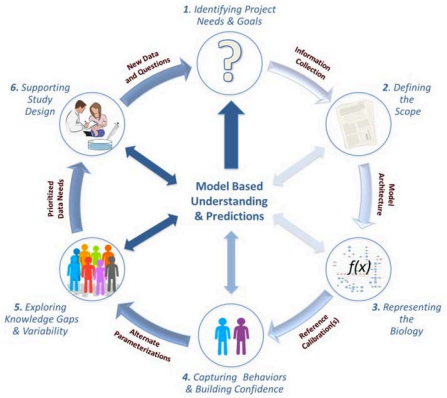


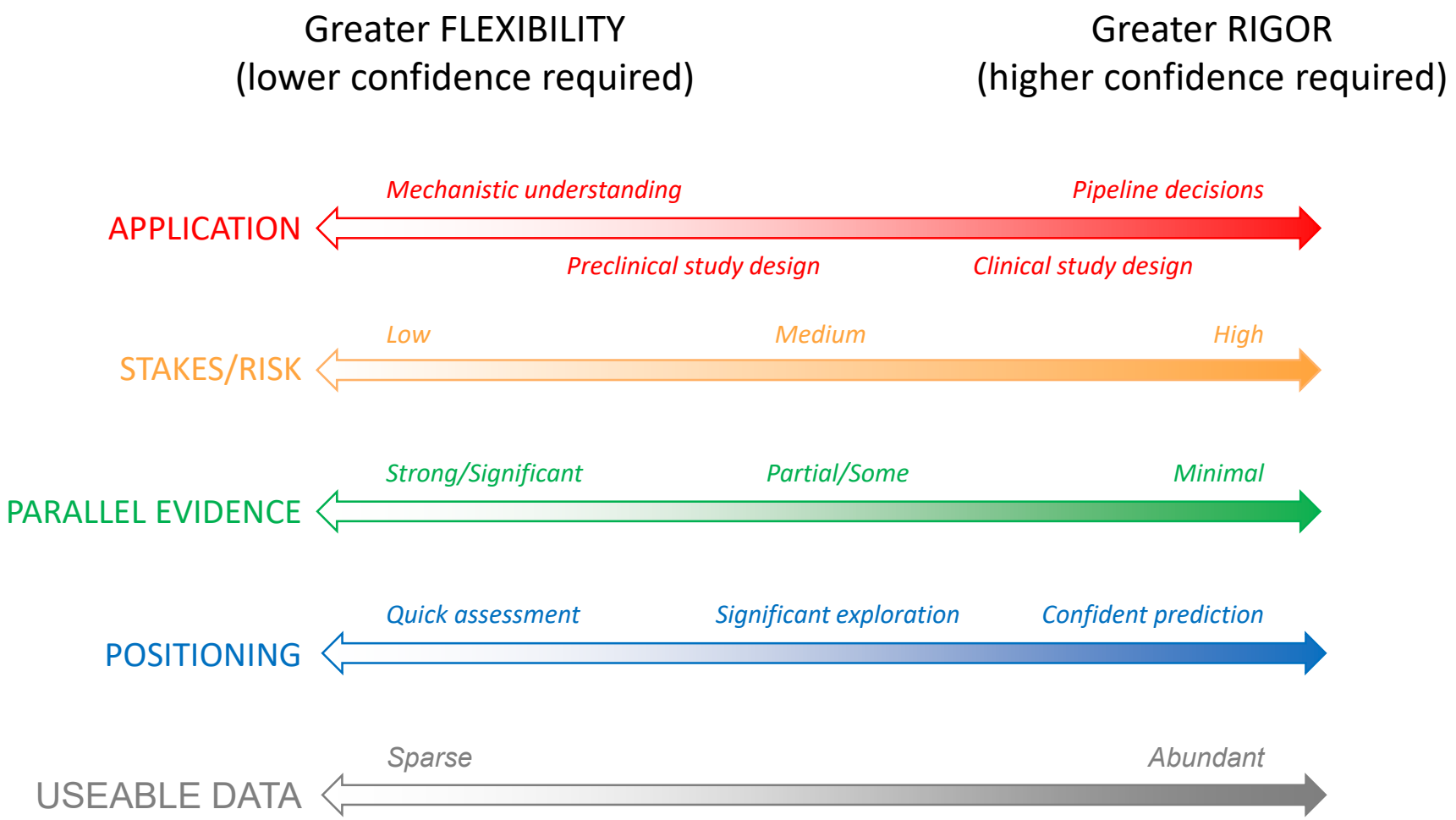
Qualification Criteria

- **Relevance**
- **Uncertainty**
- **Variability**
- **Data**

Assessment Areas

Biology (1-2)	Biological relevance & plausibility
	Main hypotheses & assumptions
	Alternate hypotheses
Implementation (3)	Technical QA/QC
	Model structure & parameter ranges
Simulation (4-5)	Sensitivities and behaviors
	Reproduction of behaviors (calibration/training)
	Prediction of behaviors (validation/testing)
Robustness (5-6)	Predictions, variability and uncertainty

Assessment MUST Be Context-Dependent



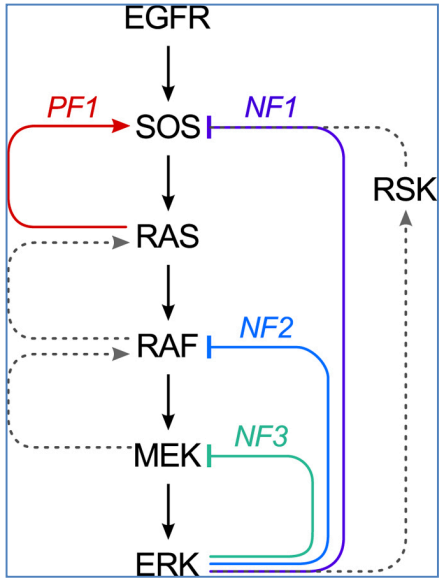
Assessment of Model Biology & Implementation

	Focus	Assessments
BIOLOGY *(1-2)*	Relevance & plausibility	• Appropriate goal/questions • Biological rationale and justification • Literature evidence • Biology/therapeutic area expert endorsement
	Main hypotheses, assumptions	
	Alternate hypotheses	

	Focus	Assessments
IMPLEMENTATION *(3-4)*	Technical QA/QC	• Appropriate modeling formalism • Appropriate representation of biology • Correct implementation: scripts to test equations, parameters, units • Appropriate and stable numerical approach
	Model structure & pameter ranges	• Dynamical features • Potential range of behaviors/outputs • Relevant range of parameters/inputs
	Sensitivities and behaviors	• Targeted/specific sensitivity • Local sensitivities (Local SA) • Global sensitivities (Global SA) • Qualitative phenotypes • Literature support, expert input on results

MAPK: Different questions require different implementations

Signaling feedbacks and complex dynamics of MAPK



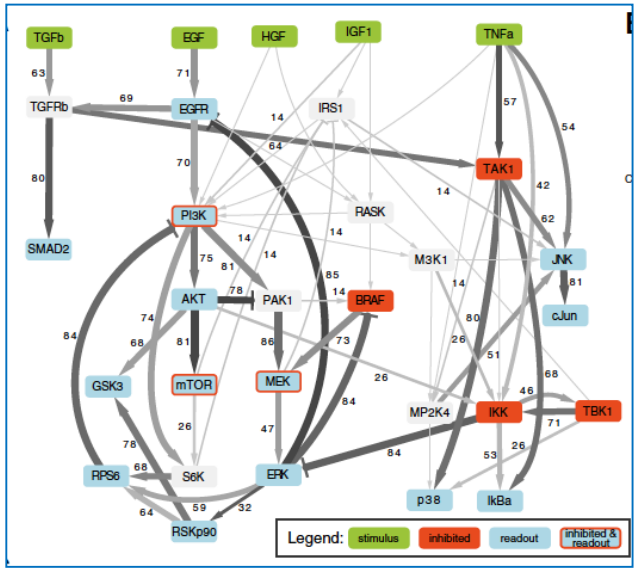
Kochańczyk et al 2017, Sci Reports

Focus: dynamical behaviors

Formulation:

- ODE for feedback dynamics
- Markov chain w stochastic for noise
- PDE for spatiotemporal exploration

Pathways influencing drug resistance in CRC



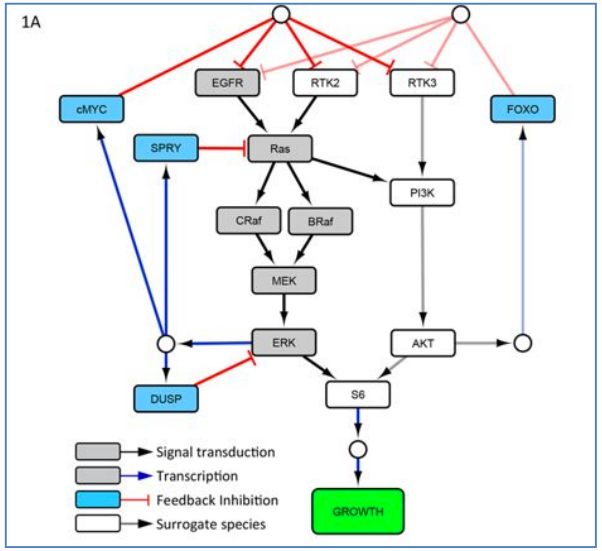
Eduati et al 2017, Cancer Res

Focus: pathways leading to resistance

Formulation:

- Logic-ODE for signaling
- elastic-net model connects to growth

Clinical MAPK targeting/rebound in BRAFmut CRC



Kirouac et al 2017, NPJ Sys Bio & App

Focus: clinical response & resistance

Formulation:

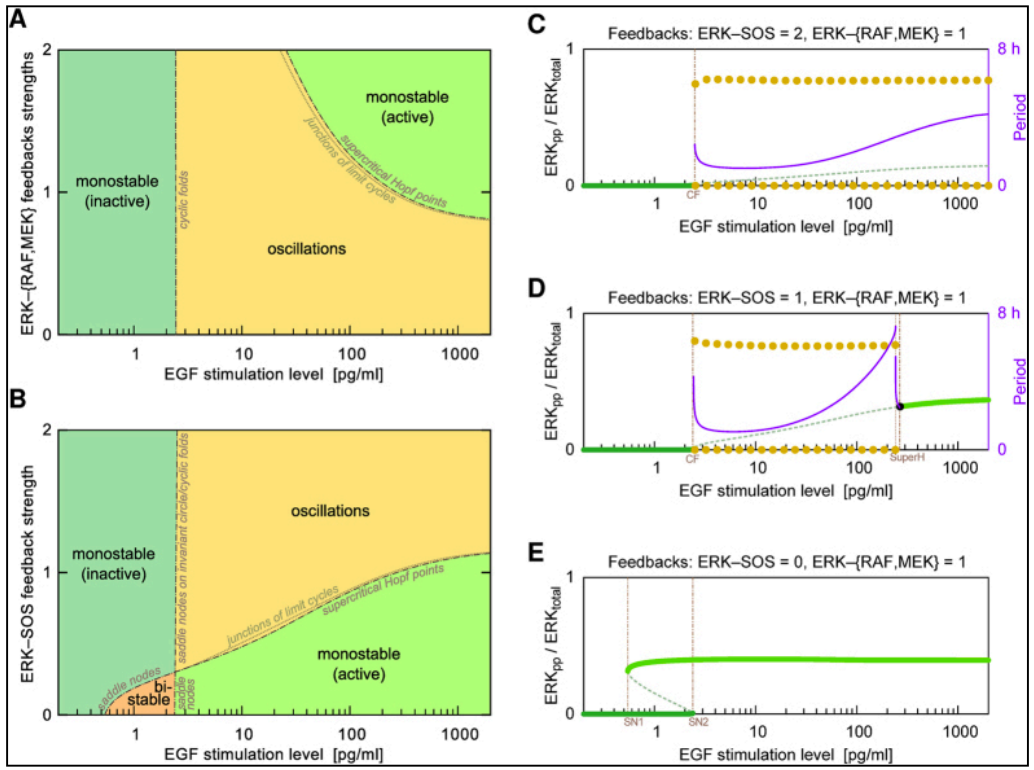
- Algebraic + ODE for signaling;
- ODE for growth

Model & Parameter analyses probe range of behaviors

- *Dynamical and/or equilibria analysis:* to assess dynamical behaviors
- *Parameter sensitivity:* to assess feasible "outcomes" and dependencies
- *Topology and network analysis:* to identify "hubs", modularity, connectivity, redundancies, etc
- *Model reduction:* to simplify model structure

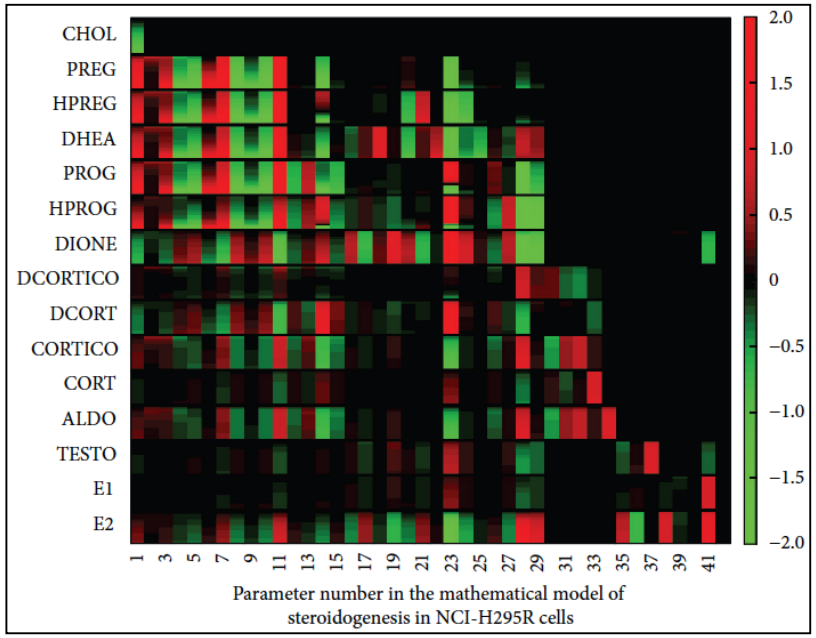
Dynamical analysis

Kochańczyk et al , Sci Reports 2017



Sensitivity analysis

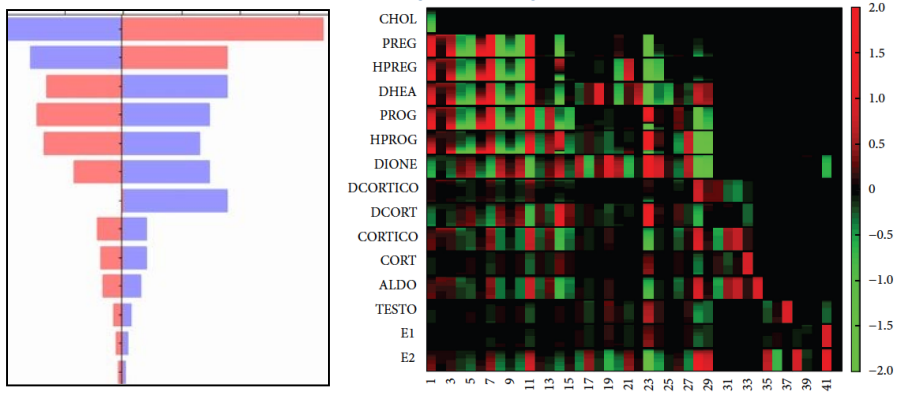
Saito et al J Tox 2016



Assessment of Model Simulation

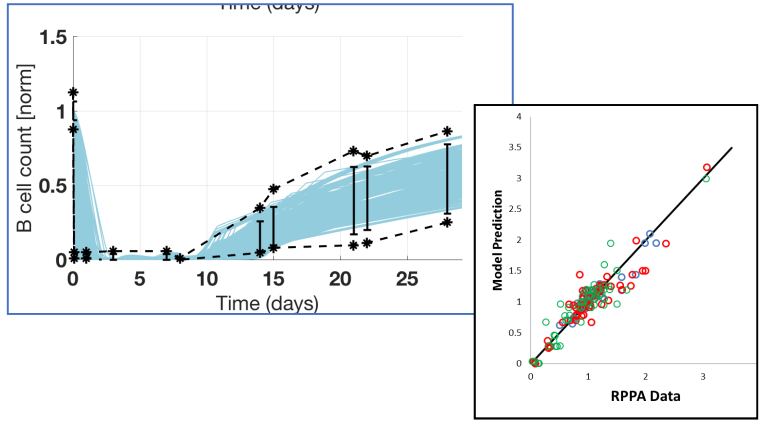
	Assessment Focus	Specific Assessments
SIMULATIONS *(4-5)*	Sensitivities and behaviors	• Targeted/specific sensitivity • Local sensitivities (Local SA) • Global sensitivities (Global SA) • Qualitative phenotypes • Literature support, expert input on results
	Reproduction of behaviors (calibration/training)	• Qualitative or quantitative comparison to calibration data (subsystem or system level)
	Prediction of behaviors (validation/testing)	• Qualitative or quantitative comparison to validation data (subsystem or system level)

Sensitivity analysis



Saito et al , J Tox 2016

Calibration

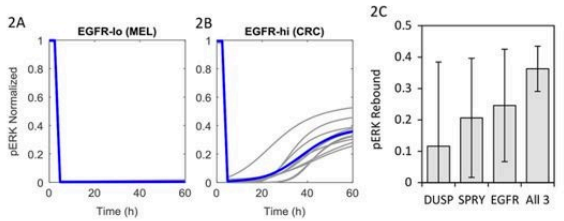


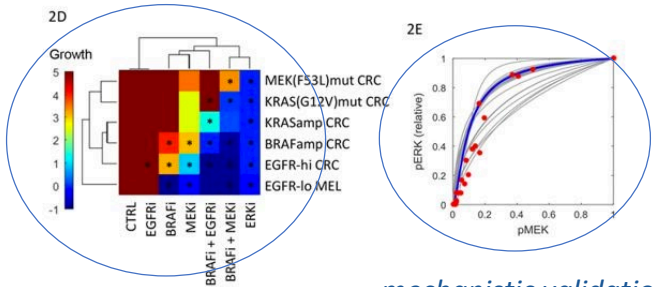
Validation

Lemaire, ASCPT 2019

Sensitivity, calibration, validation test fidelity to data/knowledge

In vitro signaling & growth



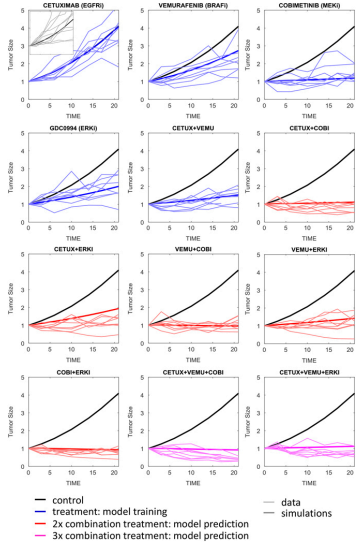


mechanistic validation

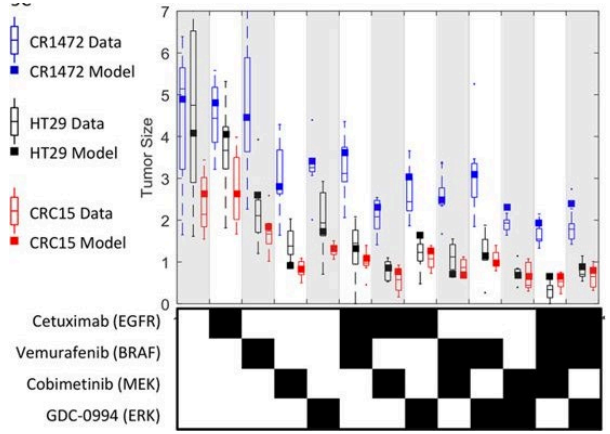
Sensitivity, calibration, validation

In vivo growth

calibration & validation of kinetics

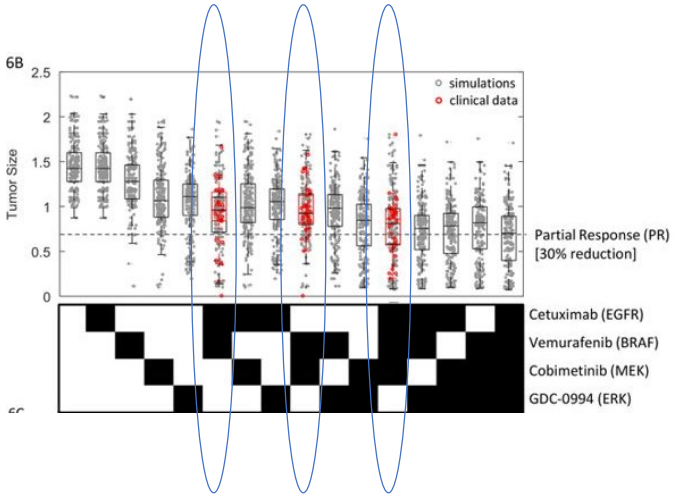


parameter exploration & preclinical variability

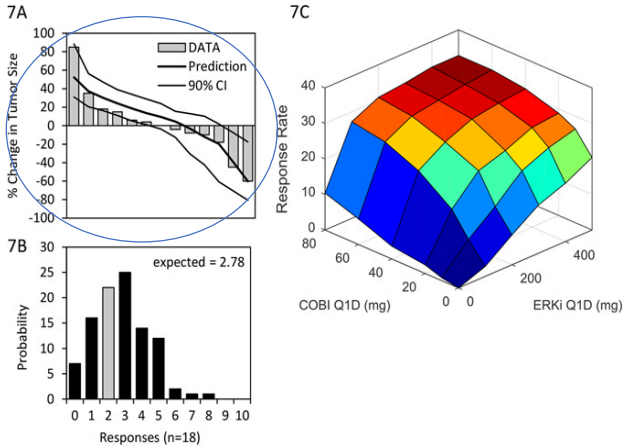


Clinical tumor response

parameter exploration & clinical calibration



Clinical validation

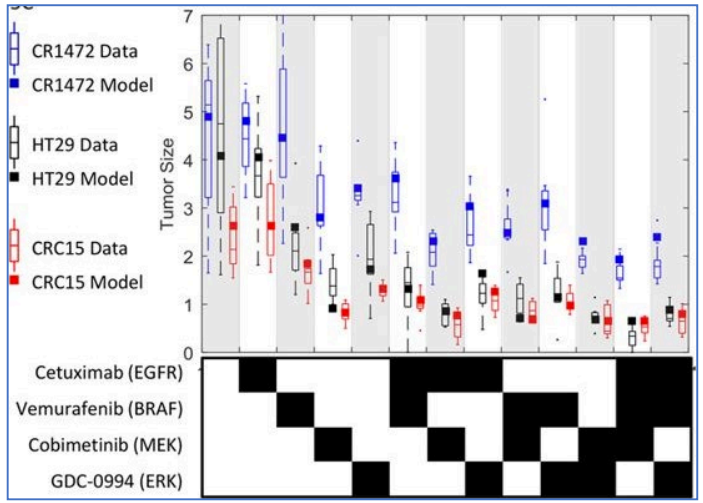


Kirouac et al 2017, NPJ Sys Bio & App

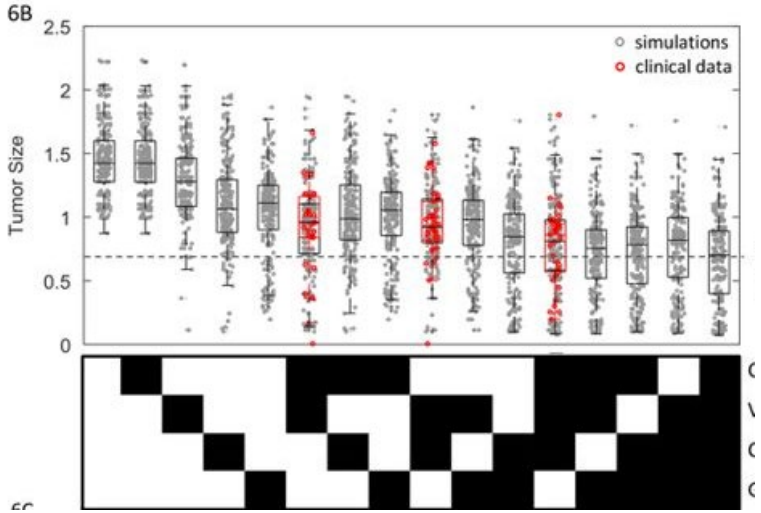
Assessment of Robustness of Predictions

	Assessment Focus	Specific Assessments
ROBUSTNESS *(5-6)*	Predictions, variability, and uncertainty	• Comparison of input/output range, distribution, etc. with data • Results with alternate parameterizations or structures

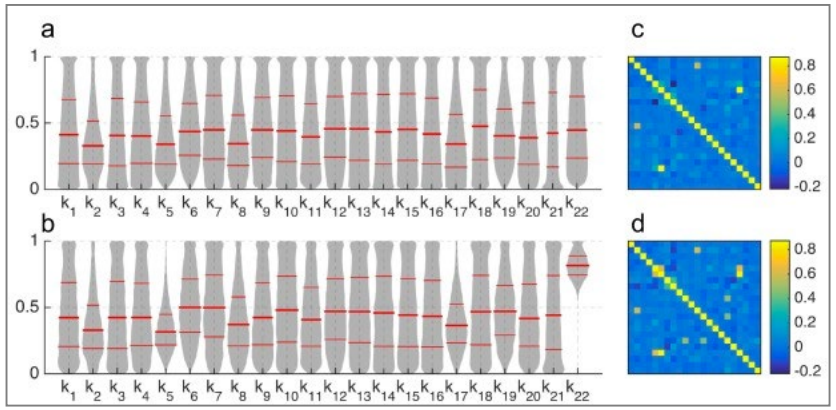
Virtual subjects for alternate phenotypes



Virtual populations: output variability



Virtual populations: Input variability



Allen et al, 2016, CPT-PSP

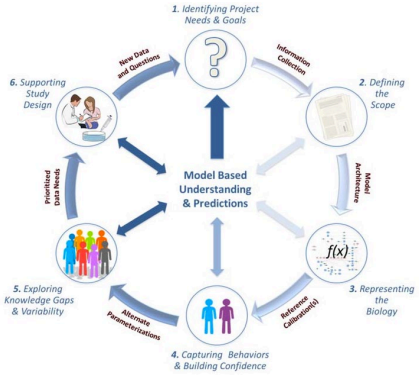
Kirouac et al 2017, NPJ Sys Bio & App

ASSESSMENT AREA *(workflow stage)*	ASSESSMENT APPROACH		
	Assessment Focus *(colored by MQM criteria)*	Specific Assessments	Reporting
BIOLOGY *(1-2)*	Relevance & plausibility Main hypotheses, assumptions Alternate hypotheses	• Appropriate goal/questions • Biological rationale and justification • Literature evidence • Biology/therapeutic area expert endorsement	• Documentation • Model schematic
IMPLEMENTATION *(3-4)*	Technicl QA/QC	• Appropriate modeling formalism • Appropriate representation of biology • Correct implementation: scripts to test equations, parameters, units • Appropriate and stable numerical approach	• Documentation • Detailed model diagram • Model equations • Variable list (definitions, units, constraints) • Parameter list (definitions, units, ranges, refs.) • Test scripts & results • Model file (executable)
	Model structure & parameter ranges	• Dynamical features • Potential range of behaviors/outputs • Relevant range of parameters/inputs	• Graphical results • Documentation/lists
	Sensitivities and behaviors	• Targeted/specific sensitivity • Local sensitivities (Local SA) • Global sensitivities (Global SA) • Qualitative phenotypes • Literature support, expert input on results	• Documentation of approach & interpretation • Tornado plots, heat maps, or similar • List of critical sensitivities & how they are explored for predictions • Example simulation plots
SIMULATIONS *(4-5)*	Reproduction of behaviors (calibration/training)	• Qualitative or quantitative comparison to calibration data (subsystem or system level)	• List of calibration experiments • Plots comparing simulation vs data (eg VPCs) • Criteria metrics if used
	Prediction of behaviors (validation/testing)	• Qualitative or quantitative comparison to validation data (subsystem or system level)	• List of validation experiments • Plots comparing simulation vs data (eg VPCs) • Criteria metrics if used
ROBUSTNESS *(5-6)*	Predictions, variability, and uncertainty	• Comparison of input/output range, distribution, etc. with data • Results with alternate parameterizations or structures	• Tabular or graphical comparison of simulated vs data variability • Graphs of variability in input (parameters) and outputs (typically states) • Documentation of critical uncertainties & variabilities

REPORTING: "Best Practices to Maximise Reuse of QSP Models: Recommendations of UK QSP Network"

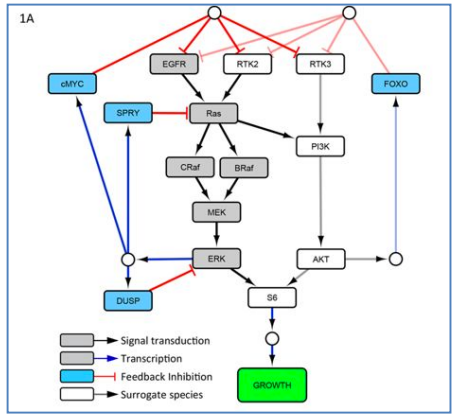
Cucurull-Sanchez et al CPT-PSP 2019, pre-print

QSP Workflow Step		Recommendations: Mathematical	Recommendations: Computational	Relevant References
1. Purpose and Context of the Model		• Ask 'Do I need a model?' and 'What is the purpose of the model?' • Engage with stakeholders: 'end users' and 'domain experts' • Formulate clearly the questions addressed, their context, expected impact of the decisions derived from the model, and rationale for the selection of QSP as modelling methodology		[11] Peterson & Riggs (2015) [26] Timmis et al. (2017) [27] Ribba et al. (2017) [28] Gadkar et al. (2016) [29] Friedrich (2016)
2. Model structure and modelling methodology	i. Model domain and general structure	• Define clearly the model domain: therapeutic area, biological scale, biological/clinical system • Provide a schematic representation of the model domain and general structure (e.g. Figure 2) • Whenever possible, follow standard graphical notation (e.g. SBGN)		[28] Gadkar et al. (2016) Figure 2 [34] Le Novère et al. (2009)
	ii. Model formulation or algorithm	• Provide all equations and boundary conditions (e.g. Box 1) • Explain all the ter… biological/pharmacologica… • Explain any abstr… • Report units for e…	• Clearly state the algorithm using …	Box 1 [26] Timmis et al. (2017)
	iii. Model solving and simulation method	• State the method… system of equations (e.g. … order implemented via th… MATLAB®) • Provide absolute… value • Provide software…		
	iv. Code files	• Share code and m… ○ supplementary m… ○ public online mo… ○ public platforms … • Ensure code is ea… • Whenever possib…		
3. Input data, knowledge and assumptions going into the model		• Use input data from systems under experimental conditions as relevant as possible to the system being modelled • Provide a detailed model parameter description, including: ○ symbol/name of parameter ○ definition ○ parameter value (or range of values) ○ units ○ sources used to obtain it (literature citation, database, derivation from other parameters, experiment presented in the same report/article, in silico estimations, etc) ○ details of how the parameter value was determined (measured directly, fitted or assumed) and whether the underlying data has any limitations (suspected errors, outliers, high variability, excluded data points, etc) • Consider using a tabular format to present this information (e.g. Table 1) • Consider providing actual data files along with code files (see section 2.iv) • Describe in detail: ○ qualitative and/or semi-quantitative knowledge obtained first-hand from stakeholders ○ assumptions (pharmacological, physiological, disease, data, mathematical, statistical), and how they were tested • Discuss potential limitations of model in the context of available input data, knowledge and assumptions	Table 1 [38] Sarkans et al. (2017) [39] Marshall et al. (2016) [27] Ribba et al. (2017) [40] Bonate et al. (2012)
4. Model verification		• Test code for consistency: ○ eliminate detected coding errors ○ ensure solutions or limit conditions reached by the model are correct (e.g. A + B -> C yields no C when A and B are set to zero) • … • respon… • i.e. not… input c… ○ identif… ○ param… • to defi… model •		[41] Anderson et al. (2007) [43] Hicks et al. (2015) [65] Nestorov et al. (1999)
5. Model validation		• Describe and clearly reference the data or knowledge used to validate the model, and explain its relevance to the model context • Plot model simulations overlaying the corresponding experimental data onto them, with measures of potential/perceived variability (e.g. standard error bars, confidence intervals, shadows from ensemble simulations)		[41] Anderson et al. (2007) [43] Hicks et al. (2015) [70] Lu et al. (2014) [71] Kanodia et al. (2014) [72] Ortega et al. (2013 [73] Karelina et al. (2012) [74] Peterson and Riggs (2012) [76] Agoram (2014)
6. Model results, application and impact		• Articulate a clear answer to the questions originally posed for the model (see section 1) • Provide the simulation plots and/or outcome numerical values that underpin those answers • Qualify the type of knowledge acquired through the modelling exercise: a positive new discovery, a confirmation and/or a learning of a misconception. • Describe the decisions that the modelling exercise enabled for the different stakeholders (user, domain expert, academic, industry, regulatory) - qualitatively and, whenever possible, quantitatively • Describe the impact of the QSP modelling exercise beyond the initial stakeholders, especially if impact is societal and/or can be translated into financial figures.		[39] Marshall et al. (2016) [77] Sheppard (2011) [11] Peterson & Riggs (2015) [75] Hendricks (2013) [78] Kansal & Trimmer (2005) [79] Milligan et al. (2013) [80] Allerheiligen (2014) [81] Bueters et al. (2013) [82] Nayak et al. (2018)

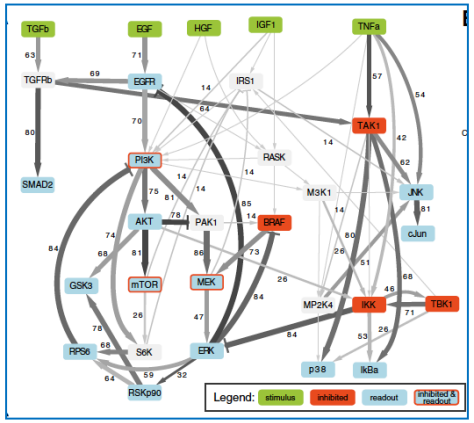


Different contexts, Different models

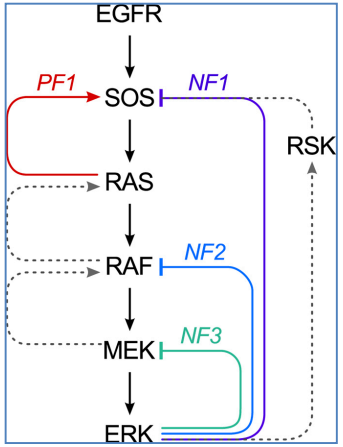
1 Clinical MAPK targeting & rebound in BRAFmut CRC



2 Pathways influencing CRC drug resistance



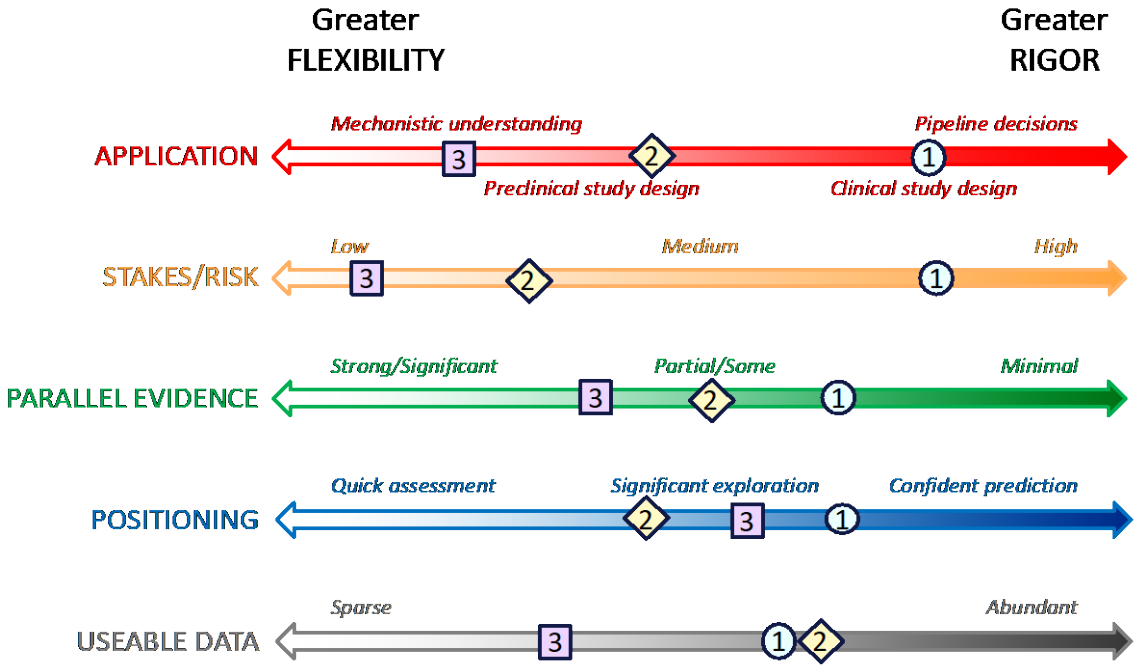
3 Complex dynamics of MAPK w feedbacks



1: *Kirouac et al 2017, NPJ Sys Bio & App*

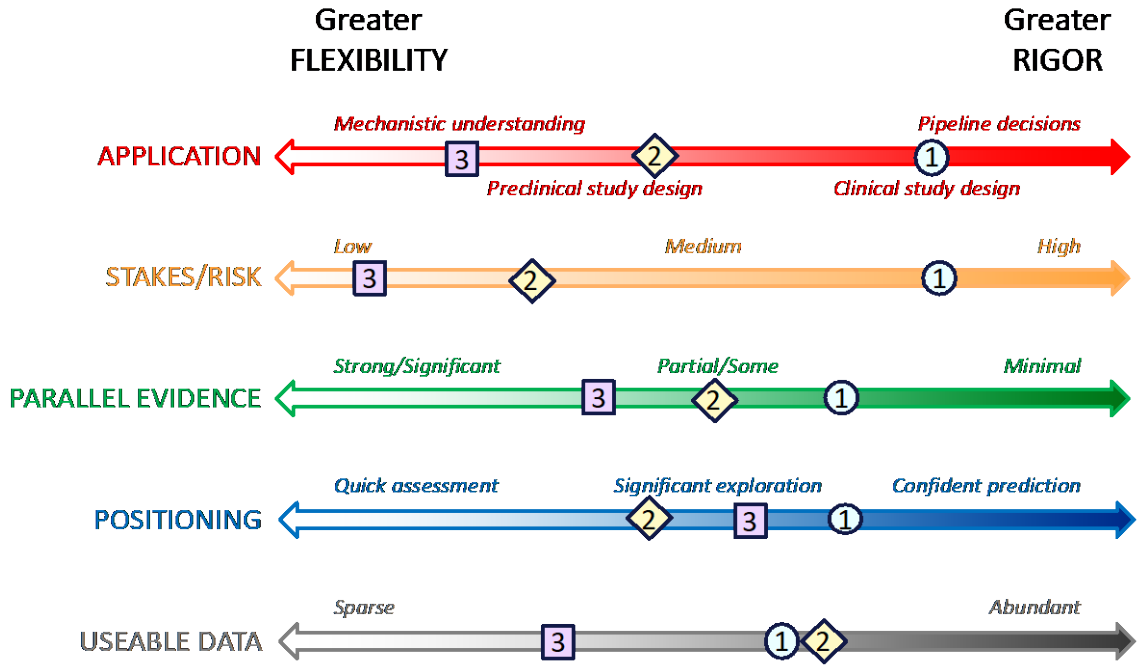
2: *Eduati et al 2017, Cancer Res*

3: *Kochańczyk et al 2017, Sci Reports*



Different contexts, Different models, Different assessment

ASSESSMENT AREA	ASSESSMENT APPROACH: Assessment Focus	1	2	3
BIOLOGY	Relevance & plausibility	hi	hi	hi
	Main hypotheses & assumptions	hi	hi	hi
	Alternate hypotheses	med	hi	hi
IMPLEMENTATION	Technical QA/QC	hi	hi	hi
	Model structure & parameter ranges	hi	hi	hi
SIMULATIONS	Sensitivities and behaviors	med	med	hi
	Reproduction of behaviors (calibration/training)	hi	hi	lo/med
	Prediction of behaviors (validation/testing)	hi	med	lo/med
ROBUSTNESS	Predictions, variability and uncertainty	hi	hi	med



We Need Common/Shared "Language" & Tools

[1]Friedrich, 2016, CPTP-PSP
[2]Gadkar et al, 2016, CPT-PSP
[3]InSysBio IRT
[4]Cheng et al, 2017, AAPS J
[5]Traynard et al, 2017, CPT-PSP
[6]Hosseini & Feigelman, ACoP 2018
[7]Bilouris et al, 2015, CPT-PSP
[8]Allen et al, 2016, CPT-PSP

General Approaches:

Documentation
Workflows
Reporting

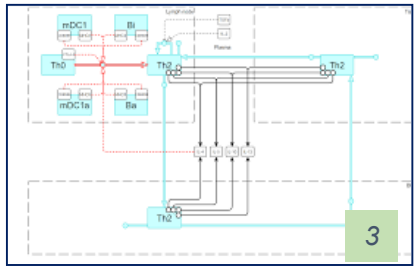
1

2

ASSESSMENT AREA	ASSESSMENT APPROACH	
	Assessment Focus	1
BIOLOGY	Relevance & plausibility	hi
	Main hypotheses & assumptions	hi
	Alternate hypotheses	med
IMPLEMENTATION	Technical QA/QC	hi
	Model structure & parameter ranges	hi
SIMULATIONS	Sensitivities and behaviors	med
	Reproduction of behaviors (calibration/training)	hi
	Prediction of behaviors (validation/testing)	hi
ROBUSTNESS	Predictions, variability and uncertainty	hi

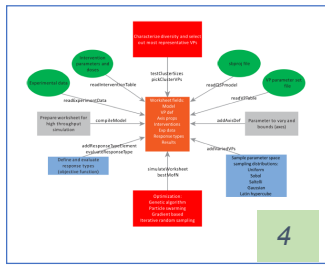
Templates, Tools & scripts

Modules & repositories
Optimization
Sensitivity analysis
QA/QC
Dynamical analysis
Model reduction analysis



3

Templates & modules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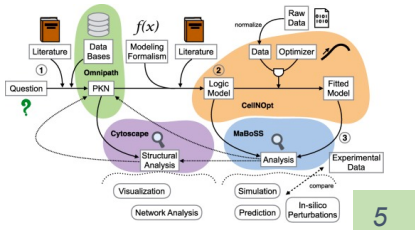

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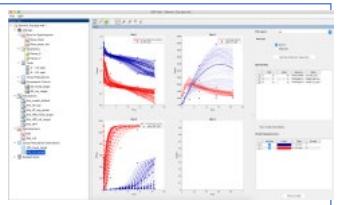
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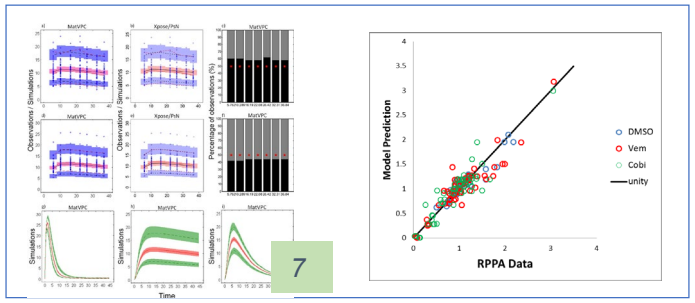
QSP toolboxes & apps

Common Metrics (?) & Visualizations

Simulation VPCs & Diagnostics



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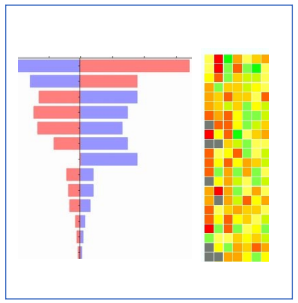
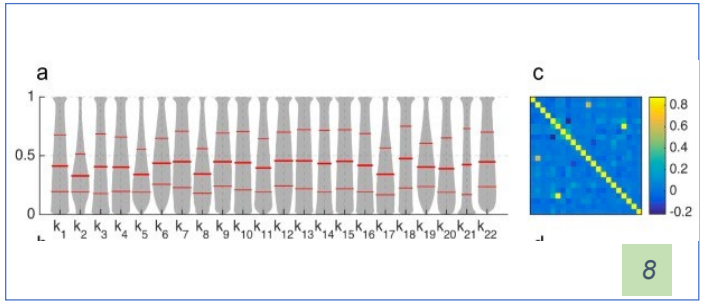
Sensitivity Analysis



Parameter variability/uncertainty



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Thank you!