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

ASCPT 2019 - QSP preconference

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IQ-CPLG-QSP assessment subteam: Jason Chan, Christina Friedrich, Craig Thalhauser
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*
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

Build on Current Guidances & Best Practices

1Gadkar et al, 2016, CPTPSP
2Friedrich, 2016, CPTP-PSP
Different “Areas” of QSP Models Require Assessment

**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?

**Qualification Criteria**
- Relevance
- Uncertainty
- Variability
- Data

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**Workflow Stages**
1. Identifying goals
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6. Supporting studies

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**Gadkar et al, 2016, CPTPSP**
**Friedrich, 2016, CPT-PSP**
Different “Areas” of QSP Models Require Assessment

<table>
<thead>
<tr>
<th>Assessment Areas</th>
<th>Biological relevance &amp; plausibility</th>
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<tbody>
<tr>
<td></td>
<td>Main hypotheses &amp; assumptions</td>
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<td>Alternate hypotheses</td>
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<td>Model structure &amp; parameter ranges</td>
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<td>Implementation (3)</td>
<td>Sensitivities and behaviors</td>
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<td>Reproduction of behaviors (calibration/training)</td>
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<td>Simulation (4-5)</td>
<td>Prediction of behaviors (validation/testing)</td>
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<td>Robustness (5-6)</td>
<td>Predictions, variability and uncertainty</td>
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**Workflow Stages**
1. Identifying goals
2. Defining scope
3. Representing biology
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6. Supporting studies

**Qualification Criteria**
- Relevance
- Uncertainty
- Variability
- Data
Greater **RIGOR**
(higher confidence required)

Greater **FLEXIBILITY**
(lower confidence required)

**APPLICATION**
- Mechanistic understanding
- Preclinical study design
- Clinical study design

**STAKES/RISK**
- Low
- Medium
- High

**PARALLEL EVIDENCE**
- Strong/Significant
- Partial/Some
- Minimal

**POSITIONING**
- Quick assessment
- Significant exploration
- Confident prediction

**USEABLE DATA**
- Sparse
- Abundant

Assessment **MUST** Be Context-Dependent
## Assessment of Model Biology & Implementation

<table>
<thead>
<tr>
<th>Focus</th>
<th>Assessments</th>
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<tr>
<td><strong>BIOLOGY</strong> (1-2)</td>
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<td>Relevance &amp; plausibility</td>
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<td>• Biological rationale and justification</td>
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<td>• Biology/therapeutic area expert endorsement</td>
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<tr>
<td><strong>IMPLEMENTATION</strong> (3-4)</td>
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<tr>
<td>Technical QA/QC</td>
<td>• Appropriate modeling formalism</td>
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<td>• Appropriate representation of biology</td>
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<tr>
<td>Model structure &amp; parameter ranges</td>
<td>• Correct implementation: scripts to test equations, parameters, units</td>
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<td>• Appropriate and stable numerical approach</td>
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<td>Sensitivities and behaviors</td>
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<td>• Potential range of behaviors/outputs</td>
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<td>• Qualitative phenotypes</td>
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<td>• Literature support, expert input on results</td>
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</table>
MAPK: Different questions require different implementations

Signaling feedbacks and complex dynamics of MAPK

Focus: dynamical behaviors
Formulation:
• ODE for feedback dynamics
• Markov chain w stochastic for noise
• PDE for spatiotemporal exploration

Pathways influencing drug resistance in CRC

Focus: pathways leading to resistance
Formulation:
• Logic-ODE for signaling
• elastic-net model connects to growth

Clinical MAPK targeting/rebound in BRAFmut CRC

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**
*Kocharńczyk et al., Sci Reports 2017*

**Sensitivity analysis**
*Saito et al J Tox 2016*
## Assessment of Model Simulation

<table>
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<tr>
<th>SIMULATIONS (4-5)</th>
<th>Assessment Focus</th>
<th>Specific Assessments</th>
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</thead>
</table>
|                   | 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](image1.png)

### Calibration

![Lemaire, ASCPT 2019](image2.png)
**Sensitivity, calibration, validation test fidelity to data/knowledge**

**In vitro signaling & growth**

- Sensitivity, calibration, validation
- Mechanistic 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

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

### Virtual subjects for alternate phenotypes

<table>
<thead>
<tr>
<th>CR1472 Data</th>
<th>CR1472 Model</th>
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<tr>
<td>HT29 Data</td>
<td>HT29 Model</td>
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<tr>
<td>CRC15 Data</td>
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- Cetuximab (EGFR)
- Vemurafenib (BRAF)
- Cobimetinib (MEK)
- GDC-0994 (ERK)

### Virtual populations: output variability

- Simulations
- Clinical data

### Virtual populations: Input variability

- Allen et al, 2016, CPT-PSP

*Kirouac et al 2017, NPJ Sys Bio & App*
<table>
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<th>ASSESSMENT AREA (workflow stage)</th>
<th>ASSESSMENT FOCUS (colored by MQM criteria)</th>
<th>ASSESSMENT APPROACH</th>
<th>REPORTING</th>
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<td>• List of critical sensitivities &amp; how they are explored for predictions</td>
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<td>• Graphs of variability in input (parameters) and outputs (typically states)</td>
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REPORTING: “Best Practices to Maximise Reuse of QSP Models: Recommendations of UK QSP Network”

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

2. Eduati et al 2017, Cancer Res
Different contexts, Different models, Different assessment

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<td>hi</td>
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**ASSESSMENT FOCUS**
- Relevance & plausibility
- Main hypotheses & assumptions
- Alternate hypotheses

**IMPLEMENTATION**
- Technical QA/QC
- Model structure & parameter ranges

**SIMULATIONS**
- Sensitivities and behaviors
- Reproduction of behaviors (calibration/training)
- Prediction of behaviors (validation/testing)

**ROBUSTNESS**
- Predictions, variability and uncertainty

**APPLICATION**
- Greater FLEXIBILITY
- Mechanistic understanding
- Preclinical study design
- Clinical study design

**STAKES/RISK**
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**PARALLEL EVIDENCE**
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- Minimal

**POSITIONING**
- Quick assessment
- Significant exploration
- Confident prediction

**USEABLE DATA**
- Sparse
- Abundant
We Need Common/Shared "Language" & Tools

General Approaches:
Documentation
Workflows
Reporting

Templates, Tools & scripts
Modules & repositories
Optimization
Sensitivity analysis
QA/QC
Dynamical analysis
Model reduction analysis

Common Metrics (?) & Visualizations

1. Friedrich, 2016, CPT-PSP
2. Gadkar et al, 2016, CPT-PSP
3. InSysBio IRT
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
Thank you!