Quantitative Systems Pharmacology (QSP) tools to aid in model development and communication: Vantage QSP Modelling Tools (VQMTools)

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VQMTools is a QSP Model development toolset, providing the QSP modeler a set of tools, that automate essential and recurrent tasks. The toolset accelerates model development, while providing a set of standardized outputs.

1. Introduction to QSP modelling

QSP models integrate data and knowledge of physiology from multiple scales, Fig 1.1[1]. The 6 stages of QSP model development is described in Gadkar et al[2] , (Fig 1.2). Although building models of complex physiology can a challenging endeavour, software tools to help automate frequently repeated tasks can accelerate development. VQMTools aims to provide such a toolset.

Fig 1.1[1] : A QSP model is built by aggregating knowledge of biological interactions to the population level outputs observed in clinical trials
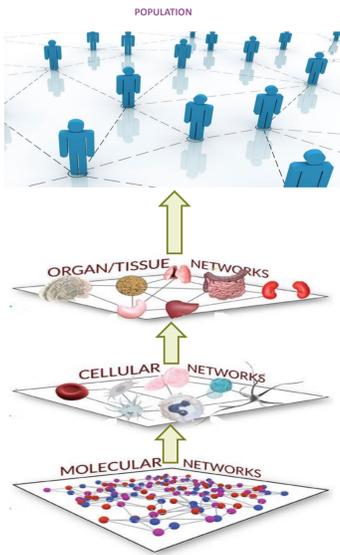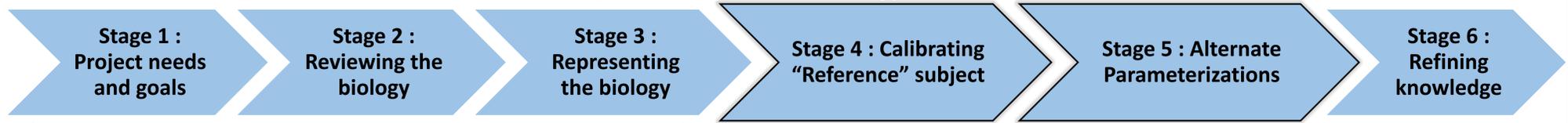

2. Need for automated tools in QSP modelling

Calibrating a Reference Virtual Subject (see Stage 4) requires **exploring model dynamics**, **Sensitivity analysis**, **Parameter estimation** and finally **verifying Reference Virtual Subject (Ref VS)** for physiological feasibility. Similarly, Stage 5 requires **creating a virtual population** and then running **diagnostics on Virtual Population (Vpop)**

Objectives for developing VQMTools

- Improve efficiency by automating recurrent QSP model development tasks. This allows the modeler to focus on model features and addressing research questions.
- Make model assumptions and constraints explicit
- Easier communication with all stakeholders

3. About VQMTools Software

- Command line interface and GUI
- Open source, free to use tools
- Currently models in SBML and Simbiology formats can be imported
- Requires MATLAB 2018, Simbiology application, Optimization toolbox
- Suitable for ODE based models

Fig 1.2 : A six stage QSP model building process

| Stage 1 : Project needs and goals | Stage 2 : Reviewing the biology | Stage 3 : Representing the biology | Stage 4 : Calibrating "Reference" subject | Stage 5 : Alternate Parameterizations | Stage 6 : Refining knowledge |

Summary of Stages 1-3

Investigate the pathophysiology, decide on complexity and accordingly pool in the quantitative information on the biological interactions. **At the end of stage 3 we have a mathematical representation of the disease**

Applications of VQMTools , Stages 4-5

Stage 4 : Calibrate the model to a reference behaviour of subjects to disease and is called as a "Reference Virtual Subject".
Stage 5 : A Virtual Population that matches selected clinical trials is created. The model validation is done by testing a new therapeutic intervention.
A validated model at the end of Stage 5 can be used to answer the project questions

4. Components of VQMTools

1. Sensitivity analysis

QSP models by design typically consist of 10-100s of parameters. While some of these are constrained by the "bottom-up" data curated from literature, there are often several parameters which need to be estimated. **A sensitivity analysis increases understanding of uncertainties in the model.**

VQMTools is useful to run **sensitivity analysis of parameters for a specified objective function.** The tool generates a tornado plot as shown (Fig 4.1)
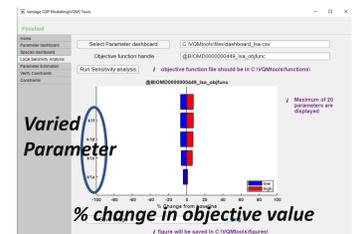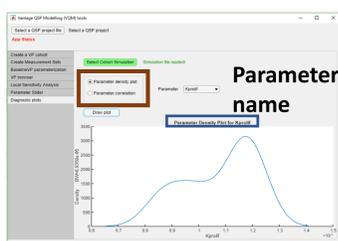

Fig 4.1 Tornado plot for parameter sensitivities

5. Population diagnostics

Understanding parameter distributions and correlations in a Vpop is an important step to evaluate the model and identify spurious parameter relations.

VQMTools allows for user to easily visualize parameter distributions across Vpop and parameter correlations .

Fig 4.4 Parameter density plot

2. Parameter estimation

After identifying under-constrained parameters from model development and sensitivity analysis, the modeller needs to estimate them by calibrating the model to a "Reference VS behaviour".

VQMTools uses methods from MATLAB optimization toolbox to estimate the set of parameters that minimizes the specified objective function

Fig 4.2 shows the interface for parameter estimation for a chosen objective function using VQMTools

Vantage QSP Modelling Tools
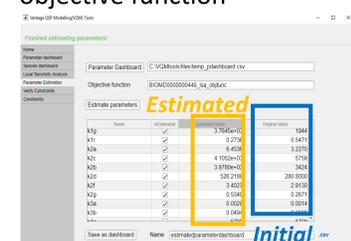
1. Sensitivity analysis
2. Parameter estimation
3. Constraint verification
4. Virtual Population
5. Population diagnostics

4. Virtual population

Creating Virtual Population is the hallmark of QSP model. The ability to replicate response/non-response to therapies, at a population level, from the biological knowledge, gives the model predictive power.

VQMTools takes a monte-carlo approach to create a cohort. User can filter this using 'measurements' to get to Virtual Population
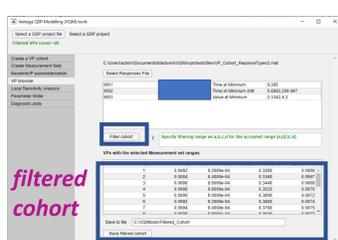

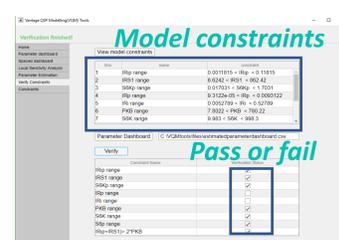*Fig 4.3 Selecting Virtual Population from a large Cohort*

Fig 4.2 VQMTools interface for model verification

3. Constraint verification

QSP models have physiological constraints (e.g., in Rheumatoid Arthritis, CD4/CD8 cell ratio is expected to be between 7 and 15) and constraints imposed by the modeller to match desired physiological mechanisms.
VQMTools allows the modeller to maintain a collection of all the constraints and verify them quickly and easily at each stage of model development

Current Applications

- VQMTools are being used in development of a Vantage Rheumatoid Arthritis QSP model. Feedback from the modelling team is informing continued development of VQMTools software

Next steps

- Add features that facilitate communication of models with non-modelling stakeholders (e.g., ability to "play" with model and visualize predictions
- Testing in multiple QSP models

References

1. Goldman et al. Bioregulatory systems medicine: an innovative approach to integrating the science of molecular networks, inflammation, and systems biology with the patient's autoregulatory capacity?. Frontiers in Physiology , 225(2015)
2. Gadkar K et al . A six-stage workflow for robust application of systems pharmacology. CPT Pharmacometrics Syst. Pharmacol. 5, 235–249 (2016)