Virtual Systems Pharmacology (ViSP) flexible web-based environment for running large multi-scale models

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INTRODUCTION

Multiple software packages available for Quantitative Systems Pharmacology (QSP) modeling are judged by their model development capabilities, user interface, available solvers, convenience of handling large number of parameters and simulations, export-import capabilities, cost of software and support, etc. Lack of a single software ranking favorably against all criteria forced us to look for a way of using several software packages while having a common tool that can be employed by any of them for running large scale simulation tasks.

This report presents a workflow and a web-based software platform which is model and therapeutic area agnostic with a database back-end that can be used to set up, manage and execute large-scale simulations for multiple models by multiple users. The platform can be adapted and deployed on an existing cluster or cloud computing environment. Its use was demonstrated with a metabolic disease systems pharmacology model.

METHODS

In order to create flexible and versatile QSP software for setting up and running large scale simulations the following requirements were formulated:

1. Handle diverse systems pharmacology models designed by different software packages
2. Be independent of the specifics of any given model and place as few general requirements as possible
3. Enable a flexible computational environment/hardware choice to run simulations (cluster, cloud, or desktop)
4. Provide an intuitive and easily configurable user interface (UI) that accommodates specifics of a particular model and the input parameters
5. Should serve as collaboration software accessible throughout the company network
6. Provide means of storing and handling large modeling projects
7. Have low deployment and maintenance costs

Virtual Systems Pharmacology (ViSP) software separates the process of constructing a QSP model from the process of running simulations originated by that model. Model file(s) are compiled into an executable code in which high-level model instructions are translated into processor commands.

In order to keep the simulation process maximally flexible all model parameters are presented as input parameters. Multiple simulation instances can be created by combining different input parameter values with executables, which can be run on a grid of processors in a cluster, in a cloud, or in a mixed environment (see Fig. 1).

ViSP is implemented as a web-based client-server application with a relational database back-end that offers the following benefits :

- Easy deployment and maintenance
- Enterprise-wide availability with controlled user access
- Rich selection of available programming tools and technologies
- Provides robust, reliable, dynamic, structured and complex relational data model

Overall ViSP workflow includes several steps (Fig. 2).

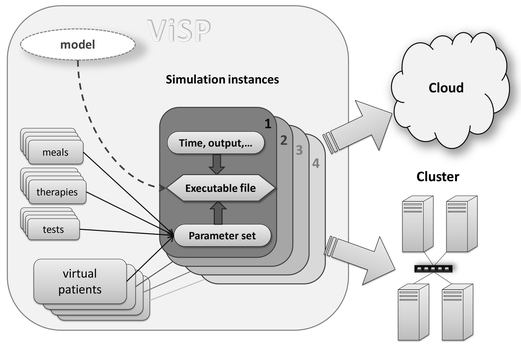

Figure 1. Components of a simulation. Input parameters are divided into Individual's specific (virtual patient), therapies and interventions (meals, clinical tests), and parameters regulating execution. Various combinations of parameters define different simulation instances.

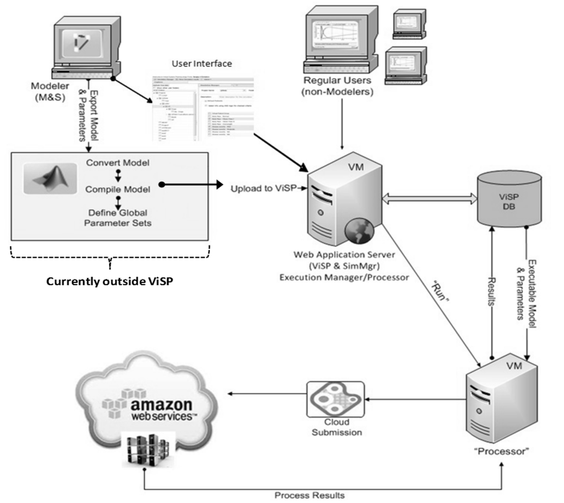

Figure 2. ViSP architecture and workflow. Mathematical model is developed by the Power User using model development software which is compiled into an executable with the 3-d party software. The Power User configures the user interface (UI) by using ViSP. Executable, full set of parameter baseline values, and Virtual Patients are uploaded by ViSP into the database. Power and Regular Users can then setup simulations through the UI and send them for execution. Dispatching software will distribute the simulations over the computational grid (cluster, cloud) and retrieve the results after simulations are completed. The latter will be available for analysis to users through the ViSP UI.

RESULTS: ViSP

The ViSP software features several primary user-interface components. **Explorer** organizes user's models and data in a tree-like hierarchical structure: projects -> models -> UIs -> parameter groups -> value sets. **Simulation Manager** provides means to customize the UI to the content of the model, prepare and launch simulation tasks. The model UI can be configured in a simple setup by creating sections according to particular aspects of the model (Fig. 3-4).

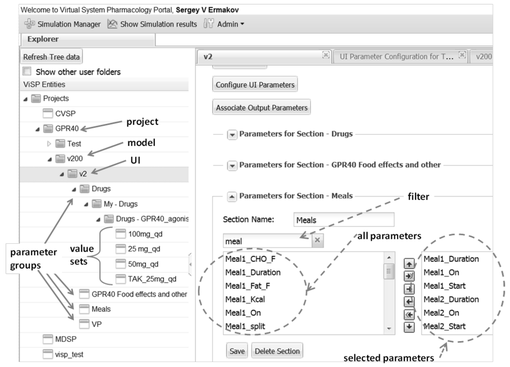

Figure 3. ViSP User Interface (UI), left pane – Explorer, right pane – configuration setup. User can configure the UI to show only relevant parameters out of many.

Figure 4. Configuration table (top) specifies position and types of controls that will be exhibited. Virtual patients can be chosen by a group or individually along with therapies, mono or combo (bottom).

MDSP MODEL

ViSP platform was used for running simulations with Metabolic Diseases Systems Pharmacology (MDSP) model. It was developed to mechanistically describe (patho)physiological processes involved in Type 2 diabetes mellitus along with the PKPD effects for several classes of antidiabetic drugs. The core of the model simulates intake and processing of nutrients, and their distribution and utilization by different body tissues and organs as schematically represented by a block diagram on (Fig.5). Model comprises 100+ ODEs, 50+ algebraic equations and 800+ parameters.

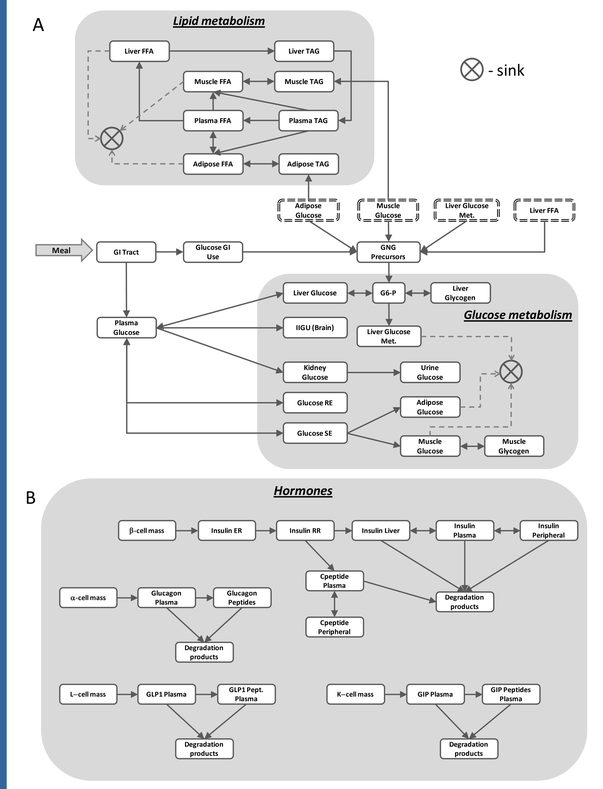

Figure 5. MDSP model block diagram

MDSP model was calibrated with several classes of antidiabetic drugs. Comparison between simulations and clinical data is presented for GPR-40 agonist Fasiglifam (TAK-875) and metformin on Fig. 6.

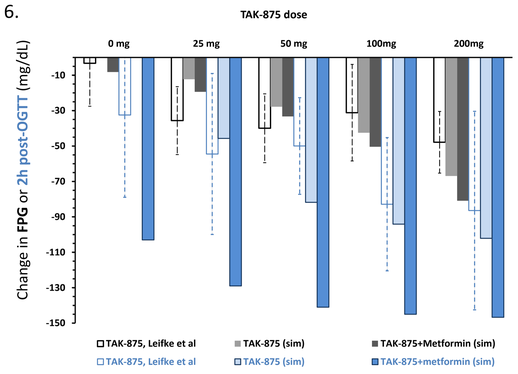

Figure 6. Effects of TAK-875 on fasting plasma glucose, **FPG** (black) and on glucose levels 2 hours after oral glucose tolerance test, **2h post OGTT** (blue). Clinical data (Leifke et al.) are compared with simulation results. Simulations are also provided for TAK-875 + Metformin 500mg bid combination.

References: Leifke, E., et al. *Clinical pharmacology and therapeutics* (2012), 92, 29-39.