

An open-source platform for Sensitivity Analysis of QSP models

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Abstract

Parameter estimation and sensitivity analysis are key aspects of model qualification process in Quantitative Systems Pharmacology (QSP), to verify that the model can capture behaviors of interest in a robust manner. In addition, models are often developed in multiple software platforms. We have developed a tool-VIPER ("Vantage Interactive Parameter Estimator"), a web interface that allows users to readily simulate an Ordinary Differential Equation (ODE) model, explore the parameter space and generate interactive plots. A QSP PKPD model of Integrated Immune Response from EMBL [5] is used as an example to showcase this tool.

Introduction

Sharing QSP models across research groups is already of interest in the field. Model repositories such as DDMore, EMBL [3] facilitate such interaction by curating and hosting models in a shared format such as Systems Biology Markup Language (SBML)[2]. Further, many software tools, public (JDesigner, R, etc.) and proprietary (Matlab Simbiology), are used for model development in various research settings. Open-source tools and package repositories are constantly upgraded with functionalities that may be relevant to QSP research work. We have integrated multiple open source resources to create an open source tool that can be customized to workflows within QSP projects (see Fig. 1).

Methods

We considered a model of immune system interaction with tumor environments, the Fully integrated Immune Response Model (FIRM) [5] which captures various cells and mediators dynamics, by integrating other published models. It predicts a generalized immune response to challenges such as infection and tumor growth. We were able to successfully use VIPER to replicate the time dynamics from [5] as shown in Fig. 2. Further, we carried out sensitivity analyses and parameter estimation to demonstrate additional capabilities.

Packages connected: RShiny and PyGMO

The powerful 'R shiny' package of Rstudio [9] provides the web interface for the tool. With limited coding for web hosting, RShiny facilitates development of web-based applications for modeling. PyGMO (Parallel Global Multiobjective Optimizer) is a scientific library for the easy distribution of massive optimization tasks over multiple

CPUs that provides the basis for parameter estimation [1]. PyGMO has several Genetic Algorithms (GA) and Differential Evolution (DE) with different mutation and crossover strategies. Laganowsky *et al* [4], showed that modified differential evolution strategy of 'PyGMO' module is well suited for biological systems. We have used a Modified differential evolution with p best crossover (MDE p BX) strategy for parameter estimation.

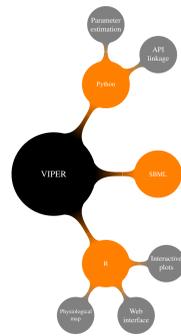


Figure 1: Representation of packages connected and functionality within VIPER

VIPER current capabilities

We visualize usage of VIPER within QSP teams to aid in model development and analysis. We aim to make the stable version of VIPER available to the community and host the code for further adaptation, if needed. The current interactive capabilities of VIPER are illustrated in Figures (2-4). It should be noted that, the model has to be uploaded into VIPER as an SBML file.

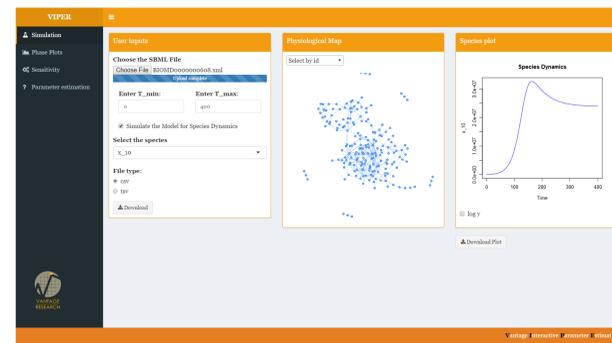


Figure 2: FIRM model output from VIPER

Model visualization:

Consistent representation of biological data such that it can be interpreted clearly into underlying mathematics can be challenging. VIPER uses "rsbml" and "graphNEL" packages to accomplish conversion from SBML to visual representation (Fig. 2).

This visualisation is still rudimentary and not optimised for QSP models and may be an area of future development.

Dynamic Simulation:

Interactive, downloadable plots of all the state variables versus time or versus other variables (2D phase plots) are available (Fig. 2).

Parameter Sensitivity Analysis:

Understanding sensitivity to parameters and distinguishing between "sloppy" and "sensitive" parameters is critical in understanding system behavior and increasing confidence in model predictions. For sensitivity analysis, Latin Hypercube Sampling of the multi-parameter space was employed within the user specified bounds for the selected parameters (pyDOE package was used). Several parameters of interest can be chosen simultaneously and the sensitivity determined.

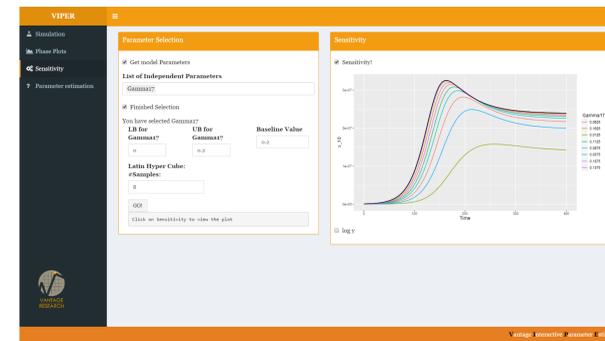


Figure 3: Sensitivity of "Mature dendritic cell in the lymphoid T cells" physiology to parameter "Maximum rate of IDC activation" in the FIRM model

Parameter estimation:

Matching model simulation to data sets of interest is often the heart of a QSP model development exercise. Identification of the right data and ensuring 'fit-for-purpose' are critical parts of design [6]. Once the right sets of data are identified, the mechanics of finding an efficient optimization algorithm and defining the right objective function that captures the modeling team's intent is part of the engineering effort. VIPER allows, at this time, to fit one data set at a time using a simple least squares objective function (Fig. 4). We plan to incorporate more sophisticated objective function definitions weighting alternate data sets differently etc., in future versions of VIPER.

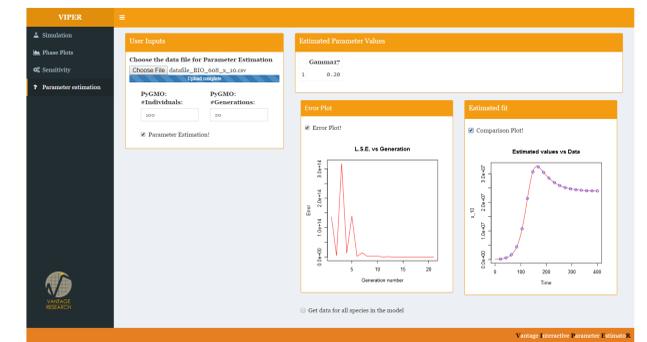


Figure 4: Fitting "synthetic" data to FIRM model

Conclusions and Next Steps

We brought together the strength of 'R' and 'python' to build a platform independent interface for workflows within a QSP project. In general, given a model in SBML format, this tool provides the following capabilities: (i) physiological map, (ii) parameter estimation through differential evolution estimation algorithms and (iii) parameter sensitivity analysis through latin hypercube sampler. Future improvements, such as additional optimization algorithms, automatic identification of sensitive parameters, generation of multiple parameter combination that match available data, could be added which can further increase the utility of such a tool. Feedback from the QSP research community is solicited to fine-tune further development.

References

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