BioModME for Building and Simulating Dynamic Computational Models of Complex Biological Networks

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Introduction and Objectives

- Biological systems and the associated regulation mechanisms and disease processes are intrinsically complex, often encompassing a vast number of interacting and redundant components that have become too exhaustive to assess experimentally.
- In addition, many of these network components are unintuitive in nature, requiring alternative approaches to determine the underlying functions of the network.
- Computational modeling, the process of simulating complex systems in silico, has emerged as a powerful tool generating testable hypotheses of these networks by predicting different possible outcomes of the network.
- However, the technical knowledge required to design and solve computational models is a barrier for most experimental and clinical investigators.
- As such, there is a significant need for software tools that package computational modeling in a language that the broader research community can use to help solve complex questions.
- Our ***objectives*** of building this application are:
  a) provide a computational model building platform that is simple and easy to use while providing higher level modeling tools that can be used by any user, regardless of model building experience.
  b) create a functional repository for model sharing, storage, and visualization, all in one online server, allowing for scientists to quickly visualize and view experimental results.
  c) provide all the tools necessary to export the model information in a variety of methods, including styled tables, pre-typed equation sheets, and functional programming code.

Materials and Methods

- Application is designed using the open-source R programming language, using the Shiny and bs4dash packages to build its web framework via JavaScript and bootstrap widgets.
- We have included the well-known ggplot2 plotting libraries for base visualization and provided Plotly, Bokeh, and Dygraph interactive plotting libraries to provide an interactive experience.
- Differential equations are generated from entered information using custom scripts and solved using DeSolve, a library containing solvers for initial value problems of differential equations.
- Software prototypes are currently available for use at https://biomodme.ctsi.mcw.edu and available for download at https://github.com/MCWComputationalBiologyLab/BioModMe.

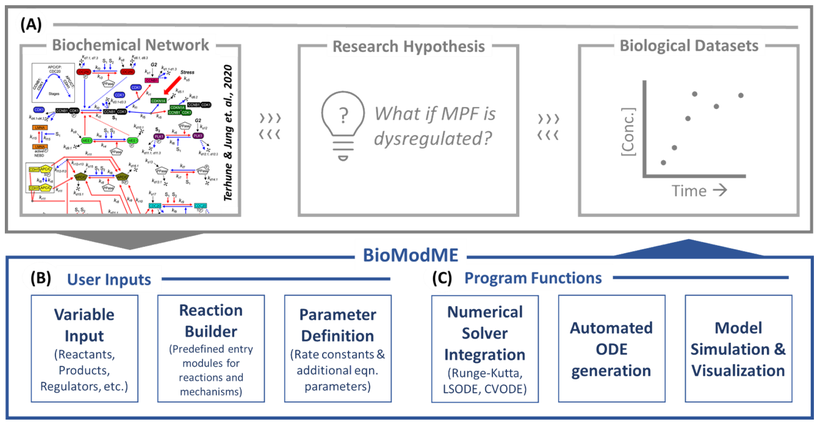

Figure 1. Overview of the proposed BioModME software tool. A complex reaction scheme such as the mitotic cell cycle[1] can be partitioned into modular user inputs that are entered into the application's UI. The applications backend formulates the model's governing differential (and algebraic) equations describing the model and provides a visualization suite for plotting the model solutions.

References - 1. Terhune, S.S., et al., *Network mechanisms and dysfunction within an integrated computational model of progression through mitosis in the human cell cycle*. PLoS computational biology, 2020. 16(4): p. e1007733.
2. Hucka, M., et al., *The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models.* Bioinformatics, 2003. 19(4): p. 524-531.

Application Layout

Figure 2. Visualized workflow of BioModME detailing the applications three main package suites. The applications first suite walks the user through the model building process, making use of commonly used web widgets. The user needs to enter their reaction system into the application along with any parameter and initial condition information. The programs backend will proceed to calculated the corresponding differential equations of the reaction network and will quickly solve the system using built in solvers written in Fortran. In the visualization suite, the user can see the time series result of their model. There are options here to create multiple instances of a model under different parameter conditions (shown above) and upload user experimental data to compare to simulated model data. The export suite provides many different export options of both the model and its information. The actual model can be stored in two different forms (SMBL[2] and RDS), the underlying data can be saved in spreadsheet or pdf form, and the entire model can be downloaded as functional code in three different programming languages.

Feature Discussion

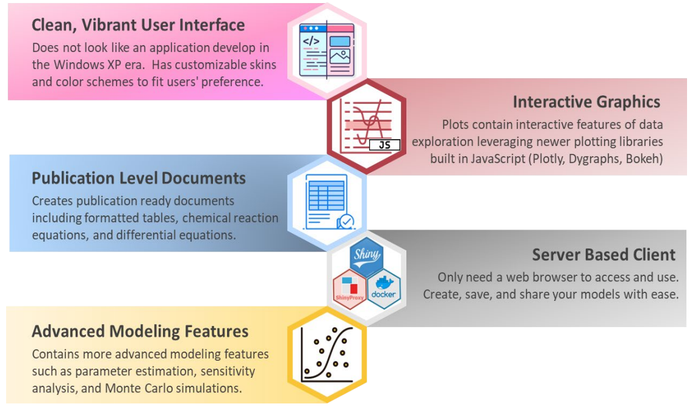

Figure 3. Overview of BioModME features. Our application provides many advancements over the current field of modeling software that exists including free, open-source software and making use of cloud technology

- BioModME provides a model building suite that allows the user to create a reaction network to describe their model, by entering the chemical reactions that surmise of their network.
- The model can be built using various chemical and physical laws, including the law of mass balance, the law of mass action, and Michaelis-Menten kinetics for enzyme-catalyzed reactions.
- The visualization suite provides the users with multiple options to present the resulting simulations including pre-built color palettes, line/axis options, and plotting themes.
- Users can implement model changes on one plot or use the application to generate multiple instances of a model under different parameter conditions, showing a set of subplots with calculated solutions. This allows the user to quickly test and compare different model states, such as diseased.
- All model tables, including parameters, equations, initial conditions, and differential equations, can be exported in the following formats as a file (csv, txt, xlsx), pre-styled tables (TEX, pdf, Rmarkdown), or into a functional programming language script.
- Future Directions: We aim to add multicompartment models, PKPD modeling with drug injections, optimize parameter estimation, and incorporate SMBL file loading.

	Price	Target Audience	Repository of Models	Availability	Required Knowledge
Ours	Free	Anyone with a scientific background	Online Server; Open Source in R; Docker Version;	Servers to save and load models from variety of sources	No computer programming needed; All equations and derivations done in app with background information provided
Others	Vary from free to 1000's of dollars	Experienced Modelers; Pharmaceutical Companies	Have to find model online or email model author	System dependency; Requires download; Uses user space	Require programming to create rules; Provide solvers with no explanation of the process

Table 1. Comparison of BioModME to current published software. Our application provides many advancements over the current modeling software including price and use of cloud technology. Other software groups contains of COPASI, CellDesigner, Berkley Madonna, and MATLAB SimBiology.

Conclusions

BioModME provides a web-application to help researchers develop mechanistic computational models without the need for complex mathematical derivations or the knowledge of coding/solving mathematical equations using a programming language. The R/Shiny interface allows for a guided model building process creating robust simulations, high-quality graphics, and summary documents.