Systems biology Gene Circuit Explorer (GeneEx): an interactive web-app for visualizing, simulating and analyzing gene regulatory circuits

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Abstract

Summary: GeneEx is an interactive web-app that uses an ODE-based mathematical modeling approach to simulate, visualize and analyze gene regulatory circuits (GRCs) for an explicit kinetic parameter set or for a large ensemble of random parameter sets. GeneEx offers users the freedom to modify many aspects of the simulation such as the parameter ranges, the levels of gene expression noise and the GRC network topology itself. This degree of flexibility allows users to explore a variety of hypotheses by providing insight into the number and stability of attractors for a given GRC. Moreover, users have the option to upload, and subsequently compare, experimental gene expression data to simulated data generated from the analysis of a built or uploaded custom circuit. Finally, GeneEx offers a curated database that contains circuit motifs and known biological GRCs to facilitate further inquiry into these. Overall, GeneEx enables users to investigate the effects of parameter variation, stochasticity and/or topological changes on gene expression for GRCs using a systems-biology approach.

Availability and implementation: GeneEx is available at https://geneex.jax.org. This web-app is released under the MIT license and is free and open to all users and there is no mandatory login requirement.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Gene regulatory circuits (GRCs) are networks of interacting genes that underpin nearly all biological processes. To deepen our understanding of the structure and function of GRCs, it has become imperative to develop computational methods and tools that can quickly and robustly model their dynamics (Alon, 2006). Here, we developed one such tool: *Gene* Circuit Explorer (GeneEx), an interactive web-app that uses an ODE-based mathematical modeling approach to simulate, visualize and analyze GRCs (Huang *et al.*, 2017; Kohar and Lu, 2018). GeneEx allows for users to then quantitatively compare the simulated gene expression data with uploaded experimental data. GeneEx also hosts a database of circuit motifs and putative biological GRCs to enable further investigation of these topologies.

2 Gene Circuit Explorer

The minimum input to GeneEx is a circuit topology that specifies all the regulators (source), their regulated gene (target) and the type of regulation (activation/inhibition). GeneEx is highly customizable and allows users to (i) input, import and modify the circuit topologies (the Circuit tab); (ii) simulate gene expression trajectories for a model with a specific parameter set (the GeneVyuha tab); (iii) simulate gene expression patterns for an ensemble of models with randomly generated parameter sets (the RACIPE tab); (iv) compare the simulations with experimental data (the Validate tab); (v) explore circuit motifs or known biological circuits (the Database tab); (vi) ask questions or discuss any feature additions (the Forum tab).

2.1 Circuit

The Circuit tab allows the user to detail a circuit for analysis. A circuit can be either built manually or uploaded as a text file. The circuit is then displayed as both a network diagram and as a searchable and editable table (Fig. 1B). Furthermore, users can import a circuit from the GeneEx database as well.

2.2 GeneVyuha

The GeneVyuha (Vyuha—a Sanskrit word that means 'pattern/formation with a specific function') tab simulates the circuit using a randomly generated parameter set and displays the time dynamics of the circuit (Fig. 1C). Users can also input their own set of model parameters obtained through statistical analysis of experimental data or through other parameter estimation methods. Users can investigate how individual parameters and/or the noise level affect the temporal evolution of gene expression by precisely controlling all the parameter values. Users may also vary any of the parameters uniformly over a range to generate the parameter perturbation diagrams of the circuit.

2.3 RACIPE

The RACIPE tab uses a recently developed mathematical modeling algorithm, named <u>random circuit perturbation</u> (RACIPE), to generate an ensemble of models with distinct random kinetic parameters (Huang *et al.*, 2017). Our previous studies have shown that the gene expression from random models form robust and functionally related clusters (Huang *et al.*, 2017, 2018; Katebi *et al.*, 2020;



Fig. 1. GeneEx features. (A) GeneEx implementation architecture. Outline of GeneEx functionalities showing: (B) circuit visualization and modification, (C) time series simulations and parametric perturbations of a single model, (D) RACIPE simulations of the circuit

Kohar and Lu, 2018; Ramirez *et al.*, 2020). GeneEx provides a convenient platform for determining how different parameters and/or noise levels affect the prevalence and stability of various gene expression clusters that emerge from the RACIPE analysis.

2.4 Validate

The Validate tab allows users to quantitatively compare RACIPEsimulated gene expression data with their uploaded experimental data to investigate whether the GRC simulations capture the essential features of the experimental data.

2.5 Database

The Database tab offers curated circuit motifs and known biological GRCs to encourage additional exploration and sharing of their simulations. The database will be expanded over time and users have the option to upload their circuits.

3 Design and implementation

GeneEx is designed for both the systems biology and bioinformatics communities and contains modular design patterns for maximal flexibility (Fig. 1). The user interface of GeneEx is provided by shiny package (Chang et al., 2016) in R (R Core Team, 2018) and the backend consists of our R/Bioconductor (Huber et al., 2015) package sRACIPE (Kohar and Lu, 2018) which relies on various R packages, such as Rcpp (Eddelbuettel and François, 2011), data.table (Dowle et al., 2017), tidyverse (Wickham and Grolemund, 2016), visNetwork (Almende et al., 2016) and so on. We extend the commonly used S4 SummarizedExperiment class data structure from Bioconductor (Huber et al., 2015) to store the GRC, the parameters and the simulated gene expressions. The stochastic and ordinary differential equations are numerically integrated in C++ using the R bindings provided by Rcpp. Comprehensive documentation (see Supplementary Information), tutorial, workflow examples and discussion forum are available and hosted at https://geneex.jax.org and the code for app is available at https://github.com/lusystemsbio/geneex.

4 Conclusion

GeneEx is a user-friendly tool that enables the integration of systems-biology-based modeling methods with experimental data for a variety of research needs. A potentially popular application of GeneEx would be to help augment or refine established GRCs by comparing their simulated expression with experimental gene expression patterns.

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Conflict of Interest: none declared.

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