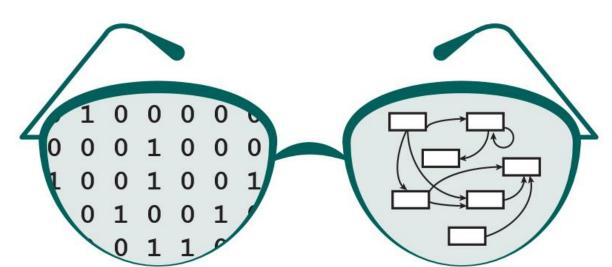
A Dynamic Gene Page Feature for GRNsight: a Web Application for Visualizing Models of Gene Regulatory Networks



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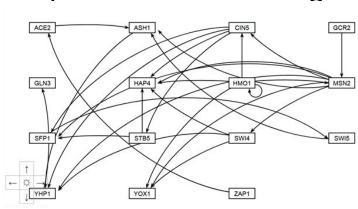


Gene Regulatory Networks Can Be Illustrated by Directed Graphs

- The central model of molecular biology states that the flow of information in a cell during gene expression is rom DNA to RNA to protein.
- Transcription factors control gene expression by binding to regulatory DNA sequences.
- Activators increase gene expression.
- Repressors decrease gene expression.
- · Transcription factors are themselves proteins encoded by genes.



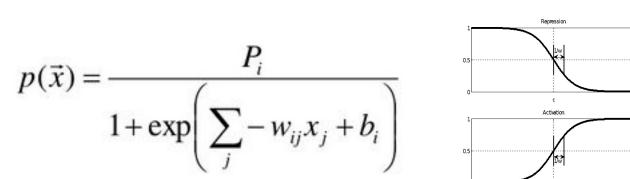
• A gene regulatory network (GRN) consists of genes, transcription factors, and the regulatory connections between them, which govern the level of expression of mRNA and proteins from those genes.



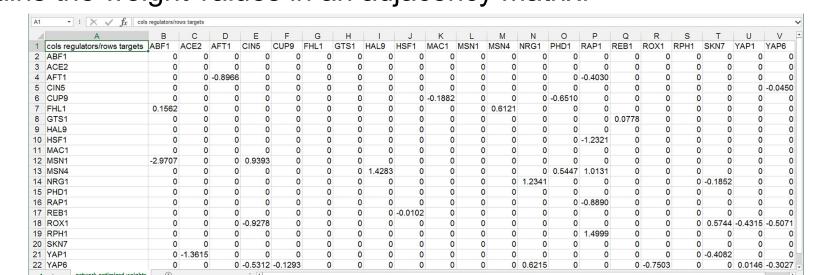
- Each node represents the gene, the mRNA, and the protein expressed from the gene.
- Each edge represents a regulatory relationship.
- All the nodes are transcription factors themselves.

GRNmap: Gene Regulatory Network Modeling and Parameter Estimation

• The MATLAB model is available at http://kdahlquist.github.io/GRNmap/



- GRNmap is a differential equations model of the changes in gene
- expression over time for a gene regulatory network (Dahlquist et al. 2015) • Each gene (node) in the network has an equation.
- The parameters in the model are estimated from laboratory data.
- The weight parameter, w, gives the direction (activation or repression) and magnitude of the regulatory relationship.
- GRNmap produces a multi-sheet Excel workbook, where one worksheet contains the weight values in an adjacency matrix.



However, GRNmap does not generate a visual representation of GRNs.

GRNsight Fulfills a Specific Software Niche for Visualizing Small- to Medium-scale GRNs

- Although other open source software, such as Cytoscape or Gephi, exist to lay out large networks, they were too cumbersome for our needs.
- GRNsight is targeted at both experienced biology investigators and novice undergraduate users and has the following requirements: Exist as a web application.
- 2. Be simple and intuitive to use.
- 3. Accept Excel (.xlsx) files directly from GRNmap, as well as, SIF (.sif), or GraphML (.graphml) input files.
- 4. Read a weighted or unweighted adjacency matrix.
- 5. Automatically lay out and display unweighted and weighted, directed network graphs.

GRNsight Automatically Lays Out Unweighted and Weighted Network Graphs

1. File Formats

- Can import and export Excel, SIF, or GraphML files.
- Demo files are provided.

2. Grid Layout

· Grid Layout button allows the users to toggle the graph between a grid layout and a force graph layout.

3. Node Colorina

- This menu allows users to modify parameters of the node coloring visualization.
- Dataset options are automatically generated from expression data sheets detected in an Excel input

4. Force Graph Parameter Sliders

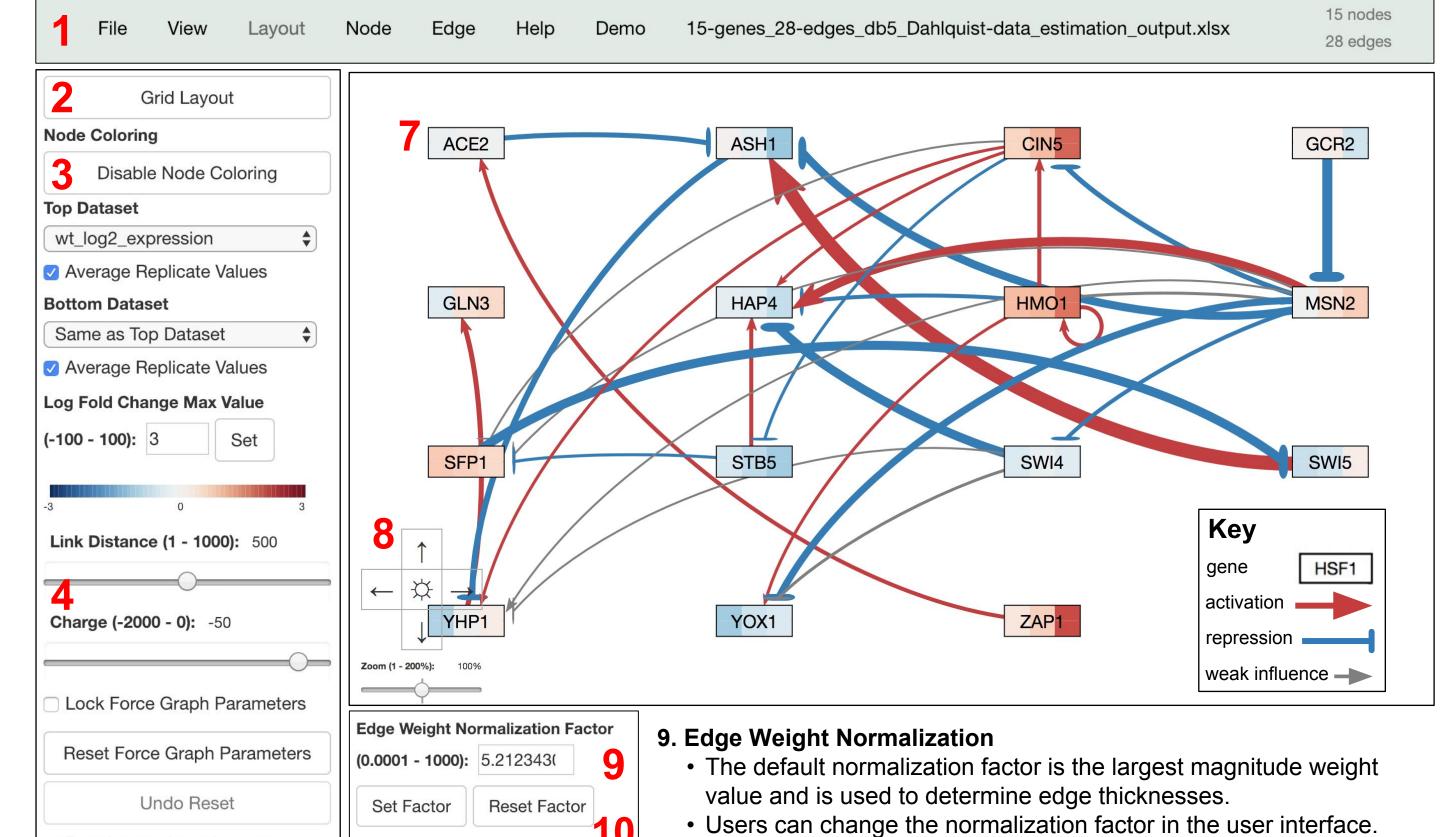
- Link distance determines the minimum distance between
- · Nodes have a charge, which repel or attract other nodes.
- Reset functionality sets all parameters to default.
- Locking the parameters prevents any further changes.

5. Viewport

- Graph bounding box can be separated from viewport.
- Multiple viewport sizes available. Zooming and scrolling enabled.
- 6. GRNsight includes options to show or hide the weight
- Buttons enable the user to always see edge weights, never see edge weights, or see edge weights upon mouseover of the edges.

7. Dynamic Gene Page

- Upon right-clicking any given node in a loaded graph, GRNsight generates a blank "gene page" in a new page tab. The gene page makes live Asynchronous Javascript and
- XML requests to four biological databases containing the species name and taxon ID from a graph's "GRNstate" data and the gene name given by the node.
- 8. Zoom and Scroll



10. Gray Edge Threshold Slider allows the gray edge threshold to be customized.

scale, facilitating accurate visual comparison.

 Gray edges allow users to visually gauge whether a particular regulatory relationship is not important.

Edge thicknesses for different graphs can be rendered on the same

- By default, edges are colored gray if the magnitude of its value is
- <= 5% of the absolute value of the maximum edge weight
- As the threshold value increases, only the highest magnitude regulatory relationships are rendered in color.
- Gray edges can also be rendered as dashed lines to further
- distinguish the edges.

When a User Selects a Node, a Gene Page Opens, Providing Information from Public Databases

Restrict graph to viewport

Small (1104 X 648 pixels)

Medium (1414 X 840 pixels)

Large (1920 X 1080 pixels)

Hide/Show Edge Weights

Always Show Edge Weights

Never Show Edge Weights

Show With Mouse Over

Viewport Size 🤚

Fit to window

Application Processing Interfaces (APIs) Allow GRNsight to

- Gather Data from Public Databases for Display on Gene Pages • AJAX commands allow GRNsight to communicate with NCBI Gene, UniProt, JASPAR, and the Saccharomyces Genome Database to
- Data are returned in either eXtensible Markup Language (XML) or
- JavaScript Object Notation (JSON) format. • Data are then rendered on the gene page as lines of text, images, and data tables
- If no data are returned from any database, an error message is given

1. Saccharomyces Genome Database (SGD)

• From SGD, GRNsight gathers the SGD ID, gene description, a list of regulators and targets, and the Gene Ontology summary and molecular function, biological process, and cellular component

2. NCBI Gene Database

 From the NCBI Database, GRNsight gathers the NCBI Gene ID, RefSeq chromosome sequence ID, and the locus tag. This locus tag is used to generate a link to the gene's corresponding page on the Ensembl Database website.

3. UniProt

 From the UniProt Database, GRnsight gathers the UniProt ID, protein type, protein sequence, and full species name.

4. JASPAR

 From the JASPAR Database, GRNsight gathers the JASPAR ID, transcription factor class name, family name, frequency matrix, and sequence logo for the DNA binding site.

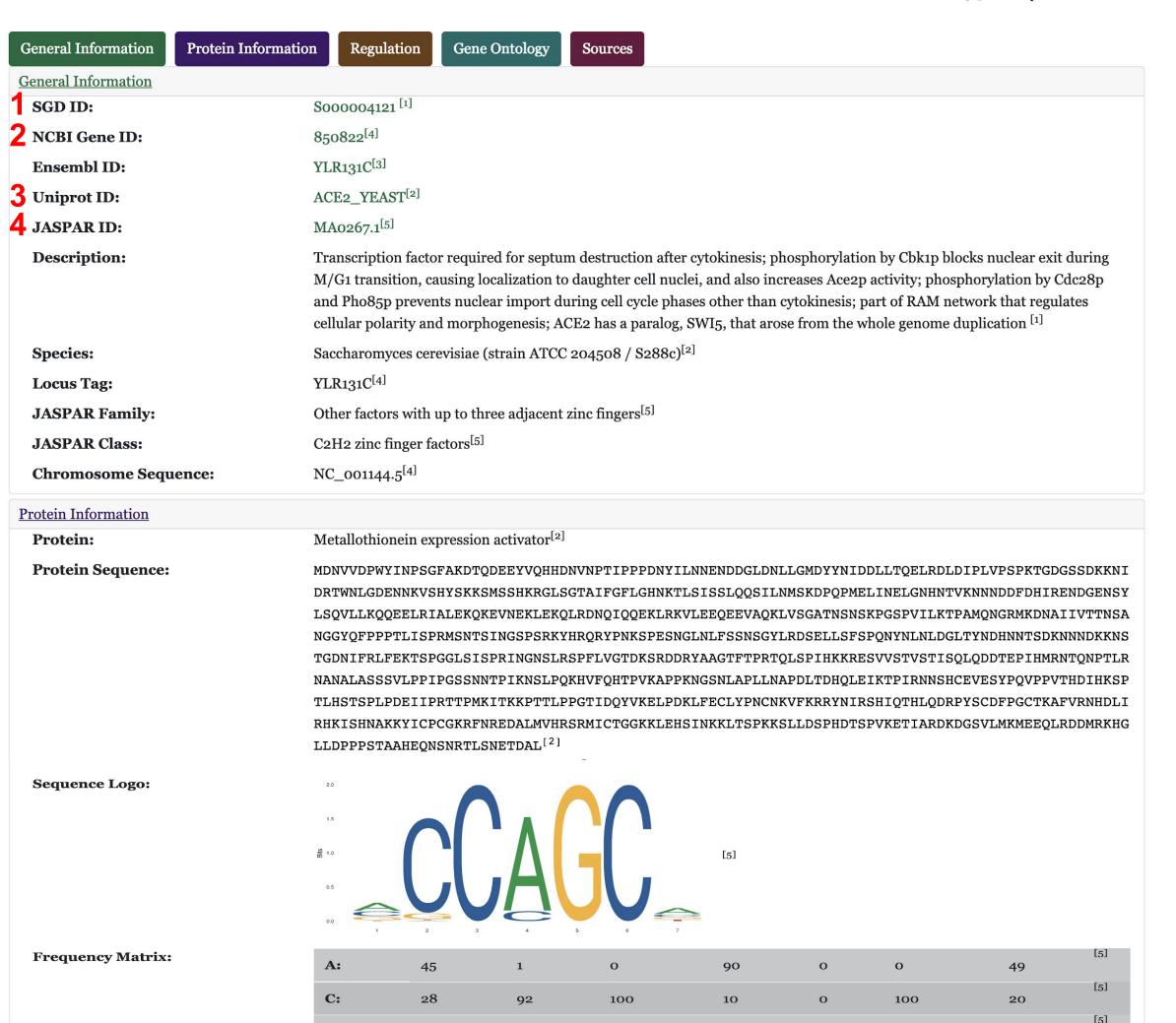
The Gene Page Uses a Variety of Modern Web Application **Technologies** • The Gene Page is partially styled using Bootstrap, a library for the

- page's Cascading Style Sheets. • The page was written using ES6 JavaScript and the jQuery library.
- To connect to the APIs, we implemented a relay from the primary GRNsight server to the API calls.

Gray Threshold (0 - 100%): 5%

Show Gray Edges as Dashed

Saccharomyces cerevisiae (strain ATCC 204508 / S288c)



New Export to Excel Feature

GRNsight can import data in a variety of formats (GRNmap Excel Workbook, SIF, GraphML) and can export to SIF and GraphML We wanted the application to export to GRNmap Excel format to facilitate creation of GRNmap input workbooks for GRNmap users.

Feature Addition

 Added an element to the user interface that gives the user the option to export GRNsight data to an Excel workbook.

Initial Errors and Troubleshooting

- Initially, exported Excel files failed to open after download.
- Once this was resolved, data that was input using GRNmap format exported correctly, but other formats failed. This problem has since been resolved.

Documentation Updates

Updated Wiki Layout

 Reorganized Wiki categories into First Steps, Instructions and Tutorials, Procedures, Design, Testing, Troubleshooting, Abstracts and Documentation, and Appendices to enhance organization and encourage continual updates to documentation.

New Documentation

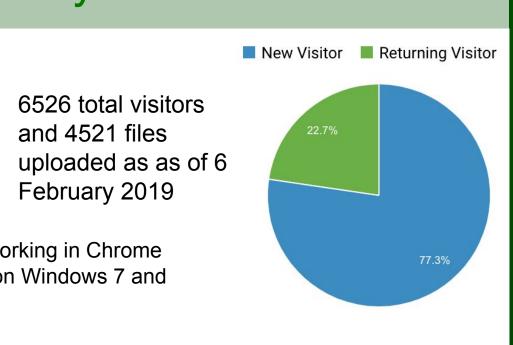
- Updated previously out-of-date library requirement guidelines.
- Added detailed instructions in Wiki to facilitate process of familiarizing new research team members with the materials and processes.
- Added Troubleshooting section to Wiki to allow for continual addition from team members on how to solve common problems.

Future Directions

- Allow the Gene Page feature to support species beyond Saccharomyces cerevisiae by identifying the species name from from user input.
- Implement tests for the Gene Page through the SinonJS testing framework.
- Add detailed tests for the Excel export feature to ensure success with all data input formats.

Availability

- GRNsight is free and open to all users and there is no
- Commons Attribution Non-Commercial Share Alike
- GRNsight code is available under the open source BSD license.
- Usage is being tracked through Google Analytics. GRNsight has been tested with and confirmed to be working in Chrome version 58 or higher and Firefox version 53 or higher on Windows 7 and Mac OS X.



Acknowledgments

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- Saccharomyces Genome Database: https://www.yeastgenome.org/ SinonJS: https://sinonjs.org/
- UniProt: https://www.uniprot.org/