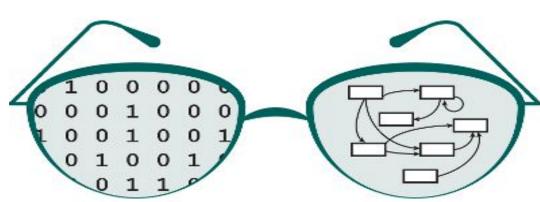
A Dynamic Gene Page Feature for GRNsight: a Web Application for Visualizing Models of Gene Regulatory Networks

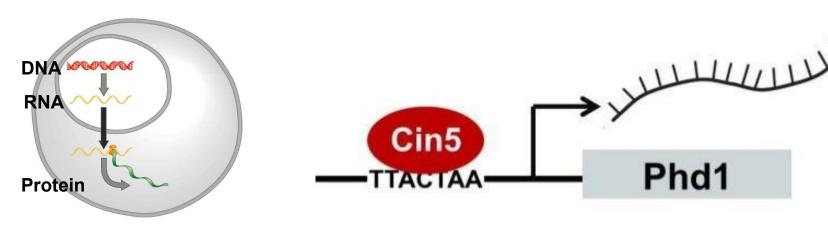


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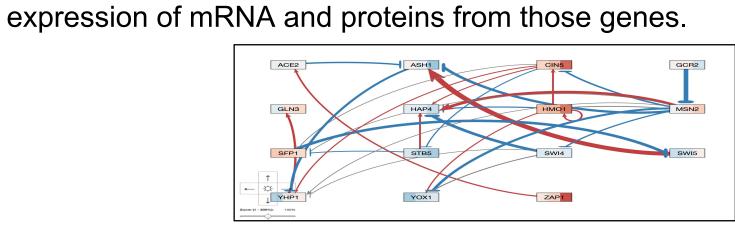


Gene Regulatory Networks Can Be Illustrated by Directed Graphs

- The central dogma of molecular biology describes the flow of information in a cell during gene expression from 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.



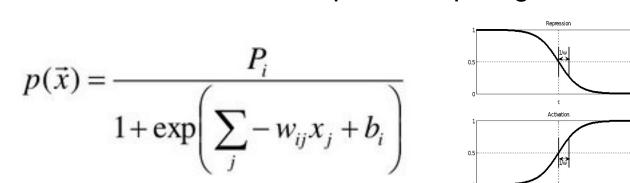
• A gene regulatory network (GRN) consists of genes, transcription factors, and the regulatory connections between them, which govern the level of



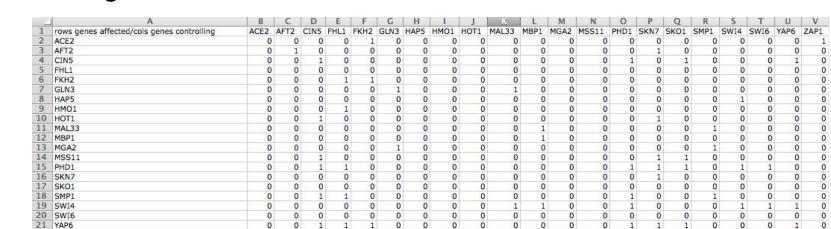
- Each node represents the gene, the mRNA, and the protein expressed from the gene.
- Each edge represents a regulatory relationship.
- All the nodes are transcription factors themselves.

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 an Excel spreadsheet with an adjacency matrix representing the network.



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

. 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

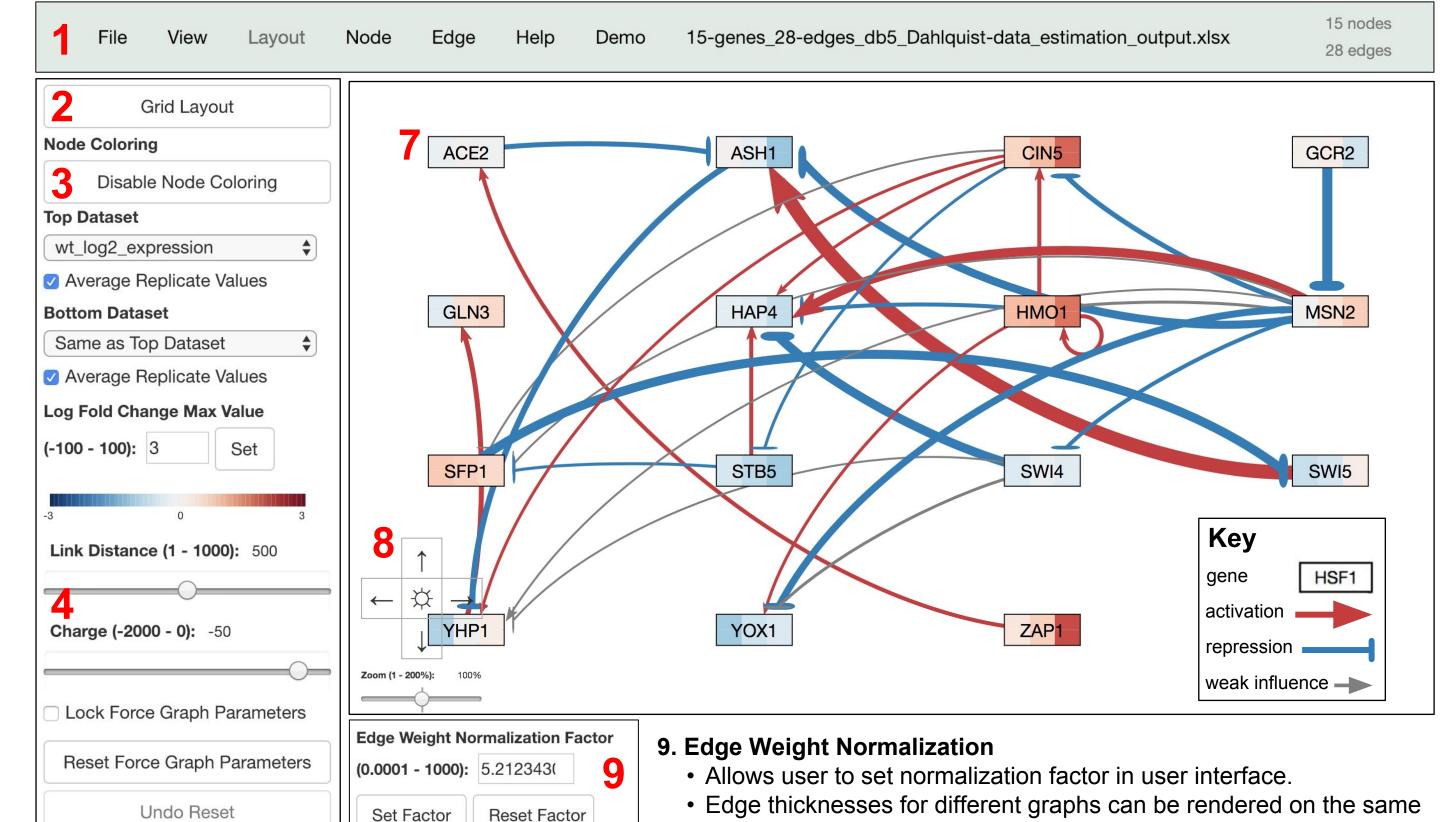
- Graph bounding box can be separated from viewport.
- Multiple viewport sizes available. • Zooming and scrolling enabled.

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



• Facilitates accurate visual comparison.

- 10. Gray Edge Threshold
- Slider allows the gray edge threshold to be customized. Gray edges allow users to visually gauge whether a particular regulatory relationship is not important.
- 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.

Gene Page Feature Presents Data for a Selected Saccharomyces cerevisiae Node

Gray Threshold (0 - 100%): 5%

Show Gray Edges as Dashed

Application Processing Interfaces (APIs) Allow the Gene Page to **Gather Data**

- AJAX requests allow gene page to communicate with the NCBI, UniProt, JASPAR, and Saccharomyces Genome databases and
- Data is returned in either eXtensible Markdown Language (XML) or JavaScript Object Notation (JSON) format.
- Data is returned as pure text, links to an image, or arrays of data which are visualized by the page into lines of text, images, and data
- If no data is returned from any database, an error message is given to the user.

1. Saccharomyces Genome Database

• From the SGD, the page gathers a list of regulators and targets in addition to the SGD ID and gene summary. SGD is also used to collect the Gene Ontology summary and lists of molecular function, biological process, and cellular component terms.

2. NCBI Gene Database

• From the NCBI Database, the page gathers the NCBI ID, chromosome sequence, and the locus tag. This locus tag is used to provide a link to the gene's corresponding page on the Ensembl

3. UniProt

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

4. JASPAR

 From the JASPAR Database, the page gathers the JASPAR ID, class name, family name, frequency matrix, and JASPAR sequence

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 the APIs, the page implements a relay from the primary GRNsight server to the API calls.

ACE₂

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

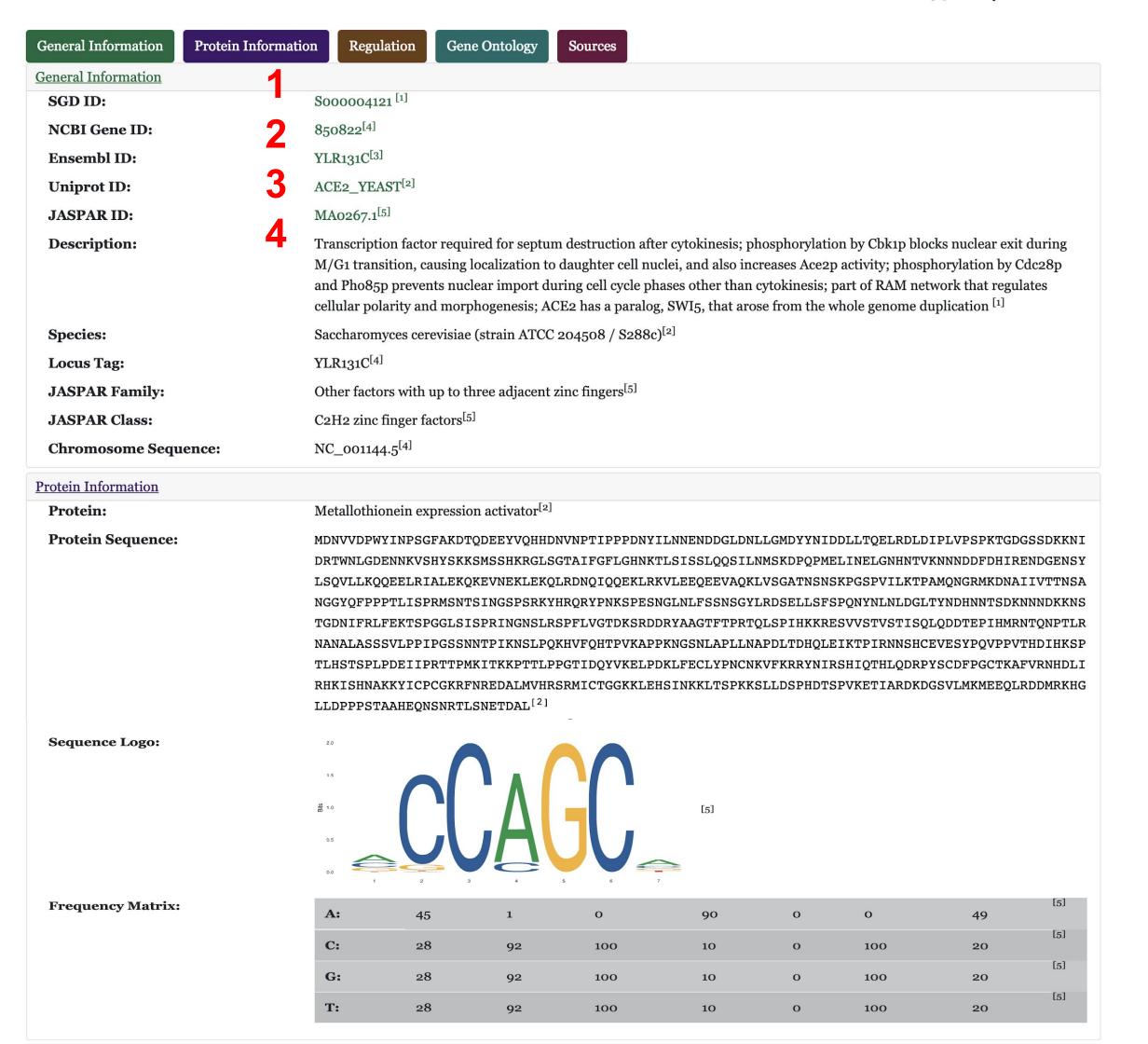
Never Show Edge Weights

Show With Mouse Over

Viewport Size 5

Fit to window

Saccharomyces cerevisiae (strain ATCC 204508 / S288c)



New Export to Excel Feature

GRNsight can import data in a variety of formats (SIF, GraphML, GRNmap), and we want this application to export to a variety of formats, as well. This has prompted the addition of the new export to Excel Workbook feature.

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 a given datasheet.
- Implement tests for the Gene Page through the SinonJS testing framework. Add detailed tests for Excel export feature to ensure success with all data

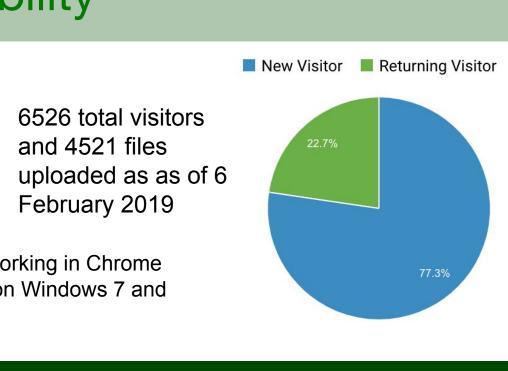
Availability

and 4521 files

- GRNsight is free and open to all users and there is no

input formats

- Commons Attribution Non-Commercial Share Alike
- GRNsight code is available under the open source 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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References

- Dahlquist KD, Dionisio JDN, Fitzpatrick BG, Anguiano NA, Varshneya A, Southwick BJ, Samdarshi M. 2016. GRNsight: a web application and service for visualizing models of small- to medium-scale gene regulatory networks. PeerJ Computer Science 2:e85 https://doi.org/10.7717/peerj-cs.85
- Ensembl: https://uswest.ensembl.org/index.html Freeman, S. (2002) Biological Science. Upper Saddle River, New Jersey: Prentice Hall. GRNmap: http://kdahlquist.github.io/GRNmap
- JASPAR: jaspar.genereg.net
- National Center for Biotechnology Information: https://www.ncbi.nlm.nih.gov/ Saccharomyces Genome Database: https://www.yeastgenome.org/
- SinonJS: https://sinonjs.org/