GRNsight v7: a web application for visualizing gene regulatory networks and protein-protein interactions

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Southern California Conference
for Undergraduate Research
November 22, 2025

Loyola Marymount University
Frank R. Seaver
College of Science
and Engineering

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Outline

- Gene Regulatory Networks (GRN) consist of genes, transcription factors, and the regulatory connections between them
- Protein-Protein Interactions (PPI) are the binding relationships between proteins
- GRNsight is an open source visualization tool that allows for easier modeling of GRNs and PPIs
- GRNsight transitioned our database source from YeastMine to AllianceMine
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3

Gene expression is the flow of information in a cell from DNA to RNA to the final protein

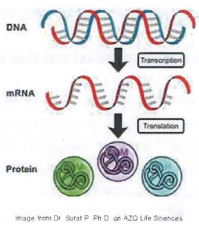
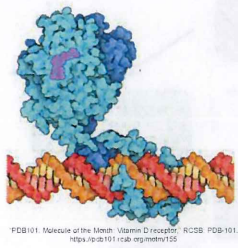


Image from Dr. Surat P. Ph.D. on AZQ Life Sciences

4

Regulatory Transcription Factors bind to DNA and turn on (activate) or turn off (repress) gene expression

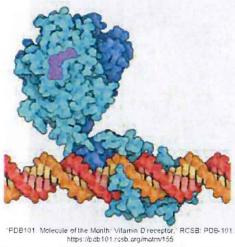


"PDB101: Molecule of the Month: Vitamin D receptor." RCSB: PDB-101. https://pdb101.rcsb.org/motm/155

- In yeast, ~250 regulatory transcription factors regulate ~6000 genes.
- In humans, ~500 regulatory transcription factors regulate ~20,000 genes.

5

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 protein from genes



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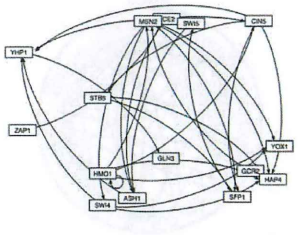

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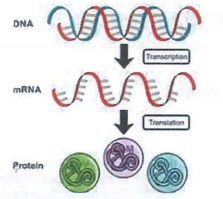
Milka

Protein-Protein Interactions refer to the physical interactions of proteins binding to each other - the basis of nearly all cell functions



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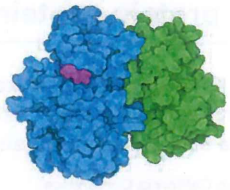

"PDB101: Molecule of the Month: Cyclin and cyclin-dependent kinase." RCSB: PDB-101. https://pdb101.rcsb.org/motm/236

8

Maiba

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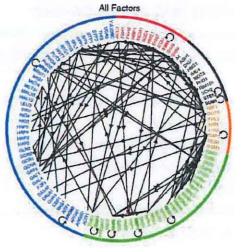
9

Maiba

Large gene regulatory networks are difficult to visualize

Gene Regulatory Network (GRN) of 106 Transcription Factors in Yeast



Lee *et al.* (2002)

10

Maiba

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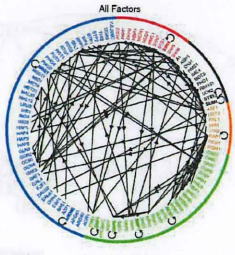

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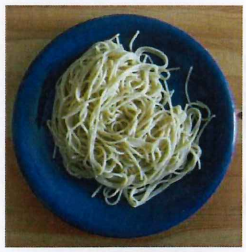
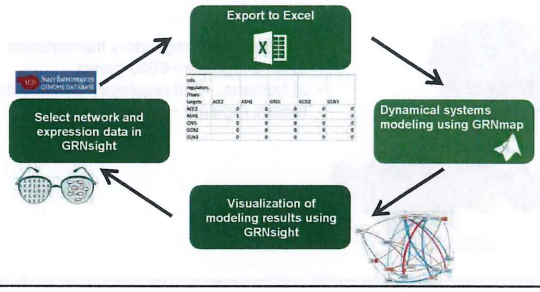


11

Maiba change title + use as summary

~~Our new integrated GRNmap – GRNsight system will speed up the rate of modeling and analysis of many networks~~



12

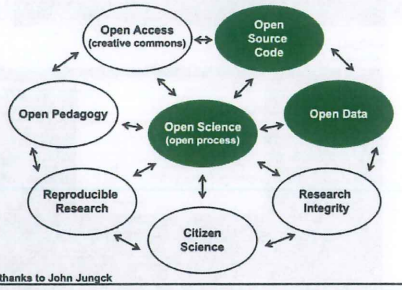
this slide seems out of place especially because people don't know what GRNmap is

maybe use at end?

this is out of place here move to after slide 62

Maria

GRNsight is part of an open science ecosystem



With thanks to John Jungck

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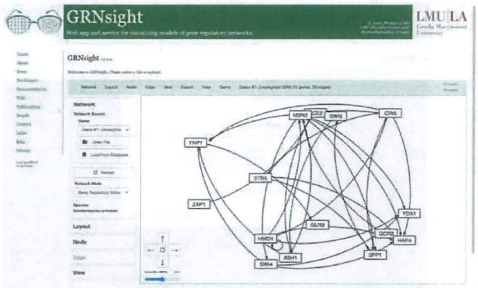
Maria

line break

GRNsight rapidly generates graphs using customizations to the Open Source D3 Library



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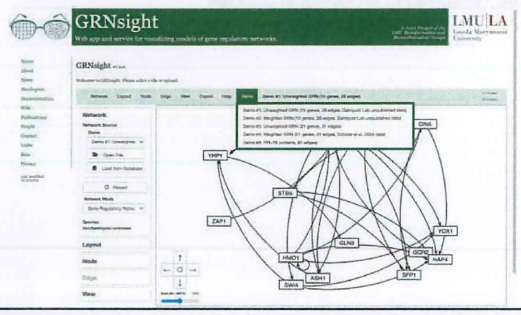
To get started quickly, GRNsight also provides different demos



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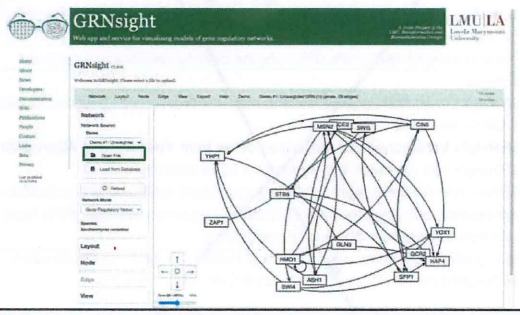
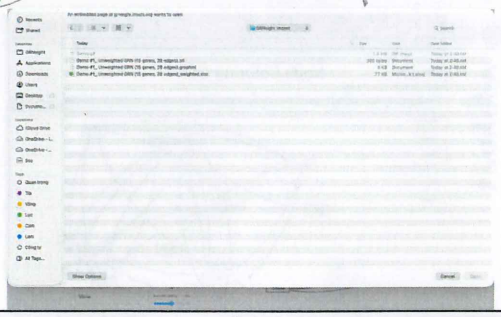
Users can import networks via File Upload



16

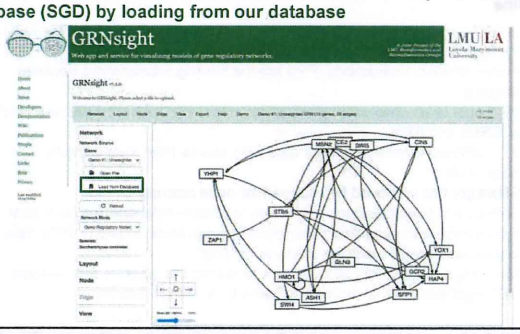
The imported file need to be in supported format (SIF, GraphML and Excel)



17

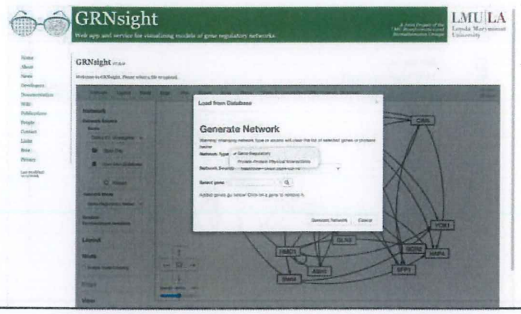
Say yeast

Users can construct custom networks from Saccharomyces Genome Database (SGD) by loading from our database



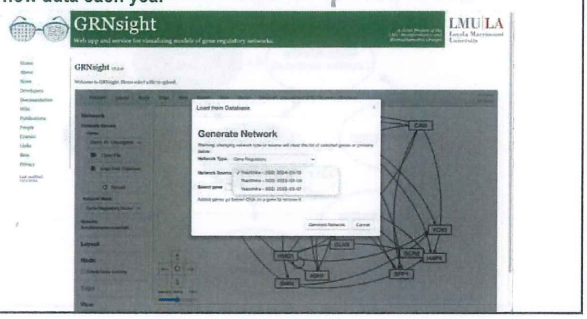
18

Users can switch different network types between GRN and PPI



19

Users can choose different network sources since GRNsight refreshes with new data each year



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Starting in 2025, AllianceMine is the GRNsight's new database source because YeastMine is no longer supported

Image TBD

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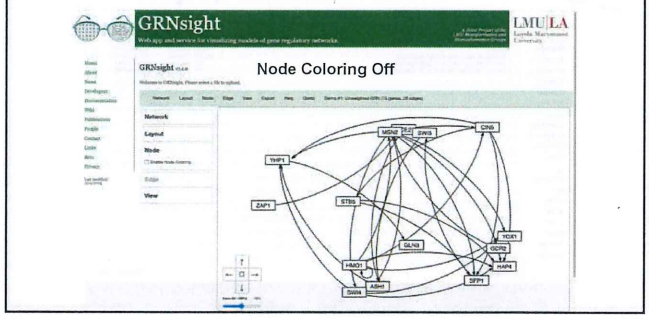
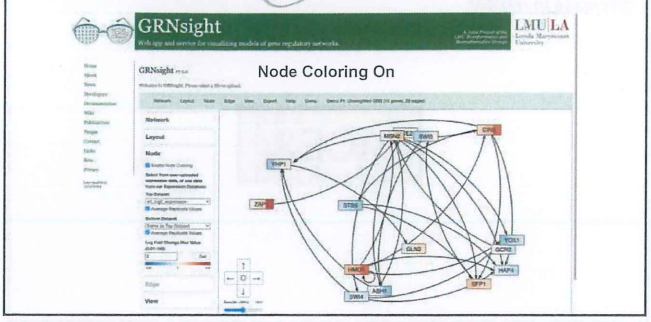
Nodes can be colored via an On/Off toggle



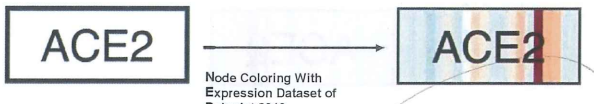
24

Nodes can be colored via an On/Off toggle



25

Nodes are colored with a heat map overlay to visualize time series expression data



Node Coloring With Expression Dataset of Dalquist 2018

26

Each vertical slides on the node represents the expression values of a transcription factor at a given time point

27

Blue slices represent negative expression values (indicating a decrease in mRNA).

28

Blue slices represent negative expression values (indicating a decrease in mRNA).

29

Blue slices represent negative expression values (indicating a decrease in mRNA).

30

Blue slices represent negative expression values (indicating a decrease in mRNA).

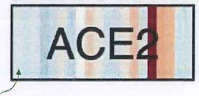
31

Blue slices represent negative expression values (indicating a decrease in mRNA).

32

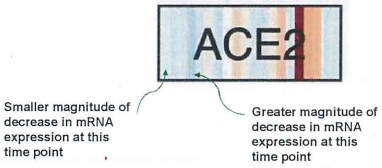
line break

The greater the magnitude of the expression value, the darker the shade of blue.



33

The greater the magnitude of the expression value, the darker the shade of blue.



34

line break

Similarly, red slices represent positive expression values (indicating an increase in mRNA)

35

Similarly, red slices represent positive expression values (indicating an increase in mRNA)

36

Similarly, red slices represent positive expression values (indicating an increase in mRNA)

37

Similarly, red slices represent positive expression values (indicating an increase in mRNA)

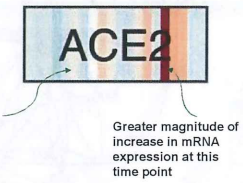
38

line break

The greater the magnitude of the expression value, the darker the shade of red.

39

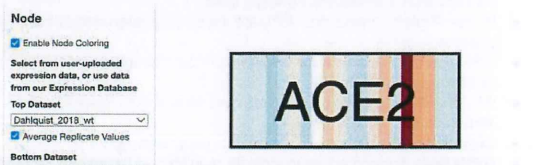
The greater the magnitude of the expression value, the darker the shade of red.



40

Multiple

Each node has top and bottom expression datasets that contribute to its coloring where it can have top and bottom have the same expression datasets



top + bottom same

41

Each node can display different datasets on the top and bottom

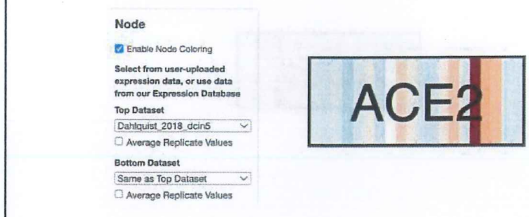
Or users can have split view visualization of differential expression datasets for easier comparison

top + bottom different

42

dcin5 wt

When checking the option "average replicate value", GRNsight will average replicate expression values taken at the same timepoint ~~for the selected half of node coloring~~



43

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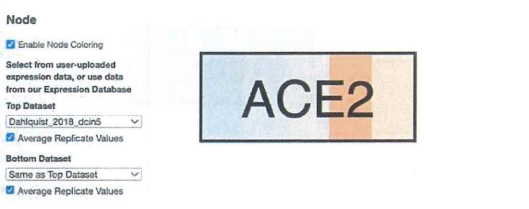
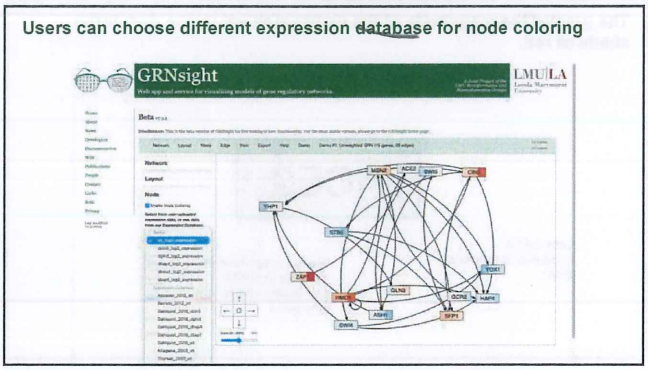


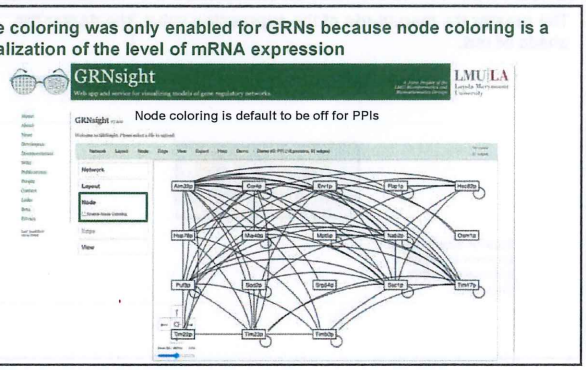
44

Users can choose different expression ~~database~~ datasets for node coloring



45

Node coloring was only enabled for GRNs because node coloring is a visualization of the level of mRNA expression previously



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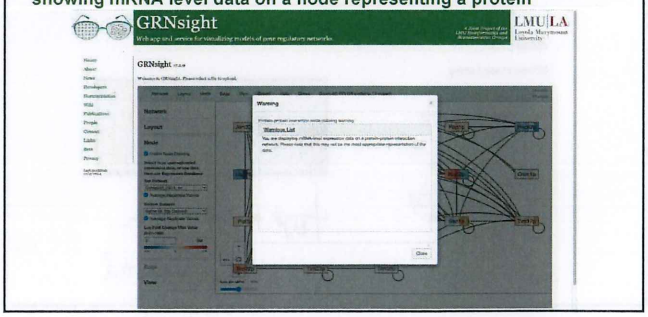
Version 7.2 allows node coloring for PPIs but with warnings, as it is showing mRNA level data on a node representing a protein



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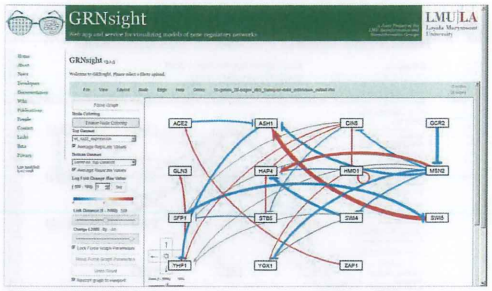
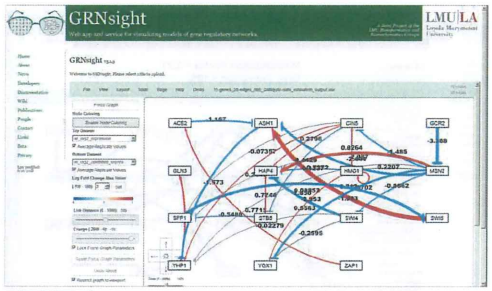
Edge weight values are indicated by color, thickness, and end marker



New color scheme in Version 3

49

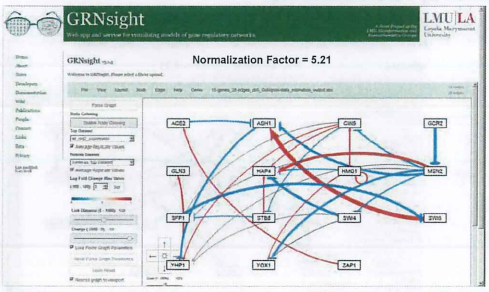
Numerical edge weight values can be displayed on the graph



New in Version 2

50

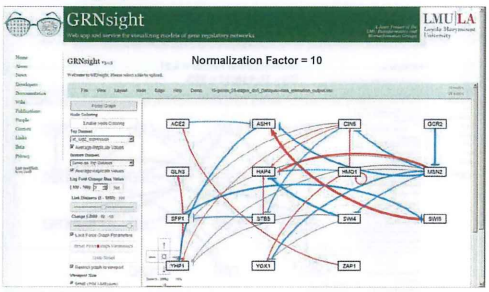
Edge thicknesses are normalized to the largest magnitude weight value



Version 1

51

Normalization factors can be modified to allow fair visual comparison between different graphs

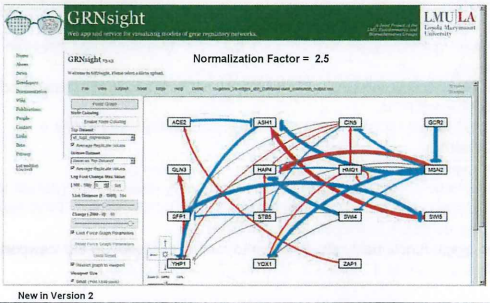


New in Version 2

52

lowercase

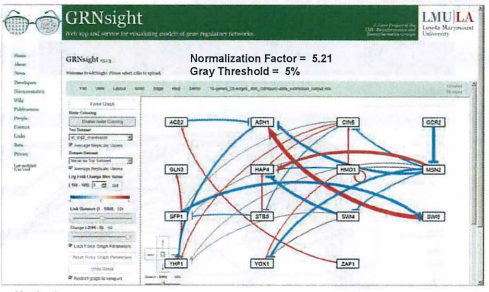
Normalization factors can be modified to allow fair visual comparison between different graphs



New in Version 2

53

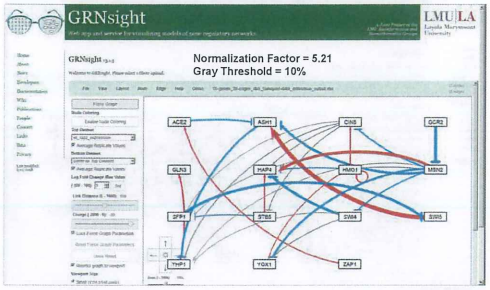
Edges with normalized weight values within 5% of Zero are displayed as gray to minimize their visual strength



Version 1

54

Users can change the gray threshold with a slider



55

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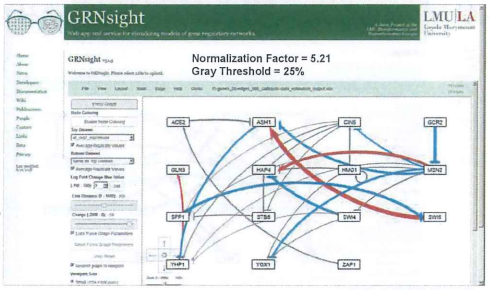
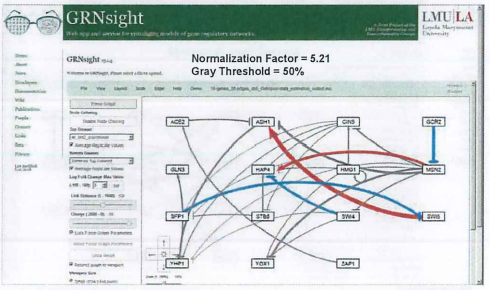


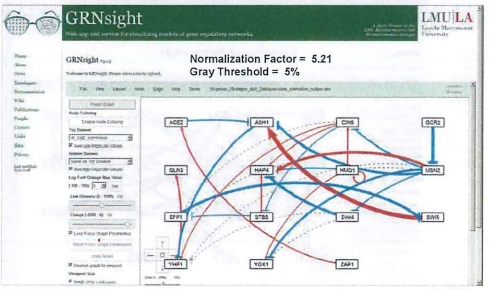
56

Users can change the gray threshold with a slider



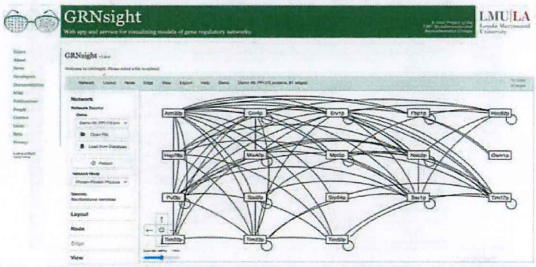
57

Gray edges can also be shown as dashed lines to facilitate visualization by color blind users



58

GRNsight displays PPI networks as undirected graphs for they are just binding relationships, not regulatory



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Outline

- Gene Regulatory Networks (GRN) consist of genes, transcription factors, and the regulatory connections between them
- Protein-Protein Interactions (PPI) are the binding relationships between proteins
- GRNsight is an open source visualization tool that allows for easier modeling of GRNs and PPIs
- V7 - GRNsight transitioned our database source from YeastMine to AllianceMine
- GRNsight has improved PPI support for node coloring
- GRNs have directed edges to indicate regulatory relationships (activation or repression), with edge thickness indicating regulation strength. PPIs have undirected edges to indicate physical binding
- New graph functionality allows users to restrict the graph to the viewport.
- GRNsight switched CI tools from Travis CI to Github Actions

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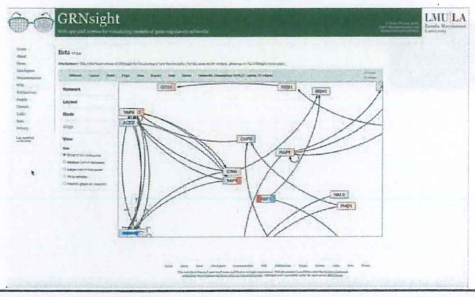
TN4

Users can choose between a small, medium or large viewport size



61

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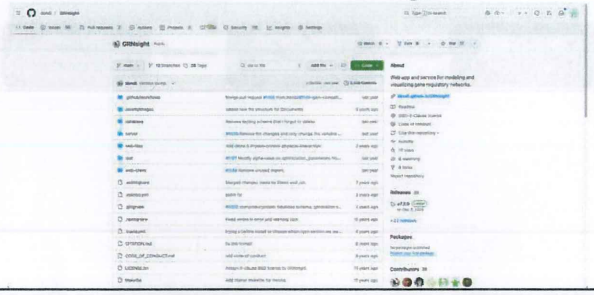
move slide 13 here

All GRNsight development occurs in an open repository

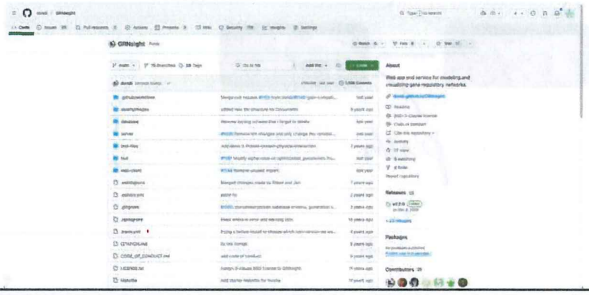
source



63

source

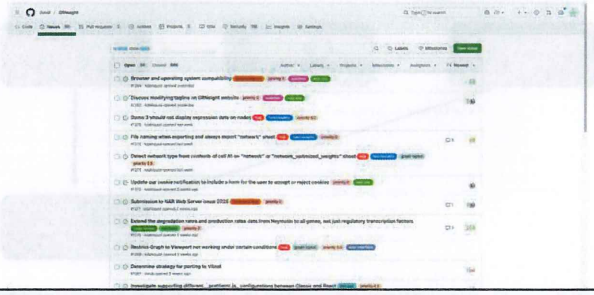
All code can be viewed in the Code ~~files~~ tab



64

tab

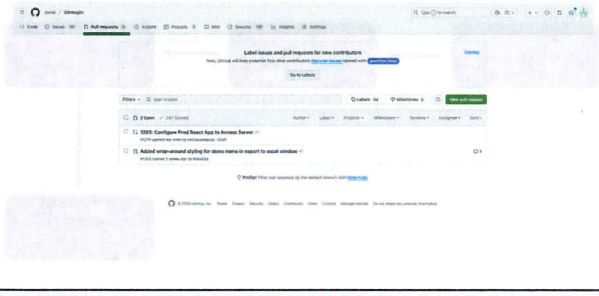
All feature requests and bugs are reported in the Issues page



65

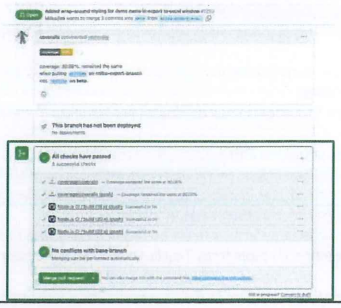
line break

Developers create pull requests when the code is ready to review and merge



66

This is where Continuous Integration (CI) plays important role



67

Continuous Integration is the practice of developers merging code into a central repository frequently

68

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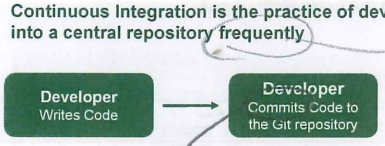
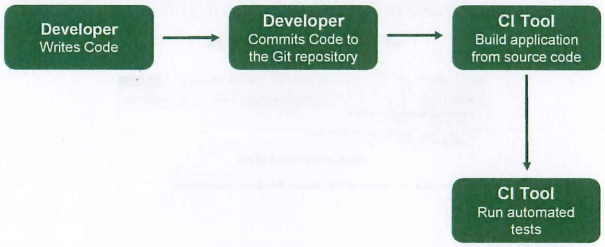


69

Every code commits triggers a build

70

The build is validated by running automated tests



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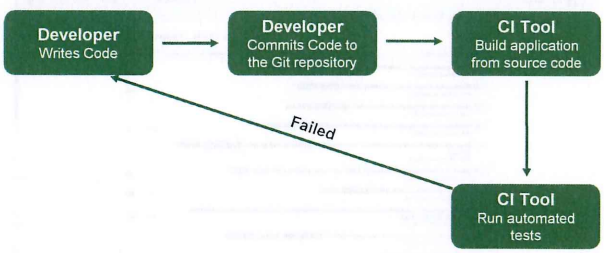
If problem detected, developers need to make changes and write code again



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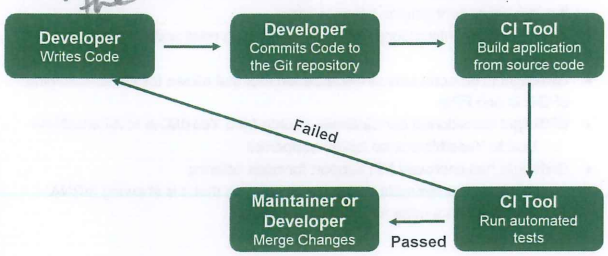
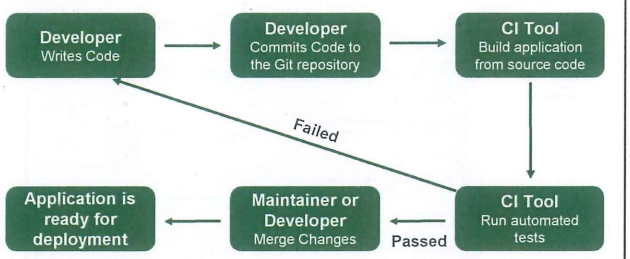
If all automated tests passed, maintainer or developers merge changes



73

After all changes got merged, application is ready for deployment



74

V7 - GRNsight migrated from Travis CI to Github Actions for CI tools due to Travis' user limit for their free plan

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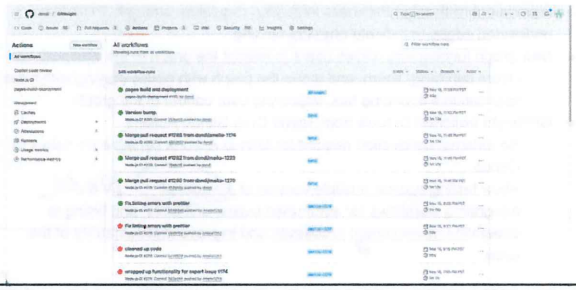
Github Actions is native to Github so no external connection is needed



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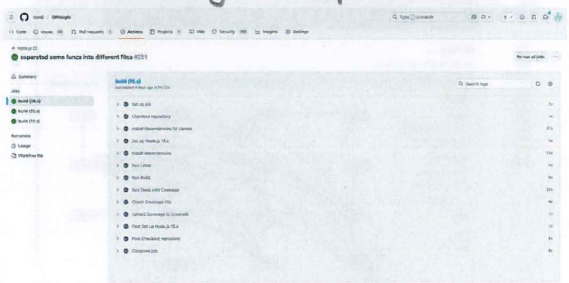
Github Actions also allows testing against multiple versions of ~~JavaScript~~ Node.js interpreter



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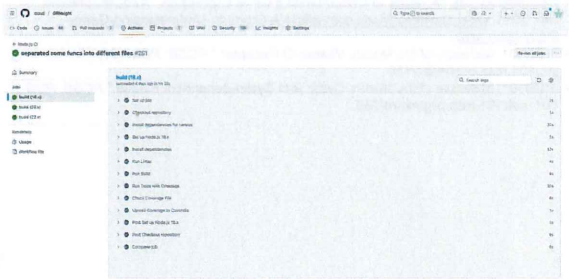
Green check indicates the code passed all the tests



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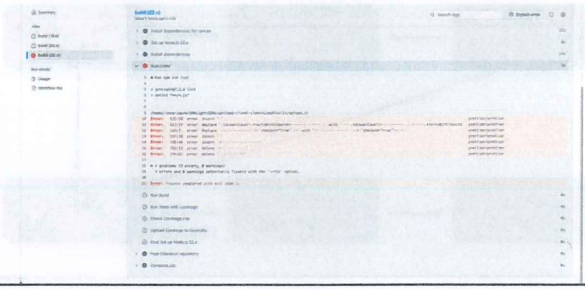
A red 'X' appears if the test failed



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Summary

- Gene Regulatory Networks (GRN) consist of genes, transcription factors, and the regulatory connections between them
- Protein-Protein Interactions (PPI) are the binding relationships between proteins
- GRNsight is an open source visualization tool that allows for easier modeling of GRNs and PPIs
- GRNsight transitioned our database source from YeastMine to AllianceMine
  - Due to YeastMine is no longer supported
- GRNsight has improved PPI support for node coloring
  - PPI is supported node coloring with warning that it is showing mRNA level data on a node representing a protein

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Summary

- GRNs have directed edges to indicate regulatory relationships (activation or repression), with edge thickness indicating regulation strength. PPIs have undirected edges to indicate physical binding.
- New graph functionality allows users to restrict the graph to the viewport.
  - Users can drag, zoom, and move the graph with nodes staying within the application's bounding box, improving user control of the graph
- GRNsight switched CI tools from Travis CI to Github Actions
  - No external connection needed for Github Actions because it's native to Github
  - Allow testing against multiple version of JavaScript
  - Integrating workflows for automated builds, unit tests, and linting to streamline development processes and improve maintainability of the code

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Acknowledgements

John David N. Dionisio
Kam D. Dahlquist
Cecilia J. Zaragoza
Nikki C. Chun
A'Kaia Phelps
Amelie Dinh
HHMI STEM Research Learning Community
LMU Department of Biology

http://dondi.github.io/GRNsight/

https://github.com/dondi/GRNsight

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References

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- "PDB101: Molecule of the Month: Vitamin D Receptor." *RCSB: PDB-101*, pdb101.rcsb.org/motm/155.
- "PDB101: Molecule of the Month: Cyclin and Cyclin-dependent Kinase." *RCSB: PDB-101*, pdb101.rcsb.org/motm/236.

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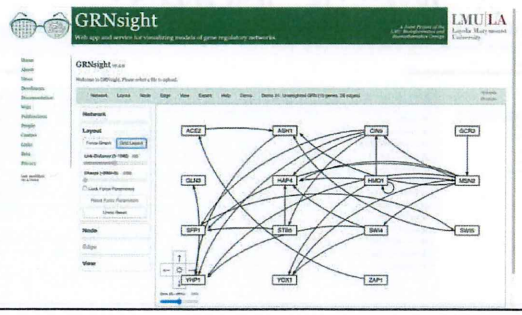
Users can choose to display the graph as grid block layout



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