Deletion of Full Strain Data from a Cold Shock Gene Regulatory Network for *Saccharomyces cerevisiae* and Re-estimation of Parameters

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Outline

1. GRNmap is a MATLAB software that uses differential equations to produce parameter estimations for GRN dynamics.
2. GRNsight can be used to visualize GRN models.
3. A previous edge deletion experiment was conducted to determine the importance of edges in a cold shock GRN.
4. The present experiment involves the deletion of full strain data from the GRN and a re-estimation of the parameters.
5. A comparison of LSE:minLSE ratio reveals the deletion of strain data affects the fit of the model to the experimental data.
6. The visualization of weight estimations on a heat map reveals no major consistencies.

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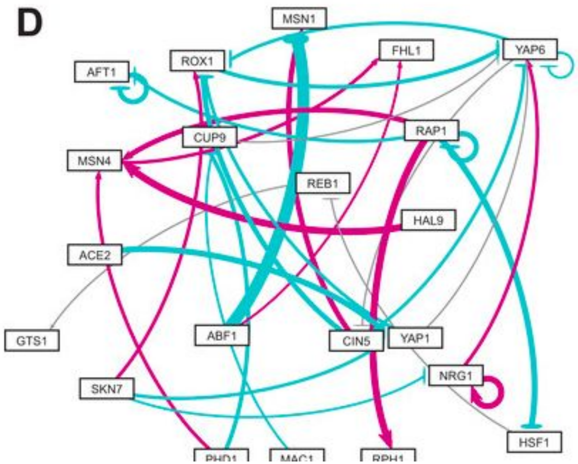
GRNmap uses differential equations to produce parameter estimations

- **GRNmap** (Gene Regulatory Networks modeling and parameter estimation)
    - Use of differential equations to model the dynamics of GRNs (Dahlquist et al., 2016)
    - Estimation of regulation weights, expression threshold, and production rates
    - LSE (Least Squares Estimation)
        - Minimize discrepancies between model and expected values (Van de Geer, 2005)
        - LSE:minLSE ratio gives the goodness of fit of the model

GRNsight offers the visualization of gene regulatory networks based on weight parameters



Cyan - Repression

Magenta - Activation

* Thickness of edge refers to weight

- **GRNsight**
  - Visualization of models for gene regulatory networks (Dahlquist et al., 2016)
  - Unweighted or weighted Simple Interaction Format (SIF) file
    - Regulatory weights of the edges from the resulting GRN

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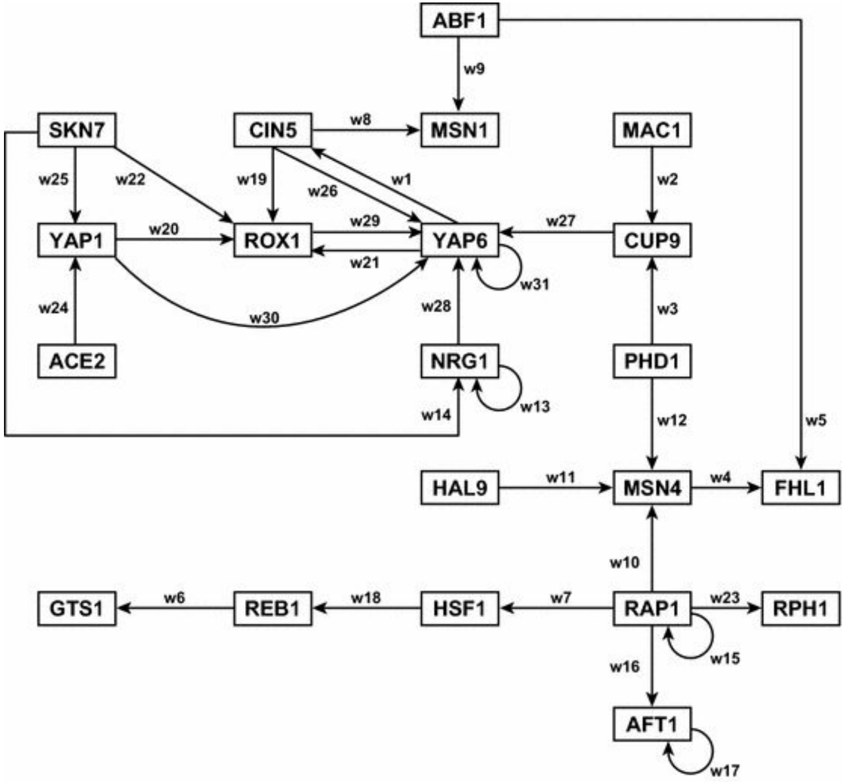
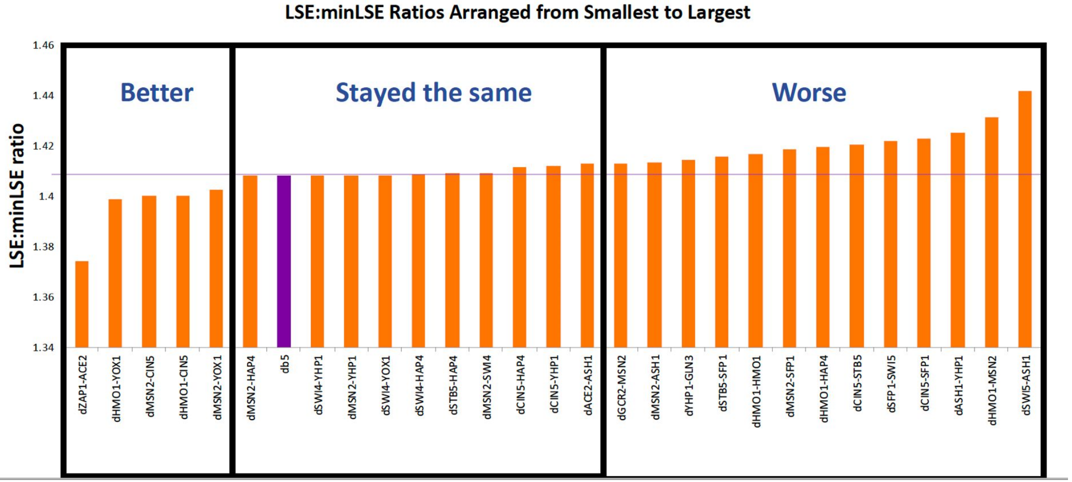
A gene regulatory network depicts the relationship between transcription factors affected by cold shock



- Cold shock gene regulatory network
  - Data from microarray experiments
  - wt, *Δcin5, Δgln3, Δhap4, Δhmo1,* and *Δzap1*
  - 15 nodes and 28 edges
- Previous experiment
  - Edge deletion

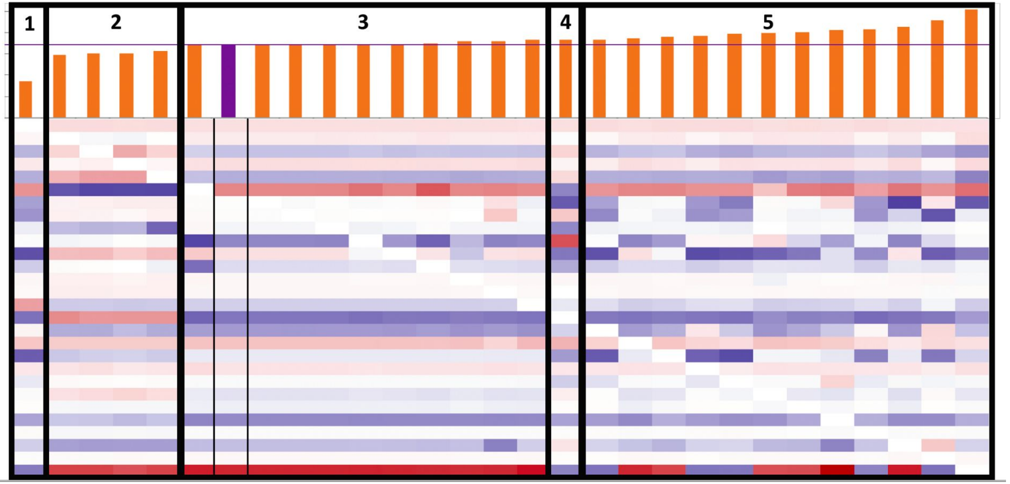
Increased LSE:minLSE ratios indicate the importance of the dSWI5 → dASH1 edge



- Systematic deletion of the edges, resulting in 28 new GRNs
- Re-estimation of the parameters using differential equations
    - LSE:minLSE ratio
- Determine the importance of each edge
    - Increased ratio indicates importance
        - dSWI5 → dASH1

(Kelly, 2019)

Re-estimated weight parameters produced groups with similar regulatory relationships



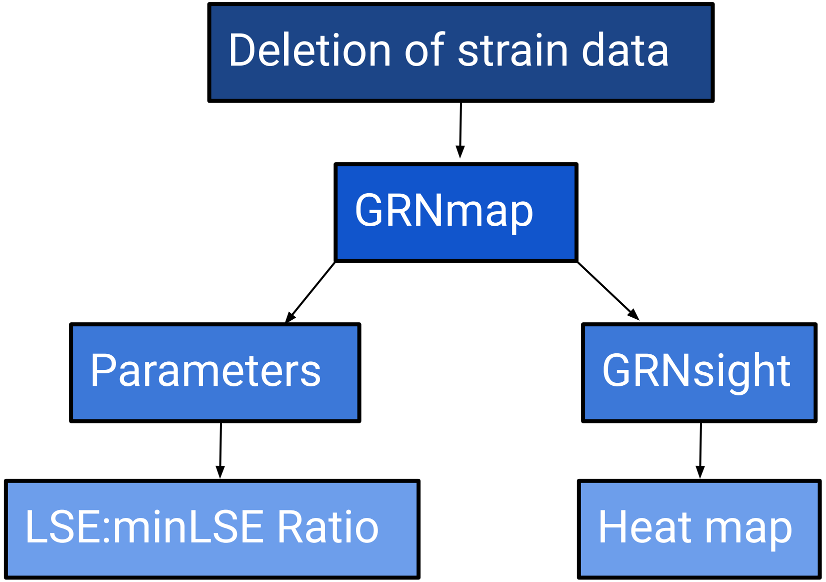
- Re-estimated weight parameters for the 28 new GRNs in a heat map
- Similarity in the activation/repression for three sets
- Changes in weights may be compensation for missing edge

(Kelly, 2019)

The current experiment involves the deletion of strain data from the analysis

- Deletion of **full strain data**
  - 32 networks
    - Wild-type only
    - Wild-type plus one strain
    - Wild-type plus two strains
    - Wild-type plus three strains
    - Wild-type plus four strains
    - All-strains

      * All-strain network is db5



Deletion of strain data

GRNmap

Parameters

GRNsight

LSE:minLSE Ratio

Heat map

* Degradation rates from Belle et al., 2006
Weight = 1
Threshold (b) = 0

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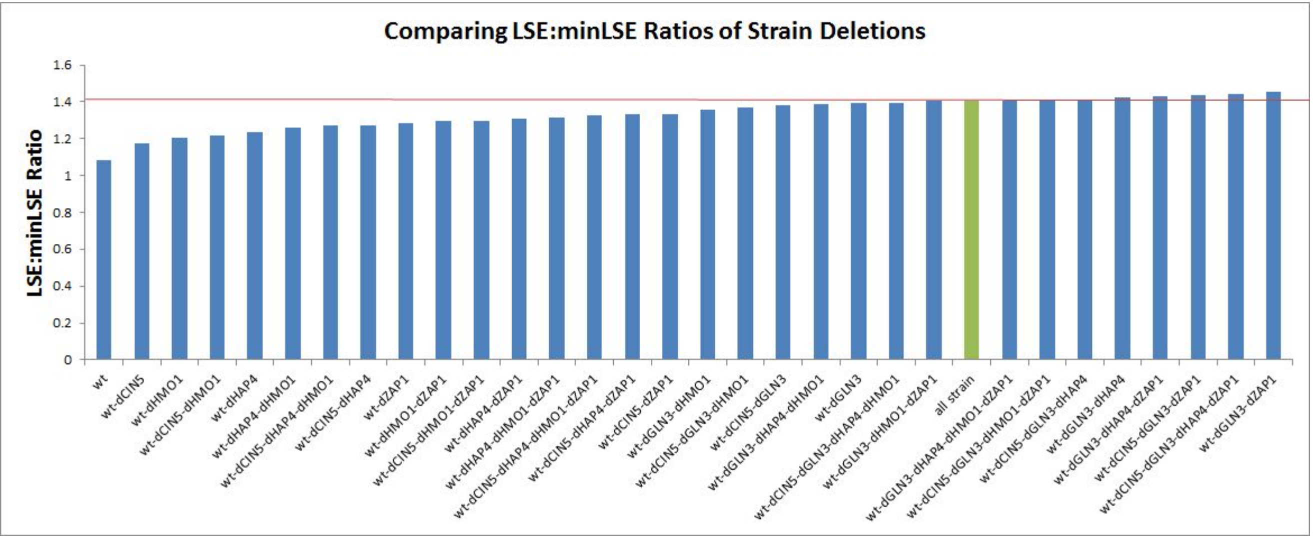
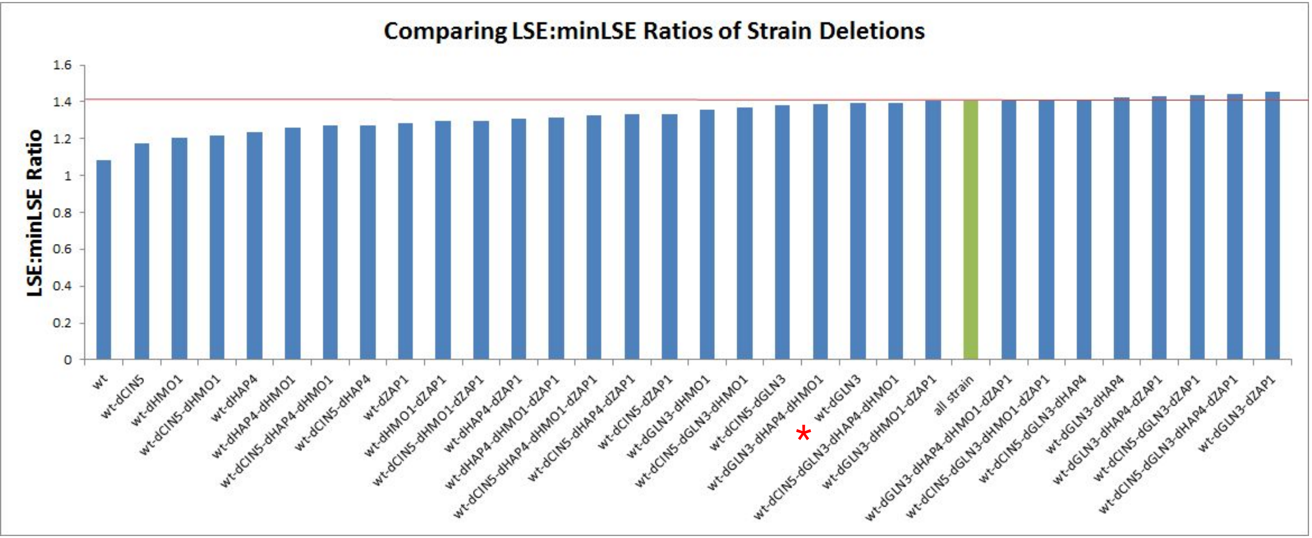
Majority of strain deletions showed a decrease in LSE:minLSE ratio compared to all-strain data



- LSE:minLSE ratio
  - All-strain: 1.408
  - 22 performed better
  - 5 performed worse
  - 4 performed about the same
- wt-plus-one-strain showed consistent decreased ratio

- 23.1% decrease in ratio for wt-only
- 2.27% increase in ratio for wt-dGLN3-dZAP1

Deletion of dGLN3 and dZAP1 strain data reduces the LSE:minLSE ratio

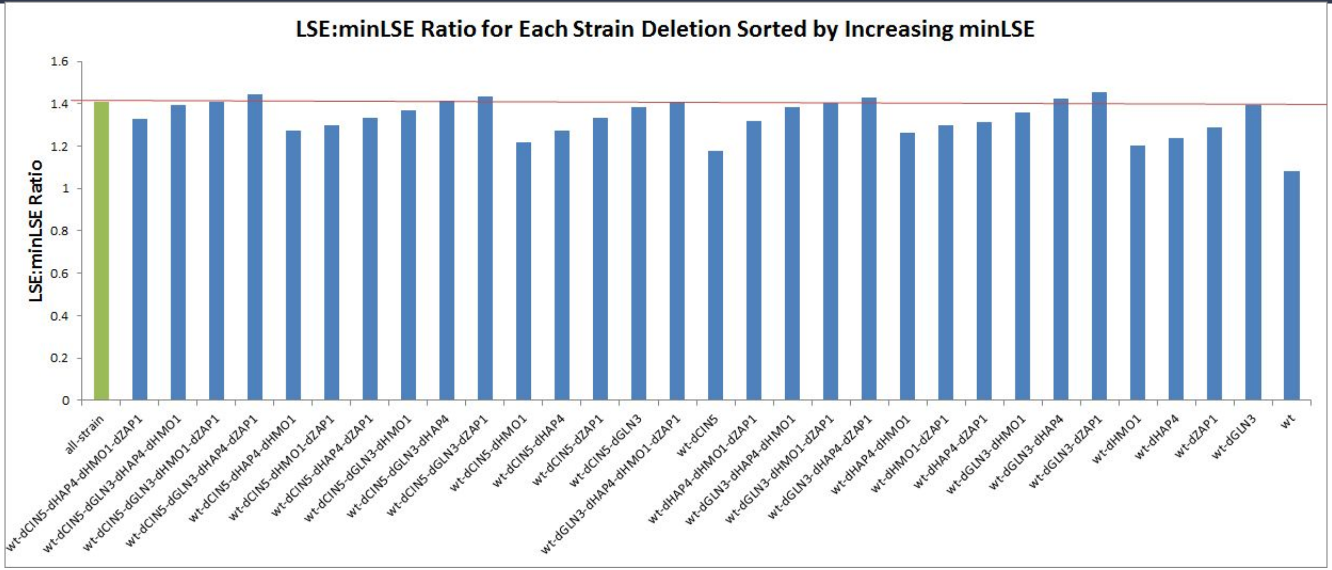


- **wt-dGLN3**
  - highest LSE:minLSE ratio of the wt-plus-one-strain
- Lowest ratio when dGLN3 and dZAP1 are deleted

Do not include:
- dGLN3
- dZAP1

All include dGLN3

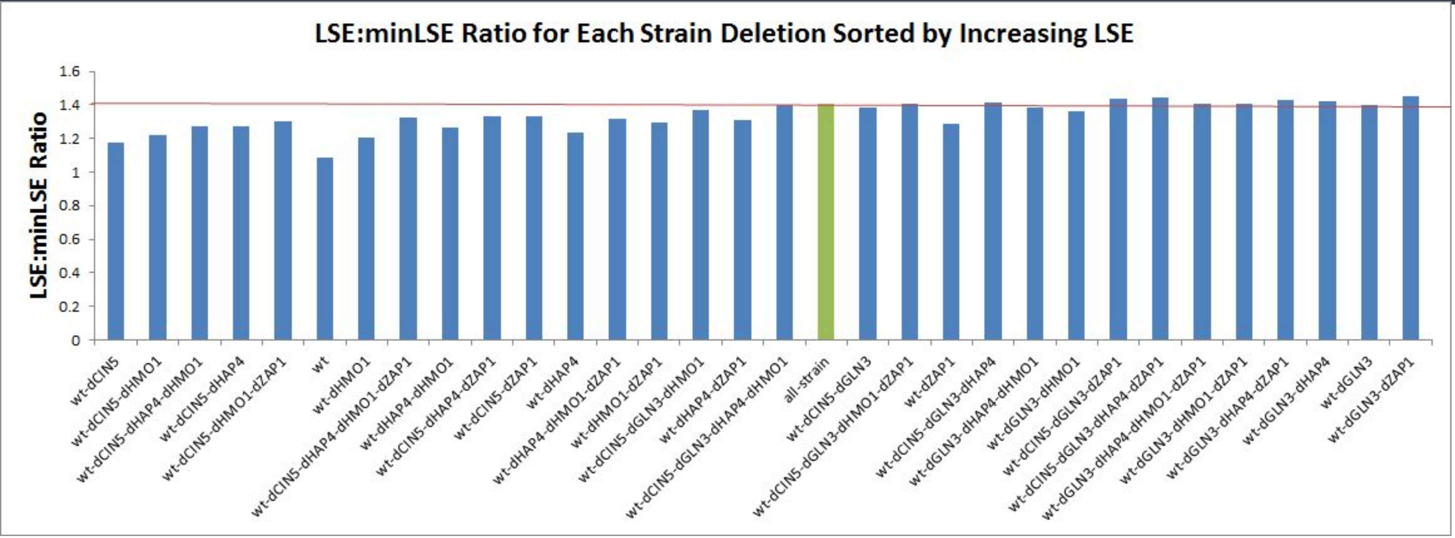
The inclusion of more strain data decreased the minLSE



All include dCIN5

- LSE:minLSE sorted by increasing minLSE
- Wild-type only had the highest minLSE
- Inclusion of more data reduced the minLSE
- All strain deletion trials showed an increase in minLSE

The strain deletions with the lowest LSE do not include dGLN3 strain data



None include dGLN3

- LSE:minLSE sorted by increasing LSE

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Heat map reveals variance in weight estimations across the strain deletions

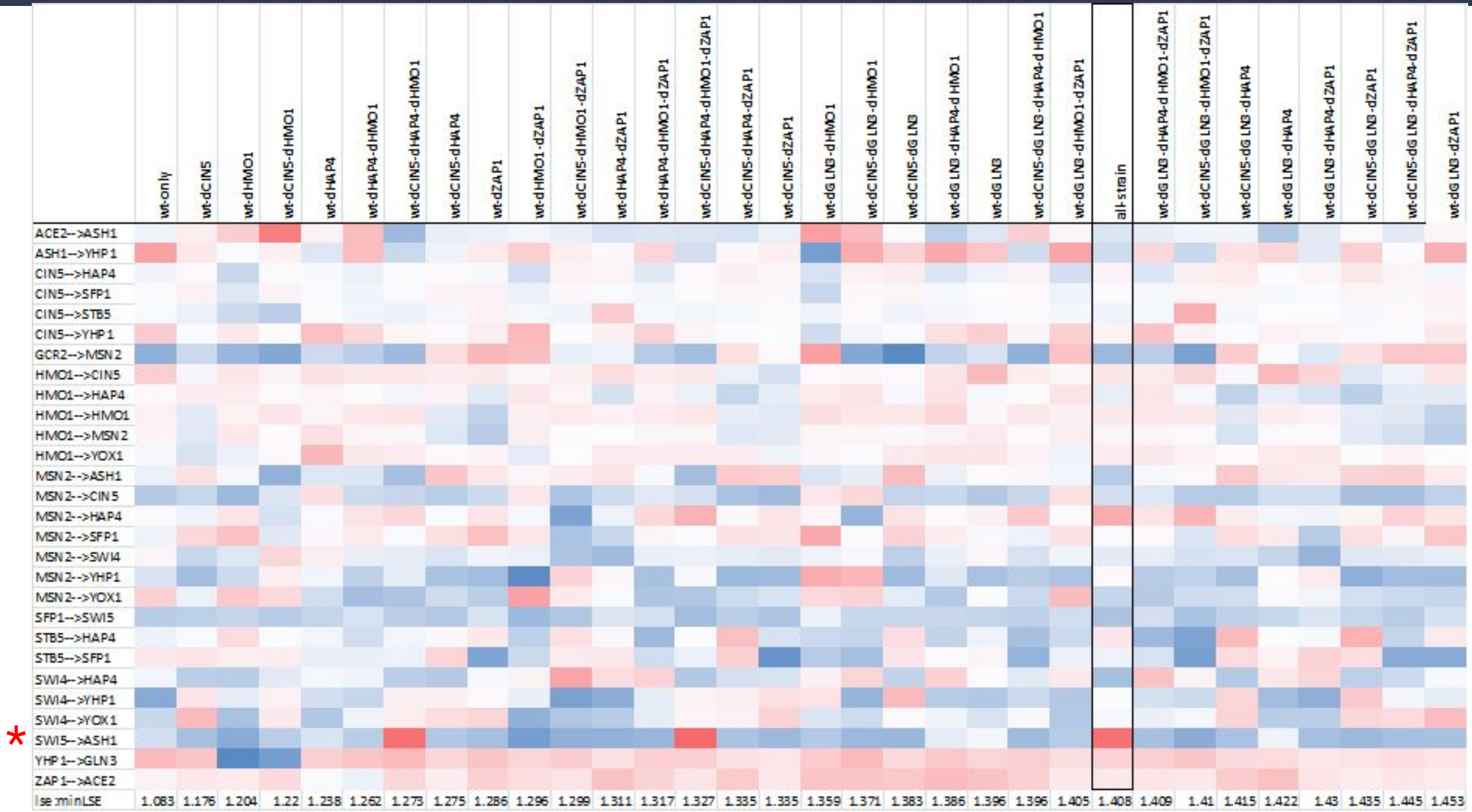
- Variance in weights from the all-strain to the strain deletions
- Red - activated

  Blue- Repressed

SFP1→ SWI5

SWI5→ ASH1
YHP1→ GLN3
ZAP1→ ACE2

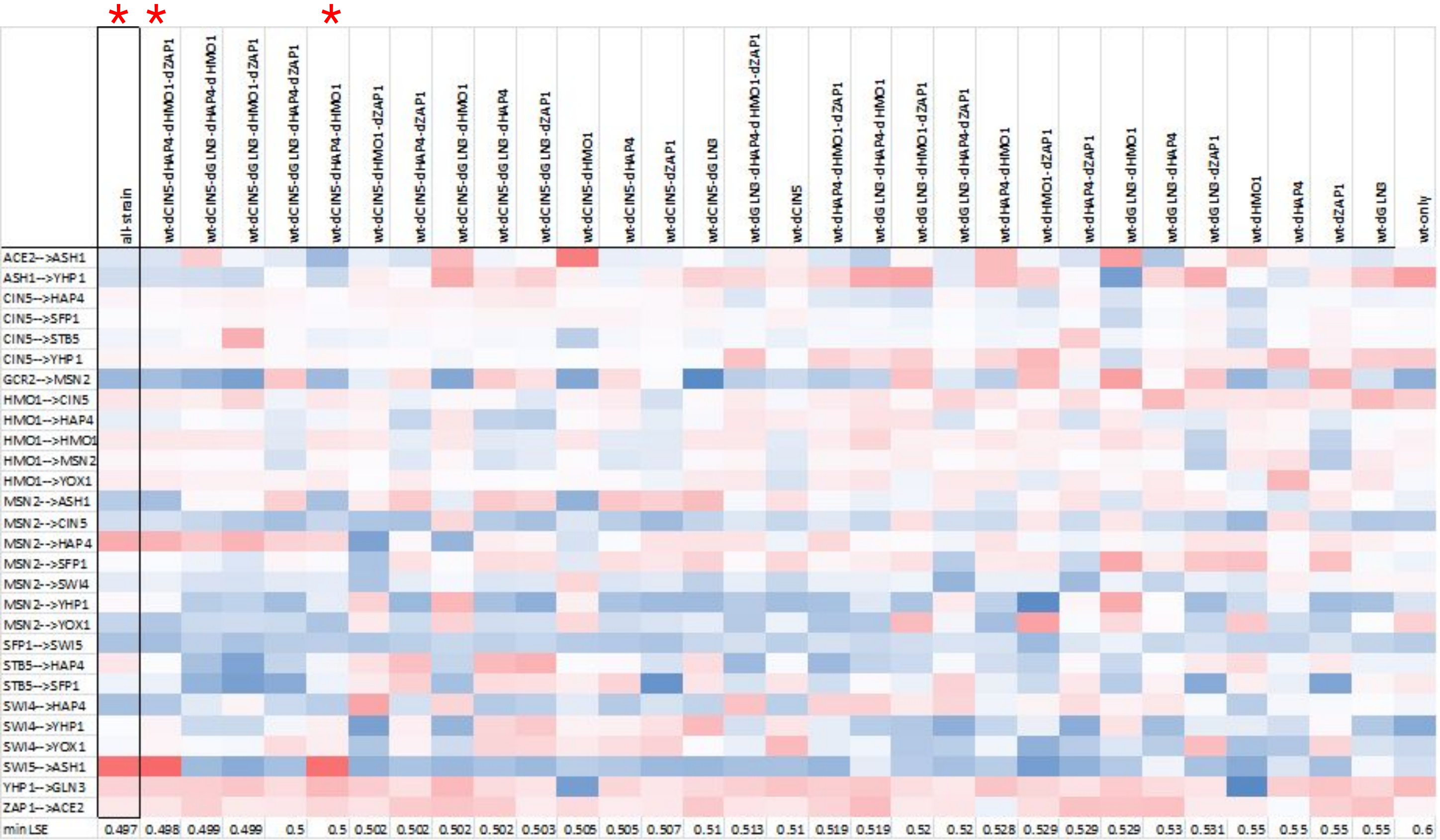
No major consistencies in weight estimation are depicted on the heat map for the strain deletions



	wt-only	wt-dCIN5	wt-dHMO1	wt-dCIN5-dHMO1	wt-dHAP4	wt-dHAP4-dHMO1	wt-dCIN5-dHAP4-dHMO1	wt-dCIN5-dHAP4	wt-dZAP1	wt-dHMO1-dZAP1	wt-dCIN5-dHMO1-dZAP1	wt-dHAP4-dZAP1	wt-dHAP4-dHMO1-dZAP1	wt-dCIN5-dHAP4-dHMO1-dZAP1	wt-dCIN5-dHAP4-dZAP1	wt-dCIN5-dZAP1	wt-dGLN3-dHMO1	wt-dCIN5-dGLN3-dHMO1	wt-dCIN5-dGLN3	wt-dGLN3-dHAP4-dHMO1	wt-dGLN3	wt-dCIN5-dGLN3-dHAP4-dHMO1	wt-dGLN3-dHMO1-dZAP1	all-strain	wt-dGLN3-dHAP4-dHMO1-dZAP1	wt-dCIN5-dGLN3-dHMO1-dZAP1	wt-dCIN5-dGLN3-dHAP4	wt-dGLN3-dHAP4	wt-dGLN3-dHAP4-dZAP1	wt-dCIN5-dGLN3-dZAP1	wt-dCIN5-dGLN3-dHAP4-dZAP1	wt-dGLN3-dZAP1
lse:minLSE	1.083	1.176	1.204	1.22	1.238	1.262	1.273	1.275	1.286	1.296	1.299	1.311	1.317	1.327	1.335	1.335	1.359	1.371	1.383	1.386	1.396	1.396	1.405	1.408	1.409	1.41	1.415	1.422	1.43	1.435	1.445	1.453

- Sorted by increasing LSE:minLSE
- SWI5→ ASH1 weight changed
- No major weight consistencies for the other edges

Few strain deletions showed similar weight estimates as all-strain



- Sorted by increasing minLSE
- Similar:
    - All-strain
    - wt-dCIN5-dHAP4-dHMO1-dZAP1
    - wt-dCIN5-dHAP4-dHMO1

The re-estimated weights are not consistent across strain deletions

- Sorted by increasing LSE
- No major patterns can be visualized

Discussion and Conclusion

1. GRNmap uses differential equations to produce parameter estimations for weight, production rate, and threshold.
2. A comparison of the LSE:minLSE ratios for each of the strain deletions revealed that the deletion of dGLN3 and dZAP1 data improved the fit of the model.
3. The heat map showed no major patterns in activation/repression for the strain deletion and edges.
    a. Few strain deletions showed similar weight estimates as the all-strain.
4. Future experiment: Clustering analysis of the data to determine similarities.

Acknowledgements

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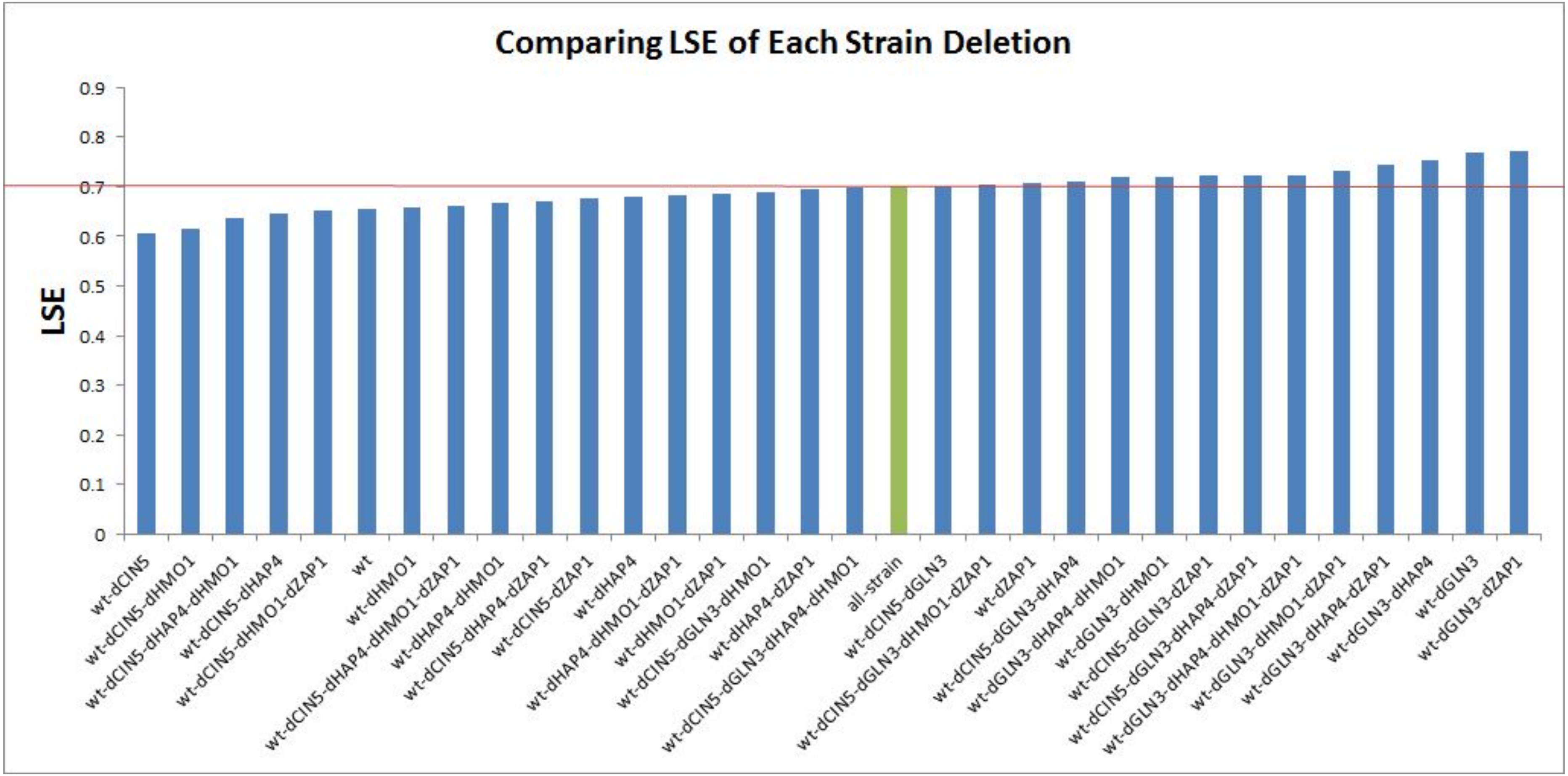
Works Cited

Kelly, L. M. (2019). *Modeling of Gene Regulatory Network Dynamics Predicts which Regulatory Relationships are Important for Controlling the Cold Shock Response in Saccharomyces cerevisiae* (Unpublished doctoral dissertation). Loyola Marymount University, Los Angeles, CA.

Dahlquist, K. D., Fitzpatrick, B. G., Camacho, E. T., Entzminger, S. D., & Wanner, N. C. (2015). Parameter estimation for gene regulatory networks from microarray data: cold shock response in Saccharomyces cerevisiae. *Bulletin of mathematical biology*, *77*(8), 1457-1492.

Dahlquist, K. D., Fitzpatrick, B. G., Dionisio, J. D. N., Anguiano, N. A., Carrillo, J. S., Hong, M. V., ... & Roque, T. A. M. (2016). GRNmap and GRNsight: open source software for dynamical systems modeling and visualization of medium-scale gene regulatory networks. *The FASEB Journal*, *30*(1_supplement), 819-16.

Van der Geer, S. (2005). Least Squares Estimation. *Encyclopedia of Statistics in Behavioral Science*.


Comparing LSE of Each Strain Deletion
LSE
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
wt-dCIN5
wt-dCIN5-dHMO1
wt-dCIN5-dHAP4-dHMO1
wt-dCIN5-dHAP4
wt-dCIN5-dHMO1-dZAP1
wt
wt-dHMO1
wt-dCIN5-dHAP4-dHMO1-dZAP1
wt-dHAP4-dHMO1
wt-dCIN5-dHAP4-dZAP1
wt-dCIN5-dZAP1
wt-dHAP4
wt-dHAP4-dHMO1-dZAP1
wt-dHMO1-dZAP1
wt-dCIN5-dGLN3-dHMO1
wt-dHAP4-dZAP1
wt-dCIN5-dGLN3-dHAP4-dHMO1
all-strain
wt-dCIN5-dGLN3
wt-dCIN5-dGLN3-dHMO1-dZAP1
wt-dZAP1
wt-dCIN5-dGLN3-dHAP4
wt-dGLN3-dHAP4-dHMO1
wt-dGLN3-dHMO1
wt-dCIN5-dGLN3-dZAP1
wt-dCIN5-dGLN3-dHAP4-dZAP1
wt-dGLN3-dHAP4-dHMO1-dZAP1
wt-dGLN3-dHMO1-dZAP1
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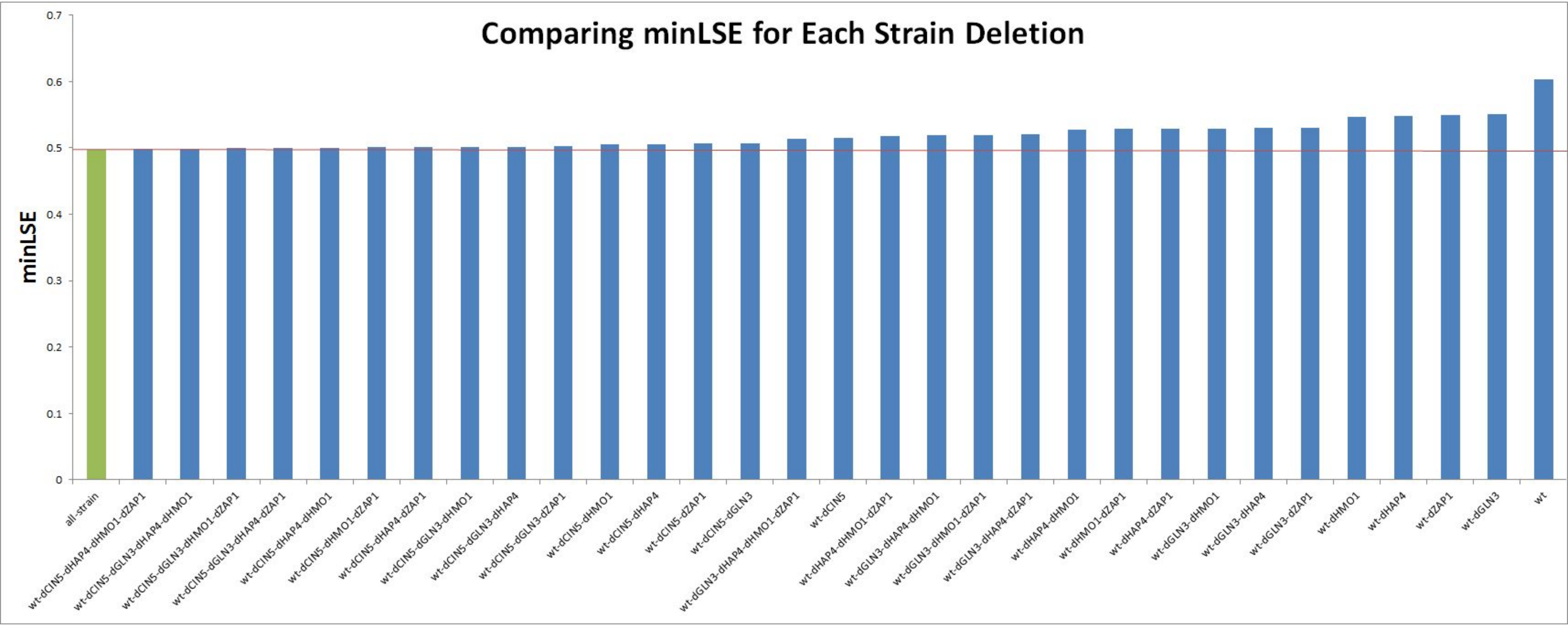
wt-dGLN3-dHAP4
wt-dGLN3
wt-dGLN3-dZAP1


Comparing minLSE for Each Strain Deletion
minLSE
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
all-strain
wt-dCIN5-dHAP4-dHMO1-dZAP1
wt-dCIN5-dGLN3-dHAP4-dHMO1
wt-dCIN5-dGLN3-dHMO1-dZAP1
wt-dCIN5-dGLN3-dHAP4-dZAP1
wt-dCIN5-dHAP4-dHMO1
wt-dCIN5-dHMO1-dZAP1
wt-dCIN5-dHAP4-dZAP1
wt-dCIN5-dGLN3-dHMO1
wt-dCIN5-dGLN3-dHAP4
wt-dCIN5-dGLN3-dZAP1
wt-dCIN5-dHMO1
wt-dCIN5-dHAP4
wt-dCIN5-dZAP1
wt-dCIN5-dGLN3
wt-dGLN3-dHAP4-dHMO1-dZAP1
wt-dCIN5
wt-dHAP4-dHMO1-dZAP1
wt-dGLN3-dHAP4-dHMO1
wt-dGLN3-dHMO1-dZAP1
wt-dGLN3-dHAP4-dZAP1
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wt-dHMO1
wt-dHAP4
wt-dZAP1
wt-dGLN3
wt