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

Alice Finton

Department of Biology
Loyola Marymount University
June 17, 2019
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.
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 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.
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

- **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

**Cyan** - Repression

**Magenta** - Activation

* Thickness of edge refers to weight
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 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.
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

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

- 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

All include dCIN5
The strain deletions with the lowest LSE do not include dGLN3 strain data.
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 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.
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.

- 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

| minLSE  | mCIN5       | mHM01      | mZAP1      | mCIN5-dHM01 | mCIN5-dZAP1 | mHM01-dZAP1 | mHM01-dCIN5 | mHM01-dZAP1 | mHM01-mZAP1 | mHM01-dHAP4 | mHM01-dHAP4-mZAP1 | mHM01-dCIN5-dHAP4 | mHM01-dCIN5-dHAP4-mZAP1 | mHM01-dHM01-dZAP1 | mHM01-dHM01-dHAP4 | mHM01-dHM01-dHAP4-mZAP1 | mHM01-dHM01-dHAP4-mZAP1 | mHM01-dHM01-dHM01-dZAP1 | mHM01-dHM01-dHM01-dHAP4 | mHM01-dHM01-dHM01-dHAP4-mZAP1 | mHM01-dHM01-dHM01-dHAP4-mZAP1 | mHM01-dHM01-dHM01-dHM01-dZAP1 |
|---------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|---------------------|-----------------------|------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| 0.497   | 0.499       | 0.499       | 0.5         | 0.5         | 0.5         | 0.5         | 0.5         | 0.5         | 0.5         | 0.5         | 0.5                 | 0.5                   | 0.5                    | 0.5                    | 0.5                    | 0.5                    | 0.5                    | 0.5                    |

- Sorted by increasing minLSE
- Similar:
  - All-strain
  - wt-dCIN5-dHAP4-dHM01-dZAP1
  - wt-dCIN5-dHAP4-dHM01
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

I would like to thank Dr. Dahlquist, the Dahlquist lab, the Rains Research Assistant program, and the LMU Biology Department.


