Lag Penalized Weighted Correlation (LPWC)

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Biological Time Series

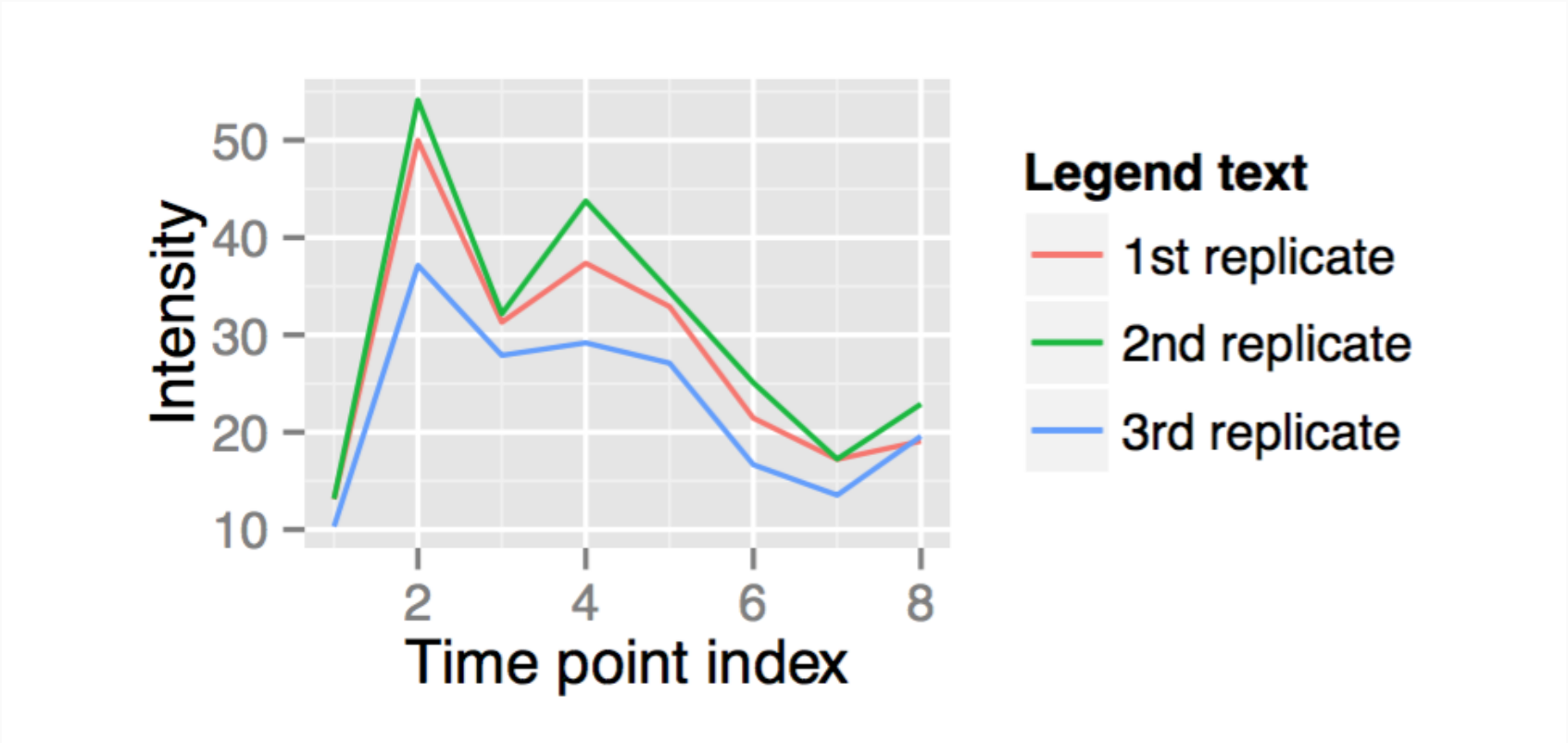
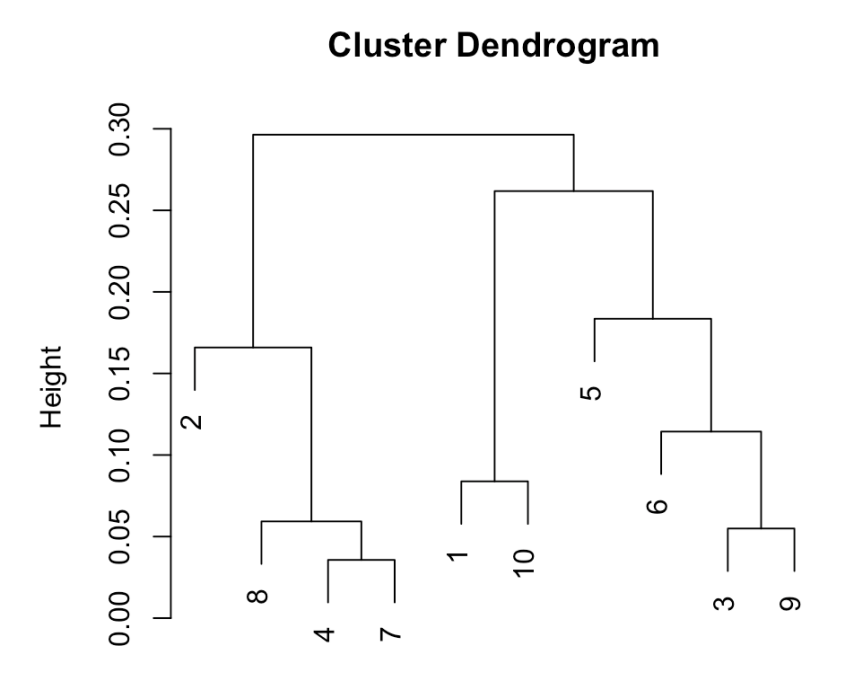


Figure 1: Simple time series plot with 8 time points and 3 replicates

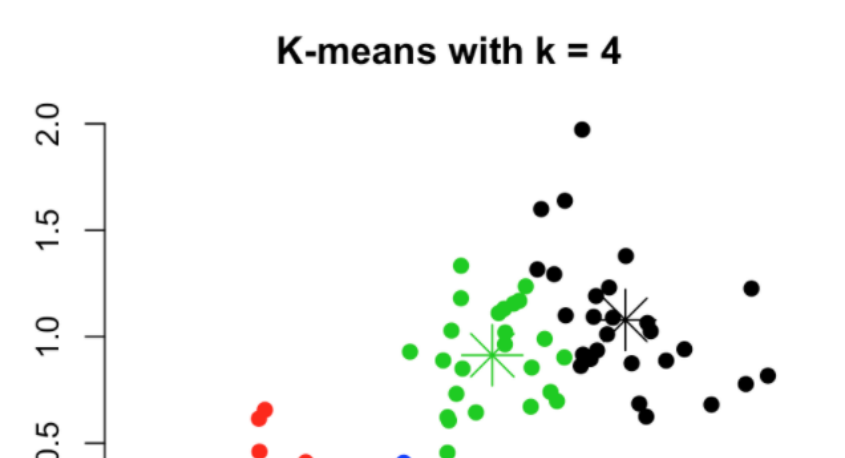
Biological Time Series

- Snapshot of biological functions over time
- Study complex and dynamic biological systems
- Tracking levels of genes/proteins reveals interactions
- Biological time series are shorter compared to time series data in other domains (5-30 time points)
- Similarity in temporal behavior may correspond to similarity in biological processes

Types of Clustering Algorithms



(a) Hierarchical-based clustering



Toy Example: Intuitive Clustering

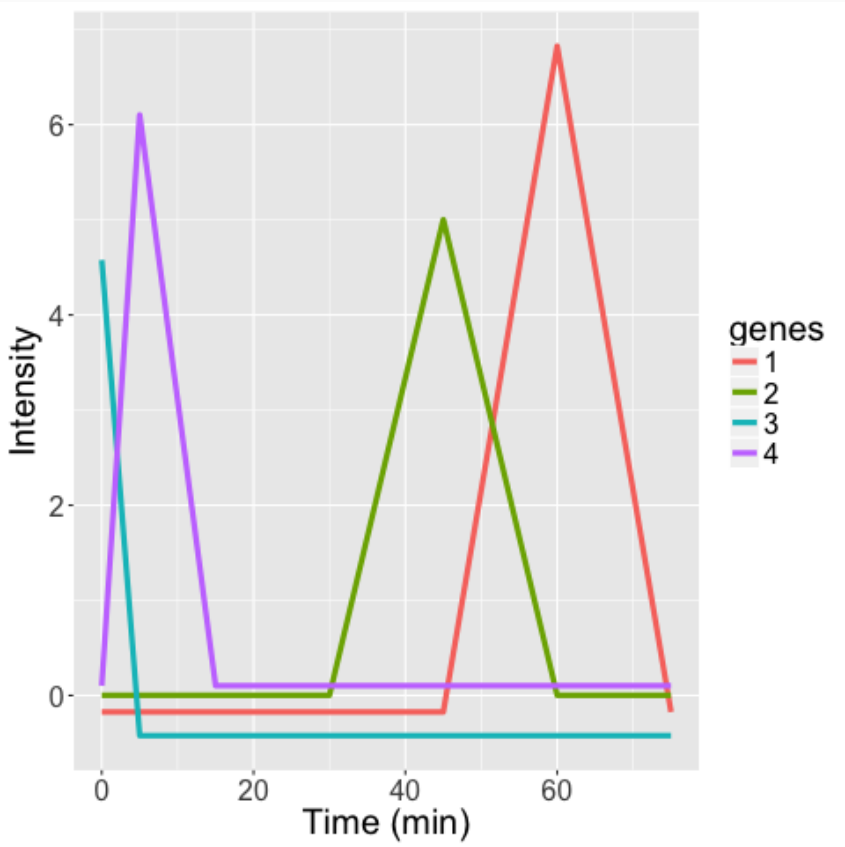
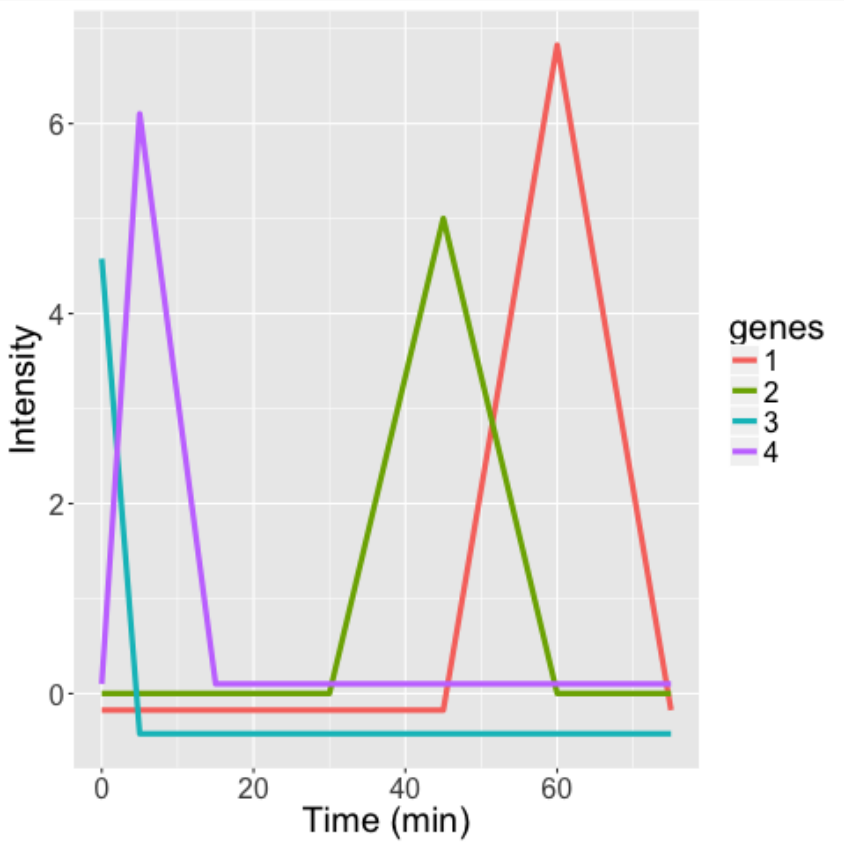


Figure 3: Hypothetical example with 4 genes

Toy Example: Algorithmic Clustering



(a) Hypothetical example with 4 genes

Clustering Algorithm	Cluster 1	Cluster 2
hLPWC/lLPWC	●●	●●
DTW	●	●●●
STS	●	●●●
heuc	●	●●●

(b) Cluster assignment of the 4 genes

Figure 4: Existing methods do not group early and late genes

Motivation

Irregular time sampling

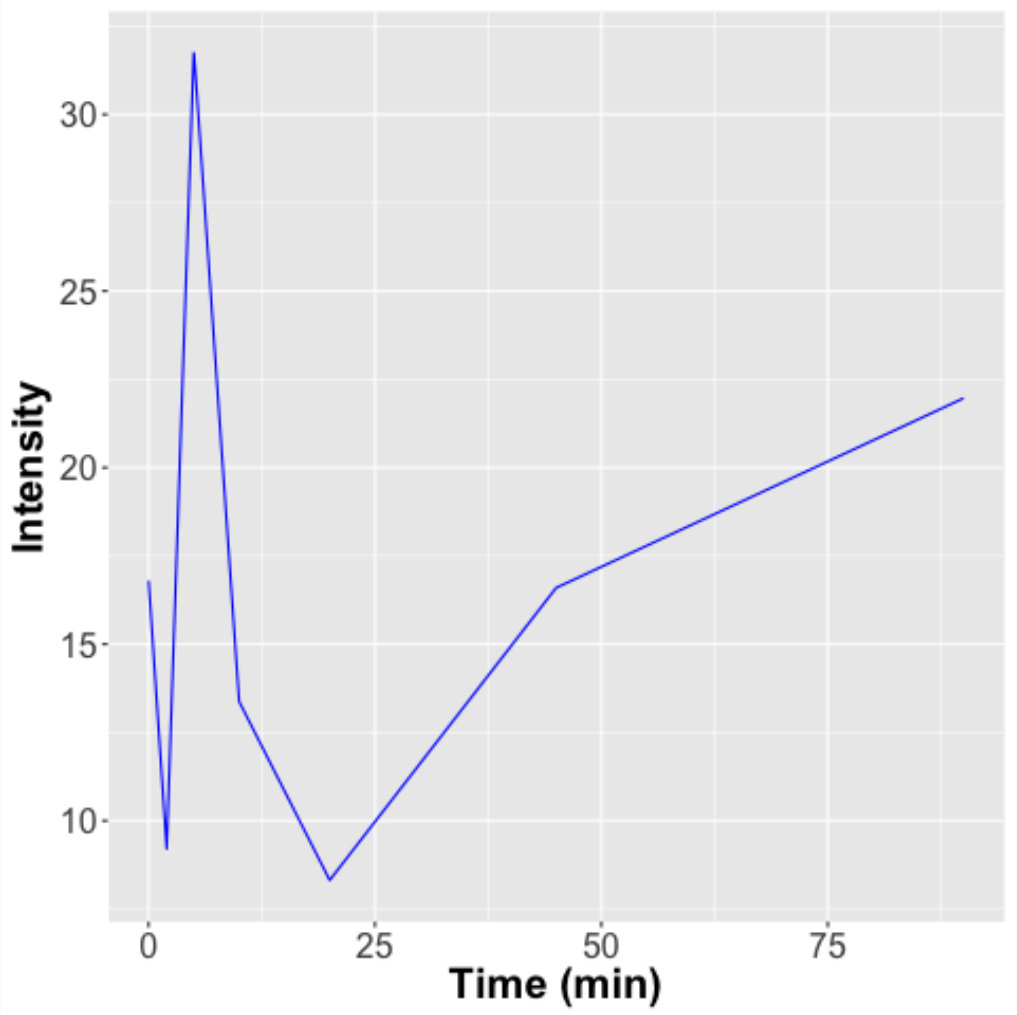


Figure 5: Irregularly sampled time series data

Motivation

Delayed response (lags)

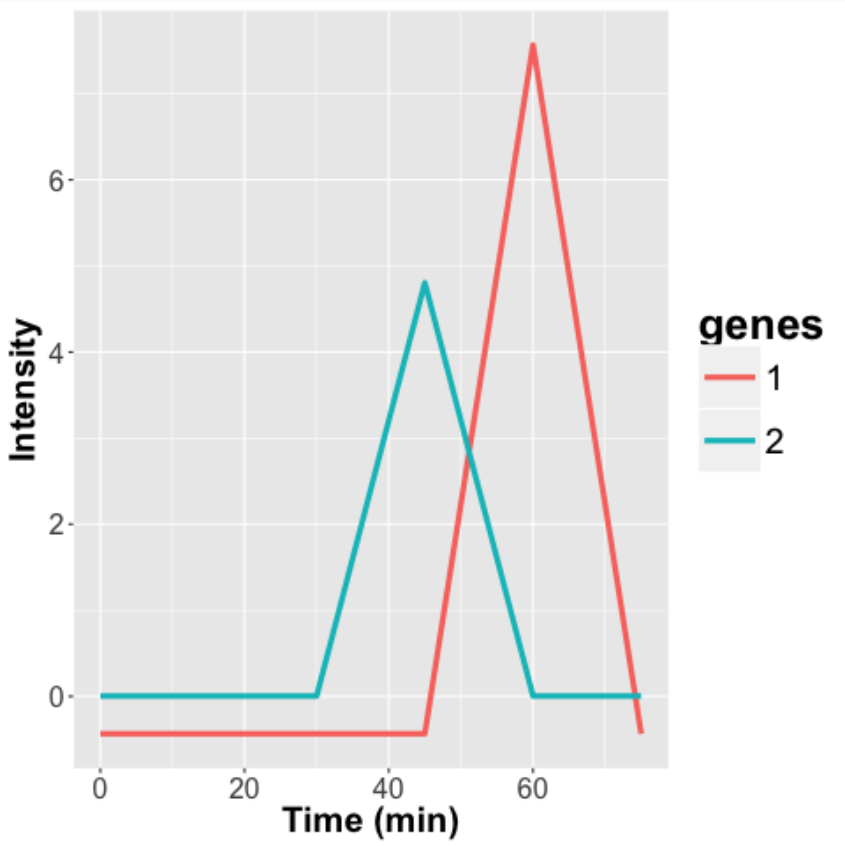


Figure 6: Gene 1 spikes after gene 2

What is a Lag?

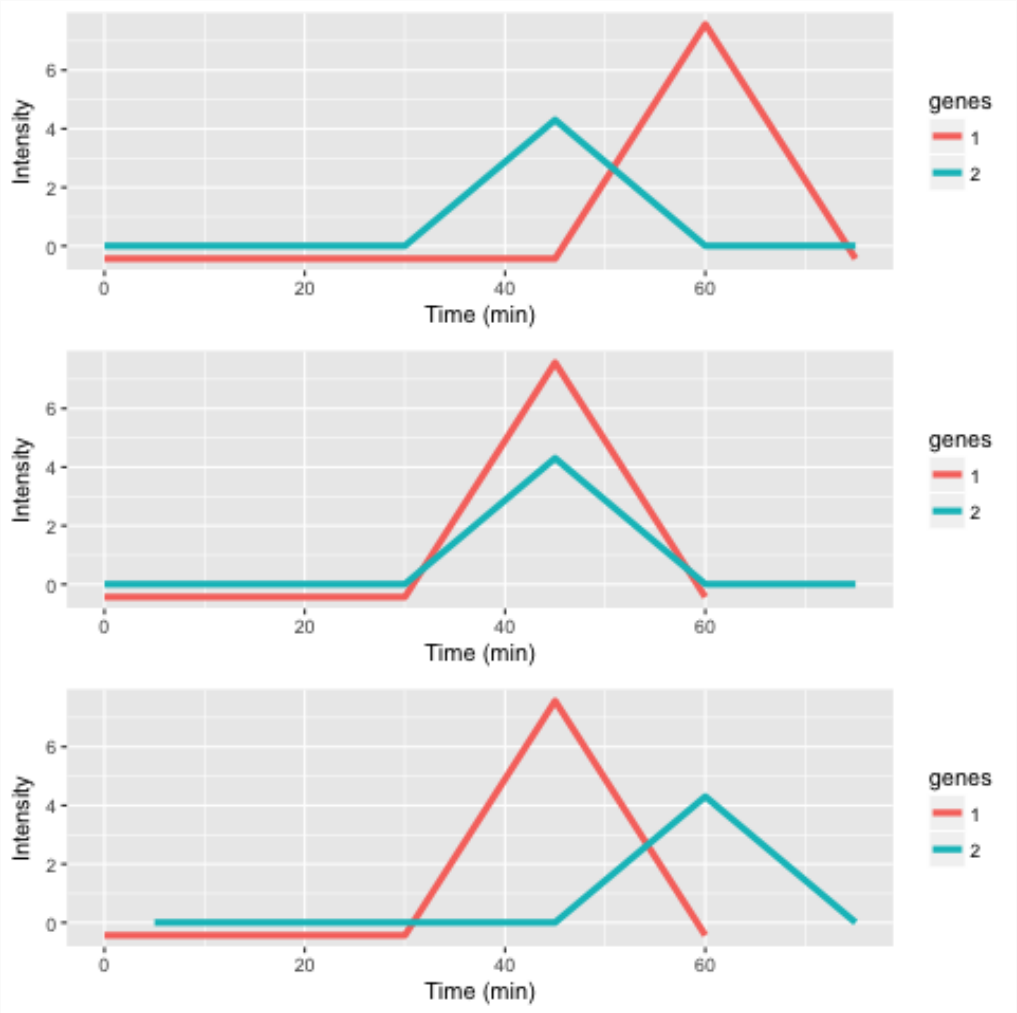


Figure 7: An example of the effects of applying different lags to genes 1 and 2. Genes 1 and 2 are not lagged (top). Gene 1 with lag -1, gene 2 with no lags (middle). Gene 1 with lag -1 and gene 2 with lag 1 (bottom).

Method Overview

LPWC is composed of two steps:

- computing optimal lags for each gene
- computing final correlation matrix for all gene

General Formula

$$corr_{LPWC}(i, j, X_i, X_j) = \underbrace{exp(\frac{-E(w)}{C})}_{\text{penalty}} * \underbrace{corr_w(L^{X_i} Y_i, L^{X_j} Y_j, exp(\frac{-w}{C}))}_{\text{weighted correlation}}$$

$$w = (L^{X_i} T_i - L^{X_j} T_j)^2$$

Algorithm

Computing optimal lag

$$score_j = \max_{X_i \in \{-m,\ldots,m\}} corr_{LPWC}(i, j, X_i, 0) \quad \forall j \neq i$$

$$lag_j = \arg\max_{X_i \in \{-m,\ldots,m\}} corr_{LPWC}(i, j, X_i, 0) \quad \forall j \neq i$$

Then, a best lag $\hat{X}_i$ for gene i assigned by

$$\hat{X}_i = \arg\max_{k \in \{-m,\ldots,m\}} \sum_{j \neq i} I(lag_j = k) * score_j$$

This is repeated to select a best lag for all genes.

Computing final correlation matrix

$$corr_{LPWC}(i, j, \hat{X}_i, \hat{X}_j) = exp(\frac{-E(w)}{C}) * corr_w(L^{\hat{X}_i} Y_i, L^{\hat{X}_j} Y_j, exp(\frac{-w}{C}))$$

Existing Time Series Clustering Methods

Partition-based

- Short Time-series Expression Miner (STEM)
- Graphical Query Language (GQL)
- Cluster Analysis of Gene Expression Dynamics (CAGED)

Hierarchical-based

- Dynamic Time Warping (DTW)
- Short Time Series Distance (STS)

Clustering Accuracy

- Adjusted Rand Index (ARI): similarity between two data clusterings and adjusted for chance
- ARI score close to 1 indicates similar clusterings, score close to 0 otherwise

Simulated Data

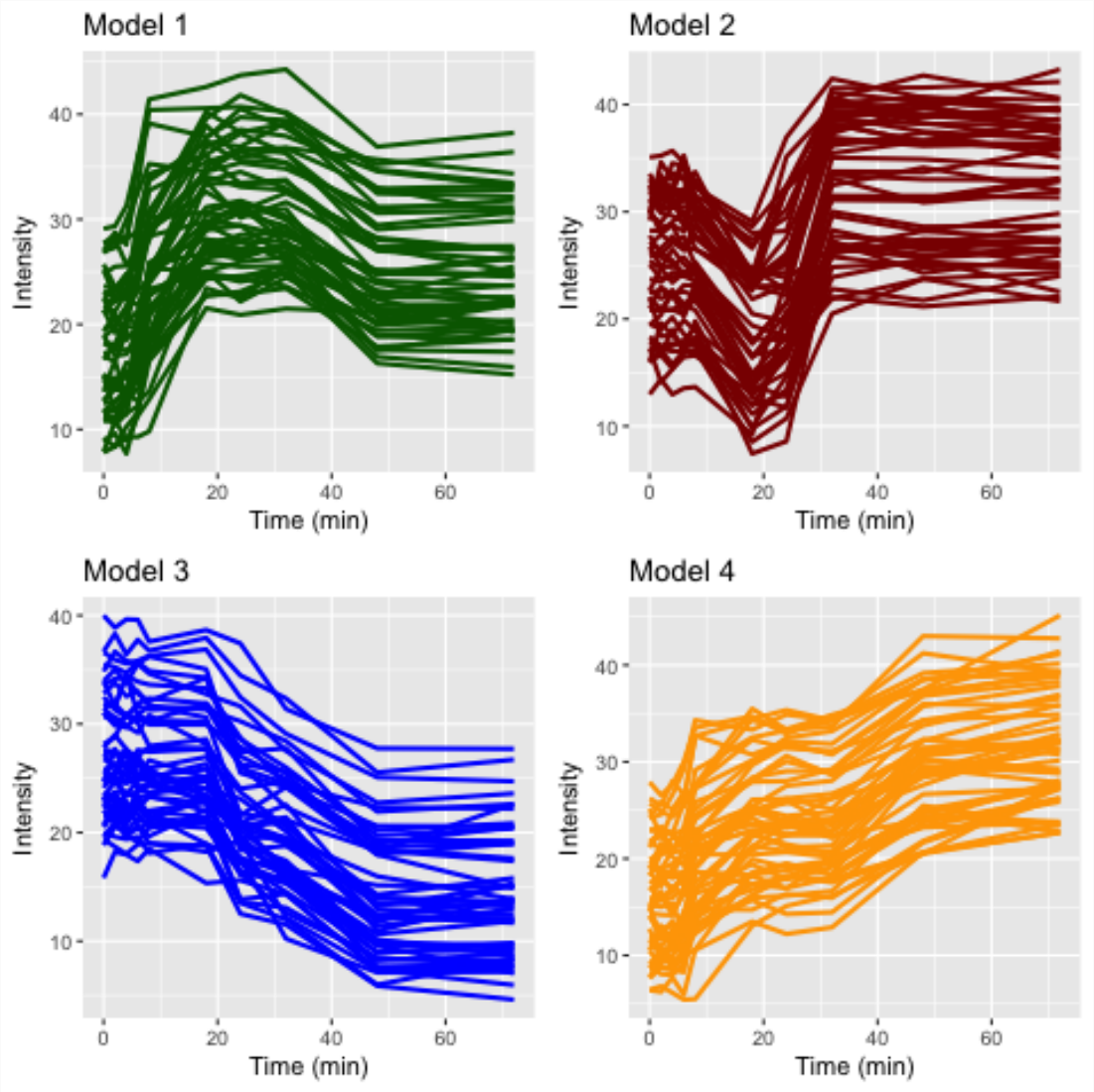


Figure 8: Four models simulated using ImpulseDE. Random noise was added to the model parameters to induce variation around a common trend.

ARI Score for Simulated Data

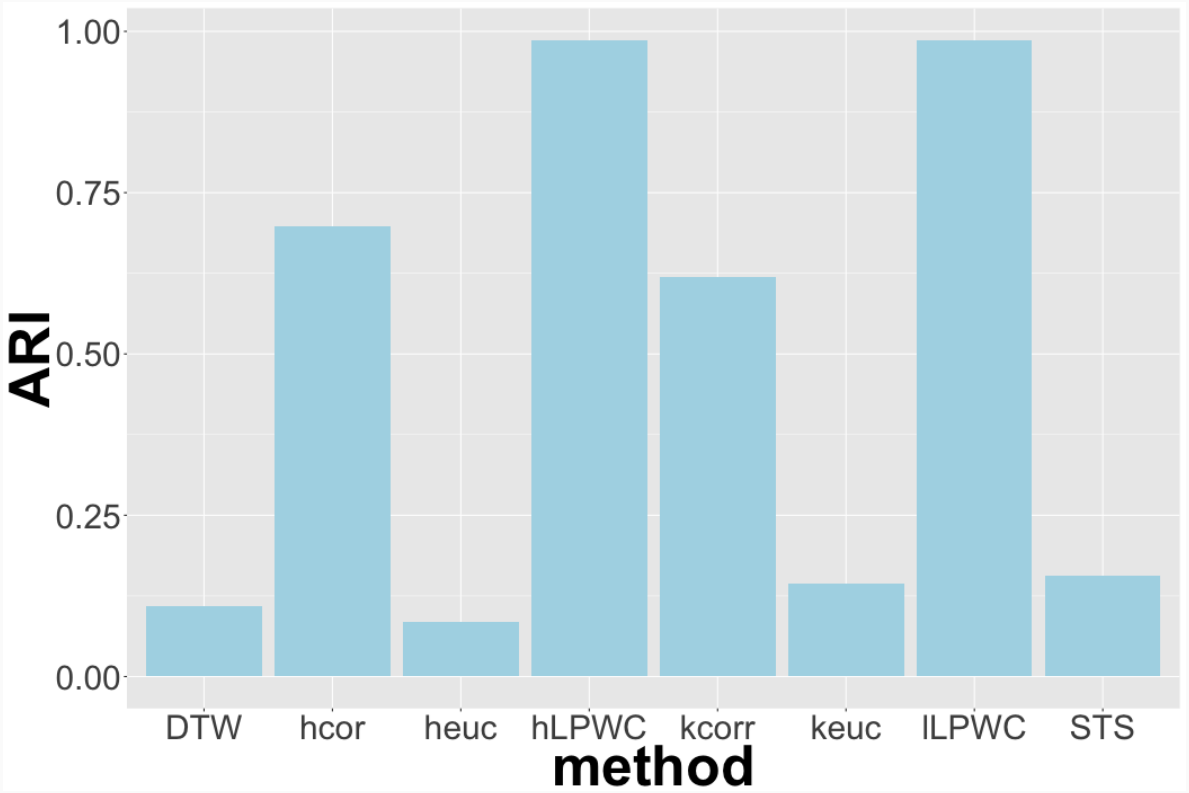


Figure 9: ARI score for different clustering methods for the simulated data where the real clusters are known.

Yeast Osmotic Stress Response Data

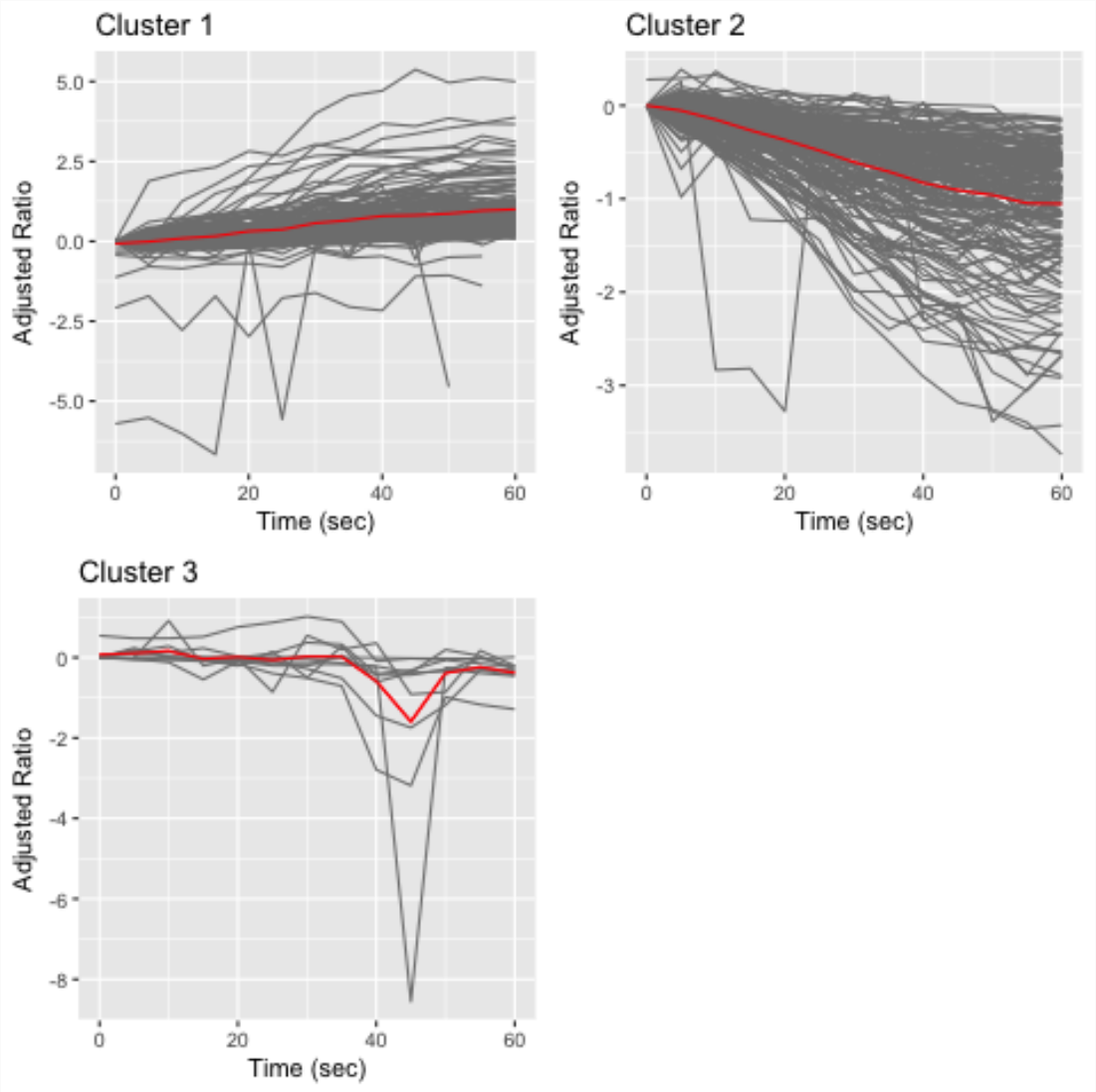


Figure 10: Clustering 344 phosphopeptides in yeast osmotic stress into 3 different clusters.

Conclusion & Future Work

- Algorithm tackles the issue of irregular time samples and delayed responses
- R package available on CRAN (LPWC) and preprint on bioRxiv
- Allow missing data (imputation) and support mixed dataset with different time points
- Improve the optimal lag assignments

Acknowledgements

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