A Bayesian Dynamical Systems Approach to Clustering Gene Expression Time Series Data

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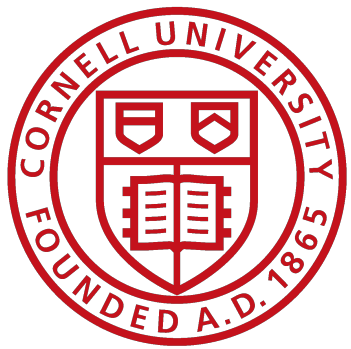
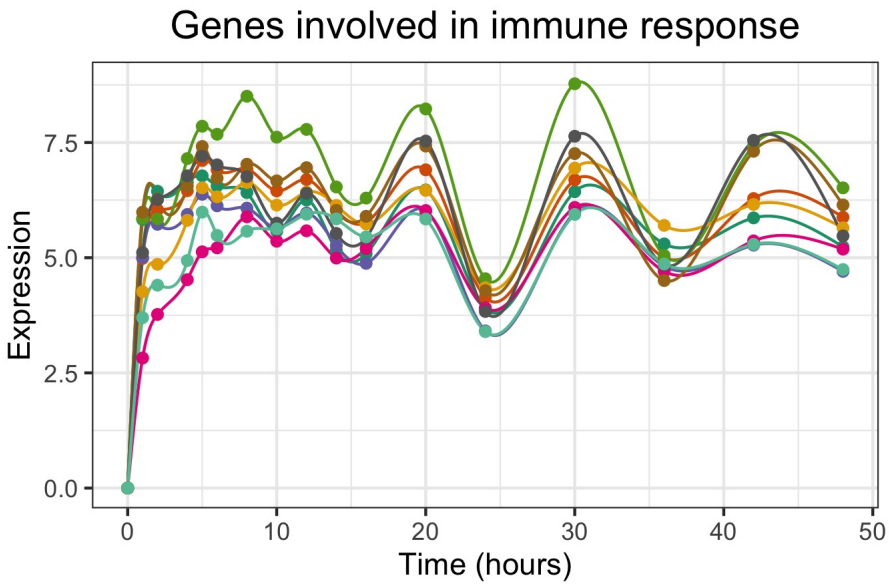


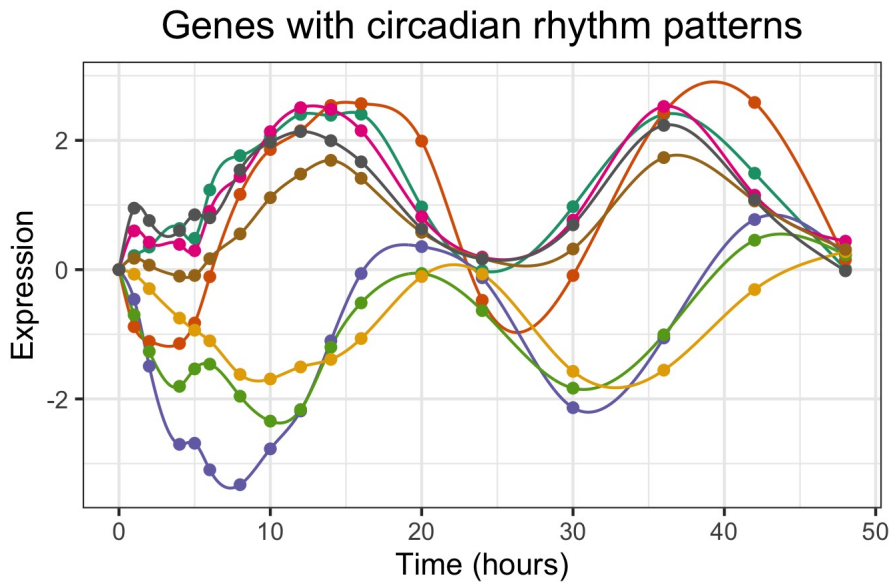
Joint work with Sumanta Basu, Andrew G. Clark,
Sofie Delbare, Myung Hee Lee, Martin T. Wells

Introduction

Time-course gene expression datasets measure expressions of thousands of genes at a few time points.

Statistical task: want to find clusters/networks of genes with similar time dynamics (either co-moving or lead-lag)





Challenges: complex time dynamics, data is high-dimensional

Challenges in cluster analysis of gene expression

How to measure "similarity" in two genes' expressions?

Idea: Derive similarity metrics from ODEs that model co-movement/lagged relationships in gene expression over time

How to find similar gene pairs within thousands of genes?

Idea: Encourage high similarity scores between genes that are known to be associated, according to prior biological information (obtained from public databases)

Gene expression as a dynamical system

How does a gene's expression vary over time?

Let $m_A(t)$ = expression of gene A at time t. Possible model:

$$\frac{\mathrm{d}m_A(t)}{\mathrm{d}t} = p(t) - \kappa_A m_A(t),$$

where $p(t)$ = some regulatory signal, κ_A = degradation rate.

[Farina et al., 2007]

How do two associated genes A and B vary over time?

$$\frac{\mathrm{d}m_A(t)}{\mathrm{d}t} = (\alpha_A\, p(t) + \beta_A) - \kappa_A m_A(t),$$
$$\frac{\mathrm{d}m_B(t)}{\mathrm{d}t} = (\alpha_B\, p(t) + \beta_B) - \kappa_B m_B(t).$$

Gene expression as a dynamical system

Rearrange/integrate ODEs to get gene A's expression in terms of B's:

$$m_A(t) = c_1 m_B(t) + c_2 \int_0^t m_B(s)\,\mathrm{d}s + c_3 \int_0^t m_A(s)\,\mathrm{d}s + c_4 t + c_5.$$

This is linear in the coefficients $c_1, \ldots, c_5$

(which are composed from parameters $\alpha_A, \alpha_B, \beta_A, \beta_B, \kappa_A, \kappa_B$).

Therefore:

- We can fit this model to time-series data $\{m_A(t_i)\}_{i=1}^n$, $\{m_B(t_i)\}_{i=1}^n$ using **linear regression**
- Then, we can use the R^2 to measure association between the temporal expressions of genes A, B

Fitting dynamical models to data

Given time-series data $\{m_A(t_i)\}_{i=1}^n$, $\{m_B(t_i)\}_{i=1}^n$, we express our model

$$m_A(t) = c_1 m_B(t) + c_2 \int_0^t m_B(s)\,\mathrm{d}s + c_3 \int_0^t m_A(s)\,\mathrm{d}s + c_4 t + c_5$$

as $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$, where $\boldsymbol{\beta} = [c_1, ..., c_5]^T$ and $\boldsymbol{\varepsilon} \sim N(\mathbf{0}, \sigma^2 \mathbf{I}_n)$, with:

$$\mathbf{Y} = \begin{bmatrix} m_A(t_1) \\ ... \\ m_A(t_n) \end{bmatrix}, \quad \mathbf{X} = \begin{bmatrix} m_B(t_1) & \int_0^{t_1} m_B(s) & \int_0^{t_1} m_A(s) & t_1 & 1 \\ ... & ... & ... & ... & ... \\ m_B(t_n) & \int_0^{t_n} m_B(s) & \int_0^{t_n} m_A(s) & t_n & 1 \end{bmatrix}$$

Then calculate: $R^2 = \underset{\text{explained by model above}}{\text{Fraction of variance in } m_A(t)} = \dfrac{\|\mathbf{X}\hat{\boldsymbol{\beta}} - \bar{Y}\mathbb{1}_n\|^2}{\|\mathbf{Y} - \bar{Y}\mathbb{1}_n\|^2}$

where $\hat{\boldsymbol{\beta}}$ = least-squares estimate of $\boldsymbol{\beta}$, and $\bar{Y}$ = mean of $\mathbf{Y}$.

Measuring similarity in time dynamics of two genes

We'll call this R^2 the lead-lag R^2.

- Measures association in temporal patterns of genes A, B
- But: does not account for prior knowledge about their relationship

Our contribution: Use empirical Bayesian regression to incorporate prior biological information into lead-lag R^2

("empirical" because hyperparameters will be chosen in a data-driven way).

Sources of biological information: pathway databases (e.g., GO, KEGG, STRING), protein-protein interaction networks

Background on Bayesian regression

Consider the linear model $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$:

- $\mathbf{X} \in \mathbb{R}^{n \times p}$ and $\mathbf{Y} \in \mathbb{R}^{n \times 1}$ are observed, $\boldsymbol{\beta} \in \mathbb{R}^{p}$ is unknown
- Assume $\boldsymbol{\varepsilon}$ are i.i.d. normal errors: $\boldsymbol{\varepsilon} \sim N(\mathbf{0}, \sigma^2 \mathbf{I}_n)$

Approaches to estimating $\boldsymbol{\beta}$:

- Frequentist approach: Use the ordinary least-squares estimate $\hat{\boldsymbol{\beta}}_{\text{OLS}} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{Y}$
- Bayesian approach: Choose prior probability distributions $p(\sigma^2)$ and $p(\boldsymbol{\beta}|\sigma^2)$.
  - Combine $p(\mathbf{Y}|\boldsymbol{\beta}, \sigma^2)$, $p(\boldsymbol{\beta}|\sigma^2)$, and $p(\sigma^2)$ via Bayes' theorem to get posterior distribution of $\boldsymbol{\beta}$
  - Can use mean of posterior distribution as an estimate of $\boldsymbol{\beta}$

Which prior distributions should we use?

The "normal-inverse gamma" prior is a common conjugate prior:

- Choose $p(\boldsymbol{\beta}|\sigma^2)$ to be the $N(\boldsymbol{\beta}_0, \sigma^2\mathbf{V}_0)$ distribution for some $\boldsymbol{\beta}_0 \in \mathbb{R}^p$ and p.s.d. matrix $\mathbf{V}_0$
- Choose $p(\sigma^2)$ to be the $\Gamma^{-1}(a, b)$ distribution for $a,\ b > 0$

If we choose $\mathbf{V}_0 = g(\mathbf{X}^T\mathbf{X})^{-1}$, for some $g > 0$. Then:

$$\mathbb{E}(\boldsymbol{\beta}|\mathbf{Y}) = \frac{1}{1+g}\boldsymbol{\beta}_0 + \frac{g}{1+g}\hat{\boldsymbol{\beta}}_{\text{OLS}}$$

This is "Zellner's g-prior".

Soon we'll see how to choose $\boldsymbol{\beta}_0$ for our gene clustering problem.

(Hint: this will be where we can incorporate prior information about the genes!)

Our Bayesian regression methodology

Given a dataset of N genes measured at T time points,

1. Define a $N \times N$ prior "adjacency matrix" $\mathbf{W}$:

$$\mathbf{W}_{ij} = \begin{cases} 1 & \text{if genes } i, j \text{ have known association} \\ \text{NA} & \text{if genes } i, j \text{ have unknown relationship} \\ 0 & \text{if genes } i, j \text{ are unlikely to be associated} \end{cases}$$

2. For each gene pair, use Bayesian regression to fit the model $m_A(t) = c_1 m_B(t) + c_2 \int_0^t m_B(s) + c_3 \int_0^t m_A(s) + c_4 t + c_5$:
   - Use $\mathbf{W}$ to set mean of prior distribution on $\beta = [c_1, ..., c_5]$: $\beta_0 = [1, 1, 0, 0, 0]$ if $\mathbf{W}_{ij} = 1$, or all 0 otherwise.

     Why: first two parameters of β link expressions of genes A, B.
   - Compute posterior mean of β, and then the lead-lag R^2.

Data-driven tuning parameter selection

Recall the posterior mean of $\boldsymbol{\beta}$ was: $\dfrac{1}{1+g}\boldsymbol{\beta}_0 + \dfrac{g}{1+g}\hat{\boldsymbol{\beta}}_{\text{OLS}}$.

How do we choose g?

- No solutions to $g_* = \text{argmin}_{g>0} \|\mathbf{Y} - \hat{\mathbf{Y}}\|^2$ (sum of squared residuals), where $\hat{\mathbf{Y}} = \mathbf{X}\boldsymbol{\beta}_*$ and $\boldsymbol{\beta}_* = \mathbb{E}(\boldsymbol{\beta}|\mathbf{Y})$
- Instead, choose g to minimize Stein's unbiased risk estimate (unbiased estimate of $\|\hat{\mathbf{Y}} - \mathbf{X}\boldsymbol{\beta}\|^2$).

Theorem

Stein's unbiased risk estimate is minimized by:

$$g_* = \frac{\|\hat{\mathbf{Y}}_{\text{OLS}} - \mathbf{X}\boldsymbol{\beta}_0\|^2 - p\hat{\sigma}^2}{p\hat{\sigma}^2},$$

where $\hat{\mathbf{Y}}_{\text{OLS}} = \mathbf{X}\hat{\boldsymbol{\beta}}_{\text{OLS}}$, $\hat{\sigma}^2 = \frac{\|\mathbf{Y} - \hat{\mathbf{Y}}_{\text{OLS}}\|^2}{n-p}$, and n, p are dims. of $\mathbf{X}$.

R^2 for Bayesian regression models

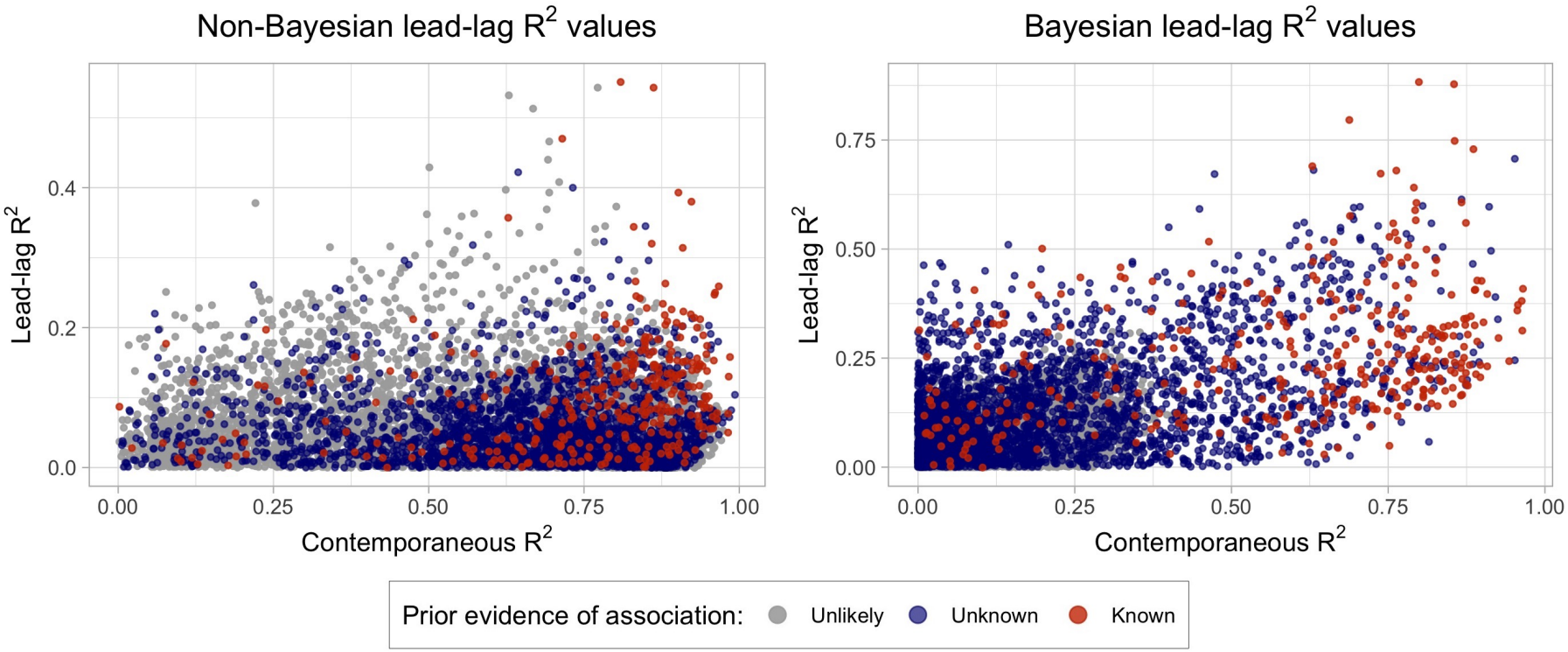
Classical definition of R^2 for ordinary least-squares may yield $R^2 > 1$ for Bayesian regression.

Instead, we define:

$$R^2 = \frac{\widehat{\mathrm{Var}}(\mathbf{X}\boldsymbol{\beta}_*)}{\widehat{\mathrm{Var}}(\mathbf{X}\boldsymbol{\beta}_*) + \widehat{\mathrm{Var}}(\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}_*)},$$

which we call the Bayesian lead-lag R^2 between genes A and B, where $\boldsymbol{\beta}_* = \frac{1}{1+g}\boldsymbol{\beta}_0 + \frac{g}{1+g}\hat{\boldsymbol{\beta}}_{\mathrm{OLS}}$ is the posterior mean of $\boldsymbol{\beta}$.

Outline of empirical results



Dataset: expressions of 1735 genes in fruit flies at 21 time points, immediately following an induced immune response.

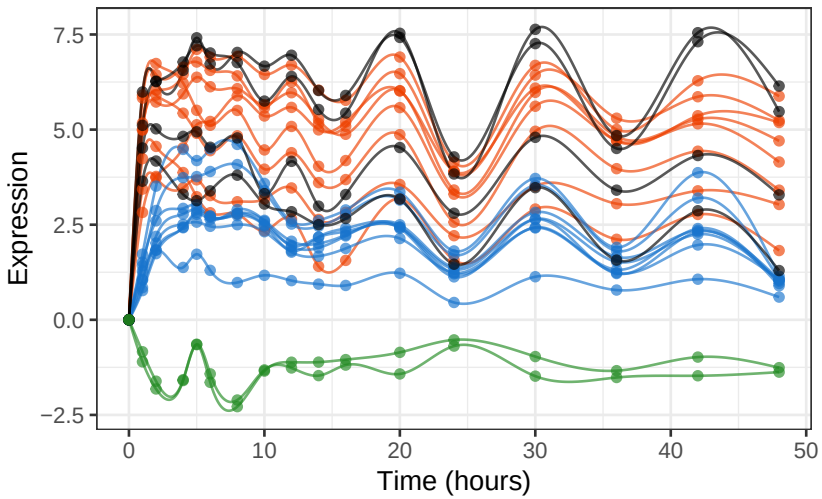
Method successfully identifies:

- Metabolism-immunity tradeoff found in previous studies
- Known groups of circadian rhythm, metabolic, immune response genes
- Novel interactions between orphan genes and known pathways

Hierarchical clustering on Bayesian lead-lag R^2 similarity matrix

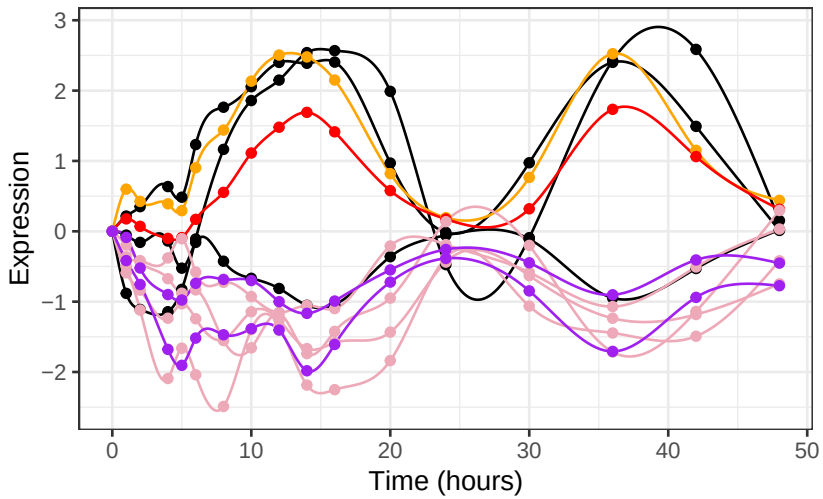
Genes involved in immune response

(Imd−regulated genes; Toll−regulated genes; cuticle proteins; genes potentially associated with Imd signaling)



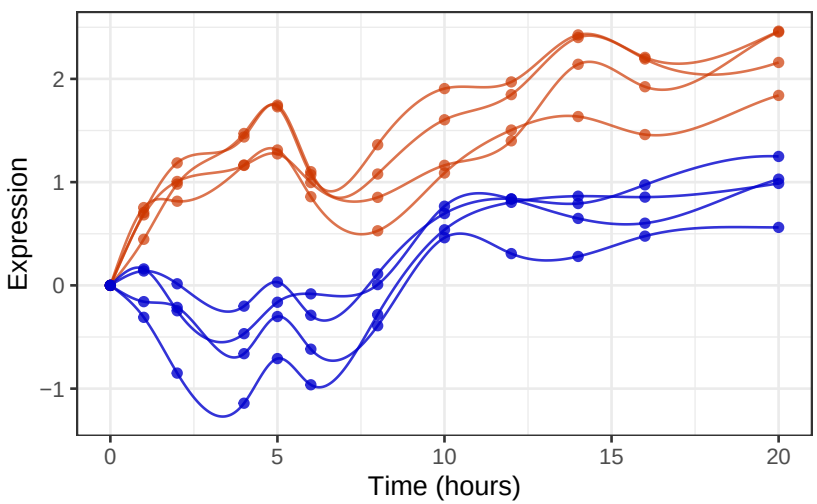
Genes exhibiting circadian rhythms

(Regulators of circadian clock: *tim, per, Clk, vri, Pdp1*; cuticle proteins; genes involved in dopamine synthesis)



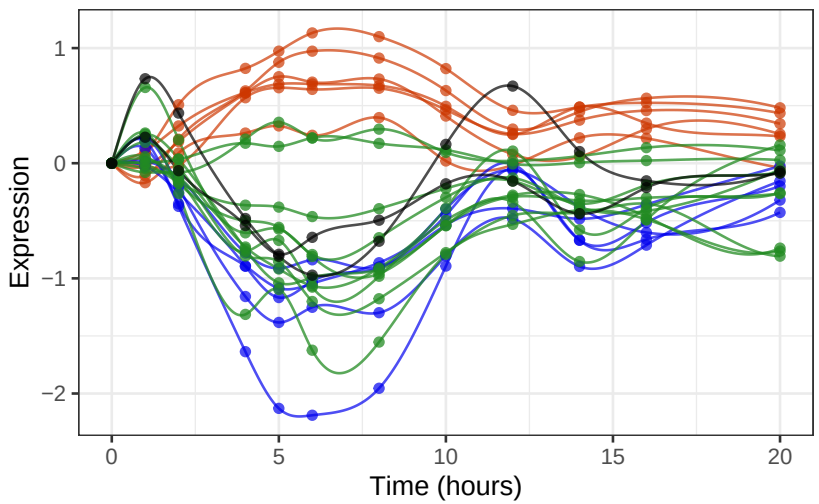
Genes involved in metabolism and immune response

(maltases; genes expressed in hemocytes)

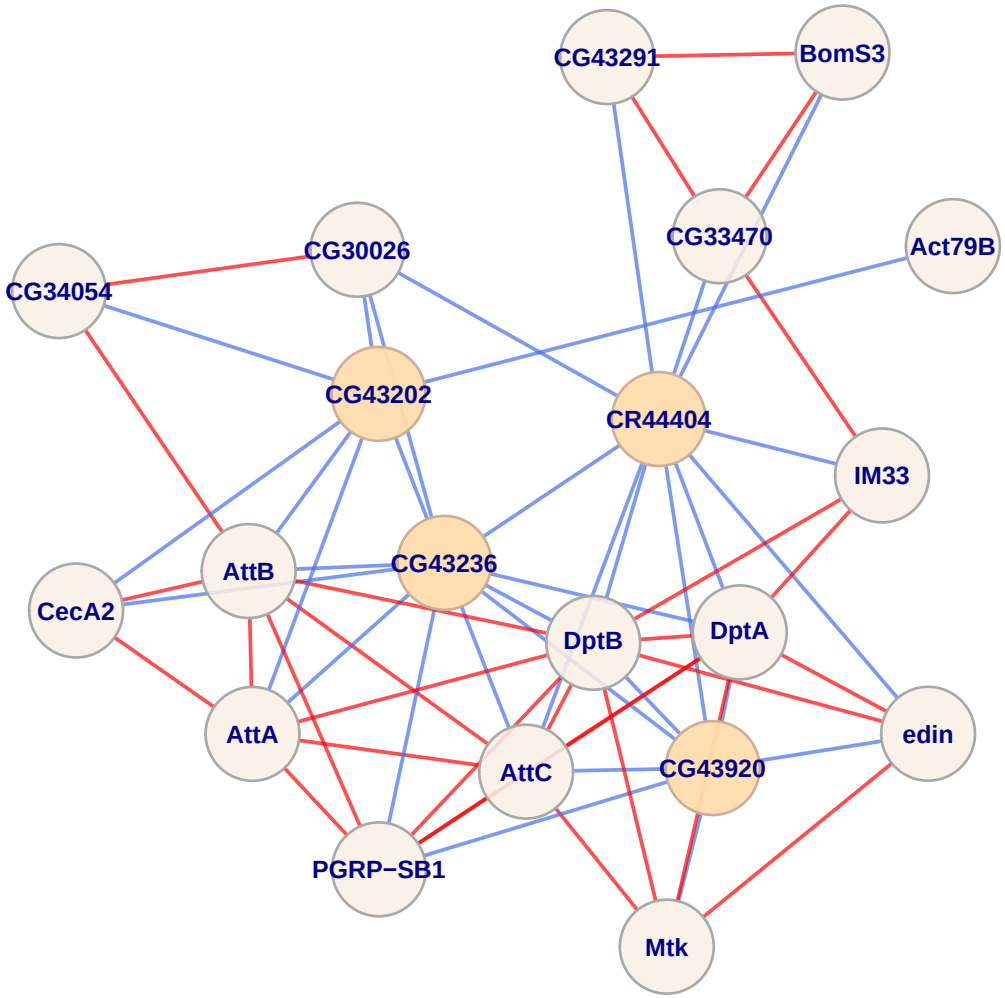


Genes involved in metabolic processes

(ribosome biogenesis; lipid catabolism; fatty acid biosynthesis; genes with uncharacterized relationships to *FASN1*)



Network reconstruction



Edge drawn between two genes if their Bayesian lead-lag $R^2 > 0.9$.

Red edges: previously known associations. Blue edges: previously unknown.

Thank you!

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Appendix: Stein's unbiased risk estimate for linear models

Theorem [Fourdrinier, Strawderman, Wells 2018]

Let $\mathbf{Y} \sim N(\mathbf{X}\beta, \sigma^2 \mathbf{I}_n)$ where $\mathbf{X} \in \mathbb{R}^{n \times p}$. Let β_* be a weakly-differentiable function of the least-squares estimator $\hat{\beta}_{\text{OLS}}$ such that $\hat{\mathbf{Y}} = \mathbf{X}\beta_* = \mathbf{a} + \mathbf{S}\mathbf{Y}$ for some vector $\mathbf{a}$ and matrix $\mathbf{S}$. Then

$$\delta_0(\mathbf{Y}) = \|\mathbf{Y} - \mathbf{X}\beta_*\|^2 + (2\text{Tr}(\mathbf{S}) - n)\hat{\sigma}^2$$

is an unbiased estimator of $\|\hat{\mathbf{Y}} - \mathbf{X}\beta\|^2$, where $\hat{\sigma}^2 = \frac{\|\mathbf{Y} - \mathbf{X}\hat{\beta}_{\text{OLS}}\|^2}{n-p}$.

In this context, $\beta_* = \mathbb{E}(\beta|\mathbf{Y}) = \frac{1}{1+g}\beta_0 + \frac{g}{1+g}\hat{\beta}_{\text{OLS}}$:

- Then $\hat{\mathbf{Y}} = \mathbf{X}\beta_* = \frac{1}{1+g}\mathbf{X}\beta_0 + \frac{g}{1+g}\mathbf{H}\mathbf{Y}$, where $\mathbf{H} = \mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T$
- Therefore $\mathbf{a} = \frac{1}{1+g}\mathbf{X}\beta_0$ and $\mathbf{S} = \frac{g}{1+g}\mathbf{H}$, whose trace is $\frac{gp}{1+g}$

Appendix: Variants of the lead-lag R^2

Recall our model of gene expression – the R^2 from this model is called the lead-lag R^2 (LLR^2):

$$m_A(t) = c_1 m_B(t) + c_2 \int_0^t m_B(s)\,\mathrm{d}s + c_3 \int_0^t m_A(s)\,\mathrm{d}s + c_4 t + c_5.$$

Consider two "sub-models":

- Sub-model 1: R^2 from this model, called $\mathrm{LL}R^2_{\text{other}}$, captures variation in gene A explained by an*other* gene B.

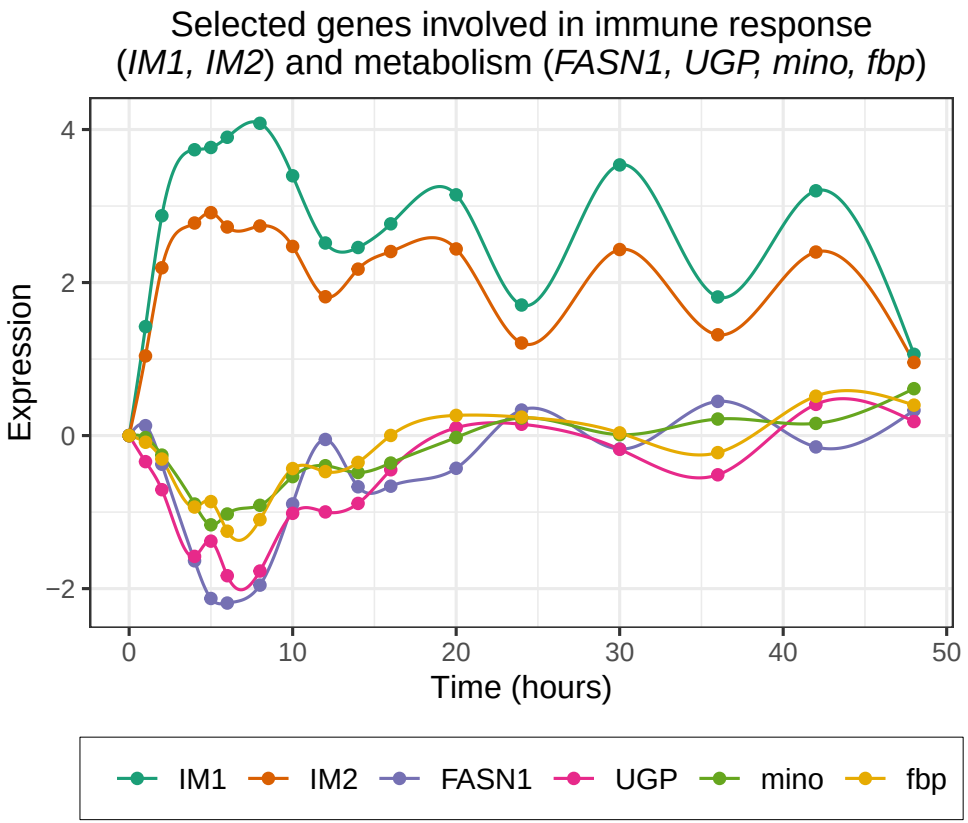
$$m_A(t) = c_1 m_B(t) + c_2 \int_0^t m_B(s)\,\mathrm{d}s + c_5$$

- Sub-model 2: R^2 from this model, called LLR^2_{own}, captures variation in gene A explained by its *own* past and linear time trends.

$$m_A(t) = c_3 \int_0^t m_A(s)\,\mathrm{d}s + c_4 t + c_5$$

In the scatterplots on slide 11, the x-axis shows $\mathrm{LL}R^2_{\text{other}}$ and the y-axis shows $\mathrm{LL}R^2 - \mathrm{LL}R^2_{\text{own}}$.

Appendix: Immune response and metabolism



Prior adjacency matrix **W**

	IM1	IM2	FASN1	UGP	mino	fbp
IM1	-	1	NA	0	0	NA
IM2	1	-	NA	0	0	NA
FASN1	NA	NA	-	NA	NA	NA
UGP	0	0	NA	-	1	NA
mino	0	0	NA	1	-	NA
fbp	NA	NA	NA	NA	NA	-

Bayesian lead-lag R^2 similarity matrix

	IM1	IM2	FASN1	UGP	mino	fbp
IM1	-	0.99	0.76	0.21	0.33	0.52
IM2	0.98	-	0.71	0.18	0.31	0.46
FASN1	0.82	0.80	-	0.77	0.97	0.78
UGP	0.30	0.30	0.83	-	0.88	0.99
mino	0.40	0.39	0.98	0.91	-	0.90
fbp	0.68	0.66	0.82	0.99	0.86	-

Red entries: previously known associations
Blue entries: previously unknown associations