Gene-specific optimization of data integration improves regression-based Gene Regulatory Network inference in Arabidopsis

LEGO

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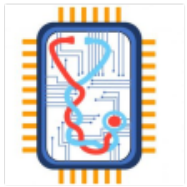


November 23

Regression-based GRN inference paradigm

Modelling assumption

The expression of regulators hold predictive and descriptive power over the expression of their target genes

Ex : GENIE3 [Huynh-Thu et al., 2010], The Inferelator [Gibbs et al., 2022]

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Limitations

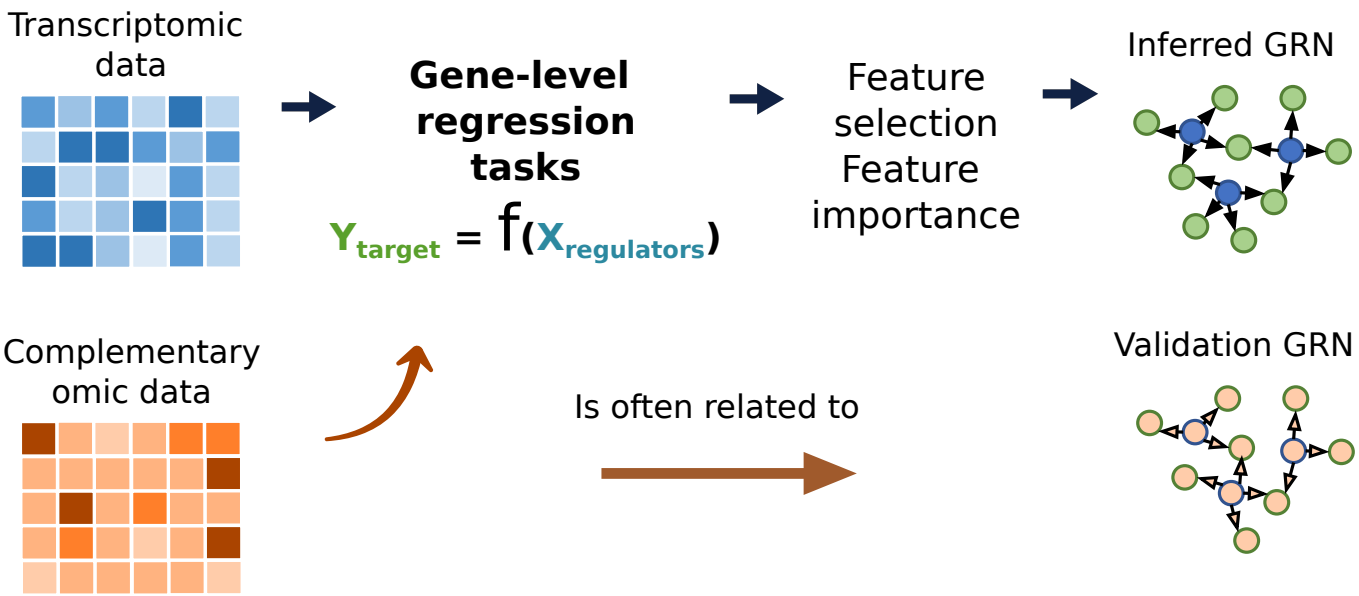
- High dimension
- High correlation among predictors
- Incomplete view of the regulation process

Data integration in regression-based GRN inference

Modelling assumption

Complementary omics can bring more causality to GRN inference

Ex : iRafNet [Petralia et al., 2015], MEN [Greenfield et al., 2013], LASSO-Stars [Miraldi et al., 2019]



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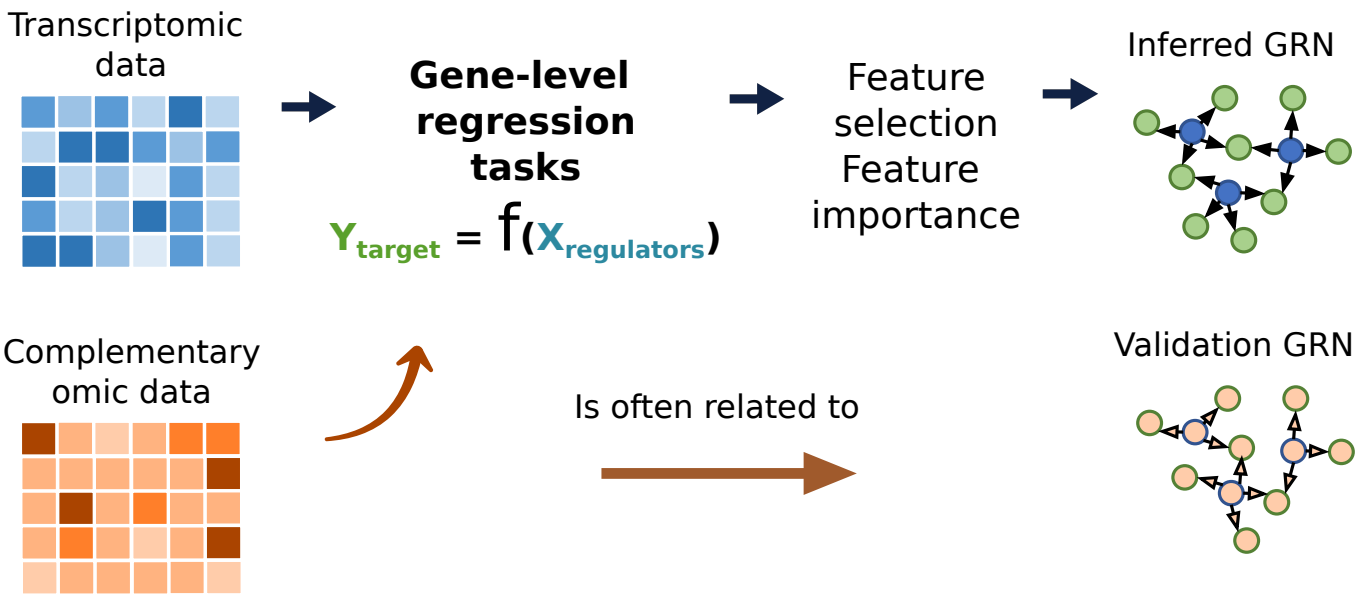

Current limitations

Omics contributions are **rarely finely tuned**.

They usually **rely on a close gold standard**.

Objectives

1. Can we define a new criterion to **robustly estimate the optimal strength of data integration** based on available data?
2. What is the benefit of optimising data integration at the **gene level**?

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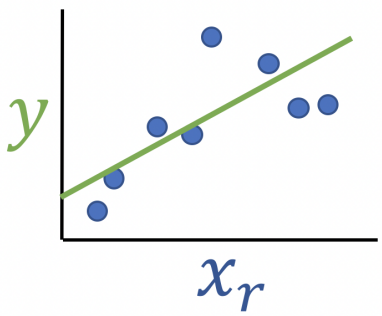
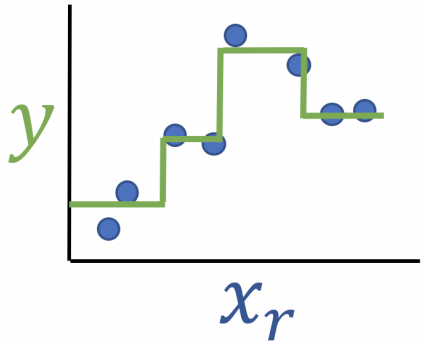
↳ Investigated for **two common forms of integrative regression**



$$Y_{target} = f(X_{regulators})$$

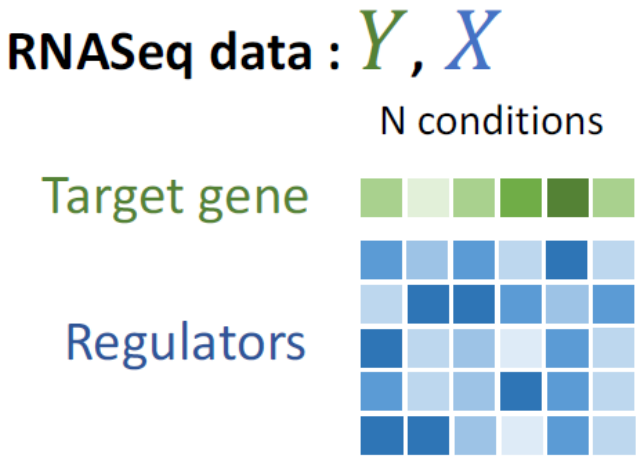
Linear
weightedLASSO
Inspired from
LASSO-Stars

Non linear
weightedRF
Inspired from
iRafNet



[Miraldi et al., 2019] [Petralia et al., 2015]

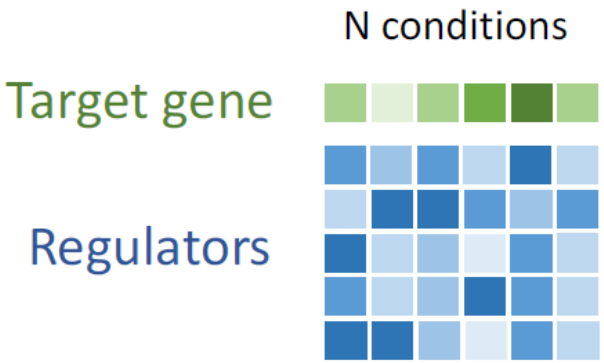
Modelling the root response to nitrate induction in *Arabidopsis thaliana*



Temporal response to nitrate induction
1426 genes, 201 regulators, $N = 45$ samples [Varala et al., 2018]

Modelling the root response to nitrate induction in *Arabidopsis thaliana*

RNASeq data : Y, X



Temporal response to nitrate induction
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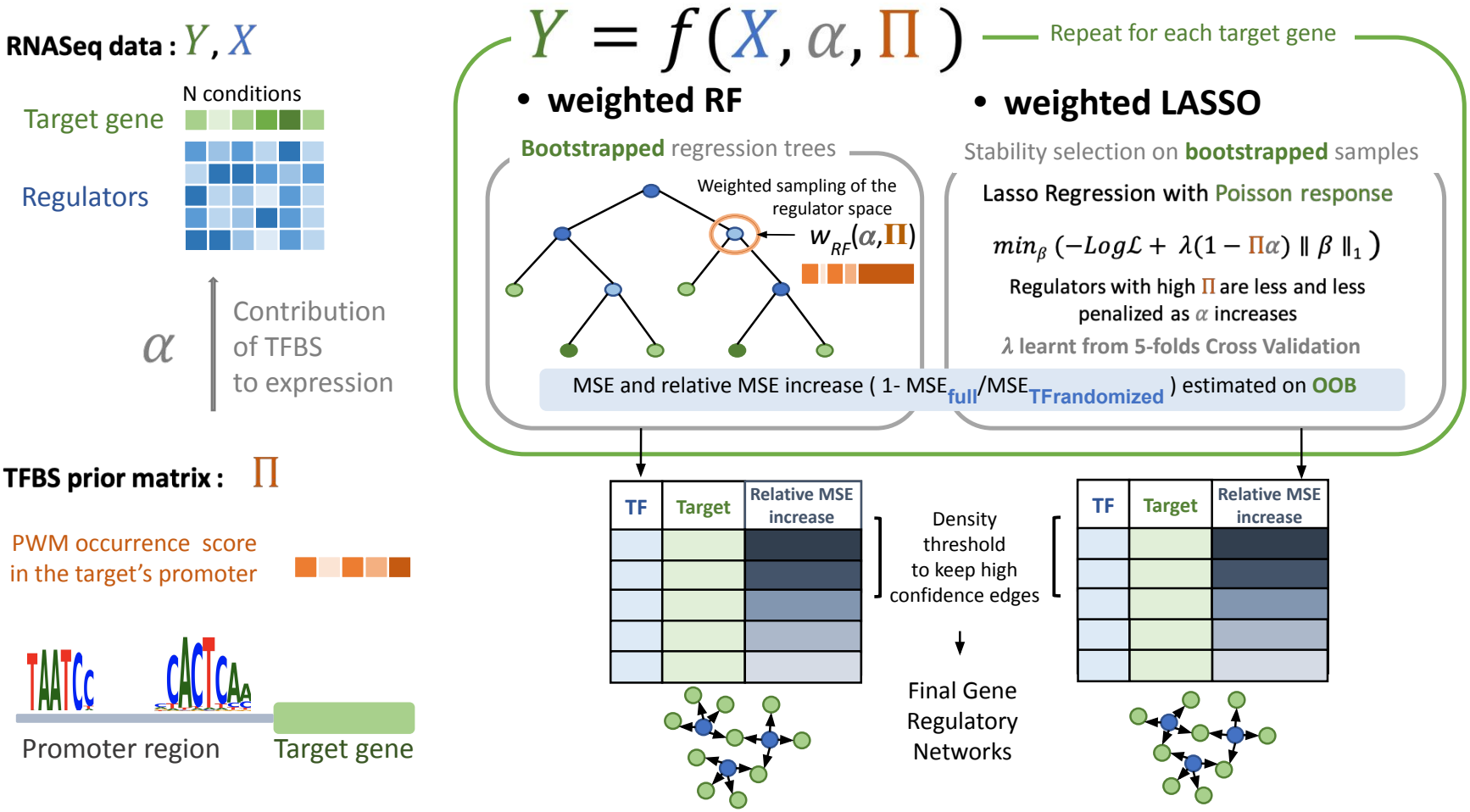
TFBM prior matrix : Π

PWM occurrence score in the target's promoter

TF binding sites from **JASPAR** and the **Plant Cistrome** Databases
[Castro-Mondragon et al., 2021, O'Malley et al., 2016]

$$\Pi_{r,t} = \begin{cases} 0 : \text{if the motif of } r \text{ is not in the promoter of } t \\ 1 : \text{if the motif of } r \text{ is in the promoter of } t \\ \frac{1}{2} : \text{if the motif of } r \text{ is missing} \end{cases}$$

Integrative regression-based GRN inference methods



iRafNet [Petralia et al., 2015] LASSO-Stars [Miraldi et al., 2019]

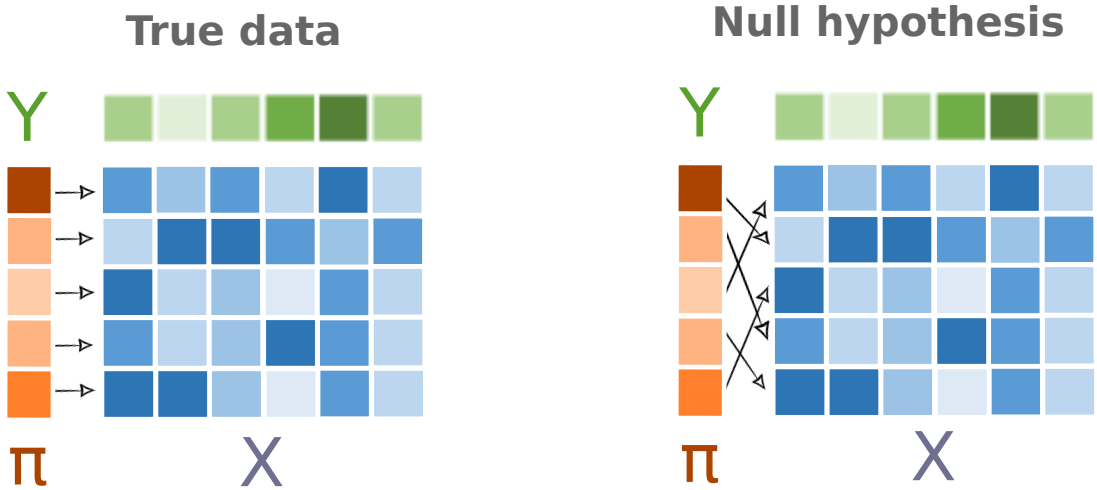
DIOgene: a gene-wise criterion to optimise data integration

Modelling assumption

We want to integrate **TFBMs while controlling that the prediction of gene expression is not deteriorated**.

A simulated null hypothesis

↳ Breaks the link between expression profiles and PWM scores, a case where **data integration is uninformative**



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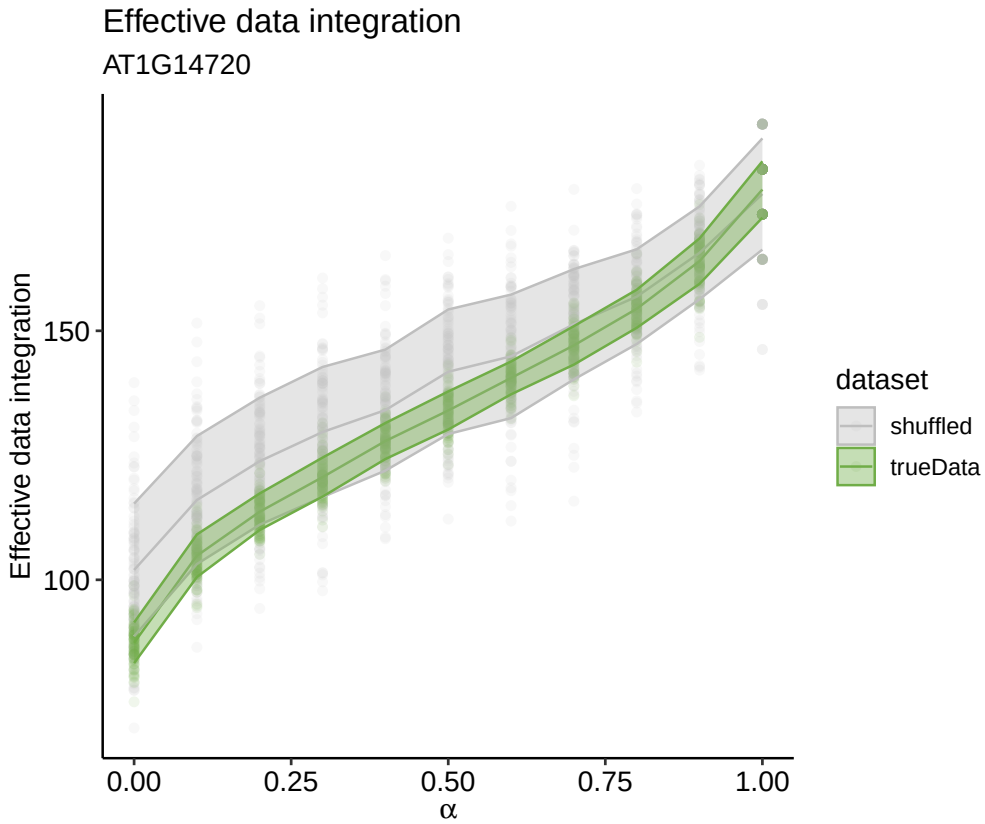
Effective data integration

Average rank of PWM-supported regulators based on their importance



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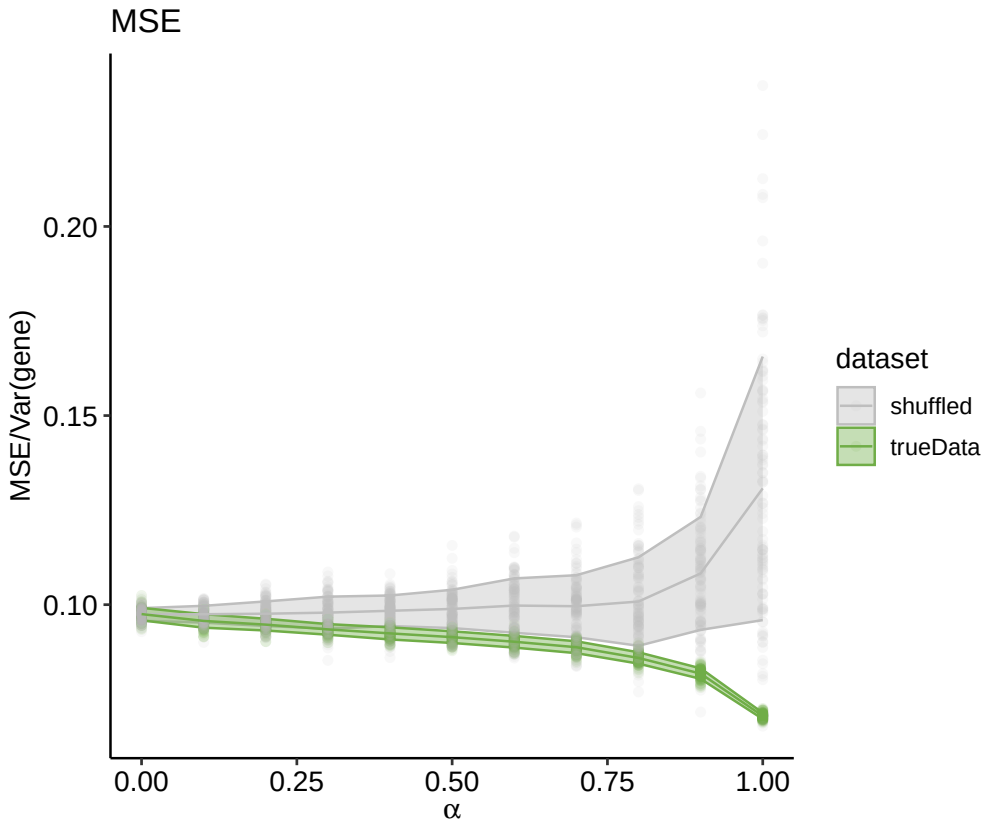
Prediction error (MSE)

Error committed by the regression model in predicting the target gene expression on test conditions



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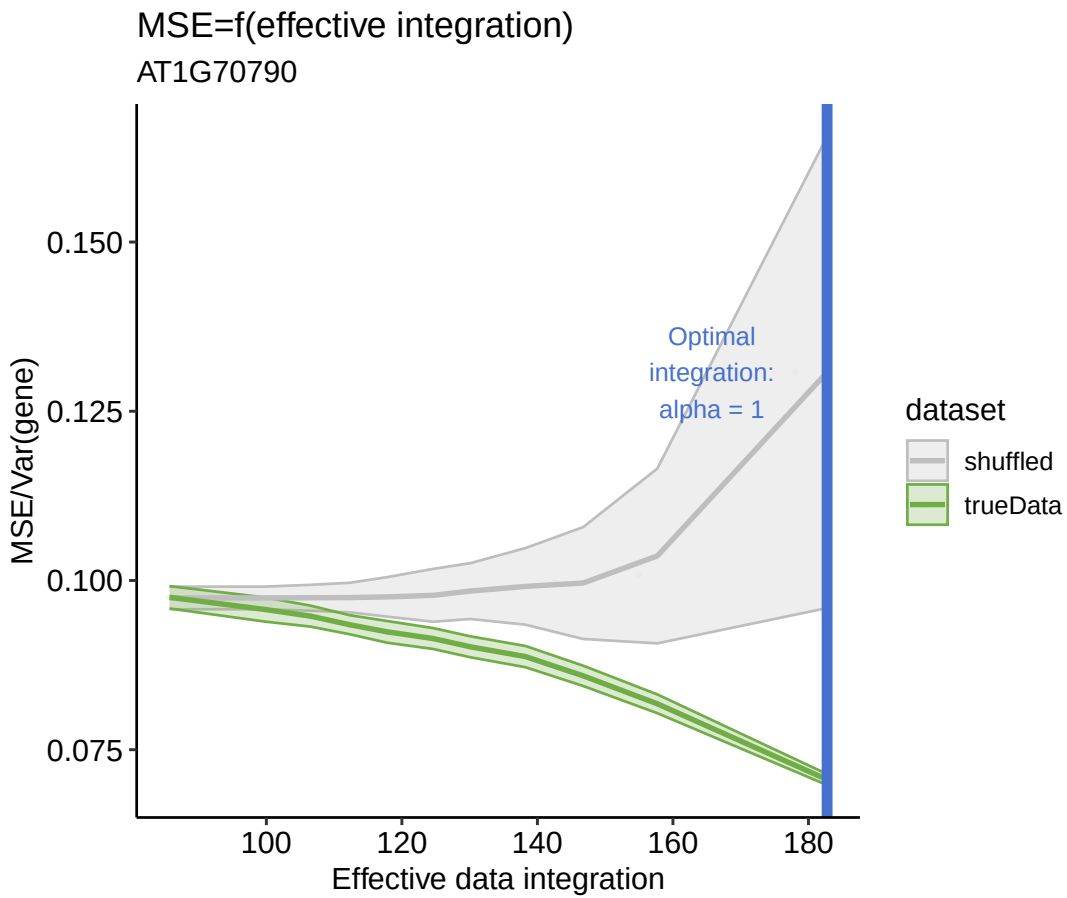
Ideal case

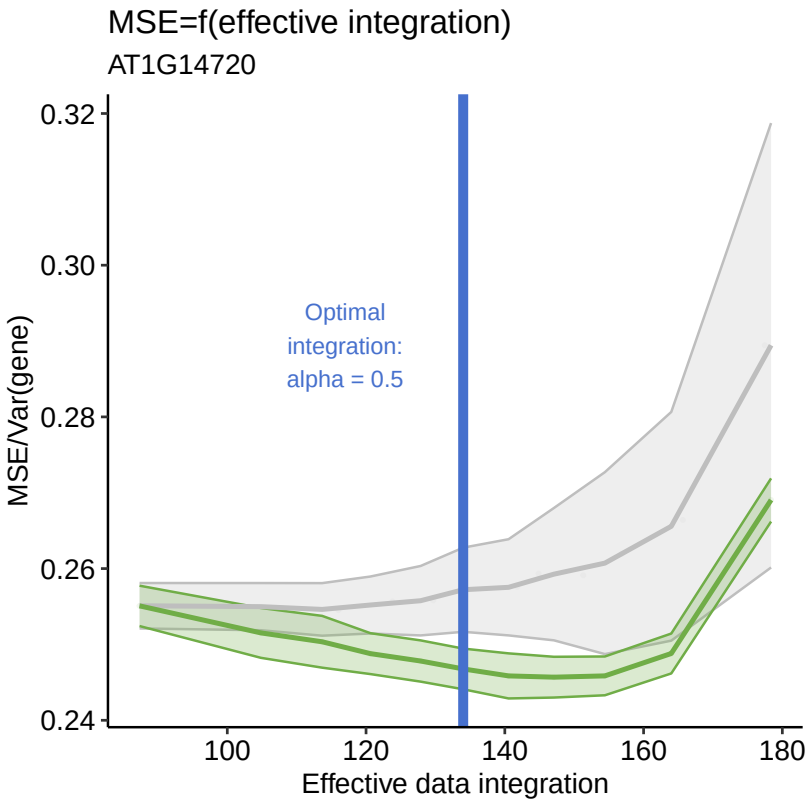
TFBM help selecting robust regulators and improve model generalisation performance

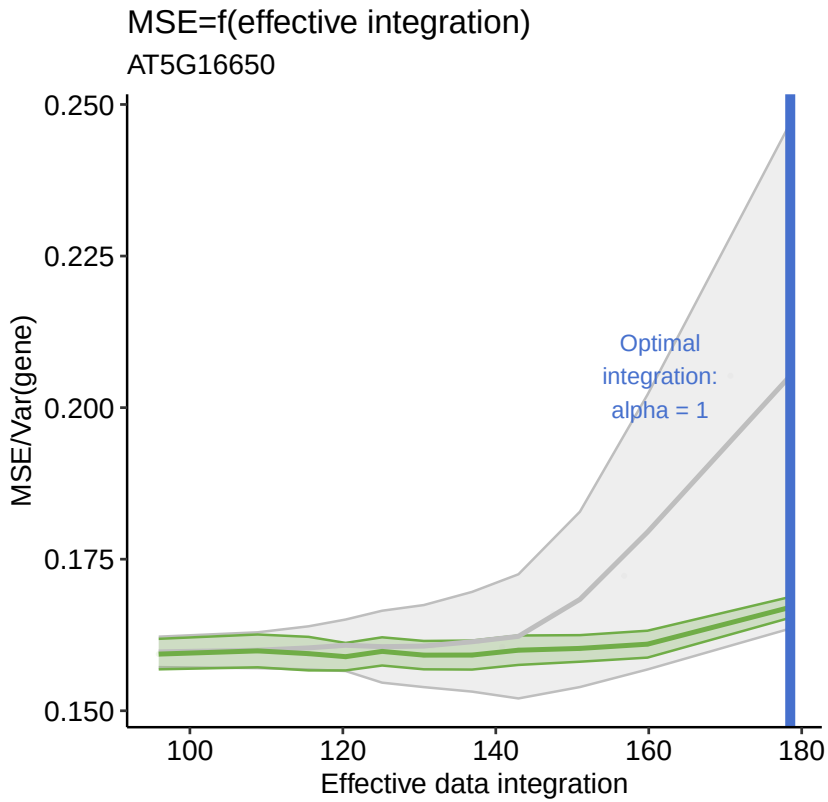


DIOgene: a gene-wise criterion to optimise data integration

Intermediate cases

The MSE reaches an optimum, or is improved over chance





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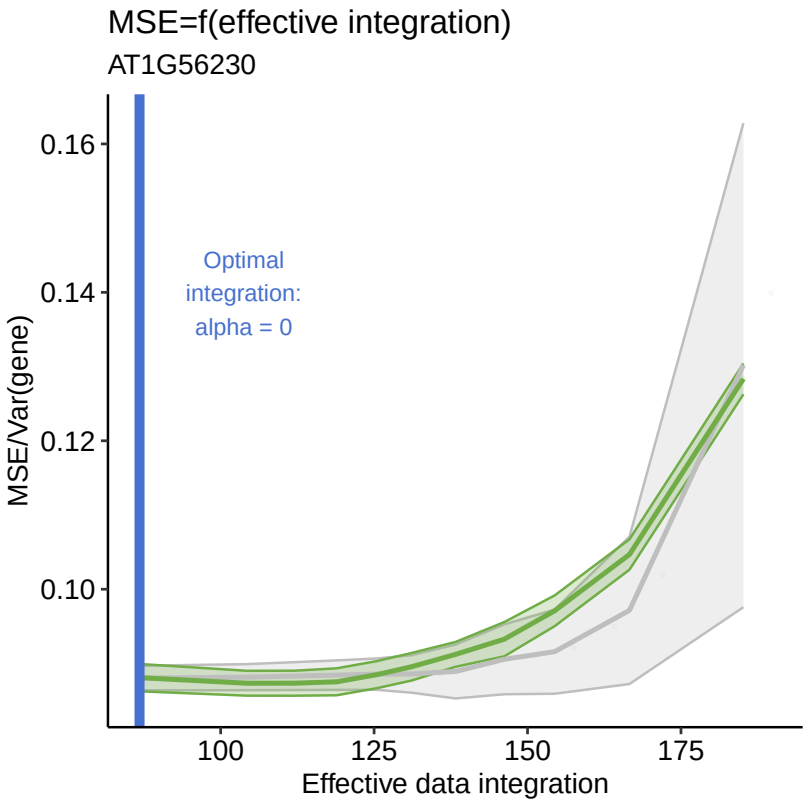
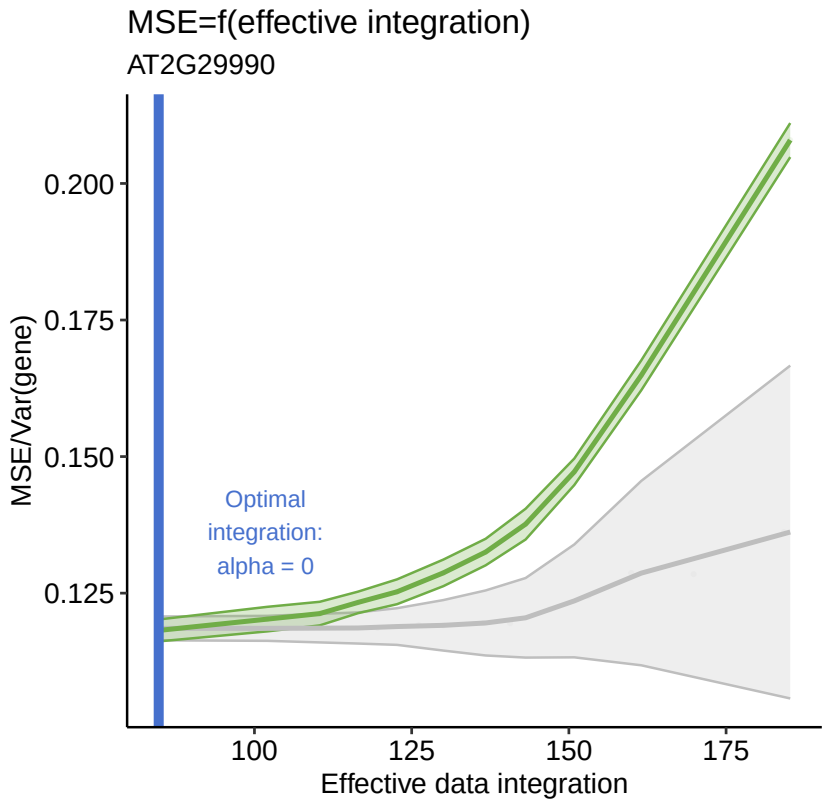
Cases where data integration should be avoided

The MSE does not differ from chance or is even higher





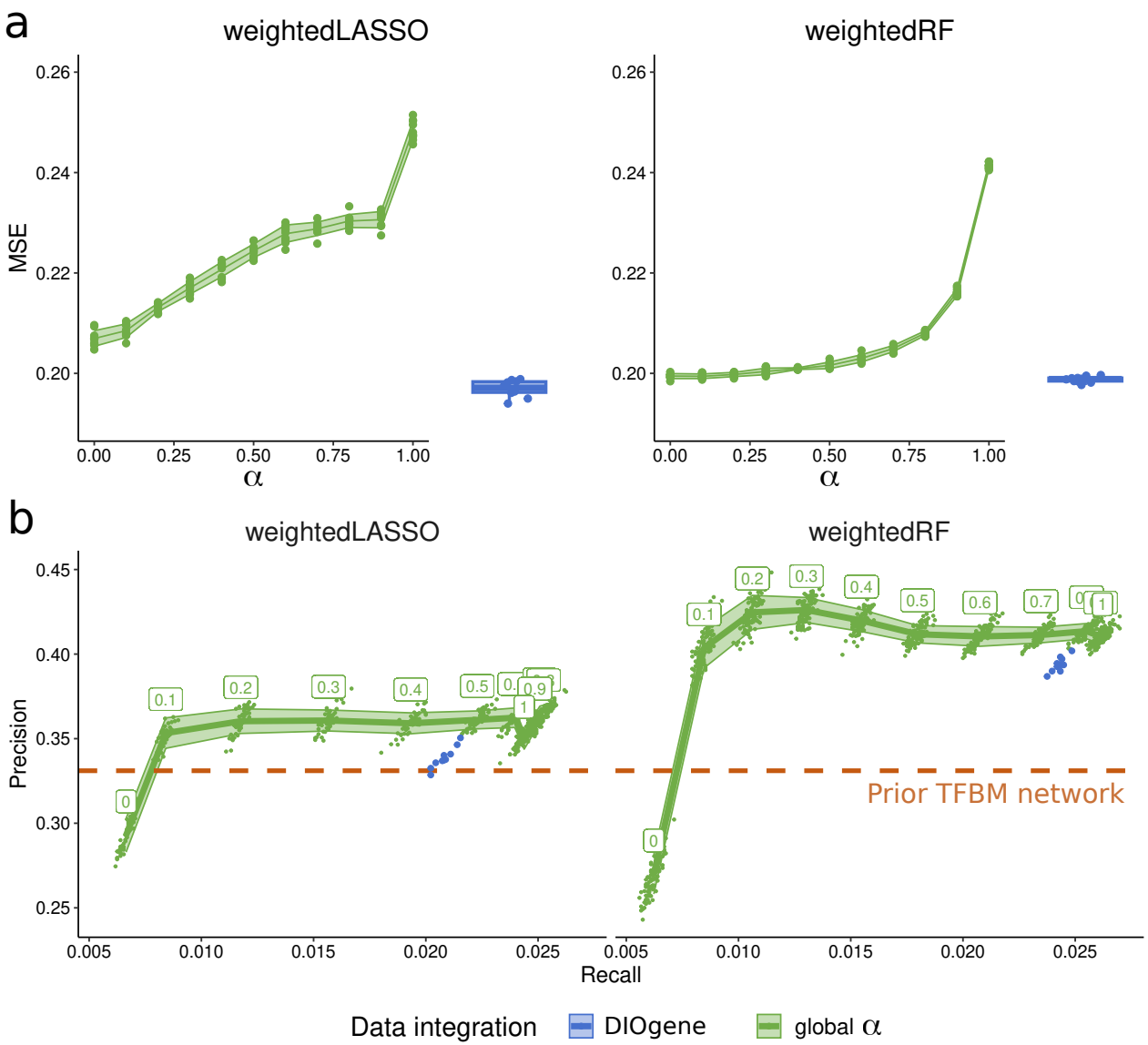
DIOgene offers low MSE, and good precision/recall

GRN reconstruction

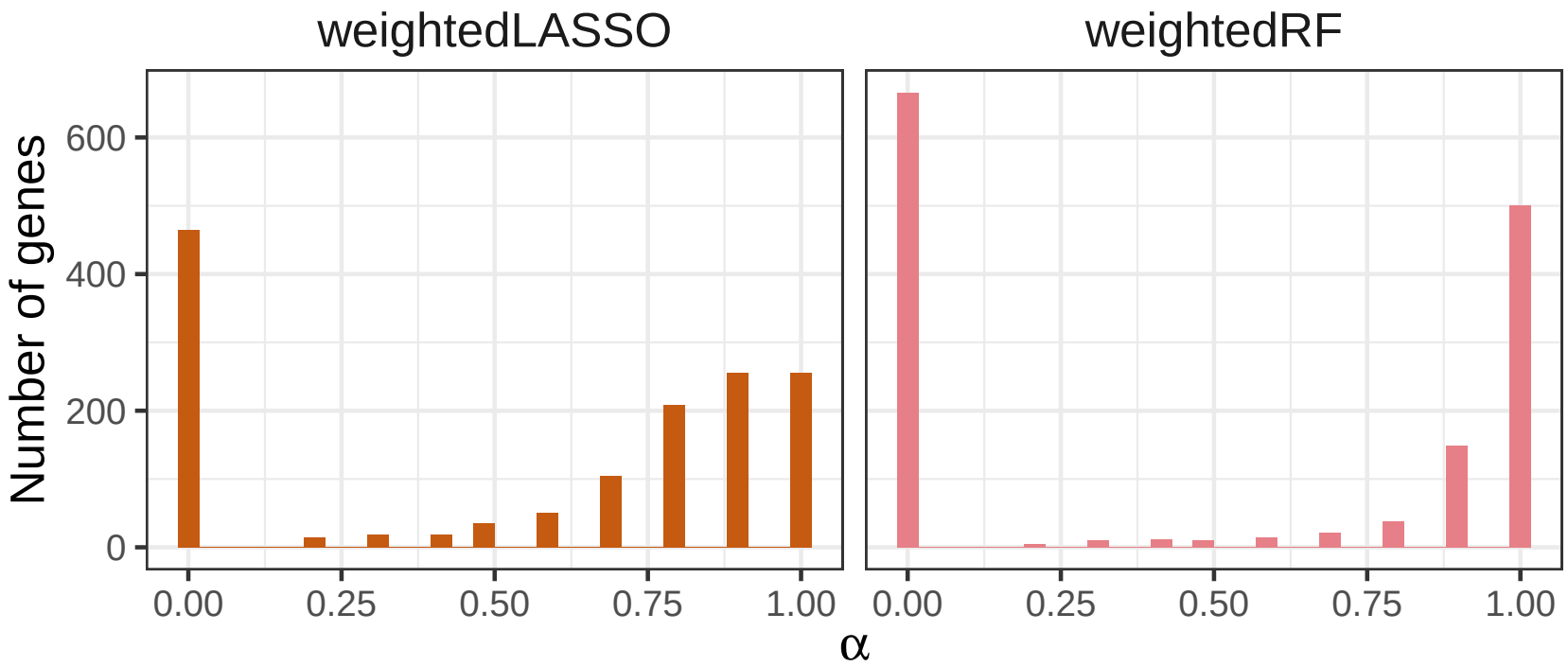
↳ 0.005 density threshold on importance-ranked edges (1432 edges)

GRN quality metrics

↳ **Median MSE**, and precision-recall curves against **DAP-Seq** in vitro TF binding [O'Malley et al., 2016]



Distributions of optimal integration strengths α_{opt}



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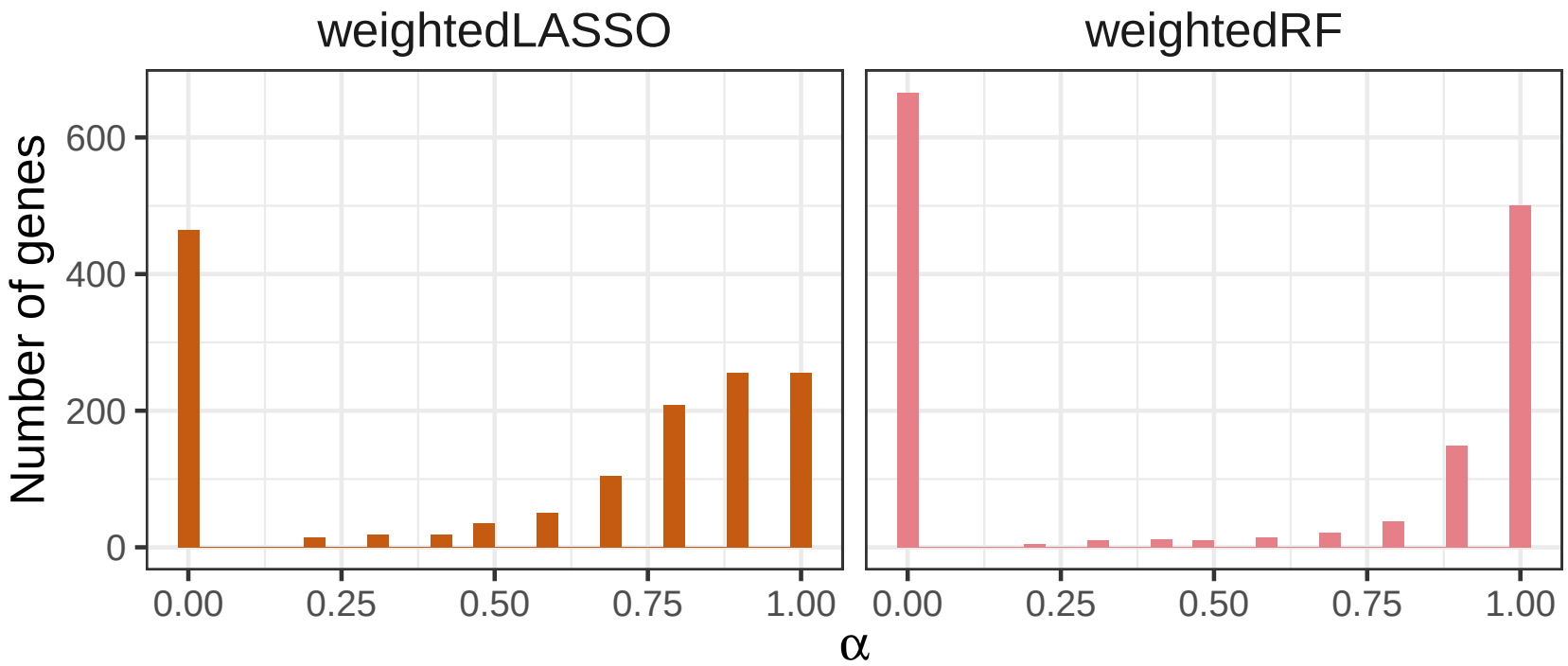

TFBM integration is not warranted for all genes

↳ Technical or biological causes? Cooperative binding events? Post-transcriptional regulations (RNA stability)?

Key message

Results of our gene-specific hypothesis-driven optimisation scheme

Indiscriminately pushing data integration to its maximal intensity is not always beneficial!

- Provides a desirable **trade-off between MSE and precision/recall**.
- Holds for both our linear and non-linear regression cases.
- Retrieves major players of nitrate nutrition in Arabidopsis.

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Code: `https://github.com/OceaneCsn/integrative_GRN_N_induction`

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Leveraging a problem-specific synthetic baseline

Importance of **in-silico controls** for causal discovery in genomic analyses (Jingyi Jessica Li's Keynote talk at ISMB 2023)

Perspectives

Limitations

- **Correlation is still a challenge**.
  ↳ Developing robust importance metrics to improve feature selection
- **Missing TFBMs**.
  ↳ Will be reduced as motif databases grow.

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Future research directions

1. Explore differences between the weightedLASSO and weightedRF and test the impact of **linearity assumptions**.
2. Extend it to **other organisms**, potentially with enhancers to scan for TFBMs, and **other types of omics and prior knowledge** to integrate.

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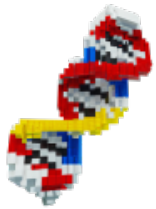
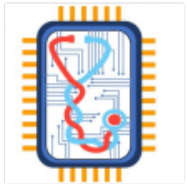


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Antoine Martin

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A gene-wise criterion to optimise data integration

Modelling assumption

We want to integrate TFBS **only if they improve prediction when used jointly with expression data**.

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Effective data integration

Importance of PWM-supported regulators :

$$\frac{\Sigma_{\Pi_{r,t}=1}\mathrm{Rank}(\mathrm{Importance}_{r,t,\alpha})}{N_{\Pi_{r,t}=1}}$$

Prediction error (MSE)

Error committed in predicting the target gene expression :

$$\frac{1}{N_{OOB}}\Sigma_{i\in OOB}(y_{t,i}-\hat{y}_{m,t,i,\alpha})^2$$

A simulated null hypothesis

↳ Breaks the link between expression profiles and PWM scores, a case where **data integration is uninformative**

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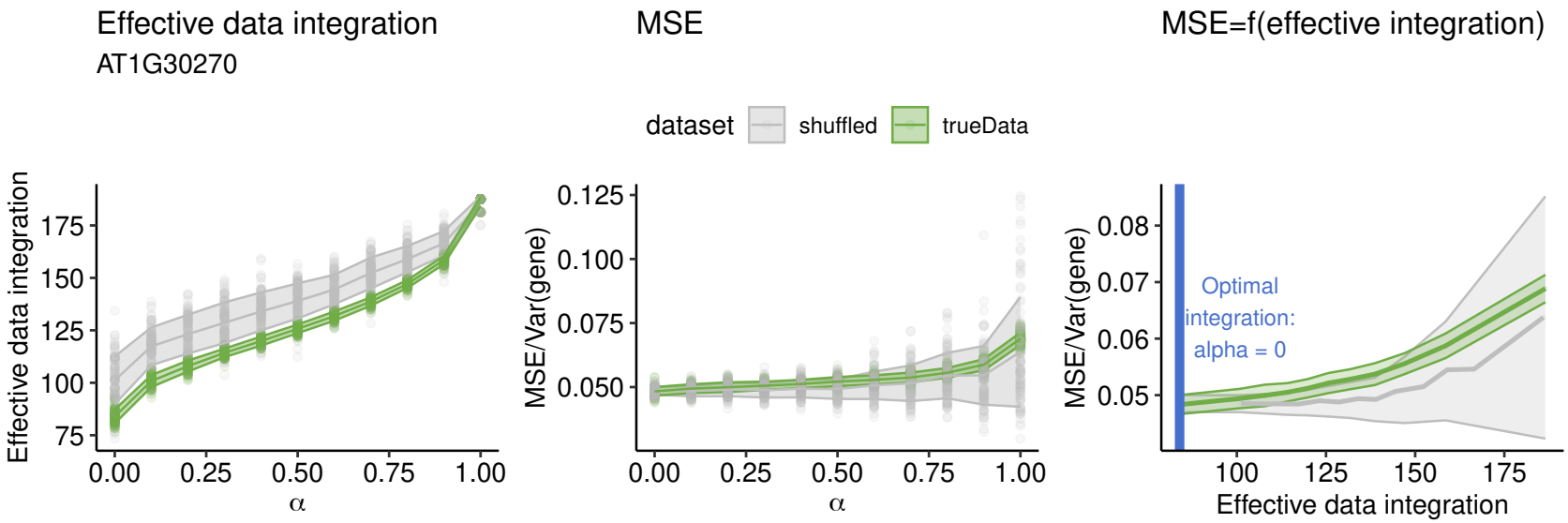

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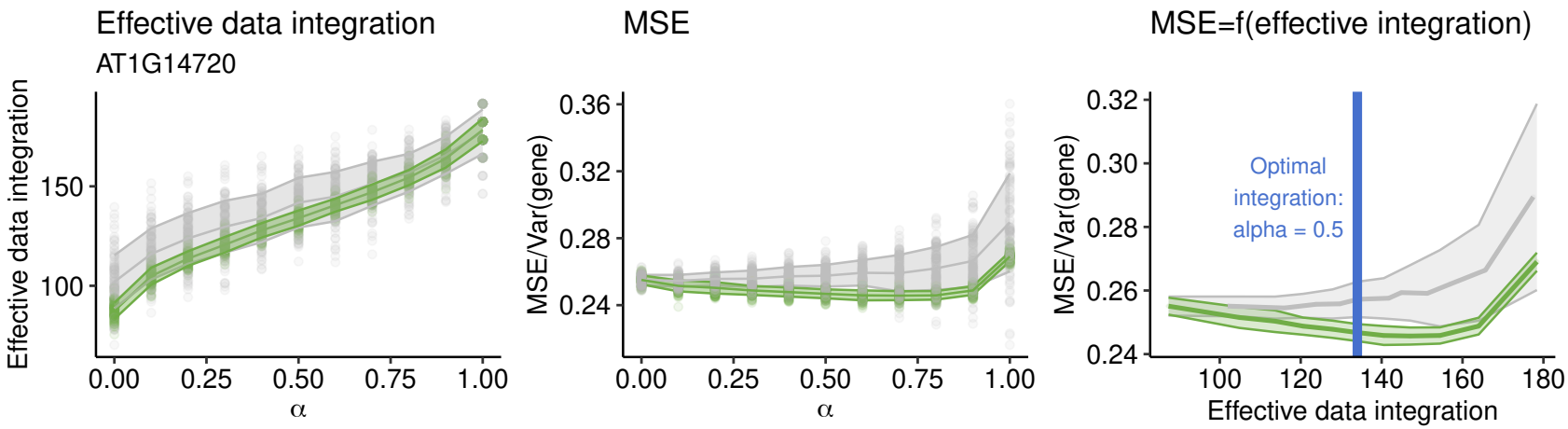

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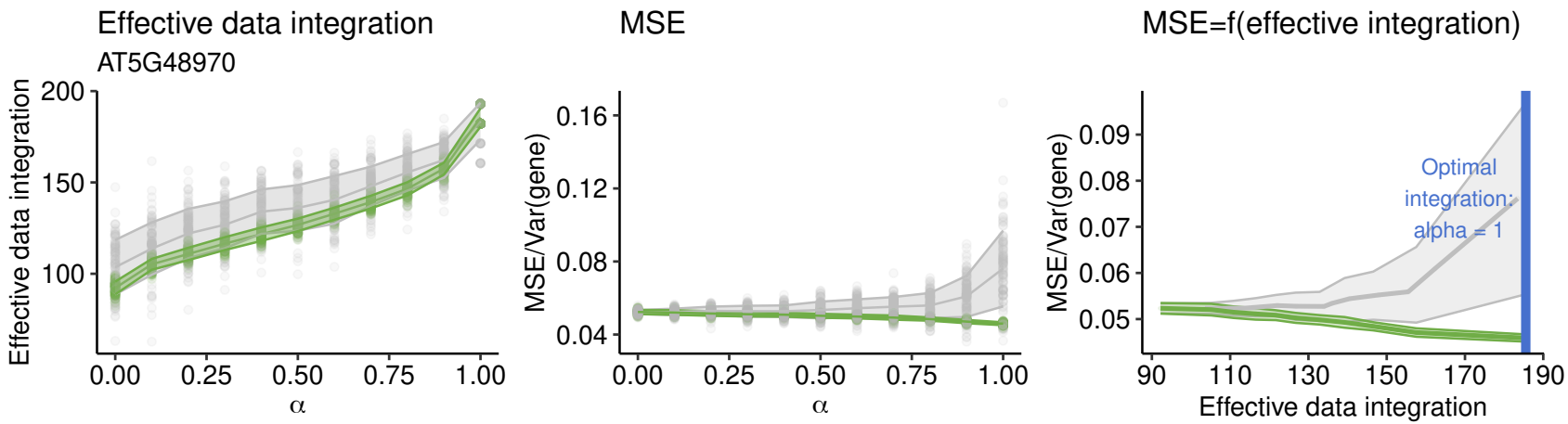

Criterion formal definition

$$\Delta_\alpha = \frac{\mu_{\text{shuffle},\alpha} - \mu_{\text{true},\alpha}}{\sigma_\alpha} \qquad \alpha_{\text{opt}} = \begin{cases} 0 & \text{if } \max\limits_{\alpha\in[0,1]} (\Delta_\alpha) \leq 1 \\ \operatorname{argmax}\limits_{\alpha\in[0,1]} (\Delta_\alpha) & \text{otherwise} \end{cases}$$

Deviation measure choice (σ_α) can modulate integration stringency:

- $\sigma_\alpha = \sigma_{\text{shuffle},\alpha} \rightarrow$ Low, stringent data integration
- $\sigma_\alpha = \frac{1}{2}(\sigma_{\text{shuffle},\alpha} + \sigma_{\text{true},\alpha}) \rightarrow$ Moderate data integration
- $\sigma_\alpha = \sigma_{\text{true},\alpha} \rightarrow$ Strong, permissive data integration

Modelling of nitrate signalling can be improved

All models capture important nitrate actors
[Bellegarde et al., 2017, Vidal et al., 2020].

Gene specific optimisation of α uniquely retrieves :

- **NPL7**[Marchive et al., 2013, Alvarez et al., 2020] and **PHL1** [Ueda et al., 2020] for **weightedLASSO**
- New candidate TFs of interest for **weightedRF**