Cross-Platform Prediction of Regulatory Activities

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Content

1. Introducution
2. Methods
3. Results
4. Application
5. Conclusion

Content

1. Introducution
2. Methods
3. Results
4. Application
5. Conclusion

Introduction

- Understand the complex regulome-transcriptome relationship
- Leverage gene expression profile to predict DNase I level

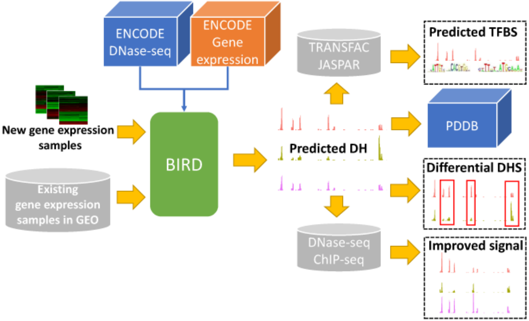


Figure: The work flow of BIRD

Introduction

- Cross-Platform?
- Expand the utility of GEO samples
- e.g. Use the human exon array data to train the prediction model and apply it to the microarray data

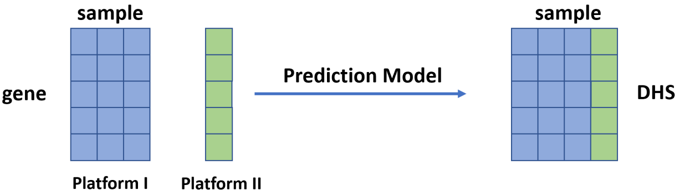


Figure: The sketch of cross-platform prediction

Content

1. Introducution

2. Methods

3. Results

4. Application

5. Conclusion

Methods: Data Preprocessing

- DNase-seq data: Bowtie
- Exon array data: The Affymetrix Human Exon 1.0 ST Array, GeneBASE
- Microarray data: Gene Expression BARCODE, GPL 96
- Training and test datasets partition

Methods: Problem Formulation and Notations

- Goal: use gene expression to predict DH level
- Let $Y^{(l)}$ be the DH level of genomic locus l, and X be the design matrix $C \times G$ of gene expression data, where C and G is the number of samples and genes respectively.
- Consider the prediction model:

$$Y^{(l)} = X\beta^{(l)} + \epsilon$$

where $l = 1, 2...L$, therefore we fit L separate regression models.

Methods: Problem Formulation and Notations

- Goal: cross-platform prediction
- Idea: apply BIRD model
- Problem: platform effect
- How to solve: normalization

Methods: Problem Formulation and Notations

- Suppose there is a new sample $\tilde{x}$ drawn from another platform, we want to apply the fitted model to predict the DH level : $\tilde{Y}^{(l)} = \tilde{x}\beta^{(l)}$?
- Assume $f(\cdot)$ is the normalization function, then we get the regression model

$$\tilde{Y}^{(l)}_{norm} = f(\tilde{x})\beta^{(l)}$$

Normalization

We introduce 4 normalization methods

- Sample-quantile method
- All-sample method
- Neighboring-sample method
- Gene-quantile method

Sample-quantile normalization

Algorithm 1 Sample-quantile normalization

```
Require: Exon array data matrix $X_e : G \times C_1$, microarray data matrix $X_m : G \times C_2$
Compute the mean quantile vector of the exon array data $X_e^q : G \times 1$
Assign the mean vector $X_e^q$ to each column of the microarray data according to its order
Obtain the normalized microarray data $X_m^{norm}$
```

All-sample normalization

Algorithm 2 All-sample normalization

```
Require: Exon array data matrix $X_e : G \times C_1$, microarray data matrix $X_m : G \times C_2$
Estimate $\mu_1, ..., \mu_G$ and $\sigma_1, ..., \sigma_G$, such that the linear transformation $T_i = \frac{x-\mu_i}{\sigma_i}, i = 1, ..., G$ applied to each row of the whole microarray samples can generate the same mean and standard deviation as exon array data.
```

Neighboring-sample normalization

Algorithm 3 Neighboring-sample normalization

```
Require: Exon array data matrix $X_e : G \times C_1$, microarray data matrix $X_m : G \times C_2$
1: For each exon array sample, select $k$ largest cross-gene correlation microarray samples and remove the duplicate samples.
2: Obtain the neighboring samples data matrix $X_m^{nbr}$
3: Estimate $\mu_1, ..., \mu_G$ and $\sigma_1, ..., \sigma_G$, such that the scaling $T_i = \frac{x-\mu_i}{\sigma_i}, i = 1, ..., G$ applied to each row of the neighboring samples $X_m^{nbr}$ can generate the same mean and standard deviation as exon array data.
4: Apply the linear transformation in step 3 to the microarray data matrix $X_m$.
```

Gene-quantile normalization

Algorithm 4 Gene-quantile normalization

```
Require: Exon array data matrix $X_e : G \times C_1$, microarray data matrix $X_m : G \times C_2$
1: Obtain the neighboring samples data matrix $X_m^{nbr}$ using algorithm 2
2: Sort the exon vector $X_{e,i}^{sort}$ and the neighboring microarray vector $X_{m,i}^{nbr,sort}$ for each row $i$.
3: Fit the LOESS regression model to $(X_{e,i}^{sort}, X_{m,i}^{nbr,sort})$
4: Given a new microarray sample, predict the normalized value for each row according to the LOESS model in step 3
```

Methods: BIRD model

Consider the prediction model:

$$Y^{(l)} = X\beta^{(l)} + \epsilon$$

- Step One: Variable Clustering
- Step Two: Fast Variable Screening

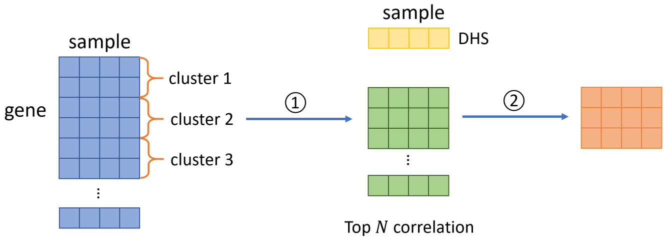


Figure: The BIRD model

Methods: Parameter Tuning

- Consist of three hyper parameters
  - the cluster number K
  - the predictor number N
  - the gene number M
- Determined by 5-fold cross-validation
- Select the genes with high cross-cell-type correlation

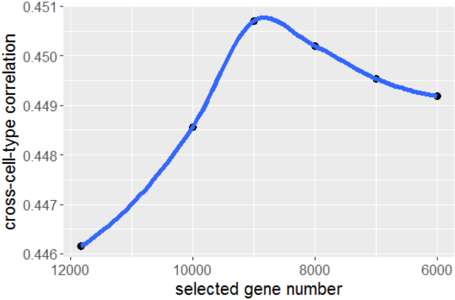


Figure: The relations between cross-cell-type correlation and gene number

Content

1. Introducution
2. Methods
3. Results
4. Application
5. Conclusion

Results

We use the following metrics to evaluate the model performance.

- Cross-locus correlation
- Cross-cell-type correlation
- Prediction squared error

Results: cross-locus correlation

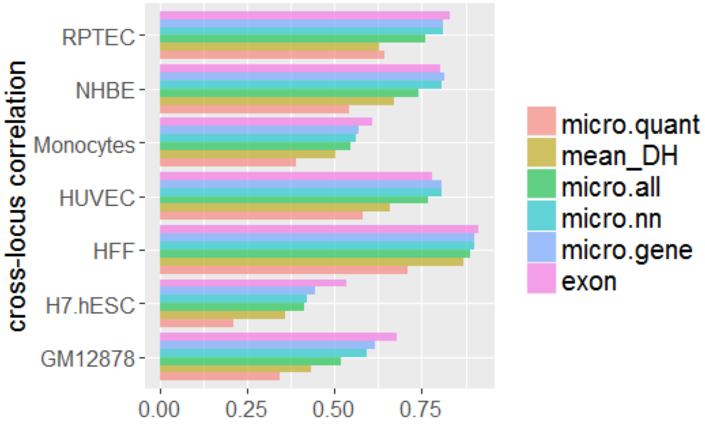


Figure: Cross-locus correlation

Results: cross-cell-type correlation

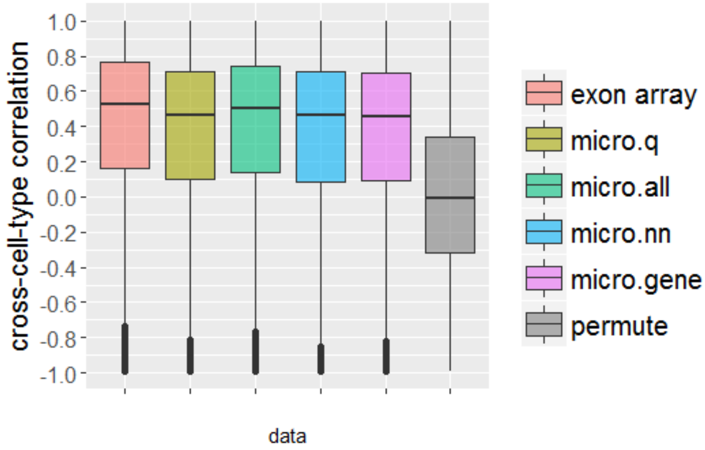


Figure: Cross-cell-type correlation

Results: prediction squared error

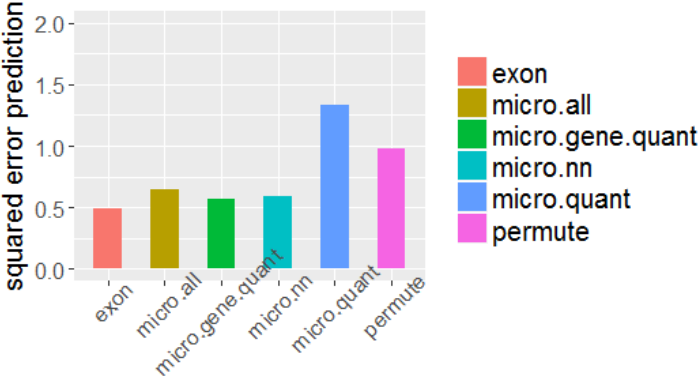


Figure: Prediction squared error

Content

1. Introducution
2. Methods
3. Results
4. Application
5. Conclusion

Application

- RNA-seq test
- Analysis of Pou5f1 binding sites

Application: RNA-seq test

- Goal: apply cross-platform prediction upon RNA sequence data
- Six samples which appear in both exon array and RNA-seq data are served as the gold standard, and the cross-cell type correlation is the evaluation metric.

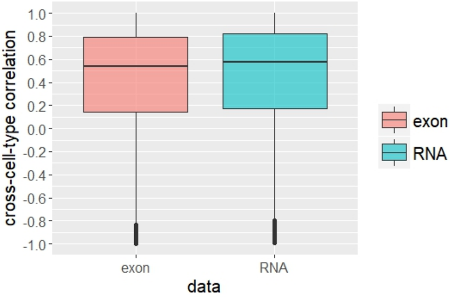


Figure: The cross-cell type correlation for exon array and RNA-seq data

Application: Pou5f1 binding sites

- Pou5f1 CHIP-seq peaks in H1-hesc
- Apply the cross-platform BIRD upon all public available GPL96 samples, and select the loci that
  - overlapped with Pou5f1 CHIP-seq peaks
  - high variability of the predicted value
- The ultimate data : 2490 DHS $\times$ 11865 samples

Application: Pou5f1 binding sites

Group both the DHS and samples into 10 clusters, and create a heatmap

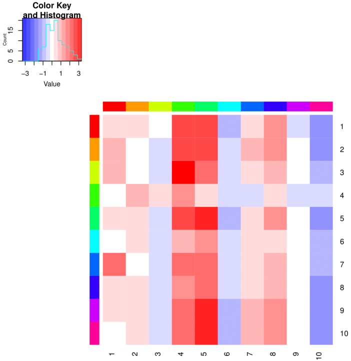


Figure: The heatmap of predicted DH level at Pou5f1 binding sites

Look up the sample annotation table

cluster id	samples
4	brain cortex hippocampus cerebellum
5	embryonic stem cells mesenchymal stem cells lung

Table: cluster id and samples

Content

1. Introducution
2. Methods
3. Results
4. Application
5. Conclusion

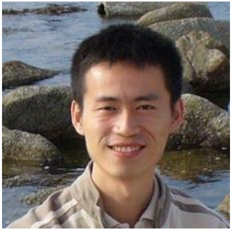
Conclusion

- The motivation of BIRD model is to predict chromatin accessibility using gene expression.
- Some normalization methods are proposed to deal with cross-platform prediction.
- Our method is further applied to some other examples.

Acknowledgement

This is joint work with Dr.Weiqiang Zhou and Dr.Hongkai Ji.

Weiqiang Zhou



Hongkai Ji

Reference I

Weiqiang Zhou, Ben Sherwood, Zhicheng Ji, Yingchao Xue, Fang Du, Jiawei Bai, Mingyao Ying, and Hongkai Ji.
Genome-wide prediction of dnase i hypersensitivity using gene expression.
Nature communications, 8(1):1038, 2017.

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