Spectral approaches to integrate gene expression and gene networks

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ARMINES contribution to ESBIC

- Develop methods for analysis of gene expression data
- Develop methods for integration of heterogeneous data, in particular expression and pathways
- Integrate these tools in the ESBIC standards
Outline

1. Classification and interpretation of microarray data

2. Including pathway information
Classification and interpretation of microarray data
Including pathway information

Classical setting

Data available

- Gene expression measures for more than 10k genes
- Measured on less than 100 samples of two (or more) different classes (e.g., different tumors)

Goal

- Design a classifier to automatically assign a class to future samples from their expression profile
- Interpret biologically the differences between the classes
Classical setting

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Linear classifiers

The approach

- Each sample is represented by a vector \( x = (x_1, \ldots, x_p) \) where \( p > 10^5 \) is the number of probes
- **Classification**: given the set of labeled sample, learn a linear decision function:
  \[
  f(x) = \sum_{i=1}^{p} \beta_i x_i + \beta_0 ,
  \]
  that is positive for one class, negative for the other
- **Interpretation**: the weight \( \beta_i \) quantifies the influence of gene \( i \) for the classification
Linear classifiers

Pitfalls

- No robust estimation procedure exist for 100 samples in $10^5$ dimensions!
- It is necessary to reduce the complexity of the problem with prior knowledge.
Classification and interpretation of microarray data
Including pathway information

Example: Norm Constraints

The approach

A common method in statistics to learn with few samples in high dimension is to constrain the norm of $\beta$, e.g.:

- Euclidean norm (support vector machines, ridge regression): $\| \beta \|_2 = \sum_{i=1}^{p} \beta_i^2$
- $L_1$-norm (lasso regression): $\| \beta \|_1 = \sum_{i=1}^{p} |\beta_i|$

Pros

- Good performance in classification

Cons

- Limited interpretation (small weights)
- No prior biological knowledge

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Spectral approaches to integrate gene expression and gene network information
Example 2: Feature Selection

The approach

Constrain most weights to be 0, i.e., **select a few genes (< 20)** whose expression are enough for classification. Interpretation is then about the selected genes.

Pros
- Good performance in classification
- Useful for **biomarker** selection
- Apparently easy interpretation

Cons
- The gene selection process is usually **not robust**
- Wrong interpretation is the rule (too much correlation between genes)
Basic biological functions are usually expressed in terms of **pathways** and not of single genes (metabolic, signaling, regulatory)

Many pathways are already known

How to use this prior knowledge to *constrain the weights to have an interpretation at the level of pathways*?
Pathway interpretation

- Glycolysis / Gluconeogenesis
- Porphyrin and chlorophyll metabolism
- Sulfur metabolism
- Riboflavin metabolism
- Folate biosynthesis
- Biosynthesis of steroids, ergosterol metabolism
- Lysine biosynthesis
- Phenylalanine, tyrosine and tryptophan biosynthesis
- Oxidative phosphorylation, TCA cycle
- Nitrogen, asparagine metabolism
- DNA and RNA polymerase subunits
- Protein kinases
- N-Glycan biosynthesis
- Purine metabolism
- Bad example
- The graph is the complete known metabolic network of the budding yeast (from KEGG database)
- We project the classifier weight learned by a SVM
- Good classification accuracy, but no possible interpretation!
Pathway interpretation

Good example

- The graph is the complete known metabolic network of the budding yeast (from KEGG database)
- We project the classifier weight learned by a spectral SVM
- Good classification accuracy, and good interpretation!
### Short description

1. Pre-process each microarray profile to filter out the high frequencies with respect to the known pathways. This involves discrete Fourier transforms + spectral graph theory.

2. Perform **classical SVM** on the smoothed expression profiles.
Spectral analysis of gene expression profiles using gene networks

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Abstract

Microarrays have become extremely useful for analysing genetic phenomena, but establishing a relation between microarray analysis results (typically a list of genes) and their biological significance is often difficult. Currently, the standard approach is to map "a posteriori" the results onto gene networks to elucidate the functions perturbed at the level of pathways. However, integrating "a priori" knowledge of the gene networks could help in the statistical analysis of gene expression data and in their biological interpretation. Here we propose a method to integrate "a priori" the knowledge of a gene network in the analysis of gene expression data. The approach is based on the spectral...
Discussion

You will always have an interpretable model because you enforce it. Can we trust it?

- Any method must use prior knowledge because of the $n << p$ problem.
- In many cases the “true” classifier is more likely to have a pathway interpretation than to be based on a few genes only.

There are many cases where smoothness is not expected on the pathway (negative regulation...)

- We just enforce a global smoothness, local jumps are possible (although penalized).
- As more data are available, a more precise estimation is possible.
Conclusion

- Manipulating gene expression data is difficult for statistical reasons.
- Inclusion of prior knowledge is required (e.g., feature selection)
- Known pathways form a natural prior knowledge
- This results in classifiers with good accuracy and interpretability.
Ongoing and future work

- Validation on tumour data
- Extension to non-smooth assumption (inhibition...)
- Integration with other softwares
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