Multiscale Bootstrap Analysis of Gene Networks Based on Bayesian Networks and Nonparametric Regression

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Introduction

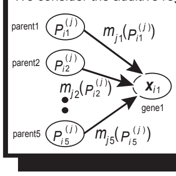
The Bayesian network [2, 3, 4] is a very powerful tool for estimating the gene network from microarray expression profiles. The estimated network is often susceptible to statistical sampling error, and thus Imoto *et al.* [3, 4] evaluated the reliability of estimation by calculating the bootstrap probabilities for the edges connecting genes. The bootstrap method, however, underestimates the probability values, and it sometimes leads to false "discovery". For improving the accuracy of the bootstrap probability, we propose the application of the newly developed multiscale bootstrap [5, 6] to the gene network estimation.

Method

1. Nonlinear Bayesian Network Model

Nonparametric Heteroscedastic Regression

We consider the additive regression model:



$$x_{ij} = \boxed{m_{j1}(P_{i1}^{(j)})} + \dots + \boxed{m_{jq_j}(P_{iq_j}^{(j)})} + \varepsilon_{ij}$$

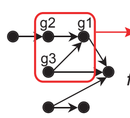
Function of the 1st parent; Function of the q_j th parent

where $\varepsilon_{ij} \sim N(0, \sigma_j^2)$

Here $m_{jk}(\cdot)$ is a smooth function from **R** to **R**.

1. What is Bayesian network?
   - DAG encoding the Markov assumption. (DAG : Directed acyclic graph)
   - The joint density can be computed by the product of the conditional densities.
2. How can we capture the nonlinear relationships between genes?
3. How can we choose the optimal graph?

Bayesian networks



$$x_{i1} \leftarrow \boldsymbol{P}_{i1} = (x_{i2}, x_{i3})^T$$

$$f(x_{i1}, \dots, x_{ip}; \boldsymbol{\theta}_G) = \prod_{j=1}^{p} f_j(x_{ij} \mid \boldsymbol{p}_{ij}; \boldsymbol{\theta}_j)$$

BNRC (Bayesian network and Nonparametric Regression Criterion)

BNRC

$$= -2\log \pi(G) \int \prod_{i=1}^{n} f(\mathbf{x}_i \mid \boldsymbol{\theta}_G)\, \pi(\boldsymbol{\theta}_G \mid \boldsymbol{\lambda}_G)\, d\boldsymbol{\theta}_G$$

$$\propto -2\log \pi(G) - r\log(2\pi n^{-1}) + \log \left| J_\lambda(\hat{\boldsymbol{\theta}}_G) \right| - 2nl_\lambda(\hat{\boldsymbol{\theta}}_G \mid \mathbf{X}_n)$$

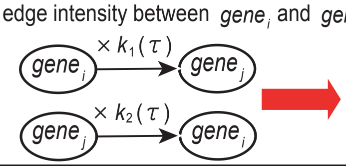
We choose the graph that minimizes the value of BNRC

2. Bootstrap and Multiscale Bootstrap Edge Intensity

We measure the intensity of the edge by the bootstrap and multiscale bootstrap method. In the multiscale bootstrap method, we generate replicates $\boldsymbol{X}^*_{n'} = (\boldsymbol{x}^*_1, \dots, \boldsymbol{x}^*_{n'})$ for several n' values from the original gene expression data $\boldsymbol{X}_n = (\boldsymbol{x}_1, \dots, \boldsymbol{x}_n)$. In other words, we alter the number of arrays from n to n' in the bootstrap replication. We will take n' values with n'/n = 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, in the example shown later. We call $\tau = \sqrt{n/n'}$ scale.

The Bootstrap Algorithm with n' arrays

Step1: Generate the bootstrap replicate $\boldsymbol{X}^*_{n'}$.
Step2: Estimate the gene network from $\boldsymbol{X}^*_{n'}$.
Step3: Iterate Step1 and Step2 B times. Then we obtain B gene networks.
Step4: If the edges $gene_i \to gene_j$ and $gene_j \to gene_i$ exists $k_1(\tau)$ and $k_2(\tau)$ times, respectively, in the B networks, we then define the bootstrap edge intensity between $gene_i$ and $gene_j$, $BP_{ij}(\tau)$, as $(k_1(\tau) + k_2(\tau))/B$.



The bootstrap edge intensity

$$\boxed{BP_{ij}(\tau) = (k_1(\tau) + k_2(\tau))/B}$$

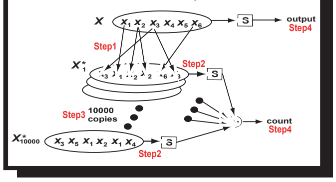


Figure1: The conceptual figure of the bootstrap method.

The bootstrap method

- We take $n' = n$.
- The bootstrap edge intensity can be written as $BP_{ij}(1)$.

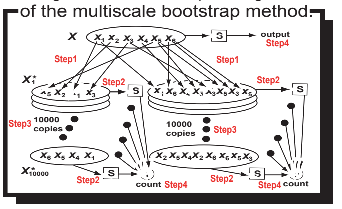


Figure2: The conceptual figure of the multiscale bootstrap method.

The multiscale bootstrap method

- We calculate $BP_{ij}(\tau)$ with several τ values by altering n'/n.
  - The very accurate edge intensiy is expressed as $MS_{ij} = 1 - \Phi(d_{ij} - c_{ij})$.
    d_{ij} : signed distance
    c_{ij} : curvature
    Φ : distribution function of standard normal distribution.
- We estimate d_{ij} and c_{ij} by fitting the theoretical curve $BP_{ij}(\tau) = 1 - \Phi(d_{ij}/\tau + c_{ij}\tau)$ to the observed $BP_{ij}(\tau)$ values calculated by the multiscale bootstrap method.

Result

- We applied the proposed method to *S.cervisiae* gene expressin data.
- We focusd on 9 genes, which are involved or putatively involved in the heat shock response.
- We took B = 10000.

Table 1: Gene pairs with high multiscale bootstrap intensities.

$gene_i$	$gene_j$	MS_{ij}	BP_{ij}
YBR072W	YBR054W	1.000	0.985
YBR072W	YPL240C	1.000	0.998
YER057C	YLL026W	0.998	0.999
YAL005C	YMR043W	0.998	0.972
YLL026W	YBR054W	0.996	0.938
YER057C	YBL075C	0.994	0.985
YPL240C	YBR054W	0.991	0.835
YBL075C	YBR054W	0.978	0.885
YER057C	YGL073W	0.928	0.642
YGL073W	YLL026W	0.918	0.922
YER057C	YMR043W	0.915	0.851

Figure 2: The resulting network.

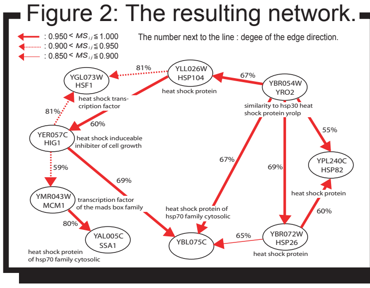
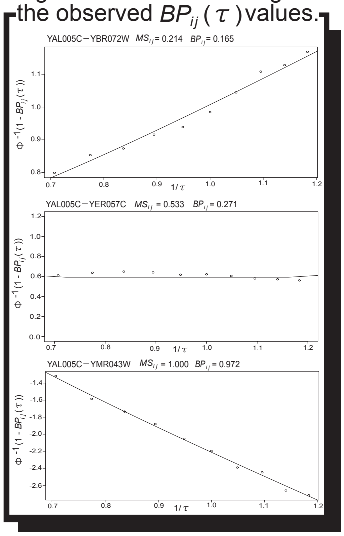


Figure 3: The curve fitting to the observed $BP_{ij}(\tau)$ values.



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