Abstract:

We present a computational tool, BNSA, Bayesian Network with Splitting-Averaging strategy for discovering gene regulatory relationships. BNSA utilises Bayesian network structure learning and extends it by considering different sample conditions in order to effectively identify both strong and subtle interactions from gene expression profiles. The tool makes use of heterogeneous data, including putative target information, gene expression profiles of both gene regulators (e.g. microRNAs, TFs) and mRNAs, and sample categories.

The R package for inferring gene regulatory network will be available through Bioconductor shortly.

BNSA: Bayesian Network with Splitting-Averaging Strategy

Methodology:

- **Data preparation for BN structure learning:**
  1) Retrieving gene expression profiles of gene regulators (e.g. miRNAs) and mRNAs, sample categories and target information of the regulators.
  2) Identifying differentially expressed miRNAs and mRNAs.
  3) Expression profiles (samples) of identified miRNAs and mRNAs are split according to categories of samples.

- **BN structure learning:**
  1) With each dataset obtained after the splitting (denoted \( D_h \)), the structure of a BN, \( G_l \), depicting the miRNA-mRNA interactions, is learned by incorporating target information.
  2) Bootstrapping is applied to alleviate the small sample problem and to generate highly confident interactions along with averaging strategy.

- **Model integration:**
  The individual structures learned from data of each category are integrated into an overall miRNA-mRNA interaction network by the designed BN averaging procedure. The belief confidence of an inferred interaction between the \( p \)-th miRNA and the \( j \)-th mRNA is estimated by a statistic model

\[
p(F_{ij}) = \sum_k \sum_l P(F_{ij} | G_k^h, p(D_k | G_k^h)) p(G_k^h)
\]

Applications of BNSA

Case 1

Data:

(I) miRNA & mRNA expression profiles for the NCI-60 dataset;
(II) miRNA-target information;
(III) two sample categories (epithelial and mesenchymal).

Results:

Fig. 3-(a) is the significant miRNA-mRNA interaction network for EMT with only down-regulated interactions. Comparing to the normal BN, BNSA captures more mRNAs that are potentially co-targeted by multiple miRNAs.

Case 2

Data:

(II) a list of TF genes;
(III) miRNA & TF target information;
(IV) sample categories.

Results:

1) Fig. 4 shows that the miR-200 family targets the ZEB1 and ZEB2 for EMT.
2) Our results, shown in Fig. 5, suggest that SNAI2 indirectly regulates ZEB1 and ZEB2 by regulating the miR-200 family transcript.

Further Information