A New System for Human MicroRNA Functional Evaluation and Network

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Abstract

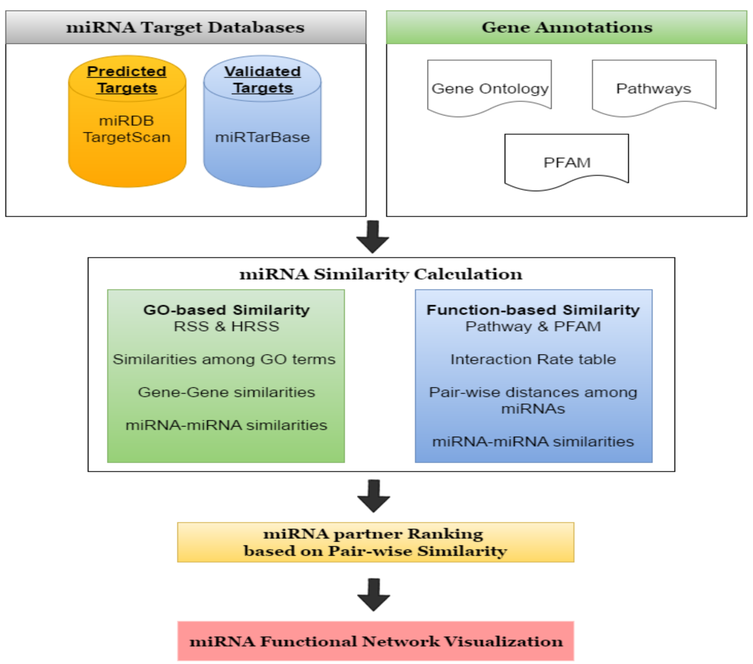
MicroRNAs are functionally important endogenous non-coding RNAs that silence host gene via destabilizing the mRNA or preventing its translation. Given the far-reaching implication of microRNAs in human health, novel bioinformatics tools that can facilitate the mechanistic understanding of microRNA-mediated gene regulation and its roles in disease development are desired. However, most state-of-art computational methods are focused on the microRNA functional inference through identifying reliable targets and none has comprehensively investigated the functional similarity among microRNAs.

We propose a new method to quantitatively measure the functional relevance among microRNAs, solely based on the Gene Ontology and integrated functional annotation data from the public pathway and gene database. Utilizing the derived pairwise similarities among microRNAs, we further investigate the cooperative microRNA modules and construct the genome scale microRNA-mediated gene network in human. The complete results and the similarity assessment system can be freely accessed at http://sbbi.unl.edu/microRNASim

Datasets

- **The miRNA-mRNA interaction data were download from the following resources:**
  - **Experimentally validated entries:**
    - **miRTarbase (582 miRNAs included)**
  - **Predicted interations:**
    - **TargetScan (686 miRNAs included)**
    - **mirDB (2,588 miRNAs included)**
- **miRNA annotation resources were downloaded from the following resources:**
  - **The whole Gene Ontology dataset was downloaded from the Gene Ontology Consortium. 42,144 terms were used in our study.**
  - **We compiled the functional annotations based on the Pfam-A set from Uniprot database.**
  - **A collection of 1,447 pathways was downloaded from the GSEA and the NPO Bioinformatics Japan Databases.**

Workflow



Method Highlights

- **Calculation of pairwise miRNA similarity based on GO through the follow steps:**
  - **The pairwise term similarity based on edge-based method/hybrid-based method**

$$s_{edge-based(t_i,t_j)} = \frac{\kappa}{\kappa+\gamma} * \frac{\alpha}{\alpha+\beta} \qquad s_{hybrid}(t_i,t_j) = \frac{1}{1+\gamma_{ic}} * \frac{\alpha_{ic}}{\alpha_{ic}+\beta_{ic}}$$

  - **The pairwise gene similarity**

$$s'(g_i,g_j) = \frac{\sum_{t_k \in T(g_i)} \max_{t_n \in T(g_j)} \{s(t_k,t_n)\} + \sum_{t_n \in T(g_j)} \max_{t_k \in T(g_i)} \{s(t_k,t_n)\}}{|T(g_i)|+|T(g_j)|}$$

  - **The pairwise miRNA similarity**

$$s^*(m_i,m_j) = \frac{\sum_{g_k \in G(m_i)} \max_{g_n \in G(m_j)} \{s'(g_k,g_n)\} + \sum_{g_k \in T(m_j)} \max_{g_n \in G(m_i)} \{s'(g_k,g_n)\}}{|G(g_i)|+|G(g_j)|}$$

- **Calculation of the miRNA similarity based on functional annotation**
  - **Pfam/pathway interaction table**

$$P(m_i) = \{\frac{G_{m_i} \cap G_{a_1}}{|G_{m_i}|}, \frac{G_{m_i} \cap G_{a_2}}{|G_{m_i}|}, ..., \frac{G_{m_i} \cap G_{a_n}}{|G_{m_i}|}\}$$

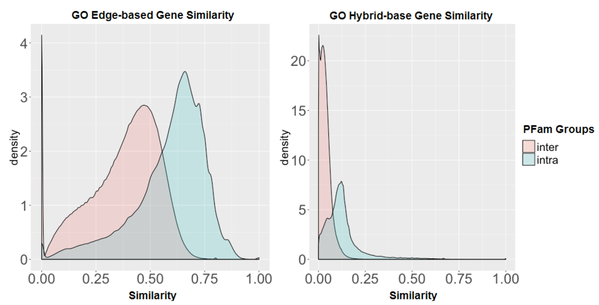
  - **The pairwise similarity** $S^{\#}(m_i,m_j) = dist(P_{m_i},P_{m_j})$
- **Integration of the similarity ranking**
  - **In order to integrate the similarity calculation from all three methods, we performed rank aggregation on three ranking lists. The 'RankAggreg' package in R was used.**

$$y = \alpha R_1 + \beta R_2 + \gamma R_3$$

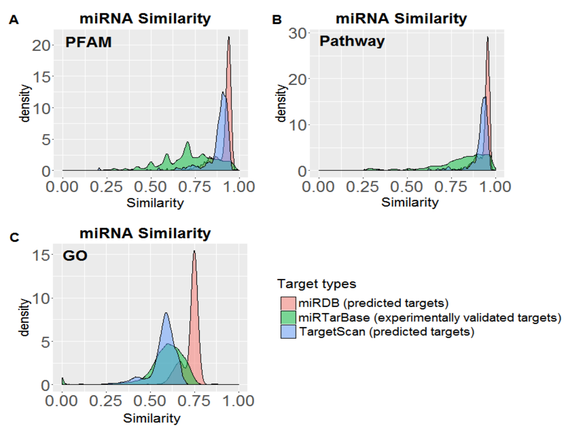
- **Detection of miRNA functional modules and Construction of the miRNA-mediated gene regulation network**
  - **Based on the similarities calculated for each pair of miRNA, we have applied Markov Cluster Algorithm (MCL) based on the pairwise similarity to identify highly associated miRNAs that work as a module. Also, we used VANESA-0.3 package to generate the visualization of the interaction of a miRNA module in each involved pathway.**

Results

- **Functional relevance among miRNA pairs**

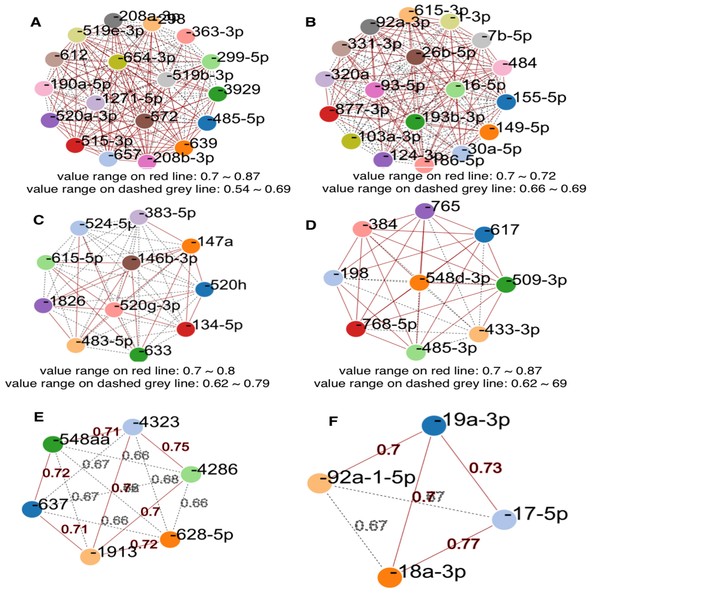


- **Go-based similarity measure complements the functional assessment**

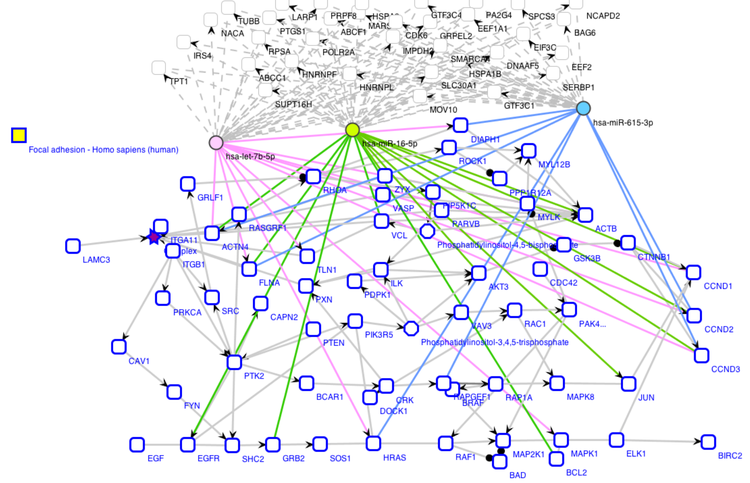


Results Continued

- **Functionally related miRNA modules**



- **MiRNA regulated network construction and visualization**



Conclusion

- **We proposed a new system for the assessment of functional relevance of human miRNAs by integrating heterogenous annotation data and different-level target information.**
- **The similarity information derived from such system can be used to identify miRNA co-regulatory modules and the construction of the miRNA-mediated gene regulation network.**
- **Stemming from this work, our next focus will be the integration of conditional dependent genomic data on both miRNA and their targets into this system that can capture the quantitative and dynamic properties of miRNA regulation and better facilitate the automatic detection of miRNA functional modules.**

Acknowledgement

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