

Identifying microRNA Networks and Motifs

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1 Introduction and Background

Complexity in higher organism genetic regulatory networks (GRNs) is thought to be achieved through sophisticated control and coordination mechanisms carried out by non-coding RNA (nc-RNA) molecules [4]. One class of small nc-RNAs are microRNAs, which destabilize and inhibit translation of selective mRNAs through complementary binding. MicroRNAs are predicted to target at least 20% of human genes. See [1] for an overview on miRNAs.

Computational models of GRNs have so far focussed on modeling control of genes by transcription factors (TFs). GRNs are modeled as graphs where nodes represent genes or modules of coregulated genes, which are combinatorially regulated by multiple input edges from TFs, and output a single protein. TF-mediated and miRNA-mediated control share many characteristics: both are *trans*-acting molecules that activate or repress genes via hardwired *cis*-regulatory binding sites, and both use coordinated and cooperative target binding to fine-tune their instructions contextually [2]. MicroRNA-mediated networks may therefore be similarly described graphically. However, RNA-mediated networks may implement additional functionality, such as controlled multitasking via nodes whose output comprise a protein-coding transcript as well as nc-RNA molecules which act as endogenous feedback signals on the cell's current state to other nodes. Determining the nature of the control structures represented in miRNA networks will help explain its observed roles in terminal differentiation and tissue specificity programs.

2 Review of Computational Methods in Detailing miRNA networks

The process for identifying and detailing miRNA-mediated networks can be described as somewhat piecemeal, with each research study leading to the addition of one likely connection (molecular interaction) across many different miRNA-mediated networks. Each study often uses computational methods to screen the genomic regions of many miRNA genes and/or of their possible binding partners for features such as complementarity, conservation, or the presence of sequence motifs, and thus infer a catalogue of likely interactions for the scanned genes. For example, catalogues have been created for TFs likely to activate miRNAs by scanning putative promoter regions of miRNA genes, and many catalogues for predicted miRNA target genes have resulted from searches for likely miRNA:mRNA complementary binding sites. Screening methods have also assisted in identifying co-regulated miRNAs which share TF binding sites (including polycistronic miRNAs), sets of miRNAs which coordinately bind and repress an mRNA target, and miRNAs that share a TF-binding site, and are thus coexpressed, with their target. The location of the miRNA gene with respect to targets is also under investigation, with some miRNAs thought to be encoded in introns of target genes, while others thought to be encoded in the antisense strand to their target genes.

Finding motifs (patterns of interconnections that recur in a network at much higher frequencies than in randomised networks) in GRNs specifying TF-mediated control has interested researchers for many years [5]. The detailing of interactions in miRNA-mediated and other ncRNA-mediated networks means there is now opportunity to perform similar analysis in such networks. A research team have studied the presence of different classes of feed-forward loops in miRNA networks [3].

3 Discussion of Open Research Questions and Planned Research

We plan to reconstruct and analyse a GRN from mRNA and miRNA microarray data, focusing on the subnetworks controlled by miRNAs. Research questions arise in terms of reconstruction methods including use of online catalogues of likely (or verified) miRNA binding interactions. We will also analyse the interaction between separate miRNA networks, and motif-finding problems. The following questions may be considered:

1. How can we model higher levels of control and coordination of microRNA subnetworks across cells? For example, can we model what determines the observed behavior of exclusive expression domains between miRNA and their targets in cells in neighbouring tissues, or mutually exclusive temporal expression of miRNAs and their targets?
2. The problem of determining graph structure when reverse-engineering GRNs from limited, microarray data is often intractable in complex networks, without good heuristics. Can we reduce the search space of features according to the likelihood of miRNA binding interactions ?
3. Algorithms used to predict miRNAs and their targets often require conservation to remove false positives. However, evidence suggests not all miRNAs or their targets are highly conserved. How should experimental design ensure lowly conserved miRNAs and targets are detected?
4. Aside from post-transcriptional repression, miRNAs have been implicated in alternative mechanisms of control including activation of genes either epigenetically or indirectly via repressing a repressor. Can we create catalogues of alternative interactions for miRNAs ?
5. Can we analyse motifs in miRNA networks against the type of miRNA network? For example, are different motifs present in networks where many intronic miRNAs are coordinately expressed with their host genes, to networks where a larger fraction of miRNAs are intergenic?
6. Can predicted miRNA-mediated networks be extended to incorporate other types of ncRNA molecular control, should such types of control be implicated in these networks?

References

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