Computational Modeling of the effect of miRNA binding sites distribution on mRNA stability
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The modeling of miRNA-mRNA interactions has various important applications in synthetic biology and human health. However, this research question is specifically challenging since the efficiency of mRNA down regulation by miRNA is affected by dozens of features including either competition or synergism among miRNAs and mRNAs.

In this project we are developing a predictive computational model that considers for the first time both the distribution of miRNA binding sites along the mRNA and their strength on the efficiency of mRNA stability regulation.

Methods

MicroRNAs (miRNAs) play key roles in post transcriptional gene regulation including mRNA degradation and translation inhibition. These short non-coding RNA strands bind to miRNAs mediating the interaction between the target mRNA and the RNA-induced silencing complex (RISC). Although a basic set of canonical rules has been established, attempts at unveiling the details of miRNA-mRNA interactions remain challenging and insufficient. Because of their important regulation role and their link to many diseases, understanding all aspects of these interactions is of interest.

Several models have attempted to predict mRNA repression levels due to miRNA-mRNA interactions. Although these models provide a strong starting point including numerous traditional features, none of the previous models look into the relationship between miRNAs, assuming each interaction is independent. Here, we aim to add another dimension to the existing models, adding binding site distribution along the mRNA and their repression strength to the total sum of influences on the efficiency of mRNA stability regulation.

In a recent study Bergman et al. [1] developed a predictive model including translational features, adding another biophysical layer to the aforementioned interplay. Unlike previous studies focusing solely on 3’UTR sites or treating different region sites equally, this study showed the importance of ORF sites. Adding these features allowed investigating the ribosomes’ effect on miRNA action, supported by ribo-seq data. The model includes:

- Thermodynamic
- Conservation
- Sequence
- Translation

Features. The model was trained on the HeLa dataset (Homo sapiens) using elastic-net regression on single sites for each mRNA-miRNA pair. Using this model, we aim to predict independent repression levels for each miRNA-mRNA binding site and create two distinct networks:

1. Relative interaction strength of potential sites: representing ORF binding sites, 3’UTR binding sites, and miRNAs as nodes, and strong and weak interactions as two distinct types of edges between nodes.
2. miRNA binding site distribution: representing binding sites as nodes, and distance between sites as edges.

Searching the networks for integrated network motifs will contribute to the understanding of miRNA-mRNA interaction, adding new aspects to existing algorithms.

Data

Human cells express more than 2000 miRNAs, each potentially binding to thousands of mRNAs. As a first step, the repression prediction was conducted on 20% of human transcripts and 20% of known mature miRNA sequences. The transcripts were chosen as the longest transcript of each gene, and the miRNAs were the top 20% with the highest 8-mer site count across the entire genome.

Future plans

- Collection of relevant experimental data.
- Combining computational models and experimental data to predict the strength of miRNA-mRNA interactions across the transcriptome.
- Inferring a network model that captures the binding sites’ distributions and strength.
- Analyzing the network to understand its’ properties.

Fig 1. Depiction of the networks we intend to build: a) miRNA binding site distribution. b) Relative interaction strength of potential sites.