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Type	Oral communication
Session	Algorithms in Bioinformatics
Title	The ComiR web-tool ready for an upgrade: the detection of new features to improve the prediction of microRNA targets
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Motivation

MicroRNAs (miRNAs) are small non-coding RNA molecules involved in the translational repression and degradation of target mRNAs in the cell [1]. The RNA-induced silencing complexes (RISCs) include mature miRNAs used as templates to recognize the complementary mRNA targets. Several prediction tools are available to predict miRNA targets, however, only a small part of the interaction pairs has been validated by experimental approaches. In addition, none of these tools does take into account the network structure of miRNA-mRNA interactions, which involves collaborative and competition [2] effects that are crucial to efficiently predict the miRNA regulatory effects in a specific cellular context. A first solution to consider collaborative effects has been given by the web tool ComiR [3], which predicts the targets of a weighted set of miRNAs, provided the miRNA expression profile of the samples/tissues of interest. The analysis of the expression profile of the RNA fraction immunoprecipitated (IP) with the RISC proteins, namely Rip-Chip or Rip-Seq, has been widely used to detect which genes are regulated by the RISC machinery. Recently, we found that AGO2 and GW182 are associated with two distinct sets of mRNA characterized by different features [4]. One of the relevant features is the presence of putative miRNA binding sites in the coding region of the mRNA, in addition to the already widely explored involvement of the binding sites in the 3'UTR. Next, we tested whether ComiR would be improved by the introduction of such features.

Methods

The training set used to train ComiR is the same used in [3]. In order to upgrade the tool, we considered new features to feed the underlying Support Vector Machine (SVM) algorithm. The new selected features are based on the binding sites of the expressed miRNAs predicted in the coding region and the 5'UTR of the mRNA. Different SVM models have been trained, each by processing different mRNA regions. We also enlarged the dataset described in [4] by performing additional RIP-Chip experiments and analyzing the AGO1 protein-associated RNAs in the MCF-7 cell line. Such analysis provided a novel dataset useful for exploring the characteristics of the mRNA regulated by RISCs different from the ones involving the AGO2 protein. We evaluated the performance of the new ComiR models in predicting the targets of the miRNAs expressed in the MCF-7 cell line by comparing the score computed for each mRNA with the fold change associated to the IP vs Input comparison related to each of the three RISC proteins (AGO1, AGO2 and GW182).

Results

We found that including the information of miRNA binding sites in the coding region of mRNA significantly increases the performance in predicting the miRNA targets. We tested whether different SVM models, compiled with different sets of features, were able to distinguish the miRNA targets associated with different RISC proteins, specifically the ones bound to AGO1 and/or AGO2. The preliminary results we obtained support our previous findings [4]. We confirmed that the GW182 associated mRNAs are scarcely characterized by miRNA binding sites, but are significantly characterized by long coding sequences. On the other hand, AGO- and AGO2-associated mRNAs share the presence of the top expressed miRNA binding sites in both 3'UTR and coding region.

[1] Bartel, D.P. (2004) MicroRNAs: genomics, biogenesis, mechanism and function. Cell, 116, 281-297
[2] Sumazin, P., et al. (2011), An Extensive MicroRNA-Mediated Network of RNA-RNA Interactions Regulates Established Oncogenic Pathways in Glioblastoma. Cell. 147(2): p. 370-381.
[3] Coronnello, C et al, (2013) Novel Modeling of Combinatorial miRNA targeting Identifies SNP with

Potential Role in Bone Density. Plos Computational Biology, 8, 12
[4] Perconti, G et al, (2019) RIP-Chip analysis supports different roles for AGO2 and GW182 proteins in recruiting and processing microRNA targets, BMC Bioinformatics, 20 (Suppl 4), 120

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Availability	-

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