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Applications Note

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Databases and ontologies

Tools4miRs – one place to gather all the tools for miRNA analysis

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Abstract

Summary: MiRNAs are short, non-coding molecules that negatively regulate gene expression and thereby play several important roles in living organisms. Dozens of computational methods for miRNA-related research have been developed, which greatly differ in various aspects. The substantial availability of difficult-to-compare approaches makes it challenging for the user to select a proper tool and prompts the need for a solution that will collect and categorize all the methods. Here, we present tools4miRs, the first platform that gathers currently more than 160 methods for broadly defined miRNA analysis. The collected tools are classified into several general and more detailed categories in which the users can additionally filter the available methods according to their specific research needs, capabilities and preferences. Tools4miRs is also a web-based target prediction meta-server that incorporates user-designated target prediction methods into the analysis of user-provided data.

Availability and Implementation: Tools4miRs is implemented in Python using Django and is freely available at tools4mirs.org.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

MicroRNAs (miRNAs) are a class of short (18–24 nt), non-coding and single-stranded RNAs that mediate the post-transcriptional gene expression regulation by promoting the cleavage or inhibiting the translation of the target mRNA (Djuranovic *et al.*, 2012; Hu and Coller, 2012). Throughout their mechanism, miRNAs control the cell development, apoptosis, proliferation, differentiation and several other essential functions in living organisms (Wienholds and Plasterk, 2005; Zhang *et al.*, 2007).

Great contributions to the current knowledge concerning miRNAs' properties and functions came not only from the development of several experimental techniques but also from computational analytical approaches, which are nowadays considered to be an almost indispensable part of any basic or applied miRNA-related research (van Rooij, 2011; Ying, 2013). The available bioinformatics methods and resources cover an impressive scope—from miRNAs identification, through the prediction of their precursors and targets, the elucidation of miRNAs functions, to databases gathering various relevant biological information (Akhtar *et al.*, 2016; Liu *et al.*, 2014). In addition to the implementation and organism specificity, the aforementioned tools differ primarily in their methodology, the features considered in the analysis and, consequently, their performance. New methods are being constantly developed, improved and published along with several useful review papers, which provide a description and evaluation of these up-to-date computational approaches (Akhtar *et al.*, 2016; Kang and Friedlander, 2015; Kleftogiannis *et al.*, 2013). Nevertheless, in this multitude of possibilities and features, reviewing several articles or websites may still be insufficient to choose a desired method. Hence, there is a need for a place that collects and categorizes all the available tools.

To address this need, **tools4miRs,** a user-friendly, manually curated and filterable service that gathers methods for miRNA analyses, was developed. In miRNA-related research, considerable importance is attached to miRNA target identification, which reflects the function of the miRNA in the cell. Therefore, **tools4miRs** also enables the prediction of miRNA targets using methods previously selected by the user.

2 Data content and organization

Throughout a comprehensive survey of the scientific literature and information available in public websites/services, data concerning over 160 tools for varied miRNA analyses were gathered. Furthermore, the methods were categorized into four general groups (Sequencing Data Analysis, All-In-One Tools, Databases and Other Tools) and seven more detailed sections: Known miRNA Identification, isomiRs Identification, Novel miRNA/Precursor Analysis, Differential Expression Analysis, Target Prediction, Target Functional Analysis and miRNA-SNP Analysis. The classification of certain collected tools may be redundant, i.e. depending on their functionality and required NGS input data, they may be assigned to several categories. Such categorization would aid the user in recognizing the methods they should consider with their data and their exact research question. The manually verified information with regard to the tools included in the **tools4miRs** and the content of currently available sections are described in detail in the Supplementary Data. All the gathered computational approaches are presented in legible tables that provide, at first glance, basic information concerning each method. Through the 'Filter Panel', the user can additionally filter the available tools according to even more specific and appropriate criteria, e.g. analysis/prediction features, collected data, organism-specificity, tool availability, reference genome/NGS data requirement and sequencing platform specificity. Clicking on the tool name leads to its extensive description, where the user can find information regarding the algorithm, ease of use/install, user adjustability, performance, last software update, user support availability, cross-references, license, analysis schemes and others. A simple example about how to find the desired tool using **tools4miRs** can be found in the Supplementary Data.

3 Target prediction meta-server

The functions of miRNAs in living organisms are associated with their binding to target mRNAs. Therefore, selecting and annotating potential miRNA targets are the first steps for determining the role of a miRNA in the cell. To facilitate this process, **tools4miRs** provides a web-based miRNA target prediction meta-server that incorporates into the analysis a suit of methods tailored by the user. Currently, the meta-server integrates 10 methods presented in a filterable table. After choosing the tools, the user is asked to provide the target mRNA and miRNA sequences as well as, **optionally**, the job name, description and e-mail address for further retrieving the calculated results. The parameters available for most of the methods can be additionally set. The possibility to submit any sequences of miRNAs and potential targets is an advantage of the **tools4miRs** meta-server over other currently available servers, which are usually implemented on a limited number of species or work on build-in databases and forces the user to select miRNA/targets from the available list of molecules. The predictions generated by the described meta-server can be presented in **basic** or **extended** mode. The **basic** mode shows individual miRNA:target pairs, along with the number of binding sites in a given target, checkmarks by the appropriate tool names and the total number of tools that predicted the given pair. In the **extended** analysis mode, the obtained predictions are grouped by unique triplets—binding site location, miRNA and target mRNA. Thus, the exact 'from:to' position in the target sequence and the total number of tools that predicted this specific site are given. Additionally, information concerning score, energy or other values calculated by the chosen approaches are provided. The 'Union', 'Consensus' and 'Intersection' of the used tools are available after the target prediction table is generated. The 'Consensus' mode returns only unique miRNA-target pairs or unique miRNA-target binding sites, predicted by minimum *X* of used tools, where *X* is number set by the user. After the target prediction table generation, the user is also able to sort and filter the obtained results, e.g. by dismissing/forcing the display of the targets predicted by the chosen method. All the results may be downloaded in CSV, XLS or XLSX format. MiRNA target prediction workflow using the **tools4miRs** meta-server can be found in the Supplementary Data.

4 Implementation and availability

Tools4miRs is freely available at www.tools4mirs.org and is intended to be systematically maintained. No registration is needed to exploit its full functionality. Researchers interested in adding their published method are encouraged to submit it through the 'Submit Tool' form. **Tools4miRs** is implemented in Python using the Django framework for the web-based frontend. Backend calculations and distributed computing are also governed by Python using common API for all the implemented software. A detailed description of the **tools4miRs** implementation can be found in the Supplementary Data.

5 Conclusions

Currently, to choose an appropriate *in silico* approach for miRNA research, it is necessary to search through a large amount of literature or existing on-line resources. Here, we describe **tools4miRs** - the first open-access platform that gathers over 160 tools dedicated for broad miRNA analysis. The presented service is also a web-based miRNA target prediction meta-server that enables the user to perform an analysis using only the desired tools. **Tools4miRs** is useful not only for bioinformaticians but also for experimental scientists in basic or applied miRNA research.

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