Evaluation of computational miRNA target predictions in human

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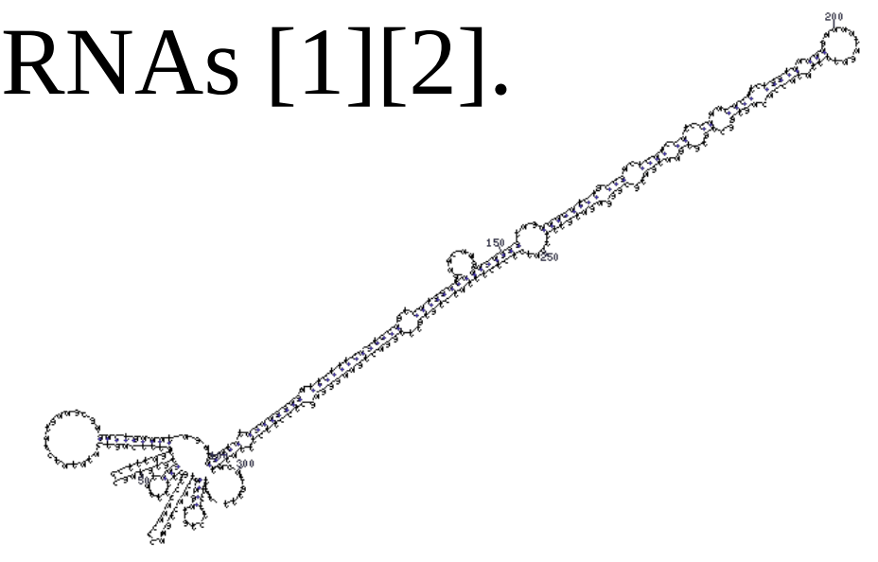
Abstract

MicroRNAs (miRNAs) are short RNAs that regulate expression through binding to the 3'UTR of mRNAs [1][2].



An important shortcoming in current miRNA research is the lack of experimentally verified mRNA targets. This initiated a surge in the development of computational methods attempting to predict miRNA target sites [3].

Here, we compare the target predictions of seven often used target prediction tools for human miRNAs: microRNA.org, MicroCosm, PITA, TargetScan, PicTar, MirZ and MicroT.

microRNA.org: A resource for predicted microRNA targets and expression
Memorial Sloan-Kettering Cancer Center
September 2008 Release Last Update: 2008-09-08 [release notes]

Results

Key statistics

Most tools cover the majority (i.e. 77%-98%) of all known miRNAs

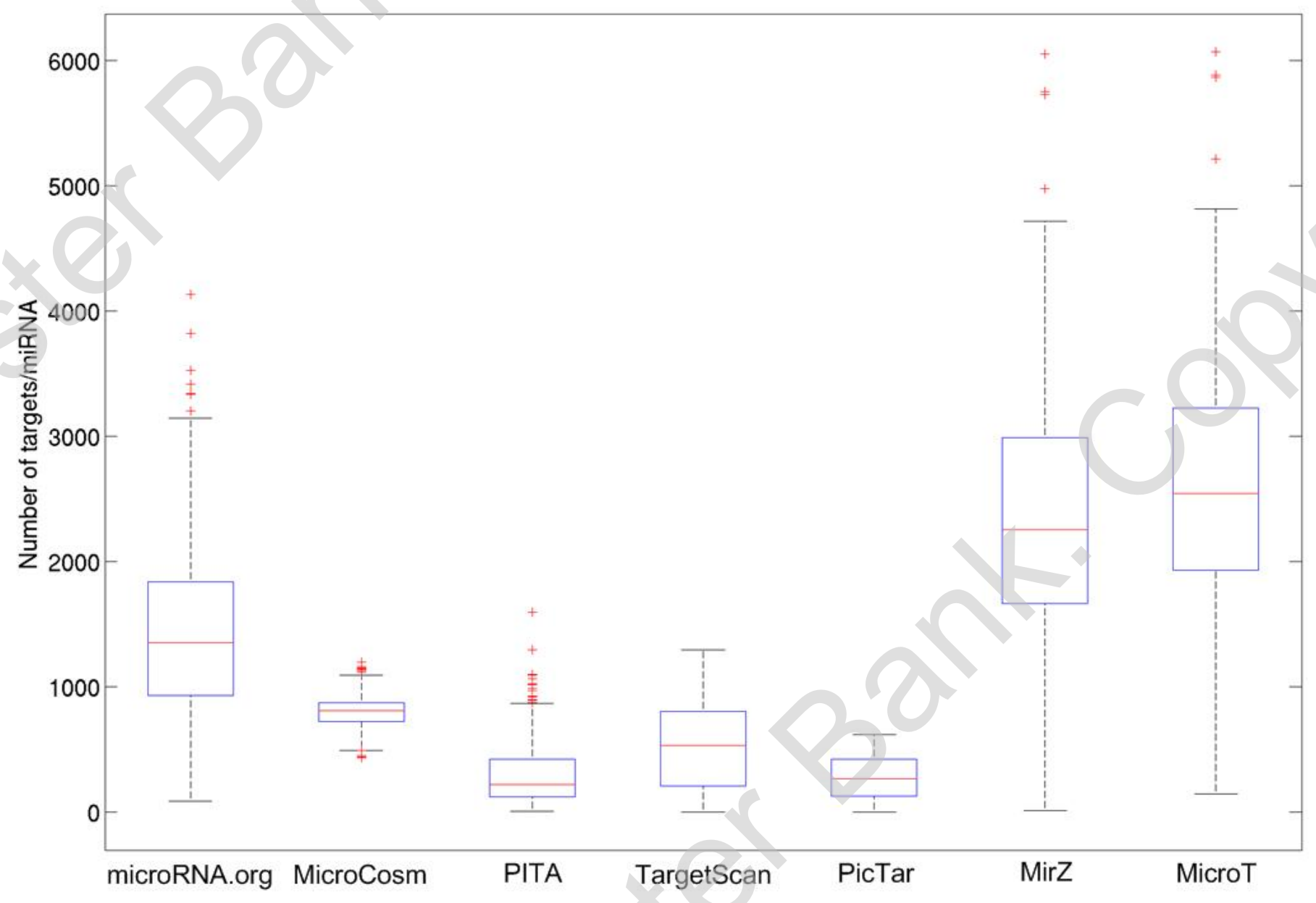
- ➢ TargetScan and PicTar only provide predictions for a subset of all known miRNAs.
- ➢ Large difference in the number of mRNAs in the human genome that are predicted as targets of at least one miRNA, ranging from 6039 for PicTar to 21111 for MicroCosm
- ➢ MicroCosm predicts that ~75% of the human genome is targeted by at least one miRNA.
- ➢ MirZ and MicroT predict the most targets per miRNA followed by microRNA.org.
- ➢ PicTar and TargetScan predict the least amount of targets per miRNA.
- ➢ MirZ predicts ~32 times more miRNA-mRNA interactions than PicTar.

	Micro-RNA.org	Micro-Cosm	PITA	Target-Scan	PicTar	MirZ	MicroT
Number miRNAs	677	711	677	171	178	683	555
Number mRNAs	16887	21111	10143	8143	6039	17375	16999
Number predicted miRNA-mRNA pairs	957253	568100	208937	88660	48800	1546406	1395638

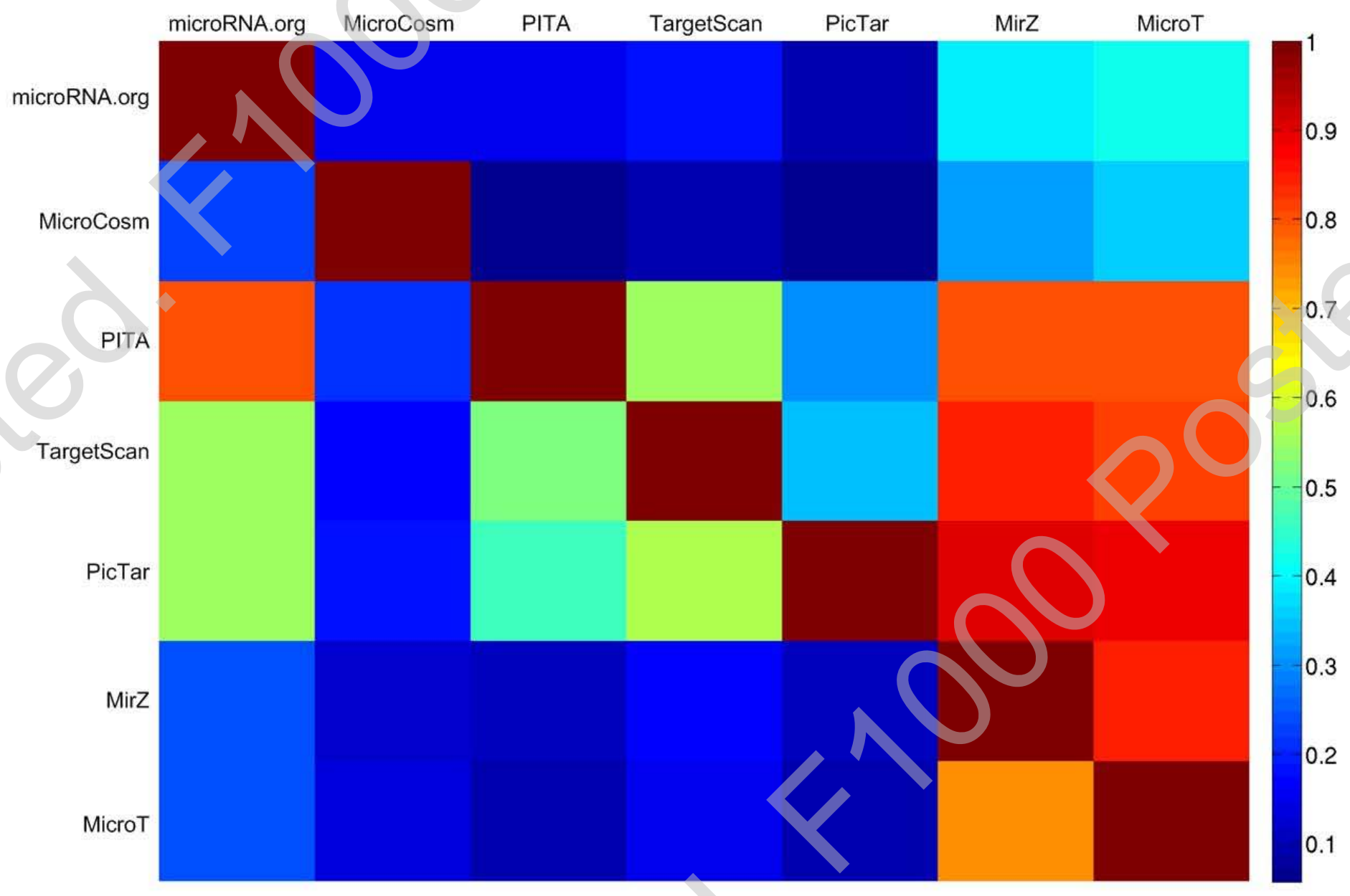
Results

Target coverage

Two classes of tools emerge: three tools, MirZ, MicroT and microRNA.org predict 1000s of targets per miRNA [4][5]. The other four tools are more conservative and have on average less than 1000 targets per database indicating a significant difference in the use of each tool. Interestingly, MicroCosm predicts relatively few targets per miRNA but predicts targets for ~75% (21000 mRNAs) of the human genome.



Target correspondence



The previous figure shows an asymmetric comparison between the average overlap in miRNA targets between all seven tools. Overall, most pair wise comparisons reveal less than 50% overlap.

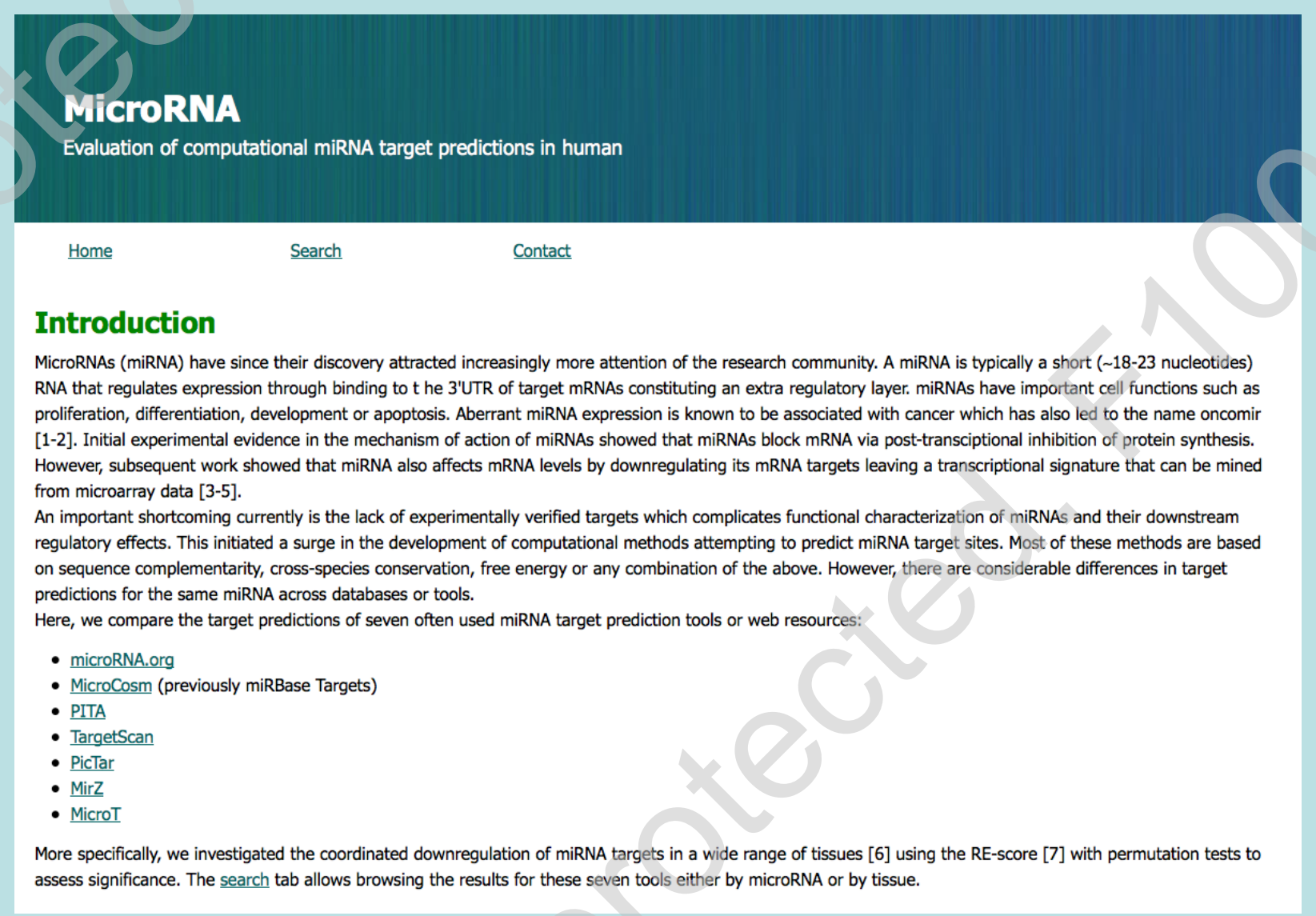
The highest overlap is observed between MirZ and PicTar, with MirZ containing 90% of PicTar's target predictions. More specifically, both MirZ and MicroT contain a high percentage of predictions from all other tools except from microRNA.org and MicroCosm.

In addition, although microRNA.org and MicroCosm are based on the same algorithm (i.e. miRanda), both tools share very few target predictions.

Web resource

The results of the coordinated downregulation of the targets of each of the seven tools in a large multi-tissue microarray data set can be browsed at our accompanying website: www.esat.kuleuven.be/~bioiuser/microRNA/

This web-resource allows, depending on the user's interest in a specific miRNA or tissue, to compare the significant target predictions of all tools.



MicroRNA
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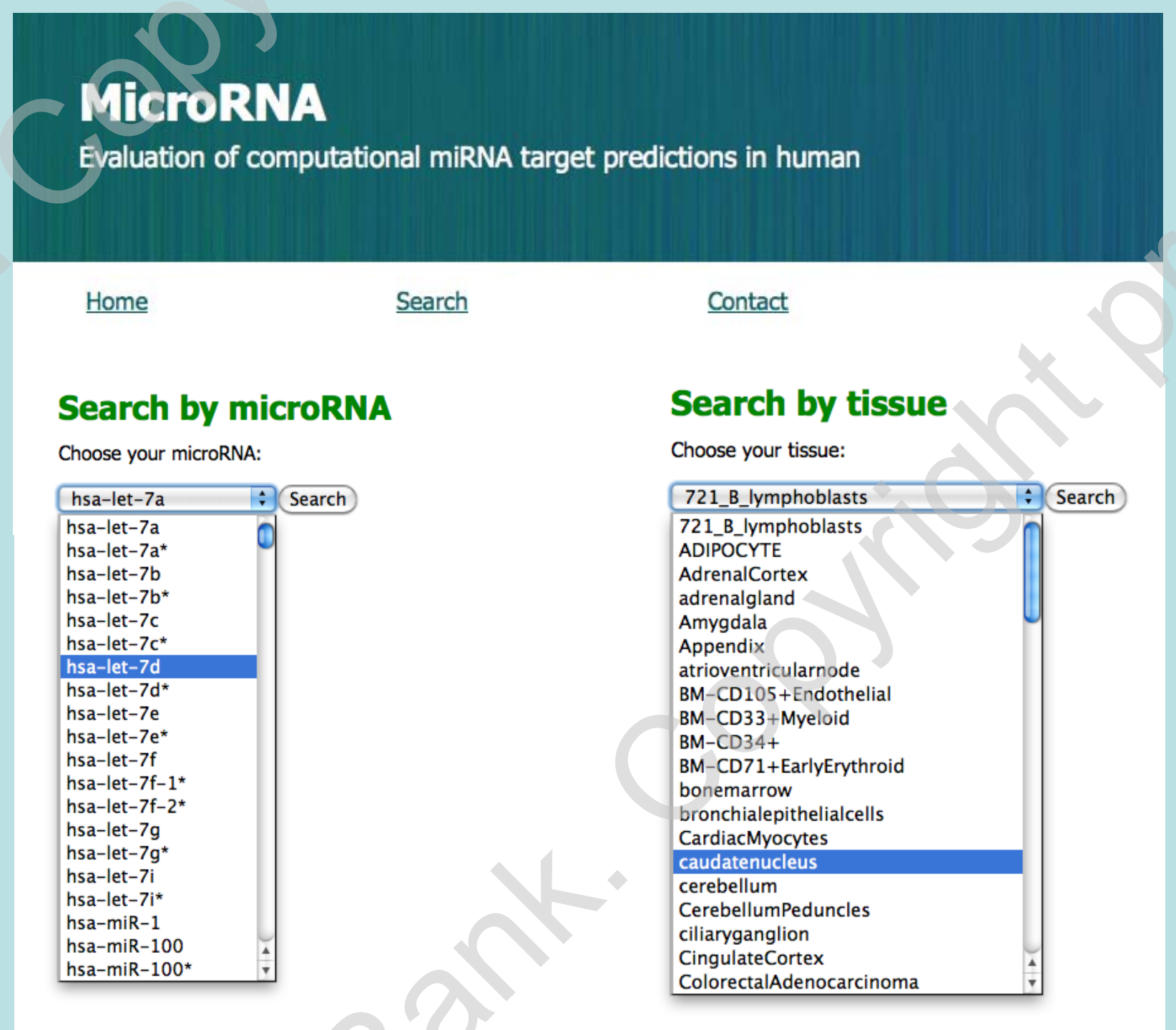
Introduction

MicroRNAs (miRNA) have since their discovery attracted increasingly more attention of the research community. A miRNA is typically a short (~18-23 nucleotides) RNA that regulates expression through binding to t he 3'UTR of target mRNAs constituting an extra regulatory layer. miRNAs have important cell functions such as proliferation, differentiation, development or apoptosis. Aberrant miRNA expression is known to be associated with cancer which has also led to the name oncomir [1-2]. Initial experimental evidence in the mechanism of action of miRNAs showed that miRNAs block mRNA via post-transciptional inhibition of protein synthesis. However, subsequent work showed that miRNA also affects mRNA levels by downregulating its mRNA targets leaving a transcriptional signature that can be mined from microarray data [3-5].
An important shortcoming currently is the lack of experimentally verified targets which complicates functional characterization of miRNAs and their downstream regulatory effects. This initiated a surge in the development of computational methods attempting to predict miRNA target sites. Most of these methods are based on sequence complementarity, cross-species conservation, free energy or any combination of the above. However, there are considerable differences in target predictions for the same miRNA across databases or tools.
Here, we compare the target predictions of seven often used miRNA target prediction tools or web resources:

- microRNA.org
- MicroCosm (previously miRBase Targets)
- PITA
- TargetScan
- PicTar
- MirZ
- MicroT

More specifically, we investigated the coordinated downregulation of miRNA targets in a wide range of tissues [6] using the RE-score [7] with permutation tests to assess significance. The search tab allows browsing the results for these seven tools either by microRNA or by tissue.

The user can search according to microRNA or tissue:



MicroRNA
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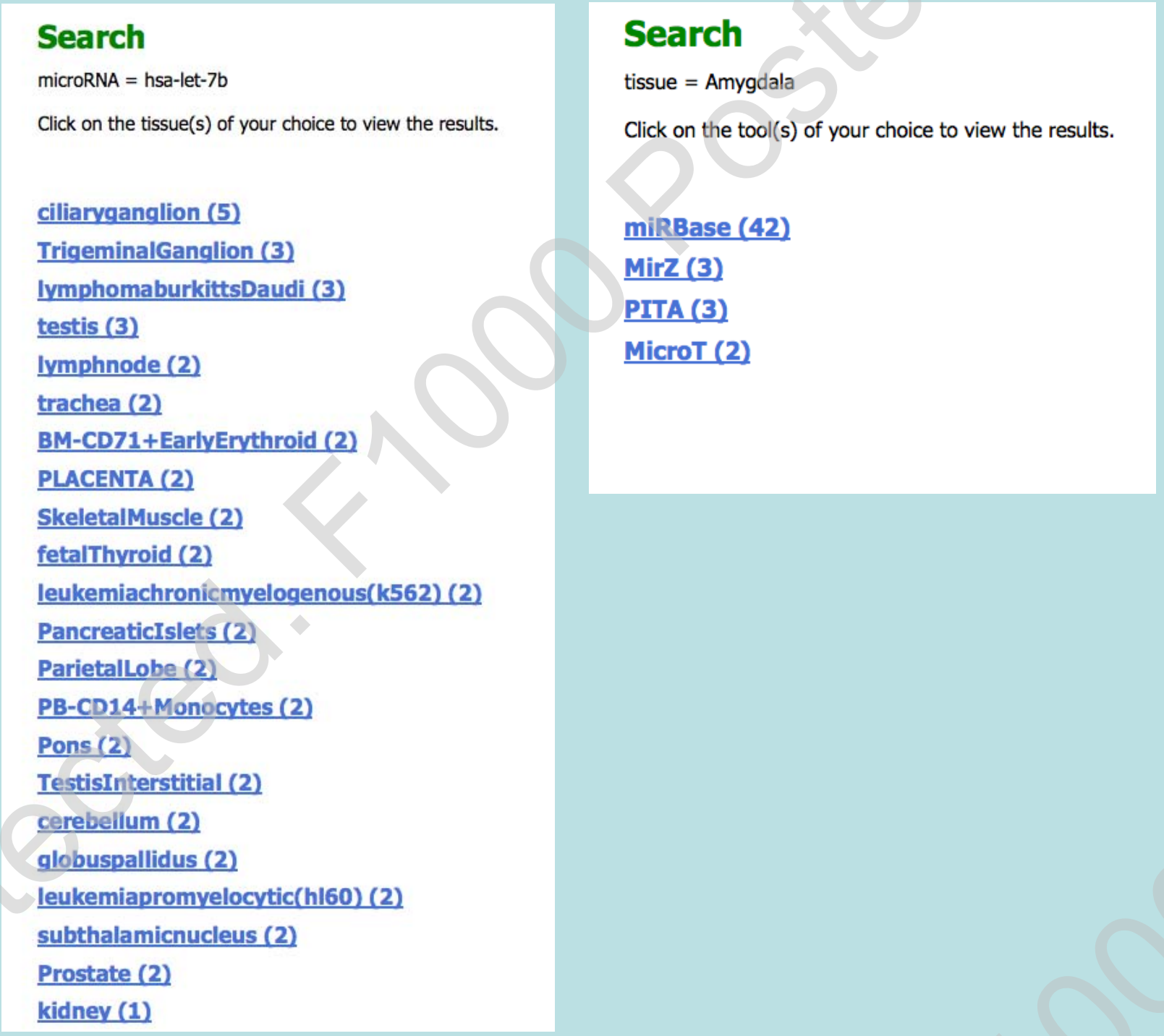
Search by microRNA
Choose your microRNA:
hsa-let-7a

Search by tissue
Choose your tissue:
721_B_lymphoblasts

When selecting microRNA, the user gets a list of tissues where the microRNA is expressed together wit the number of tools that supported this prediction.

When selecting tissue, the user gets a list of the number of microRNAs expressed in each tissue.



Search
microRNA = hsa-let-7b
Click on the tissue(s) of your choice to view the results.

- ciliaryganglion (5)
- TrigeminalGanglion (3)
- lymphomaburkittsDaudi (3)
- testis (3)
- lymphnode (2)
- trachea (2)
- BM-CD71+EarlyErythroid (2)
- PLACENTA (2)
- SkeletalMuscle (2)
- fetalThyroid (2)
- leukemiachronicmyelogenous(k562) (2)
- PancreaticIslets (2)
- ParietalLobe (2)
- PB-CD14+Monocytes (2)
- Pons (2)
- TestisInterstitial (2)
- cerebellum (2)
- globuspallidus (2)
- leukemiapromyelocytic(hl60) (2)
- subthalamicnucleus (2)
- Prostate (2)
- kidney (1)

Search
tissue = Amygdala
Click on the tool(s) of your choice to view the results.

- miRBase (42)
- MirZ (3)
- PITA (3)
- MicroT (2)

Results

Multi-tissue comparison

We used the RE-score which measures the expression difference between the targets and non-targets of a miRNA in an expression profile to assess the differential expression in multiple tissues [6][7]. The significance of the RE-score was assessed using 1000 randomly drawn and equally large sets of targets from the genes represented in the microarray data set.

Tool	Average number of significant microRNAs per tissue	Average Pvalue score per tissue
microRNA.org	11.6	77.2
MicroCosm	10.7	76.2
PITA	9.5	76.4
TargetScan	1.6	69.4
PicTar	2.8	50.8
MirZ	20.8	114.8
MicroT	17.7	112.7

Conclusions

Our results showed that most tools provide target predictions for the majority of currently known miRNAs but large differences where observed in the number of targets predicted on average.

In addition, we investigated the coordinated downregulation and showed that MirZ and MicroT captured more significant miRNA mediated down-regulation compared to the other tools in a wide range of tissues. We conclude that many of the tools predict less than half of the experimental observations. In addition, many tools predict different targets for the same miRNA.

References

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