

miRViz: a novel webserver application to visualize and interpret microRNA datasets

Authors:

Pierre GIROUX^{1,†}, Ricky BHAJUN^{2,†}, Stéphane SEGARD², Claire PICQUENOT², Céline CHARAVAY², Lise DESQUILLES¹, Guillaume PINNA³, Christophe GINESTIER⁴, Josiane DENIS¹, Nadia CHERRADI¹, Laurent GUYON* ^{1,2}

1. Univ. Grenoble Alpes, CEA, INSERM, IRIG, Biology of Cancer and Infection UMR_S 1036, F-38000 Grenoble, France

2. Univ. Grenoble Alpes, CEA, INSERM, IRIG, BGE UMR 1038_S, F-38000 Grenoble, France

3. Plateforme ARN Interférence, Service de Biologie Intégrative et de Génétique Moléculaire (SBIGeM), I2BC, CEA, CNRS, Université Paris-Saclay, F-91191 Gif-sur-Yvette, France.

4. Aix Marseille Univ., CNRS, INSERM, Institut Paoli-Calmettes, CRCM, Epithelial and Cancer Stem Cells lab, F-13273 Marseille, France

* To whom correspondence should be addressed. Tel: (+33)438 780 453; Fax: (+33)438 785 058; Email: laurent.guyon@cea.fr

[†] The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

Abstract

MicroRNAs (miRNAs) are small non-coding RNAs that are involved in the regulation of major pathways in eukaryotic cells through repression of their target genes at the post-transcriptional level¹. While high-throughput approaches are broadly used to decipher the biological relevance of miRNAs, extraction of significant information from large miRNA datasets remains challenging. For example, sequencing technologies can quantify the relative expression of up to thousands of mature miRNAs under various experimental conditions. However, in such datasets, small subsets of miRNAs can often show significant differential expression, and deciding which one(s) should be further analyzed can prove difficult. Thus, the current challenge resides in objective analysis, interpretation and visualization of these large datasets, for which specifically suited methods are lacking.

Here, we present miRViz (<http://mirviz.prabi.fr/>), a webserver application designed to visualize and interpret large miRNA datasets, with no need for programming skills. MiRViz has two main goals: (1) to help biologists to raise data-driven hypotheses; and (2) to share miRNA datasets in a straightforward way through publishable quality data representation, with emphasis on relevant groups of miRNAs.

Results

As summarized in **Figure 1**, datasets loaded into miRViz can be overlaid onto five proposed miRNA networks (described below), to display graphical representations in which each node corresponds to a given miRNA. MiRViz is designed to work with 11 different species, including human (hsa), mouse (mmu), *C. elegans* (cel) and *Drosophila* (dme). Practical examples, and step-by-step procedures to produce figures are provided as **Supplementary Notes 1-5**.

The first network used by miRViz, “Seed2_7”, allows direct visualization of miRNA families by connecting pairs of miRNA nodes that share the same seed sequence. In **Supplementary Figure and Note 1**, we show a practical example of using this network to analyze the cooperative export of the whole hsa-miR-320 family in exosomes².

The two miRViz networks entitled “Genomic_distance” connect neighboring miRNA genes on the genome (**Supplementary Note 2**). **Supplementary Figure 2** shows direct identification and visual representation of the 14q32 cluster of miRNAs with miRViz. This cluster corresponds to loss of heterozygosity of this genomic region for patients with adrenocortical carcinoma with good prognosis³. MiRViz enables clear visualization and direct identification of the miRNA cluster.

The last two miRViz networks connect miRNA nodes that share common mRNA targets⁴ (**Supplementary Note 3**). As proof-of-concept, **Supplementary Figure 3** compares two datasets and highlights a cluster of overexpressed miRNAs in pluripotent stem cells⁵, which are active *in vitro* to maintain the equilibrium of breast cancer stem cells⁶.

MiRViz provides various tools for in-depth analysis of miRNA datasets. It might also prove extremely useful in the analysis of data from emerging technologies, like single-cell miRNA-seq experiments, for which proof of concept was recently established⁷, or for profiling rare materials, such as human liquid biopsies.

References:

1. Bartel, D. P. *Cell* **173**, 20–51 (2018).
2. Ji, H. *et al.* *PLoS One* **9**, (2014).
3. Assié, G. *et al.* *Nat. Genet.* **46**, 607–612 (2014).
4. Bhajun, R. *et al.* *Sci. Rep.* **5**, 8336 (2015).
5. Laurent, L. C. *et al.* *Stem Cells* **26**, 1506–16 (2008).
6. El Helou, R. *et al.* *Cell Rep.* **18**, 2256–2268 (2017).
7. Faridani, O. R. *et al.* *Nat. Biotechnol.* **34**, 1264–1266 (2016).

Data availability:

All of the datasets analyzed during this study are publicly available and are described in detail in **Supplementary Note 4**. In addition, we have described all of the steps to reproduce the Supplementary Figures (**Supplementary Note 5**).

Code availability:

The webserver miRViz, <http://mirviz.prabi.fr/>, is freely available without login requirements. The source code is available under the Open Source CECILL-B license in the download section.

Acknowledgements:

We thank C. Cochet and JJ. Feige for helpful discussion, and all external testers of miRViz. We thank Christopher Berrie for scientific English editing.

Author contributions:

LG and CC designed the webserver. LG, PG and RB built the miR networks. SS conceived the architecture of the webserver. SS and CP coded the webserver. CC and LG carried out functional tests of the webserver. LG and LD analyzed the miR datasets. GP, CG, JD and NC performed the experiments. LG wrote the manuscript with input and approval from all authors.

Competing interests:

The authors declare that they have no competing interests.

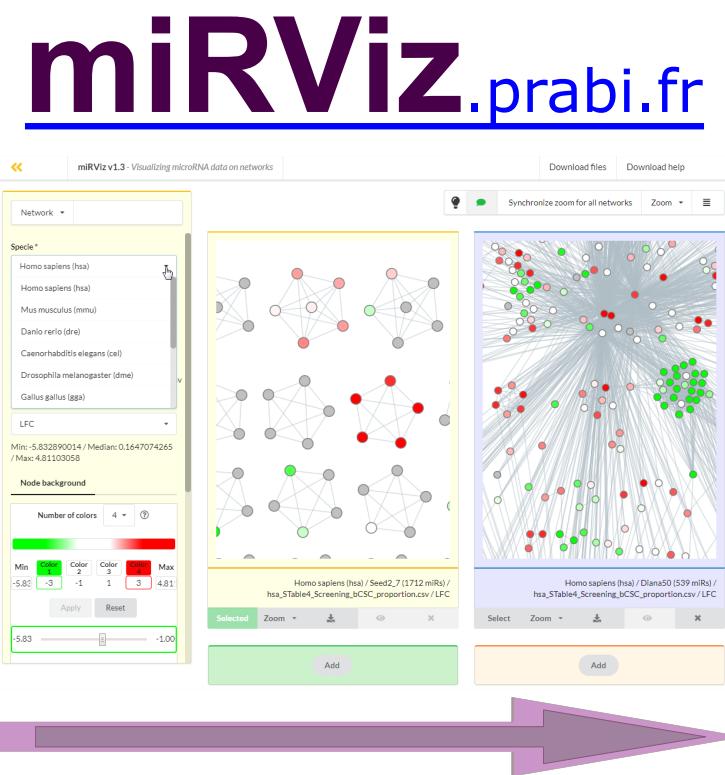
Figure 1. Users load their own datasets in comma-separated values (csv) format through the 'Load data' menu, and can choose from among the five different miRNA networks. They can also choose the color code for the nodes, to depict the quantitative values of their data. To compare datasets, up to four windows can be displayed concurrently, and can be manipulated synchronously.

Visualize and interpret microRNA datasets with networks

Input

Large-scale microRNA table (miR-seq, screening, etc.)

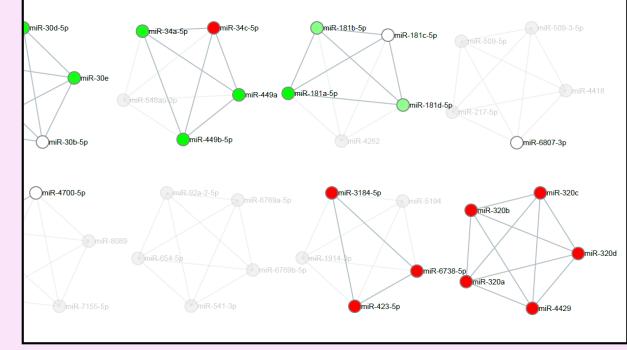
MIMAT	mir	R2_LNA	Ilc_LNA	poorest_ln	lnpoorln_R2_mimic	Ilc_mimic	poorest_ln
MIMAT000008	hsa-let-7b	-4.215567	-1.273018	18	0.449661	0.762007	1.1
MIMAT000008	hsa-let-7c	-4.046345	-1.195076	19	0.449661	-0.28864	2.7
MIMAT000008	hsa-let-7d	-3.203031	-0.857981	2.4	0.449661	-5	-1
MIMAT000008	hsa-let-7e	-1.141446	-0.409876	3.5	0.449661	-2	-0.26303
MIMAT000008	hsa-let-7f	-3.203031	-0.857981	2.4	0.449661	-1.08857	-0.57374
MIMAT000008	hsa-miR-15a	-0.337245	-0.085591	4.1	0.449661	3.575877	1.489563
MIMAT000008	hsa-miR-16	-0.505668	-0.120105	4	0.4496545	1.487665	6.4
MIMAT000007	hsa-miR-17	1.7640528	0.5380593	5.3	0.449647	-2.02347	-0.848
MIMAT000007	hsa-miR-17	-0.539593	-0.239466	4.8	0.449647	-1.48935	0.61
MIMAT000007	hsa-miR-19a	-0.539593	-0.239466	3.8	0.449647	1.21025	1.238051
MIMAT000007	hsa-miR-19a	-0.539593	-0.239466	3.6	0.449647	16.39710	1.567
MIMAT000007	hsa-miR-19b	-1.253049	-0.602036	2.8	0.449647	26.17024	1.97544
MIMAT000007	hsa-miR-20a	0.803389	0.2630344	5.1	0.449647	-2.02347	-3.3396
MIMAT000007	hsa-miR-21	-0.629525	-0.280108	3.5	0.449647	-1.15627	-1.1324
MIMAT000007	hsa-miR-22	0.803389	0.2630344	5.1	0.449647	2.19828	0.952171
MIMAT000007	hsa-miR-23a	-1.348582	-0.654503	2.7	0.449647	5.353513	0.658211
MIMAT000007	hsa-miR-24-T	-1.259049	-0.602036	2.8	0.449647	-3.82211	-0.96438
MIMAT000007	hsa-miR-24	1.6602849	0.4150375	6.2	0.449647	-3.42817	-0.7746
MIMAT000008	hsa-miR-25	-0.539593	-0.239466	3.6	0.449647	10.52206	1.076816
MIMAT000008	hsa-miR-26a	-0.393253	-0.455195	3.1	0.449647	17.82583	3.17706
MIMAT000008	hsa-miR-26b	-1.528846	-0.602036	2.5	0.449647	33.05005	2.944853
MIMAT000008	hsa-miR-27	-1.027074	-0.455195	2.1	0.449647	1.12024	0.449623
MIMAT000008	hsa-miR-28-5p	-0.539593	-0.239466	3.6	0.449647	0.389067	1.48863
MIMAT000008	hsa-miR-29a	-0.285736	0.123893	3.1	0.449647	11.231	1.784271
MIMAT000008	hsa-miR-30a	-0.629525	-0.280108	3.5	0.449647	42.04326	4.81031
MIMAT000008	hsa-miR-30a*	-0.539593	-0.239466	3.6	0.449647	3.709659	0.325999
MIMAT000008	hsa-miR-31	-0.207536	-0.797727	4.4	0.449647	3.709659	6.1610053
MIMAT000009	hsa-miR-32	0.5058681	0.134301	4.5	0.449647	10.79185	1.752907
MIMAT000009	hsa-miR-33a	-0.281038	-0.09624	3.8	0.449647	1.758027	5.7
MIMAT000009	hsa-miR-32a	2.473128	0.1740234	4.4	0.449647	11.46634	1.77361
MIMAT000009	hsa-miR-33	8.387128	0.4547878	5.7	0.449647	-2.02347	-0.80735
MIMAT000009	hsa-miR-35	-0.747449	-0.455195	4.7	0.449647	2.807028	1.19265
MIMAT000009	hsa-miR-36	1.020739	0.078386	4.1	0.449647	0.16446	0.063931
MIMAT000009	hsa-miR-38	-6.530077	-0.700441	2.4	0.449647	0.388533	0.06306
MIMAT000009	hsa-miR-39a	-0.674451	-0.075859	3.7	0.449647	1.348882	0.065069
MIMAT000009	hsa-miR-101	-1.17604	-0.355881	3.4	0.449647	29.45276	4.327071
MIMAT000010	hsa-miR-25b	-1.348892	-0.654503	2.7	0.449647	4.817791	1.659537
MIMAT000010	hsa-miR-103	2.192095	0.334419	2.3	0.449647	7.824933	0.854548
MIMAT000010	hsa-miR-105	0.2248303	0.01543	4.7	0.449647	-6.52008	-2.23447
MIMAT000010	hsa-miR-106a	2.8017308	0.7874554	6.3	0.449647	-1.66823	-0.6742
MIMAT000010	hsa-miR-107	4.61E-16	-0.07939	3.6	0.449647	0.9635598	0.498806
MIMAT000022	hsa-miR-192	1.4527493	0.3677316	6	0.449647	-6.74491	-3.19265
MIMAT000022	hsa-miR-196a	-0.359728	-0.16463	3.8	0.449647	12.33355	2.710058
MIMAT000022	hsa-miR-197	2.423027	0.626335	5.9	0.449647	0.41491	0.25302
MIMAT000022	hsa-miR-198	-2.337953	-0.456195	4.1	0.449647	0.674491	0.363059
MIMAT000022	hsa-miR-199a-5p	-0.289736	-0.123893	3.9	0.449647	24.55146	1.008871
MIMAT000022	hsa-miR-199a-3p	2.0234723	0.140625	4.3	0.449647	77	3.264703
MIMAT000024	hsa-miR-208a	-0.539593	-0.239466	3.6	0.449647	67.44908	3.12534
MIMAT000024	hsa-miR-123-5p	-2.360718	-0.584963	2.3	0.449647	0	0.6742
MIMAT000024	hsa-miR-148a	-2.866586	-0.742054	2.6	0.449647	4.336028	1.535254
MIMAT000024	hsa-miR-30c	-0.056208	-0.305624	4	0.449647	37.54685	4.656693
MIMAT000024	hsa-miR-30d	-1.180359	-0.450661	3	0.449647	46.40496	2.647458
MIMAT000024	hsa-miR-133-5p	-1.348582	-0.31666	3.5	0.449647	3.035208	0.736966
MIMAT000024	hsa-miR-147	0.6744906	0.075551	4.3	0.449647	-0.96356	-0.67371



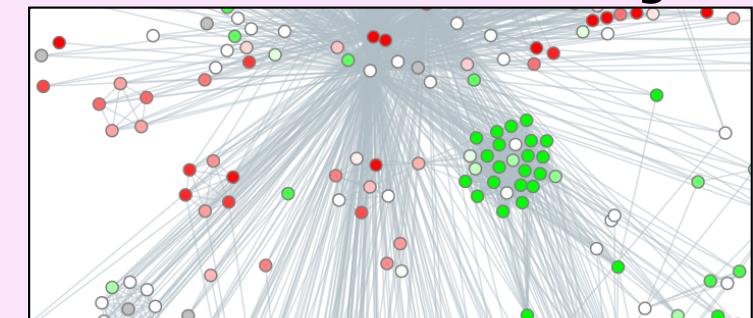
Human chromosome X

Outputs

Families of microRNAs



MicroRNAs sharing similar set of mRNA targets



Clusters of microRNAs on DNA

hsa-miR-514a-5p
UACUCCUGG
chrX
miRBase