A comparative study of unsupervised machine learning methods for mircoRNA sequence-based clustering

Samuel Acosta-Melgarejo
Supervisor: Sam Griffiths-Jones

Faculty of Biology, Medicine and Health, University of Manchester

BIOL61230/Research Project 1

Background

MicroRNAs

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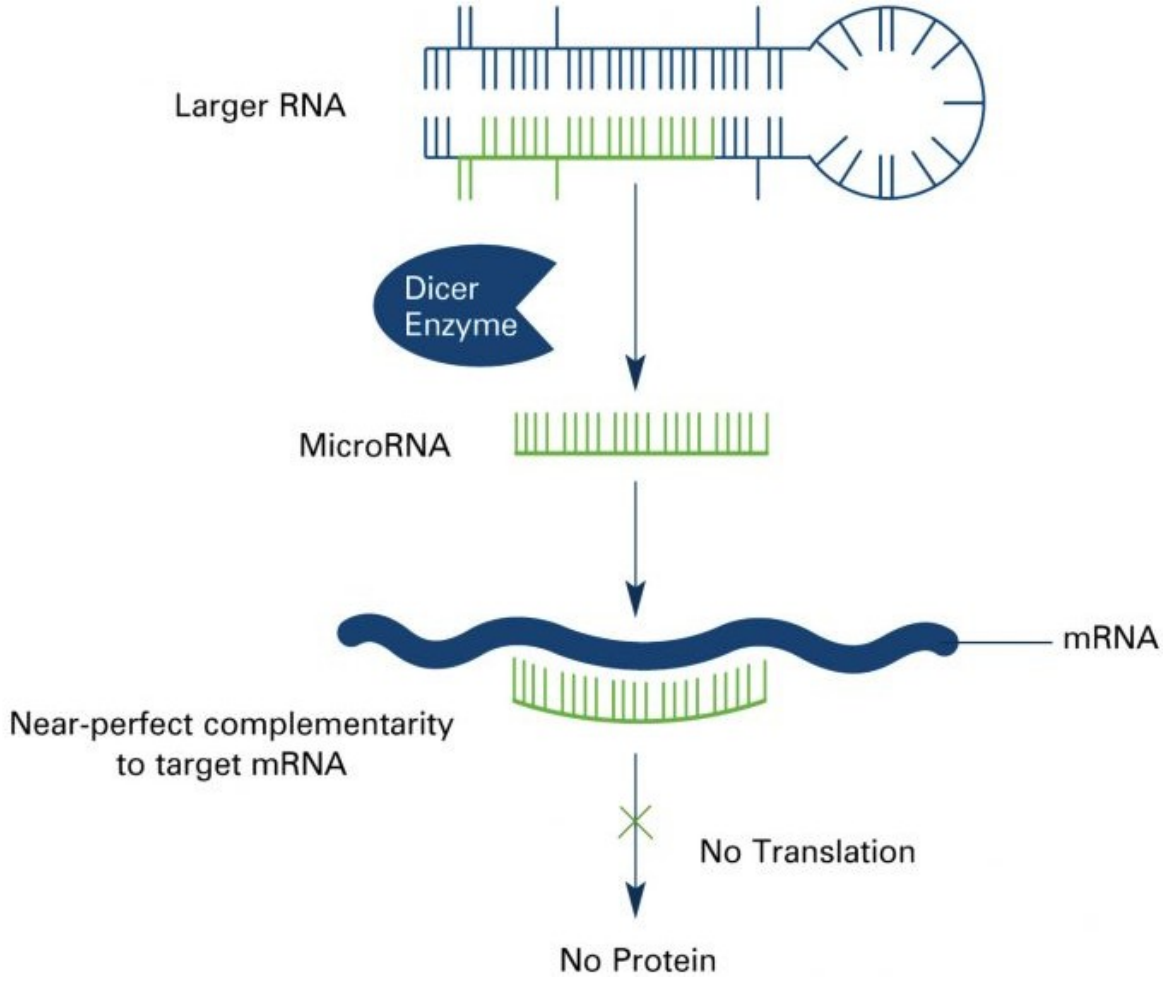
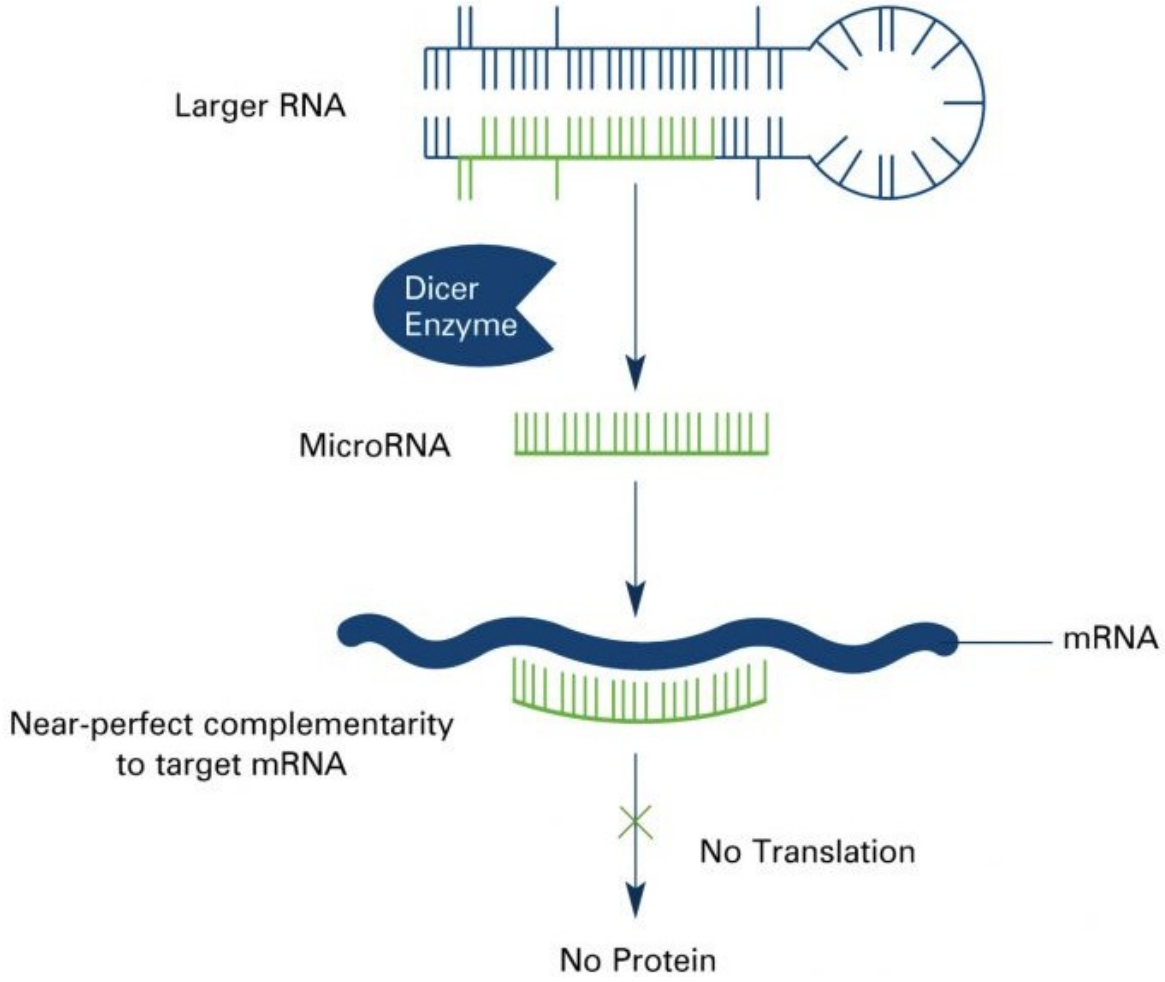
- Important post-transcriptional functions in gene expression, (developmental timing, cell death, cell proliferation...).
- Research and annotation centralised in the miRBase database.

Background


Larger RNA
Dicer
Enzyme
MicroRNA
mRNA
Near-perfect complementarity
to target mRNA
No Translation
No Protein

Background



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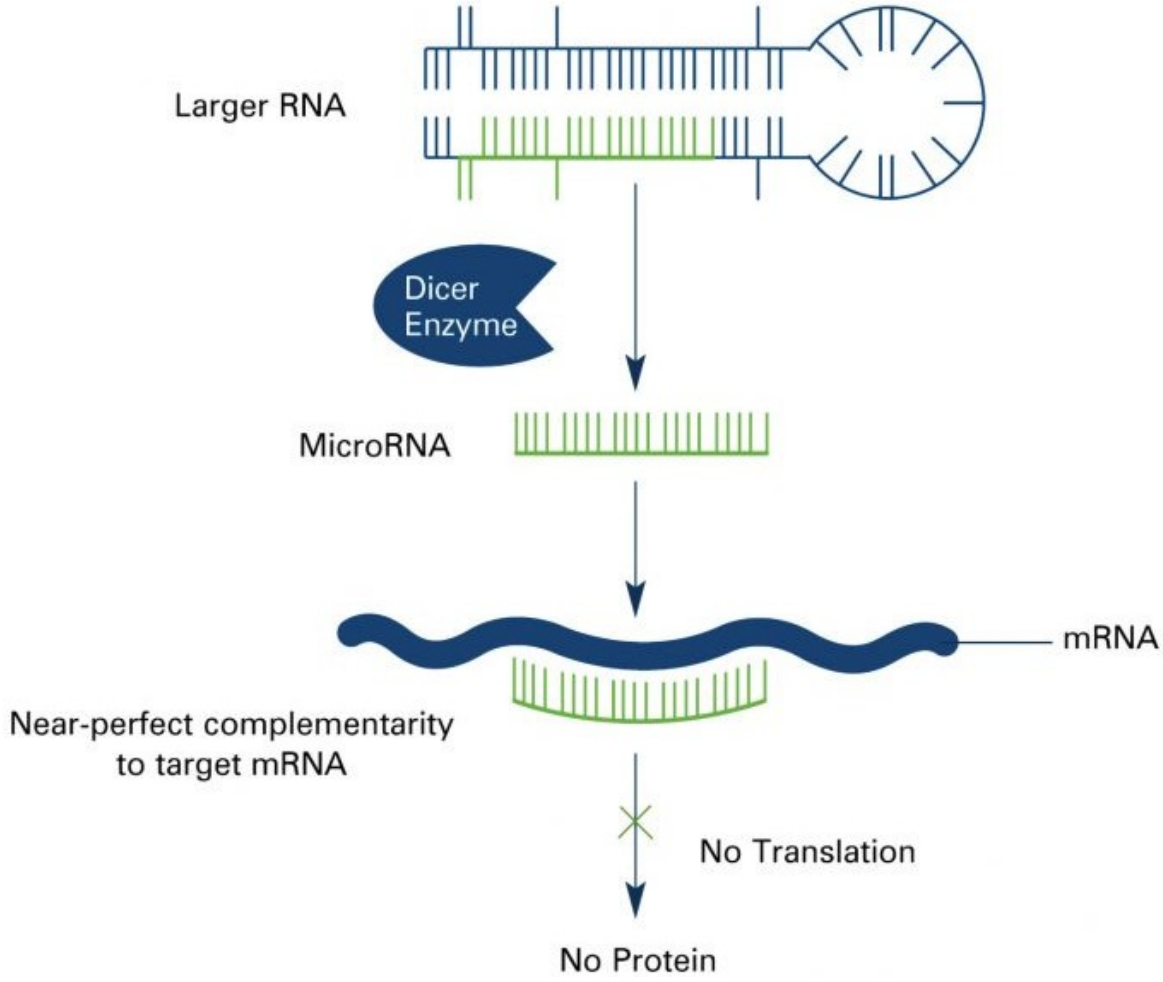

- Excised by enzymes from longer precursors.
- Precursors folded into hairpin-like secondary structures.

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MiRNA families

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Why are they important?

- Valuable information about biological functions.
- Amount of information about different miRNAs is variable; families useful for hypothesising characteristics of less known miRNAs.
- New miRNAs discovered at a fast rate; even low confidence families still useful for researchers (available way before biological validation).

Introduction

Project aims

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- Establish quality and significance of detected families.
- Compare different computational approaches and determine the most suitable.

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Requirements

- It was desirable that the tool could predict without human intervention $\rightarrow$ unsupervised machine learning
- Complete miRBase dataset, so results could be objectively compared to real families in miRBase $\rightarrow$ algorithms able to cluster large datasets

Methods: Algorithms

Unsupervised machine learning: Identifies groups of elements based on a similarity measure (obtained by embedded vectors/all-to-all BLAST).

1. Centroid-based clustering (*k-means++*, ClustalΩ impl.)
   Finds the k cluster centres and assigns the elements to their nearest cluster centre, minimising squared distances from the cluster.

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   Finds clusters in graphs using stochastic matrices (Markov matrices) to model the mathematical concept of random walks on a graph.
3. Density-based clustering (DBSCAN, scikit-learn impl.)
   Represents clusters as areas of higher density within a dataset. Starts from arbitrary point, evaluates if surrounding neighbour elements comply requirements set by the parameters, and if they do, a cluster is formed.

Methods: Statistical validation

1. Fowlkes-Mallows score

External similarity measure, expressed as the geometric mean of the pairwise precision and recall.

Definition

$$\mathrm{FMS} = \frac{\mathrm{TP}}{\sqrt{(\mathrm{TP}+\mathrm{FP})(\mathrm{TP}+\mathrm{FN})}} \tag{1}$$

- TP = true positives
- FP = false posititves
- FN = false negatives

Methods: Statistical validation

2. Adjusted Rand index

Similar external similarity measure function, a version of the Rand index corrected for chance.

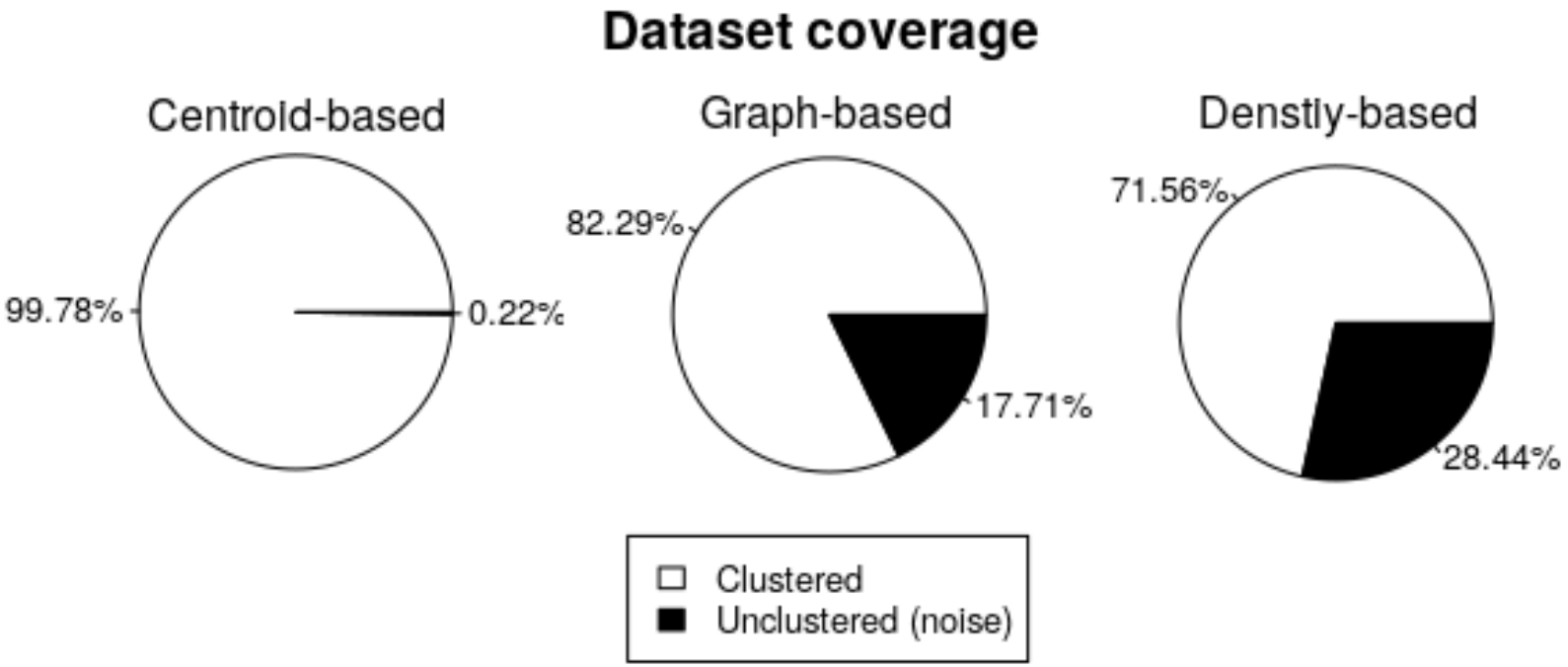
Definition

$$\mathrm{RI} = \frac{a+b}{C_2^{n_{samples}}} \quad ; \mathrm{ARI} = \frac{\mathrm{RI} - E[\mathrm{RI}]}{\max(\mathrm{RI}) - E[\mathrm{RI}]} \tag{2}$$

- a = true positives
- b = true negatives
- $C_2^{n_{samples}}$ = total number of possible pairs
- $E[\mathrm{RI}]$ = expected index of random labellings

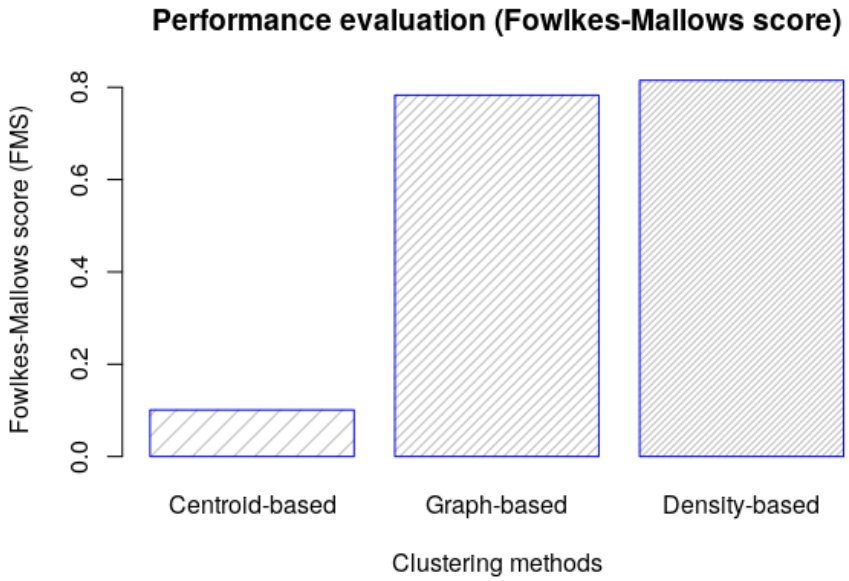
Results: Data coverage

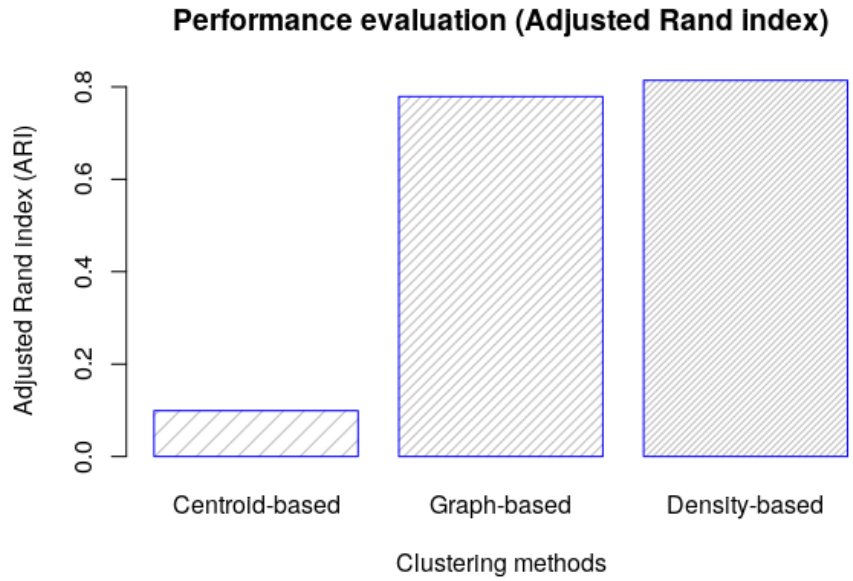
- Ref: 28645 miRNAs in 1983 families in miRBase (69.49% coverage).
- About 10% difference among graph and density-based algorithms.
- Centroid-based algorithm very different, clusters almost all the sequences.



Results: Quality assessment

- Similar patterns observed in FMS and ARI, the former tends to evaluate more positively.
- The centroid-based algorithm had a much lower score in both.
- The density-based algorithm had the best score in both measures, followed closely by the graph-based algorithm.





Results: Clustering overview

- Low performance of centroid-based algorithm explained by noise sensitivity and hard-wired cluster size threshold in implementation.
- Good performance of graph and density-based algorithms can be explained by their sparse-graph-oriented design.
- Stochastic graph-based algorithm has more coverage and clusters, implementation has better biological data support.
- ε value parameter in density-based algorithm increases noise detection and improves results.

Conclusions

- Unsupervised machine learning methods proven very useful for miRNA family detection in large datasets.
- Stochastic graph-based clustering, and specially, density-based clustering are the most suitable.
- The developed tool can be effectively used as an automated aid for automatic miRNA family detection or to complement, adjust or improve the miRBase original family predictions.
- The tool is publicly available under an open source license at GitHub (www.github.com/samuacosta/miRNACluster)

Thank you.

samuel.acostamelgarejo@postgrad.manchester.ac.uk

- References:

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