# Strategies for the selection of miRNA candidates for the treatment of Sarcopenia using network-based analysis and differential expression scoring

**Sarcopenia is a progressive muscle wasting and it is a natural consequence of aging. There is no cure for muscle loss. Target identification and validation is a pressing challenge, with many targets failing or showing poor association with the disease. This project aims to create models of miRNA:target interactions in sarcopenia based on differentially expressed (DE) miRNAs and genes**

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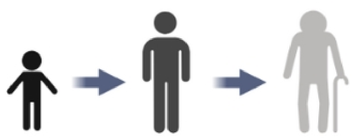
## MicroRNA (miRNAs)

MicroRNAs (miRNAs) are small single stranded RNAs (ssRNAs), which are produced from hairpin shaped precursors [Wahid et al., 2010].

They are conserved small non-coding RNAs that play a role in the regulation of gene expression [Wu et al., 2018]. miRNAs have been found to regulate almost all cellular functions [Ranganathan and Sivasankar, 2014]

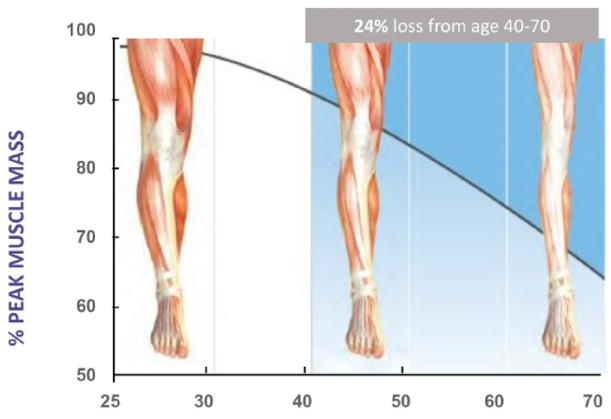
## Aging and Sarcopenia



**Aging** is a time--dependent functional decline of an organism at all levels.

**Sarcopenia** is an age-related disease characterized by the loss of muscle mass and muscle function.

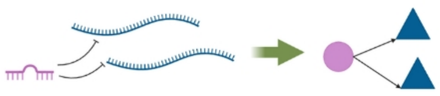
Muscle mass decreases approximately **3-8% per decade** after the age of 30 and this rate of decline is even higher after the age of 60 [Brocklehurst, 1976].
miRNAs as therapeutics are appealing given the potential to target multiple genes and pathways [Badalian-Very and Hydbring, 2013].




Source: https://waytowellness.co.za/

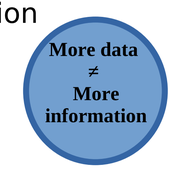
Target identification and validation is a pressing challenge, with many targets failing for efficacy reasons or showing poor association with the disease. Computational prediction of therapeutic targets could significantly decrease the attrition rates in the drug discovery pipeline by significantly reducing the initial search phase.

## Network density



The miRNA:Target interactions can be represented as a graph where both miRNAs and mRNAs are nodes and the edges are the relationship they have.

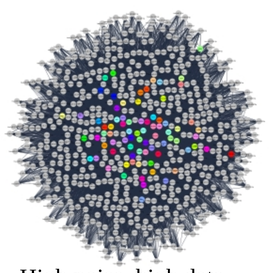
A miRNA can have thousands of targets and an mRNA can be targeted by multiple miRNAs. If we account for every possible target, we can easily pass from graph **A** on the picture below to graph **B**. Selection techniques, such as the one proposed here, can allow the filtering of nodes increasing the information the graph gives and reducing noise as shown in graph **C**.




**A)** Starting mRNAs and their interactions

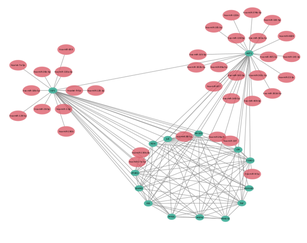
Low noise, low data

**B)** mRNAs with all miRNAs that targets them



High noise, high data

**C)** mRNAs and miRNAs classified as “relevant”



Low noise, high data

## General pipeline

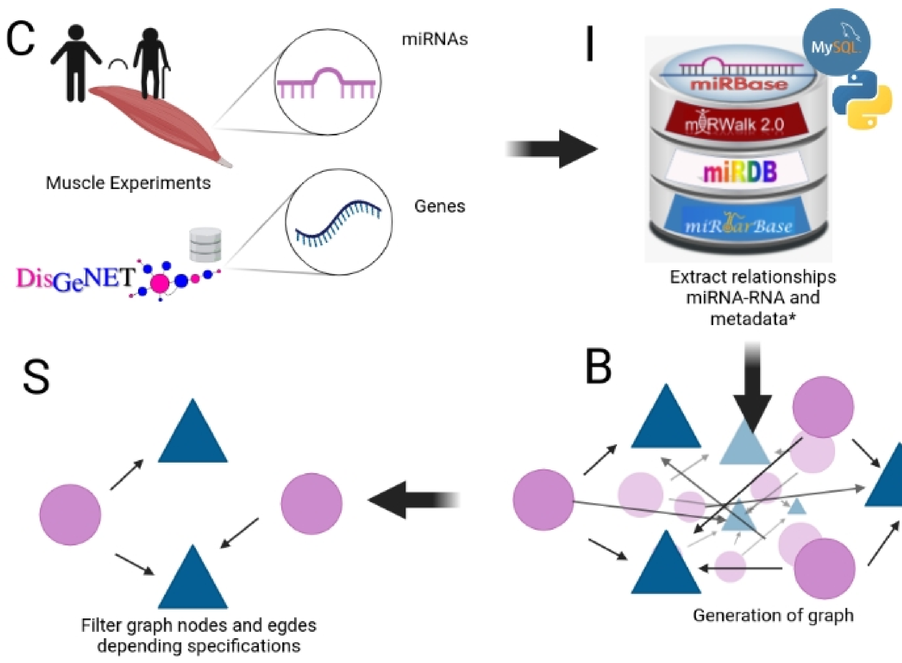
To create a graph with relevant nodes, we follow a 4 step methodology; **Collect (C)**, **Increase (I)**, **Build (B)**, and **Select (S)**.

We **Collect** an initial set of nodes (mRNA and/or miRNAs) from databases or experiments from literature.

We then **Increase** the information by using different miRNAs databases. The main attribute we consider is the binding affinity of a pair of nodes, their abundance in muscle, and the impact they have on aging muscle (from Differential Expression Analysis).

Next, we **Build** the network, and calculate the shortest paths and scores (as described in the next panel).

Finally, we can set a threshold to **Select** the nodes considered relevant by this algorithm.

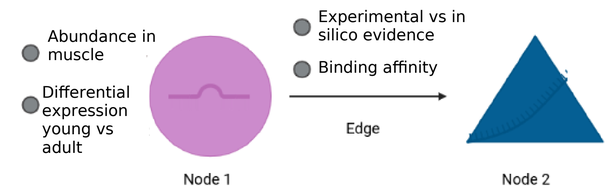



## Building the network

Each node (regardless if it is miRNA or mRNA) has a **normalized abundance** in the muscle in the range 0 to 1.

We define a threshold for the abundance to label the node as a “muscle node”.

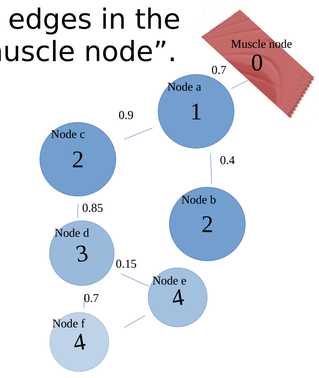
Nodes also have a **normalized differentiation** score in the range -1 to 1 based on their old vs young muscle DE.




Edges are weighted with the binding affinity and a binary label; 1 if it is validated experimentally and 0 if not.

To evaluate the nodes in the network, we consider two scores; **muscle relevance** and **age impact**.

**Muscle relevance** is calculated by the product of the edges in the shortest path to a “muscle node”.




In the example of the right, node c and b have 2 nodes in their paths, with muscle relevance of 0.63 and 0.28 respectively.

If the first node in the path is a muscle node, then the muscle relevance is set to 1.

**Age impact** of a node is calculated as the eigenvector centrality based on the average absolute value of the normalized DE of a pair of nodes as weight. This indicates the relevance of a particular node in the network.

## Future work

There are a total of 11 experiments with more than 300 samples from young vs old muscle waiting to be added to the model, this includes both mRNAs and miRNAs.

We are currently working on developing a metric for overall network 'quality'.

Tunning of the threshold is needed in order to improve node selection and interpretability.

## References and Acknowlegements

References:

[Badalian-Very and Hydbring, 2013] Badalian-Very, G. and Hydbring, P.(2013). Clinical applications of microRNAs. F1000Research, 2.
[Brocklehurst, 1976] Brocklehurst, G. (1976). The structure of the rhomben-cephalic roof in the frog. Acta neurochirurgica, 35(1-3):205–214.
[Dragomir et al., ] Dragomir, M., Carolina Mafra, A. P., G Dias, S. M.,Vasilescu, C., and Calin, G. A. Molecular Sciences Using microRNA Net-works to Understand Cancer.1

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**Poster presented by**

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