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 not a cure for muscle loss. Target identification and validation is a pressing challenge, with many targets failing in clinical trials or showing poor association with the disease. This project aims to create model(s) of microRNA:target interactions for more efficient in silico selection of potentially therapeutic targets for sarcopenia.

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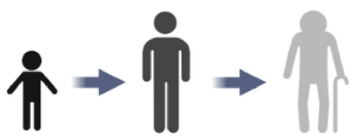
MicroRNA (miRNAs)

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]

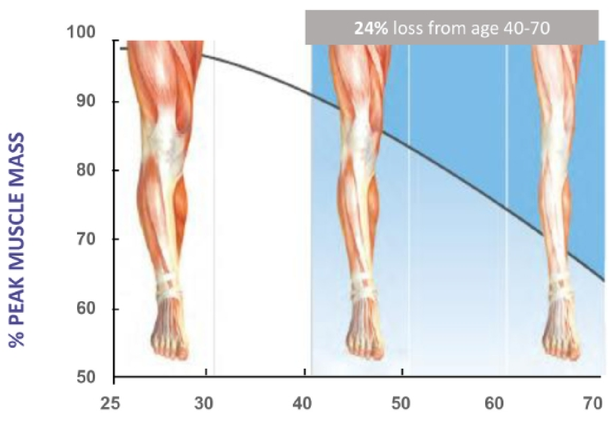
Aging and Sarcopenia



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.

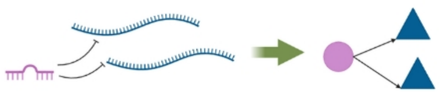
Muscle mass decreases approximately **3-8% per decade** after the age of 30 and this rate of decline is even higher after the age of 60 [Brocklehurst, 1976].
miRNAs as therapeutics are appealing given the potential to target multiple genes and pathways [Badalian-Very and Hydbring, 2013].



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

Target identification and validation is a pressing challenge, with many targets failing in preclinical trials 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.

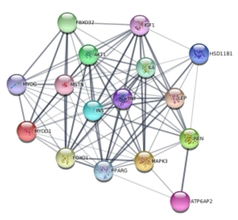
Network density



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.

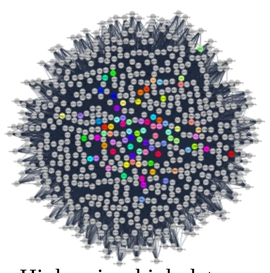
A miRNA can have thousands of targets and an mRNA can be targeted by multiple miRNAs. If we account for every possible target, we can easily pass from graph **A** on the picture below to graph **B**. Selection techniques, such as the one proposed here, can allow the filtering of nodes increasing the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

A) Starting mRNAs and their interactions



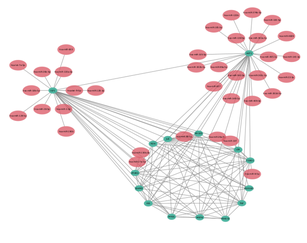
Low noise, low data

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

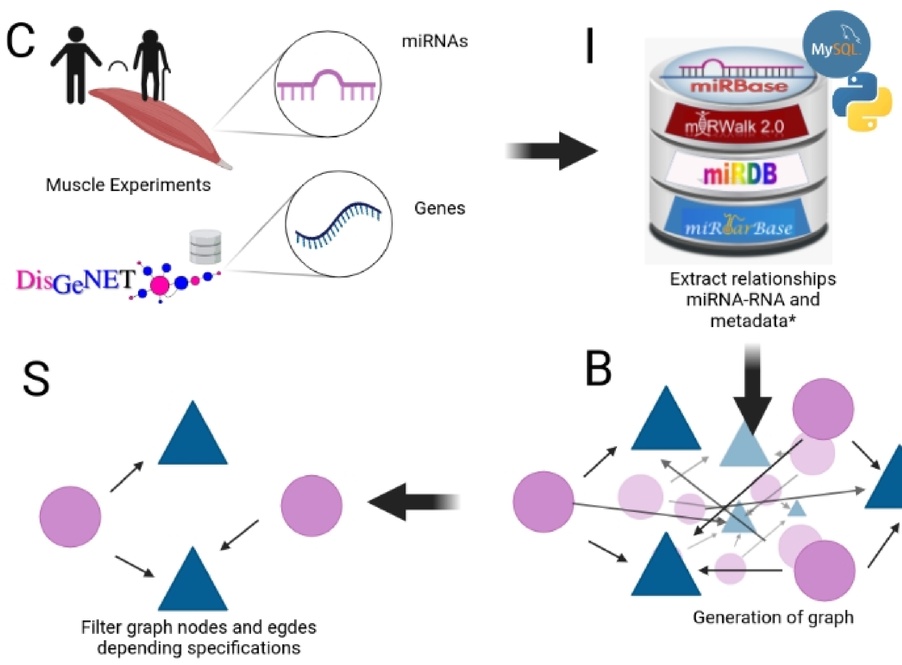
We aim create a graph with relevant nodes, for this, we follow a 4 step methodology; **Collect (C)**, **Increase (I)**, **Build (B)**, and **Select (S)**.

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.

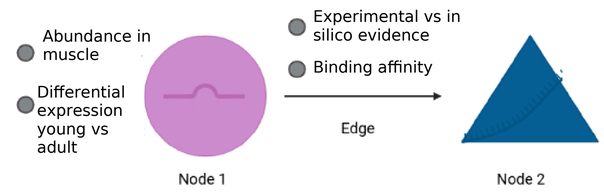


Building the network

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 (mirWalk/mirDB) 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 node with abundance in muscle biger than a threshold (muscle node).

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.

RNA-Seq

In order to create the microRNA:target network we need an initial set of nodes; genes and miRNAs.
For this, a Differential Expression Analysis (DEA) was done based on 3 RNA-Seq experiments in the literature for skeleton muscle in old vs young; GSE152558, GSE164471, and GSE157585.

Future work

In addition to DEA, we will add miRSeq (2) and microarray (5) experiments as well.

We will analyze the pathways that the union of all the experiments DE genes and microRNA alter, focosig in how individualy they up or downregulate those pathways.

The resulting microRNA:target intera-ctions modeled within the network presented in this poster will serve to select the microRNA to be study as Sarcopenia treatment

References and Acknowlegements

References:

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[Brocklehurst, 1976] Brocklehurst, G. (1976). The structure of the rhomben-cephalic roof in the frog. Acta neurochirurgica, 35(1-3):205–214.
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