Mathematical modelling of tissue specific miRNA effects

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This project aims to develop a mathematical model to predict the changes in gene expression induced by manipulations of miRNAs across multiple tissues or cell types.
This prediction is especially relevant because several miRNAs have been considered as potential therapeutic targets, but their applicability may be compromised by effects in off-target tissues or cell types.
miRNAs are small non-coding RNAs that repress target mRNAs by inhibiting translation and promoting target degradation. miRNA repression implies forming a RISC complex with the Argonaute protein and binding to its targets by complementary base pairing at miRNAs responsive elements (MREs). Each miRNA is able to bind multiple target RNAs and each mRNA can be regulated by multiple miRNAs, establishing complex miRNA-target regulatory networks (miRTRNs). Additionally, other RNA molecules with MREs (as long non-coding RNAs and circular RNAs) may act as miRNA sponges and counteract their effects. The relative abundances of mRNA targets, sponges and other miRNAs change from tissue to tissue, modulating the effective impact of a miRNA on its targets [1].
We will develop our model by expanding a previous miRTRN dynamic model developed by Miotto and colleagues [2]. This model was used to study the competing endogenous RNA hypothesis, according to which mRNAs that are targets of the same miRNA have a correlated expression, even if the miRNA abundance does not change. In this project, we want to use the model to predict the effect of changes in miRNA abundances in specific tissues. For that, we need to parameterize the model with tissue specific transcriptomic data. We also want to include extra features in the model, such as 1) allowing for cooperativity or competition when multiple miRNAs bind to the same mRNA target, 2) considering that different mRNAs vary in their intrinsic degradation rate, and 3) make the miRNA-mediated target degradation rate dependent on the miRNA-target binding affinity.
The expanded versions of the model will be simulated to predict tissue specific miRNA effects and to analyze the molecular determinants that contribute more significantly to the variability across tissues.

Students selected for this project, after thesis registration, are eligible to apply to the BioISI Programme (supporting 8 students with a 6-month Scholarship(BII), being the selection criterium the academic merit of the candidates

Bibliography:

1.Marques, T. M. & Gama-Carvalho, M. Network Approaches to Study Endogenous RNA Competition and Its Impact on Tissue-Specific microRNA Functions. *Biomol* **12**, 332 (2022).
2.Miotto, M., Marinari, E. & Martino, A. D. Competing endogenous RNA crosstalk at system level. *PLoS Computational Biology* **15**, e1007474-24 (2019). 10.1371/journal.pcbi.1007474