MATHEMATICAL MODELING OF MICRO-RNA CONTROL OF TRANSCRIPT LEVELS AND TRANSLATION EFFICIENCY IN IRRADIATED CELLS

The functioning of the cell does strongly depend on the level of gene expression. Changing gene expression can be induced by both external and intracellular factors. Endogenous molecules that play a significant role in post-transcriptional regulation of gene expression include microRNAs (RNA molecules composed of about 22 nucleotides). The microRNA binds to the mRNA leading to mRNA degradation or to inhibiting translation. High-throughput techniques used in biological research and medicine allow determining global changes of mRNA and miRNA in the course of normal and disease processes, but it is not easy to determine the effect and weight of individual miRNAs on changes caused by a specific factor or process.
The mathematical model developed by us has made it possible to identify miRNA groups of the greatest importance for transcriptome changes in irradiated cells [Mura et al. BMC Genomics, 2019]. Conducting model simulations under the assumption that only single miRNAs affect the transcriptome changes and determining the correlation of such simulations with the results of the experiment allows building a ranking list of all miRNAs operating in the studied population and identify those that have the greatest impact on changes in expression under certain conditions.

The model is based on the assumption that all changes in the level of transcripts result from changes in the miRNA - mRNA interaction. In simulations, we take into account only the initial state determining the levels of mRNA and miRNA and knowledge of the final state of mRNA levels is used to determine the model parameters and determine the correlation between the results obtained from the model and the actual ones. This forms the basis for identifying the miRNA playing the most-important role in mRNA expression changes. Because the earlier model uses data from only one time point and does not take into account the cause of change in miRNA-RNA interaction, the main goal of this project is to extend the current short-time effect miRNA - mRNA model to include longer-term dynamics and, combining experimentation with modeling to determine whether the weight of individual miRNAs in changes in mRNA levels at different times and conditions is characteristic of the type of cells or of the type of stimulus acting on cell. In order to obtain the necessary experimental data, deep miRNA and mRNA sequencing will be performed. RNAs will be isolated from two different cell lines exposed to ionizing radiation. Simulations of the model will be used to determine model parameters, using the Approximate Bayesian Computation (ABC) techniques.

As part of this project, we also we plan to extend our modeling effort to include determining the effect of miRNAs of high significance for transcriptome changes on the translation process and protein production. Based on preliminary research, we propose to devise a mathematical model that allows predicting the role of miRNA in changes of translation efficiency over time in forced situations, including specific changes caused by cancer therapies.

The additional goal of this project is to examine the biological mechanisms that control changes in model parameters over time, depending also on cell type and type of stimulus. We plan to study a relationship between the rank of different miRNAs and their nucleotide sequence and the sequence of their pre-miRNAs. We plan to run a series of experiments with reporter genes with various combinations of miRNA target sequences. The obtained results will be used to validate the mathematical models developed under this project.