Sphingolipids are molecules whose properties have forced scientists to reconsider their views on the metabolic function of lipids. According to its name (the prefix “sphingo” comes from the legendary Sphinx) are the source of many puzzles. The discoveries made in the last three decades have proven their key role in cell signaling and control of cell fate. Disturbances of sphingolipid metabolism underlie many of the pathological conditions, including neurodegenerative diseases. It should be stressed that progress in basic research on understanding the complex molecular mechanisms governing sphingolipidomics is dependent on the existence of adequate and comprehensive metabolic models.

Our research is the response to the growing need for the development of formal computational models that describe molecular processes and also tools to effective adaptation of experimental data to the modelling. Specifically, we are interested in the complexity of the metabolism of sphingolipids in human nerve cells and the global metabolism of nerve cells under apoptosis (neurodegeneration).

Consequently as the main objective of this project we plan to develop a multiscale model of metabolic and signalling pathways that are modulated by bioactive lipids from sphingolipid family.

We would like to use an inclusive approach that gives high hopes for obtain of biologically important applications. Integration involves the use of various biotechnological high throughput data (transcriptomic, proteomic and lipidomic). By multiscaleness we understand the synthesis of several formal models involving biological phenomena occurring in a scale of a single signal or metabolic pathway, on a larger cellular scale, then the level of the whole organism.

The most detailed model will be based on our recently developed a kinetic model of the metabolism of sphingolipids (mathematically represented by the system of ordinary differential equations). This model will be integrated with the global reconstruction of cellular metabolism Recon 2, which in turn will allow the prediction of the level of individual metabolites. Another model (pharmacokinetic) based on differential equations (PB-PD Pharmacokinetic/Pharmacodynamic modelling) will allow to characterize compounds secreted into the body fluids and their distribution tissue distribution. The next research task is to match the models of metabolic networks with data on the expression levels of specific enzymes in the cell. We believe, it will help us to come up with specific metabolom profiles for particular patogennic states. Synergy between metabolom and trancriptom will be achieved thanks to Bayesian approach along with MCMC (Markov Chain Monte Carlo) methods. New and general methods for integration of high-throughput data that we plan to derive will hopefully give us a chance to investigate biomedical problems from various perspectives at once. At the end of our research we plan to apply lipidomic data gathered by our collaborators from European Centre of Bioinformatics and Genomic in Poznan. Our goal is to validate the mathematical model in terms of consistency between its predictions and actual levels of lipids concentration in a cell.

In summary, in the framework of this project we will create mathematical metabolic models, corresponding to different scales and levels of the examined phenomenon – neurodegeneration. To achieve this, we will propose innovative methods for statistical analysis, and integration of high throughput data with computational models. Thanks to the systemic approach, we hope to provide a new tools for wide range of applications in both bioinformatics and the so-called molecular medicine. We hope that the use of our models to investigate the process of neurodegeneration will be an important step in understanding the mechanisms of diseases such as Alzheimer's or Parkinson's.