

Postgraduate student: **Eleftherios Ouzounoglou**

Thesis Title:

## **Application of Systems Biology methods in the elucidation of alpha-synuclein's role in the pathogenesis of Parkinson's Disease**

Abstract:

Systems Biology is the most rapidly evolving field of Computational Biology. Its main objective is to make optimal use of the available qualitative knowledge and the increasing availability of a wide variety of heterogeneous biological data from the molecular level, in order to create mathematical and/or computational models that allow the study of the dynamic behavior of biological systems and also facilitate the more efficient research on these systems using in-silico methods, such as simulation and hypothesis testing.

In recent years, important findings about the molecular mechanisms involved in the development of Parkinson's Disease have been presented in the literature. Among these, key successes have to do with the elucidation of the contribution of alpha-synuclein (ASYN) and the consequences of its mutation or overexpression in neurodegeneration. This important protein has been genetically associated with Parkinson's Disease and experimental findings suggest that the central mechanism of pathogenesis is related to the creation of oligomeric molecular species of alpha-synuclein. A consequence of the abnormal function of ASYN is the death of neurons where the protein is over-expressed, or expressed in a mutant form. Furthermore ASYN has also been found to affect in significant ways several key cell operations, most notably the proteolytic mechanism. However, the verification of the alpha-synuclein related biological phenomena that lead to neurodegeneration is a very difficult process, so the contribution of computer science, through systems biology, is crucial so as to make manageable the complexity of the problem and handle the heterogeneity of information on the observed phenomena.

In this Master's thesis, we take the first steps towards creating a Systems Biology oriented computational model, capable to simulate the alpha-synuclein over-expression related dynamic phenomena in the cell and especially those concerning its oligomerization, the degradation by different proteolytic mechanisms and the inhibition of those due to pathogenic behavior of this protein.

The developed biomolecular reactions model was trained by using the available experimental data from the laboratory. Despite the relatively limited amount of data, the model simulates particularly well the observed phenomena. An important accomplishment is the ability of the model to predict the dynamic behavior of the biological system when various experimental interventions are applied, although no parameter learning procedure has been applied specific to these cases. This result is a positive indication for the accuracy of the model and for its predictive capabilities. Starting from this accomplishment, a multi-scale model that will simulate additional alpha-synuclein related phenomena (e.g. the secretion of the protein and its actions in the intercellular space etc.) is planned, aiming to assist in the search for the mechanisms that contribute to the development of Parkinson's Disease.

SUBJECT AREA: SystemsBiology

KEYWORDS: Parkinson's Disease, alpha-synuclein, biochemical networks, modeling, in silico experiments.

### Examining Committee

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