

Project Overview

The aim of our research is to enhance our understanding of the molecular mechanisms underlying the behavior of complex living systems. In particular, we investigate how large and complex regulatory networks control the response of a living cell to its ever-changing environment. The stress response to environmental events is induced by the interaction of several interwoven modules with complex dynamic behavior, acting on different time scales. To deal with this complexity we need mathematical modeling and computer-supported analysis. So far, the methods of systems biology are mostly applied to individual modules, such as particular metabolic pathways and genetic networks. But to understand the global behavior, we need an integrated description of the regulatory network. We must develop new, scalable methods for modeling and analysis of integrated networks. We will apply our methods to the stress response system of the enterobacterium *Escherichia coli*, one of the best studied organisms and a model for several pathogenic bacteria. In the project, we will develop an integrated model of the stress response system of *E. coli*, including key metabolic, genetic and signaling modules. We also develop methods to reduce high-dimensional nonlinear systems of equations, and to approximate them by discrete automata. Parallel model checking algorithms will be developed for verifying specific properties at the model. So we can explore the models and predict the outcome of experiments. Finally, we will validate our model by experimentally testing predicted properties in our labs. Our cross-disciplinary European team of biologists, mathematicians and computer scientists will develop a coherent and generic methodology, generalizable to other complex (biological) systems. Our models will be accessible via the Silicon Cell and the International *E. coli* Alliance. They could improve many medical and biotechnological applications, e.g. strain improvement and rational drug design.