The term signaling pathways refers to cascades of biochemical processes resulting in change of gene expression in response to changes in intra- or extracellular environment conditions. Discovery of processes that form these cascades is a key to understanding intracellular regulatory mechanisms and, consequently, is the first step toward our controlling these processes. Such control may take form of a therapies targeted at particular diseases. It should be stressed that it is not just the knowledge which molecular players are involved in signaling pathways that is important, but also the dynamics of the processes under consideration.

In recent years signaling pathways have been the subject of extensive research, both experimental and theoretical. These studies led to discovery of new interactions between proteins, protein complexes, mRNAs and oter molecules as well as development of original mathematical models that describe them and help I analysis of dynamical properties of processes involved in signaling pathways and predict cellular responses to external stimuli. This, in turn, yielded new ways of influencing cells behawior – in terms of therapeutical actions. Mathematical methods facilitated faster progress in the field, since at least some of time- and resource-consuming experiments could be replaced by computer simulations and formal mathwamatical analysis of systems described by mathematical equations.

It should be noted, however, that usually researchers focus only on a small fragment of an extremely large number of intracellular processes. Even in these cases, mathematical models are very complex and their simulation requires large computational power. If one aims at investigating interactions between two such fragments, the computational power requirements increase even farther. Therefore it is crucial to develop new methods that facilitate effective merging of existing models and algorithms for simulations of their dynamics. These are te two main topics of the proposed project.

The project consists of four intertwinned tasks: (1) Development of original methods for simulations of the mathematical models of stochastic processes into the signaling pathways that take into account heterogeneous cellular responses to external stimuli; (2) Development of original methods for merging chosen signaling pathways models; (3) Experimental identification of parameters characterizing activation of the considered signaling pathways and (4) Identification of key interactions between NFκB and HSF1 pathways at the protein and transcription regulation levels. First two tasks belong to the fields of computational biology and system engineering and constitute the main part of the project. However, theoretical work in these fields should be related to practical applications. Therefore, two other tasks have been planned, of experimental and bioinformatical nature. The third of aforementioned tasks will provide data for estimation of parameters of the mathematical models, whereas the last one will allow to determine specific structure of the chosen biological systems.

The methods developed in the project will be tested on analysis of signaling pathways, in which p53 and NFkB proteins are key elements. These pathways are involved in regulation of inflammatory and immune responses, apoptosis, carcinogenesis, control of cell cycle progression, angiogenesis and metastasis. Additionally, heat-shock HSF1-dependent pathways will be merged with them, as they potentially may be utilized to sensitize cancer cells to radio- or chemotherapy.

New methods and computational tools developed in the project will facilitate expansion of knowledge on regulatory mechanisms of biological processes and, due to the nature of the pathways under consideration, may ultimately lead to potential clinical applications. New computational methods developed in the project will be general enough to support research on crosstalk between other pathways as well. Development of new techniques of analysis of mathematical models should also result in increasing of costs effectiveness of biological experiments due to new model-based experimental protocols. Moreover, results obtained in the project will elucidate important issues concerning the mechanisms of the interactions between pathways critical for cellular response to stress. As a result, acquired knowledge will pave the way for modulating cell resistance to cytotoxic factors used in anticancer therapies and, consequently, provide hints on possible changes in currently used therapy protocols.