The recent progress in molecular biology has made it possible to determine elementary components of complex biochemical networks in living cells, and it has allowed detailed system level cellular modeling. This promises for example to predict properties of genetically modified organisms and effects of drugs on cellular functions.

The intrinsic property of chemical reactions in living cells is their "mesoscopic" character. The word mesoscopic is taken from physics, where it is coined for systems of intermediate sizes between elementary ones i.e. with only a few degrees of freedom and macroscopic ones that can be treated in the limit of infinite sizes and number of states. An example in microbiology is a prokaryotic cell of E.Coli. It has a size of about 1mc that allows about 1 million of protein molecules to be inside. The DNA of E.Coli encodes several thousands of various proteins, that means that in average there are only about a hundred of molecules of the same kind per cell. This number can be even much smaller for many important molecules. Thus there is only one DNA molecule per cell.

The small number of proteins of the same kind per cell assumes their strong fluctuations due to the stochastic nature of chemical reactions and discreteness of molecules. Such fluctuations do not merely lead to smearing of the behavior expected from the thermodynamic limit. Several important processes, such as an escape from a metastable state cannot be understood without proper accounting for the mesoscopic fluctuations. An example in prokaryotes is the lac operon in E. coli, where, in response to lactose-like inducers, the operon often acts as a bistable switch, whose switching rate is controlled by mesoscopic fluctuations.

In our research we focus on the analysis of specific biochemical networks, progressing from simple to more realistic models. We start with a rigorous stochastic treatment of Michaelis-Menten and Hill dynamics, deriving the spectrum of noise and its effects on the deterministic components of the reactions. In spite of their text-book status, such equations are to be generalized in applications to mesoscopic biochemistry. The Michaelis-Menten equations have been derived only to describe the average rates of chemical reactions mediated by enzymes. In this theory strong simplifications in quantifying such chemical reactions follow after enzymes are assumed to be at local equilibrium. This allows to reduce the number of independent variables and to derive effective rates of chemical reactions. In several work such effective rates have been used in application to bistable switches in biochemical networks. The estimated rates, however, often have been far from experimentally measured ones. According to our theory, at least partly this can be explained by the fact that enzymes not only affect the average rates of reactions but also modify fluctuations. Integrating over enzyme fast degrees of freedom we found that resulting fluctuations in the number of substrate molecules are no longer Poissonian. This can result in considerable suppression of switching rates.

To fully account for fluctuations in Michaelis-Menten-Hill dynamics we should design new theoretical approaches that would allow to separate fast and slow degrees of freedom. This can be achieved using the stochastic path integral techniques, recently devised to study shot noise in mesoscopic physics. Under stationary conditions one can derive the full counting statistics of the enzyme interaction events. This in turn can be incorporated into the effective Hamiltonian in the stochastic path integral for slow substrate variables. Its evaluation at a saddle point leads to equations that describe not only the evolution of an average number of particles in substrate but rather the evolution

of the whole generating function, which contains information both about average number of molecules and their fluctuations. The instanton-like saddle points describe transitions among metastable states. The evaluation of the path integral will provide estimates of the switching rates that properly account for the non-Poisson character of enzyme mediated reactions.

Our theory of rigorous separation of fast and slow variables on the level of the entire probability generating functions will allow considerable reduction in the number of independent variables in fully stochastic numerical modeling of biochemical networks, because multiple fast degrees of freedom will be possible to integrate analytically prior to running numerical simulations.

Our research on fluctuations at Michaelis-Menten-Hill dynamics can be facilitated by exact treatment of several simple models. One such example is the case with a single enzyme molecule, for which exact evolution of the generating function of substrate number of molecules is possible. Such exact results will improve our knowledge about applicability of various approximation techniques and provide valuable tool to test numerical codes.

The next step in our research is to consider stochastic networks of realistic sizes. This will require further theoretical incite since nonlinear effects of evolution and adaptation, ubiquitous in life, have not been addressed in mesoscopic physics. One of the directions is to look for field theoretical models that mimic evolution and adaptation processes. The techniques, described above, then should be applicable for their study.

The final goal is direct applications of our techniques to explain and predict experimental results determined for real living cells.