# DOMINANT PATHS AND SYSTEMS IN MULTISCALE REACTION NETWORKS

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## EXTENDED ABSTRACT

We develop the classical idea of limiting step to the asymptotology of multiscale reaction networks. The concept of limit simplification is proposed. For multiscale reaction networks the dynamical behavior is to be approximated by the system of simple dominant networks. The dominant systems can be used for direct computation of steady states and relaxation dynamics, especially when kinetic information is incomplete, for design of experiments and mining of experimental data, and could serve as a robust first approximation in perturbation theory or for preconditioning. They give an answer to an important question: given a network model, which are its critical parameters? Many of the parameters of the initial model are no longer present in the dominant system: these parameters are non-critical. Parameters of dominant systems indicate putative targets to change the behavior of the large network.

Following Kruskal [1], asymptotology is "the art of describing the behavior of a specified solution (or family of solutions) of a system in a limiting case." We analyze dynamics and steady states of multiscale reaction networks. We focused mostly on the case when the elementary processes have significantly different time scales. In this case, we obtain "limit simplification" of the model: all stationary states and relaxation processes could be analyzed "to the very end", by straightforward computations, mostly analytically. For any ordering of reaction rate constants we look for the dominant kinetic system. The dominant system is, by definition, the system that gives us the main asymptotic terms of the stationary state and relaxation in the limit for well separated rate constants.

The theory of dominant systems for linear reaction networks and Markov chains is well developed [2; 3]. Complete theory for linear networks with well separated reaction rate constants allows us to elaborate algorithms for explicit approximations of eigenvalues and eigenvectors of kinetic matrix. We found the explicit asymptotics of eigenvectors and eigenvalues. All algorithms are represented topologically by transformation of the graph of reaction (labeled by reaction rate constants). The reaction rate constants for dominant systems may not coincide with constant of original network. In general, they are monomials of the original constants. In the simplest cases, the dominant system can be represented as dominant path in the reaction network. In the general case, the hierarchy of dominant paths in the hierarchy of lumped networks is needed.

Accuracy of estimates is proven. Performance of the algorithms is demonstrated on simple benchmarks and on multiscale biochemical networks [4]. These methods are applied, in particular, to the analysis of microRNA-mediated mechanisms of translation repression [5; 6; 7]. Although remarkable progress has been made in deciphering the mechanisms used by miRNAs to regulate translation, many contradictory findings have been published that stimulate active debate in this field. There is a hot debate in the current literature about which mechanism and in which situations has a dominant role in living cells. The same experimental systems dealing with the same pairs of mRNA and miRNA can provide ambiguous evidences about which is the actual mechanism of translation repression observed in the experiment. We analyse dominant systems for the reaction kinetic network that includes all known mechanisms of miRNA action and demonstrate that among several coexisting miRNA mechanisms, the one that will effectively be measurable is that which acts on or changes the sensitive parameters of the translation process. This analysis of dominant systems explains the majority of existing controversies reported.

For general nonlinear systems, the problem of dominant systems is still open. It is discussed in the framework of the modern theories of tropical asymptotic [8; 9]. For nonlinear reaction networks, we present a new heuristic algorithm for calculation of hierarchy of dominant paths. Our approach is based on the asymptotic analysis of fluxes on the Volpert graph [10; 11].

The results of the analysis of the dominant systems often support the observation by Kruskal [1]: "And the answer quite generally has the form of a new system (well posed problem) for the solution to satisfy, although this is sometimes obscured because the new system is so easily solved that one is led directly to the solution without noticing the intermediate step."

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