Modeling high-dimensional and uncertain dynamical systems: Application to the Iron Homeostasis Network.

Eric Fanchon, TIMC, Université Grenoble Alpes, Eric.Fanchon@imag.fr.

Understanding the biological mechanisms at work within cells is a fundamental issue for improved diagnosis and the development of new therapeutic strategies (e.g. combinatorial therapies). The agents of biological processes at the molecular level are metabolites, proteins and other macromolecules interacting one with the other. Such systems have complex dynamics due to the nonlinearity of the basic kinetic laws, and the presence of numerous feedback loops. It is well recognized that two main features make the building and analysis of models of biological networks very difficult: (i) the state and parameter spaces are high-dimensional ; (ii) the numerical values of many model parameters are poorly known, and biological data on behavior are often of a qualitative nature, and heterogeneous.

Our approach is based on the intuitive formalism of temporal logic (specifically Signal Temporal Logic, STL), to express in a rigorous manner complex dynamical properties. This is an adaptation to biological modeling of formal methods developed in Computer Science for the development and verification of software and hardware systems. Due to their heterogeneity and qualitative nature, the constraining power of biological data is generally not sufficient, with respect to the complexity of the model, to define reliably a unique model. We acknowledge this situation by producing not a unique set of parameter values but a region of parameter space. Our approach performs an efficient sampling of the parameter space in order to define feasible regions in which the model exhibits hypothesized or experimentally observed behaviors expressed with STL. We then try to characterize the diversity of dynamical behaviors associated to it.

We apply this methodology in an effort to model and better understand the complex network of cellular iron homeostasis in mammals with focus on progenitors of erythroid cells, in the context of (phenotypically similar) blood cancers called Acute Myeloid Leukemia. Iron homeostasis is central to many biological functions, including erythropoiesis, resistance against infections, and proliferation of cancer cells as in the pathologies considered herein.