ABSTRACT

Systems theoretic description of biology has opened up a new paradigm of prediction and control in biomedical research. The 'systems biology' approach is particularly effective when used to develop a personalized therapy for complex systemic diseases like cancer. The ability to evolve and to grow drug resistance makes cancer an ideal choice for studying dynamic therapy design problems. A real-time 'prediction and validation' based 'drugs combination' approach can provide a better response than relying on a single miracle drug. A fundamental requirement to develop this methodology is the modeling of a disease-free system along with the modeling of possible mutations that can cause increased cell proliferation to induce carcinogenesis.

This dissertation takes a Boolean approach to model the cellular regulatory system. A Boolean network can model the cell cycle regulation with decent success. The proposed scheme considers Boolean maps for non-feedback systems and Boolean control networks for feedback systems. Somatic mutations can be modeled as stuck-at faults in the network. A semi-tensor product approach has been taken to define a Boolean system along with faults in a linear way. The existence and uniqueness theorems for the fault analysis and therapeutic intervention (drugs combination) design and algorithms for improvement in observability and controllability have been carefully prepared to solve the problem in the most general way. Additionally, it has been observed that fault analysis and drug design problems can be mapped as Boolean satisfiability functions. Heuristic methods for fault analysis and intervention problems based on the SAT algorithms have also been discussed for a real-time solution of the problem. The theoretical and simulation results on fault analysis and optimal therapeutic intervention have been discussed for different biological networks for both these approaches.

Keywords: Boolean networks; Fault analysis; Intervention; Observability; Controllability; Semi-tensor product; Satisfiability; Cancer.