Preface

In the quest to understand cell behavior and cure genetic diseases such as cancer, the fundamental approach being taken is undergoing a gradual change. It is becoming more acceptable to view these diseases as an engineering problem, and systems engineering approaches are being deployed to tackle genetic diseases. In this light, we believe that logic synthesis techniques can play a very important role. Several techniques from the field of logic synthesis can be adapted to assist in the arguably huge effort of modeling cell behavior, inferring biological networks, and controlling genetic diseases. Genes interact with other genes in a Gene Regulatory Network (GRN) and can be modeled as a Boolean Network (BN) or equivalently as a Finite State Machine (FSM). As the expression of genes determine cell behavior, important problems include (i) inferring the GRN from observed gene expression data from biological measurements, and (ii) using the inferred GRN to explain how genetic diseases occur and determine the “best” therapy towards treatment of disease.

We report results on the application of logic synthesis techniques that we have developed to address both these problems. In the first technique, we present Boolean Satisfiability (SAT) based approaches to infer the predictor (logical support) of each gene that regulates melanoma, using gene expression data from patients who are suffering from the disease. From the output of such a tool, biologists can construct targeted experiments to understand the logic functions that regulate a particular target gene. Our second technique builds upon the first, in which we use a logic synthesis technique, implemented using SAT, to determine gene regulating functions for predictors and gene expression data. This technique determines a BN (or family of BNs) to describe the GRN and is validated on a synthetic network and the p53 network. The first two techniques assume binary valued gene expression data. In the third technique, we utilize continuous (analog) expression data, and present an algorithm to infer and rank predictors using modified Zhegalkin polynomials. We demonstrate our method to rank predictors for genes in the mutated mammalian and melanoma networks. The final technique assumes that the GRN is known, and uses weighted partial Max-SAT (WPMS) towards cancer therapy. In this technique, the GRN is assumed to be known. Cancer is modeled using a stuck-at fault model, and ATPG techniques are used to characterize genes leading to cancer and select drugs to treat cancer. To steer the GRN state towards a desirable healthy state, the optimal
selection of drugs is formulated using WPMS. Our techniques can be used to find a set of drugs with the least side-effects, and is demonstrated in the context of growth factor pathways for colon cancer.

This monograph is organized as follows. After an introductory chapter in which we provide the relevant background from the areas of genomics and logic, we present (in Part I) a set of techniques to infer the predictor set and gene regulatory network (GRN) from gene expression data. This is done for binary-valued as well as continuous gene expression data. Part II describes a logic based approach to do GRN control and intervention, using ideas from the area of VLSI testing.

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Sept 2013                                      Sunil P. Khatri
Logic Synthesis for Genetic Diseases
Modeling Disease Behavior Using Boolean Networks
Lin, P.-C.K.; Khatri, S.P.
2014, XXI, 100 p. 28 illus., 8 illus. in color., Hardcover
ISBN: 978-1-4614-9428-7