Title: Identification and robustness of phenotypes in complex gene regulatory networks

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Subject Headings: Mathematics, Dynamical Systems, Systems Biology, Gene Regula- tory networks

Project Summary:

How genotype is transformed into phenotype is a fundamental question of systems biology. We will use mathematical models in an attempt to address at least a part of this question.

We use networks to model how genes regulate: the nodes are the genes and the edges indicate interactions. In turn the interactions (edges) provide structure to differential equations that govern the activation and inactivation of genes and hence the quantities of proteins in the organism. These different levels of proteins correspond to different functions and physiological expression, i.e. phenotypes of the organism. The simplest dynamical expression to identify is that of a steady state or fixed point, and thus in our mathematical model different fixed points correspond to different phenotypes.

There are two classical approaches to this problem. First, assume an explicit differential equation and solve for the equilibria. The challenge in this setting is that for large networks finding all the equilibria is computationally expensive. To a large extent this is due to the fact that these biological systems involve many unknown parameters and the associated dynamics depends on the parameters. Second, assume that the genes have a boolean behavior, either on or off. This allows for extremely fast computations. The disadvantage is that the associated parameter space is extremely restrictive.

A new modeling approach based on combinatorics and algebraic topology combines the speed of boolean computations with the richness of parameter space associated with differential equations. The goal of this project is twofold. First, to use this new approach and the associated software DSGRN to identify fixed points (phenotypes) for complex net- works and understand how robust these fixed points are, e.g. are the fixed points preserved over large regions of parameter space. Second, to relate these findings back to classical differential equation models.

Applicant GPA and other requirement(s): 3.5 GPA

Applicant Responsibilities: The student will learn how to run the DSGRN code and to apply it to large networks. As a consequence the student will have to learn how to organize and interprete large data sets. The student will learn how to run Matlab or Julia code to find zeros of functions over regions of parameter space.

Thus, the student is expected to have familiarity with using computers (previous pro- gramming experience is helpful, but not required) and an interest in data science. The student will learn about gene regulatory networks as models in systems biology. This learning will be done via a combination of reading papers, direct tutoring by mentors, and participation in group meetings.

By the end of the summer the student will be able to understand the relationship be- tween fixed points of the combinatorial models with fixed points for the classical differential equation models.

Mentoring Plan: The faculty mentors will be Konstantin Mischaikow, Mathematics. In addition to informal interactions with the mentors on a daily basis, there will be formal meetings at least once a week. The student will also be expected to attend the group meetings where broader applications of DSGRN and development are discussed. This will introduce the student to typical activities associated with applied mathematics, mathe- matical biology, and more generally interdisciplinary science. The student will be given access to sufficient computing resources to carry out this effort and will be provided office space with other members of the research group.