BBSI Summer Research proposal

Intro

In our efforts to expand the human understanding of medicine, scientists look to the building block of life as we know it, the cell. On the most basic level the cell dictates the health of the rest of the body. Knowing how to control the inner workings of the cell gives the doctors of tomorrow the best shot of fighting the world’s deadliest diseases. One obvious starting point for such a project, Biological signaling pathways, gives us insight into cell activities including differentiation, migration, or growth. Indeed, understanding of biological signaling pathways has already been successful made in treating many diseases, like chronic myelogenous leukemia. [1] [2].

Biological signaling pathways

Signaling pathways work through the aggregation of protein and ligands binding into complexes that communicate transcription factors and other cell controls [2]. Often the complexes span many states and thus the precise nature of the effect these along the signaling path can be difficult to predict with out the use of mathematics [1]. One method breaks the various reactions in to chemical reactions with substrates products and a reaction rate, and reduces the construction of signaling pathways into a set of ODEs [3]. This method however, generally falls into problems due to the combinatorial explosion in ODEs resulting in all but the simplest pathways, and with known complexes of $10^{19}$, $10^8$, and $10^{23}$ different states one realizes that large complexes are the standard not the
exception [2] [3]. Clearly a new analytical method, which maintains enough detail to be reliable but is also computationally efficient, must be considered [1]. As of today only k-calculus and BioNetGen offer such solutions and my relative distance to BioNetGen make it the practical choice for my research.

BioNetGen

BioNetGen, assembles proteins and ligands into mathematical graphs with a set of “graph-rewriting” rules representing sets of reactions and is capable of predicting system behavior by generating a model of the signaling pathway from a given set of rules and initial species [1] [4]. Additional advantage of the rule based modeling in BioNetGen come with the ease associated with editing and revising models. A new reaction can be incorporated with only a small amount of new code [1]. This being said, BioNetGen still has areas to improve in that I hope to address during my time with BBSI.

Proposal

1. BioNetGen currently lacks the mathematical strictness desired. A formalized language of the terms and relations in BioNetGen would standardize the communication between researching groups and would accelerate the distribution of BioNetGen. Furthermore advances in mathematical strictness give BioNetGen a structure to build theorems and conjectures and increase our knowledge and control of the system.

2. BioNetGen faces a specific problem with infinite state spaces from a set of rules. When confronted with a set of rules BioNetGen fails to recognize that rules generate an infinite set and runs until the computer uses up all the memory and crashes. Once
crashed, one can assume the infinity of their set, but ideally coming to this conclusion could be made without wasting the time and resources of the scientist. Developing and programming an algorithm that would provide a computationally efficient check to size of the space state, will be my primary goal this summer. Initially I would explore the ideas, first described by Vincent Danos, of describing the complexes, finite or infinite, with a finite set of views, the set of radius one neighborhoods around each protein or ligand and then identifying patterns in the set of views to determine if the complex is finite[2].

3. Additional problems of interest include using formal description to describe transformation from system that allows symmetry (shared component names) and one that does not, formalizing existing model reduction algorithms, develop new model reduction algorithm, and exploring topological constraints on complexes [5].
Reference


