An Inverse Problem for Estimating Parameter Models for Mammalian Cell Cycle Entry

Zack Jones[1,2], Zachariah Sinkala[1], and Shawn Garbett[3]

***Short Abstract* — Parameter estimation is an important task in modeling biochemical systems. Our work focuses on studying the Rb-E2F network which has been verified as a critical component in regulating the initiation of DNA replication. In this study, we apply an inverse problem to the Rb-E2F network in an attempt to extract parameter values from experimental data through a Bayesian inference approach. Using these extracted values, we hope to gain insight on the individual activities of the proteins that comprise the Rb-E2F network and their significance in driving cell cycle entry to commitment through the R-point.**

***Keywords* — Parameter estimation; bistable switch; Rb-E2F pathway; cell cycle**

I. Background

Cancer, by definition, is a group of diseases characterized by uncontrolled cell growth and spread of abnormal cells. Our work focuses on studying the Rb-E2F network which has been verified as a critical component in regulating the initiation of DNA replication. It is well known that the control of this pathway is disrupted in virtually all human cancers. Animal cells commit to the cell cycle at the restriction point (R-point), and this point of commitment has been well identified by scientists as being regulated by the Rb-E2F network through a bi-stable switch mechanism [1].

The mathematical model of the Rb-E2F network presented by Yao *et al* contains a combination of 26 different parameters for a system of three ordinary differential equations. A range for each parameter value is provided; we are interested in applying an inverse problem for estimating parameter models for mammalian cell cycle entry. Using observed experimental data and Yao *et al* published model, we attempt to estimate the parameter vales that are representative of the observed data using a Bayesian inference approach. Using these extracted values, we hope to gain insight on the individual activities of the proteins that comprise the Rb-E2F network and their significance in driving cell cycle entry to commitment through the R-point.

[1]Department of Computational Sciences, Middle Tennessee State University

[2]E-mail: zwj2a@mtmail.mtsu.edu

[3]Department of Cancer Biology, Vanderbilt University Medical Center, Quaranta Lab

II. Preliminary Results

We have implemented the model presented by Yao *et al* into MATLAB for computational analysis to confirm that we can achieve resettable bistability for a given set of random parameters by obtaining a time series plot for the output of the Rb-E2F network (EE node) [1]. Over the coming months, we plan to use a Bayesian inference approach and apply an inverse problem to the model presented by Yao *et al* to estimate parameter values based on observed experimental data that produces resettable bistability.

III. Conclusion

Since the model presented by Yao *et al* contains up to 26 different parameters, we feel that it is important to get a sense of the values these parameters hold for a given set of observed experimental data. Through use of Bayesian inference, it is our goal that we will gain better insight on the individual activities of the proteins that comprise the Rb-E2F network by applying an inverse problem to the system.

References

[1] Yao G, Tan C, West M, Nevins JR, You L (2011) Origin of bistability underlying mammalian cell cycle entry. *Mol Syst Biol* **7**: 485