



CALIFORNIA SCIENCE & ENGINEERING FAIR 2019 PROJECT SUMMARY

Name(s) Samuel Alber	Project Number S0804
Project Title Developing and Applying a Novel Stochastic Model to Increase Production of Functional Cardiomyocytes via DNA Methylation	
<p style="text-align: center;">Abstract</p> <p>Objectives Heart disease is currently the leading cause of death throughout the world; however, an upcoming frontier in regenerative involves engineering patient-specific functional cardiomyocytes from induced pluripotent stem cells to treat many forms of heart disease. The goal of this project is to build a novel computational framework capable of describing large gene regulatory networks such as the developmental gene regulatory network within cardiomyocyte. This model is then used to provide novel insight into how DNA methylation perturbations could be used to increase the probability of obtaining a functional contractile cardiomyocyte which will make modern heart tissue engineering approaches more efficient. My hypothesis is that inhibiting global DNA methylation levels will increase the probability of producing a functional cardiomyocyte.</p> <p>Methods Using a MATLAB script, I converted the gene interactions within a known 29-gene cardiomyocyte gene regulatory network into a set of biochemical rules that were then stochastically simulated via BioNetGen. Additionally, I included a parameter responsible for the level of DNA methylation within my network model. I then incorporated the weighted-ensemble method to increase the efficiency of my model through using the WESTPA package in conjunction with BioNetGen. Finally, I ran my model simulations on the High Processing Computing Cluster at the University of California, Irvine, with varying levels of DNA methylation and visualized my large 29-dimensional data set using the t-SNE algorithm.</p> <p>Results The stochastic model coupled with the weighted ensemble method was able to successfully describe the cardiomyocyte gene regulatory network. The level of DNA methylation determined which phenotypes were expressed and at what probabilities. Inhibiting the global level of DNA methylation was shown to cause the network to favor the contractile cardiomyocyte phenotype.</p> <p>Conclusions My model is the first biologically relevant model to demonstrate that global DNA methylation perturbations can be used to increase the production of functional contractile cardiomyocytes, which is crucial in treating many forms of heart disease. Furthermore, my model is the most computationally complex model so far to successfully incorporate the weighted ensemble method. This novel framework can be extended to make other large-scale biochemical models significantly more efficient.</p>	
Summary Statement I constructed a novel stochastic model with the weighted ensemble method that demonstrates how inhibiting global DNA methylation levels could increase the production of functional cardiomyocytes.	
Help Received I met with Professor Read of the University of California, Irvine, weekly to discuss the progress of my project and I met several times with graduate student Cameron Gallivan who helped me with debugging some of my code.	