Creating a Computational Model of the DREAM Complex to Understand the Dynamics of Cardiomyocyte Renewal
(Technical Report)

Presenting the Body Mass Index through a Data Feminism Lens
(STS Topic)

A Thesis Prospectus in STS 4500 Presented to
The Faculty of the School of Engineering and Applied Science
University of Virginia

In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

Catherine Zhao
November 1, 2021

Technical Team Members:
Michelle Wu

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

ADVISORS

Sean Ferguson, Department of Engineering and Society

Jeffrey Saucerman, Department of Biomedical Engineering

Introduction

Approximately every 39 seconds an American will have a heart attack, costing $12.1 billion USD in the U.S. alone (*Heart Disease and Stroke Statistics—2021 Update*, 2021). In the heart, cardiomyocytes are the cells responsible for contracting the myocardium and generating cardiac output (Woodcock & Matkovich, 2005). After a heart attack, or myocardial infarction (MI), there is a progressive death of cardiomyocytes without a counteracting force of sufficient renewal. A pressing issue in the field of cardiology is to identify strategies that enhance adult cardiomyocyte renewal. That is why therapeutic strategies that can target cardiac regeneration are considered the holy grail for cardiologists and pharmaceutical companies.

The field has now identified a number of cell signaling pathways and genes that could stimulate cardiac regeneration. However, these studies by themselves do not provide a framework for prioritization of one pathway or gene over the other. As a result, computational modeling methods are needed to unravel the interplays between various regulators of cardiomyocyte renewal. By knocking down or overexpressing certain genes, proteins, and molecules in the cardiac model, the downstream significance on other nodes can be revealed. Further experimentation that replicates the simulated conditions can provide novel insight into adult cardiomyocyte behavior. The goal of this Capstone project is to develop a computational model that visualizes signaling pathways or complexes to allow researchers to predict targets for cardiomyocyte regeneration.

The STS topic that will be explored in this prospectus surrounds the body mass index (BMI), and how it is a flawed metric that remains in use by both physicians and researchers

today. Although it can lead to misinterpretations of an individual's fatness, the BMI remains the single most cost-effective tool for measuring the obesity levels of a population. However, without knowing the context of the BMI—including but not limited to the history of its invention, popularization, and misconceptions—there can be adverse personal and societal implications.

Any MI patient treated within the U.S. healthcare system could be informed of their BMI. With the continued use of this metric, physicians are contributing to a trend of increased medicalization and over-measurement that has overtaken the traditional physician-patient interaction and led to reduced quality of care (Reilly, 2003). By working towards novel computational modeling tools to improve MI treatment as well as exploring the ways in which data contextualization can challenge the societal narratives surrounding BMI, we can move towards engineering better therapies and solutions for our society.

Technical Report

After myocardial infarction (MI), colloquially known as a heart attack, both necrosis and apoptosis contribute to loss of cardiomyocytes in the myocardium (Orogo & Gustafsson, 2013). This can lead to decreased heart function, since less than half of cardiomyocytes undergo regeneration throughout a person's lifetime (Bergmann et al., 2009). This limited capacity for regeneration and proliferation by adult cardiomyocytes cannot compensate for the significant loss of cardiomyocytes in a single heart attack (Cui et al., 2018). Within the past few years, the dimerization partner, retinoblastoma-like, E2F, and MuvB (DREAM) complex has shown tremendous promise in adult cardiomyocyte regeneration. The DREAM complex plays an

important role in the cell cycle by linking together p130, p107, E2F, BMYB, and FOXM1, coordinating gene repression during G0 and periodic gene expression, especially during G1/S and G2/M transitions. Experiments related to the DREAM complex have found that previously quiescent cardiomyocyte conditions can be shifted towards proliferation, contributing to increased mitotic gene expression levels (Sadasivam & DeCaprio, 2013).

It is known that neonatal cardiomyocytes can undergo regeneration, but recently the field of cardiology has found that adult cardiomyocytes have regenerative capabilities as well, albeit a lot more slowly. Thus, the DREAM complex holds great therapeutic potential post-MI. For this Capstone project, the species and reactions involved in the DREAM Complex will form a computational model in order to provide a framework to unravel the interplays between various regulators of cardiomyocyte renewal. The specific aims of this project are enumerated below:

Aim 1: Create a computational model that helps explain the dynamics of cardiomyocyte proliferation through the DREAM Complex that may lead to cardiac regeneration

A. Define all molecular interactions in the pathway and visualize the network of the model using Netflux, a software for developing dynamic computational models of biological networks using logic-based ordinary differential equations (ODEs)
B. Examine network dynamics by manipulating regulators or nodes through gene knockdown and overexpression

Aim 2: Validate the computational model through comparisons with experimental data in literature

A. Review literature in the fields of cardiology, pharmacology, and systems biology with experimental data
B. Perform sensitivity analysis to examine the model's robustness by comparing knockdown regulators with interconnected regulators in the same pathway
C. Utilize model-driven experimental design to facilitate further cardiac systems pharmacology research

Aim 3: Transition the existing Netflux workflow from MATLAB to Python

A. Recreate the current Netflux framework such that one can import data, simulate the model, and export ODEs for further manipulation and visualization entirely through Python

Currently, the Cardiac Systems Pharmacology Group led by Jeffrey Saucerman, PhD, has created several computational models using Netflux that model cardiomyocyte hypertrophy and death, extracellular matrix remodeling by fibroblasts and macrophages, and cardiomyocyte proliferation. This project is related to the lab's third area of research, cardiomyocyte proliferation. Pre-existing models created by current and former graduate students will serve as examples of the final model for this project. Additionally, this model will be incorporated into a current model of the cardiomyocyte cell cycle that a current graduate student is working on. The final goal for this project is for both models to be published together in Spring 2022.

The author's first role for this project is to perform a literature search to determine the species and reactions of the DREAM complex, as discussed in Aim 1. This information will be

populated into an Excel spreadsheet, imported into Netflux, and exported as ODE code files for graphical visualizations of the reactants over time and the whole model. Aim 1 will be complete by the end of the Fall 2021 semester. As for Aim 2, a more thorough process of model validation will occur in the Spring 2022 semester, and will be a group effort. Finally, for Aim 3, the author has also taken on the responsibility of converting the existing Netflux files from MATLAB to Python. This is because Python is a more universal language than MATLAB for sharing computational models, and the field of computational biology has shifted towards it. Once the code is in Python, more researchers will be able to utilize the Netflux tool. By the end of Fall 2021, the author will have completely converted all existing Netflux code in MATLAB to Python, and others in the Saucerman Lab should be able to start using the new code for their own models by Spring 2022.

STS Topic

The body mass index (BMI) is used to define anthropometric height and weight characteristics in adults and categorize populations into groups. Since its popularization in the 1970s, this metric has formed the basis of collective knowledge about the epidemiology of obesity in the U.S. and abroad. However, on an individual level, BMI is a poor indicator of one's body fat percentage. In particular, BMI does not distinguish between the mass of fat at different locations on the body (Nuttall, 2015). An individual can have a high BMI without having a high percentage of body fat, but for many people – especially women and those of racial and ethnic minorities– having an above average BMI can very easily lead to negative body image and mental health. Despite its drawbacks, such as misdiagnosis of comorbidities, BMI has largely

remained in use for 50 years by many medical professionals, health researchers, and governmental agencies, likely because it is the most simple and cost-effective metric for tracking obesity at the population level (Gutin, 2018).

Thus, when presenting an individual's BMI, the individual should also learn the context surrounding this metric, such as its limitations and the context in which the data was collected. According to D'Ignazio and Klein, the data feminism framework asserts that "data are not neutral or objective. They are the products of unequal social relations, and this context is essential for conducting accurate, ethical analysis." In today's age when data can be found virtually everywhere, D'Ignazio and Klein describe taking a feminist approach: Data must be examined alongside its context to realize the differentials of power and the misaligned collection incentives that are almost always built into data, but not often taken into account (D'Ignazio & Klein, 2020). BMI is one notable example of this, since it is still used by doctors today despite its questionable origin and tendency to be presented without context. In this paper, the data feminism framework will be applied to explore the personal and social implications that our society faces as a result of the mainstream use of the BMI in medical practice. Then, this paper will explore how doctors and patients alike can work together to challenge the use of BMI data sans contextualization and ensure that it is always presented alongside its context so it is not misunderstood.

Physicians have used BMI as a risk factor for the onset of several health-related issues, such as Type II diabetes, hypertension, and even asthma (Pantalone et al., 2017; Scott et al., 2012). Researchers have used BMI for population studies due to its wide acceptance of defining

categories of body mass as a health issue. While the BMI's usefulness on a population level has been established, its limitations on a doctor-to-patient level can be explored further. The diagnostic characteristics attached to BMI are the result of BMI as a measure becoming confounded with 'healthy weight' as a societal ideal. Since the evidence-based medicine movement that began in the 1960s, the desire to quantify a patient's body and locate numbers on a chart can lead to simple diagnoses and new developments being overlooked, while tests, consultations, and procedures that might not be needed are ordered. This reflects the increased medicalization and over-measurement that has slowly overcome the traditional physician-patient interaction and led to reduced quality of care (Reilly, 2003).

This is not to mention that the BMI was invented by the white, male Belgian statistician Lambert Adolphe Jacque Quetelet at the turn of the 19th century, who used it as a statistic that could be applied towards populations, not individuals. Quetelet hoped to determine the 'average' man, and formulated the Quetelet formula, which is now known as the BMI. Even more, the statistician cited this metric as a measure of one's fitness to parent, and thus a scientific justification for eugenics (Humphreys, 2010).

Research into the necessary context of the BMI in contemporary medical practice through a data feminism lens is an important area of research for groups that the BMI was not designed for, and continues to fail to take into account. Thus, such a glib understanding of BMI can be harmful to the health of a significant proportion of patients in the U.S. healthcare system. Both literature-based and empirical evidence will be used to develop strategies to challenge the use of BMI, including ways in which the provider can alter the clinical environment to bypass negative

social stigmas surrounding high BMI as well as how the patient can be empowered in discouraging situations to attain high-quality health care.

Next Steps

The specific aims are enumerated in the Technical Report above. Aims 1 and 3, which relate to creating the model itself and converting the Netflux software from MATLAB to Python, respectively, will be completed before the end of the Fall 2021 semester. Aim 2, which involves validation of the computational model, will be an involved process that involves in-depth literature review and potentially wet-lab experiments for which there is insufficient literature online related to cardiomyocytes specifically (as opposed to evidence for cancer cells instead). Additionally, this model will be published alongside a model for the cardiomyocyte cell cycle that a current graduate student is working on. The DREAM complex model for this project will be incorporated into the larger model, and both will be published together.

Finally, the rightmost column details the STS-related deliverables and due dates, with the items for STS 4600 in the Spring 2022 semester still to be determined. Further exploration of the themes presented in the prospectus will be determined, and evidence from epigenomic case studies and case studies that link the use of BMI and mental health will be explored.

Date	*Capstone*	*STS*
End of Fall 2021 Semester	• Complete Aims 1 and 3	• Complete Draft Prospectus • Peer Review of Two Draft Prospecti • Complete Final Prospectus • Present STS Research Project
End of Spring 2022 Semester	• Complete Aim 2 • Publish model alongside cell cycle model	• TBD

References

Bergmann, O., Bhardwaj, R. D., Bernard, S., Zdunek, S., Barnabé-Heider, F., Walsh, S., Zupicich, J., Alkass, K., Buchholz, B. A., Druid, H., Jovinge, S., & Frisén, J. (2009). Evidence for cardiomyocyte renewal in humans. *Science (New York, N.Y.)*, *324*(5923), 98–102. https://doi.org/10.1126/science.1164680Cui, B., Zheng, Y., Sun, L., Shi, T., Shi, Z., Wang, L., Huang, G., & Sun, N. (2018). Heart Regeneration in Adult Mammals after Myocardial Damage. Acta Cardiologica Sinica, 34(2), 115–123. https://doi.org/10.6515/ACS.201803_34(2).20171206A

D'Ignazio, C., & Klein, L. (2020). 6. The Numbers Don't Speak for Themselves. In Data Feminism. https://data-feminism.mitpress.mit.edu/pub/czq9dfs5/release/3

Gutin, I. (2018). In BMI We Trust: Reframing the Body Mass Index as a Measure of Health. Social Theory & Health : STH, 16(3), 256–271. https://doi.org/10.1057/s41285-017-0055-0

Heart Disease and Stroke Statistics—2021 Update. (2021). https://doi.org/10.1161/CIR.0000000000000950

Humphreys, S. (2010). The unethical use of BMI in contemporary general practice. The British Journal of General Practice, 60(578), 696–697. https://doi.org/10.3399/bjgp10X515548

Nuttall, F. Q. (2015). Body Mass Index. Nutrition Today, 50(3), 117–128. https://doi.org/10.1097/NT.0000000000000092

Orogo, A. M., & Gustafsson, Å. B. (2013). Cell Death in the Myocardium: My Heart Won't Go On. IUBMB Life, 65(8), 651–656. https://doi.org/10.1002/iub.1180

Pantalone, K. M., Hobbs, T. M., Chagin, K. M., Kong, S. X., Wells, B. J., Kattan, M. W.,

Bouchard, J., Sakurada, B., Milinovich, A., Weng, W., Bauman, J., Misra-Hebert, A. D., Zimmerman, R. S., & Burguera, B. (2017). Prevalence and recognition of obesity and its associated comorbidities: Cross-sectional analysis of electronic health record data from a large US integrated health system. BMJ Open, 7(11), e017583. https://doi.org/10.1136/bmjopen-2017-017583

Reilly, B. M. (2003). Physical examination in the care of medical inpatients: An observational study. Lancet (London, England), 362(9390), 1100–1105. https://doi.org/10.1016/S0140-6736(03)14464-9

Sadasivam, S., & DeCaprio, J. A. (2013). The DREAM complex: Master coordinator of cell cycle dependent gene expression. Nature Reviews. Cancer, 13(8), 585–595. https://doi.org/10.1038/nrc3556

Scott, S., Currie, J., Albert, P., Calverley, P., & Wilding, J. P. H. (2012). Risk of misdiagnosis, health-related quality of life, and BMI in patients who are overweight with doctor-diagnosed asthma. Chest, 141(3), 616–624. https://doi.org/10.1378/chest.11-0948

Woodcock, E. A., & Matkovich, S. J. (2005). Cardiomyocytes structure, function and associated pathologies. The International Journal of Biochemistry & Cell Biology, 37(9), 1746–1751. https://doi.org/10.1016/j.biocel.2005.04.011