Functional Specification

1. **Background to area of interest.**

Crossbridge cycling is one of the most conserved biochemical processes in mammalian biology. This complex biomechanical cycling involves the interactions of multiple sarcomeric proteins, each having their unique activation and deactivation kinetics. Here, I will be highlighting the beautifully efficient dance that induces heart contraction through the development of my Model Verification tool, MyosinCK, to visualize the many steps taken in sarcomeric contraction. This model will focus on the concentrations, binding affinities, and enzymatic rate constants of the following proteins/ small molecules: Actin, Myosin, Actomyosin Complex, ADP, and ATP. These values will be derived from their cardiac isoforms found in the literature. The goal of this program is to establish a visualization tool tailored to describing cardiac-specific muscle dynamics and how the alterations of parameters mentioned above (due to disease mutations, drug therapies, etc.) can impact the efficiency of muscle dynamics. The proposed program pipeline is as follows:

1. Formulate Python code describing and visualizing the cardiac crossbridge cycling of wild-type cells.
    a. These rates will be pulled from biophysical and structural biology literature.
    b. This will produce a graph of all products accumulated and used over time. I will also create and save separate graphs of each product for comparison when a turbulent is introduced into the system.
        i. This is important as mutations or drug therapies are not garunteed to effect every part of the crossbridge cycle.
2. Identify SARCOMERIC DISEASE CAUSING MUTATIONS and how alterations in protein concentration/ binding affinities reflect these rates.
    a. HCM mutation: R403Q
    b. DCM mutation: S532P
3. Identify how FDA approved/ in development drug therapies act to correct disease phenotype.
    a. HCM: Mavacamten
    b. DCM: Omecamtiv Mecarbil

This work has great promise as a foundational visualization tool for it's user friendly interface as well as possible adaptation to the field of muscle biology. These rates and concentration may be altered for the field of skeletal muscle research as these muscles share identical proteins but different isotopes.

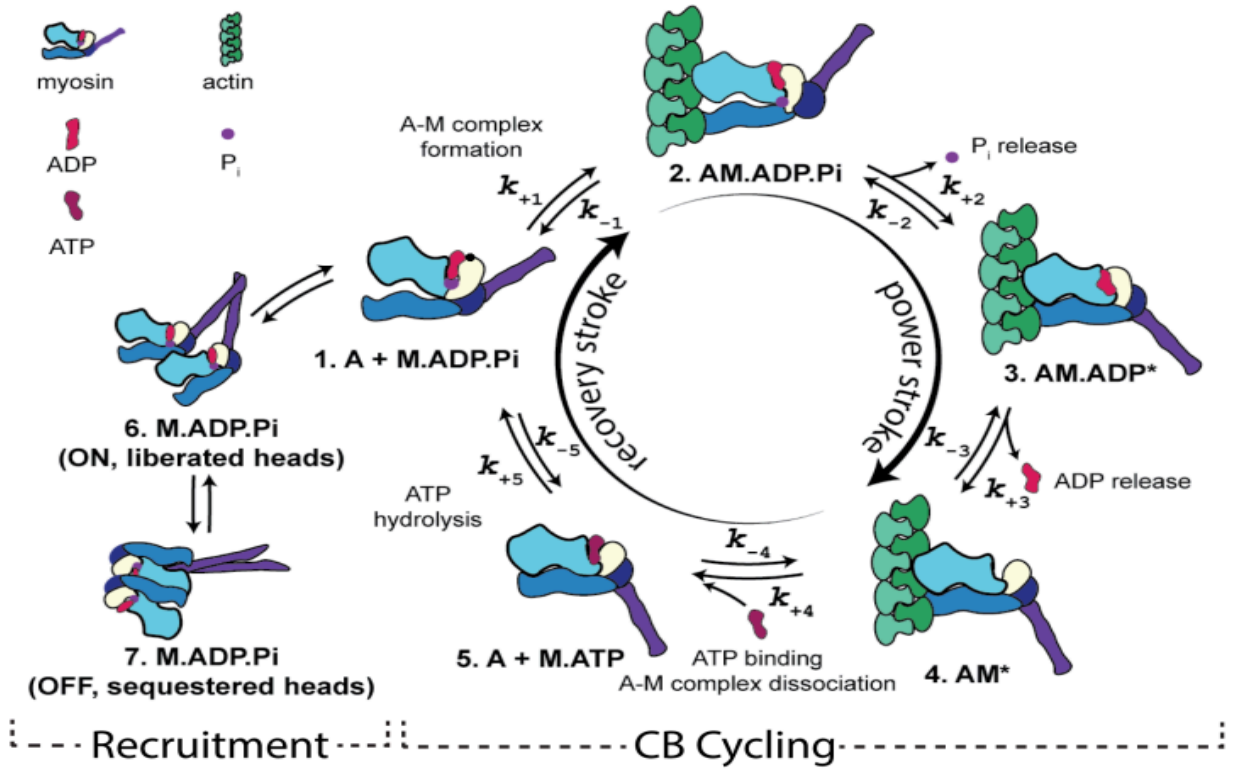

Figure 1: Actomyosin Crossbridge Cycling. The proposed model verification tool will breakdown this complex interaction into simple data visualizations that can be used as controls for mutation/ drug applications.

2. User Profile

This software package will be useful for structural biologist that specialize in in-silico modeling. This group will have extensive knowledge in computer software and will be able to utilize this code as a proof of concept as it probes how changes in protein concentration/ availability, equilibrium rates, and ATP can alter crossbridge cycling dynamics. This could be used in parallel with clinical data in hopes of response curves matching with disease phenotypes. For example, hypercontractility caused by HCM disease causing mutations would perhaps show slower myosin release (larger slope) as a result of higher myosin concentration.

3. Use Cases

As explained above in a more global scope, this program will be capable of the following tasks:
- Calculates the slopes in varying enzymatic reactions with differing concentrations over time
- Create a dose-response curve for myosin-targeted therapies that affect myosin activation, constant rates, etc.
- Creates a 2 2-dimensional plot for each specialized parameter model run. This can be done by altering constants and pushing concentrations together.