I spent this summer working in the Computational Biology and Complex Systems Lab in the Department of Physics at the Polytechnic University of Catalonia in Barcelona, Spain. Here, I was exposed and involved in an interesting area of cardiovascular research as well as exposed myself to a new subset of research in general. By exploiting more computational and mathematical techniques, I am able to translate these skills into my current and future research endeavors.

Alongside Professor Blas Echebarria, I assisted in developing mathematical models of the cAMP-PDE signaling pathway in atrial myocytes in atrial fibrillation (AF) risk variant rs13143308T. We organized my time in the lab into four different parts: 1) a bibliographic search of mathematical models of cAMP signaling in, preferentially atrial, myocytes, 2) implementing several of those models into a computer framework, 3) studying how the system behaves for different sets of parameters, and 4) studying the consequences for AF due to these varied conditions. Our overall goal was to identify what conditions and concentrations of major regulators of the cAMP-PDE pathway dramatically impacted the AF.

I began with understanding each component making up the cAMP-PDE pathway in AF. From reading various literature, I came to understand that the adenosine receptor agonist (A_2A) upregulates cyclic-AMP (cAMP), which in turn phosphorylates/activates PKA. This enzyme then phosphorylates the RyR2 receptor to let in more calcium into the sarcoplasmic reticulum. This is all important to note as the specific risk type focused on in this research has a dysfunctional/high calcium concentration. With this in mind, A_2A has been seen as a model of this risk type. However, it was interesting to find that the risk type had the same amount of RyR2 but differed in its phosphorylation amounts to produce more calcium, indicating that this might be independent of A_2A. Another factor that may be contributing to this is phosphodiesterase (PDE), which contributes to the breakage of cAMP to AMP. However, A_2A and PDE do form a macromolecular cluster together, so what my lab currently focuses on is studying how this macromolecular cluster affects calcium levels with spatial resolution models.

In order to contribute to this research and extend off this topic, I was tasked to identify these parameter values upon different conditions, for example when a certain enzyme is low in concentration, via MatLab. With this, I conducted additional literature reviews to identify and develop new differential equations and other mathematical models that represented these concentrations as well as their rate of phosphorylation and constants like the Michaelis-Menten constant to represent this pathway. The proteins studied include [PDE], [ATP], [A_2AR], [AC], [cAMP], [$PKA_{inactive}$], [PKA_{active}], [$RyR2_{inactive}$], and [$RyR2_{active}$].

Then, I learned how to input these formulas and concentrations into MatLab. I used the method of trial and error as well as discussions with Professor Echebarria to understand which variables were best to include in the model, which parameters were to be kept constant, and which proteins were helpful in the output of the model. With more and more trials of this model, it became clearer that the model was always going to be underdetermined. However, I came to realize that the goal was less for certain exact quantitative estimates but more for how ranges of

values/concentrations for certain proteins changed the output of the model as a whole in distinguishing ways.

While this model was more for the use of my peers alongside their spatial resolution displays of these pathways, it was interesting to see how this information of this pathway can be collected and represented. It was definitely interesting to be able to represent concentrations and these protein amounts within these differential equations and create a system of differential equations which made these concentrations dependent on each other. This tied everything up nicely and definitely served as a good skill builder for my current research at Feinberg.

I can now apply these skills to the concentrations of SERPINE1 mRNA binding protein 1 (SERBP1) to the plasminogen activator inhibitor type-1 (PAI-1) as well other proteins involved in regulating PAI-1 in cardiac fibrosis models. This will help me further uncover the mechanisms in which these proteins regulate each other and contribute to age-related cardiac fibrosis. Furthermore, adding the complexity of the prion-like abilities of this mRNA binding protein make these skills even more helpful: I can model the speed in which the β–structures analogous to the fibrils in traditional prion diseases, formed by SERBP1 analogs, form and produce a form of epigenetics beyond the chromosome.