**Implementation of Terkildsen et al. (2007) Model**

**Introduction:**

We successfully implemented Rodriguez et al. (2002) model [1] earlier where authors claimed KATP channel is primarily responsible for extracellular K accumulation. In this study, we are dealing with Terkildsen et al. model (2007) [2]. In this model, authors claimed that sodium-potassium (Na-K) pump is responsible for the major K accumulation in the extracellular space and argued that KATP cannot account for the biggest proportion of K accumulation. Hence they focused on the dominant mechanisms acting within early ischemic, namely the roles of the Na-K pump, KATP channel, and changing cellular volume in the development of the triphasic profile. Our goal here is to implement Terkildsen et al.’s model and reproduce some of the plots of their paper. Our ultimate goal is to compare the Terkildsen et al. and Rodriguez et al models by examining the challenge-response behavior of cardiac tissue to ischemia.

**Method:**

Terkildsen et al. developed a model based on the Luo-Rudy dynamic (LRd) [3] modeling framework of guinea pig cardiomyocyte with the modification and development in Na-K pump, KATP channel, and volume regulation model. They used the updated form of the Smith-Crampin model (2004) [4] to represent Na-K pump. Smith-Crampin model represents the 15 states of the Post-Albers cycle and is responsive to both intracellular and extracellular sodium and potassium concentrations, transmembrane potential (Vm), and different metabolite concentrations including intracellular ATP, ADP, Pi (inorganic phosphate), and hydrogen. Michailova et al. model (2005) [5] is used to represent the ATP-sensitive potassium current. It describes the biological interactions between channel subunits and ligands such that channel conductance is dependent on the concentration of ATP, ADP and [K]e. A comprehensive model of cell volume regulation is implemented to account for the shrinkage of extracellular space. To create a mathematical description of the metabolite concentration (a model of ischemia), they used metabolite data obtained from the guinea pig P NMR spectroscopy experiments of Befroy et al. (1999) [6] during 15 min of ischemia. Ischemia alters the metabolite time courses of intracellular ATP concentration, P, PCr (phosphocreatine), and pH, thereby affecting the KATP channel and Na-K pump.

**Results:**

We run the program for 1000 sec and get the steady-state normaxic condition. Our steady state values are slightly different than Terkildsen et al.’s steady state values. Under normaxic conditions, the extracellular ion concentrations are fixed.

The cell model is then paced with the period of 300 ms using a potassium current stimulus of 15 μA/μF for 0.2 ms. For our study, we run the simulation for a minute under normaxia before we apply ischemia for 15 minutes. During ischemia, extracellular ion concentrations are varied dynamically and the concentrations of the metabolites are changed in the time dependent manner as shown in Figure 1.

Figure 1: Reproduction of Figure 5 in Terkildsen et al. (2007) paper. Phosphocreatine (PCr; A), ATP (B), intracellular PH (PHi; C), ADP (D) and inorganic phosphate (Pi) are calculated during 15 minutes of ischemia.

Figure 2 demonstrates the potassium accumulation in the extracellular space when all the condition (except volume regulation) of ischemia is imposed in the cell model. It shows the triphasic accumulation of extracellular K during myocardial ischemia.

Figure 2: Reproduction of figure 6(A) of Terkildsen et al. (2007) paper. It shows the extracellular K concentration during 15 min of myocardial ischemia.

Figure 3 illustrates the action potential duration (90% repolarization) during 15 minutes of myocardial ischemia. Our APD is relatively shorter than the APD showed in Figure 6(A) of Terkildsen et al.’s model.

Figure 3: Reproduction of Figure 7(A) from Terkildsen et al.’s (2007) paper. The figure shows the action potential duration as function of time.

Figure 4 shows the Na-K pump current as function of time which is responsible for extracellular K accumulation and its triphasic nature.

Figure 4: Figure showing INa-k vs time. This is not exact representation of Figure 8 from Terkildsen et al.’s paper because they took average pump current (% normoxic).

**Conclusion:**

We successfully implemented and reproduced Terkildsen et al. (2007) model to find the triphasic accumulation of extracellular potassium concentration ([K]e) during myocardial ischemia.

**References:**

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