Project Title: Theoretical study of $Ca^{2+}$ ion dependent cardiac thin filament activation using opened Ising chain with nearest-neighbor cooperative interaction.

Project Acronym: CaCTFI

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**Project summary** [600 words]: The cardiac thin filament activation process is currently open problem in regard of theoretical description. Several studies have been made on the actin-myosin cross-bridges in myosin fiber. Yet only a few considered a dependency of myofilament activation on concentration of $Ca^{2+}$ ions. Presence of $Ca^{2+}$ ions in troponin-tropomyosin complex significantly improves chance of muscle filament contraction. 1D Ising model, which describes cardiac thin muscle fiber as a sequence made of 26 troponin-tropomyosin units was first time introduced by Rice et al. (Rice et al., 2003). Our aim is to improve the theoretical model by discarding periodic boundary approximation, which is in discrepancy with physiological description of cardiac muscle thin filament. We will show a method, which will allow us to calculate contraction force of cardiac muscle thin filament with open boundaries. With experimental data provided by work of Dobesh et al. (Dobesh, 2001). we will look for optimal set of parameters for our improved model.

**EXCELLENCE**

**Present state of subject** [800 words]:
Experimental evidence shows cooperativity between neighboring cross-bridges so that an attached cross-bridge may facilitate binding of nearby cross-bridges. One possible mechanism is that strongly bound cross-bridges hold the tropomyosin in permissive conformation to facilitate attachment of nearby cross-bridges. For example, in vitro studies suggest that binding of isolated myosin heads can produce activation of the thin filament even in the absence of Ca (Bremel and Weber, 1972; Swartz and Moss, 1992; Trybus and Taylor, 1980). Also, the forces from a bound cross-bridge may produce significant realignment of actin-binding sites along compliant thick and thin filaments to increase the binding of nearby cross-bridges (Daniel et al., 1998). Another proposed cooperative mechanism involves end-to-end interactions of the regulatory troponin/tropomyosin (T/T) units along the thin filament. The T/T units overlap by several residues, a feature thought to mediate end-to-end interactions that increase apparent cooperativity (Johnson and Smillie, 1977; Pan et al., 1989). There have been many attempts to model cardiac myofilaments based on one or more of the cooperative mechanisms (Dobrunz et al., 1995; Landesberg and Sideman, 1994; Razumova et al., 2000; Rice et al., 1999; Zou and Phillips, 1994). Unfortunately, many of the modeling efforts are hampered by the paucity of direct experiment estimates of the cooperative mechanisms, especially with regarding nearest-neighbor cooperative effects (Razumova et al., 2000; Rice et al., 1999). Moreover, the models fail to reproduce basic cooperative behavior as characterized by F-pCa relations. Specifically, the models have failed to provide a framework to understand why F-pCa relations are closely approximated by Hill functions and why Hill plots show two slopes (Dobesh, 2001). Work by Rice et al. addresses these issues by proposing a model of cardiac thin filament activation using an Ising model approach from equilibrium statistical physics.

Similar Ising models published previously have focused on simulating cooperative binding of S1 myosin heads to skeletal muscle, a related but critically different manifestation of thin filament cooperative behavior (Hill et al., 1980; Tobacman and Butters, 2000). 1D Ising model introduced by Rice (Rice et al., 2003) shows good result with comparison to experimental data. To use transition matrix method, a periodic boundary approximation was proposed. However, periodic boundary condition disregards finite size and open boundaries of the cardiac muscle thin filament. Our further work will focus on improving their model by discarding periodic boundary condition and describing randomness of states of the statistical model using information entropy.

**Scientific goal(s)** [400 words];
Aim of this proposal is to improve simple descriptive model of dependence of thin filaments contraction on concentration of $Ca^{2+}$ ions. The model together with experimental data should provide us more detailed picture of heart muscle fibers on microscopic scale and role of the $Ca^{2+}$ ions in the contraction mechanism. We will show a method, which allows a choice of open boundaries within the theoretical model used for a computation of a normalized contraction force of a cardiac muscle thin filament.

**Research methodology** [500 words]:
Processes present in thin filament are commonly described by kinetic (4-states Markov) model, which describes transition processes occurring on each troponin-tropomyosin (further only T/T) unit, such as $Ca^{2+}$ binding and releasing and changing conformational state of the unit. However, this model does not provide information about the filament behavior. If an assumption is made, that the number of T/T units in permissive state is proportional to normalized contraction force of the filament, we can introduce a Hamiltonian describing cardiac thin filament as an Ising-Lenz 1D model. Then a probability, that the thin filament can be found in a specific configuration is proportional to Boltzmann weight. The probability is normalized to the partition function, which is often found using transition matrix method. For usage of transition matrix method, a choice of periodic boundary condition is made, and partition function can be found in a form of trace of the transition matrix with eigenvalues to the power of number of T/T units in thin filament.
This approach is used in models when number of units are large, and the effect of the boundaries is negligible. However, for a small number of units such as 26 it is no longer true. We can expect that the ends of the filament will have different contribution to the total contraction force. We will show how partition function can be found using transition matrix but with open boundaries.

**IMPACT OF RESEARCH**

**Enhancing the potential and future career prospects** [400 words]:
In my previous work I was mainly focused on statistical model applications on various biological systems in equilibrium. Support of this proposal will provide me an opportunity to further broaden my knowledge in this topic. The obtained results presented on conferences could help us find potential collaborators with expertise in this field, if possible, with an ability to execute a detailed experiment. With twenty years of progress in experimental technology and methodology, the measurement of cardiac thin filament contraction force could provide us more precise data. Furthermore, new measurement methods were developed, which are able to measure correlations of muscle nodes contraction, which could give us more insight on cooperativity effects in cardiac muscle thin filament.

**Exploitation and dissemination of results** [400 words]:
From perspective of biology we acquire a rather simple model. The proposed model should describe Ca ion dependent process of cardiac thin filament activation with a good agreement with the experiment.
In statistical physics in order to compute partition function, many works have to assume periodic boundary condition or propose thermodynamical limit (sending number of units to infinity). We will introduce approach of improved transfer matrix method, which can discard this approximation and make the computation more exact.

**IMPLEMENTATION**

**Work plan and tasks** [600 words]:
In the first step we will focus on understanding of thin filament physiology and its activation process and the role of Ca cation. In the second step will analytically compute the statistical quantities such as mean values and correlation functions. In the third step we will look for a method for finding new set of parameters, for which would model give us good agreement with experiment. Next, we will compare results for periodic and open boundary condition and analyze corresponding Shannon's entropies for both cases. In the final step, if the results will be satisfactory, they will be refactored to the publishable article. With this workflow intervened with our other projects we can estimate whole process to take approximately one and half year.

**Risk management** [400 words]:
We expect possible problems when finding optimal set of parameters for our model using experimental data. The method for finding new parameters can be computationally demanding and we yet do not know if the comparison with the experiment will be satisfactory.
Then next question is if 26 T/T units will create noticeable effect of the open boundaries.