Modeling of cardiac muscle contraction regulation at the mesoscale: a combined experimental and theoretical approach

Masters' internship and PhD thesis proposal

Within the project **MesoCardio**, funded by PEPR MATHS-VivES.

Position between MSME, Université Paris-Est Créteil (France) and PhysioLab, University of Florence (Italy), under the supervision of Matthieu Caruel at MSME, jointly with Marco Linari and Pasquale Bianco at the PhysioLab.

Starting date: April 2026 for the internship, October 2026 for the PhD thesis.

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The MesoCardio project

The PhD is part of a large-scale initiative: the MesoCardio project. This project sets an interdisciplinary consortium to develop models of the cardiac contraction at the mesoscale, aiming at understanding the physiological mechanisms behind the regulation of the contraction. The consortium involves three mathematics labs (CERMICS, École nationale des ponts et chaussées; CMAP, École polytechnique; MΞDISIM, Inria Saclay), one biomechanics lab (MSME, Université Paris-Est Créteil) and one physiology lab (PhysioLab, University of Florence). The work program encompasses statistical mechanical modeling, mathematical analysis of stochastic systems, non-linear continuum mechanics and homogenization, the development of innovative numerical methods, and experiments both in situ and on in vitro biomimetic nanosystems.

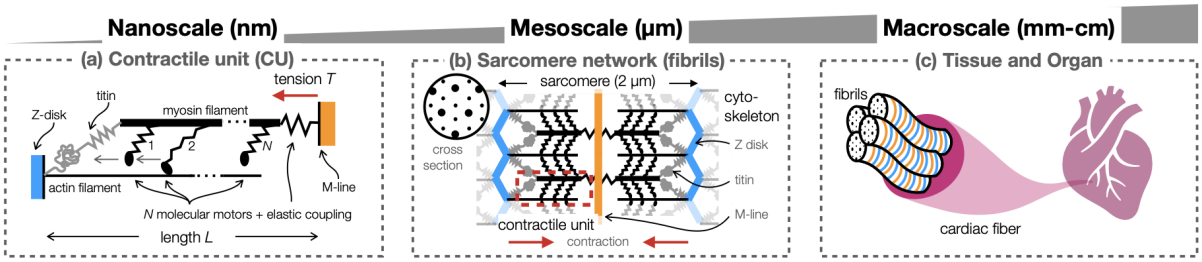

Figure 1: General context of the project. Muscle contraction is generated at the nanoscale by coupled molecular motors forming contractile units (a). These units for a regular network at the mesoscale (b), that constitutes the contractile apparatus of the tissue at the macroscale (c).

Muscle contraction and its regulation

Muscle contraction is generated by ATP-driven nanoscale molecular motor proteins assembled in contractile units [Fig. 1 (a)]. These motors emerge from myosin (thick) filament and pull on surrounding actin (thin) filaments. At the mesoscale, the contractile units form a chain of sarcomeres supported by elastic cytoskeletal proteins [titin, M-line, Z disks, see Fig. 1 (b)]. This network is the main constituent

of the muscle fibers at the macroscale [Fig. 1 (c)]. The sarcomere activity is controlled by a dual filament regulation: rapid Ca^{2+}-dependent thin filaments activation, making actin sites available for myosin binding, and stress-dependent myosin filament activation, adapting to load and recruiting myosin motors from their energetically convenient OFF state [3, 6]. Other accessory and cytoskeleton proteins like titin also control the regulatory state of the thick filament, by inducing positive mechanical feedback [7, 4]. Mutations in regulatory proteins on thin or thick filaments cause filament activation deterioration, leading to myopathies and heart failure.

Currently, most mechanical models of the muscle tissue do not take into account the mesoscale level, and directly couple nanoscale mean-field-type molecular motor models with macroscale continuum mechanics balance laws. This approach is insufficient to model systems with low number of motors (fluctuations), and to understand the contraction regulation mechanisms. The MesoCardio project aims at developing mathematical models able to capture these phenomena operating at the mesoscale.

The project has three main objectives, organized in work packages (WP):

WP1. Develop a model reduction strategy to derive an effective model of a finite size contractile unit with several motors. This model can be used to represent in an efficient way biological situations with a low number of motors involved (e.g. during activation) or specific in vitro experiments.

WP2. Use a combined experimental and modeling approach to formulate a model of interacting contractile units incorporating the molecular mechanisms regulating cardiac muscle contraction and related myopathies. The reduced formulations from WP1 can be implemented in this model to reduce the simulation cost.

WP3. Propose an homogenized formulation of this network of contractile units to be coupled with macroscopic balance laws in the framework of continuum mechanics.

Regulation mechanisms within contractile units network: Experiments and Modeling

The internship and PhD project is at the core of WP2 with strong interaction with WP1. The objective is to define and model thick filament regulation mechanisms in cardiac muscle and their alterations in myopathies. The model should also describe mechanisms involved in cooperative thin filament activation by Ca^{2+} and cardiomyopathy caused by regulatory proteins mutations. The research work will be carried between MSME, for the modeling part, and the PhysioLab, for the experimental part.

The tasks in this PhD work are:

1. Formulate a mechanical model of the cytoskeletal proteins (titin) at the level of a single contractile unit by drawing from the models introduced in Refs. [1, 2], see Fig. 1(a).

2. Conduct experimental studies to characterize the regulation mechanisms operating at the level of interacting contractile units, see Fig. 1(b). These experiments will be performed (i) on intact or demembranated myocytes by combining sarcomere-level mechanics and synchrotron-light small angle X-ray diffraction [3, 6], and (ii) in vitro on a re-assembled myosin-based synthetic nanomachine tested with a Dual Laser Optical Tweezers setup [5].

3. Use the data gathered from the two kind of experiments to feed a model of interacting contractile units that incorporate mechanical feebacks in regulation mechanisms.

Organization of the work

The 6-month Masters' internship will essentially be dedicated to the understanding of the stochastic modelling of contractile units, and on learning basic muscle regulation physiology. The work with then alternate between MSME (Créteil, France) and the PhysioLab (Sesto Fiorentino, Florence, Italy), with a stays of about 6 months in each institution. The project will provide funding for travel and accommodation expenses during the stays in Italy.

The MesoCardio project is strongly interdisciplinary. The person recruited will interact with the doctoral candidate who will work in parallel on the formulation of mathematical and numerical methods for deriving reduced contractile units models (WP1). The results of WP2 will benefit from the model reduction strategy developed in WP1 and, in return, the person recruited on WP2 will provide physiological background and corresponding modeling elements to be included in WP1's model reduction pipeline.

Candidate profile

Candidates should be in the process of completing a Master's degree (M2) or an equivalent qualification in mechanical engineering, biomechanics or physics. Some experience in statistical mechanics and stochastic processes will be appreciated. Familiarity with programming in Python, particularly for scientific computing, is also required. No prior knowledge of biology or physiology is necessary; however, candidates should demonstrate a genuine interest in the project's experimental and applicative aspects.

Practical aspects

The MSME laboratory is located on the UPEC central campus in Créteil (20 min from downtown Paris by metro). In Italy, the PhysioLab is located in the department of biology in the Sesto Fiorentino scientific campus of UNIFI (30 min from downtown Florence). The gross monthly salary is about 600 € for the internship, and 2300 € for the PhD thesis.

References

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