Machine learning of multiscale active force generation models for the efficient simulation of cardiac electromechanics

Regazzoni, F.; Dede’, L.; Quarteroni, A.
Machine learning of multiscale active force generation models for the efficient simulation of cardiac electromechanics

F. Regazzoni¹, L. Dedè¹, and A. Quarteroni¹,²

¹MOX - Dipartimento di Matematica, Politecnico di Milano, P.zza Leonardo da Vinci 32, 20133 Milano, Italy
²Mathematics Institute, École Polytechnique Fédérale de Lausanne (EPFL), Av. Piccard, CH-1015 Lausanne, Switzerland (Professor Emeritus)

Abstract

High fidelity (HF) mathematical models describing the generation of active force in the cardiac muscle tissue typically feature a large number of state variables to capture the intrinsically complex underlying subcellular mechanisms. With the aim of drastically reducing the computational burden associated with the numerical solution of these models, we propose a machine learning technique that builds a reduced order model (ROM). In our approach, the latter is obtained as the best-approximation of the HF model within a class of candidate models represented by means of Artificial Neural Networks (ANNs). The ANN is trained to learn the dynamics of the HF model from input-output pairs generated by the HF model itself from which the ROM is built in a non-intrusive (black-box) way. Moreover, the learning machine is informed with some a priori knowledge on the HF model, in a semi-physical (gray-box) way. A drastic reduction in both computational cost and memory storage is achieved with respect to the HF model. This is crucial when performing numerical simulations of the cardiac function, that is when active force models are exploited in the multiscale problem of cardiac electromechanics. As a matter of fact, we achieve a computational speedup of about one order of magnitude, while preserving almost the same accuracy of the HF solution.

Keywords Data-driven modeling, Machine Learning, Model Order Reduction, Cardiac simulations, Sarcomere modeling, Artificial Neural Networks

1 Introduction

Numerical simulations of the cardiac function require coupling different mathematical models representing processes taking place at different spatial scales [78, 76, 30, 68, 37, 16]. Cardiac tissue mechanical activation, which is responsible for the generation of active force and for the contraction of the myocardium, is driven by a subcellular mechanism with characteristic spatial scales of micrometers or less. Hence, when the target is a three-dimensional Finite Element simulation of the heart integrated function [77, 17, 91, 22], like for cardiac electromechanics, the mathematical model describing the activation of the cardiac contractile cells should be solved virtually in any point of the computational domain and practically at each nodal point or at every quadrature node of the computational mesh. Since capturing the complexity of realistic heart models requires as many as $10^5$–$10^6$ mesh elements, the computational complexity may dramatically become an issue, both because of computing time and memory storage.

Moreover, the intrinsic complexity of the subcellular processes leading to the mechanical activation of the tissue makes difficult to build activation models, namely systems of ODEs, featuring a reduced dimension without compromising the richness of the most detailed models; see e.g. [88, 85, 98]. This harms the accomplishment of a well balanced trade off between model computational complexity and model reliability.

In this paper, we propose a multiscale approach to cardiac electromechanics (EM) wherein active force generation at the subcellular level is modeled by a ROM built by means of Artificial
Neural Networks (ANNs). We aim at reducing the computational burden associated to EM of the heart wherein complex sarcomere models should be used for accurate simulations. We show, both qualitatively and quantitatively, that our approach and our reduced model realize a very good trade-off between computational efficiency and accuracy.

We build the ANN-based reduced model by enriching the method proposed in [84], which is a fully black-box approach. The latter, indeed, does not require any knowledge of the high-fidelity (HF) model but only a collection of input-output pairs generated by the HF model. In this work, we move instead towards a grey-box approach (or semi-physical approach), by feeding the ANN learning process with some a priori knowledge on the HF model: we employ this method to reduce the dimensionality and the computational complexity of the cardiac activation model proposed in [83] and we compare the results of simulations performed with the HF and the reduced model.

The paper is organized as follows. In Sec. 2 we briefly review the mechanism of cardiac force generation and the associated mathematical models, highlighting the difficulties in finding a low dimensional model for this process. Then, we review the available literature on the reduction of computational complexity of activation models. In Sec. 3 we recall the activation model proposed in [83], which we consider here as the HF model to be reduced and, in Sec. 4, we present the reduction strategy. In Sec. 5 we provide the technical details on the ANN training, we show the results obtained, and we validate the ANN-based ROM by means of single cell simulations, under both physiological and pathological conditions. In Sec. 6 we consider multiscale three-dimensional cardiac EM simulations and we compare the results obtained with the HF activation model and our reduced model. We critically discuss the results obtained in Sec. 7 and we draw our conclusions in Sec. 8.

2 Cardiac activation models and Model Order Reduction

The fundamental contractile unit of the cardiac muscle tissue is the sarcomere, a cylindrical structure nearly 2 µm long, made of two families of filaments – known as thin and thick filaments – arranged in a highly organized structure [51, 11, 96, 49, 15]. Myosin, the principal constituent of thick filaments, is a molecular motor able to bind to actin, which is located on thin filaments, and to generate force by pulling thin filaments towards the centre of the sarcomere. When the tissue is at rest, however, the regulatory units (i.e. troponin-tropomyosin complexes located on thin filaments) are in a non-permissive configuration that blocks actin binding sites, preventing myosin from generating force.

Cells contraction is triggered by an increase of the intracellular concentration of calcium ions (that we denote by the variable \(c\)), which bind to troponin thus making the permissive configuration energetically favourable for the associated regulatory unit. When a regulatory unit is in the

Figure 1: The cardiac force generation process is split into two parts: first, the regulatory units located on the thin filament (troponin-tropomyosin protein complexes) are activated as a consequence of an increase of intracellular calcium concentration \(c\) and regulated by the sarcomere elongation \(SL\); then, when tropomyosin switches to the permissive configuration, actin and myosin undergo the so-called Lymn-Taylor cycle and generate active force [51].
permissive configuration, myosin is free to bind to the actin binding sites regulated by that unit, forming the so-called crossbridges and generating active force (see Fig. 1). A regulatory unit acts indeed as a microscopical on-off switch for the generation of force. When calcium concentration goes back to the presystolic level, calcium ions detach from troponin and the regulatory units move back to the non-permissive configuration, thus hindering further force generation.

Besides calcium concentration, the activation mechanism is regulated by the local stretch of the tissue, which affects the sarcomere length (here denoted by $SL$). The main consequences of an increment of $SL$ (in the physiological range) are an increase of maximal force at saturating calcium concentrations and an enhanced sensitivity to calcium. This is linked to the Frank-Starling law, for which an increased presystolic volume (at the microscopical level, larger $SL$) translates into a higher generated force (linked to higher tissue activation at the microscale) [51, 11].

Mechanical activation models aim at linking the time evolution of $c(t)$ and of $SL(t)$ (regarded as the two inputs of the model) to the level of activation, measured by the so-called permissivity – denoted by $y(t) \in [0,1]$ – that is the fraction of regulatory units in permissive state. This is assumed to be proportional to the active force generated by the muscle tissue [83].

2.1 Modeling cardiac mechanical activation

Mathematical models of cardiac muscle cells activation are typically represented by Continuous-Time Markov Chains describing the transitions of the regulatory units proteins [57, 81, 86, 89]. In such stochastic models, a single representative regulatory unit is considered, thus adopting a mean-field approach, to contain computational complexity.

As shown in the seminal contribution of [85], mean-field models are however unable to reproduce the steep nonlinear response of tissue activation to an increase of calcium concentration, which features a Hill coefficient (i.e. a measure of ultrasensitivity of a protein to a ligand, see e.g. [51]) significantly larger than one [53, 26, 93, 94]. Indeed, the large Hill coefficient reveals an apparent cooperative behaviour between the different units and this cannot be captured by a mean-field model, which considers instead only a single unit. On the contrary, the experimentally observed force-calcium dependence can be recovered by explicitly considering a spatial distribution of regulatory units, which allows to model nearest-neighbouring interactions [88].

The drawback of spatially explicit models is their overwhelming computational complexity since the number of degrees of freedom grows exponentially with the number of regulatory units, reaching the order of $10^{21}$ and even larger [83]. This issue is typically tackled by sampling the solution of spatially-explicit models by the Monte Carlo method, which is however time-consuming and exhibits a slow convergence towards accurate results [85, 46, 99, 100]. With Monte Carlo method a set of possible trajectories of the system, whose state is represented by just a few tens of variables, is simulated and the results are averaged. However, in order to reach statistical convergence, as much as $10^4$ trajectories may be required (see e.g. [98, 83, 100]), raising again the issue of memory storage in three-dimensional realistic cardiac simulations.

2.2 Reducing computational burden of cardiac cells activation models

Several attempts have been made to reduce the computational complexity of spatially-explicit models while preserving their reliability, in particular for reproducing the physiological force-calcium relationship [85]. In [88] an exact solution for a spatially-explicit model was proposed, which is however limited to the steady-state. In [13] the large complexity of the proposed reduced model limits its applicability to a small number of regulatory units. In [98] the authors propose an integro-differential system derived from the Forward Kolmogorov Equation associated with the Markov Chain describing the transition of the regulatory units: this system comprises a set of parameters which have to be estimated by a least-squares fitting over a collection of simulations obtained by means of the Monte Carlo method. In [55], aiming at reducing the complexity of a spatially-explicit model, the authors grouped the states of the model by the number of units being in a given state, regardless of their position. Then, the position of units is again taken into account when the transition probabilities are computed by averaging, with Monte Carlo random sampling, over all configurations of the considered group. However, in this model the spatially-explicit description is lost and length dependent effects cannot be captured.
In [83], we introduced a physically motivated assumption of conditionally independence on specific sets of events, which allowed to derive a system of ordinary differential equations (ODEs) for the time evolution of the probability of the states of triplets of consecutive neighboring regulatory units. This model allows to accurately reproduce the results of the original model (with a relative error of order of $10^{-2}$) more efficiently than with a Monte Carlo approximation (to get the same error, the latter requires more than 10000 times of computational time). Moreover, a thorough validation of the model in [83] shows a good qualitative and quantitative agreement with experimental measurements under various settings. In particular, the force-calcium relationship is accurately reproduced, a significantly important achievement for cardiac electromechanics.

2.3 Model Order Reduction techniques

The model that we proposed in [83] accomplishes a significant reduction of the computational burden, both in terms of model size and of computational time, with respect to spatially-explicit models. However, this model still features 2176 internal variables, that describe all the possible combinations of triplets of adjacent regulatory units. In a full-organ three-dimensional simulation with a space discretization featuring $10^6$ degrees of freedom, the total number of variables associated to the muscle cells activation would be of the order of $10^9$. A further significant reduction of the dimensionality of this model is thus desirable, if not necessary. This is precisely our goal in this paper.

We consider therefore general purpose Model Order Reduction (MOR) reduction techniques to derive a computationally tractable, lower dimensional counterpart of a HF model, yet accurately reproducing its results [3, 9, 74, 73]. MOR techniques can be classified as model-based or data-driven. With the former strategy, the reduced formulation is derived from the HF model, by projecting it onto a smaller space [3, 9, 8, 1]. In this framework, the space of the full-order state is approximated by a lower dimensional subspace, which can be obtained through different techniques, including Moment-Matching [5, 6, 32], Balanced-Truncation [1, 64] and Proper Orthogonal Decomposition (POD, see [44, 1, 29, 70, 72]), as in the case of the Reduced Basis (RB) method [73, 65]. Projection-based methods are tailored on linear models; if applied to nonlinear models they need to be suitably adapted [73, 65, 61, 19, 28].

On the other hand, data-driven MOR approaches build the reduced model from a collection of input-output pairs, from which they attempt to infer the dynamics of the HF model. The Loewner framework [60, 62, 59] and the orthonormal vector fitting (OVF) method [24, 25] are data-driven MOR techniques for linear systems based on an approximation of the transfer function of the HF model in the frequency domain. Data-driven MOR techniques for nonlinear models are, e.g.: dynamic mapping kriging (DMK) [43], which approximates the right-hand side of a nonlinear system by Gaussian Process (GP) regression [80, 63]; Sparse Identification of Nonlinear Dynamics (SINDy) [12], which seeks an approximation of the system right-hand side as a combination of a predetermined collection of linear and nonlinear terms; a generalization of the Loewner framework to analytic nonlinear models with affine input dependence [2, 38, 39]; Multistep Neural Networks, trained to minimize the residuals of a given multi-step time-stepping scheme on a collection of available snapshots of the full-order state [79]. However, the latter mentioned techniques are aimed to reduce the computational effort of the evaluation of the right-hand side of the HF model and not to reduce its dimensionality. In [40], the authors proposed a MOR technique based on a combination of projection-based methods with GP regression, which is however restricted to parametric differential equations and cannot be easily extended to models with a time-dependent input.

In [84] we proposed a data-driven MOR technique, based on ANNs, which is suitable for nonlinear models with time-dependent inputs and can provide a significant reduction of dimensionality of the HF model. Our approach consists in reformulating the model reduction problem as a maximum-likelihood problem, where one looks for the model which best approximates, inside a class of candidate models, a collection of input-output pairs. Specifically, the set of candidate models consists in systems of ODEs whose right-hand side is represented by an ANN that is trained to learn from the collection of input-output pairs – generated by the HF model – the underlying physics of the HF model itself. We will recall our data-driven MOR technique in Sec. 4.1 and we will extend it in Sec. 4.2 by the introduction of suitable penalization terms that enforce some a
priori knowledge on the HF model into the learning process.

### 3 The high fidelity model for cardiac activation

In this work our HF model is the activation model for cardiac muscle cells proposed in [83], describing the time evolution of the probabilities associated to the possible states of triplets of adjacent regulatory units on a myofilament. We have describing the time evolution of the probabilities associated to the possible states of triplets of adjacent regulatory units on a myofilament. We have $n_{RU} = 36$ units, each having 4 possible states given by the combination of the two conditions of being bound to calcium or not and of being in permissive state or not. Since each triplet can be in $4^3$ possible states and we have $(n_{RU} - 2)$ different triplets of adjacent units, the size of the internal state of the model is $N = (n_{RU} - 2) \cdot 4^3 = 2176$. We denote by $Z(t) \in \mathbb{R}^N$ the internal state of the HF model, that is the vector collecting all such variables.

The HF model for cardiac activation can be written in the following form:

$$
\begin{align*}
\dot{Z}(t) &= F(Z(t), u(t)), \quad t \in (0, T] \\
Z(0) &= Z_0 \\
y(t) &= G(Z(t)), \quad t \in (0, T],
\end{align*}
$$

(1)

where the input is given by $u(t) = (c(t), SL(t))^T$ and the output is the permissivity $y(t)$. The right-hand side $F$ and the output function $G$ are nonlinear and linear functions, respectively; we refer the interested reader to [83] for the definition of these terms. For the sake of simplicity, we decided in this paper to avoid reporting the full details of the activation model, which can be recasted in the form of (1).

Following [88], we assume that each cycling crossbridge can exert a fixed amount of force. As the fraction of cycling crossbridges corresponds to the permissivity, the total active tension ($T_a$) is proportional to $y$:

$$
T_a = \hat{T}y,
$$

(2)

where $\hat{T}$ is the force generated for $y = 1$. We remark that we neglect shortening velocity-related effects [51, 52], which require an explicit representation of crossbridges to be modeled [18, 14, 54] and which we will include in a future work.

### 4 The model reduction strategy

Within a data-driven framework, we carry out $N_s$ experiments (i.e. numerical simulations) with the HF model and we collect a set of $N_s$ outputs $y(t)$, each one obtained with a different input $u(t)$. As our goal is to obtain a reduced model to be exploited in multiscale cardiac simulations, our inputs will span the range of values possibly covered during the cardiac activity. In particular, since calcium concentration during each heartbeat varies between 0.1 μM (micromolar) and 1.2 μM and the working range of sarcomeres spans a length from 1.7 μm to 2.3 μm [11, 51], our input takes values in $U = [c_{\text{min}}, c_{\text{max}}] \times [SL_{\text{min}}, SL_{\text{max}}]$, where we prudentially set $c_{\text{min}} = 0$ μM, $c_{\text{max}} = 1.5$ μM, $SL_{\text{min}} = 1.6$ μM, $SL_{\text{max}} = 2.4$ μM. Since the output of the model represents the fraction of units in permissive state, we define the space of output values as $Y = [0, 1]$.

Hence, for $j = 1, \ldots, N_s$, we consider a time interval $[0, T_j]$ and an input function $\hat{u}_j : [0, T_j] \rightarrow U$ and we define $\hat{y}_j : [0, T_j] \rightarrow Y$ as the solution of the HF model (1) associated to the input $\hat{u}_j$. The $j$-th training experiment (where $j = 1, \ldots, N_s$) consists of the pair $(\hat{u}_j, \hat{y}_j)$.

The solution of the HF model (1) also depends on the initial condition $Z_0$. Because of the non-intrusive nature of our approach, a unique initial condition must be used in each experiment, otherwise the input-output map that we aim to learn would not be well-defined (see [84] for more details). Specifically, we set as initial condition for each training experiment the steady-state of the cell in pre-systolic conditions, that is when calcium concentration is $c_0 = 0.1$ μM and the sarcomere length is $SL_0 = 2.2$ μm. The corresponding state can be numerically computed by solving the HF model with input $u(t) = u_0 := (c_0, SL_0)^T$, until a steady-state is reached.
4.1 Black-box model reduction

Our ROM will approximate the HF model in the following form:

\[
\begin{align*}
\dot{z}(t) &= f(z(t), u(t)), \quad t \in (0, T_j] \\
z(0) &= z_0 \\
y(t) &= z(t) \cdot e_1, \quad t \in (0, T_j],
\end{align*}
\]

where the reduced state \( z(t) \) belongs to a lower dimensional subspace \( \mathbb{R}^n \) such that \( n \ll N \). By setting \( y(t) = z(t) \cdot e_1 \), where \( e_1 = (1, 0, \ldots, 0)^T \in \mathbb{R}^n \), we are forcing the first entry of the reduced state to coincide with the output itself. It follows that the first entry of the initial reduced state \( z_0 \) (here denoted by \( (z_0)_1 \)) must coincide with the output associated with the initial full-order state \( Z_0 \), which represents the pre-systolic permissivity and is given by \( y_0 := G(Z_0) \approx 1.5 \cdot 10^{-3} \). As discussed in [84], we can set, without loss of generality, \( (z_0)_i = 0 \) for \( i = 2, \ldots, n \) as this choice does not reduce the set of candidate reduced models. To sum up, we set the initial reduced state as \( z_0 = (y_0, 0, \ldots, 0)^T \).

The right-hand side \( f: \mathbb{R}^n \times U \to \mathbb{R}^n \) is the unique element in (3) still to be defined. This therm is, in fact, what the machine learning algorithm will learn from the training input-output pairs. Our strategy is that of fixing the dimension \( n \) of the ROM, selecting a candidate class of functions \( \mathcal{F} \), and interpreting the model reduction problem as a best-approximation problem, in which we look for the function \( f \in \mathcal{F} \) such that the input-output map represented by the model (3) best fits the input-output pairs belonging to the training set. Basically, within all the possible models with \( n \) state variables, we are looking for the one which best approximates the HF model. More precisely, we consider the following optimization problem, in which we minimize the distance, in the least-squares sense, between the HF output and the output obtained by the ROM:

\[
\begin{align*}
\min_{f \in \mathcal{F}} \quad & \frac{1}{2} \sum_{j=1}^{N_s} \int_0^{T_j} |\hat{y}_j(t) - y_j(t)|^2 dt \\
\text{s.t.} \quad & \dot{z}_j(t) = f(z_j(t), \hat{u}_j(t)), \quad t \in (0, T_j], \quad j = 1, \ldots, N_s \\
& z_j(0) = z_0, \quad j = 1, \ldots, N_s \\
& y_j(t) = z_j(t) \cdot e_1, \quad t \in (0, T_j], \quad j = 1, \ldots, N_s.
\end{align*}
\]

Because of their universal approximation properties [23] and their well assessed ability of learning manifolds from data [90, 42], we set as candidate function space \( \mathcal{F} \) the space of functions represented by ANNs with a prescribed architecture. ANNs are functions from \( \mathbb{R}^p \) to \( \mathbb{R}^q \) (in our case, \( p = n + 2 \) and \( q = n \)), parametrized by a finite number of parameters (representing the weights and biases), which are collected in a real valued vector \( \mu \in \mathbb{R}^k \), for \( k \geq 1 \) (see e.g. [103]). To stress the dependence of \( f \) on the parameters \( \mu \), we will use henceforth the notation \( f(z, u; \mu) \).

In this manner, the optimization problem (4) can be written as an optimization problem in \( \mathbb{R}^k \) and standard optimization techniques can be employed for its solution. In particular, we use the Levenberg-Marquardt algorithm [67], specifically designed for least-squares problems, which requires the computation of the gradients of the least-squares terms with respect to the design variables \( \mu \). For the computation of the gradients, by using the Lagrange multipliers formalism, an adjoint backward equation is solved at each iteration of the optimization algorithm. We refer the interested reader to [84] for the technical details.

4.2 Feeding the learning process with a priori knowledge

The approach presented so far is fully black-box, that is it does not require any knowledge about the HF model but for a collection of input-output pairs generated by the HF model itself. However, as for the application considered in this paper, we may actually have some insight into the HF model that we aim to reduce. Such a priori knowledge can be exploited in the learning process by adding to the cost functional of problem (4) suitable penalization terms.

4.2.1 The cycle condition

As explained in [84], with the proposed black-box approach it is not possible to give a physical meaning to all the entries of the reduced state \( z(t) \) (apart from \( (z(t))_1 \), which coincides with the
permissivity $y$). Nonetheless, the reduced state $z$ is a compact representation of the full-order state $Z$: we may suppose that there exists a map between the full-order and the reduced state. Hence, the initial state $Z_0$ is mapped, by construction, into the reduced initial state $z_0$.

This implies that, whenever for some input $\tilde{u}_j(t)$ the HF model returns, at the final time $T_j$, to the initial state (that is $Z(T_j) = Z_0$), also the ROM should satisfy $z(T_j) = z_0$. To enforce this condition, which we call cycle condition, we insert in the training set some experiments, labelled by the indexes $j \in J_r$, such that at final time $T_j$ the full-order state coincides with the initial state $Z_0$. Then, we add to the cost functional of problem (4) the following term:

$$E_c^2 = a_c^{-1} \sum_{j \in J_r} \sum_{i=2}^{n} \frac{(z_j(T_j) \cdot e_i)^2}{\int_0^{T_j} (z_j(t) \cdot e_i)^2 \, dt}, \quad \text{(5)}$$

where $a_c = |J_r|/(n-1)$ is a normalization factor, whose role will be discussed later. We remark that $E_c$ does not involve $(z)^1$ since it is already accounted for in the cost functional of problem (4). We also notice that in (5) we normalize with respect to the $L^2$ norm of the history of $z(t)$, otherwise the introduction of the penalization term (5) would be useless. Indeed, by performing a change of variable the internal state by multiplying its entries, but for the first one, by a small constant $\alpha \ll 1$, the quantity $\sum_{j=1}^{N_s} \sum_{i=2}^{n} (z_j(T_j) \cdot e_i)^2$ can be made arbitrary small, without changing the input-output map represented by the model.

### 4.2.2 The equilibrium condition

In Sec. 4 we have defined the initial full-order state $Z_0$ as the steady-state associated to the input $u_0$. Therefore, such state is by definition an equilibrium solution (i.e. $F(Z_0, u_0) = 0$), a condition that should be satisfied also by the ROM (i.e. $f(z_0, u_0) = 0$). To enforce this condition (which we call equilibrium condition), we envisage two alternative strategies. The first one, which we call weak imposition, consists in adding to the cost functional the following further penalization term:

$$E_e^2 = a_e^{-1} |f(z_0, u_0)|^2,$$  \quad \text{(6)}

where the normalization factor is defined as $a_e = n$. The second one consists in manipulating the ANN architecture in such a way that the equilibrium condition is exactly satisfied. Specifically, we redefine $f$ as $f(z,u) = \hat{f}(z,u) - f(z_0, u_0)$, where $\hat{f}$ stands as the ANN to be trained (from which we remove the last layer of biases since it is canceled by the subtraction). We call this second approach strong imposition of the equilibrium condition as the latter is satisfied by construction. In other words, we train the ANN weights and biases, but for the biases of the output layer, which are defined in such a way that the equilibrium condition is satisfied. The reduction of the number of the unknowns is a consequence of the reduction of the space of candidate solutions (we have excluded the functions not satisfying the equilibrium condition).

### 4.3 Grey-box model reduction

The introduction of the cycle condition and of the equilibrium condition, made in Sec. 4.2, would not be possible in a strict black-box framework since the internal state would not be observable. We have thus moved towards a grey-box approach since we have mixed a black-box technique with some insight on the HF model. Before stating the formulation of the grey-box model reduction problem, we introduce the following notation to denote the cost-functional of the black-box formulation (4), which penalizes the error between the HF model and the ROM

$$E^2 = a_b^{-1} \sum_{j=1}^{N_s} \int_0^{T_j} (\hat{y}_j(t) - y_j(t))^2 \, dt,$$ \quad \text{(7)}

where $a_b = \sum_{j=1}^{N_s} \int_0^{T_j} (\hat{y}_j(t))^2 \, dt$. Then, the grey-box MOR problem reads:

$$\min_{\mu \in \mathbb{R}^n} \frac{1}{2} w_0^2 E_0^2 + \frac{1}{2} w_c^2 E_c^2 + \frac{1}{2} w_e^2 E_e^2$$

s.t.  

$$\begin{aligned}
\hat{z}_j(t) &= f(z_j(t), \tilde{u}_j(t); \mu), \quad t \in (0, T_j], \quad j = 1, \ldots, N_s \\
\hat{z}_j(0) &= z_0, \quad j = 1, \ldots, N_s \\
y_j(t) &= z_j(t) \cdot e_1, \quad t \in (0, T_j], \quad j = 1, \ldots, N_s.
\end{aligned} \quad \text{(8)}$$
The weight factors $w_i, w_c, w_e \in \mathbb{R}^+$ allow to tune the contribution of the different terms. The normalization factors $a_i, a_c$ and $a_e$ allow to keep the relative weight of the different terms unaffected by changes in the number of training samples, in $J_r$ or in $n$. When the strong imposition of the equilibrium condition is employed, we set $w_e = 0$ and we modify the architecture of $f$ accordingly.

4.4 Discrete version of the MOR problem

We discretize in the problem (8) both for the state equation and the objective functional. As in [84], we consider uniform subdivisions of the time intervals $[0, T_j]$ with step-size $\Delta t$; then, we discretize the state equation by a Forward Euler scheme and the objective functional in (8) by the composite trapezoidal rule [75].

We notice that all the terms of the objective functional of problem (8) can be written as sum of squares. The optimization problem retains a least-squares structure and the Levenberg-Marquardt algorithm can thus be applied. The unique change with respect to the solution of the fully black-box problem (4) is that it requires the calculation of the gradient of the terms $E_c$ and $E_e$ with respect to the design variables $\mu$, which can be performed by means of the Lagrange Multiplier method (as in [84]) and by differentiation with respect to $\mu$, respectively.

5. The reduced cardiac activation model

To train the ANN we generate a training set by means of the HF model, i.e. a collection of input-output pairs $(\hat{u}_j, \hat{y}_j)$, for $j = 1, \ldots, N_s$. In such training set we insert three kind of input functions:

- 50 step responses of duration $T = 3 \text{s}$, in the form of $u(t) = u_0 + (\hat{u} - u_0) I_{[t_1, t_2]}(t)$, where $t_1 = 0.2 \text{s}$, $t_2 = 2 \text{s}$ and where $\hat{u}$ is randomly selected. Specifically, we put into the training set 40 inputs where the values $u$ are selected by Latin Hypercube Sampling (LHS) of the input set $U$ and 10 additional inputs obtained by LHS of the subset $[0.3, 0.6][\mu M] \times [2.15, 2.25][\mu M] \subset U$, a region where the steady-state force-length relationship has a non regular shape and thus requires a better resolution to be appreciated. The samples belonging to this set are such that the full set of solutions $Z(T)$ virtually coincides (with a relative error lower that $10^{-4}$) with $Z_0$. Therefore, we set the corresponding indexes into the set $J_r$.

- 45 oscillating inputs of duration $T = 1 \text{s}$, in the form of $u(t) = (c_{\text{min}} + A \sin(\frac{2\pi}{T_1} t))^2, B + C \sin(\frac{2\pi}{T_2} t))^2$, where the periods $T_1$ and $T_2$ are randomly selected in the range $0.1 - 0.8 \text{s}$ and the constants $A, B$ and $C$ are randomly selected, with the constrain that the function values belong to the set $U$.

- 60 randomly generated inputs of duration $T = 1 \text{s}$.

For selecting the hyperparameters, we proceed by a trial-and-error approach. Aiming at a drastic reduction of dimensionality of the HF model, we set $n = 2$ internal variables for the ROM. For this choice we found that two hidden layers of 6 neurons each yield accurate results without a significant overfitting, as we will show later (Table 1). Finally, we set $w_h = 1$, $w_e = 10^{-1}$ and, for the weak imposition of the equilibrium condition, $w_e = 10^{-1}$.

To evaluate the accuracy of the ROM, we build a testing set with a collection of step inputs, randomly generated inputs and the physiological and pathological inputs described in Sec. 5.1. Moreover, in order to evaluate the reliability of the ROM over time intervals longer than the one used for the training, we also test the ROM with random inputs of duration $T = 10 \text{s}$.

Therefore, the ANN is trained based on the input-output pairs generated by the HF model under fundamental regimes (step responses, frequency responses) and random inputs. Then, the learned model is tested on different test cases, including physiological samples. If the ANN model, which has been exposed during the training stage only to fundamental inputs, is able to reproduce the results of the HF model also for physiological inputs, we can conclude that the ANN has really learned the dynamics of the system, and it is not simply interpolating between a database of precomputed solutions.
In Table 1 we compare the training and testing errors obtained with and without imposition of the equilibrium condition (in weak or strong form) and with or without imposition of the cycle condition.

We conclude that the best strategy consists in introducing in the learning process both the cycle condition and the equilibrium condition (the latter with strong imposition). In the following we will further validate the ROM obtained with this strategy. For simplicity, we will refer to this model as the ANN model. The trained ANN is publicly available online (see App. A).

### 5.1 Validation of the reduced model

We perform with the HF and the ANN models some of test cases typically employed to validate microscopic cardiac force generation models and we check that the ANN model did not lose the capability of the HF model to reproduce the experimentally observed features of cardiac force generation. The results, reported in Fig. 2 and briefly commented in the next sections, show a remarkably good match.

#### 5.1.1 Steady-state force-calcium-length relationships

An important characterization of muscle tissue models is the dependence of the steady-state force on the two inputs, $c$ and $SL$ (see Fig. 2a and Fig. 2b respectively). The force-calcium relationship reveals the characteristic sigmoidal shape, with a steep slope in proximity of half activation. An increase in $SL$ leads to an increase of plateau force and to an increase of calcium sensitivity, which translates in a leftward shift of the curve. Conversely, the force-length relationship features increasing curves for $SL < 2.2 \mu m$, with a change of convexity as $c$ increases (from convex to concave), and a plateau for $SL > 2.2 \mu m$ (see e.g. [26, 93, 94]).

#### 5.1.2 Isometric twitches

Then, we consider isometric twitches, i.e. force transients in response to the calcium wave occurring at each heartbeat, at constant $SL$. We impose the following calcium transient (from [98]):

$$c(t) = c_0 + \frac{c_{\text{peak}} - c_0}{\beta} \left[ e^{-\frac{t-t_0}{\tau_1}} - e^{-\frac{t-t_0}{\tau_2}} \right] \mathbb{1}_{t \geq t_0},$$

where

$$\beta = \left( \frac{\tau_1}{\tau_2} \right) - (\frac{\tau_2}{\tau_1})^{-1} = \left( \frac{\tau_1}{\tau_2} \right) - (1 - \frac{\tau_1}{\tau_2})^{-1}$$

and $c_0 = 0.1 \mu M$, $t_0 = 0.1 \, s$, $\tau_1 = 0.02 \, s$, $\tau_2 = 0.11 \, s$. In Fig. 2c, we set $c_{\text{peak}} = 1.2 \mu M$ and we consider different values of $SL$. Conversely, in Fig. 2d, we set $SL = 2 \mu m$ and we let $c_{\text{peak}}$ vary. In both cases, by increasing either $c_{\text{peak}}$ or $SL$, three effects can be observed: (1) the peak force increases; (2) the activation time is not significantly affected; (3) the relaxation time increases (see e.g. [47, 27]).

<table>
<thead>
<tr>
<th>Equilibrium condition</th>
<th>Cycle condition</th>
<th>Train error</th>
<th>Test error</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>1.62 $\times$ $10^{-2}$</td>
<td>2.66 $\times$ $10^{-2}$</td>
</tr>
<tr>
<td>weak ($w_e = 10^{-1}$)</td>
<td>-</td>
<td>1.52 $\times$ $10^{-2}$</td>
<td>2.10 $\times$ $10^{-2}$</td>
</tr>
<tr>
<td>strong</td>
<td>-</td>
<td>1.70 $\times$ $10^{-2}$</td>
<td>3.10 $\times$ $10^{-2}$</td>
</tr>
<tr>
<td>weak ($w_e = 10^{-1}$)</td>
<td>$w_c = 10^{-1}$</td>
<td>1.48 $\times$ $10^{-2}$</td>
<td>2.35 $\times$ $10^{-2}$</td>
</tr>
<tr>
<td>strong</td>
<td>$w_c = 10^{-1}$</td>
<td>1.44 $\times$ $10^{-2}$</td>
<td>1.97 $\times$ $10^{-2}$</td>
</tr>
</tbody>
</table>

Table 1: Training and testing relative errors obtained by training the ANN model with or without imposition of the equilibrium condition (in either weak or strong form) and with or without imposition of the cycle condition.
5.1.3 Sudden development of tension

Experiments show that the rate of tension development following a sudden rise of \( c \), starting from its presystolic value of near 0.1 \( \mu \text{M} \), increases with the calcium level ([31, 95, 4, 102]). To replicate this phenomenon, we apply a step change in calcium at different levels, with \( SL = 2.2 \mu \text{m} \). The results are shown in Fig. 2e.

5.1.4 Isometric versus shortening twitches

The systolic contraction of the myocardium leads to a shortening of the muscle fibers and, as a consequence, to a decrease of \( SL \). Therefore, in the normal cardiac activity, shortening twitches, rather than isometric twitches, are observed. To investigate the difference between the two settings, we consider the experimentally measured \( c \) and \( SL \) transients reported in [48]. The results of the simulation, shown in Fig. 2f, show that the decrease of \( SL \) leads to a decrease of force peak and to a slight decrease of duration of activation (see e.g. [51, 11]).

5.1.5 Long-term twitches

The normal cardiac activity features a nearly periodic behavior. To test the capability of our model to sustain a periodic input after several cycles, we perform 10 s long simulations by applying the calcium transient (9), with \( c_{\text{peak}} = 1.1 \mu \text{M} \) and \( SL = 2 \mu \text{m} \), with different periods, ranging from 0.3 to 1.5 s (see Fig. 2g). We notice that for the highest frequency the wave summation phenomenon occurs, by which the effect of consecutive twitches sum up in a sustained contraction state (see e.g. [51, 11]).

6 Three dimensional cardiac electromechanics

We present our approach to reduce the computational burden associated to the numerical approximation of multiscale cardiac EM, where we describe force generation at the microscopic level by means of the reduced ANN model developed in Sec. 5. First, we introduce the EM problem (Sec. 6.1) and its numerical discretization (Sec. 6.2). Then, we illustrate our multiscale strategy (Sec. 6.3) and we assess the results, both in terms of efficiency and accuracy with three test cases (Secs. 6.4–6.5).

6.1 The EM problem

We consider a reference computational domain \( \Omega_0 \), representing the left ventricle (LV) muscle tissue, and a final time \( T = 0.8 \text{s} \) (the characteristic duration of a heartbeat). We define the following functions, defined over the space-time domain \( \Omega_0 \times (0, T] \) (in the following the dependence on \((x, T)\) will be implicit): the transmembrane potential \( v \), the ionic variables \( w \), the activation variables \( Z \) and the displacement \( d \). By using a standard notation, we denote by \( F = I + \nabla d \) the deformation gradient in the reference configuration and by \( J = \det F \) its Jacobian. To account for the anisotropic properties of the cardiac tissue, we define a local frame of reference by means of the mutually orthogonal vector fields \( f_0, s_0 \) and \( n_0 \), denoting respectively the fibers direction, the sheets directions and a direction normal to the previous ones [34].

6.1.1 Electrophisiology

To model the propagation of the action potential, we consider the monodomain equation, which reads (see e.g. [20, 21]):

\[
\begin{align*}
\frac{\partial v}{\partial t} &= C_m \left( \frac{\partial v}{\partial t} + I^{\text{ion}}(v, w) \right) - \nabla \cdot \left( J F^{-1} D_m F^{-T} \nabla v \right) + I_{\text{app}} \quad \text{in } \Omega_0 \times (0, T] \\
\frac{\partial w}{\partial t} &= h(v, w) \quad \text{in } \Omega_0 \times (0, T] \\
(J F^{-1} D_m F^{-T} \nabla v) \cdot N &= 0 \quad \text{on } \partial \Omega_0 \times (0, T] \\
v &= v_0, \quad w = w_0 \quad \text{in } \Omega_0 \times \{0\},
\end{align*}
\]
Figure 2: Comparison between the results of the HF model (colored solid lines) and the ANN-based reduced model (black dashed lines) for different test cases, discussed in Sec. refsec:validation.
where $\mathbf{N}$ denotes the outer normal versor at the surface. The functions $I^{\text{ion}}$ and $h$ are specified according to the ionic model. In this work we consider the ten Tusscher-Panfilov model with 18 variables in the M cells setting [92]. To reduce the number of parameters, we divide the first equation by the membrane surface to volume ratio $\chi_m$ and by the membrane capacitance $C_m$, obtaining:

$$\frac{\partial v}{\partial t} + I^{\text{ion}}(v, w) = \nabla \cdot \left( J F^{-1} \hat{D}_m \mathbf{F}^{-T} \nabla v \right) + I^{\text{app}}$$

where $I^{\text{ion}} = C_m^{-1} I^{\text{ion}}$, $I^{\text{app}} = C_m^{-1} \chi_m^{-1} I^{\text{app}}$ and $\hat{D}_m = C_m^{-1} \chi_m^{-1} D_m$. To account for the anisotropic properties of the tissue, we write the diffusion tensor as $D_m = \sigma_{\text{iso}} (\mathbf{I} - f_0 \otimes f_0) + \sigma_1 f_0 \otimes f_0$. The electrical signal is triggered by the applied current $I^{\text{app}}$. In this work, we do not explicitly model the Purkinje network and consider instead a collection of points $x_1, \ldots, x_{N_p}$ where the electrical stimulus is applied, yielding

$$I^{\text{app}}(x, t) = I^{\text{max}} \sum_{j=1}^{N_p} \exp \left( \frac{|x - x_j|}{\delta^2} \right) \mathbb{I}_{[0,t_{\text{app}}]}(t).$$

### 6.1.2 Cardiac tissue activation

Among the ionic variables of the ten Tusscher-Panfilov model, there is the intracellular calcium concentration. To recover the other input variable of the cardiac activation model proposed in [83], namely the local sarcomere length $SL$, we assume that the sarcomere deformation is proportional to the local deformation in the fiber direction, i.e. $SL = SL_0 \sqrt{I_{4, f}}$. To regularize the $I_{4, f}$ field, which may be irregular, especially on coarse FEM computational meshes, we define $SL$ as solution of the following differential problem:

$$\begin{cases}
(SL - SL_0 \sqrt{I_{4, f}}) - \delta_{SL}^2 \Delta SL = 0 & \text{in } \Omega_0 \times (0, T) \\
\epsilon^2 \nabla SL \cdot \mathbf{N} = 0 & \text{on } \partial \Omega_0 \times (0, T)
\end{cases}$$

(11)

where $\delta_{SL}$ is the regularization parameter. Then, the activation equation, by employing the model proposed in [83], reads:

$$\begin{cases}
\frac{\partial Z}{\partial t} = F(Z, (c, SL)^T) & \text{in } \Omega_0 \times (0, T) \\
Z(0) = Z_0 & \text{in } \Omega_0 \times \{0\}.
\end{cases}$$

(12)

The active tension field is then computed as $T_a = T G(Z)$

### 6.1.3 Mechanics

The balance of momentum written in the reference domain reads as follows (see e.g. [69]):

$$\begin{align*}
\rho \frac{\partial^2 \mathbf{d}}{\partial t^2} - \nabla \cdot \mathbf{P}(\mathbf{d}) &= 0 & & \text{in } \Omega_0 \times (0, T) \\
\mathbf{P}(\mathbf{d}) = N + (N \otimes N) \left( K_{\text{epi}}^\perp \mathbf{d} + C_{\text{epi}}^\perp \frac{\partial \mathbf{d}}{\partial t} \right) + (I - N \otimes N) \left( K_{\text{epi}}^\parallel \mathbf{d} + C_{\text{epi}}^\parallel \frac{\partial \mathbf{d}}{\partial t} \right) &= 0 & & \text{on } \Gamma_{\text{epi}}^0 \times (0, T) \\
\mathbf{P}(\mathbf{d}) = \frac{\|J F^T \mathbf{N}\|}{\int_{\Gamma_{\text{epi}}^0} \|J F^T \mathbf{N}\| \, d\Gamma_0} \int_{\Gamma_{\text{endo}}^0} p \mathbf{J} F^T \mathbf{N} d\Gamma_0 & & \text{on } \Gamma_{\text{endo}}^0 \times (0, T) \\
\mathbf{d} = \mathbf{d}_0, & & \frac{\partial \mathbf{d}}{\partial t} = \mathbf{d}_0 & & \text{in } \Omega_0 \times \{0\},
\end{align*}$$

(13)

where the total Piola-Kirchhoff stress tensor $\mathbf{P}$ is splitted, by adopting an active stress approach [36], into a passive and an active contribution as $\mathbf{P} = \mathbf{P}^{\text{pass}} + \mathbf{P}^{\text{act}}$. The passive term is defined as the differential of the hyperelastic energy $\mathbf{W}$ with respect to the deformation gradient ($\mathbf{P}^{\text{pass}} = \frac{\partial \mathbf{W}}{\partial \mathbf{F}}$).
We consider a quasi-incompressible exponential material model [97] with the hyperelastic energy defined by

$$\mathcal{W} = \frac{C}{2} (e^Q - 1) + \frac{B}{2} (J - 1) \log J$$

$$Q = b_{ff} E_{ff}^2 + b_{ss} E_{ss}^2 + b_{nn} E_{nn}^2$$

$$+ b_{fs} (E_{fs}^2 + E_{sf}^2) + b_{fn} (E_{fn}^2 + E_{nf}^2) + b_{sn} (E_{sn}^2 + E_{ns}^2),$$

(14)

where $E_{ab} = E_{a0} \cdot b_{0b}$, for $a, b \in \{f, s, n\}$, are the entries of the Green-Lagrange strain tensor $E = \frac{1}{2} (C - I)$ in the $(f_0, s_0, n_0)$ frame of reference and $B$ is the bulk modulus. On the other hand, the active stress tensor is defined as:

$$\mathbf{P}^{\text{act}} = T_a \mathbf{F}_{f0} \otimes f_0 \sqrt{J_{a,f}}.$$

To model the effect of pericardium on the cardiac wall, we set generalized Robin boundary conditions at the epicardium $\Gamma_{\text{epi}}^0$ (see [71, 34]). The boundary condition at the base, accounting for the effect of the neglected part of the domain on the artificial boundary $\Gamma_{\text{base}}^0$, is derived in Appendix C. Finally, the action of the fluid at the endocardium ($\Gamma_{\text{endo}}^0$) is modeled by the pressure $p(t)$ (see below).

### 6.1.4 Blood external circulation

To close the problem, the LV activity must be coupled with the external circulation. With this aim, we consider a lumped description, as done in [34], consisting of four phases, where we conventionally start with systole:

1. In the isovolumic contraction phase, the pressure $p(t)$ starts from its end-diastolic value ($\bar{p}_{\text{ED}}$) and then raises in such a way that the ventricular volume $V$ is kept constant.

2. When $p(t)$ reaches the aortic valve opening pressure value $\bar{p}_{\text{AVO}}$ (we define such time instant as $t = T_{\text{AVO}}$), the ejection phase starts. In this phase, the evolution of $p(t)$ is modeled by a two-elements Windkessel model [101] as:

$$\left\{ \begin{array}{l}
C \frac{dp}{dt} = -\frac{p}{R_{\text{circ}}} - \frac{dV}{dt} \\
p(T_{\text{AVO}}) = \bar{p}_{\text{AVO}}
\end{array} \right. \quad t \in [T_{\text{AVO}}, T_{\text{AVC}}]$$

(15)

where $T_{\text{AVC}}$ (aortic valve closing time) is the first time, after $T_{\text{AVO}}$, when the negative flux $\frac{dV}{dt}$ changes sign.

3. At this stage, another isovolumic phase begins. This phase ends when $p(t)$ reaches $\bar{p}_{\text{MVO}}$, the value of the mitral valve opening pressure.

4. In the filling phase, we linearly increase $p(t)$ so that it reaches $\bar{p}_{\text{ED}}$ at final time $T$.

To compute the ventricular volume $V$ we employ the following formula, that is derived in Appendix B:

$$V(t) = \frac{1}{3} \int_{\Gamma_{\text{endo}}^0} J(t) (\mathbf{X} + \mathbf{d}(t) - \mathbf{b}(t)) \cdot \mathbf{F}^{-T}(t) \mathbf{N} \, d\Gamma_0,$$

where

$$\mathbf{b}(t) = \frac{1}{|\Gamma_{\text{base}}^0|} \int_{\Gamma_{\text{base}}^0} (\mathbf{X} + \mathbf{d}(t)) \, d\Gamma_0.$$
6.1.5 The coupled EM problem

We report here for completeness the coupled EM problem:

\[
\begin{align*}
\lambda_m \left( C_m \frac{\partial v}{\partial t} + \mathcal{I}^{ion}(v, w) \right) &= \nabla \cdot (J F^{-1} D_m F^{-T} \nabla v) + \mathcal{I}^{app} & \text{in } \Omega_0 \times (0, T] \\
\frac{\partial w}{\partial t} &= h(v, w) & \text{in } \Omega_0 \times (0, T] \\
(J F^{-1} D_m F^{-T} \nabla v) \cdot N &= 0 & \text{on } \partial \Omega_0 \times (0, T] \\
v &= v_0, \ w = w_0 & \text{in } \Omega_0 \times \{0\} \\
\left( SL - SL_0 \sqrt{T_{4,f}} \right) - \mathcal{L} SL \Delta SL &= 0 & \text{in } \Omega_0 \times (0, T] \\
\varepsilon^2 \nabla SL \cdot N &= 0 & \text{on } \partial \Omega_0 \times (0, T] \\
\frac{\partial Z}{\partial t} &= F(Z, (c, SL)^T) & \text{in } \Omega_0 \times (0, T] \\
Z(0) &= Z_0 & \text{in } \Omega_0 \times \{0\} \\
\rho \frac{\partial^2 d}{\partial t^2} - \nabla \cdot \left( p^{pass}(d) + T G(Z) \frac{F_0 \otimes f_0}{\sqrt{T_{4,f}}} \right) &= 0 & \text{in } \Omega_0 \times (0, T] \\
P(d)N + (N \otimes N) \left( k_{epi}^d \frac{\partial d}{\partial t} + c_{epi}^d \frac{\partial d}{\partial t} \right) + (I - N \otimes N) \left( k_{epi}^d \frac{\partial d}{\partial t} + c_{epi}^d \frac{\partial d}{\partial t} \right) &= 0 & \text{on } \Gamma_0^{epi} \times (0, T] \\
P(d)N &= \frac{\| J F^{-T} N \|}{J F^{-T} N} \int_{\Gamma_0^{endo}} p J F^{-T} N d \Gamma_0 & \text{on } \Gamma_0^{endo} \times (0, T] \\
P(d)N &= -p J F^{-T} N & \text{on } \Gamma_0^{endo} \times (0, T] \\
d = d_0, \ \frac{\partial d}{\partial t} = d_0 & \text{in } \Omega_0 \times \{0\},
\end{align*}
\]

where the endocardial pressure \( p \) has to be determined, depending on the cardiac cycle phase, either as Lagrange multiplier for the isovolumetric phases, or as solution of the circulation model (15). In Tab. 2 we report the full list of parameters used in the EM model.

6.2 Numerical discretization

For the spatial discretization of the first equation of Eq. (10), for Eqs. (11)-(13) and for the generation of fibers fields, we employ \( P^1 \) linear Finite Elements on a tetrahedral meshes. Moreover, we discretize the ionic variables \( w \) and the activation variables \( Z \) by means of \( P^1 \) linear Finite Elements, and we solve the associated ODE models (i.e. the equation for \( w \) of Eq. (10) and Eq. (12)) at each nodal point of the computational mesh. As for the time discretization, we consider a uniform subdivision \( 0 = t_0 < t_1 < \cdots < t_M = T \) of the time interval \([0, T]\) with step \( \Delta t = 2 \times 10^{-4} \text{s} \). To denote the unknown at the \( k \)-th time step, we use a superscript (e.g. \( v^{(k)} \approx v(t_k) \)). For the discretization of time derivatives, we use first order finite difference schemes [75].

To couple the different models, we employ the segregated strategy presented in [35]. Specifically, at each time step \( t_k \), we orderly perform the following steps:

I. We update the ionic variables of the ten Tusscher-Panfilov model [92], with an IMEX scheme, to deal with the stiff nature of the equations.

II. We update the potential field \( v^{(k)} \) by solving the monodomain equation (Eq. (10)), with implicit treatment of the potential and by employing an extrapolation of the displacement \( d \) consistent with the order of the time derivative discretization.

III. We recover the local sarcomere length by solving Eq. (11) and we update the activation variables by solving Eq. (12), with explicit treatment of the unknown \( Z \). Since the solution of the activation model requires a smaller time step \((2.5 \times 10^{-5} \text{s})\), at this step we perform an inner iteration.
### Electrophysiology

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_{\text{iso}}$</td>
<td>$1.204 \times 10^3$</td>
<td>mm$^2$s$^{-1}$</td>
<td>Normalized electrical diffusivity in fiber direction</td>
</tr>
<tr>
<td>$\sigma_{\text{iso}}$</td>
<td>$0.1761 \times 10^3$</td>
<td>mm$^2$s$^{-1}$</td>
<td>Normalized electrical diffusivity in transverse direction</td>
</tr>
<tr>
<td>$I_{\text{max}}$</td>
<td>$100$</td>
<td>V$s^{-1}$</td>
<td>Applied current value</td>
</tr>
<tr>
<td>$\delta$</td>
<td>$14$</td>
<td>mm</td>
<td>Applied current radius</td>
</tr>
<tr>
<td>$t_{\text{app}}$</td>
<td>$2 \times 10^{-3}$</td>
<td>s</td>
<td>Applied current duration</td>
</tr>
</tbody>
</table>

### Activation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T$</td>
<td>$700$</td>
<td>kPa</td>
<td>Active tension per unit area if $y = 1$</td>
</tr>
<tr>
<td>$SL_0$</td>
<td>$2.0$</td>
<td>$\mu$m</td>
<td>Reference sarcomere length</td>
</tr>
<tr>
<td>$\delta_{SL}$</td>
<td>$5$</td>
<td>mm</td>
<td>$SL$ regularization radius</td>
</tr>
</tbody>
</table>

### Mechanics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho$</td>
<td>$1 \times 10^3$</td>
<td>kg m$^{-3}$</td>
<td>Tissue density</td>
</tr>
<tr>
<td>$B$</td>
<td>$50$</td>
<td>kPa</td>
<td>Bulk modulus</td>
</tr>
<tr>
<td>$C$</td>
<td>$2$</td>
<td>kPa</td>
<td>Material stiffness</td>
</tr>
<tr>
<td>$b_{ff}$</td>
<td>$8$</td>
<td>-</td>
<td>Hyperelastic parameter</td>
</tr>
<tr>
<td>$b_{ss}$</td>
<td>$6$</td>
<td>-</td>
<td>Hyperelastic parameter</td>
</tr>
<tr>
<td>$b_{nn}$</td>
<td>$3$</td>
<td>-</td>
<td>Hyperelastic parameter</td>
</tr>
<tr>
<td>$b_{fs}$</td>
<td>$12$</td>
<td>-</td>
<td>Hyperelastic parameter</td>
</tr>
<tr>
<td>$b_{fn}$</td>
<td>$3$</td>
<td>-</td>
<td>Hyperelastic parameter</td>
</tr>
<tr>
<td>$b_{sn}$</td>
<td>$3$</td>
<td>-</td>
<td>Hyperelastic parameter</td>
</tr>
<tr>
<td>$K_{epi}^\perp$</td>
<td>$2 \times 10^{-1}$</td>
<td>kPa mm$^{-1}$</td>
<td>Robin boundary condition</td>
</tr>
<tr>
<td>$C_{epi}^\perp$</td>
<td>$2 \times 10^{-2}$</td>
<td>kPa s mm$^{-1}$</td>
<td>Robin boundary condition</td>
</tr>
<tr>
<td>$K_{epi}^\parallel$</td>
<td>$2 \times 10^{-2}$</td>
<td>kPa mm$^{-1}$</td>
<td>Robin boundary condition</td>
</tr>
<tr>
<td>$C_{epi}^\parallel$</td>
<td>$2 \times 10^{-3}$</td>
<td>kPa s mm$^{-1}$</td>
<td>Robin boundary condition</td>
</tr>
</tbody>
</table>

### Circulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{\text{circ}}$</td>
<td>$3.5 \times 10^{-2}$</td>
<td>Pa s mm$^{-3}$</td>
<td>Windkessel model parameters</td>
</tr>
<tr>
<td>$C_{\text{circ}}$</td>
<td>$4.5$</td>
<td>mm$^3$Pa$^{-1}$</td>
<td>Windkessel model parameters</td>
</tr>
<tr>
<td>$\bar{p}_{\text{ED}}$</td>
<td>$1.333$</td>
<td>kPa</td>
<td>End-diastolic pressure</td>
</tr>
<tr>
<td>$\bar{p}_{\text{AVO}}$</td>
<td>$9.333$</td>
<td>kPa</td>
<td>Aortic valve opening pressure</td>
</tr>
<tr>
<td>$\bar{p}_{\text{MVO}}$</td>
<td>$0.667$</td>
<td>kPa</td>
<td>Mitral valve opening pressure</td>
</tr>
</tbody>
</table>

Table 2: Parameters of the EM problem.
IV. We update the displacement by Eq. (13), with implicit treatment of the unknown $d^{(k)}$.

To deal with the nonlocal nature of the boundary condition on $\Gamma_{\text{base}}^0$, we adopt a quasi-Newton strategy, by computing the Jacobian matrix only with respect to the local terms. In the isovolumic phases of the heartbeat, we solve Eq. (13) together with the equation $V^{(k)} = V^{(k-1)}$. This is a saddle-point problem in the unknowns $d^{(k)}$ and $\rho^{(k)}$ and we solve it by Schur complement reduction [10]. On the other hand, during the ejection phase, the pressure is updated before solving the mechanical problem with an implicit treatment of $p$.

In Test Case 3, to lower the computational burden due to the fine mesh, for the solution of the mechanical problem we employ a 5 times larger time step (see [35, 33]).

6.3 ANN-based efficient EM simulations

The computational cost associated with the numerical approximation of the EM problem is strongly affected by the solution of the 2176-variables activation model (12), both in terms of memory storage and computational time (we provide quantitative indications in Secs. 6.4–6.5). To lower such computational burden, we replace the HF activation model (12) with its surrogate given by the 2-variables ANN model (3). This can be easily done thanks to the fact that the two models share the same inputs and outputs. In the following, we compare the results of EM simulations obtained by employing the HF activation model and by employing the ANN model, which we will respectively denote by HF-EM and ANN-EM.

6.4 Test Case 1: cardiac slab

We consider a slab of cardiac tissue, defined by the computational domain $\Omega_0 = (0, 40 \text{ mm}) \times (0, 20 \text{ mm}) \times (0, 8 \text{ mm})$. We consider a fiber field $f_0 = e_1$ aligned as the x-axis and a sheet field $s_0 = e_3$ aligned as the z-axis. We consider a unique stimulus location $x_1 = (0, 0, 0)^T$ (point A of Fig. 4). Due to the simple domain employed, in this test case the three boundaries ($\Gamma_{\text{base}}^0$, $\Gamma_{\text{epi}}^0$, and $\Gamma_{\text{endo}}^0$) are not defined. Thus, we change the boundary conditions of the mechanical
Figure 4: Test Case 1: comparison of the time course of quantities of interest in three points (indicated in the top image) obtained with the simulations performed with HF-EM (solid colored lines) and with ANN-EM (black dashed lines).
problem (13), by imposing $d \cdot N = 0$ and a no-stress condition in tangential direction on the three faces passing through the origin (i.e. $\{x : x \cdot e_j = 0\}$, for $j = 1, 2, 3$). In the remaining subset of the boundary, we impose a generalized boundary condition with $K_\perp = 5 \times 10^{-1}$ kPa mm$^{-1}$, $C_\perp = 1 \times 10^{-1}$ kPa s mm$^{-1}$ and $K_\parallel = C_\parallel = 0$.

We consider a structured computational mesh with a uniform subdivision in 16, 8 and 3 elements along the cartesian directions $x, y, z$, respectively, for a total of 2304 tetrahedra and 612 dofs. In Figs. 3–4 we show a comparison between the HF-EM and the ANN-EM results. The computational costs are compared in Tab. 4.

6.5 Test Cases 2 and 3: idealized and patient-specific left ventricle

We consider an idealized LV (Test Case 2) and a patient-specific LV derived from the Zygote CAD [104] (Test case 3). The idealized computational mesh consists of 6500 tetrahedra and 1827 degrees of freedom, whereas the patient-specific one accounts for $354 \times 10^3$ tetrahedra and $65 \times 10^3$ degrees of freedom. The electrical stimulus $I_{app}$ is applied at three points, located on the endocardial surface close to the apex. We generate the fibers and sheets distribution according to the rule-based algorithm proposed in [7], by setting $\alpha_{endo} = -60^\circ$, $\alpha_{epi} = +60^\circ$. The fibers, sheets and normal fields are displayed (just for the patient-specific geometry) in Fig. 6. In Test Case 2 we set the parameter $\bar{T}$ to 480 kPa, to obtain realistic pressure values.

The stress-strain relationship defined by (14) is referred to the natural configuration. However, in practical applications, the natural stress-free configuration is unknown since an internal pressure $p$ is always present in each phase of the heartbeat. In Test Case 2, we assume that the computational domain is referred to the end dyastolic phase. Therefore, we recover the natural configuration as
the domain such that by applying the pressure \( p = \bar{p}_{\text{ED}} \), one recovers the given computational domain as steady-state solution. Then, we employ such deformation as initial condition for the mechanical problem (13). On the other hand, as the computational domain of Test Case 3 is associated to a phase of the heart cycle such that the diastolic filling is not fully completed (more precisely, the beginning of the atrial kick), we recover the natural configuration by assuming that the computational domain is at equilibrium with an intermediate pressure between \( \bar{p}_{\text{ED}} \) and the pressure at the end of the second isovolumetric phase (specifically we take \( p = 5.6 \text{ mmHg} \)). Then, we passively inflate the ventricle until we reach the pressure \( \bar{p}_{\text{ED}} \), and we employ the obtained displacement as initial condition for the mechanics problem (13).

In Fig. 7 and Fig. 8 we show the propagation of the \( v \) and the \( c \) fields, respectively, for Test Case 3. The active tension field \( T_a \) is visualized, at different time steps, in Fig. 9, where three sections at different quotes along the apex-base coordinate allow to appreciate the distribution of active stress across the transmural coordinate. Finally, in Fig. 10 (Test case 2) and in Fig. 11 (Test case 3), we show the displacement field and the contraction of the LV. The top and frontal sections highlight the torsion that the LV undergoes during the heartbeat and the wall thickening.

Then, in Fig. 12 (Test case 2) and Fig. 13 (Test case 3), we compare the results obtained within the HF-EM and the ANN-EM frameworks. In the top row, we show the time evolution, of the average, minimum and maximum value over the domain of \( c, SL \) and \( T_a \). In the bottom row we show the time evolution of the macroscopic quantities \( p \) and \( V \) and the LV pressure-volume loop. All the curves show a good match between the results obtained in the HF-EM and the ANN-EM frameworks.

The main cardiac indicators, some of them clinically meaningful, computed in the HF-EM and ANN-EM frameworks, are reported in Tab. 3. For all the indicators, the error between HF-EM and ANN-EM is even smaller than the train and of the test error associated with the ANN model. We will comment on this in Sec. 7.

Finally, in Tab. 4, we report the computational times associated with the numerical approxi-
Figure 9: Test Case 3: active tension at different times.

Figure 10: Test Case 2: deformed geometry and magnitude of displacement at different times. Top row: full geometry. Middle row: half domain (top view). Bottom row: half domain (frontal view).
Figure 11: Test Case 3: deformed geometry and magnitude of displacement at different times. Top row: full geometry. Middle row: half domain (top view). Bottom row: half domain (frontal view).

<table>
<thead>
<tr>
<th>Indicator</th>
<th>HF-EM</th>
<th>ANN-EM</th>
<th>Relative error</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Case 2 (idealized LV, 1827 dof)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>63.33</td>
<td>63.57</td>
<td>$3.71 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>46.63</td>
<td>46.80</td>
<td>$3.71 \times 10^{-3}$</td>
</tr>
<tr>
<td>Maximum pressure (mmHg)</td>
<td>112.96</td>
<td>113.91</td>
<td>$8.38 \times 10^{-3}$</td>
</tr>
<tr>
<td>Work (mJ)</td>
<td>766</td>
<td>773</td>
<td>$9.08 \times 10^{-3}$</td>
</tr>
<tr>
<td><strong>Test Case 3 (patient-specific LV, 65476 dof)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>56.64</td>
<td>56.39</td>
<td>$4.33 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>44.48</td>
<td>44.29</td>
<td>$4.33 \times 10^{-3}$</td>
</tr>
<tr>
<td>Maximum pressure (mmHg)</td>
<td>108.94</td>
<td>109.10</td>
<td>$1.52 \times 10^{-3}$</td>
</tr>
<tr>
<td>Work (mJ)</td>
<td>662</td>
<td>659</td>
<td>$4.85 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

Table 3: Test Case 2 and 3: main cardiac indicators. Comparison between the HF-EM and the ANN-EM frameworks and corresponding relative errors.
Figure 12: Test Case 2: comparison of the time evolution of quantities of interest and of the pressure-volume loop obtained with the simulations performed with HF-EM (solid colored lines) and with ANN-EM (black dashed lines). In (a)-(b)-(c) the three lines refer to the minimum, maximum and mean value over the computational domain.

Figure 13: Test Case 3: comparison of the time evolution of quantities of interest obtained in the HF-EM and the ANN-EM frameworks (see caption of Fig. 12).
Table 4: Comparison of the computational times associated to the four physics and the total wall time between HF-EM and ANN-EM, for both test cases.

<table>
<thead>
<tr>
<th>Simulation type</th>
<th>Ionic (%)</th>
<th>Potential (%)</th>
<th>Activation (%)</th>
<th>Mechanics (%)</th>
<th>Wall time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Case 1 (cardiac slab, 612 dof, 1 core)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF-EM</td>
<td>6.3%</td>
<td>0.3%</td>
<td>89.0%</td>
<td>4.5%</td>
<td>3h 16’</td>
</tr>
<tr>
<td>ANN-EM</td>
<td>53.0%</td>
<td>2.7%</td>
<td>3.3%</td>
<td>41.1%</td>
<td>22’</td>
</tr>
<tr>
<td><strong>Test Case 2 (idealized LV, 1827 dof, 1 core)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF-EM</td>
<td>4.27%</td>
<td>0.29%</td>
<td>91.94%</td>
<td>3.40%</td>
<td>9h 31’</td>
</tr>
<tr>
<td>ANN-EM</td>
<td>53.38%</td>
<td>3.31%</td>
<td>3.74%</td>
<td>39.57%</td>
<td>46’</td>
</tr>
<tr>
<td><strong>Test Case 3 (patient-specific LV, 65476 dof, 20 cores)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF-EM</td>
<td>3.14%</td>
<td>0.47%</td>
<td>83.07%</td>
<td>13.33%</td>
<td>20h 18’</td>
</tr>
<tr>
<td>ANN-EM</td>
<td>41.21%</td>
<td>4.80%</td>
<td>2.54%</td>
<td>51.46%</td>
<td>2h 04’</td>
</tr>
</tbody>
</table>

7 Discussion

7.1 Computational gain

The ANN-EM framework accomplishes a significant reduction of the computational cost of the HF-EM framework. The solution of the activation model, which accounts for most of the computational time of the whole simulation, highlights a gain nearly of a factor 300 in all test cases, reducing the overall computational times by one order of magnitude. The computational speedup is slightly smaller for finer grids, for which the relative weight of the mechanical subproblem is more pronounced. However, whereas the approximation of the electrophysiology subproblem (10) requires a finer grid for the convergence of the solution [78], the computational mesh used in Test Case 3 features a large enough number of elements to get accurate results for the mechanics subproblem (13) and to capture the complexity of patient-specific domains [78, 55]. Therefore, since when different meshes are employed for the different physics the activation subproblem (12) is typically solved on the mesh used for the mechanics [78], we expect that the speedup obtained in Test Case 3 is representative for the computational gain one can obtain for HF simulations of patient-specific EM.

With the ANN-EM approach, the number of variables for each degree of freedom of the domain is 24 (18 ionic variables, the transmembrane potential, 2 activation variables, 3 components of the displacement), significantly lower than the number of variables with the HF-EM approach (18+1+2176+3 = 2198).

Finally, we remark that in this work we considered a staggered approach [35, 33], where the four different physics are solved in sequence. The results could vary with other numerical coupling approaches. In particular, with a monolithic approach (where the 4 physics are solved simultaneously in a strongly coupled manner [34]), the computational gain is expected to be even greater since the size of the Jacobian matrix scales as the square of the number of variables.

7.2 Approximation accuracy

The zero-dimensional simulations obtained with the reduced ANN model (see Sec. 5.1) are accurate with respect to the ones obtained with the HF model (relative error of order 10^{-2}). Nevertheless, when the activation model is embedded in the EM coupled system, the model output (i.e. active force) has a feedback on its inputs (mostly on SL, as it causes the tissue contraction, but also on c, due to the mechano-electrical feedback). Therefore, one should check whether such feedback has the effect of amplifying the error introduced by the ANN reduced model, or not.

Numerical results show that, on the contrary, by embedding the ANN model in a EM setting, the errors are dampen by one order of magnitude (order of 10^{-3}). As a matter of fact, the feedback
7.3 Comparison with phenomenological models

The ANN model is built from data generated by the HF model. This is somehow similar to the way the so-called phenomenological models, i.e. models built by fitting the experimental observations with a few number of variables (see e.g. [45, 66, 87, 56]), are built. A natural question is how those models compare with the ANN model.

Building a model consists in the solution of an inverse problem: starting from experimental observations, one looks for a law, written in mathematical terms, and a set of parameters describing the phenomenon that generated the observations themselves. However, experimental data are typically noisy and defective (this is particularly evident in the case considered in this work, due to the microscopic scale at which force is generated and to the intrinsic difficulties in measuring the internal properties of myofilaments without damaging them [53, 26, 94]). In the context of inverse problems and statistical learning, the action of compensating for noise and deficiency of data is known as regularization (see e.g. [41, 58]). Regularization is typically performed either by suitable penalization of the unknown variables, or by restricting the set of candidate solutions [50].

Phenomenological models are derived by finding the best fit of experimental data with a simple law chosen a priori. Such a priori assumptions allow for a lumped description of the phenomenon with a small number of parameters to be tuned from experimental data. This is crucial, due to the noisy and defective nature of data. In fact, such a priori assumptions are a way of performing regularization. For instance, to reproduce the nonlinear response of activation to calcium concentration – consequence of the nearest-neighborhood interaction within units – without explicitly representing the units themselves, a power law dependence on $c$ is typically assumed, and the exponent is estimated by fitting experimental data. However, this law has a phenomenological basis and it is not derived by first principles [87].

With our approach, instead, regularization is performed during the construction of the HF model thanks to the introduction of physics first principles and to a detailed description of the microscopic arrangement of the contractile system. In such a way, indeed, the set of possible relationships among the variables is restricted to those satisfying some physical principles. However, a detailed physics-based description leads to complex models (in the previous example, a physics-based description of nearest-neighborhood interactions within units is not possible without a spatially-explicit description of the filament). On the other hand, establishing a model on physics principles clearly enhances its predictive power. Then, in a second stage, the ROM is learned from the HF model, which does not suffer from the problems affecting experimental data: training data can be generated from the HF model without noise and without constraints on the quantity. This allows to fit data within a much wider class of candidate solutions (specifically, we fit training data with ANN-based models, which are able to virtually represent all ODE models, if a sufficient number of neurons is used, as proved in [84]).

To summarize, whereas phenomenological models are directly derived from experimental observations, with our approach the process is splitted into two stages. First, we build an HF model, by compensating for the deficiency and bad quality of experimental data thanks to physics. Then, in a second stage, we build a ROM, by fitting data (no more noisy nor defective) generated by HF model. Thus, the ROM should be seen merely as a way of efficiently solving the physics-based model itself.

A further advantage of building a model on the ground of a microscopical description is this allows to investigate the effects of microscopical properties on the macro-level tissue features (e.g. study the effect of drugs affecting the binding rate of myofilament proteins), whereas the parameters...
of phenomenological models may not have a clear physical interpretation.

8 Conclusions

We proposed a novel strategy to reduce the computational burden of cardiac multiscale EM simulations, wherein the intrinsically complex subcellular mechanisms leading to the activation of the muscular tissue make it difficult to trade off the detail of description of activation models (and thus their reliability) with computational efficiency. Specifically, we built an ANN-based ROM of a complex and detailed model of cardiac activation, featuring more than 2000 variables. This operation, thanks to the scale separation between the organ and the myofilaments, can be performed offline, without any dependence on the three-dimensional setting where we later embed the ROM. The ANN learns, within a gray-box approach, the dynamics of the HF model from a collection of input-output pairs, generated by the HF model itself, combined with some a priori knowledge, enforced during the learning process. In such a way we have derived a 2-variables ROM, capable of reproducing the results of the HF model with a relative error of about $10^{-2}$. Moreover, we have validated the results of the ANN-based model, by checking that it is still able to reproduce the experimental characterizations that the HF model can reproduce.

By employing the ANN-based ROM in the context of multiscale EM, the computational time associated to the solution of the activation subproblem is reduced by nearly 300 times, leading – in the case of the computational grids employed in this work – to a one order of magnitude decrease of the overall computational time required to approximate the EM problem. Moreover, the number of variables for each degree of freedom reduces from 2198 to just 24, a significant gain, especially when large-scale simulations are addressed. Remarkably, thanks to the stabilizing effect of the $SL$ feedback on the activation dynamics, the relative error introduced by employing the ANN-based ROM in the context of EM is just of about $10^{-3}$. We conclude that, in virtue of the offline ANN learning of the complex activation subproblem, a very favorable balance between reliability and computational efficiency is achieved, without any compromise with the detail of description of the microscopic phenomena pertaining the generation of force.

Acknowledgments

This project has received funding from the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme (grant agreement No 740132, iHEART - An Integrated Heart Model for the simulation of the cardiac function, P.I. Prof. A. Quarteroni). The authors gratefully acknowledge Dr. M. Fedele (MOX, Politecnico di Milano) for having provided the computational mesh of Test Case 3 and Dr. A. Gerbi (EPFL) for the interesting discussions about integrated cardiac modeling.

Appendix A The ANN-based model

The ANN-based model considered in this paper can be written in the form of (3), where the right hand side is given by the following ANN:

$$f(z, u) = W_2 \tanh(W_1 \tanh(W_0 (z^T, u^T)^T - \vartheta_0) - \vartheta_1) - \vartheta_2).$$

The application of the operator $\tanh$ has to be intended componentwise. The value of the weight matrices $W_j$ and of the bias vectors $\vartheta_j$ (where $j = 1, 2, 3$) are made available in the following online repository, together with a code to perform numerical simulations with the ANN model:

https://github.com/FrancescoRegazzoni/cardiac-activation-ANN.

The training of the ANNs has been carried out with the MATLAB library model-learning, which is also available online [82]:

Appendix B  Ventricular volume computation

In order to compute the ventricular volume \( V \) (i.e. the volume of the ventricular cavity), we proceed as follows. First, we identify the center point of the base as:

\[
b(t) = \frac{1}{|\Gamma^\text{base}_0|} \int_{\Gamma^\text{base}_0} (X + d(t)) d\Gamma_0,
\]

where \( X \) denotes the material coordinate and we close the ventricular cavity by the surface \( \Gamma^\text{cap}_t \), defined as the surface connecting the point \( b(t) \) with the orifice ring. The ventricular volume is thus defined as the measure of the volume \( \Omega^\text{fluid}_0 \), delimited by \( \Gamma^\text{endo}_t \) and \( \Gamma^\text{cap}_t \). By exploiting the identity \( \nabla \cdot (x - b(t)) = 3 \), where \( x \) denotes the spatial coordinate, we have:

\[
3V(t) = \int_{\Omega^\text{fluid}_t} dV = \int_{\Omega^\text{fluid}_t} \nabla \cdot (x - b(t)) dV = \int_{\Gamma^\text{endo}_t} (x - b(t)) \cdot n(t) d\Gamma + \int_{\Gamma^\text{cap}_t} (x - b(t)) \cdot n(t) d\Gamma,
\]

where \( n(t) \) and \( N \) denote the outer normal at the surface in the actual and reference domains respectively. Since, by construction, \( (x - b(t)) \perp n(t) \) on \( \Gamma^\text{cap}_t \), the second term vanishes, leading to the formula:

\[
V(t) = \frac{1}{3} \int_{\Gamma^\text{endo}_t} J(t) (X + d(t) - b(t)) \cdot F^{-T}(t) N d\Gamma_0,
\]

Appendix C  Boundary conditions for the mechanics problem

The base \( \Gamma^\text{base}_t \) is an artificial boundary and, as such, it must be provided with boundary conditions which account for the effect of the neglected part of the domain on the considered part. We respectively denote by \( \Omega_t \) and \( \Omega^\text{fluid}_t \) the solid and fluid domains located above the base, and by \( \Gamma^\text{endo}_t \), \( \Gamma^\text{epi}_t \) the endocardial end epicardial surfaces located above the base. By considering a quasistatic approximation and by denoting the Cauchy stress tensor by \( T = T^\text{pass} + T^\text{act} \), the momentum equation in the current configuration entails:

\[
0 = \int_{\tilde{\Omega}_t} \nabla \cdot T d\mathbf{x} = \int_{\Omega^\text{pass}_t} T n d\Gamma_t = \int_{\Gamma^\text{epi}_t} T n d\Gamma_t + \int_{\Gamma^\text{endo}_t} T n d\Gamma_t + \int_{\Gamma^\text{base}_t} T n d\Gamma_t.
\]

We assume that the epicardial surface located above the base is unloaded [71], that is \( T n = 0 \) on \( \Gamma^\text{epi}_t \). On \( \Gamma^\text{endo}_t \), which is in contact with the fluid, we have \( T n = -p n \). Moreover, we have the following identity:

\[
0 = \int_{\Omega^\text{fluid}_t} \nabla p d\mathbf{x} = \int_{\Gamma^\text{endo}_t} p n d\Gamma_t + \int_{\Gamma^\text{epi}_t} p n d\Gamma_t,
\]

which entails:

\[
\int_{\Gamma^\text{base}_t} T n d\Gamma_t = - \int_{\Gamma^\text{base}_t} T n d\Gamma_t = \int_{\Gamma^\text{endo}_t} p n d\Gamma_t = \int_{\Gamma^\text{endo}_t} p J F^{-T} n d\Gamma_0.
\]  \hspace{1cm} (17)

Equation (17) allows to derive the total stress applied on the boundary \( \Gamma^\text{base}_t \), but not its pointwise distribution. This is the price to pay as we do not explicitly include the domain \( \Omega_t \) into the EM model. Nonetheless, if we assume that the stress is uniformly distributed, we get:

\[
T n = |\Gamma^\text{base}_t|^{-1} \int_{\Gamma^\text{endo}_t} p J F^{-T} n d\Gamma_0 \quad \text{on} \quad \Gamma^\text{base}_t.
\]  \hspace{1cm} (18)
which reads, in the reference configuration:

$$\mathbf{PN} = \frac{\|J'F \mathbf{F}^{-T} \mathbf{N}\|}{\int_{\Gamma_{0}^{\text{base}}}} \frac{\|J'F \mathbf{F}^{-T} \mathbf{N}\| d\Gamma_0}{\int_{\Gamma_{0}^{\text{endo}}}} pJ'F \mathbf{F}^{-T} \mathbf{N} d\Gamma_0 \quad \text{on } \Gamma_{0}^{\text{base}}. \quad (19)$$

We notice that thanks to Eq. (19) the net force exerted by the fluid on the solid is null since the stress on $$\Gamma_{0}^{\text{base}}$$ perfectly balances the stress exerted on $$\Gamma_{0}^{\text{endo}}$$. This is coherent with the hydrostatic nature of the pressure force, which contributes to the energy of the system, but not to its momentum.

Appendix D   Error estimation of ANN-EM vs HF-EM in 1D

To gain some insight on the effect of the feedback of mechanics on activation, we consider a one-dimensional steady-state version of equation (13), which can be regarded as a simple model for the tissue deformation along the direction of the active force (i.e. the fibers direction). By denoting by $$d$$ the one-dimensional displacement and by $$e = \frac{d}{dx} d$$ the one-dimensional strain, we consider an elastic energy $$W(e)$$ and we define the passive stress as $$P_{\text{pass}}(e) := W'(e)$$, while we denote by $$P_{\text{act}}$$ the active stress. The mechanical equilibrium equation in the domain $$(0, L)$$ reads as follows:

$$\begin{cases} 
-\frac{d}{dx} \left( P_{\text{pass}} \left( \frac{d}{dx} d(x) \right) + P_{\text{act}}(x) \right) = 0 & \text{for } x \in (0, L) \\
\frac{d}{dx} d(0) = 0 \\
P \left( \frac{d}{dx} d(L) \right) + P_{\text{act}}(L) = p, 
\end{cases} \quad (20)$$

where we set a symmetry boundary condition at one side and a load $$p$$ at the other side. Coherently with model (1), the active stress is a function of calcium concentration and sarcomere length: $$P_{\text{act}}(x) = T_a(c(x), SL(x)) = T_a(c(x), SL_0(1 + e(x)))$$. The solution of Eq. (20) satisfies:

$$P_{\text{pass}}(e(x)) + T_a(c(x), SL_0(1 + e(x))) = p \quad \forall x \in (0, L)$$

Consider now a perturbed version of Eq. (20), where the function $$T_a$$ is replaced by a surrogate $$\tilde{T}_a = T_a + \eta$$, affected by the error $$\eta$$ (in our case, $$\eta$$ can be regarded as the approximation error associated with the reduced ANN model). By asymptotic analysis, the perturbed solution $$\tilde{d}$$ satisfies:

$$\frac{d}{dx} \tilde{d} - \frac{d}{dx} d \sim \eta \left( \frac{\partial T_a}{\partial SL} SL_0 + W''(c) \right)^{-1}.$$

Hence, the active stress in the perturbed problem is linked with the HF one by:

$$\tilde{T}_a(c, SL_0(1 + \tilde{e}(x))) - T_a(c, SL_0(1 + e(x))) \sim \eta \left( 1 + \frac{\partial T_a}{\partial SL} SL_0 \right)^{-1} \frac{W''(c)}{W''(e)}.$$

Being the elastic energy convex, the term $$W''(c)$$ is positive. Thus, on the ascending limb of the force-length relationship ($$\frac{\partial T_a}{\partial SL} > 0$$), the error $$\eta$$ is attenuated; conversely, on the descending limb ($$\frac{\partial T_a}{\partial SL} < 0$$) it is amplified.

References


33
MOX Technical Reports, last issues
Dipartimento di Matematica
Politecnico di Milano, Via Bonardi 9 - 20133 Milano (Italy)

31/2019  Pagani, S.; Vitulano, G.; De Blasi, G.; Frontera, A.
High density characterization of the atrial electrical substrate during sinus rhythm in patients with atrial fibrillation

32/2019  Fedele, M.
Polygonal surface processing and mesh generation tools for numerical simulations of the complete cardiac function.

30/2019  Pagani, S.; Manzoni, A.; Quarteroni, A.
Forward uncertainty quantification in cardiac electrophysiology by reduced order modeling and machine learning

Reduced order modeling for applications to the cardiovascular system

28/2019  Infantino, M.; Mazzieri, I.; Ozcebe, A.G.; Paolucci, R.; Stupazzini, M.
Physics-based probabilistic seismic hazard assessment in Istanbul

27/2019  Tantardini, M.; Ieva, F.; Tajoli, L.; Piccardi, C.
Comparing methods for comparing networks

26/2019  Antonietti, P. F.; Bonaldi, F.; Mazzieri, I.
Simulation of 3D elasto-acoustic wave propagation based on a Discontinuous Galerkin Spectral Element method

25/2019  Gigante, G.; Vergara, C.
On the stability of a loosely-coupled scheme based on a Robin interface condition for fluid-structure interaction

21/2019  Martino, A.; Guatteri, G.; Paganoni, A.M.
Hidden Markov Models for multivariate functional data

22/2019  Gigante, G.; Sambataro, G.; Vergara, C.
Optimized Schwarz methods for spherical interfaces with application to fluid-structure interaction