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DEEP-LEARNING-ASSISTED CARDIAC ELECTROPHYSIOLOGY SIMULATION

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ABSTRACT

Simulation built upon partial and ordinary differential equations has been a classic approach to modeling cardiac electrophysiological dynamics. However, mitigating the computational burden of differential equations is still a challenging problem. This paper provides a novel alternative utilizing data-driven recurrent neural networks for cardiac electrophysiological dynamic simulation. Specifically, we develop a long short-term memory (LSTM)-assisted simulation to capture the underlying dynamics of cardiac electrophysiology while preserving computational efficiency. Experimental results demonstrate the efficiency and effectiveness of the proposed method, which outperforms the differential equation-based simulation approach while significantly reducing the computational cost. The proposed method offers a promising alternative to traditional simulation and may contribute to the development of more efficient and accurate approaches for simulating cardiac electrophysiology.

1 INTRODUCTION

The heart plays a vital role in delivering oxygen and nutrients by pumping blood throughout the body. As a result, cardiac health plays a crucial aspect in human well-being. Unfortunately, cardiac disease remains one of the leading causes of death in the United States (Wang and Xiang 2023). To improve the treatment of cardiac diseases, researchers are increasingly interested in understanding the mechanism of the heart. One research area is investigating how computational models can simulate the biophysical processes of a heart, providing an in-depth understanding of how cardiac cells and tissues work. Existing simulation methods adopt partial differential equations (PDEs) and ordinary differential equations (ODEs) to model the ionic currents in the cells and tissue (Sundnes et al. 2007). These equations are solved using the finite element method (FEM) to simulate the dynamic processes of the heart. However, FEMs are often computationally expensive (Bucelli et al. 2021), especially when simulating a large number of cells and ionic currents. For example, simulating a complete heartbeat may cost thousands of iterations and four hours on a supercomputer with 32 cores (Niederer et al. 2011; Regazzoni et al. 2022). Therefore, it is critical to improve the computational efficiency of cardiac electrophysiology simulation, while preserving accurate simulation outcomes.

Various solutions have been proposed to mitigate the computational burden of cardiac electrophysiology simulation. Reduced-order model (ROM) is one of the commonly used solutions and employs a small set of parameters to approximate high-fidelity models (HFMs). Traditional ROMs often reduce the number of parameters through projection-based reduction which projects the solution onto a lower-dimensional basis from the original solution space (Benner et al. 2015). There are two major approaches to projection-based reduction: model-based reduction and data-driven reduction. Model-based reduction keeps the mathematical form of differential equations and replaces the full-order solution with low-order ones (Hochbruck and Lubich

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1997; Bai 2002; Boulakia et al. 2012; Quarteroni et al. 2015). However, none of these methods adapts well to complex cardiac electrophysiology systems with nonlinear manifolds of solutions. In recent years, there are various research adopting data-driven reduction with artificial neural networks (ANNs) to reduce the dimension of computational components in HFMs, which significantly improves computational efficiency than model-based reduction (Regazzoni et al. 2020; Regazzoni 2020; Regazzoni et al. 2022). Specifically in cardiac electrophysiology simulation, data-driven ROMs, such as neural ODE (Chen et al. 2018), can estimate differential equations with the assistance of data-driven components, which significantly accelerate the computational speed. However, Neural ODE still assumes the time-varying system behavior follows a fixed function (e.g., PDEs, ODEs), which can easily cause accuracy issues when various applications' underlying true functions deviate.

A large part of the discrepancies between the real systems' underlying functions and simulations' adopted function often stems from model uncertainties, caused by inadequate knowledge of reality and/or using oversimplified models. Model uncertainty is inevitable in simulations using differential equations, as PDEs and ODEs are often only partially understood and merely approximate the real system dynamics with closure parameters. To address this limitation, we propose to replace the differential equations with data-driven recurrent networks. Specifically, we propose a data-driven and long short-term memory (LSTM)-assisted simulation method to model cardiac electrophysiological dynamics. Due to their capability of learning long-term dependencies, LSTMs do not rely on any fix-form differential equations and can simulate long-term behaviors with sparse input data. Furthermore, data-driven models generate significantly less computational cost compared to differential equation-based models. In the experiment, we benchmark the proposed simulation method with a differential equation-based simulation. The proposed method outperforms the benchmark both in accuracy and computational time. The contributions of this paper are summarized as follows:

- The proposed LSTM-assisted simulation model allows us to simulate the long-term variation of cardiac electrophysiological signals.
- By replacing the differential equations with data-driven models, the proposed methodology can bring the tissue-level electrophysiology simulation into a more flexible model form to capture the true input-output relationships.
- The LSTM-assisted simulation greatly improves the simulation accuracy and efficiency, which is conducive to improving treatment planning and decision-making.

The remainder of the paper is organized as follows: Section 2 outlines the current practice of ROMs and its application in cardiac electrophysiology; Section 3 presents the methodology of LSTM-assisted cardiac electrophysiology simulation; Section 4 evaluates and validates the proposed methodology; Section 5 concludes the research.

2 RESEARCH BACKGROUND

In the current practice, ROM is a commonly used approach to reducing the computational burden. The drawback of ROM lies in the use of differential equations, which can not fully address the discrepancies between the simulated and real system and result in model uncertainty.

2.1 Projection-based ROMs and Cardiac Electrophysiology Applications

Reduced-order models (ROMs) reduce the dimension of the original system representation by projecting the governing equations onto a low-dimensional subspace. ROMs can be approached from a variety of viewpoints, of which the most commonly used are projection-based approaches. Specifically, the full-order state space $\mathbf{X} \in \mathbb{R}^N$ is approximated by a low-dimensional subspace $\mathbf{V} \in \mathbb{R}^{N \times n}$, of which the columns are the basis functions of the subspace. The full-order state at a certain time step is then modeled as

$\mathbf{X}_t \simeq \mathbf{V}\mathbf{x}_t, \mathbf{x}_t \in \mathbb{R}^n$, and the HFM is formulated using the Galerkin (or Petrov-Galerkin) method as:

$$\begin{cases} \dfrac{d\mathbf{x}}{dt} = \mathbf{W}'\mathbf{F}(\mathbf{V}\mathbf{x}_t), t \in [0,T] \\ \mathbf{x}_0 = \mathbf{W}'\mathbf{X}_0 \end{cases} \tag{1}$$

where $\mathbf{F}(\cdot)$ is a function of the time-varying full-order state, and $\mathbf{V}$ and $\mathbf{W}$ are a pair of Hilbert spaces. With the Explicit Euler method, the dynamic of the reduced-order state is approximated as $\mathbf{x}_{t+1} = \mathbf{x}_t + (t_{j+1} - t_j) \times \frac{d\mathbf{x}}{dt}$, where t_{j+1} and t_j are two consecutive time steps. A variety of projection-based approaches exist, including proper orthogonal decomposition (POD) (Boulakia et al. 2012), reduced basis methods (Quarteroni et al. 2015), and Krylov subspace methods (Hochbruck and Lubich 1997; Bai 2002), which differ in the procedure of selecting bases for $\mathbf{V}$ and $\mathbf{W}$.

To simulate cardiac electrophysiology, complex ROMs are proposed by coupling ODEs with PDEs (Quarteroni et al. 2015; Pagani et al. 2018). POD has been applied in cardiac electrophysiology to compress snapshots over time (Boulakia et al. 2012). A POD–Galerkin method is also developed to project a set of snapshots of the HFM onto low-dimensional subspaces by POD (Pagani et al. 2018; Bonomi et al. 2017). Moreover, a lax-Pairs approach is proposed as an alternative to ROM, where the basis functions change with respect to time according to the traveling front (Gerbeau and Lombardi 2014; Gerbeau et al. 2015). However, due to the large set of solutions to HFM, traditional projection-based ROM is computationally expensive to simulate complex cardiac electrophysiological dynamics.

2.2 Data-driven Projection-based ROMs and Cardiac Electrophysiology Applications

Different from traditional projection-based ROM, data-driven projection-based ROM reduces the computation efforts using the inferential power of machine learning models (Regazzoni et al. 2019; Regazzoni et al. 2020; Regazzoni 2020; Regazzoni et al. 2022). For example, in data-driven projection-based ROM, a reduced basis can be constructed based on full-order data with POD. Then, projection coefficients onto the reduced basis are mapped with time using a regression model (Guo and Hesthaven 2019). A general mathematical formulation is:

$$\begin{cases} \dfrac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{q}(\mathbf{X}_t)), t \in [0,T] \\ \mathbf{x}_0 = \mathbf{0}^T \\ \widetilde{\mathbf{X}}_{t+1} = \lambda(\mathbf{x}_{t+1}) \end{cases} \tag{2}$$

The dynamics of reduced-order state is still updated as $\mathbf{x}_{t+1} = \mathbf{x}_t + (t_{j+1} - t_j) \times \frac{d\mathbf{x}}{dt}$. $\mathbf{f}(\cdot)$, $\lambda(\cdot)$ and $\mathbf{q}(\cdot)$ are data-driven models. $\mathbf{q}(\cdot)$ is an encoder that maps full-order state $\mathbf{X}$ to reduced-order state $\mathbf{x}$. Researchers also incorporate physical information into data-driven ROMs (Raissi et al. 2019). Data-driven ROM reduces the computational expense with a relatively low-dimension solution space.

However, when applying data-driven ROM in simulating cardiac electrophysiology, the data-driven model can only replace the ODE of cardiac electrophysiology simulation, while the PDE is preserved as in traditional projection-based ROM (Regazzoni et al. 2019). Therefore, FEM still needs to rebuild the full-order solution space, which leads to huge computational efforts. Furthermore, this ODE solver can only deal with a dynamic system that has time-dependent inputs, whereas in cardiac electrophysiology no inputs are provided because of the all-or-none basis of neural spiking (Lucas 1909).

A recent study makes it possible to learn the dynamics of cardiac electrophysiology all at once. Neural ODE (Chen et al. 2018) offer a continuous-time generative method for representing time series data. It embeds $\mathbf{f}(\cdot)$, $\lambda(\cdot)$, and $\mathbf{q}(\cdot)$ in one neural network and trains them simultaneously. Its performance on cardiac electrophysiology simulation can be improved considering the physical information of HFM (Kashtanova et al. 2022). However, these methods still rely on differential equations to capture the temporal

dynamics of the system, while the real system may not vary with time following certain patterns described by differential equations.

2.3 Learning the HFM with Deep Neural Networks

Therefore, researchers start considering approximating full-order models without any finite differential equations, such as non-finite-differential approaches, to capture the complete temporal dynamics of the real system. A general formulation of the non-finite-differential approach is represented as:

$$\begin{cases} \widetilde{\mathbf{X}}_{t+1} = \mathbf{F}(\widetilde{\mathbf{X}}_t), t \in [0, T] \\ \mathbf{X}_0 \leftarrow \text{Initialization} \end{cases} \tag{3}$$

where we can model $\mathbf{F}(\cdot)$ as deep neural networks. In doing so, $\mathbf{F}(\cdot)$ directly outputs the results at a certain time step without any presumed differential equations.

Several papers have explored the use of deep neural networks to predict differential equation systems. These systems often exhibit chaotic behavior, where the system's state can undergo significant changes based on different initial conditions. Previous study by Shahi et al. (2021) have treated the prediction of action potentials as a multivariate time series prediction problem. The authors introduced information about the pacing stimulus timing as an additional input to the network, alongside the cardiac electrophysiology time series. Another study by Shahi et al. (2022) conducted a comparative analysis of RNN, reservoir network, and NVAR techniques for predicting Mackey-Glass, Lorenz-63 systems, and cardiac electrophysiology time series. Both papers approached the time series problem as an online prediction task, where the model's output could be used as input for subsequent predictions in an autoregressive manner. However, these studies only focused on time sequence data from individual cardiac cells, neglecting the exploration of cardiac tissue data. On the other hand, the simulation of electrophysiology in a square cardiac tissue slab is achieved using Convolutional LSTM (Shi et al. 2015), as discussed in Cantwell et al. (2019). Nevertheless, the training of the model followed a sequence-to-sequence approach, limiting its ability to make predictions with newly generated data. Consequently, this model was unable to perform long-term predictions effectively.

To address these limitations, our paper proposes a deep learning method called LSTM-assisted simulation, which overcomes the aforementioned challenges. This approach enables the autoregressive simulation of cardiac electrophysiology at the tissue level, which has a greater potential for various applications compared with previous simulation in studying pathology and medical decision-making.

3 RESEARCH METHODOLOGY

In this paper, our goal is to develop an LSTM-assisted simulation to capture tissue-level dynamics of cardiac electrophysiology. We will explain the core research components in the following sections.

3.1 Data Preparation for LSTM-assisted Simulation

Cardiac electrophysiology explores cardiac electrical behavior, such as action potential, membrane potential, refractory period, and ion channels. Membrane potential, as a significant component of cardiac electrophysiology, represents the difference in electrical charge between the interior and exterior of a cardiac cell. The distribution of ions, such as sodium (Na+), potassium (K+), and calcium (Ca2+), move in response to various stimuli, such as the opening and closing of voltage-gated ion channels. These activities are responsible for the coordination and contraction of cardiac muscle. Therefore, accurately simulating the dynamics of membrane potential is of great help in studying cardiac electrophysiology without conducting extensive human experiments.

We define the data collected from the simulation as the "Golden Standard". This simulation data represents an idealized version of the cardiac electrophysiology being simulated, as it is generated based

on known mathematical models that describe the behavior of the cardiac system. By comparing the outputs of the LSTM-assisted simulation with the known simulation data, one can assess the accuracy of the LSTM-assisted method in capturing the underlying patterns and behaviors of cardiac electrophysiology.

During the simulation, we adopt 24-by-24 square grids to represent the heart tissue. We define a dataset $\{\mathbf{x}_0, \mathbf{x}_1, \cdots, \mathbf{x}_{T-1}\}$, where $\mathbf{x} \in \mathbb{R}^{N\times 4}$ represents snapshots of four critical attributes in the cardiac electrophysiological dynamics. $N = 576$ is the number of cells contained within the 24-by-24 square grid. T is the duration of the simulation. The four critical attributes include the membrane potential and three other variables summarizing Ca2+ ionic dynamics (Ten Tusscher and Panfilov 2006):

- **Cai** represents the intracellular calcium concentration in the cytosol of the ventricular cell. It is primarily regulated by the L-type Ca2+ current and the sodium-calcium exchanger (NCX).
- **CaSR** represents the intracellular calcium concentration in the sarcoplasmic reticulum (SR), which is a specialized organelle in the cell that sequesters and releases Ca2+ ions. CaSR is primarily regulated by the SR Ca2+ ATPase (SERCA) and the ryanodine receptor (RyR) channels.
- **Cass** represents the intracellular calcium concentration in the submembrane space. Submembrane space is the region where sarcolemmal membrane and membrane of the SR are in close proximity.

To develop the LSTM-assisted simulation model, 80% of snapshots within the duration T is sampled into a set of N_s finite-time training sequences $\mathscr{X} = \{\mathbf{X}^1, \mathbf{X}^2, \cdots, \mathbf{X}^{N_s}\}$, where each training sequence $\mathbf{X}^i = \{\mathbf{x}_0, \mathbf{x}_1, \cdots, \mathbf{x}_{N_t-1}\} \in \mathbb{R}^{N\times 4\times N_t}$ consists of sequential N_t snapshots. Then, we split $\mathbf{X}^i$ into an input sequence $\mathbf{X}_{in}$ and a target sequence $\mathbf{X}_{out}$ to train the LSTM model. The input sequence $\mathbf{X}_{in}$ is regarded as a set of past membrane potential values, whereas the target sequence $\mathbf{X}_{out}$ is considered as the current membrane potential values. Therefore, the length of $\mathbf{X}_{in}$ and $\mathbf{X}_{out}$ are $N_t - 1$:

$$\begin{aligned} \mathbf{X}_{in} &= \{\mathbf{x}_t, \mathbf{x}_{t+1}, \cdots, \mathbf{x}_{t+N_t-2}\} \\ \mathbf{X}_{out} &= \{\mathbf{x}_{t+1}, \mathbf{x}_{t+2}, \ldots, \mathbf{x}_{t+N_t-1}\} \end{aligned} \tag{4}$$

3.2 LSTM-assisted Simulation of Cardiac Electrophysiological Dynamics

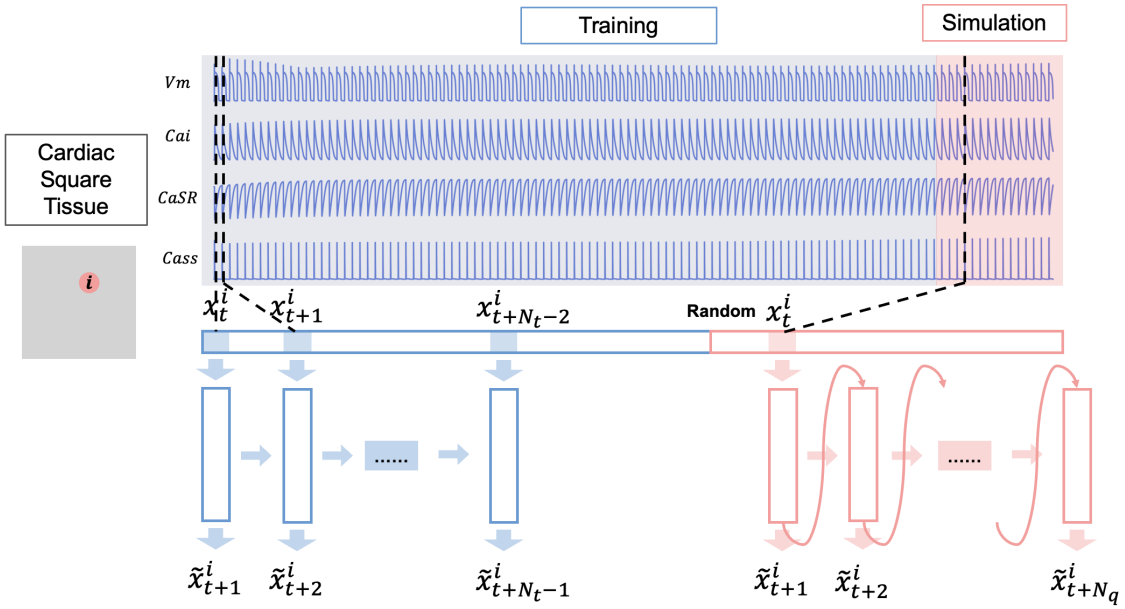


Figure 1: LSTM-assisted simulation workflow.

The proposed LSTM-assisted simulation contains multiple LSTM layers and a dense output layer. The workflow of simulation is as shown in Figure 1. The blue component in the figure represents the training process of the LSTM model. A trained model can continuously simulate sequences of membrane potentials (or the other three attributes) for any cell i as shown in the red component. N_q represents the length of the output. The simulation model is mathematically formulated as:

$$\begin{cases} \mathbf{h}_{t+1} = \mathscr{NN}_{LSTM}(\mathbf{x}_t, \mathbf{h}_t), t \in \{0, 1, \cdots, N_t - 2\} \\ \mathbf{h}_0 = \mathbf{0}^T \\ \mathbf{x}_0 \leftarrow \text{Initialization} \\ \widetilde{\mathbf{x}}_{t+1} = \mathbf{g}(\mathbf{h}_{t+1}), t \in \{0, 1, \cdots, N_t - 2\} \end{cases} \tag{5}$$

where $\mathscr{NN}_{LSTM}$ represents the LSTM cell that maps a current hidden vector $\mathbf{h}_t$ to its subsequent state representation $\mathbf{h}_{t+1}$ given input $\mathbf{x}_t$. By feeding $\mathbf{h}_{t+1}$ to a dense neural layer $\mathbf{g}(\cdot)$, we can estimate $\widetilde{\mathbf{x}}_{t+1}$.

We define the loss function of LSTM as the error between the estimated value $\widetilde{\mathbf{X}}_{out}$ and the true value $\mathbf{X}_{out}$ in Equation 6. We use backpropagation through time (BPTT) and Adam optimizer to update the LSTM network parameters, through which the network learns to simulate $\mathbf{X}_{out}$ accurately.

$$L = \frac{\sum_{i=1}^{N_s} (\mathbf{X}_{out} - \widetilde{\mathbf{X}}_{out})^2}{N_s} \tag{6}$$

3.3 Offline Training and Online Simulation Algorithms

Algorithm 1: Offline Training Algorithm

Data: Training dataset $\mathscr{X} = \{\mathbf{X}^1, \mathbf{X}^2, \cdots, \mathbf{X}^{N_s}\}$, number of train-epochs N_{ep}, batch size N_b, flatten input size $N_{in} = N \times 4$

Result: Tuned model parameters θ^*

Randomly initialize θ;
for $i \leftarrow 0$ **to** N_{ep} **do**
  Shuffle $\mathscr{X}$;
  for $j \leftarrow 0$ **to** $N_s \mid N_b$ **do**
    Sample a batch $\mathscr{X}_b \subset \mathscr{X}$;
    Stack and reshape $\mathscr{X}_b$ as $\mathbf{X}_b \in \mathbb{R}^{N_b \times N \times 4 \times N_t}$;
    Split $\mathbf{X}_b$ along the time dimension into input sequence and target sequence: $\mathbf{X}_{b\_in} = \{\mathbf{x}_0, \mathbf{x}_1, \cdots, \mathbf{x}_{N_t-2}\}$ and $\mathbf{X}_{b\_out} = \{\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_{N_t-1}\}$, where $\mathbf{x} \in \mathbb{R}^{N_b \times N \times 4}$;
    Initialize hidden state $\mathbf{h}_0 \leftarrow \mathbf{0} \in \mathbb{R}^{N_b \times N_{in}}$;
    for $t \leftarrow 0$ **to** $N_t - 2$ **do**
      $\mathbf{x}_t \in \mathbb{R}^{N_b \times N \times 4} \leftarrow \mathbf{X}_{b\_in}$;
      $\mathbf{h}_{t+1} \leftarrow \mathscr{NN}_{LSTM}(\mathbf{x}_t, \mathbf{h}_t)$;
      $\widetilde{\mathbf{x}}_{t+1} \leftarrow \mathbf{g}(\mathbf{h}_{t+1})$
    end
    Stack $\widetilde{\mathbf{x}}_t$ for $t \in \{1, 2, \cdots, N_t - 1\}$ as $\widetilde{\mathbf{X}}_{b\_out} \in \mathbb{R}^{N_b \times N \times 4 \times (N_t - 1)}$;
    Use $\widetilde{\mathbf{X}}_{b\_out}$ and $\mathbf{X}_{b\_out}$ to calculate approximate gradient $\hat{\mathbf{g}}$ of Equation 6 ;
    Update parameters: $\theta \leftarrow \text{ADAM}(\hat{\mathbf{g}})$;
  end
end

We propose both offline training and autoregressive online simulation strategies in this paper. Algorithm 1 outlines the offline training of the LSTM network in more detail. During offline training, the LSTM model $\mathscr{NN}_{LSTM}$ takes a batch of the sampled sequence $\mathscr{X}_b$ from the training set $\mathscr{X}$. We split $\mathscr{X}_b$ into input sequence and target sequence to train $\mathscr{NN}_{LSTM}$ and $\mathbf{g}(\cdot)$, which are $\mathbf{X}_{b\_in} = \{\mathbf{x}_0, \mathbf{x}_1, \cdots, \mathbf{x}_{N_t-2}\}$ and $\mathbf{X}_{b\_out} = \{\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_{N_t-1}\}$, where $\mathbf{x} \in \mathbb{R}^{N_b \times N \times 4}$. Then $\mathscr{NN}_{LSTM}$ together with $\mathbf{g}(\cdot)$ output $\widetilde{\mathbf{x}}_t$ for $t \in \{1, 2, \cdots, N_t - 1\}$, where $\widetilde{\mathbf{x}}_t$ are the subsequent state of the input sequence. While optimizing the error between output sequence $\widetilde{\mathbf{X}}_{out} = \{\widetilde{\mathbf{x}}_1, \widetilde{\mathbf{x}}_2, \cdots, \widetilde{\mathbf{x}}_{N_t-1}\}$ and $\mathbf{X}_{out} = \{\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_{N_t-1}\}$, parameters in $\mathscr{NN}_{LSTM}$ and $\mathbf{g}(\cdot)$ are learned.

Given the well-tuned parameters θ^* and an initial condition $\mathbf{x}_0 \in \mathbb{R}^{N \times 4}$, we can iteratively update $\widetilde{\mathbf{x}}_t$ for next $N_q \in \mathbb{Z}^+$ steps with the simulation model in Equation 5. Specifically, the proposed LSTM-assisted simulation can reconstruct dynamics $\widetilde{\mathbf{x}}_t$ autoregressively for any number of time steps. The online simulation algorithm is outlined in Algorithm 2.

Algorithm 2: Online Simulation Algorithm

Data: Initial condition $\mathbf{x}^0 \in \mathbb{R}^{N \times 4}$, number of prediction steps $N_q \in \mathbb{Z}^+$
Result: Simulation sequence $\mathscr{X}_s = \{\mathbf{x}^1, \mathbf{x}^2, \cdots, \mathbf{x}^{N_q}\}$

```
Load trained parameters θ*;
Initialize LSTM input x_in ← x^0, hidden state h_0 ← 0;
for t ← 0 to N_q − 1 do
    h_{t+1} ← NN_LSTM(x_in, h_t) ;
    x̃_{t+1} ← g(h_{t+1});
    x_in ← x̃_{t+1}
end
```

4 EXPERIMENTAL RESULTS

4.1 Data Sampling from Cardiac Electrophysiology HFM

In this paper, we define a time interval $(0, T]$ and a computational domain $\Omega = [0,1] \times [0,1]$ which represents a square mesh. The time interval is set to be $T = C \times N_c$ ms, where C is the simulation cycle length and N_c is the number of heartbeat cycles. Based on suggestions from the paper by Ten Tusscher and Panfilov (2006), we determine the cycle length to be $C = 500$ ms. Moreover, we define a stimulus of strength 100 mV and duration 1 ms, located in the area of $\Omega_0 = [0.8, 1] \times [0.8, 1]$.

To sample the data, we simulate the behavior of cardiac tissue using a monodomain model coupled with an ionic model proposed by Ten Tusscher and Panfilov (2006). The latter is a continuum approach that enables us to describe the tissue as a single entity. We simulate 109 heartbeat cycles and collect four critical attributes, including membrane potential, Cai, CaSR, and Cass, at all cell locations (c_i, c_j) within domain Ω.

4.2 Setting up Benchmark model – Neural ODE Model

We benchmark the proposed LSTM-assisted simulation with a Neural ODE (Chen et al. 2018), which we consider as the state-of-the-art data-driven ROM with a black-box differential equation solver. With the differential equation solved, Neural ODE updates cardiac electrophysiology dynamics with the Explicit Euler method.

Model structure Neural ODE model is built upon variational auto-encoder (VAE), which learns to represent the underlying distribution of training data with a lower-dimensional space, known as the latent space (Kingma et al. 2014). Specifically, Neural ODE maps snapshots of cardiac electrophysiology $\mathbf{X} = \{\mathbf{x}_0, \mathbf{x}_1, \cdots, \mathbf{x}_{N_t-1}\}$ at each time step to a latent trajectory $\{\mathbf{z}_0, \mathbf{z}_1, \cdots, \mathbf{z}_{N_t-1}\}$ with an encoder and rebuilds the snapshots

Table 1: Performance comparison between the proposed model and benchmark model.

	MSE				Generation
	Vm	Cai	CaSR	Cass	time (ms)
Neural ODE Simulation	0.4560	0.2532	0.1297	0.6458	604.17
LSTM-assisted Simulation	0.0247	0.0053	0.0119	0.0238	104.17

$\widetilde{\mathbf{X}} = \{\widetilde{\mathbf{x}}_0, \widetilde{\mathbf{x}}_1, \cdots, \widetilde{\mathbf{x}}_{N_t-1}\}$ with a decoder. Mathematically, the encoder and decoder in Neural ODE are formulated as:

$$\begin{aligned} \mathbf{z}_0 &\sim RNN(\mathbf{X}) \\ \mathbf{z}_1, \mathbf{z}_2, \cdots, \mathbf{z}_{N_t-1} &= ODESolver(\mathbf{z}_0, t_0, t_1, \cdots, t_{N_t-1}, \mathbf{f}) \\ \widetilde{\mathbf{x}}_i &= \lambda(\mathbf{z}_i), \text{ for } i \in \{0, 1, \cdots, N_t - 1\} \end{aligned} \tag{7}$$

where *RNN* is the encoder, and *ODESolver* and $\lambda(\cdot)$ are decoders. The initial state $\mathbf{z}_0$ is obtained by passing the input sequence $\mathbf{X}$ through the *RNN*. Then, *ODESolver* outputs subsequent latent states $\{\mathbf{z}_1, \mathbf{z}_2, \ldots, \mathbf{z}_{N_t-1}\}$. Specifically, $\mathbf{f}(\cdot)$ in the *ODESolver* outputs gradient $\frac{d\mathbf{z}_t}{dt} = \mathbf{f}(\mathbf{z}_t)$, and $\mathbf{z}_{t+1}$ is updated as $\mathbf{z}_{t+1} = \mathbf{z}_t + (t_{j+1} - t_j) \times \mathbf{f}(\mathbf{z}_t)$, where t_{j+1} and t_j are two consecutive time steps. Finally, we obtain output sequence $\widetilde{\mathbf{X}}$ by passing the resulting latent trajectory through neural network $\lambda(\cdot)$.

Loss function Neural ODE is trained by maximizing the likelihood over a set of time steps in the interval $[t_{start}, t_{end}]$:

$$\log p(t_0, \ldots, t_{N_t-1} | t_{start}, t_{end}) = \sum_{i=0}^{N_t-1} \log \lambda(\mathbf{z}_i) - \int_{t_{start}}^{t_{end}} \lambda(\mathbf{z}_t) dt \tag{8}$$

4.3 Performance Comparison between LSTM-assisted Simulation and Neural ODE

With the Adam optimizer, we set hyper-parameters as follows: learning rate is 10^{-3}, the batch size is 16, the number of hidden layers in LSTM is 2, and training epoch N_{ep} is 3. The LSTM-assisted model and Neural ODE are implemented using PyTorch deep learning framework and trained on an NVIDIA GeForce RTX 3070.

We compare the performances of simulating long-term dynamics of cardiac electrophysiology between the proposed LSTM-assisted simulation and Neural ODE via mean squared error (MSE) on the same testing set $\widetilde{\mathbf{X}}_{out}$. MSE is formulated as:

$$MSE = \frac{(\mathbf{X}_{out} - \widetilde{\mathbf{X}}_{out})^2}{C \times N} \tag{9}$$

MSE is utilized to quantify the discrepancy between the output sequence and input sequence. As shown in Table 1, the proposed model outperforms the Neural ODE in terms of both accuracy and efficiency. The LSTM-assisted model achieves a much lower MSE than the Neural ODE for all four attributes. On the other hand, the LSTM model takes only 104.17 milliseconds to simulate one heart cycle, while the Neural ODE takes 604.17 milliseconds.

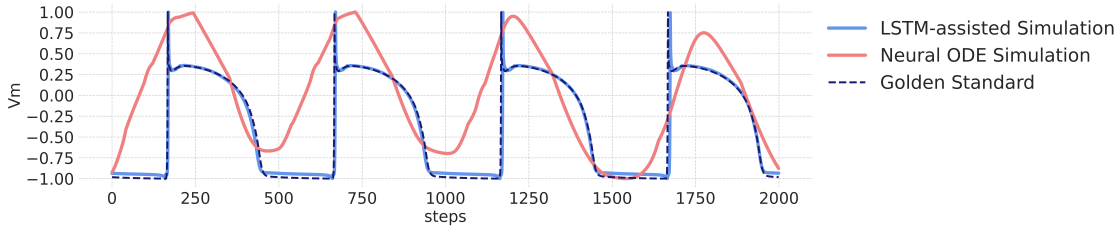


Figure 2: Comparison between normalized membrane potentials sampled from HFM and simulated by both LSTM-assisted and Neural ODE models.

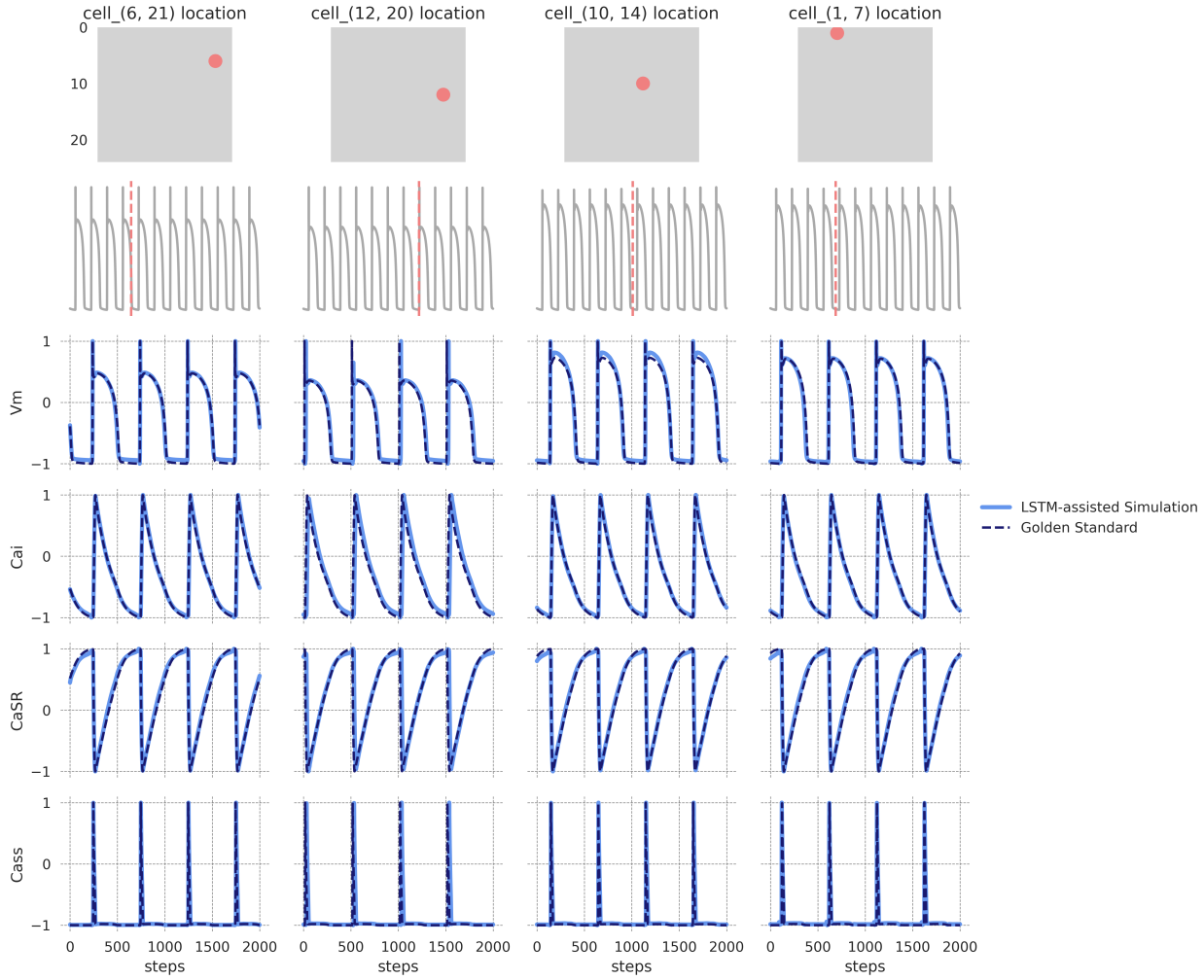
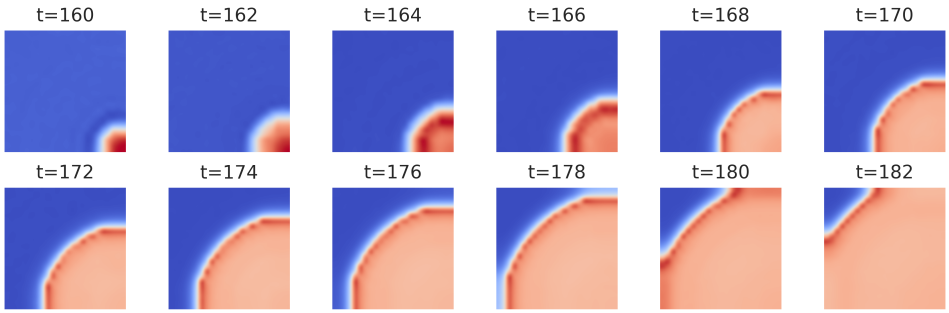


Figure 3: Simulations of four normalized attributes (i.e., membrane potential (Vm), Cai, CaSR, and Cass) for four different cells at various starting time points.

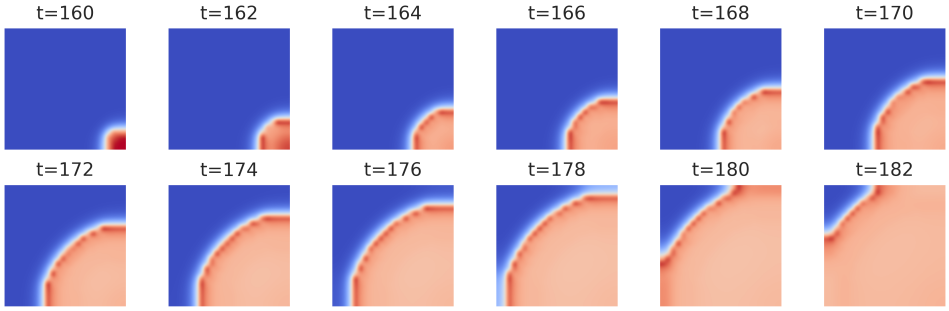
Moreover, as shown in Figure 2, the proposed LSTM-assisted simulation outputs nearly the same waveform of membrane potentials as the golden standard, which is the membrane potential signal sampled from HFM. As a comparison, the Neural ODE can only capture the rough pattern of the membrane potential waveform. This further validates that the proposed LSTM-based model can learn and reproduce membrane potentials accurately. In addition, the learning capability of Neural ODE degrades drastically as time goes on, while LSTM-assisted simulation can still reconstruct membrane potential precisely.

The proposed LSTM-assisted simulation has the ability to remember and incorporate past inputs into their current output, which is attained by maintaining a cell state that can carry information forward in time. As a result, the proposed method can learn complex temporal dependencies and make accurate long-term predictions. In Figure 3, we simulate the long-term dynamics of four critical attributes, i.e., membrane potential, Cai, CaSR, and Cass, for different cells at various starting time points. The signals of four attributes simulated by the LSTM-assisted model almost overlay the golden standard sampled from HFM. Results shown in Figure 3 suggest that the proposed model can accurately simulate the dynamics of cardiac electrophysiology at any cell location, and it is flexible to start the simulation at any time point.

In the experiment, we also compare action potential propagations simulated by the LSTM-assisted model with HFM. We select 12 time steps within a propagation cycle. In Figure 4, the LSTM-assisted



(a) LSTM-assisted simulation



(b) Golden standard

Figure 4: Comparison of membrane potential (normalized) propagation between (a) LSTM-assisted simulation and (b) the golden standard.

simulation result at each time step looks nearly identical to HFM. The proposed simulation provides a flexible tool for cardiologists to investigate the long-term cardiac signals at any cell location, which is conducive to detecting the origin of abnormal cardiac signals and helps with treatments of heart diseases, such as atrial fibrillation.

5 CONCLUTIONS

Cardiac electrophysiology simulation is critical for us to understand the mechanism of the heart. The literature has been adopting ODEs and PDEs as the backbone for simulation. To mitigate the time-consuming calculation of ODE-based and PDE-based FEM, researchers introduced ROM-based approaches in the past.

However, traditional ROMs assume that cardiac electrophysiology follows pre-determined differential equations, which is not always the case. This paper replaces the differential equations in ROMs with an LSTM-assisted simulation method. The proposed method not only identifies a compact and low-dimensional representation of the original high-dimensional space but also models the dynamics of low-dimensional space. To validate the performance of the proposed model, we apply it to cardiac electrophysiology simulation, where complex spatiotemporal patterns of four critical attributes should be captured.

The experimental results show that LSTM-assisted simulation outperforms differential equation-based simulation in accuracy and efficiency. Due to the long-term memory of LSTM cells, LSTM-assisted simulation can capture long-term dependencies in cardiac electrophysiological dynamics. Furthermore, the proposed method provides a fast and reliable simulation of cardiac electrophysiology, which further helps with cardiac disease diagnosis and treatment planning.

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