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APHYN-EP: Physics-based deep learning framework to learn and forecast cardiac electrophysiology dynamics

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Abstract. Biophysically detailed mathematical modeling of cardiac electrophysiology is often computationally demanding, for example, when solving problems for various patient pathological conditions. Furthermore, it is still difficult to reduce the discrepancy between the output of idealized mathematical models and clinical measurements, which are usually noisy. In this paper, we propose a fast physics-based deep learning framework to learn cardiac electrophysiology dynamics from data. This novel framework has two components, decomposing the dynamics into a physical term and a data-driven term, respectively. This construction allows the framework to learn from data of different complexity. Using 0D *in silico* data, we demonstrate that this framework can reproduce the complex dynamics of transmembrane potential even in presence of noise in the data. Additionally, using *ex vivo* 0D optical mapping data of action potential, we show the ability of our framework to identify the relevant physical parameters for different heart regions.

Keywords: Physics-based learning · Deep Learning · Electrophysiology · Simulations.

1 Introduction

Multi-physics phenomena involved in cardiac function can be studied using mathematical models of different complexity. Among them, several electrophysiology (EP) models can accurately reproduce the electrical behaviour of the heart at cellular, tissue or organ level. For instance, in order to describe the dynamics of transmembrane voltage, current and different ionic concentrations in the cardiac cell, detailed biophysical models such as the Ten Tusscher-Panfilov model [21, 22] have been proposed. However, these models are intricate and computationally expensive, and have numerous hidden variables which are nearly impossible to measure all, making the model parameters difficult to personalise.

Alternatively, one can use phenomenological models that involve simplified descriptions derived from biophysical models. Examples of such models are the FitzHugh-Nagumo, Aliev-Panfilov, and Mitchell-Schaeffer models [6, 13, 1, 14, 12], which all employ fewer variables and parameters, and are therefore especially useful for rapid computational modelling of wave propagation at tissue and organ level. However, these are less realistic and, consequently, need a complementary mechanism to enable their fitting to measured data. Machine learning and in particular deep learning (DL) approaches could help provide such correction mechanisms. Thus, the combination of rapid phenomenological models and machine learning components may allow the development of rapid and accurate models of transmembrane dynamics.

For this reason, researchers have started to use coupled physico-statistical approaches for cardiac electrophysiology simulations with a high precision and at low cost. For example, one group designed a neural network that approximates the FitzHugh-Nagumo model [5], others used a physics-informed neural network for cardiac activation mapping accounting for underlying wave propagation dynamics [20], while another group proposed an approach to create a nonlinear reduced order model with the help of deep learning algorithms (DL-ROM) designed for cardiac EP simulations [7]. Lastly, other researchers presented a physics-informed neural network for accurate simulation of action potential and correct estimation of model parameters [9]. However, the majority of these coupled approaches is based on high-fidelity physical models. Fitting those to the data could be not only computationally expensive but also difficult to properly manage large discrepancies between simulated and real data.

To alleviate this limitation, here we propose to use the APHYN-EP framework, a DL framework based on a fast low-fidelity (or incomplete) physical model. This framework has two components, decomposing the dynamics into a physical term and a data-driven term, respectively. Notably, the data-driven deep learning component is specifically designed to capture only the information that cannot be modeled by the incomplete physical model. In our previous paper [10] we showed that this framework is able to reproduce with good precision the 2D dynamics simulated by the Ten Tusscher – Noble – Noble – Panfilov ionic model. But we applied the framework only on simulated data and on the depolarisation part of a cardiac action potential cycle, neglecting the repolarisation part.

In this paper, we specifically explore the capability of APHYN-EP framework to learn the full cardiac action potential cycle (i.e., depolarisation and repolarisation phases). Using 0D *in silico* data, we demonstrate that our framework can reproduce the complex dynamics of transmembrane potential even in presence of noise in the data. Additionally, using *ex vivo* 0D epicardial optical fluorescence mapping data, we show the capability of this framework to identify relevant physical parameters for different anatomical zones of the heart.

2 Learning Framework

In order to learn the cardiac electrophysiology dynamics (X_t), here we solve an optimization problem via our physics-based data-driven APHYN-EP framework. This particular framework combines a physical model (F_p) representing an incomplete description of the underlying phenomenon with a neural network (F_{dl}), where the latter complements the physical model by capturing the information that cannot be modeled by the physics-described component:

$$\min_{F_p \in \mathcal{F}_p, F_{dl} \in \mathcal{F}_{dl}} \|F_{dl}\| \quad \text{subject to } \forall X \in \mathcal{D}, \forall t, \frac{dX_t}{dt} = F(X_t) = (F_p + F_{dl})(X_t). \quad (1)$$

Our incomplete physical model is the two-variable (v, h) model by [12] for cardiac EP simulations (2). The variable v represents a normalised ($v \in [0, 1]$) dimensionless transmembrane potential while the ‘‘gating’’ variable h controls the repolarisation phase (i.e, the return to initial resting state):

$$\begin{aligned} \frac{dv}{dt} &= \frac{hv^2(1-v)}{\tau_{in}} - \frac{v}{\tau_{out}} + J_{stim}(t) \\ \frac{dh}{dt} &= \begin{cases} \frac{1-h}{\tau_{open}} & \text{if } v < v_{gate} \\ \frac{-h}{\tau_{close}} & \text{if } v > v_{gate} \end{cases} \end{aligned} \quad (2)$$

where J_{stim} is a transmembrane potential activation function, which is equal to 1 during stimulation time (t_{stim}). This physical model has been successfully used in patient-specific modelling [19], covering general EP dynamics. Furthermore, in contrast to very detailed ionic/cellular models, this model is flexible in terms of spatial and temporal steps. Thus, assuming the initial conditions for this system (2) $v(t=0) = 0$ and $h(t=0) = 1$ we can calculate an approximation of h for any time point t with the help of a simple integration scheme.

The framework’s deep learning component (F_{dl}) is a Residual Network (ResNet) [8], because it can accurately reproduce a complex dynamics due to residual connections in its architecture. The choice of data-driven component is not limited by ResNet architecture. We performed preliminary experiments with other types of networks (out of scope for this paper), but overall the ResNet model was the most stable along the different simulations.

In APHYN-EP framework the physical and the data-driven components are trained simultaneously using automatic differentiation tools provided by the Pytorch library [17]. Here, the Loss function (\mathcal{L}) for training consists of 2 parts: trajectory-based loss and loss on norm of F_{dl} , being represented as following:

$$\mathcal{L} = \lambda * \mathcal{L}_{traj} + \|F_{dl}\| = \lambda * \sum_{i=1}^N \sum_{h=1}^{T/\Delta t} \|X_{h\Delta t}^{(i)} - \tilde{X}_{h\Delta t}^{(i)}\| + \|F_{dl}\|$$

where each state $\tilde{X}_{h\Delta t}^{(i)} = \int_{X_0^{(i)}}^{X_0^{(i)} + h\Delta t} (F_p^{\theta_p} + F_a^{\theta_a})(X_s) dX_s$ is calculated from the initial state $X_0^{(i)}$ via a differentiable ODE solver [4, 3]. The role of the λ coefficient

is to balance the two parts of the loss. During training, we use λ in the dynamic mode as $\lambda_{j+1} = \lambda_j + \gamma \mathcal{L}_{\text{traj}}(\theta_{j+1})$ (j is an epoch number) to artificially increase the importance of $\mathcal{L}_{\text{traj}}$ at the beginning of training and gradually decrease it, changing the focus of optimization on norm of F_{dl} . This training algorithm is described in detail in [23, 10].

3 Experimental settings

To test the performance of APHYN-EP framework, we chose two types of experiments. First, using *in silico* data, we tested the ability of the framework to reproduce the complex dynamics of transmembrane potential even in the presence of noise in the data. Second, using *ex vivo* optical mapping data, we showed that our framework can identify the relevant physical parameters for different anatomical zones of the unhealthy heart. The details of data collection and training settings used for the experiments are included below.

3.1 *In silico* data

Data collection To evaluate our method, we used a dataset of transmembrane potential activation simulated with a monodomain reaction-diffusion equation and the Ten Tusscher – Panfilov ionic model [22], which represents 12 different transmembrane ionic currents. The simulations were performed with finetwave software⁷, described in detail in the second chapter of [15]. The computational domain represents a 2D slab of cardiac tissue (isotropic), with 24×24 elements in size. One stimulation was applied for 1 ms in the selected area (left top corner for training and near the center for validation datasets, see Figure 1) for transmembrane potential activation. Simulations were conducted for 400 ms (of a heart beat) to achieve full depolarization-repolarization cycle (videos showing simulated dynamics across time can be seen in the Supplementary Material). Next, we saved a time sequence for each pixel of the cardiac slab in separate files, creating two databases: for training and validation, respectively. To simplify the workflow for our framework, we removed the section of time sequences where the potential is equal to zero (Figure 1(c)). To test the ability of the framework to operate with noisy data we add to each time sequence a 5 percent random noise with normal Gaussian distribution.

The data simulated via the Ten Tusscher – Panfilov model with added noise were considered here as the ground truth. The objective was then to learn the complex dynamics generated via this model with the APHYN-EP framework, combining a simplified physics description with a deep learning component. This should result in a low computational cost surrogate model of the computationally intensive biophysically detailed Ten Tusscher – Panfilov model.

⁷ <https://github.com/TiNezlobinsky/Finitewave>

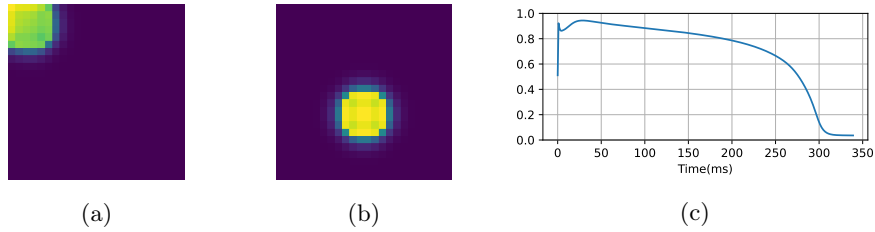


Fig. 1: (a,b) 2D cardiac slab with transmembrane potential activation (yellow) and resting phase (dark blue), for train and validation dataset, respectively. (c) Typical temporal sequence for the experiment (without noise), normalised amplitude of the transmembrane potential on the Y-axis and time (ms) on the X-axis.

Training settings The physical model (F_p) of Eq. (2) was implemented with a standard finite-difference scheme. We estimated only τ_{in} , τ_{out} and τ_{close} as unknown parameters in (2), since they control the major part of model dynamics and thus the main difference between the Mitchell–Schaeffer and the Ten Tusscher – Panfilov models in our simulations. The initial Mitchell-Schaeffer model parameters were taken as in the original paper [12]: $\tau_{in} = 0.3$, $\tau_{out} = 6$, $\tau_{open} = 120$, $\tau_{close} = 150$, $v_{gate} = 0.13$ and $t_{stim} = 1$. For the deep learning component (F_{dl}) of the framework, we used a ResNet with 8 filters at the initial stage and 3 intermediary blocks, and started with a re-weighted orthogonal initialisation for its parameters.

We used a time resolution of 0.1 ms to compute the forecast given by APHYN-EP framework. The training was performed using a horizon of 350 ms. We trained the framework until full model convergence (about 100 epochs) using an ADAM optimiser [11] with initial learning rate of 10^{-3} . The hyper-parameters λ_0 and γ of the algorithm were set to 1 and 10, respectively.

It is important to notice that, while the framework takes a few hours to train (about 2h on Nvidia Quadro M2200 GPU), once this is done the inference is quick (less than 10 sec to compute 350 ms of forecasting) and does not require any recalibration.

3.2 *Ex vivo* data

Data collection We tested APHYN-EP framework performance on *ex vivo* datasets from optical fluorescence imaging of action potential. Briefly, the optical signals were recorded *ex vivo* on an heart explanted from a juvenile swine (25kg in weight). The heart was attached to a Langendorff perfusion system and a voltage sensitive dye (i.e., di-4-ANEPPS) was injected into the perfusate. In order to avoid cardiac motion artifacts during the electrophysiological recordings, the heart contraction was suppressed by a bolus of saline and Cytochalasin D (an electro-mechanical uncoupler). All optical images were acquired epicardially

using a high-speed CCD camera (MICAM02, BrainVision Inc. Japan), with high-temporal resolution (3.7ms) as well as a high-spatial resolution (i.e., pixel size 0.7mm). The action potential was then derived at each pixel from the relative change in the intensity of fluorescence signal. The experiments are described in more detail in [18]. The recorded signals were exported from the BV-Ana acquisition software and further signal analysis was performed using in-house scripts written in Matlab and Python.

For this experiment, we used a heart with an ischaemic region. We manually selected two rectangular regions of interest (ROIs) with different action potential dynamics across time (see Figure 2). Next, we normalised the optical signal, to obtain a $[0, 1]$ min/max interval for transmembrane potential (while keeping the noise in the data). We took a first full cardiac cycle and removed the parts with zero potential keeping only time-sequences of 300 ms per experiment. Then, we saved a time sequence for each pixel from each ROI in separate files, creating two databases (ROI A and ROI B) containing each about 10 and 5 time-sequences for training and validation respectively.

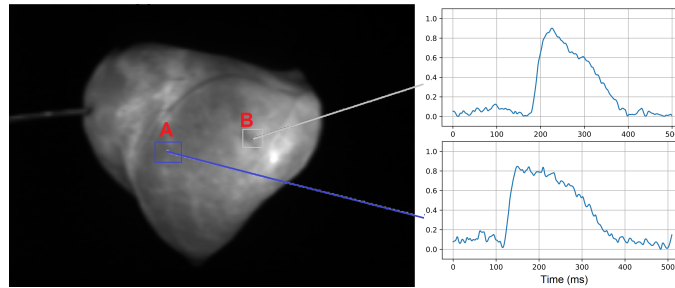


Fig. 2: Example of optical mapping data (tracings of action potential waves) recorded ex vivo in a porcine heart. ROI B represents an ischaemic region characterized by a shortened action potential duration (APD) compared to the normal APD recorded in ROI A.

The optical data were considered here as the ground truth. Our specific objective was to learn the complex dynamics of measured action potential, and then to identify the relevant physical parameters for different parts of the heart.

Training settings The training settings for this experiment were similar to the ones described in section 3.1, except for training horizon (300 ms) and parameter γ , which was set to 1 for better equilibrium.

4 Results

4.1 *In silico* data

Results demonstrated that APHYN-EP framework was able to accurately reproduce several key features, the wave morphology and the electrical conduction properties of the transmembrane potential generated by the Ten Tusscher – Panfilov model (see Figure 3), even in presence of noise in data. Figure 3(a) shows that in absence of parameter τ_{close} (controlling the repolarisation), the data-driven component (ResNet model) completed the dynamics generated by physical component. In the presence of τ_{close} the error of dynamics learned by data-driven component is minimal (Figure 3(b)). The predicted dynamic was generated via an Euler integration scheme, by assimilating only one first measurement of the transmembrane potential dynamics. The framework showed robust resistance to noise in the data, and, as a result, it neglected rapid changes in transmembrane potential activation (see Figure 3, first 40 ms).

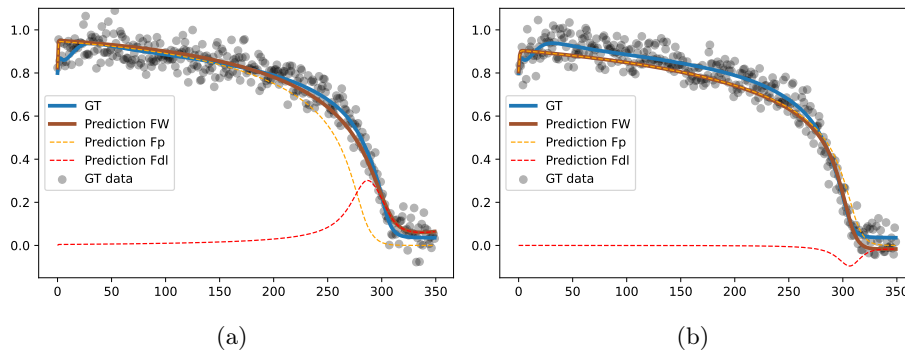


Fig. 3: Validation results of trained framework with learning of (a) 2 (τ_{in} and τ_{out}) and (b) 3 (τ_{in} , τ_{out} and τ_{close}) physical parameters. Ground truth (GT), prediction of the framework (Prediction FW), decomposition of prediction on physical (F_p) and DL (F_{dl}) parts.

4.2 *Ex vivo* data

Using optical imaging mapping data, APHYN-EP framework was able to reproduce the observed action potential dynamics for different ROIs within the heart, identifying the 3 major physical dynamics parameters (τ_{in} , τ_{out} and τ_{close}). Figure 4 demonstrates that the framework correctly estimated the difference in value of parameter τ_{close} which increases APD or shortens it, respectively.

Table 1 shows the mean squared error (MSE) results for our framework forecasting on train and validation data samples. To calculate this error, for each

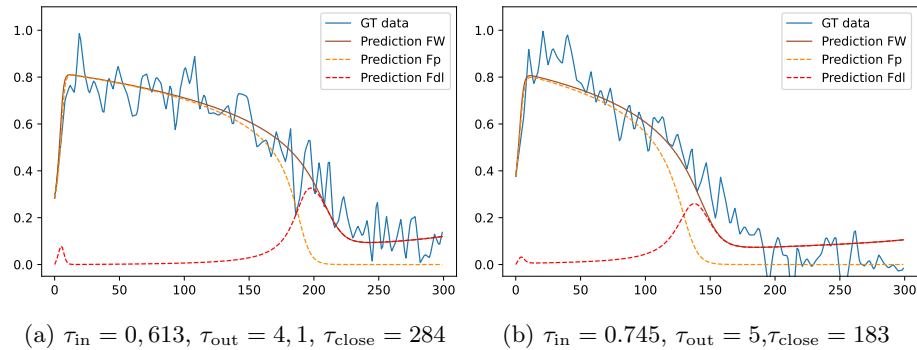


Fig. 4: Validation results of the framework trained on: (a) ROI A data and (b) ROI B data. Ground truth (GT) data, prediction of the framework (Prediction FW), decomposition of prediction on physical (F_p) and DL (F_{dl}) parts.

data sample, we fed the framework with only one initial measurement, then let it predict 300 ms forward without any additional information. We also added for comparison a baseline model corresponding to the “incomplete” physical model trained alone on the same dataset as APHYN-EP framework, described in 3.2. As we can observe, our framework outperform the physical model for every dataset, while the contribution of F_{dl} component is still minimal.

Table 1: Mean-squared error (MSE) of normalised transmembrane potential forecasting (forecasting horizon of 300 ms).

	ROI A		ROI B	
	Train	Validation	Train	Validation
APHYN-EP framework ($\ F_{dl}\ ^2$)	$9.12 * 10^{-3}$ ($1.6 * 10^{-4}$)	$5.72 * 10^{-3}$ ($8 * 10^{-5}$)	$1 * 10^{-2}$ ($8 * 10^{-5}$)	$8 * 10^{-3}$ ($7 * 10^{-5}$)
Physical model only	$1.4 * 10^{-2}$	$1 * 10^{-2}$	$1.45 * 10^{-2}$	$9.3 * 10^{-3}$

It is important to notice that we cannot use the Ten Tusscher – Panfilov ionic model [22] applied on *ex vivo* data as a baseline model due its parameter personalisation difficulties [2]. Despite the expectations and suggestions indicated in [2, 16], these difficulties have not been overcome. Complex biophysical models have too many parameters and instabilities to enable robust parameter estimation from such data.

5 Discussion and Conclusion

In this work, we presented a learning framework that is able to learn the considered dynamics. Overall, our results suggest that automated learning of cardiac

electrophysiology dynamics is feasible and has great potential. We showed that APHYN-EP framework can learn and forecast the EP data of different origin (i.e, data simulated via the Ten Tusscher – Panfilov ionic model, as well as real optical mapping data), even in presence of noise in the data. This may be useful for applications concerning fast parameterization of computational heart models.

The main advantage of our proposed framework is its coupled architecture, which allows us to use a simplified low-fidelity electrophysiological model as a physical component of the framework. Such framework opens up possibilities in order to introduce prior knowledge in deep learning approaches through explicit equations, as well as to correct physical model errors from data.

However, we acknowledge some limitations of our model. For instance due to data-driven architecture of the framework, its training is not regular. This could lead to the local minimum for the parameters of the physical component and additional involvement of the deep learning component. A solution for this problem may be given by a more advanced training protocol, rigid boundaries on physical model parameters and performing ablation studies including deep learning component architectural changes, which will be addressed in our future work.

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References

1. Aliev, R.R., Panfilov, A.V.: A simple two-variable model of cardiac excitation. *Chaos, Solitons & Fractals* **7**(3), 293–301 (1996)
2. Camara, O., Sermesant, M., Lamata, P., Wang, L., Pop, M., Relan, J., De Craene, M., Delingette, H., Liu, H., Niederer, S., Pashaei, A., Plank, G., Romero, D., Sebastian, R., Wong, K., Zhang, H., Ayache, N., Frangi, A., Shi, P., Smith, N., Wright, G.: Inter-model consistency and complementarity: Learning from ex-vivo imaging and electrophysiological data towards an integrated understanding of cardiac physiology. *Progress in Biophysics and Molecular Biology* **107**(1), 122–133 (2011), experimental and Computational Model Interactions in Bio-Research: State of the Art
3. Chen, R.T.Q., Amos, B., Nickel, M.: Learning neural event functions for ordinary differential equations. *ICRL* (2021)
4. Chen, R.T.Q., Rubanova, Y., Bettencourt, J., Duvenaud, D.: Neural ordinary differential equations. *Adv Neural Inform Process Syst* (2018)
5. Court, S., Kunisch, K.: Design of the monodomain model by artificial neural networks. *arXiv preprint:2107.03136* (2021)

6. FitzHugh, R.: Impulses and physiological states in theoretical models of nerve membrane. *Biophysical Journal* **1**(6), 445–466 (1961)
7. Fresca, S., Manzoni, A., Dedè, L., Quarteroni, A.: POD-enhanced deep learning-based reduced order models for the real-time simulation of cardiac electrophysiology in the left atrium. *Front. Physiol.* **12** (2021)
8. He, K., Zhang, X., Ren, S., Sun, J.: Deep residual learning for image recognition. In: *IEEE conf. CVPR.* pp. 770–778 (2016)
9. Herrero Martin, C., Oved, A., Chowdhury, R.A., Ullmann, E., Peters, N.S., Bharath, A.A., Varela, M.: EP-PINNs: Cardiac electrophysiology characterisation using physics-informed neural networks. *Front. Cardiovasc. Med.* **8** (2022)
10. Kashtanova, V., Ayed, I., Arrieula, A., Potse, M., patrick gallinari, Sermesant, M.: Deep learning for model correction in cardiac electrophysiological imaging. In: *Medical Imaging with Deep Learning* (2022)
11. Kingma, D.P., Ba, J.: Adam: A method for stochastic optimization. *arXiv preprint:1412.6980* (2014)
12. Mitchell, C.C., Schaeffer, D.G.: A two-current model for the dynamics of cardiac membrane. *Bull. Math. Biol.* **65**(5), 767–793 (2003)
13. Nagumo, J., Arimoto, S., Yoshizawa, S.: An active pulse transmission line simulating nerve axon. *Proceedings of the IRE* **50**(10), 2061–2070 (1962)
14. Nash, M.P., Panfilov, A.V.: Electromechanical model of excitable tissue to study reentrant cardiac arrhythmias. *Prog. Biophys. Mol. Biol.* **85**(2), 501–522 (2004)
15. Nezhobinsky, T.: Software for cardiac modelling and patch clamp experiments, and its application to study conduction in the presence of fibrosis. Ph.D. thesis, Ghent University (2021)
16. Niederer, S., Mitchell, L., Smith, N., Plank, G.: Simulating human cardiac electrophysiology on clinical time-scales. *Frontiers in physiology* **2**, 14 (2011)
17. Paszke, A., Gross, S., Massa, F., Lerer, A., Bradbury, J., Chanan, G., Killeen, T., Lin, Z., Gimelshein, N., Antiga, L., et al.: Pytorch: An imperative style, high-performance deep learning library. *Adv. Neural Inf. Process. Syst.* **32** (2019)
18. Pop, M., Sermesant, M., Lepiller, D., Truong, M.V., McVeigh, E.R., Crystal, E., Dick, A., Delingette, H., Ayache, N., Wright, G.A.: Fusion of optical imaging and mri for the evaluation and adjustment of macroscopic models of cardiac electrophysiology: A feasibility study. *Medical Image Analysis* **13**(2), 370–380 (2009), includes Special Section on Functional Imaging and Modelling of the Heart
19. Relan, J., Chinchapatnam, P., Sermesant, M., Rhode, K., Ginks, M., Delingette, H., Rinaldi, C.A., Razavi, R., Ayache, N.: Coupled personalization of cardiac electrophysiology models for prediction of ischaemic ventricular tachycardia. *Interface Focus* **1**(3), 396–407 (2011)
20. Sahli Costabal, F., Yang, Y., Perdikaris, P., Hurtado, D.E., Kuhl, E.: Physics-informed neural networks for cardiac activation mapping. *Front. Phys.* **8**, 42 (2020)
21. Ten Tusscher, K.H.W.J., Noble, D., Noble, P.J., Panfilov, A.V.: A model for human ventricular tissue. *Am. J. Physiol. - Heart Circ. Physiol.* **286**, H1573–H1589 (2004)
22. Ten Tusscher, K.H.W.J., Panfilov, A.V.: Alternans and spiral breakup in a human ventricular tissue model. *Am. J. Physiol. - Heart Circ. Physiol.* **291**(3), H1088–H1100 (2006)
23. Yin, Y., Le Guen, V., Dona, J., Ayed, I., de Bezenac, E., Thome, N., Gallinari, P.: Augmenting physical models with deep networks for complex dynamics forecasting. In: *Int. Conf. ICRL* (2021)