33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Identification of nonlinear cardiac cell dynamics using radial basis function regression

Samir Kanaan-Izquierdo, Susana Velazquez and Raul Benitez, Member, IEEE

Abstract— **We present a novel method for the identification of the dynamics of physiological cardiac cell models. The main aim of the technique is to improve the computational efficiency of large-scale simulations of the electrical activity of the heart. The method identifies the dynamical attractor of a detailed physiological model using statistical learning techniques. In particular, a radial basis function regression method is used to capture the intrinsic dynamical features of the model, thus reducing the computational cost to quantitatively generate cardiac action potentials in a wide range of pacing conditions. The approach permits to recover key properties such as the action potential morphology and duration in a wide range of pacing frequencies.**

I. INTRODUCTION

Modeling the electrical activity of the heart is essential in order to gain further insight into the biophysical mechanisms underlying heart function and disease. At the cellular level, single-cell models describe the evolution of the cell membrane potential in terms of a set of ionic currents flowing across the myocyte.

Since the first model of a cardiac cell by Noble [1], an increasing number of cardiac cell models have been proposed in the literature [2]. Realistic single-cell models include detailed biophysical mechanisms of the membrane channels, providing a powerful tool to study clinical conditions associated to anomalous function of specific ion channels [3].

The incorporation of additional features, however, increases the complexity of the model which in turn raises the computational demand of multidimensional simulations of the cardiac tissue [4], [5]. Therefore, the complexity of the model should be chosen in terms of the particular questions to be addressed, assuming a compromise between the scale of the multicellular simulations and the level of detail of the single cell model.

A recent approach to address these problems is to formulate either empirical or simplified models [6]–[8]. Multidimensional optimization methods are then used to determine the model parameters that optimally reproduce the observed action potential (AP) morphology under different conditions. This approach presents two main drawbacks. On one hand, both simplified and empirical models typically use effective transmembrane currents which might not be related to ionic species, making it difficult to analyze the results. On the other, simple models contain some dynamical regimes of the observed system but are not necessarily able to explore the whole dynamical richness observed experimentally. Indeed, since single-cell APs present a variety of morphologies depending on the past and present pacing conditions, these methods tend to fail when predicting the emergence of new dynamical scenarios such as oscillatory regimes or cardiac alternans.

A practical approach to reduce the computational cost of realistic, large-scale simulations is to avoid the integration of the single-cell models by using a pattern recognition method to identify the intrinsic dynamical features of the cell response [9]. In a first stage, an identification system learns the dynamics of the biophysical model under different scenarios. Once the response of the model has been identified, the recognized dynamics can be used to predict future values of the membrane potential [10]. Identification of unknown nonlinear systems is also widely used in control engineering [11] and has been successfully used in the prediction of nonlinear time-series in areas such as weather forecasting [12]. Recent attempts to use similar methods in the area of cell modeling can be found in Ref. [13]. This approach requires ensuring the generalization of the procedure, namely that the method is able to provide correct predictions in situations that have not been explicitly included during the learning stage.

In this work we combine statistical learning and phase-space reconstruction methods to identify the nonlinear system underlying the generation of cardiac action potentials (AP) in cardiac single-cell models. Phase-space reconstruction methods are based in Taken's theorem, which states that under certain conditions the multidimensional structure of a nonlinear dynamical system can be identified from observed data [14]–[17].

The structure of the paper is organized as follows: In Section II we provide a detailed description of the model identification method and introduce the reference biophysical model used for testing the performance of the approach. The main capabilities of the technique are described in Sec. III, where we report examples of estimated AP morphology and duration under different pacing regimes. Finally, a discussion about the potentialities of the method and an exposition of further improvements is presented in Section IV.

II. MATERIALS AND METHODS

A. Model Identification method

The support vector regression (SVR) method performs a linear regression of the data in a feature space [10]. In a first stage, a mapping function is used to project the data into a

S. Kanaan-Izquierdo is with the Department of Software, Universitat Politecnica de Catalunya, Comte Urgell 187, 08036 Barcelona, Spain. S. Velazquez and R. Benitez are with the Department of Automatic Control, Universitat Politecnica de Catalunya, Comte Urgell 187, 08036 Barcelona, Spain. {samir.kanaan, susana.velazquez, raul.benitez}@upc.edu

978-1-4244-4122-8/11/$26.00 ©2011 Crown

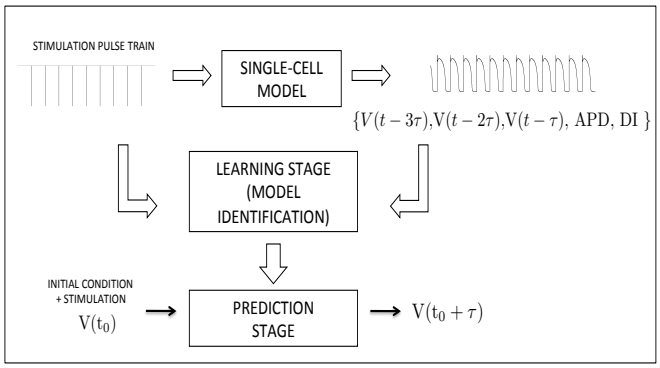

Fig. 1. Description of the basic stages of the method.

higher dimensional feature space. Next, linear regression in the feature space is performed in order to construct a model of the observed data. More specifically, ε-SV regression constructs a function in the feature space whose deviation from the projected objective function is at most ε. Such method yields a set of support vectors that define a tube of radius ε around the function being estimated [18]. SVR has been widely used to estimate non-linear time series [19] since it avoids overfitting of the training data while exhibiting a good overall performance.

The proposed method comprises two stages: training and prediction. A general description of the approach is described in Fig. 1. On the training stage, the training data provided to the SVR method consists in a set of results from the numerical simulation of the model to be studied. Since in our case the objective function is the membrane potential $V(t)$, we provide a set of time-delayed values of the model simulation, more specifically the three past cell membrane potential values $V(t-3\tau), V(t-2\tau), V(t-\tau)$, the action potential duration (APD) and diastolic interval (DI) of the last stimulation cycle, the stimulation current, and the time elapsed since the last stimulus. The delay time τ is chosen heuristically from a knowledge of the internal time scales of the model, thus providing a set of weakly correlated simulation samples [17]. The rationale behind using a time-delayed set of previous membrane potential values to forecast $V(t)$ is inspired in phase embedding methods where the attractor dynamics is identified from a set of time delayed values of the scalar measurements [14]–[17]. The SVR then computes a set of support vectors in the kernel space that allow it to estimate the function $V(t)$.

In the prediction stage, an estimate of $V(t_0+\tau)$ is obtained from the support vectors and a set of initial data $V(t_0-3\tau), V(t_0-2\tau), V(t_0-\tau)$, APD and DI of the last stimulation cycle, the stimulation current, and the time elapsed since the last stimulus. From this time on, the method uses its own predicted values in order to predict future values.

We have used an implementation of the ε-SVR method included in the package Kernlab [20] of the R [21] environment, with a Gaussian radial basis kernel function and with error radius $\varepsilon = 0.01$.

B. Case example: Identification of ten Tusscher's model

The ten Tusscher model provides a detailed description of human ventricular tissue and can be used to simulate epicardial, endocardial, and midmyocardial cells [22], [23]. The model has a total of 17 variables among which 12 correspond to the dynamics of ion channels. It is widely used in the area since it closely reproduces experimental measures and simulates the electrical activity of single cells as well as 1D cell rings and 2D tissue sheets. Therefore we have chosen ten Tusscher's model as the reference model for testing our approach.

In particular, we have used the model configuration that corresponds to epicardial cells with a maximum restitution slope of 1.1. Restitution measures the relationship between APD and DI. This relationship strongly depends on the stimulation sequence applied to the cell model. Two of the most commonly used stimulation protocols are the dynamic stimulation protocol [24] and the S1-S2 restitution pacing protocol. We have numerically simulated ten Tusscher model with both stimulation protocols in order to obtain a predictor as general as possible. Specifically, dynamic protocol has been applied with stimulation periods ranging from 1000 ms to 200 ms whereas S1-S2 protocol has been applied with a basic cycle length (BCL) of 600 ms and S2 diastolic intervals ranging from 700 ms to 20 ms. In both cases we have followed the parameters used in [23] in order to obtain comparable results. A combination of data from simulations using both dynamic and S1-S2 stimulation protocols is used for training, so that a single SVR is trained for both protocols.

An integration step of $\Delta t = 0.02$ ms has been used to integrate the ten Tusscher model with suitable precision. To construct the embedding training data we have chosen a time-lag $\tau = 1$ ms.

III. RESULTS

A. AP morphology

Dynamic protocol: The AP data predicted by our method as a response to a dynamic stimulation protocol accurately reproduces the AP simulated by ten Tusscher's model as can be seen in Fig. 2. Note that both normal (Fig. 2a) and alternans (Fig. 2b) AP cycles are properly estimated. The normalized root mean square error (NRMSE) is 1.57%, with 1134 support vectors.

S1-S2 protocol: The AP prediction for S1-S2 stimulation protocol at BCL=600 ms also reproduces the AP of ten Tusscher's model, as displayed in Fig. 2c. Both S1 and S2 cycles are accurately estimated, with a NRMSE of 3.84%. Apparently S1-S2 cell response is harder to predict than dynamic protocol response, as the only clue of a new S2 cycle is a different DI in the previous cycle. In our opinion this is the cause of the slightly larger prediction error on S1-S2.

B. APD restitution

Dynamic protocol: The restitution curves obtained by our prediction method accurately recover the dynamic restitution

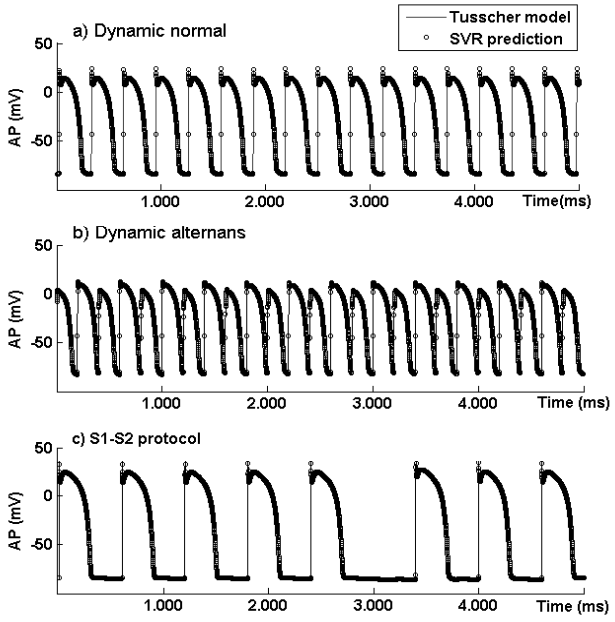

Fig. 2. Estimated AP morphology under different stimulation protocols.

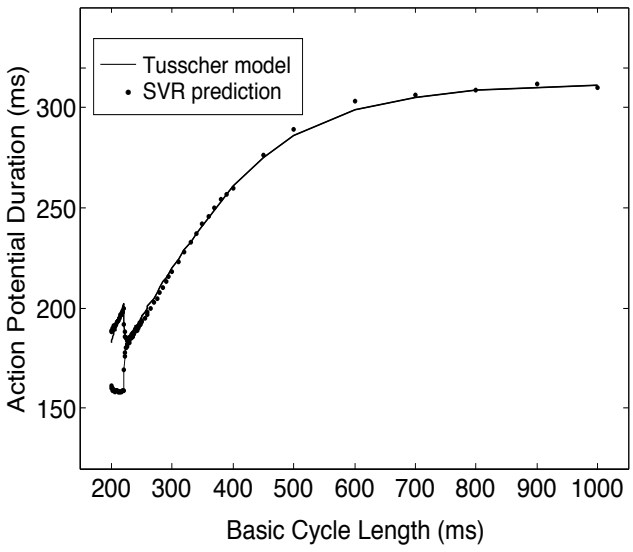

Fig. 3. Simulated and predicted APD restitution curves of the dynamic pacing protocol.

curves of ten Tusscher model as can be seen in Fig. 3. Remarkably, our approach predicts AP alternans as shown by the bifurcation at the lower left corner of Fig. 3. In summary, our prediction method properly reproduces the restitution of cardiac cells under dynamic stimulation protocol, presenting a NRMSE of 1.182%.

S1-S2 protocol: Our prediction method also reproduces APD restitution curve under S1-S2 protocol with accuracy, as depicted in Fig. 4. The overall error in APD restitution under S1-S2 stimulation protocol is 1.437%, while the error in estimating the diastolic interval is 1.225%.

C. Adaptation to different stimulation conditions

A final experiment has been performed to predict the cardiac cell response at pacing frequencies that have not been previously used in the training stage. The results for both dynamic protocol (NRMSE=1.72%) and S1-S2 protocol (NRMSE=6.24% at BCL = 420 ms) indicate that our method correctly generalizes the model dynamics, being able to reproduce responses to different stimulation sequences.

IV. CONCLUSIONS AND DISCUSSION

A. Conclusions

In this paper a new approach is presented to reproduce the dynamics of a cardiac cell electrical activity by learning it from sample data. The approach accurately reproduces the AP morphology with a low error rate, as well as the APD restitution curves, for the two main stimulation protocols. It is also able to generalize and predict the cell response under different pacing frequencies, correctly identifying and reproducing cell dynamics under different conditions.

B. Discussion

Although we have used ten Tusscher's model to test the performance of the method, the approach could also be used to identify the dynamics of more detailed models and even to directly learn from electrophysiological recordings at the cellular level. It is also possible to incorporate more physiological variables to the training stage so that the method can predict the behavior of myocytes of different species.

One of the most promising features of our method is that it provides detailed cell simulations at very low computational cost. Indeed, the time step of both learning and reconstruction stages is τ, much larger than the time step required to simulate ten Tusscher's model. In our simulations, $\tau = 1$ ms whereas $\Delta t = 0.02$ ms, which scales down the computational cost by a factor of 50. However, direct runtime comparisons are not yet available since ten Tusscher's model has been implemented in C and our method in R.

Furthermore, due to the simplicity of the method's internal state (three last potential values, last APD and DI and time since last stimulus), it should be easy to parallelize its execution, or even to keep a cache of the most frequent states and their output. These techniques would further reduce the time required to run large scale simulations at tissue level. Moreover, it is also possible to start a simulation at the desired pacing frequency, thus avoiding the usual procedure

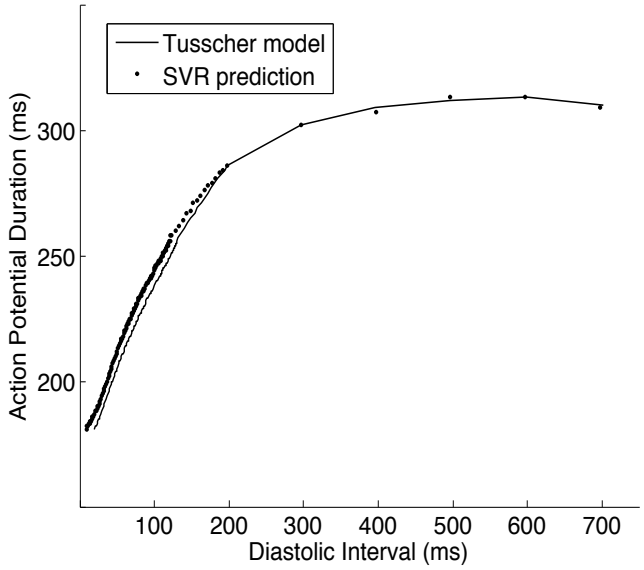

Fig. 4. Simulated and predicted APD restitution curves corresponding to the S1-S2 stimulation protocol

of starting simulations of the model at lower frequencies and slowly increase them to let the model adapt its internal state.

C. Further work

Once we have tested our method using a detailed cell model, we plan to use our approach to identify other physiological models or even use experimental data to drive the training stage. Further improvement can be achieved by computing the time-delayed mutual information of the simulated data [17] to automatically determine an optimal time lag τ for the embedding approach.

Finally, we plan to perform 1D tissue simulations to determine conduction velocity and to further validate the method. Afterwards, we would develop 2D tissue simulations to study spiral waves, which are important for fibrillation and arrhythmias. Indeed, both 2D and organ-level 3D simulations would take advantage of the performance improvements of our method.

V. ACKNOWLEDGMENTS

This work was supported by the Spanish Ministry of Education (MICINN) through project DPI 2009-06999.

REFERENCES

[1] D. Noble, "A modification of the hodgkin–huxley equations applicable to purkinje fibre action and pacemaker potentials." *J Physiol.*, vol. 160, pp. 317–52., 1962.

[2] F. H. Fenton and E. M. Cherry, "Models of cardiac cell," *Scholarpedia, 3(8):1868*, 2008.

[3] F. M. Ashcroft, *Ion channels and disease: channelopathies*. San Diego: Academic Press, 2000.

[4] A. Garny, D. Noble, and P. Kohl, "Dimensionality in cardiac modelling," *Progress in Biophysics and Molecular Biology*, vol. 87, no. 1, pp. 47 – 66, 2005, biophysics of Excitable Tissues.

[5] N. A. Trayanova, "Whole-heart modeling: applications to cardiac electrophysiology and electromechanics." *Circ Res*, vol. 108, no. 1, pp. 113–128, 2011.

[6] A. Bueno-Orovio, E. M. Cherry, and F. H. Fenton, "Minimal model for human ventricular action potentials in tissue," *J Theor Biol*, vol. 253, no. 3, pp. 544–60, Aug 2008.

[7] J. M. Rogers, "Modeling the cardiac action potential using b-spline surfaces," *IEEE Trans Biomed Eng*, vol. 47, no. 6, pp. 784–91, Jun 2000.

[8] S. Dokos and N. H. Lovell, "Parameter estimation in cardiac ionic models," *Prog Biophys Mol Biol*, vol. 85, no. 2-3, pp. 407–31, 2004.

[9] R. O. Duda, P. E. Hart, and D. G. Stork, *Pattern classification*, 2nd ed. New York: Wiley, 2001. [Online]. Available: http://www.loc.gov/catdir/bios/wiley041/99029981.html

[10] V. N. Vapnik, *The nature of statistical learning theory*, 2nd ed. New York: Springer, 2000. [Online]. Available: http://www.loc.gov/catdir/enhancements/fy0816/99039803-d.html

[11] O. Nelles, *Nonlinear system identification: from classical approaches to neural networks and fuzzy models*. Berlin: Springer, 2001.

[12] D. Tao and X. Hongfei, "Chaotic time series prediction based on radial basis function network," *Software Engineering, Artificial Intelligence, Networking, and Parallel/Distributed Computing, ACIS International Conference on*, vol. 1, pp. 595–599, 2007.

[13] C. Seijas, A. Caralli, and S. Villazana, "Estimation of action potential of the cellular membrane using support vectors machines," in *Engineering in Medicine and Biology Society, 2006. EMBS '06. 28th Annual International Conference of the IEEE*, 30 2006-sept. 3 2006, pp. 4200 –4204.

[14] H. D. I. Abarbanel, *Analysis of observed chaotic data.* New York: Springer, 1996.

[15] H. D. I. Abarbanel, R. Brown, J. J. Sidorowich, and L. S. Tsimring, "The analysis of observed chaotic data in physical systems," *Rev. Mod. Phys.*, vol. 65, no. 4, pp. 1331–1392, Oct 1993.

[16] R. Hegger, H. Kantz, and T. Schreiber, "Practical implementation of nonlinear time series methods: The tisean package," *Chaos*, vol. 9, no. 2, pp. 413–435, Jun 1999.

[17] H. Kantz and T. Schreiber, *Nonlinear time series analysis*, 2nd ed. Cambridge, UK: Cambridge University Press, 2004. [Online]. Available: http://www.loc.gov/catdir/samples/cam041/2003044031.html

[18] A. J. Smola and B. Schölkopf, "A tutorial on support vector regression," *Statistics and Computing*, vol. 14, pp. 199–222, August 2004.

[19] K. Lau and Q. Wu, "Local prediction of non-linear time series using support vector regression," *Pattern Recognition*, vol. 41, no. 5, pp. 1539 – 1547, 2008. [Online]. Available: http://www.sciencedirect.com/science/article/B6V14-4PK7P2X-2/2/ed347f53a80f34f6f11c6fb755dfe1f6

[20] A. Karatzoglou, A. Smola, K. Hornik, and A. Zeileis, "kernlab – an S4 package for kernel methods in R," *Journal of Statistical Software*, vol. 11, no. 9, pp. 1–20, 2004. [Online]. Available: http://www.jstatsoft.org/v11/i09/

[21] R Development Core Team, *R: A Language and Environment for Statistical Computing*, R Foundation for Statistical Computing, Vienna, Austria, 2009, ISBN 3-900051-07-0. [Online]. Available: http://www.R-project.org

[22] K. H. W. J. ten Tusscher, D. Noble, P. J. Noble, and A. V. Panfilov, "A model for human ventricular tissue," *Am J Physiol Heart Circ Physiol*, vol. 286, no. 4, pp. H1573–89, Apr 2004.

[23] K. H. W. J. ten Tusscher and A. V. Panfilov, "Alternans and spiral breakup in a human ventricular tissue model," *Am J Physiol Heart Circ Physiol*, vol. 291, no. 3, pp. H1088–100, Sep 2006.

[24] M. L. Koller, M. L. Riccio, and R. F. G. Jr., "Dynamic restitution of action potential duration during electrical alternans and ventricular fibrillation," *American Journal of Physiology - Heart and Circulatory Physiology*, vol. 275, no. 5, pp. H1635–H1642, 1998. [Online]. Available: http://ajpheart.physiology.org/content/275/5/H1635.abstract