Reconstruction from experimental data of a mathematical model of cardiac tissue: A feasibility study

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Abstract

The aim of this work is to study the feasability of reconstruction mathematical model of cardiac tissue from intracellular recordings. It is studied using simulated data and the presented method is applied to the Aliev-Panfilov model. A dissociated scheme is proposed and the estimation of some parameters is investigated in case of ideal or noisy data. The influence of the number and distribution of electrodes is then studied.

1. Introduction

Multielectrodes arrays (MEAs) are widely used in experimental investigation of cellular activities in cardiac domains [1–4]. The MEAs allow extracellular potential recordings of cardiac cells in culture in vitro. Recorded signals can be analyzed by mathematical models. Usually, these models use normalized parameters and describe qualitatively the dynamics of the cardiac cells electrical activities. Another approach is to identify intrinsic parameters resulting of experimental signals and to establish a cardiac cell inspired model. This approach is based on estimation and identification of parameters largely used in the optimization theory. The methodology consists firstly on a choice of an adequate model. Then, an enough number of signals must be recorded to identify the unknown parameters of the model. However, the number, the size and the distance between electrodes are limited because of physical constraints (surface, types of electrodes, price, acquisition setup). The proposed method focused on the estimation of the intracellular coupling and the parameter describing the sodium current (conductance and threshold). Furthermore, in this paper, the relation between the number of electrodes and the accuracy of estimated parameters is investigated. Our results suggest that there exists a compromise between the number of electrodes and the values of model parameters which emulate closely the cardiac cells electrical activities. The effect of noise, usually present in experimental data, is measured.

2. Methods

2.1. Model description

Although there exist methods to construct models without no a-priori knowledge about the system [5], it is usually preferable to use already existing ones especially if one wants to relate the estimated parameters to a biophysical analysis. Therefore, the problem consists to find a good correlation between obtainable experimental data, such as intracellular potentials, and parameters describing a reasonable mathematical model. A generic representation of the electrical activity in cardiac tissue can be written [6, 7] so that

$$C\frac{\partial u}{\partial t} = \nabla[D\nabla u] + I_{ion}\ , \tag{1}$$

where u is the transmembrane voltage, C the capacitance of the membrane of cardiac cells, D corresponds to the coupling between cells due to gap junction and I_{ion} represents the total ionic current flowing through the membrane. It is composed of individual ionic currents which are often dynamic functions of u itself.
In space-clamped mode, system (2) reduces to

$$C\frac{du}{dt} = I_{ion}\ . \tag{2}$$

The number of ionic currents and their related expressions define the model under investigation. For every kind of current description, the problem of correlating them to experimental data corresponds to identify the parameters used in the considered model. In every case, they are constant parameters. A major step has been performed in [8] where the authors proposed successfully a method to estimate these parameters in the case of space-clamped mode. They applied it to obtain a good estimation of the 63 parameters used in the Beeler-Reuter model. All ionic currents could be reasonably reconstructed using an experimental design consisting of action potential recordings perturbed by pseudo-random injection currents. The estimation process used a least squares fit approach and assumed that only the transmembrane action potential waveform is recorded. This method is applied to the Beeler-Reuter model but could be generalized to others. Although

opening up the possibility of formulating cell-specific reconstructions of underlying ionic mechanisms, the fact that it is based on the space-clamped method forbids extracting information about the coupling between cells, that is the strength of connexons and how they weave the cardiomyocytes networks. Actually the MEA technology allows us to investigate this missing spatial dimension, due its periodically distributed numerous electrodes. The recorded data are field potentials but it is possible to reach experimental transmembrane voltages, as in a first approximation by integrating them over time. A first question arises about how to take benefit from the method proposed in [8] while adding a spatial dimension to the reconstruction problem. In order to keep this ionic currents identification method, a dissociated scheme is proposed and presented in the next paragraph. It is applied to the Aliev-Panfilov model [9], but could be also generalized to other models. This model can be expressed such as

$$\begin{cases} \dfrac{\partial u}{\partial t} = \nabla[D\nabla u] - ku(u-a)(u-1) - uv \\ \dfrac{\partial v}{\partial t} = \varepsilon(u,v)[-v - ku(u-a-1)] \ , \end{cases} \tag{3}$$

where $\varepsilon(u,v) = \varepsilon_0 + \mu_1 v/(u+\mu_2)$.

2.2. A dissociated scheme

A choice of parameters in system (3) leading to a biophysically reasonable action potential shape is so that $\varepsilon_0 \ll 1$ while $\mu_1 \approx 0.1$ and $\mu_2 \approx 0.2$. Furthermore, in this normalized model, the resting state of the system is such as $(u,v) = (0,0)$. It implies that, as $u > v$, system (3) is a slow-fast system where the fast variable is u and the slow one v. It yields the fact that the leading edge of the pulse which is a fast process is mainly obtained by the bistable equation [10] :

$$\frac{\partial u}{\partial t} = \nabla[D\nabla u] - ku(u-a)(u-1) \ . \tag{4}$$

In this system, the cubic function corresponds to the contribution of the sodium current and a leak potassium one and is completely defined by the parameters k and a. It keeps the coupling between cells, given by D.
Figure 1 shows a good match between the leading edge of the action potential obtained with eq. (3) (straight line) and the corresponding leading edge resulting from eq. (4) with the same parameters (dashed line).

Assuming that the slow-fast property is assured in biological conditions, it is therefore possible to split the problem of identification into two parts : In a first place, by focusing on the leading edge of the action potential, a method can be designed to estimate the values of the parameters involved in eq. (4), that is k, a and D. This estimation process is presented in the next section. Then, these parameters known, one can use the method proposed in [8] to obtain the remaining parameters in system (3). It could be performed on the whole signal. As this method has already been fully described in [8], we will focus only on the first part of this process. Note that this dissociated method can be applied to any system described by

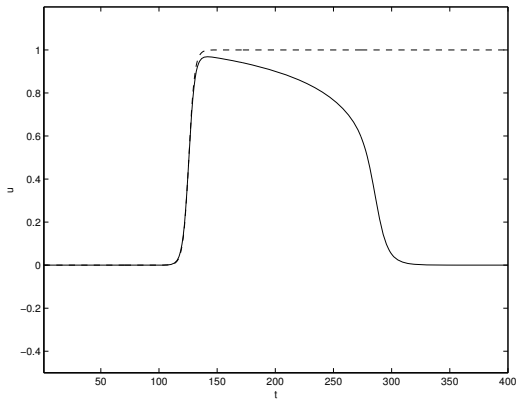

Figure 1. Action potential shape (straight line) obtained by integrating eq. (3) and leading edge shape obtained from eq. (4). A square tissue of 200×200 cells has been simulated in both cases with Neumann conditions on its border. The initial conditions led to a planar propagation. The presented signals correspond the transmembrane voltage of cell $(100,100)$ at the middle of the tissue. Parameters : $D = 1$, $a = 0.1$, $k = 1$, $\varepsilon = 0.005$, $\mu_1 = 0.1$ and $\mu_1 = 0.2$.

$$\frac{\partial u}{\partial t} = \nabla[D\nabla u] - ku(u-a)(u-1) + I_{slow} \ , \tag{5}$$

where I_{slow} corresponds to ionic currents varying slowly in time. These currents can be identified with the method described in [8], while the parameters of the bistable equation are obtained as presented in the next section.

2.3. Estimation and identification methods description

The state equation of model (5) is given in a discrete functional framework and the identification problem will be considered in this framework. A descent method will then be used in order to find a numerical solution to the problem. The cost functional to be minimized is quadratic function. The discrete approximation approach permits the exact numerical computation of the cost functional gradient. Potential and current measures are used and results of identification obtained with removing the contours and electrode's matrix sparseness are compared. The system identification problem consists of estimating parameters

based on observed input-output data using the model structure described above. A quadratic criterion is used to select particular parameters set which gives good approximation of the process behaviour. In general terms, an identification experiment was performed by exciting the system and observing its input and output over a time interval. These signals were recorded. Then a parametric model of the process was fitted to the recorded input and output sequences. For the identification task, two approaches are used. The first one consists on defining a matrix of electrodes and removing contours until have a matrix of dimensions 1×1 (meaning one electrode surrounded by its four nearest neighbouring electrodes) or 2×2. The parameters identification is performed for each matrix found. The second approach consists on electrode's matrix sparseness by removing a pair of lines and columns gradually until the matrix is completely sparse, as illustrated in figure (2).

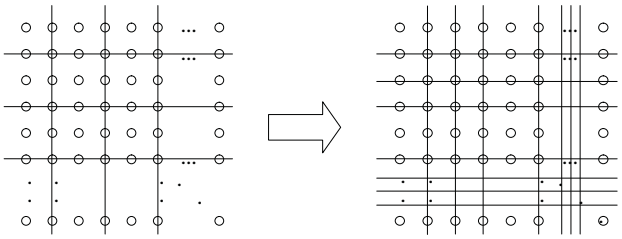

Figure 2. Scheme of sparsing electrode matrix ($\circ$ symbols). The removed electrodes are striped.

Both approaches were applied on a simulated cardiac tissue modeled by the Aliev-Panfilov model with following fixed parameters: $D = 1$, $a = 0.15$, $k = 8$, $\varepsilon_0 = 0.002$, $\mu_1 = 0.2$ and $\mu_2 = 0.3$, which satisfies the conditions of the dissociated scheme. In order to estimate D, a and k, initial conditions have been set so that a planar action potential could propagate through the simulated tissue. The border of the medium follows zero-flux (Von Neumann) conditions and is not taken into account in the identification process : No electrode lies on the edge.

3. Results

3.1. Estimation with fixed density of electrodes

In this section, the first approach has been used: The density of electrodes is kept constant (one electrode for each cardiac cell) but their number is decreased by removing contours. The results are presented on Fig. 3.

All the parameters are well estimated whatever the number of electrodes used. Nevertheless, more electrodes leads to a faster convergence. This result shows the feasability of the method when the data used are ideal.

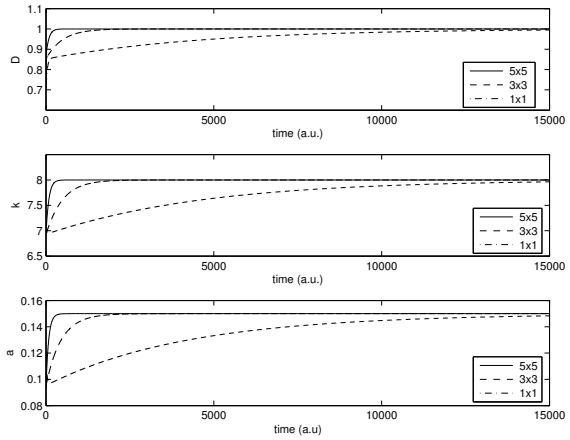

Figure 3. Estimated parameters with local fixed density of electrodes in function of the number of electrodes.

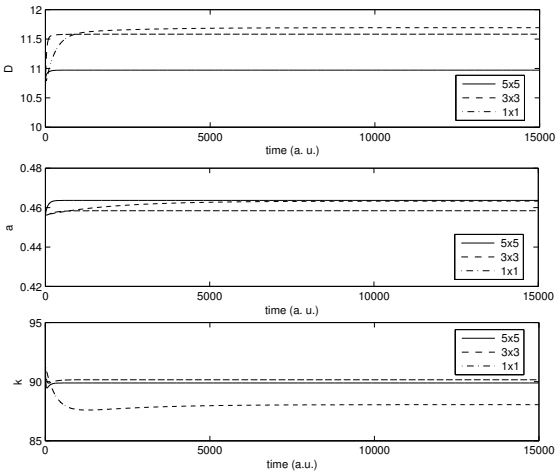

Figure 4. Estimated parameters in case of noise with local fixed density of electrodes in function of the number of electrodes.

Biological systems are usually perturbated by intrinsic or extrinsic noise. In order to study the sensibility to noise of this method, we added 5% of white noise independently on each electrodes. The influence of this perturbation on the identification process is given in Fig. 4 for which the estimated parameters converge to unexpected and false values. Note that the exact profile of the leading edge was obtained when the model was simulated with these values. In order to minimize these effects, a simple first order filtering on the signal has been applied, which improved the

estimation, as illustrated in Fig. 5, especially when enough electrodes are used. Not that in the case 1×1, the estimation is correct but not accurate, which forbids a good identifiaction in case of inhomogeneous coupling.

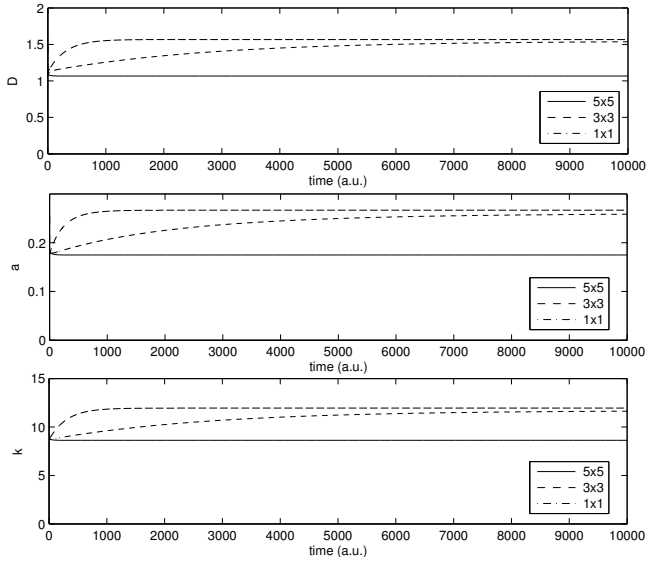

Figure 5. Estimated parameters in case of noise with prefiltering with local fixed density of electrodes in function of the number of electrodes.

3.2. Estimation with sparsing matrix of electrodes

The influence of sparsing of electrodes, that is an increased distance between electrodes has been investigated and the results are presented in Fig. 6. An increased distance between electrodes does not seem to affect the estimation, although it implies a slower convergence. The effect of noise is similar to the case of section 3.1 but is well minimized by a prefiltering stage.

4. Conclusion

A study on the feasability of reconstruction of model from experimental data has been presented. It is based on a dissociated scheme and focused on some parameters including the coupling strength between cells. We conclude frome the results obtained on a simulated tissue that it is possible to reach an accurate estimation, especially when the signal are ideal. In case of noise, a prefiltering is needed. An increased but reasonable distance between electrodes is not cumbersome, which opens up the possibility to apply this method to data from MEA, for which a typical distance between electrodes could correspond to

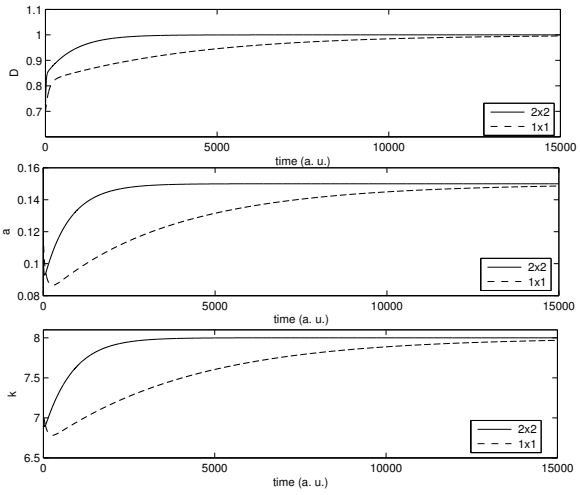

Figure 6. Estimated parameters in case of sparsing matrix of electrodes in function of the number of electrodes.

five size of cardiac cells. Further work will be devoted to study this possibility.

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