Cardiomyocyte calcium dynamics

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Contraction of the cardiac muscles starts with an action potential acting as a signal, which depolarizes myocytes, making them to contract. Ca^{2+} is key in both processes, signaling and contraction; in this work we are going to focus in the role its concentration plays in contraction of cardiomyocytes, and therefore beating of the heart. A cardiac cell can be modelled as an array of Calcium Release Units (CaRUs), each of which present five different compartments and calcium concentration; the response of this concentrations to the external action potential determines the cardiac contraction.

Keywords: cardiomyocyte, alternans

I. MYOCYTE STRUCTURE AND MUSCLE CONTRACTION

Muscle tissue (both the voluntary and the involuntary) is made of myocytes, the muscle cell; these are made of myofibrils, whose basic unit is the sarcomere, the minimum unit capable of contracting, and, with it, making a force. Our object of study and simulation will be cells of the heart, also called cardiomyocytes. In the heart, the parts that contract synchronously at the beating are the atrium and the ventricle. The basic structure of myocytes in this two sites consists on the sarcolemma (cell external membrane) surrounding the myofibers formed of sarcomeres; between sarcomeres an inward projection of the sarcolemma, T-tubules in the case of ventricle and Z-tubules for atrium, studded with L-type Voltage Operated Calcium Channels (VOCCs or LCCs), which are near, in a cytosol cleft referred as dyadic junction, of Ca^{2+} release channels known as ryanodine receptors (RyRs), attached to a membrane bound structure, the sarcoplasmic reticulum (SR); the density of RyRs varies along the SR, and is higher near the sarcolemma, at the dyadic junction, located close and opposite to the VOCCs.

As the action potential depolarizes the myocyte, VOCCs channels open, allowing Ca^{2+} to flow into the dyadic junction, activating RyRs through a process called Ca^{2+} induced-Ca^{2+} release (CICR); this way, the original calcium signal gets amplified.

The central part of the sarcomere consist on two types of filaments; actin, which are attached to the side limits, and myosin, that appear at the middle. When Ca^{2+} diffuse out of the dyadic junction, it binds to troponin C, displacing tropomyosin and making possible to myosin and actin filaments to engage and slide, contracting the sarcomere and therefore the whole myocyte.

Ca^{2+} levels go back to the resting ones due to an enzyme, sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA), that pumps it again into the SR; and Na^{+}/Ca^{2+} exchanger (NCX), a membrane protein that takes Ca^{2+} out of the cell.

II. CALCIUM CYCLE MODEL FOR CARDIAC CELLS

We should take the cardiac cell as an array of Calcium Release Units (CaRUs), each of this situated in the T-tubules and presenting a group RyRs in front of one of LCCs. These CaRUs influence its neighbors by calcium diffusion and have also some internal dynamics in the presence of an action potential; we will focus in this last part, taking into account one CaRU at a time and neglecting diffusion between different units. The model and most of the constants will be taken from [1].

Each CaRU consists of five different compartments and their calcium concentrations; dyadic (c_d), subsarcolemma (c_s), cytosol (c_i), network sarcoplasmic reticulum (c_{SR}) and junctional SR (c_{jSR}). Dynamics of calcium fluxes for each compartment is deterministic, and its evolution is given by the following equations:

$$\frac{dc_d}{dt} = -J_{CaL} + J_{rel} - J_{ds}$$
$$\frac{dc_s}{dt} = \beta(c_s)[\frac{v_d}{v_s}J_{ds} - J_{si} + J_{NaCa} - J_{TCs}^{buff}]$$
$$\frac{dc_i}{dt} = \beta(c_i)[\frac{v_s}{v_i}J_{si} - J_{TCi}^{buff} - J_{up}]$$
$$\frac{dc_{SR}}{dt} = \frac{v_i}{v_{SR}}J_{up} - J_{tr}$$
$$\frac{dc_{jSR}}{dt} = J_{tr} - \frac{v_d}{v_{jsr}}J_{rel}$$

Where v_i, v_s, v_d, v_{SR} and v_{jSR} represent the volume of each compartment; J_{ds}, J_{di} and J_{tr} the diffuse current among compartments, J^{buff} are due to the attachment to

calcium buffer Troponin C; J_{CaL} corresponds to the calcium current from extracellular medium through LCCs, J_{NaCa} the flux from the subsarcolemma through the Na-Ca exchanger to the extracellular medium, J_{up} due to the SERCA pump, from cytosol to SR, and J_{rel} the release of calcium from jSR into dyadic space.

The action potential (corresponding to the electrical signal that our heart receives periodically and makes it beat) that stimulates the cell with a certain period T can be modeled as it follows:

$$V(t) = (V_{max} - V_{rest})\sqrt{1 - [\frac{\tilde{t}}{APD}]^2} + V_{rest} \quad if\ \tilde{t} < APD$$
$$V(t) = V_{rest} \quad if\ \tilde{t} > APD$$

where $\tilde{t} = t - nT,\ n = 0, 1, 2, \ldots,$ and $APD = 100T/(100 + T)$, T in ms. This will go from the resting potential to a maximum value, to later decrease to the resting potential before the next burst, similar to the form of actual action potentials.

Each CaRU has a cluster of 50 RyRs, following a four state model; Open (O), Close (C) and two inactivated (I_1 and I_2). Transition between states is stochastic with a certain rate at each step; for the RyR, all rates are constant except the one going from close state to open, which depends on the square of the calcium concentration in the dyadic space (c_d), meaning that in the presence of an action potential that makes LCC to inject calcium from the exterior to the dyadic junction, RyR will be more likely to be open and release Ca^{2+}.

The model for LCCs will be similar, with a group of 5 and five possible states; two closed (C_1 and C_2), two inactivated (I_1 and I_2) and one open (O). Rates depend on the voltage, making LCC to open with membrane depolarization, and on calcium concentration, inactivating it at high concentrations.

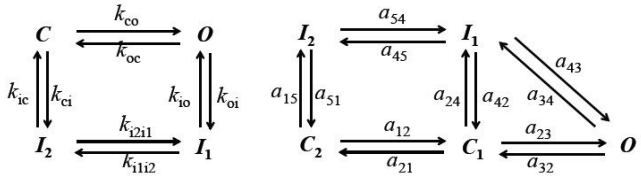

FIG. 1. Markov models for RyR and LCC states.

III. MAIN RESULTS

With a step time (in ms) of 0.005 and a total time of simulation of 2.5×10^4 ms, we computed the total dynamics starting from all RyR and LCC in close state and a period for the action potential of 1000 ms.

We obtained the following results.

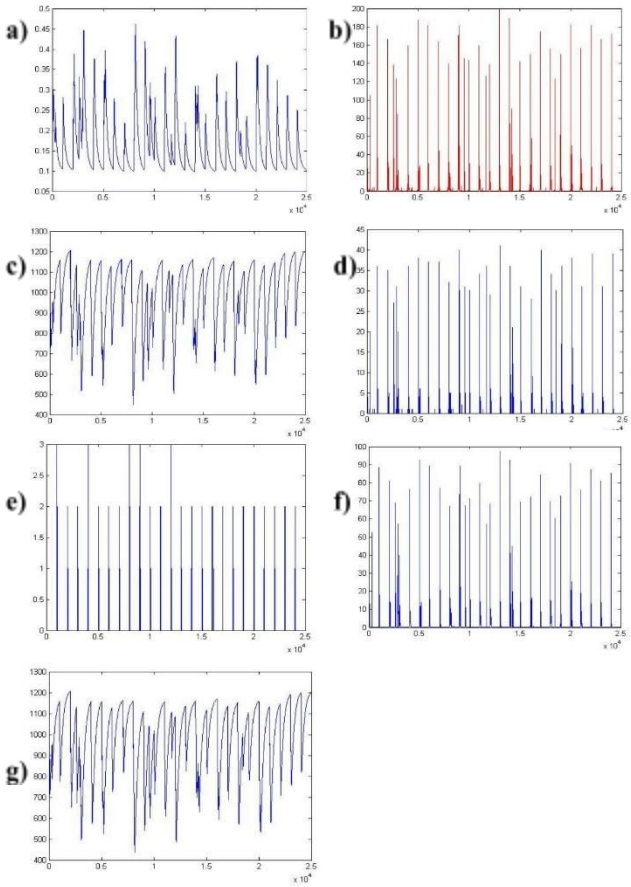

FIG. 2. a) Cytosol calcium concentration, b) dyadic, c) junctional SR, d) RyR in open state, e) LCC in open state, f) subsarcolemma calcium concentration and g) SR calcium concentration.

RyR and LCC are open in the presence of the voltage (the number that are opened varies due to its stochastic nature), causing the calcium concentration to rise in every compartment but junctional and non-junctional SR, to later going down to the resting concentration as the voltage decreases (going up to them in the case of SR and jSR). Concentration does not always rise back to the same value than before; this depend on some parameters and may cause alternans to appear; this will be briefly discussed later. This dynamic repeats periodically with the voltage, representing the beating of the heart.

From all calcium concentrations, the one in the dyadic junction may be the most important, since it is the one that may or not burst RyR to release the Ca^{2+} needed for the contraction. Because of that, it is interesting to study how it behaves under changes of some parameters of the equations.

For this, we consider that RyRs opening is activated (as it is a stochastic process, activation means that an important

quantity of RyRs open in a short period of time) when c_d is above a certain value (the activation of RyR rise drastically the concentration of c_d, we took 100 based on several simulations), and, taking steps in a certain parameter, we run the simulation several times for each step, and compute the probability that RyR opens.

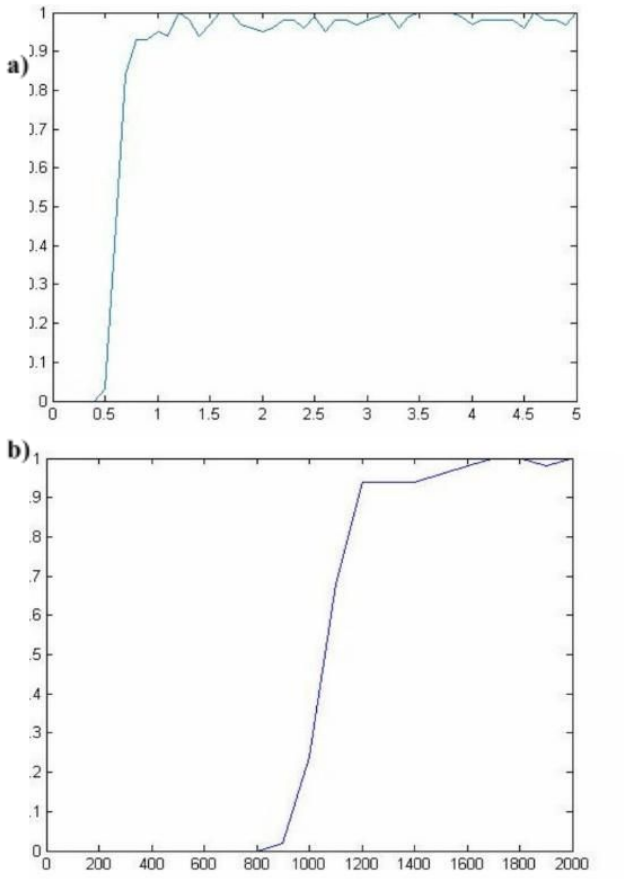

FIG. 3. a) varying grel (weight of J_{rel}) from 0 to 5; b) with c_{SR} constant in the dynamic equations, vary it from 0 to 2000.

From these results we see that these parameters act like a switch on of the contraction, since the probability of activation increases rapidly from almost 0 to almost 1 within certain values.

We also observed a similar performance when changing two parameters at the same time. For example, for the number of ryanodine receptors and a constant Csr for each simulation we obtained the following probability density:

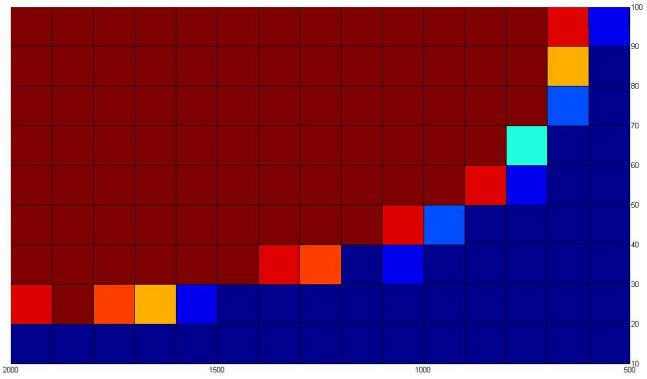

FIG. 4. Probability density as a function of NRyR (vertical axis) and c_{SR} (in micromolar, horizontal axis). More blue means less probability.

From this idea of the probability of opening RyRs and release of calcium from junctional SR into the dyadic space, we can discuss about alternans.

With certain values of grel and k, and a period for the potential action of 800ms, doing an average of multiple simulations we obtained a dynamics for the calcium concentration in the dyadic space that presents similar performances with the same periodicity as the potential. Holding parameters constant, only decreasing the periodicity to 200ms we observed some tendency to alternans:

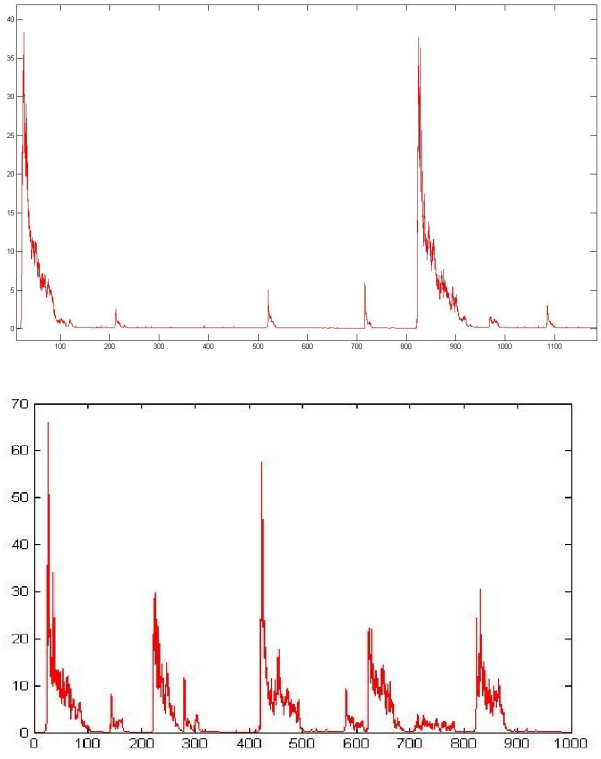

FIG. 5. C_d with no alternans (T=800ms) and with

alternans (T=200ms).

This tendency to the alternans given by a variation of the periodicity of the action potential can be explained by the fact that the calcium concentration in the sarcoplasmic reticulum does not reach the same resting concentration, being lower than the concentration with higher periodicity, and then the probability observed in figure 4 or figure 3b fits well with this performance. That is: it is not in a situation where the probability is almost 1, but lower, thus releasing less calcium to the dyadic space at some excitations.

IV. CONCLUSIONS

In this article it has been shown the first steps in the simulation of atrial cardiomyocyte cells so it can be studied their behaviour and how it is changed depending on the parameters. It has been observed the periodicity in the different concentrations due to the periodic electric impulse and the stochastic character of the response (it's never the same) and the switch behaviour of some parameters in the activation of Ca^{2+} sparks (release from SR), that would rise the cytosolic concentration producing the activation of actin and thus the contraction of the cell.

It has been also observed the tendency to the alternans while varying the periodicity of the excitations and in this way also the resting c_{SR} (and cj_{SR}). It could be studied also this tendency while varying other parameters in the dynamics.

The implementation of different compartments as the one studied in this article with diffusion of cytosolic calcium would be the last part to observe how now the stochastic character of the response fades away to give a deterministic response that ensures the beating of the heart.

The results obtained are quite satisfactory comparing them to what we know of the cardiomyocytes behaviour, this is, they represent realistically the response of the heart cells to a periodic potential excitation.

ACKNOWLEDGEMENTS

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[1] E. Álvarez-Lacalle, J. Spalding, B.Echebarria and Y. Shiferaw: *Materials and methods.*