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Bifurcations, chaos, and sensitivity to parameter variations in the Sato cardiac cell model

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ABSTRACT

The dynamics of a detailed ionic cardiac cell model proposed by Sato et al. (2009) is investigated in terms of periodic and chaotic action potentials, bifurcation scenarios, and coexistence of attractors. Starting from the model's standard parameter values bifurcation diagrams are computed to evaluate the model's robustness with respect to (small) parameter changes. While for some parameters the dynamics turns out to be practically independent from their values, even minor changes of other parameters have a very strong impact and cause qualitative changes due to bifurcations or transitions to coexisting attractors. Implications of this lack of robustness are discussed.

1. Introduction

Mathematical modelling has become an important tool in the life sciences to address problems that are not approachable experimentally. For example, to investigate cardiac arrhythmias or sudden cardiac death, models have been developed to describe cardiac dynamics from gene to organ level [2,3]. Therefore, many models exist to describe the action potentials (AP) of single ventricular cells. For better comparison with experimental results, these models are often developed to represent dynamics of specific mammals: For example, the well-known Luo–Rudy model [4] can be used to model guinea pig ventricular cells, while the model used by Wang and Sobie [5] describes mouse ventricular action potentials, and the one used by Sato et al. [1] (first AP model, in the following referred to as the Sato model) models ventricular rabbit myocytes.

However, many of these models share the feature of consisting of a great number of equations and parameters. For example, the Sato model uses 27 variables whose calculation requires 118 equations and 177 parameters. Therefore, the exact implementation of these models as given in the original publications is quite error-prone, and since changes in parameters can dramatically alter the dynamics of the model, reproducing results from former studies can be a challenging task.

Studies analysing the parameter sensitivity of electrophysiological models are still rare [6,7]. Therefore, in this paper we use the Sato model to investigate the sensitivity of the dynamics to parameter variations. This cardiac cell model was used to provide an explanation for ventricular tachycardia and ventricular fibrillation originating from early afterdepolarisations at the cellular level by a chaos synchronization mechanism [1,8]. As will be shown in the following sections this model

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exhibits chaotic action potentials as well as coexistence of different types of periodic and chaotic attractors. To investigate the robustness of the dynamics given by the standard parameter set of this model [1], bifurcation diagrams are computed showing dynamical changes when going below or above the standard parameter values and it turns out that for some parameters already minor deviations from the standard value lead to qualitatively different dynamics.

2. Methods

The Sato model, which is given in detail in Appendix A, describes the action potentials in the membrane voltage $V(t)$ of ventricular rabbit myocytes. It uses 27 variables that can be described by 118 equations involving 177 parameters. Besides ionic concentrations, channel conductances or physical constants, many of these parameters are coefficients, obtained from fitting mathematical models to experimental data. Since the sensitivity of the model dynamics to changes of these fitted parameters is to be examined as well, all fit coefficients were labelled (see Tables A.3–A.6) and included in the total list of model parameters.

The cardiac cell model is given as a set of ordinary differential equations (ODE's)

$$\begin{aligned} \frac{\mathrm{d}V(t)}{\mathrm{d}t} &= -\frac{I_{\mathrm{ion}}(\boldsymbol{h},t)+I_{\mathrm{stim}}(t)}{C_{\mathrm{m}}} \\ \frac{\mathrm{d}\boldsymbol{h}(t)}{\mathrm{d}t} &= \boldsymbol{F}(\boldsymbol{h},V,t) \end{aligned} \tag{1}$$

where C_{m} is the membrane capacity and I_{stim} the external stimulation current with pulses of 1 ms duration and amplitudes of $-40\ \mu\mathrm{A/cm^2}$. I_{ion} is the sum of all considered transmembrane or intracellular ionic currents. The state vector $\boldsymbol{h}$ includes all additionally needed, time dependent variables like gating variables or ionic concentrations. The ODE system (1) was solved in C++, using the Nordsieck BDF method with adaptive time steps implemented in the GNU Scientific Library [9]. The maximum absolute and relative error tolerances were set to 10^{-8} with a maximum allowed time step of 0.5 s. Since this ODE solver requires the Jacobian matrix of the ODE system (1), the symbolic Jacobian was calculated using the GiNaC framework [10].

For the Sato model, no initial conditions were given in the original publications [1,11]. We obtained steady state initial conditions by setting all 27 variables to 0.1 prior to pacing the system with a constant PCL of 0.8 s until a steady state was reached, which took about 300 s of simulated cell activity. The initial conditions obtained by this procedure are given in Table A.2.

The model was originally designed to reproduce cardiac dynamics at fast pacing [11] and includes modifications to be capable of generating early afterdepolarisations (EADs) [1], which are known to be potential triggers of lethal cardiac arrhythmias [12,13]. A detailed description of EADs and the underlying ionic mechanisms can, for example, be found in Ref. [14]. Briefly, an EAD is an abnormal depolarisation during the plateau phase of an AP, which essentially prolongs the action potential duration (APD). The APD for each AP is defined here as the time duration where $V > -85$ mV. To analyse the action potentials and the appearance of EADs, we also introduced a Poincaré section to the 27-dimensional state space such that every action potential is represented by the values of the 27 variables at a fixed phase after the initial depolarisation of the AP. These chosen state space points need to reflect the dynamics during the plateau phase of the action potential. Since the shape and duration of the action potential are PCL-dependent, we defined the phase space point v_n^{p} of the nth action potential of variable v as

$$v_n^{\mathrm{p}} := v(t_0 + (n+0.3)\mathrm{PCL}) \tag{2}$$

where t_0 is the time of the depolarisation of the first AP considered. Thus, the phase increases linearly with PCL. Furthermore, for calculating Lyapunov exponents, a discrete QR decomposition based method as described in [15] was implemented.

3. Results

3.1. Periodic and chaotic action potentials

Fig. 1 shows the temporal evolution of the membrane voltage $V(t)$ for three different PCLs: For PCL = 1.100 s and PCL = 1.370 s, the APD is in each case constant for every AP. While for PCL = 1.100 s no EADs occur at all, however, for PCL = 1.370 s EADs occur at each beat. For intermediate PCLs, in this case 1.282 s, EADs occur irregularly on some beats.

Fig. 2 shows a three dimensional projection of the chaotic attractor underlying the time series shown in the middle panel of Fig. 1. Colours indicate the average concentration c_j of free Ca^{2+}in the sarcoplasmic reticulum (SR).

To investigate the occurrence of EADs for a larger PCL range, we calculated the APD for 200 APs for 1.1s < PCLs < 1.4 s with a step size of $\Delta\mathrm{PCL} = 0.5$ ms. Prior to the APD calculation, we paced the system for 500 s of cell activity and for the nth PCL_n, we used the final state vector of the previous $\mathrm{PCL}_{n-1} = \mathrm{PCL}_n - \Delta\mathrm{PCL}$ as initial condition. The resulting bifurcation diagram in Fig. 3A shows that for a certain PCL range, the APD takes many different values, which shows the irregular behaviour in the appearance of EADs. Note that an APD value larger than about 0.5 s represents an EAD. For smaller and larger PCL values the APD does not vary, which indicates periodic behaviour. Furthermore, the irregular behaviour in the intermediate PCL range is interrupted by periodic windows. Fig. 3B shows a bifurcation diagram where instead of APDs