Bifurcations, sustained oscillations and torus bursting involving ionic concentrations dynamics in a canine atrial cell model

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ABSTRACT

Atrial fibrillation is a disorganization of the electrical propagation in the atria often initiated by ectopic beats. This spontaneous activity might be associated with the appearance of sustained oscillations in some portion of the tissue. Adrenergic stress and specific gene polymorphisms known to promote atrial fibrillation are notably related to calcium and potassium channel conductances. We performed codimension-one and two bifurcation analysis along these conductances in an ionic canine atrial myocyte model. Two Hopf bifurcations were found, related to two distinct mechanisms: (1) a fast calcium gating-driven oscillator, and (2) a slow concentration-driven oscillator. These two mechanisms interact through a double Hopf bifurcation (HH) in a neighborhood of which a torus (Neimark–Sacker) bifurcation leads to bursting. A complex codimension-two theoretical scenario was identified around HH, through systematic comparison with the attractors found numerically. The concentration oscillator was further decomposed to reveal the minimal oscillating subnetwork, in which the Na^+/Ca^{2+} exchanger plays a prominent role.

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1. Introduction

Neural and cardiac excitable cells can exhibit a wide range of oscillatory regimes, from simple sustained oscillations to complex bursting. Major pathologies and in particular cardiac arrhythmias are often triggered by abnormal automaticity from some part of the tissue [1,2].

The most prevalent cardiac arrhythmia in North America is atrial fibrillation [3]. It consists of a general disorganization of electrical activity in the atrial tissue. Fibrillation is often initiated by ectopic focus originating from abnormal automatic activity or afterdepolarization in cardiac myocytes. In terms of nonlinear dynamics, afterdepolarization is a transient oscillation while automaticity consists of sustained oscillations. Bursting and other complex spatio-temporal dynamics have also been reported in cultured myocytes [4].

Increase of membrane Ca^{2+} conductance and decrease of K^+ membrane current conductance are known to promote oscillations in ventricular myocyte models [5,6]. Various K^+ channels may also be blocked in some genetic polymorphisms leading to afterdepolarizations [7,8]. Ca^{2+} conductance is enhanced under adrenergic

stress [9] and this condition promotes ectopic focus in ventricular [10] and atrial cell models [11]. Another major mechanism of oscillation in atrial cell is the so-called spontaneous Ca^{2+} release (Sp-CR) from the sarcoplasmic reticulum (SR) [12]. It has recently been introduced in two models of human atrial myocytes [11,13,14] but their respective representations of the sarcoplasmic calcium handling are still debated [11]. Although the Sp-CR mechanism is gaining interest, it is yet not clear if mechanisms involving only membrane currents and cytoplasmic ion concentrations dynamics can elicit sustained oscillations in cardiac cells.

Classical cardiac and neural Hodgkin–Huxley type models [15] do not include dynamics of ion concentrations. Na^+ and K^+ dynamics have recently been found to be able to yield bursting in a neural model [16,17]. Bursting involving slow oscillations of Na^+ and Ca^{2+} has also been observed in a ventricular model [18]. While most of recent ionic cardiac myocyte models incorporate ion concentration dynamics [19,20], the question of their ability to cause oscillations and bursting has rarely been addressed.

The purpose of this paper is to investigate where and how oscillations may be elicited in a canine atrial myocyte model lacking the Sp-CR mechanism. We first perform bifurcations analyses as a function of the conductance of a Ca^{2+} (g_{Ca}) and K^+ (g_{Ks}) current. Two independent mechanisms of oscillation are identified, each being associated with a Hopf bifurcation. One of the Hopf bifurcations is linked to the calcium current gating variables, while the

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second one is associated with the dynamics of the cytoplasmic ionic concentrations. Bursting-like activity is shown to result from the interaction of these mechanisms through a double Hopf bifurcation (HH). Afterward, the details of each of these mechanisms are investigated using reduced models.

2. Methods

2.1. Complete model

We used the Ramirez–Nattel–Courtemanche model of canine atrial cells (RNC) [21], with parameters as in [22]. The original model encompasses some Cl^- dynamics, but no volume regulation through osmosis. Since anionic dynamics is thought to be of little relevance unless volume regulation is included [23], Cl^- currents were removed. A background K^+ current I_{bK} was added to restore the original RNC resting state.

In the resulting "Complete Model", the evolution of the membrane voltage (V) and of the cytoplasmic sodium (Na_i) and potassium concentrations (K_i) are governed by differential equations representing the ionic flows through the cell membrane. The calcium (Ca_i) also takes into account the fluxes associated with the sarcoplasmic reticulum (I_{SR}) as well as to the cytosolic troponin (Ca_{Tpn}) and calmodulin (Ca_{Cmdn}) buffers ($I_{buffers} \propto C\dot{a}_{Csqn}$ and $C\dot{a}_{Cmdn}$). The sarcoplasmic reticulum (SR) consists of a Ca^{2+} uptake (Ca_{up}) and release compartments (Ca_{rel}), the latter including a calsequestrin buffer (Ca_{Csqn}), such that I_{SR} is a combination of $C\dot{a}_{up}$, $C\dot{a}_{Csqn}$ and $C\dot{a}_{rel}$. The equation for $C\dot{a}_{rel}$ includes the dynamics of Ca^{2+} release from the SR through the ryanodyne receptors (RyR). The model also incorporates the Na^+/Ca^{2+} exchanger ($I_{NaCa}(V, Na_i, Ca_i)$), Na^+/K^+ pump ($I_{NaK}(V, Na_i)$) and Ca^{2+} pump ($I_{pCa}(Ca_i)$). The final set of equations for V, Na_i, K_i and Ca_i is:

$$\dot{V} = \frac{-I_{ion}}{C_m}; \quad N\dot{a}_i = \frac{-\Sigma I_{Na}}{FV_i}; \quad \dot{K}_i = \frac{-\Sigma I_K}{FV_i};$$
$$C\dot{a}_i = \frac{-\Sigma I_{Ca}}{2FV_i} + I_{SR} + I_{buffers}; \tag{2.1.1}$$

$$\Sigma I_{Ca} = -2I_{NaCa} + I_{pCa} + I_{CaL} + I_{bCa};$$
$$\Sigma I_{Na} = 3I_{NaK} + 3I_{NaCa} + I_{Na} + I_{bNa};$$

$$\Sigma I_K = -2I_{NaK} + I_{K1} + I_{to} + I_{Kurd} + I_{Kr} + I_{Ks} + I_{bK};$$
$$I_{ion} = \Sigma I_{Na} + \Sigma I_K + \Sigma I_{Ca}$$

Dynamics of currents and RyR involve 14 V-dependent and one Ca-dependent gating variables, all of them governed by an equation of the form $\dot{y} = (y_\infty - y)/\tau_y$. Some stationary functions $y_\infty(V)$ are piecewise defined with a discontinuity. These were made smooth and continuous by connecting the two pieces by a sigmoid function as in [24]. The resulting differentiability of the vector field is a condition for uniqueness of the solutions and makes ODE systems more amenable to bifurcation analysis [25]. All details of the mathematical formulations of the complete model are provided in Appendix C.

As a result of the relation between the concentrations and voltage [26],

$$V = C_2(Na_i + K_i + 2Ca_i + 2Ca_{up} + 2Ca_{rel} + 2Ca_{Cmdn}$$
$$+ 2Ca_{Tpn} + 2Ca_{Csqn}) + C_1 \tag{2.1.2}$$

the model becomes a differential–algebraic system [27] with 23 differential variables and one linear algebraic constraint. Because of its linearity, the algebraic constraint is always invertible with respect to any variables and the chosen algebraic variable may be eliminated from the system of differential equations. It is then possible to solve the system as mere ODE rather than DAE.

2.2. Reduced submodels

Simplified models are used to investigate the respective contributions of gating and concentrations subsystems to the oscillatory dynamics of complete model. They are chosen as simple as possible to capture the essential mechanisms of oscillation. All the reduced models share the following features:

- I_{Na} gating variables (m, h, j) are stationary: $m = m_\infty(V)$, $h = h_\infty(V)$, $j = j_\infty(V)$.
- The Ca^{2+} charges of the SR and buffers are fixed at a constant value, corresponding to the locus of saddle-node bifurcation (SNF, see Fig. 1). Then, in Eq. (2.1.2): $Ca_{up} + Ca_{rel} + Ca_{Cmdn} + Ca_{Tpn} + Ca_{Csqn} = const$ such that $I_{SR} = I_{Buffers} = 0$.
- In all reduced models, the Ca^{2+}-dependent-inactivation gating variable f_{Ca} of I_{CaL} is fixed at stationary value $f_{Ca}(Ca_i)$. As discussed later, f_{Ca} is not essential for the loss of stability and oscillations observed in the complete model.

The specific reduced models are:

- *Vgates model:* Model of V with gating dynamics: total of nine differential equations, for V and the gating variables of I_{CaL} (d, f) and potassium channels (x_s, x_r, o_a, o_i, u_a, u_i). Ca_i, Na_i and K_i concentrations are frozen at their values at each equilibrium point of the Comp model, such that it remains an equilibrium point in the Vgates model.
- *Vf/Vd models:* Only two differential variables: V and one of the gating variables among $\{d, f\}$. All other gating variables are fixed at their stationary values. Concentrations are as in Vgates model.
- *VConc model:* Only the dynamics of concentrations: three differential variables and one algebraic variable among $\{V, Ca_i, Na_i, K_i\}$. All gating variables are fixed at their stationary values. We use in particular the version with V, Ca_i, K_i as differential variables and Na_i as algebraic equation in Section 6.4.
- *VCai model:* Only $\{V, Ca_i\}$ as differential variables. No algebraic relation. All gating variables are fixed at their stationary values. Na_i and K_i are frozen as in Vgates model at their values of equilibrium point of the Comp model, for each value of the parameter.

2.3. Parameters of control: g_{Ca} and g_{Ks}

Adrenergic stimulation has been shown to increase g_{Ca} often more than twofold in human atrial myocyte [28] and up to fivefold in canine ventricular myocyte [29]. In the latter, it can also increase up to eightfold the I_{Ks} maximum conductance [30]. Some mutations also disrupt the β-adrenergic regulation of I_{Ks} [8] or even provoke a complete blockade. Other K^+ currents, such as I_{Kr} and I_{Kur}, are also augmented under adrenergic stimulation [28] or affected by similar loss of function mutations [31]. Herein, I_{Ks} was chosen as a paradigmatic example. Normal conductances in the model are g_{Ca} = 26.4 nS, and g_{Ks} = 5.61 nS [21]. For bifurcation analysis, g_{Ca} was varied from one to twice the normal value, and g_{Ks} from 0 (complete blockade) to twice its normal value.

2.4. Numerical simulation

Numerical simulations were performed to identify stable limit cycles (sustained oscillations) in all models. Numerical computations were performed with *Matlab*, using a modified – Euler method as in [21,22]. Step was generally $\Delta t = 10^{-2}$ ms, but was adapted to stiffness for long transient trajectories.