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Cardiac Electrophysiology: The Sinoatrial Node in Focus

Nzerem Francis Egenti*, Ugorji Hycinth Chimezie

Department of Mathematics and Statistics, University of Port Harcourt, Port Harcourt, Nigeria

Email address:
frankjournals@yahoo.com (N. F. Egenti)

*Corresponding author

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Abstract: The integrity of the cardiac cells and muscles is essential for quality of life. The sinoatrial node cells are the definitive cells of cardiac electrophysiology. They are the primary source of action potentials. Lamentably, the question of ion currents that generate the much needed cardiac action potentials is yet to be resolved. The nagging issue of the presence or otherwise of the sodium ion (Na^+) in the sino-atrial node cells may cast doubts at the propriety of clinical measures that target some cardiac events. Some literatures suggest the presence of the said ion at the periphery of the sino-atrial node while contending that it is totally absent in the node centre. Other literatures hold that it is present the entire sino-atrial node. In the light of these, this paper proposed a refined model equation of the cardiac sino-atrial node membrane current. The node centre, known to be the origin of cardiac action potential, was given a bit closer look. Physiological delay arising from the flow of a class of calcium ion current (L-Type calcium current), the bastion of the sino-atrial node centre action potential, was also considered. Ostensibly, the timing of specific ion currents during action potentials may furnish some clues on cardiac conditions.

Keywords: Action Potentials, Cardiac, Delay, Ion Channels, Mathematical, Equations, Periodic, Physiological

1. Introduction

One of the beautiful endowments to animated life is the heart. It has the cardinal task of circulating blood around the body. It follows therefore that the integrity of the heart is required for the organs of the body to function. The heart contains numerous cells, each of which is detailed for specific function. Cardiac electrophysiology deals on the forces that drive ions across cell membranes. Maex [1] supposed that ions rather than electrons are responsible for electrical currents that pervade excitable tissue of the cardiac cells and muscles. The notable ions that suffuse the cardiac cells, and other body cells, are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and chlorine (Cl^-). In the seminal works of Hodgkin and Huxley [2] and Hodgkin *et al* [3] on nerve impulses there was the hypothesis that the transport of potassium and sodium ions in excitable biological membranes occurs in selective ionic paths. Those paths, according to them, differ for different ions. Mathematical physiologists (see Keener and Sneyd [4] acclaim the yet to be controverted veracity of those works is. The work by Hodgkin and Huxley [2] is the basis of the present-day ion channels nomenclature. Ionic currents flow through the channels of the cell membranes due to potential difference across the cell membranes. Membrane potential is used by neurons, cardiac cells, muscle cells and a number of other cells in propagating electrical signals. Nonetheless, ion channels mediate passive transport rather than active transport since, as indicated by Liberman and Adams [5]; they cannot be coupled to an energy source. Channel *gating* enhances brief openness and closeness of the channels as the need arises. Here, *voltage-gated* channel was specifically discussed.

The membrane potential of cardiac cells are among the *excitable* cells known for induced action potential (AP). Electric excitability occurs when cells are activated to change their transmembrane potential so as to relate to other cells or to propagate signals to their neighbourhoods. Cardiac AP is known to differ from those of other body cells in a number of ways (see Keener and Sneyd [4], Pinnel *et al*. [6]) while a typical neural AP has about 1ms duration, and while the APs of skeletal muscles last for 2-5ms, the cardiac APs have a

duration of 200-400ms. The cardiac AP duration gives the cardiac muscles AP the unique characteristic of the *plateau phase* – the maintenance of the AP at a positive level. The cardiac cells consists of variety of cell types and different types of ionic channels. On this note Keener and Sneyd [7] was uncertain about the level of successes Hodgkin *et al* [3] would have recorded if their *de novo* investigation had applied to the cardiac cells.

This work dwells on a particular part of the cardiac cells- the sinoatrial node (SAN) cells. The SAN, located at the right atrium of the heart, is the normal natural pacemaker of the heart. Tatiana *et al*. [8], among other physiology literatures, hold that the SAN ionic current induces overall cardiac membrane AP. It is responsible for the initiation of the cardiac cycle (heartbeat). Hearts beats result from a sequence of electrochemical excitation waves that are initiated from the sinoatrial node. The generating and conduction of spontaneous electrical impulse by the SAN- a process, known as excitation-contraction coupling (ECC) causes the heart muscle to contract. Although the SAN fibres have some contractile filaments, they do not contract appreciably. Nervous and hormonal influences affect the heart rate. Without such influences, a heart rate (HR) of more than 100 beats per minute (bpm) will be generated by cells in the SA node. The parasympathetic nervous system is such that slows down HR to about 70 - 75 bpm. Therefore mechanical variations that respond to neural and hormonal influences also affect the electrical properties of the heart in a complementary manner called mechano-electric feedback. In general, the basis of cellular action potential is the transmembrane potential difference. This potential difference is assumed negative inside the cell membrane relative the outside. Depolarization (diastolic depolarization DD, in the case of the SAN) occurs when membrane potential tends towards less negative values; hyperpolarization is the case in which membrane potential tends towards more negative values. Physiological details underlying the general cardiac AP are awash in literatures, which include those of Pinnel [6], Richard [9] and Katz [10].

A contentious issue on cardiac electrophysiology is the presence or absence of the sodium ion (Na^+) in the SAN cells. In fact there is a litany of opposing literatures on this issue. While Katz [10], Arie [11] and several literatures posit the presence of Na^+ ion in the cells, Richard [9], Wu and Cui [12] are of the contrary view. Such uncertainty precludes mathematical details and predictions pertaining to physiology and medicine (see Keener and Sneyd: [4] ((1998), section 4.3.2., p.148) vs [7] ((2009), section 12.2.2, p.541)). The node has central and peripheral regions. The centre of the SAN is normally the leading pacemaker site and the source of cardiac APs. The periphery of the SAN is the conduit for the action potential from the main pacemaker site in the centre to the atrial muscle. Cohort studies by Honjo *et al*.[13] and Zang *et al*. [14] in line with Inada *et al* [15] suggested the absence of sodium ion at the SAN centre and the substantial presence of the same at the periphery. The latter hypothesised that the crucial feature of peripheral cells is attributable to the presence of the sodium current (i_{Na}). Action potential at the centre of the SAN is long with relatively positive maximum diastolic potential, MDP (∼−60 mV) (Inada *et al*. [15]. The pace making activity at the centre is quite slow.

2. Cardiac Excitation

The heart is always in a state of systematic electrical arousal. Intriguingly enough, it has an autonomous capacity to generate such arousal. The bastion of cardiac excitation is the SAN.

2.1. SAN Centre as a Point Source

The SAN recruits steady excitation through the atria to the adjoining atrial cells. Theoretically the SAN centre is the *point source* of excitation. This work considered the case where an electrical current I from a source is being introduced into a cardiac cell with resistivity κ, at position $(x, y, z) = (x_0, 0, 0)$, say. Assuming the cell conserves current, then a current density J which flows radially outwards from the source, is given by

$$J = \frac{I}{4\pi R^2}, \tag{1}$$

where R is the distance from the source to a point P, and $4\pi R^2$ is the area of the neighbourhood of the point source. The point P is of an abutting cell to the SAN. Using Faraday's law of electrostatics, the scalar electric potential V can be obtained by integrating the electric field from R to ∞, which reads

$$V = -\int_R^\infty \vec{E}.d\vec{l} = -\int_R^\infty \frac{\kappa I}{4\pi r^2} dr = \frac{\kappa I}{4\pi R}, \tag{2}$$

where $\vec{E} = \kappa \vec{J}$. If $r < x_0$ we have

$$\frac{1}{R} = \frac{1}{x_0} \sum_{n=0}^{\infty} \left(\frac{r}{x_0} \right)^n P_n \cos\theta, \tag{3}$$

or for $r > x_0$

$$\frac{1}{R} = \sum_{n=0}^{\infty} \left(\frac{x_0}{r} \right)^n P_n \cos\theta \tag{4}$$

where $P_n cos\theta$ is the Legendre polynomial of order n. The infinite series in (3) and (4) are each bounded and converge as $n \to \infty$ since Legendre polynomials have magnitudes less than unity for $n > 0$.

The electric scalar potential $V(r)$ can be expressed as an infinite sum of spherical harmonic modes given by

$$V(r) = \frac{\kappa I}{4\pi} \sum_{n=0}^{\infty} \frac{r^n P_n cos\theta}{x_o^{n+1}} \text{ for } r < x_0 \tag{5}$$

and

$$V(r)=\frac{\kappa I}{4\pi}\sum_{n=0}^{\infty}\frac{x_0{}^{n}P_n cos\theta}{r^{n+1}} \text{ for } r > x_0 \tag{6}$$

For r = 0 a bounded and convergent series may be sought differently. Intuitively, one may consider the cell as cylindrical in shape. Assume the cylinder is bounded above and below by the planes z = L and z = - L respectively, and on the sides by the cylinder ρ = a [16]. Since the potential must be zero at the origin, we take the function Pn(k ρ) to be the usual Bessel function Jn (k ρ) [32], which must be chosen so that one of its zeroes falls on the bounding cylinder. Taking the limit as L approaches infinity, and using the cylindrical coordinate (ρ,φ,z), we get the field of the point source inside a conducting cylinder as [32]:

$$V(\rho,\varphi,z)=\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}A_{nm}J_n(k_{nm}\rho)\cos\left(n(\varphi-\varphi_0)\right)e^{-k_{nm}|z-z_0|}$$
$$A_{nm}=\frac{2(2-\delta_{n0})}{a^2}\frac{J_n(k_{nm}\rho_0)}{k_{nm}\left[J_{n+1}(k_{nm}a)\right]^2}, \tag{7}$$

where *Anm* are constants regarding the cylindrical coordinates which evolves from the orthogonality relationships for each of the functions, and $k_{nm}a$ is the *m*-th zero of $J_n(z)$.

2.2. The SAN Currents

Here the emphasis was not on the cable theory as proposed by Poznanski [17] and by Wilfrid [18] which suppose a thin long cell with axial symmetry with extra-cellular uniform potential. The cardiac membranes consist of several cells many of which do not possess the axial symmetry and length that are amenable to the cable theory. Consider the intra-cellular and extra-cellular (i.e. non-SAN) domain D, of cardiac cells which consists of ion species (Figure 1). Let A be the intra-cellular region consisting of the SAN and Ao the centre (core) of the SAN. Thus, D\A denotes the region where all ion species suffuse. Define the presence or otherwise of an ion species, sp_i in the region A by the related Dirac measure

$$\delta_{sp_i}(\mathrm{A})=\begin{cases}1, \text{if } spi \in \mathrm{A}\\ 0, \text{if } spi \notin \mathrm{A}\end{cases} \tag{8}$$

The absence of any species in the SAN centre means

$$\mathscr{A}\backslash\mathscr{A}_o=\{sp_i : sp_i \in \mathscr{A}\,;\, sp_i \notin \mathscr{A}_o\} \tag{9}$$

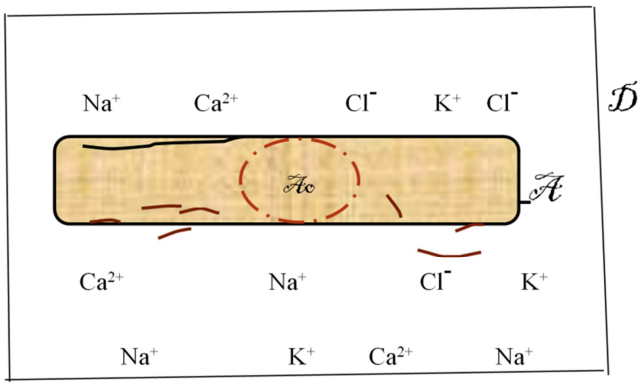

Figure 1. *Schematic of the SAN core.*

At the extra-cellular region D\A the motion of the ions does not impact the stimulus that evoke a full-blown excitation [1]. Assume a one-dimensional spatial motion along *x*, at time, *t*. As usual, molecules and ions move down their concentration gradient - a diffusion process. By Fick's second law we have the relation

$$\frac{\partial c(x,t)}{\partial t}=D\frac{\partial^2 c(x,t)}{\partial x^2} \tag{10}$$

In the above equation, *c*(*x, t*) is the space-time-dependent concentration and *D* is the ion-particular diffusion coefficient. The dynamics of diffusion is marked by random migration of ions/molecules and therefore has a probability current Nzerem [19]. The migration toward the membrane is governed by the stochastic differential equation

$$\frac{\partial}{\partial t}p(x,t|x_0,t_0)=-\frac{\partial}{\partial x}\left[D^1 p(x,t|x_0,t_0)\right]+D\frac{\partial^2}{\partial x^2}p(x,t,|x_0,t_0) \tag{11}$$

In the above equation, D^1 is some distribution representing the drift process, *D* is the diffusion coefficient and *p*(*x, t*) is the probability density function associated with the ionic space-time dynamics. Equation (4) above would furnish, as it were, the likelihood of obtaining the spatio-temporal situation of an ionic species when the initial space and time are known.

The interest is more on the ionic currents that pervade the SAN. In Zhang *et al.* [14] the ion currents observed from rabbit SAN cells are i_{Na}, $i_{Ca,L}$, $i_{Ca,T}$, i_{to}, 4-AP-sensitive sustained outward current (i_{sus}), $i_{K,r}$, $i_{K,s}$, and i_f. Let us employ the seminal Hodgkin and Huxley [2] equation

$$I=C_M\frac{dV}{dt}+I_i\,, \tag{12}$$

where:

I is the total membrane current density;

I_i is the ionic current density;

V is the displacement of the membrane potential from its resting value

(depolarization negative);

C_M is the membrane capacity per unit area (assumed constant);

t is time.

In cardiac tissue, equation (2) may be extended into a reaction-diffusion form to accommodate spatial diffusion of currents [20]

$$\frac{dV}{dt}+\frac{I_{ion}}{C_m}-\nabla\mathbf{x}.(\mathbf{D}.\nabla\mathbf{x}V)=0$$

where x is the spatial coordinate of each material point in the heart; D is the diffusion tensor, which controls the transduction orientation and speed of the electrical wave of excitation in the cardiac tissue. The equation of SAN current density may be written in a more simplified form, though with no loss, as

$$\frac{dV}{dt}=-\frac{1}{C_m}\left(i_{Ca,L}+i_{Ca,T}+i_{Kr}+i_{Ks}+i_{Na}[\delta_{\mathrm{Na}}(\mathrm{A}\backslash\mathrm{A0})]+i_{to}+i_f+i_{sus}\right), \quad (13)$$

where $i_{Ca,L}$, i_{CaT} are *L*- and *T*-type Ca^{2+} currents, $i_{K,r}$, $i_{K,s}$ are rapid and slow delayed rectifying K^+ currents, i_f is the hyperpolarization-activated current, i_{sus} is the sustained current, and i_{to} is the transient outward current. (Note that $\delta_{Na}(A\backslash A_0)$ sets i_{Na} to 1or 0 as the case may be, as indicated by equation (8)). This measure is intended to arrest the sodium ion controversy. However, more is to be done about the expression for the Na^+ ion current; the hyperpolarization current i_f, known as the *funny current*, consists of the Na^+ and K^+ ions. It is therefore split into its constituents (see equations (21) and (22) below).

Define the individual currents, in line with Zang *et al*. [14]:

$$i_{Na}=g_{Na}m^3h\left[Na^+\right]_o\frac{F^2}{RT}\frac{e^{(V-E_{Na})F/RT}-1}{e^{VF/RT}-1}V\ , \quad (14)$$

where g_{Na} is the Na^+ conductance, and subsequently g_i represents conductance for the ion *I*, *m* is the activation variable for i_{Na}, *h* is the deactivation variable given by

$$h=(1-F_{Na})h_1+F_{Na}h_2\ , \quad (15)$$

F is Faraday's constant, *R* is universal gas constant, *T* is Absolute temperature, F_{Na} is the fraction of inactivation of i_{Na} that occurs slowly. As was proposed of the Na^+ current (see Hodgkin and Huxley [2] conductance is controlled by the activation variable *m* and the deactivation variable *h* (h_1 and h_2 are the fast and slow deactivation variables respectively).

$$i_{Ca,L}=g_{Ca,L}\left[f_Ld_L+\frac{6\times10^{-3}}{1.0+e^{-(V+14.1)/6}}\right](V-E_{Ca,L}), \quad (16)$$

$$i_{Ca,T}=g_{Ca,T}d_Tf_T(V-E_{Ca,T}), \quad (17)$$

where d_L and d_T are the activation variables for $i_{Ca,L}$ and $i_{Ca,T}$ respectively, and f_L and f_T are the deactivation variables for $i_{Ca,L}$ and $i_{Ca,T}$ respectively.

$$i_{K,r}=g_{K,r}p_ap_i(V-E_K)\ , \quad (18)$$

where p_a is the general activation variable for $i_{K,r}$ given by

$$p_a=(1-F_{K,r})p_{a,f}+F_{K,r}p_{a,s}, \quad (19)$$

where $p_{a,f}$, $p_{a,s}$ are the fast and slow activation variables for $i_{K,r}$ respectively (see Shibasaki [21])

$$i_{K,s}=g_{K,s}x_s^{\,2}(V-E_{K,s}) \quad (20)$$

$$i_f=i_{fNa}+i_{fK} \quad (21)$$

$$=gf_{Na}y(V-E_{Na})+f_Ky(V-E_K) \quad (22)$$

where *y* is the activation variable for i_f (see Pan et al. [22]; Arie and Ronald [23]). The equilibrium potentials for Na^+, Ca^{2+}, and K^+, E_{Na}, E_{Ca}, E_K are respectively given by

$$E_{Na}=\frac{RT}{zF}In\left(\frac{[Na^+]_o}{[Na^+]_i}\right) \quad (23)$$

$$E_{Ca}=\frac{RT}{zF}In\left(\frac{[Ca^{2+}]_o}{[Ca^{2+}]_i}\right) \quad (24)$$

$$E_K=\frac{RT}{zF}In\left(\frac{[K^+]_o}{[K^+]_i}\right) \quad (25)$$

It is of note that the density of each of the ion currents is proportional to membrane capacitance C_M. In line with Inada *et al.* [15], conductance *g* of the ion currents can be expressed as a linear function of C_M in one dimension. At the at periphery and in the centre of the SAN the conductance has the form

$$g(C_M)=\left(g_p-g_c\right)\frac{C_M-C_c}{C_d}+g_c\ , \quad (26)$$

where g_P and g_C are the conductance for the peripheral and central SAN respectively, C_c is the capacitance, in *pF*, of the SAN centre and C_d is the difference between the peripheral and central capacitance. From equation (26) above we deduce that the linear representation of the conductance can be obtained by the join of the points

$$g_c=\frac{-(C_M-C_c)}{C_d-(C_M-C_c)}g_p \text{ and } g_p=\frac{(C_M-C_c)-C_d}{C_M-C_c}g_c\ . \quad (27)$$

2.3. SAN Centre/Periphery Ion Currents

Consider equation (13). The constituent Na^+ current is

$$i_{Na}[\delta_{\text{Na}}(\text{A})] + i_f = i_{Na}[\delta_{\text{Na}}(\text{A})] + gf_{Na}[\delta_{\text{Na}}(\text{A})] \\ y(V - E_{Na}) + f_K y(V - E_K) \quad (28)$$

The absence of Na^+ ion at the SAN centre Ao means that the part of permeating i_f is the i_K. Thus,

$$i_K \epsilon i_f(\text{Ao}) = f_K y(V\text{-}E_K) \quad (29)$$

If the absence of this sodium ion at the centre is assumed, then the SAN has regional sodium ion concentration basically at the periphery. The time derivative of this concentration $[Na^+]$ of the Na^+ is measured by

$$\frac{d\left[Na^+\right]}{dt} = -\frac{i_{Na}}{z_{Na}FV_r} \quad (30)$$

where: z_{Na} is the valence of the sodium ion; F is Faraday's constant; V_r is the volume of the region where Na^+ is distributed.

The proportion of this Na^+ ion pervading the region A\Ao is

$$Q = c_1 \exp[z_{Na}E/kT],\ c_1 = \text{constant} \quad (31)$$

By equating the right-hand-sides of equations (23) and (24) the resulting Na^+ ion current flowing across the peripheral region ($i_{Na,p}$) is

$$i_{Na,p} = -c_1 z_{Na} tFV_r e^{\frac{z_{Na}E}{kT}}. \quad (32)$$

The above equation determines the quantity of sodium ion firing across the SAN periphery, which can therefore recruit the much required action potential.

With this absence at the centre and the presence elsewhere in the SAN, at least at the periphery equation (13) is modified as

$$\frac{dV_m}{dt} = -\frac{1}{C_m}\left(i_{Ca} + i_K + i_{Na}(\delta_{Na}(\mathscr{A} \setminus \mathscr{A}_\circ)) + (i_{f_K} + i_{f\,Na,p}) + i_{to} + i_{sus}\right), \quad (33)$$

where $i_{fNa,p}$ is the sodium ion component of i_f at least at the periphery but not at the centre, i_{Ca} and i_K represent lumped Ca^{2+} and lumped K^+ currents respectively. (At present, the 4-aminopyridine (4-AP)-sensitive transient outward current, i_{to} is yet to be seen as physiologically important, as claimed by Vladimir *et al*. [24] 4-AP is used in studies in the characterization of the potassium channel subtypes, though Kenyon and Gibbon [25] asserted that there is no reason to claim that i_{to} contains potassium current. 4-AP blocks potassium channels and prolongs action potentials).

2.4. Coupling Conductance

Away from here [31], the cardiac conduction system treated conductance as a source-sink phenomenon, with the SAN as the primary source. The SAN is coupled to the right atrium by means of gap junction. The equation for the SAN centre membrane current together with coupling to the abutting cells is

$$\frac{dV_m}{dt} = -\frac{1}{C_m}\left(i_{Ca} + i_K + i_{f_k} + i_{to}\right) - \sum_i g_c(V_m - V_{m,i}) \quad (34)$$

where V_m is the SAN centre cell's membrane potential, $V_{m,i}$ is the membrane potential of cells connected to the SAN centre cell. In the above equation g_c is the coupling conductance (low g_c enhances the SAN pace making, albeit reduced coupling current required to recruit atrial firing). The gap-junctional coupling conductance is directly dependent on the difference of the potentials. The coupling from cell j to cell i is a discretized form of the Laplacian:

$$I_{coupling} = g_{ij}(V_j\text{-}V_i) \equiv g_c(V_1\text{-}V_2)$$

The associated coupling function is (Kopell and Ermentront [26])

$$H_1(\phi) = \frac{g_{ij}}{T}\int_0^T V^*(t)(V_0(t+\phi) - V_0(t))dt.$$

where $V_0(t)$ is the voltage component of the periodic trajectory of the uncoupled system , and $V^*(t)$ is the voltage component of the adjoint. At the gap junction, $H_1(0) = 0$, but for synapses $H_i(0)$ will not vanish in general. Suppose there are two cells, the SAN centre $cell_1$ and an abutting $cell_2$, of isopotential compartments with gap-junctional current $I_{2,1}$ flowing from $cell_1$ to $cell_2$. The representative current $g_c(V_1\text{-}V_2)$ is seen as a source term in the current balance equation for $cell_2$, with the current issuing from $cell_1$. It is likened to a sink term for $cell_1$. Thus, $g_c(V_2\text{-}V_1)$ is a source term into $cell_1$ (see Ritzel [27]). The equations of the coupled system becomes

$$C_m\frac{dV_1}{dt} = -I_{ions,1} + I_{app,1} + g_c(V_2 - V_1) \quad (35)$$

$$C_m\frac{dV_2}{dt} = -I_{ions,2} + I_{app,2} + g_c(V_1 - V_2) \quad (36)$$

where $I_{\text{ions},1}$ is a function of V_1. A large gap junctional conductance causes the cells to be tightly electrically coupled. Subtract (35) from (36), after dropping the term of order $1/g_c$ to get

$$\lambda_c\frac{dV_{1,2}}{dt} \cong -V_{1,2} \quad (37)$$

where $V_{1,2} = V_1\text{-}V_2$, $V_{2,1} = V_2\text{-}V_1$ and $\lambda_c = C_m/g_c$. From the above equation we get

$$V_{1,2} \cong V_0 e^{-t/\lambda_c}, \quad (38)$$

when evaluated at $V_{1,2}(0) = V_0$.

2.5. Centre is Dependent on Calcium ion (Ca^{2+})

Cardiac calcium ion, Ca^{2+} consists of the long-lasting current $i_{Ca,L}$, and the transient current $i_{CA,T}$. while the former is found in all cardiac cell types, the latter is specific to the SAN, the Purkinje cells and the atria. $i_{Ca,L}$ is very important in pace-making; it is activated at the level of membrane potential above -55mV (see Chapman et al. [28]). $i_{Ca,L}$ channel is slow to open but remains open for a long time afterwards. The cardiac delayed rectifier potassium currents consist of the fast type i_{Kr} and the slow type i_{Ks}.

The $i_{Ca,L}$ and i_{Ks} are ion-carrying currents with physiological (harmless) delay. In what follows, $i_{Ca,L,}$ the long-lasting Ca^{2+} current is given a closer look. The Ca^{2+} current lasting duration, owing to the opening of the *L*-type calcium channel, induces an influx of calcium into the cardiomyocyte which initiates cardiac excitation/contraction coupling. This is a time-hallowed physiological phenomenon. The evident delay in the channel closure typically reflect a combination of transmission times- processing time and the delivery time. A characteristic feature of Na^+-driven AP of a typical cardiac cell is an overdrive (rapid stimulation). This requires that pacemaker activity may be inhibited for several minutes. In effect, a periodic response may cease to be tenable. The Na^+ absence in the SAN centre, together with the $i_{Ca,L}$-driven SAN centre AP reinforce the harmless time delay evident in the SAN AP.

The response of *L*-type Ca^{2+} current (now, for ease, indicated by C_i) to the opening of its channel obeys the single-species delay differential equation

$$\dot{C}_i(t) = C_i(t)\left[k(t) - l(t)C_i(t) + m(t)C_i(t-\tau(t))\right], \quad (39)$$

where:

$k(t)$ is the rate of calcium release from the sarcoplasmic reticulum during spontaneous Ca^{2+} spark that marks the onset of AP;

$l(t)$ is the net calcium current sink to the right atrium- the major cause of delayed depolarisation rate (since the SAN is electrically coupled to the right atrium)

$m(t)$ is the calcium sustainability factor during delayed depolarisation;

$\tau(t)$ is the time-dependent delay.

In virtue of the oscillatory nature of the SAN cells' APs, it is noteworthy that $k(t)$, $l(t)$, $m(t)$ and $\tau(t)$ are continuously differentiable ω-periodic functions and $k(t) > 0$, $l(t) > 0$, $m(t) \geq 0$, $\tau(t) \geq 0$ for $t \in R = (-\infty, +\infty)$. The delay in the term $m(t)C_i(t-\tau(t))$ is physiological (harmless) due to time needed for SAN electrical coupling to the right atrium. With the probability of gate being open, and using equation (16) we write

$$\begin{aligned}\dot{C}_i(t) = g_{Ca,L}[d_L+\eta](V(t)-E_{Ca,L})\{k(t) - l(t)g_{Ca,L}[d_L+\eta](V(t)-E_{Ca,L}) \\ + m(t)g_{Ca,L}[d_L+\xi](V(t-\tau(t))-E_{Ca,L}\}\end{aligned} \quad (40)$$

where $\eta = \dfrac{6\times10^{-3}}{1.0+e^{-(V+14.1)/6}}$, $\xi = \dfrac{6\times10^{-3}}{1.0+e^{-(V(t-\tau(t))+14.1)/6}}$.

Following Freedman and Jianhong [29], suppose $\tau\max = \max_{t\in[0,\omega]}\tau(t)$. Then, for any given $\phi \in ([-\tau_{\max}, 0]; R)$, there exist $\lambda \in (0,\infty)$ and a unique solution $C_i(t) = C_i = (t;\phi)$ of equation (3.1) on $[-\tau_{\max}, \lambda)$. Thus, $C_i(t)$ is continuous on $[-\tau_{\max}, \lambda)$, continuously differentiable, and satisfies equation (40) on $(0,\lambda)$ and $C_i(\theta) = \phi(\theta)$ on $[-\tau_{\max}, 0)$. Besides, if $\phi(t) \geq 0$ on $[-\tau_{\max}, 0]$, then $C_i(t)$ remains nonnegative for all $t \in (0,\lambda)$. It can be shown (see: Freedman and Jianhong [29] Shigui [30]) that if the equation

$$k(t) - l(t)B(t) + m(t)B(t-\tau(t)) = 0 \quad (41)$$

has a positive, ω-periodic, continuously differentiable solution $B(t)$, then the equation (40) has a positive ω-periodic solution $S(t)$. Besides, if $l(t) > m(t)S(t-\tau(t))/S(t)$ for all $t \in [0,\omega]$, then $S(t)$ is globally asymptotically stable with respect to the positive solution of equation (39). This is likened to a physiological state of the SAN if each of the other individual ionic current is associated with similar condition as the $i_{Ca,L}$ under consideration.

In the above equation $B(t)$ is, in the present context, the SAN calcium current-carrying capacity. The carrying capacity is the primary generator of periodic oscillations of the SAN AP. It is noteworthy that the action potential of peripheral SAN tissue depends on i_{Na}, while that of central SAN tissue depends on $i_{Ca,L}$, rather than $i_{Na.}$ We assume $k(t)/(l(t)-m(t))$ is not a constant since $B(t)$ must be an ω-periodic function, in which case the periodic solution $S(t)$ is non-constant. The location of the periodic solution $S(t)$ may be approximated. To do this, the constants ε and some constant $N > 0$ may be roughly estimated, as shown in Freedman and Jianhong [29] such that

$$\varepsilon \leq \frac{S(t)}{B(t)} \leq N \text{ for } t \in [0,\omega]. \quad (42)$$

In the event of pathological delay, the ratio $S(t)/B(t)$ will be nowhere the interval [ε , N].

3. Conclusion

This paper considered an aspect of electrophysiology that relates to the cardiac membrane and cells. It is untenable to undertake a lumped study of cardiac cells due to their characteristic peculiarities and heterogeneities. In the light of this, this work was particular on the electrophysiology of the

sino-atrial node (SAN). The membrane and cells of SAN are a sine-qua-non to cardiac pacesetting and ionic action potential. The SAN centre is the origin of action potential; the SAN as a whole is the source of entire cardiac action potential.

Mathematical analysis of electrophysiology is often faced with the problem of inadequate and authentic information about cellular composition of ions. This is serious setback on the much needed mathematical models. The most excruciating irritation regarding cardiac electrophysiology is what we may call *the sino-atrial dilemma*. The issue of the presence or lack of the sodium ion (Na^+) in the SAN is still a contestation. Mathematical exactitude require unassailable details in cases where experimentations precede analysis. In literature (part of which is contained here), what appears clearer is the presence of the said ion at the periphery and the dearth of the same at the centre. All the same, this work is a bit pacifying. Any school of thought as regards the sino-atrial dilemma may see the modified equation(s) of cardiac membrane current here as *not offensive* (?).

The SAN centre, which is the origin of cardiac action potential, induced more insight into the calcium ion. At the onset of action potential calcium is released from its warehouse, known as the *sarcoplasmic reticulum*. The *L*-Type calcium ion current, $i_{Ca,L}$ is known to be critical to the recruitment of action potential. $i_{Ca,L}$ channel is slow to open but remains open for a long time afterwards. This property brings to understanding the physiological (harmless) delayed diastolic depolarisation that is due to SAN coupling to the right atrium.

The event in calcium current delay may be described by suitable delay differential equation with periodic content. A single-species delay differential equation that describes the situation was therefore furnished. The single-species equation was to cater for the $i_{Ca,L}$ dynamics only, as it is not the only ion current of the SAN centre. Stability of the periodic solution of the equation is descriptive of physiological state of $i_{Ca,L}$ flow, all else being equal. The solution space indicates the permissible time interval within which delay is not dangerous, that is when delay is harmless. Away from this solution space, there is the likelihood of pathophysiology. Specialized cardiac cells, including the SAN, are conduction sources and sinks. Flows involving sources and sinks in terms of cardiac cell membranes are amenable to periodic delays. Delay differential equations, including the one presented here are therefore utilized and analysed for physiological purposes.

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