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Mathematical Modeling of Neuron Using Hodgkin-Huxley Model

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Abstract:

The growing rate of mental illnesses has brought the idea of curing anxiety disorders by altering heart rate variability using sympathetic and parasympathetic stimulations. The parasympathetic activity in the sinoatrial node that is responsible for arrhythmia has been considered in the already existing cardiovascular model. This study presents a mathematical model of a single neuron and simulates its activity for a single burst to be amalgamated in a closed-loop system of the heart and uses heart rate variability as a control variable to treat anxiety disorders and decrease the rate of increasing mental disorders in the world population. The proposed study shows the results that rise from 7mV and go up to 107mV and then again fall back to 7mV depicting a single burst. These results are being validated by comparing the model of neurons presented in the classical Hodgkin-Huxley model using MATLAB.

Keywords: *Anxiety, Heart rate variability, Sinoatrial node, Mathematical model, Neuron, Mental disorders*

I. INTRODUCTION

Lower heart rate variability (HRV) is an indication of poor cardiovascular health which leads to anxiety and ultimately to cardiovascular death. Anxiety is caused by irregular rhythms of the heart rate also known as arrhythmia. This anxiety can be modelled mathematically as a disturbance signal in the closed-loop feedback system of the heart via state-space methods. The parasympathetic nervous system activity is a good representation of anxiety signal which can be modeled as an activity of neuron firing action potential signal in the sinus node of the heart (as illustrated in Figure 1). These models can be translated as a 4th-order model of the heart combined with voltage signals of the heart to treat anxiety disorder through means of a feedback controller. In this paper, the heart is first represented as a 4th-order mathematical model followed by a mathematical model of voltage signals generated by a single neuron. Simulation results have been presented in the Results and Discussion section. Finally, the paper has been concluded by presenting the future direction of the work.

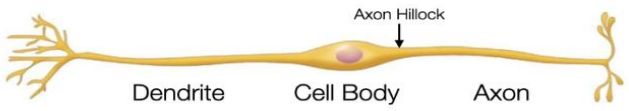

Figure 1: Neuron Structure

II. LITERATURE REVIEW

More than 450 million population in the world suffer from mental illnesses which comprise 6% approximately. The increasing rate of mental illnesses has brought the need to cure them. For this purpose, many techniques have previously been applied which include computational and analytical methods, and invasive and noninvasive controller-based techniques [1].

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It was earlier believed that mental illnesses arise in the brain which can be diagnosed through brain scans, MRIs etc. but Weir [2] contradicts this idea and claims that the root cause of mental illnesses is arrythmia, which means that mental disorders are caused by irregularities in the heart instead of the brain. The physiology of the heart helps in the analysis and treatment of mental illnesses and somehow heart rate variability serves as a control variable for our purpose [3]. It is possible to map brain-heart interactions to study the underlying reasons behind them [4]. Keeping the fact in mind that the brain and the heart have their distinct physiological dynamics, their interaction can still be learned through invasive, minimally invasive and noninvasive methods such as 7T magnetic resonance imaging [1]. Advanced signal and neuroimage processing methods can be deployed for timely detection of pathophysiological changes arising in the brain and the heart [4].

Addressing mental issues requires a thorough understanding of symptoms and causes, for this purpose, monitoring of physiological variables through sensing devices such as mobile phones and wearables has increased over the decade. Physiological signals such as facial expressions, eye movement, HRV, and electrodermal activity are positive in monitoring illnesses [3].

The analysis of ejection fraction as a measure of heart rate turbulence is greater than 30% on average in the meta-analysis of 9 out of 10 control groups of post-acute myocardial infarction, it is also a predictive of the final stage of heart failure patients [5]. Since heart rate turbulence (HRT) has been useful in predicting the behaviour of baroreflex, it can be deployed in risk assessment of cardiac death, and heart failure and taking preemptive measures in clinical setup [6].

Too much attention is being paid to HRV to treat Bipolar Disorder (BD), Social Anxiety Disorder (SAD), Borderline Personality Disorder (BPD), Post Traumatic Stress Disorder (PTSD) etc, recently, a Guideline for Reporting Articles on Psychiatry and Heart rate variability checklist assessing HRV in BD and BPD patients has been proposed which may accelerate the comparison between studies of the behaviour of HRV in for BD and BPD [7]. The reduced autonomic nervous system activity is linked to psychopathology and heart disease. The relationship between the two helps diagnose and treat coronary heart diseases caused by reduced autonomic control. The sympathetic activation increases the release of catecholamines which increases the heart rate during periods of stress, and, the decrease of parasympathetic activity also increases the heart rate. In either of the states, there is a risk of increased arrythmia [8]. The reduced HRV is a measure of autonomic control activity and is indicative of sudden cardiac death in patients with social anxiety disorder followed by impairment in stress regulation, and behavioral inhibition. It has been deduced that females exhibit higher levels of social anxiety disorder as compared to males [9]. The rate of social anxiety disorder was three times higher in patients with coronary heart disease [10]. This leads towards an urgent need to prevent anxiety disorders, especially in patients with heart diseases.

Anxiety being the key component of mental illnesses can be addressed by modeling fear circuits in the brain since activation in the insular cortex is increased at levels in anxiety disorders [11].

The model of arterial pressure and elastance function as a representation of the heart has been described in detail to model the activity of sinus nerves in vagotomized subjects [12]. It has been observed that the carotid baroreceptor function follows a sigmoidal curve and adapts mean carotid sinus pressure during the cycle continuously in agreement with [13].

The analogy between the electrical model of the heart and cardiovascular system has been clearly explained by Creigen [14], the classical Wind Kessel model as a resistance in parallel with a capacitor[15], lumped parameter models by Ottesen et al [16] etc. We choose the 4th-order lumped heart model representing compliances as capacitances, inertance as inductance, resistances to blood flow as electrical resistances and valves as diodes in terms of a state-space model. Also, the baroreflex has been modelled as an electrical circuit by representing valves, systemic resistances, pressures and permeabilities as diodes, resistors, currents and voltages etc. [17]. This model helps in understanding the changes in baroreceptor firing rates in terms of a function of varying blood pressure.

As determined by the baroreflex, a controller has already been proposed also known as the Left Ventricular Assist Device (LVAD) that responds to changes in physiological states adjusting according to the flow of the pump based on the heart rate [18]. A full-state feedback method has been devised to control cardiac output in case of vasodilation during posture change in humans that mimics the Starling law which derives the flow of LVAD to preload [19].

The firing frequency of baroreceptors can be modelled as a function of arterial pressure through a mathematical equation to describe the behavior of arterial baroreceptors [20].

The capacitor-switch model of neurons is an extension of the classical integrate and fire model with a capacitor, a floating DC source, a trashing path and other outgoing paths consisting of a resistor, a diode, and a voltage-gated switch [21]. The traditional Hodgkin-Huxley model of neurons has been incorporated which generates an action potential signal corresponding to the firing activity of neurons. Membrane potential for each of Na, K and Ca ions has been obtained by deriving differential equations of each channel [22]. The ganglions present in the vagus nerve (XIth cranial nerve) are responsible for activating action potential through the sinoatrial node which eventually activates the parasympathetic nervous system and regulates HRV, thus controlling the anxiety [23].

III. MATERIAL AND METHODS

A. Cardiovascular System

We have taken the 4th order cardiovascular model from Chen's thesis as a foundation for our simulation work [18]. The lumped parameter model comprises of different states of blood flow modelled as different state equations which are elaborated as follows:

Starting with left ventricular elastance $E(t)$ as a time-varying function of capacitance

$$E(t) = \frac{LVP(t)}{LVV(t)-V_o} = \frac{1}{C_1(t)} \qquad (1)$$

Here, LVP is Left Ventricular Pressure, and LVV is the Left Ventricular Volume and V_o is reference volume which is 5ml for a normal heart. Elastance function $E(t)$ may be defined as

$$E(t) = (\,E_{max} - E_{min}\,)E_n(t_n) + E_{min} \qquad (2)$$

where, E_{max} is end systolic pressure-volume relationship and E_{min} is end diastolic relationship. $E_n(t_n)$ is the normalized time-varying elastance, also known as the double hill function

$$E_n(t_n) = 1.55 * \left[\frac{\left(\frac{t_n}{0.7}\right)^{1.9}}{1+\left(\frac{t_n}{0.7}\right)^{1.9}}\right] * \left[\frac{1}{1+\left(\frac{t_n}{1.17}\right)^{21.9}}\right] \qquad (3)$$

t_n has been defined as $t_n = \frac{1}{T_{max}}$, and $T_{max} = 0.2 + 0.15t_c$ such that t_c is the cardiac cycle

For E_{max} = 2.0 and $E_{min} = 0.6$, the elastance function has been plotted in Figure 3.

The following equation is valid for each phase of the cardiac cycle:

$$\frac{dx}{dt} = A(t)x \qquad (4)$$

$A(t)$ is different for each phase, x can be defined as

$$x = [x_{c1} \;\; x_{c2} \;\; x_{c3} \;\; x_{c4}]$$

We have the following states defined for our cardiovascular model in Table 1:

Table 1: State Variables for Cardiovascular System

Variables	Physical Terminologies
x_{c_1}	Left Ventricular Volume (ml)
x_{c_2}	Left Atrial Pressure (mmHg)
x_{c_3}	Arterial Pressure (mmHg)
x_{c_4}	Aortic Flow (ml/sec.)

During the isovolumic phase of the cardiac cycle, mitral and aortic valves are closed, and aortic flow is zero, therefore we have,

$$A(t)=\begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -\frac{1}{R_1C_2} & \frac{1}{R_1C_2} & 0 \\ 0 & \frac{1}{R_1C_3} & -\frac{1}{R_1C_3} & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

During the ejection phase, the aortic valve is open and the mitral valve is closed, the left ventricle pumps blood into the circulatory system, so we have,

$$A(t)=\begin{bmatrix} 0 & 0 & 0 & -1 \\ 0 & -\frac{1}{R_1C_2} & \frac{1}{R_1C_2} & 0 \\ 0 & \frac{1}{R_1C_3} & -\frac{1}{R_1C_3} & \frac{1}{C_3} \\ \frac{E(t)}{L} & 0 & -\frac{1}{L} & -\frac{(R_3+R_4)}{L} \end{bmatrix}$$

In the filling phase, blood goes from the left atrium into the left ventricle. The mitral valve is opened, and the aortic valve is closed which implies that $x_{c4}=0$. Thus, we have,

$$A(t)=\begin{bmatrix} -\frac{E(t)}{R_2} & \frac{E(t)}{R_2} & 0 & 0 \\ \frac{E(t)}{R_2C_2} & -\frac{(R_1+R_2)}{R_1R_2C_2} & \frac{1}{R_1C_2} & 0 \\ 0 & \frac{1}{R_1C_3} & -\frac{1}{R_1C_3} & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

Both of the valves open is the case which never occurs in the heart. The final states of any cardiac cycle are the initial states for the next cycle.

B. Neuron

If we model neurons using the state-space method then, we have Hodgkin-Huxley's model of the neuron as the building block of modelling anxiety. A neuron can be stimulated by a signal through external means or neighboring neurons. There are concentration gradients across the cell membrane at resting state which is more sodium(Na) and calcium(Ca) ions outside the cell and more potassium(K) ions inside the cell maintained by pumps that allow the flow of ions in and out of the membrane. The brief reversal of polarity caused by voltage-gated ion channels is called action potential. When the membrane voltage increases and becomes less negative, the cell is said to be polarized, and, when the membrane potential decreases, it becomes more negative, the cell is said to be repolarized. For action potential to be generated, the cell must polarize to a 'threshold' value. This voltage starts at -60mV and rises spontaneously until it reaches -40mV. At the threshold value, the Ca channels open to allow the flow of Ca ions into the cell depolarizing the membrane. This is known as the rising phase of action potential in the sinus node. At the peak of depolarization, K channels open, Ca channels are inactivated, K ions leave the cell and the voltage finally returns to -60mV corresponding to the falling phase. At this stage, the original ionic gradients are restored and the cycle repeats.

For a mathematical model of neurons, Consider the circuit in Figure 2. We have Na, K and leak conductances g_{Na}, g_K and g_L respectively, each with an associated battery connected in parallel to each other. We define total membrane current as the sum of the sodium current, the potassium current and a leak current. The Na current and K current are

time-dependent whereas, the leak current is a fixed quantity, and has a battery of -50mV keeping the cell hyperpolarized.

$$I_m = I_{Na} + I_K + I_L \tag{5}$$

where,

$$I_{Na} = G_{Na}(V,t)(V - E_{Na})$$
$$I_K = G_K(V,t)(V - E_K)$$
$$I_L = G_L(V - E_L)$$

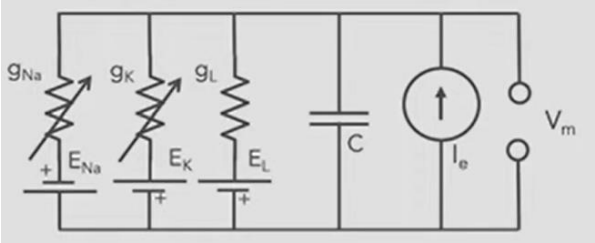

Figure 2: Equivalent Circuit for a Neuron

The membrane potential depends upon the membrane current as described by the following differential equation

$$I_m(t) + C\,\frac{dV(t)}{dt} = I_e(t) \tag{6}$$

The membrane currents depend upon the conductances which in turn are dependent upon the voltage.

The sodium (Na) and potassium (K) conductances are off at negative potentials, they turn on at positive voltages and remain constant. The moment this voltage is turned on, it rises gradually with a delay and reaches a constant K conductance in time while the Na conductance first turns on(activation) and then turns off(inactivation). To explain the voltage and time-dependence of K conductance, let P_K be the probability that the K channel is open and N_K is the total number of ion channels, then K conductance may be defined as,

$$G_k = P_K(V,t)N_K\hat{g}_K \tag{7}$$

K channel is formed by four identical subunits, each subunit having a voltage sensor which allows it to either turn on or off. For a channel to be open, all four of the subunits must be in open state. If n is the probability that a subunit is open then,

$$P_K = n^4 \tag{8}$$

So,

$$G_K = \bar{\bar{G}}_K n^4 \tag{9}$$

Therefore, the K current can be written as

$$I_K = \bar{\bar{G}}_K n^4 (V - E_K) \tag{10}$$

Using the Boltzmann equation to find out the ratio of probabilities of being in an open or closed state.

$$\frac{P_{open}}{P_{closed}} = e^{-\left(\frac{Uopen - Uclosed}{kT}\right)} = e^{-\left(\frac{w - q_g V_m}{kT}\right)} \tag{11}$$

Thus, we have,

$$n = P_o = \frac{P_o}{P_o + P_c} = \frac{1}{1 + \frac{P_c}{P_o}} = \frac{1}{1 + e^{\left(\frac{w - q_g V_m}{kT}\right)}} \tag{12}$$

Let n be the probability of the ion channel being in an open state, and then the probability of the subunit being in a closed state is $(1 - n)$. Also, let be α the transition state of a channel to open and β be the transition state to close, these transition rates are voltage- dependent.

So, we have

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n$$
$$= \alpha_n - \alpha_n n - \beta_n n$$
$$= \alpha_n - (\alpha_n + \beta_n)n \quad \frac{1}{(\alpha_n + \beta_n)}\frac{dn}{dt} = \frac{\alpha_n}{\alpha_n + \beta_n} - n \tag{13}$$

which is the steady- state solution of this differential equation.

If $\frac{dn}{dt} = 0$, then $n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$ and $\frac{1}{\alpha_n + \beta_n}$ is a time constant called τ_n, so we can rewrite the differential equation as,

$$\tau_n \frac{dn}{dt} = n_\infty - n \qquad (14)$$

The gating variable n rises exponentially when the voltage rises from negative value to zero and dies out exponentially when the voltage again switches to negative, but the conductance goes as the gating variable to the fourth power and turns on gracefully.

$$P_K(t) = [n(t)]^4 \qquad (15)$$

Again, to explain the voltage and time dependence of Na conductance, let m be the probability the Na subunit is open, and then the probability of the subunit being closed is $(1 - m)$. A similar kind of equation for m managing variable

$$\tau_m \frac{dm}{dt} = m_\infty - m \qquad (16)$$

where, $m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}$.

In Na conductance, all four subunits are not independent of each other so,

$$P_{Na}(t) \propto [m(t)]^3$$

$$P_{Na}(t) = [m(t)]^3 h \qquad (17)$$

The process of turning m on is called activation, m turning off is called deactivation and G_{Na} turning off is called inactivation. Here, h is the inactivation gating variable for Na.

Na channel inactivation can be described by a first-order linear differential equation,

$$\tau_h \frac{dh}{dt} = h_\infty - h \qquad (18)$$

h is a bigger value for lower voltages and smaller for high voltages. So, h turning on is called inactivation and h turning off is called deactivation.

Therefore, Na conductance can now be defined as,

$$G_{Na} = \bar{\bar{G}}_{Na} m^3 h \qquad (19)$$

such that m and h are independent. The Na current may be written as,

$$I_{Na} = \bar{\bar{G}}_{Na} m^3 (V - E_{Na}) \qquad (20)$$

IV. RESULTS AND DISCUSSION

Following is the plot for left ventricular elastance as a function $E(t)$ of time which is according to the results stated in [18]

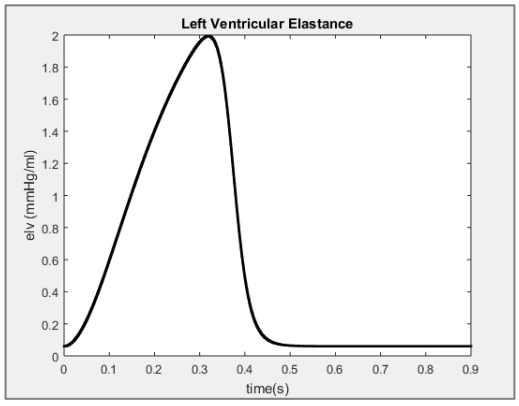

Figure 3: Plot for Left Ventricular Elastance
Source: Author's Estimation

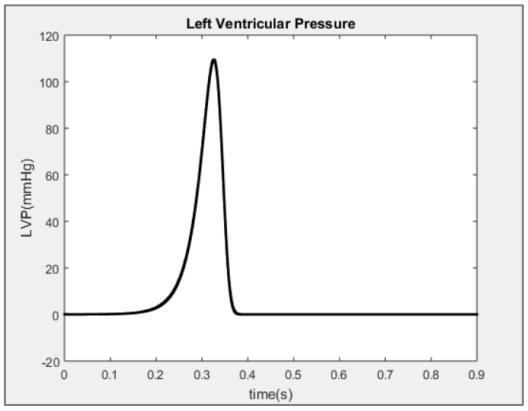

Figure 4: Plot for Left Ventricular Pressure
Source: Author's Estimation

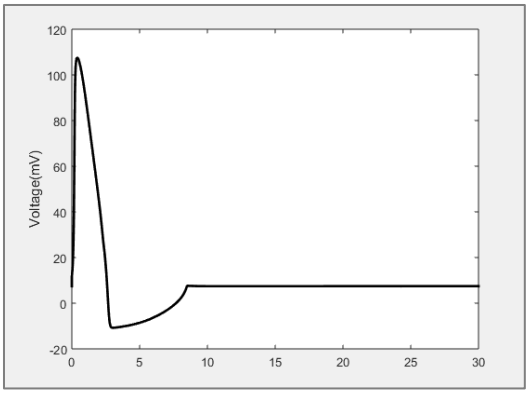

Figure 5: Plot for Action Potential of a Single Neuron Source: Author's Estimation

If we plot the Left Ventricular Pressure using our cardiac model then we can see that it rises from 0mmHg and goes through 110mmHg which verifies the veracity of our model as presented in Figure 4. The electric generation of potential across the membrane of the SA node can be seen in Figure 5: It rises from 7mV and goes up to 107mV and then again falls back to 7mV depicting a single burst.These results are being validated by comparing the model of neurons presented in the classical Hodgkin-Huxley model [22].

V. CONCLUSION AND FUTURE RECOMMENDATIONS

The cardiovascular model can be combined with the neuron's action potential to obtain a disturbed representation of signals of the heart. Also, a closed-loop feedback controller can be incorporated to rectify the pressures of blood flow to treat arrhythmia. Moreover, now we have online heart monitoring devices based on IoT for blood pressure, heart rate, blood oxygen saturation levels, and body temperature whether it be wearables or implanted in human bodies.

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CONFLICT OF INTEREST

There is no conflict of interest between all the authors.

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