Chapter 7

Implementation of Mathematical Model

The chapter includes:

- Functioning of left ventricle
- Effect of acetylcholine on left ventricular function
- Reduced neuron conduction in diabetic condition
- Effect of changes in left ventricular geometry on the performance of heart

Mathematical model is implemented to quantify the physiological processes. It provides complete understanding about the process and effect of every parameter on the process. States and state transitions are clear from the mathematical model.

7.1 Mathematical model to demonstrate the functioning of left ventricle

The pulsatile model describing cardiovascular dynamics is as shown in the figure-7.1 is a lumped parameter RC network system. [63] The functioning of the model is similar to left ventricle. The ideal diodes D1 and D2 (analogous to mitral valve and aortic valve) ensure that the blood flow (analogous to current) travels in the direction shown in the diagram. The quantities $V_v(t)$, $V_h(t)$ and $V_a(t)$ are the pressure due to volume (ml) of blood in the veins is analogous to voltages, ventricle and arteries respectively. The condition for current $I_1(t)$ to flow is $V_v(t) > V_h(t)$ and $I_2(t)$ to flow is $V_a(t) > V_h(t)$. The difference in volumes is analogous to difference in voltages. The difference in voltage levels initiates the current flow. $C_a(t)$ is arterial compliance and $C_v(t)$ is venous compliance. The quantity compliance is analogous to capacitor. The compliance is fulfilled only when the volume is filled to full capacity (analogous to capacitor charge in electrical circuits). Once the compliance (capacitance) reaches the maximum, discharge starts. The elastance goes on increasing as the compliance reaches its minimum (negative pressure initiates ventricular filling is similar to zero charge in capacitor initiate the current flow in it). The behavior of compliance in relation to elastance is shown in figure-7.2. $R_1$ and $R_2$ are the inflow and the outflow resistance of the left ventricle. $R_a$ is the total peripheral resistance. The negative pressure creates the filling of the left ventricle by pulmonary vein at the
left ventricular diastole. The negative pressure is created till the ventricle gets filled. When the ventricular compliance is fulfilled, the ventricle starts ejecting the blood in arteries where there is less pressure. Unless the compliance is not met the current $I_1(t)$ and $I_2(t)$ does not flow. The ventricular compliance will be fulfilled when only the ventricular filling is complete. The elastance of left ventricles increases till the compliance reaches a steady negative value that ensures the ventricular filling.

![Electrical circuit model representing the left ventricle](image)

Figure-7.1-Electrical circuit model representing the left ventricle. Figure adapted from [63].

**Conclusion:**

The HRV indices can diagnose the shift in the neuro-humoral balance, the increase in parasympathetic power and decrease in total power in diabetic condition.

Shift in the neuro-humoral balance indicates inadequacy of the blood supply. The reduced blood supply indicates the compromised performance of the target organ.

Increase in parasympathetic power reduces the diastolic filling rate and indicates necrosis.

Reduced total power at SA node indicates the compromised performance of heart and insufficient pumping.

Increase in heart rate indicates the insufficient blood supply and overload on heart.
In case of hypertensive subjects, increase in sympathetic power is an early indicator of compromised heart performance.

Increase in SDNN is one of the significant markers in case of hypertensive subjects. SDNN in maintained at lower values by pharmacological intervention so that heart is not strained. Hence, SDNN cannot be considered as reliable marker.

Regular HRV analysis of diabetic, diabetic and hypertensive subjects can control the mortality and morbidity rate due to myocardial ischemia/infarction.

Figure 7.2- Relation between compliance and elastance function for T=1 sec. Figure adapted from [63].

The behavior is modeled with the following equations.

\[ I_1 = \frac{V_v - V_h}{R_1} \quad \text{if} \quad V_v > V_h \quad \text{--------------------------- (1)} \]

\[ = 0 \quad \text{otherwise.} \]

\[ I_2 = \frac{V_h - V_a}{R_2} \quad \text{if} \quad V_h > V_a \quad \text{--------------------------- (2)} \]

\[ = 0 \quad \text{otherwise.} \]

\[ I_a = \frac{V_a - V_v}{R_a} \quad \text{--------------------------- (3)} \]

\[ \frac{dQ_h}{dt} = I_1 - I_2 \quad \text{--------------------------- (4)} \]

Where, \( Q_h \) is the quantity of blood in left ventricle.

\[ \frac{dV_a}{dt} = \frac{I_2 - I_a}{C_a} \quad \text{--------------------------- (5)} \]
\[
\frac{dV_v}{dt} = \frac{l_2-l_1}{C_v} \tag{6}
\]

\[
E_{h(t)} = \frac{3(\text{Es}-\text{Ed})}{T} + \text{E}_d \text{ for } 0 < t < \frac{T}{3} \tag{7}
\]

\[
E_{h(t)} = \frac{6(\text{Es}-\text{Ed})(\frac{T}{3}-t)}{T} + \text{Es} \text{ for } \frac{T}{3} < t < \frac{T}{2} \tag{8}
\]

\[
E_{h(t)} = \text{Ed} \text{ for } \frac{T}{2} < t < T \tag{9}
\]

\[
E_{h(t)} = \frac{1}{C_{h(t)}} \tag{10}
\]

Where, \( E_s \) and \( E_d \) are end-systolic and end-diastolic elastance and \( E_{h(t)} \) is the time varying left ventricular elasticity. The systolic elastance is at minimum and diastolic elastance is at the maximum value.

The elastance values formulated as discrete piecewise linearization. The unit for compliance is ml/mm Hg i.e. volume per (negative) pressure. The left ventricular elastance is reciprocal of left ventricular compliance. The left ventricular piecewise linear elastance of normal subject is for systole and diastole is in the range of 0.1 to 2.5 mm Hg/ml.

**Conclusion:** The healthy heart expands and contracts accordance with the electric stimulation and ventricular elastance is maximum at ventricular diastole.

7.2 Effect of acetylcholine on functioning of heart

Mathematical model of based on Hodgkin and Huxley-type equations of time- and voltage-dependent membrane currents is used to analyze effects of acetylcholine on electrical activity of SA node. [64] The basic electrical properties of a patch of cell membrane can be described by an equivalent electrical circuit which assumes a membrane capacitance in parallel with several time and voltage-dependent membrane resistances as stated by Hodgkin and Huxley. The total membrane current (IM) across such a patch is equal to the sum of the capacitive current (IC) and the total ionic current (IT).

Thus, the total ionic current (IT) can be written as -

\[
I_M = I_C + I_1 \tag{11}
\]

The capacitive current can be described as a function of membrane capacitance (CM) and membrane potential (EM) as
\[ I_c = C_M \frac{dEM}{dt} \]  
Therefore equation (1) can be written as-

\[ I_M = -C_M \frac{dEM}{dt} + I_T \quad \text{(12)} \]

If membrane potential is constant then \( I_M = 0 \). Therefore equation (2) can be written as-

\[ I_T = -C_M \frac{dEM}{dt} \quad \text{(13)} \]

The total current is also sum to ionic current flow through the channels connected to the membrane. They are represented as-

A slow inward current - \( i_s \)
Current in sodium channel - \( i_{na} \)
Current in Potassium channel - \( i_k \)
Current due to leakage - \( i_l \) and
Current due to hyperpolarization \( i_h \)

\[ I_T = i_s + i_{na} + i_k + i_h + i_l \quad \text{(14)} \]

The \( i_{ach} \) can be added to the above equation, by giving an acetylcholine pulse. [65] The changes in the membrane potential and different currents are shown graphically in Figure 7.3. The top trace shows membrane potential and the lower traces illustrate the time course of the individual membrane currents. The first cycle shows control conditions. The pacemaker period was 318 millisecond, maximum diastolic potential was -59.6 mV, overshoot was 20.8 mV, and action potential amplitude was 80.4 mV. The algebraic sum of the six membrane currents as described in the present model is represented by the total current. Positive deflections are outward current. Negative deflections are inward currents. The period of the action potential due to \( i_{ach} \) is changed to 548 millisecond. Whereas, next interval is reduced to 310 millisecond. Major change is observed in the total current reduced.
Figure 7.3 Effect of adding pulse of acetylcholine on SA node membrane potential and different currents flowing in and out of membrane. Figure adapted from [65].

From the diagram it is clear that the depolarization rate is delayed by increase in acetylcholine concentration at SA node. Also the subsequent interval is reduced. Effect of different concentrations of acetylcholine on diastolic depolarization rate is plotted in figure-7.4. [67] The graph shows more or less linear relationship between the acetylcholine concentrations to diastolic depolarization rate.
Conclusion: Increased Acetylcholine reduces the diastolic depolarization rate by increase in parasympathetic power.

7.2.1 Effect of increased concentration of Acetylcholine

This signifies that in prolonged diabetic condition, with poor glycemic control, the diastolic depolarization rate is significantly reduced. The reduced depolarization rate is associated with reduced relaxation time. This reduces the blood volume filled from pulmonary vein reducing the $V_v$ and $I_1$ referring to equation (1)

It can be deduced from equations (1) and (2) that at given time, either $I_1$ or $I_2$ exists. Equation (4) either represents flow rate of either deoxygenated blood coming from pulmonary artery or oxygenated blood pumped into aorta. Reduced flow rate reduces the cardiac throughput and LVEF.

Acetylcholine secretion is also associated with release of $Ca^{2+}$- $Na^{2+}$ that enhances the contractility thereby reducing the relaxation period required for ventricular filling. [67] Also acetylcholine facilitates vasodilatation that affects the ventricular filling from pulmonary artery. All the above stated facts combine to reduce the LVEF as shown in Figure-7.4.

The same is phenomenon is observed from the analysis of results. Table 7.3-B shows the average LVEF in different cohorts. IHD and INHD cohort records the minimum LVEF with higher concentration of Acetylcholine is associated with poor glycemic control and hence the cardiac complications.
Table-7.1- Relationship between acetylcholine and DDR.

<table>
<thead>
<tr>
<th>Diastolic depolarization rate mv/ses</th>
<th>Acetylcholine concentration nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>100+/-10</td>
<td>0</td>
</tr>
<tr>
<td>75+/-5</td>
<td>5</td>
</tr>
<tr>
<td>80+/-10</td>
<td>10</td>
</tr>
<tr>
<td>40+/-10</td>
<td>30</td>
</tr>
<tr>
<td>40+/-10</td>
<td>40</td>
</tr>
<tr>
<td>30+/-10</td>
<td>50</td>
</tr>
</tbody>
</table>

Table-7.2- Sympathetic, parasympathetic power, LVEF and contractility.

<table>
<thead>
<tr>
<th>Cohort Type</th>
<th>Average parasympathetic Power</th>
<th>LVEF</th>
<th>Average Contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>128.037</td>
<td>0.67</td>
<td>0.3949</td>
</tr>
<tr>
<td>Diabetic</td>
<td>179.9</td>
<td>0.64</td>
<td>0.3608</td>
</tr>
<tr>
<td>IHD and INHS</td>
<td>240.75</td>
<td>0.4</td>
<td>0.3274</td>
</tr>
<tr>
<td>D &amp; H</td>
<td>174.1481</td>
<td>0.65</td>
<td>0.3901</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>122.6087</td>
<td>0.68</td>
<td>0.4199</td>
</tr>
</tbody>
</table>

Conclusion: The higher neural stimulation in diabetic neuro pathology, increases the diastolic depolarization rate and reduces the blood volume collected in left ventricular diastole, thereby reducing the blood supply.

7.3 Mathematical model to demonstrate the reduced signal conduction in neurons in diabetic condition

The SA node triggers a pulse that results into an R peak depending upon the inputs it receives from the following. The heart rate is an output that depends upon the different inputs. [63] The most prominent are listed as-

1) Arterial blood pressure (ABP) from baroreceptors located in the peripheral organs.
2) Instantaneous lung volume (ILV) from volume receptors located in the alveoli of lungs.
3) The variation in hormonal level from parasympathetic and sympathetic control from chemoreceptors located in the central nervous system.
4) The oxygen concentration level in the blood plasma from the chemoreceptors located in the peripheral circulatory system.
5) Temperature changes from the thermo sensors located all over the body.
6) Stress hormonal level from the chemoreceptor located in the brain.
7) The relaxed status of the heart wall from the stretch receptors located in the heart wall to check whether ventricular diastole has occurred before.
8) The time at which the previous R peak is fired.

With all the above inputs, SA node fires as an autonomous system. If any of the inputs are more than the qualifying threshold level, SA node triggers an input resulting into R peak. Since the triggering/not triggering of SA node depends on different input conditions, the process control can be effectively modeled by a neural network simulator as shown in figure 7.5. By keeping the subject relaxed by prior intimation, by maintaining the temperature at comfortable level, by allowing the patient in a steady position either sitting or supine and by requesting the subject to breathe steadily, all the actuator of the feedback loops other than hormonal triggering of SA node can be assumed to be giving constant input.

The pacemaker (SA node) of heart is continuously controlled by sympathetic and parasympathetic hormonal secretion. In resting condition, the parasympathetic activity is more predominant whereas any physical, mental activity shows the dominance of sympathetic hormone.
Baro-receptor Input for arterial blood pressure

Atria stretch receptors input for sensing ventricular relaxation state

Chemo-receptor input for input for hormonal conduction from preganglionic neuron

Volume receptor input for lung volume status

Thermo receptor input for body temperature regulation

Chemo receptors input Stress sensing in the brain

Chemo receptor for sensing oxygen level in the cells of the peripheral circulatory system

Comparator with threshold reference level

Autonomically controlled SA node

Previous R peak instance

R peak/no R peak

Figure - 7.5-Block diagram showing the SA node firing.
The data collection process of doctoral studies, RR interval series of different types of subjects for 3-5 minutes are collected. The temporal details are required for the evaluation of heart rate at every instance.

By instructing the subject to maintain steady position and relax with uniform breathing rate, closed control loops other than the chemoreceptor driving sympathetic and parasympathetic variation can be safely assumed to be constant. Parameters that determine the instantaneous firing of SA node can be modeled as shown in figure 7.6. The weights \( W_1 \) to \( W_7 \) show the neural conduction coupling of the hormone released by the pituitary gland. The feedback control system can be represented as below with only \( W_3 \) variation.

\[
R_n = h_{pn} \times W_n - R_{n-1} - \frac{(h_{pn} \times W_n - R_{n-1})}{0}
\]

if the least time interval has elapsed.

Else \( R_n = 0 \)

The hormonal input, \( h_{pn} \) is an outcome of complex interaction of parasympathetic and sympathetic neural signal which can be simulated by a random number sequence.

\( R_n \) and \( R_{n-1} \) can be obtained from R-R sequence of the data samples collected. The weigh samples computed for different categories are obtained. The table for average is shown in the table-7.4 and Figure-7.7 representing the mean value graphically.
The above outcome of the mathematical model can be explained with pathophysiological facts as under:

The prevailing diabetic condition, the blood circulation is observed to be restricted in micro and macro level. The prevailing vasoconstrictor condition reduces supply of blood to the different organs. As a result the hormone transport from the blood plasma also gets reduced. Prolonged Diabetes and hyperglycemia develop the autonomous neuropathy that results in reduced conduction from neurons. Hence the preganglionic hormones secreted in pituitary gland are poorly conducted by the post ganglionic neurons of SA node. [3] This is demonstrated mathematically by the implementing the equation (15).

The results in table 7.4 show that neural conduction is reduced the most in
diabetics with myocardial ischemia/infarction and by diabetics. In case hypertensive subjects since some subjects are in early stage of left ventricular hypertrophy the neural conduction is higher than normal subjects. [33] Also it is observed to be higher in diabetic and hypertensive subjects.

The deteriorated neuron conduction manifests into low total power in decreasing order in case of diabetic, diabetic with myocardial ischemia infarction subjects and slightly reduced in case of diabetic with hypertensive subjects as can be verified from the table-7.4 and figure-7.8 shows the graphical representation of the same.

Table 7.4 -The average of total power at the SA node.

<table>
<thead>
<tr>
<th>Type of category</th>
<th>Average Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1827.556</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1591.45</td>
</tr>
<tr>
<td>Diabetic with Ischemic heart disease and infarcted heart disease</td>
<td>689.3</td>
</tr>
<tr>
<td>Diabetic &amp; Hypertensive</td>
<td>1430.444</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>1495.174</td>
</tr>
</tbody>
</table>

Figure-7.8 – Mean total power at SA node.

**Conclusion:** prevailing diabetic condition reduces the neural signal conduction and the total power at the SA node.
7.4 **Mathematical model to demonstrate the change in autonomous power in diabetic condition**

The parasympathetic and sympathetic power is continuously modulating the heart rate even at resting condition. The sympathetic power is found to be more in case of any external /internal stimulus. Normally the ratio of both in resting condition is slightly less than unity. In case of diabetic subjects, it is found that parasympathetic power is dominating and the ratio of sympathetic to parasympathetic power is reduced. In frequency domain techniques, the HF band (0.15-0.4 Hz) represents the parasympathetic band whereas LF band (0.04-0.15 Hz) represents the sympathetic power. There is some controversy found in literature stating the LF band represents both the power.

Hence a novel and simple technique is used to separate and quantify sympathetic and parasympathetic power from the given RR interval series. [9]

The algorithm is as follows-

1. Acquire RR interval samples of equal length from the ECG sample acquired from the data acquisition equipment.

2. Compute the average RR interval.

3. Compute the deviation from the average value for all the RR interval values.

   If the corresponding RR interval is greater than average the resulting value is negative. Store it in array1.

   Else if the value is positive, store it in array2.

4. Compute the distance of each point from the average of the two arrays. The distance represents the power of the two bands. Average SD1up represents the sympathetic power and average SD1down represents the parasympathetic power.

5. The deviation from the average value of the R-R interval gives the sympathetic and parasympathetic power of the corresponding class.

6. Compute the average of the both the two for all the datasets of the ECG acquired.

The table 7.5 represents the average sympathetic and parasympathetic powers for all the categories. Figure 7.9 gives the graphical representation of the same.
Note: Since the deviation from average RR interval is equated to power, the unit of power is not mentioned.

Table 7.5 - The average sympathetic and parasympathetic power.

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of subjects</th>
<th>Average sympathetic</th>
<th>Average parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>26</td>
<td>145.1111</td>
<td>128.037</td>
</tr>
<tr>
<td>Diabetic</td>
<td>20</td>
<td>144.05</td>
<td>179.9</td>
</tr>
<tr>
<td>Diabetic with Ischemic heart disease and infarcted heart disease</td>
<td>20</td>
<td>163.40</td>
<td>240.75</td>
</tr>
<tr>
<td>Diabetic &amp; Hypertensive</td>
<td>27</td>
<td>137.8889</td>
<td>174.1481</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>23</td>
<td>151.3913</td>
<td>122.6087</td>
</tr>
</tbody>
</table>

Figure 7.9 - Mean sympathetic and parasympathetic power.

Conclusion: The shift in the neuro-humoral balance is observable at preclinical stage and parasympathetic predominance is found in the diabetic subjects.
Mathematical model for quantitative assessment of cardiac performance based upon the changes in left ventricular geometry during systole and diastole

The left ventricular wall can be viewed as a cylinder with expansion and contractions in diastole and systole. The changes in the wall geometry can be approximated based on the assumption that net volume is unchanged. The figure 7.10 demotes the geometrical details of the left ventricle. The mid wall radius is R, length of the wall L, the relative changes in wall thickness is h. [18]

![Figure-7.10 – Simplified left ventricle](image)

The changes in dimension that occur are assumed due to the changes in the dimensions are denoted by ΔR, ΔL and Δh. Since there is no change in volume and mass during diastole and systole, equation 16 shows the changed dimensions during diastole.

\[
\frac{R}{\Delta R} + \frac{L}{\Delta L} + \frac{h}{\Delta h} = 1
\]

are negative during contraction where as Δh/h is positive.

If a is the internal radius of left ventricle, in echocardiography, LVID_d and LVID_s represent the left ventricular internal dimension in diastole and systole respectively. TW_s and TW_d are diastolic and systolic wall thickness.

\[
\frac{\Delta a}{a} = \frac{LVID_d - LVID_s}{\frac{LVID_d}{2}} \quad \text{-----------------------------}17
\]

\[
\frac{\Delta h}{h} = \frac{TW_s - TW_d}{\frac{TW_d}{2}} \quad \text{-----------------------------}18
\]
\[ \frac{\Delta R}{R} = \frac{LVIDd + TWd - LVIDs + TWs}{2LVIDd + TWd} \]

Equation 19 shows the ratio of change in the ventricular internal radius during diastole and systole. Equations 17 and 18 represent the change in the change in the ventricular internal radius of and ventricular wall height and the of the ventricular with the wall. The Left posterior ventricular wall thickness changes i.e. \( \frac{\Delta R}{R} \) contribute by 25.35% to the contractility outcome in diabetic condition.

Ventricular expansion/contraction rate, wall expansion/contraction rate can be computed by the systolic and diastolic time gap information. Performance of heart ejection fraction of heart is directly related to the expansion and contraction rate. The intra ventricular and posterior wall motion velocities indicate the manifestation of neuro-humoral changes due to prevailing diabetic, hypertensive and diabetic and hypertensive conditions. The table-7.7 and figure-7.11 show the average posterior and intra-ventricular wall velocities and average left ventricular ejection fraction for all the categories of subjects. Due to parasympathetic domination in diabetic conditions, the wall velocities are found to be reduced in case of diabetic cohorts, diabetic and hypertensive cohorts and more reduction is observed in diabetic cohorts with myocardial ischemia/infarction. The wall velocities and ejection fraction are higher in hypertensive subjects. The left ventricular contraction and relaxation follows the electrical signal stimulation. The reduction in the wall velocities reduce the LVEF due to inefficient pumping.

Table-7.7 -The average posterior and intra ventricular velocities and ejection fraction for all categories.

<table>
<thead>
<tr>
<th>Class of subject</th>
<th>Average Posterior wall velocity cm/sec.</th>
<th>Average Intra-ventricular wall velocity cm/sec.</th>
<th>Ejection fraction</th>
<th>Average Contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.45</td>
<td>1.12</td>
<td>0.67</td>
<td>0.3949</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.15</td>
<td>0.7</td>
<td>0.64</td>
<td>0.3608</td>
</tr>
<tr>
<td>IHD &amp; INHD</td>
<td>0.74</td>
<td>0.38</td>
<td>0.4</td>
<td>0.3274</td>
</tr>
<tr>
<td>Diabetic and Hypertensive</td>
<td>0.799082</td>
<td>1</td>
<td>0.65</td>
<td>0.3901</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>0.99</td>
<td>1.03</td>
<td>0.68</td>
<td>0.4199</td>
</tr>
</tbody>
</table>
Conclusion: The modified geometry in diabetic condition is contributes to the LVEF outcome by 25.35%.