A simple model for ECG Simulation from pairs of action potentials, Normal subject

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Abstract
A simple technique is described for simulation of electrocardiogram (ECG) in terms of the myocardium action potential. The difference in potentials between different regions of ventricular wall at any time will create currents in the surrounding volume conductor. Endocardial and epicardial action potentials are constructed from four ionic currents. The magnitude of the gradient of these two action potentials in different parts of the ventricular wall define electrogram. In this study, ECG has been described as a weighted sum of the gradient of these pairs of action potential over the ventricular wall.

1 Introduction
The electrocardiogram continues to be a valuable, noninvasive, easily repeatable, and inexpensive means of diagnosing many cardiac abnormalities, such as myocardial infarction, ischemia, and ventricular hypertrophy, and it is unequalled in the analysis of cardiac arrhythmias. Also, in the past few decades the clinical information that can be derived from the electrocardiogram has grown continually. Modeling of the electrical activation of the heart allows us to test if our knowledge of small-scale phenomena, such as the behavior of the cardiac membrane, suffices to explain large scale phenomena, such as the ECG. If our models prove to be capable of this, we may also use them to predict the effect that modifications on the cellular level have on the ECG. One may, for example, modify a model of the cell membrane so as to imitate the implications of a genetic defect, and observe the specific changes in the ECG. Such prediction can help us to improve diagnostic methods.

It is well established that the electrocardiogram is the result of action potentials produced in different parts of the heart. The difference in potentials between different regions at any time will create currents in the surrounding volume conductor. This study is based on the idea that ECG can be constructed by
calculating the magnitude of the gradient of action potential shapes produced in different parts of the heart over the ventricular wall. This gradient is important for the generation of T wave [1]. To elaborate on this idea, [2] has created a simple model based on endocardial and epicardial action potentials. This model describes electrical coupling in the heart on the action potential duration.

Any model with the purpose of generating ECG has to be based on a number of simplification and assumption. There are difficulties in describing both the generators of the signal and the inhomogeneity of the surrounding volume conductor. Basically, the inhomogeneities are of smaller importance than the properties of the generator itself [2]. In the classical literature, [3] and [4] have looked at the heart as a dipole or multipole and the human body as a volume conductor of definite geometrical shape. Similarly, [5] presented a digital computer model for the simulation of the body surface electrocardiogram (ECG) during ventricular activation and recovery. The model has calculated the potentials on the surface of a bounded homogeneous volume conductor with the shape of an adult torso. However, the aim of simulation presented here is to provide a simple electrophysiological background to ECG. [2] has considered only two pairs of action potential for simulation of ECG. But, in order to make the model more complex and accurate, I have considered the influence of fifty pairs of action potential from superior part of the right ventricle and lateral aspects of the left ventricle on ECG. As a result, ECG from left and right precordial leads have been generated.

2 Background

The heart consists of three tissue layers: endocardium, myocardium, and pericardium. Myocardium is the thick layer of cardiac muscle which is responsible for the contraction and relaxation of the ventricles and atria. This layer is composed almost completely of cardiomyocytes. The outside of the myocardium is covered with a thin layer called the Epicardium. This thin layer consists mostly of connective tissue and fat. The inner lining of the heart is called the Endocardium. It is a smooth membrane of endothelial cells that lines not only the chambers of the heart, but the valves as well. This is the same layer that covers the inside of all of the blood vessels of the cardiovascular system. During depolarization the impulse is carried from endocardium to epicardium, and during repolarization the impulse moves from epicardium to endocardium. Measurements of functional refractory periods at various sites in the ventricular myocardium have indicated that the durations of the cellular action potentials are generally shorter near the epicardium than near the endocardium, and shorter near the base than near the apex [5].

An ECG is a commonly used tool in medicine, rehabilitation, and physiology to understand both the structure and function of the heart. By definition, an ECG is a recording of the variations in voltage that are produced by depolarization.
and repolarization of the myocardium (muscle of the heart). The variations in voltage are measured at the surface of the body using surface electrodes [6]. Traditionally, 12 leads are recorded, 6 leads on the extremities and 6 on the precordium. This has been the standard approach for almost half a century. The extremity leads give a more distant image of the electrical activity of the heart. For example, leads II and III record electrical activity from the inferior wall. The precordial leads, because they are unipolar and closer to the heart, primarily reflect the cardiac electrical activity directly beneath the electrode. Therefore, because of their position on the chest wall, leads V2 to V6 primarily give information on the process of activation and repolarization of the anterior and lateral aspects of the left ventricle. Lead V1 provides information on the interventricular septum and the superior part of the right ventricle. The placement of the electrodes is presented in Fig. 1.

3 Methods
A simple model has been presented for simulation of ECG. The model is based on the idea that ECG can be broadly described as a weighted sum of opposing areas of the myocardium. The normal ECG is simulated using a gradient of action potentials over ventricular wall. The ventricular action potential is simply described by four ionic currents. For simplicity we have divided the model of generating ECG into two simple models. In the first model, the ventricular action potential has been calculated from four ionic currents [7]. By means of several pairs of action potential generated in the first model, ECG can be described as a weighted sum of the gradient of these pairs of action potential in the second model [2].

A. First model
In the first model, Fig. 2a, 10000 iteration has been used for time loop which is going from \( t=0 \) to \( t=500 \)ms. The iteration begins with the initial values for instantaneous activation and inactivation variables and membrane voltage at time \( t_0 \). In each iteration, steady state activation and inactivation for each Na, Ca, K, and background currents have been calculated from previous value of
membrane voltage using Eq. 1-5. The instantaneous activation and inactivation variable values at time \( t(\Delta t, \text{where } \Delta t \text{ is } 0.02 \text{ ms}) \) consequently approach new \( P_x \) by using Eq. 6-10.

\[
P_{Na} = \frac{1}{1 + e^{-\alpha(v_m+40)}} \tag{1}
\]

\[
P_{Na} = \frac{1}{1 + e^{-\alpha(v_m+80)}} \tag{2}
\]

\[
P_{Ca} = \frac{1}{1 + e^{-\alpha(v_m+30)}} \tag{3}
\]

\[
P_{Ca} = \frac{1}{1 + e^{-\alpha(v_m+60)}} \tag{4}
\]

\[
P_{K} = \frac{1}{1 + e^{-\alpha(v_m+20)}} \tag{5}
\]

\[
\frac{dX_{Na}}{dt} = (P_{Na} - X) \tag{6}
\]

\[
\frac{dZ_{Na}}{dt} = 0.3((1 - P_{Na}) - Z_{Na}) \tag{7}
\]

\[
\frac{dX_{Ca}}{dt} = 0.1(P_{Ca} - X) \tag{8}
\]

\[
\frac{dZ_{Ca}}{dt} = 0.02((1 - P_{Ca}) - Z_{Ca}) \tag{9}
\]

\[
\frac{dX_{K}}{dt} = 0.02(P_{K} - X_{K}) \tag{10}
\]

In the same iteration in next step, four ionic currents are calculated. The electrochemical driving force for each current has been measured as the difference between membrane potential \( V_m \) and the equilibrium potential (\( E \)). The instantaneous activation \( X \) and inactivation \( Z \) are used for calculation of the currents as function of time. A constant has been introduced in each equation to define the maximum current. The following equations define the various currents:

\[
I_{Na} = 5X_{Na}Z_{Na}(V_m - E_{Na}) \tag{11}
\]

\[
I_{Ca} = 0.04X_{Ca}Z_{Ca}(V_m - E_{Ca}) \tag{12}
\]

\[
I_k = (1 - 0.075P_k)0.03(V_m - E_k) \tag{13}
\]

\[
I_K = (1 - 0.075P_k)0.05(V_m - E_K)X_K \tag{14}
\]

Besides the above equation for ionic currents as function of time, the ionic currents can also be derived as function of voltage Eq. 15-18.
\[ I_{Na} = 5PNa(V_m - E_{Na}) \]  
\[ I_{Ca} = 0.04P_{Ca}(V_m - E_{Ca}) \]  
\[ I_b = (1 - 0.075P_k)0.03(V_m - E_K) \]  
\[ I_K = (1 - 0.075P_k)0.05(V_m - E_K)P_K \]

The instantaneous value of membrane voltage \( V_m \) within the time loop for time \( t \) is calculated using Eq. 19. After 10000 iterations, a ventricular action potential will be generated.

\[ \frac{dV_m}{dt} = \frac{1}{c}(I_{Na} + 2I_{Ca} + I_b + I_K + J_s) \]  

The \( c \) value is equal to 0.01 F. Current injection is simulated with the variable \( J_s \), which is equal to -1.7 during stimulation.

**B. Second model**

In the second model, the electrical coupling between two instantaneous action potentials \( V_{m1}, V_{m2} \) at time \( t \), generated in the first model, are investigated. The model presented in [2] is very simple as ECG is generated by only two pairs of action potentials. By making the model more complex, 50 pairs of action potential are also considered to describe the ECG from two precordial leads: \( V_1, V_2 \). The entire model describing simulation of ECG from both two pairs and fifty pairs of action potentials is shown in Fig. 2b.

Each pair of action potentials is generated in separate loop. On the other hand, the 2nd action potential for each pair is calculated in an analogous way within the same time loop. However, for each pair the Na current is increased for the 2nd action potential (from 5.3 to 8) and the background current is also increased by changing the term 0.08 to 0.09. The term \( J_{12} \) is also described as the difference between two action potentials in each pair, Eq. 20:

\[ J_{12} = 0.05(V_{m1} - V_{m2}) \]

As the term \( J_{12} \) has been added to Eq. 19, the new instantaneous membrane voltage corresponding to the second action potential is changed by Eq. 21

\[ \frac{dV_m}{dt} = \frac{1}{c}(I_{Na} + 2I_{Ca} + I_b + I_K + J_s) \]

There is (10 iterations) delay between activation of each pair of action potentials. For each pair, electrogram (EG) is then simulated as the difference between the two action potentials from endocardial and epicardial in a segment of the ventricular wall.
In case that only two pairs of action potential are considered, the ECG from two precordial leads, $V_1, V_2$, is computed by using Eq. 23-24

\[
EG = V_{m1} - V_{m2} \quad (22)
\]

\[
ECG_L = -0.2EG_1 + 1.0EG_2 \quad (23)
\]

\[
ECG_R = 0.5EG_1 - 1.0EG_2 \quad (24)
\]

$EG_1$ and $EG_2$ represent respectively the difference between the two action potentials from superior part of the right ventricle and lateral aspects of the left ventricle.

Eq. 27-28 indicate the formula used for the calculation of ECG from 50 pairs of action potential in the developed model. 50 electrograms are generated in this study from Eq. 22. The magnitude of the gradient of the electrical potential of the 25 regions of the Septum and right ventricle (R) are calculated as the sum of first 25 pairs of electrogram. Similarly, left ventricle (L) electrical activities are calculated as the sum of other 25 pairs of electrogram by Eq. 25-26. Eq. 27-28 show computed ECG from left and right precordial leads.

\[
EG_L = \sum_{k=1}^{25} EG_k \quad (25)
\]

\[
EG_R = \sum_{k=26}^{50} EG_k \quad (26)
\]

\[
ECG_L = -0.002EG_R + 0.01EG_L \quad (27)
\]

\[
ECG_R = 0.005EG_R - 0.01EG_L \quad (28)
\]

4 Results

All simulations are done in MATLAB 7.5.0(R2007b). Steady State activation and inactivation curves as function of membrane voltage for the various ionic currents are shown in Fig. 3. The maximum activation of Na at different voltage has sigmoid shape. For larger membrane voltage, the activation is larger. On the contrary, inactivation curve for Na will be decreased as the membrane voltage is increased. During stimulation, activation of the Na current is followed by a Ca current.

Fig. 4 illustrates four ionic currents during depolarization and repolarization of
Figure 2: a) The first model, in this model the ventricular action potential has been calculated from four ionic currents, b) The second model, ECG from right and left precordial lead has been generated by using two pairs and fifty pairs of action potentials.
membrane voltage vs. time. The changes of membrane voltage from -90 to +30 cause a rapid opening of Na channels followed by fast increase in the membrane conductance to Na and thus a rapid influx of Na ions ($I_{Na}$) into the cell. The rapid Na current inactivation followed by slow Ca current activation and inactivation. The K current is gradually activating during whole depolarization. K ions carry a background current which does not exhibit activation and inactivation kinetics. The two K currents decrease during repolarization.

In order to obtain a relation between current and membrane voltage, the maximum current is plotted vs. the peak membrane voltage, Fig. 5. Na current is activated around -60 mv, it has a peak around -30 mv, and it becomes zero at +50 mv. The Ca current is activated around -50 mv and the equilibrium potential is at +80 mv. The equilibrium potential for both K and background currents is -90 mv. As it is shown in the Fig. 5, the curve for background current goes towards the voltage axes for greater depolarization, this means that Ohm’s law cannot be applied to background current.

The action potential shown in Fig. 6 has been calculated from integration of four membrane currents. The cardiac action potential is a specialized action potential in the heart, with unique properties necessary for function of the electrical conduction system of the heart. In our model, it is excited by simulating a current injection in order to depolarize the cell membrane. This stimulates the inward Na current. After a couple of moments, the Ca current will be evoked. As indicated in Fig. 5, during the action potential, there is a continuous rise in the K current. However, background current is increased during the peak of action potential and reduced during plateau phase. During repolarization of action potential, background current is increased again due to inward rectification.

The first step of the second model is based on the idea that electrogram can be constructed by calculating the difference between one endocardial and one epicardial action potentials in a segment of the heart wall at any time [8]. The configuration of the action potential varies between different parts of the ventricle. Measurements of functional refractory periods at various sites in the ventricular myocardium have indicated that the endocardial action potential exhibits a longer duration than the epicardial one. There is also a difference in duration of the action potential between base and apex of the heart so that longer action potentials are generally recorded at the base [5]. This difference in duration seems to be dependent on the excitation interval. It is also known that the action potential of the right ventricle is shorter than in the left ventricle. Fig. 7 demonstrates a simulated endocardial and epicardial action potentials. It is apparent from the figure that the duration of epicardium action potential is shorter than that of endocardial. In the simulation, the duration of action potential has been reduced by increasing the background current. Moreover, as the wall of the heart ventricle is normally activated from the endocardium towards the epicardium [9],[10], there is a delay between the activation time of endocardium and epicardium action potentials. This delay is also clear in the
There is some mechanism behind these gradients. The electrogram is generated by flow of currents in the conductor surrounding the myocardium. The currents cause potential differences between various recording places and these potential differences can be picked up by the extracellular electrodes. The extracellular currents are in turn the result of currents within the myocardial tissue. The driving force is the difference in membrane potential between regions of the tissue. The difference in potential between the two sites generates current that flows between the regions. In case that two myocardial cells are considered, the current flows in the gap junction between the cells and the gap junctions behave like resistors. Neighbor cell in heart are tightly coupled because of the presence of gap junctions between them. This has the effect of clamping the cells towards the same membrane potential in the same way. However, in the present model the endocardial site is too heavily coupled to the epicardial site, since only two action potentials are considered. In our simulation, the first action potential (endocardial) has been triggered by means of a simulated current injection. The second action potential (endocardial) has been triggered by the first action potential by means of a current flowing between the two sites.

The electrogram as the difference between two myocardial action potentials is shown in the Fig. 8. The electrogram shows a 'QRS-complex' followed by a flat ST-segment and a flat T-wave.

Each site of myocardial wall can be regarded as the generator of current and ECG follows from currents in the conductor surrounding the heart. The localization of sites depend on the lead the ECG is computed from. In the simulation here, only the superior part of the right ventricle and lateral aspects of the left ventricle have been represented by means of several pairs of action potentials. Each pair is considered to represent activation of the endocardium followed by an activation of epicardium in one region of the ventricular wall with all characteristics explained in previous paragraph. Finally, ECG can be broadly described as a weighted sum of these electrograms representing two opposing areas of the myocardium (left and right).

In a basic simulation of ECG, one electrogram represents the difference between two action potentials in one pair from the region in right ventricle and the other electrogram represents the electrical potential of the opposing region in the left ventricle which is obtained by the difference of the latter pair of action potential Fig. 9. However, in the developed model, it is assumed that 25 pairs of action potentials represent the changes of electrical potential of the 25 regions of septum and right ventricle (R), and the other 25 pairs represent the changes in 25 regions of left ventricle (L) electrical potentials. Furthermore, each pair of action potential activate somewhat later than the previous pair of action potential. Fig. 10 shows few electrograms as the difference between few pairs of myocardial action potentials.

ECG can be computed as a summation of the obtained electrograms shown.
in Fig. 9 and Fig. 10. In the basic model, as there is only two electrograms, ECG has been calculated from the summation formulas presented in Eq. 23-24. For the developed model, the ECG is the product of the summation of all fifty electrograms. Simulated left lateral lead and also right precordial lead are demonstrated respectively in Fig. 11 and Fig. 12 for both two and fifty pairs of action potentials. It can be seen in Fig. 11 that the left precordial lead started with a small q-wave (septal q, originating from the right action potential pairs) followed by a tall R. The ST-segment is rising and the T-wave is positive. The right precordial lead, Fig. 12 shows a small r followed by a deep S and a negative T (due to the influence from the left ventricle electrical potential). The simulation of ECG from both two pairs and fifty pairs of action potentials are also compared in Fig. 11 and Fig. 12. It is clear from both figures that the QRS-complex could be more accurate in case that more than two action potentials are used in simulation. For instances, in the basic model simulation for both precordial leads, the S wave is not clear and the T wave needs to be more stronger. In a brief, the ECG simulated from the developed model is closer to basic shape and clinical features of the original ECG than the simple model.

5 Discussion

A simple model has been presented for simulation of ECG. The model is divided into two basic models. The first model describes the ventricular action potential
Figure 4: Simulation of four ionic currents during membrane voltage depolarization and repolarization as function of time. The scale of the amplitudes are not real.

Figure 5: Simulated current-voltage relations for the four ionic currents. The scale of the amplitudes are not real.
Figure 6: The ventricular action potential.

Figure 7: Simulated endocardial and epicardial action potentials.
Figure 8: The electrogram as the difference between two myocardial action potentials.

Figure 9: Left and right ventricle electrograms as the difference between two pairs of myocardial action potentials.
Figure 10: Few electrograms as the difference between few pairs of myocardial action potentials.

Figure 11: Basic and developed simulation of ECG generated from Left precordial lead.
from its main ionic currents and the second model is based on the idea that ECG can be described as a weighted sum of two or more electrograms of two opposing areas of myocardium. The influence of each action potential pair depends on which recording lead should be generated. Electrogram is identified as the difference between two simulated action potential representing endocardium and epicardium site of septum. The action potential generated from ionic currents indicates activation and inactivation as a function of time and membrane voltage. The difference between the actual membrane potential and the equilibrium potential, for each current is the driving force for each current.

Both models are made of simple mathematics like straight lines and single exponential functions. The model is intended to be qualitative rather than quantitative, therefore, several assumption have been considered. For example, in the purpose of generation an action potential, only four currents are considered. In reality, there are many potassium currents but, in our model only the sum of all potassium currents is incorporated. Moreover, the model does not consider the sodium/calcium exchange mechanism.

The activation variables for the various currents in the model were assumed to approach a theoretical steady-state value described by the steady-state activation and inactivation curves. on the contrary of classical simulation by [11], the time constants for the activation and inactivation variables to reach steady-state are supposed to be fixed. The current-voltage relations are simulated by

Figure 12: Basic and developed simulation of ECG generated from Right precordial lead.
having the activation variables at the steady state without considering the inactivation variables.

Another hypothesis which is used for the generation of simulation is that T wave could be simulated by assuming the presence of longer action potentials on the right side of septum compared to the left side. The model is based on the fact that endocardial action potential is longer than epicardial action potential. By changing the ionic constant factor during simulation, the duration of action potential has been changed. For simplicity, the action potential gradient was simulated by having a more intense background current in the epicardial action potential in comparison with the endocardial action potential. It is also possible to create the gradient by varying the calcium currents and the delayed potassium current. Apparently, the T wave is dependent on differences in activation and on action potential shapes in the ventricle wall. Basically, the T-wave is a very sensitive measure of these differences in repolarization.

Model presented in [2] includes only 2 different cell types: endocardial and epicardial. It is assumed that epicardial and the endocardial site is too heavily coupled to the epicardial site, hence, only two action potentials are considered. These two action potentials consist one pair of action potential. An electrogram is defined as the gradient of pairs of action potential. Actually, the value of electrogram will be more accurate as the number of action potentials in each pair increases. By considering more than two cell types, for instances, endocardial, midmyocardial(M cell) and epicardial, the number of action potentials will be changed to three for each pair. However, there is another way to improve the model, which is implemented in this study. By increasing the number of action potential pairs over the right and left ventricular wall, we can track the electrical activities over the ventricular wall in different segment of the heart. In our simulation, fifty pairs of action potential representatives of the electrical changes of fifty part of the ventricular wall from right to left have been generated. The ECG generated from two pairs of action potential has been compared to the ECG generated from fifty pairs of action potentials. More details have been seen in an improved ECG in comparison with the simple ECG. However, both models are based on several assumption and the purpose of the paper is to simulate a simple model.

6 Conclusion

Simulation of ECG based on a simple model of the myocardium action potential has been done successfully in this project. This model contains two different cells; Endocardial and epicardial. Myocardium action potentials are simulated from four ionic currents. The magnitude of the difference between each endocardial and epicardial action potentials in different parts of the ventricular wall makes electrogram. This study is based on the fact that the duration of epicardial action potential is longer than endocardial. Finally, ECG has been
described as a weighted sum of the gradient of these pairs of action potential over
the ventricular wall. By developing the simple model more complex and consid-
ering the influence from more than two pairs of action potential, more extensive
simulation was produced. For instances, by considering fifty pairs representing
fifty parts of ventricular wall, the simulated QRS-complex was more accurate.

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