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# Sensitivity Analysis of the Electrocardiogram in Mouse Heart

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**Abstract:** The function of the heart is contracting and pump oxygenated blood to the body and deoxygenated blood to the lungs. To achieve this goal heart must beat regularly and continuously for entire life and respond to the changing requirements by the body. In this paper, we consider a mathematical model to produce ECG and analyze how the parametric variation can modify the electrocardiogram signal in the mouse heart. Numerical simulations were analyzed in detail, and compared with the control experiment, changes in frequency and ECG characteristics were evaluated. In agreement with physiological function, we find that the frequency of pacemaker cells can vary significantly, whereas electrical conducting cells maintain ECG characteristics in the face of parametric variations. P-wave, QRS complex, and T-wave can vary significantly in myocardial cells to parametric variations.

*Keywords:* Control of physiological variables, bio-signals analysis and interpretation, systems biology, physiological model, modeling and identification, isolated heart.

## 1. INTRODUCTION

It is well known that in the cardiovascular system, each heartbeat is the result of electrical activity originates in a specialized pacemaker region called the sinoatrial node (SAN). Pacemaker cells generate spontaneous rhythmic changes of their membrane potential, thereby producing normal automaticity. These cells are located high up in the right atrium and generate beats at varying rates during the human life span depending upon the activity of the autonomic nervous system, Kapa et al. (2018), Gordan et al. (2015). This electrical activity then spreads through atria, then through the atrioventricular node (AVN) and His-Purkinje system (HPS), to produce orderly contractions of the cardiac muscle. Cardiac muscle forms both the atria (AT) and the ventricles (VN) of the heart and constitutes the largest part of the heart tissue. They are responsible for repeatedly contracting and relaxing in order to deliver blood to the rest of the body, Fig. 1a.

An electrocardiogram (ECG) is a measure of the electrical activity of the heart, is a graph of voltage versus time. Each time the heartbeat, an electrical signal travels through the heart. An ECG permit obtaining information about the heart state and its abnormalities can be associated with diseases AlGhatrif and Lindsay (2012).

Several robustness definitions have been given depending upon the context and level of biological organization under consideration. Here robustness is defined as the invariance of ECG characteristics in the face of parametric perturbation, Kitano (2007).

A hallmark of mechanistic research is to understand a complex whole by decomposing it into parts, and by localizing phenomena of interest to certain parts of the system Kitano (2002). Ryzhii and Ryzhii presented a novel model of heart formed by the cardiac conduction system, including main pacemakers and heart muscles. They obtained synthetic ECG as a combined signal of atrial and ventricular muscles and analyzed it against real patient responses Ryzhii and Ryzhii (2014). However, the understanding of the effects of parametric variation in ECG has received little attention. In this paper, we experimentally obtained ECG signals to an isolated mouse heart and modified the Ryzhii and Ryzhii model to obtain a mouse heart rate. We studied how parametric variations in the different cell types that conform the heart affect the ECG.

## 2. METHODOLOGY

### *2.1 Experimental setup*

A typical experiment was conducted as follows. Isolated heart was placed in a Langendorff system Skrzypiec-Spring et al. (2007), and platinum electrodes were placed to obtain electrocardiogram recordings. ECG was obtained placing the negative electrode in the sinoatrial node and the positive electrode in the left ventricle. Einthoven's triangle was implemented Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., & Barker (1946), and the Lead II was obtained, which is the addition of the Lead I and III. ECG acquisition was made following electrocardiography procedures based on Kolárová et al. (2010) and Zabel et al. (1995). Experimental series data were recorded by an

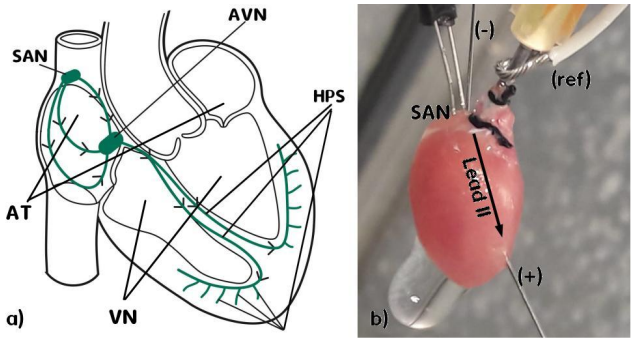


Fig. 1. The mouse heart a) Schematic representation of pacemakers cells (SAN), electrical conducting cells (AVN and HPS), and myocardial cells (AT and VN) b) Experimental setup illustration to obtain the ECG

acquisition system (Biopac MP36, USA) and subsequently analyzed with the WPI DataTrax2 software with a sample rate of 100 data/s, see Fig. 1b. Hearts were allowed to beat spontaneously (380 $beats\ min^{-1}$) (6.33 Hz) for 30 min, Bell et al. (2011).

### *2.2 Mathematical model*

We modified the mathematical model presented by Ryzhii et al., which consists of a set of heterogeneous nonlinear oscillators representing the cardiac conduction system, including main pacemakers and heart muscles. Sinoatrial node, atrioventricular node, and His-Purkinje system are represented by modified Van der Pol-type oscillators connected with time-delay velocity coupling, Ryzhii and Ryzhii (2014). The model is formed by 14 equations; the model is divided into two sets of differential equations, a time-delayed differential equation for the electrical system of the heart and ordinary differential equations that represent the AT and VN muscles.

The electrical system of the heart is given by the equations (1) and (2). The index $i = 1, 2, 3$ corresponds to SAN, AVN and HPS oscillators, respectively. Where $x_i$ represents their action potential.

$$\dot{x_i} = y_i \tag{1}$$

$$\dot{y_i} = -F(x_i)y_i - G(x_i) + K_{node}(y_{i-1}^{\tau_{node}} - y_i). \tag{2}$$

Function $F(x_i) = a_i(x_i - u_{i1})(x_i - u_{i2})$ is the damping term and function $G(x_i) = f_i x_i(x_i + d_i)(x_i + e_i)$ corresponds to the harmonic force term; the functions $F(x_i)$ and $G(x_i)$ have the improved form postulated by Postnov et al. (1999) and Grudziński and Zebrowski (2004).

Here, function $y_{i-1}^{\tau_{node}} = y_{i-1}(t - \tau_{node})$ denotes the time-delayed coupling components, where $\tau_{node}$ is the time delay corresponding to each coupling ($\tau_{avn\_san}$, $\tau_{san\_avn}$ and $\tau_{avn\_hps}$). Parameter $K_{node}$ is the coupling constant between each node($K_{avn\_san}$, $K_{san\_avn}$ and $K_{avn\_hps}$).

Equations (3) and (4) correspond to model used by Ryzhii and Ryzhii (2014) to represent cardiac muscles, which are stimulated by SAN and HPS, respectively. This model is based on modified FitzHugh-Nagumo oscillators reported by FitzHugh (1961); Nagumo et al. (1962); Rogers and McCulloch (1994).The index $i = 1, 2, 3, 4$ corresponds to P-wave, Ta-wave, QRS complex and T-wave, respectively.

$$\frac{dz_j}{dt} = k_j(-c_j z_j(z_j - w_{j1})(z_j - w_{j2}) - b_j v_j - g_j v_j z_j + I_j), \tag{3}$$

$$\frac{dv_j}{dt} = k_j h_j(z_j - v_j). \tag{4}$$

The P-wave corresponds to atrial depolarization, the Ta-wave is the atrial repolarization, the QRS complex corresponds to the ventricular depolarization, and the T-wave is the ventricular repolarization.

Function $I_j = C_j Y_j H(Y_j)$ is the magnitude of the stimulation current that couples the SAN and HPS pacemaker to AT and VN muscles, respectively. Parameter $C_j$ corresponds to coupling coefficients. Function $H(Y_j)$ is the Heaviside step function, $Y_1 = y_1, Y_2 = -y_1, Y_3 = y_3, Y_4 = -y_3$. The parameters $k_j, c_j, w_{j1}, w_{j2}, b_j, h_j$ and $g_j$ control the rest state, the excitability, the duration of the action potential, the excitation threshold and excited state of each oscillator.

The ECG waveform is calculated as a composition of electrical muscle responses, as follows,

$$ECG = z_0 + z_1 - z_2 + z_3 + z_4. \tag{5}$$

Where $z_0$ is the baseline value of the ECG signal.

We modified some parameters from Ryzhii and Ryzhii (2014) to obtain an ECG with the frequency of an isolated mouse heart Bell et al. (2011) ($6.33Hz$). All parameters in equations and functions given by Eqs. (1)-(4) are tabulated in Table 1, Table 2, and Table 3.

Table 1. Parameter values of the conduction system

| Parameter | value | From |
|---|---|---|
| $a_1$ | 440 | ts |
| $a_2$ | 340 | ts |
| $a_3$ | 240 | ts |
| $u_{i1}$ | 0.9 | ts |
| $u_{i2}$ | -0.8 | ts |
| $f_1$ | 975 | ts |
| $f_2$ | 515 | ts |
| $f_3$ | 202 | ts |
| $d_{1,2,3}$ | 3 | Ryzhii and Ryzhii (2014) |
| $e_1$ | 3.5 | Ryzhii and Ryzhii (2014) |
| $e_{2,3}$ | 3.5 | ts |
| $K_{avn\_san}$ | 0 | Ryzhii and Ryzhii (2014) |
| $K_{san\_avn}$ | $f_1$ | Ryzhii and Ryzhii (2014) |
| $K_{avn\_hps}$ | $f_1$ | Ryzhii and Ryzhii (2014) |
| $\tau_{avn\_san}$ | 0 | Ryzhii and Ryzhii (2014) |
| $\tau_{san\_avn}$ | 0.0127 | ts |
| $\tau_{avn\_hps}$ | 0.0127 | ts |

*ts = this study*

Table 2. Parameter values of the AT muscle cells

| Atrium | | |
|---|---|---|
| Parameter | value | From |
| $k_1$ | 3000.0 | ts |
| $c_1$ | 0.26 | Ryzhii and Ryzhii (2014) |
| $w_{11}$ | 0.22 | ts |
| $w_{12}$ | 1.9 | ts |
| $b_1$ | 0.0 | Ryzhii and Ryzhii (2014) |
| $d_1$ | 0.4 | Ryzhii and Ryzhii (2014) |
| $h_1$ | 0.004 | Ryzhii and Ryzhii (2014) |
| $g_1$ | 1.0 | Ryzhii and Ryzhii (2014) |
| $K_{AT\_De}$ | $16 \times 10^{-6}$ | ts |
| $k_2$ | 400.0 | Ryzhii and Ryzhii (2014) |
| $c_2$ | 0.26 | Ryzhii and Ryzhii (2014) |
| $w_{21}$ | 0.31 | ts |
| $w_{22}$ | 2.2 | ts |
| $b_2$ | 0.0 | Ryzhii and Ryzhii (2014) |
| $d_2$ | 0.09 | ts |
| $h_2$ | 0.004 | Ryzhii and Ryzhii (2014) |
| $g_2$ | 1.0 | Ryzhii and Ryzhii (2014) |
| $K_{AT\_Re}$ | $26 \times 10^{-6}$ | ts |

*ts = this study*

Table 3. Parameter values of the VN muscle cells

| Ventricle | | |
|---|---|---|
| Parameter | value | From |
| $k_3$ | 30000.0 | ts |
| $c_3$ | 0.125 | ts |
| $w_{31}$ | 0.177 | ts |
| $w_{32}$ | 1.38 | ts |
| $b_3$ | 0.004 | ts |
| $d_3$ | 0.0927 | ts |
| $h_3$ | 0.0148 | ts |
| $g_3$ | 1.0 | Ryzhii and Ryzhii (2014) |
| $K_{VN\_De}$ | $14.0 \times 10^{-6}$ | ts |
| $k_4$ | 2000.0 | Ryzhii and Ryzhii (2014) |
| $c_4$ | 0.1 | Ryzhii and Ryzhii (2014) |
| $w_{41}$ | 0.4 | ts |
| $w_{42}$ | 2.6 | ts |
| $b_4$ | 0.0 | Ryzhii and Ryzhii (2014) |
| $d_4$ | 0.1 | Ryzhii and Ryzhii (2014) |
| $h_4$ | 0.008 | Ryzhii and Ryzhii (2014) |
| $g_4$ | 1.0 | Ryzhii and Ryzhii (2014) |
| $K_{VN\_Re}$ | $57.0 \times 10^{-6}$ | ts |

*ts = this study*

### *2.3 Parametric robustness*

To study the parametric robustness each parameter was modified in the range from $-30\%$ to $30\%$ times its nominal value.

The simulations were performed by numerically solving the set of time-delay differential equations. To do this we used the fourth-order Runge-Kutta method implemented in MATLAB (The MathWorks, Natick, MA, USA).

## 3. RESULTS

To obtain an ECG reference signal, we employed the experimental procedure described above. The electrocardiogram in an isolated mouse heart was recorded. A typical ECG is depicted in Fig. 2. As can be seen, electrical signal shows a physiological response formed by several PQRS complex and a frequency of 6.3 Hz.

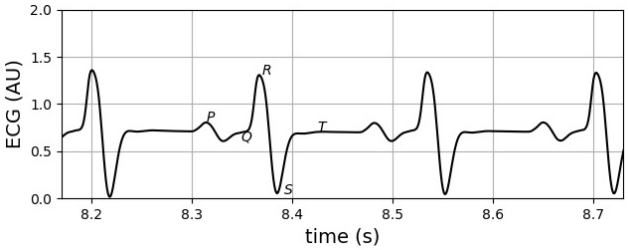


Fig. 2. An illustrative example of an ECG experimentally obtained in isolated mouse heart

According to our hypothesis we consider that the heart consists of three cells types pacemaker cells, electrical conducting cells and myocardial cells. We studied ECG dynamics in mouse model by numerically solving the system of time delay differential equations in Eqs. 1-4 by mean of Python Ansmann (2018). Figure 3 shows a ECG signal. The AT and VT waveforms are shown in dotted lines. Comparing Figures 2 and 3, we observed similar PQRS waveforms.

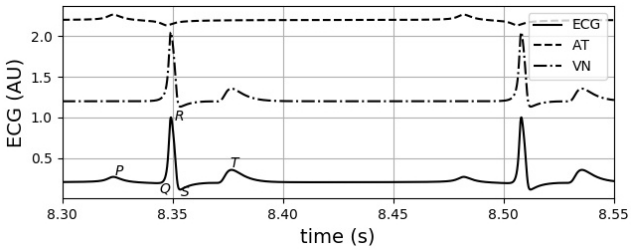


Fig. 3. An illustrative example of an ECG *in silico* obtained by solving Eqs.(1)-(5).

We further analyzed how changes in parameter values affects the ECG dynamics. This was done by modifying each parameter value in the range [0.7,1.3] times its nominal value. The obtained results are shown in Fig. 4. We can see there that, when the parameter $d_1$ that corresponds to the harmonic force term in pacemaker cells is modified produces abnormal heart rate. As the parameter is decreased bradycardic response increases. Further notice that the QRS complex is lost, Fig. 4b. As $d_1$ parameter is increased tachycardia increases, Fig. 4c.

When the parameter $w_{32}$ that corresponds to FitzHugh-Nagumo in AT muscle cells is modified produces alterations in QRS complex. As the parameter is decreased QRS amplitude decreases, Fig. 4d. As $w_{32}$ parameter is increased QRS amplitude increases, Fig. 4e.

When the parameter $w_{41}$ that corresponds to FitzHugh-Nagumo in AT muscle cells is modified produces alterations in T wave. As the parameter is decreased T wave amplitude and duration increases, Fig. 4f. As $w_{41}$ parameter is increased T wave amplitude and duration decreases, Fig. 4g. The results of the parametric robustness analysis corresponding to the rest of the parameters are summarized in Table 4.

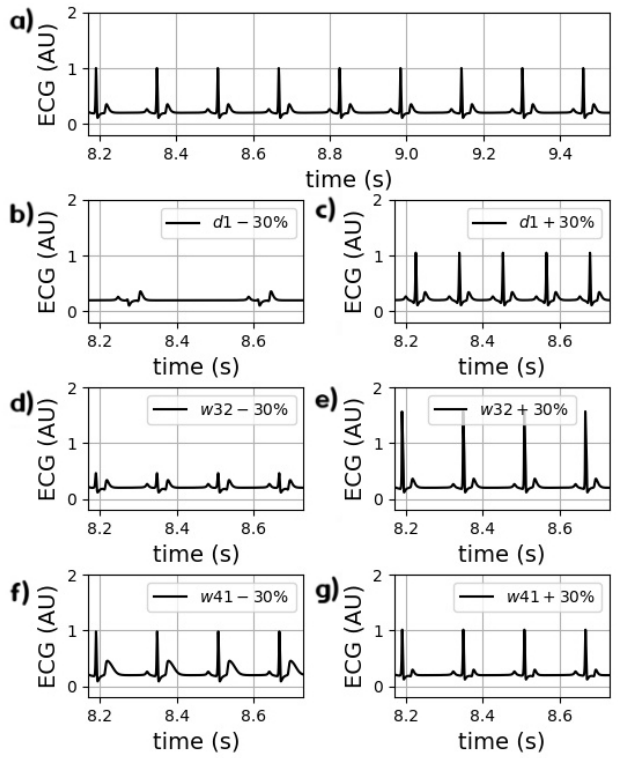


Fig. 4. Effect of parameter variation on the ECG. a) Control experiment. Parameter $d_1$ in pacemaker cells effect. The simulations in the plot b) were carried out considering parameter increased, c) parameter decreased. Parameter $w_{32}$ in muscle cells effect. The simulations in the plot d) were carried out considering parameter increased, e) parameter decreased. Parameter $w_{41}$ in muscle cells effect. The simulations in the plot f) were carried out considering parameter increased, g) parameter decreased.

## 4. DISCUSSION

By treating the heart as a set of three cell types pacemaker cells, electrical conducting cells, and myocardial cells, we studied how parametric variations in the different cell types that conform the heart affect the ECG characteristics. We did this through experiments and deterministic simulations. Experimentally, we obtained ECG recordings in an isolated mouse heart. Theoretically, the mathematical model presented by Ryzhii and Ryzhii (2014) was modified in its parameter values to obtain an ECG in the mouse basal frequency. Model parameters may be broadly associated with pacemakers cells, electrical conducting cells, and myocardial cells. Each value of the parameter was randomly increased (decreased) until 30% of its nominal value. This was performed one parameter at a time, while the rest of the parameters was kept without change. Then, the ECG was numerically obtained.

Figure 2 shows the experimental response and Fig. 3 shows the ECG obtained whit the mathematical model. As can be seen, the frequencies and PQRS responses are similar. These results are consistent with results reported by Bell et al. (2011), Peña-Romo et al. (2016) and Zabel et al. (1995).

Table 4. Measurement of the parametric variation on ECG characteristics.

| Group | Parameter | Modification | |
|---|---|---|---|
| | | −30% | +30% |
| SAN | $a_1$ | s⇑F | s⇓F |
| | $u_{11}$ | s⇑F | s⇓F |
| | $u_{12}$ | s⇑F | s⇓F, s⇓A-QRS |
| | $f_1$ | ⇓F | ⇑F |
| | $d_1$ | ⇓F, L⇓A-QRS | ⇑F |
| | $e_1$ | ⇓F, L⇓A-QRS | ⇑F |
| AVN | $a_2$ | n/e | n/e |
| | $u_{21}$ | | |
| | $u_{22}$ | | |
| | $f_2$ | | |
| | $d_2$ | | |
| | $e_2$ | | |
| HPS | $a_3$ | n/e | n/e |
| | $u_{31}$ | | |
| | $u_{32}$ | | |
| | $f_3$ | | |
| | $d_3$ | | |
| | $e_3$ | | |
| P-wave | $k_1$ | n/e | n/e |
| | $c_1$ | s⇑A | s⇓A |
| | $w_{11}$ | s⇑A | s⇓A |
| | $w_{12}$ | s⇑A | s⇓A |
| | $b_1$ | n/e | n/e |
| | $d_1$ | n/e | n/e |
| | $h_1$ | n/e | n/e |
| | $g_1$ | n/e | n/e |
| | $K_{AT\_De}$ | s⇓A | s⇑A |
| Ta-wave | $k_2$ | n/e | n/e |
| | $c_2$ | | |
| | $w_{21}$ | | |
| | $w_{22}$ | | |
| | $b_2$ | | |
| | $d_2$ | | |
| | $h_2$ | | |
| | $g_2$ | | |
| | $K_{AT\_Re}$ | | |
| QRS Complex | $k_3$ | n/e | n/e |
| | $c_3$ | L⇓A | s⇑A |
| | $w_{31}$ | s⇑A | L⇓A |
| | $w_{32}$ | L⇓A | L⇑A |
| | $b_3$ | n/e | n/e |
| | $d_3$ | s⇑A | L⇓A |
| | $h_3$ | s⇑A | s⇓A |
| | $g_3$ | s⇑A | s⇓A |
| | $K_{VN\_De}$ | L⇓A | n/e |
| T-wave | $k_4$ | s⇑A | s⇓A |
| | $c_4$ | s⇓A | s⇑A |
| | $w_{41}$ | L⇓A | L⇑A |
| | $w_{42}$ | s⇓A | s⇑A |
| | $b_4$ | n/e | n/e |
| | $d_4$ | n/e | n/e |
| | $h_4$ | n/e | n/e |
| | $g_4$ | n/e | n/e |
| | $K_{VN\_Re}$ | s⇑A | s⇓A |

$\Uparrow$= *Increase*, $\Downarrow$= *Decrease*, $s$ = *Small*, $L$ = *Large*, $n/e$ = *No Effect*, $A$ = *Amplitude*, $F$ = *Frequency*.

It is known that the pacemaker cells are able to depolarize spontaneously. The rate of depolarization is determined by the electrical characteristics and by the autonomic nervous system. The autonomic nervous system affects the rate and force of heart contractions. Acetylcholine is a neurotransmitter associated with these modifications Gordan et al. (2015). On the other hand, the electric conduction system formed by atrioventricular cells, and

His-Purkinje system are specialized to carry current to myocardial cells. Our results are in agreement with this. We can see that the variation of $a_1$, $u_{11}$, $u_{12}$, $f_1$, $d_1$, $e_1$, parameters that the ECG can modify in duration. Then, the SAN was strongly sensitive. Furthermore, the effect in ECG of variations in the model parameters that represent the AVN and HPS is null.

According to our results, myocardial cells are sensitive to parametric variations. The ECG can modify in amplitude. The model presents sensitivity to the parameters associated with the QRS complex, which correspond to the ventricular depolarization. Furthermore, the ECG is robust to parameter variations associated with the P-wave, and the Ta-wave.

Additionally, the model presents sensitivity to the parameters associated with the T-wave which corresponds to the ventricular repolarization. The physiological effects correspond with an amplification of the T-wave. The physiological effects are shown in Table 4. It is known that the T wave is highly susceptible to hormonal, neurologic influences, Becker (2006). Our results are in agreement with this.

This study opens several lines of research worth pursuing in future work. It would be worthwhile to extend a similar investigation considering the mechanisms related to heart diseases, and arrhythmias. Furthrmore, theoretical analysis could better elucidate the role of noise in ECG dynamics.

## 5. CONCLUSION

We have characterized the effect of parametric variation on the electrocardiogram signal in the mouse heart. We experimentally obtained ECG signals to an isolated mouse heart to compare with numerical simulations. Our results provide evidence that electrical conducting cells maintain ECG characteristics in the face of parametric variations.

## ACKNOWLEDGEMENTS

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