Motions of the human cardiac cell electrophysiology model

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Abstract. One of the many processes in the human body on which our lives depend is the proper propagation of the electrical signal in the heart tissue. This propagation is dependent on the work of each heart cell, and even small variations in the synchronous work of these cells can lead to life-threatening conditions. A proper understanding of cardiac electrophysiology is therefore essential to understanding heart function and treating heart disease. In this work, cardiac electrophysiology is investigated using a mathematical model of a human ventricular cell (Bueno-Orovio-Cherry-Fenton model). This model is paced by regular stimulation impulses, and its responses to this stimulation are analyzed in terms of their dynamic properties, and the dependence of its dynamic parameters for the frequency and amplitude of stimulation. For this analysis, classical and modern tools from the field of dynamic systems theory (e.g. entropy measures, Fourier spectra, the 0-1 test for chaos) are used.

1. Introduction
The heart is a very complex organ on which work each person’s life depends. It is controlled by electrical signals that determine our heart rate. With an improperly given electrical signal, the heart can enter a state of ventricular fibrillation that is incompatible with life. From the dynamic systems point of view, ventricular fibrillation is spatiotemporal chaos [1]. The dynamic properties of cardiac tissue are therefore examined in detail and many papers are dealing with this topic [2, 3, 4, 5]. Among such studies, we can mention, for example, works in which parameters are sought in which chaotic and regular responses of cardiac cell models occur [2, 3] or describes the transitions between the different types of the dynamic behavior of these models [5]. Researchers are also describing the behavior of ventricular fibrillation [4], and designing a control scheme to prevent instability in cardiac tissue [6].

In this work, the dynamic properties of the Bueno-Orovio-Cherry-Fenton model [7] are investigated. This model is paced by different amplitude and frequency settings. The responses of this model are then examined in terms of their regularity and complexity.

The paper is organized as follows. In Section 2, the Bueno-Orovio-Cherry-Fenton model is introduced. In Section 3, the main findings of this study are summarized. These main findings include time and frequency domain signal analysis in Subsection 3.1. Then using the 0-1 test for chaos for detection of chaotic and regular data in Subsection 3.2. The results of the complexity analysis of the obtained time series by entropy measure can be found in Subsection 3.3. Section 4 summarizes the main results of this study.
2. Bueno-Orovio-Cherry-Fenton model

The Bueno-Orovio-Cherry-Fenton model of human ventricular cell [7] was designed in 2008 and is defined by 4 differential equations (see Equation (1)). With this model, 5 different sets of parameters are defined (see table 1) approximating the behavior of the epicardial, endocardial, and midmyocardial cells, as well as two other ionic models of human ventricular cells (Priebe-Beuckelmann and Ten Tusscher et al. models). In this work, a parameter set describing the epicardial cell is used.

\[
\begin{align*}
\partial_t u &= J_{stim} - (J_{fi} + J_{so} + J_{si}) \\
\partial_t v &= (1 - H (u - \theta_v)) (v_{\infty} - v) / \tau_v^- - H (u - \theta_v) v / \tau_v^+ \\
\partial_t w &= (1 - H (u - \theta_w)) (w_{\infty} - w) / \tau_w^- - H (u - \theta_w) w / \tau_w^+ \\
\partial_t s &= ((1 + \tanh (k_s (u - u_{so}))) / 2 - s) / \tau_s
\end{align*}
\]

Equation (1)

The equation describing the time derivation of the transmembrane potential \( \partial_t u \) is described by ionic currents \( J_{fi} \) (defining membrane depolarization), \( J_{so} \) (defining membrane repolarization), and \( J_{si} \) (balances the current \( J_{so} \) during the plateau phase). The definitions of these ionic currents can be seen in Equation (2).

\[
\begin{align*}
J_{fi} &= -v H (u - \theta_v) (u - \theta_v) (u_a - u) / \tau_{fi} \\
J_{so} &= (u - u_a) (1 - H (u - \theta_w)) / \tau_o + H (u - \theta_w) / \tau_{so} \\
J_{si} &= -H (u - \theta_w) w s / \tau_{si}
\end{align*}
\]

The stimulation function \( i_{ext} \) for \( A = 80 \mu A/cm^2 \), and \( c = 20 \) ms. Parameter \( c \) is labeled by red color.

\[
i_{ext} = \begin{cases} 
A \sin(\pi(t - n(c + 1))), & t \in [n(c + 1), n(c + 1) + 1], \ n \in \mathbb{N} \cup \{0\}, \\
0, & t \notin [n(c + 1), n(c + 1) + 1], \ n \in \mathbb{N} \cup \{0\}.
\end{cases}
\]

Equation (3)

In these equations, there are several time parameters described as a function of the transmembrane potential \( u \). These functions are defined as follows:

\[
\begin{align*}
\tau_v^- &= (1 - H (u - \theta_v)) \tau_{v1} + H (u - \theta_v) \tau_{v2} \\
\tau_w^- &= \tau_{w1} + (\tau_{w2} - \tau_{w1}) (1 + \tanh (k_w (u - u_w))) / 2 \\
\tau_o &= \tau_{o1} + (\tau_{o2} - \tau_{o1}) (1 + \tanh (k_{so} (u - u_{so}))) / 2 \\
\tau_s &= (1 - H (u - \theta_w)) \tau_{s1} + H (u - \theta_w) \tau_{s2} \\
\tau_0 &= (1 - H (u - \theta_0)) \tau_{01} + H (u - \theta_0) \tau_{02}.
\end{align*}
\]

Equation (4)
Table 1. Model parameters [7].

| Parameter       | EPI | ENDO | M   | PB  | TNNP |
|-----------------|-----|------|-----|-----|------|
| $u_o$           | 0   | 0    | 0   | 0   | 0    |
| $u_u$           | 1.55| 1.56 | 1.61| 1.45| 1.58 |
| $\theta_v$      | 0.3 | 0.3  | 0.3 | 0.35| 0.3  |
| $\theta_w$      | 0.13| 0.13 | 0.13| 0.13| 0.015|
| $\theta_v^+$    | 0.006| 0.2  | 0.1 | 0.175| 0.015|
| $\theta_o$      | 0.006| 0.006| 0.005| 0.006| 0.006|
| $\tau_{v1}$     | 60  | 75   | 80  | 10  | 60   |
| $\tau_{v2}$     | 1150| 10   | 1.4506| 1150| 1150 |
| $\tau_v^+$      | 1.4506| 1.4506| 1.4506| 1.4506| 1.4506|
| $\tau_{v1}$     | 60  | 6    | 70  | 140 | 70   |
| $\tau_{v2}$     | 15  | 140  | 8   | 6.25| 20   |
| $k_v$           | 65  | 200 | 200 | 65  | 65   |
| $u_w$           | 0.03| 0.016| 0.016| 0.015| 0.03 |
| $\tau_w^+$      | 200| 280 | 280 | 326 | 280  |
| $\tau_{fi}$     | 0.11| 0.1 | 0.078| 0.105| 0.11 |
| $\tau_{o1}$     | 400 | 470 | 410 | 400 | 6    |
| $\tau_{o2}$     | 6   | 6   | 7   | 6   | 6    |
| $\tau_{so1}$    | 30.0181| 40   | 91  | 30.0181| 43  |
| $\tau_{so2}$    | 0.9957| 1.2  | 0.8 | 0.9957| 0.2 |
| $k_{so}$        | 2.0458| 2    | 2.1 | 2.0458| 2   |
| $u_{so}$        | 0.65| 0.65| 0.6 | 0.65| 0.65 |
| $\tau_{s1}$     | 2.7342| 2.7342| 2.7342| 2.7342| 2.7342|
| $\tau_{s2}$     | 16  | 2   | 4   | 16  | 3    |
| $k_s$           | 2.0994| 2.0994| 2.0994| 2.0994| 2.0994|
| $u_s$           | 0.9087| 0.9087| 0.9087| 0.9087| 0.9087|
| $\tau_{si}$     | 1.8875| 2.9013| 3.3849| 1.8875| 2.8723|
| $\tau_{w∞}$     | 0.07| 0.0273| 0.01 | 0.175| 0.07 |
| $w_{∞}$         | 0.94| 0.78| 0.5 | 0.9 | 0.94 |

The values $v_∞$ and $w_∞$ are defined as

$$
v_∞ = \begin{cases} 
1, & u < \theta_v^- \\
0, & u \geq \theta_v^- 
\end{cases}
$$

$$
w_∞ = (1 - H(u - \theta_o)) (1 - u/\tau_{w∞}) + H(u - \theta_o) w_∞^*.
$$

In these equations $H(x)$ stands for standard Heaviside function.

3. Main results

In this work, the Bueno-Orovio-Cherry-Fenton model was paced using a stimulation current defined by Equation (3), and the influence of the amplitude and frequency of the stimulation current (parameter $A$ and $c$) was investigated. The amplitude of the stimulation was varied from 0.45 to 1.00 in 0.025 steps. The $c$ parameter was examined in the range of 30 to 117.5 ms with a step of 2.5 ms. Each simulation was numerically calculated in the time range from 0 to 500 s using the explicit Runge-Kutta (4,5) formula as a $ode45$ solver in MATLAB. Due to the elimination of transients, the responses of the model in times from 0 to 250 s were removed. The time series thus obtained were subsampled using the stimulation frequency (1 sample was left in each stimulation period for future analysis).
Figure 2. Results for $A = 0.45$, and $c = 110$ ms. Left figure: modeled action potential (blue) with depicted points, that are analyzed (red); middle figure: analyzed time series (red); right figure: Fourier spectrum of analyzed time series.

Figure 3. Results for $A = 0.65$, and $c = 30$ ms. Left figure: modeled action potential (blue) with depicted points, that are analyzed (red); middle figure: analyzed time series (red); right figure: Fourier spectrum of analyzed time series.

3.1. Time series, Fourier spectra, and bifurcation analysis

The responses of the examined model can be divided into 4 categories.

- In the first category, the stimulus current was not strong enough to create an action potential (mainly simulations where $A < 0.5$). Only the triangular signal generated by insufficient cell stimulation can be seen in the simulated transmembrane potential. The frequency spectrum consists only of discrete spikes, which imply the regular motion of a dynamic system in phase space. Examples of these time series can be seen in Figures 2 and 3.
- The second group is also formed by a current that insufficiently stimulates the heart cell (mostly $A < 0.5$). In these cases, however, the frequency spectrum is continuous, which indicates the irregular movement of the dynamic system. This case is shown in Figure 4.
- An action potential has already been created in this category and the responses of the model form a regular motion represented by a discrete frequency spectrum. These time series can be found mainly for $A < 0.5$ and $c \geq 60$ (see Figure 5).
- The action potential is formed by an irregular motion that forms a continuous frequency spectrum. These responses are typical for pacing delay $c < 60$ and pacing amplitude $A > 0.5$. An example of this time series can be found in Figure 6.

Next, bifurcation diagrams were plotted for 3 stimulation amplitudes $A = 0.55, 0.85, 1$ (see Figure 7). It can be seen from these diagrams that the irregular movement of the action potential is concentrated at higher stimulation frequencies and the regular movement is detected at higher values of the stimulation delay $c$ (the bifurcation diagram is formed by individual points for these values of $c$). This corresponds to time series exploration.
3.2. The 0–1 test for chaos

The 0-1 test for chaos was performed to detect chaotic movements in the investigated time series. This test was introduced in 2004 in the article [8] (see also [9]). One of the advantages of this test is that it works directly with the time series and therefore it is not necessary to reconstruct the motion of the dynamic system in phase space. The output value of this test is between 0 and 1. In the case of the resulting values approaching 0, we consider the examined time series to be regular. For a final value approaching 1, we consider the time series to be chaotic. If the final value of this test is not close to 0 or 1((0.05, 0.95)) it is not possible to decide whether it is
Figure 7. Bifurcation diagram of analyzed time series for $A = 0.55$ (left), $A = 0.85$ (middle), and $A = 1$ (right).

a chaotic or regular movement.

This test has been used in many different studies to detect chaotic motion in data. An example is [10], where the author investigated the motion of a double pendulum forced by biharmonic excitation or paper [11] where it is used to find chaotic and regular motions of atomic force microscopy in tapping mode.

The 0-1 test for chaos is calculated in the following way. For a given set of observations $\phi(j)$ for $j \in \{1, 2, \ldots, N\}$ the translation variables $p_b(n) = \sum_{j=1}^{N} \phi(j) \cos(j b)$, and $q_b(n) = \sum_{j=1}^{N} \phi(j) \sin(j b)$ are calculated for a suitable set of values in $b \in (0, 2\pi)$. Subsequently, the mean square displacement is calculated using the following equation.

$$M_b(n) = \lim_{N \to \infty} \frac{1}{N} \sum_{j=1}^{N} [p_b(j + n) - p_b(j)]^2 + [q_b(j + n) - q_b(j)]^2$$

here $n \leq n_{cut}$ where $n_{cut} \ll N$. Next, the modified mean square displacement is estimated.

$$D_b(n) = M_b(n) - \left( \lim_{N \to \infty} \frac{1}{N} \sum_{j=1}^{N} \phi(j) \right)^2 \frac{1 - \cos(nb)}{1 - \cos(b)}.$$

Next, the correlation coefficients of $\xi$ and $\Delta$ for the fixed parameter $b$ are calculated.

$$K_b = \text{corr}(\xi, \Delta)$$

where $\xi = (1, 2, \ldots, n_{cut})$ and $\Delta = (D_b(1), D_b(2), \ldots, D_b(n_{cut}))$. Finally, the resulting value of the 0-1 test for chaos is obtained as the median of $K_b$.

$$K = \text{median}(K_b).$$

The resulting values of the 0-1 chaos test can be found in Figure 8. In this figure, it can be seen that chaotic movements occur mainly at low values of stimulation amplitudes ($A \leq 0.5$) or very fast stimulation frequencies ($c \leq 57.5$ ms). An example of these time series can be found in Figure 4, and 6. This chaotic area is disturbed by the regular movement detected especially at the stimulation delay $c = 50$ and $c = 52.5$ ms. Furthermore, a larger amount of regular behavior can be observed at the lowest investigated amplitude $A = 0.45$ (see Figure 2). Next, it can be noticed that the vast majority of regular behavior is concentrated in the region with a higher stimulation period and higher amplitude. An example of this time series can be found in Figure 5. In the figure, it can be also noticed several examples where it is not possible to decide on the regularity or chaos of the movement (points that are not drawn in red or blue). These time series occur mainly during transitions between regular and chaotic motion.
3.3. Entropy

Entropy calculations do not focus on the detection of regular and chaotic data but assess the overall complexity of the investigated time series. Therefore, using this method, it is not possible to decide whether it is a chaotic or regular movement of a dynamic system. The larger the value of entropy, the greater the complexity of the investigated time series. There are several types of entropies. For example, can be mentioned are topological entropy [12], Kolmogorov-Sinai entropy [13], approximate entropy [14] and sample entropy [15]. Sample entropy (SampEn) is a modification of approximate entropy (ApEn) developed by Steve M. Pincus [14]. The main difference between a sample and approximate entropy is that SampEn does not include self-similar patterns as ApEn does. The definitions of ApEn and SampEn can be found in [16]. Sample and approximate entropy are used in this work for the analysis of the investigated time series.

The results of these tests can be found in Figure 9. In this figure can be seen that the results obtained with SampEn and ApEn are very similar. The highest complexity of the analyzed time series is concentrated in two areas of higher stimulation frequencies. One area is the amplitude of less than 0.65 (A < 0.65) and has a stimulation delay of less than 35 ms (c < 35). Another area can be found for A ≥ 0.65 and c < 50. Higher data complexity can also be seen for stimulation amplitudes at which no cell stimulation occurs (A < 0.5). By comparing the results of the 0-1 test for chaos (see Figure 8) and entropy (see Figure 9) it can be noticed that the parameters where the higher entropy (data complexity) was measured are also parameters that the 0-1 test for chaos evaluated as chaotic.

4. Conclusions

In this study, the dynamic properties of the Bueno-Orovio-Cherry-Fenton model depending on the pacing amplitude and stimulation frequency were investigated. It has been shown that for regular stimulation, the model shows both regular as well as chaotic responses. These chaotic responses were detected using the 0-1 test for chaos. Furthermore, the complexity of the modeled action potential was investigated by calculating the approximate and sample entropy. It was found, that the modeled action potential reaches the highest complexity at high stimulation frequencies. By comparing the results of the 0-1 test for chaos and entropy was proved that time series with high signal complexity is also chaotic.

By comparing the results of this work with the dynamic properties of the improved Fenton-Karma model [2] and Beeler-Reuter model [3] it can be seen that the responses of the investigated
model are more chaotic at low stimulation amplitudes. Furthermore, it can be noted that the action potential of the Bueno-Orovio-Cherry-Fenton model is not chaotic for the stimulation delay of \( \geq 60 \) (unlike other models). These differences in dynamic parameters can have several causes. These may be the properties of parametric sets examined in these works. Furthermore, this phenomenon can be caused by the way of evaluating the dynamic properties of a given model, or it can be the properties of the modeled equations.

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